Abstract

The origin of the carbophilic and oxophilic behavior of gold (Au) catalyst is described. The strength and utility of Au catalysts to various organic transformations is also shown. The usefulness of gold-catalyzed transformations to the construction of some interesting biologically active molecules is also briefed.
1.1 Introduction

1.1.1. The Gold

Gold belongs to the group 11 elements in modern periodic table with symbol \text{Au} and atomic number 79. The electronic configuration of Au is: \([\text{Xe}]\ 4f^{14} 5d^{10} 6s^1\). \text{Gold} metal is dense, soft, malleable and ductile with an attractive bright yellow color. Chemically it is unaffected by air, moisture and corrosive reagents; therefore Au-metal is used in coin and jewellery item.\textsuperscript{2a} The impact of \textit{relativistic effect} largely contributes to the chemical and physical property of gold (Figure 1.1).\textsuperscript{2b} As atomic nuclear charge (Z) increases, the penetration ability of s electrons to the nucleus also increases. This relativistic effect therefore causes the s electrons (a lesser extent for the p electrons) occupying in a smaller orbitals, whereas the absence of relativistic effect did not affect the size of the s-orbital. Thus, in case of heavier elements where the relativistic effect seems to be prominent; the s electrons are bound strongly and shield the nuclear charge from other electrons (especially from d and f electrons) more effectively, whereas the d and f electrons are less bound and occupy in larger orbitals (Figure 1.1).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{image1.png}
\caption{Relativistic effect on s and d orbitals}
\end{figure}

1.1.2. Homogeneous gold catalysis

Gold is soft and carbophilic Lewis acid; it activates carbon-carbon \(\pi\)-bonds, allows forming C–C, C–O, C–N, and C–S bonds by the attack of corresponding nucleophiles to the gold activated C–C multiple bonds.\textsuperscript{2,3} Thus the attack of nucleophile to the Au-activated alkyne 2 delivers \textit{trans}-alkenyl gold intermediate 3 (Scheme 1.1). Finally, replacement of vinylic Au–C bond by different electrophiles furnishes functionalized alkene derivatives 4 and 5.
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**Scheme 1.1: Activation of alkynes by gold**

On the basis of the computed enthalpy of formation, it has been observed that the binding energy of complex obtained from alkyne and gold is stronger than the complex generated from an alkyne and different electrophiles (Brønsted acids, iodine, and iodonium compounds). This observation clearly reflects that gold is a powerful activator to carbon-carbon triple bond. Apart from the activation of C–C multiple bonds, the carbonyl functional groups are also activated by gold-catalyst, offering opportunities in the exploration of novel organic transformations. Furthermore, the gold-catalyzed transformations have been used in the construction of complex molecular entities as well as cascade or domino reactions.

The gold-catalyzed transformations generally occur with the active involvement of non-classical carbocation or carbenoid intermediates; this leads to the formation of products with controlled selectivity. Moreover, the carbon-gold bonds are labile toward protodeauration but not susceptible to β-hydride eliminations. Gold exhibits +1 and +3 oxidation states; these two oxidation states are therefore involved in the Au-catalyzed reactions. The gold catalysts are active even in ppm level without the assistance of ligands. The heterogeneous gold nanoparticles are found to be very active and selectively used in accomplishing oxidation, hydrogenation, and redox reactions. Apart from all these chemical benefits, gold is more abundant than platinum, palladium, rhodium, and other metals.

1.2. Gold-Catalyzed Transformations

1.2.1. Nucleophilic Addition to Alkynes

The carbon-oxygen bond is present in a wide range of organic molecules. Gold catalysts play important role in the development of new methods for C–O bond formations. The cationic gold is soft Lewis acid and a high π-acid with low oxophilicity; as a consequence, cationic gold selectively activates unsaturated C–C bonds in the presence of different
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oxygen containing nucleophiles such as H₂O, alcohols, diol etc. Due to π-acidic nature of Au, it first coordinates to the triple bond of alkynes to form a gold-alkyne complex 2. The attack of nucleophile to the Au-activated alkyne delivers trans-vinyl gold species 3 (Scheme 1.2). The trapping of gold-vinyl species with proton or other electrophiles affords diverse range of products. For example: addition of water to alkyne in the presence of Au-catalyst provides carbonyl derivatives. The Au-catalyzed addition of aliphatic or aromatic alcohols to alkyne lead to enol ethers. The intramolecular addition of oxygen nucleophile to alkyne generates oxygen containing benzofuran, dihydropyran, benzopyran, and furan heterocycles. The intra- or intermolecular addition of carbon or nitrogen bearing nucleophiles to alkynes is broadly employed for the synthesis of various complex molecules.

Scheme 1.2: Addition of different nucleophiles to alkynes

1.2.2. Gold-Catalyzed 1,2- or 1,3-Migration of Propargyl Ester

The Au-catalyzed intramolecular 1,2- or 1,3-migration of propargyl ester is successfully employed for the synthesis of complex molecular frameworks. Generally, the terminal or electron-deficient alkynes undergo 1,2-migration of ester moiety, whereas internal alkynes prefer 1,3-migration. Under the influence of Au-catalyst, the terminal and/or electron deficient propargyl ester forms carbenoid intermediate 13 in situ; this transformation proceeds with the participation of five-membered transition state 12 (path
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a; Scheme 1.3). The trapping of reactive gold-carbenoid species 13 lead to novel products.\(^6\) Whereas the propargyl esters having internal alkynes undergo 1,3-shift of ester moiety producing allene intermediate 16 (path b; Scheme 1.3). Complex molecular entities are synthesized by arresting reactive allenolate 16.\(^7\)

**Scheme 1.3**: Rearrangement of propargyl carboxylates by gold catalyst

**1.2.3. Gold-Catalyzed Meyer-Schuster Rearrangement**

The Meyer-Schuster rearrangement of secondary or tertiary propargyl alcohols 18 to \(\alpha,\beta\)-unsaturated carbonyls 21 is successfully conducted in the presence of Au-catalyst at room temperature.\(^8\) The activation of alkyne moiety in 18 by Au delivers allenol intermediate 20 \(in\ situ\). The tautomerization of 20 instantaneously delivered 21 (Scheme 1.4).

**Scheme 1.4**: Meyer-Schuster rearrangements under gold catalyst

**1.2.4. Nucleophilic Substitution at Propargylic and Benzylic Position**

Nucleophilic substitutions at propargylic and benzylic position of propargyl and benzyl alcohol with the aide of Au(III) catalyst affords the corresponding propargyl and benzyl substituted compounds 23 and 26, respectively (eq 1 and 2, Scheme 1.5).\(^9\)
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1.2.5. Gold-Catalyzed Oxidation of Alkynes

The intra- or intermolecular oxidation of alkynes furnishes α-oxo metal carbene via oxide transfer from the oxidant (Scheme 1.6). The gold-carbene intermediate successfully undergoes C–H insertion, nucleophilic addition, and cyclopropanation reactions.

![Scheme 1.6: Oxidative rearrangement of alkynes by gold catalyst](image)

1.2.6. Activation of Allenes by Gold

Allenes are valuable substrates in organic chemistry. The activation of allenes with Bronsted or Lewis acid triggers the attack of nucleophile in inter- or intramolecular fashion and allows creating C–C or C–heteroatom bonds. Importantly, the transfer of chirality of allenes is successfully employed in accessing stereoselective target-oriented synthesis of natural products. The gold catalysts are selectively used for the activation of allenes. The gold catalyst coordinates with allene to form an active intermediate or . The attack of nucleophile to the intermediates delivers functionalized alkene (Scheme 1.7).

![Scheme 1.7: Gold-catalyzed addition of nucleophiles to allenes](image)
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1.2.7. Activation of Alkenes by Gold

Gold catalyst also activates the unactivated and activated alkenes. The intra and intermolecular addition of carbon, oxygen and nitrogen nucleophiles to Au-activated alkenes lead to carbon-carbon and carbon-heteroatom bond formations with ease (Scheme 1.8).²¹,¹²

![Scheme 1.8](image)

**Scheme 1.8:** Activation of alkene by gold catalyst

1.2.8. Glycosylation of Sugar Derivatives by Gold

The alkynyl-functionality bearing O-protected benzoate leaving group in sugar derivatives easily undergo glycosylation with nucleophile in the presence of gold catalyst.¹³ The reaction begins with the activation of triple bond by Au(I) catalyst forming complex 36. Attack of proximal carbonyl oxygen to gold-activated triple bond followed by cleavage of glycosidic bond provides the oxocarbenium intermediate 37 with expulsion of gold–isocoumarin complex 39 (Scheme 1.9). The addition of nucleophile to the glycosyl acceptor affords the corresponding glycoside product 38.

![Scheme 1.9](image)

**Scheme 1.9:** Glycosylation reaction of sugar derivatives

1.2.9. Gold-Catalyzed Direct Alkynylation of Arene Ring

The alkyne functionality is found in large variety of molecules of biological and material applications.¹⁴ The Sonogashira cross-coupling is commonly used and trustworthy methods for installing the alkyne moiety in the arenes.¹⁴b Interestingly Nevado group demonstrated an alternate route to aryl-alkyne synthesis involving the dehydrogenative coupling between electron-rich arenes 40 and electro-deficient alkynes 41 under gold catalyst (eq 1, Scheme 1.10).¹⁴c The Au-catalyzed coupling between hypervalent iodine
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reagent TIPS-EBX (44) and heteroaryls lead to heteroaryl-alkyne moiety 45. This strategy has successfully been employed for the regioselective alkynylation of thiophene, furan, pyrrole and indoles (eq 2, Scheme 1.10).\(^{14d-i}\)

![Scheme 1.10: Alkynylation of arene ring by gold catalyst](image)

**Scheme 1.10:** Alkynylation of arene ring by gold catalyst

1.2.10. Gold-Catalyzed Bromination of Arenes

Direct halogenation of aromatic compounds with \(N\)-bromo-, \(N\)-chloro-, and \(N\)-iododsuccinimide (NBS, NCS, and NIS, respectively) delivers aryl halide derivatives and the inert succinimide by-product. The halogenation of unactivated aromatic ring proceeds in the presence of strong Lewis acids.\(^{15}\) Recently, Wang group reported Au(III)-catalyzed direct bromination of unactivated arenes \(^{46}\) with NBS \(^{47} \).\(^{15}\) An aryl-gold(III) species \(^{49}\) is presumably participated in this bromination reaction (Scheme 1.11).

![Scheme 1.11: Direct bromination of arenes by gold catalyst](image)

**Scheme 1.11:** Direct bromination of arenes by gold catalyst

1.2.11. Gold Catalysis in Total Synthesis

The use of gold catalysis in the total synthesis of biologically active molecular entities has been increasing. Owing to the mild nature of catalytic conditions, the gold-catalyzed transformations has been successfully employed in building total synthesis of natural products (Figure 1.2 and 1.3).\(^{2c}\) We recently demonstrated the synthesis of rac-actinopolymorphol B (51) using Au-catalyzed regioselective hydration of propargyl acetate as a key step.\(^{16a}\) The Au-catalyzed spiroketalization of alkynes with tethered...
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hydroxy or mixed hydroxy/alkoxy moieties is used in the fabrication of various natural products, for instance: okadaic acid (52) and cephalosporolide H (53).\textsuperscript{16b–d} The Au-catalyzed intramolecular hydroamination of alkynes is successfully employed for the synthesis of nitrogen bearing heterocycles; the utility of this strategy is shown in the formal total synthesis of antitumor drug nitidine (54) and first enantioselective total synthesis of indole alkaloid (-)-mersicarpine (55).\textsuperscript{16e,f} The Mayers–Schuster rearrangement of propargyl carboxylates by gold-catalyst was applied for the total synthesis of prostaglandin (56) and $\alpha$-ionone (57).\textsuperscript{16g,h} The formal synthesis of racemic clavukerin A (58) is demonstrated involving the Au-catalyzed addition of –OMe to alkyne followed by [3,3]-sigmatropic rearrangement.\textsuperscript{16i}

Figure 1.2: Biologically active molecules

Synthesis of biologically active bejarol (59), funebrine (60), swainsonine (61) and porantheridine (62) were accomplished using Au-catalyzed intramolecular hydroalkoxylation, hydrocarboxylation and hydroamination to the tethered allenes.\textsuperscript{16j–m} The Au-catalyzed intramolecular hydroarylation to allenes is employed for the synthesis of
flinderoles B and C \((63)\)^{16a} The furano-sesquiterpenes **crassifolone** \((64)\) and **dihydrocrassifolone** \((65)\) were accomplished involving intramolecular Au-catalyzed Michael addition of furan to conjugated ynone.\(^{17a}\) The cyclization of monoallylic diols is used for the enantioselective total synthesis of (-)-**isoaltholactone** \((66)\).\(^{17b}\) The rearrangement of propargyl carboxylate moiety has been successfully used for the total synthesis of complex molecular entities. The utility of rearrangement of propargyl acetate for the synthesis of sesquisabinene and sesquithujene terpenoids is reported by Fürstner group.\(^{17c}\) Formal total synthesis of **frondosins A and B** \((67)\) is demonstrated using vinyl gold carbenoid intermediate.\(^{17d}\)

**Figure 1.3:** Pharmaceutically important compounds
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The gold-catalyzed oxidation of alkynes to oxo-gold carbene concept was applied to construct the core ring of cermizine C (68) and lentiginosine (69 and 70). The Au-catalyzed intramolecular cyclization of enyne, allenene and diynes is applied successfully in the construction of several bioactive molecules GSK 1360707 (71), ventricos-7(13)-ene (72), orientalol F (73) and englerin A (74). A formal total synthesis of imidazole alkaloid isocynometrine (75) is achieved using the hydrative cyclization of allenenes. The Au-catalyzed glycosylation of sugar derivatives is utilized for the synthesis of novel sugar derivatives. The biologically active molecules JBIR-68 (76) and ginsenoiside Rh2 (77) were synthesized involving Au-catalyzed O- and N-glycosylation of protopanaxadiol and uracil, respectively.

1.3. Conclusion and Expectations

It is apparent from the above discussion that the development of novel Au-catalyzed transformations and their utility to the construction of complex molecular entities of biological and material applications offers abundant opportunities and cummulative challenges. Inspired from these challenges, we thus became interested in the explorations of novel and efficient Au-catalyzed transformation.

1.4. References


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