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Gold-catalyzed reactions of C–H bonds

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1. Introduction

At the beginning of the last century, organic chemists began to use transition metal catalysts for forming carbon–carbon and carbon–heteroatom bonds. Since then, the formation of these bonds by using various transition metals such as Pd, Ni, Ru, Rh has been extensively investigated and documented in the literature.[1] Recent years have witnessed a tremendous growth in the number of gold-catalyzed highly selective chemical transformations.[2] The catalysis of organic reactions by gold compounds has been shown to be a powerful tool in organic synthesis.[3] Although gold was considered to be an inert metal for a long time, its ability to behave as a soft Lewis acid has only been recognized recently. Such a property allows gold to activate unsaturated functionalities such as alkynes, alkenes, and allenes, to create carbon–carbon and carbon–heteroatom bonds under extremely mild conditions.[4,5] Moreover, by pre-coordination gold may activate sp, sp^2, and sp^3 carbon–hydrogen bonds efficiently. This may provide new opportunities in organic chemistry using gold as catalyst. In 1986, the Ito–Hayashi asymmetric aldol reaction catalyzed by homogeneous gold was successfully reported for the first time.[6] Thereafter, Utimoto,[7] Teles[8] as well as the Hashmi group[9] and others[10] initiated an impressive growth of activities on homogeneous gold catalysis. The recent enormous interest on gold catalysis has been reflected in a number of excellent reviews already published on the subject.[1–5]

As part of our ongoing studies on metal-catalyzed atom-economical reactions,[11] we have been interested in using gold to facilitate the conversion of C–H bonds into other bonds. This report is focused on gold-catalyzed conversion of C–H bonds to form carbon–carbon and carbon–heteroatom (oxygen and nitrogen) bonds (Fig. 1). These approaches are summarized based on their reaction types. We apologize in advance for possible neglect on any relevant work on the subject. Due to their special reactivities, α-C–H bonds of carbonyl compounds has not been included.

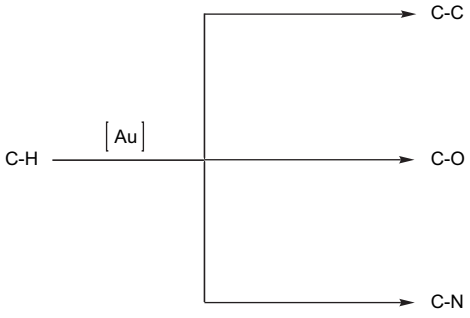


Figure 1. Gold-catalyzed reaction of C–H bonds.

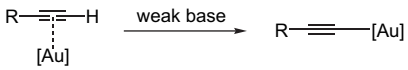


Figure 2. Gold–acetylide complex.

2. Gold-catalyzed C–C bond formations

2.1. C–C bond formation via the reaction of terminal alkyne C–H bonds

2.1.1. Addition of ortho-alkynylaryl aldehydes and terminal alkynes

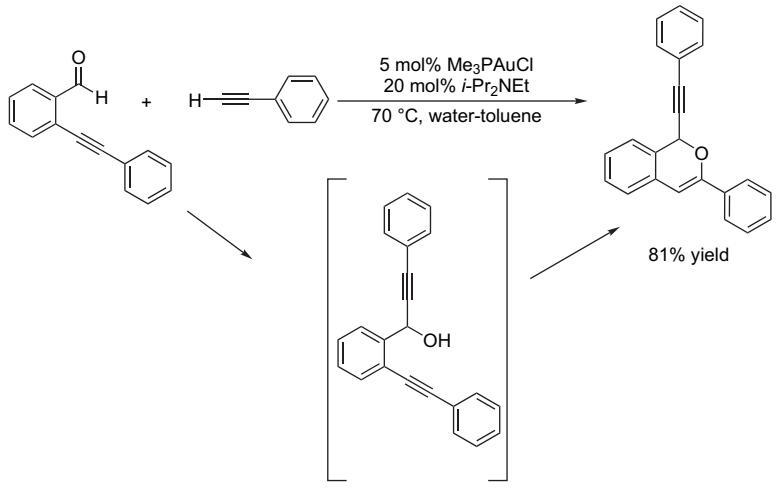
Alkynyl C–H bonds are weakly acidic. The strong coordination of terminal alkynes to gold catalyst pulls electron density away from the triple bond to gold, which will significantly increase the acidity of the alkynyl C–H bond. Consequently, gold–acetylides can be generated readily (Fig. 2).

Furthermore, there has been significant interest in recent years in developing organometallic reactions in aqueous media, which has the potential of simplifying synthesis (e.g., elimination of protection–deprotection steps) and minimizing environmental impacts.[6] The soft-nature of gold–alkyne coordination suggests that the formation of gold–acetylide (an organometallic reagent) and the further reaction of such organometallic reagents will tolerate water (a hard acid and base). Indeed, Li and Yao[12] developed a highly efficient gold-catalyzed Grignard-type alkynylation of *ortho*-alkynylaryl aldehydes in water in the presence of a catalytic amount of a tertiary amine base, *i*-Pr_2NEt. In addition, gold further catalyzed an intramolecular cyclization of the hydroxyl-alkyne intermediate, leading to 1-alkynyl-1*H*-isochromenes directly (Scheme 1). Such isochromenes are common structural units in natural products and exhibit interesting biological activities such as antibiotic properties.[13] The reaction was found to be dually promoted by an electron-donating phosphine ligand and the presence of the *ortho*-alkyne. In addition, water was found to be essential to obtain high conversions.

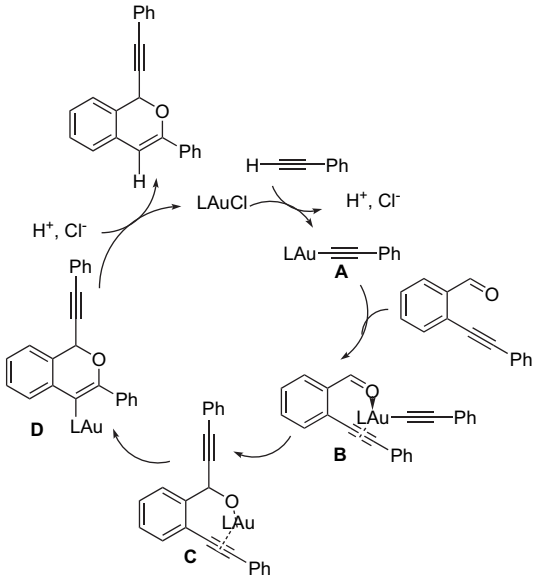
The reaction was proposed to proceed by the initial reacting of terminal alkynes with $ClAuPMe_3$ in the presence of a weak base, generating the gold(I)–acetylide species **A** (Scheme 2). Then, formation of intermediate **B** through chelation activated the carbonyl group. Addition of the acetylide to aldehyde gave intermediate **C**, which then cyclized to give the vinyl–gold intermediate **D**. Protonolysis of the carbon–gold bond gave the final product and regenerated the catalyst.[14,15]

2.1.2. Addition of aldehydes, terminal alkynes, and amines

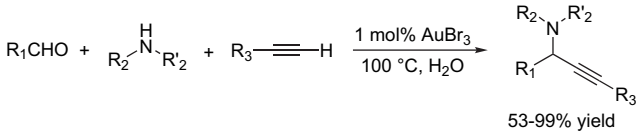
The formation of propargylamines via the addition of acetylenic moiety to a C=N bond is a useful method in synthesis.[16] Instead of using tertiary amines, primary amines and secondary amines can form imines and iminium ions. In water, equilibriums exist between their formations and hydrolysis. The imine and iminiumintermediates are possible to react with gold–acetylide intermediate in situ, which can drive the reaction to give alkyne-imine and alkyne-iminium addition products in water. Recently, Li and Wei[17] developed a highly efficient direct coupling of aldehyde, alkyne, and a secondary amine (A^3-coupling) catalyzed by both Au(III) and Au(I) under such conditions (Scheme 3). Au(0) was found to be inactive. In addition to gold, the reaction can also be catalyzed by other transition metals such as Cu(I),[18] [Cu–Ru],[19] Ir(I),[20] and Ag(I)[21] under neat conditions,[19] in organic solvents,[20] in ionic liquids,[21] and in water.[19,21] The gold-catalyzed A^3-coupling



Scheme 1.



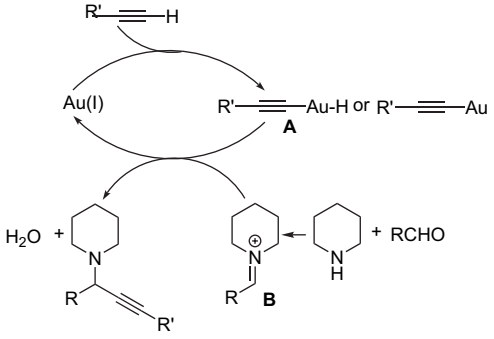
Scheme 2.



Scheme 3.

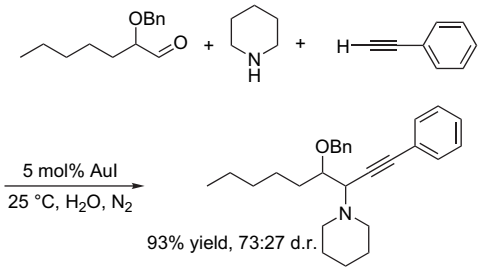
appears particularly effective. No co-catalyst or activator is needed for the gold-catalyzed reaction. The corresponding propargylamine products were obtained in excellent yields using less than 1 mol % of catalyst. The gold-catalyzed A^3-coupling tolerates the use of both aromatic and aliphatic aldehydes with alkynes and amines. With aromatic aldehydes, the A^3-coupling proceeded efficiently (95–99% yield). Whereas aliphatic aldehydes, gave the propargylamine products with modest yields (53–75%) in some cases due to the trimerizations of some aliphatic aldehydes. The A^3-coupling was efficient only with dialkyl amines. Anilines gave the corresponding products in lower yields and no desired products were observed with *N*-alkylanilines. The reaction was very clean with almost quantitative yield when water was used as solvent, while the reaction resulted in low conversions and undefined by-products when organic solvents such as THF, toluene, and DMF were used.

The reaction mechanism was proposed involving the activation of the C–H bond of alkyne by a Au(I) species[22] (for $AuBr_3$-catalyzed, Au(I) can be generated in situ from reduction of Au(III) by the alkyne) (Scheme 4). The gold–acetylide intermediate **A** thus generated reacted with the iminium ion **B** generated in situ from aldehydes and secondary amines to give the corresponding propargylamine and regenerated the Au(I) catalyst for further reactions. Alternatively, a simple substitution of H by Au(I) or Au(III) ion will also generate a gold–acetylide intermediate, which can react with the iminium intermediate to give the addition product.



Scheme 4.

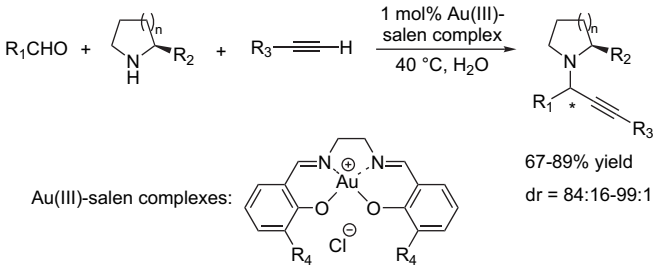
When the three-component coupling was carried with α-oxyaldehydes, alkynes, and amines in water by using gold, silver, and copper catalysts, gold(I) was found to be the most effective catalyst in this reaction to afford propargylamines in good yields and moderate diastereoselectivities[23] (Scheme 5). On the other hand,



Scheme 5.

silver catalysts showed the best catalytic activities on non-coordinating α-alkyl-substituted aldehydes.[23]

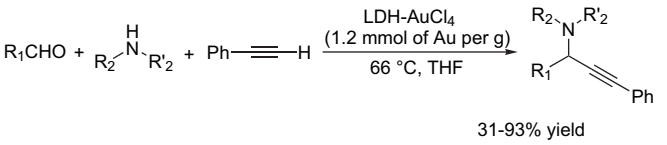
Later Che et al.[24] reported that 1 mol % of gold(III)–salen complexes catalyzed the three-component coupling reaction of aldehydes, chiral amines, and alkynes in water at 40 °C (Scheme 6). They prepared and characterized the gold(III)–salen complexes according to a known literature procedure.[25] The salen ligand was refluxed in CH_2Cl_2/EtOH with $KAu(III)Cl_4$ in the presence of NH_4PF_6. The addition of diethyl ether induced the precipitation of the desired gold(III)–salen complexes. The latter catalyzed three-component coupling reaction efficiently to afford a variety of propargylamines with excellent yields and excellent diastereoselectivity (67–89% yield; dr: up to 99:1). In addition this reaction allowed the synthesis of new propargylamine-modified artemisinin derivatives with modest yield (up to 59%). Their cytotoxicities were obtained with IC_{50} values up to 1.1 μM against a human hepatocellular carcinoma cell line (HepG2).



Scheme 6.

The one-step synthesis of 1-substituted 3-aminoindolizines (Scheme 7) using 1 mol % $NaAuCl_4$-catalyzed three-component reactions of aldehydes, amines, and alkynes followed by cycloisomerization reaction under solvent free or in H_2O at 60 °C was successfully reported by Liu and Yan.[26] Other gold catalyst such as $AuCl_3$ and AuCl afforded the desired product at 60 °C with 86% and 20% yields, respectively. However, at room temperature a longer reaction time was required and lower product yields were observed using $NaAuCl_4$. With respect to amines, secondary amines afforded moderate to excellent yields of indolizine derivatives (68–98%); however, similar to earlier reports primary amines such as $PhNH_2$ could not be used for this reaction. On the other hand, no electronic effect was noticed on the arylalkynes and the reaction gave a high reactivity in most cases (88–95%). Alkyl alkynes such as 1-octyne or functionalized alkyne could also be successfully incorporated into the indolizine products (54–66%). The use of pure α-amino acid derivatives with aldehydes and alkynes produces the corresponding indolizines without loss of enantiomeric purity (ee=99%).

Kantam et al.[27] reported the use of layered double hydroxide-supported gold (LDH–$AuCl_4$) as heterogeneous catalyst for the generation of propargylic amines in nearly quantitative yields via three-component coupling of aldehydes, amines, and an alkyne (Scheme 8). This reaction was highly efficient with a variety of aromatic, aliphatic, cyclic, and heterocyclic aldehydes. In addition, cyclic and aromatic amines gave excellent yields of propargylamines, whereas the yield was moderate with morpholine (60%). On the other hand, the yields were lower with aliphatic alkynes such as 1-octyne and 1-decyne (30% and 50% yield, respectively). The heterogeneous catalyst (LDH–$AuCl_4$) was prepared based on the literature method.[28] The catalyst can be recovered quantitatively and reused twice. The efficiency decreased in the second and third cycles from 83% to 40%, respectively, probably due to the generation of non-active Au(0) species. The non-catalytic activity with Au(0) in the three-component coupling of aldehydes, amines, and alkynes was already reported by Li and Wei.[17]

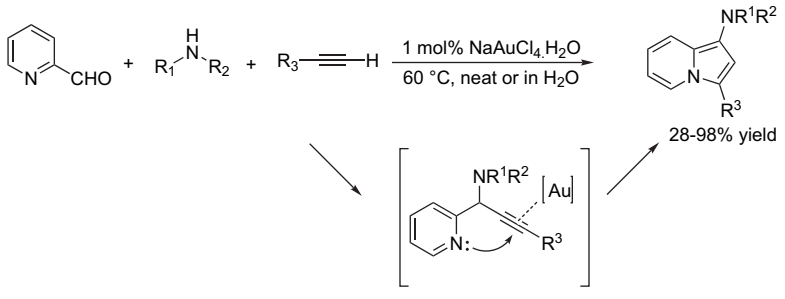


Scheme 8.

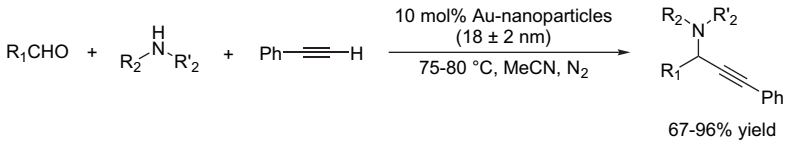
Kidwai et al.[29] reported an efficient and recyclable Au-nanoparticle catalyst for the A^3-coupling reaction of aldehyde, amine, and alkyne via C–H activation (Scheme 9). The reaction catalyzed by Au-nanoparticle required higher temperatures (80 °C) and coordinating polar solvents such as MeCN, MeOH, and THF. They showed that the catalytic activity of Au-nanoparticles was depending on the nanoparticles' size. Therefore Au-nanoparticles with 18±2 nm particle size were the most efficient and gave excellent yields (92%). The catalyst was successfully recycled and reused with only slight drop in activity although the rate of the reaction decreased. Heterocycles and electron-deficient aromatic aldehydes gave better yields compared to electron-donating aromatic aldehydes, which slow down the rate of the reaction. In this study, only cyclic secondary amine substrates such as piperidine, morpholine, and pyrrolidine were reported with high yields (67–97%).

2.1.3. *Addition of imines, acyl chlorides, and terminal alkynes*

N-Acylimines and *N*-acyliminium ions are relatively more electron-deficient than the corresponding imines and iminium ions. Such structures are more reactive towards electron-rich nucleophiles such as organometallic reagents than the imine and iminium counterparts. Indeed, in 2002 Li et al. reported the first coupling of alkynes with *N*-acylimines and *N*-acyliminium ions, generated in situ in water, to produce propargyl amide derivatives catalyzed by CuBr.[30] Alternatively, Arndtsen and Black[31] reported an efficient method for the synthesis of propargylamides in a one-pot catalytic synthesis from imines, acid chlorides, and terminal alkynes in dry CH_3CN catalyzed by CuI at room temperature. A similar coupling reaction of alkyne with acyliminiums catalyzed by zinc was reported by Carreira.[32] In 2005, Li and Wei[33] reported a gold-catalyzed direct addition of alkynes to an active acyliminium ion, which was generated in situ from an imine and an acid

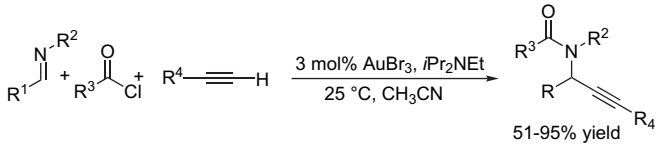


Scheme 7.



Scheme 9.

chloride, to afford propargylamides (Scheme 10). The reaction was efficiently catalyzed with 3 mol % of $AuBr_3$ in the presence of *i*-Pr_2NEt base in acetonitrile. Other solvents such as hexane, toluene, DCM, and THF are less effective. In the presence of aromatic aldehyde and aromatic acyl chloride, aliphatic amines gave higher yields (51–95%) than aromatic amines (48–54%). The best results were obtained with benzoyl chloride and *p*-toluoyl chloride as the acylation reagents.

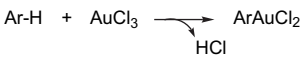


Scheme 10.

2.2. C–C bond formation via the hydroarylation of alkynes

2.2.1. Intermolecular addition of arenes to terminal alkynes

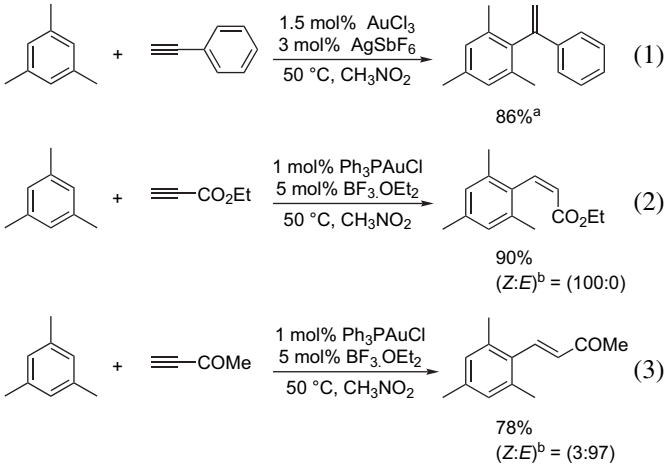
The coordination of alkyne to gold activates alkynes and renders them prone towards nucleophilic attacks. Previously, various oxygen and nitrogen nucleophiles have been added efficiently to alkynes catalyzed by gold.[1–5] In addition to oxygen and nitrogen-based nucleophiles, various carbon-nucleophiles also added efficiently to alkynes catalyzed by gold. The direct addition of arenes to alkynes to form C–C bonds via C–H functionalization provides efficient and atom-economical synthetic methods.[34] Such reactions have attracted extensive research efforts. In 1931, Kharasch and Isbell demonstrated that anhydrous gold(III) chloride can react with neat benzene, toluene, or other aromatic compounds to form arylgold(III) complexes at room temperature[35] (Scheme 11). Subsequent studies of this chemistry led to the isolation and characterization of several arylgold(III) species generated from the reaction.[36] This auration reaction was shown to proceed in an electrophilic manner.[37] In one case, arylgold(III) species were shown to be stabilized by binding to 2,6-lutidine. This lutidine-bound phenylgold(III) complex reacted with phenylacetylene in a stoichiometric manner upon heating to give high yields of diphenylacetylene product.[38] The mechanism of this reaction, however, is still not clear.



Scheme 11.

Reetz and Sommer[39] reported the direct addition of arenes to triple bonds with different gold catalysts. For example, 1,3,5-trimethylbenzene added to the internal alkyne carbon in the presence of $AuCl_3/AgSbF_6$ (Eq. 1, Scheme 12). Both the regio- and stereoselectivities of hydroarylation have been completely reversed with different electron-deficient terminal alkynes; the use of ethyl propiolate in the presence of $Ph_3PAuCl/BF_3{\cdot}OEt$ gave exclusive (*Z*)-selectivity (Eq. 2, Scheme 12) whereas in case of 3-butyne-2-one (*E*)-selectivity was observed (Eq. 3, Scheme 12).

Depending on the nature of the alkynes used, Reetz and Sommer[39] proposed two plausible mechanisms. The regioselectivity of the addition was suggested to be determined by

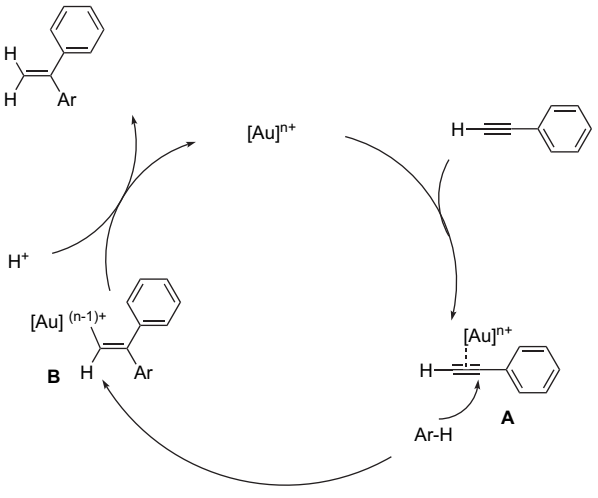


[a] GC yield (determined with n-hexadecane as an internal standard).
[b] Determined by GC or NMR spectroscopy.

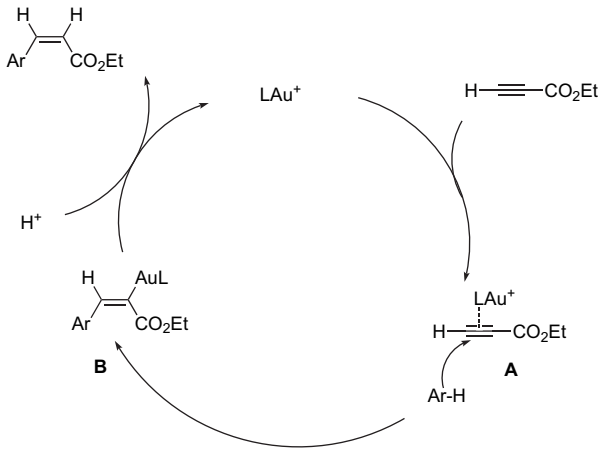
Scheme 12.

electronic factors. In the case of phenylacetylene, the π complex **A** undergoes electrophilic aromatic substitution with the electron-rich arene to form a vinyl–Au intermediate **B** (Markovnikov-type addition was observed). The simultaneously released H^+ protonates this intermediate, setting free the product as well as regenerating the catalyst (Scheme 13).

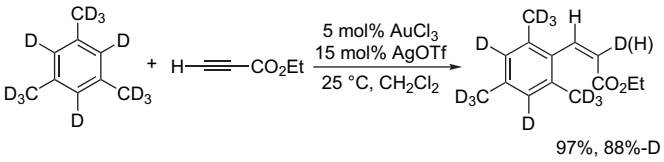
In the case of acetylenecarboxylic acid ester (ethyl propiolate) the mechanism is proposed in Scheme 14. The cationic gold complex coordinates to alkyne **A**, and nucleophilic attack of the arene from the opposite side leads to the formation of a vinyl–gold intermediate **B**, which is stereospecifically protonated with final formation of the (*Z*)-olefin. The regioselectivity is dominated by electronic factors in a gold-catalyzed Michael addition (anti-Markovnikov-type addition was observed). The formation of (*E*)-double bonds with ketone is due to isomerization of the initially produced (*Z*)-isomer (Eq. 3 in Scheme 12). Based on the proposed mechanism,



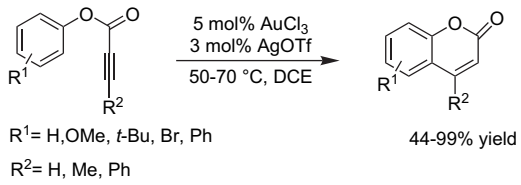
Scheme 13.



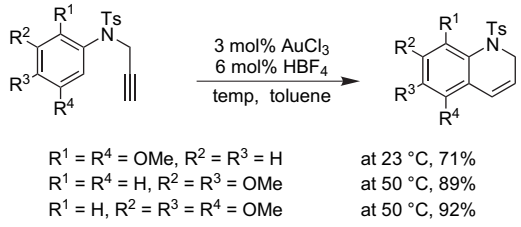
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

auration of arenes as a key step in the hydroarylation seems unlikely. It is believed that activation of the alkyne by Au-π complexation is involved, as has been postulated for other nucleophilic addition reactions such as oxygen, nitrogen, and sulfur.

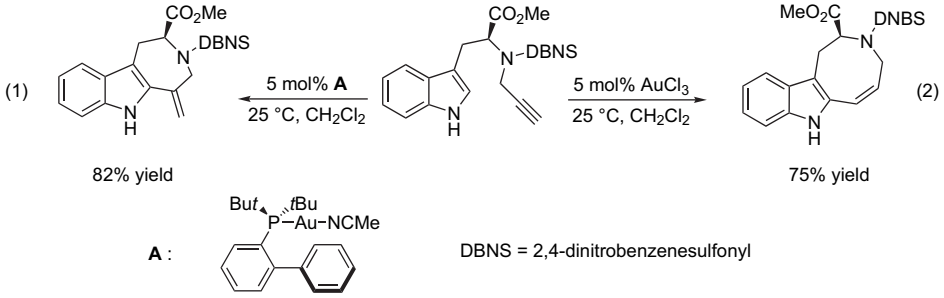
Shortly afterward, He and Shi[40] used a combination of $AuCl_3$/3×$AgSbF_6$ and $AuCl_3$/3×AgOTf as catalysts for the hydroarylation of electron-deficient alkynes, which showed enhanced activity and were effective for various arene substrates. In order to gain further insight of the mechanism, they performed an isotope experiment on the reaction of the deuterium-labeled mesitylene with an electron-poor terminal alkyne such as ethyl propiolate. The result showed that the D (H) incorporated into the vinyl part of the product comes mainly from the aromatic substrate (Scheme 15). These results seemed to support the involvement of a direct metalation of electron-rich arene groups by gold(III) species to form arylgold(III) and 1 equiv of acid. The silver salt might help to generate a more electrophilic gold(III) species from $AuCl_3$. $AuCl_3$ alone also worked but it gave a low yield of the product. The formed arylgold(III) species could add to electron-deficient alkynes to give the final products. This step could be aided by Lewis acid activation of the alkynes by metal ions or acid present in the reaction solution. However, they did not exclude the possibility that gold(III) simply works as Lewis acid to activate alkynes as Reetz and Sommer have proposed.[39]

2.2.2. *Intramolecular addition of arenes to alkynes*

He and Shi also described an efficient method for the preparation of coumarins from aryl alkynoates[40] (Scheme 16). This intramolecular addition was catalyzed by the more electrophilic gold species, generated in situ from 5 mol % of $AuCl_3$ and 15 mol % of AgOTf, in dichloroethane at room temperature. Various aryl alkynoates bearing electron-donating substituents on the aryl ring underwent intramolecular cyclization smoothly to give coumarins in good yields (44–99%). Mechanistically, auration of the arene was suggested as a key step in these hydroarylations.

Echavarren and Nevado[41] reported a similar intramolecular cyclization of *N*-propargyl-*N*-tosylanilines catalyzed by the electrophilic gold species, generated in situ from 3 mol % of Au(PPh_3)Me and 6 mol % of HBF_4, in toluene at different temperatures (Scheme 17). Only aryl alkynoates bearing electron-donating substituents were shown in this intramolecular cyclization and excellent yields were obtained in all cases (71–99%). Similar efficiency was also shown using Pt(II) as a catalyst but at a higher reaction temperature (100 °C).

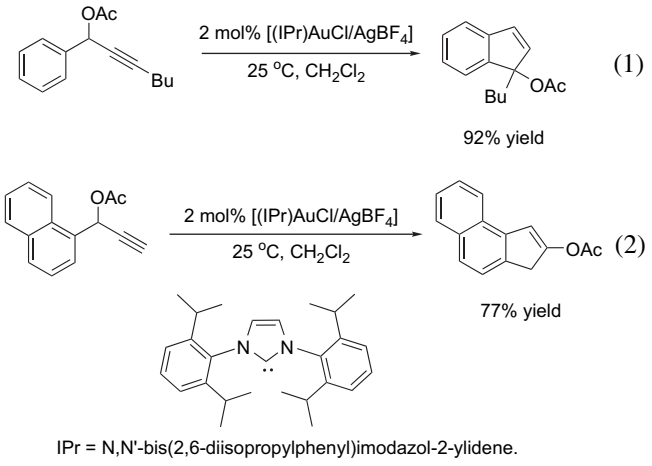
Echavarren et al.[42] also reported a facile annulation of seven- and eight-membered rings on indoles by cyclization with alkynes using Au(I) or Au(III) species as catalyst (Scheme 18). Various gold complexes and salts bearing bulky phosphanes[43] and *N*-heterocyclic carbene ligands,[44] were synthesized and tested in the intramolecular reaction of indoles with alkynes. They found that cationic Au(I) complex **A**, in CH_2Cl_2, was the best catalyst for the formation of seven-membered rings through 7-*exo*-*dig* cyclizations



Scheme 18.

(Eq. 1, Scheme 18); whereas the use of Au(III)Cl_3 catalysts in CH_2Cl_2 led to the formation of eight-membered rings through 8-*exo*-*dig* cyclizations (Eq. 2, Scheme 18).

At the same time, Nolan et al.[45] described a novel type of catalytic formation of various substituted indenes in the presence of 2 mol % of (IPr)AuCl/$AgBF_4$ in CH_2Cl_2. This chemoselective transformation proceeds under extremely mild reaction conditions using *N*-heterocyclic carbene ligands (NHC) (Scheme 19). In case of internal alkynes, the desired 3-butyl-3-yl acetate indene was obtained via a 1,3-migration of the acetate group followed by a cyclization through C–H activation of the arene (Eq. 1, Scheme 19). In the case of a terminal alkyne there was an initial 1,2-migration of the acetate group followed by an internal hydroarylation via C–H activation to afford the indene derivative (Eq. 2, Scheme 19). In general, the desired substituted indenes were not obtained in the presence of AuCl alone or AuCl/$AgBF_4$; while with $AgBF_4$ alone, only the equivalent allene was isolated and no cyclic product was observed. Various (NHC)AuCl complexes were synthesized[46] and used in the presence of silver tetrafluoroborate. Sterically demanding NHCs such as *N*,*N*′-di-adamantyl-imidazol-2-ylidene decreased the rate of the reaction. On the other hand, less encumbered NHCs such as 1,3,4,5-tetramethyl-2,3-dihydro-1*H*-imidazole as well as PPh_3 led to poor selectivity. Both tetrafluoroborate and hexafluorophosphate were suitable counterions whereas hexafluoroantimonate gave the desired product with a lower yield.



Scheme 19.

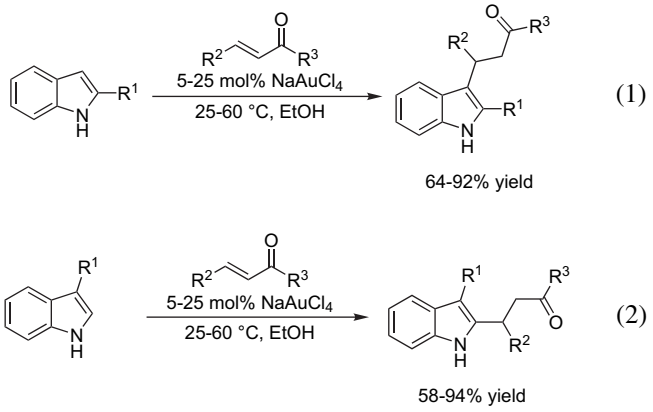
Wang et al.[47] reported the synthesis of indene derivatives by mixing propargylic dithioacetals with 5 mol % of AuCl in toluene at 80 °C (Scheme 20). The five-membered dithioacetal ring was expanded to a six-membered ring through vinylcarbenoids. In addition, AuCl(PPh_3) and $AuCl_3$ also afforded the corresponding product as the only isomer. The $PtCl_2$-catalyzed reaction gave a complicated mixture while Ru(II) and Rh(II) catalysts were not reactive and the starting material was recovered. Various substrates gave the corresponding indene derivatives in high yields (91–99%).

Scheme 20.

2.3. Addition of arenes/heteroarenes to alkenes

2.3.1. *Addition of indoles to α,β-unsaturated ketones*

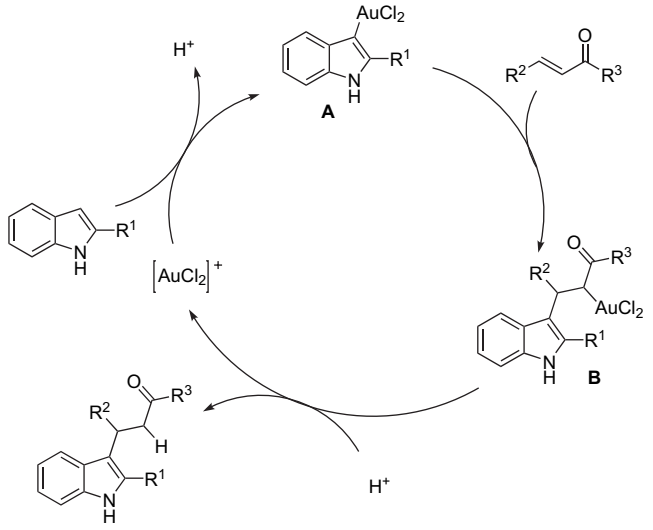
Similar to the addition of arenes to alkynes, Arcadi et al.[48] have shown an efficient gold-catalyzed conjugate addition of indole derivatives to α,β-enones using $NaAuCl_4$ as a catalyst (Scheme 21). In 2006, they reported the gold-catalyzed reactions of indoles/pyrroles with 1,3-dicarbonyls[49] and 7-aza-indole with α,β-enones.[50] The method has high functional group tolerance and regioselectivity, as well as wide substrate scope under relatively mild conditions.



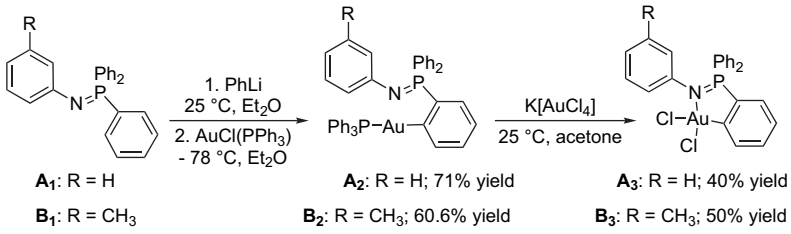
Scheme 21.

A tentative mechanism for this addition is illustrated in Scheme 22. Regioselective direct electrophilic attack of the gold catalyst at the indole forms an indolyl–gold species **A**, which subsequently undergoes addition reaction to α,β-enones to give the σ-alkyl–gold species **B**. In contrast to the behavior of similar σ-alkyl-palladium intermediates,[51] which undergo a β-H elimination reaction, the organogold derivative is prone to protonation by the proton set free during the electrophilic aromatic substitution step. β-H elimination reactions are slow with gold catalysis.[52] Protonolysis of **B** liberates the desired product and recycles the catalyst.

Recently, He and Shi[53] reported a similar gold(III)-catalyzed addition of various heterocycles to activated olefins and alkynes. A variety of function groups such as aldehyde, carboxylic acid, and nitrile could be tolerated under mild conditions (acetonitrile at room temperature) and afforded the desired products in high yields (41–97%).



Scheme 22.



Scheme 23.

2.3.2. Addition of furans and arenes to α,β-unsaturated ketones

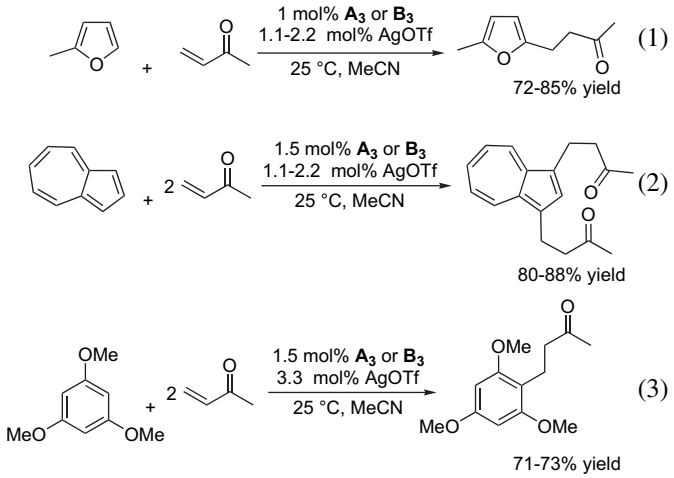
In 2007, Urriolabeitia et al.[54] synthesized new organogold(III) iminophosphorane complexes based on C, N-pincer ligands (Scheme 23). The air-stable white solid gold(I) compounds **A_3** and **B_3** were obtained in two steps in modest yields. Lithiation of the iminophosphorane ligands (**A_1** and **B_1**) followed by reacting with $AuCl(PPh_3)$ at low temperature gave compounds **A_2** and **B_2** in 71% and 60.6% yields, respectively. Transmetalation with organogold derivatives **A_2** and **B_2** with $KAuCl_4$ afforded cycloaurated gold(III)[55] compounds **A_3** and **B_3** in 40% and 50% yields, respectively (Scheme 23).

These cycloaurated gold(III) compounds **A_3** and **B_3** catalyzed the addition of 2-methylfuran to methyl vinyl with yields up to 85% (Eq. 1, Scheme 24). They also reported the addition of an electron-rich arene such as azulene (Eq. 2, Scheme 24) or 1,3,5-trimethoxybenzene (Eq. 3, Scheme 24) to methyl vinyl ketone in good yields. In all examples only 1–1.5 mol % of the cycloaurated gold(III) catalysts and 1.1–3.3 mol % of AgOTf were necessary to obtain high yields of the desired products (71–88%). These results showed clearly that the C, N-pincer ligands stabilize the gold(III) center and generate active catalytic species in the addition reaction. The most likely mechanism of the addition involves the electrophilic auration of C–H bonds of 2-methylfuran and the electron-rich arenes as a first step.

2.4. C–C bond formation by hydroarylation of others via C–H bond functionalization

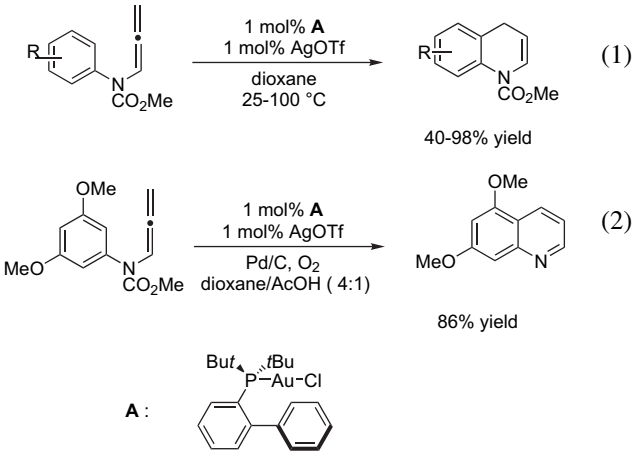
2.4.1. Intramolecular addition of electron-rich arenes to allenes

Very recently Ohno et al.[56] reported a gold-catalyzed intramolecular hydroarylation of allenes for the synthesis of dihydroquinoline derivatives (Scheme 25). Among the catalysts investigated, the combination of 1 mol % of gold complex **A** with 1 mol % of AgOTf in dioxane was the most effective and produced the desired products in good yields (Eq. 1, Scheme 25). Other



Scheme 24.

catalysts such as AuCl, $AuCl_3$, and $PtCl_2$ are slightly less effective for the desired cyclization (yields 29–77%). $(Ph_3P)AuCl$ in the presence of AgOTf gave 56% of the desired product; whereas $Pd(OAc)_2$, $CuBr_2$, and AgOTf afforded a mixture of various by-products as well as the recovered starting material. In case of *N*-allenylaniline, and using the optimum conditions (**A**/AgOTf), the hydroarylation took place selectively at the terminal allenic carbon leading to a highly selective formation of six-membered rings. A one-pot synthesis of quinoline was reported in high yield (86%) by adding a reagent (Eq. 2, Scheme 25). Using AcOH as a co-solvent accelerated the reaction. Finally, such an intramolecular hydroarylation was also applied in the synthesis of chromene derivatives.

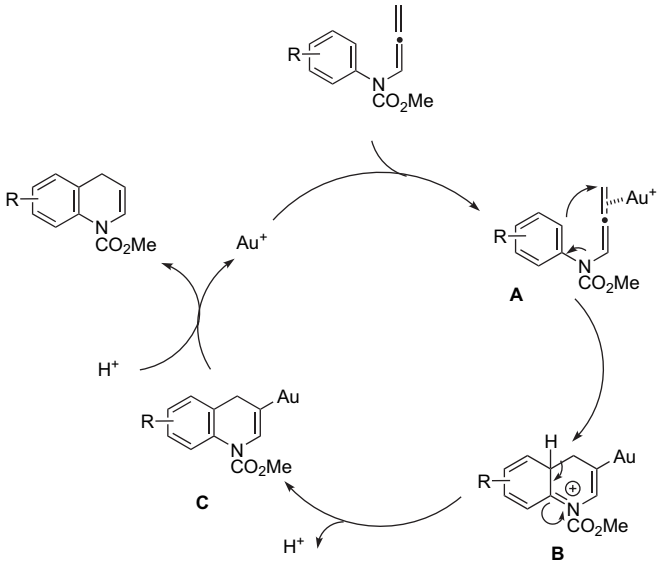


Scheme 25.

Mechanistically, coordination of the allene with the cationic gold(I) activated the allene **A**. Nucleophilic attack of **A** by an electron-rich arene afforded vinyl–gold complex **B**. Deprotonation of the vinyl–gold complex **B** gave the vinyl–gold intermediate **C**. Reaction of the gold–carbon bond with the proton generated in the previous step afforded the desired cyclic product and regenerated the cationic gold catalyst (Scheme 26). A deuterium experiment using AcOD showed that the presence of AcOH as co-solvent accelerated the protonation step from **C** and enhanced the overall rate of the reaction.

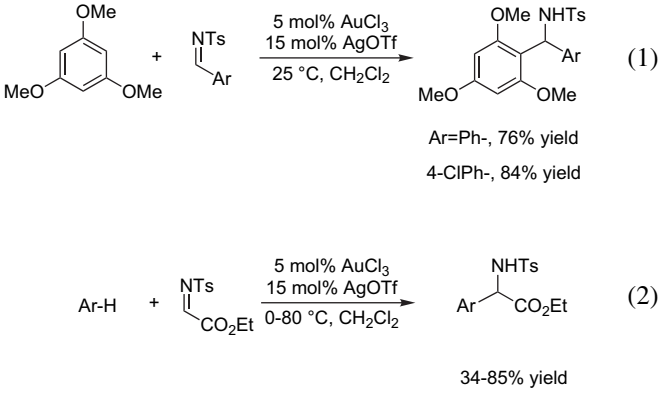
2.4.2. Intermolecular addition of electron-rich arenes to imines

In spite of extensive studies on the Friedel–Crafts-type addition of arenes to aldehydes, related reactions to imines are very rare. The prospect of an efficient aryl C–H auration followed by a nucleophilic addition to imines provided a possible alternative strategy to generate an equivalent of imino Friedel–Crafts reaction product. Following this reasoning, Li and Luo[57] recently reported an efficient gold/silver-catalyzed imino Friedel–Crafts-type reaction (Scheme 27). With 5 mol % of AuOTf as a catalyst, the reactions of electron-rich arenes and readily available imines proceeded efficiently (Eq. 1, Scheme 27). The process is simple and can be applied to a wide range of electron-rich arenes. In addition, various amino acid derivatives were synthesized under the same conditions in high



Scheme 26.

yields (Eq. 2, Scheme 27). The reaction was efficient with both aromatic and heteroaromatic compounds. However, under the same conditions highly electron-rich indole did not react and the starting material was recovered.



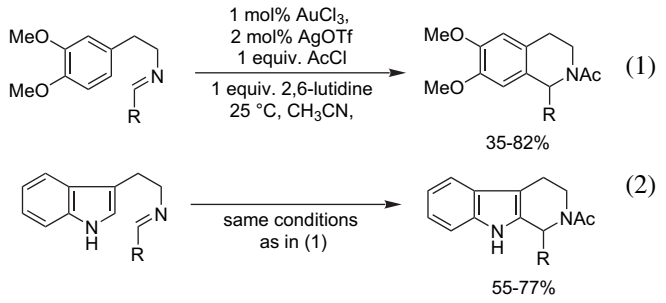
Scheme 27.

2.4.3. Intramolecular addition of electron-rich arenes to activated imines

Youn[58] has shown that gold(III) complexes can be used as catalysts for the Pictet–Spengler reaction. A variety of tetrahydroisoquinoline (Eq. 1, Scheme 28) and tetrahydro-β-carboline derivatives (Eq. 2, Scheme 28) could be obtained in good yields by using 1 mol % of $AuCl_3$ and 2 mol % of AgOTf as a combined catalyst system in acetonitrile in the presence of a base. The use of an acylating agent such as AcCl and Ac_2O was crucial to activate the imines. In the absence of an acylating agent, the reactivity decreased and the corresponding products were obtained in low yields. It was proposed that the reaction involved an imine activation by coordinating with the gold(III) complex.

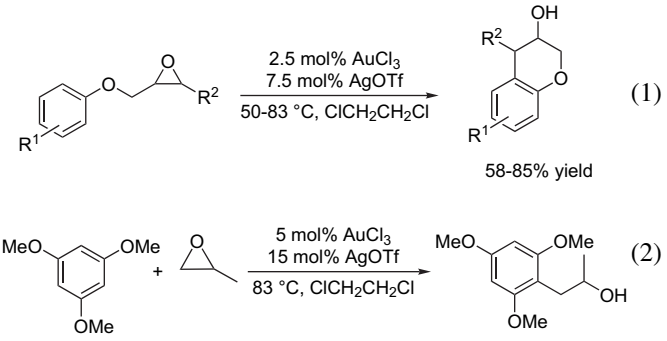
2.4.4. Addition of electron-rich arenes to epoxides

In addition to addition reactions, gold was also reported to be an efficient catalyst in the nucleophilic substitution of C–O bond by arenes. In 2004, He and Shi[59] reported a cyclization of electron-rich arenes with tethered epoxides catalyzed by gold(III) (Eq. 1, Scheme 29). With 2.5 mol % of AuOTf in dichloroethane, the reaction was



R = COOEt, Ph, *p*-NO_2-C_6H_4, *p*-OMe-C_6H_4, 2-(5-methylfuran-2-yl), 2-(6-methylpyridin-2-yl), cinnamyl, ^{n}pent

Scheme 28.

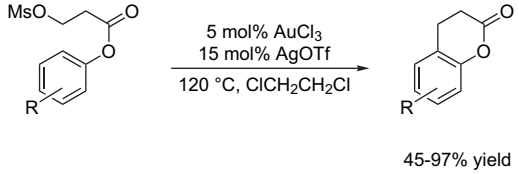


Scheme 29.

stereospecific and gave only *endo* addition products in good yields (58–85%); whereas using $AuCl_3$ alone as a catalyst gave only 10–20% yield of the desired products. For electron-rich arene substrates, the starting materials were converted in 4 h at 50 °C. On the other hand, a higher temperature and a longer reaction time were required for less electron-rich substrates (48 h at 83 °C). For the intermolecular reaction, it was necessary to increase the catalyst loading to 5 mol % in order to obtain the desired product. The S_N2 type addition of the trimethoxybenzene proceeded exclusively at the less hindered primary carbon of propylene oxide (Eq. 2, Scheme 29).

2.4.5. Intramolecular addition of electron-rich arenes to primary alcohol mesylate (S_N2 type reaction)

He and Shi[60] reported a gold(III)-catalyzed functionalization of aromatic C–H bond with primary alcohol triflate or methanesulfonate esters to construct C–C bonds. Linear substituted arene products were prepared efficiently using 5 mol % of AuOTf in dichloroethane at 120 °C. Chroman and benzopyranone derivatives were obtained in good yields by this method (Scheme 30). Mechanistic studies indicated the involvement of an arylgold(III) species as the reaction intermediate rather than a delocalized carbocation in a typical Friedel–Crafts-type reaction. The arylgold intermediate then reacted with the sulfonate ester to give the final product.

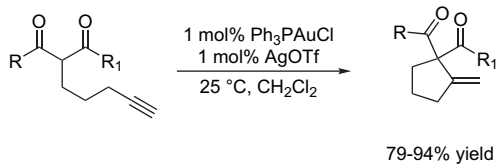


Scheme 30.

2.5. C–C bond formation via the addition of activated methylenes to alkynes and alkenes

2.5.1. Intramolecular addition of activated methylene to alkynes

Recently, Toste et al.[61] reported an intramolecular addition of 1,3-dicarbonyl compounds to alkynes using $Ph_3PAuCl/AgOTf$ as a catalyst in CH_2Cl_2 at room temperature (Scheme 31). This reaction did not work with Ph_3PAuCl alone as a catalyst. Only 1 mol % of the catalyst was required and a variety of β-ketoester substrates reacted efficiently. Steric effect was noticed only on the rate of the reaction and the yields were excellent in all cases (81–93%). In addition, the method was efficient for forming a variety of bicyclic rings, although an increased catalyst loading (5 mol %) was necessary to obtain high yields.

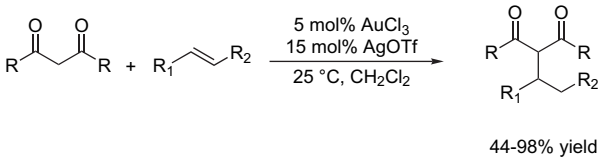


Scheme 31.

Two possible mechanisms for the Au-catalyzed addition of β-ketoesters to alkynes were proposed (Scheme 32). In mechanism **A**, the Au(I)–alkyne complex was attacked by the enol form of the ketoester, resulted in vinyl–Au intermediate $\mathbf{A_1}$, which was protonated to form the product. An alternative mechanism **B** proceeded by forming an Au-enolate, by direct auration of the α-ketoester, followed by a cis-carboauration of the alkyne to produce vinyl–Au intermediate $\mathbf{B_1}$, which was protonated to form the same desired product.

2.5.2. Intermolecular addition of activated methylene to acyclic alkenes

Nearly at the same time as Toste's alkyne addition,[61] a highly effective intermolecular addition of activated methylene compounds to alkenes was developed by Li and Yao[62] using $AuCl_3$/3×AgOTf in CH_2Cl_2 at room temperature (Scheme 33). In the absence of AgOTf, $AuCl_3$ did not catalyze the reaction. The active species appeared to be the gold(III)-cation. Replacing $AuCl_3$ by $(PPh_3)AuCl$ or *cyclo*-hexNCAuCl decreased the reactivity of the reaction. The use of CH_2Cl_2 as solvent gave the highest yield of the desired product compared to DCE and nitromethane. With THF or water as solvent, only a trace amount of or no product was obtained. Acyclic 1,3-diketones reacted with styrene and styrene derivatives more efficiently than cyclic 1,3-diketones. Only decomposition of the starting material was observed with esters such as dimethyl malonate and β-ketoesters, possibly due to the high Lewis acidity of $Au(OTf)_3$.

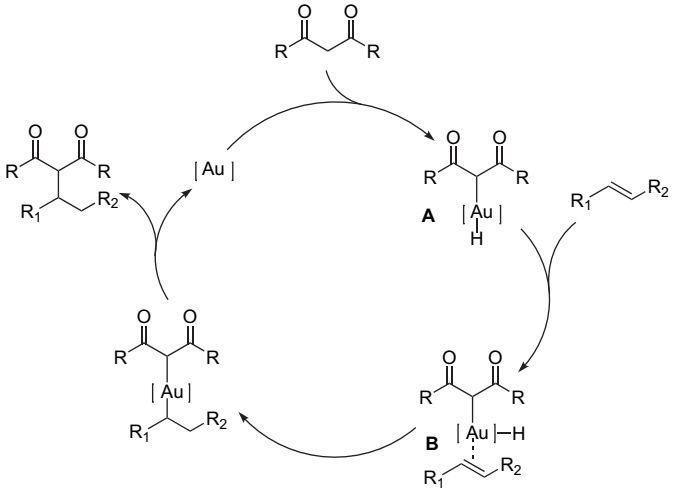


Scheme 33.

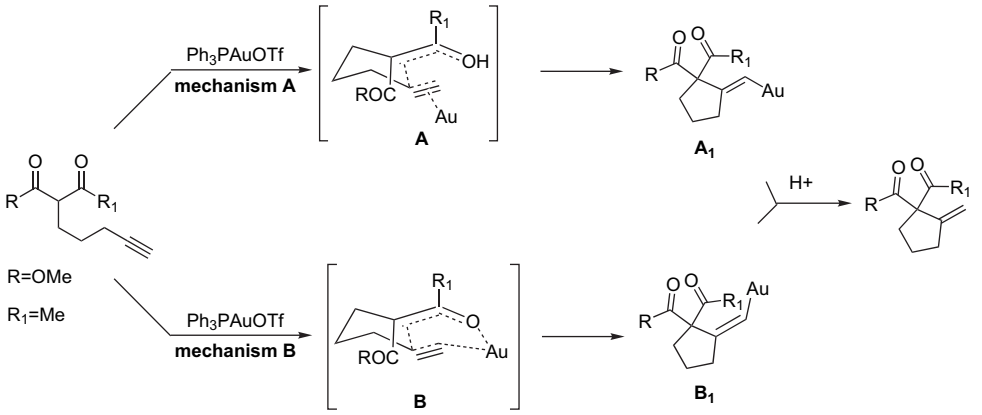
A tentative mechanism was proposed involving the activation of the C–H bond of the activated methylene by a Au(I) species **A** (generated in situ from the reduction of Au(III) by the activated methylene). The alkylgold hydride intermediate **B** then reacted with styrene to give the hydroalkyation product and regenerated the Au(I) catalyst for further reactions (Scheme 34). However, an alternative mechanism involving a Wacker's type activation of alkene by gold followed by a nucleophilic attack with 1,3-dicarbonyl cannot be excluded.

2.5.3. Intermolecular addition of activated methylene to cyclic alkenes

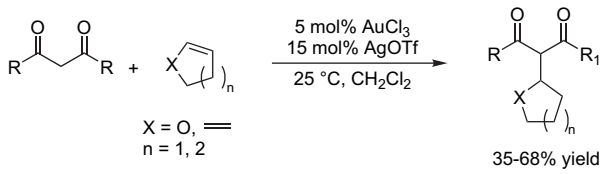
In 2005, Li and Nguyen[63] extended the intermolecular addition of activated methylene compounds to cyclic alkenes and dienes using $AuCl_3/3\times AgOTf$ in CH_2Cl_2 at room temperature (Scheme 35). The use of $(PPh_3)AuCl$ instead of $AuCl_3$ as catalyst led to a very low conversion. Compared to more coordinating solvents such as



Scheme 34.



Scheme 32.



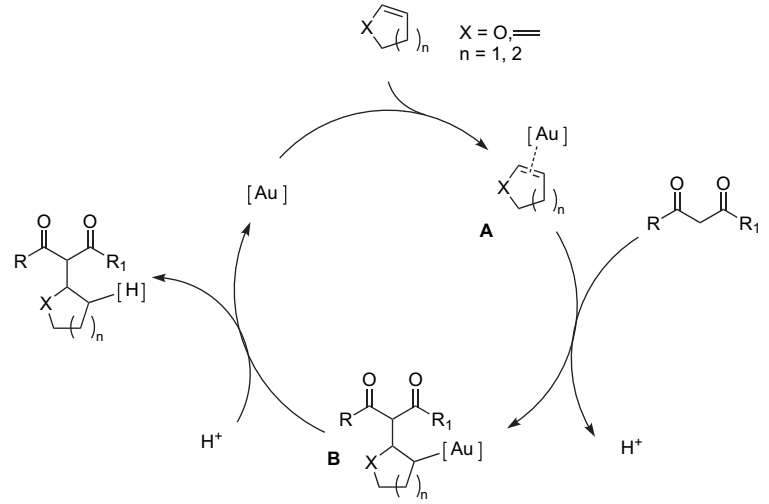
Scheme 35.

MeCN, $MeNO_2$, and dioxane, CH_2Cl_2 gave the highest yield of the desired product. The reaction is selective to cyclic dienes, cyclic triene, and cyclic enol ethers. Both mono- and bis-alkylation products were isolated in the reaction of dibenzoylmethane with cyclic enol ethers such as 2-methoxy-3,4-dihydro-2*H*-pyran. Only trace amounts of the desired products were observed when simple cyclic and acyclic alkenes were used, while with acyclic conjugated dienes, undefined mixtures of products were observed. A tentative mechanism of this transformation was proposed involving the coordination of electron-rich alkenes with Au(III) activated the alkenes **A**. Addition of 1,3-diketone–Au(III) complex to **A** generated gold intermediate **B**. Protonolysis of the C–Au bond generated the final product (Scheme 36).

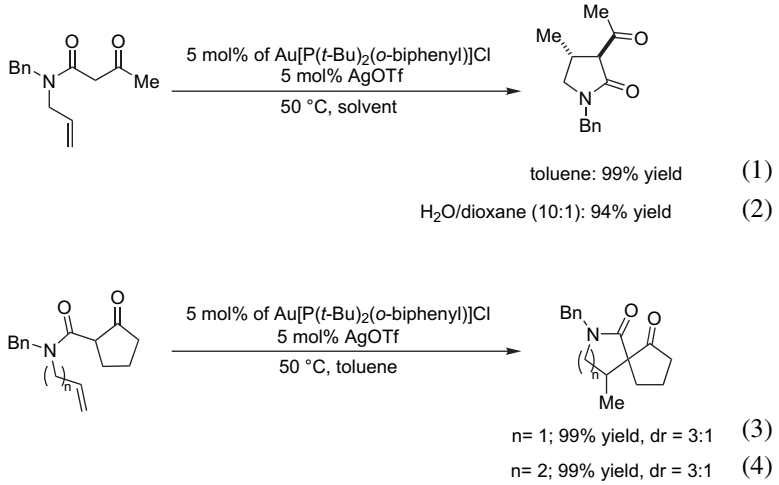
2.5.4. Intramolecular addition of activated methylene to alkenes

In 2007, Che and Zhou[64] reported a preparation of substituted lactams by an intramolecular addition of β-ketoamide to unactivated alkenes using 5 mol % of ClAuP(*t*-Bu)$_2$(*o*-biphenyl)/AgOTf in toluene (Eq. 1, Scheme 37). The use of AgOTf and Au(PPh_3)Cl alone or a combination of $AuCl_3$/AgOTf as catalysts did not give the desired product. Toluene was the best solvent compared to 1,4-dioxane, dichloroethane, and acetonitrile. In addition, the reaction was also efficient in H_2O/dioxane (10:1) (Eq. 2, Scheme 37). This method allowed the synthesis of spirolactams with modest to high diastereoselectivities. A variety of substrates underwent Au(I)-catalyzed *exo-trig* cyclization (no *endo* cyclization was observed) to give highly substituted five-membered ring lactams (Eq. 3, Scheme 37). In case of β-ketoamides containing a butenyl chain, the reaction furnished six-membered ring lactams (Eq. 4, Scheme 37). Variation at the amide and ketone moieties had only a slight impact on the reaction time and the product yield. On the other hand cyclization of amide esters or diamides was not observed; presumably, the presence of an ester and an amide functionality decreased the enol concentration.

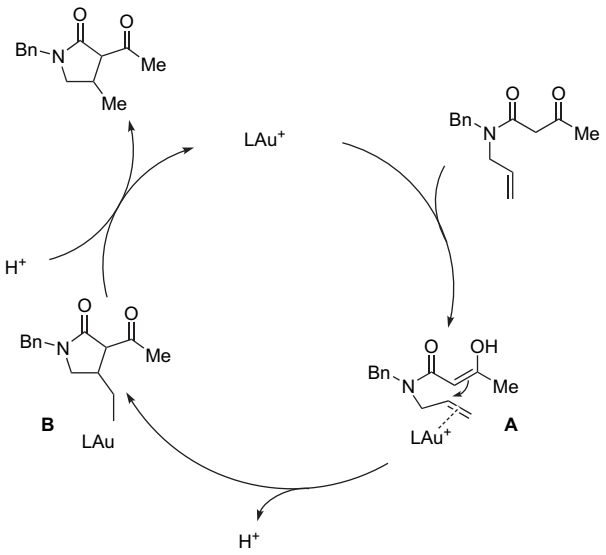
A tentative mechanism was proposed in Scheme 38. The cationic gold(I) coordinates to alkene to give intermediate **A**, which was followed by an *exo-trig* addition of the enol form of the β-ketoamide



Scheme 36.



Scheme 37.



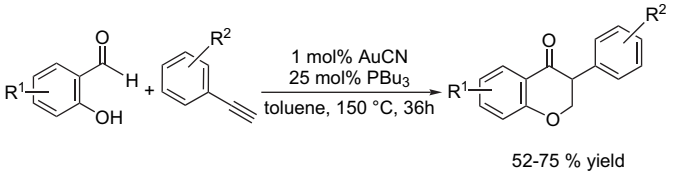
Scheme 38.

to generate intermediate **B**. Protonolysis of the carbon–gold bond gave the desired lactam and regenerated the catalyst.

2.6. Tandem reactions

2.6.1. Annulation of o-hydroxyaldehydes with terminal alkynes

Isoflavanones[65] are prevalent in nature and possess a wide range of biological activities. Recently, Li and Skouta[66] developed an annulation of simple *o*-hydroxyaldehydes with alkynes catalyzed by gold(I) (Scheme 39). The reaction did not work with Au(III)X_3 (X=Cl, Br), while the use of Au(I)X (X=Cl, Br, CN) gave the desired product in modest to high yields. The use of a coordinating solvent such as DMF, THF, dioxane or acetonitrile afforded only a trace amount of or no product. On the other hand, under aqueous media the desired annulation was not observed and the *o*-hydroxyaldehyde was recovered. Among the various organophosphine ligands used, PBu_3 gave the highest yield (78%) of the isoflavanone derivatives. Various arylalkynes with both electron-withdrawing and electron-donating substituents were used to afford the



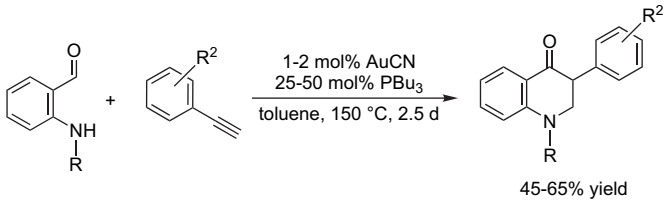
Scheme 39.

corresponding products in good yields (55–75%). The use of an aliphatic alkyne such as 1-hexyne led to the recovery of starting material under the same conditions. The annulation may involve a gold–carbene intermediate[67] or the activation of a formyl C–H bond, assisted by the neighboring phenolic hydroxy group through chelation.[68]

The annulation efficiently generates isoflavanone-type structures, which have many possible applications in the synthesis of isoflavanone natural products. Indeed, very recently they reported rapid syntheses of (±)-pterocarpans, isoflavones, and their analogues[69] (Scheme 40) by applying the gold-catalyzed annulation.

2.6.2. Annulation of 2-tosylaminobenzaldehyde with terminal alkynes

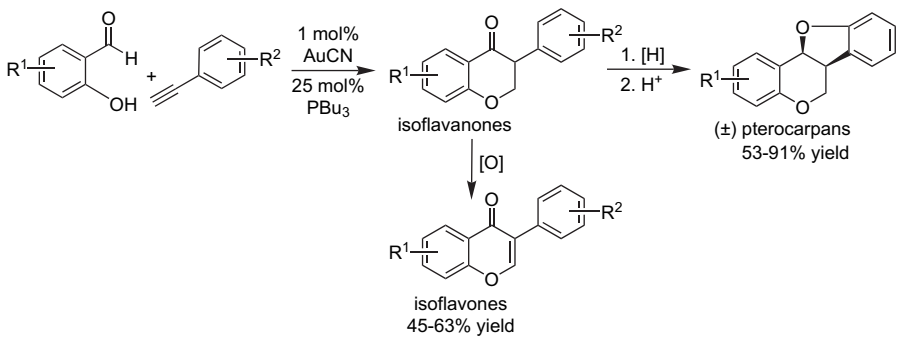
Recently, Li and Skouta[70] extended the Au(I)-catalyzed annulation of 2-tosylamino-benzaldehyde and alkynes. This annulation required a long reaction time (2.5 days) in order to obtain the 2,3-dihydro-1-tosylquinolin-4(1*H*)-one derivatives (45–65%) (Scheme 41). The reaction of 2-aminobenzaldehyde did not afford the corresponding aza-isoflavanone whereas the use of 2-acylaminobenzaldehyde gave the desired product in low yield together with a mixture of other unidentified by-products. In addition, non-aromatic alkynes such as ethynylcyclohexane, 1-ethynylcyclohex-1-ene, and hex-1-yne did not give the desired products and only the starting materials were recovered. Various arylalkynes bearing electron-rich and electron-deficient substituents were used successfully in the annulation.



Scheme 41.

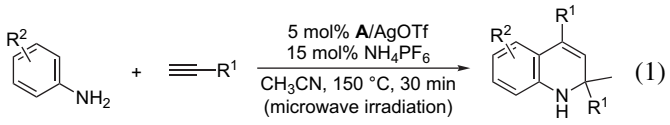
2.6.3. Annulation of arylamines with terminal alkynes

Recently, Che et al.[71] described a gold(I) complex-catalyzed tandem hydroamination–hydroarylation as an efficient synthetic strategy for substituted 1,2-dihydroquinolines using 5 mol % of **A**/AgOTf with 15 mol % of NH_4PF_6 as an additive in CH_3CN under microwave irradiation at 150 °C (Eq. 1, Scheme 42). Under similar conditions, the **A**/AgOTf-catalyzed reaction of alkynes and with primary arylamines bearing an *o*-alkylcarbonyl or *o*-arylcarbonyl group produced 2,4-disubstituted quinolines in 65–94% yields within 30 min (Eq. 2, Scheme 42). Similar chemical transformation shown in Eq. 1, Scheme 42 was reported first, in 2005, by Li et al.[72] using only $AgBF_4$ as a catalyst at 140–190 °C. The addition of various



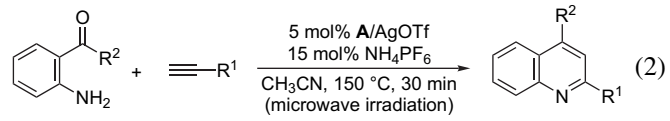
Scheme 40.

arylalkynes and arylamines gave the desired products efficiently in one-pot reaction (60–88% yield).

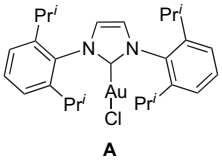


42-94% yield

R^1= Ph, Aryl, n-Bu, *n*-hexyl, alkynyl etc...
R^2= Me, Ph



65-93% yield



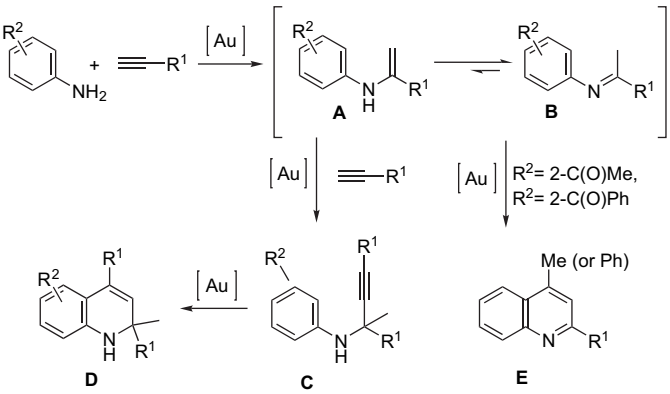
A

Scheme 42.

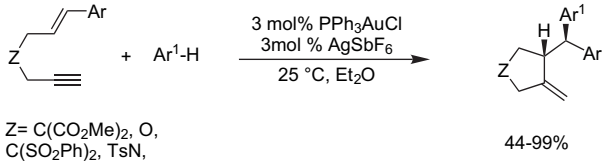
Mechanistically, Au(I) catalyzed a hydroamination of the first equivalent of alkyne to generate an enamine intermediate **A**, which might tautomerize to ketimine **B**. Addition of the second equivalent of the alkyne to the enamine **A** or ketimine **B** gave a propargylamine intermediate **C**. Then, an intramolecular hydroarylation of **C** produced the desired 1,2-dihydroquinoline **D**. In the case of *o*-alkylcarbonyl and *o*-arylcarbonyl anilines, ketimine **B** underwent a condensation/annulation reaction to produce 2,4-disubstituted quinolines **E** (Scheme 43).

2.6.4. Addition of arenes to 1,6-enynes

Genet et al.[73] reported an intermolecular addition of arenes to unactivated alkenes in the presence of a second electrophilic moiety such as an alkyne (Scheme 44). This diastereoselective cycloisomerization of the enynes using 3 mol % of the commercially available $ClAuPPh_3$ with 3 mol % of $AgSbF_6$ in ether at room temperature afforded the desired products in high yields (63–99%). The use of $AuCl_3$, AuCl, $PtCl_2$, or $Sc(OTf)_3$ alone did not give the desired product. The addition of the aromatic ring was completely chemoselective to the alkene and no product resulted from addition of the aromatic ring to the alkynyl moiety was observed. The reaction was also applicable to electron-rich heteroaromatic derivatives to give the desired products in high yields (44–99%).

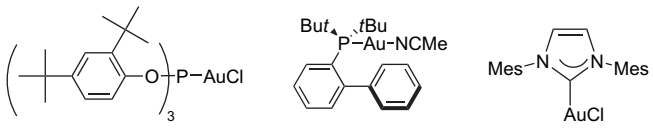


Scheme 43.



Scheme 44.

A similar gold(I)-catalyzed addition of electron-rich arenes and heteroarenes to 1,6-enynes was reported by Echavarren et al.[74] (Scheme 44). They have shown that among gold(I) complexes **A**, **B**, and **C** (Scheme 45), complex **A** with $AgSbF_6$ was the most selective and efficient catalyst in Et_2O at room temperature. The active gold(I) catalyst was generated in situ from 5 mol % of complex **A** and 5 mol % of $AgSbF_6$. Neutral complex **A**, AuCl, and $AuCl_3$ were not effective as catalyst for the reaction. The reactivity of the cationic complex **B** was similar (74% yield) to that of the catalyst formed from complex **C** and $AgSbF_6$ (72% yield).[46]



A **B** **C**

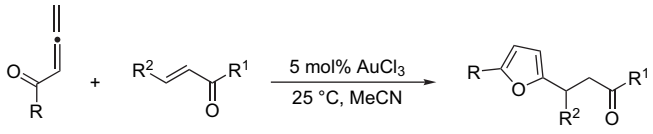
Scheme 45.

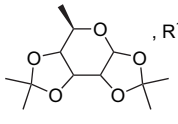
2.6.5. Cycloisomerization of allenyl ketone followed by addition to α,β-unsaturated ketones

In 2000, Hashmi et al.[75] reported tandem C–O/C–C bond formations of allenyl ketone and α,β-unsaturated ketones catalyzed by $AuCl_3$ in acetonitrile at room temperature (Scheme 46). These sequential cyclization/alkylation reactions provided an access to various C-5 substituted furans in good yields (46–74%). Mechanistically, cycloisomerization of allenyl ketone catalyzed by gold afforded the 2-substituted furan, which subsequently added to α,β-unsaturated ketones. There are two possible mechanisms for the second step: gold may activate the α,β-unsaturated ketone followed by an electrophilic substitution at the 5-position of the furan; alternatively, a direct Michael addition of the aurated furan **A**, formed in situ, with α,β-unsaturated ketones generated gold intermediate **B**. Deprotonation of the C–Au bond formed in both cases gave the desired product and regenerated the gold catalyst (Scheme 47).

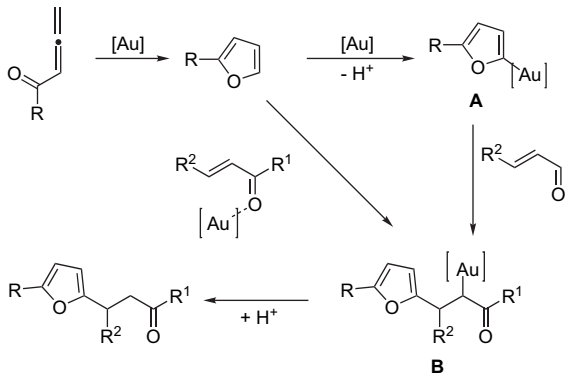
2.6.6. Annulation of phenols and naphthols with cyclic dienes

In 2006, Li et al.[76] reported the direct annulation of phenols and naphthols with cyclic dienes using $AuCl_3/3\times AgOTf$ in CH_2Cl_2. The



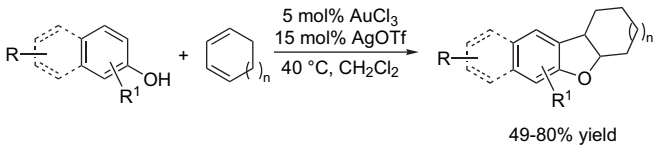
R = 4-methoxybenzyl, R^1 = Me, R^2 = H	74%
R = 4-methoxybenzyl, R^1 = Et, R^2 = Me	64%
R = 3-methoxyphenyl, R^1 = Me, R^2 = H	46%
R =  , R^1 = Me, R^2 = H	62%

Scheme 46.



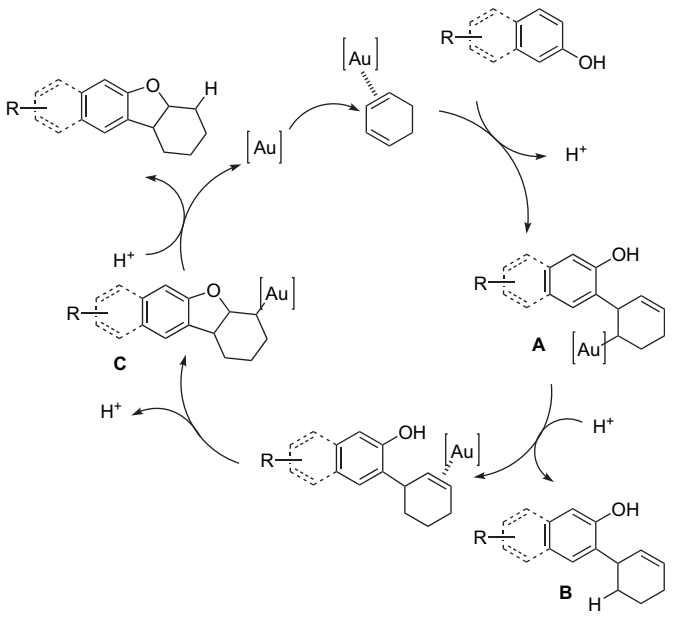
Scheme 47.

annulation led to a highly efficient synthesis of dihydrobenzofurans (Scheme 48). The use of $AuCl_3$ or AgOTf alone, or AuCl/AgOTf as catalyst gave only a trace amount of or no product. In addition, no desired product was obtained with a cationic gold(I)–triphenylphosphine complex (PPh_3AuOTf). The use of an excess amount of dienes in the presence of 5 mol % of $AuCl_3/3\times$AgOTf led to a high yield of the desired product. The rate and conversion of the reaction was controlled by electronic effects. The presence of electron-donating groups on phenols and naphthols was beneficial and increased the conversion of the reaction significantly. On the other hand, acyclic diene did not give the desired product under similar conditions.



Scheme 48.

Mechanistically, coordination of the double bond with Au(III) followed by an intermolecular addition of the aryl C–H bond generated a gold intermediate **A**. A protonation of the C–Au bond generated intermediate **B** (Scheme 49). Then, Au(III) (or triflic acid) recoordinated to the remaining double bond, which was followed by an intramolecular addition of the phenol O–H bond to generate gold intermediate **C**. Protonation of the C–Au bond generated the product and regenerated the Au(III) catalyst.



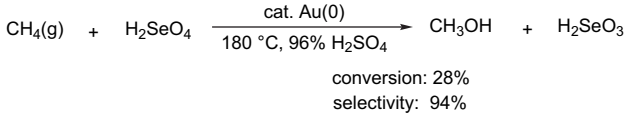
Scheme 49.

3. Gold-catalyzed C–O bond formations

3.1. Selective oxidation of alkanes

3.1.1. Selective oxidations of methane

During the last two decades, activation of C–H bonds in alkanes was successfully achieved under mild conditions[77] using several catalysts such as Hg,[78] Pd,[79] and Pt.[80] Periana et al.[81] reported a catalytic oxidation of methane to methanol using the combination of metallic gold as catalyst and selenic acid (H_2SeO_4) as oxidant in 96% of sulfuric acid (H_2SO_4) as solvent at 180 °C with a TON up to 30 (Scheme 50). This catalytic reaction resulted in a 94% selectivity of CH_3OSO_3H at 28% methane conversion. Enriched ^{13}C methane and NMR studies confirmed that only a small amount of methane selenoic acid ($^{13}CH_3SeO_3H$) was detected and $^{13}CH_3OSO_3H$ was the major product in the liquid phase. In addition, both gold and selenic acid were necessary for this reaction. In the absence of Se(VI) ions with or without Au(0), no methanol was observed. Only small amounts of methanol were formed in the presence of selenic acid alone. The reaction was not sensitive toward the use of O_2 as an additive under the same conditions. The catalytic transformation and the DFT study of the mechanism were highlighted recently by De Vos.[82]

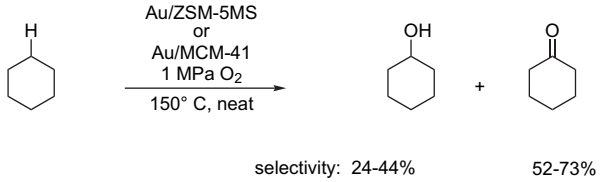


Scheme 50.

3.1.2. Selective oxidations of cycloalkanes

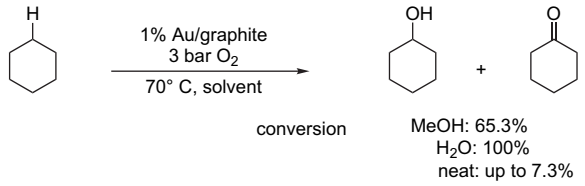
The oxidation of cyclic alkanes was also explored through the activation of C–H bonds. Suo et al.[83] reported an efficient oxidation of cyclohexane at 150 °C using calcined gold supported on nanocrystalline ZSM-5 (Au/ZSM-5) as catalyst with 1 MPa of oxygen as a source of oxidant (Scheme 51). In the absence of the oxygen atmosphere, the oxidation reaction did not take place. This transformation afforded, under solvent-free conditions, quantitative oxidation of cyclohexane with 90% selectivity for cyclohexanol and cyclohexanone. The catalyst was prepared with different loading of Au (0.51–1.30 wt %) and was recovered and reused twice without loss of activity. The same research group also reported the use of gold-containing mesoporous molecular sieves (Au/MCM-41) as catalyst in the presence of O_2 for the same oxidation reaction (Scheme 51). The selectivity to cyclohexanol and cyclohexanone was up to 94% and the catalyst was also reused efficiently.

Suo's studies showed that supported gold catalysts were efficient for the activation of C–H bonds at high temperatures (140–160 °C) and under high pressures (1–2 MPa O_2). Hutchings et al.[84] reported that gold catalyst supported on graphite (Au/C) was active



Scheme 51.

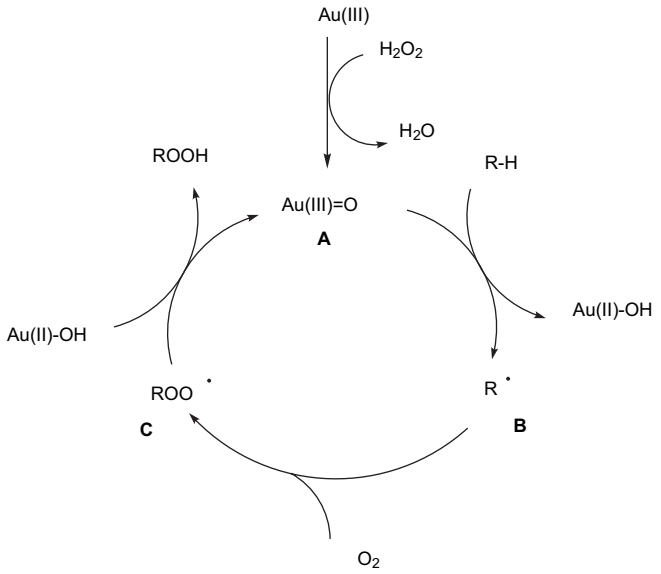
and selective in the oxidation of cyclohexane to cyclohexanol and cyclohexanone under exceptionally mild conditions (70 °C and 3 atm O_2) (Scheme 52). However, the selectivity of the Au/C catalyst changed with the proceeding of the reaction. In addition, the supported gold catalyst gave reactivity similar to supported Pt or Pd catalysts. Protic solvents such as methanol and water gave 65.3% and 100% of conversions, respectively, without partial oxidation product. On the other hand, at 70 °C under neat conditions, very low conversion (7.3%) was observed with *tert*-butyl hydroperoxide as an initiator. Addition of bismuth (Bi) to Au/graphite led to a more active but less selective catalyst. It appears that extremely high selectivity of the oxidation of cyclohexane to cyclohexanol and cyclohexanone can be obtained in short-time reaction in the presence of water while additives such as bismuth did not improve the activity of the catalyst significantly.



Scheme 52.

Shul'pin et al.[85] reported the oxidation of cyclooctane, through C–H activation, using $NaAuCl_4$ as a catalyst and H_2O_2 as an oxidant in acetonitrile at 75 °C. This reaction gave cyclooctyl hydroperoxide as a major product (Eq. 1, Scheme 53). In addition, cyclooctanol and cyclooctanone were also observed as minor products. The total turnover number (TON) was 520 after 144 h. They used triphenylphosphine[86] to reduce the excess hydrogen peroxide to water and the alkyl hydroperoxide to the corresponding alcohol. This method allowed the determination of the *real* concentrations of the alkyl hydroperoxide, formed from the alkane, as well as those of the alcohol and the ketone. The presence of $AgClO_4$ in the reaction mixture showed an acceleration of the oxidation. In addition, the gold(I) complex $ClAuPPh_3$ alone also catalyzed this reaction efficiently. On the other hand, oxidation of cyclooctane by air at room temperature catalyzed by $NaAuCl_4$ with Zn/CH_3COOH as a reducing agent and methylviologen (MV^{2+}) as an electron-transfer agent gave cyclooctanol (0.001 M) as the major product together with a very small amount (0.0001 M) of cyclooctyl hydroperoxide with TON=10 (Eq. 2, Scheme 53).

A possible pathway for the Au-catalyzed alkane hydroperoxidation was suggested in Scheme 54. The gold(III) reacted with hydrogen peroxide (H_2O_2) to generate the gold(III)–oxo complex **A**, which might be the oxidizing species. Then the high-valent gold–oxo complex **A** attacked the C–H bond of the alkane (RH), leading to the alkyl hydroperoxide through intermediates **B** and **C**.



Scheme 54.

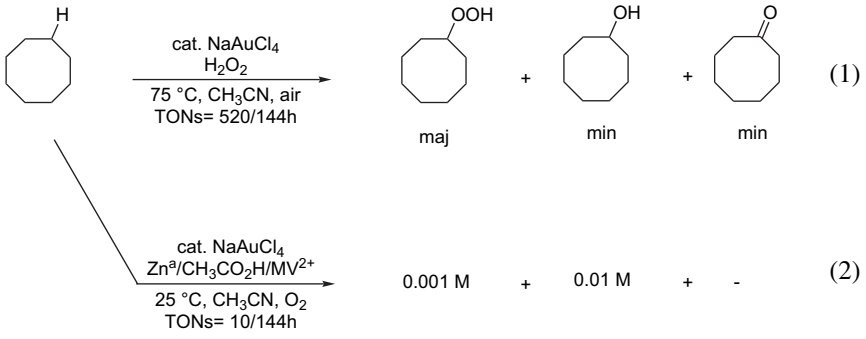
3.1.3. Selective oxidations of cycloalkenes

Shul'pin et al.[85] also reported the oxidation of cyclohexene catalyzed by $NaAuCl_4$ using H_2O_2 as an oxidant with a high total turnover number (TON=654 after 48 h). The reaction gave cyclohexen-3-ol as the main product (0.050 M) together with smaller amounts of 3-hydroperoxycyclohexene (0.003 M), cyclohexene-3-one (0.012 M), and the epoxide (0.0004 M) (Eq. 1, Scheme 55). The concentration of cyclohexene-3-ol decreased by half when the oxidant was O_2 instead of H_2O_2 (Eq. 2, Scheme 55).

3.2. Selective oxidations of alcohols

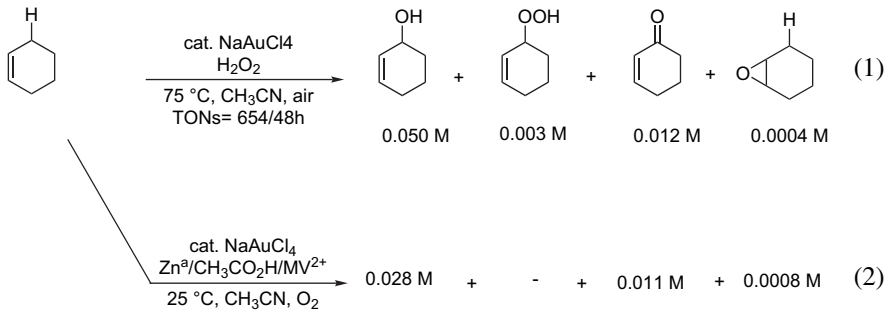
3.2.1. Homogeneous Au-catalysis

Shi et al.[87] reported a selective oxidation of primary alcohols to aldehydes using a gold-catalyst with dioxygen as an oxidant in toluene at 90 °C (Scheme 56). The catalyst (prepared in situ from 5 mol % of AuCl and 6.3 mol % of electron-donating β-diketiminate anions **A** as the ligand) gave a quantitative conversion (100%) of the alcohols to aldehydes in high selectivity (99%). No trace amount of acids was detected. In addition, oxidation of secondary alcohols

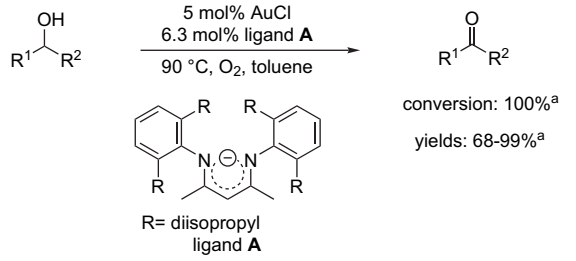


[a]Zn/CH3COOH as a reducing agent and methylviologen (MV^{2+}) as electron-transfer agent

Scheme 53.



Scheme 55.



Scheme 56.

gave ketones as sole products with 100% conversion under the same conditions. The use of 4 Å molecular sieves was beneficial to this reaction and no additive was required. The use of TBHP, H_2O_2, and air as oxidants also afforded the desired products although the efficiency and the reaction rate decreased. Various ligands such as triphenylphosphine, pyridine, and bipyridine in organic solvents gave trace amounts of the carbonyl compound when THBP or H_2O_2 was used instead of O_2. The gold–ligand complex was detected by ESI mass spectroscopy at different stages of the reaction. A variety of alcohols such as primary and secondary benzyl and allylic alcohols gave the desired aldehydes and ketones as sole products with excellent conversions (100%) and selectivity (68–99%). Neither electron-donating nor electron-withdrawing substituents affected the efficiency of the oxidation. However, the reaction rate decreased with electron-deficient substrates. For primary aliphatic alcohols, α,β-unsaturated aldehyde was observed as a by-product in addition to the desired aldehyde, which affected the efficiency of the reaction.

3.2.2. Heterogeneous Au-catalysis

In the last two decades, heterogeneous gold catalysts have been used extensively in the selective oxidation of alcohols. Choudhary et al.[88] prepared various recyclable nano-gold catalysts supported on different metal oxides such as Au/MgO, Au/Al_2O_3, Au/ZrO_2, and Au/U_3O_8. The catalysts were prepared by a homogeneous deposition precipitation (HDP) method for depositing nano-gold on the supports.[88a] Among the supported nano-gold catalysts, Au/U_3O_8 showed the best performance[88b] in the oxidation of substituted benzyl alcohols to the corresponding aldehydes using O_2 (1.5 atm) at 130 °C in neat reactions. The conversion and selectivity to the corresponding aldehydes were up to 67% and 62%, respectively. In addition, small amounts of esters were isolated in longer reaction time, due to the reaction between the substituted benzoic acid formed and the reactant (substituted benzyl alcohol). The presence of solvents such as toluene, *p*-xylene, DMF, and DMSO lowered both the conversion and the selectivity.[88c]

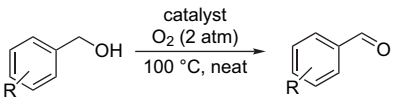
Stucky and Zheng[89] reported the use of a trace amount of metal carbonate (K_2CO_3), acetate ($Co(OAc)_2\cdot 4H_2O$; NaOAc) or borate ($K_2B_4O_7\cdot 10H_2O$) to promote the gold nanocatalysts in selective aerobic oxidation of benzyl alcohols under solvent-free conditions at 100 °C. For example, the use of NaOAc during the selective oxidation of benzyl alcohol afforded benzaldehyde with 74.6% selectivity; whereas the use of $Co(OAc)_2\cdot 4H_2O$ instead of NaOAc afforded a higher selectivity to aldehyde (93.8%) and a high efficiency (TOF=353 h^{-1}) at 100 °C. Such an improvement in both alcohol conversion and product selectivity is not achievable by OAc^- or Co^{2+} alone.

Hutchings et al.[90] reported various catalytic systems based on Au-metal nanoparticles such as $Au–Pd/TiO_2$, Au/TiO_2, and Au/zeolite (ZSM-5, zeolite β, and zeolite Y) for the selective oxidation of benzylic alcohol (Table 1). They showed that TiO_2-supported Au–Pd alloy nanocrystals gave significantly enhanced activity for alcohol oxidation using O_2 as an oxidant at 100 °C under solvent-free conditions. The $Au–Pd/TiO_2$ catalysts were very active for this reaction, and the selectivity to benzaldehyde was 91.6% in 8 h, with only benzyl benzoate as by-product. On the other hand, the use of Au/TiO_2 or Pd/TiO_2 alone gave 63.9% and 54.4% selectivities in 8 h, respectively. When compared with monometallic supported Au[2] and Pd,[91] the Au–Pd nanocrystals give TOFs that are increased by a factor of 25. The selectivity of the Au/TiO_2 catalyst for benzaldehyde decreased with the reaction time (96.7% in 1 h to 63.9% in 8 h, Table 1).

Baiker et al.[92] reported a highly selective oxidation of benzylic alcohols using gold supported on TiO_2 (Au/TiO_2) in supercritical carbon dioxide (sCO_2). Using 1 mol % of the catalyst, benzyl alcohol was converted into benzaldehyde in 16% conversion and 99% selectivity. The combination of gold-based catalysts and sCO_2 offered an interesting alternative to the known methods of alcohol oxidation. In addition, the reaction rate in sCO_2 (in expanded phase) was higher than under solvent-free conditions.

Corma et al.[93] used a combination of nano-gold crystals (2–5 nm) and nanocrystalline ceria (5 nm) to obtain a highly active,

Table 1

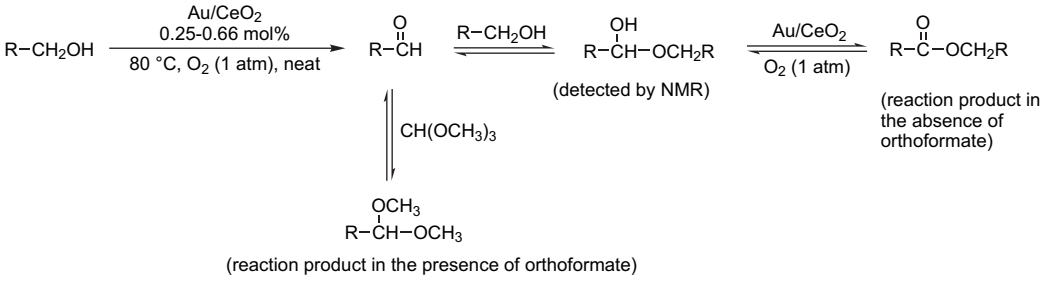


Catalyst	Conversion (%)		Benzaldehyde selectivity (%)	
	0.5 h	8 h	1 h	8 h
2.5% Au–2.5%Pd/TiO_2	3.7	74.5	95.2	91.6
2.5% Au/TiO_2	0.6	15.3	96.7	63.9
2.5%Pd/TiO_2	13.4	60.1	51.3	54.4

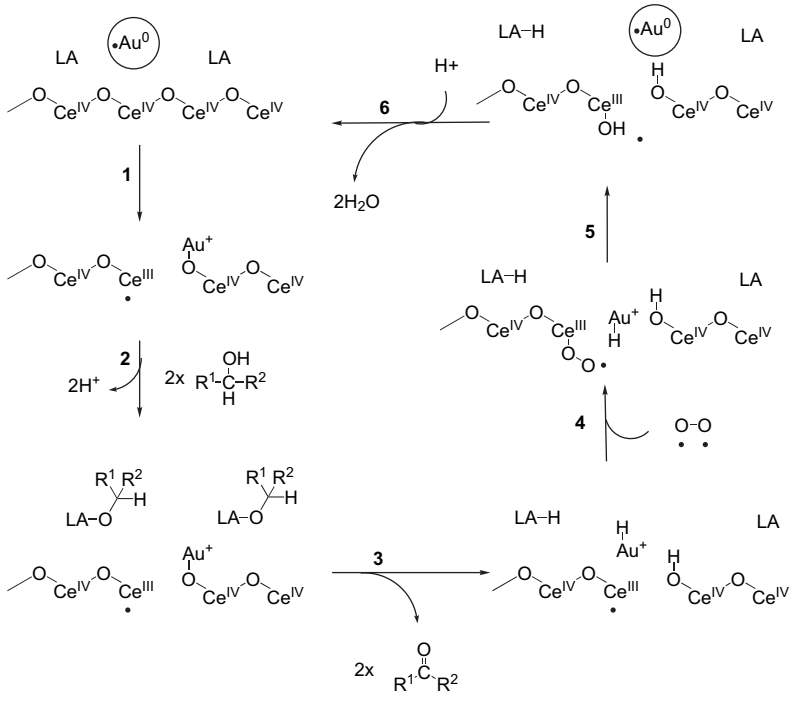
selective and recyclable catalyst (Au/CeO_2, TON=250,000 after 3 recycles) for the oxidation of alcohols into aldehydes and ketones by using oxygen at the atmospheric pressure as oxidant under solvent- and base-free conditions at 80 °C. Benzylic and allylic alcohols were selectively oxidized to the corresponding aldehydes in high conversions (66–99%) and selectivities (51–99%). In the case of aliphatic primary alcohols, trimethyl orthoformate was added to trap the generated aldehydes. The corresponding masked aldehyde, dimethyl acetal, was obtained in very high selectivity and the formation of the esters was completely inhibited (Scheme 57). In addition, NMR spectroscopy studies showed that the esters were formed via the hemiacetal. In basic aqueous solution and in the absence of trimethyl orthoformate, the oxidation of primary alcohols gave carboxylic acids rather than esters. The oxidation of 1-phenylethanol into acetophenone with Au/CeO_2 at 160 °C gave the desired product in 99% selectivity with a TOF of 12,500 h^{-1} while the use of Pd supported on hydroxypatite[94] gave a TOF of 9800 h^{-1}.

Based on infrared (IR) and X-ray photoelectron diffraction (XPD) studies, the mechanism for the catalytic reaction was proposed in Scheme 58: (1) the interaction between gold and ceria gave Au^+ and Ce^{3+} species (as observed by XPD); (2) the alcohol reacted with the Lewis acidic sites of Au/CeO_2 to give a metal alkoxide; (3) the metal alkoxide underwent a rapid hydride transfer from C–H of the alcohol to Ce^{3+} and Au^+ to give the ketone and Ce–H (indicated as LA–H in Scheme 58) and Au–H (as observed by IR spectroscopy); (4) a cerium-coordinated superoxide (Ce–OO•) species was formed in the presence of O_2;[95] (5) hydrogen abstraction from Au–H afforded cerium hydroperoxide; (6) reduction of Ce^{IV} regenerated the initial Au^+ species.

Biffis et al.[96] reported the oxidation of alcohols to the corresponding aldehydes and ketones with dioxygen (3 atm) catalyzed by 'quasi-homogeneous' microgel-stabilzed Au nanoclusters[97] in the presence of NaOH and water at 50 °C. The reaction gave a quantitative selectivity for ketone in case of 1-phenylethanol (75% conversion with TOF=375 h^{-1}) whereas only 48% conversion and 49% selectivity for benzyl alcohols to aldehydes with a high TOF=960 h^{-1}. In case of aliphatic alcohols such as 1-octanol, the carboxylic acid was formed as a major product with 59% conversion and 84% selectivity but with a low TOF=74 h^{-1}. In addition, trace amounts of the corresponding esters were detected. This tendency toward further oxidation of the intermediate aldehyde can be expected, because aldehydes forms hydrate readily in water. The hydrate can be oxidized more efficiently than the starting alcohol by gold catalysis. The method can be applied to the oxidation of glycerol and glucose under the same conditions. The efficiency of this system was related to the basicity of the media (highly efficient at pH=9.5). Glycerol gave a mixture of glycerate and glycolate, while glucose gave gluconate with up to 99% selectivity and 35% conversion.

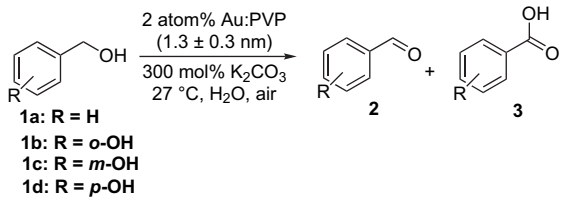


Scheme 57.



Scheme 58.

Table 2

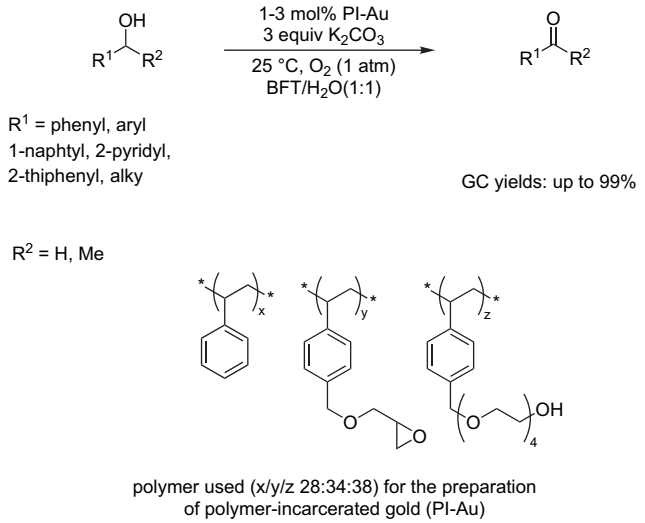


Entry	Substrate	Time (h)	Yield[a] (mol %)		
			1	**2**	**3**
1	**1a**	6	0	0	85
2	**1b**	24	34	54	0
3	**1c**	8	3	34	52
4	**1d**	8	3	91	0

[a] Detected by gas chromatography (GC).

Tsukuda et al.[98] reported the first selective oxidation of alcohols using poly(*N*-vinyl-2-pyrrolidone) (PVP)-stabilized Au nanoclusters (NCs) in the presence of 3 atm of O_2 or air and a base (K_2CO_3) in water at ambient temperature (Table 2). The gold NCs with an average diameter of 1.3±0.3 nm favored the O_2 adsorption onto the catalyst and gave high catalytic activities. In the absence of either molecular oxygen or base, the PVP/AuNCs catalyst did not catalyze the oxidation. For benzyl alcohol **1a**, the reaction gave the corresponding acid as a major product with a 85% selectivity together with 10% ester. Aldehyde was not detected by GC. Oxidation of *ortho*- and *para*-hydroxybenzyl alcohols **1b** and **1d** gave the corresponding aldehydes selectively in 54% and 91% yields, respectively, while oxidation of *meta*-hydroxybenzyl alcohols **1c** gave a mixture of the corresponding aldehyde and acid in 34% and 52% yields, respectively. The low conversion of **1b** was related to the steric hindrance by the quasi-two-dimensional NC surface[99] and/or the chelating effect by the OH group at the *ortho* position.

The efficiency of Au–Pd/TiO_2,[90] Au/CeO_2,[93] and other gold catalysts for the aerobic oxidation of alcohols required high temperatures (100–160 °C) in most cases. Kobayashi et al.[100] reported a room temperature oxidation of alcohols to aldehydes and ketones using a polymer-incarcerated-gold (PI-Au) as catalyst with O_2 (1 atm) in the presence of 3 equiv of K_2CO_3 and benzotrifluoride/H_2O (ratio 1:1) (Scheme 59). The polymer-incarcerated[101] gold nanocluster catalysts (PI-Au) were prepared by mixing $AuClPPh_3$ with the polymers and $NaBH_4$ in a small amount of THF. The mixture was heated at 150 °C for 5 h to cross-link the side chains and then washed with THF and water to afford PI-Au. This catalytic reaction did not proceed at all in the absence of water or base. However, increasing the temperature to 160 °C the PI-Au catalyzed the oxidation of 1-phenylethanol under solvent- and base-free conditions with a very high turnover frequency (TOF) of an average 2.0×10^4 h^{-1} after the initial 30 min, which exceeded that achieved by the Au/CeO_2 catalyst.[93] The catalyst was reused without significant loss of activity. This method tolerates a broad range of substrates such as aromatic and aliphatic secondary alcohols. In addition aromatic and allylic primary alcohols were oxidized smoothly in the presence of a weak base (K_2CO_3) to afford the corresponding aldehydes in good yields, although the products were accompanied by small amounts of carboxylic acids or esters. Moreover, alcohols that contained heteroatoms such as S and N, which are well known to coordinate strongly to gold nanoparticles, were also oxidized smoothly to give the desired ketones in high yields (94% and 99%, respectively) without leaching of the metal.



Scheme 59.

4. Gold-catalyzed C–N bond formations

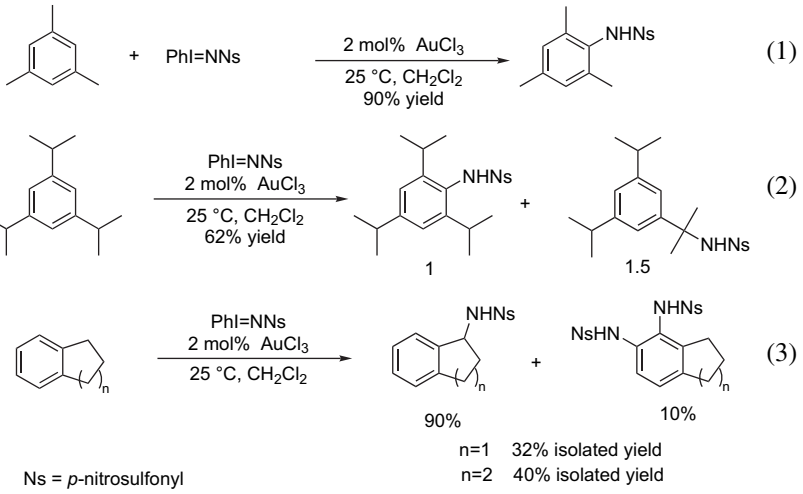
4.1. Nitrene insertion via aryls and benzyl C–H activation

Arylgold(III) catalysts have been successfully used for C–C bond formations.[40] Very recently He et al.[102] expended the use of arylgold(III)[35–38,55] to C–N bond formations via the activation of aromatic or benzylic C–H bonds using 2 mol % of $AuCl_3$ in CH_2Cl_2 at room temperature (Scheme 60). The addition of mesitylene to PhI=NNs (ratio 8:1) in the presence of $AuCl_3$ as catalyst gave only the aromatic C–N bond formation in 90% yield (Eq. 1, Scheme 60). The tri-, tera- and penta-methylbenzenes gave the desired aromatic C–N bond formation products in high yields (61–90% yield), while di- and mono-substituted benzene as well as benzene gave less than 5% yield of the desired products. The use of metal salts such as $PdCl_2$, $ZnCl_2$, $FeCl_2$, $Cu(OTf)_2$ or HCl did not give the desired product. In addition, electron-rich heterocycles such as indole and furan showed no reactivity under the same conditions. In case of 1,3,5-triisopropylbenzene (which contains weak benzylic C–H bonds), the reaction gave a mixture of aromatic and aliphatic C–N bond formation products with a ratio of 1:1.5 (Eq. 2, Scheme 60). When the more activated benzylic C–H bonds such as indane and tetrahydronaphthalene were used as substrates, in addition to aromatic C–H insertion, high percentages of benzylic nitrene insertion were observed (Eq. 3, Scheme 60).

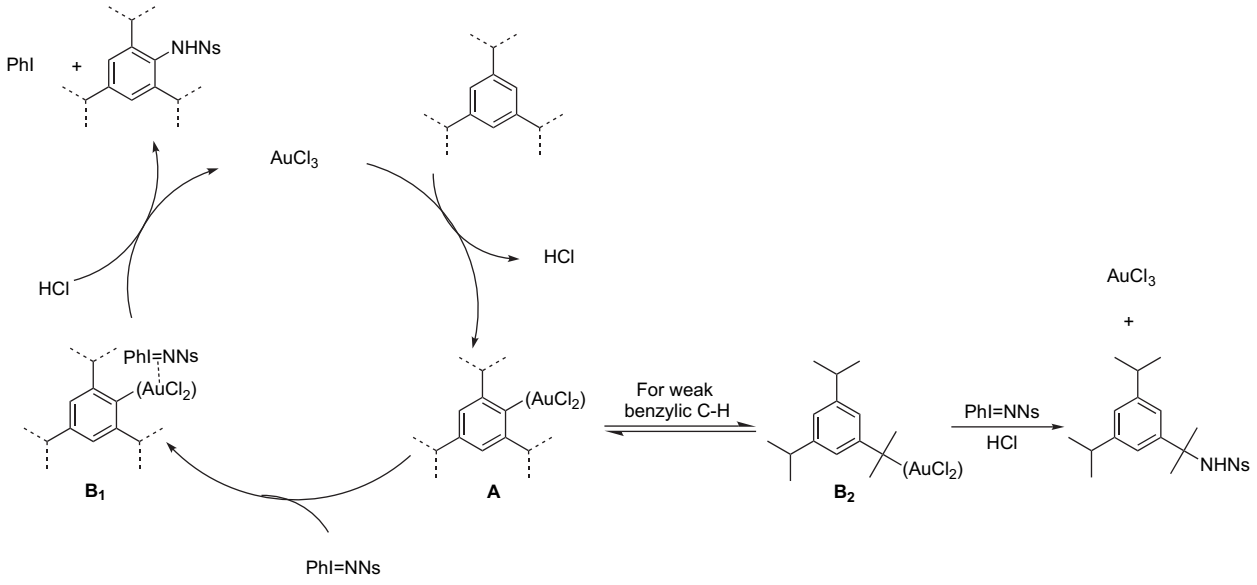
Deuterium studies showed that the C–H functionalization step might not be rate determining. They proposed that $AuCl_3$ reacted with aromatic C–H bond to generate the arylgold(III) **A** as the first step (Scheme 61). Activation of the PhI=NNs via gold(III) $\mathbf{B_1}$ led to attack on the carbon of the arylgold(III) species to give the desired product and generate $AuCl_3$. In the presence of very weak benzylic C–H bonds, gold(III) displaced a weak benzylic proton first to form carbon–gold(III) species $\mathbf{B_2}$, which subsequently underwent the nitrene insertion. Based on He's studies, it is possible that arylgold(III) may be formed first and chemoselectively before gold(III) migrated to the very weak benzylic C–H position.

5. Concluding remarks

Over the last two decades, gold catalysis has demonstrated high efficiency in a variety of different chemical transformations compared to other transition metals such as Pd and Pt. In addition, Au(I) and Au(III) complexes were highly useful for generating new C–C, C–O, C–N, and C–S bonds under mild conditions. Gold catalysis has



Scheme 60.



Scheme 61.

also been used as key steps in the synthesis of natural products and as a powerful tool for cascade or domino reaction processes. Recently gold-catalyzed C–H bond activations showed promising efficiency in chemical transformations. However, numerous problems still need to be solved: (1) in spite of the extensive C–C bond formations from C–H bond catalyzed by gold, related C–X (O, N, S) bond formations involving C–H bond activation is very rare; (2) enantioselective transformations of C–H bonds catalyzed by chiral gold complexes is virtually untouched; (3) rational ligand design for specific reactions are needed; (4) currently the exact nature of the catalytically active species is still not known in many chemical transformations and extensive mechanistic studies are needed. We believe that this field of chemistry will continue to be an attractive topic and will grow rapidly.

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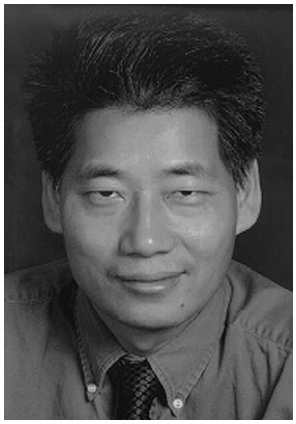
Biographical sketch



Chao-Jun Li (born in 1963) received his B.S. degree from Zhengzhou University (1983), M.S. degree from the Chinese Academy of Sciences in Beijing (1988), and Ph.D. degree at McGill University (1992) (with T.H. Chan and D.N. Harpp). He was a NSERC Postdoctoral Fellow with B.M. Trost at Stanford University from 1992–1994. He was an Assistant Professor (1994), Associate Professor (1998), and Full Professor (2000–2003) at Tulane University. He was a visiting faculty (with Robert G. Bergman) at the University of California at Berkeley (2002) and at Nagoya University (2007) (R. Noyori Laboratory). In 2003, he became a Canada Research Chair (Tier I) in Organic/Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts are focused on developing innovative and fundamentally new organic reactions that will defy conventional reactivities and have high synthetic efficiency. His widely recognized research includes the development of Grignard-type reactions in water, transition metal catalysis in air and water, alkyne–aldehyde–amine coupling (A^3-coupling), asymmetric alkyne–aldehyde–amine coupling (AA^3-coupling), and cross-dehydrogenative-coupling (CDC) reactions via C–H activations.

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