Gold-catalyzed reactions of oxo-alkynes

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Dedicated to Professor Lutz Tietze on the occasion of his 65th Birthday


Abstract

Gold (I) and gold (III) complexes show unique catalytic activities toward alkynes; both inter and intramolecular addition of nucleophiles to alkynes is promoted in the presence of gold catalysts. This review focuses on the gold catalyzed reactions of alkynes tethered with carbonyl groups along with their interesting mechanistic aspects.

Keywords: Gold catalysis, alkynals, alkynones, domino reactions

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Introduction

The formation of C-C and C-X bonds by the use of transition metal catalysts is one of the most interesting and intriguing subjects in organic chemistry. 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] The catalysis of organic reactions by gold compounds has recently been shown to be a powerful tool in organic synthesis.[2] This chemistry is also valuable in constructing complex molecules. Although gold is considered as an expensive metal, the unique catalytic properties exhibited by the various gold complexes have encouraged organic chemists to explore the viability of these complexes as catalysts. Likewise other transition metals, gold salts are capable of forming several bonds in one pot, without isolating any intermediates, commonly referred as domino[3] or tandem reactions. It is obvious that this type of reactions would allow the minimization of waste elements and most importantly the reaction can be performed with high atom economy.[4] Over the decades the usefulness of gold catalyst has been realized and has drawn the attention of numerous research groups, which has been reflected in a number of research publications in the literature. Cationic gold (I) and gold (III) show unique activities toward alkynes, promoting the nucleophilic addition of a variety of functional groups both inter- and intramolecularly. As a part of continuing interest on gold catalysis, we were

interested in summarizing the gold catalyzed processes of alkynals, alkynones and alkynoates since the products obtained through these processes are valuable building blocks. This review focuses on the gold catalyzed reactions of alkynes tethered with carbonyl groups (Fig 1) along with their interesting mechanistic aspects.
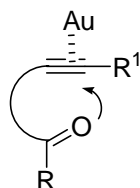

R = H, alkyl, *O*-alkyl

Figure 1

Recently, we reported AuCl$_3$-catalyzed formal [4 + 2] benzannulation between *o*-alkynylbenzaldehydes **1** and alkynes **2** (eq 1).[5] Various naphthyl ketones **3a**/**3b** were obtained in good to high yields. It was found that regioselectivity was strongly dependent on the substituent on alkynes. For instance when $R^1 = C_3H_7$ and $R^2 = H$, the regioisomer **3a** predominates, on the other hand, when $R^1 = COCH_3$ and $R^2 = H$, the regioisomer **3b** predominates.
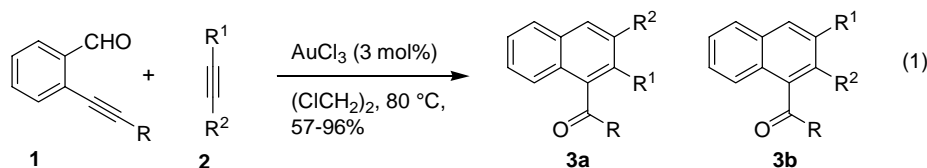

A plausible mechanism for the AuCl$_3$-catalyzed formal [4 + 2] benzannulation is shown (Scheme 1). The coordination of the triple bond of **1** to AuCl$_3$ enhances the electrophilicity of alkyne and the subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne would form the intermediate auric ate complex **5**.[6] The Diels-Alder type [4 + 2] cycloaddition of **5** with an alkyne **2** would occur as shown in **6** to form the intermediate **7**. The subsequent bond rearrangement, as shown in **7** with arrows, would afford the naphthalene derivatives **3** and regenerate AuCl$_3$.
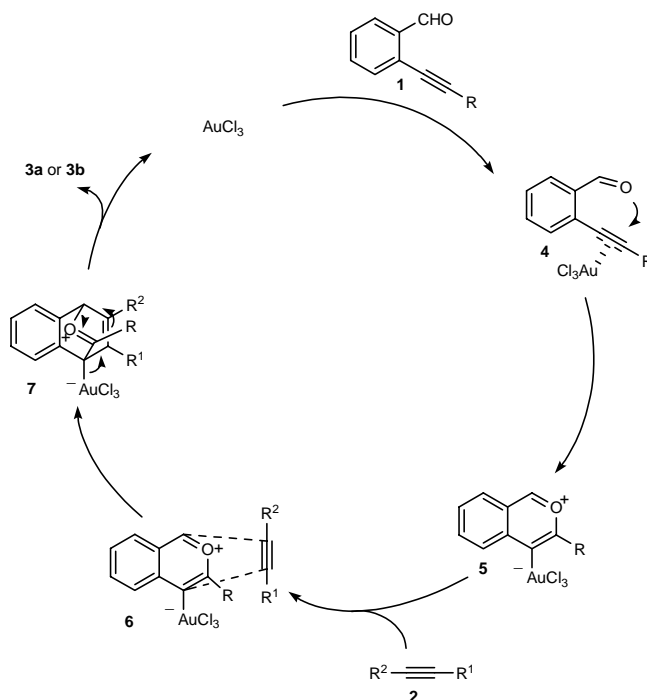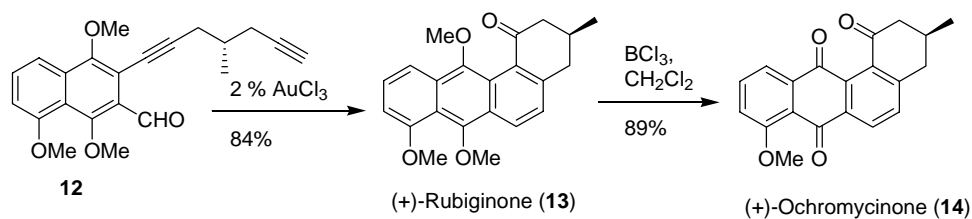
Scheme 1

The intramolecular version of this reaction was also reported by us (eqs 2 and 3).[7] Treatment of the tethered alkynyl enynones **8**, in which a carbon chain is attached to the carbonyl group, with a catalytic amount of AuBr$_3$ in (ClCH$_2$)$_2$ gave the naphthyl ketones **9** in good to high yields (eq 2, top-down approach). Analogously, the AuBr$_3$-catalyzed benzannulations of **10**, in which a carbon tether is extended from the alkynyl terminus, also proceeded smoothly, and the cyclized naphthyl ketones **11** were obtained in high yields (eq 3, bottom-up approach).
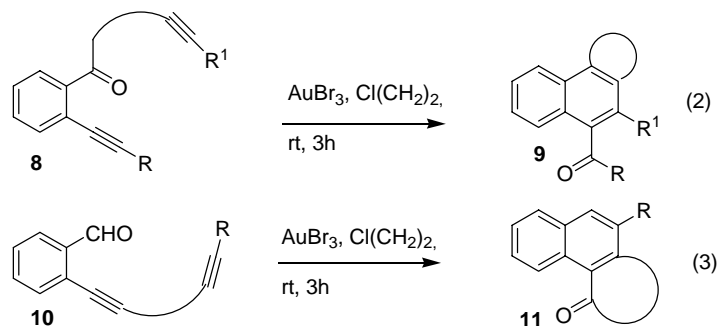

A successful application of this methodology has been made for total synthesis of (+)-ochromycinone and (+)-rubiginone B$_2$.[8] The chiral alkynal **12** was subjected to intramolecular [4+2] benzannulation reaction in the presence of 2 mol.% AuCl$_3$ to afford (+)-Rubiginone **13**. (+)-Ochromycinone **14** was easily obtained *via* demethylation of –OMe group by BCl$_3$.

12   2 % AuCl₃   84%   (+)-Rubiginone (**13**)   BCl₃, CH₂Cl₂   89%   (+)-Ochromycinone (**14**)
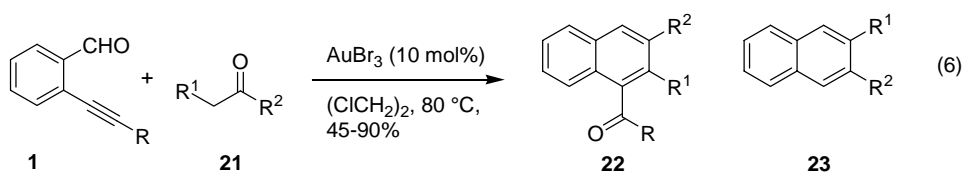
Scheme 2

The application[9] of this methodology has also been reported recently by Dyker *et al.* for the total synthesis of *rac*-heliophenanthrone **15** (eq 4). It was found that gold catalyst gave lower yield (34%) for the benzannulation of **16**, however, the use of PtCl₂ proved beneficial giving the product in 71% yield. The benzannulation product **17** thus obtained was converted into heliophenanthrone **15**.

Heliophenanthrone (**15**)

**16** mixture of diastereomers   AuCl₃, 34% PtCl₂, 71%   **17**   (4)
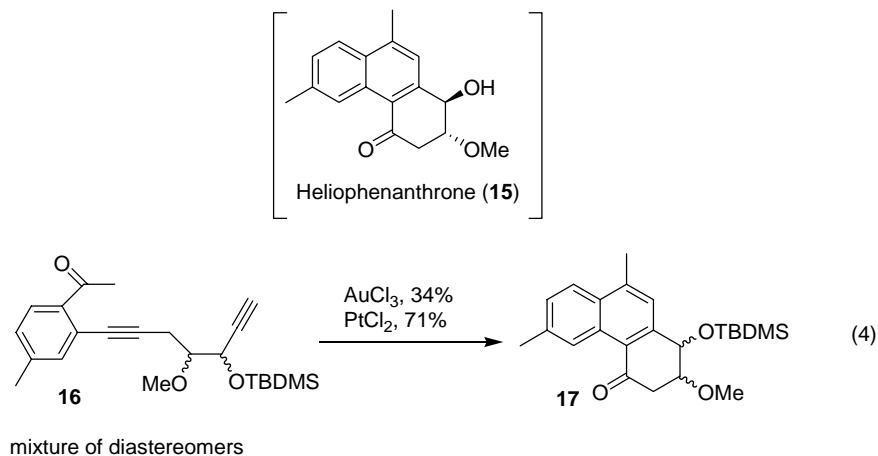
An innovative extension of the above approach by Oh and coworkers involved the synthesis of [6,7,*n*] tricyclic compounds **19** *via* [3+2] cycloaddition of **18** (eq 5).[10] It is interesting to note that only trace amounts of [4+2] benzannulation products were obtained in each case. Since the main structural feature distinguishing **18** from **10** is the gem-ester group, the author argued that Thorpe-Ingold effect might be playing some role in favoring the formation of the five membered ring products *via* intermediate **20**.

(5)
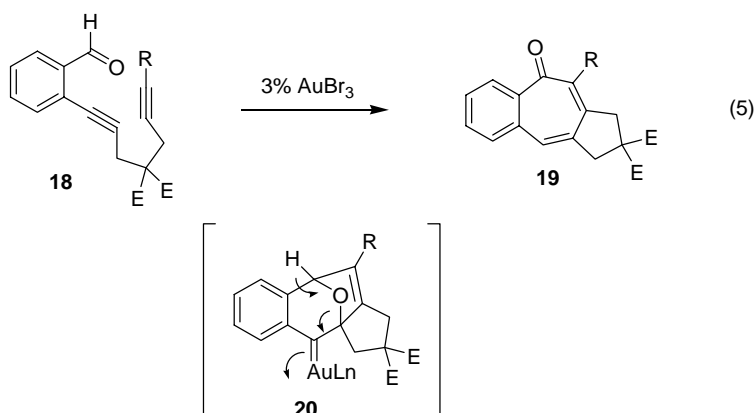
We have reported [4+2] benzannulation between the pyrylium intermediates, formed by the nucleophilic attack of carbonyl oxygen to gold- coordinated alkyne in **1**, with carbonyl compounds **21**.[11] Functionalized naphthalenes **22** or **23** were obtained in good to high yields by heating the substrates at 100 °C in 1,4-dioxane in the presence of AuBr$_3$ (eq. 6).


(6)

A plausible mechanism for the present benzannulation is shown in Scheme 3. The gold ate complex **5** was generated from **1** as described previously. The reverse-electron-demand-type Diels-Alder reaction of **5** with the enol **24**, derived from **21**, followed by dehydration would generate the intermediate **26** through **25**. The subsequent bond rearrangement, as shown in **26** with arrows, would afford the naphthyl ketone derivative **22** or **23** with regeneration of AuBr$_3$.
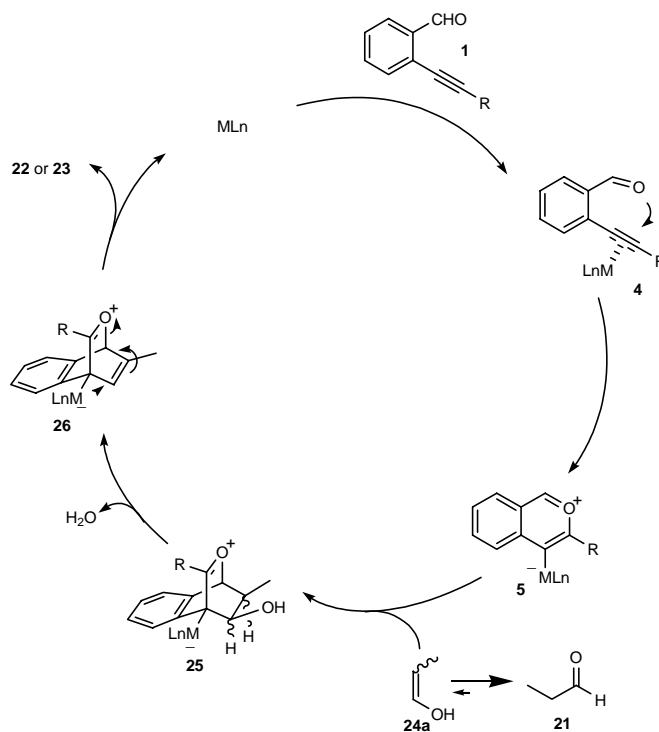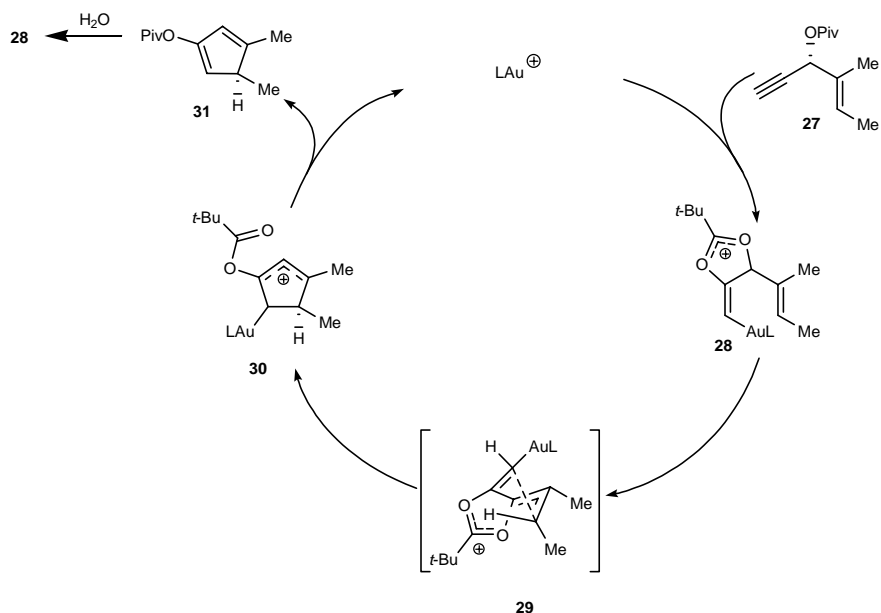
Scheme 3

Toste *et al*. developed[12] Au(I) catalyzed synthesis of cyclopentenones **28** by the rearrangement of 1-ethynyl-2-propenyl pivaloates **27** (eq. 7). The reactions are tolerant of substitutions at the acetylenic and olefinic positions (except for *Z*-olefins) providing access to a wide range of cyclopentenones under exceptionally mild conditions. One of the important features of this reaction is that enantio-enriched cyclopentenones could be prepared by cyclization of enantiomerically enriched propargyl alcohols. The high degree of chirality transfer in these rearrangements was observed.
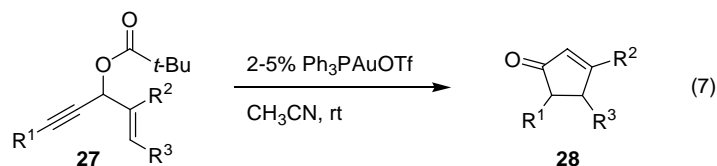

Mechanistically the reaction is quite interesting (Scheme 4). Intramolecular 1,2-addition of the ester oxygen onto the alkyne, induced by coordination of the alkyne to a cationic gold(I) complex, affords the vinyl gold species **28**. This cyclization of **28** produces the cationic intermediate **30** *via* the transition state **29**, which upon elimination of cationic gold(I) affords the diene **31**. Finally, the cyclopentadiene **31** is hydrolyzed to the cyclopentenone **28**.
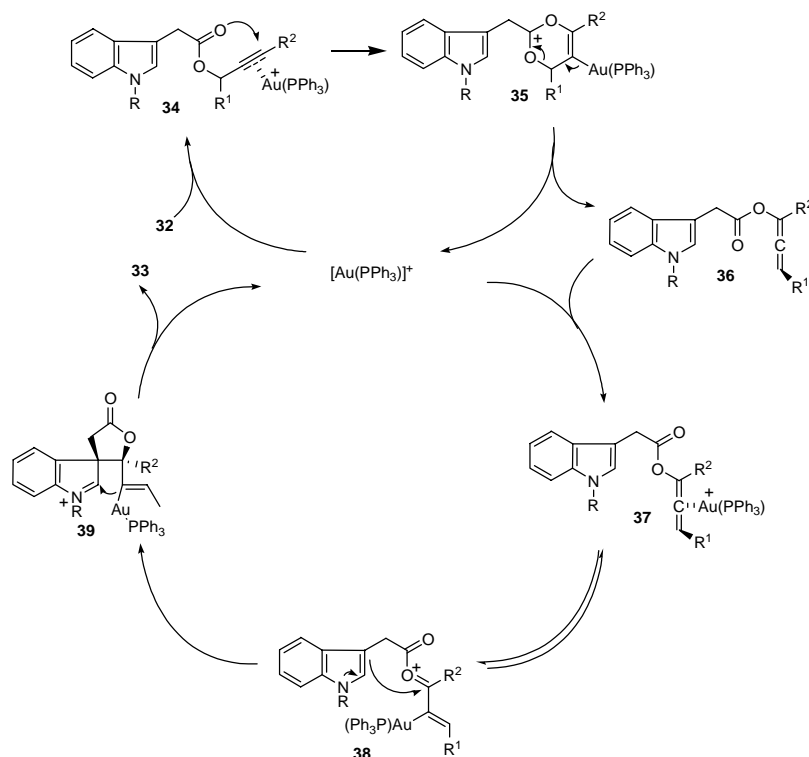
Scheme 4

Zhang reported the synthesis of highly functionalized 2,3-indoline-fused cyclobutanes **33** from **32** catalyzed by cationic gold (eq 8).[13] It was proposed that the catalyst played dual role for activating both propargylic esters and the *in situ* generated allenylic esters.
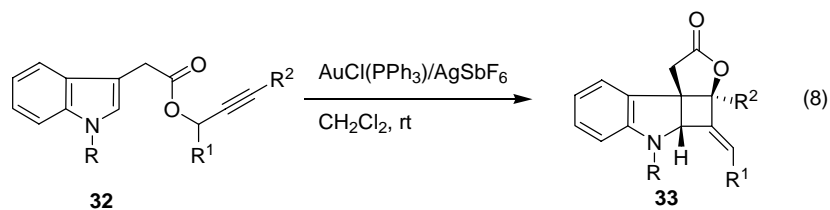

The proposed mechanism for the formation of the cyclobutane **33** is shown in Scheme 5. Activation of the C-C triple bond in propargylic ester **32** by [Au(PPh₃)]⁺ promotes a 3,3-rearrangement of the indole-3-acetoxy group, which leads to the formation of allenylic ester **37**. The allene moiety of **37** was further activated by the cationic Au(I) complex, resulting in the formation of oxonium ion **38**. The cyclobutane **33** is produced *via* the C-C bond formation between the oxonium carbon of **38** and the C-3 carbon of the indole ring, followed by intramolecular trapping of the iminium with the alkenylgold(I).
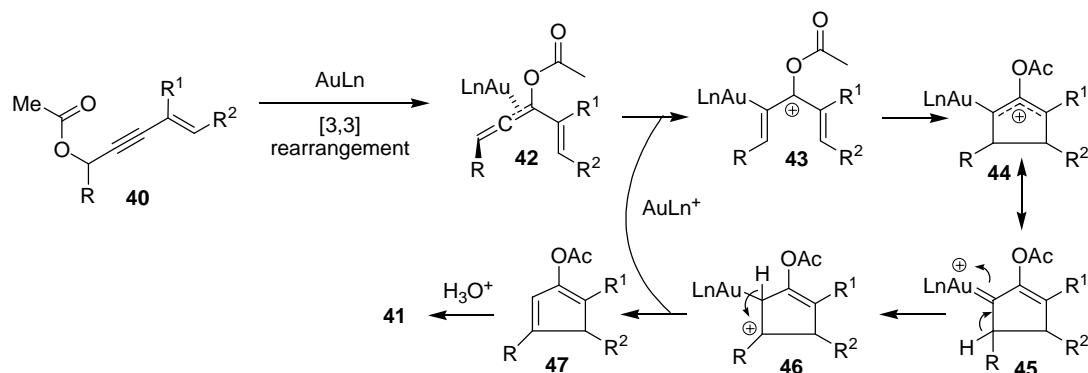
Scheme 5

A recent report by the same author described gold catalyzed highly efficient synthesis of cyclopentenones **41** from propargylic esters **40** *via* tandem 3,3-rearrangement and the Nazarov reaction (eq 9).[14]
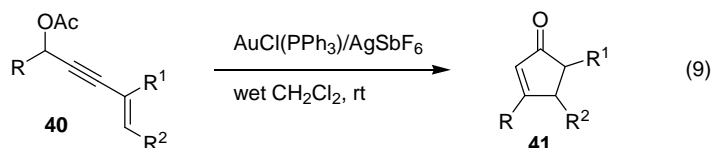

The mechanism of the reaction is presented in Scheme 6. The allenylic acetate **42** generated in situ *via* cationic Au(I)-catalyzed [3,3]-rearrangement of the corresponding propargylic acetate is further activated by the Au(I) catalyst leading to pentadienylic cation **43**. 4π-Electron closure of **43** forms the Au- containing cyclopentenylic cation **44**, which is in resonance with Au carbenoid species **45**. [1,2]-Hydride shift in **45** gives **46** after subsequent elimination and regeneration of the cationic Au(I) catalyst.

Scheme 6

Furstner *et al.* described the AuCl$_3$ catalyzed rearrangement of propargylic acetates for the synthesis of terpene derivatives (eq 10).[15] Complexation of gold catalyst to alkyne renders alkynes susceptible to attack the carbonyl oxygen to form gold carbene **52** through intermediate **50** and **51**. The insertion of carbene **52** was then took place into the tethered alkene to form the product **49**.
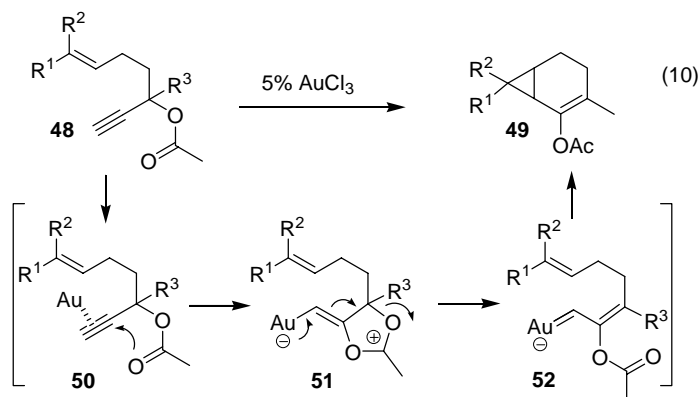
Recently, Toste has developed a gold(I)-catalyzed cyclopropanation of olefins **54** using propargyl esters **53** as gold-(I)-carbene precursors (eq 11).[16] The attack of carbonyl oxygen to the gold coordinated alkyne would produce intermediate **57** *via* **56,** which on subsequent rearrangement as shown by the arrow would provide gold carbene complex **58**. The carbene complex **58** thus formed could then be inserted into the olefin to provide cyclopropanation products. The highest enantioselectivity of 85% was achieved using DTBM-SEGPHOS-gold (I) catalyst.

$$(11)$$

R = Piv, Ac, Bz
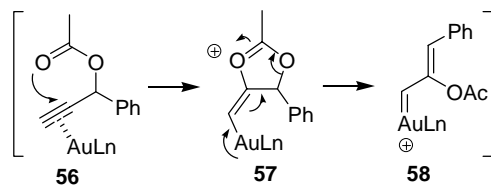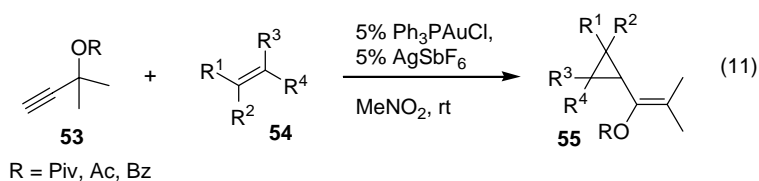
The chemistry has also been applied by Porco for the synthesis of various azaphilones, which are known to be a component of many natural products. Gold catalyzed cyclo-isomerization of *O*-alkynylbenzaldehydes **59** into 2-benzopyrylium salts and subsequent oxidation by using IBX in conjunction with phase transfer catalyst provided products **60** in high yields (eq 12).[17]

$$(12)$$
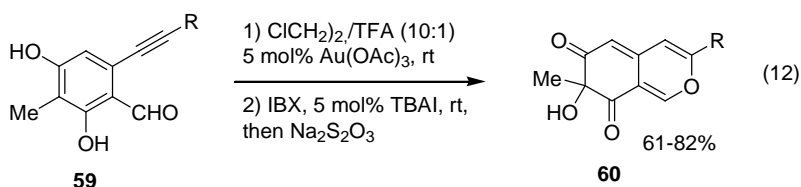
The reaction of propargyl ketones such as **61** in the presence of 0.1 mol. % $AuCl_3$ gave the furan **62** in essentially quantitative yield (eq 13).[18] On the other hand, with palladium as a catalyst, 100 °C temperature is needed in order to proceed the reaction. A novel cascade cyclization of the propargyl ketone **63** in the presence of $AuCl_3$ was also reported (eq. 14). The author proposed the intermediacy of **64** for this cascade cyclization.

$$(13)$$

$$(14)$$
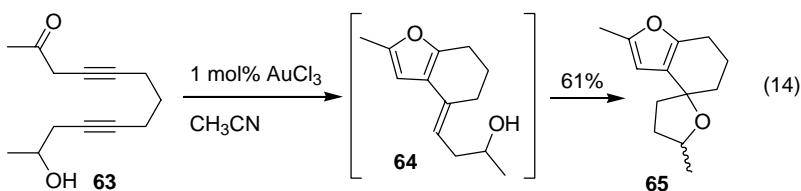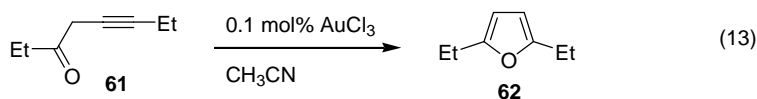
Recently, Larock reported an entirely new approach for the novel cyclization of 2-(1-alkynyl)-2-alken-1-ones **66** with nucleophiles in the presence of catalytic amounts of $AuCl_3$ which led to the formation of highly substituted furans **67** (eq 15).[19] An example of nucleophiles

includes alcohol, activated methylene and electron rich arenes such as *N,N*-dimethylaniline and *N*-methyl indole.
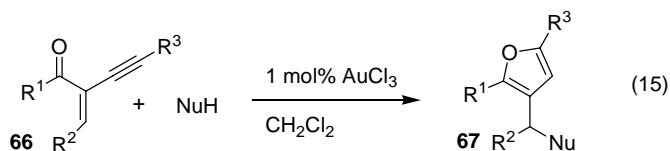
The mechanism of the reaction is depicted in Scheme 7. The coordination of the triple bond of **66** to AuCl$_3$ enhances the electrophilicity of the triple bond, and subsequent nucleophilic attack of the carbonyl oxygen on the electron-deficient triple bond generates carbocation **69**. Intermolecular nucleophilic attack on the carbocation and subsequent protonation of the carbon-gold bond afford furan **67** and regenerate the catalyst AuCl$_3$. The authors ruled out the possibility of an alternative mechanism wherein AuCl$_3$ first acts as a Lewis acid, forming a complex with the carbonyl oxygen thereby facilitating Michael addition since 1% AuCl$_3$ failed to catalyze the 1,4-addition of methanol to 2-cyclohexenone and methyl vinyl ketone under the standard conditions.
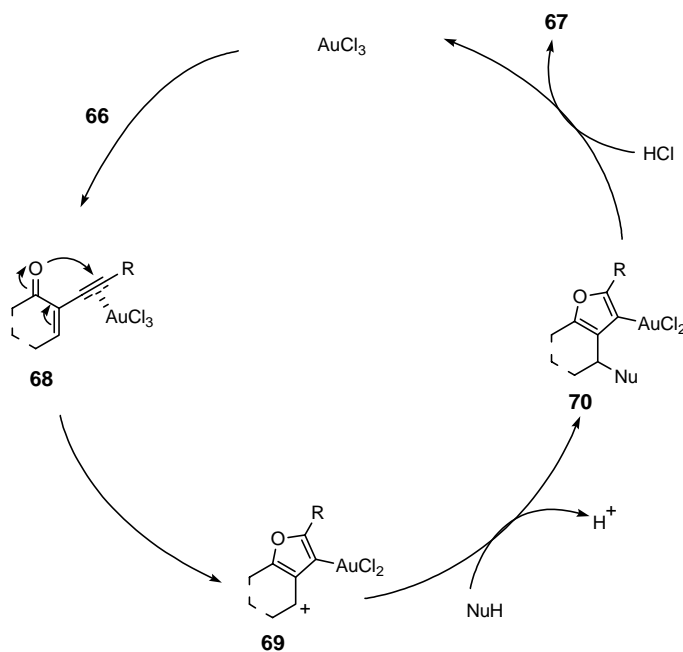

Scheme 7

Recently, Hashmi and coworkers reported gold catalyzed synthesis of 2,5-disubstituted oxazoles **72** from the corresponding propargylcarboxamides **71** (eq 16).[20] The addition of amide oxygen to gold co-ordinated alkyne is highly stereospecific as shown is **73** to form the vinyl gold species **74** which on protonation and regeneration of catalyst gave products **72**.
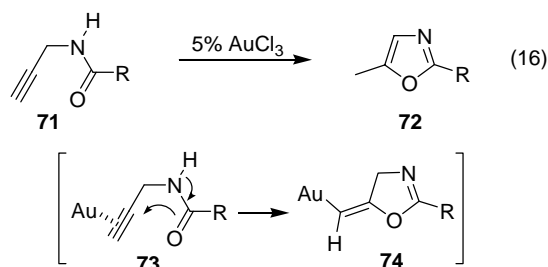
The gold catalyzed rearrangement of propargylic *tert*-butyl carbonates **75** and **77** into 4-alkylidene-1,3-dioxolan-2-ones **76** and **78** was described by Gagosz and Buzas (eqs 17 and 18).[21] A variety of cyclic carbonates were synthesized under these milder conditions.
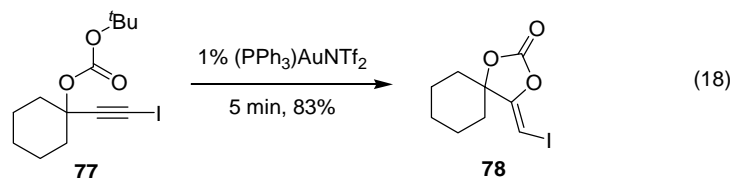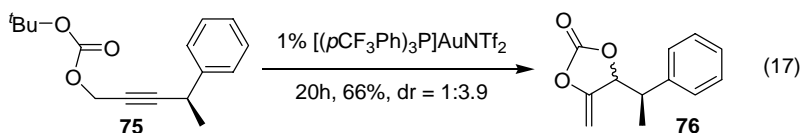
In summary, we have discussed the gold catalyzed reactions of carbonyl compounds tethered with alkynes. Other transition metals are also known to activate alkynes allowing the nucleophilic attack of carbonyls to metal co-ordinated alkynes. However, gold is now becoming more popular because of its efficiency in performing reactions at lower catalyst loading and at room temperature.

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Nitin Patil was born in Achegaon (a small village in the Jalgaon district of Maharashtra) in India in 1975. After completing his master studies in 1997 at North Maharashtra University, he joined Dr. Dilip Dhavale's research group as a CSIR-JRF at University of Pune for his Ph.D. work. He completed his doctoral study in 2002 on the synthesis of polyhydroxylated piperidine and indolizidine alkaloids. After working for nine months as a postdoctoral fellow at Goettingen University, with Professor Christoph Schneider on enantioselective opening of epoxides, he

shifted to Tohoku University, Japan, as a JSPS Postdoctoral Fellow to work with Professor Yoshinori Yamamoto. Presently, he has been working as Assistant Professor of Organic Chemistry in the same laboratory. His research interest includes transition metal and Lewis acid mediated development of new synthetic methods, asymmetric catalysis, and synthesis of biologically important natural and unnatural compounds. He has more than 30 research publications in international peer-reviewed journals including book chapters and reviews.

Yoshinori Yamamoto was born in Kobe, Japan, and received his M.S. and Ph.D. degrees from Osaka University. In 1970 he was appointed as an Instructor at Osaka University, after which he went to Professor H. C. Brown's research group at Purdue University, as a Postdoctoral Associate (1970-1972). In 1977 he was appointed as an Associate Professor at Kyoto University. In 1986 he moved to Tohoku University to take up his present position, Professor of Chemistry. He also holds a Professorship at IMRAM, Tohoku. He was awarded the Chemical Society of Japan Award for Young Chemists (1976), the Chemical Society of Japan Award (1996), and the Humboldt Research Award (2002). He is the Regional Editor of Tetrahedron Letters and Volume Editor of Science of Synthesis, and he was the President of the International Society of Heterocyclic Chemistry (2000-2001). He is the project leader of the 21 Century COE Program of MEXT "Giant Molecules and Complex Systems, Chemistry Group of Tohoku University" (2002-2006). He has a wide range of research interests in synthetic organic and organometallic chemistry. His recent work focused on the use of transition-metal complexes and Lewis acids as catalytic reagents in organic synthesis and synthesis of complex natural products.