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Gold as a catalyst. Part I. Nucleophilic addition to the triple bond

Sergey B Alyabyev,[a] Irina P Beletskaya [b]

[a] *Eurasian Patent Organization*
Malyi Cherkassky per. 2, 109012 Moscow, Russian Federation
[b] *Department of Chemistry, Lomonosov Moscow State University*
Leninskie Gory 1, stroenie 3, 119991 Moscow, Russian Federation

This paper is the first in a series of reviews of the state of-the-art in gold catalysis in organic synthesis and covers the literature over the past decade. The first review addresses the problem of the nucleophilic addition to the triple bond. Gold catalysts used in the hydroamination of alkynes and the addition of oxygen-containing nucleophiles and thiols are considered. The data concerning intra- and intermolecular types of transformations are given separately. The α,α-nucleophilic addition and Au carbene intermediates are discussed.
The bibliography includes 568 references.

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I. Introduction

Gold has always played a significant role in natural science. In 1911, Ernest Rutherford used gold foil (gold leaf) to establish the theory of the nuclear atom.[1] However, gold has long been considered as an inert, unreactive and chemically uninteresting element. Available gold compounds were few in number. Many of these compounds were unstable even at moderate temperatures and decomposed to form elemental gold. This metal was mainly used as a financial safe haven and for jewellery fabrication. The technological applications of gold were limited to its use as an electrical conductor and an inert coating.[2] Until 2000, handbooks and manuals for organic synthesis did not include data on the use of gold in organic reactions. For example, the monograph by Dzhemilev *et al.*[3] published in 1999 gives no examples of application of gold-containing catalysts in organic synthesis. In the manual by Larock[4] devoted to transformations of functional groups published in 1999, examples of the use of gold as a catalyst are also absent.

The situation changed radically in the 21st century. Investigations performed in the past 15 years demonstrated the incredibly wide use of gold in catalytic processes. The work by Hutchings,[5] who showed that gold is the best catalyst for the hydrochlorination of acetylenes, and the study by Haruta *et al.*,[6] who investigated the oxidation of CO on gold nanoparticles (AuNP) at low temperature, are key publications, which have changed views on this noble metal. In the past decades, the field of application of gold-containing catalysts steadily expanded,[7] which was accompanied by an explosive growth of the number of publications.

Reactions catalyzed by Au^{I}, Au^{III} and AuNP are rapidly developed. The growing field of applications for gold as a catalyst can be called a gold rush. This is attributed to interesting properties of gold complexes, their selective Lewis acidity and ability to catalyze various chemical transformations with high product yields and excellent selectivity. Gold complexes are distinguished from other transition metal complexes by different affinities for nitrogen and oxygen atoms. Besides, they are not prone to β-hydride elimination. The latter difference is particularly pronounced

S.B.Alyabyev. PhD, Chief Expert at the Department of Chemistry and Medicine of the Eurasian Patent Organization.
Telephone: +7(495) 411 – 6161, e-mail: salyabyev@eapo.org
Current research interests: organic chemistry; chemistry of biologically active heterocyclic compounds, dyes; organic synthesis, metal-complex catalysis.
I.P.Beletskaya. Academician, Doctor of Chemical Sciences, Professor, Head of the Laboratory of Organoelement Compounds at the Department of Chemistry, MSU.
Telephone: +7(495) 939 – 3618, e-mail: beletska@org.chem.msu.ru
Current research interests: metal-complex and organic catalysis, chemistry of macrocyclic compounds and the design of chemosensors based on them, chemistry of porphyrins and steroids, metal-centred nucleophiles.

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in C(sp^3)–H-activation reactions. Gold complexes can activate multiple bonds, particularly the triple bond, due to which gold is sometimes called a carbophilic or even alkynophilic catalyst. The triple bond activation by gold followed by the intra- or intermolecular nucleophilic attack provides a route to the formation of new C–C and C–heteroatom bonds, in particular in the synthesis of heterocycles.

Due to the successful use of gold-based catalysts in numerous reactions, they had a significant impact on modern organic synthesis.[8] Currently, Au catalysts are extensively investigated by researchers worldwide.[9] There is a specialized journal devoted to the properties of this metal and a wide range of its possible applications.[10] Two monographs on gold, its properties and applications in modern chemistry were published[11,12] in 2012. Different aspects of gold catalysis are covered in several reviews.[13–17]

Gold has only one isotope (see p. 67 in the handbook[18]), resulting in the absence of a peak family characteristic of a mixture of isotopes in the mass spectrum.[19] The nuclear spin of gold is 3/2. However, because of low sensitivity and the quadrupole moment, only several ^{197}Au NMR spectra in a highly symmetric environment were described.[20–24] Due to the diamagnetic character of Au^{I} and Au^{III}, the catalytic reactions can be monitored by NMR spectroscopy of the substrate, the intermediate and the product. Mössbauer spectroscopy provides information on the oxidation state of gold (see pp. 238, 420 in the monograph[25]). The unexpected and in some ways unique catalytic properties of gold are attributable to the operation of a relativistic effect, which stabilizes the outermost $6s^2$ electron pair so that the reactivity and catalytic activity are determined by its high-energy 5d orbitals.[26]

It is impossible to cover in detail the published data on gold-catalyzed reactions even in several reviews. However, we will try to classify these transformation and consider at least the most important reactions. We will begin with the most studied reactions involving alkynes, which exhibit a huge potential associated with the catalysis by Au^{I} and Au^{III} complexes and, in some cases, by gold nanoparticles. Despite the fact that the nucleophilic addition to alkynes is catalyzed by a wide range of catalysts, including strong bases,[27,28] gold catalysis has a number of advantages, such as mild reaction conditions (low temperature, the absence of strong bases or acids), high selectivity and the possibility of cooperative catalysis.

The gold catalysis is helpful in solving main problems of modern organic synthesis, being useful in the development of methods for chemo-, regio- and stereoselective transformations. The next section briefly describes gold as a catalyst.

II. Homogeneous Au catalysts

This section is devoted to the data on catalysts used, in particular, in hydroamination and addition of oxygen-containing nucleophiles. Although we intend to write a separate review on the state-of-the-art gold-based catalysts, the below data, which are related mainly to catalysts for the reactions considered in the present review, will be useful for a better understanding of the issues under consideration.

In catalysts, gold can exist in different oxidation states — Au^0, Au^{I} and Au^{III}. Gold salts, *e.g.*, AuCl, $AuCl_3$ and $AuBr_3$, can serve as catalysts.[29] In aqueous solutions in the absence of stabilizing ligands, Au^{I} undergoes self-disproportionation to Au^{III} and Au^0.

The structures of most gold-based precatalysts were established; however, in most cases the real structure of active species is unknown. In this case, unknown active gold-containing species in intermediates are denoted by the symbol [Au]. When comparing the same reactions, gold-based catalysts are often significantly more active than complexes of other transition metals.[13]

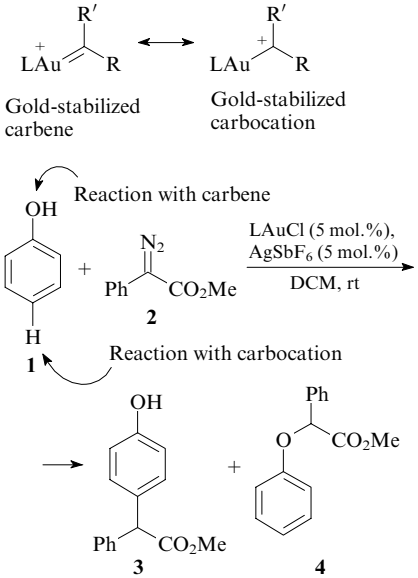
II.1. Effect of the ligand nature

The nature of the ligands involved in active gold(I) complexes often plays a key role in the activity of the corresponding complex and determines the direction of the transformation.[26,30–35] For example, gold(I) complexes with N-heterocyclic carbenes,[36–38] phosphites,[39,40] as well as with bidentate,[41] electron-deficient[42,43] and bulky[44–46] phosphines can exhibit different activity and selectivity. Examples of the effect of the ligand nature on the catalytic reaction product are given in the studies,[47,48] where it was shown that the reaction pathway of the condensation of phenol (**1**) with α-phenyl α-diazoacetate (**2**) depends on the nature of the ligand (Scheme 1).

The effect of the ligand on the catalytic properties of gold was comprehensively examined and described in a number of publications.[31,49–53] Besides, the activity of the catalyst is influenced by the oxidation state of gold and the nature of the counterion.[11] All this makes it possible to choose the optimal combination of the above factors favourable for the catalysis under mild conditions with the highest efficiency.

Gold(I), like Ag^{I}, exhibits strong Lewis acidity[54] with respect to both unsaturated carbon–carbon bonds (π-electrophilicity) and lone pairs of heteroatoms (σ-electrophilicity). Due to these properties, gold can be used as a catalyst

Scheme 1



L	Yield of **3** (%)	Yield of **4** (%)
(2-biph)Cy_2P	39	49
(2,4-$Bu^t_2C_6H_3O)_3P$	99	0

DCM = CH_2Cl_2, Cy is cyclohexyl, biph is biphenyl

for the addition of N-, O-, S- and C-nucleophiles to unsaturated C–C bonds, Friedel–Crafts-type reactions, the activation of carbonyl and imine groups, enyne and heteroenyne cycloisomerization, the C–H bond activation of terminal alkynes, the oxidation of unsaturated bonds in homogeneous catalysis reactions and reactions in the presence of gold nanoparticles. Asymmetric gold complexes proved to be highly efficient in asymmetric synthesis.[55]

Some reactions, for example, the addition of nucleophiles to alkynes, proceed with ease due to high catalytic activity of gold. Another advantage of gold-based catalysts is their high tolerance to different substituents, which is attributed to mild reaction conditions. In addition, the use of gold as a catalyst enables one to substantially increase the molecular complexity in one step, for example, to prepare a polyheterocyclic system from the acyclic starting compound. Such transformations can be a challenge for retrosynthetic analysis because it is not always easy to reveal relationships between the product and the starting compound. The gold-catalyzed reaction was applied for the synthesis of natural products, *e.g.*, (+)-conolidine.[56]

The search for stable and efficient catalysts remains an important challenge in modern organic synthesis because such catalysts provide a higher efficiency of a catalytic process, resulting in its lower cost.[57] In the presence of some organic substrates, gold-based catalysts are prone to decompose to an inactive form of gold.[58] Ligands that form complexes with gold play a key role in stability and efficiency of homogeneous gold catalysts.

Organic cationic gold(I) complexes contain monodentate ligands, the Au^I atom being linearly coordinated by two ligands. Phosphines were the first to be widely used as ligands in gold complexes employed as catalysts.[31] According to theoretical concepts, the R_3PAu^+ cation is isolobal to H^+ and LHg^{2+} (see Refs 59–63). In the Periodic Table, relativistic effects reach a maximum for gold,[64–66] resulting, for example, in that Au^I complexes can be of smaller size than related Ag^I complexes.[67]

The gold(I)-containing cationic catalyst $[Ph_3PAu]^+$ is used for a wide range of transformations. This complex can be synthesized by at least two methods: by the reaction of $(Ph_3P)AuMe$ with acid[68] and by the exchange reaction of $(Ph_3P)AuCl$ with the silver salt AgX,[69] where X is a soft non-coordinating anion (TfO^-, Tf_2N^-; $Tf = CF_3SO_2$). The latter approach is more commonly applied because it is efficient with acid-sensitive substrates and, in some cases, it is more efficient due to silver cocatalysis. The catalyst $(Ph_3P)AuNTf_2$ was synthesized by Gagosz and co-workers[70] by the reaction of $(Ph_3P)AuCl$ with $AgNTf_2$ and was then isolated in the individual state (white powder) and characterized by ^1H and ^{31}P NMR and IR spectroscopy. This catalyst is stable in air. The cationic catalyst $(Ph_3P)AuBF_4$ is generated *in situ* from $(Ph_3P)AuCl$ and $AgBF_4$.[71]

Malhotra *et al.*[72] investigated the effect of the nature of phosphine ligands for gold(I) on the catalytic activity, in particular, in the intermolecular hydroamination reaction of phenylacetylene (**5a**) (Fig. 1). The ligand Ph_3P, which is commonly used in gold catalysis, proved to be inefficient in this reaction. Thus, the substrate conversion was 20% after 18 h. The researchers[72] attributed this fact to weak donor ability of this ligand and to catalyst deactivation. The replacement of one phenyl group in the ligand by the *o*-biphenyl (2-biph) moiety (ligand **L1**) resulted in a substantial improvement of the efficiency of the reaction, the conversion being nearly 100% after 18 h. Increasing the electron density on the ligand by introducing two electron-rich *tert*-butyl groups (ligand **L2**) led to 100% conversion of the substrate in less than 3 h (see Fig. 1). An analysis of numerous experimental data demonstrated that the presence of the *o*-phenyl moiety adjacent to the gold cation prevents deactivation of the latter,[53] while the presence of electron-donating substituents in the ligand is favourable for the catalyst regeneration in the protodeauration step of the σ-complex, resulting in an increase in TOF (turnover frequency) of the catalyst.

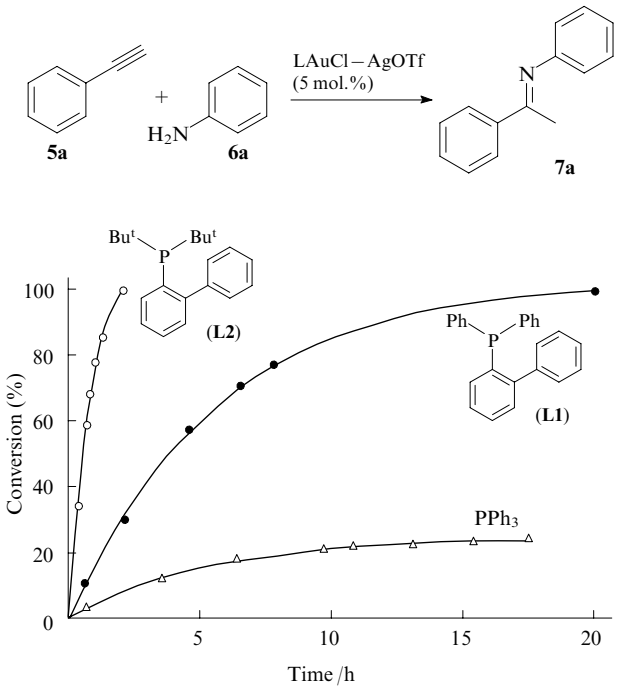


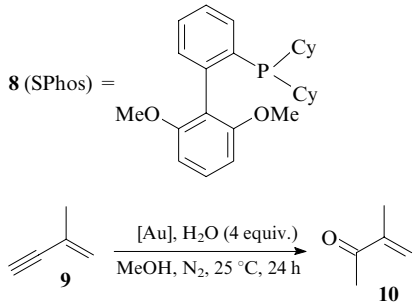
Figure 1. Conversion in the hydroamination reaction of phenylacetylene (**5a**) depending on the nature of the ligand for the gold(I) cation.[72]

Leyva and Corma[73] synthesized (in a nearly quantitative yield) the air-stable cationic Au^I catalyst $(SPhos)AuNTf_2$ (**8**), which proved to be efficient in the hydration of a wide range of alkynes, including enynes (*e.g.*, compounds **9**), internal alkynes (**11**) and propargyl alcohols (**13**). This catalyst is used in smaller amounts compared to $(Ph_3P)AuNTf_2$ and it is more active (Scheme 2).

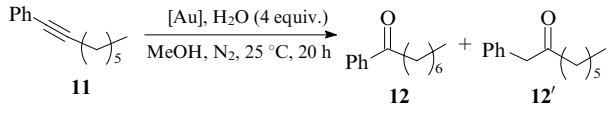
Later on, N-heterocyclic carbenes (NHC) were employed as ligands for gold.[74–78] These carbenes became very popular as ligands for Au^I complexes because they exhibit unprecedented σ-donor ability and create steric hindrance, resulting in an increase in stability of catalytic intermediates.[38, 79]

N-Heterocyclic carbene Au^I complexes **17** can be prepared in the catalytically active form (as complexes with a weakly coordinating anion) from appropriate chloride **15** using two alternative procedures: 1) by the exchange reaction with silver salt and 2) through the intermediate formation of the corresponding hydroxide **16** (see Refs. 68 and 80) (Scheme 3). For instance, it was demonstrated[81] that [Au(IPr)(OH)] (**16a**) can react with $HNTf_2$ in benzene to form $[Au(IPr)(NTf_2)]$ (**17a**) in 91% yield (see Scheme 3).

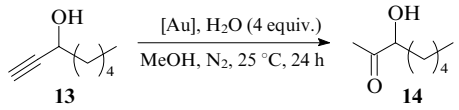
Scheme 2



[Au] (mol.%)	Yield of **10** (%)
$(Ph_3P)AuNTf_2$ (5)	73
(SPhos)$AuNTf_2$ (5)	90

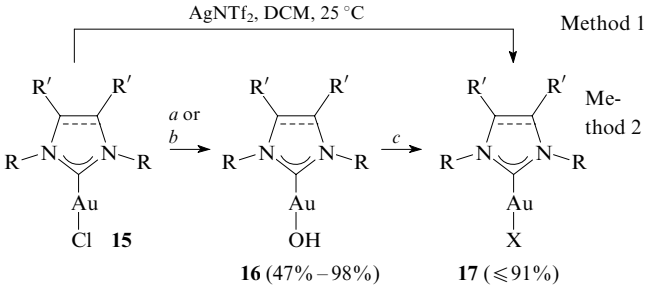


[Au] (mol.%)	Yield of **12** + **12′**, % (**12** : **12′**)
$(Ph_3P)AuNTf_2$ (1)	30 (50 : 50)
(SPhos)$AuNTf_2$ (1)	100 (60 : 40)

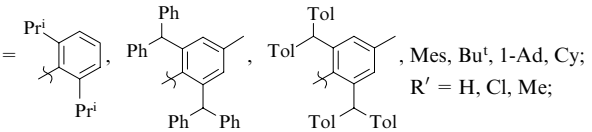


[Au] (mol.%)	Yield of **14** (%)
$(Ph_3P)AuNTf_2$ (1)	30
(SPhos)$AuNTf_2$ (1)	> 95

Scheme 3



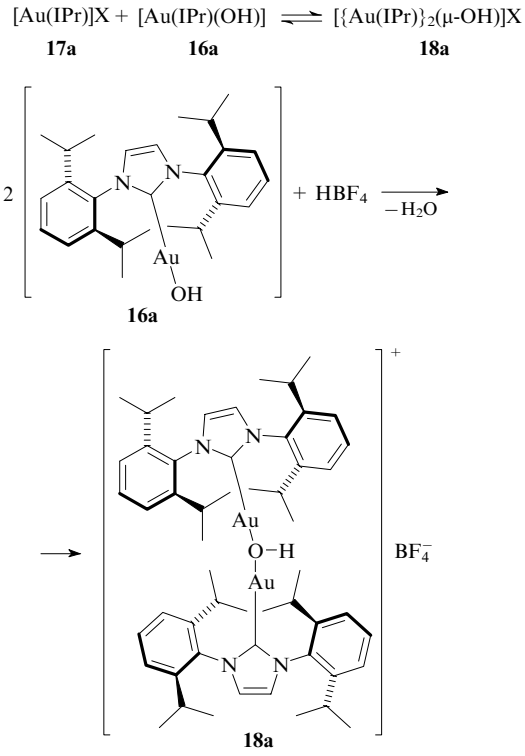
(*a*) KOH (10 equiv.), THF, in air, 30 °C, 2 h; (*b*) CsOH (10 equiv.), C_6H_6, argon, 30 °C, 20 h; (*c*) HX, C_6H_6, 25 °C;



X = SbF_6^-, NTf_2^-; Tol = 4-MeC_6H_4, Mes = 2,4,6-$Me_3C_6H_2$, Ad is adamantyl; R′ = H: R = 2,6-$Pr^i_2C_6H_3$ (**a**, IPr), 1-Ad (IAd), Mes (IMes)

Nolan and co-workers[82] applied complex **17a** for the hydration of a wide range of terminal and internal alkynes. Complex **17a** exhibits catalytic activity in the absence of silver salts. For efficient catalysis, excess acid should be used to prevent the equilibrium transformation of hydroxide **16a** into the dinuclear complex [{Au(IPr)}$_2$(μ-OH)][X] (**18a**), which is less active in the hydration reaction (Scheme 4).[82]

Scheme 4



The second method has a theoretical and practical significance. Since this method does not require the presence of silver salts as a cocatalyst, it is less expensive and more simple (due to insensitivity to light and moisture). Besides, the use of gold-based catalysts in the absence of other ions (in particular, silver) provides a better insight into the mechanism of the catalyzed reaction. Therefore, it is important to be sure that the gold-based catalyst contains no silver.[83,84] The simple synthesis under mild conditions in the absence of silver salts was proposed for [Au(NHC)Cl] **15**.[85,86]

The first mononuclear Au-NHC hydroxide complex [Au(IPr)OH] (**16a**) was synthesized by the treatment of [Au(IPr)Cl] (**15a**) with potassium hydroxide (2 equiv.) at 60 °C in a THF – toluene (1 : 1) mixture.[81] This complex was prepared in an aqueous KOH solution.[87] Recently, a new method was proposed for the synthesis of hydroxide **16a** using 10 equiv. of KOH at a temperature below 30 °C, which made it possible to avoid the decomposition of thermally labile intermediates.[88] The latter method was extended to other NHC ligands (see Scheme 3). In this reaction, CsOH can be used instead of KOH; in this case, the reaction is performed in benzene, due to which the next step can be accomplished without additional treatment.

It was shown that hydroxy complex **16** can be successfully applied as a catalyst for the synthesis of a gold acetylene complex,[89] carboxylation and decarboxylation,[90,91] the development of new silver-free protocols of gold catalysis[82,92] and many other transformations.[93–99] The synthesis of gold hydroxy complexes **16** offers considerable scope for the preparation of gold-containing cata-

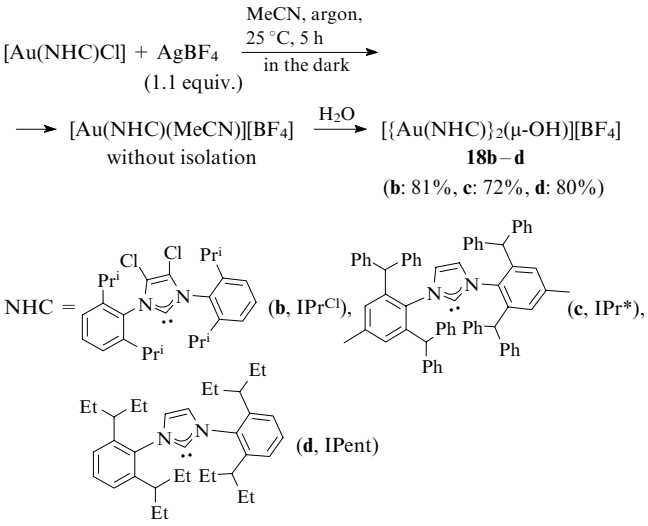
lysts without impurities of transition metals (in particular, silver). The synthesis of gold-containing catalysts through hydroxy complexes often provides higher yields compared to the procedure using $AgNTf_2$.[80, 81, 88, 100, 101]

Apart from catalytic activity, many Au-NCH hydroxide complexes **16** are known to act as external bases.[102] N-Heterocyclic carbene ligands were applied for the stabilization of the hydroxy group in complexes of gold,[81, 88] copper,[103] rhodium,[104] ruthenium,[105] palladium [106] and iridium.[107]

Later on, Gómez-Suárez and Nolan [108] synthesized a series of dinuclear gold complexes, in particular, the dinuclear hydroxy complex [{Au(IPr)}$_2$(μ-OH)][BF_4] (**18a**).[92, 109] Good results were achieved using the [BF_4]$^-$ anion as the counterion X [92, 109, 110] in the hydration of internal alkynes in the absence of silver and acids.[110, 111] Catalyst **18a** can be prepared using 0.5 equiv. of acid to neutralize OH-complex **16a** (see Scheme 4).

A series of analogues **18b** – **d** were synthesized by the exchange reaction with silver salt followed by washing of the product solution with water (Scheme 5).[110]

Scheme 5



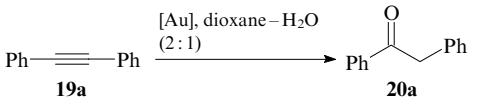
Gold complexes **18b** – **d** exhibited high activity in alkyne hydration, for example, in the hydration of diphenylacetylene (**19a**), their activity being higher than that of complex **18a** described above (Scheme 6). Besides, complexes **18** can be applied for the nitrile hydration and Meyer – Schuster rearrangement.[110]

The complex [{Au(NHC)}$_2$(μ-OH)][BF_4] **18** can be considered as a combination of [Au(NHC)OH)] **16** and [Au(NHC)][BF_4] **17**.[92, 109] Under appropriate reaction conditions, the dinuclear complex is present in dynamic equilibrium with mononuclear complexes **16** and **17**, which are Brønsted base and Lewis acid, respectively (Scheme 7).

The equilibrium formation of complexes **16** and **17** gives rise to a synergistic effect and an increase in the catalytic activity of the complex.

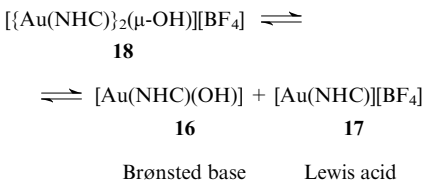
In recent years, there has been growing interest in the synthesis of N-heterocyclic carbene complexes [73, 112 – 115] with reduced heteroatom stabilization.[116 – 118] As opposed to complexes with normal NHC having structures **I** (*e.g.*, complex **17**), unsaturated abnormal NHC (aNHC), for example with structure **II**, are bound to the metal atom through the carbon atom adjacent only to one of the two nitrogen atoms of the ring rather than through the carbon

Scheme 6



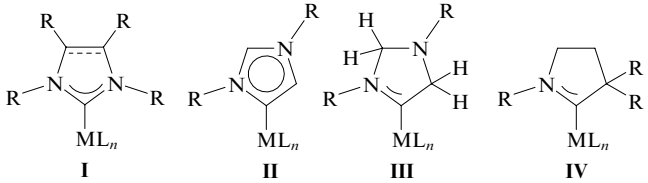
Catalyst (mol.%)	Temperature, time	Yield of **20a** (%)	Ref.
[(IPr)AuOH] (**16a**) + $HSbF_6$ (0.1)	120 °C, 24 h	70	84
(IPr)AuCl (**15a**) + $AgSbF_6$ (0.1)	120 °C, 24 h	77	103
[{Au(IPr)}$_2$(μ-OH)][BF_4] (**18a**) (0.5)	80 °C, 3 h	92	102
[{Au(IPr^{Cl})}$_2$(μ-OH)][BF_4] (**18b**) (0.5)	80 °C, 3 h	91	102
[{Au(IPr*)}$_2$(μ-OH)][BF_4] (**18c**) (0.5)	80 °C, 3 h	55	102
[{Au(IPent)}$_2$(μ-OH)][BF_4] (**18d**) (0.5)	80 °C, 3 h	74	102
[{Au(IPr)}$_2$(μ-OH)][BF_4] (**18a**) (0.1)	120 °C, 24 h	57	102
[{Au(IPr^{Cl})}$_2$(μ-OH)][BF_4] (**18b**) (0.1)	120 °C, 24 h	95	102
[{Au(IPr^{Cl})}$_2$(μ-OH)][BF_4] (**18b**) (0.05)	120 °C, 24 h	95	102

Scheme 7



atom located between two nitrogen atoms. Their saturated analogues — saturated aNHC (structure **III**, *e.g.*, complex **23** in Scheme 8) — are very similar in the electron density distribution to commonly used cyclic alkyl(amino)carbene complexes (CAAC, structure **IV**; an example is given in Section IV.2, structure **201**).[119, 120]

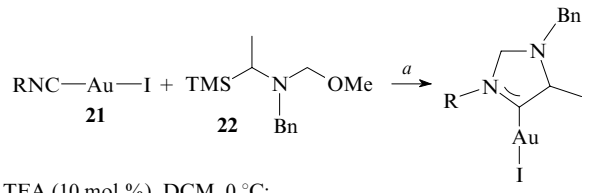
Structures I – IV



Complexes **III** and **IV** contain only one nitrogen atom adjacent to the carbene atom; saturated aNHC have one additional nitrogen atom in the ring.

First metal complexes with unsaturated aNHC were reported by research groups headed by Crabtree,[121, 122] Lassaletta [123] and Nolan.[124] Once free isolated unsaturated aNHC were synthesized,[125] some of them were used for the synthesis of complexes of a series of d elements, including palladium,[126 – 130] iridium,[131 – 135] ruthenium,[136] iron,[137] rhodium,[138] zinc,[139] and main group elements — boron,[140] aluminium [141] and phosphorus.[142] The resulting complexes exhibited high activity as catalysts for the Suzuki – Miyaura cross-coupling,[124, 126, 130] hydrogen transfer reactions [131, 132, 138] and other transformations. It was found

Scheme 8



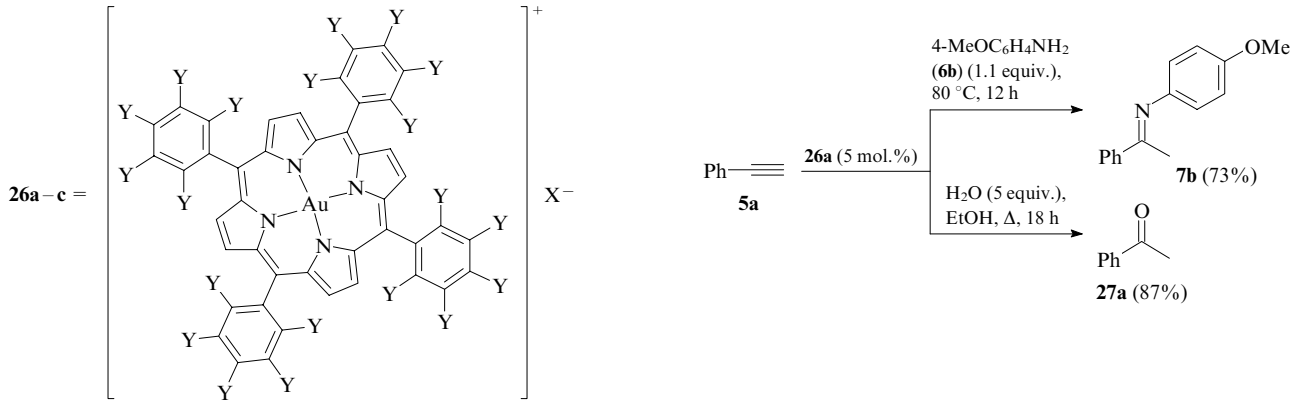
(*a*) TFA (10 mol.%), DCM, 0 °C;
R = Bu^t, 2,6-Pr$^i_2$C$_6$H$_3$, 2,4,6-Me$_3$C$_6$H$_2$,
2,6-Me$_2$C$_6$H$_3$, 2-Me-6-ClC$_6$H$_3$, Bn; TMS = SiMe$_3$, TFA = CF$_3$CO$_2$H

that unsaturated aNHC are stronger donors than their normal analogues.[116–118]

New abnormal N-heterocyclic carbene gold(I) complexes **23** were synthesized[75] in moderate yields by the 1,3-dipolar cycloaddition[143,144] of azomethine ylide, which was generated *in situ* from compound **22**, with isocyanogold(I) halide **21** (Scheme 8). The best yields were achieved for the corresponding iodide. Complexes **23** immobilized onto a solid support demonstrated good activity, for example, in the intramolecular reaction of furan with alkyne.[145]

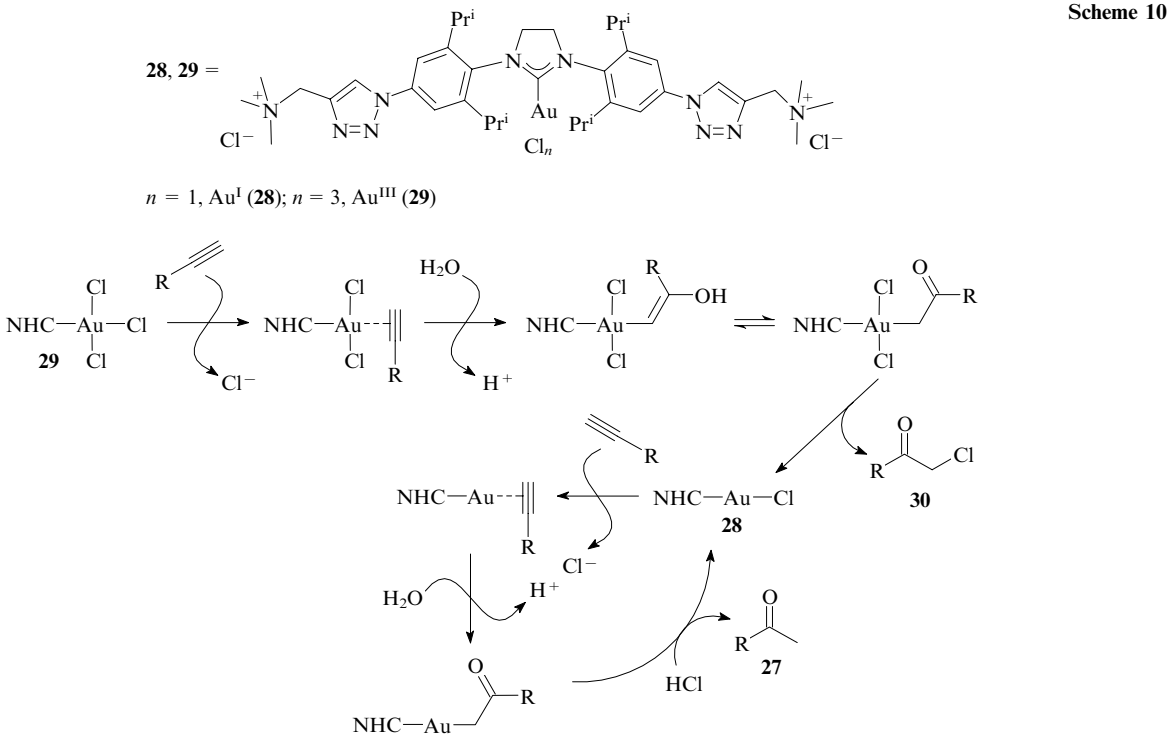
Gold(I) complexes, usually of the [LAuX] type, in which the ligand L is phosphine[146,147] or N-heterocyclic carbene[31,74,77,148–150] and X is a weakly coordinating anion (generally, TfO$^-$ or PF_6^-),[80] are applied for a wide range of gold-catalyzed reactions. Inorganic Au^{III} compounds, *e.g.*, $AuCl_3$ and $Na[AuCl_4]$, can be used for similar transformations.[151–157] Until recently, Au^{III} complexes with organic ligands have received much less attention. A few examples of such complexes were described, in particular compounds **24** and **25a**,**b** containing pyridine-substituted iminophosphorane[158] and *o*-pyridylcarboxylates,[159] respectively, as ligands.

Scheme 9

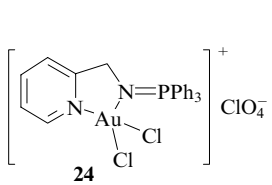


Y = H: X = Cl (**a**; [Au(TPP)]Cl), OTf (**b**; [Au(TPP)]OTf); Y = F, X = Cl (**c**; [Au(F$_{20}$-TPP)]Cl)

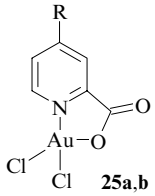
Scheme 10



Structures 24, 25



24



25a,b

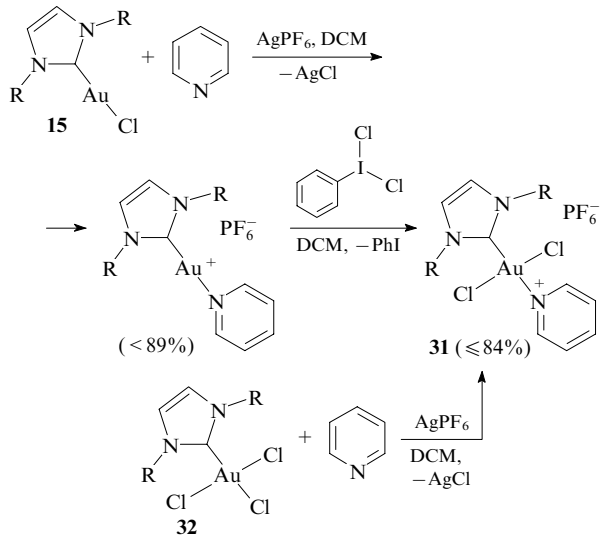
R = H (**a**), CO_2H (**b**)

It was demonstrated that Au^{III} can catalyze, as a Lewis acid, nucleophilic substitution reactions [160–162] and other transformations.[163–166] For example, the hydration and hydroamination of alkyne **5a** catalyzed by gold(III) porphyrin complexes **26a–c** gave products **27a** and **7b** in good yields (Scheme 9).[167]

Gold(I) and gold(III) compounds often exhibit different behaviours in catalytic reactions. The difference in the intermediate steps of the catalytic cycle results in the formation of different reaction products.[168–172] Meanwhile, gold(III) can serve as a precatalyst and is transformed into gold(I) during the reaction, as it was demonstrated by Ibrahim *et al.*,[173] who reported the synthesis of water-soluble N-heterocyclic carbene gold(III/I) complexes **28** and **29** for the hydration of terminal alkynes in water in the absence of acidic or silver activators. High solubility of carbene gold complexes in water was achieved by introducing methylenetrimethylammonium groups into the ligand, which is a rather common practice in modern organic synthesis (see, *e.g.*, Ref. 174). In both cases, Au^{I} complex **28** acts as a catalyst for alkyne hydration. This complex is generated in reactions performed in the presence of an Au^{III} complex as a result of reduction of the latter with alkyne in the reaction mixture. This reaction gives chloroketone **30** as a by-product (Scheme 10).

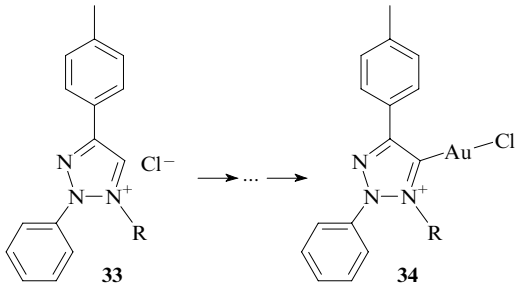
Cationic NHC gold(III) pyridine complexes **31** were synthesized by two methods (Scheme 11).[175] Complexes **31** proved to be efficient catalysts for a number of reactions, for example, the halogenation of aromatic substrates, nucleophilic addition of the carbonyl oxygen atom to the

Scheme 11



R = Pr^{i}, 2,4,6-$Me_3C_6H_2$, Bu^{t}, Cy

Scheme 12



R = Me (59% yield), Cy (35%)

triple bond, hydroarylation of the triple bond and some other transformations. However, Au^{III} complexes **31** exhibit activity only in the presence of silver salts. Complexes containing two or three pyridine molecules as ligands were not synthesized.

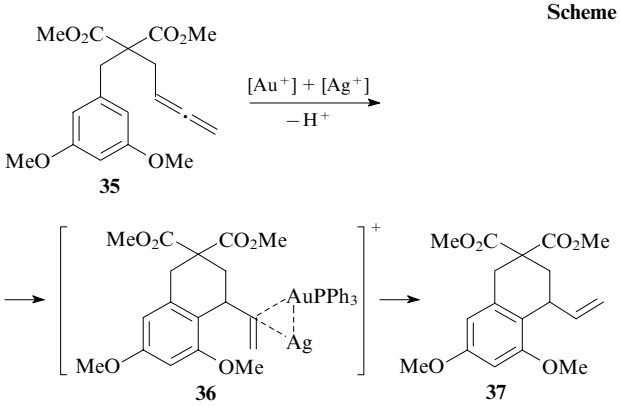
Schaper *et al.*[176] used triazolium salts **33** to synthesize a new type of catalysts **34** (Scheme 12), which proved to be highly efficient in intramolecular hydroamination reactions.

The review [177] considers some aspects of the synthesis of efficient catalysts and the corresponding ligands for enantioselective gold catalysis and adresses the influence of different ligands on the diastereoselectivity and regioselectivity of gold-catalyzed reactions.

II.2. Activation of gold by silver

It was demonstrated [178–183] that in some cases the simultaneous use of two different metals can provide catalytic activity and selectivity unreachable in the catalysis by one metal. In the homogeneous catalysis by gold compounds, derivatives of other metals are often employed. In partic-

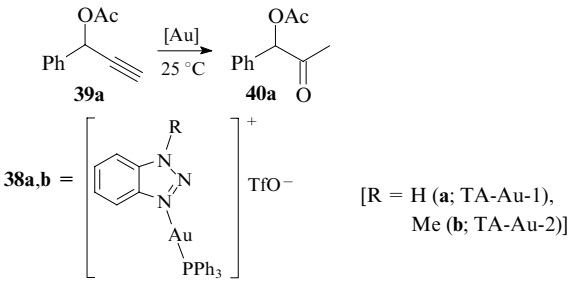
Scheme 13



ular, catalysis by gold halides in the presence of silver salts is widely applied.[184] In most cases, silver salts alone do not catalyze the reaction. These salts activate the catalyst precursor (precatalyst). Weber and Gagné [185] demonstrated that the silver ion is involved together with gold in the formation of intermediate active dinuclear complex **36** (Scheme 13).

Wang *et al.*[83] studied the hydration of propargyl ethers. Different gold-based catalysts were examined. Complexes **38a,b** (TA-Au) proved to be efficient catalysts (Scheme 14), while the complexes [(Ph_3P)Au]OTf, [(Ph_3P)Au]SbF_6 and [(IPr)Au]SbF_6 did not exhibit activity in this reaction.

Scheme 14



[Au]	Solvent	Time /h	Yield of **40a** (%)
$[(Ph_3P)Au]^+TfO^-$	Dioxane	12	0
$[(Ph_3P)Au]^+SbF_6^-$	Dioxane	12	0
$[(IPr)Au]^+SbF_6^-$	Dioxane	12	0
38a (TA-Au-1)	Dioxane	12	87
38b (TA-Au-2)	Dioxane	12	85
38a (TA-Au-1)	DCM	12	32
38a (TA-Au-1)	THF	12	< 5
38a (TA-Au-1)	MeOH	12	24
38a (TA-Au-1)	DMF	12	< 5
38a (TA-Au-1)	$MeNO_2$	12	11
38a (TA-Au-1)	MeCN	4	89
38a (TA-Au-1)	Acetone	4	99

A year earlier, Ghosh *et al.*[186] reported the use of the $(Ph_3P)AuCl-AgSbF_6$ mixture as a catalyst for the transformation shown in Scheme 14. In order to address the possible causes of the conflicting results obtained in the same reaction catalyzed by the same gold-based catalyst — $[(Ph_3P)Au]SbF_6$, Wang *et al.*[83] performed further investigations. They demonstrated that the striking difference in the activity of the catalyst is due to different procedures applied for their preparation. In both cases, the catalyst was prepared by mixing the complex $(Ph_3P)AuCl$ with the salt $AgSbF_6$. Wang *et al.*[83] filtered the thus-prepared catalyst solution through Celite to remove the AgCl precipitate and obtained the silver-free complex $[(Ph_3P)Au]SbF_6$. Ghosh *et al.*[186] used the complex, which was prepared by mixing the components, as-is without the separation of AgCl. Therefore, in the latter case the catalyst was a mixture of gold and silver salts. This example demonstrates the cooperative catalytic action of silver and a gold-containing catalyst.

The electronic nature of the gold cation in solution was studied by ^{31}P NMR spectroscopy. The spectra are shown in Fig. 2.[83] After the filtration through Celite, the complex $[(Ph_3P)Au]SbF_6$ has a ^{31}P NMR chemical shift of 27.1 ppm (spectrum *d*), which is consistent with the assumption of the formation of the cationic species $[(Ph_3P)Au]^+$. Meanwhile, the complex obtained without filtration gives a different ^{31}P NMR chemical shift of 28.1 ppm (spectrum *c*), which is attributed to the effect of silver on gold ions in solution. A similar situation is observed for other gold complexes prepared with and without filtration. The addition of AgOTf to the gold complex, which was prepared by the filtration of AgCl that formed, led to a change in the ^{31}P NMR chemical shift. The TA-Au-1 catalyst, like the $(Ph_3P)AuCl-AgSbF_6$ mixture, is also characterized by a downfield shift of the ^{31}P NMR signal, which is consistent with the activity exhibited by these catalysts in the reaction presented in Scheme 14. In the TA-Au catalyst, the activation of the gold ion *via* changes in the HOMO and LUMO energies is mediated by the ligand coordinated to the gold ion, while the silver ion acts as an activation factor in the mixture.

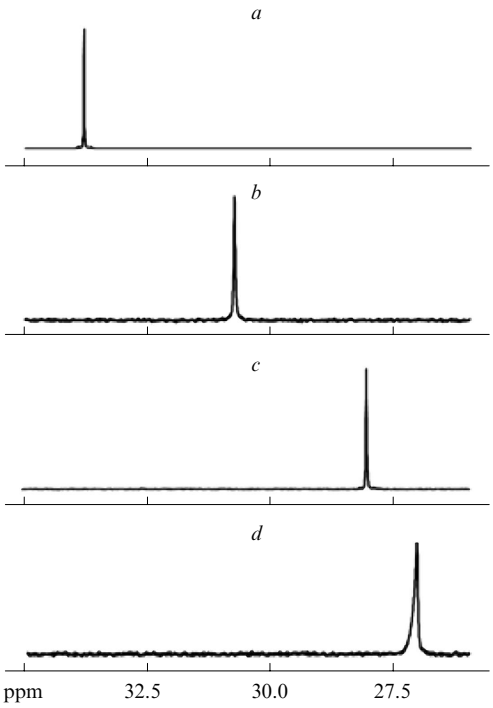
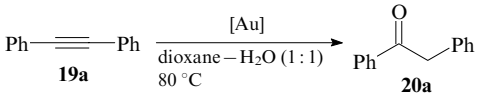


Figure 2. ^{31}P NMR spectra of gold(I) complexes with different ligands: $(Ph_3P)AuCl$ (*a*), TA-Au-1 (**38a**) (*b*), $(Ph_3P)AuCl-AgOTf$ (*c*), $[(Ph_3P)Au]OTf$ (*d*).[83]
85% H_3PO_4 as the internal standard; a solution of the gold complex (0.05 mol litre^{-1}) in $CDCl_3$.

Another example of the influence of silver on the catalytic activity of gold in the intermolecular hydration of simple alkynes [*e.g.*, diphenylacetylene (**19a**), Scheme 15] is also presented in the study cited.[83] The Celite-filtered complex $[Au(IPr)]SbF_6$ did not exhibit catalytic activity in this transformation, like the silver salt used alone. The activity of the catalytic system decreases with a decrease in the fraction of silver in this system.

Scheme 15



Catalyst	Time /h	Yield of **20a** (%)
$[Au(IPr)]Cl + AgSbF_6$ (2 mol.%) without filtration	2	97
$[Au(IPr)]SbF_6$ (5 mol.%)	24	0
$AgSbF_6$ (5 mol.%)	24	0
$[Au(IPr)]SbF_6$ (2 mol.%) + $AgSbF_6$ (2 mol.%)	12	95
$[Au(IPr)]SbF_6$ (2 mol.%) + $AgSbF_6$ (1 mol.%)	24	88
$[Au(IPr)]SbF_6$ (2 mol.%) + $AgSbF_6$ (0.5 mol.%)	24	67

Based on the analysis of the state-of-the-art of gold catalysis, Wang *et al.*[83] separated all gold-catalyzed reac-

tions into three groups depending on the influence of the Ag cocatalyst:

— 'genuine' gold catalysis: reactions are catalyzed by gold in the absence of silver; the addition of Ag^+ does not lead to a change in the activity of the catalyst or the gold catalysis is more efficient than the Au + Ag mixture;

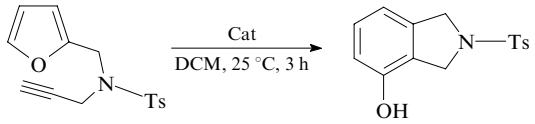
— bimetallic catalysis: reactions are promoted exclusively by a mixture of gold and silver; neither gold nor silver alone catalyze these reactions, only a combination of these two metals produces an efficient catalytic system;

— silver-assisted gold catalysis, where silver acts as a cocatalyst: reactions are catalyzed by gold, but proceed with higher yields, under milder conditions, *etc*. when performed in the presence of both gold and silver ions. This group of reactions can, in turn, be divided into two subgroups: 1) reactions catalyzed by gold alone, but the presence of silver leads to some advantages; 2) reactions catalyzed by either silver or gold alone, but a mixture of catalysts brings about a certain synergistic effect.

Table 1 gives examples of reactions of all three types listed above.

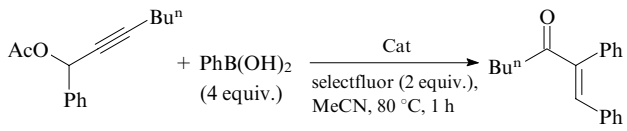
The effect of the acidic activation in the gold catalysis has been considered in detail.[194]

Table 1. Examples of different types of gold-catalyzed reactions in the presence of silver.

Type of catalysis	Examples of reactions	Ref.
Gold catalysis		159

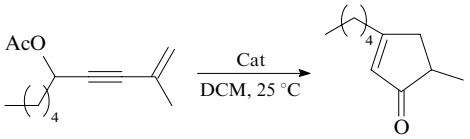
	Au alone	Ag alone	Au + Ag
Cat	(XPhos)AuNTf$_2$	AgNTf$_2$	(XPhos)AuNTf$_2$ + AgNTf$_2$
Yield (%)	88	0	89

Ts = 4-MeC$_6$H$_4$SO$_2$, XPhos = PCy$_2${C$_6$H$_4$(2,4,6-Pr$^i_3$C$_6$H$_2$)-2}

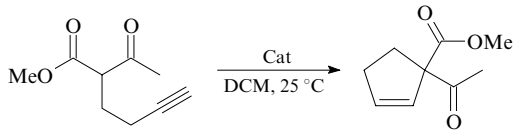


selectfluor is 4-chloromethyl-1-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

	Au alone	Ag alone	Au + Ag
Cat	(Ph$_3$P)AuNTf$_2$	AgNTf$_2$	(Ph$_3$P)AuNTf$_2$ + AgNTf$_2$
Yield (%)	59	0	61

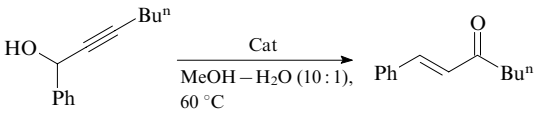
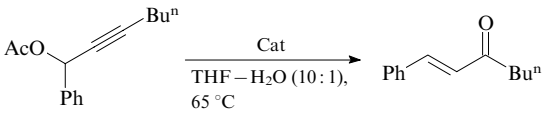
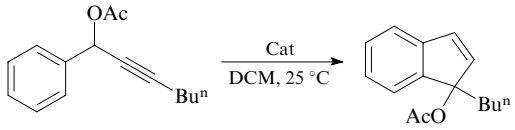
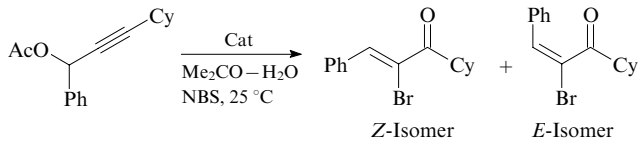
Bimetallic catalysis		188

	Au alone	Ag alone	Au + Ag
Cat	(Ph$_3$P)AuSbF$_6$	AgSbF$_6$	(Ph$_3$P)AuCl + AgSbF$_6$
Yield (%)	0 (24 h)	0 (24 h)	92 (0.5 h)



	Au alone	Ag alone	Au + Ag
Cat	(Ph$_3$P)AuSbF$_6$	AgSbF$_6$	(Ph$_3$P)AuCl + AgSbF$_6$
Yield (%)	0 (24 h)	0 (24 h)	88 (0.5 h)

Table 1 (continued).

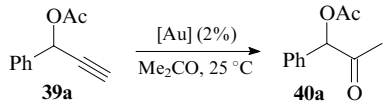
Type of catalysis	Examples of reactions	Ref.
Silver-assisted gold catalysis (type 1)		190
	Au alone / Ag alone / Au + Ag	
	Cat: [Au(IPr)]SbF_6 / $AgSbF_6$ / [Au(IPr)]Cl + $AgSbF_6$	
	Yield (%): 26 (4 h) / 0 (24 h) / 90 (4 h)	
		191
	Au alone / Ag alone / Au + Ag	
	Cat: [Au(IPr)]BF_4 / $AgBF_4$ / [Au(IPr)]Cl + $AgBF_4$	
	Yield (%): 19 (4 h) / 0 (24 h) / 92 (24 h)	
Silver-assisted gold catalysis (type 2)		192
	Au alone / Ag alone / Au + Ag	
	Cat: [Au(IPr)]BF_4 / $AgBF_4$ / [Au(IPr)]Cl + $AgBF_4$	
	Yield (%): 87 (10 min) / 83 (6 h) / 90 (10 min)	
	 *Z*-Isomer *E*-Isomer	193
	NBS is *N*-bromosuccinimide	
	Au alone / Ag alone / Au + Ag	
	Cat: $(Ph_3P)AuNTf_2$ / $AgNTf_2$ / $(Ph_3P)AuCl + AgNTf_2$	
	Yield (%): 84 (2 h) ($Z : E$ = 1 : 3) / 89 (2 h) ($Z : E$ = 1 : 10) / 86 (2 h) ($Z : E$ = 1.5 : 1)	

II.3. Effect of the nature of the counterion

Apart from ligands and Ag^+ ions, the nature of the counterion has also a considerable effect on the activity of the catalyst. For example, the complex $(Ph_3P)AuNTf_2$ is characterized by a ^{31}P NMR signal with a chemical shift of 31.1 ppm [195] similar to that observed for complexes **38** (30.8 ppm), which implies the coordination of Tf_2N^- to $[(Ph_3P)Au]^+$ in solution. Examples of reactions, in which $(Ph_3P)AuNTf_2$ proved to be efficient as a catalyst, are shown in Scheme 16.[83] It can be seen that the complex $(Ph_3P)AuNTf_2$ is much more active than the complex $(Ph_3P)AuOTf$.

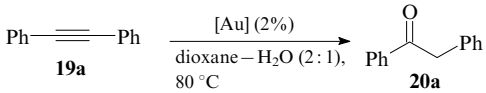
The nature of the anion of the silver salt can have an effect on the direction of the gold(I)-catalyzed reaction in the presence of silver.[196] The corresponding example is given below in Section IV.1.b (see Scheme 34). Thus, indole derivative **105** undergoes 6-*endo-dig* N-cyclization and

Scheme 16



39a **40a**

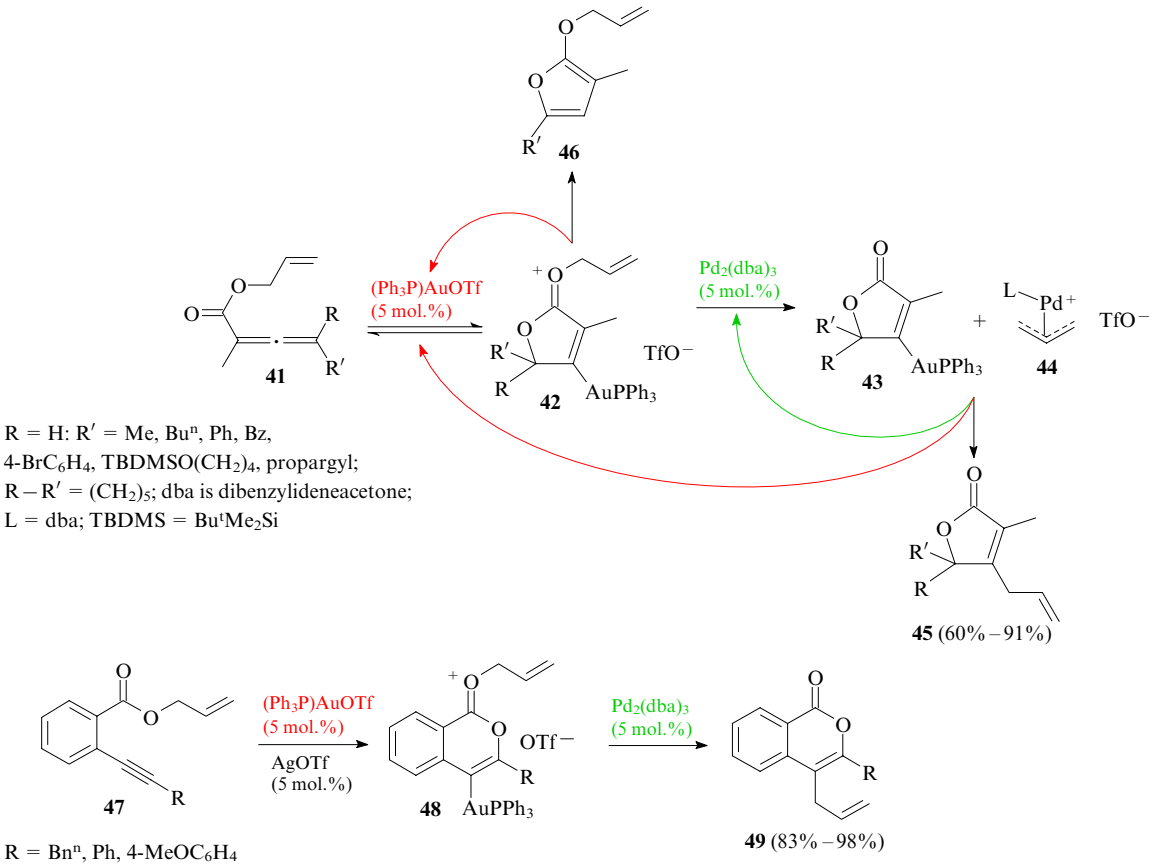
[Au]	Time /h	Yield (%)
$(Ph_3P)AuOTf$	10	0
$(Ph_3P)AuNTf_2$	6	93



19a **20a**

[Au]	Time /h	Yield (%)
$(Ph_3P)AuOTf$	24	0
$(Ph_3P)AuNTf_2$	8	88

Scheme 17



6-*endo-dig* O-cyclization in the presence of silver triflate and silver nitrate, respectively, as the cocatalyst. In both cases, the reaction is performed in dichloroethane. The formation of different reaction products was explained [196] in terms of the hard-soft acid-base theory.

II.4. Cooperative catalysis

Blum and co-workers [197, 198] described a strategy for gold catalysis in the presence of another catalyst called the 'catalyzed catalysis'. They used a gold complex — Lewis acid — for the catalysis of the cross-coupling and simultaneously a palladium complex — Lewis base — for the catalysis of isomerization of a gold-containing intermediate *via* an intramolecular rearrangement. The authors succeeded in preparing furan **46** (Scheme 17) by means of transformations, which previously involved the protodemetallation as the final step.[13, 53] The Au/Pd cross-coupling reaction was shown to be applicable to the synthesis of substituted butenolides and isocoumarins, the structural motifs of which are present in many biologically active compounds.[199, 200] This is an example of the sequential involvement of metals in the catalytic cycle.

The gold-catalyzed rearrangement of allenoate **41** (see Scheme 17) produces allyl oxonium triflate **42** (its formation was confirmed by ^{1}H NMR spectroscopy [201]). Shi *et al.*[198] hypothesized that this rearrangement would increase the reactivity of this ester towards deallylation involving Pd^0 because of enhanced affinity of Pd^0 for allylic substrates bearing positively charged leaving groups.[202] The subsequent reaction between gold complex **43** and π-allyl Pd complex **44** results in the C – C bond formation and produces substituted butenolide **45** *via* the reductive elimination accompanied by regeneration of two catalysts. A similar situation was observed for the cyclization of ester **47** (see Scheme 17).

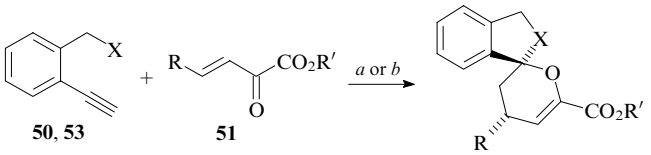
This method provides a new synthetic route to numerous known organogold intermediates, which earlier undergo protodemetallation. The reactions, resulting in the formation of a large number of new bonds in high yield by a one-pot process, are of great importance in modern synthetic chemistry because they do not require the isolation of intermediates,[203] which often leads to a substantial increase in the synthesis time and makes the process much more expensive.[204] A mixture of catalysts is employed in one of approaches, which utilizes the advantages of reactions resulting in the formation of numerous new bonds.[178, 180, 198, 205 – 226] For instance, the gold- and palladium-catalyzed cross-coupling reaction provides new opportunities as compared to the catalysis by each metal alone and makes it possible to bypass the isolation and purification of intermediates.

Xu and co-workers [227] synthesized various spiroaminals **52** and spiroketals **54** by a combination of the intramolecular 5-*exo-dig* cyclization † of alkynes **50** and **53** and the lanthanum or yttrium triflate-catalyzed inverse electron demand hetero-Diels – Alder reaction (Scheme 18). Scheme 18 also presents the reaction mechanism proposed by the authors.

Another example of the involvement of a gold-activated intermediate in a different catalytic cycle was described by Shi and co-workers.[228] They proposed a method for the

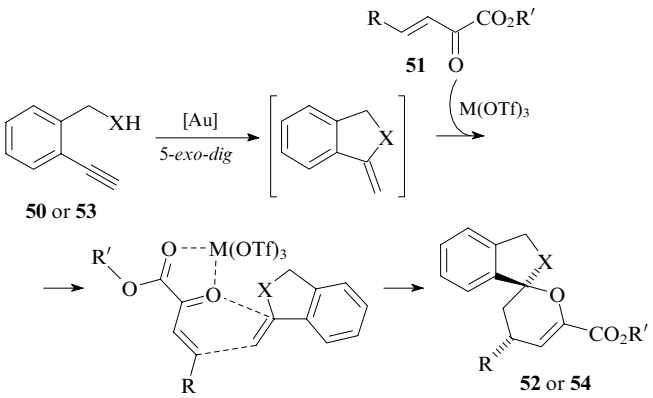
† For the nomenclature for cyclization reactions, see Section IV.1.a.

Scheme 18



50, **53** **51** **52** (71%–90%), **54** (81%–91%)

(*a*) [Au(IPr)]Cl–AgOTf (5 mol.%), $La(OTf)_3$ (10 mol.%), MeCN, 0 °C, 1 h;
(*b*) $Au(PPh_3)NTf_2$ (5 mol.%), $Y(OTf)_3$ (10 mol.%), MeCN, 25 °C, 1 h;
50, **52**: X = NTs, conditions *a*; **53**, **54**: X = O, conditions *b*

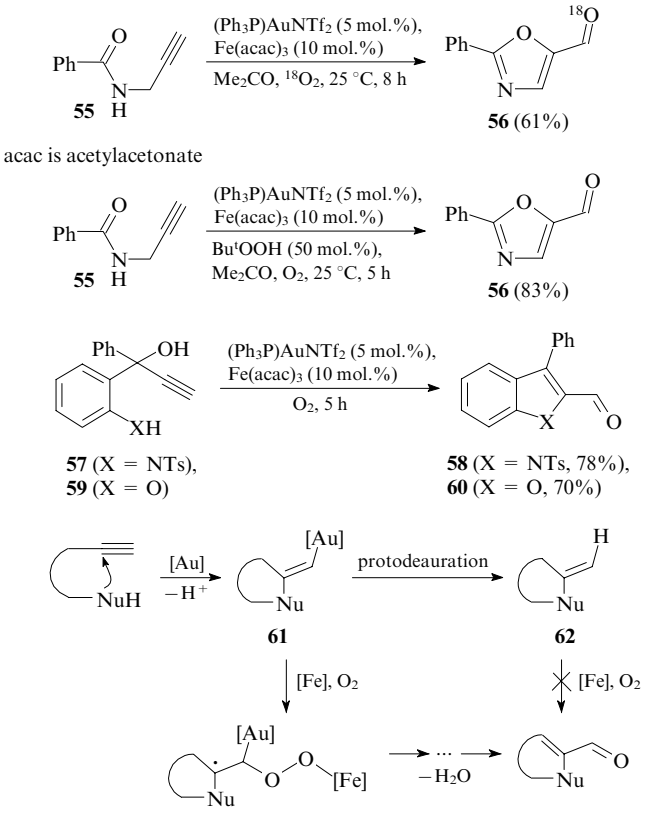


50 or **53** **52** or **54**

R = Ar, Het, PhCH=CH$_2$; R′ = Me, Bn

synthesis of substituted heterocyclic aldehydes *via* the oxygen radical addition to a vinyl gold intermediate under iron catalyst assistance. This method shows high efficiency in the synthesis of substituted oxazole- (**56**), indole- (**58**) and benzofurancarbaldehydes (**60**) (Scheme 19). It was found that the oxygen addition to vinyl gold complex **61** occurs in the presence of iron as a catalyst. It is interesting that only Ag derivatives are oxidized, whereas protodeauration product **62** remains intact. Therefore, the cooperative action of Au and Fe takes place.

Scheme 19



55 **56** (61%)

acac is acetylacetonate

55 **56** (83%)

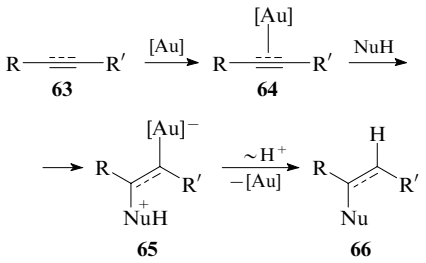
57 (X = NTs), **59** (X = O) **58** (X = NTs, 78%), **60** (X = O, 70%)

61 **62**

III. Nucleophilic addition to the triple bond

A carbon–carbon multiple bond of alkynes, allenes and alkenes is coordinated to gold complexes, resulting in its activation towards nucleophilic attack. As shown in Scheme 20, gold interacts with the π-electron system of substrate **63** to form intermediate **64**, which is subjected to nucleophilic attack. It was experimentally confirmed that the nucleophilic addition occurs in the *anti* position with respect to gold. Meanwhile, norbornenes undergo *syn*-addition.[229] Then intermediate **65** is transformed into addition product **66** *via* protodemetallation accompanied by elimination of the gold-containing catalyst.

Scheme 20



63 **64** **65** **66**

Since gold has high affinity for alkynes as a Lewis acid,[32] *i.e.*, displays alkynophilic properties, it catalyzes a wide diversity of alkyne transformations. Due to the ability to activate the triple bond, gold can be advantageously used in various reactions of alkynes with different reagents. This review presents recent advances in gold catalysis of reactions with alkynes as the substrate.

IV. Hydroamination of alkynes

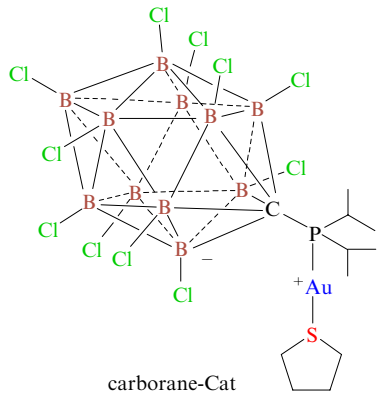
The condensation of carbonyl compounds with primary amines is a well-known conventional method for the synthesis of imines.[230] In recent years, a number of new alternative procedures were developed for the preparation of imines by alkyne hydroamination,[231–233] which are preferable in the context of environmental protection. The catalyzed intermolecular hydroamination of alkynes with primary amines is of great importance in modern organic synthesis,[232] because it provides an efficient approach to the synthesis of substituted amines, imines and enamines, which are essential structural moieties of drugs, detergents, additives and dyes.[234–238]

The addition of nucleophiles, such as amines, to the carbon–carbon multiple bond is a slightly exothermic or nearly thermoneutral reaction.[238,239] However, there are kinetic limitations because of the mutual repulsion between a high electron density on the nucleophile and π-electrons of the multiple bond. Consequently, a high energy barrier has to be overcome for the reaction to proceed. However, a high temperature required for overcoming this barrier leads to a shift of the equilibrium towards the reactants because the reaction is characterized by a negative entropy.[239–241] Alkynes have a higher π-electron density compared to alkenes, which implies stronger electrostatic repulsion of

the nucleophile. Despite this fact, the metal-catalyzed addition of a nucleophile to the C≡C triple bond is more efficient compared to the related addition reaction to the C=C double bond, which is attributed to the formation of a much weaker π-bond between the metal atom of the catalyst and alkyne compared to alkene.[242] The strong π-coordination of metal in the transition complex leads to inhibition of the catalyst. Besides, the triple bond in alkynes is sterically more accessible to nucleophilic attack.

The hydroamination of the carbon – carbon multiple bond can be performed using electron-deficient early and late transition metal and lanthanide complexes. In particular, Pd, Ru, Ag, Pt, Ir, Rh, Ni and Au compounds were applied as catalysts for hydroamination of alkynes.[243 – 251] It should be noted that the hydroamination catalyzed by lanthanides, alkali metals and early transition metal complexes usually involves the N – H bond activation.[251] The hydroamination catalyzed by late transition metals, such as Pd, Ru, Au, Pt, Ir, Rh, Ni and Ag, preferentially entails the activation of the C≡C triple bond followed by the nucleophilic attack of the amino group.[232, 251, 252] Cationic complexes with ligands having low electron density usually exhibit the highest activity. The subsequent protonolysis gives an amino derivative and leads to catalyst regeneration. This process is weakly sensitive to the presence of oxygen in the molecule, as well as to atmospheric oxygen and moisture. However, since the amines thus produced often have high complexation ability towards late transition metals, these reactions usually require the use of a stoichiometric amount of the catalyst.[253 – 256] Another complication is the possible β-hydrogen elimination. Gold-based catalysts are mostly free from these drawbacks. However, amines with strong donor ability form complexes with gold, for example, $[LAuNH_2R]^+$, resulting in catalyst deactivation.[257] The gold-based catalyst carborane-Cat containing the carborane cluster exhibited an extremely high TON (turnover number) value (higher than 95 000) in the hydroamination of alkynes.[258]

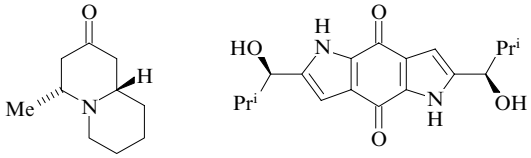
Structure of carborane-Cat



carborane-Cat

The gold-catalyzed hydroamination was applied for the preparation of a number of biologically active compounds. For example, the alkaloid (–)-epimyrtine (**67**), which was isolated from *Vaccinium myrtillus* and which exhibits anticancer, antibacterial, antiviral and anti-inflammatory activities, was synthesized by the gold-catalyzed intramolecular 6-*endo-dig* hydroamination of alkynes.[259]

Structures 67, 68



67 [(–)-epimyrtine] **68** [(+)-terreusinone]

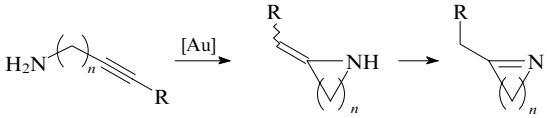
Another example of this reaction is the synthesis of the dipyrrolobenzoquinone derivative — (+)-terreusinone (**68**) — isolated from the marine algicolous fungus *Aspergillus terreus*. The key step of the synthesis involves the gold-catalyzed intramolecular hydroamination giving the pyrrolo[2,3-*f*]indole derivative followed by its oxidation to the final product.[260]

IV.1. Intramolecular reactions

IV.1.a. Amino group as a nucleophile

In the general form, these processes are presented in Scheme 21.

Scheme 21



Here, we remind the nomenclature of cyclization reactions proposed by the British chemist Baldwin in 1976.[261, 262] Baldwin's rules include the following abbreviations:

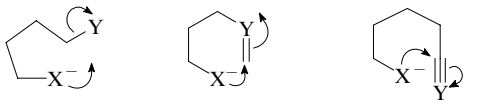
— the size of the ring formed is indicated by the numerical prefix 3-, 4-, 5-, 6-, 7-;

— the prefix *exo* is used when the breaking bond is exocyclic to the ring formed during cyclization; when the endocyclic bond is broken, the process is indicated by the prefix *endo*;

— hybridization of the electrophilic carbon atom (Y) is designated as follows: sp^3-*tet* (tetragonal), sp^2-*trig* (trigonal), sp-*dig* (digonal).

Structures V – VII are given as examples.

Structures V – VII

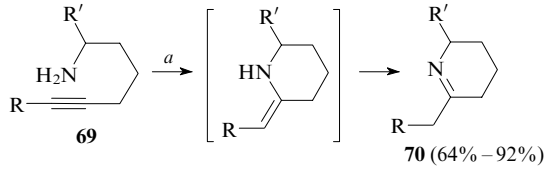


V (5-*exo-trig*) **VI** (6-*endo-trig*) **VII** (6-*exo*-dig)

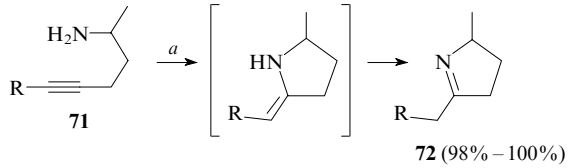
In 1987 Utimoto and co-workers[263, 264] demonstrated that $Na[AuCl_4]$ can act as a catalyst for the hydroamination reaction. The intramolecular hydroamination of 5-alkynylamines **69** was used to prepare tetrahydropyridine derivatives **70** in high yields (Scheme 22). It was found[263, 264] that gold(III) surpasses a Pd^{II} catalyst in the intramolecular hydroamination reaction of alkynes resulting in 6-*exo-dig* cyclization.

The reaction proceeds even at room temperature, but it is performed under reflux in order to reduce the reaction time (from 12 to 2 h). The cyclization of 1-undecylhex-5-enylamine under these conditions affords 2,6-disubstituted tetrahydropyridine — a precursor of (±)-solenop-

Scheme 22



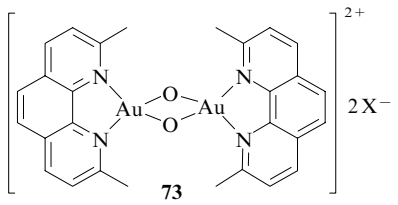
(*a*) $Na[AuCl]_4$ (5 mol.%), MeCN or THF, Δ, 1 h;
R = H, Et, n-C_5H_{11}, n-C_6H_{13}, $H_2C{=}CH(CH_2)_2$, Ph;
R′ = H, Me, n-C_6H_{13}, n-$C_{11}H_{23}$



(*a*) $Na[AuCl_4]$ (5 mol.%), MeCN, 79 °C;
R = n-C_6H_{13}, n-C_7H_{15}, n-C_8H_{17}

sin A[265, 266] — in 90% yield. The 5-*exo-dig* cyclization of substrates **71** gave pyrrolines **72** in even higher yields compared to tetrahydropyridines **70** (see Scheme 22). The use of dimeric Au^{III} oxy complex **73** as the catalyst makes it possible to perform this reaction at room temperature.[267, 268]

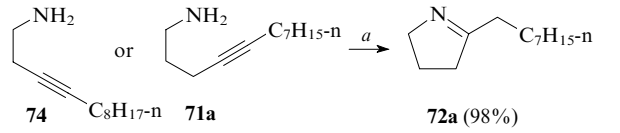
Structure 73



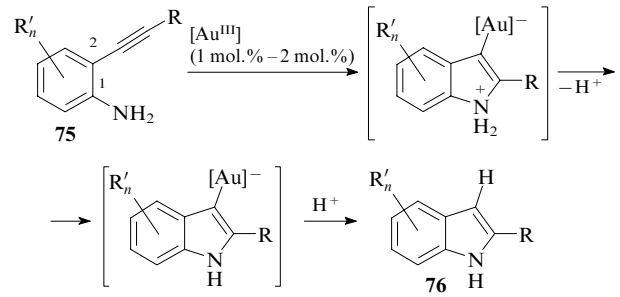
The method proved to be efficient in the synthesis of dihydropyrroles (*e.g.*, **72a**) *via* 5-*endo* cyclization of alk-3-ynylamines (**74**) or 5-*exo* cyclization of alk-4-ynylamines (**71a**) (R′ = H) (Ref. 252) (Scheme 23). The amino group in the *ortho* position with respect to the alkynyl group of arenes **75** can also be involved in the formation of five-membered heterocycles **76** *via* 5-*endo-dig* cyclization (see Scheme 23).[269] The use of an ethanol – water system as the solvent extends substantially the scope of this $Na[AuCl_4]$-catalyzed reaction.[269] An example is the transformation of arene **75b**.

In some case, the intramolecular hydroamination of alkynes giving five- or six-membered rings proceeds even in the presence of simple acidic or basic catalysts.[238] The cyclization of 2-alkynylanilines or 2-alkynylureas takes place in the presence of Bu^tOK (see Ref. 270) or TfOH.[271] However, the application of gold-based catalysts has a number of advantages, such as the possibility of using substrates containing substituents labile under acidic or basic conditions and the opportunity to prepare four- and seven-membered heterocycles.[242] For instance, the gold-catalyzed hydroamination of 2-alkynylanilines **75** is tolerant to the presence of electron-donating and electron-withdrawing groups in the aniline moiety, as well as to the presence of aromatic, secondary and tertiary alkyl groups and alkenyl groups bound to the carbon atom at the alkyne triple bond. This method is efficient for the cyclization of *N*-acetamide- and *N*-methylcarbamate-protected 2-alkynylanilines.[269, 272]

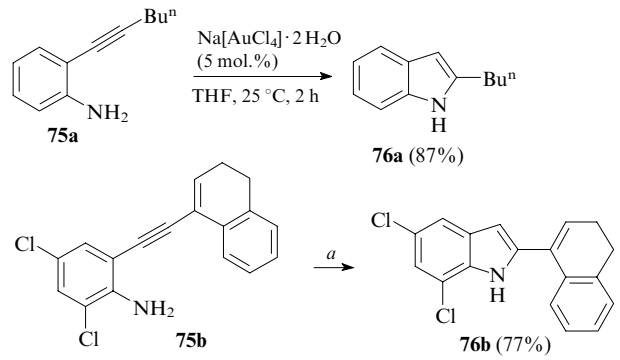
Scheme 23



(*a*) $Na[AuCl_4]\cdot 2H_2O$ (5 mol.%), MeCN, Δ



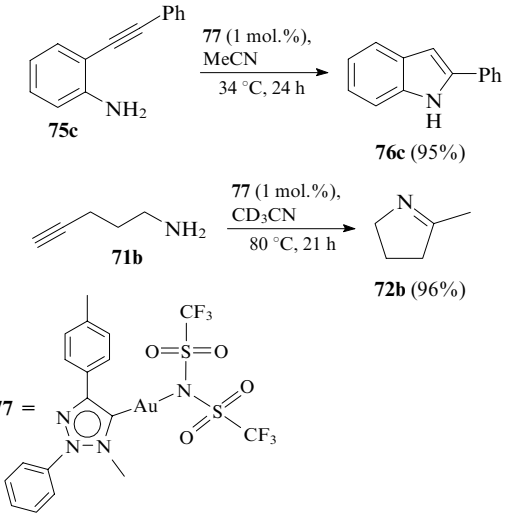
for **75**: R = 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, Bu^n, PhCH=CH, 2-Th, *etc.*; R'_n = 4,6-Cl_2, 4-NO_2-6-Cl, 5-CF_3, 4,6-F_2, *etc.*; Th is thienyl



(*a*) $Na[AuCl_4]$ (5 mol.%), EtOH – H_2O (20 : 1), 25 °C, 20 h

Gold complex **77** with a strong electron-donating carbene ligand is an efficient catalyst for the intramolecular hydroamination of *o*-aminoalkynylbenzenes, *e.g.*, **75c**, and linear aminoalkynes, *e.g.*, **71b** (Scheme 24).[176]

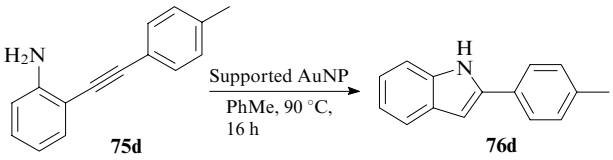
Scheme 24



A similar transformation can be accomplished in the presence of gold nanoparticles.[273] For example, the cyclo-

isomerization of 2-(*p*-tolylethynyl)aniline (**75d**) in toluene at 90 °C using gold nanoparticles on different supports gives the corresponding substituted indole **76d** (Scheme 25), the yield of which depends on the nature of the support.[274, 275]

Scheme 25

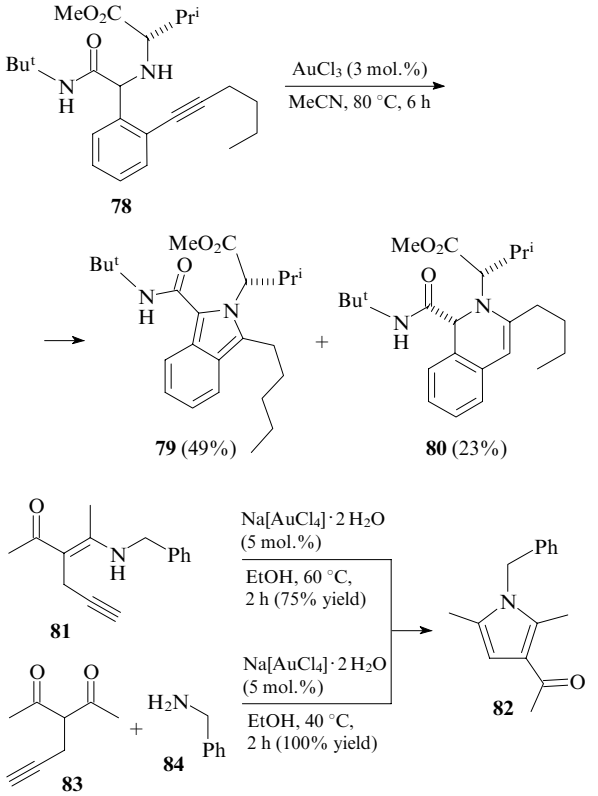


Support	Yield (%)
TiO_2	13
CeO_2	51
C (activated)	96

Several examples of the successful use of Au^{III} catalysts for the intramolecular hydroamination of alkynes giving heteroaromatic compounds were reported. For instance, the heating of alkynylamine **78** in acetonitrile under reflux in the presence of a catalytic amount of $AuCl_3$ for 6 h produced a mixture (2 : 1) of isoindole **79** (5-*exo* cyclization) and dihydroisoquinoline **80** (6-*endo* cyclization) in a total yield of 72% (Scheme 26).[276] Another example is the intramolecular hydroamination of enaminone **81** producing 1,2,3,5-tetrasubstituted pyrrole **82** in 75% yield (see Scheme 26).[277, 278]

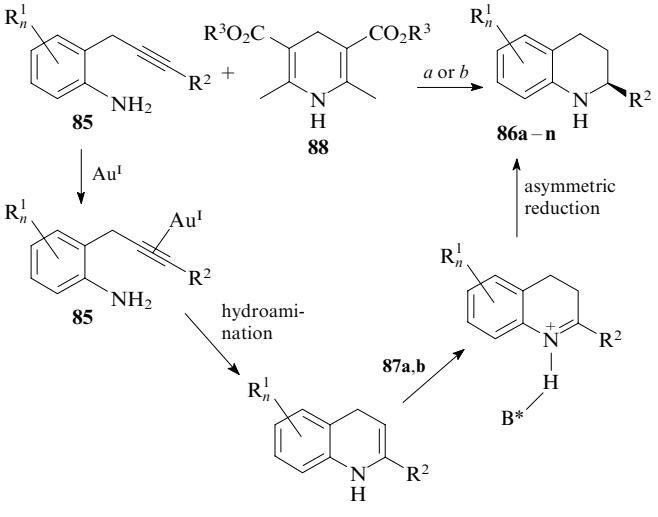
It is interesting to note that the one-pot reaction sequence involving the intramolecular cyclization followed by hydroamination (the reaction of compounds **83** and **84**) gives product **82** in 100% yield (see Scheme 26).[277, 278] The method can be applied to prepare pyrroles using different amines. Prop-2-ynyl-1,3-dicarbonyl compounds can serve as substrates. However, the method is limited only to terminal alkynes.

Scheme 26

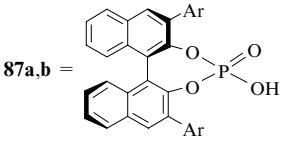


Gong and co-worker[279] developed a method for the direct one-pot transformation of 2-(prop-2-ynyl)anilines **85** into tetrahydroquinolines **86** with high enantioselectivity. The reaction proceeds in the presence of the achiral gold complex (Ph_3PAuMe), chiral phosphoric acid — BINOL derivative **87** (B*H) — and Hantzsch ester **88** as the reducing agent (Scheme 27). This approach allows the

Scheme 27



(*a*) $(Ph_3P)AuMe$ (5 mol.%), **87a** (15 mol.%), PhMe, 25 °C, 16 h;
(*b*) (IMes)AuMe (0.2 mol.%), **87b** (0.2 mol.%), PhMe, 90 °C, 16 h;

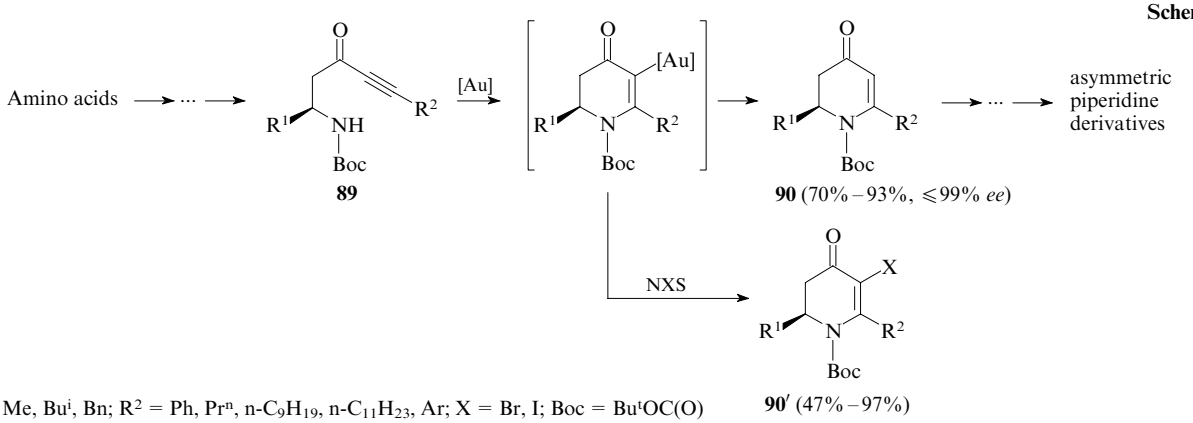


[Ar is phenanthren-9-yl (**a**), 2,4,6-$Pr^i_3C_6H_2$ (**b**)]

Product **86**	R^1_n in **85**	R^2	Conditions *a*		Conditions *b*	
			yield (%)	*ee* (%)	yield (%)	*ee* (%)
a	H	4-MeC_6H_4	99	98	86	96
b	H	3-MeC_6H_4	99	94	83	96
c	H	4-BrC_6H_4	99	> 99	85	98
d	H	4-FC_6H_4	> 99	99	87	99
e	H	4-$MeOC_6H_4$	> 99	98	—	—
f	H	2-Naph	99	99	—	—
g	H	2-MeC_6H_4	85	94	—	—
h	H	2-FC_6H_4	—	—	87	99
i	H	Pr^n	—	—	87	61
j	H	Bu^n	98	87	82	43
k	H	n-C_5H_{11}	94	88	—	—
l	4,5-(OCH_2O)	Ph	96	91	70	96
m	4-Ph	Ph	> 99	95	—	—
n	5-Cl	Ph	> 99	90	83	97

Naph is naphthyl.

Scheme 28



R^1 = H, Me, Bu^i, Bn; R^2 = Ph, Pr^n, n-C_9H_{19}, n-$C_{11}H_{23}$, Ar; X = Br, I; Boc = Bu^{t}OC(O)

stereoselective synthesis of tetrahydroquinolines **86** in high yields (conditions *a*). The relay catalysis using achiral gold complexes (intramolecular hydroamination of the triple bond) and chiral Brønsted acid (enantioselective hydrogen transfer) was demonstated to have a great potential. Chiral 1,2,3,4-tetrahydroquinolines **86** are not only present in a series of naturally occurring alkaloids but are also important building blocks in modern medicinal chemistry.[280]

The drawback of the method is that it requires relatively large amounts of gold (5 mol.%) and chiral phosphoric acid **87** (15 mol.%), which reduces its practical value. More recently, Gong and co-workers [281] proposed a more efficient method (conditions *b*) for the enantioselective cascade hydroamination followed by asymmetric hydrogen transfer using only 0.2 mol.% of each catalyst (see Scheme 27).[282]

The intramolecular hydroamination of alkynes underlies the enantiospecific synthesis of dihydropyridinones **90** from amino acids (Scheme 28).[283]

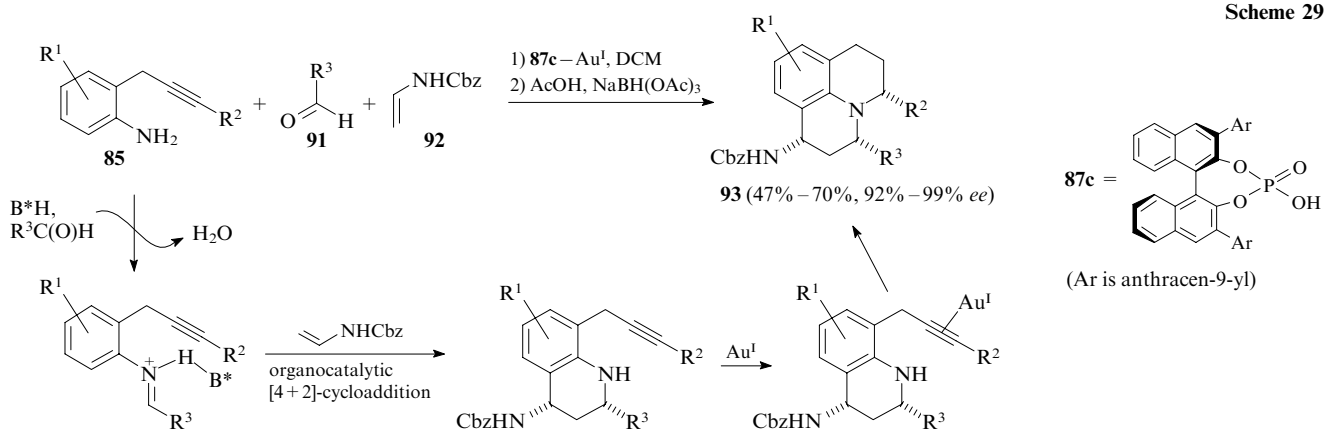
The piperidine ring is an important structural moiety that is present both in natural and synthetic compounds exhibiting a broad range of biological activity.[284,285] The $(Ph_3P)AuCl-AgSbF_6$ system (5 mol.% of each component) proved to be the most efficient catalyst for this transformation; the enantioselectivity of the reaction was higher than 99%. Each salt alone does not catalyze the reaction. A modification of this reaction was used to synthesize chiral 5-halopyridones **90′** from β-amino-ynones **89** in one step.[286] Appropriate *N*-halosuccinimides (NXS, see Scheme 28) served as a source of a halogen atom. The optimal yields of the reaction product were achieved with the $(Ph_3P)AuCl-AgSbF_6$ system and NXS (*e.g.*, NIS) as an electrophile and a source of halogen, respectively. The reaction was performed in 1,2-dichloroethane at room temperature. The highest yields in the reactions with the same substrate **89** using different NXSs were obtained for NBS. Chloro and fluoro derivatives were not synthesized.

Wang *et al.* [287] developed a method for the synthesis of various julolidine derivatives **93** with high optical purity (Scheme 29). The method is based on the three-component cascade reaction consisting of the enantioselective [4 + 2]-cycloaddition catalyzed by chiral phosphoric acid and subsequent intramolecular hydroamination catalyzed by a Au^I complex.

The study of the reaction kinetics demonstrated that Brønsted acid not only catalyzes the [4 + 2]-cycloaddition but also activates the gold complex in the hydroamination step.

The intramolecular hydroamination reaction, the regioselectivity of which is determined by the nature of the catalyst used, was described by the Belgian research group headed by Van der Eycken.[288] In the presence of AuCl – TFA, *o*-alkynylaniline **94** undergoes 5-*endo-dig* cyclization to form product **95**, whereas the use of the

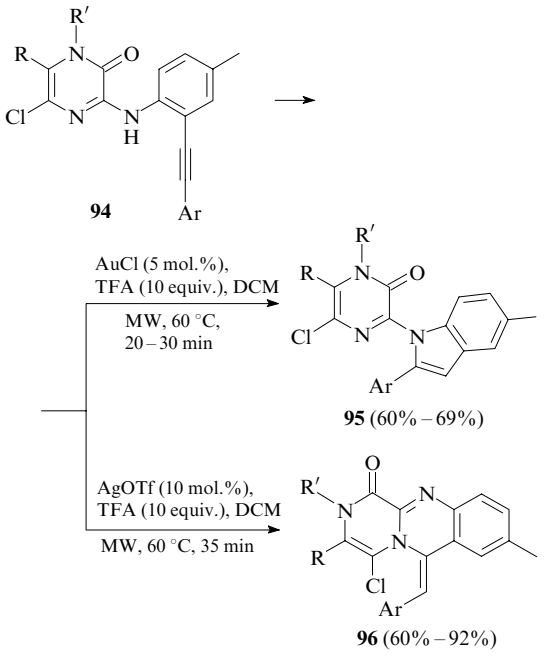
Scheme 29



R^1 = H, 4-Cl; R^2 = Ph, 4-FC_6H_4; R^3 = Ph, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-NCC_6H_4, 4-$MeO_2CC_6H_4$, 4-$O_2NC_6H_4$, 3-ClC_6H_4, 3-$O_2NC_6H_4$, $PhCH_2CH_2$; B*H = **87c**; Cbz = BnOC(O)

AgOTf – TFA system resulted in the formation of 6-*exo-dig* cyclization product **96** (Scheme 30).

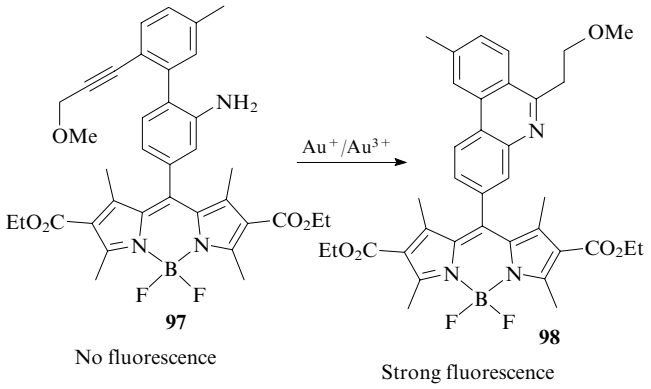
Scheme 30



R = H, Ph; R′ = Me, Bn, 4-MeC$_6$H$_4$; MW is microwave irradiation

The intramolecular hydroamination reaction was applied [289] for the fluorescence detection of gold ions in living cells. The 6-*exo-dig* cyclization of substrate **97** catalyzed by gold ions (Au^+/Au^{3+}) gives product **98** exhibiting strong fluorescence (Scheme 31).

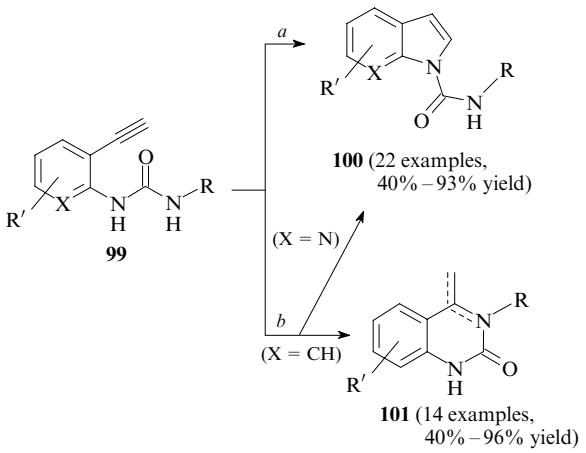
Scheme 31



IV.1.b. Amides and imides as nucleophiles

The annulation of *o*-alkynylaniline derivatives **75** is commonly used for the preparation of indoles *via* a 5-*endo-dig* process.[269, 290 – 295] Ye *et al.*[296] applied the (Ph$_3$P)AuCl (10 mol.%) – Ag$_2$CO$_3$ (10 mol.%) system for the cyclization of 1-(*o*-alkynylaryl)ureas **99**. The reaction was performed in water under microwave irradiation (150 °C) for 10 min and produced N-substituted indoles **100** (Scheme 32). The reaction in the presence of the gold carbene complex [(IPr)AuCl] (**15a**) (5 mol.%) as the catalyst results in the transformation of substrates **99** into 6-*exo-dig* cyclization products **101** [297] due apparently to steric effects. The reaction was performed in DMF at 60 °C for 5 h. This method can be applied to synthesize 4-methylene-3,4-dihydroquinazolin-2-ones **101**; it is much simpler than the procedures developed previously with the use of palladium compounds [298] or TfOH as the catalysts.[299] However, if X = N, the more electron-deficient pyridine ring directs the reaction towards 5-*endo-dig* N(1)-attack product **100** in this case as well (see Scheme 32). In some cases, the presence of an electron-withdrawing substituent R′ in the benzene ring (*e.g.*, the Cl atom) results in the formation of indole as the second product. Starting 1-(*o*-alkynylaryl)ureas **99** can be easily synthesized from aniline and isocyanate.

Scheme 32

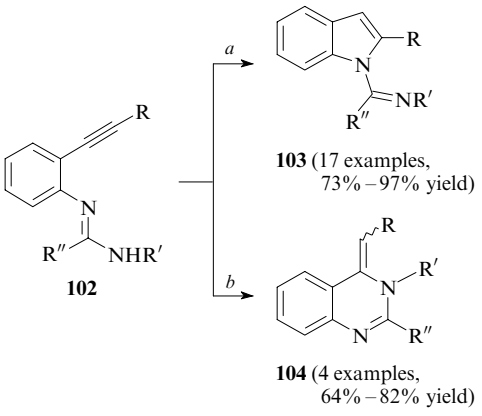


(*a*) (Ph$_3$P)AuCl – Ag$_2$CO$_3$, 5-*endo-dig* N(1)-attack
(*b*) [(IPr)AuCl] – AgSbF$_6$, 6-*exo-dig* N(3)-attack;
100: X = CH, N; R = Alk, Ar, Het; R′ = Me, Cl, F;
101: R = H, Alk, Ar; R′ = H, Br, Cl, Alk, MeO

The Au$^{\mathrm{I}}$-catalyzed hydroamination of (2-alkynyl)benzyl carbamates produces different 1,2-dihydroisoquinolines, including nitidine alkaloids, *via* 6-*endo-dig* cyclization.[300]

In the presence of Na[AuCl$_4$]·2H$_2$O as the catalyst, acetamidines **102** undergo 5-*endo* cyclization to form N-substituted indoles **103**. Under basic catalysis conditions, acetamidines **102** undergo 6-*exo* cyclization involving the nitrogen atom, which is capable of being deprotonated,[301] to form quinazoline derivatives **104** (Scheme 33).

Scheme 33

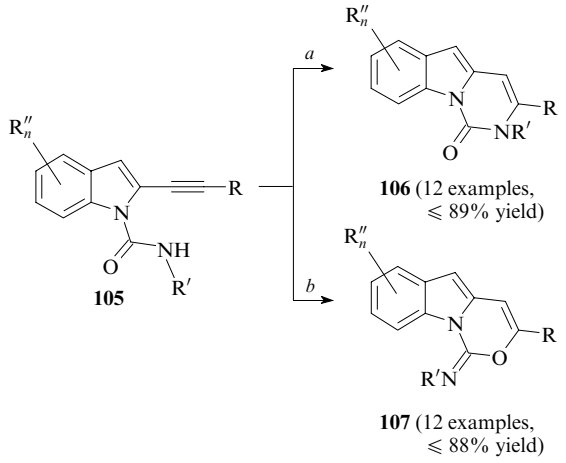


(*a*) Na[AuCl$_4$]·2H$_2$O (5 mol.%), PhMe, 25 °C, 1 h;
(*b*) K$_2$CO$_3$ (2 equiv.), MeCN, 80 °C, 2 h;
R = Ar, Alk; R′ = Alk; R″ = CF$_3$, CF$_2$Br

The cyclization of indole derivative **105** is an example of the effect of the counterion on the direction of the gold-

catalyzed reaction. Gupta *et al.*[302] demonstrated that 6-*endo-dig* N-cyclization giving product **106** proceeds in the presence of $Au^I - AgOTf$, whereas the $Au^I - AgNO_3$ system affords product **107** *via* 6-*endo-dig* O-cyclization (Scheme 34).

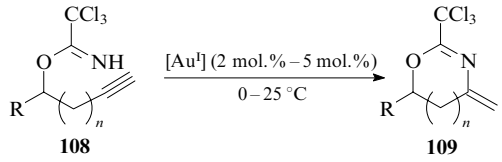
Scheme 34



(*a*) $(Ph_3P)AuCl$ (5 mol.%), AgOTf (20 mol.%), DCE, 25 °C, 5 min;
(*b*) $(Ph_3P)AuCl$ (5 mol.%), $AgNO_3$ (20 mol.%), DCE, 25 °C, 4 h;
105: R, R′ = Ar, Alk; R''_n = H, 5-Cl, 5,6-OCH_2O; DCE = $ClCH_2CH_2Cl$

Trichloroacetimidate derivatives of propargyl and homopropargyl alcohols **108** undergo intramolecular hydroamination under mild conditions[303] to form five- and six-membered heterocycles **109**, respectively (Scheme 35). The complexes $\{(C_6F_5)_3P\}AuSbF_6$ and $(Ph_3P)AuBF_4$ proved to be the most efficient catalysts.

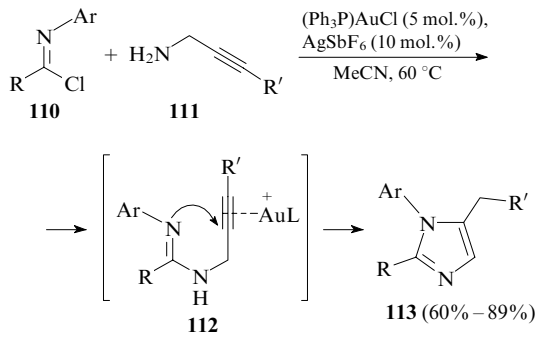
Scheme 35



R = H, Alk, cyclo-Alk, Ar, Bn; *n* = 0, 1

Amidines **112**, which can be easily prepared by the reaction of imidoyl chlorides **110** with prop-1-yn-3-ylamine and 1-phenylprop-1-yn-3-ylamine **111**, undergo gold-catalyzed 5-*exo* cyclization to form imidazole derivatives **113** (Scheme 36).[304]

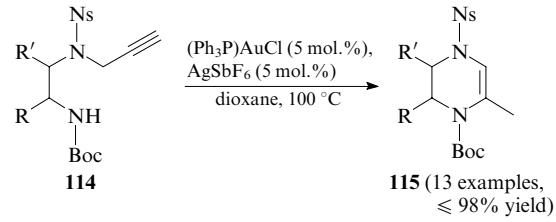
Scheme 36



R = CF_3, CF_2Br, CF_2H, CO_2Et; R′ = H, Ph

The cationic gold complex $(Ph_3P)AuCl$ catalyzes 6-*exo* cyclization of Boc-protected substrates **114** to form the corresponding dehydropiperazines **115** (Scheme 37).[305]

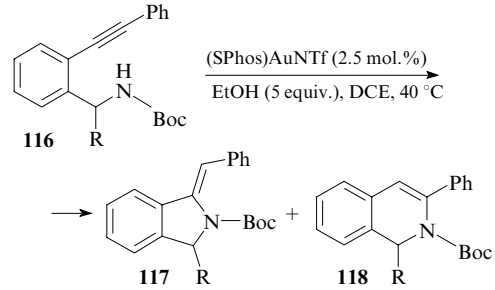
Scheme 37



R, R′ = H, Alk; Ns = 4-$O_2NC_6H_4SO_2$

The hydroamination of *o*-alkynylbenzyl carbamates **116** proceeds through either 5-*exo* or 6-*endo* cyclization depending on the nature of the substrate (a substituent at the α position with respect to the amido group) (Scheme 38).[306, 307]

Scheme 38



R	5-*exo* (**117**) : 6-*endo* (**118**)	R	5-*exo* (**117**) : 6-*endo* (**118**)
H	0 : 100	CHF_2	85 : 15
Me	40 : 60	CF_3	80 : 20
CH_2F	40 : 60	CF_2CF_3	80 : 20

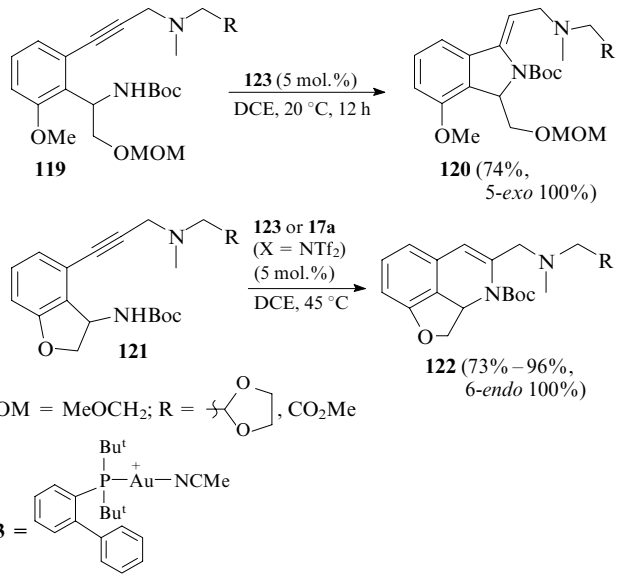
Another example of the effect of the substrate nature on the regioselectivity of intramolecular hydroamination was reported by Chiba *et al.*[308, 309] The reaction with open-chain ether **119** as the substrate affords 5-*exo* cyclization product **120**. The reaction with cyclic ether derivative **121** yields 6-*endo* cyclization product **122** (Scheme 39).

The selective intramolecular 7-*endo* hydroamination in the presence of a gold complex with electron-rich phosphine or carbene NHC was described by Wilckens *et al.*[310] The reaction yielded oxazepines **126** — kinetically controlled products (6-*exo* cyclization is thermodynamically more favourable) (Scheme 40). Unprotected primary amines and carboxamides (*e.g.*, benzamides and trifluoroacetamides) are involved in the reaction under the same conditions.

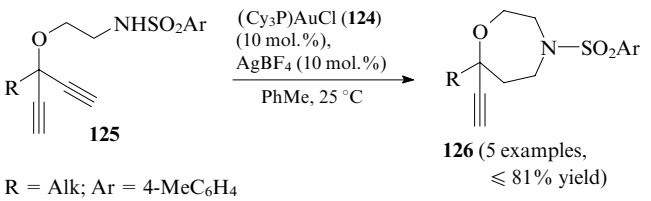
Gold triethynylphosphine complex **127** catalyzes 7-*exo* cyclization of Ts-protected aminoalkynes **128** giving azepine and benzazepine derivatives **129**, which are difficult to synthesize by other methods (Scheme 41).[311]

Substrate **130** undergoes both 6-*exo* hydroamination[312] and 7-*endo* hydroamination.[313] The reaction pathway depends on the nature of the catalyst used.[314] Thus, the

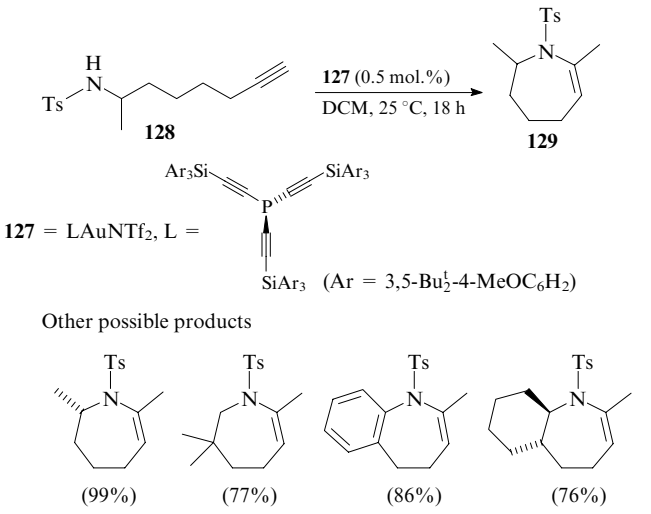
Scheme 39



Scheme 40



Scheme 41

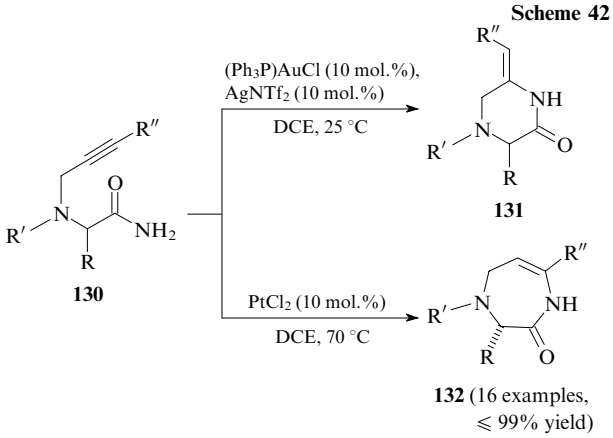


former reaction is catalyzed by the cationic gold complex; the latter one is catalyzed by $PtCl_2$ (Scheme 42).

The 7-*endo* cyclization of aryl-substituted 2-(alk-1-ynyl)-phenylacetamides **133** proceeds in the presence of an anionic gold complex as the catalyst to give 3-benzazepinones **134** (Scheme 43).[315]

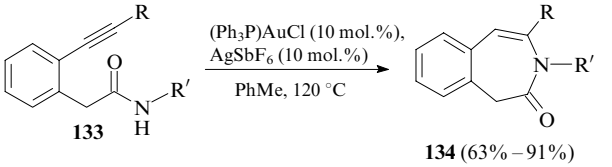
The corresponding alkyl-substituted 2-(alk-1-ynyl)phenylacetamides (**133**, R = Alk) undergo 7-*endo* cyclization mediated by the complex $(Ph_3P)_2Pd(OAc)_2$ (see Ref. 316) or $(PhCN)_2PdCl_2$.[317]

Scheme 42



131: R = Alk; R″ = Ph: R′ = pNs (88% yield), CO_2Me (84%);
132: R = Bn, Alk; R′ = Ns, Ts, Cbz, Boc; R″ = Ar, Me

Scheme 43



R = Ar; R′ = Alk

The hydroamination of substrate **135** is accompanied by the sulfonyl group migration.[318] The plausible reaction mechanism is shown in Scheme 44.

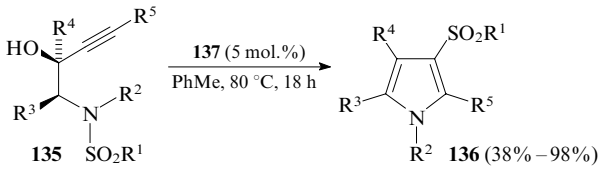
The cyclization of 2-alkynylanilides **138** accompanied by the sulfonyl group migration is yet another example of this type of processes. The reaction is catalyzed by $AuBr_3$ and is accompanied by the sulfonyl group migration from the nitrogen atom to position 3 of the resulting substituted indole **139** (Scheme 45).[293] It is interesting that, if X = OMe, the $InBr_3$-catalyzed reaction involves the migration of the sulfonyl group to position 6 to form product **140** (see Scheme 45).[293]

The intramolecular hydroamidation of internal alkynes **141** accompanied by the cyclopropane ring opening was described by Fernández-García *et al.*[319] The reaction proceeds with substrates containing an electron-donating (OMe) or electron-withdrawing [$C(O)NR_2$] substituent in the cyclopropane ring to give seven-membered cyclic dienamide **142** (Scheme 46).

The highly enantioselective cascade hydroamination – N-sulfonyliminium cyclization reaction of substrate **143** was performed also using a combination of gold(I) complex **123** and chiral phosphoric acids **87c – f**.[320] The reaction mechanism and examples of products **144a – k** are shown in Scheme 47.

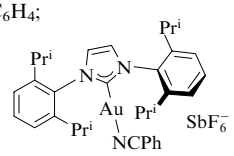
The synthesis of substituted pyrroles by the gold-catalyzed intramolecular 5-*endo-dig* hydroamination – elimination of homopropargyl amine derivatives **145** was described in several publications. For instance, the Au^I/Ag^+-catalyzed hydroamination – dehydration of amines **145** was reported (Scheme 48).[321, 322] Surmont *et al.*[323] performed the Au^{III}-catalyzed hydroamination – dehydrofluorination of amines **145** (see Scheme 48). Shu *et al.*[324] described the synthesis of diiodopyrrolidin-2-ols. Trisubstituted pyrroles

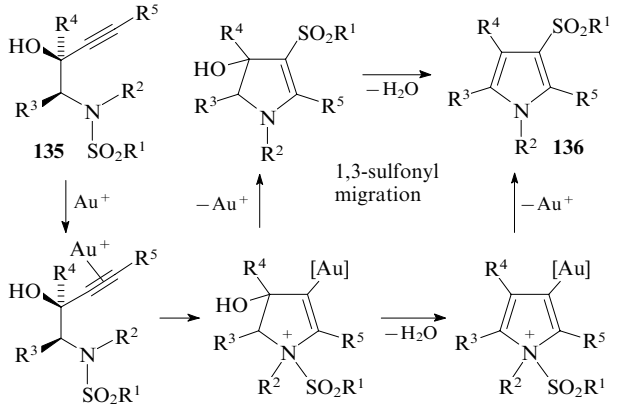
Scheme 44



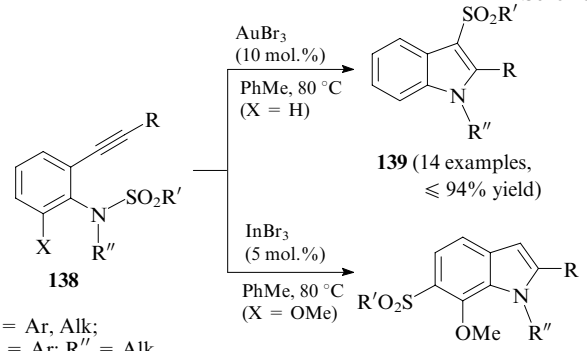
R^1 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, Me; R^2 = All, Me, Bu^n, Bn;
R^3 = Bn, Pr^i; R^4 = Et, Ph, 4-MeC_6H_4, 4-ClC_6H_4,
2-HSC_6H_4; R^5 = H, Bu^n, cyclo-C_3H_5, Ph, 4-MeC_6H_4, 4-BrC_6H_4,
3-HSC_6H_4;

137 =



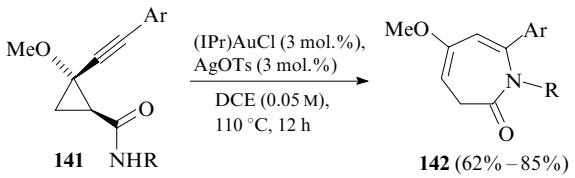


Scheme 45



R = Ar, Alk;
R′ = Ar; R″ = Alk

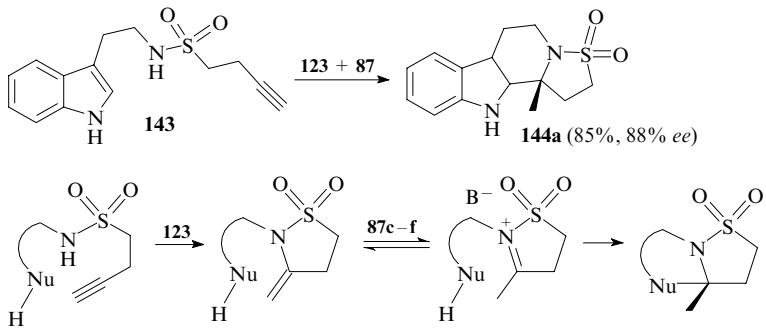
Scheme 46



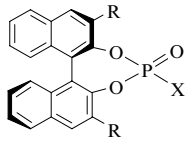
R = H, Me, Ar

150 were synthesized[325] from simple *N*-sulfonylated propargylic amines **148** through the Rh^I-catalyzed dimerization and Au^{III}-catalyzed selective intramolecular 5-*endo* hydroamination of adduct **149** (see Scheme 48).

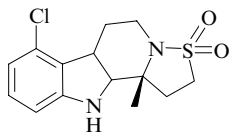
Scheme 47



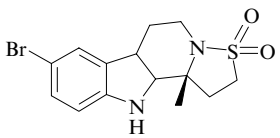
87c – f =



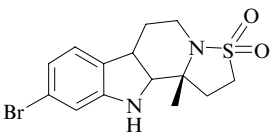
X = OH: R is anthracen-9-yl (**c**), $SiPh_3$ (**d**), $SiPr^i_3$ (**f**); X = NHTf, R = $SiPh_3$ (**e**)



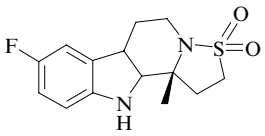
144b (77%, 95% *ee*)



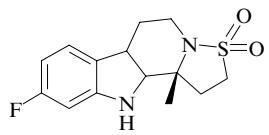
144c (81%, 90% *ee*)



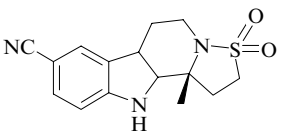
144d (81%, 91% *ee*)



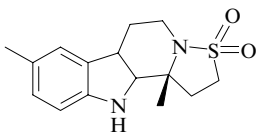
144e (85%, 92% *ee*)



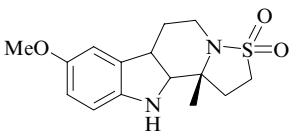
144f (85%, 84% *ee*)



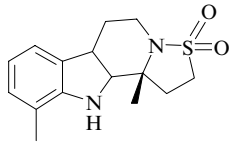
144g (60%, 96% *ee*)



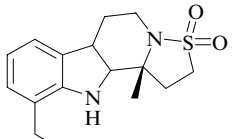
144h (75%, 81% *ee*)



144i (84%, 88% *ee*)

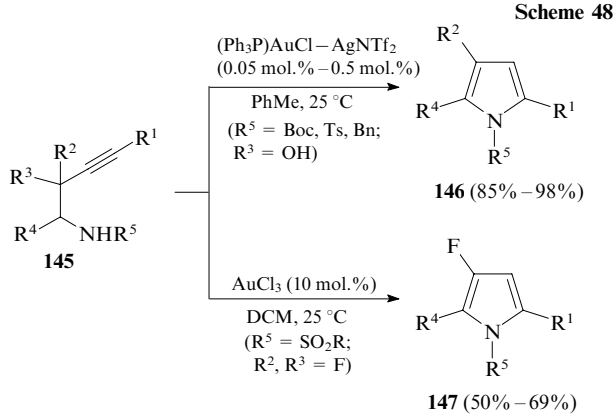


144j (85%, 92% *ee*)

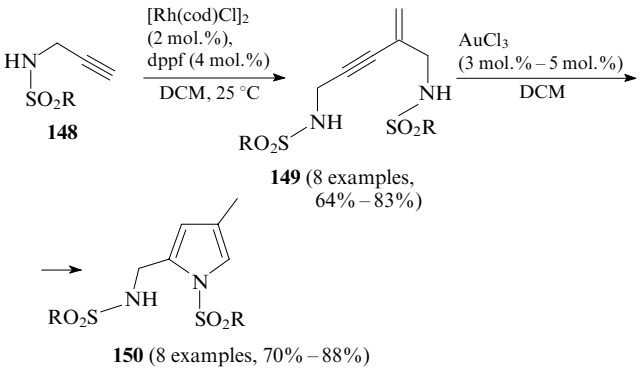


144k (83%, 95% *ee*)

Scheme 48



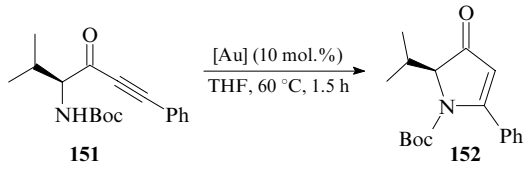
146: R^1 = H, Bu^t, n-C_8H_{17}, Bn, Ph; R^2 = H, Me; R^4 = H, Bn;
147: R^1 = H, Ph; R^4 = Ph, 4-XC_6H_4 (X = Me, MeO, Cl)



R = Me, Bu^n, Bn, Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4;
cod is cycloocta-1,5-diene, dppf is 1,1-bis(diphenylphosphino)ferrocene

Depending on the nature of the Au catalyst used, the intramolecular hydroamination of α-amino-ynone **151** proceeds with different degrees of retention of configuration of the chiral centre (Scheme 49).[326]

Scheme 49

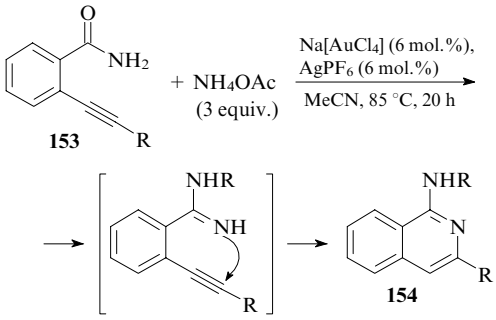


Au	Yield of **152** (%)	*ee* (%)
AuCl	88	0
AuCl – K_2CO_3 (2 equiv.)	90	60
Au_2O_3	95	99

The Au^{III}-catalyzed consecutive condensation – hydroamination starting from 2-alkynylbenzamides **153** and ammonium acetate was used to synthesize 1-aminoisoquinolines **154**,[327] which are of interest as pharmacologically active compounds (Scheme 50).

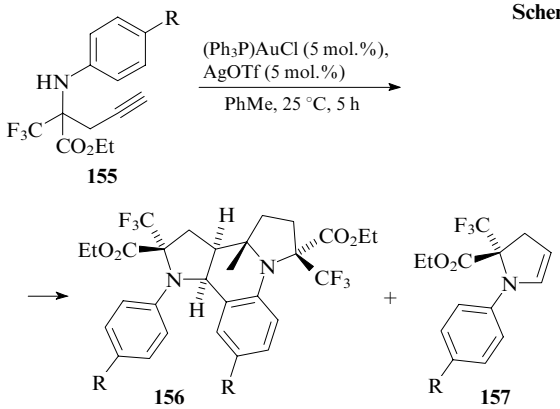
Under gold catalysis conditions, homopropargyl amino esters **155** undergo the tandem hydroamination – formal aza-Diels – Alder reaction,[328] resulting in the formation of four new bonds and five stereocentres. The process is characterized by high diastereoselectivity (*ee* > 99%) (Scheme 51).

Scheme 50



R = Ph (92% yield), 3-Th (96%), Bu^t (85%), cyclohex-1-enyl (80%)

Scheme 51

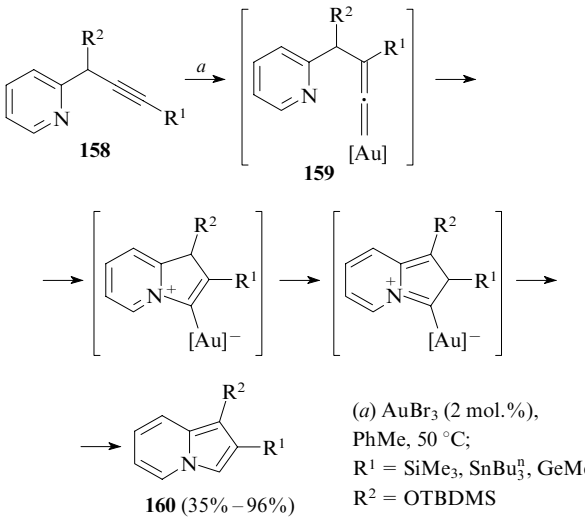


R	Yield of **156** (%)	Yield of **157** (%)
MeO	76	13
Me	34	34
H	14	64

IV.1.c. Heterocyclic nitrogen atom as a nucleophile

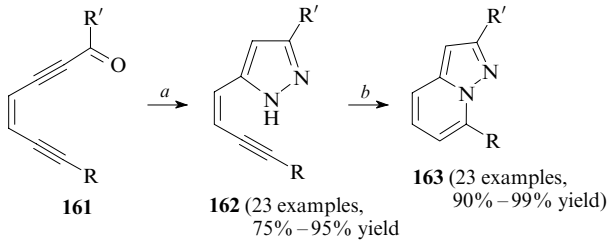
In the presence of $AuBr_3$ as the catalyst, pyridine substrate **158** is transformed into indolizine **160**; the reaction proceeds through vinylidene carbene complex **159** (Scheme 52).[329] A similar reaction can be catalyzed by silver triflate.[330]

Scheme 52



Wu *et al.*[331] developed an efficient method for the synthesis of pyrazolo[1,5-*a*]pyridines **163** in nearly quantitative yield under mild conditions in the presence of a cationic gold complexes (Scheme 53). The starting compounds **162** for the hydroamination of alkynes are prepared by the treatment of enediynones **161** with hydrazine (2 equiv.).

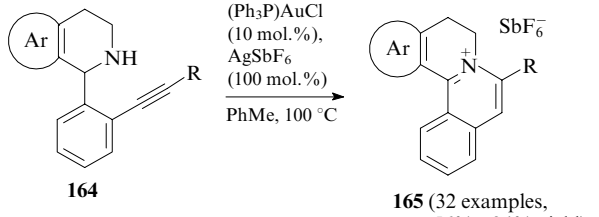
Scheme 53



(*a*) N_2H_4, MeCN, 60 °C, 30 min; (*b*) $(Ph_3P)AuCl$ (3 mol.%), $AgSbF_6$ (10 mol.%), THF, 25 °C, 5 h; R = H, Ar, Alk; R′ = Me, Ar

The $(Ph_3P)AuCl-AgSbF_6$-catalyzed intramolecular reaction of cyclic amines **164** produced tetracyclic derivatives **165** (Scheme 54).[288] The reaction requires a stoichiometric amount of the silver salt for the oxidation of the cyclic intermediate.

Scheme 54



R = Ar, Alk

Crawley and Funk[332] described an interesting hydroamination reaction of alkynes in the presence of gold-containing catalysts, which allows the synthesis of a complex fused system **167** with high stereoselectivity (Scheme 55).

Scheme 55

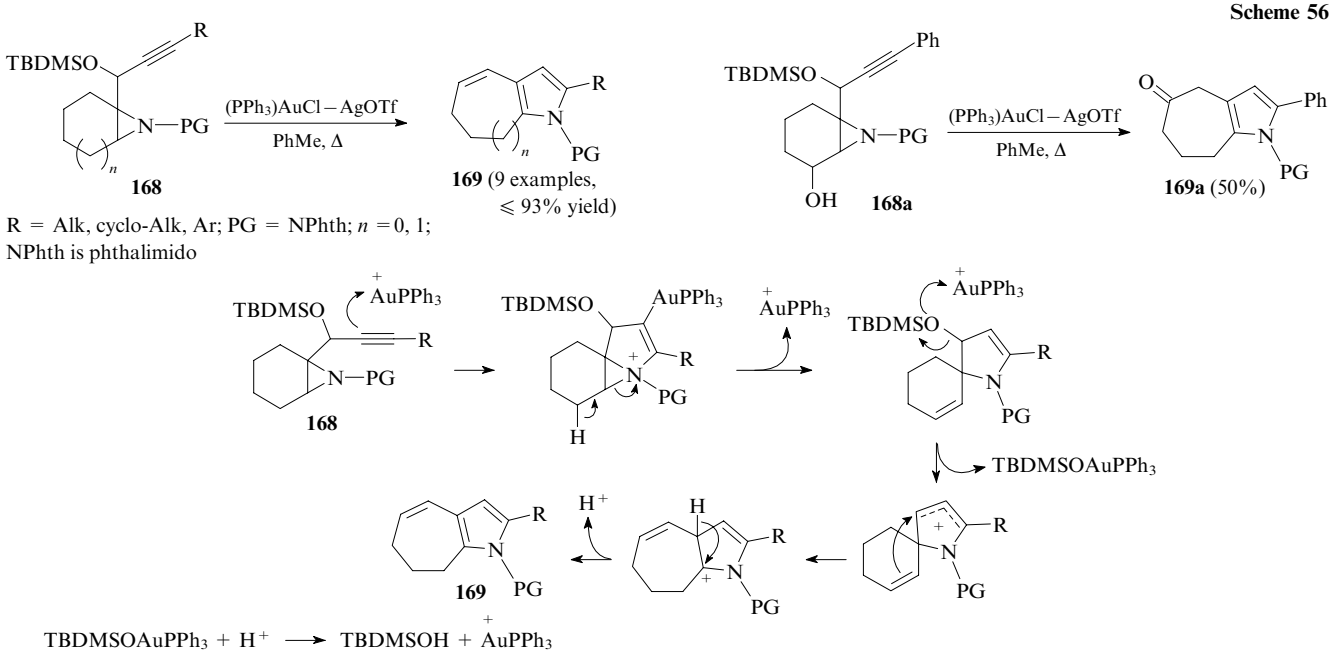


Zhao *et al.*[333] investigated the rearrangement of propargyl-substituted aziridine **168** catalyzed by the $(Ph_3P)AuCl-AgOTf$ system. The reaction affords trisubstituted cycloalkene-annulated pyrroles **169** (Scheme 56). If the starting compound contains a hydroxy group at the α position with respect to the aziridine ring (compound **168a**), this group is transformed into the oxo group to form product **169a** (see Scheme 56). The reaction involves an unusual sequence consisting of the addition of the nitrogen atom to the triple bond and the aziridine ring opening followed by the Wagner – Meerwein rearrangement. Based on the analysis of the available data[334 – 336] and the results of investigation of reaction intermediates, Zhao *et al.*[333] proposed the mechanism of transformations shown in Scheme 56. The reaction products can be used to synthesize structural analogues of alkaloids.

IV.1.d. Azides as nucleophiles

In 2005, Toste and co-workers[41] demonstrated that azide can act as a nucleophile in the reaction with alkynes catalyzed by a cationic Au^I complex. In this reaction, gold serves, on the one hand, as a π-acid and, on the other hand, as an electron donor, thus activating alkyne and facilitating elimination of N_2, respectively (Scheme 57). This method was used to prepare pyrroles **171** and **173**.

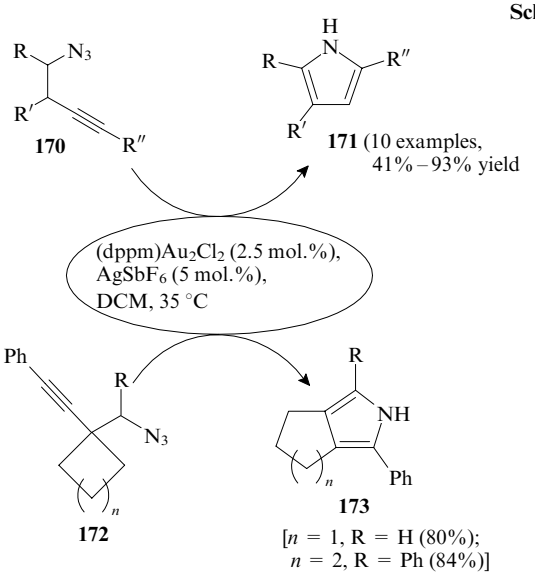
Scheme 56



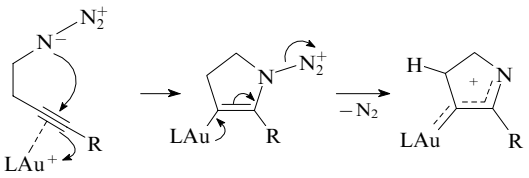
R = Alk, cyclo-Alk, Ar; PG = NPhth; $n = 0, 1$; NPhth is phthalimido

$TBDMSOAuPPh_3 + H^+ \longrightarrow TBDMSOH + {}^+AuPPh_3$

Scheme 57

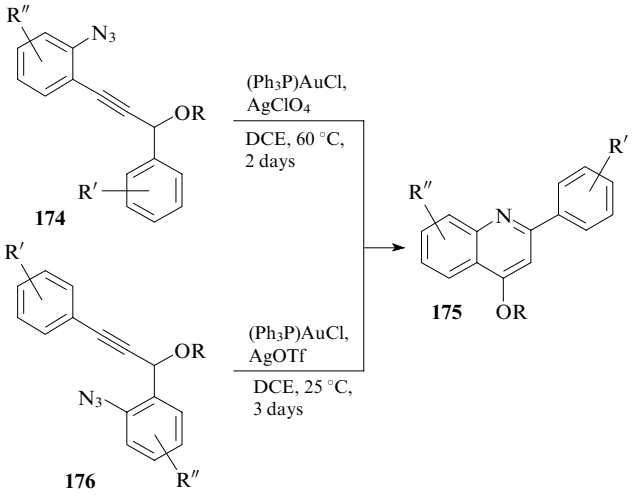


170: R′ = H: R = H, Bu^n; R – R′ = $(CH_2)_4$; R″ = Alk, cyclo-Alk, Ar, Het; dppm is bis(diphenylphosphino)methane



Substituted quinolines **175** were synthesized by the cyclization of 3-(2′-azidoaryl)-1-arylpropargyl carbonates **174**.[337] The reaction proceeds through the consecutive 3,3-rearrangement and 6-*endo-trig* cyclization followed by deazotization. The same quinolines **175** can be prepared from 1-(2′-azidoaryl)-3-arylpropargyl carbonates **176** under other reaction conditions. The latter reaction proceeds through the consecutive 6-*endo-dig* cyclization, deazotization and 1,2-H-shift (Scheme 58).

Scheme 58

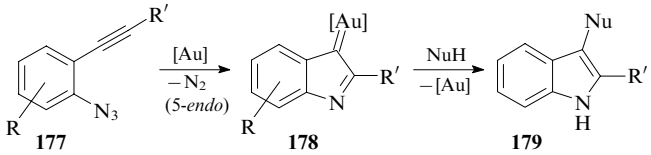


R = CO_2Me, Ar; R′ = H, Hal, CF_3, Me; R″ = H, Cl, Me

The former process involves the 3,3-rearrangement of propargyl ether to gold-activated allene intermediate as the first step. This intermeduate undergoes nucleophilic attack of the azido nitrogen atom. The latter reaction proceeds *via* a different mechanism involving the nucleophilic attack on the activated triple bond as the first transformation step. The nitro group in the *ortho* position of the benzene ring can serve as a nucleophile; in this case, isatins and anthranils were synthesized.[196]

2-Alkynylaryl azides **177** can be transformed into indoles **179** through carbenoid intermediate **178**, which reacts with a nucleophile.[338 – 341] In the first step, substrate **177** undergoes 5-*endo* cyclization through the nucleophilic attack of the azide nitrogen atom on the gold-activated triple bond (Scheme 59).

Scheme 59



R = H, Alk, cyclo-Alk, Ar; R′ = H, Alk; Nu or anisole, *etc.*

Attempts were made[338 – 341] to extend the range of substrates involved in this reaction by introducing an acyloxy group into the propargyl moiety of substrate **180**. In this case, the reaction proceeds *via* a different mechanism to form substituted quinolines **186**. Intermediate **181** undergoes 1,3-acetoxy shift to give allene **182**,[342, 343] this process being thermodynamically more favourable than the 5-*endo* cyclization. The nucleophilic addition of azide to activated allene produces cyclic intermediate **183**, and the latter is transformed into quionoline **186** *via* the 1,2-shift of the group R^2 accompanied by regeneration of the catalyst. Cationic intermediate **184** is generated either directly from intermediate **183** (path *a*, Scheme 60) or alternatively through gold carbenoid **185** (path *b*, see Scheme 60).

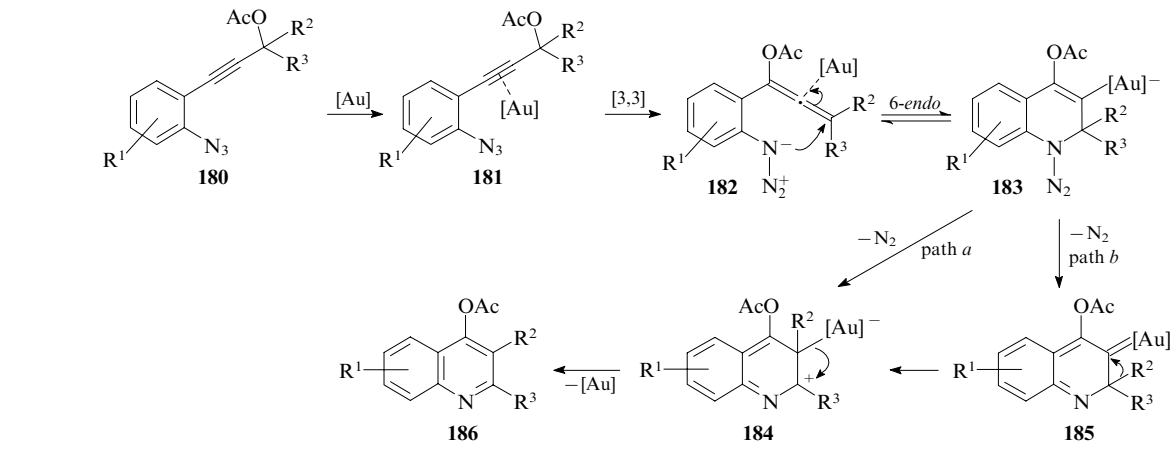
The reaction proceeds with different 2-alkynylaryl azides, including those with substituents R^2 and R^3 that are involved in ring closure (substrates **180′**). In most cases, the reaction produces substituted quinolines **186′** in high yields (see Scheme 60). The table in Scheme 60 gives the structures of selected products **186′** and their yields. If the substituents R^2 and R^3 are different, the ratio of products **186** and **186″** depends on the ability of the groups R^2 and R^3 to undergo migration (1,2-shift). If one of these groups in substrate **180** is unable to migrate, the reaction affords a mixture of quinoline **186** and indole **187** (Scheme 61).

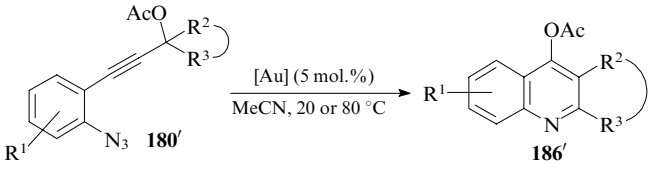
IV.1.e. Hydrazine as a nucleophile

Pyrazole derivatives **189** were synthesized[344] by the gold-catalyzed 5-*endo-dig* cyclization of hydrazine derivatives **188** (Scheme 62).

The synthesis of fluorinated pyrazoles **191** by the gold-catalyzed intramolecular aminofluorination of substrates **190** using a selectfluor as a source of fluorine was described in 2011.[345] A series of fluorinated pyrazoles **191** (Scheme 63) were prepared in good yields. The reaction mechanism proposed by Qian *et al.*[345] is shown in Scheme 63.

Scheme 60





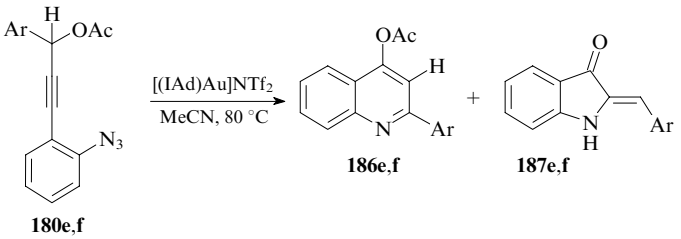
[Au] = $AuCl_3$ or $[(IAd)Au]NTf_2$

Substrate **186** : **186″**	R	Conditions	Yield (%)	Time /h	Ratio **186** : **186″**
180a	$Ph(CH_2)_2$	*a*	60	20	2 : 1
		b	71	0.25	5 : 1
180b	$H_2C{=}CH(CH_2)_2$	*a*	59	0.25	2.5 : 1
		b	64	0.25	7.5 : 1
180c	$H_2C{=}CH$	*a*	79	0.25	3.2 : 1
		b	74	0.25	1 : 0
180d	$(MeO)_2CHCH_2$	*a*	89	0.25	1 : 0
		b	0	substrate decomposition	

(*a*) $[(IAd)Au]NTf_2$ (5 mol.%), MeCN (substrate concentration is 0.2 mol litre^{-1}), 80 °C;
(*b*) $AuCl_3$ (5 mol.%), MeCN (0.2 mol litre^{-1}), 80 °C

Product	Yield (%) (time /h)	Product	Yield (%) (time /h)	Product	Yield (%) (time /h)	Product	Yield (%) (time /h)
186′a	*a*: 93 (0.5) *b*: 82 (0.25)	**186′c**	*a*: 52 (1.0) *b*: 88 (0.5)	**186′e**	*a*: 84 (4.0) *b*: 72 (0.5)	**186′g**	*a*: 71 (0.5) *b*: 83 (0.25)
186′b	*a*: 93 (0.5) *b*: 80 (0.5)	**186′d**	*a*: 96 (14.0) *b*: 85 (0.5)	**186′f**	*a*: 90 (0.5) *b*: 85 (0.5)	**186′h**	*a*: 27 (24.0) *b*: 0 (decomposition of **180′**)

Scheme 61

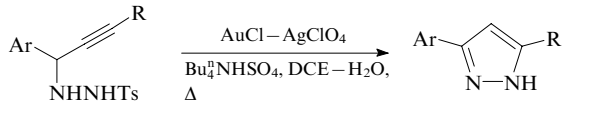


Substrate	Ar	Time /h	Yield of **186** (%)	Yield of **187** (%)
180e	Ph	20	51	46
180f	$4\text{-}ClC_6H_4$	16	40	40

Organic molecules containing an amino group and a halogen atom occur in nature as secondary metabolites, and many synthetic compounds of this type exhibit important biological activity.[346]

In 2013, Bouvet *et al.*[347] developed the gold-catalyzed synthesis of chiral azaproline derivatives **194** based on the 5-*exo*-*dig* cyclization of enantiomerically enriched α-hydrazino esters **193** containing the alkynyl group (Scheme 64).

Scheme 62

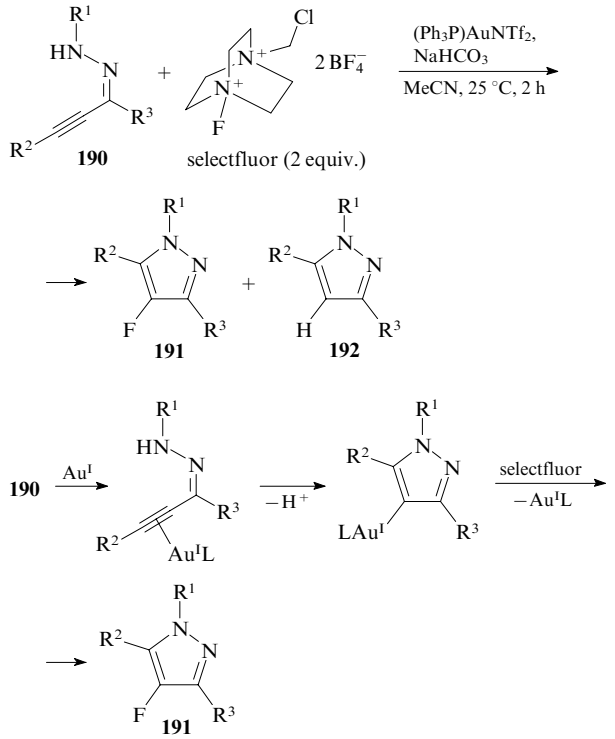


188

189 (10 examples, 61% – 98% yield)

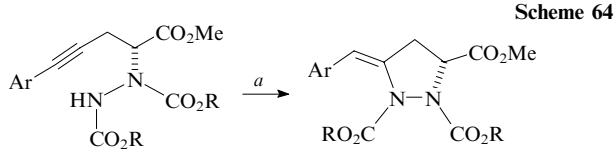
R = Ph, Bu^n, PhS

Scheme 63



R^1	R^2	R^3	Ratio **191** : **192**	Yield (%)
Ph	4-MeC$_6$H$_4$	Me	7.2 : 1	85
Ph	Bu^n	Me	4.5 : 1	78
Ph	Bu^t	Me	5.1 : 1	75
H	Ph	Me	2.1 : 1	45
Ph	Ph	H	only **191**	90

Scheme 64



193

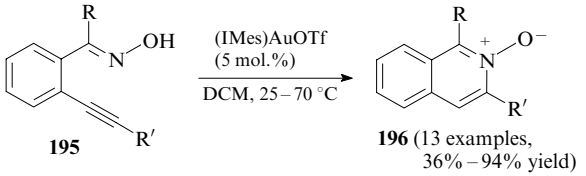
194 ($\leqslant$ 82% yield, *ee* $\leqslant$93%)

(*a*) (Ph$_3$P)AuCl (5 mol.%), AgBF$_4$ (5 mol.%), DCM, 25 °C, 6 – 24 h, *Z* selectivity

IV.1.f. Hydroxylamine as a nucleophile

The cyclization of 2-alkynyl benzaldoximes **195** in the presence of (IMes)AuOTf produces the corresponding isoquinoline *N*-oxides **196** (Scheme 65).[348, 349] The reaction proceeds under mild conditions.

Scheme 65



195

196 (13 examples, 36% – 94% yield)

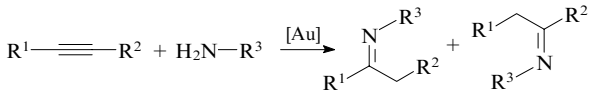
R, R′ = Ph, Alk

IV.2. Intermolecular reactions

IV.2.a. Amines as nucleophiles

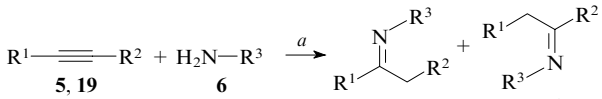
In the general form, the transformation is presented in Scheme 66.

Scheme 66



The first intermolecular hydroamination reaction was described by Tanaka and co-workers[350] in 2003. Alkynes **5** and **19** react with anilines **6** under solvent-free conditions (Scheme 67). The activity of the complex (Ph$_3$P)AuMe in the presence of an acidic activator (chosen from a group of heteropoly acids) surpasses that of the previously known catalysts for the intramolecular hydroamination of alkynes.

Scheme 67



5, **19** **6** **7** **7′**

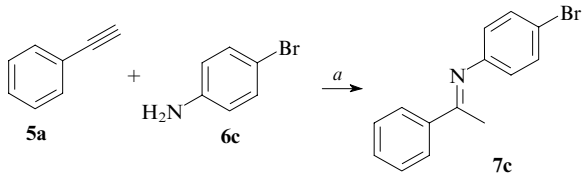
(28% – 99% total yield)

(*a*) (Ph$_3$P)AuMe (0.01 mol.% – 0.5 mol.%), acidic activator (0.05 mol.% – 1 mol.%), solvent-free conditions, 70 °C; R^2 = H: R^1 = Ar, Alk; R^1, R^2 = Alk; R^3 = Ar

The efficient hydroamination requires the use of a catalyst and acid, the process being sensitive to the nature of the acidic activator. The reaction can be carried out with aryl- and alkyl-substituted terminal alkynes, 2-ethynylthiophene and dialkyl-substituted internal alkynes (in the latter case, the reaction time is longer). The method is efficient for arylamines containing electron-donating and electron-withdrawing groups in the aromatic ring, sterically hindered primary arylamines and phenylhydrazine, but it is not efficient for alkylamines. Electron-rich aryl alkynes proved to be more reactive than aryl alkynes containing electron-withdrawing substituents. The catalyst is characterized by high stability: TOF is about 9000 h^{-1} for the reaction of phenylacetylene with 4-cyanoaniline or 4-bromoaniline (Scheme 68).

All reactions were carried out under solvent-free conditions and gave Markovnikov products. Besides, it was found that phenylhydrazine also adds to phenylacetylene under these conditions to form the corresponding phenylhydrazone (in 99% yield), which can be used in the Fischer indole synthesis. Scheme 68 gives the yields of the products obtained by the reaction of phenylacetylene (**5a**) with 4-bromoaniline (**6c**) using different acidic activators.

Scheme 68

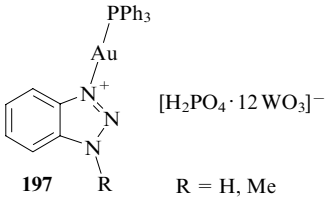


(*a*) $(PPh_3)AuMe$ (0.1 mol.%), activator (0.5 mol.%), 70 °C, 2 h

Activator	Yield of **7c** (%)	Activator	Yield of **7c** (%)
–	0	n-$C_{12}H_{25}C_6H_4SO_3H$	72
$H_3PW_{12}O_{40}$	97	$MeSO_3H$	26
$H_3MoW_{12}O_{40}$	95	NH_4PF_6	56
$H_4SiW_{12}O_{40}$	97	NH_4BF_4	7
CF_3SO_3H	88	Nafion-SAC13	19

Silica-supported gold nanoparticles encapsulated within micelles were applied as the catalyst to perform the hydroamination of alkynes **5** with anilines **6** at room temperature.[351] Gold(I) complexes with benzotriazoles **197** were proposed as highly efficient thermally stable catalysts for intermolecular hydroamination of alkynes.[195] These catalysts give good results in intermolecular hydroamination reactions of internal alkynes with arylamines. Besides, an increase in the catalyst loading to 10 mol.% made it possible to perform the hydroamination of alkynes with aliphatic amines with moderate yields.

Structures 197

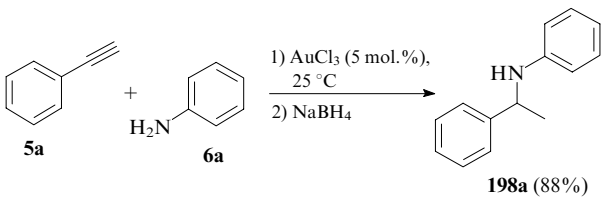


The target products were synthesized in yields of up to 98% using the $(Ph_3P)AuOTf$ – **197** catalytic system (0.1 mol.% of each component). This reaction can be accomplished at 50 °C using the cationic gold complex with the cyclohexylbis(2′,6′-diisopropoxybiphenyl-2-yl)phosphine ligand at a loading of about 0.0025 mol.%, the TON value being as high as 31 200.[72] The intermolecular hydroamination of terminal alkynes **5** with anilines **6** was also successfully catalyzed using gold(I) N-heterocyclic carbene complexes.[352 – 354] Imino derivatives **7** can be prepared in good yields by the hydroamination of alkynes using gold(III) porphyrin complexes **26**.[167]

Similar reactions of terminal alkyl- and arylacetylenes with anilines (*e.g.*, compounds **5a** and **6a**) were described by Li and co-workers.[355] The reactions of arylacetylenes were catalyzed by $AuCl_3$ (5 mol.%) or $AuCl_3 – AgOTf$ (5 mol.% – 15 mol.%) (Scheme 69).

Based on the analysis of the data published in the literature and own experimental results, the authors revealed the following facts. The choice of substrates for intermolecular hydroamination reactions is mostly limited to terminal alkynes (aromatic and aliphatic) and aromatic amines (anilines). The reactions with cyclic secondary

Scheme 69

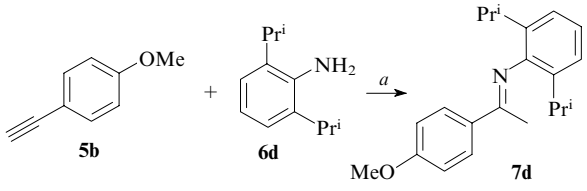


amines (*e.g.*, morpholine and piperidine) are somewhat more difficult to perform.[356] This is attributed to the donor properties of amine, which should not be strong; otherwise, the amine forms a stable complex with a gold atom and deactivates the latter. Meanwhile, the nucleophilicity of amine with very weak donor properties is insufficient for the attack on the gold-activated triple bond. The hydroamination of terminal alkynes **5** with primary aromatic amines (anilines) **6** usually follows Markovnikov's rule. Enamines that are formed as intermediates undergo rapid tautomerization to the corresponding imines **7**, due to which the dihydroamination product is not generated.[242]

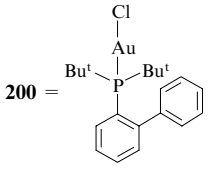
The intermolecular hydroamination of terminal alkynes **5** (R = Ph, Cy, cyclo-C_5H_9) was performed using both carbon-supported and mesoporous zeolite-supported gold nanoparticles; in the latter case, the catalyst can be recycled.[356, 357] The optimal reaction conditions were found using the model reaction of phenylacetylene (**5a**) with morpholine (**199a**). The best results with the catalyst Au/MCM-41 (5 mol.%) were obtained by performing the reaction in the ionic liquid (bmim)PF_6 (bmim is 1-n-3-methylimidazolium) (95.5% yield). It was found that the nature of the ionic liquid, more precisely the nature of the counterion, plays a role in this process. For instance, the use of BF_4^- instead of PF_6^- led to a decrease in the yield to 88%. Initially, the reaction was performed in the ionic liquid at high temperature (150 °C). Later on, a modified procedure was proposed. The reaction was accomplished without the formation of by-products by using a support impregnated with an ionic liquid and performing the process in toluene at 100 °C. It was hypothesized[356, 357] that cationic gold on the AuNP surface is the true catalyst.

Fang *et al.*[358] described the gold-catalyzed intermolecular hydroamination using a Lewis acid — copper(II) triflate — instead of silver salt as the cocatalyst (Scheme 70).

Scheme 70

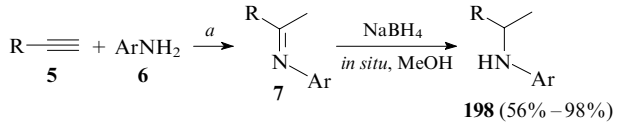


(*a*) **200** (0.1 mol.%), $Cu(OTf)_2$ (1 mol.%), PhMe, 24 h (100% conversion);



Anokhin *et al.*[359] reported the reaction of alkynes **5** (both aromatic and aliphatic) with different anilines **6** catalyzed by the cationic gold complex $\{(C_6F_5)_3P\}AuNTf_2$ with weak electron-donating phosphine as the stabilizing ligand (Scheme 71). The reaction was carried out under solvent-free conditions at room temperature to form imines **7**, which were reduced with sodium borohydride to give amines **198** in nearly quantitative yield without isolation (one-pot procedure).

Scheme 71



(*a*) $\{(C_6F_5)_3P\}AuNTf$, solvent-free conditions, 25 °C; R = n-C_6H_{11}, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4; Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,5-$Me_2C_6H_3$

The catalyst $\{(C_6F_5)_3P\}AuNTf_2$ can be quantitatively precipitated from the reaction with hexane and, after washing and drying, reused. This procedure can be repeatedly performed without loss of catalytic activity. In intramolecular reactions, the complex $\{(C_6F_5)_3P\}AuNTf_2$ proved to be too active, resulting in the formation of a gold mirror through reduction of Au^+.

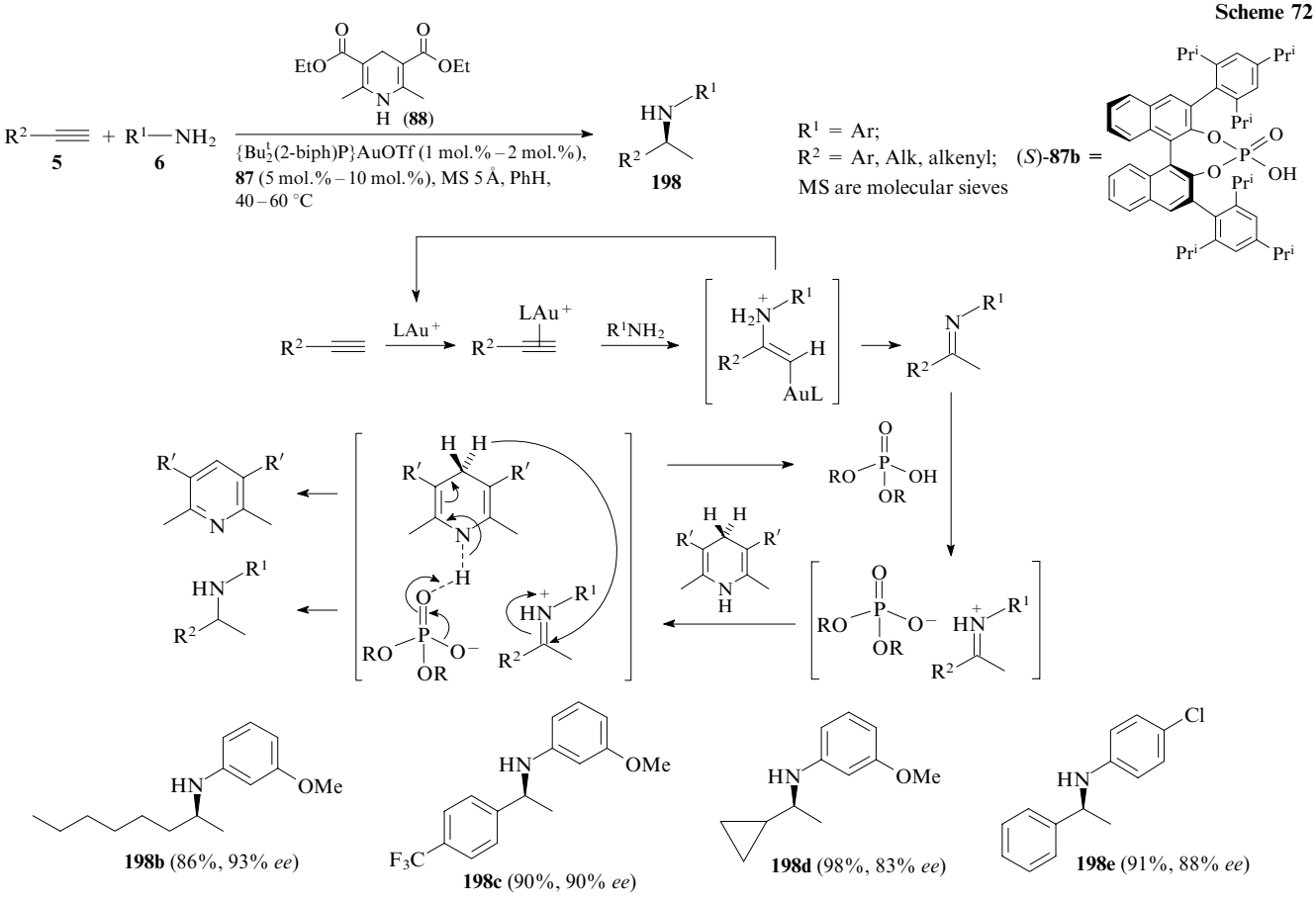
The highly enantioselective tandem intermolecular hydroamination – hydrogenation reaction of alkynes **5** was accomplished using a gold(I) complex as the catalyst in the presence of chiral Brønsted acid (*S*)-**87b** (Scheme 72).[360] The reaction proceeds with high yield and combines the advantages of metal catalysis and organocatalysis, thus allowing the synthesis of chiral highly enantiomerically enriched secondary amines **198**. Good results were obtained with aryl-, alkenyl- and alkyl-substituted alkynes **5** and with anilines **6** bearing substituents with different electronic properties. Examples of products **198** obtained in this reaction and the reaction mechanism are presented in Scheme 72.

There are some difficulties when using secondary amines in the hydroamination reaction of alkynes. First, secondary amines are stronger nucleophiles than primary ones and their coordination bond with metal ions is stronger, which hinders their transfer to the carbon centre. Second, the electrostatic repulsion between the π-electron system of the alkyne and electron-rich secondary amine is stronger compared to primary amines. Finally, there is steric hindrance in the reaction of secondary amines with gold-activated alkynes.

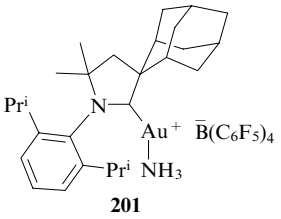
In 2009, Bertrand and co-workers[243] used cationic Au^I complex **201** with the cyclic alkyl(amino)carbene ligand for the hydroamination of both terminal and internal alkynes with secondary amines **198** and **199** in good yields with moderate regioselectivity.

The addition of cyclic secondary amines **199** to unsymmetrical internal aryl alkynes was performed in moderate yield and with moderate selectivity using Au^I complex **202** with the bulky P,N-ligand Mor-DalPhos.[361] The reaction proceeded in toluene at 110 °C for 16 h. The catalytic system included 5 mol.% complex **202** and 5 mol.% $Ag[B(C_6F_5)_4]$. The C – N bond formation occurs mainly

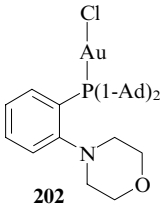
Scheme 72



Structures 201, 202



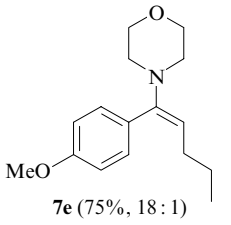
201



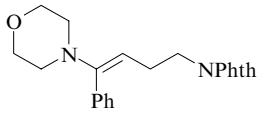
202

with the carbon atom bound to the aryl substituents, except for 2-alkynylpyridines, which undergo the Michael reaction. The reaction proceeds through a transition complex that is formed through the coordination of alkyne to the Au amine adduct to give a vinyl Au intermediate *via* insertion of alkyne followed by the proton migration. The *E* configuration of enamine results from the stereoselective protodeauration. Structures **7e – h** are examples of products **7** (the yields and selectivity of the addition are given).

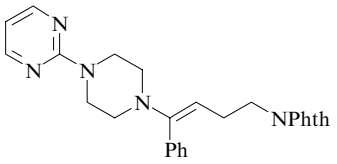
Structures 7e – h



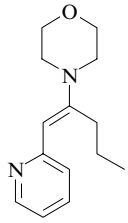
7e (75%, 18 : 1)



7f (73%, > 20 : 1)



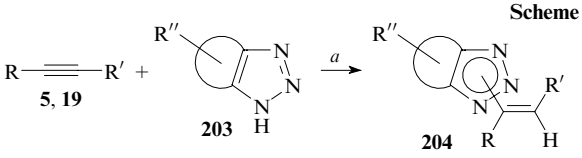
7g (88%, > 20 : 1)



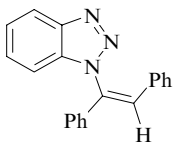
7h (80%, > 20 : 1)

In the same 2009 year, Shi and co-workers [362] proposed an efficient method for the synthesis of vinyl-substituted triazoles **204** based on the gold(I)-catalyzed hydroamination of alkynes **5** and **19** with triazoles **203**, which follows Markovnikov' rule. The reaction of alkynes with benzotriazoles affords N(1)-substituted benzotriazoles **204a – c**, whereas carbonyl-substituted NH-triazoles give N(2)-addition products (*e.g.*, derivative **204d**) (Scheme 73).

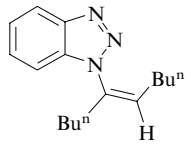
Scheme 73



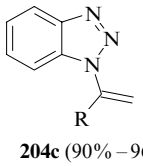
(*a*) $(Ph_3P)AuOTf$ (0.2 mol.%), PhMe, 80 °C



204a (70%)

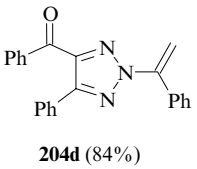


204b (90%)



204c (90% – 96%)

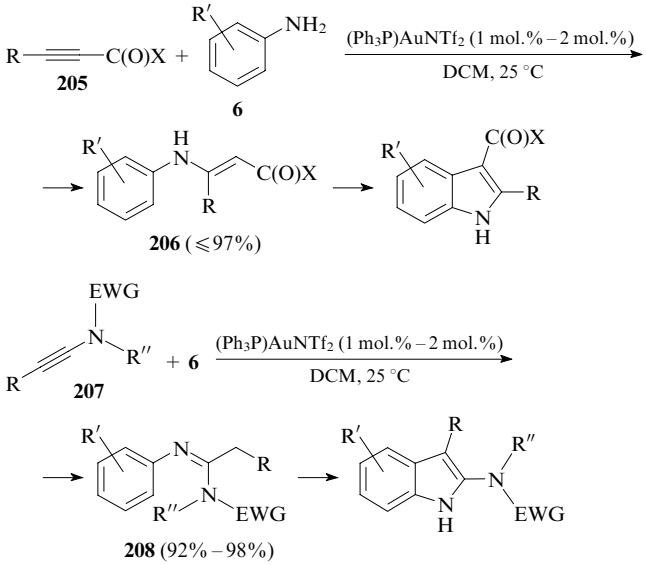
(R = Ar, Alk)



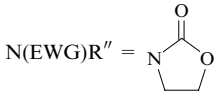
204d (84%)

Kramer *et al.* [363] reported the highly regioselective hydroamination of propiolic acid derivatives **205** and ynamides **207** having the strongly polarized triple bond. The reaction proceeds in the presence of $(Ph_3P)AuNTf_2$ as the catalyst at room temperature (Scheme 74).

Scheme 74



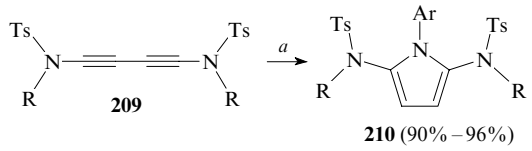
R = Ar, Alk; X = OMe, OEt, amine moiety; R′ = H, Cl, I, Me, OMe; EWG is an electron-withdrawing group;



N,*N*-Disulfonyl ynamides **207** (R″ = EWG = SO_2Ph) activated by two potent electron-withdrawing groups undergo the catalyst-free Michael addition of aniline at room temperature.[364]

In the case of the alkadiyne system, the nucleophile that is initially bound to one of the triple bonds can interact with the second triple bond in an intramolecular fashion to form a cyclic structure. For example, the Au^I-catalyzed hydroamination of 1,3-diynes **209** affords 2,5-diamidopyrroles **210** (Scheme 75).[365]

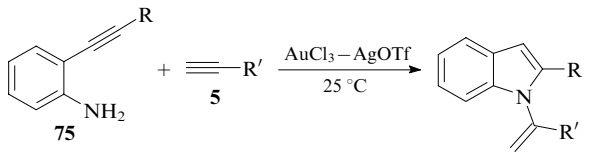
Scheme 75



(*a*) $ArNH_2$ (1.05 equiv.), $(PPh_3)AuNTf_2$ (1 mol.%), DCM, 30 °C, 30 min; R = Pr^n, Ph, Bn

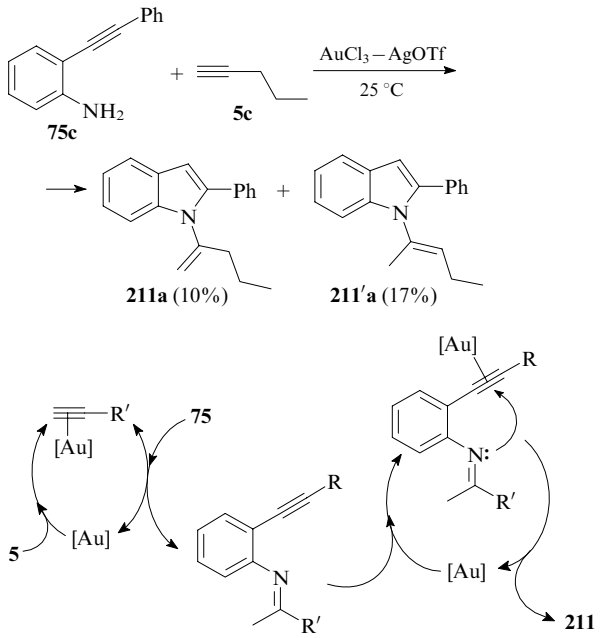
Zhang *et al.* [366] reported the Au^{III}-catalyzed sequential intermolecular and intramolecular hydroamination of terminal alkynes **5** with *o*-alkynylanilines **75** giving *N*-vinylindoles **211** under solvent-free conditions (Scheme 76). The product yields are 69% – 82% in the case of aromatic substituents R and R′ and are not higher than 67% if one of the substituents is not aromatic.

Scheme 76



211 (25% – 82%)

R = Ph, cyclohex-1-enyl, Pr^n, Bu^n;
R′ = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 1-Naph, cyclohex-1-enyl, Pr^n, Bu^n



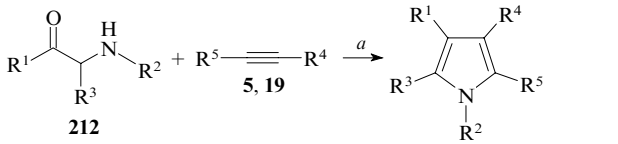
If R′ = Alk, the reaction can produce a mixture of isomers (*e.g.*, indoles **211a** and **211′a**) (see Scheme 76). Since 2-phenyl-1*H*-indole (**76c**) does not react with phenylacetylene (**5a**) under these reaction conditions, Zhang *et al.*[366] concluded that gold initially catalyzes the intermolecular amination of alkyne **5** followed by the intramolecular nucleophilic attack of arylimine as a nucleophile on the triple bond, as shown in Scheme 76.

The formation of product **103** analogous to product **211** in the intramolecular hydroamination of acetamidines **102** is considered above (see Scheme 33) and provides support for the proposed reaction mechanism. This reaction is an example of double hydroamination, in which one nucleophilic centre interacts with two triple bonds. It is also possible that two nucleophiles react sequentially with one triple bond (the nucleophilic addition to alkyne followed by the addition to the imine that formed). This situation will be considered below.

The cascade hydroamination – cyclization – aromatization reactions of alkynes **5** and **19** with α-amino ketones **212** produce pyrroles **213** (Scheme 77).[367] In some cases, this process occurs at room temperature. The reaction mechanism is shown in Scheme 77. It can be seen that gold catalyzes two steps of the reaction, displaying carbophilic and oxophilic behaviour in the first and second steps, respectively.

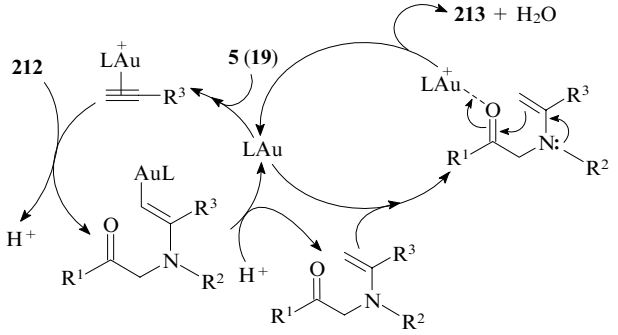
The gold-catalyzed intermolecular reaction of alkynes **5** with *o*-phenylenediamines **214** underlies the direct synthesis of 1,5-benzodiazepine **215** (Scheme 78),[368] which is present in a number of biologically active compounds: anti-inflammatory and sedative agents and antidepressants.[369, 370] The screening of a series of catalysts demonstrated that {(2-biph)Cy_2P}$AuNTf_2$ [with an SPhos analogue as the ligand (**8**)] is the most effective one. A combination of {(2-biph)Cy_2P}AuCl and $AgNTf_2$ gave the same result. The application of {(2-biph)Cy_2P}AuCl resulted in the

Scheme 77

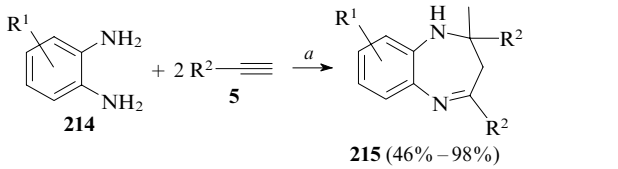


213 (40% – 94%)

(*a*) **123** (5 mol.%), MgO (3 equiv.), DCM, 100 °C, closed vessel, 1 – 31 h; R^1 = Me, Ph, PhCH=CH, 4-FC_6H_4, 4-$MeOC_6H_4$, 1-Naph; $R^1 - R^3$ = $(CH_2)_4$; R^3 = H, Me; R^2 = Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$EtO_2CC_6H_4$, 4-MeC_6H_4, 3,4,5-$(MeO)_3C_6H_2$, 1-Naph; R^4 = H, CO_2Et; R^5 = Ph, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeO_2CC_6H_4$, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, 1-Naph, 2-Th, cyclo-C_3H_5, EtO_2C

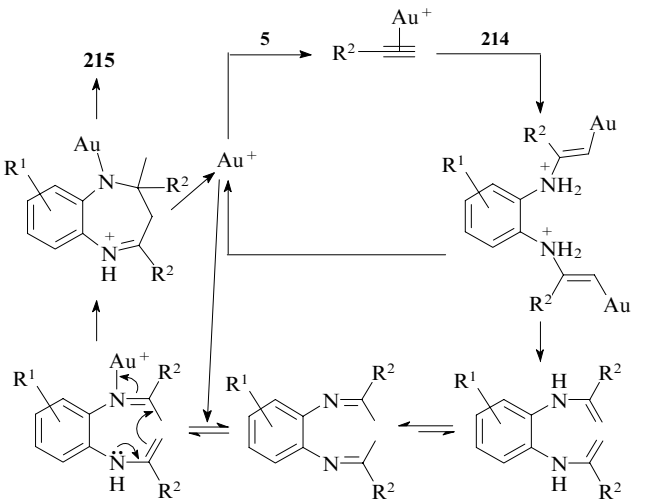


Scheme 78



215 (46% – 98%)

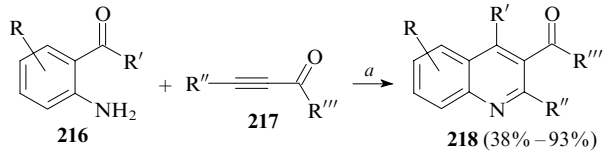
(*a*) {(2-biph)Cy_2P}$AuNTf_2$ (5 mol.%), $CHCl_3$, 60 °C, 6 h; R^1 = Me, Cl, Br, NO_2; R^2 = Ph, Ar, cyclo-C_3H_5, n-Alk



formation of only trace amounts of product **215**; the target product was not obtained when using $AgNTf_2$ alone. Attempts to perform this reaction in the presence of other Lewis or Brønsted acids, such as CuI, $PdCl_2$, $BiCl_3$, $ZnCl_2$, $FeCl_3$, $Cu(OTf)_2$, HOTf, $HNTf_2$ or HCl, failed, and the target product was not prepared. If R^2 = Alk, the reaction product was obtained in 46% – 48% yield. Qian *et al.*[368] proposed the reaction mechanism involving the hydroamination of two activated acetylene molecules by two amino groups of *o*-phenylenediamine. The subsequent closure of the seven-membered heterocycle is also catalyzed by gold, which is bound to the nitrogen atom (see Scheme 78).

The intermolecular cycloaddition of 2-aminoarylcarbonyl compound **216** and internal alkyne **217** produced[371] substituted quinolines **218** in yields of up to 93% (Scheme 79). The plausible reaction mechanism involves the nucleophilic addition of the amino group of aniline **216** to the gold-activated triple bond of alkyne **217** as the first step followed by intramolecular condensation.

Scheme 79



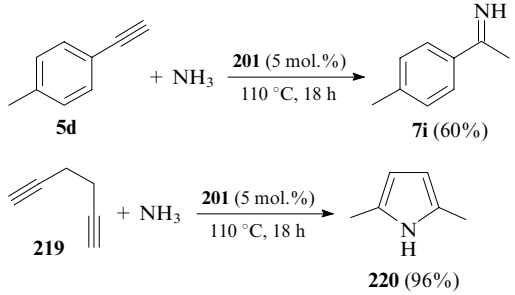
216 + **217** → **218** (38% – 93%)

(*a*) $(Ph_3P)AuCl$, AgOTf, DMF, 100 °C;
for **216**: R = H, 4-Me, 3-Cl, 3-NO_2; R′ = H, Me, Bu^n, Ph, XC_6H_4 (X = H, 4-Br, 4-Cl, 2-F);
for **217**: R″ = Me, Pr^n, n-C_6H_{13}, 4-YC_6H_4 (Y = H, Me, Br, NO_2, OMe); R‴ = OEt, Me, piperidino

IV.2.b. Addition of ammonia

Ammonia is a cheap and available source of nitrogen, and its application for the C – N bond formation is of great interest in modern organic synthesis.[372, 373] However, there is difficulty in using ammonia as a substrate for hydroamination because it combines moderate nucleophilicity and strong complexing properties. Bertrand and co-workers[37] found that cationic Au^I complex **201** with the cyclic alkyl(amino)carbene (CAAC) ligand catalyzes the addition of ammonia to alkyne **5d** to form Markovnikov product **7i**. The double hydroamination of diyne **219** with ammonia provides a route to pyrrole **220** (Scheme 80). This cationic gold complex can also be used for the addition of ammonia to terminal and internal allenes. The reaction proceeds through the intermediate, in which NH_3 and alkyne are bound to the gold complex.

Scheme 80



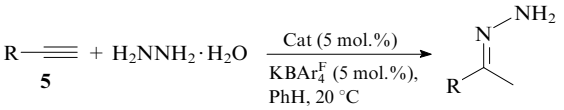
5d + NH_3 → **7i** (60%)

219 + NH_3 → **220** (96%)

IV.2.c. Addition of hydrazines

The reactions of terminal alkynes with substituted hydrazines by using cationic gold complexes follow Markovnikov's rule.[374, 375] The addition of unsubstituted hydrazine was described by López-Gómez *et al.*[375] This reaction was catalyzed by CAAC-Au^I **201** and proceeded at 100 °C with anhydrous hydrazine. In 2014, Hashmi and co-workers[376] proposed the addition reaction of hydrazine hydrate at room temperature in the presence of gold complex **23** (R = 2,6-$Pr^i_2C_6H_3$) with a saturated abnormal N-heterocyclic carbene ligand (Scheme 81).

Scheme 81

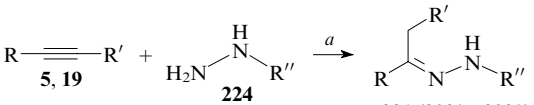


5 + $H_2NNH_2 \cdot H_2O$ → **221** (10 examples, ⩽ 90% yield)

R = Alk, Ar; Cat = **23** (R = 2,6-$Pr^i_2C_6H_3$); Ar^F = 3,5-$(CF_3)_2C_6H_3$

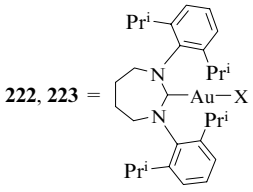
In 2016, Morozov *et al.*[377] developed a new highly efficient procedure for hydrohydrazination of alkynes (mainly of terminal aryl alkynes) both in solvent and under solvent-free conditions (Scheme 82). New gold carbene complexes **222** and **223** with the TDH-Dipp ligand served as the catalysts.[378] The TDH-Dipp ligand is characterized by strong electron-donating properties and the presence of bulky substituents causing steric hindrance. The reaction follows Markovnikov's rule. In the case of R′ = CO_2Et (alkyne **225**), 2*H*-pyrazol-3-ones **226** are produced in high yield.

Scheme 82

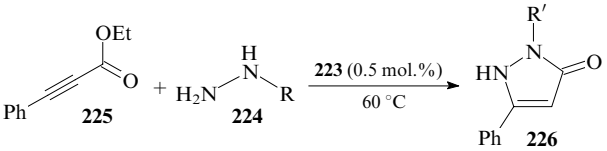


5, **19** + **224** → **221** (23% – 98%)

(*a*) **222** (2 mol.%) and AgOTf or **223** (2 mol.%), solvent, Δ, 2 h or **223** (0.25 mol.%), 100 °C; R = n-C_6H_{13}, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-$PhOC_6H_4$, 4-ClC_6H_4, 4-$Me_2NC_6H_4$, 1-Naph, 4-$MeO_2CC_6H_4$; R′ = H, Ph; R″ = H, Ph, Boc, Ts; solvent: MeOH, EtOH, PhMe, MeCN, $CHCl_3$



222, **223** = [X = Cl (**222**), OTf (**223**); (TDH-Dipp)AuX]



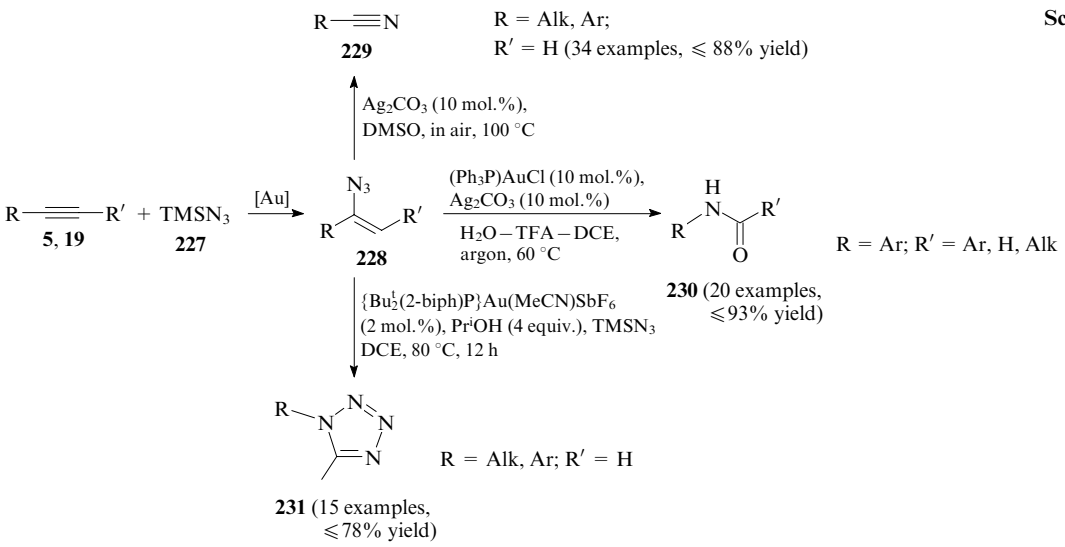
225 + **224** → **226**

R = Boc, Ph; R′ = H (89% yield), Ph (86%)

IV.2.d. Addition of azides

Azides **228**, which were synthesized by the gold-catalyzed addition of trimethylsilyl azide (**227**) to alkynes **5** and **19**,

Scheme 83

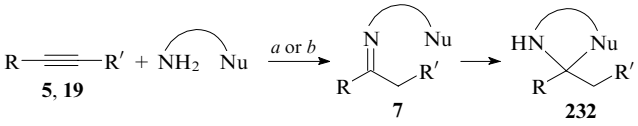


can be transformed into nitriles **229**,[379] amides **230** (Ref. 380) or tetrazoles **231** (Ref. 381) (Scheme 83).

IV.3. Double hydroamination and hydroamination–hydroarylation of terminal alkynes

The reaction of gold-activated alkyne **5** or **19** produces imine **7**, which is a new electrophilic precursor capable of interacting with the second nucleophile (an amino group or an aryl moiety) present in molecule **7** (Scheme 84).

Scheme 84



(*a*) R′ = H, Alk; R = $(CH_2)_nCH_2OH$: $PtBr_2$, MeOH, 800 °C;
(*b*) R = Alk, Ar; R′ = H: $(Ph_3P)AuNTf_2$, PhMe, 100 °C; Nu = NH_2, Ar

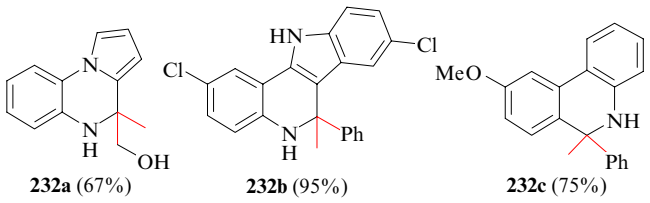
These consecutive double hydroamination and hydroamination–hydroarylation reactions produce nitrogen-containing heterocycles, *e.g.*, **232a–f**. Patil *et al.*[382–384] used platinum compounds ($PtBr_2$ and $PtCl_4$) as catalysts for these reaction. Both terminal and disubstituted alkynes were involved in the reaction, good yields being obtained only with substrates containing a hydroxy group in the substituent [R = $(CH_2)_nCH_2OH$]. The reaction was performed in methanol at 80 °C. The complex $(Ph_3P)AuNTf_2$ catalyzes this type of transformations with terminal alkynes **5** (R′ = H) as substrates.[385] The presence of a hydroxy group in substrate **5** is not necessary. This reaction can be carried out with substrates bearing a broad range of substituents. Toluene proved to be the solvent of choice. In some cases, AgOTf was applied as the cocatalyst.

Patil *et al.*[385] proposed the reaction mechanism. According to this mechanism, the second step resulting in the ring formation is catalyzed by gold, which activates the imine moiety by binding to the lone pair of the nitrogen atom (Structure **233**).

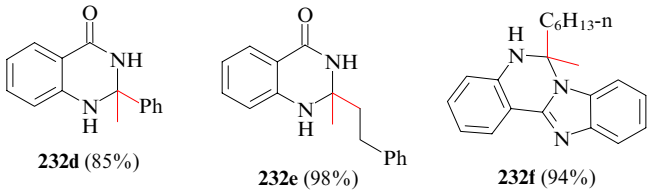
An efficient method for the synthesis of substituted 1,2-dihydroquinolines **234** and **234′** and quinolines by the

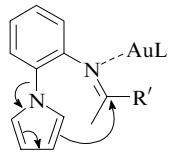
Structure 232, 233

Hydroamination–hydroarylation products



Double hydroamination products

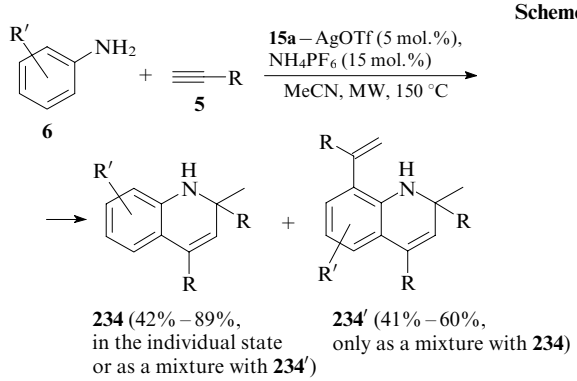




microwave-assisted tandem hydroamination–hydroarylation reaction using Au^I catalyst **15a** was reported by Liu *et al.*[386] This method has a number of advantages, such as a short reaction time (usually 10–70 min) and a broad range of possible substrates (Scheme 85).

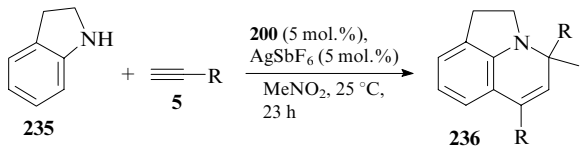
Compounds containing the partially hydrogenated quinoline moiety possess valuable therapeutic properties. They are lipid peroxidase and HMG-CoA reductase inhibitors and progesterone agonists and antagonists.[387–391] This reaction with indoline (**235**) affords tricyclic product **236** (Scheme 86).[386]

Scheme 85



R = Alk, Ar; R′ = H, Hal, Me, OMe, OPh

Scheme 86



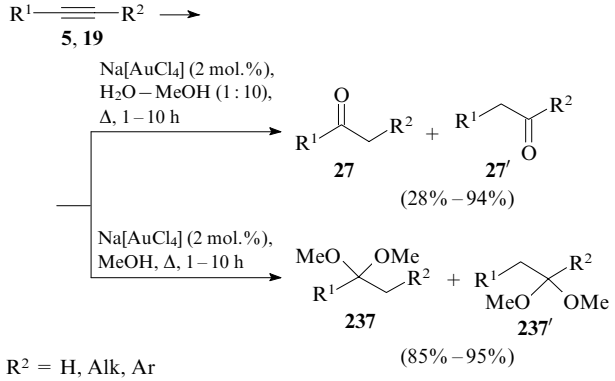
R = Ph, 4-MeC_6H_4, 4-$F_3CC_6H_4$, 4-FC_6H_4, 4-$MeOC_6H_4$, Bu^n, n-C_6H_{13}; **236**: R = Ar (68% – 95% yield), Alk (58% – 63%)

V. Nucleophilic addition of oxygen-containing nucleophiles to the triple bond

The hydration of alkynes is a known and well-characterized reaction allowing the synthesis of oxygen-containing compounds. It can be catalyzed by salts and complexes of different metals, such as Hg,[392, 393] Ru,[394, 395] Rh,[396] Pd,[397, 398] Pt.[399, 400] For example, toxic mercury(II) salts in a strongly acidic medium or transition metal complexes were used as catalysts for these reactions. These catalysts are insufficiently efficient and generally have low TOF values.[401] Thus, the highest TOF value for the hydration of pent-3-yn-1-ol catalyzed by [*cis*-$PtCl_2(tppts)_2$] [tppts = $P(C_6H_4SO_3Na\text{-}3)_3$] is 550 h^{-1} in the beginning of the reaction, while the average value is not higher than 100 h^{-1} (see Ref. 400).

The gold-catalyzed hydration of alkynes was described for the first time almost 120 years ago.[402] Interestingly, since then the use of gold in this type of reactions was not mentioned in research papers over a long period of time. In 1976, Norman *et al.*[403] demonstrated that phenylacetylene is transformed into acetophenone in the presence of $HAuCl_4$ as the catalyst. In the 1990s, Fukuda and Utimoto [157] found that $Na[AuCl_4]$ (2 mol.%) catalyzes the addition of oxygen-containing nucleophiles (such as water and alcohols) to alkynes (Scheme 87).

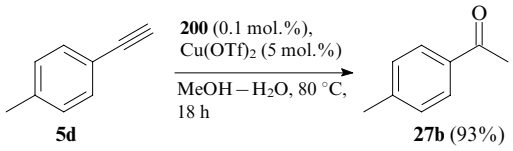
Scheme 87



R^1, R^2 = H, Alk, Ar

The hydration of 4-methylphenylacetylene (**5d**) in the presence of trifluoromethanesulfonic acid (10 mol.%) as the catalyst affords the corresponding ketone in a low yield (10%).[404] In the presence of the gold – copper catalytic system, this reaction produces ketone **27b** in 93% yield;[69] the copper salt acts as the cocatalyst (Scheme 88).

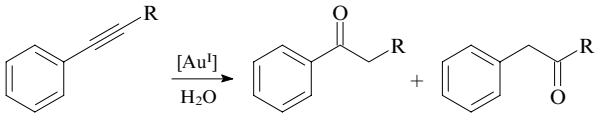
Scheme 88



The transformation of terminal alkynes into the corresponding methyl ketone follows Markovnikov's rule,[405] because, according to calculations, a gold ion binds to terminal alkynes in an asymmetric mode:[406, 407] the bond between the metal and the internal sp-carbon atom is longer than the distance to the terminal sp-carbon atom.

Internal alkynes exhibit moderate regioselectivity, the direction of the reaction being often determined by the nature of the catalyst. For instance, the hydration of alkyne $PhC{\equiv}CC_6H_{13}$-n (**19b**) in the presence of $(Ph_3P)AuNTf_2$ as the catalyst produces two regioisomeric ketones **27** and **27′** in equimolar amounts.[73] The (IPr)AuCl – $AgSbF_6$-catalyzed hydration of $PhC{\equiv}CEt$ (**19c**) affords an anti-Markovnikov product as the major one (**27** : **27′** = 1 : 4) (Scheme 89).[111]

Scheme 89



Compound **19**	R	[Au^I]	Ratio **27** : **27′**
b	C_6H_{13}-n	$(Ph_3P)AuNTf_2$	1 : 1
c	Et	(IPr)AuCl – $AgSbF_6$	1 : 4

The hydration of alkynes using an Au^I-containing catalyst was described by Tanaka and co-workers [401] in 2002. The reaction was catalyzed by the complex $(Ph_3P)AuMe$ combined with different acids (H_2SO_4, CF_3SO_3H, $H_3PW_{12}O_{40}$), which react to form the Ph_3PAu^+ cation and to give off methane.[68] In aqueous methanol, the reactions of terminal and internal alkynes afford products in yields from moderate to high (53% – 99%) with high TOF (3500 – 15 600 h^{-1}). However, the reaction is not regioselective. In some cases, the hydration of terminal alkynes, as well as internal alkynes, gives considerable amounts of anti-Markovnikov addition products.

The hydration of alkynes was performed using catalysts based on Au^I (see Refs 73, 110, 111, 186, 408 – 410), Au^{III}

(see Refs. 157, 165, 406, 411) and Au^{I} combined with an acid,[68, 401, 412 – 414] the bimetallic $Au^{I}-Ag^{I}$ system[83] and gold nanoparticles.[415] Compared to gold(III), gold(I) exhibits its catalytic activity towards a wider range of substrates at lower loadings.[416] The mechanism proposed[417] for the double activation involves the formation of *gem*-diaurated intermediates. It was noted that protic solvents play a key role in the energy profile of this reaction.[418, 419] In recent years, it was reported[418, 420, 421] that the regioselectivity of reactions with internal alkynes can be substantially improved under carefully developed conditions. Of particular interest are studies by Nolan and co-workers,[110, 111] who used gold carbene complexes for the efficient and selective hydration of alkynes. These catalysts not only give higher regioselectivity but also can be used at lower loadings. Stable gold carbene complexes substantially improve the efficiency of the catalytic process because the reaction is not accompanied by the decomposition of the gold-containing catalyst giving catalytically inactive elemental gold.

The gold-catalyzed hydration of alkynes affording carbonyl compounds is of great practical value.[421, 422] This reaction is described in several reviews[13, 420, 423] and is applied to synthesize natural products.[424 – 426] The hydration of alkynes catalyzed by gold-containing catalysts has attracted considerable attention of chemists primarily due to mild reaction conditions.[69, 427]

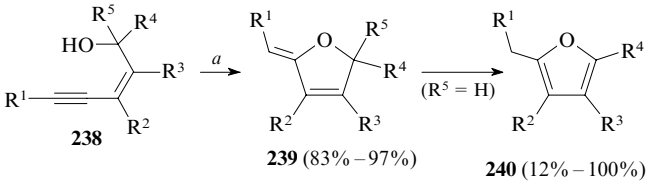
Like hydroamination, the reaction with oxygen-containing nucleophiles can proceed in both an intermolecular and intramolecular fashion. In the latter case, the entropy factor favours the reaction that gives oxygen-containing heterocycles. We begin our consideration of this issue with this type of reactions.

V.1. Intramolecular reactions

V.1.a. Addition of an alcoholic hydroxy group

An example of this type of reactions is the transformation of (*Z*)-3-ethynylallyl alcohols **238** into furan **240** (Scheme 90).[151, 428] The reaction is catalyzed by Au^{I} and Au^{III} in different solvents (acetonitrile, dichloromethane and THF). The geometry of the double bond in the product corresponds to *anti*-oxyauration. The cyclization in the I_2 – base system gives a product with inverse geometry of the double bond.[429]

Scheme 90

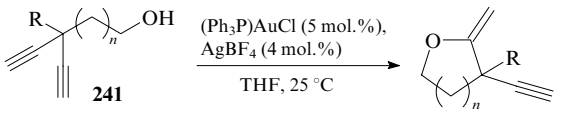


(*a*) [Au] (0.1 mol.% – 1 mol.%); R^1-R^5 = Alk, Ar, H

Another example of the intramolecular nucleophilic attack of the hydroxy group on the triple bond to form cyclic products **242** (Scheme 91) was described by Rüttinger *et al.*[52]

A series of cyclization reactions of di- and triols containing a triple bond to form different cyclic products were reported. For example, the double cyclization of ethynyldiol **243** afforded bicyclic ketal **244** (Scheme 92).[430]

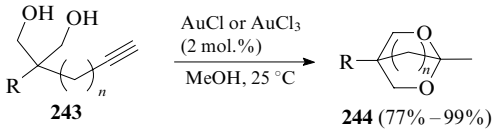
Scheme 91



242 (62% – 99%)

R = Cy, Bn, Ar; *n* = 1, 2

Scheme 92

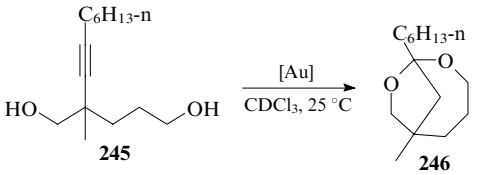


244 (77% – 99%)

R = Alk, All, Bn, Ar; *n* = 1, 2

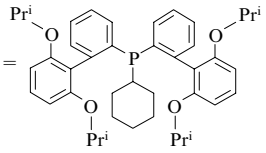
The cyclization of diol **245** proceeds in the presence of AuCl (2 mol.%) over 0.2 h.[431] The use of aryl-substituted phosphine **L3** as the ligand in the presence of $AgSbF_6$ made it possible to decrease the catalyst loading to 0.002 mol.%.[72] The reaction brings about high product yield, although the reaction time increases to 24 h (Scheme 93).

Scheme 93



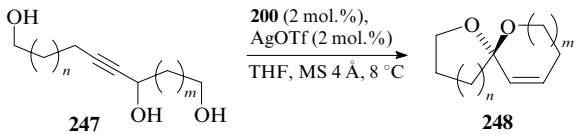
Catalyst (mol.%)	Time /h	Yield of **246** (%)
AuCl (2)	0.2	91
(**L3**)AuCl – $AgSbF_6$ – $KCTf_3$ (0.002)	24	92

L3 =



The gold-catalyzed cyclization of monopropargylic triols **247** affords spiroketals **248** containing the double bond (Scheme 94).[432] Aponick *et al.*[432] proposed two alternative mechanisms of product formation. Both mechanisms involve the formation of an active complex, in which gold is coordinated to the triple bond, as a key step followed by the nucleophilic attack of the hydroxy group.

Scheme 94

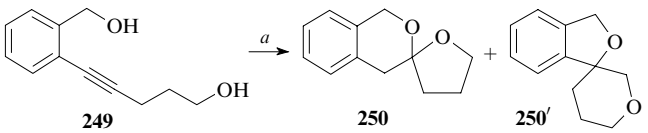


m = 0, 1; *n* = 1, 2

The intramolecular hydroalkoxylation of diol **249** was accomplished using a copper salt instead of a silver salt as the cocatalyst (Scheme 95).[358]

Jung and Floreancig[148] reported the synthesis of oxygen-containing cyclic compounds with different ring sizes (*e.g.*, compounds **252a**) starting from homopropargyl ethers

Scheme 95

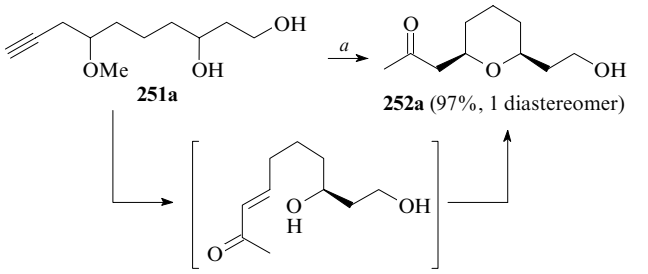


(63% yield, 1.5 : 1)

(*a*) **200** (0.1 mol.%), $Cu(OTf)_2$ (1 mol.%), PhMe, 24 h

(*e.g.*, **251a**) in the presence of a Au^I complex as the catalyst (Scheme 96). The procedure proposed by the authors of the cited study is operationally simple and tolerant to function-

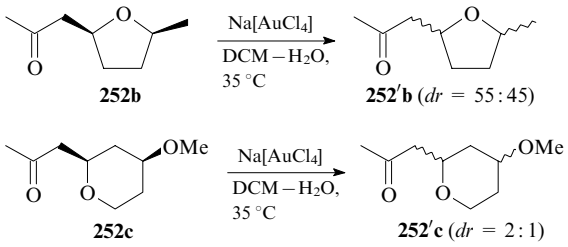
Scheme 96



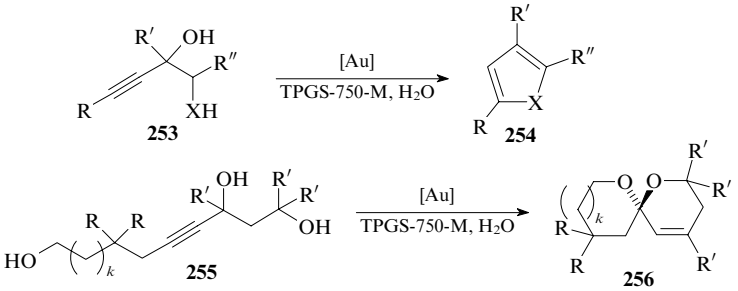
(*a*) $(Ph_3P)AuCl-AgSbF_6$, $DCM-H_2O$

ality and ambient atmosphere. The diastereoselectivity of the process is achieved due to relative stability of the products. The latter are involved as structural units in a number of natural compounds.[433] Under the reaction conditions, thermodynamically less stable diasteroemer **252** can be transformed into more stable isomer **252′** (Scheme 97).

Scheme 97



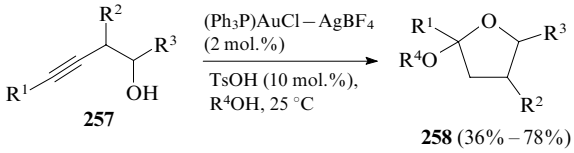
The gold-catalyzed cyclization of diols **253** and triols **255** producing hetero- and spirocycles (**254** and **256**, respectively) in an aqueous medium at room temperature under



micellar catalysis conditions was described for the first time by Lipshutz and co-workers[434] (Scheme 98). In this reaction, $AuBr_3$, AuCl, $(Ph_3P)AuCl-AgOTf$, $(Ph_3P)AuCl-AgBF_4$ and $AuBr_3-AgOTf$ were applied as gold-containing catalysts with comparable efficiency.

A combination of the intramolecular and intermolecular addition reactions (Scheme 99) was described by Belting and Krause.[435]

Scheme 99



R^1, R^3 = Ar, Alk, H; R^2 = Ar, H; R^4 = Alk

A series of control experiments showed a combination of two different catalytic cycles. The gold-catalyzed formation of dihydrofuran *via* the fast intramolecular reaction is followed by the slow acid-catalyzed intermolecular addition of alcohol. The reaction can be performed with primary and secondary (but not tertiary) alcohols in different solvents (toluene, dichloromethane, THF or diethyl ether, but not in acetonitrile). Both terminal and internal alkynes can be involved in the reaction. An additional methylene unit can be present between the triple bond and the hydroxy group (in this case, the reaction gives rise to a six-membered ring).

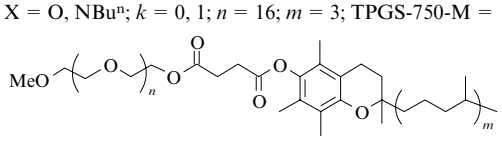
In the reactions with HXYH-type binucleophiles (*e.g.*, hydrazine, hydroxylamine), nucleophilic substitution products of propargyl alcohols **260** undergo subsequent cyclization to form heterocyclic structures **261** (*e.g.*, 2,3-dihydropyrazine, 2,3-dihydroisoxazole)[436] (Scheme 100). The system composed of $NaAuCl_4 \cdot 2H_2O$ and $FeCl_3$ as the cocatalyst exhibited the highest efficiency in this reaction. Examples of products **261** are shown in Scheme 100.[436]

Iron(III) catalyzes the nucleophilic substitution in propargyl alcohol **259**. In the presence of DMAP, Au^{III} catalyzes the subsequent nucleophilic addition to the triple bond in hydroxylamine **260**. The subsequent nucleophilic addition to the double bond in 2,3-dihydroisoxazole **261** giving disubstituted product **262** in good yield was also observed (Scheme 101).

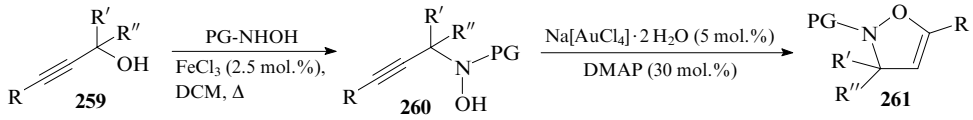
Besides, Au^I catalysts were employed in the hydroamination – cyclization reactions giving 2,5-dihydroisoxazoles[437] and in the gold(III)-catalyzed one-pot synthesis of isoxazoles from alkynes and nitric acid.[438]

It was found that the ether group of benzyl ethers **263** is an appropriate nucleophile for this type of reactions (Scheme 102).[439]

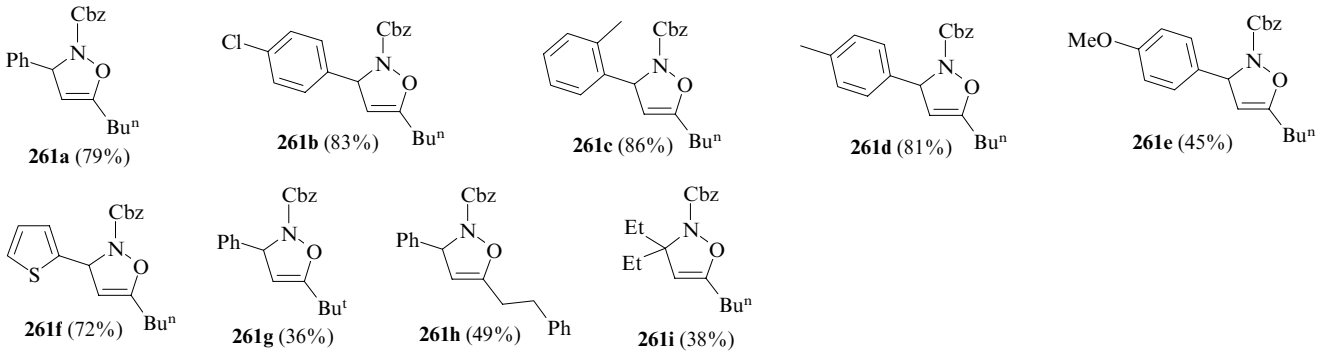
Scheme 98



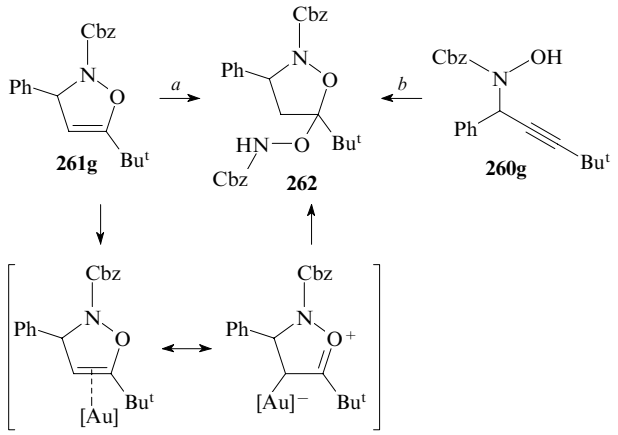
Scheme 100



PG is a protecting group, *e.g.*, Cbz; DMAP is 4-dimethylaminopyridine

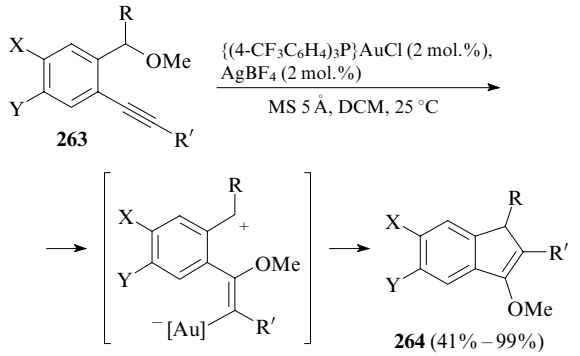


Scheme 101



(*a*) CbzNHOH (1 equiv.), $Na[AuCl_4]\cdot 2H_2O$ (10 mol.%), DCM, 25 °C (yield of **264** is 74%); (*b*) CbzNHOH (1.1 equiv.), $Na[AuCl_4]\cdot 2H_2O$ (5 mol.%), DCM, 25 °C, 2 h (81%)

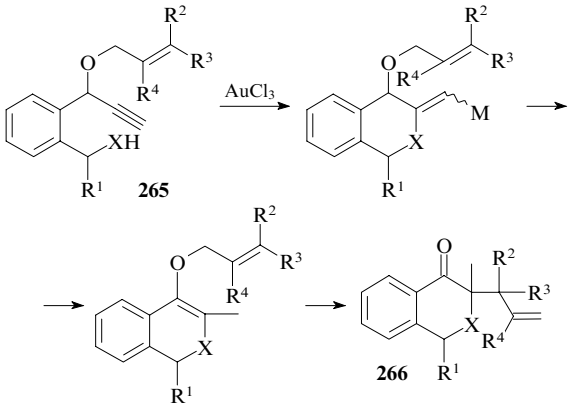
Scheme 102



X, Y = H, CF_3, OMe; R = Ar, vinyl; R′ = Alk, Ar, CO_2Me

The $AuCl_3$-catalyzed reactions produce isochromanones and isoquinolines **266** (Scheme 103) containing a quaternary carbon atom with high diastereoselectivity and in high yield (60% – 95%).[440] The alkynyl moiety may be disubstituted. This reaction proceeds *via* the tandem intramolecular *exo-dig* heterocyclization – enol isomerization – Claisen rearrangement sequence, with the attack of the nucleophile X on the gold-activated triple bond being the first step.

Scheme 103



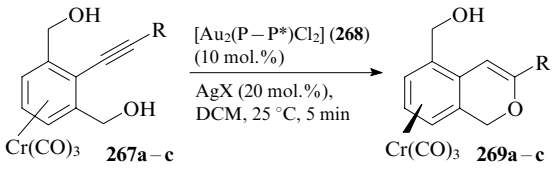
X = O, NR^5; R^1 = Et, Ph, $CH_2{=}CH$, MeO; R^2, R^3 = H, Me, Ph; R^4 = H, Me; M = Au, H

Murai *et al.*[441] demonstrated that the reaction of substrate **267** in the presence of the Au^I complex $[Au_2(P-P^*)Cl_2]$ **268** with axially chiral diphosphine (P – P*) and silver salt produces fused six-membered heterocycle **269** with high enantioselectivity (Scheme 104). The application of a system composed of $(SEGPHOS)(AuCl)_2$ and $AgBF_4$ resulted in the formation of the corresponding antipode.

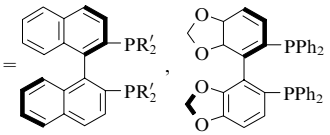
Scheme 105 displays the results of the cyclization of compound **270**, which has a chirality centre at the benzylic position. The reaction produced optically active isochromene chromium complex **271** with high enantioselectivity.

Under these conditions, the cyclization of free ligand *meso*-**272** to isochromene proceeds with low enantioselectivity and gives lower yields because of the formation of a large amount of by-products. However, under other conditions (lower temperature), the reaction affords isochro-

Scheme 104

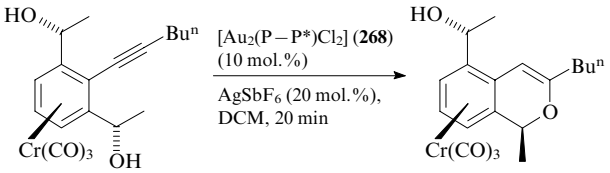


267, **269**: R = Me (**a**), Bu^n (**b**), Ph (**c**);
268: (P–P*) = (*R*)-BINAP (**a**), (*R*)-XylylBINAP (**b**), (*R*)-3,5-Me$_2$-4-MeO-BINAP (**c**), (*R*)-SEGPHOS (**d**);
X = BF_4, NTf_2, OTf, SbF_6;

(P–P*) = 

R′ = Ph [(*R*)-BINAP], 3,5-Me$_2$C$_6$H$_3$ [(*R*)-XylylBINAP], 3,5-Me$_2$-4-MeOC$_6$H$_2$ [(*R*)-3,5-Me$_2$-4-MeO-BINAP]

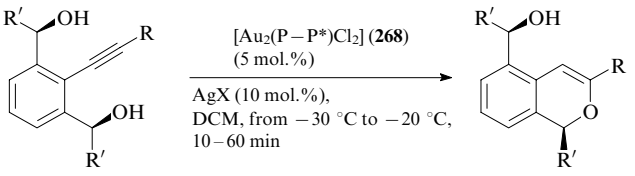
Scheme 105



Catalyst **268**	Temperature /°C	Yield of **271** (%)	*ee* (%)
a	25	24	96
b	25	43	98
	40	34	97
c	25	59	99

menes **273** in high yields and with excellent stereoselectivity (Scheme 106).[442]

Scheme 106

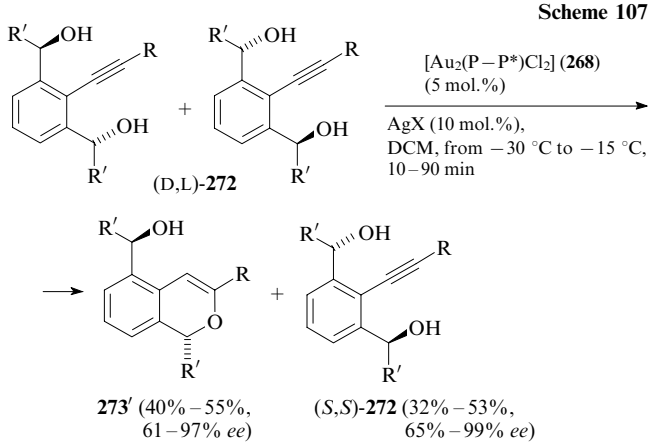


R = Me, Bu^n, Ph; R′ = Me, Pr^i, Ph, Bn; X = NTf_2, OTf, SbF_6, BF_4

This reaction can be used for the kinetic resolution of a racemic mixture of diastereomers (D,L)-**272** (Scheme 107).[442]

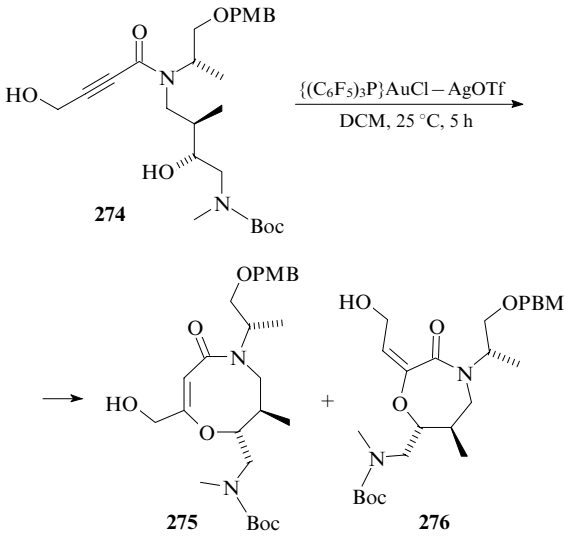
The gold-catalyzed intramolecular hydroalkoxylation reactions were successfully applied to prepare different heterocyclic compounds,[435, 443, 444] including natural[424] and biologically active substances.[425] For example, oxazocenone **275** pharmacologically active against type 1 diabetes was synthesized by the Au^I-catalyzed 8-*endo-dig* hydroalkoxylation[425] (Scheme 108).

Scheme 107



R = Me, Bu^n, Ph; R′ = Me, Ph, Bn; X = NTf_2, OTf

Scheme 108

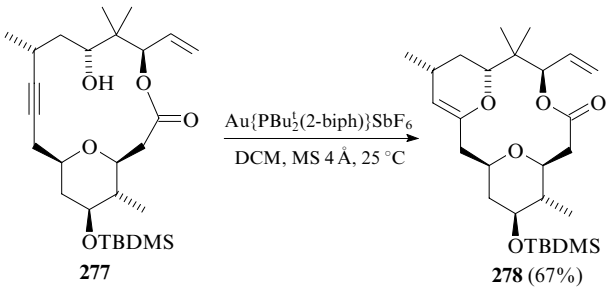


(83%, **275** : **276** = 6.2 : 1; yield of **275** is 77%)

PMB = 4-MeOC$_6$H$_4$CH$_2$

Another example of the application of gold-catalyzed intramolecular hydroalkoxylation in the synthesis of the natural product (–)-polycavernoside A was reported by Woo and Lee.[426] They described the synthesis of intermediate **278** (Scheme 109), which can be further transformed into the target product.

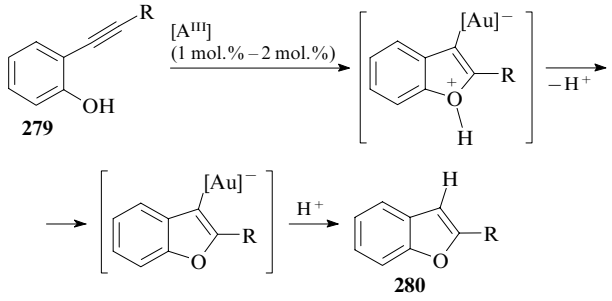
Scheme 109



V.1.b. Phenolic hydroxy group as a nucleophile

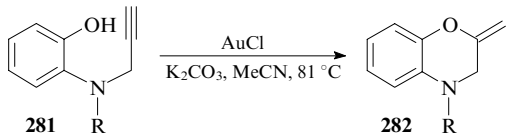
The hydroxy group in the *ortho* position with respect to the alkynyl group of arene **279** can be involved in the formation of five-membered heterocycle **280** *via* the 5-*endo-dig* cyclization (Scheme 110).[445]

Scheme 110



The intramolecular hydroxyarylation of 2-alkynylamino-substituted phenols **281** proceeds *via* the 6-*exo-dig* cyclization to form the corresponding cyclic enol ethers **282** (Scheme 111).[446]

Scheme 111

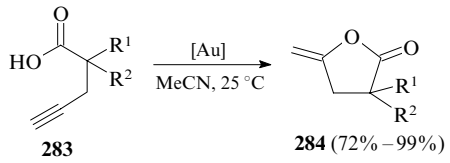


R = H (72% yield), Bz (63%), Ac (61%), Ts (91%)

V.1.c. Hydrocarboxylation of alkynes

Carboxylic acids are weak nucleophiles. The first example of the intermolecular addition of acetic acid was reported by Schmidbaur and co-workers.[412] Thus, the reaction of acetic acid with hex-3-yne produced, apart from enol ether, hexan-3-one due to the presence of traces of water. The intramolecular hydrocarboxylation to form lactones **284** was described in several publications.[447–450] This reaction was catalyzed by AuCl, as well as by $AuCl_3$ or Au_2O_3. A substantially lower catalyst loading is required when using the sterically hindered phosphine ligand **L3** (see Scheme 93) containing an electron-donating substituent, the high yield of the product being retained (Scheme 112).[72]

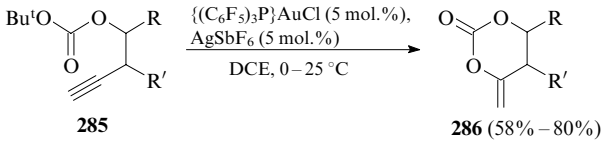
Scheme 112



R^1 = H, CO_2R, CH_2OBn, Ph; R^2 = H, Alk, All, Bn, $HC{\equiv}CCH_2$, Cl, vinyl, Ar; [Au] = AuCl (5 mol.%), or Au_2O_3 (0.5 mol.%), or (**L3**)AuCl–AgOTf–$KCTf_3$ (0.01 mol.%)

The AuCl–K_2CO_3 system in MeCN was used[451] to synthesize five-, six- and even seven-membered lactones. Bromoalkynes react stereoselectively to form *Z*-diastereomers. Shin and Kang[452,453] demonstrated that appropriate *tert*-butyl esters **285** can be utilized instead of free carboxylic acids (Scheme 113).

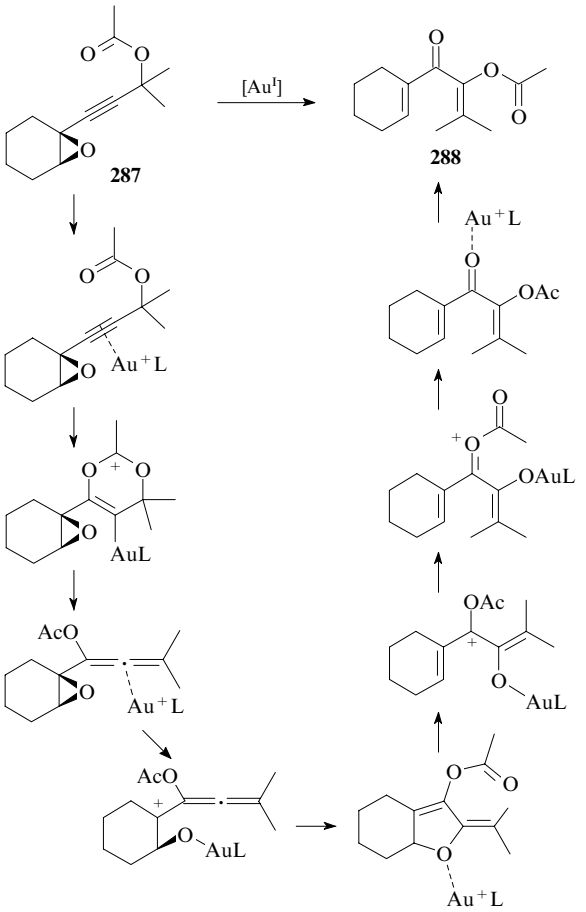
Scheme 113



R = Alk, Ar; R′ = H, Alk

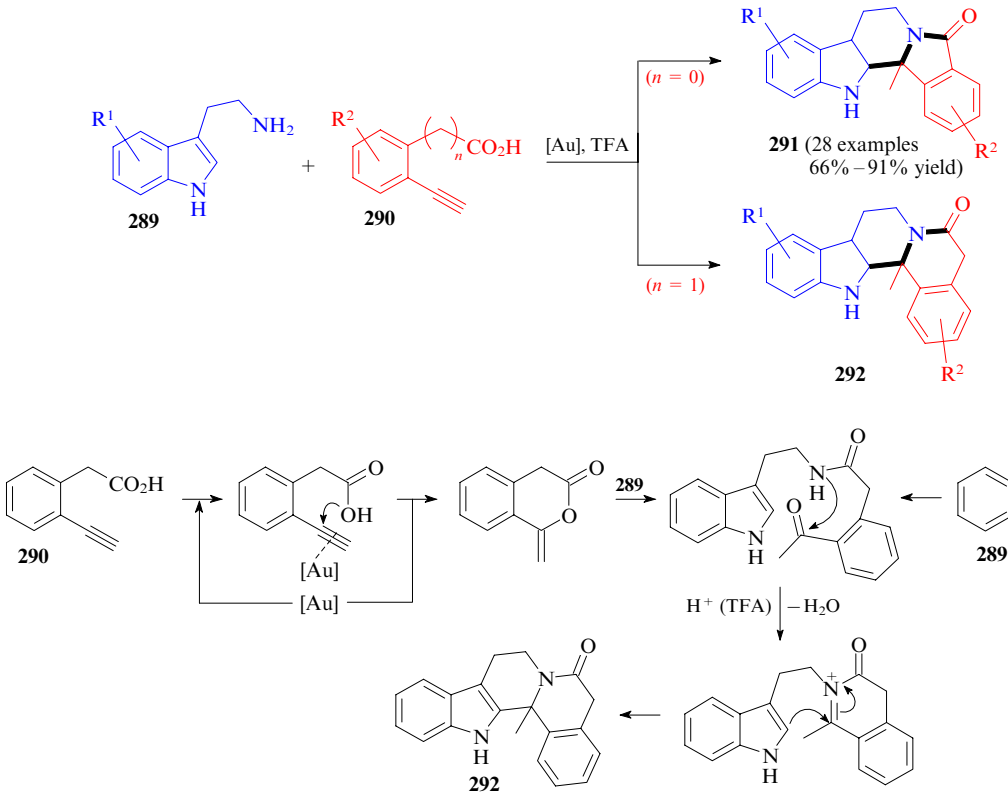
Three competitive alternative mechanisms of the transformation of substrate **287** into product **288** were considered by González-Pérez *et al.*[454] The most favourable mechanism was shown to involve a cascade of nine steps (Scheme 114). All functional groups in the substrate and the lone pair of the epoxide oxygen atom play an important synergistic role in the successive coordination of gold to both π systems of the substrate. Scheme 114 displays the mechanism of this transformation, which was proposed based on the activation free energies calculated at the B3LYP/6-31G(d)-LANL2DZ level of theory.

Scheme 114



The one-pot cascade reaction, which involves the gold-catalyzed addition of an oxygen atom to the triple bond as the key step, was applied to synthesize polycyclic structures **291** and **292** based on substituted tryptamines **289** (Scheme 115).[455] This scheme also shows the reaction mechanism proposed by the authors. The process involves the one-pot formation of one C–C bond and two C–N bonds without the isolation of intermediates. The reaction was

Scheme 115

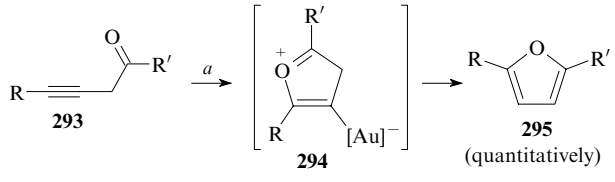


found to be tolerant to a wide range of substituents and can be used to synthesize target products in high yields.

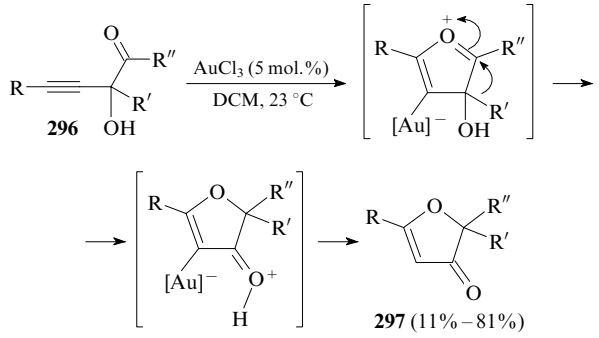
V.1.d. Ketones as nucleophiles

Hashmi *et al.*[151] found that Au^{III}, unlike Pd^{II}, triggers the cycloisomerization of propargyl ketone **293** *via* the initial nucleophilic attack of the carbonyl group followed by the aromatization of ion **294** to furan **295** (Scheme 116). Kirsch and co-workers[456] performed a similar reaction with α-hydroxypropargyl ketone **296** to prepare 3(2*H*)-furanones **297** (see Scheme 116).

Scheme 116



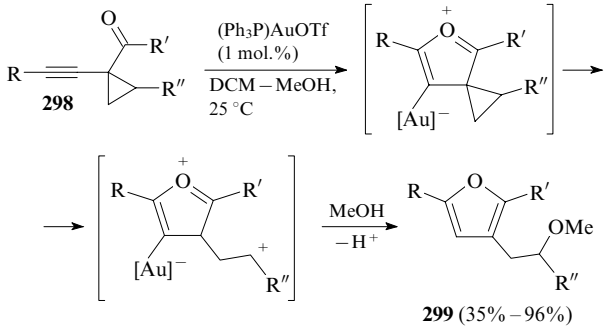
(*a*) $AuCl_3$ (0.1 mol.%), MeCN, 25 °C; R, R′ = Alk



R, R′ = Alk; R″ = Alk, Ar

Zhang and Schmalz[457] applied this procedure to synthesize polysubstituted furans **299** from alkynylcyclopropanones **298** (Scheme 117).

Scheme 117

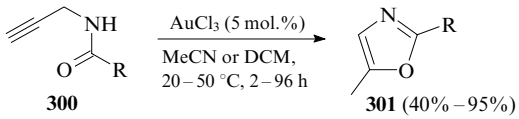


R = H, Alk, vinyl, Ar, $SiMe_3$; R′ = Alk, Ar; R″ = Alk, Ar, OAlk

V.1.e. Amide oxygen atom as a nucleophile

2,5-Disubstituted oxazoles **301** were synthesized from appropriate acylated propargylamines **300** under mild reaction conditions *via* homogeneous catalysis by $AuCl_3$ (Scheme 118).[458]

Scheme 118



R = Me, Ph, 1-Ad, 2-furyl, 2,5-dimethylfuran-3-yl, HC═CHPh, $(CH_2)_2CO_2Me$

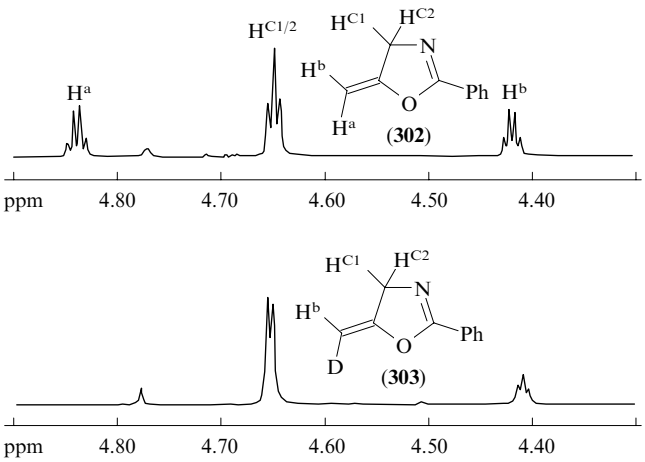
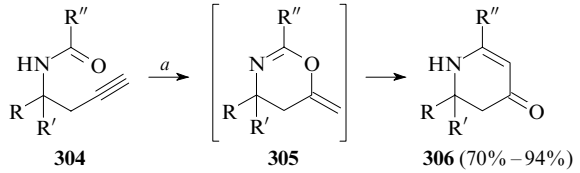


Figure 3. Fragments of the ^{1}H NMR spectra of the reaction mixture, which show the formation of intermediate **302** (**303**).[458]

The reaction proceeds through the formation of intermediate **302** (**303** in the reaction with the deuterated analogue), as shown in Fig. 3.

Spanish chemists[459] developed a method for the synthesis of 2,3-dihydropyridin-4(1*H*)-ones **306** from appropriate amides **304** containing the propargyl group through the cyclization consisting of the nucleophilic addition of the amide oxygen atom to the triple bond followed by the Petasis – Ferrier rearrangement (Scheme 119). Both reactions are catalyzed by the same catalyst under identical conditions. Gold successively behaves as a soft π-Lewis acid and a hard σ-Lewis acid. The 2,3-dihydropyridin-4(1*H*)-one moiety is present in intermediates for the synthesis of a number of piperidine, indolizine and quinolizidine alkaloids.[460 – 463]

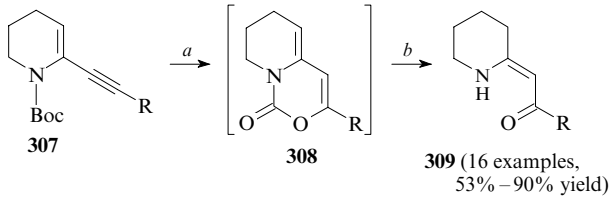
Scheme 119



(*a*) $(Ph_3P)AuCl$ (5 mol.%), AgOTf (5 mol.%), MeOH, 25 °C, 4 h;
R = CF_3, CF_2Ph, CF_2Bn, $CF_2CH_2CH{=}CH_2$, Ph;
R′ = CO_2Et, Ph; R″ = Me, Et

The gold(I)-catalyzed cyclization of N-Boc-protected 6-alkynyl-1,2,3,4-tetrahydropyridines **307** affords conjugated amides (vinylogous amides) **309** (Scheme 120), which are intermediates in the synthesis of natural compounds.[464]

Scheme 120

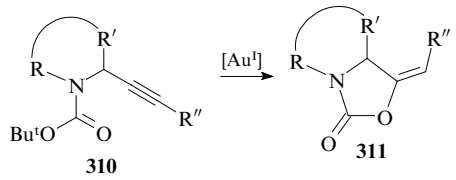


(*a*) $(Ph_3P)AuOTf$ (2 mol.%), PhMe, Δ, 20 – 60 min;
(*b*) KOH, Bu^{t}OH, 85 °C, 1 h; R = Alk, cyclo-Alk, Ar, *etc.*

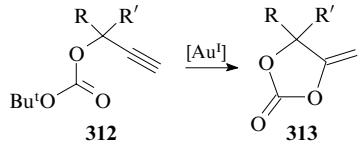
The complex $(Ph_3P)AuOTf$ served as the catalyst. The reaction proceeds through the 6-*endo-dig* cyclization to form the Au vinyl complex, which is subjected to protodeauration to give cyclic carbamate intermediate **308**. The latter is quantitatively transformed, without isolation, into conjugated amide **309** upon the addition of a base. 2-Alkynylphenylcarbonyl derivatives also undergo 6-*endo-dig* cyclization, which was observed in the synthesis of isocoumarins.[198, 465 – 468]

The cycloisomerization of N-Boc-protected propargylamines **310** to oxazolidinones **311**,[468 – 471] as well as the cyclization of propargyl carbonates **312** (Refs 452, 472, 473) proceed through the 5-*exo-dig* cyclization (Scheme 121).

Scheme 121



R – R′ closes a saturated or unsaturated ring

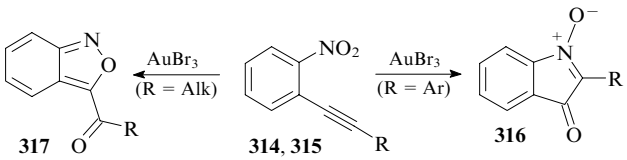


R = H, Alk, Bn; R′ = H, Alk

V.1.f. Nitro group oxygen atom as a nucleophile

Yamamoto and co-workers[196] synthesized isatogens (2-substituted 3*H*-indol-3-one *N*-oxides) **316** and anthranils **317** in good to high yields by the cyclization of *o*-(arylalkynyl)nitrobenzenes **314** and *o*-(alkylalkynyl)nitrobenzenes **315**, respectively (Scheme 122).

Scheme 122



[R = Pr^n (52%),
Bu^t (83%)]

[R = Ph (81%),
2-Py (86%)]

R = Ar (**314**), Alk (**315**)

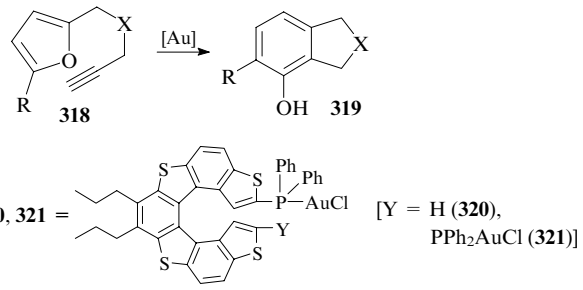
The cyclization of *o*-(arylalkynyl)nitrobenzenes **314** is accompanied by the formation of a small amount of anthranils **317**. The cyclization of *o*-(alkylalkynyl)nitrobenzenes **315** proceeds selectively.

V.1.g. Heterocyclic oxygen atom as a nucleophile

The gold-catalyzed synthesis of phenols **319** was shown to be accompanied by the intramolecular oxygen migration (Scheme 123).[445] This transformation is catalyzed also by some other transition metals with d^8 configuration. How-

ever, gold is the most active one and its use allows the synthesis of the target product with high purity.

Scheme 123

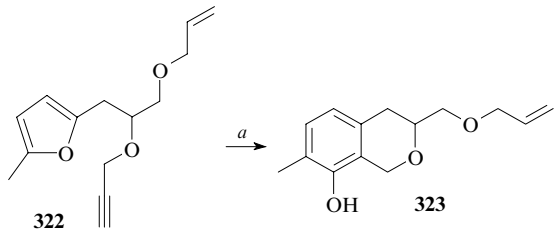


R	X	Reaction conditions	Yield of **319** (%)	Ref.
Me	NTs	$AuCl_3$ (2 mol.%), MeCN	92	445
2-ClC_6H_4	NTs	$AuCl_3$ (2 mol.%), MeCN	84	445
Me	O	**320** (0.25 mol.%), $AgNTf_2$ (0.25 mol.%)	18	474
Me	O	**321** (0.25 mol.%), $AgNTf_2$ (0.25 mol.%)	4	474
Me	O	**321** (2 mol.%), $AgNTf_2$ (2 mol.%)	23	475
Me	O	aNHC – Au^I (0.25 mol.%), $AgNTf_2$ (0.25 mol.%), CD_2Cl_2, rt	63 – 78	75
Me	NTs	Au/CeO_2 (1.8 mol.%), CD_3CN, 60 °C	100	475

The reaction was carried out in the presence of different gold-based catalysts, which exhibited different efficiency. Gold(III) catalysts proved to be much more active than Au^I-based catalysts. For example, phenol was synthesized in 84% – 92% yield by the reaction catalyzed by $AuCl_3$ (2 mol.%), whereas complexes **320** and **321** were inefficient.[474] Gold(I) complexes with saturated abnormal NHC ligands exhibited good efficiency in this reaction; the TON values were up to 252 – 380.

The reaction can proceed stereoselectively with retention of configuration of the stereocentre in the position adjacent to the group X.[476] If the alkynyl ether chain of the substrate contains an additional methylene unit (substrate **322**), the reaction produces bicyclic system **323** composed of two six-membered rings (Scheme 124).[75]

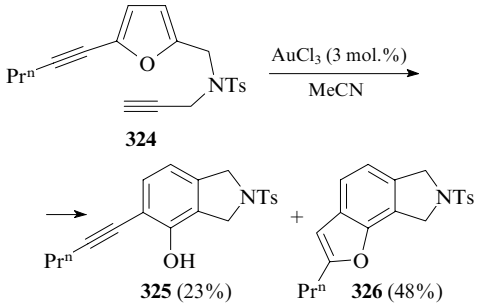
Scheme 124



(*a*) aNHC – Au^I (0.25 mol.%), $AgNTf_2$ (0.25 mol.%), DCM, 25 °C, 0.5 – 8 h (conversion > 95%)

If the substrate contains a second alkynyl substituent (substrate **324**), the second ring closure can take place under the reaction conditions to form doubly annulated arene **326** (Scheme 125).[474]

Scheme 125



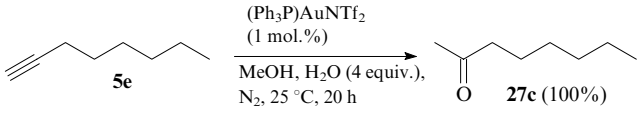
Hashmi and co-workers[475] compared the homogeneous and heterogeneous gold catalysis of the cyclization of ω-alkynylfurans to phenols. Gold nanoparticles supported on CeO_2 (Au/CeO_2) displayed high activity, phenol being produced in a yield of up to 100% (see Scheme 123). Since leaching of gold was observed in $CDCl_3$, CD_3CN was used as the solvent to maintain the heterogeneity of the system. In the latter case, an analysis revealed the presence of 0.0025 mol.% gold in solution. Taking into account that the TON value for the heterogeneous gold-catalyzed reaction was similar to TON for the homogeneous gold-catalyzed reaction,[477] it was hypothesized that Au^I species that are formed on the surface of gold nanoparticles serve as active species in the heterogeneous catalysis as well.

V.2. Intermolecular reactions

V.2.a. Hydration

In 2009, Leyva and Corma[73] published a work devoted to the hydration of alkynes **5** of different nature at room temperature. The reactions were performed using various catalysts in different solvents, and the optimal conditions for the hydration of alkynes were found in relation to model oct-1-yne (**5e**) (Scheme 126).

Scheme 126

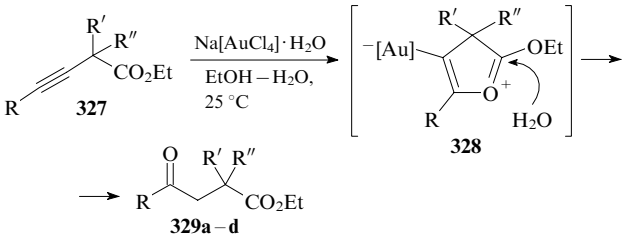


Good results (the yield of the product was 76% – 90%) were also obtained in the reactions performed in THF in the presence of 1 equiv. of water using $(Ph_3P)AuOTf$, $(Bu^t_3P)AuOTf$ or $(Ph_3P)AuNTf_2$ as the catalyst. It was found[73] that water-miscible solvents, as expected, are more efficient in this reaction because they allow for an increase in the concentration of water in the reaction mixture, which was observed in the series dichloromethane – THF – methanol. However, the use of methanol homologues — ethanol and isopropyl alcohol — led to a decrease in the yield of ketone due to the formation of ketals. The application of sterically hindered donor phosphines as ligands enhances the catalytic activity of gold. Weakly-coordinating counterions have a similar effect; however, the presence of $[B(C_6F_5)_4]^-$ inhibits the reaction.

As mentioned above, the pathway of the hydration of internal alkynes substantially depends on the nature of the catalyst. It is also influenced by the substituents in the substrate molecule. For example, the ester group in the α position with respect to the triple bond is responsible for the selective formation of the hydration product, which is

attributed to the initial attack of the ester group on the triple bond under the reaction conditions to form cyclic intermediate **328** *via* the 5-*endo-dig* cyclization.[478] The hydrolysis of this oxonium ion and protodeauration afford γ-keto ester **329** (Scheme 127).

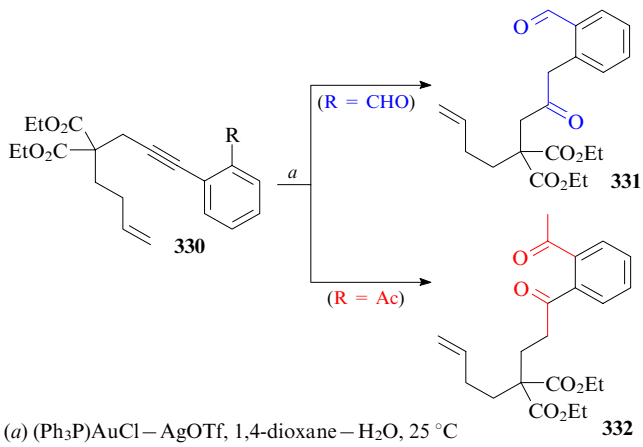
Scheme 127



Compound **329**	R	R′	R″	Yield (%)
a	Ph	Me	All	58
b	Me	Me	$(CH_2)_2CO_2Me$	80
c	n-C_6H_{13}	H	H	74
d	n-C_6H_{13}	Me	Et	78

A similar situation is observed in the hydration of substrate **330** (Scheme 128).[479] The 6-*endo-dig* cyclization of *o*-alkynylaryl aldehyde **330** (R = CHO) results in the selective formation of product **331**. In the presence of the acetyl group instead of the aldehyde moiety, the selective formation of product **332** takes place. This fact is attributed to a change in the reaction mechanism. The latter reaction proceeds *via* the 5-*exo-dig* cyclization to give a cyclic intermediate. The latter is hydrolyzed to form regioisomer **332**. In the absence of a directing group in the substrate, the reaction does not take place under the conditions presented in Scheme 128.

Scheme 128



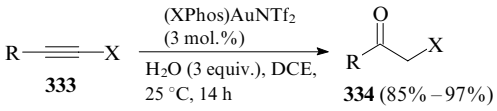
(*a*) $(Ph_3P)AuCl - AgOTf$, 1,4-dioxane – H_2O, 25 °C

R	Yield (%)	Product
CHO	87	**331**
Ac	85	**332**
H	0	–

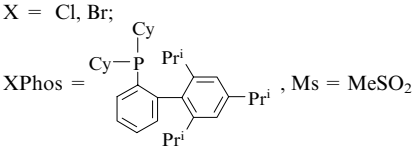
More examples of the regioselective hydration of internal alkynes can be found, in particular, in the review by Goodwin and Aponick.[420]

The hydration of 2-substituted haloalkynes **333** catalyzed by $(XPhos)AuNTf_2$ produces α-halomethyl ketones

Scheme 129



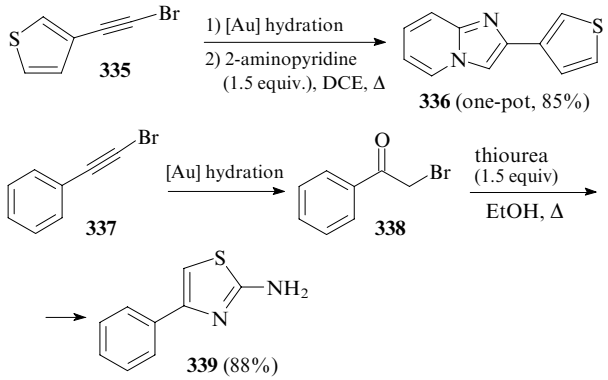
R = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-$Bu^tC_6H_4$, 4-$MeOC_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4, $PhCH_2CH_2$, 3-Th, n-$C_{10}H_{21}$, n-C_8H_{17}, $Z(CH_2)_4$ (Z = AcO, BnO, BzO, MsO, BzNH, NPhth, Cl, Br, TsO), Cy, cyclohex-1-enyl;
X = Cl, Br;



334 in high yields under mild conditions (Scheme 129).[480] The nature of the substituents R in haloalkynes can be varied in a wide range without a substantial effect on the yield of the target product.

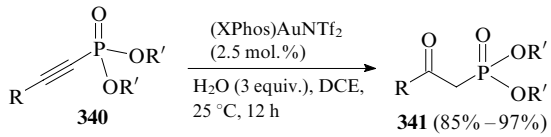
α-Halomethyl ketones **334** are important intermediates in the synthesis of a number of heterocyclic compounds.[481] A modification[480] of this reaction allows the one-pot or stepwise synthesis of heterocyclic compounds, *e.g.*, products **336** and **339**, in high yield (Scheme 130).

Scheme 130



Another example of the hydration of alkynes containing a heteroatom substituent in the α position was reported by Xie *et al.*[482] The authors proposed a simple and efficient method for the regioselective hydration of alkynylphosphonates **340** using the cationic gold(I) catalyst (Scheme 131). The reaction proceeds under mild conditions, thus making it possible to employ substrates containing different functional groups and prepare target products in high yield.

Scheme 131



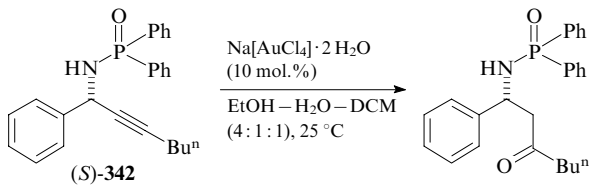
R = Ar, Alk, cyclo-Alk; R′ = Et, Pr^i, Bu^n, Bn

The resulting β-ketophosphonates **341** and their derivatives exhibit a wide range of biological activity,[483] can be used as complex-forming agents for different metals[484] and are intermediates in organic synthesis.[485]

The gold(III)-catalyzed regiosepecific hydration of *N*-(diphenylphosphinoyl)propargylamine **342** produces

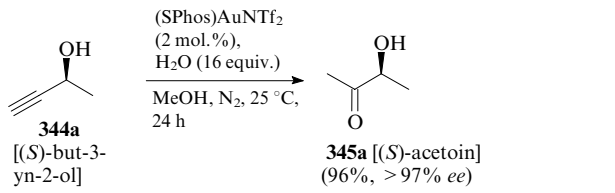
β-aminoketone **343** with retention of chirality (Scheme 132).[486]

Scheme 132



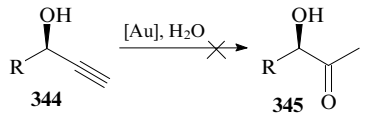
α-Hydroxymethyl ketones **345** play an important role in modern medicinal chemistry,[487,488] particularly in the synthesis of chiral molecules containing an asymmetric centre at the carbon atom bound to the hydroxy group. These ketones can be prepared from chiral propargyl alcohols **344** or their derivatives. In 2009, Leyva and Corma[73] synthesized the (SPhos)AuNTf$_2$ catalyst (**8**) and used it to accomplish the hydration of two enantiomers of chiral propargyl alcohol **344a** under mild conditions in excellent yields and with high enantioselectivity (Scheme 133, one enantiomer is shown as an example). Similar results were obtained for other *S*- and *R*-propargyl alcohols.

Scheme 133



In 2012, Wang *et al.*,[83] who were apparently not aware of the study of Leyva and Corma,[73] made an attempt to prepare α-hydroxymethyl ketones by the hydration of available enantiomerically pure propargyl alcohols **344** using different Au catalysts. The screening of a number of Au^{I} complexes, including TA-Au (**38**), did not reveal catalysts, in the presence of which this transformation can be performed even at 80 °C (Scheme 134).

Scheme 134

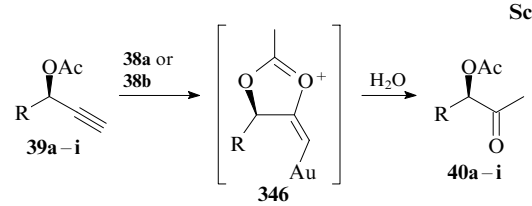


Shi and co-workers[83] knew[489] that propargyl ethers **39** with the terminal triple bond can undergo 1,2-migration. The application of the complex TA-Au (**38**) as the catalyst allowed this research team to hydrate the resulting oxonium cation **346** with retention of chirality (Scheme 135).

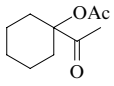
The best results were achieved with acetone as the solvent; the reaction was performed at room temperature.

It should be noted that the pathway of the transformation of 1,4-enyne **347** depends on the nature of the catalyst (Scheme 136). In the presence of the (Ph$_3$P)AuCl – AgSbF$_6$ (2 mol.%) system, the reaction produces cyclopentenone **348** through the carbene-like intermediate.[489] The use of complex **38a** (1 mol.%) as the catalyst dramatically changes the reaction pathway, resulting in the formation of product **349** in excellent yield.

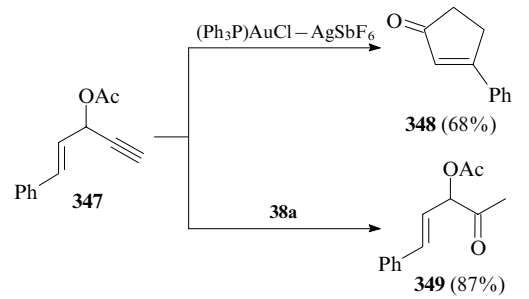
Scheme 135



Compound **40**	R	Yield (%)	Compound **40**	R	Yield (%)
a	Ph	96	**e**	See [a]	93
b	3-$O_2NC_6H_4$	98	**f**	4-FC_6H_4	90
c	Bn	94	**g**	4-$MeOC_6H_4$	95
d	Pr^n	91	**h**	4-$MeO_2CC_6H_4$	93
			i	4-ClC_6H_4	91

[a] **40e** = 

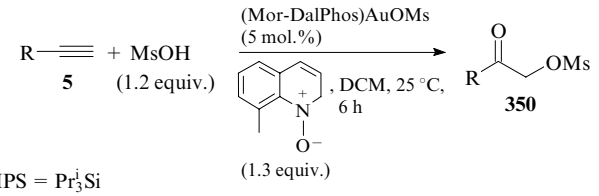
Scheme 136



Other propargyl ethers were transformed into products of type **348** in the presence of the (Ph$_3$P)AuCl – AgSbF$_6$ system as the catalyst.[186]

Zhang and co-workers[481] proposed a new approach to the synthesis of methanesulfonyloxymethyl ketones **350** containing a good leaving group in the α position with respect to the oxo group *via* the gold-catalyzed oxidation–nucleophilic addition reactions (Scheme 137). These ketones have a high synthetic potential.[490,491]

Scheme 137



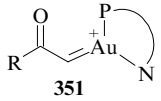
TIPS = Pr^i_3Si

R	Yield of **350** (%)	R	Yield of **350** (%)
$(CH_2)_4Cl$	84	Cyclohex-1-enyl	92
Cy	79	$(CH_2)_2Ph$	75
Ph	80	cyclo-C_3H_5	88
$(CH_2)_4OTIPS$	74	$C(=CH_2)Me$	89
		$CH(OMe)(CH_2)_4Me$	70

The reaction is characterized by high regioselectivity and proceeds through the formation of gold α-oxocarbene complexes **351** stabilized by the bidentate P,N-ligand Mor-

DalPhos (see complex **202**).[492, 493] Complexes **351** exhibit high electrophilic activity and can react even with weak nucleophiles, such as carboxamides,[492] carboxylic acids[493] and thioamides.[481]

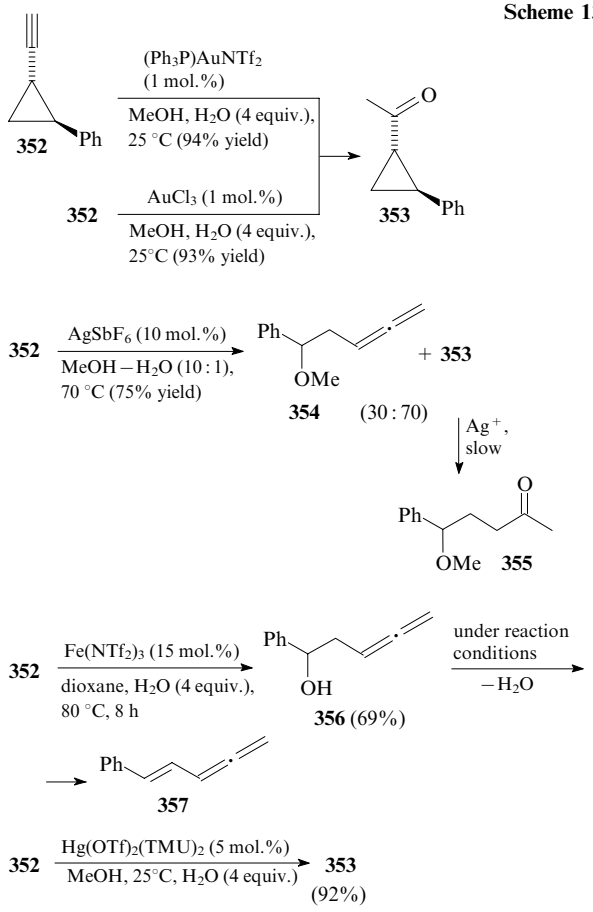
Structures 351



351

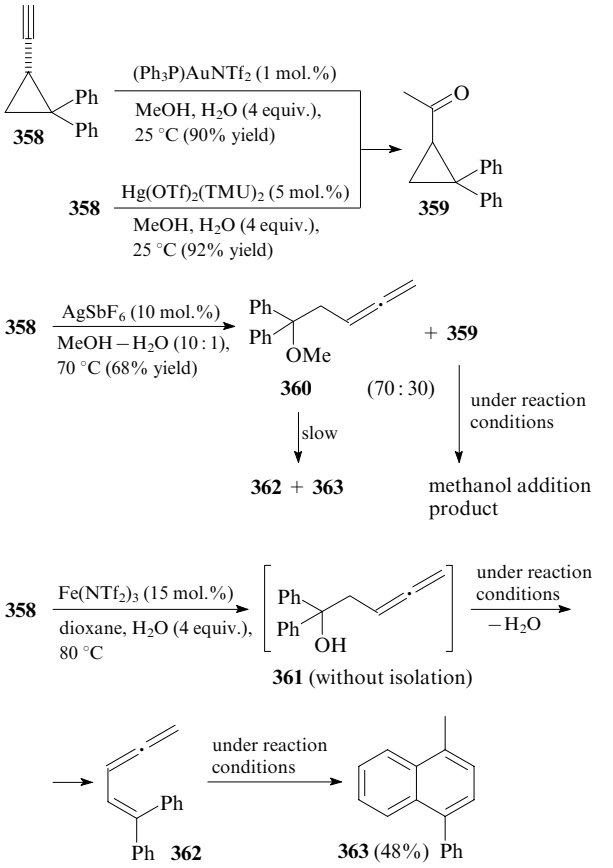
The hydration of cyclopropylalkyne **352** affords different products in the presence of different catalysts.[494] Under gold catalysis conditions, substrate **352** is quantitatively transformed into methyl ketone **353**. No rearrangement products were detected. Different products (**354** – **357**) were synthesized using the $AgSbF_6$ or $Fe(NTf_2)_3$ catalyst (Scheme 138). Similar results were obtained with diphenyl-substituted substrate **358** (Scheme 139).

Scheme 138



TMU is tetramethylurea

Scheme 139

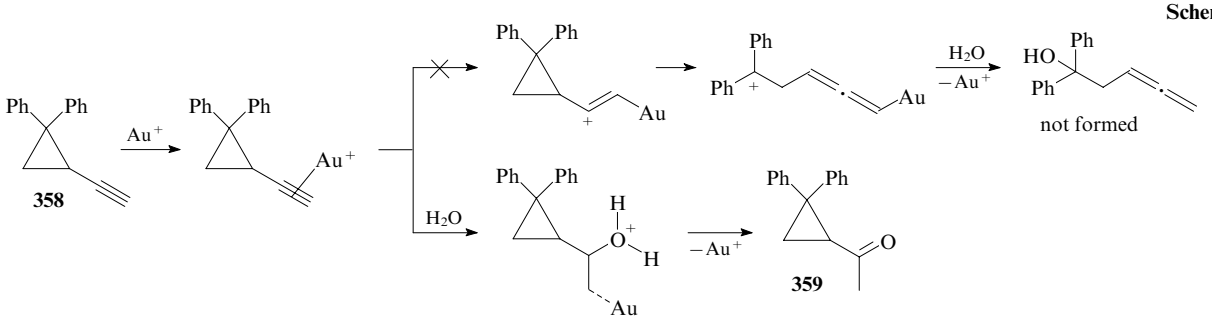


The absence of by-products in the gold-catalyzed reaction is in sharp contrast to the results of the reactions catalyzed by Brønsted acids.[495] Velegraki and Stratakis[494] attributed this fact to a much stronger coordination of the gold ion by the triple bond, which does not give rise to a carbocation, thus preventing the formation of the corresponding rearrangement products (Scheme 140).

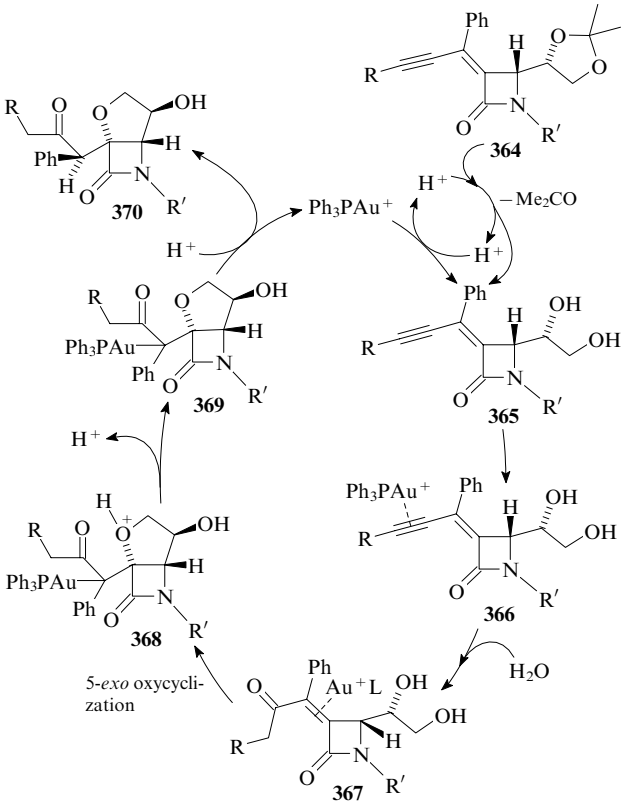
Substrate **364** can be transformed into bicyclic compound **370** *via* the successive hydration of the triple bond and *5-exo* oxycyclization of gold-activated alkene (Scheme 141).[496]

Catalyst **17** (NHC = IPr; X = SbF_6, NTf_2) taken in an amount of 0.01 mol.% – 0.1 mol.% exhibits high activity[82] in the absence of silver as the cocatalyst. The reaction is performed in methanol – water or 1,4-dioxane – water systems (2 : 1 in both cases, Scheme 142).

Scheme 140

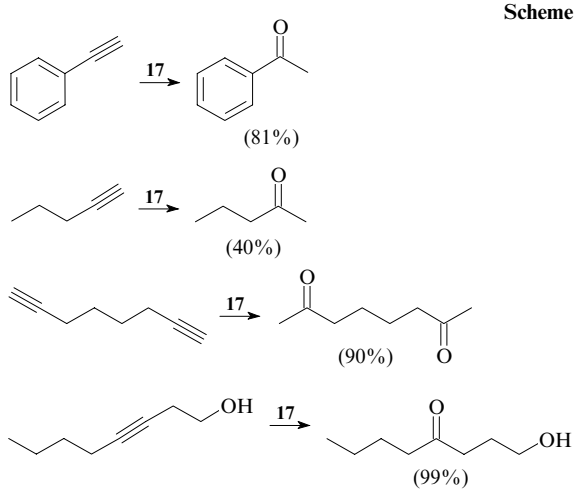


Scheme 141



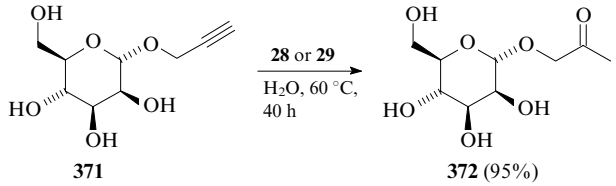
R = H, D, Hal; R′ = PMP, Bn; L = PPh_3

Scheme 142



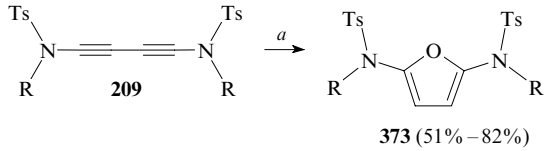
The hydration of labile substrates (*e.g.*, mannose derivative **371**) can be performed in water in the absence of acid and silver salts using complex **28**(**29**) as the catalyst to prepare the reaction product in good yield with high regioselectivity (Scheme 143).[173]

Scheme 143



When using the alkadiyne system, the nucleophile that initially adds to one of the triple bonds can interact with the second triple bond of the molecule to form a cyclic structure. For example, the Au^I-catalyzed hydration of diamino derivatives of 1,3-diynes **209** affords 2,5-diamidofurans **373** (Scheme 144).[365]

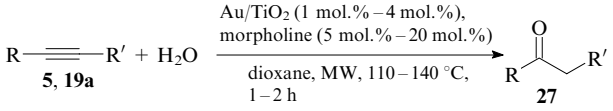
Scheme 144

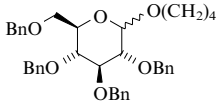


(*a*) $(Ph_3P)AuNTf_2$ (2 mol.%), H_2O (1.4 equiv.), THF, 60 °C, 45 min; R = Pr^i, Ph, Bn

The intermolecular hydration of alkynes **5** and **19a** is catalyzed by gold nanoparticles supported on TiO_2 in the presence of morpholine as a basic cocatalyst (Scheme 145).[415] This catalyst can be reused (it can be easily isolated by the filtration); besides, this catalyst can be applied in a flow reactor. The reaction proved to be particularly useful with substrates containing groups labile under acidic conditions. The pH value of the reaction mixture remains at 8 – 9, which accounts for the fact that the reaction is successfully performed with substrates labile in an acidic medium. It is interesting that the addition of morpholine to the reaction mixture used for the hydration of phenylacetylene in the presence of a homogeneous catalyst leads to deactivation of the latter[194, 258] and the termination of the reaction (Scheme 146).

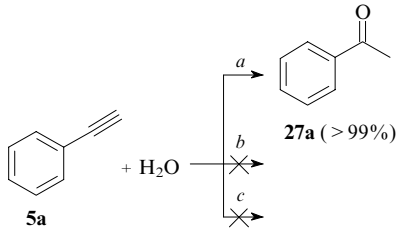
Scheme 145



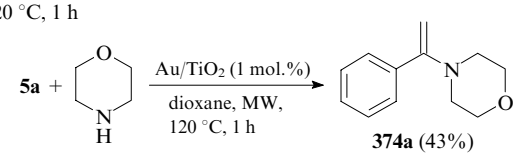
R	R′	Yield of **27** (%)	R	R′	Yield of **27** (%)
Ph	H	87	$AllO(CH_2)_4$	H	92
4-$MeOC_6H_4$	H	89	$THPO(CH_2)_4$	H	90
4-FC_6H_4	H	80	$(MeO)_2CH(CH_2)_8$	H	88
2-MeC_6H_4	H	90			
n^z6H_{13}	H	92			
$Ph(CH_2)_3$	H	90		H	91
$NC(CH_2)_3$	H	76			
$BzO(CH_2)_4$	H	84			
$TIPSO(CH_2)_4$	H	97	Cyclohex-1-enyl	H	89
$TBDMSO(CH_2)_4$	H	95	2-Pyridyl	H	75
$TBDPSO(CH_2)_4$	H	93	Ph	Ph	80
$Ph_3CO(CH_2)_4$	H	89	4-(CH≡C)C_6H_4	H	65[a]

Note. TBDPS = Bu^tPh_2Si, THP is tetrahydropyran-2-yl. [a] The yield of the double hydration product is given.

Scheme 146



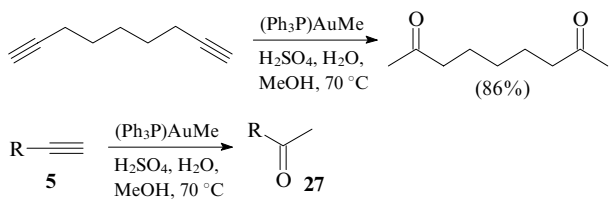
(*a*) $(Ph_3P)AuNTf_2$ (1 mol.%), MeOH, 25 °C, 24 h;
(*b*) $(Ph_3P)AuNTf_2$ (1 mol.%), morpholine (5 mol.%), MeOH, 25 °C, 24 h;
(*c*) $(Ph_3P)AuNTf_2$ (1 mol.%), morpholine (5 mol.%), dioxane, MW, 120 °C, 1 h



Liang *et al.*[415] hypothesized that the role of morpholine is to produce enamine intermediate **374a**,[351] the formation of which was detected under the water-free reaction conditions (see Scheme 146).

Mizushima *et al.*[497] showed that the $(Ph_3P)AuMe$ – acid system can be applied as the catalyst for the hydration of alkynes **5** to prepare methyl ketones **27** in high yields. The nature of the solvent substantially affects the reaction. Thus, methanol was found to be the solvent of choice. In this solvent, TOF is 15 600 h^{-1}. In some cases, the reaction was performed under a CO atmosphere. Under the reaction conditions, the C=C and C≡N groups of the molecule remain intact. Some examples are given in Scheme 147.

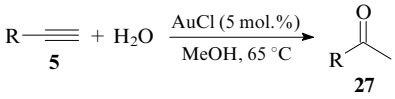
Scheme 147



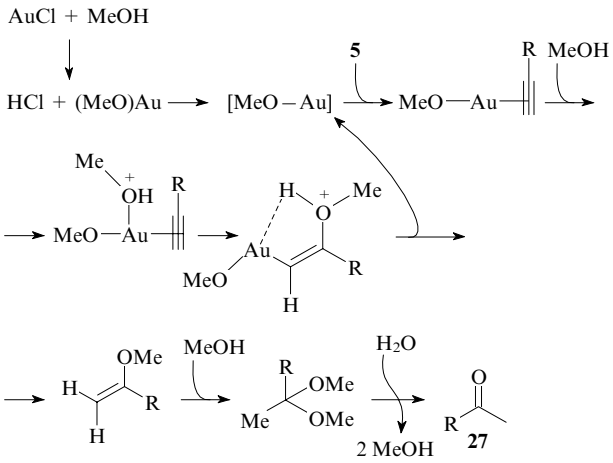
R = Bu^n (99% yield), $NC(CH_2)_3$ (83%), $Cl(CH_2)_3$ (72%), cyclohex-1-enyl (90%), Ph (98%), 2-Th (92%)

Korean researchers[416] showed that high yields can be achieved in the hydration of terminal alkynes by using AuCl as the catalyst. The nature of the solvent substantially affects the product yield. Thus, the hydration of phenylacetylene (**5a**) in methanol produces ketone **27a** in 98% yield; in water, dichloromethane and a methanol – water mixture (1 : 1), the product is not formed; in acetonitrile and THF, only traces of the product are detected; in ethanol and isopropyl alcohol, the yield of ketone **27a** is lower (88% and 72%, respectively). Based on these data and taking into account the change in the position of the signal of the methyl group of methanol in the reaction mixture, Das *et al.*[416] proposed the mechanism of hydration, in which methanol is coordinated to Au^I and is involved in the formation of a transition complex (Scheme 148). The involvement of methanol in the formation of intermediates in gold-catalyzed reactions was described by Chabanas and co-workers[68] as early as 1998.

Scheme 148



R = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$Me_2NC_6H_4$ (95% – 99% yields), 4-ClC_6H_4, 4-BrC_6H_4 (67% – 70%), Bu^n, n-C_6H_{13} (82% – 87%), $HOCH_2CH_2$ (21%)



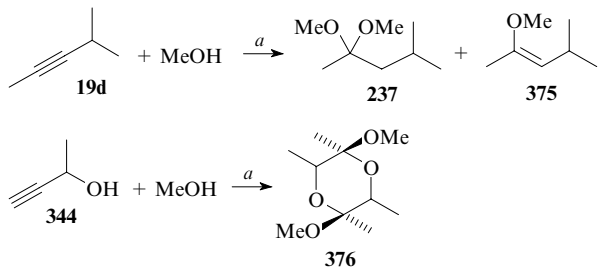
V.2.b. Hydroalkoxylation

The first example of intermolecular hydroalkoxylation was described by Chabanas and co-workers[68] in 1998. This reaction was catalyzed by the cationic complex $[(Ph_3P)Au]^+$, which was prepared by the treatment of $(Ph_3P)AuMe$ with sulfuric acid. Later on, the addition of secondary and tertiary alcohols and phenols to internal alkynes was reported.[498, 499] As expected, internal alkynes are less reactive than terminal alkynes. Besides, the issues of chemoselectivity, stereoselectivity and regioselectivity are encountered in reactions with internal alkynes.

In the same year, 1998, a highly active catalyst was proposed for the addition reaction of alcohols to alkynes (*e.g.*, to compound **19d**) (TON > 10^5, TOF > 5400 h^{-1}) (Scheme 149).[68, 500] This cationic triphenylphosphine gold complex $(Ph_3P)Au^+X^-$ has been commonly recognized. The addition of alcohols to alkynes can produce a small amount of enol ether **375**. Under these conditions, propargyl alcohol **344** is transformed into one diastereomer of cyclic acetal **376** (see Scheme 149).

The initial TOF values for the addition reaction of methanol to propyne depend on the nature of the ligand:

Scheme 149



(*a*) $(Ph_3P)AuMe$, $MeSO_3H$, solvent-free conditions, 20 – 50 °C

Ph_3As ($430\ h^{-1}$) < Et_3P ($550\ h^{-1}$) < Ph_3P ($610\ h^{-1}$) < $(4\text{-}FC_6H_4)_3P$ ($640\ h^{-1}$) < $(MeO)_3P$ ($1200\ h^{-1}$) < $(PhO)_3P$ ($1500\ h^{-1}$). The stability of the corresponding gold complexes increases in the reverse order. Apparently, this is the common trait in the catalytic chemistry of gold. Thus, the extremely stable complex $K[Au(CN)_2]$, which is among the first that were examined, did not exhibit catalytic activity. In the reaction under consideration, the TOF value is proportional to the proton concentration in the reaction mixture.

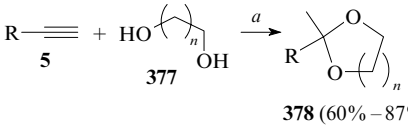
The *syn* addition of oxygen and gold atoms during the C–O bond formation and the solvent assistance in the hydrogen migration were established.[501] Alkynes can contain functional groups, such as CN, Hal and AlkO, and the trisubstituted double bond. This hydroalkoxylation method was used with *ortho*,*ortho*-disubstituted aryl alkynes.[502]

Attempts were made to utilize gold(III) complexes in ionic liquids in the synthesis of acetophenone (**27a**) from phenylacetylene (**5a**).[503] The activity of the catalyst proved to be lower than that described earlier for Au^I. Different organometallic gold complexes with mesityl and pentafluorophenyl substituents [165] were tested both in the presence and in the absence of the acid. The catalysts were found to have high activity and give good product yields. The activity of Au^I N-heterocyclic carbene complexes with acetate as the counterion in the presence of $B(C_6F_5)_3$ was investigated.[504] In some cases, the catalyst was able to be recycled.[412]

The application of Au^I as the catalyst for the addition reaction of diol **377** to alkyne proved to be much more efficient compared to Brønsted acids.[505] In the presence of the $(Ph_3P)AuCl-AgBF_4$ system as the catalyst, cyclic acetals **378** were synthesized from diols **377** by the reactions with different alkynes **5**, for example, with phenylacetylene (**5a**), benzylacetylene and hex-1-yne, at 100 °C without the addition of acid. Terminal alkynes (both aromatic and aliphatic) are characterized by high degrees of alkyne conversion and give high product yields (Scheme 150).

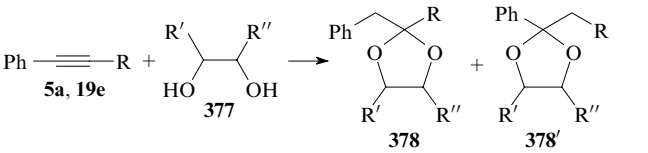
The reaction of internal alkynes with substituted diols **377** affords a mixture of products **378** and **378′**, the degree

Scheme 150



(*a*) $(Ph_3P)AuCl$ (2 mol.%) – $AgBF_4$ (2 mol.%), PhMe, N_2, 100 °C; R = Ph, Bn, Bu^n, Bu^t, 1-Naph; *n* = 1 – 3

Scheme 151



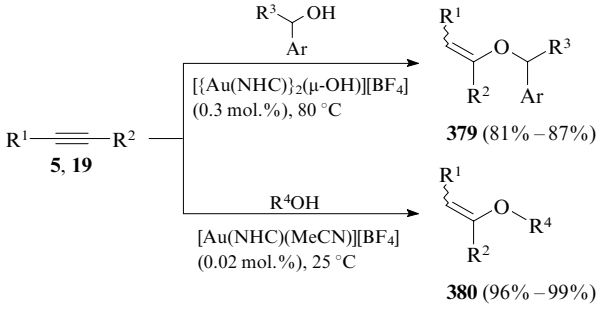
R	R′	R″	Conversion (%)	Yield (%)	Ratio **378** : **378′**
Me	H	H	15	–	68 : 32
Me	H	Et	60	35	66 : 34
H	Me	Me	100	78	97 : 3
H	H	Et	100	85	94 : 6

of alkyne conversion and the product yield being lower (Scheme 151).

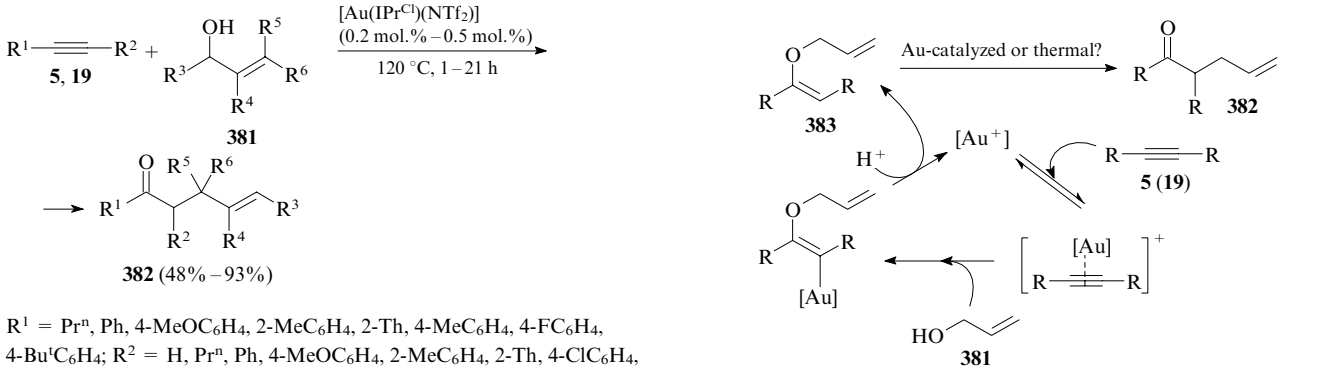
The addition of a catalytic amount of *p*-toluenesulfonic acid to the Au^I-Ag^I system leads to an increase in the rate of acetalization, *i.e.*, Brønsted acid acts as a cocatalyst. In the reactions performed in the presence of *p*-toluenesulfonic acid alone (2 mol.% – 5 mol.%), a low conversion and, correspondingly, a low product yield are observed.[505] The reactions using AuCl, $AuCl_3$ or $Na[AuCl_4]$ as the catalyst did not give the target products even in the presence of $AgBF_4$ or $CuCl_2$.[152]

The cationic gold carbene complexes, *e.g.*, $[Au(NHC)(MeCN)]BF_4$ or $[\{Au(NHC)\}_2(\mu\text{-}OH)][BF_4]$, proved to be efficient catalysts for the hydroalkoxylation of internal alkynes.[506] The reaction was accomplished under solvent-free conditions with primary and secondary alcohols using a catalyst in an amount of 0.3 mol.% for secondary alcohols and 0.02 mol.% for primary alcohols (the TON was 35 000 and TOF 2188 h^{-1}, respectively). A

Scheme 152



Scheme 153



R^1 = Pr^n, Ph, $4\text{-}MeOC_6H_4$, $2\text{-}MeC_6H_4$, 2-Th, $4\text{-}MeC_6H_4$, $4\text{-}FC_6H_4$, $4\text{-}Bu^tC_6H_4$; R^2 = H, Pr^n, Ph, $4\text{-}MeOC_6H_4$, $2\text{-}MeC_6H_4$, 2-Th, $4\text{-}ClC_6H_4$, $4\text{-}O_2NC_6H_4$; R^3, R^4, R^6 = H, Me; R^5 = H, Me, $4\text{-}MeOC_6H_4$, $4\text{-}O_2NC_6H_4$

broad range of *Z*-vinyl ethers **379** and **380** were synthesized in excellent yields with high stereoselectivity (Scheme 152).

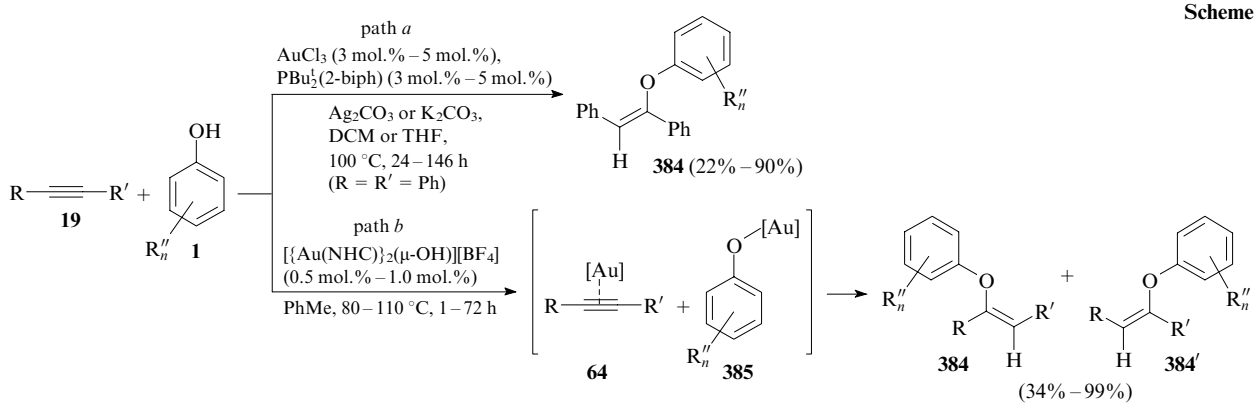
The reaction of allyl alcohol **381** at higher temperature produces homoallyl ketones (γ,δ-unsaturated carbonyl compounds),[507] which are structural units present in a number of natural products and are useful building blocks in organic synthesis.[508, 509] Allyl ether **383** is postulated as an intermediate. The plausible reaction mechanism is shown in Scheme 153. The involvement of gold in the rearrangement of allyl ether to ketone is an open question because the Claisen rearrangement can be a thermal process.

V.2.c. Hydroaryloxylation

In 2010, Sahoo and co-workers[498] described for the first time the reaction between internal alkynes **19** and phenols **1** (2 equiv.) using $AuCl_3$ (3 mol.% – 5 mol.%) in the presence of K_2CO_3 or Ag_2CO_3 (2 equiv.) under rather drastic conditions (Scheme 154).

In 2013, Nolan and co-workers[510] proposed a new, more efficient procedure for the hydroaryloxylation of internal alkynes with phenols taking into account that the digold hydroxide $[\{Au(NHC)\}_2(\mu\text{-}OH)][BF_4]$ (**18**) can be viewed as a combination of the Lewis acid $[Au(NHC)][BF_4]$ and the Brønsted base [Au(NHC)(OH)].[109] The hydrophenoxylation was shown to proceed *via* a double activation mechanism consisting of the coordination of the $[Au(NHC)][BF_4]$ unit to alkyne **19** to form π-complex **64** and the deprotonation of phenol **1** by the [Au(OH)(NHC)] unit to give gold phenoxide **385** (see Scheme 154).[511, 512] This reaction is the first example of the formation of two independent gold-activated centres in two different substrates involved in the intermolecular reaction. The reaction was studied in detail, in particular by quantum chemical methods, by Gómez-Suárez *et al.*[513] The substrates utilized in this reaction and the product yields are given in the table in Scheme 154.

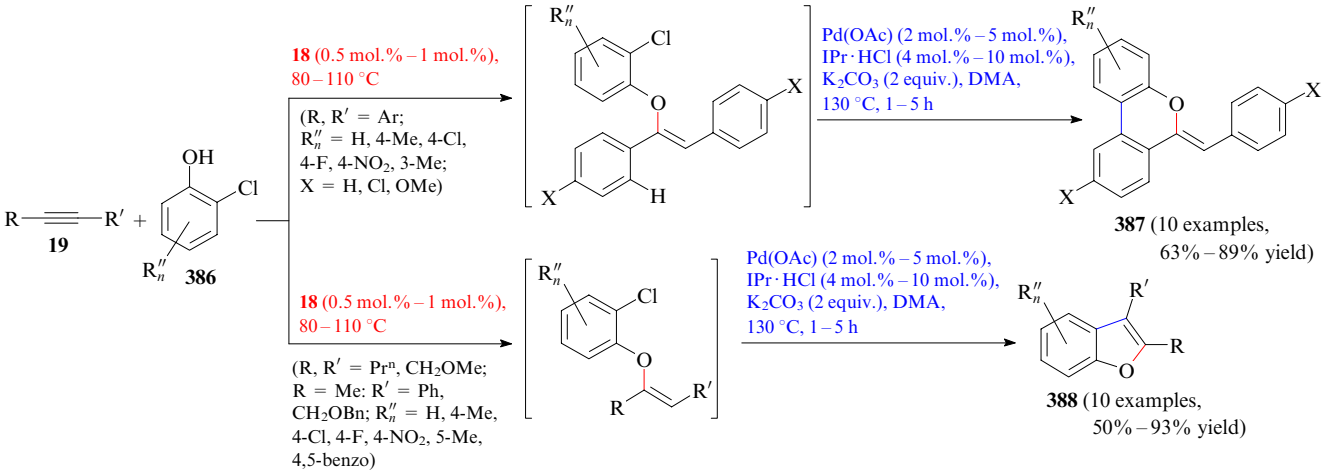
Scheme 154



R	R′	R''_n	Path *a*[498]		Path *b*[510]		
			reaction time /h	yield of **384** (%)	reaction time /h	yield of **384** + **384′** (%)	ratio **384** : **384′**
Ph	Ph	H	144	35	1[a]	96	–
Ph	Ph	4-MeO	96	83	1	98	–
Ph	Ph	4-Me	96	69	1	97	–
Ph	Ph	4-F	84	90	1	98	–
Ph	Ph	4-Cl	46	88	2	94	–
Ph	Ph	4-CF_3	24	82	4	91	–
Ph	Ph	4-NO_2	24	86	24	97	–
Ph	Ph	3-Me	–	–	2	97	–
Ph	Ph	3-F	96	72	2	95	–
Ph	Ph	2-Me	146	45	19	99	–
Ph	Ph	2-Ph	144	68	24	89	–
Ph	Ph	2,6-Me_2	146	0	24	67	–
Pr^n	Pr^n	H	–	–	24	94	–
4-$MeOC_6H_4$	Ph	H	–	–	1	93	1 : 0.28
Ph	4-ClC_6H_4	H	–	–	2	93	1 : 0.65
4-$MeOC_6H_4$	4-ClC_6H_4	H	–	–	1	94	1 : 0.24
Me	Ph	H	–	–	6	90	1 : 0.18
Me	Ph	4-NO_2	–	–	6	90	1 : 0.35
Bu^n	2-Py	H	–	–	72	62	1 : 0
Ph	2-Py	H	–	–	72	34	1 : 0

[a] TON = 3400.

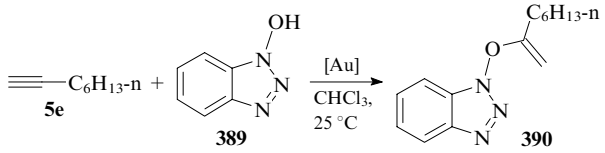
Scheme 155



The procedure developed by Nolan and co-workers[514] for the addition of phenols to alkynes allowed the authors to prepare benzo[*c*]chromenes and benzo[*b*]furans by the one-pot process based on the concept of consecutive catalysis. The intermediate generated *via* the nucleophilic addition of phenol **386** to alkyne **19** catalyzed by the dinuclear gold complex is involved in the subsequent palladium-catalyzed reaction. The process occurs under solvent-free conditions. The reaction pathway and the reaction product are determined by the nature of substituents at the alkyne triple bond. The reaction of diaryl alkyne **19** affords benzo[*c*]chromene **387** as the final product that is formed through C–H-activation by palladium. The reaction of alkyl-substituted alkyne **19** gives benzo[*b*]furan **388** as the final product through the palladium-catalyzed Mizoroki–Heck reaction (Scheme 155).

The intermolecular addition of *N*-hydroxybenzotriazole (**389**) to alkyne **5e** proceeds similarly to the reaction of phenols. The addition follows Markovnikov's rule in the presence of the $(Ph_3P)AuCl–AgOTf$ system and gives products in high yield.[515] The use of the ligand **L3** (see Scheme 93) made it possible to substantially decrease the required amount of the catalyst and retain a high yield of target product **390** (Scheme 156).

Scheme 156

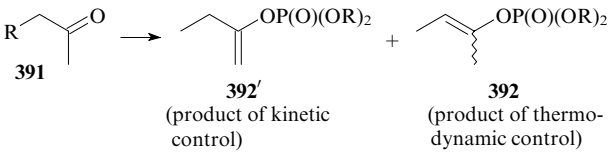


[Au] (mol.%)	Time /h	Yield of **390** (%)
$(Ph_3P)AuCl–AgOTf$ (5)	12	94
(**L3**)AuCl–AgOTf (0.1)	24	95

V.2.d. Addition of diphenyl phosphate

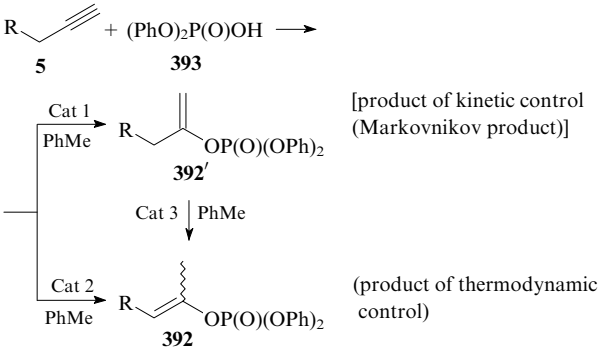
The preparation of enol phosphates **392** from carbonyl compounds **391** is of great importance in organic synthesis because these enol phosphates are versatile intermediates capable of various transformations.[516–518] A known method for the synthesis of enol phosphates **392** involves the reaction of lithium enolate with dialkyl phosphorochloridates.[519] The main issue of this transformation is to achieve selectivity. Thus, under thermodynamic control, more highly substituted enol **392** is usually generated as the major, but not the only, product from unsymmetrical ketones **391** (Scheme 157). Consequently, the synthesis of enol **392** with high selectivity is a challenge in modern organic synthesis.

Scheme 157



The gold-catalyzed addition of diphenyl phosphate **393** to terminal alkynes **5** affords both the product of kinetic control **392′** and the product of thermodynamic control **392** (Scheme 158).[520]

Scheme 158

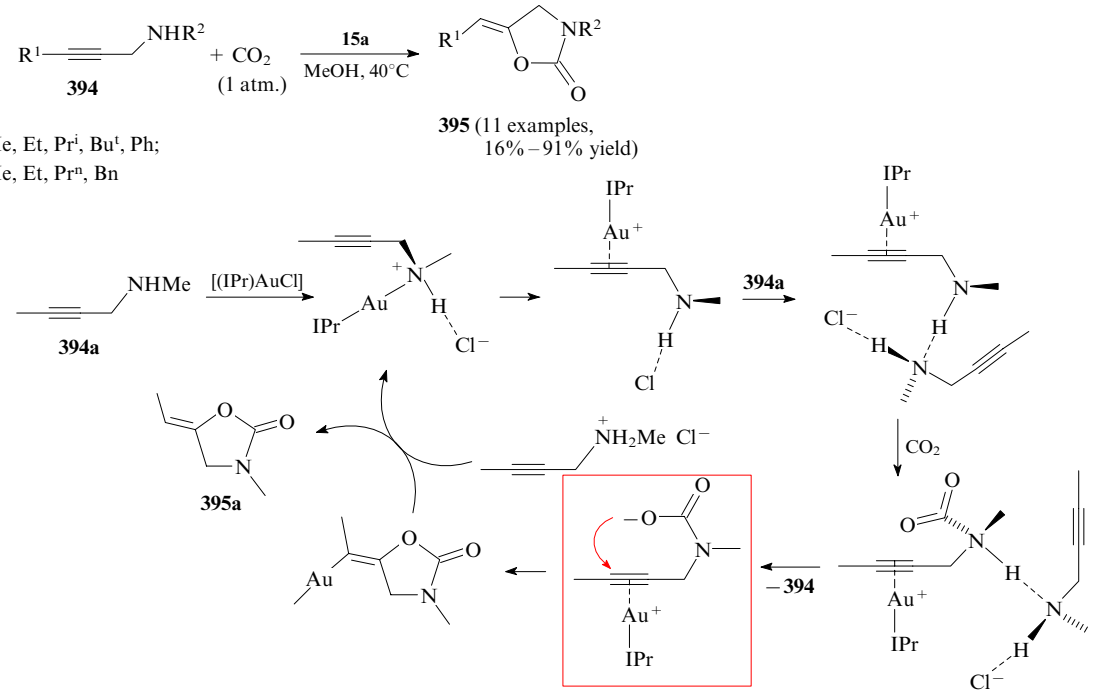


Cat 1: $(Ph_3P)AuCl–AgPF_6$; Cat 2: $[\{(C_6F_5)_3P\}AuCl]–AgOTf$; Cat 3: $[\{(C_6F_5)_3P\}AuOTf]$; R = n-C_5H_{11}, Cy, Ph, $PhCH_2CH_2$, $ClCH_2CH_2$, *etc.*

The following systems exhibited the highest efficiency: $(Ph_3P)AuCl–AgPF_6$ (Cat 1), which catalyzes the selective preparation of enol phosphate **392′** in 88% yield, and $[\{(C_6F_5)_3P\}AuCl]–AgOTf$ (Cat 2), which catalyzes the selective formation of the product of thermodynamic control **392** in 88% yield. Toluene proved to be the solvent of choice.

In addition, the gold catalysis can be applied for the isomerization of kinetic enol phosphate **392′** to thermodynamically favourable product **392**. The screening of catalysts revealed that $[\{(C_6F_5)_3P\}AuOTf]$ (Cat 3) is the most

Scheme 159



active one for this process. The reaction proceeds even at room temperature; the heating of the reaction mixture to 70 – 100 °C can be used to reduce the reaction time.

V.2.e. Addition of carbon dioxide

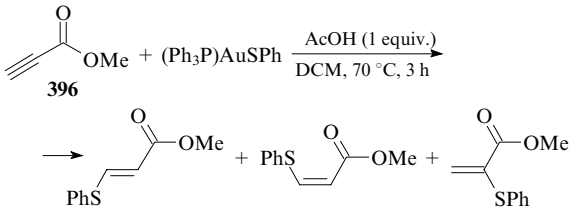
The reaction of propargylamines with CO_2 catalyzed by Lewis acids affords cyclic carbamates.[521 – 523] The application of Au^I NHC complexes allows the synthesis of *exo* products **395** in yields of up to 91% (Scheme 159).[524]

Yuan and Lin[525] performed DFT (density functional theory) quantum chemical calculations for the reaction of propargylamines **394** with carbon dioxide giving cyclic carbamates **395** and proposed the reaction mechanism, which involves the nucleophilic attack of the oxygen atom of the CO_2 molecule on the gold-activated triple bond (see Scheme 159).

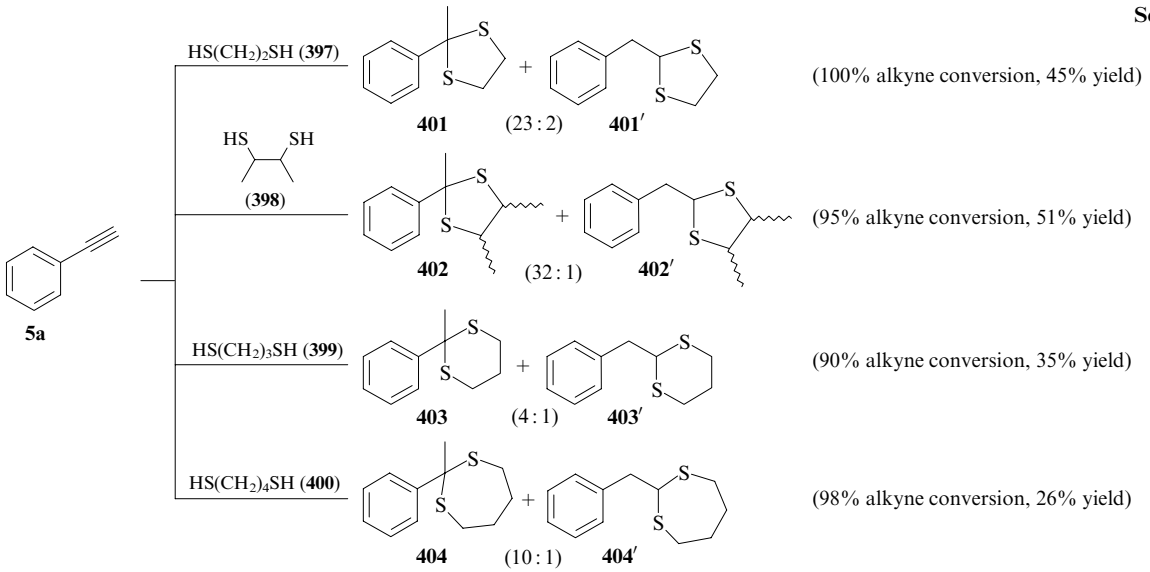
VI. Addition of thiols to the triple bond

Catalytic systems based on Ni,[526 – 529] Pd,[530 – 533] Rh[534 – 537] and Cu[538] for the efficient addition of thiols to alkynes are well known. Recently, several attempts were made to use gold catalysis in these reactions.[468, 539 – 542] In particular, Zalesskiy *et al.*[543] studied in detail the mechanism of

Scheme 160



Scheme 161



hydrothiolation of alkynes **396** (Scheme 160), in particular by quantum chemical modelling (DFT).

Phenylacetylene (**5a**) can be easily and regioselectively transformed into cyclic thioacetals by the reactions with dithiols **397**–**400** in the presence of the $(Ph_3P)AuCl-AgBF_4$ system at 100 °C in toluene.[505] As compared with the synthesis of the corresponding acetals, the synthesis of thioacetals **401**–**404** requires the use of a large amount of the catalyst and a longer reaction time, and the reaction gives a large amount of anti-Markovnikov addition products — compounds **401′**–**404′**. The long reaction time results also in the formation of a large amount of by-products *via* alkyne polymerization (Scheme 161), thus decreasing the yields of the target products. Besides, the reaction produces a mixture of regioisomers.

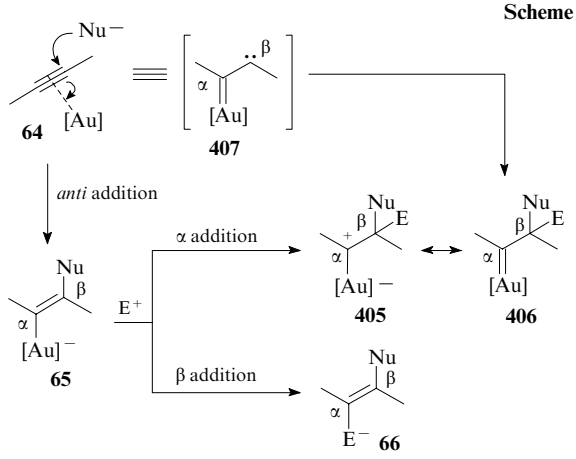
Brønsted acids, for example, *p*-toluenesulfonic acid, can also act as catalysts for the thioacetalization of alkynes; however, poor regioselectivity and the formation of large amounts of anti-Markovnikov addition products are observed in most cases.

Thiols, like amines, can deactivate Au^I catalysts through the complexation, for example, through the formation of the cationic bridged complex $[\{Au(L)\}_2(\mu\text{-}SR)]^+X^-$ (see Ref. 257).

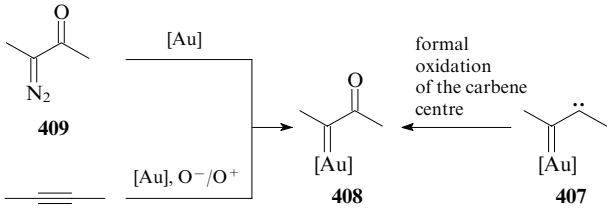
VII. α,α-Nucleophilic addition. Gold carbene intermediates

The homogeneous gold catalysis has found wide acceptance in modern organic synthesis due to soft Lewis acidity of the Au^I cation with respect to alkynes and allenes. In the nucleophilic addition reactions considered above, the nucleophile adds to the β-carbon atom of gold-activated alkyne **64** followed by deauration of intermediate **65** and the addition of an electrophilic species at the α position of the triple bond of the starting alkyne to form the corresponding alkene **66** (see Scheme 20). However, the possible addition of an electrophilic species to the same β-carbon atom to form gold-substituted carbocation **405** cannot be ruled out (Scheme 162; here and in Scheme 163, the substituents in the alkyne and the diazo carbonyl compound are omitted for clarity). The back donation of electron density from the metal centre stabilizes the electron-deficient trivalent carbon centre (for example, as it is shown above in Scheme 57), giving rise to carbenoid intermediate **406**. Although gold is the most electronegative metal on the Pauling scale,[18, 544] DFT quantum chemical calculations demonstrated that this electron density shift can take place.[545] Formally, the formation of carbenoid **406** can be represented as the successive addition of the nucleophile and electrophile to hypothetical carbene **407** (see Scheme 162). Hypothetical carbene **407** is used for the interpretation of a number of reactions of gold-activated alkynes, in particular, enyne cycloisomerization.[546, 547] The opportunity to synthesize gold carbene intermediates and perform their subsequent various transformations, which open access to a broad range of functionalized products starting from simple substrates, is a second essential factor making homogeneous gold catalysis widely applicable.[548] If both the nucleophile and electrophile *en route* to carbenoid **406** are oxygen atoms, the reaction produces α-oxo gold carbenoids **408** (Scheme 163). Formally, this can be viewed as the oxidation of the carbene centre of **407**.

Scheme 162



Scheme 163



α-Oxo carbenoids **408** are versatile intermediates, which can undergo different synthetic transformations, such as C–H insertion, the ylide formation or cyclopropanation reactions.[549] In the practice of organic synthesis, these carbenoids are prepared by the metal-catalyzed deazotization of diazo carbonyl compounds. In particular, the deazotization catalyzed by Rh compounds is of practical value. In the presence of chiral ligands, these catalysts enable enantioselective transformations.

The drawback of this method is that it requires the use of explosive substrates, which poses difficulties in the industrial-scale organic synthesis.[550, 551] Besides, the preparation of diazo carbonyl compounds necessitates the use of highly energetic unstable reagents and generally involves several additional synthetic steps.[549] Therefore, the development of new methods for the synthesis of equivalents of diazo carbonyl compounds is a challenge in synthetic organic chemistry.

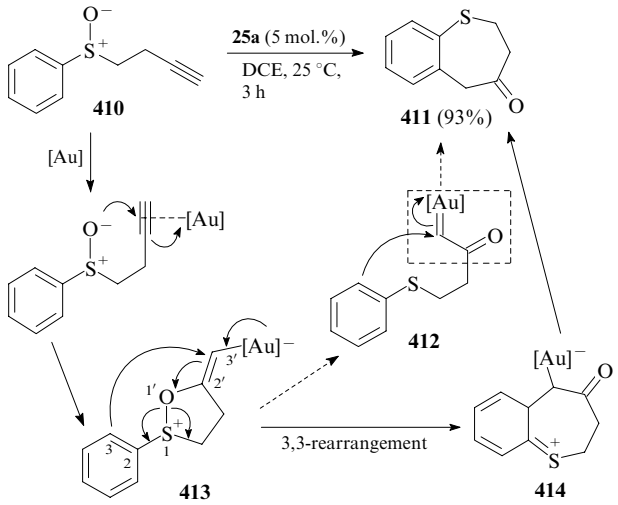
A series of α-oxo gold carbenoids **408** were synthesized using diazo carbonyl compounds **409**.[552–556] The oxidation of the intermediate generated from alkyne affords α-oxo carbenoid **408** without using a diazo compound (Scheme 163). This reaction pathway is safer and cheaper.

Both the intramolecular oxidation of gold-activated alkyne giving gold α-oxo carbenoid and then its transformation product and intermolecular processes using an external oxidant are known.

VII.1. Intramolecular oxidation

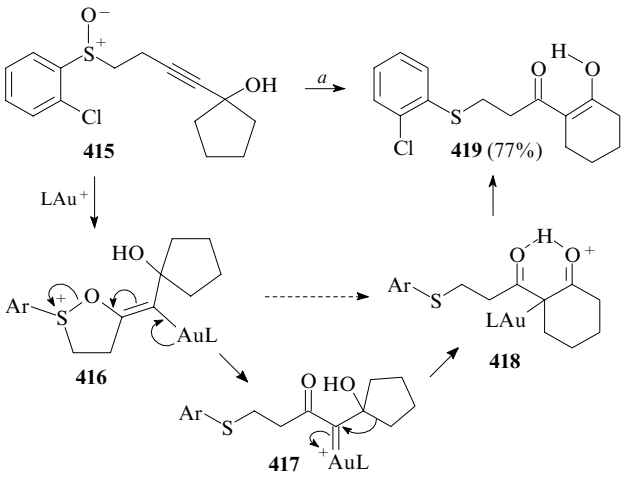
Based on the available data on gold-catalyzed transformations of alkynes, Li and Zhang[557] hypothesized that the most efficient oxidant for the synthesis of α-oxo gold carbenoids should first act as a nucleophile and then as an electrophile. Sulfoxide, being a weak oxidant, meets these requirements. The Au^{III}-catalyzed intramolecular reaction of sulfoxide **410** affords 2,3-dihydrobenzo[*b*]thiepin-4(5*H*)-one (**411**) in good yield (Scheme 164).

Scheme 164



It should be noted that in this case, the reaction pathway through α-oxo carbenoid intermediate **412** is only hypothetical. A more detailed study of the reaction [558] and DFT quantum chemical calculations demonstrated that the reaction proceeds *via* the 3,3-sigmatropic rearrangement of intermediate **413** to form bicyclic intermediate **414**. If this sigmatropic rearrangement cannot take place, for example, in the presence of a substituent in the *ortho* position with respect to sulfoxide (substrate **415**), the reaction proceeds through carbenoid intermediate **417**.[557] However, the direct transformation of intermediate **416** into intermediate **418** (Scheme 165) cannot be ruled out.[559]

Scheme 165

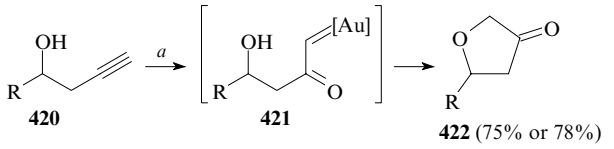


(*a*) [(IPr)Au(NTf$_2$)] (5 mol.%), DCE, 25 °C, 3 h

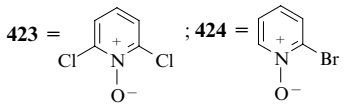
VII.2. Intermolecular oxidation followed by intramolecular cyclization

α-Oxo carbenoid **421** can be synthesized using an external oxidant (*e.g.*, N-oxide **423** or **424**) and then this carbenoid can be subjected to transformations, for example, intramolecular cyclization to form dihydrofuranone **422** (Scheme 166).[560]

Scheme 166

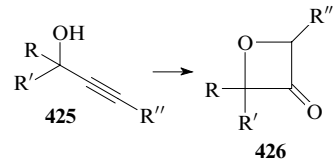


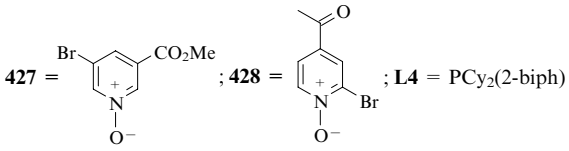
(*a*) (Ph$_3$P)AuNTf$_2$ (5 mol.%), **423** or **424** (2 equiv.), MsOH (2 equiv.), DCE, 25 °C, 2.5 h;



This approach was applied to synthesize oxetan-3-ones **426** from propargyl alcohols **425** (Scheme 167). Both secondary or tertiary alcohols can be utilized and the triple bond can be either terminal or that bound to an electron-with-

Scheme 167



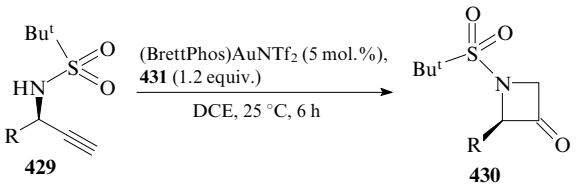


Conditions	R	R′	R″	Yield of **426** (%)
(**L4**)AuNTf$_2$	$H_2C{=}CH(CH_2)_3$	H	H	65
(5 mol.%),	Cy	H	H	73
Tf$_2$NH (1.2 equiv.),	$N_3(CH_2)_4$	H	H	81
427 (2 equiv.),	$Br(CH_2)_4$	H	H	70
DCE, 25 °C,				
3 – 4 h				
(IPr)AuNTf$_2$	Me	Me	CO_2Et	82
(5 mol.%),	Me	Pr^i	CO_2Et	72
Tf$_2$NH (1.2 equiv.),	Adamantane-2,2-diyl		CO_2Et	92
428 (2 equiv.),				
DCE, 25 °C,				
20 – 24 h	$(CH_2)_6$		CO_2Et	75

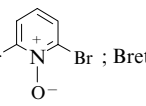
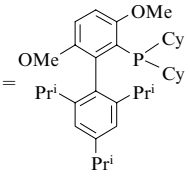
drawing group.[561] Besides, this approach was used for the one-pot stereoselective synthesis of azetidin-3-ones **430** from propargylamides [562] (Scheme 168). The *tert*-butylsulfonyl group served as a protecting group. The latter was prepared by the oxidation of the *tert*-butylsulfinyl group in the substrate synthesized by the highly selective Ellman process.[563]

A carbonucleophile can serve as a nucleophile that attacks α-oxo gold carbenoid, as it is observed, for example, with phenylpropargyl ethers **432**, which are transformed into chroman-3-ones **433** in good yield under the reaction conditions (Scheme 169). The presence of electron-withdrawing groups leads to a decrease in the yield of the product (*e.g.*, chromanone **433e**). On the whole, the reaction is characterized by high regioselectivity (products **433a**, **433c** and **433f**).[564]

Scheme 168

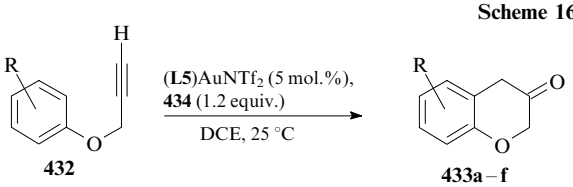


429 **430**

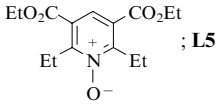
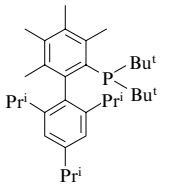
431 =  ; BrettPhos = 

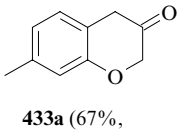
R	Yield of **430** (%)	*ee* (%)
$PhCH_2CH_2$	82	99
cyclo-C_3H_5	81	> 99
$N_3(CH_2)_4$	67	98
$BocHN(CH_2)_3$	84	98

Scheme 169

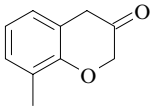


432 **433a – f**

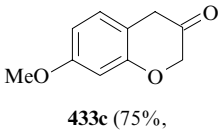
434 =  ; **L5** =  (Me_4Bu^tXPhos)



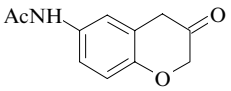
433a (67%, *p* : *o* = 12 : 1)



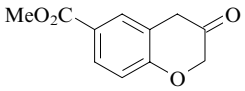
433b (78%)



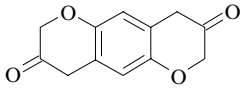
433c (75%, *p* : *o* = 11 : 1)



433d (81%)



433e (43%)

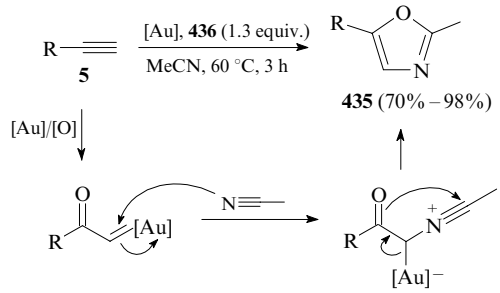


433f (60%, linear : angular = 8 : 1)

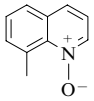
VII.3 Intermolecular oxidation and intermolecular reaction of carbenoid

The intermolecular reaction of α-oxo gold carbenoid is complicated by its high reactivity, in particular, by high electrophilicity of the carbene centre, which often triggers numerous side reactions, including those with the solvent (*e.g.*, dichloroethane). One way of addressing this problem is to use the reagent as the solvent, for example, by performing the reaction in nitrile (acetonitrile). The oxidation of a series of alkynes **5** in acetonitrile produced 2,5-disubstituted oxazoles **435** in nearly quantitative yields [565] (Scheme 170). In this case, 8-methylquinoline *N*-oxide (**436**) is the oxidant of choice.

Scheme 170

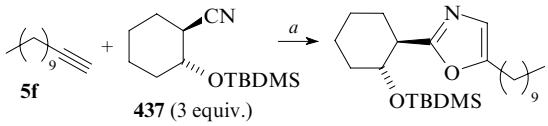


R = n-$C_{10}H_{21}$, $Ph(CH_2)_2$, $HO(CH_2)_4$, $HO_2C(CH_2)_4$, $CH_2{=}C(Me)$, cyclo-C_3H_5, 4-$OHCC_6H_4$; [Au]: $(Ph_3P)AuNTf_2$, $(IPr)AuNTf_2$, $(BrettPhos)AuNTf_2$;

436 = 

If nitrile cannot be used as the solvent (for example, because of its high price), the reaction is performed under solvent-free conditions in the presence of a threefold excess of nitrile (*e.g.*, compounds **437**), which can be recycled and reused (Scheme 171).

Scheme 171

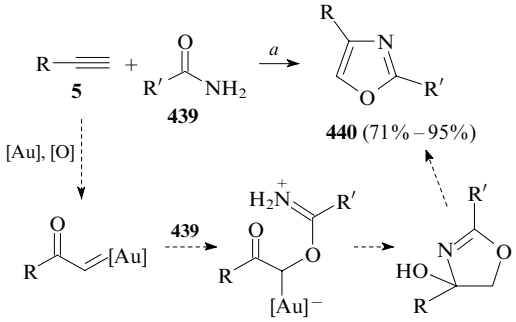


438 (64% relative to alkyne, 81% relative to recycled nitrile)

(*a*) $(BrettPhos)AuNTf_2$ (1 mol.%), **428** (1.3 equiv.), solvent-free conditions, 60 °C, overnight

The reaction of α-oxo gold carbenoid with a stoichiometric amount of the external nucleophile does not afford the target product in a significant yield (generally, the yield is not higher than 4%). However, the application of the ligand Mor-DalPhos (complex **202**) [361] leads to a substantial

Scheme 172



(*a*) (Mor-DalPhos)AuCl (**202**) (5 mol.%), $NaBAr^F_4$ (10 mol.%), **428** (2.2 equiv.), PhCl, 60 °C, 16 h; R = n-$C_{10}H_{21}$, $(CH_2)_4NPhth$, $TBDMSO(CH_2)_4$; R′ = 2-Fu, 2-Th, $Me_2C{=}CH$, $PhCH{=}CH$, 4-$MeOC_6H_4$; Ar^F = 3,5-$(CF_3)_2C_6H_3$

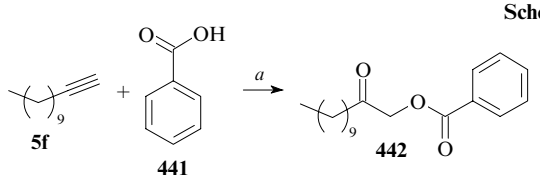
increase in the product yield. For instance, the reaction of terminal alkyne **5** with primary amide **439** gave target 2,4-disubstituted oxazoles **440** in a yield of about 87% through [3 + 2]-annulation (Scheme 172).[492]

The efficiency of the ligand Mor-DalPhos is associated with its bidentate behaviour (N and P), resulting in the formation of the tris-coordinated gold atom in carbenoid **351** characterized by lower electrophilicity. The carbenoid is more stable and reacts selectively.

Other examples of the intermolecular reactions are the reactions of oxo gold carbenoid with carboxylic acids[493] and methanesulfonic acid[481] considered above.

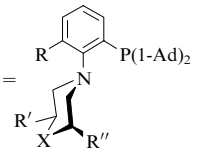
The optimization of the ligand (Scheme 173) made it possible to increase the yield of target product **442** *via* stabilization of the chair conformation of the piperidine ring, which leads to steric stabilization of gold carbenoid, a decrease in its activity and an increase in the selectivity of the reaction, thus improving the yield of product **442**. The reaction proceeds with different carboxylic acids and alkynes.

Scheme 173



(*a*) LAuCl (5 mol.%), **428** (1.5 mol.%), PhCl, 25 °C, 12 h;
L = Mor-DalPhos, **443** – **447**

Mor-DalPhos, **443** – **447** =



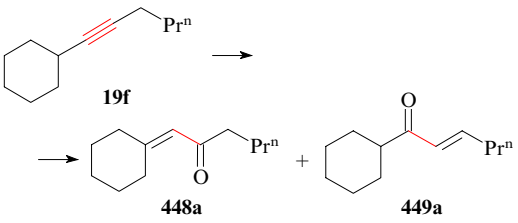
L	X	R	R′	R″	Yield of **442** (%)
Mor-DalPhos	O	H	H	H	68
443	CH_2	H	H	H	68
444	CH_2	H	H	Me	75
445	CH_2	H	Me	Me	84
446	CH_2	Me	H	H	83
447	CH_2	Me	Me	Me	83

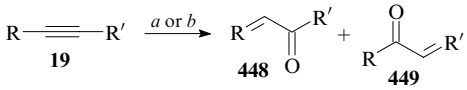
VII.4. Regioselectivity

The structure of the oxidation product formed from a terminal alkyne is unambiguously defined. The regioselectivity of the reaction involving alkyne with the disubstituted triple bond is an important problem in the efficient catalysis. The reaction of alkyne **19f** containing primary and secondary alkyl groups as substituents at the triple bond can be cited as an example of the successful transformation of this type. This reaction affords enone **448a** in a larger amount compared to its regioisomer **449a** (Scheme 174).[566] Enones are produced through 1,2-CH insertion into isomeric α-oxo carbenoids. The regioselectivity of this process is achieved due to the binding of the oxidant to the less hindered end of the triple bond and the possible stabilization of the most substituted alkene. It is noteworthy that minor product **449a** is generated exclusively as the *E* isomer in contrast to the decomposition of α-diazo carbonyl compounds in the presence of Rh catalysts, resulting in the selective formation of *cis*-enones.[567, 568] A similar regioselectivity was observed in the reaction with a substrate containing methyl and primary alkyl groups (**448b**, **449b**) or the functionalized primary group and the cyclohexyl moiety (**448d**,**e**, **449d**,**e**) as substituents (see Scheme 174). If the substrate contains the methyl group and the bulky cyclohexyl moiety as two substituents, the regioselectivity is > 50 : 1 (**448c**, **449c**). The conjugation in the product (**448f**,**g**, **449f**,**g**) also affects the regioselectivity. Aryl alkynes are characterized by lower reactivity and they react under different conditions: the application of stronger Lewis acid and another oxidant (products **448h** – **j**, **449h** – **j**).

The oxidation of propargyl acetate **451** produced enones **452** and **453** in 11% and 82% yields, respectively (Scheme 175).[566]

Scheme 174





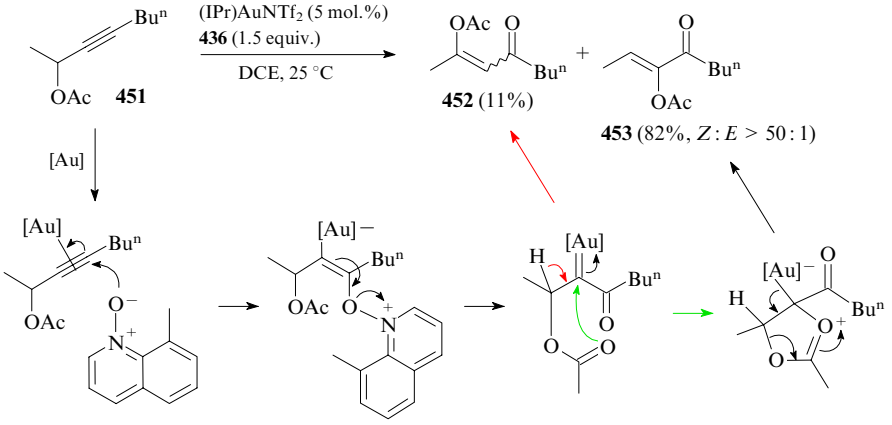
(*a*) (IPr)AuNTf$_2$ (5 mol.%), [O], THF; (*b*) {(2,4-$Bu^t_2C_6H_4O)_3P$}AuNTf$_2$ (5 mol.%), [O], THF

450 =



Compounds **448**, **449**	R	R′	[O]	Conditions	Yield, %	Ratio **448** : **449**
a	Cy	Bu^n	**450**	*a*, −20 °C, 14 h	90	13 : 1
b	n-C_6H_{13}	Me	**450**	*a*, −20 °C, 48 h	71	11 : 1
c	Cy	Me	**450**	*a*, 0 °C, 3 h	91	> 50 : 1
d	Cy	$(CH_2)_4$OTBDMS	**450**	*a*, −20°C, 14 h	90	14 : 1
e	Cy	$(CH_2)_4CH{=}CH_2$	**450**	*a*, 0 °C, 48 h	78	10 : 1
f	$CH_2{=}C$(Me)	CH_2CH_2OBn	**450**	*a*, 40 °C, 20 h	81	10 : 1
g	Cyclohex-1-enyl	Bu^n	**450**	*a*, 25 °C, 1 h	85	> 50 : 1
h	Bu^n	Ph	**424**	*b*, 25 °C, 26 h	84	11 : 1
i	Cy	Ph	**424**	*b*, 25 °C, 26 h	85	> 50 : 1
j	Bu^n	4-$MeOC_6H_4$	**424**	*b*, 25 °C, 4 h	92	> 50 : 1

Scheme 175



Both products (**452** and **453**) are formed through the initial attack of the oxidant on the distal end of the triple bond with respect to the acetoxy group. The product of regioisomeric attack was not detected, which is attributed to the inductive effect of the electron-withdrawing acetoxy group.

* * *

Efficient methods for the synthesis of a great diversity of compounds were developed based on the addition of various nucleophiles to the triple bond catalyzed by Au^{I} and Au^{III} complexes with different ligands and by AuNP nanoparticles. These methods are particularly useful in the synthesis of heterocycles. The diversity of reactions, which can be accomplished under gold catalysis distinctively different from the known palladium catalysis, is impressive. We hope that this and subsequent reviews on the chemistry of gold will attract the attention of readers of the journal 'Russian Chemical Reviews' to this fascinating area of chemistry.

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