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Gold-catalysed reactions of alcohols: isomerisation, inter- and intramolecular reactions leading to C–C and C–heteroatom bonds

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Abbreviations: aq, aqueous; bmim, 1-butyl-3-methylimidazolium; Bn, benzyl; cat., catalytic; Cy, cyclohexyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereoisomeric excess; dr, diastereoisomeric ratio; ee, enantiomeric excess; equiv, equivalent; MOM, methoxymethyl; MS, molecular sieves; Boc, *tert*-butoxycarbonyl; PPTS, pyridinium *p*-toluenesulfonate; rt, room temperature; TBS, *tert*-butyldimethylsilyl; Tf, trifluoromethanesulfonyl; THP, tetrahydropyranyl; TIPS, triisopropyl; TMS, trimethylsilyl; TOF, turnover frequency; TON, turnover number; Ts, 4-methylphenylsulfonyl.

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1. Introduction

Homogeneous catalysis by gold has emerged over the last 20 years. After the long-held assumption of the unreactivity of gold, a gold rush is occurring, as exemplified by the number of reports,[1] highlights[2] and reviews[1,3] on the Au-catalysed organic reactions that recently appeared. I have always been fascinated by the rich chemistry of alcohols under catalytic conditions[4,5] and, here, the aim is to give an overview of their reactions, except oxidations,[6] in the presence of Au catalysts. Such a topic has never been specifically reviewed. Recently, I reviewed the Pd-catalysed reactions of alcohols:[5] they require either a Pd^0 or a Pd^{II} catalyst, most of them involve β-H eliminations and, when mediated by Pd^{II} compounds, require oxidants to regenerate active Pd^{II} species from the Pd^0 that is produced in the course of the catalytic cycle.[7] In contrast, Au-catalysed reactions can often occur efficiently using gold salts of both stable oxidation states, i.e., Au^I and Au^{III}. Moreover, gold intermediates do not tend to undergo β-H eliminations and no reoxidant is required.

Since gold has high alkynophilicity, many reported Au-catalysed reactions of alcohols involve also alkynyl groups and begin by coordination of the C≡C bond to the catalyst. Other unsaturated functions can also participate in the reaction before that of the alcohol. Consequently, this review is organised by the type of substrate with, mainly, a chronological account of the reports.

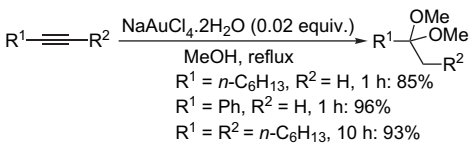
2. Formation of C–O bonds from the addition of exogenous alcohols to unrearranged unsaturated substrates

This section exclusively concerns processes in which the intermolecular addition of the alcohol to the substrate occurs prior to any intramolecular reaction. Other sections will contain examples of alcohol addition that proceeds after a gold-catalysed evolution of the substrate.

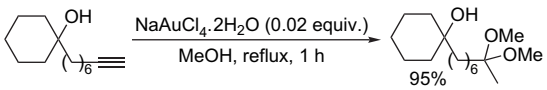
2.1. Alkynes

2.1.1. *Using Au^{III} catalysts*

In 1976, Thomas et al. disclosed that the reaction of aliphatic and aromatic alkynes with $HAuCl_4$ in refluxing methanol afforded the corresponding ketones as the main compounds, but also small amounts of the methyl vinyl ethers.[8] Fifteen years later, Fukuda and Utimoto, who apparently were not aware of the above Thomas study, reported the Au^{III}-catalysed acetalisation of alkynes in refluxing anhydrous MeOH (Eqs. 1 and 2).[9] In contrast, the use of a 1:10 mixture of H_2O/MeOH led, in most cases, to ketones, with no hydration occurring with a gold^I catalyst such as $KAu(CN)_2$.[9] Fukuda and Utimoto have also observed that the treatment of alkynes with 1 equiv of a diol and catalytic amounts of $NaAuCl_4$, to produce cyclic acetals, was unsuccessful. Subsequently, the same team obtained α,β-unsaturated ketones with only traces of β-methoxy ketones from methyl propargyl ethers using aqueous methanol and catalytic $NaAuCl_4$ (Eq. 3).[10] In fact, Au^{III}-catalysed reactions of alkynes in aqueous methanol led, in most cases, to ketones.[10,11]



(1)



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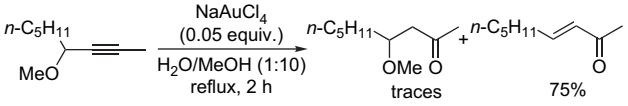
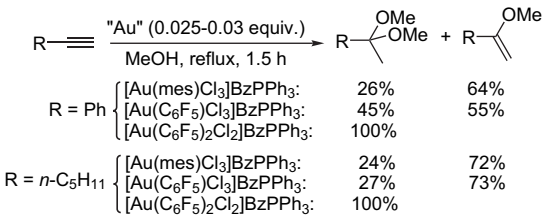


(3)

According to Fukuda and Utimoto, the α,β-unsaturated ketone depicted in Eq. 3 is produced by hydration of the alkyne affording the β-methoxy ketone followed by elimination of MeOH.[10] As the starting substrate was quantitatively recovered when aqueous tetrahydrofuran or acetonitrile was used instead of aqueous methanol,[10] we suspect rather a methoxylation reaction of the C≡C bond generating the dimethylketal or the methyl vinyl ether, followed by their hydrolysis and then elimination of MeOH, these two last reactive steps being mediated by the acidity of the catalyst. This possible reactive pathway is in agreement with a previous proposal from Thomas team.[8]

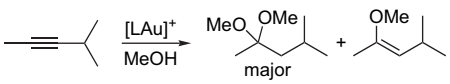
Using anionic organometallic Au^{III} complexes, $[Ar_nAuCl_{4-n}]Q$ (n=1, 2), as catalysts in anhydrous MeOH, Laguna et al. have obtained acetals and enol ethers from phenylacetylene and 1-heptyne, the ratio between the two adducts depending upon the structure of the catalyst (Eq. 4).[12] A comparison of the results from phenylacetylene (Eqs. 1 and 4) also highlights the catalyst dependence. Laguna et al. pointed out that 1-(1-methoxyvinyl)benzene is sensitive to the workup conditions in leading to acetophenone.



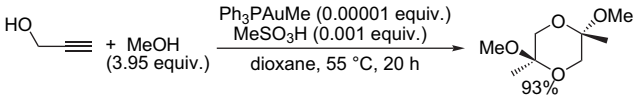
(4)

2.1.2. Using Au^I catalysts

While an Au^I catalyst such as $KAu(CN)_2$ was not able to induce hydration of alkynes,[9] cationic Au^I complexes, $[LAu]^+$, obtained from the addition of Brønsted acids to LAuMe (L=Ph_3As, Et_3P, Ar_3P, $(MeO)_3P$ or $(PhO)_3P$) catalyse the addition of methanol, ethanol, isopropanol and allyl alcohol to acetylene, as well as to mono- and disubstituted acetylenes, as disclosed by Teles et al. in 1997.[13,14] The nature of the ligand has a considerable influence on the catalytic activity: TONs of up to 10^5 and TOFs of up to 5400 h^{-1} have been obtained. The nature of the alcohol also influenced the reactivity: a reactivity decrease by a factor of about 10 when going from a primary to a secondary alcohol was observed, while tertiary alcohols were unreactive. Acetals are the major products in the presence of excess alcohol (Eq. 5), except from diphenyl acetylene that mainly leads to the corresponding enol ether. Enol ethers can become the main products in the presence of excess alkyne. An equilibrium between the acetal and the corresponding enol ethers has been observed from 3-hexyne.[14] The methoxylation of propargylic alcohol has been accompanied by intermolecular reaction with the hydroxyl group of the substrate affording a dimeric compound (Eq. 6). Such a reaction did not occur from 2-butyne-1,4-diol (Eq. 7): the carbonyl group of the isolated compound could come from the corresponding acetal while the methoxy substituent is due to the reaction of one hydroxyl with MeOH, these reactions being possibly induced by the acidic medium.



(5)



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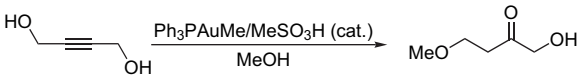
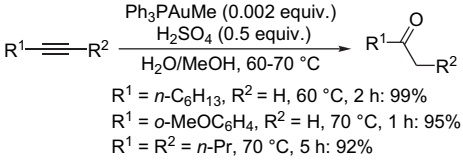
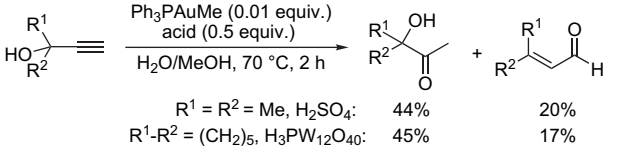


(7)

Under similar conditions, but using aqueous methanol, Tanaka et al. obtained only ketones (Eq. 8) and pointed out that the reaction did not proceed in the absence of either the Au catalyst or the protic acid. When a terminal tertiary propargylic alcohol was used as the substrate, some cleavage of the C–OH bond leading to the α,β-unsaturated aldehyde was observed (Eq. 9).[15]



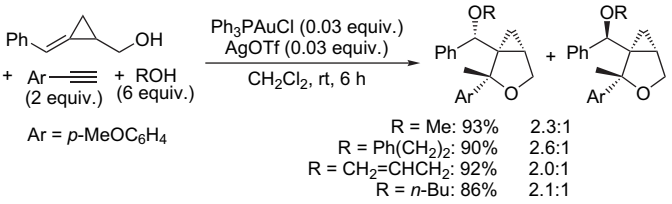
(8)



(9)

In contrast to LAuMe that required H^+ as a co-catalyst to mediate a reaction,[14] the $Ph_3PAuOCOC_2F_5$-catalysed reaction of 3-hexyne, in MeOH at 45 °C, led to a 98:2 mixture of 3-hexanone and 3-methoxy-3-hexene.[16]

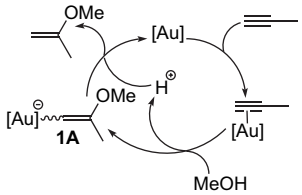
Recently, Tian and Shi have reported the synthesis of heterocycles via multicomponent reactions involving the Au^I-catalysed addition of 2-(arylmethylene)cyclopropylcarbinols to terminal arynes (Eq. 10).[17]



(10)

2.1.3. Mechanism

A simplified mechanism leading to 2-methoxypropene from the methanol addition to propylene catalysed by, indifferently, an Au^I or Au^{III} complex (noted [Au]) is depicted in Scheme 1. The decrease of the electronegativity of the triple bond by coordination to [Au] permits the nucleophilic attack of the alcohol, leading to an anionic species **1A**, the protodeauration of which liberates the organic compound and regenerates the catalyst. 2,2-Dimethoxypropane could then be obtained from 2-methoxypropene through a similar reactive pathway.

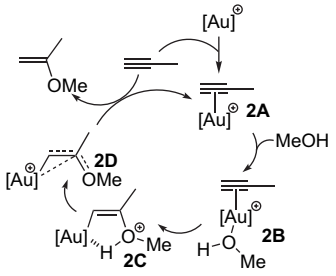


Scheme 1.

According to Laguna et al., the reactions mediated with Au^I and Au^{III} are, however, mechanistically distinct.[12] This could be exemplified by the hydration of propargylic alcohols, which is sluggish with $NaAuCl_4$,[9] but efficient with cationic Au^I complexes.[15]

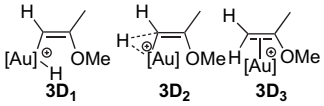
Laguna's team suggested that, in the case of anionic organometallic Au^{III} complexes, $[Ar_nAuCl_{4-n}]Q$ (n=1, 2), the first step is the dissociation of one chloride ligand to afford QCl and the active Ar_nAuCl_{3-n} catalytic species, the coordination of the alkyne to this Au^{III} compound leading to Ar_nAuCl_{3-n}(alkyne).[12] Consequently, a catalytic cycle as illustrated in Scheme 1 is envisageable.

Theoretical[14,18] and mass spectroscopic[18] studies have been devoted to the use of cationic Au^I complexes, and a catalytic cycle, that involves the *syn*-addition of gold and alcohol to the triple bond, has been proposed by Teles et al[14] (Scheme 2). As mono- and disubstituted alkynes are, from ab initio calculations, better ligands for cationic Au^I complexes than MeOH, the first step is the formation of an Au–π-alkyne complex **2A**. MeOH would coordinate to gold leading to **2B**, before its addition to the triple bond to afford the *Z*-isomer **2C**. From **2C**, **2D** illustrates the intermediate leading to 2-methoxypropene and **2A** via a ligand exchange. 2,2-Dimethoxypropane could be obtained from **2D** by the addition of a second mole of MeOH followed by protodeauration.[14]



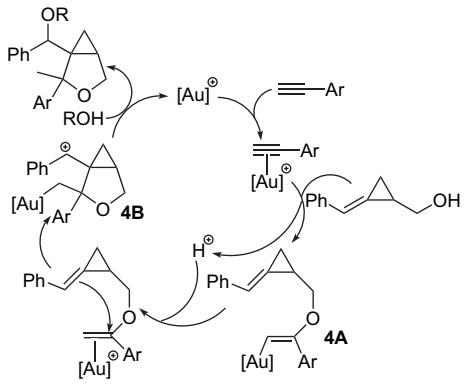
Scheme 2.

Agreeing with the Teles catalytic cycle, Schröder et al. illustrated the proton shuttle function of gold, i.e., **2D**, with intermediates **3D$_1$**, **3D$_2$** and **3D$_3$** pictured in Scheme 3.[18] These authors, however, suspected that the solvent assists the hydrogen migration or the deprotonation/protonation sequences.



Scheme 3.

As for the three-component addition reaction shown in Eq. 10, Tian and Shi proposed a mechanism based on deuterium labelling experiments and on the use of both (*E*)- and (*Z*)-2-(arylmethylene)cyclopropylcarbinol.[17] The addition of the cyclopropylcarbinol to the activated triple bond affords the vinylgold species **4A** that suffers a cascade rearrangement leading to an alkylgold cation **4B** (Scheme 4). The trapping of **4B** by the alcohol and the protodeauration affords the three-component adduct and the cationic catalyst.



Scheme 4.

2.2. Alkenes

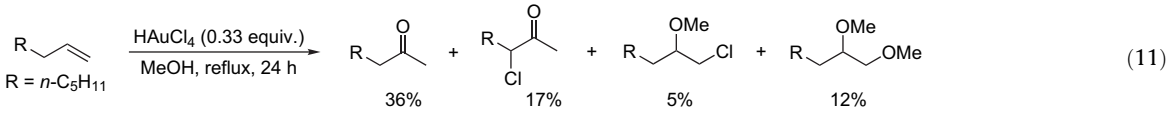
In 1976, Thomas et al. described the oxidation of various terminal alkenes using $HAuCl_4$ in MeOH: mixtures of ketones, α-chloroketones, 1-chloro-2-methoxyalkanes and 1,2-dimethoxyalkanes were obtained in most cases (Eq. 11).[19] In contrast, the use of $NaAuCl_4$ in H_2O/MeOH at reflux led to an almost quantitative recovery of the alkene.[9] As illustrated in Section 3.3 (Eq. 38),[20] the selective methoxylation of a methylenecyclohexane-type compound seems to be feasible in the presence of $AuCl_3$.

The Au^I-catalysed formation of 3-(2-hydroxyethyl)-5-methyleneoxazolidin-2-one from *tert*-butyl 2-hydroxyethylprop-2-ynylcarbamate is accompanied by the production of its *tert*-butyl ether as the main compound (Eq. 12). As the cyclisation process concomitantly generates isobutene, the primary alcohol function reacts with this alkene under the reaction conditions. In agreement with this proposal, the formation of 3-(2-*tert*-butoxyethyl)-5-methyleneoxazolidin-2-one was precluded in the presence of 10 equiv of MeOH.[21]

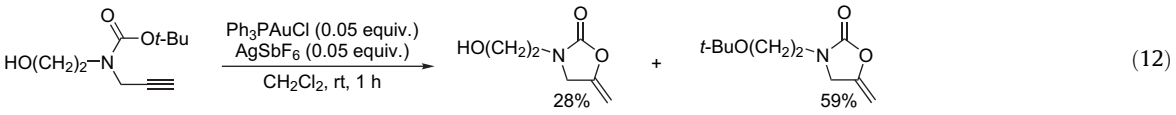
The above results indicated that the intermolecular addition of alcohols to alkenes in the presence of suitable Au catalysts could be more common than was usually suspected.[22] In fact, Zhang and Corma disclosed, in 2007, the effective $Au^{III}/CuCl_2$-catalysed addition of primary and secondary alcohols to alkenes (Eq. 13).[23] A possible mechanism is shown in Scheme 5. The coordination of both the alcohol and the substrate to Au^{III} leads to **5A**, and induces the insertion of the C=C bond into the O–Au bond to generate **5B**. Protolysis of the C–Au bond of **5B** affords the final ether and regenerates the catalyst. The role of $CuCl_2$ is to stabilise the catalyst in decreasing its propensity to be reduced into the less active Au^I and non-active Au^0.[23,24] Other possible intermolecular additions of alcohols to intermediates bearing a C=C bond are shown in Section 6.2.

2.3. Allenes

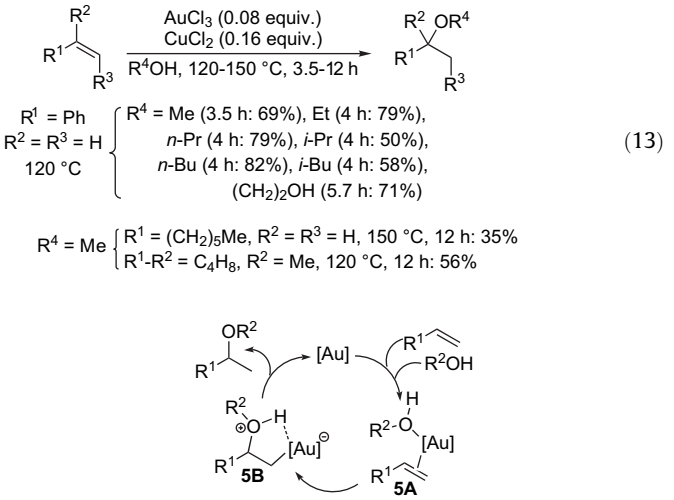
The addition of primary and secondary alcohols to allenes to form the corresponding vinylic ethers using Au^I complexes, e.g.,



(11)



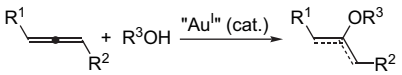
(12)



(13)

Scheme 5.

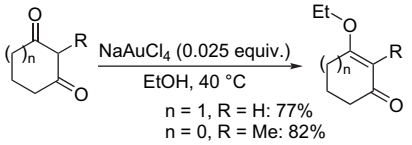
Ph_3PAuNO_3, as catalysts was mentioned in a patent from the BASF company (Eq. 14).[13]



(14)

2.4. Ketones

The Au^{III}-catalysed addition of EtOH to cyclic β-diketones involves the enolic form of the substrate, and affords the corresponding β-ethoxy-α,β-unsaturated ketones (Eq. 15).[25]



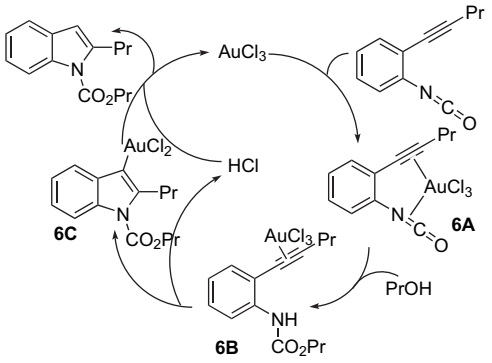
(15)

2.5. Isocyanates

In the absence of a catalyst, the treatment of 2-(1-pentynyl)-phenyl isocyanate with propanol led to the corresponding carbamate, i.e., a well-known reaction of isocyanates with alcohols.[26] The presence of an Au^{III} catalyst accelerates the addition of the alcohol to the NCO group and induces the formation of an indole derivative (Eq. 16).[27] A possible mechanism involves the dual role of the catalyst (Scheme 6). Both the alkynyl and isocyanate groups will coordinate to the gold centre to form **6A**. The Lewis acidic properties of Au^{III} would facilitate the addition of propanol, leading to **6B**, which is prone to intramolecular amination. This gives the alkenyl gold intermediate **6C** and HCl to finally yield the indole derivative and the starting catalyst.

3. Addition of exogenous alcohols to rearranged 'non-hydroxylated' enynes and allenenes

This section summarises processes for which the rearrangement of the enyne occurs before the addition of an exogenous alcohol,

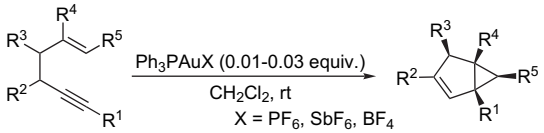


Scheme 6.

and will be limited to substrates without a hydroxy group or without the participation of such a substituent in the rearrangement pathway.

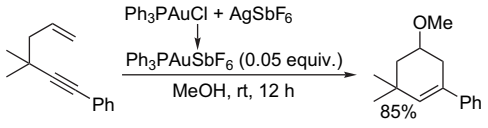
3.1. 1-En-5-ynes

In the course of their study of the Au^{I}-catalysed isomerisation of 1,5-enynes to bicyclo[3.1.0]hexenes (Eq. 17), Toste et al. used MeOH as a solvent to trap intermediates.[28] With 1-(3,3-dimethylhex-5-en-1-ynyl)benzene as the substrate and a cationic catalyst Ph_3AuSbF_6, obtained from a mixture of Ph_3AuCl and $AgSbF_6$, they isolated a cyclohexenyl methyl ether in good yield (Eq. 18). To obtain such a compound, a quaternary carbon at the propargylic position is required to prevent the competing formation of the bicyclo[3.1.0]hexene. It seems that Ph_3PAuCl or $AuCl_3$ as the catalyst was less efficient.



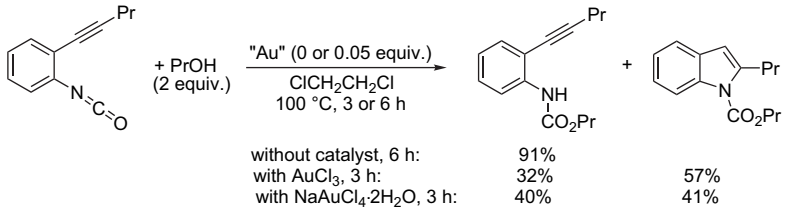
R1 = H, R2 = Ph, R3 = R4 = R5 = H, X = PF_6: 99%
R1 = R2 = Ph, R3 = R4 = R5 = H, X = SbF_6: 94%
R1 = H, R2 = Ph, R3 = H, R4 = CH_2OAc, R5 = H, X = SbF_6: 96%
R1 = R2 = H, R3 = Bn, R4 = R5 = H, X = SbF_6: 82%
R1 = R2 = R3 = R4 = H, R5 = CH_2OTIPS, X = SbF_6: 61%

(17)

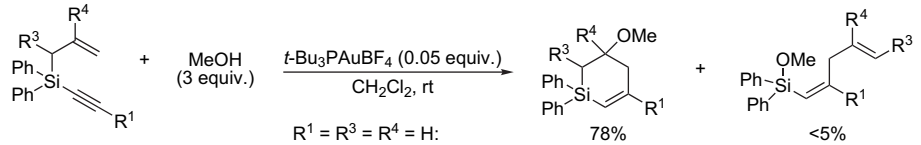


(18)

Toste's team has subsequently exploited this MeOH addition for the synthesis of vinylic diphenylsilanes (Eqs. 19 and 20).[29] The ratio of the cyclic and acyclic products depended upon the nature of both the substituents (Eq. 19) and the catalyst anion (Eq. 20). It was noted that the process is not affected by a propargylic hydroxyl (Eq. 19). Since the expected products were not isolated when dimethylsilanes instead of diphenylsilanes were used, the authors surmised that the desired rearrangement is followed by a rapid protodesilylation of the resulting vinylic dimethylsilanes.

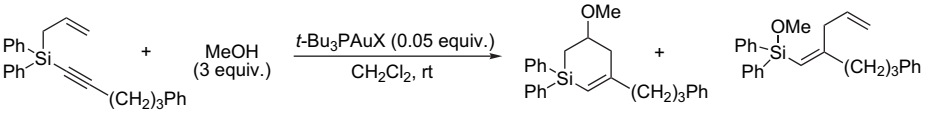


(16)



$R^1 = R^3 = R^4 = H$:	78%	<5%
$R^1 = CH_2OBn$, $R^3 = R^4 = H$:	74%	5%
$R^1 = CH(OH)Ph$, $R^3 = R^4 = H$:	76%	0%
$R^1 = CHPh(allyl)$, $R^3 = R^4 = H$:	68%	0%
$R^1 = CO_2Me$, $R^3 = H$, $R^4 = Me$:	75%	0%
$R^1 = Ph$, $R^3 = H$, $R^4 = Me$:	33%	64%
$R^1 = (CH_2)_3Ph$, $R^3 = Me$, $R^4 = H$:	0%	66%

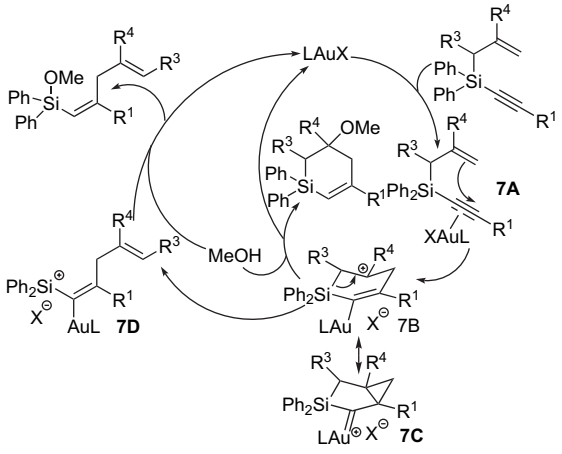
(19)



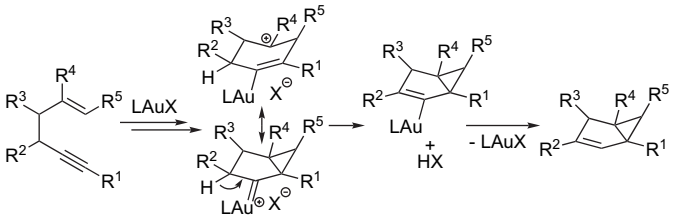
X = SbF_6, 20 min:	52%	48%
X = BF_4, 50 min:	78%	12%

(20)

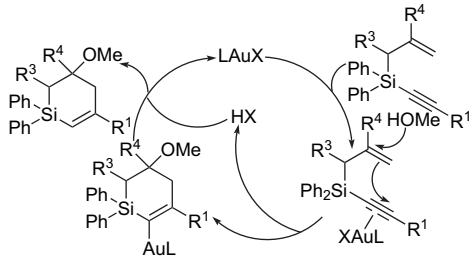
The proposed mechanism (Scheme 7) involves the S_E2' addition of the allylsilane to the Au^I-complexed alkyne **7A**, affording a stabilised cationic complex **7B** (gold carbene **7C** as a resonance structure).[29,30] Two reactive pathways can occur from this intermediate: trapping by MeOH that affords the cyclic silane, or fragmentation of an Si–C bond leading to a silyl cation **7D**. The reaction of **7D** with MeOH provides the acyclic silane. The substituent-dependent steric interactions developed at the level of **7B**/**7C** can explain the observed selectivities, in particular, when R^3=Me, the steric clash between the methyl group and the silicon substituents increases the relative rate of the fragmentation and, consequently, leads only to the acyclic silane. This mechanistic proposal is in agreement with the formation of the bicyclo[3.1.0]-hexenes outlined in Eq. 17. Indeed, with the CHR^2 group instead of $SiPh_2$, the key intermediate evolves towards the bicyclic compound via a formal 1,2-hydrogen shift (Scheme 8). A possible mechanism, as shown in Scheme 9, has not been suggested for the formation of the cyclic silane, probably because of the anteriority of the metal-catalysed isomerisation of 1,5-enynes to bicyclo[3.1.0]hexenes,[28,31,32] for which deuterium labelling has provided evidence for the cationic intermediates.[3e,28]



Scheme 7.

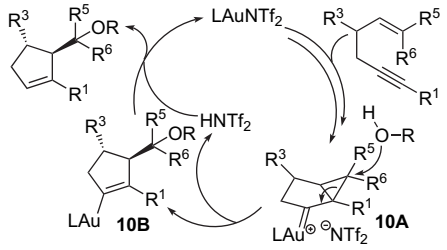


Scheme 8.

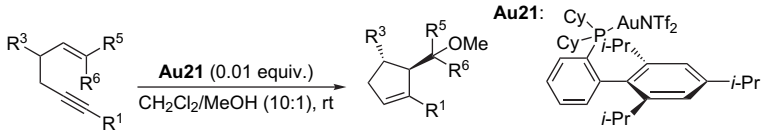


Scheme 9.

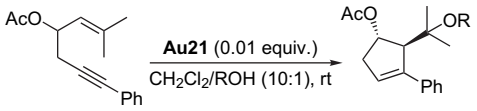
Almost simultaneously, Gagosz et al. disclosed a different reaction course: functionalised cyclopentenes were efficiently obtained from the reaction between various 1,5-enynes and alcohols (Eqs. 21 and 22) in the presence of, mainly, **Au21** as the catalyst, with $Ph_3PAuNTf_2$ and [*n*-BuP(adamantyl)$_2$]$AuNTf_2$ leading to lower yields and to by-products derived from the alkoxylation of the alkyne.[33] The mechanistic scheme proposed by the authors involves the addition of the alcohol to a gold carbene intermediate **10A** (Scheme 10). This leads to the cleavage of the weakest bond of the cyclopropyl ring to afford a vinylgold species **10B**, which is protodemetallated to deliver the organic compound. When the substrate bears a propargylic hydroxy substituent, the competitive formation of the bicyclo[3.1.0]hexanone (see Section 8.3.1) was not observed, but this group was etherified (Eq. 23). According to the authors, the absence of the bicyclic ketone is due to the rapid attack of methanol on intermediate **10A**, while the introduction of a methoxy unit in the hydroxyl position results from either an Au-catalysed propargylic substitution of the substrate or an Au-catalysed substitution of the intermediate allylic alcohol, both by methanol. Given the results depicted in Eqs. 126 and 127 (see Section 8.3.1) for reactions carried out between −20 °C and room



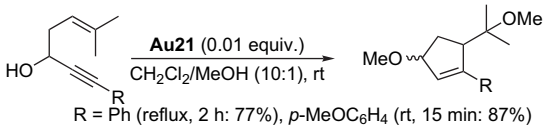
Scheme 10.



(21)



(22)

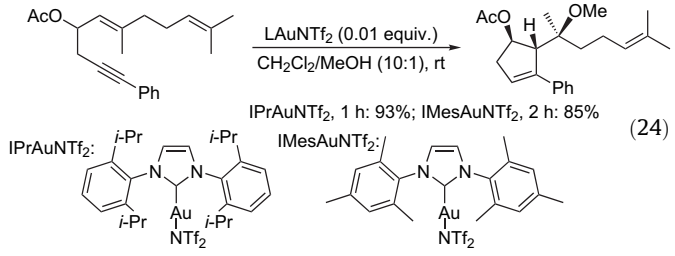


(23)

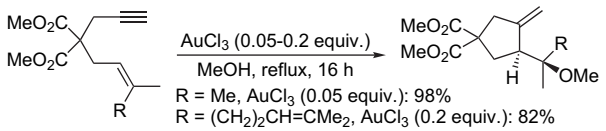
temperature, we suspect, however, that the non-formation of the bicyclo[3.1.0]hexanone is rather due to other factors, possibly the nature of the catalyst.

Subsequently, Ricard and Gagosz have synthesised air-stable *N*-heterocyclic carbene Au^{I} bis(trifluoromethanesulfonyl)imidate complexes that are effective for the catalysed methoxylation of 1,5-enynes (Eq. 24).[34]

A rationalisation of the differences of the reaction courses illustrated by Eqs. 18–20 versus Eqs. 21–24 is not obvious. A plausible explanation could be based on the substitution of the substrates: Toste's 1,5-enynes (Eqs. 18–20) are terminal alkenes, while the C=C bond of Gagosz's 1,5-enynes (Eqs. 21–24) is di- or trisubstituted. An alternative explanation is based on the nature of the catalyst. Both catalysts are cationic phosphinated Au^{I} complexes, but the phosphine ligands as the counteranions are different. Given the results depicted in Eq. 20, the counteranion may have a determinant role.



(24)

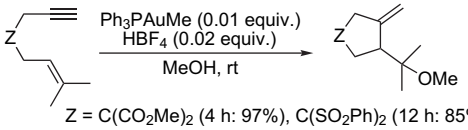


(25)

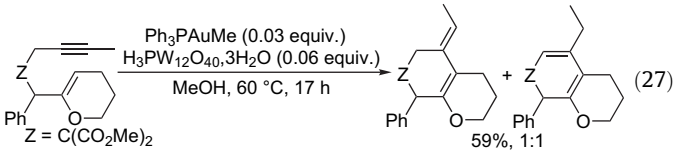
Moreover, it is known that NTf_2^- is a weakly coordinating anion,[35] and the difference of reactivity between $Ph_3PAuSbF_6$ and $Ph_3PAuNTf_2$ towards enynes has been exemplified.[36]

3.2. 1-En-6-ynes

In 2001, Echavarren et al. reported that $AuCl_3$ catalysed the methoxycyclisation of a few 1-en-6-ynes (Eq. 25),[37,38] but with erratic results that could be attributed to the hygroscopic nature of this metal chloride.[37] The reaction became more efficient, requiring lower amount of catalyst and room temperature instead of reflux, with the use of an Au^{I} catalyst generated from Ph_3PAuMe and a protic acid such as CF_3CO_2H, HBF_4 or $H_3PW_{12}O_{40}\cdot 3H_2O$ (Eq. 26).[39,40] Ethanol instead of methanol has also been used[41] and the cationic complexes $[Ph_3PAu(ROH)]^+$ were presumably formed.[39,41] These Au^{I}-catalysed conditions have led to the synthesis of a panel of functionalised compounds;[39–41] an example of cyclisation without alkoxylation has, nevertheless, been reported (Eq. 27).[42]



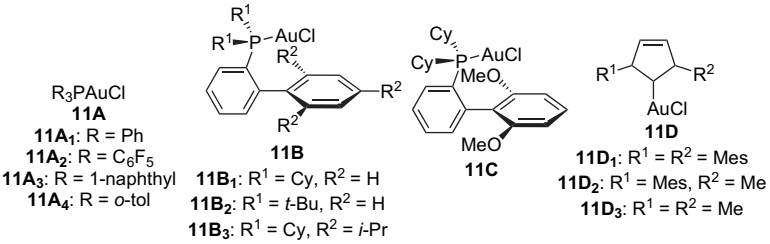
(26)



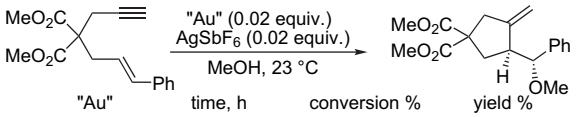
(27)

The superiority of the cationic Au^{I} complexes over the neutral Au^{I} and Au^{III} complexes[37,39] led Echavarren et al. to experiment with various catalysts obtained from mixtures of $AgSbF_6$ and LAuCl. Scheme 11 and Eq. 28 illustrate some of these LAuCl complexes **11A$_1$**–**11A$_4$**, **11B$_1$**–**11B$_3$**, **11C** and **11D$_1$**–**9D$_3$** and their influence on the results.[41,43,44] As exemplified by a comparison of the methoxycyclisations depicted in Eqs. 28 and 29, the substituents at the alkene dictate the regioselectivity in the C–C bond formation. When the C=C bond is substituted by a CH_2SiMe_3 group, as shown in Eq. 30, the desilylation takes place, leading to a 1,4-diene without incorporation of the alkoxy unit.[41]

Echavarren's team has also reported enantioselective alkoxycylisations of 1-en-6-ynes.[45] A number of chiral Au^{I} complexes have

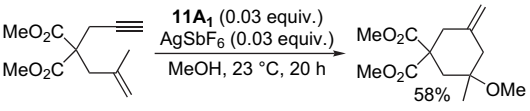


Scheme 11.

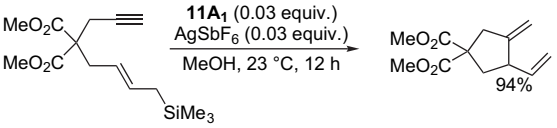


"Au"	time, h	conversion %	yield %
AuCl	48	50	35
11A$_1$	18	93	70
11A$_2$	48	66	44
11A$_4$	30	>98	79
11B$_1$	18	>98	68
11B$_3$	18	>98	94
11D$_1$	20	>98	76
11D$_2$	24	73	51
11D$_3$	48	84	48

(28)



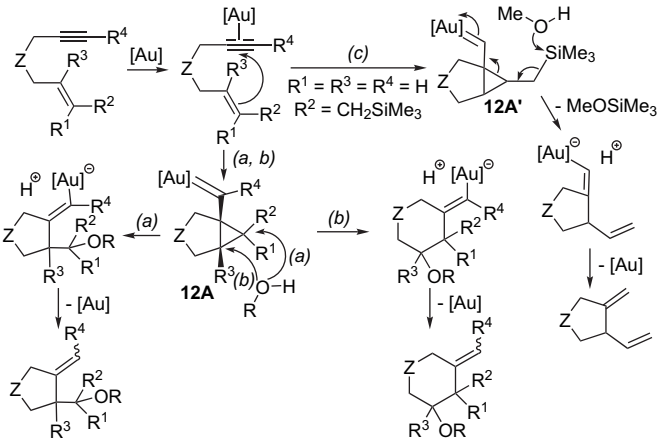
(29)



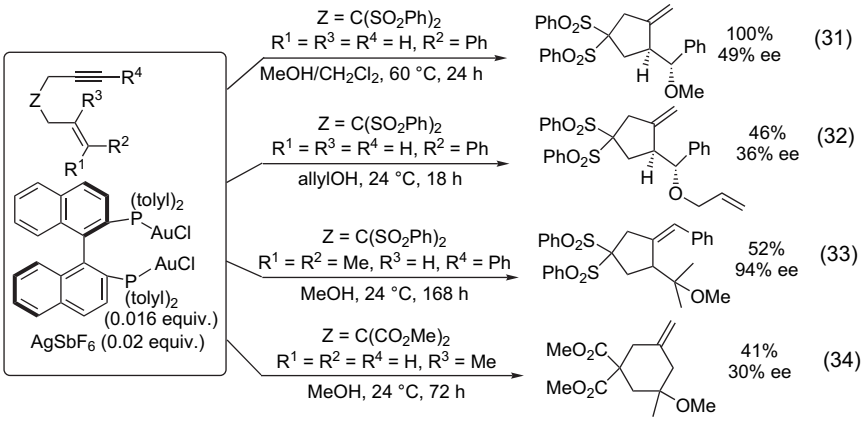
(30)

been tested, one of which, associated with $AgSbF_6$, has led to enantioselectivities up to 94% (Eqs. 31–34).

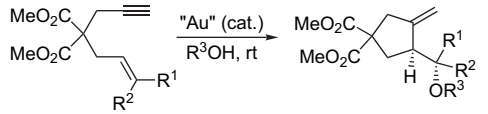
The alkoxycyclisations of 1-en-6-ynes summarised in the above equations can occur as illustrated in Scheme 12 and this agrees with deuteration studies and DFT calculations.[37] The coordination of the triple bond of the substrate promotes the 5-*exo*-*dig* cyclisation, leading to a cyclopropyl gold carbene complex **12A**. The addition of ROH to **12A** following path a or b affords either the five-membered (path a) or six-membered (path b) heterocycle. According to



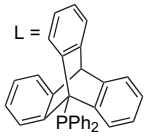
Scheme 12.



Gagosz et al. have developed cationic Au^I complexes having NTf_2 as the counteranion; these complexes would be more convenient to prepare, store and handle and, moreover, have a good catalytic activity (Eq. 35).[36] Recently, Genêt, Michelet and co-workers have, nevertheless, described the alkoxycyclisation of various 1-en-6-ynes using a mixture of $AuCl_3$, $AgSbF_6$ and PPh_3: high yields were also obtained, but to the detriment of the amount of catalyst (Eq. 35).[46] Subsequently, Ricard and Gagosz have reported the use of their air-stable *N*-heterocyclic carbene Au^I bis(trifluoromethanesulfonyl)imidate complexes to catalyse these reactions (Eq. 35; see Eq. 24 for the structure of $IPrAuNTf_2$).[34]



$LAuNTf_2$ (0.01 equiv.), 75 min:
$R^1 = R^2 = R^3$ = Me: 97%
$AuCl_3$ (0.1 equiv.), $AgSbF_6$ (0.3 equiv.), PPh_3 (0.1 equiv.), 20-24 h:
R^1 = Ph, R^2 = H, R^3 = Et: 98%, allyl: 99%
$R^1 = R^2 = R^3$ = Me: 98%
$IPrAuNTf_2$ (0.01 equiv.),
$R^1 = R^2 = R^3$ = Me, 30 min: 96%
R^1 = Ph, R^2 = H, R^3 = Me, 1.5 h: 95%



(35)

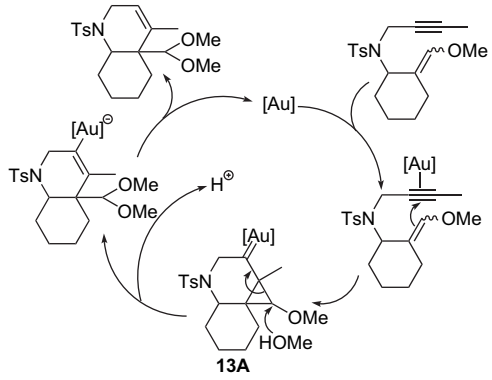
Echavarren et al., the selectivity, i.e., the nucleophilic attack of **12A**, is controlled by the electronegativity of Z,[37] but, given the results shown in Eqs. 25, 26, 28, 29 and 31–34, it seems that the nature of R^3 is the determining factor. The formation of the 1,4-diene when R^2=CH_2SiMe_3 (Eq. 30) is due to desilylation by attack of MeOH on the intermediate **12A′** (path c).[41]

Although the $AuCl_3$-catalysed methoxycyclisation of 1-en-6-ynes could afford erratic results,[37] $AuCl_3$ is effective when the C=C bond belongs to an enol ether group (Eqs. 36 and 37).[38,47] At first sight, the difference of regioselectivity in the C–C bond formation illustrated in Eqs. 36 and 37 is attributable, as envisaged above, to the difference of substitution of the C=C bonds, but, in fact, the processes would be different. Indeed, the reactions depicted in Eq. 36 are explained via 5-*exo*-*dig* cyclisations, as shown in Scheme 12 (path a), while the methoxycyclisation of Eq. 37 would involve the 6-*endo*-*dig* process leading to intermediate **13A** (Scheme 13).

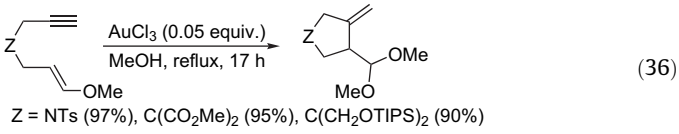
Hotha et al. have reported the alkoxylation of 1-en-6-ynes bearing a propargylic oxygen atom. These reactions, involving the cleavage of the C–(OCH_2C≡CH) bond, will be reported in Section 5.

3.3. 1-En-7-ynes

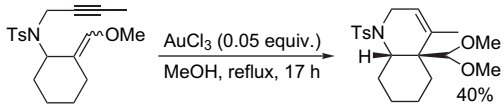
In 2003, Echavarren, Genêt and co-workers isolated 1-methoxy-1,5-dimethyl-2-(prop-1-en-2-yl)cyclohexane from the Au^{III}-



Scheme 13.

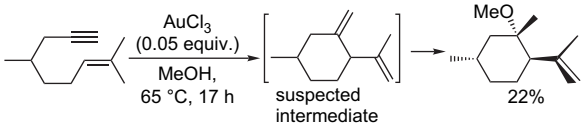


(36)



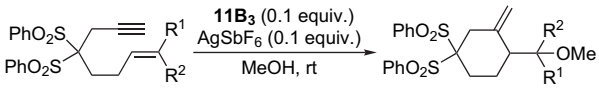
(37)

catalysed methoxycyclisation of 4,8-dimethylnon-7-en-1-yne (Eq. 38).[20] These authors suggest 4-methyl-2-methylene-1-(prop-1-en-2-yl)cyclohexane as the intermediate and the addition, catalysed by the Lewis acid $AuCl_3$, of MeOH to its exocyclic methylene.



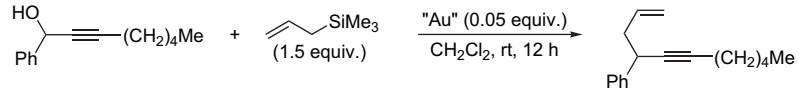
(38)

Recently, a different reaction course of 1-en-7-ynes was reported by Echavarren et al. under cationic Au^I catalysis (Eq. 39).[48] The efficiency of this methoxycyclisation is sensitive to the nature of the ligand: no conversion was initiated by the Au^I complex in situ generated from $(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3PAuCl$ and $AgSbF_6$. As for alkoxycyclisations described in Section 3.2, the product would be realised from the reaction between the alcohol and a cyclopropyl gold carbene intermediate.



(39)

$R^1 = R^2 = Me$, 36 h: 70%
$R^1 = (CH_2)_2CH{=}CMe_2$, $R^2 = Me$, 15 h: 72%

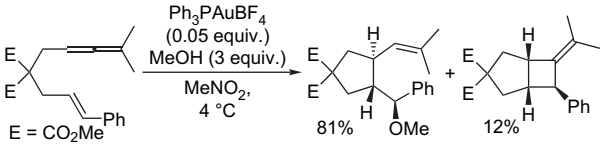


(41)

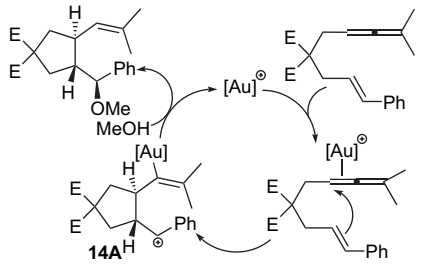
$NaAuCl_4{\cdot}2H_2O$: 82%, $AuBr_3$: 68%, $AuCl_3$: 65%, $HAuCl_4{\cdot}3H_2O$: 60%
AuCl: 30%, Ph_3PAuCl: 0%

3.4. 1-En-6-allenes

The cationic intermediate **14A**, formed from the Au-catalysed intramolecular addition of the C=C bond to the allenic moiety of a 1-en-6 allene, is effectively trapped by methanol (Eq. 40 and Scheme 14).[49]



(40)



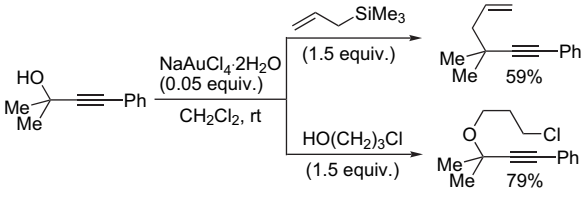
Scheme 14.

4. Formation of C–C or C–heteroatom bonds involving cleavage of C–OH bonds

The formation of ethers from the intermolecular dehydration of alcohols will be documented in Section 12.

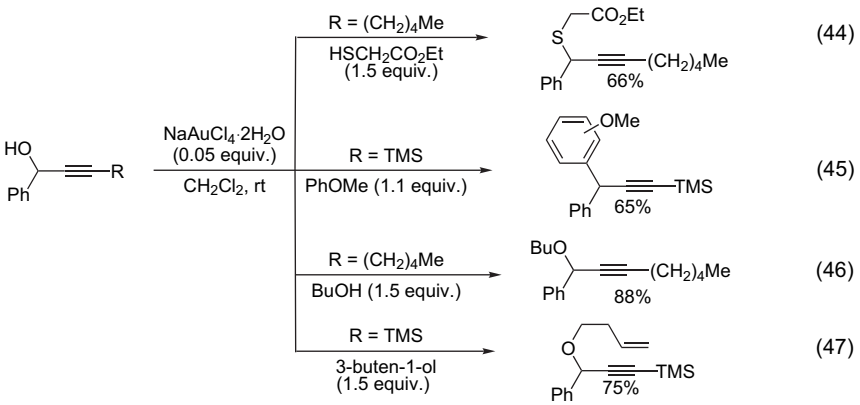
4.1. Intermolecular reactions

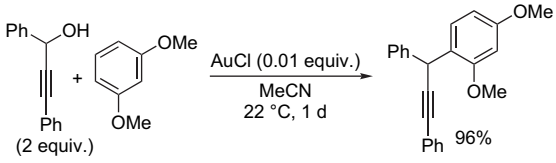
Although the formation of methoxy ethers depicted in Eqs. 7 and 23 can be envisaged as the result of propargylic substitutions, the discovery of the Au-catalysed nucleophilic substitution of propargylic alcohols has to be attributed to Campagne et al.[50] The screening of different catalysts has shown that the formation of the C–C bond from the reaction between 1-phenyloct-2-yn-1-ol and allyltrimethylsilane occurred more efficiently with Au^{III} than with Au^I catalysts (Eq. 41). The 1,5-enyne thus obtained is stable under the experimental conditions, except in the presence of $HAuCl_4{\cdot}3H_2O$ that promotes its cycloisomerisation into the corresponding bicyclo[3.1.0]hexane, a reaction already described by Toste et al. (Eq. 17).[28] Tertiary propargyl alcohols (Eqs. 42 and 43) and various nucleophilic species such as aromatic compounds, thiols and alcohols have been used (Eqs. 44–47). It was anticipated that the substitution process occurs after coordination of both the triple bond and the hydroxyl group to the catalyst, but the formation of the racemic adduct from an enantiomerically enriched propargylic alcohol has suggested a mechanism through a carbonium intermediate.[50] This agrees with the subsequent report of Dyker et al., who considered that the Au^I-catalysed substitutions of 1,3-diphenylprop-2-yn-1-ol with 1,3-dimethoxybenzene (Eq. 48), 1,3,5-trimethoxybenzene, 2,4-dimethoxybenzaldehyde or azulene are Friedel–Crafts-type reactions.[51] Consequently, these substitution reactions are probably due to the Lewis acid properties of the catalyst.[52]



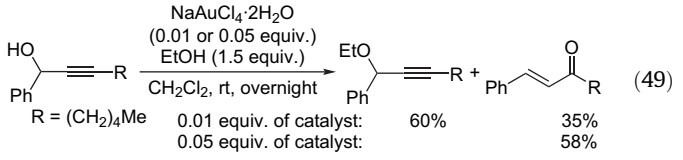
(42)

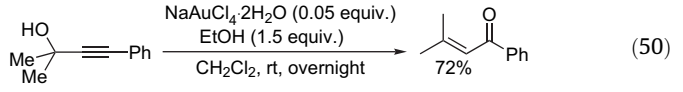
(43)



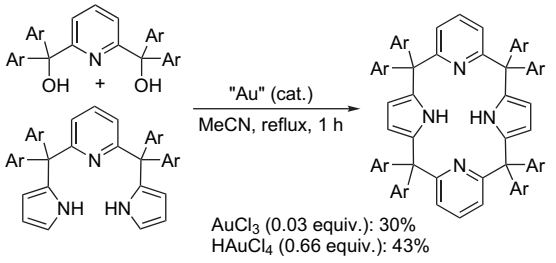


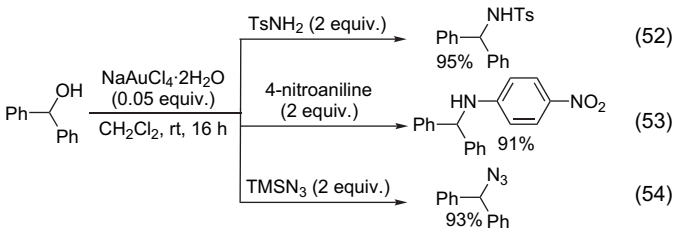
For the addition of ethanol to a secondary propargylic alcohol under Campagne's conditions, a low amount of catalyst has to be used to obtain the propargylic ether, an increase promoting the evolution of the product towards an unsaturated ketone (Eq. 49).[50,53] The formation of an unsaturated ketone from the $NaAuCl_4$-catalysed reaction of ethanol with a tertiary propargylic alcohol has also been reported (Eq. 50),[50,53] but this is not the rule.[54]

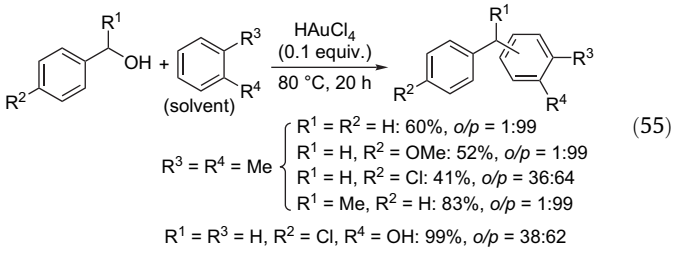




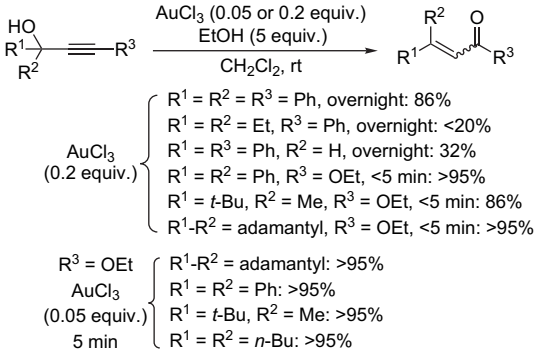
The teams of Dyker[51] Campagne and Prim[55] have exploited the Lewis acid properties of Au^{III} salts to cleave the C–OH bond of benzhydryl alcohols. Thus, Dyker et al. succeeded in the synthesis of a heterocalixarene (Eq. 51), while Campagne, Prim and co-workers effected the amination of a variety of aromatic and heteroaromatic substrates with tosylamine, 4-nitroaniline and trimethylsilyl azide (Eqs. 52–54). It has been observed that (i) an Au^{I} catalyst such as Ph_3PAuCl was inefficient and (ii) the $NaAuCl_4$-catalysed amination with $TsNH_2$ also occurred from 1-phenylethanol, but led to unchanged benzyl alcohol.[55] In contrast, $HAuCl_4$-catalysed benzylation of arenes occurs with both 1-phenylethanol and benzyl alcohol, as reported by Beller et al. (Eq. 55).[56,57]



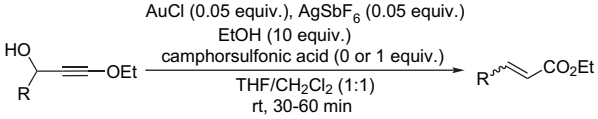




The possibility of a carbonium intermediate from the Au-catalysed reaction of propargylic alcohols[50,51] led Dudley et al. to study their Meyer–Schuster rearrangement.[58–60] It was firstly proved that $AuCl_3$ in the presence of ethanol (Eq. 56) is much more effective as a catalyst than protic acids.[58] The efficiency depended, however, on the substituents and was low from secondary propargylic alcohols. According to a subsequent report, mainly devoted to the rearrangement of secondary ethoxyalkynyl carbinols, a cationic Au^{I} catalyst ($AuCl/AgSbF_6 > AuCl_3$, AuCl, Ph_3PAuCl) with ethanol ($EtOH \gg CF_3CH_2OH$, AcOH, PhOH) as additive in a THF/CH_2Cl_2 mixture ($THF/CH_2Cl_2 > THF$, CH_2Cl_2, EtOH, H_2O) is the optimum system.[58] Inclusion of camphorsulfonic acid in the reaction mixture improved the stereoselectivity of most rearrangements (Eq. 57). A reasonable mechanistic sequence, that, in fact, does not involve a carbonium intermediate, has been proposed (Scheme 15).[59] The coordination of the substrate to the catalyst promotes the substitution by the alcohol to generate a diethoxyallenic complex **15A** and water. The reincorporation of water produces **15B**, the protolysis of which yields **15C** that evolves to the enoate. It has been envisaged that diethoxyallene could be liberated from **15A** and that the reincorporation of water led to **15C** without gold assistance.[59] According to the authors, the formation of a mixture of α,β-unsaturated ethyl and *n*-propyl esters, when *n*-propanol instead of ethanol was used, is consistent with the intermediate **15A** (see, however, Section 14, Eq. 173).[59]



(56)



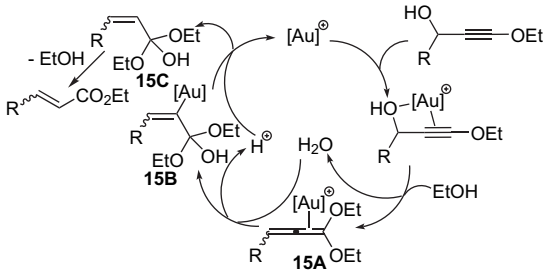
without camphorsulfonic acid:

R = cyclohexyl (75%, *E*/*Z* = 57:43), 1-cyclohexenyl (72%, *E*/*Z* = 40:60), *t*-Bu (91%, *E*/*Z* = 97:3), $Ph(CH_2)_2$ (80%, *E*/*Z* = 94:6), $Me(CH_2)_7$ (91%, *E*/*Z* = 63:37), Ph (90%, *E*/*Z* = 47:53)

(57)

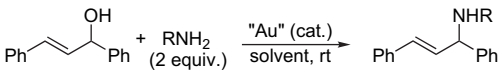
with camphorsulfonic acid:

R = cyclohexyl (78%, *E*/*Z* = 70:30), 1-cyclohexenyl (70%, E/Z = 40:60), *t*-Bu (93%, *E* only), $Ph(CH_2)_2$ (82%, *E*/*Z* = 99:1), $Me(CH_2)_7$ (90%, *E*/*Z* = 86:14), Ph (92%, *E*/*Z* = 91:9)



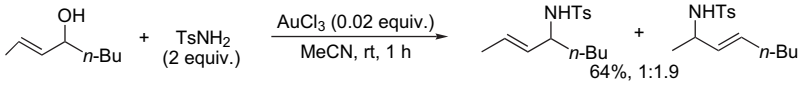
Scheme 15.

In 2007, Liu et al. disclosed the gold-catalysed substitution of secondary and tertiary allylic alcohols with tosylamine or arylamines. As outlined in Eq. 58, $AuCl_3$ is a better catalyst than a cationic Au^I complex.[61] The formation of regioisomers from dissymmetric substrates (Eq. 59) and the non-amination of primary allylic alcohols lead the authors to suspect that the reaction occurred via an allylic cation. Subsequently, Liang et al. reported the amination of 1-en-4-yn-3-ols (Eq. 60).[62] Under the reaction conditions, the enynamines evolve with time towards the corresponding pyrroles.

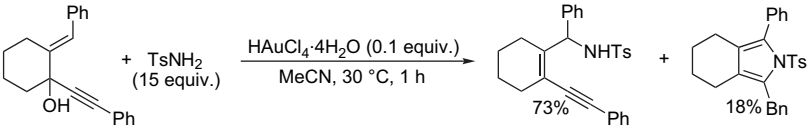


(58)

R = Ts, $AuCl_3$ (0.02 equiv.), MeCN, 30 min: 87%
R = Ts, Ph_3PAuCl/AgOTf (0.05 equiv.), THF, 12 h: 76%
R = *p*-$NO_2C_6H_4$, $AuCl_3$ (0.02 equiv.), MeCN, 30 min: 92%

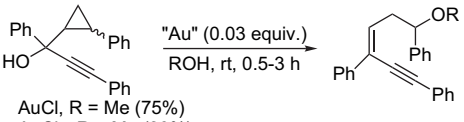


(59)



(60)

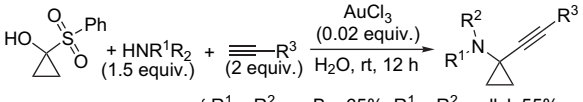
Liang et al. have, moreover, developed the synthesis of (*Z*)-conjugated enynes via the Au-catalysed addition of various alcohols to 1-cyclopropyl-2-yn-1-ols (Eq. 61).[63] The authors suggest that the reaction is initiated by the gold activation of the cyclopropanol unit. As all of the reported substrates bear a triple bond, we, nevertheless, suspect the role of this unsaturation.



AuCl, R = Me (75%)
$AuCl_3$, R = Me (80%)
$HAuCl_4·4H_2O$, R = Me (90%), Et (82%), *i*-Pr (88%), *t*-Bu (80%)*, $Cl(CH_2)_2$ (85%), CH_2=$CHCH_2$ (82%), CH≡CCH_2 (78%), Bn (80%)
*at 60 °C

(61)

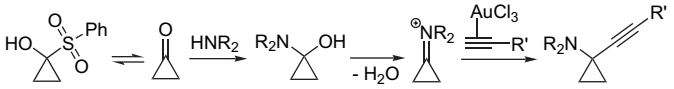
Recently, Chen et al. reported the synthesis of 1-alkynyl cyclopropylamines from the Au^{III}-catalysed reaction, in water, between 1-(arylsulfonyl)cyclopropanol, a terminal alkyne and a secondary amine (Eq. 62).[64] According to the proposed mechanism (Scheme 16), the cleavage of the C–O bond of the cyclopropanol would, in fact, not be mediated by the Au salt.



R3 = Ph { R1 = R2 = *n*-Bu: 65%, R1 = R2 = allyl: 55%; R1-R2 = $(CH_2)_4$: 55%, R1-R2 = $(CH_2)_5$: 62%

R3 = 1-cyclohexenyl { R1 = R2 = *n*-Bu: 48%; R1-R2 = $(CH_2)_5$: 62%

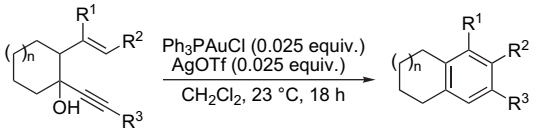
(62)



Scheme 16.

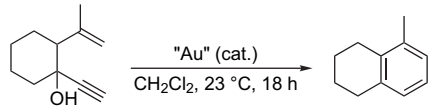
4.2. Intramolecular reactions

The Au-catalysed benzannulation of tertiary 3-hydroxy-1,5-enynes has been carried out by Barriault et al., with an efficiency depending upon the nature of the substituents (Eq. 63) and the catalyst, the best catalyst being the cationic Au^I complex obtained from Ph_3PAuCl and AgOTf (Eq. 64).[65,66] Through different mechanistic possibilities, the authors retain the scenario shown in Scheme 17.[66] The 6-*endo*-*dig* attack of the C=C bond to the coordinated alkyne affords the cationic vinylgold complex **17A**, and the subsequent deprotonation, protonation and aromatisation sequences yield the aromatic compound.



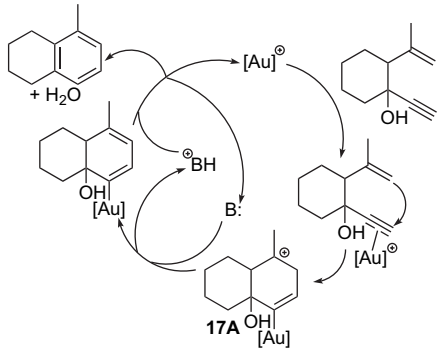
n = 0
R^1 = Me, R^2 = R^3 = H: 28%
n = 1
R^1 = R^2 = R^3 = H: 10%; R^1 = Ph, R^2 = R^3 = H: 84%
R^1 = R^3 = Me, R^2 = H: 77%; R^1 = Me, R^2 = H, R^3 = Ph: 86%
R^1-R^2 = $(CH_2)_4$, R^3 = H: 70%; R^1-R^2 = $(CH_2)_4$, R^3 = Ph: 81%
R^1 = OEt, R^2 = R^3 = H: 12%; R^1-R^2 = OCH=CH, R^3 = H: 57%
n = 2
R^1 = Me, R^2 = R^3 = H: 51%; R^1 = Me, R^2 = H, R^3 = Ph: 65%

(63)



$AuCl_3$ (0.025 equiv.): 22%
AuCl (0.025 equiv.): 22%; Ph_3PAuCl (0.025 equiv.): 0%
Ph_3PAuCl + AgX (0.05 equiv. each), X = SbF_6: 22%, X = BF_4: 42%
Ph_3PAuCl + AgOTf (0.025 equiv. each): 84%
Ph_3PAuCl + HOTf (0.025 equiv. each): 79%
Ph_3PAuCl + CCl_3CO_2H (0.025 equiv. each): 38%
Ph_3PAuCl + CF_3CO_2H (0.025 equiv. each): 0%
AuCl + HOTf (0.025 equiv. each): 29%

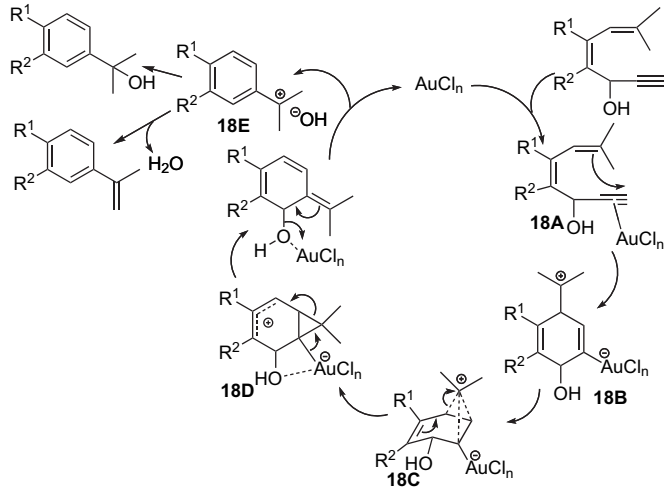
(64)



Scheme 17.

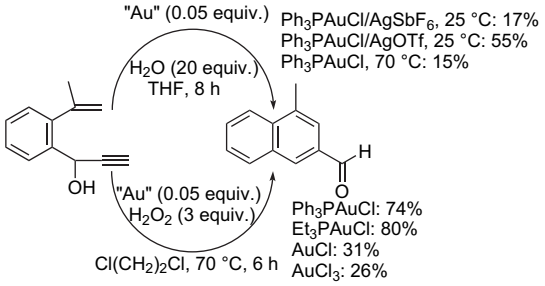
Benzannulations from secondary *cis*-4,6-dien-1-yn-3-ols have been reported by Liu et al. (Eq. 65).[67,68] The suspected mechanism of this reaction, that is efficiently catalysed with Au^I and Au^{III} chlorides, is depicted in Scheme 18.[67] The 6-*endo*-*dig* cyclisation of the π-alkyne complex **18A** gives **18B**, which forms the non-classical carbocation **18C** via a through-space overlap of the tertiary cation with the C=C–Au double bond. This leads to the allylic cation **18D**. Cleavage of the cyclopropane ring of **18D** followed by the Au-assisted cleavage of the C–OH bond generates the cationic species **18E** that evolves towards the products.

When the internal C=C bond of the substrate belongs to an aromatic ring, the Au catalysis, in the presence of water or hydrogen peroxide, leads to naphthyl aldehydes or ketones (Eq. 66).[69] This oxidative benzannulation involves the 6-*exo*-*dig* cyclisation of **19A** giving **19B** (Scheme 19). The deprotonation of **19B** followed by proton-assisted dehydroxylation of the vinylgold complex **19C**



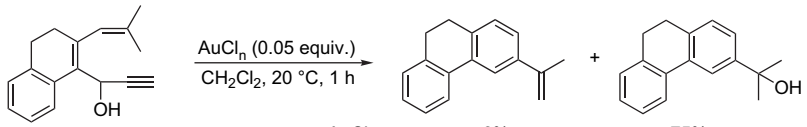
Scheme 18.

leads to the carbene **19D** that is oxygenated with H_2O or H_2O_2 to afford the corresponding carbonyl compound. In the absence of added H_2O or H_2O_2, it has been shown that **19D** evolves towards the olefin product when R is an alkyl group. Since water is released from **19C** before the formation of **19D**, the oxidative step should proceed in the absence of added water, but its reaction rate would be decreased.



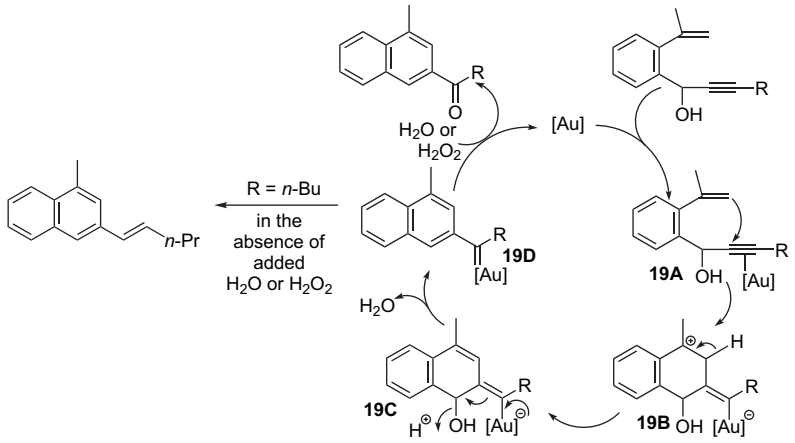
(66)

Liu's team has also synthesised naphthyl ketones from the Au-catalysed cycloisomerisation of 1,6-diyne-4-en-3-ols (Eq. 67). This process is very sensitive to the nature of the catalyst: the Ph_3PAuCl/AgOTf mixture led to good yields, while no reaction or decomposition products were observed with AuCl, $AuCl_3$, Ph_3PAuCl and $Ph_3PAuCl/AgSbF_6$.[70] The first step of the reaction would be the coordination of the propargylic alcohol moiety to the cationic catalyst to form a chelate **20A** (Scheme 20). The 6-*endo*-*dig* attack of the free alkyne group to the π-alkyne would generate the vinylgold intermediate **20B**, which would be captured by water to yield **20C** on liberating a proton. The enol/ketone tautomerisation of **20C** could induce the expulsion of water to generate **20D**, the proto-deauration of which affords the naphthyl ketone and the starting catalytic species. A trace amount of water is sufficient for this catalytic sequence because 1 equiv of water is released in the final step.[70] This contrasts with the benzannulation conditions of Eq. 66 that use an excess of water.

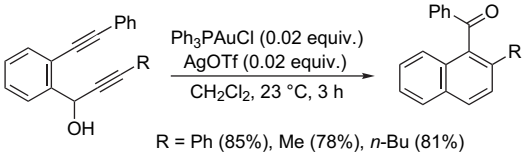


AuCl: 6% 75%
AuCl + MS 4 Å: 81%
$AuCl_3$: 6% 83%

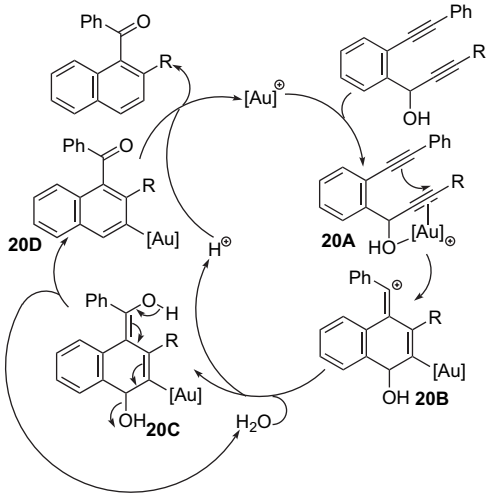
(65)



Scheme 19.



(67)



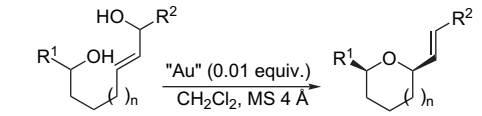
Scheme 20.

Other transformations of propargylic alcohols into α,β-unsaturated ketones, for which a mechanism involving the cleavage of the C–OH bond has been proposed,[61] are included in Section 6.1.1 (see Eqs. 77–82).

Recently, Aponick et al. disclosed the synthesis of 2-alkenyltetrahydro-pyrans and -furans from monoallylic diols using Au^{I} and Au^{III} catalysts and, in particular, the in situ produced cationic $Ph_3PAuOTf$ (Eq. 68). The proposed mechanism would involve the addition of the pendent hydroxyl group to the Au-coordinated allylic alcohol rather than to an allylic carbocation intermediate.[71]

5. Formation of C–O bonds involving cleavage of C–OR bonds (R≠H)

Hotha and Kashyap have exploited the alkynophilicity of $AuCl_3$ for the addition of various alcohols to a 3-*O*-propargyl protected glucal (Eq. 69).[72] Instead of the formation of heterocycles as expected from the reactions of 1-en-6-ynes depicted in Section 3.2, this

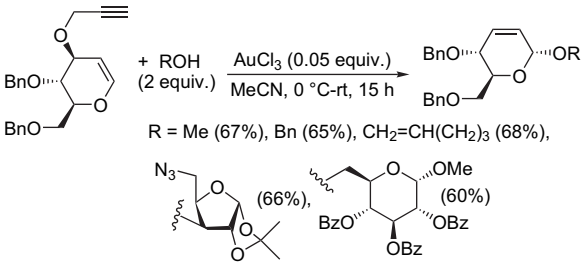


n = 1, R^1 = H, R^2 = Cy, rt:
- $AuCl_3$, 100 min: 87%
- AuCl, 16 h: 41%
- Ph_3PAuCl, 16 h: 0%
- Ph_3PAuCl/AgOTf, 40 min: 96%

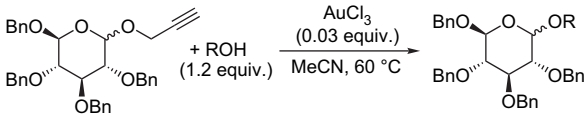
Ph_3PAuCl + AgOTf:
- n = 1, R^1 = H, R^2 = Ph, rt, 0.5 h: 89%
- n = 1, R^1 = Cy, R^2 = H, rt, 0.33 h: 95%, 11:1 dr
- n = 1, R^1 = Cy, R^2 = H, -50 °C, 8 h: 80%, >25:1 dr
- n = 1, R^1 = $EtOCOCH_2$, R^2 = H, rt, 0.5 h: 96%, 6:1 dr
- n = 1, R^1 = $BnOCH_2$, R^2 = H, -50 °C, 24 h: 97%, 8:1 dr
- n = 0, R^1 = Cy, R^2 = H, rt, 0.5 h: 89%, 5:1 dr

(68)

reaction leads to the addition of the alcohol to the C=C bond and to the elimination of the propargyloxy unit. Subsequently, the same authors disclosed the transglycosylation of per-*O*-benzylated saccharides having a propargyl group at the anomeric position using a panel of alcohols and catalytic amounts of $AuCl_3$ (Eq. 70).[73] Surprisingly, the transglycosylation of per-*O*-acetylated or per-*O*-benzoylated propargyl glucosides did not occur. The advanced mechanism proposes that the formation of a π-alkyne gold complex **21A**, formed by coordination of the C≡C bond to $AuCl_3$, is followed by the formation of a cyclopropyl gold carbene intermediate **21B** and then **21C** (Scheme 21). The expulsion of the alkenyl gold complex **21D** leads to an oxocarbenium ion **21E** that is trapped by ROH to yield the glycoside **21F** and HCl. The protodemetallation of **21D** mediated by this acid extrudes methyleneoxirane and regenerates the catalyst. According to the authors, the formation of **21B** increases the electrophilicity and would allow the generation of **21C**. A cyclopropyl gold carbene as intermediate has previously been proposed by Zhang and Kozmin.[74] Nevertheless, the formation of **21C** directly from **21A** is envisageable. The above Hotha mechanistic proposal led us to suspect the intermediates shown in Scheme 22 for the reaction depicted in Eq. 69.

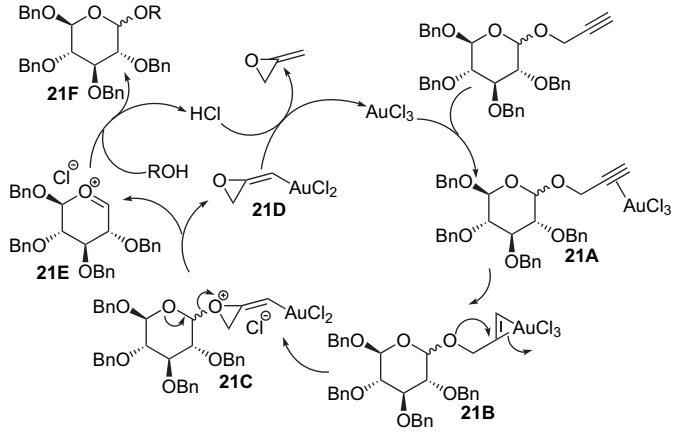


(69)

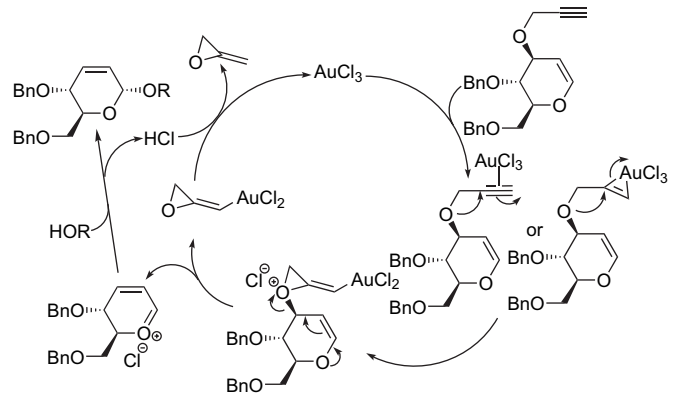


(70)

ROH = $Cl(CH_2)_3OH$ (6 h: 80%), $PhCH_2OH$ (4 h: 92%), menthol (6 h: 68%), $CH_2{=}CH(CH_2)_3OH$ (10 h: 95%), cholesterol (15 h: 39%)

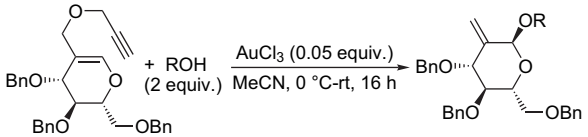


Scheme 21.



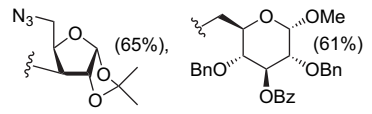
Scheme 22.

Hotha et al. have also carried out the addition of alcohols to per-*O*-benzylated *C*-2-propargyloxymethyl glycals (Eq. 71).[75]

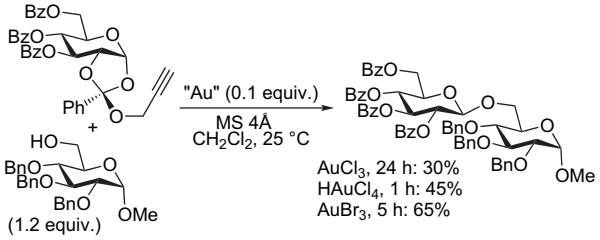


(71)

R = Me (63%), Bn (61%), $CH_2{=}CH(CH_2)_3$ (72%),

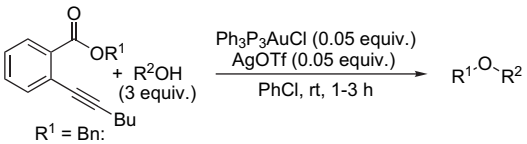


Another method, also disclosed by Hotha's team, for the addition of alcohols to the anomeric position is the use of propargyl 1,2-orthoesters, as illustrated in Eq. 72.[76] A gold^{III} halide catalyst and CH_2Cl_2 as the solvent are required, no reaction occurring with AuCl or Au_2O_3, or in MeCN. As above, the process is compatible with a variety of aglycones comprising aliphatic, alicyclic, steroidal and sugar alcohols. The suggested mechanism involves the attack of the alcohol on the 1,2-dioxonium ion formed after coordination of the C≡C bond to the catalyst.



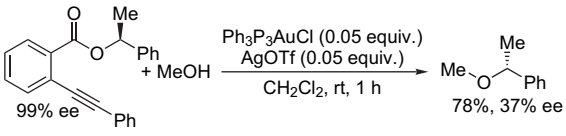
(72)

Recently, Asao et al. described the etherification of a variety of alcohols using alkyl *ortho*-(alkynyl)benzoates and catalytic amounts of both Ph_3PAuCl and AgOTf (Eq. 73), this catalytic system being much more efficient than $AuBr_3$ and Ph_3PAuCl.[77] This process could involve the gold complex **23A** and its nucleophilic attack by the alcohol, which yields the ether, the isocoumarin derivative (that has been isolated in a few cases) and the cationic gold catalyst (Scheme 23). The formation of the C–O bond from **23A** is, probably, an S_N1 reaction having some S_N2 character since the alkylation of MeOH by (*S*)-1-phenylethyl 2-(2-phenylethynyl)benzoate led to partially racemised (*R*)-(1-methoxyethyl)benzene (Eq. 74). The intramolecular version of this reaction has been reported (Eq. 75).[77]

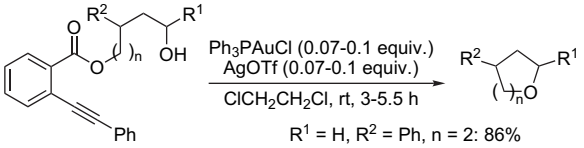


(73)

R^1 = Bn:
R^2 = $Ph(CH_2)_2$ (87%), Cy (70%), *t*-Bu (90%), $AcO(CH_2)_2$ (70%), $NC(CH_2)_2$ (75%)
R^1 = *p*-$MeO(C_6H_4)CH_2$:
R^2 = $Ph(CH_2)_2$ (92%), $EtOCOCH_2$ (70%)

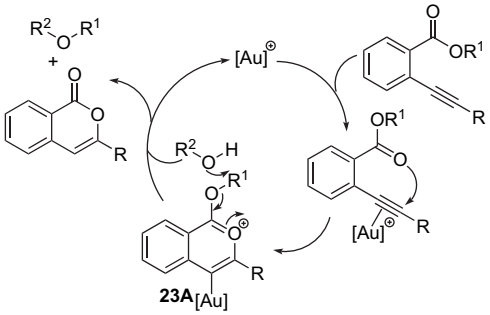


(74)



(75)

R^1 = H, R^2 = Ph, n = 2: 86%
R^1 = Ph, R^2 = H, n = 1: 90%
R^1 = Ph, R^2 = H, n = 2: 100%



Scheme 23.

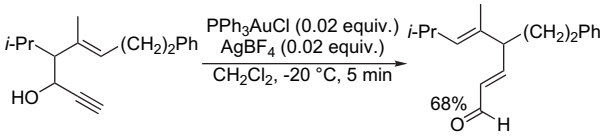
6. Isomerisation of hydroxyalkynes

6.1. Without exogenous alcohol addition

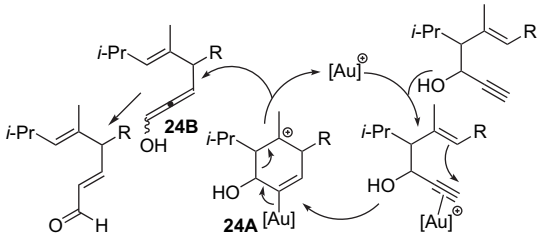
6.1.1. Propargylic alcohols

The transformation of secondary and tertiary propargylic alcohols into the corresponding α,β-unsaturated ketones has been described in Eqs. 9 (see Section 2.1.2), 49 and 50 (see Section 4.1) and will also be illustrated in Eq. 154 (see Section 10.1), but the mechanism of these reactions, carried out in the presence of alcohols or water, probably involves addition/elimination sequences rather than a simple isomerisation.[78,79]

Gagosz has isolated an α,β-unsaturated aldehyde from the reaction, at low temperature, of (*E*)-4-isopropyl-5-methyl-8-phenyl-oct-5-en-1-yn-3-ol with a cationic Au^I catalyst (Eq. 76).[80] According to the mechanism suggested by the author, this isomerisation requires the presence of the C=C bond (Scheme 24). Indeed, the transformation would occur via the 6-*endo*-*dig* cyclisation leading to the vinylic gold intermediate **24A**, the fragmentation of which generates an allenol **24B** that tautomerises into the unsaturated aldehyde.

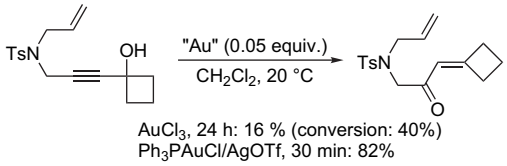


(76)

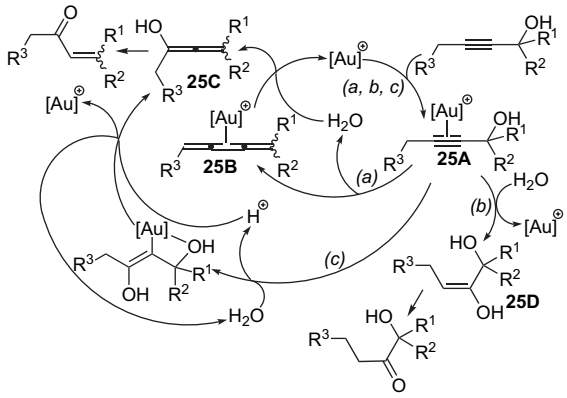


Scheme 24.

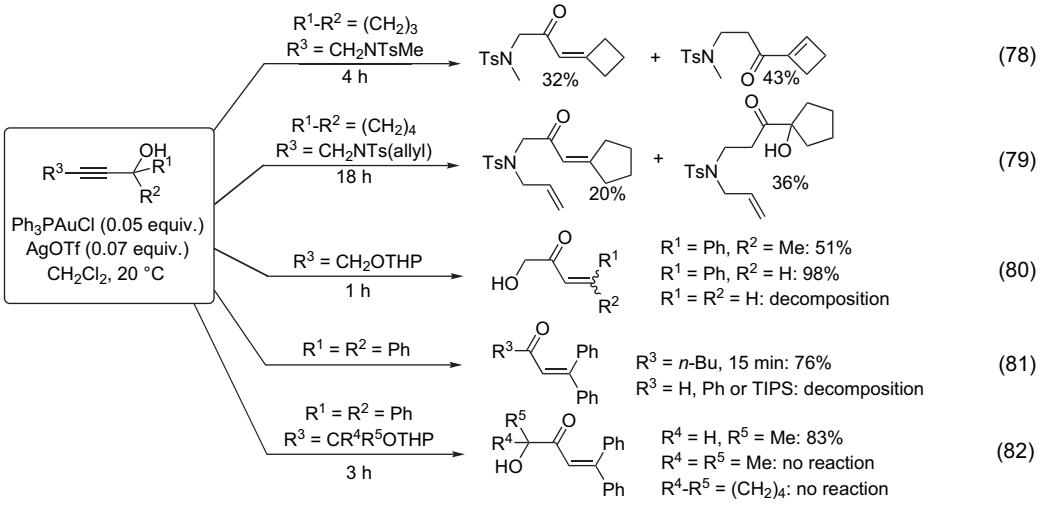
Studying the catalytic isomerisation of a range of propargylic alcohols into α,β-unsaturated ketones (Eqs. 77–82), Chung et al. have observed that a cationic Au^I complex, namely $Ph_3PAuOTf$, is much more efficient than $AuCl_3$ (Eq. 77).[81] The OTHP protective group does not survive in the experimental conditions (Eqs. 80 and 82) and a concurrent reaction is the formation of an α-hydroxyketone (Eq. 79). As illustrated by the results of Eqs. 80 and 81, the isomerisation compounds are isolated only from secondary and tertiary alcohols bearing non-terminal alkynes. Furthermore, the substituent R^3 has to bear a hydrogen atom in the α-position of the alkyne (Eqs. 81 and 82). This observation led the authors to suspect the formation of an allene intermediate and to propose the mechanism pictured in Scheme 25, paths a and b. Dehydration of the π-alkyne complex **25A** leads to the cumulene **25B** that reacts with water to close the catalytic cycle in giving **25C** that tautomerises into the α,β-unsaturated ketone. As for the α-hydroxyketone, this compound will be obtained from the addition of adventitious water to **25A** that generates **25D** as an intermediate. This isomerisation of propargylic alcohols into α,β-unsaturated ketones is reminiscent of the Meyer–Schuster-type rearrangement depicted in Section 4.1 (see Eqs. 56 and 57, and Scheme 15). This led us to envisage path c as an alternative mechanism, but this possible reaction pathway does not rationalise the importance of the existence of a hydrogen atom in the α-position of the alkyne.



(77)

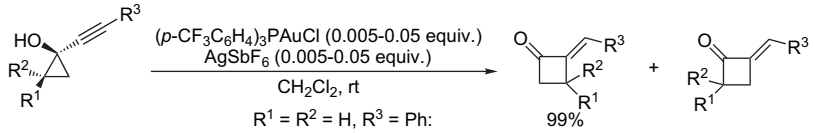


Scheme 25.



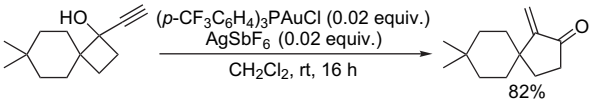
Toste et al. have reported the cationic Au^I-catalysed ring expansion of alkynylcyclopropanols (Eq. 83), and pointed out that the yields and the reaction rates are highly dependent upon the nature of the ligand.[82] Their experimental conditions were found to be viable for the efficient isomerisation of terminal alkynylcyclobutanols (Eq. 84). These authors envisaged two possible mechanisms (Scheme 26). Mechanism a involves a 1,2-alkyl shift at the level of the π-alkyne complex **26A**. This generates a vinylic gold intermediate **26B**, the protolysis of which leads to the alkylidenecycloalkanone. Mechanism b also provides **26B**, but via the activation of the cycloalkanol, giving an alkylgold intermediate **26C**, and the subsequent insertion of the alkyne into the C–Au bond. Given the *E*-geometry of the alkylidenecycloalkanones (Eq. 83), and the selective migration of the more substituted cycloalkanol carbon (Eq. 83, with R^1 and/or $R^2 \neq H$, and Eq. 84), Toste et al. concluded that mechanism a is more consistent with the results.

Subsequently, Shin et al. studied the rearrangement of 1-(3-hydroxypropynyl)cycloalkanol derivatives induced by cationic Au^I catalysts. Ring-expansion products and/or spirocyclic furans have been obtained with selectivities depending upon the catalyst ligand, the protective group and the ring size (Eq. 85).[83] The synthesis of 2,5-dihydrofurans from butynediol monoesters, previously disclosed by Gagosz et al., is a similar reaction (Eq. 86),[84] for which the mechanism shown in Scheme 27 has been suggested. The complexation of the C≡C bond induces the [3,3]-sigmatropic rearrangement[85] leading to the hydroxyallene **27A**. The addition of the alcohol to the extremity of the allene generates **27B**, the protodeauration of which liberates the dihydrofuran and the catalyst. In agreement with this mechanism, the gold intermediate **27B** can be trapped by iodide prior to protonation (Eq. 87).

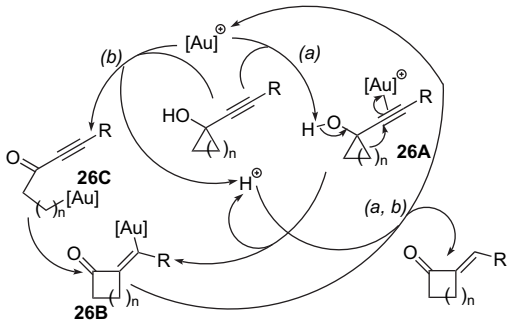


$R^1 = R^2 = H$, R^3 = Ph:	99%	
$R^1 = R^2 = H$, R^3 = I:	88%	
$R^1 = R^2 = H$, R^3 = n-hexyl:	81%	
$R^1 = R^2 = H$, R^3 = *t*-Bu:	98%	
$R^1 = R^2$ = Me, R^3 = Ph:	0%	61%
R^1 = *i*-Pr, $R^2 = R^3 = H$:	80%	0%
R^1 = *i*-Pr, $R^2 = H$, R^3 = Ph:	67%	15%
$R^1 = H$, R^2 = *i*-Pr, R^3 = Ph:	0%	91%
$R^1 = H$, R^2 = Bn, $R^3 = H$:	55%	33%

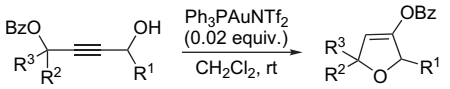
(83)



(84)

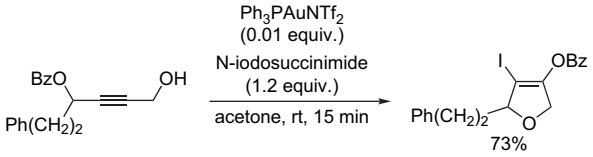


Scheme 26.



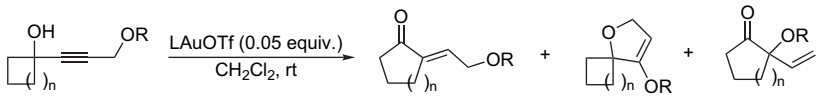
$R^1 = R^2 = R^3 = H$, 80 min: 83%
$R^1 = R^2$ = Me, $R^3 = H$, 15 min: 95%
R^1 = *i*-Pr, $R^2 = H$, R^3 = Me, 20 min: 92%
$R^1 = R^2 = H$, $R^3 = (CH_2)_2Ph$, 5 min: 95%
$R^1 = R^2 = H$, $R^3 = CH_2OBn$, 20 min: 99%
$R^1 = R^2 = H$, $R^3 = (CH_2)_4Bz$, 10 min: 99%

(86)



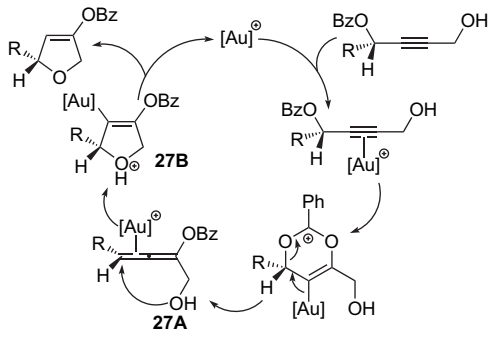
(87)

Interestingly, complete transfer of chirality and high diastereoselectivity can be obtained under the Gagosz conditions (Eq. 88).[84] A limitation of the method is the rearrangement into the α,β-unsaturated ketone when the hydroxyl group is tertiary (Eq. 89).

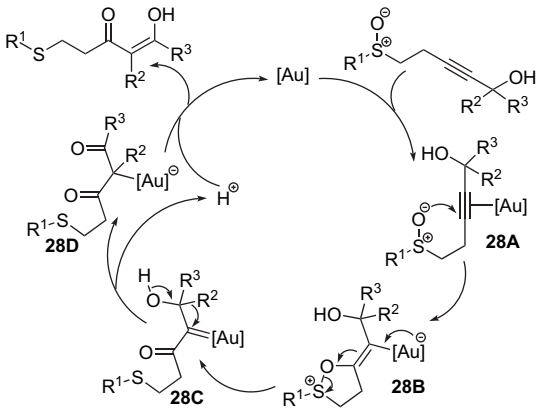


n = 1	R = Ac, L = PPh_3*:	96%	
	R = Piv, L = PPh_3:	60%	
	R = Piv, L = o-biphenylP(*t*-Bu)$_2$:	73%	
	R = Boc, L = PPh_3:	68%	
	R = Bz, L = PPh_3:	66%	
	*0.01 equiv. of $Ph_3PAuOTf$ was used		
n = 2	R = Ac, L = PPh_3:	16%	5%
	R = Ac, L = o-biphenylP(*t*-Bu)$_2$:	61%	
	R = Ac, L = $P(C_6F_5)_3$: 11%	2%	
	R = Bz, L = o-biphenylP(*t*-Bu)$_2$:	98%	
n = 3	R = Ac, L = o-biphenylP(*t*-Bu)$_2$:	92%	
	R = Boc, L = o-biphenylP(*t*-Bu)$_2$:	63%	

(85)

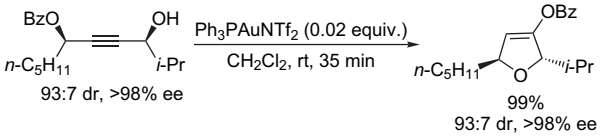


Scheme 27.

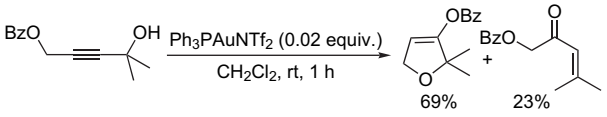


Scheme 28.

Such a reaction of propargylic alcohols has been exemplified above (see Section 4.1, Eqs. 49, 50 and 56).



(88)

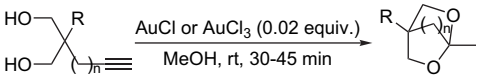


(89)

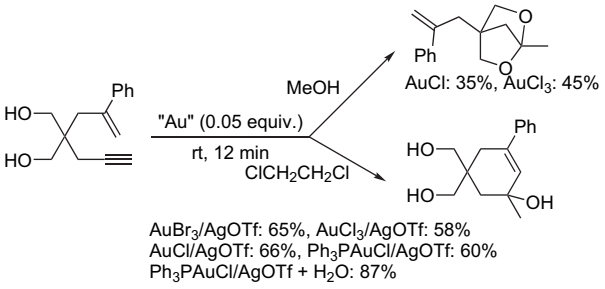
Li and Zhang have disclosed that catalytic amounts of gold can induce the reduction of the sulfoxide moiety of sulfinyl propargylic alcohols with concomitant oxidation of the C≡C bond to afford β-diketones.[86] The screening of Au^{I} and Au^{III} catalysts has led to the choice of the $IPrAuNTf_2$ carbene complex as the most suitable. β-Diketones were selectively obtained from arylsulfinyl substrates (Eqs. 90 and 91), while alkylsulfinyl propargylic alcohols can lead to other compounds (Eqs. 92 and 93). The diketone would be obtained from the π-alkyne complex **28A** via the 5-*exo*-*dig* cyclisation leading to **28B** (Scheme 28). Pushing out the sulfide moiety yields the α-oxo gold carbenoid **28C**. The subsequent 1,2-alkyl shift followed by the protodeauration of **28D** provides the β-diketone.

6.1.2. Others

In 2005, Michelet et al. disclosed the Au-catalysed synthesis of bicyclic ketals from bis- and tris-homopropargylic diols.[87] As illustrated in Eq. 94, the process occurs in MeOH under Au^{I} and Au^{III} catalyses, and is compatible with the presence of C=C bonds. The authors suggested that the coordination of both one alcohol and the triple bond to the catalyst, to form **29A**, occurs before the formation of the first C–O bond that leads to **29B** (Scheme 29). The protolysis of **29B** affords the enol ether **29C**, another addition of the remaining alcohol to which leads to the bicyclic ketal. Oh et al. have observed that, in 1,2-dichloroethane, the addition of AgOTf to the Au catalyst leads to the participation of a tethered C=C bond and traces of water to afford a triol (compare Eqs. 95 and 96).[88] As expected, the formation of the carbocycle was improved when water was intentionally added to the solvent (Eq. 96).

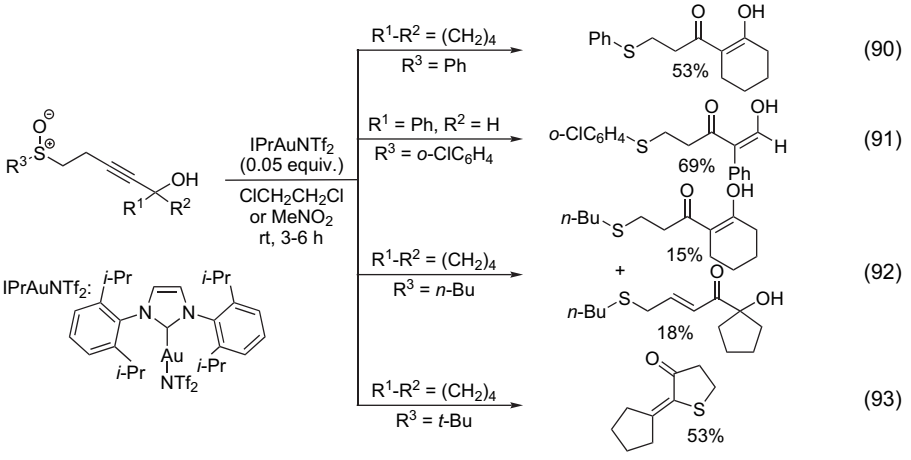


(94)



(95)

(96)

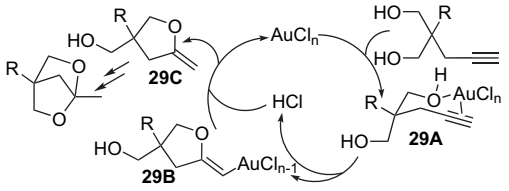


(90)

(91)

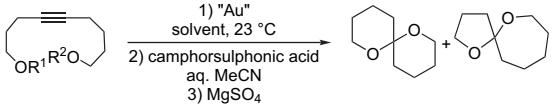
(92)

(93)



Scheme 29.

Liu and De Brabander have carried out the cyclisation of 4-nonyne-1,9-diol and its monoprotected forms under the conditions shown in Eq. 97.[89] Mixtures of [5,5]- and [4,6]-spiroketal resulting from 6-*exo*-*dig* and 7-*endo*-*dig* cyclisations, respectively, were obtained, the ratio between the two isomers as the yield depending upon the nature of the catalyst. Camphorsulfonic acid and $MgSO_4$ were added at the end of the reaction to ensure complete conversion into the spiroketals. Given the above Chung's report[81] (Eqs. 80 and 82), we suspect that the cleavage of the OTHP protective group is mainly due to the Au catalysts.

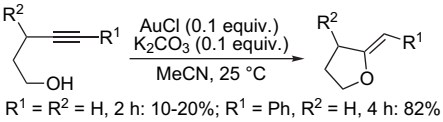


R^1 = H: R^2 = H, Ph_3PAuCl: 0%; R^2 = H, $Ph_3PAuCl/AgPF_6$ (0.01 equiv.), *i*-Pr_2O, 30 min: 92%, 1:3.7; R^2 = TBS, $Ph_3PAuCl/AgPF_6$ (0.05 equiv.), *i*-Pr_2O, 13 h: 73%, 1:6.6

R^1 = THP, R^2 = H: $AuCl_3$ (0.05 equiv.), Et_2O, 30 min: 41%, 2.2:1; $Ph_3PAuCl/AgOTf$ (0.05 equiv.), Et_2O, 30 min: 36%, 2:1; Ph_3PAuMe (0.01 equiv.), TfOH (0.1 equiv.), Et_2O, 30 min: 40%, 1.3:1

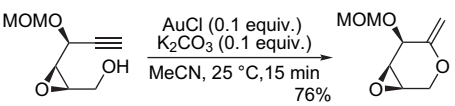
(97)

Functionalised tetrahydrofurans and pyrans have been regio- and stereoselectively obtained by Pale et al. via cyclisation, catalysed by a 1:1 mixture of AuCl and K_2CO_3, of primary 4(or 5)-yn-1-ols (Eqs. 98 and 99).[90] Only decomposition products were observed in the absence of the base, or with $AuCl_3$ or Ph_3PAuCl as the catalyst. Given the stereoselectivity of the cycloisomerisation, the authors suggested a trans-addition of the alcohol to the Au-coordinated C≡C bond (Scheme 30).[91] They also proposed that K_2CO_3 participates in the deprotonation of the intermediate **30A** and the C–Au bond cleavage. We suspect that K_2CO_3 would rather increase the nucleophilicity of the hydroxyl group and thus facilitates the alcohol addition.

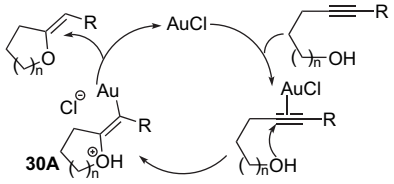


$R^1 = R^2$ = H, 2 h: 10-20%; R^1 = Ph, R^2 = H, 4 h: 82%
R^1 = H, R^2 = OBn, 1 h: 90%; R^1 = Br, R^2 = OBn, 1 h: 84%
R^1 = H, R^2 = OSiPh_2*t*-Bu, 2 h: 80%

(98)

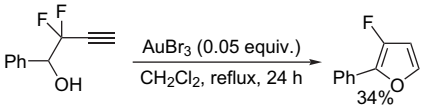


(99)



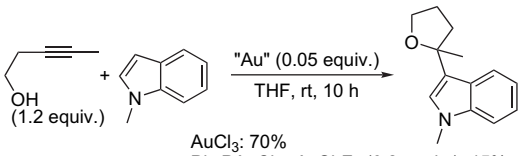
Scheme 30.

The cyclisation of 2,2-difluoro-1-phenylbut-3-yn-1-ol mediated by catalytic amounts of $AuBr_3$ affords 3-fluoro-2-phenylfuran instead of the expected 3,3-difluoro-2,3-dihydro-2-phenylfuran (Eq. 100).[92]



(100)

The formation of both C–O and C–C bonds from the Au-catalysed reaction of pent-3-yn-1-ol with *N*-methyl indole (Eq. 101) would, first, involve the cyclisation of the alcohol to 2,3-dihydro-5-methylfuran and, subsequently, the addition of the indole to this unsaturated ether.[93]

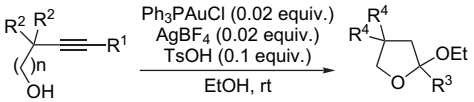


$AuCl_3$: 70%
$Ph_3PAuCl + AgSbF_6$ (0.2 equiv.): 45%

(101)

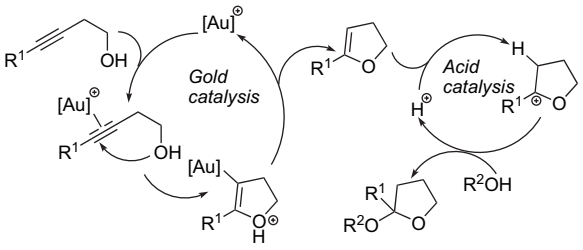
6.2. With exogenous alcohol addition

While a propargylic alcohol is reluctant to react with MeOH using *t*-Bu_3PAuBF_4 as the catalyst (Eq. 19),[29] Belting and Krause have selectively prepared tetrahydrofuranyl ethers from the cycloisomerisation/hydroalkoxylation domino reaction, in alcohols, of homo- and bis-homopropargylic alcohols catalysed by a dual catalyst, consisting of an Au compound and TsOH (Eqs. 102 and 103).[94] The hydroalkoxylation step occurs with methanol, ethanol, 2-propanol and 2-methoxyethanol, but not with *tert*-butanol. In the absence of the Brønsted acid, the main product was the dihydrofuran derivative, but the subsequent addition of *p*-TsOH strongly increased the quantity of the tetrahydrofuranyl ether (Eq. 104). Consequently, the authors proposed a mechanism involving two successive catalytic cycles, one mediated by gold and the other by the Brønsted acid (Scheme 31). Note that $HAuCl_4$ (Eq. 105)[94] and the cationic complex $Ph_3PAuSbF_6$ (Eq. 106)[95] can play the two roles.

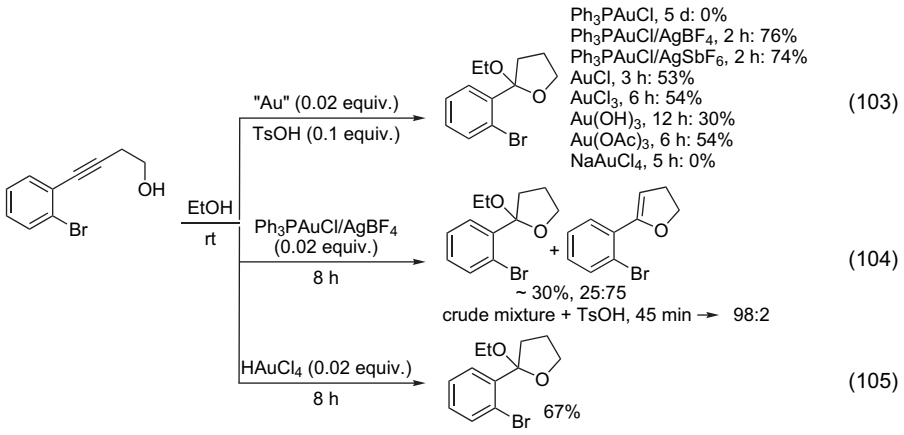


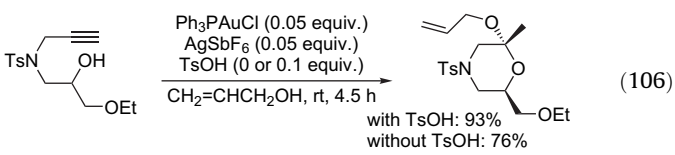
n = 1, R^1 = H, R^2 = Ph, 5 h → R^3 = H, R^4 = Ph: 53%
n = 2, R^1 = Ph, R^2 = H, 1 h → R^3 = CH_2Ph, R^4 = H: 67%

(102)

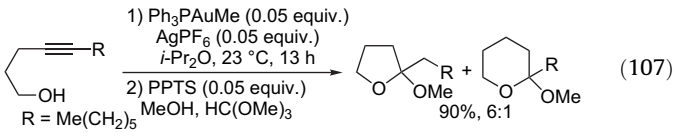


Scheme 31.



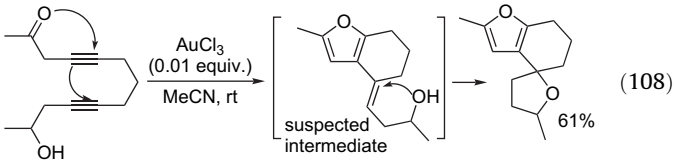


In agreement with the above mechanism, Liu and De Brabander have prepared cyclic acetals through a two-step reaction: firstly, an Au-catalysed cycloisomerisation and, secondly, an acidic treatment with MeOH/HC(OMe)$_3$ (Eq. 107).[89]

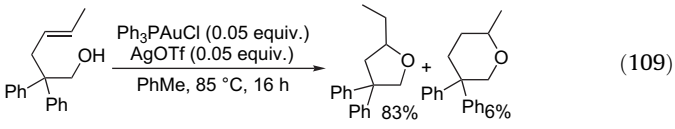


7. Isomerisation of hydroxyalkenes

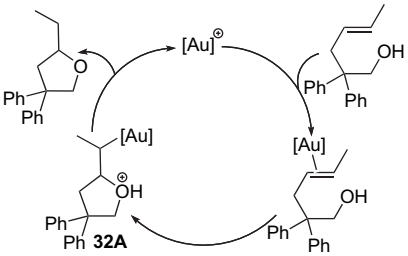
The possible Au-catalysed reaction of alkenylalcohols has first been suggested by Hashmi et al., who have proposed that the spirocyclisation step of the domino reaction shown in Eq. 108 occurs, in MeCN, via a homoallylic alcohol intermediate.[96]



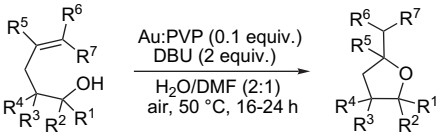
Hashmi's hypothesis was, five years later, exemplified by Yang and He with the formation of a mixture of five- and six-membered heterocycles from the cyclisation, mediated by a cationic Au^{I} catalyst, of (*E*)-2,2-diphenylhex-4-en-1-ol (Eq. 109).[97] As illustrated in Scheme 32, the activation of the C=C bond by coordination promotes the nucleophilic addition of the alcohol to generate a σ-alkylgold intermediate **32A**, the protodeauration of which delivers the oxygen heterocycle.



Subsequently, Sakurai et al. carried out the cycloisomerisation of a variety of γ-hydroxy alkenes, under an air atmosphere, using a gold nanocluster, denoted Au/PVP,[98] as the catalyst, in an H$_2$O/DMF mixture containing DBU (Eq. 110).[99] Under these widely different conditions, the hydrogen atom required for the deauration of the σ-alkylgold intermediate is, according to the authors, provided by DMF via a radical process.

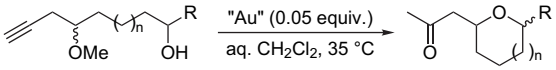


Scheme 32.



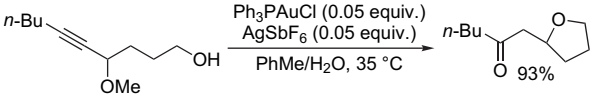
$R^1 = R^2 = Ph$, $R^3 = R^4 = R^5 = R^6 = R^7 = H$: 87%
$R^1 = Ph$, $R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = R^7 = H$: 0%
$R^1 = \alpha$-naphthyl, $R^2 = Me$, $R^3 = R^4 = R^5 = R^6 = R^7 = H$: 62%
$R^1 = R^2 = Ph$, $R^5 = Me$, $R^3 = R^4 = R^6 = R^7 = H$: 38%
$R^1 = R^2 = Ph$, $R^6 = Me$, $R^3 = R^4 = R^5 = R^6 = R^7 = H$: 8%
$R^1 = R^2 = Ph$, $R^6 = R^7 = Me$, $R^3 = R^4 = R^5 = H$: 0%
$R^3 = R^4 = Ph$, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = H$: 93%
R^3-$R^4 = (CH_2)_5$, $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = H$: 33%
$R^1 = Me$, $R^3 = R^4 = Ph$, $R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = H$: 93%
(110)

The Au-catalysed synthesis, in an aqueous medium, of heterocycles from terminal homopropargylic methyl ethers with a pendant hydroxy group (Eq. 111) involves hydroxyalkene intermediates (Scheme 33).[100,101] According to Jung and Floreancig, the hydration of the C≡C bond is followed by elimination of methanol to give the hydroxyenone **33A**. From **33A**, the cyclisation occurs as already shown in Scheme 32 and with a diastereocontrol resulting from product equilibration under the reaction conditions. In agreement with the proposed mechanism, the reaction of 9-hydroxynon-3-en-2-one under the same experimental conditions has led to the corresponding seven-membered heterocycle. When the triple bond of the homopropargylic ether is internal, a mixture of products was produced.[101] In contrast, the intramolecular alkoxycyclisation succeeded in high yield from a non-terminal propargylic ether, as depicted in Eq. 112.[101]

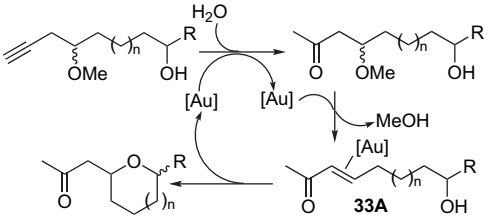


n = 0, R = H, $NaAuCl_4$: 85%
n = 1, R = H, $NaAuCl_4$: 91%
n = 1, R = H, $Ph_3PAuCl/AgSbF_6$: 100%
n = 1, R = Me, $NaAuCl_4$: 79%
n = 2, R = H, $NaAuCl_4$: 52%
n = 1, R = $(CH_2)_2OH$, $NaAuCl_4$: 70%
n = 1, R = $(CH_2)_2OH$, $Ph_3PAuCl/AgSbF_6$: 97%

(111)

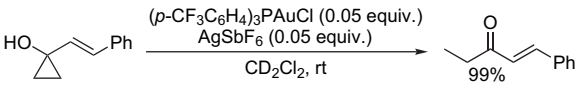


(112)



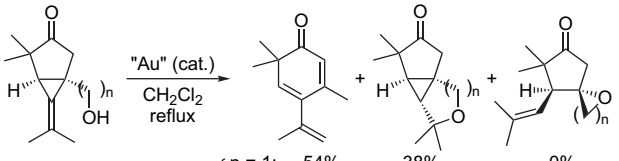
Scheme 33.

Toste et al. have briefly reported the cationic Au^I-catalysed rearrangement of 1-styrylcyclopropanol into 1-phenylpent-1-en-3-one (Eq. 113).[82] The coordination of the allylic alcohol moiety could facilitate the cleavage of the cyclopropyl ring to afford the corresponding gold homoenolate, the protolysis of which leads to the product. Given the formation of gold homoenolates from cyclopropanol derivatives,[102] we, nevertheless, suspect that such a cleavage would occur in the absence of the C=C bond.



(113)

Fensterbank, Malacria and co-workers have recently disclosed Au^I-catalysed transformations of methylenecyclopropanes bearing a hydroxylated tether. As exemplified in Eq. 114, the selectivity depends upon both the length of the tether and the nature of the catalyst, the mechanistic proposals being shown in Scheme 34.[103]



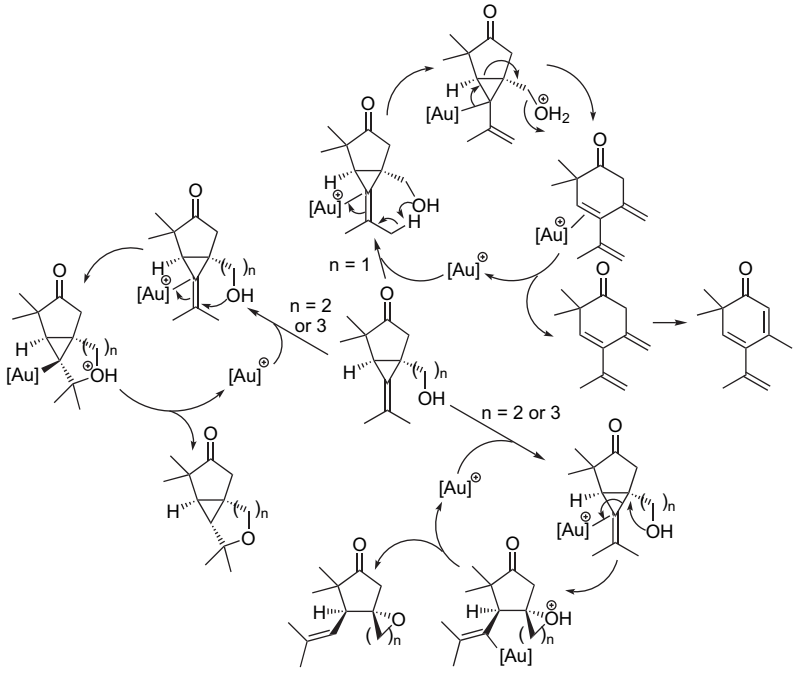
AuCl (0.05 equiv.), 2 h	n = 1:	54%	38%	0%
	n = 2:	0%	44%	0%
	n = 3:	0%	0%	80%
$AuCl(PPh_3)$ (0.02 equiv.), $AgSbF_6$ (0.02 equiv.), 1 h	n = 1:	77%	0%	0%
	n = 2:	0%	42%	30%
	n = 3:	0%	0%	74%

(114)

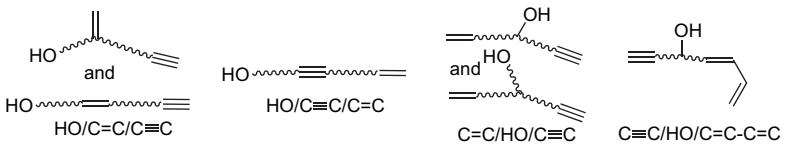
8. Cycloisomerisation of hydroxyenynes and hydroxydienynes

Before beginning this section, it seems of interest to remember the reactions involving the cleavage of the C–OH bond of hydroxyenynes that were illustrated in Section 4.2 (Eqs. 63–67), and the intramolecular dialkoxylations of dihydroxy-enynes depicted in Eq. 94, for which neither the hydroxylic solvent nor the C=C bonds participate in the process. The possible non-participation in a cycloisomerisation of either the hydroxy or the C=C bond of hydroxyenynes using specific substrates or conditions is also exemplified in Eqs. 23, 76 and 95.

The course of the cycloisomerisation of hydroxyenynes depends greatly upon the relative position of the alcohol. Consequently, this topic is subdivided into three main sections. The first section, denoted HO/C=C/C≡C, concerns substrates for which the hydroxyalkyl chain is a substituent of the C=C bond, while for the second, denoted HO/C≡C/C=C, the hydroxyalkyl chain is a substituent of the C≡C bond. In the third section, denoted C=C/HO/C≡C, the substrates have the tether connecting the C=C and C≡C bonds substituted by a hydroxyl or a hydroxyalkyl chain. Scheme 35



Scheme 34.



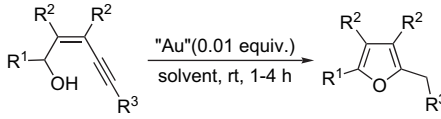
Scheme 35.

illustrates this differentiation. Examples of substrates in which the double bond belongs to an aromatic group are included. The isomerisation of hydroxydienynes is then summarised in the section denoted C≡C/HO/C=C–C=C.

8.1. HO/C=C/C≡C

8.1.1. 2-En-4-yn-1-ols

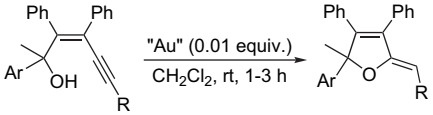
After the brief description, by Hashmi's team, of the $AuCl_3$-catalysed cycloisomerisation of (*Z*)-2-methylpent-2-en-4-yn-1-ol into 2,4-dimethylfuran,[96] Liu et al. synthesised a panel of furans and 5-ylidene-2,5-dihydrofurans from (*Z*)-enynols containing a secondary or tertiary alcoholic group, respectively.[104] As exemplified in Eqs. 115 and 116, the reaction also proceeds with a cationic Au^I catalyst. These cycloisomerisations would occur via the *anti-exo-dig* nucleophilic attack of the alcohol on the activated alkyne to form an ate complex **36A** (Scheme 36).[91] The protonolysis of **36A** affords the alkylidene dihydrofuran **36B**. When the substrate is a secondary alcohol, the furan is formed either by acidic isomerisation of **36B** (path a) or through the isomerisation of **36A** and then protonolysis (path b).



$AuCl_3$, CH_2Cl_2:
- R^1 = *p*-MeC_6H_4, R^2 = Pr, R^3 = Ph: 92%
- R^1 = *p*-$MeOC_6H_4$, R^2 = Pr, R^3 = Bu: 85%
- R^1 = Pr, R^2 = Ph, R^3 = *p*-$MeOC_6H_4$: 79%

$Ph_3PAuCl/AgOTf$, THF:
- R^1 = Ph, R^2 = Bu, R^3 = *p*-$MeOC_6H_4$: 85%
- R^1 = *p*-$CF_3C_6H_4$, R^2 = Et, R^3 = *p*-MeC_6H_4: 64%

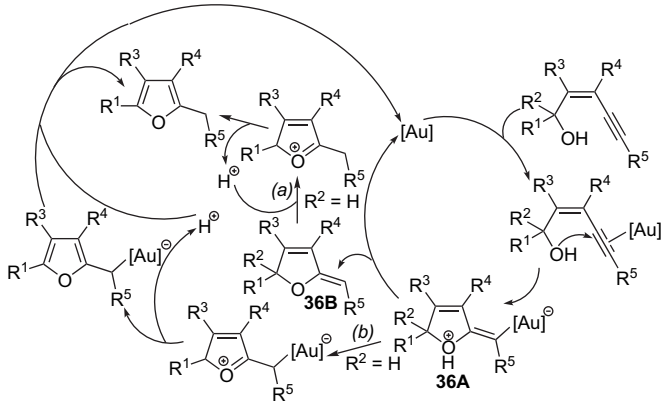
(115)



$AuCl_3$:
- Ar = *o*-ClC_6H_4, R = Ph: 97%
- Ar = *o*-ClC_6H_4, R = Bu: 83%
- Ar = R = Ph: 91%
- Ar = Ph, R = 1-cyclohexenyl: 92%

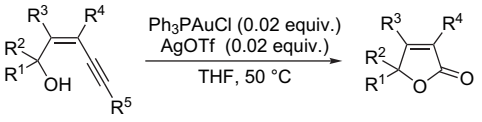
Ph_3PAuCl + AgOTf:
- Ar = *p*-FC_6H_4, R = Ph: 84%
- Ar = 2-thienyl, R = *p*-MeC_6H_4: 87%

(116)



Scheme 36.

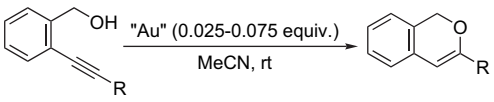
When the above cyclisation of the tertiary substrates is carried out at 50 °C under bubbling of oxygen, oxidative cleavage of the C≡C bond leading to butenolides is observed, in particular, when using a cationic Au^I complex as the catalyst and THF as the solvent (Eq. 117). Under these conditions, a partial oxidation of THF was observed and the domino reaction was completely suppressed in the presence of a radical scavenger. Furthermore, the same oxidative treatment of the above 5-ylidene-2,5-dihydrofurans induced cleavage of the exocyclic C=C bond to also afford the butenolides.[105]



- R^1 = Me, R^2 = R^3 = R^4 = R^5 = Ph, 17 h: 97%
- R^1 = Me, R^2 = R^3 = R^4 = Ph, R^5 = *p*-$MeOC_6H_4$, 4 h: 81%
- R^1 = Me, R^2 = *p*-ClC_6H_4, R^3 = R^4 = Ph, R^5 = Bu, 3 h: 82%
- R^1 = Me, R^2 = Ph, R^3 = Me, R^4 = TMS, R^5 = Bu, 1.5 h: 41%
- R^1-R^2 = $(CH_2)_5$, R^3 = R^4 = Ph, R^5 = Bu, 3 h: 66%

(117)

In contrast to the above 5-*exo-dig* cyclisations (Eqs. 115–117), the teams of Hashmi and Laguna have observed 6-*endo-dig* pathways from primary benzylic alcohols bearing an *o*-alkynyl substituent.[106] The reactions were more efficient under Au^I than Au^{III} catalysis (Eq. 118) and their course was sensitive to the substitution of the alkynyl group (see Section 10.1, Eq. 156).

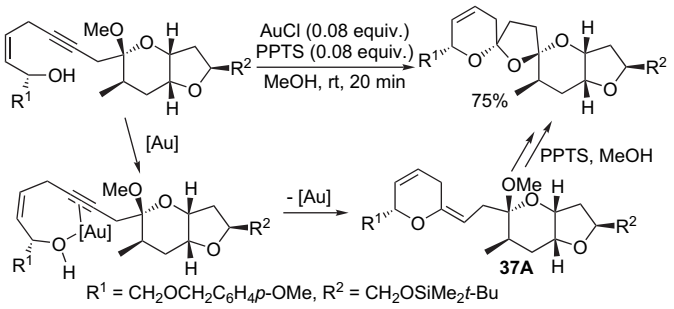


$AuCl_3$, R = *n*-Pr (27%), *t*-Bu (24%), Ph (36%)
$[(Mes_3PAu)_2Cl]BF_4$, R = *n*-Pr (31%), *t*-Bu (95%), Ph (75%)

(118)

8.1.2. 2-En-5-yn-1-ols

According to Forsyth et al., the formation of the dispiroketal pictured in Scheme 37 involves, probably, the coordination of both the hydroxyl group and the triple bond to gold as the first step. This would allow the *syn*-addition leading, after protodeauration, to the enol ether **37A**. The subsequent steps are induced by the methanolic PPTS mixture.[107]

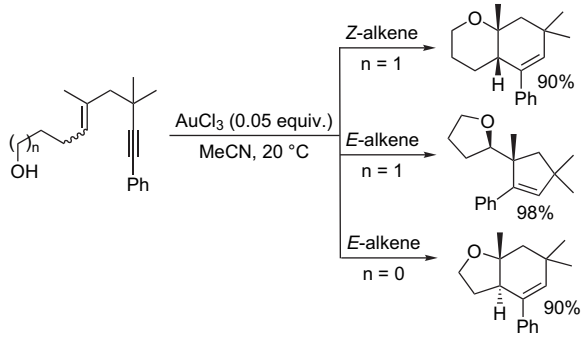


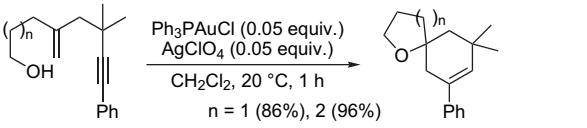
R^1 = $CH_2OCH_2C_6H_4$*p*-OMe, R^2 = CH_2OSiMe_2t-Bu

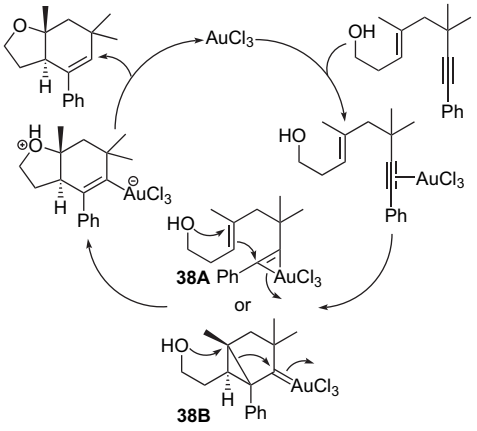
Scheme 37.

8.1.3. Others

Zhang and Kozmin have synthesised heterobicyclic compounds from various 1,5-enynes armed with a primary alcohol, using $AuCl_3$ or $Ph_3PAuClO_4$ as the catalyst.[74] As exemplified in Eqs. 119–122, the structure of the isolated product depends upon both the geometry of the alkene and the length of the hydroxylated tether. The proposed mechanism of the $AuCl_3$-catalysed double cyclisation of (*E*)-4,6,6-trimethyl-8-phenyloct-3-en-7-yn-1-ol involves a concerted process from **38A** or the opening of the cyclopropyl gold carbene intermediate **38B** (Scheme 38). Such gold carbenes were already implicated as reactive intermediates in various cyclisations,[28,32,39] but a number of observations have led the authors to prioritise the concerted pathway.[3c,74]

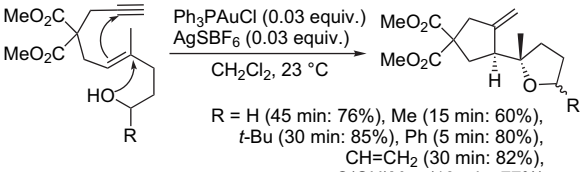




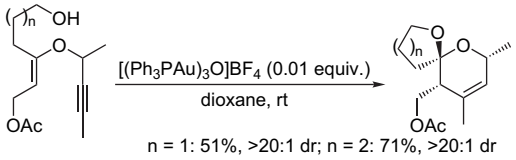


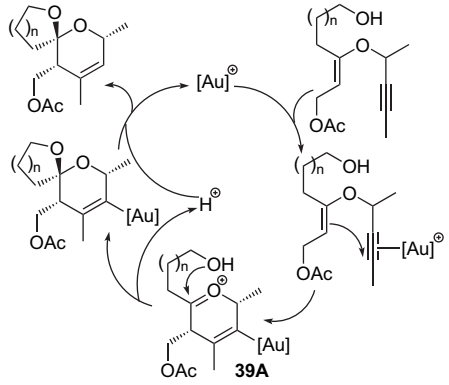
Scheme 38.

The double cyclisation of 1,6-enynes armed with a primary or secondary alcohol has been reported by Echavarren et al. (Eq. 123).[41] A possible mechanism is similar to that illustrated in Scheme 38, but with a formal 5-*exo-trig* addition of the alcohol to the double bond and a 5-*exo-dig* addition to the triple bond.



Using hetero 1,5-enynes bearing a hydroxyalkyl chain, Toste et al. have diastereoselectively prepared substituted 5,6- and 6,6-spiroketal (Eq. 124).[108] The proposed mechanism of this double cyclisation (Scheme 39) differs strongly from that depicted in Scheme 38. Indeed, it was suggested that the spirocyclisation step occurs by intramolecular trapping of an oxocarbenium intermediate **39A**.

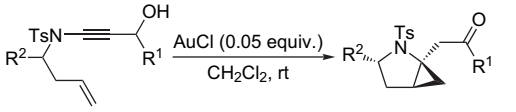




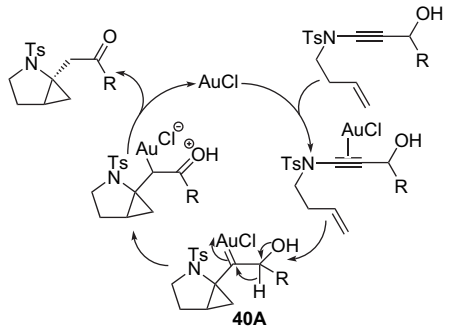
Scheme 39.

8.2. HO/C≡C/C=C

Cossy et al. have reported the diastereoselective Au^I-catalysed cycloisomerisation of ene–ynamides bearing a propargylic alcohol moiety (Eq. 125).[109] This reaction, that leads to carbonyl compounds incorporating a 2-azabicyclo[3.1.0]hexane framework, involves a 1,2-hydride shift from the cyclopropyl gold carbene intermediate **40A** followed by protodemetallation (Scheme 40).



$R^1 = R^2 = H$: 40%; R^1 = Me, R^2 = H: 60%; R^1 = *i*-Pr, R^2 = H: 42%
R^1 = H, R^2 = Ph: 61%; $R^1 = R^2 = CH_2OBn$: 51%



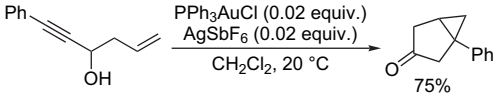
Scheme 40.

8.3. C≡C/HO/C=C

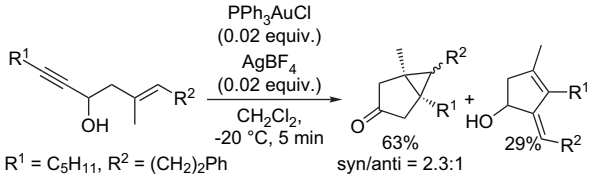
8.3.1. Without exogenous alcohol addition

After the brief Fürstner report on the cationic Au^I-catalysed cycloalkoxylation of 1-phenylhex-5-en-1-yn-3-ol into

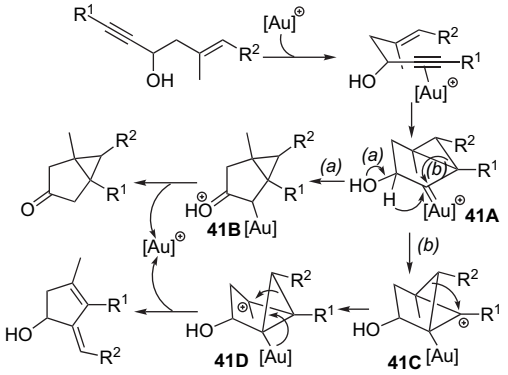
1-phenylbicyclo[3.1.0]hexan-3-one (Eq. 126),[31] this method has been exploited by Gagosz, who has observed the concomitant formation of alkylidene-hydroxycyclopentenes (Eq. 127) and the non-cyclisation of a substrate having a terminal alkyne (Eq. 76, Section 6.1.1).[80] Both cyclic compounds would be obtained through the 5-*endo-dig* cyclisation generating the intermediate **41A** (Scheme 41). A 1,2-hydrogen shift affords **41B** that collapses to the corresponding ketone (path a), while a double 1,2-alkyl shift leads successively to **41C**, **41D** and the alkylidene-cyclopentenol (path b).



(126)

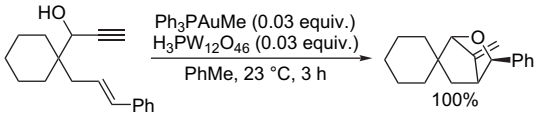


(127)

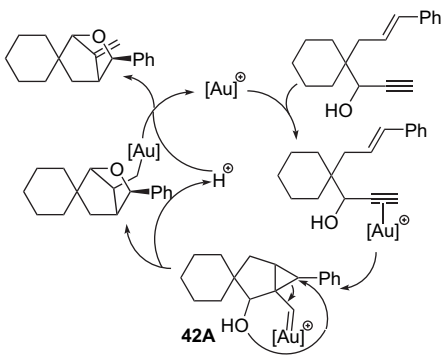


Scheme 41.

Using a 6-en-1-yn-3-ol instead of a 5-en-1-yn-3-ol as the substrate, Echavarren et al. obtained a hetero tricycle (Eq. 128).[39,41] These authors asserted that the tricycle results from intramolecular attack of the hydroxy group on a cyclopropyl gold intermediate.[41] Consequently, the mechanism shown in Scheme 42, where the key intermediate **42A** is obtained via a 5-*exo-dig* cyclisation, is proposed.

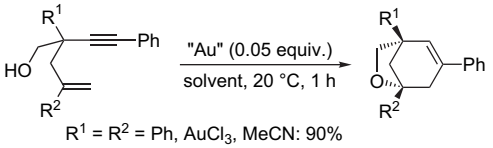


(128)



Scheme 42.

The use of 1,5-enynes having the propargylic carbon substituted by a hydroxymethyl group affords oxabicyclic alkenes (Eq. 129).[74] According to Zhang and Kozmin, the reaction involves a 6-*endo-dig* carbocyclisation of the enyne with a concomitant intramolecular formation of the C–O bond.

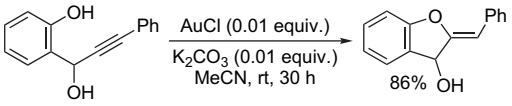


(129)

$R^1 = R^2$ = Ph, $AuCl_3$, MeCN: 90%
R^1 = 3,5-$(MeO)_2C_6H_3$, R^2 = Me, $AuCl_3$, MeCN: 92%
R^1 = H, R^2 = Me, $Ph_3PAuCl/AgClO_4$, CH_2Cl_2: 89%

An attempt to obtain cyclisation products from (*E*)-3-benzylidene-1,1,1-trifluoro-5-phenylpent-4-yn-2-ol in the presence of catalytic amounts of $NaAuCl_4$ has led to an inseparable mixture.[110]

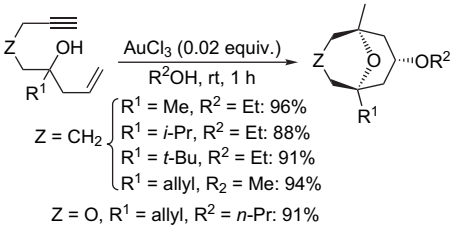
Although the hydroxyl group of the C≡C/HO/C=C system is not involved in the process, the recent report from Pale et al. on the efficient Au^I-catalysed cyclisation of 2-(1-hydroxy-3-phenylprop-2-ynyl)phenol is included here (Eq. 130).[111]



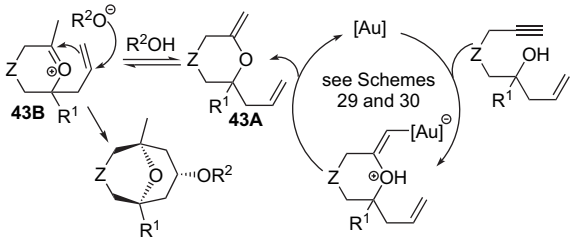
(130)

8.3.2. With exogenous alcohol addition

Barluenga et al. have examined the metal-catalysed cycloisomerisation of 1-en-8-yn-4-ols using alcohols as the solvents.[112] The use of $AuCl_3$ catalyses effectively a domino reaction leading to a bicyclic compound with the incorporation of one molecule of solvent (Eq. 131), while the transformation has a low efficiency with AuCl, and was not observed with Ph_3PAuCl. Experiments carried out from deuteriated substrates and deuteriated alcohols, but under Pt-catalysis, support the 6-*exo-dig* cyclisation leading to an exocyclic enol **43A** that, under the reaction conditions, is in equilibrium with the oxocarbenium **43B** (Scheme 43). Addition of the counterion to the C=C bond induces the final Prins-type cyclisation step.[113]



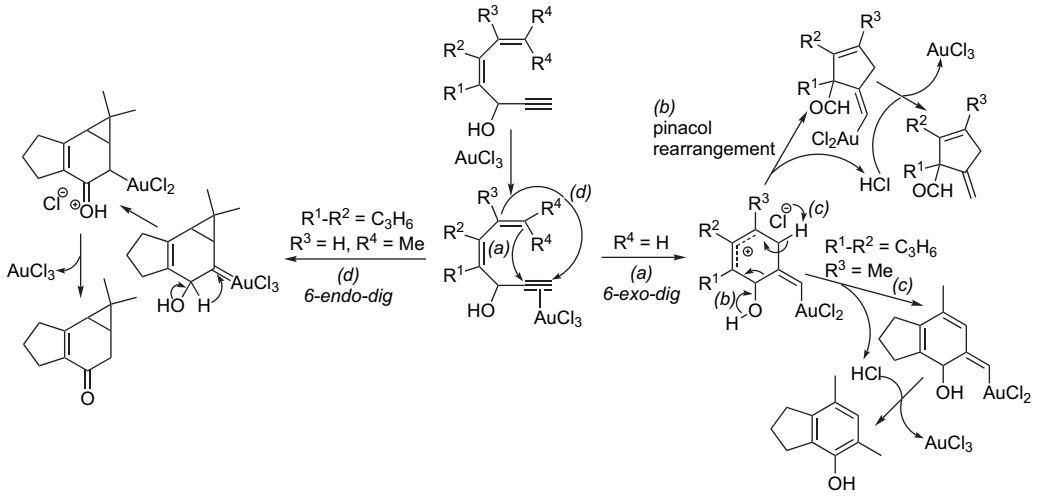
(131)



Scheme 43.

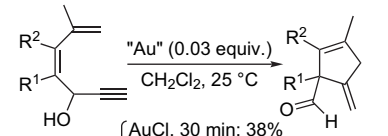
8.4. C≡C/HO/C=C–C=C

The structure of the products obtained from the Au-catalysed reaction of *cis*-4,6-dien-1-yn-3-ols depends greatly upon their substitution pattern.[67,68] The 6-substituted substrates undergo rearrangement leading, in most cases, to aldehydes as the main



Scheme 44.

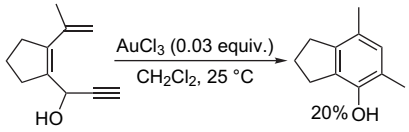
products (Eq. 132), except when the internal C=C bond belongs to a cyclopentene (Eq. 133).[68] As for the 7,7-disubstituted compounds having the internal C=C bond also belonging to a cyclopentene, they afford tricyclic ketones (Eq. 134).[68] Moreover, the cleavage of the C–OH bond occurs from 7,7-disubstituted compounds bearing an internal C=C bond belonging to a cyclohexene, as documented in Section 4.2 (Eq. 65).[67] The different possible reactive pathways leading to the isomerisation products are suggested in Scheme 44.



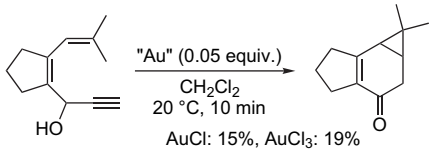
R^1-R^2 = C_4H_8: AuCl, 30 min: 38%; PhP_3AuCl, 3 d: 3%; $PhP_3AuCl/AgOTf$, 10 min: 58%; $AuCl_3$, 10 min: 74%

R^1 = H, R^2 = Ph, $AuCl_3$: 71%

R^1 = Me, R^2 = Ph, $AuCl_3$: 76% (132)



(133)

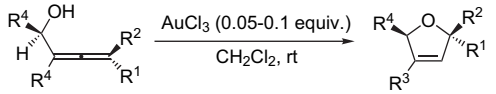


AuCl: 15%, $AuCl_3$: 19% (134)

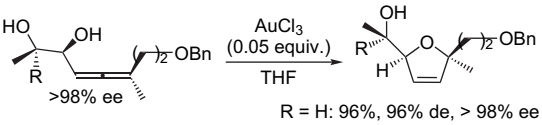
9. Cycloisomerisation of hydroxyallenes

9.1. α-Hydroxyallenes

In 2001, Krause's team disclosed the $AuCl_3$-catalysed cycloisomerisation of α-hydroxyallenes into 2,5-dihydrofurans (Eq. 135)[114] using mainly CH_2Cl_2[114–116] or THF[116–118] as the solvent. The possible excellent stereoselectivity without loss of optical purity and the participation of a second hydroxy group in the β-position have been pointed out by the authors (Eq. 136).[118] Nevertheless, the efficiency of the chirality transfer depends upon the substrate substitution and, in order to be high, requires, in most cases, the optimisation of the reaction conditions.[116]

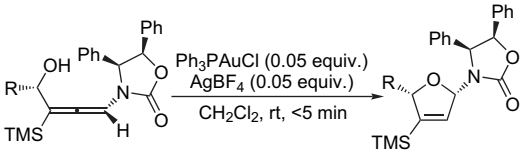


R^1 = *t*-Bu, R^2 = Me, R^3 = H, R^4 = CO_2Et: 74%
R^1 = *t*-Bu, R^2 = *n*-Bu, R^3 = H, R^4 = CO_2Et: 100%
R^1 = *t*-Bu, R^2 = R^3 = Me, R^4 = CO_2Et: 94%
R^1 = *t*-Bu, R^2 = H, R^3 = Me, R^4 = CH_2OTBS: 95%
R^1 = H, R^2 = *n*-hex, R^3 = Me, R^4 = CH_2OTBS: 65%
R^1 = $H_2C=CH(CH_2)_2$, R^2 = Me, R^3 = Me, R^4 = CH_2OMe: 86% (135)



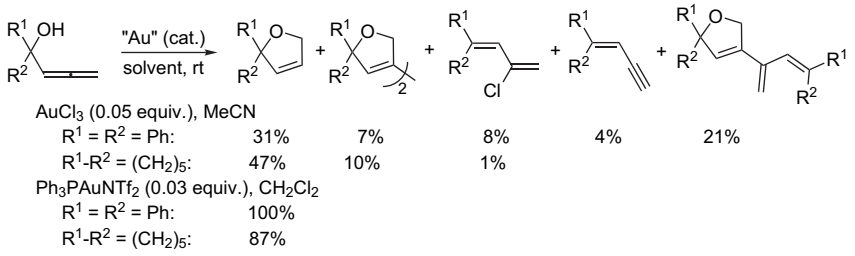
R = H: 96%, 96% de, > 98% ee
R = Me: 97%, 96% de, > 98% ee (136)

The cycloisomerisation of α-hydroxyallenes also proceeds with other Au catalysts such as $AuBr_3$, AuCl and cationic Au^I complexes (Eq. 137).[116,119] Hashmi et al. observed the formation of various side products when tertiary 2,3-dien-1-ols reacted under $AuCl_3$ catalysis in MeCN at room temperature, while 2,5-dihydrofurans were obtained in high yields with $Ph_3PAuNTf_2$ in CH_2Cl_2 (Eq. 138).[120] The increase in coupling products proportional to the amount of $AuCl_3$ used has suggested the in situ reduction of the Au^{III} catalyst.[120]



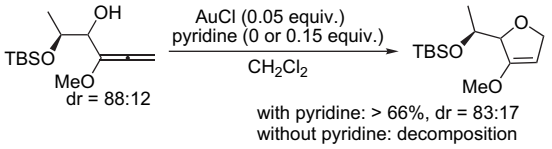
R = Ph (80%), *i*-Pr (87%), $H_2C=CH(CH_2)_2$ (86%), MeCH(OBn) (78%), $TBSOCH_2$ (81%) (137)

The $AuCl_3$-catalysed cyclisation of 2-(*tert*-butyldimethylsilyloxy)-4-methoxyhexa-4,5-dien-3-ol has required the presence of pyridine as additive (Eq. 139),[121] possibly to preserve the allenic and/or vinylic ether function. Brasholz and Reissig have successfully applied this procedure to substrates with a ketal or *N*-Boc protected oxazolidine unit.[121] In contrast, with $Ph_3PAuOTf$ as the catalyst, an allenic ether can be used without an additive as shown, from 1-(1-(benzyloxy)propa-1,2-dienyl)cyclobutanol as the substrate, by Shin et al., who, however, obtained a completely different reaction (Eq. 140).[83] Scheme 45 illustrates a possible pathway that affords

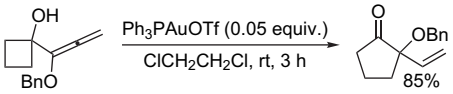


(138)

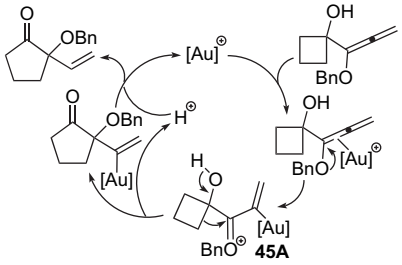
1-benzyloxy-1-vinyl-cyclopentanone: the coordination of the allene to the catalyst generates **45A** and the subsequent 1,2-alkyl shift is followed by protodeauration.



(139)

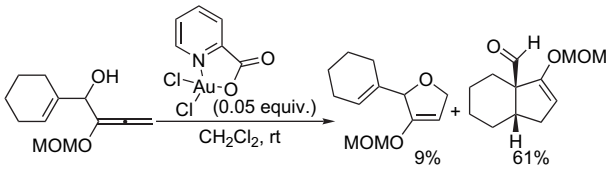


(140)



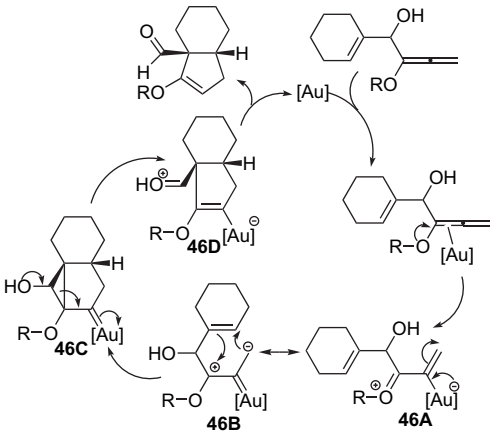
Scheme 45.

Instead of a dihydrofuran, Huang and Zhang recently obtained a substituted bicyclo[4.3.0]nonene as the main compound from the Au^{III}-catalysed isomerisation of 1-cyclohexenyl-2-(methoxymethoxy)buta-2,3-dien-1-ol (Eq. 141)[122] and its formation has been rationalised as shown in Scheme 46. The selective gold activation of the enolic double bond of the allenyl ether moiety generates the oxocarbenium species **46A**, which is in resonance with the 1,3-dipole **46B**. The subsequent 1,3-dipolar cycloaddition led to a strained Au carbenoid **46C**. The OH-assisted fragmentation of the cyclopropane ring affords **46D**, the protodeauration of which liberates the organic compound and the catalyst.

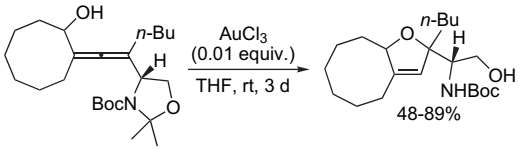


(141)

As illustrated above, various functional groups survive in the presence of Au catalysts. Nevertheless, the $AuCl_3$-catalysed heterocyclisation shown in Eq. 142 leads to the concomitant cleavage of the oxazolidine unit.[123]



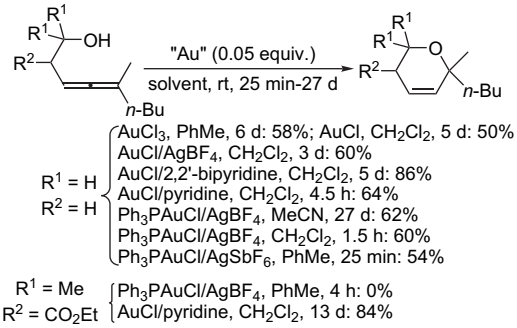
Scheme 46.



(142)

9.2. β-Hydroxyallenes

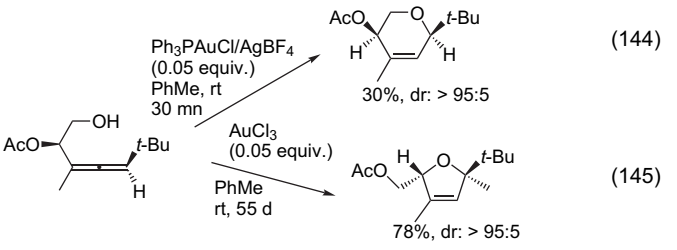
Testing various conditions to perform the cyclisation of 5-methylnona-3,4-dien-1-ol, Gockel and Krause have observed that the reaction time to obtain the 6-*endo*-cyclisation product depended greatly upon the nature of both the catalyst and the solvent (Eq. 143).[124] Furthermore, with a tertiary β-allenyl alcohol bearing an ester group in the α-position, the success of the cyclisation was dependent upon the catalyst/solvent combination (Eq. 143). Functionalised dihydropyrans have been prepared from chiral substrates with, in most cases, a complete chirality transfer.



(143)

While 1-hydroxy-3,6,6-trimethylhepta-3,4-dien-2-yl acetate afforded the corresponding dihydropyran with Ph_3PAuBF_4 as the catalyst, switching to $AuCl_3$ led to a 2,5-dihydrofuran, both reactions being conducted in the same solvent at room temperature (Eqs. 144 and 145). The formation of the dihydrofuran is best explained by an acetate migration, possibly $gold^{III}$ catalysed, from

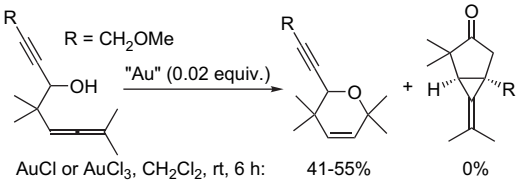
the secondary to the primary hydroxyl group, and the cyclisation of the resulting α-hydroxyallene.[124]



(144)

(145)

When the hydroxyl group is substituted by an alkynyl unit, 6-methylenebicyclo[3.1.0]hexan-3-one derivatives instead of the oxygenated heterocycles can be obtained, depending upon the experimental conditions (Eq. 146). This transformation involves the intramolecular attack of the allene moiety on the activated triple bond and the formation of the cyclopropyl gold carbene intermediate **47A** (Scheme 47),[103] i.e., a reactive pathway similar to that of some hydroxylated enynes (see Sections 8.2 and 8.3, and Schemes 40 and 41).[125]



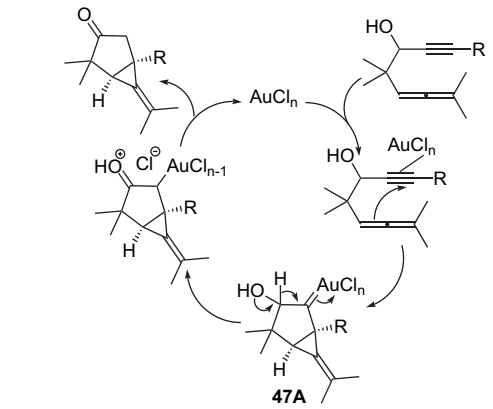
AuCl or $AuCl_3$, CH_2Cl_2, rt, 6 h:	41-55%	0%
AuCl or $AuCl_3$, PhMe, reflux, 6 h:	0%	45-58%
$Ph_3PAuCl/AgBF_4$, CH_2Cl_2, reflux or PhMe, rt, 1 h:	55-73%	0%

(146)

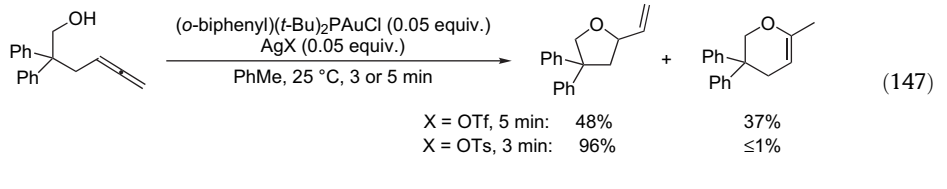
9.3. γ-Hydroxyallenes

A 1.3:1 mixture of tetrahydrofuran and dihydropyran derivatives has been obtained by Widenhoefer et al. from a toluene solution of 2,2-diphenyl-4,5-hexadien-1-ol containing a catalytic 1:1 mixture of (*o*-biphenyl)(*t*-Bu)$_2$PAuCl and AgOTf. Switching from AgOTf to AgOTs to form the cationic Au^I catalyst has led almost exclusively to the five-membered cyclic compound (Eq. 147).[126] Under these latter conditions, the hydroalkoxylation of an enantiomerically enriched terminal monosubstituted allenyl carbinol occurs with near-complete chirality transfer, and generates a mixture of *E*- and *Z*-2-alkenyltetrahydrofuran (Eq. 148). Subsequently, enantioselective hydroalkoxylations have been carried out with ees of up to 99% using cationic Au^I catalysts having chiral ligands[127,128] or, more originally, chiral counterions (Eq. 149).[128] Furthermore, Toste et al. have highlighted 'matched' and 'mismatched' effects[129] from the combination of chiral counterions and chiral ligands.[128]

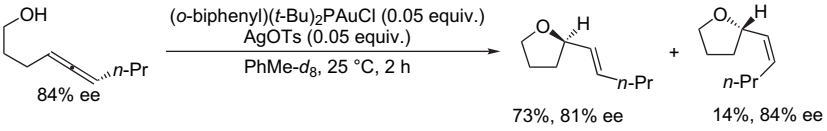
Recently, Alcaide et al. have carried out the Au^{III}-catalysed cyclisation of γ-hydroxyallenes substituted in the α-position by a protected hydroxyl moiety.[130] While the TBS protecting group was stable under their experimental conditions (Eq. 150), MOM cleavage was observed, leading to a reaction occurring at the level of the α-hydroxyallene (Eq. 151).



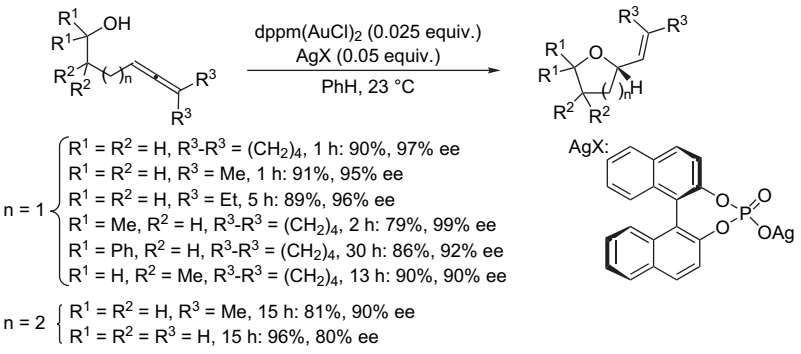
Scheme 47.



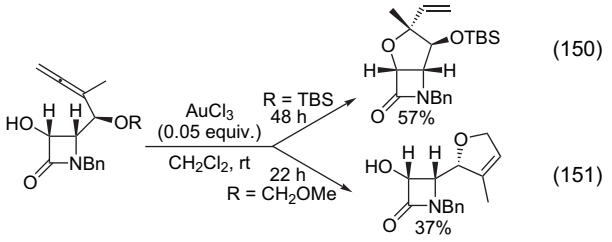
(147)



(148)



(149)

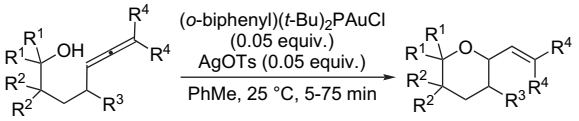


(150)

(151)

9.4. δ-Hydroxyallenes

A number of 2-alkenyl tetrahydropyrans have been prepared from 5,6-heptadien-1-ols under achiral (Eq. 152)[126] and chiral (Eq. 149)[127,128] experimental conditions.

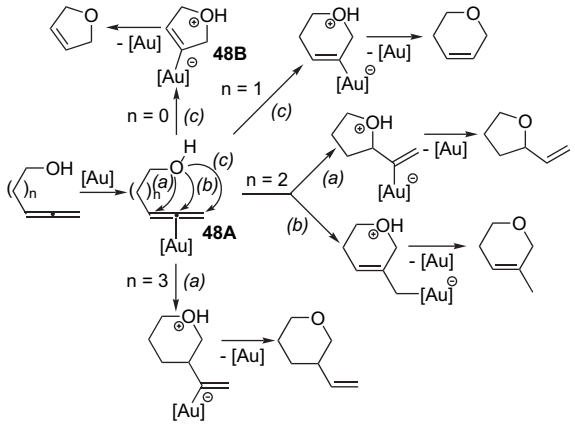


(152)

$R^1 = R^2 = R^3 = R^4 = H$: 98%; $R^1 = R^3 = R^4 = H$, $R^2 = Ph$: 98%
$R^1 = R^4 = H$, $R^2 = Ph$, $R^3 = Me$: 96%; $R^2 = R^3 = R^4 = H$, $R_1 = Me$: 97%
$R^1 = R^3 = R^4 = H$, $R^2 = Ph$, $R^4 = Me$: 96%

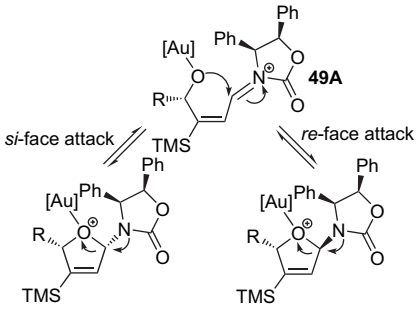
9.5. Mechanism

A simplified common mechanism for the hydroalkoxylation of allenyl carbinols is shown in Scheme 48. From the π-complex **48A**, the preference for an *exo*- or *endo*-cyclisation governing the size of the formed heterocycle is related to the length of the carbon tether linking the hydroxyl group and the diene unit. As illustrated in Eq. 147, the cyclisation selectivity can also be catalyst dependent. Attempts to trap intermediates **48B** with methyl vinyl ketone[119] or an α-acetylallene[131] have been unsuccessful.



Scheme 48.

The teams of Krause[116] and Hegedus[119] have observed the Au-catalysed epimerisation of 1,4-disubstituted dihydrofurans, a reaction sensitive to the nature of catalyst, substrate and solvent.[116] With α-hydroxyallenamides as the substrates (Eq. 137), Hyland and Hegedus, having observed (i) the cis-to-trans isomerisation of the corresponding dihydrofurans over extended periods of reaction times in the presence of the cationic Au^I catalyst, and (ii) the more rapid formation of the *trans* diastereoisomer with $AuCl_3$, suggested an equilibrium via an iminium species **49A** (Scheme 49).[119]

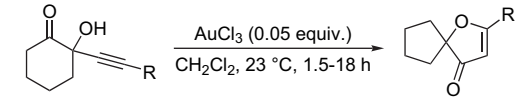


Scheme 49.

10. Cycloisomerisation of alkynyl-ketones and -esters

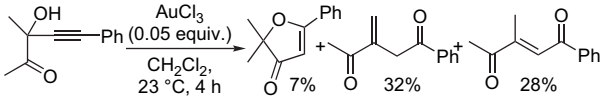
10.1. With participation of an internal hydroxyl group

Kirsch et al. have prepared spirocyclic 3(2*H*)-furanones from the $AuCl_3$-catalysed rearrangement of 2-(1-alkynyl)-2-hydroxycyclohexanones (Eq. 153).[132,133] The use of Au^I catalysts such as Ph_3PAuBF_4 and Ph_3PAuCl led mainly to decomposition products. The proposed mechanism involves the 5-*endo-dig* addition of the carbonyl to the coordinated triple bond leading to the oxonium species **50A** (Scheme 50). This triggers a 1,2-alkyl shift that allows the ketonisation of the hydroxyl and the protodeauration delivering the hetero spirocyclic compound and the initial catalyst. Complex reaction mixtures were obtained from a substrate such as 3-hydroxy-3-methyl-5-phenylpent-4-yn-2-one (Eq. 154), or when the alkynyl moiety contains an OTHP protective group (Eq. 153).[133] Reactions in the presence of primary amines, to in situ generate the iminium intermediates corresponding to **50A**, have led to the expected 3-pyrrolones in poor yields (Eq. 155).[133]

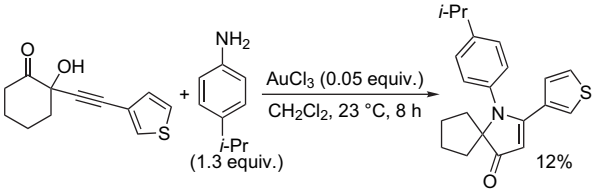


(153)

R = Ph (1.5h, 83%), *p*-FC_6H_4 (4 h, 70%), *o*-$MeOC_6H_4$ (5 h, 81%), *p*-(*t*-Bu)C_6H_4 (4 h, 75%), 3-thienyl (5 h, 76%), $Me(CH_2)_4$ (2 h, 66%), cyclohexyl (7 h, 25%), $(CH_2)_3OTHP$ (6 h, 11%), CH_2OTHP (18 h, 33%)

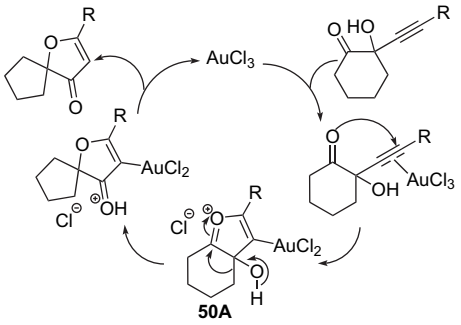


(154)

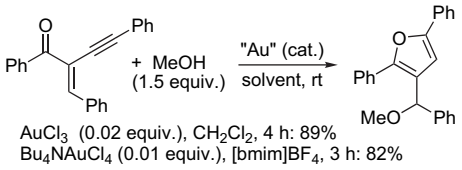


(155)

In Section 8.1.1, the 6-*endo-dig* cyclisation of primary benzylic alcohols bearing an *o*-alkynyl substituent has been illustrated (Eq. 118). When the alkynyl moiety contains an ester or an amide moiety, this additional nucleophilic group mediates a concurrent reaction leading to an unexpected dimeric compound (Eq. 156).[106] According to the mechanism suggested by Hashmi, Laguna and co-workers, this concurrent reaction, that forms eight new bonds, involves firstly the 6-*endo-dig* attack of the coordinated triple bond by the C=O group and, in one of the next steps, the activation of the benzylic C–H bonds by the catalyst.

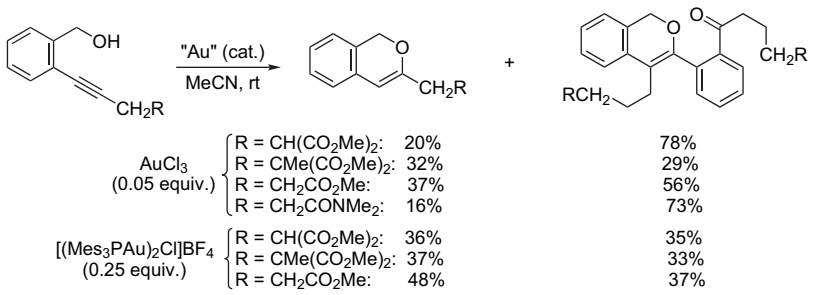


Scheme 50.



(158)

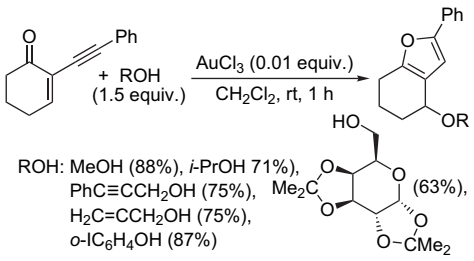
Zhang and Schmalz have carried out similar reactions, but with substrates possessing a cyclopropyl ring instead of the C=C bond. The cascade reaction occurred from a variety of substrates and alcohols, including *t*-BuOH, and with Au^{III} or Au^{I} catalysts, in particular, $Ph_3PAuOTf$ (Eq. 159).[138] The authors suspected two mechanisms (paths a and b in Scheme 52) similar to those shown in Scheme 51.



(156)

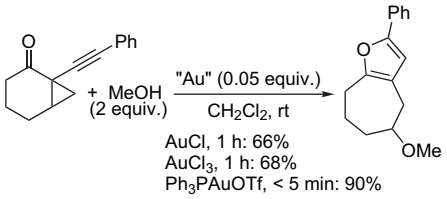
10.2. With addition of an exogenous alcohol

In 2004, Larock et al. disclosed the synthesis of substituted furans from the $AuCl_3$-catalysed reaction between 2-(2-phenylethynyl)cyclohex-2-enone and alcohols (Eq. 157).[134] The method has been successfully extended to a panel of 2-(1-alkynyl)-2-alken-1-enones and alcohols (Eqs. 157 and 158).[134,135] Recently, Liang et al. carried out these reactions using a recyclable catalytic system comprising Bu_4NAuCl_4 in an ionic liquid, namely [bmim]BF_4 (Eq. 158).[136] According to Larock et al., at least two mechanisms are plausible (Scheme 51). The dual role of Au^{III} as a Lewis acid and as a transition-metal catalyst is illustrated in Scheme 51, path a. Acting as a Lewis acid, $AuCl_3$ forms a complex **51A** with the carbonyl oxygen. This facilitates the 1,4-addition of the alcohol to the C=C bond giving **51B**. The subsequent addition of $AuCl_3$ to the C≡C bond generates **51C**, inducing the cyclisation that leads to **51D** and HCl. The protonation of **51D** affords the furan with regeneration of the catalyst. In the second mechanism (path b), $AuCl_3$ functions simply as a transition metal to firstly produce **51E**. The nucleophilic attack of carbonyl oxygen on the electron-deficient C≡C bond affords the carbocationic species **51F**, the reaction of which with the alcohol produces **51D**. The latter mechanism appeared to be more likely to the authors, since no 1,4-addition of MeOH to 2-cyclohexenone occurred under their standard experimental conditions.[134,135] It should be noted that Yamamoto et al., who have obtained the same reactions using CuBr as the catalyst in DMF, have also preferred such a mechanism.[137]



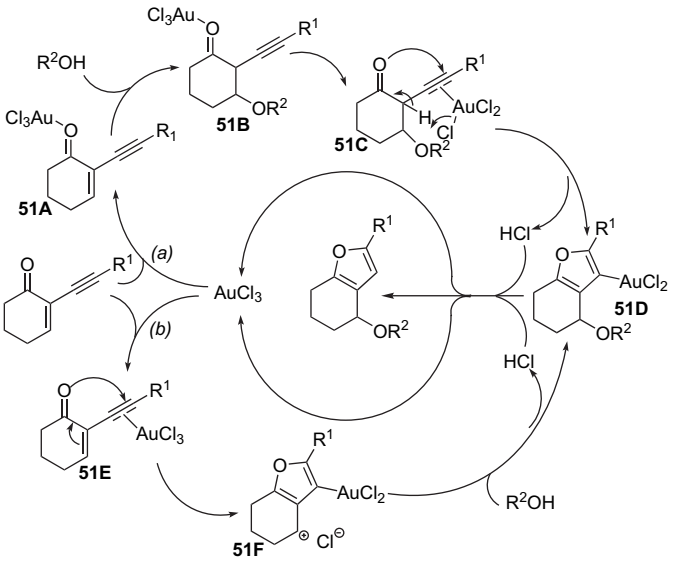
(157)

They point out, however, that the lack of reaction in the absence of a nucleophile, or when using Et_3SiH instead of MeOH, contradicts the mechanism involving a carbocation intermediate (path b).



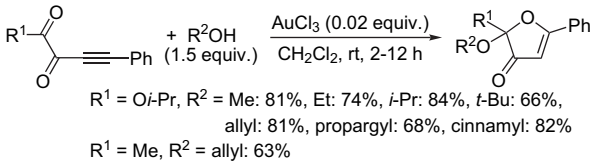
(159)

Liu et al. disclosed an efficient access to 3(2*H*)-furanones from the reaction between 2-oxo-3-butynoic esters or 1,2-dioxo-3-ynes and alcohols in the presence of catalytic amounts of $AuCl_3$ (Eq. 160) or $Ph_3PAuCl/AgOTf$.[139] The reaction involves either the nucleophilic

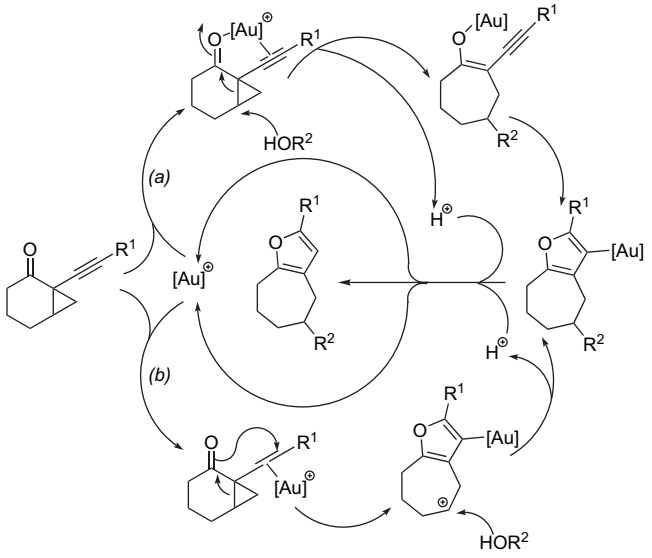


Scheme 51.

addition of R^2OH to the R^1CO moiety and the concomitant 5-*endo-dig* cyclisation, or the 5-*endo-dig* cyclisation followed by the addition of R^2OH to the resulting oxonium ion.

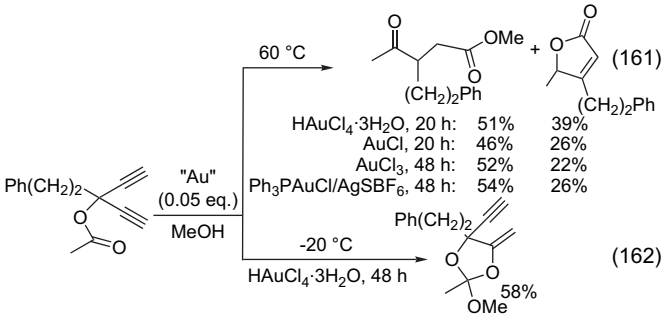


R^1 = O*i*-Pr, R^2 = Me: 81%, Et: 74%, *i*-Pr: 84%, *t*-Bu: 66%, allyl: 81%, propargyl: 68%, cinnamyl: 82%
R^1 = Me, R^2 = allyl: 63% (160)

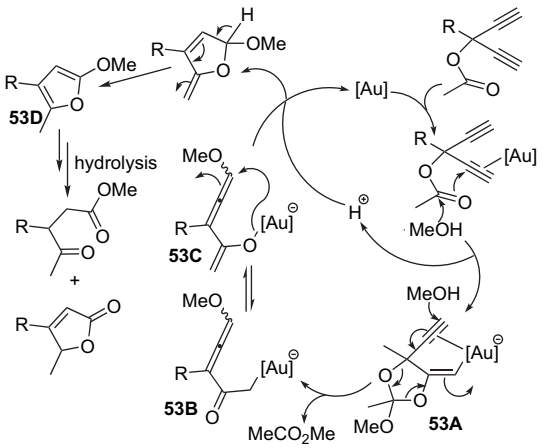


Scheme 52.

The treatment, at 60 °C in MeOH or *i*-BuOH, of 1,1-diethynyl acetates with catalytic amounts of an Au catalyst provides a mixture of γ-ketoesters and lactones (Eq. 161).[140] Kato et al. proposed that the activation of one of the two C≡C bonds induces the 5-*exo-dig* cyclisation and the alcohol addition leading to **53A** (Scheme 53). The *anti*-Markovnikov addition of MeOH to the second triple bond and the elimination of AcOMe give **53B**/**53C**. The cyclisation followed by protolysis and isomerisation affords **53D**, the hydrolysis of which yields the products. In agreement with this mechanism, the orthoester resulting from the protolysis of the reaction intermediate **53A** has been isolated on decreasing the reaction temperature to −20 °C (Eq. 162).

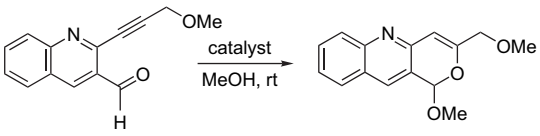


Belmont et al. have recently disclosed the synthesis of pyranoquinolines from the catalysed reaction between 1-alkynyl-2-carbonyl-quinolines and methanol.[141] While no reaction or low yields were obtained using $AuCl_3$ or Ph_3PAuCl as the catalyst, the acetalisation/cycloisomerisation process was efficiently promoted

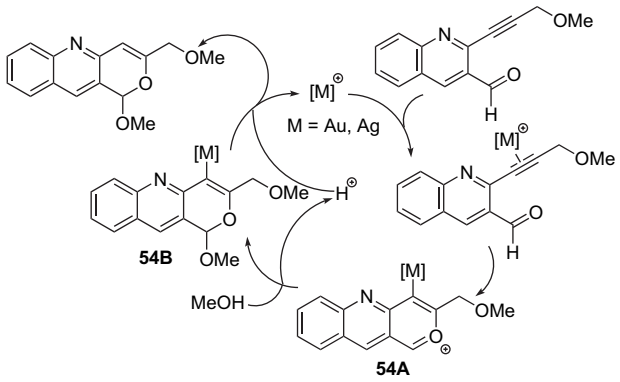


Scheme 53.

with a 1:1 mixture of Ph_3PAuCl and $AgSbF_6$. A similar result was, however, attained when using only the silver salt (Eq. 163). A possible mechanistic pathway is shown in Scheme 54. The increase of the electrophilicity of the triple bond by coordination gives rise to the nucleophilic attack of the carbonyl oxygen to generate the gold ate complex **54A**. This 6-*endo-dig* cyclisation is followed by the attack of MeOH to give **54B**, the protodeauration of which liberates the organic product.



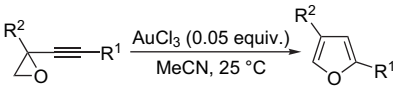
$AuCl_3$ (0.05 equiv.): 0%
Ph_3PAuCl (0.05 equiv.): 25%
Ph_3PAuCl (0.05 equiv.) + $AgSbF_6$ (0.05 equiv.): > 95%
$AgSbF_6$ (0.05 equiv.): > 95% (163)



Scheme 54.

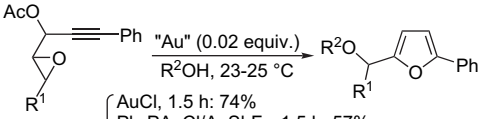
11. Cycloalkoxylation of epoxy alkynes

Hashmi and Sinha have obtained furans in 25–84% yields from the treatment, with catalytic amounts of $AuCl_3$, of α-epoxy alkynes substituted by a hydroxyalkyl moiety (Eq. 164).[142] No product involving a reaction of the alcohol was isolated, but the dependence of the yields upon the substitution position suggests its participation in the formation of the side products.



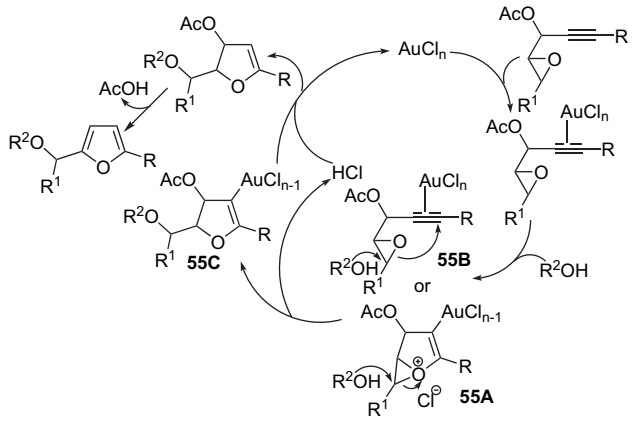
R^1 = Me, R^2 = $(CH_2)_3OH$: 80%
R^1 = Me, R^2 = $(CH_2)_4OH$: 84%
R^1 = $(CH_2)_2OH$, R^2 = Ph: 56%
R^1 = $(CH_2)_2OH$, R^2 = $(CH_2)_2Me$: 25% (164)

In 2007, Liang et al. reported the cycloisomerisation/alkoxylation of alkynyloxiranes, using Au^I or Au^{III} catalysts and primary, secondary or tertiary alcohols (Eq. 165).[143] According to the authors, the cyclisation may precede the alcohol addition (**55A**) or may occur simultaneously (**55B**), as illustrated in Scheme 55. This gives the gold intermediate **55C**, the protodeauration of which, followed by elimination of AcOH, produces the 2,5-disubstituted furan.



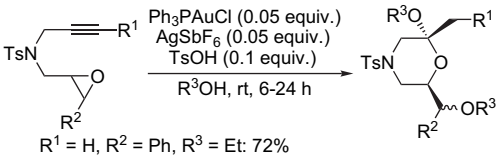
R^1 = Ph, R^2 = Me: AuCl, 1.5 h: 74%; $Ph_3PAuCl/AgSbF_6$, 1.5 h: 57%; $HAuCl_4{\cdot}4H_2O$, 20 h: 74%; Bu_4NAuCl_4, 24 h: 74%; $AuCl_3$, 1.5 h: 93%

R^1 = Ph, $AuCl_3$: R^2 = Me (2 h: 78%), Et (6 h: 70%), *i*-Pr (6 h: 62%), *t*-Bu (6 h: 60%), allyl (6 h: 60%), Bn (6 h: 61%) (165)



Scheme 55.

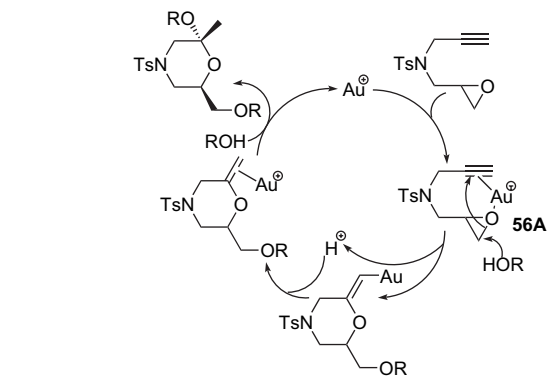
Simultaneously to Liang et al., Shi et al., independently, disclosed the synthesis of ketal skeletons from the Au-catalysed double intermolecular addition of an alcohol to alkynyl epoxides (Eq. 166).[95] A plausible mechanism (Scheme 56) involves alcohol addition to the complex **56A** formed by the coordination of both the triple bond and the oxirane, followed by protodeauration, and then re-coordination to promote the addition of a second molecule of alcohol.



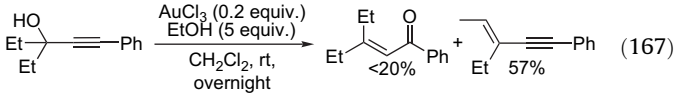
R^1 = H, R^2 = Ph, R^3 = Et: 72%
R^1 = Me, R^2 = H, R^3 = Et: 65%
R^1 = R^2 = H, R^3 = Me: 75%, Et: 70%, *i*-Pr: 44%, allyl: 68% (166)

12. Dehydration of alcohols

The Au^{III}-catalysed Meyer–Schuster rearrangement of tertiary propargylic alcohols leads usually to α,β-unsaturated ketones (see Section 4.1). Under such conditions, 3-ethyl-1-phenylpent-1-yn-3-ol is, however, mainly dehydrated (Eq. 167).[58] The $AuCl_3$-mediated dehydration and the subsequent hydration of the triple bond have been invoked to rationalise the formation of 3-methylene-1-phenylpentane-1,4-dione, depicted in Eq. 154, and this is followed by migration of the C=C bond.[133] Dehydration of saturated tertiary alcohols has also been reported, in the presence of $Ph_3PAuOTf$, at 60 °C in 1,2-dichloroethane.[144]

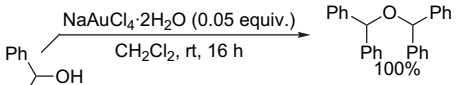


Scheme 56.

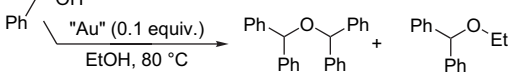


(167)

Gold salts are able to promote the intermolecular dehydration of alcohols, affording symmetric and unsymmetric ethers (Eqs. 168 and 169).[23,55,145] With diphenylmethanol as the substrate, a key intermediate is the corresponding benzylic cation.[55,145]



(168)



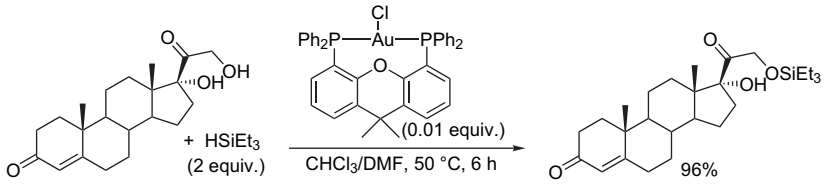
AuCl, 5.5 h:	21%	75%
$AuCl_3$, 5.5 h:	85%	12%
$NaAuCl_4$, 24 h:	8%	76%

(169)

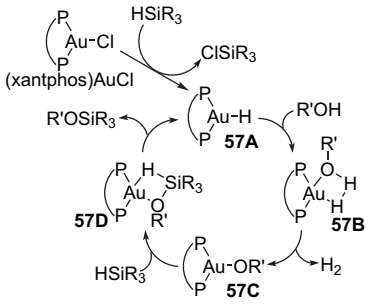
Gagosz et al. have suggested that the dissymmetric ether formed under cationic Au^I catalysis (Eq. 23) results from the substitution of the propargyl or allylic alcohol,[33] but an intermolecular dehydration is, nevertheless, envisageable. Note that the formation of a dissymmetric ether has also been reported using a $gold^I$ complex, methanol and a primary propargyl alcohol (Eq. 7),[14] or $NaAuCl_4$, ethanol and a tertiary propargyl alcohol,[54] but without mechanistic comment.

13. Silylation of alcohols

The chemoselective silylation of a broad range of alcohols with $HSiR_3$ (R_3=Et_3, Ph_3, Me_2Ph, Me_2t-Bu) has been carried out in high yields by Ito et al. using (xantphos)AuCl as the catalyst.[146] Although the silylation of primary, secondary and tertiary alcohols effectively occurs, the selective reaction of a primary alcohol in the presence of a tertiary alcohol has been successful (Eq. 170). The real catalyst would be the gold hydride **57A** that undergoes reaction with the alcohol through a σ-bond metathesis involving **57B** and leading to **57C** (Scheme 57). The reaction between **57C** and the hydrosilane provides the silyl ether and **57A** via a second σ-bond metathesis (**57D**).

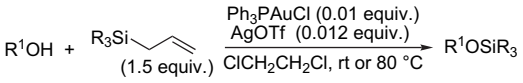


(170)



Scheme 57.

Subsequently, Shibata et al. have used allylsilanes and a cationic Au^{I} catalyst for the silylation of primary and secondary alcohols (Eq. 171).[144] According to the authors, the reaction proceeds owing to the Lewis acid properties of the catalyst.

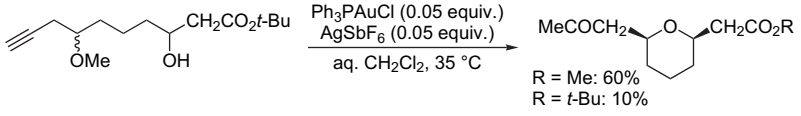


R^1 = $Ph(CH_2)_3$, R_3 = Me_2t-Bu, 80 °C, 0.5 h: 94%
R^1 = $Ph(CH_2)_3$, R_3 = Et_3, rt, 3 h: 84%
R^1 = $Ph(CH_2)_3$, R_3 = i-Pr_3, 80 °C, 10 h: 91%
R^1 = $Me(CH_2)_5CHMe$, R_3 = Me_2t-Bu, 80 °C, 1 h: 90%
R^1 = $Ph(CH_2)_2CHMe$, R_3 = Me_2t-Bu, 80 °C, 10 h: 93%
R^1 = $Ph(CH_2)_2CHMe$, R_3 = i-Pr_3, 80 °C, 10 h: 91%

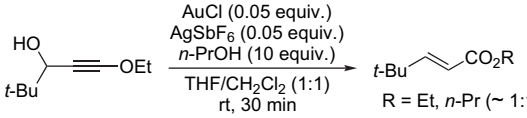
(171)

14. Transesterification

The alcoholysis of esters in the course of Au-catalysed reactions has been reported, but this was not the aim of the studies; two possible examples are shown in Eqs. 172 and 173. The methanolysis depicted in Eq. 172[100,101] is due to the MeOH that is released in the course of the reaction (see Scheme 33, Section 7). As for Eq. 173, the formation of a mixture of ethyl and propyl esters could be due to the addition of propanol to a reaction intermediate (see Scheme 15, Section 4.1), as suggested by the authors,[59] and/or also to propanolysis of the ethyl ester. The alcoholysis of esters under Au-catalysed reactions is, however, not a general process even when the alcohol is used as the solvent (see Eqs. 35 and 174, Sections 3.2 and 15, respectively).



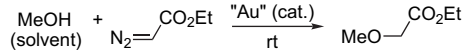
(172)



(173)

15. Insertion into O–H bonds

The insertion of the :$CHCO_2Et$ unit of ethyl diazoacetate into the O–H bond of methanol and ethanol is catalysed by various carbene gold^{I} complexes (Eq. 174; for the structure of the IPr ligand, see Eq. 24, Section 3.1).[34,147,148] According to Nolan et al., the alcohol coordinates to the catalyst[147] and the counterion plays an important role in the process.[148]



IPrAuCl/[3,5-$(CF_3)_2C_6H_3]_4$BNa (0.05 equiv. each), 1 h: 99%[147]
IPrAu(NCMe)PF_6 (0.04 equiv.), 12 min: 99%[148]
IPrAuNTf_2 (0.02 equiv.), 5 min: 89%[34]

(174)

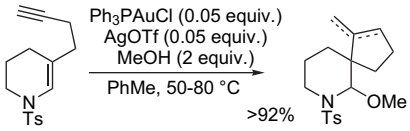
16. Conclusions

In the context of 'Green Chemistry', one of the main interests of most above Au^{I}- and Au^{III}-catalysed transformations is their high atom efficiency under moderate conditions. In some cases, the presence of a Brønsted acid as co-catalyst or promoter is required. Some of the above reactions occur, nevertheless, under gold-free conditions using only Brønsted acids or other Lewis acids. This has been pointed out by different authors, in particular, by Hashmi in a recent report.[149] Moreover, since the used cationic Au^{I} catalysts are often obtained from the in situ metathesis reaction between a neutral gold^{I} complex and a silver^{I} salt, the resulting Ag^{I} species may not be innocent in some of the corresponding catalysed reactions. These remarks indicate that the intimate mechanisms of these reactions still require further clarification, but, nevertheless, do not detract from the interest in the atom-economical methods mediated by gold catalysts, since good-to-high yields and selectivities are usually obtained.

The homogeneous gold catalysis has attracted growing interest during the last few years. The potential of gold to efficiently induce domino reactions will, without any doubt, lead the retrosynthetic analyses to take, more and more, into account the gold methods, resulting in increased applications in multi-step organic synthesis of natural and unnatural products.

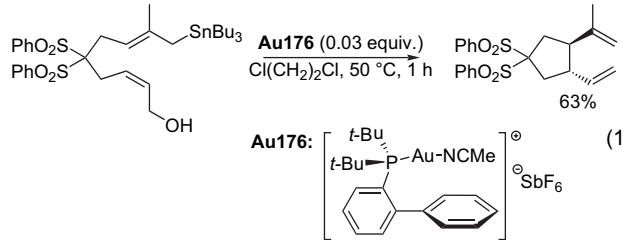
17. Addendum

As shown in Eq. 175, Dake et al. have disclosed the methoxylation/cyclisation of an enesulfonamide tethered to an alkyne.[150]

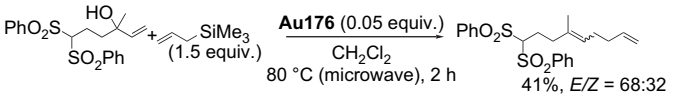


(175)

Intra- and intermolecular couplings of allylic alcohol fragments with allylic tin or silicium units have been disclosed by Echavarren et al. (Eqs. 176 and 177).[151]

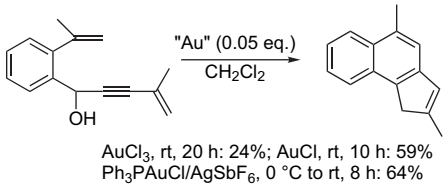


(176)



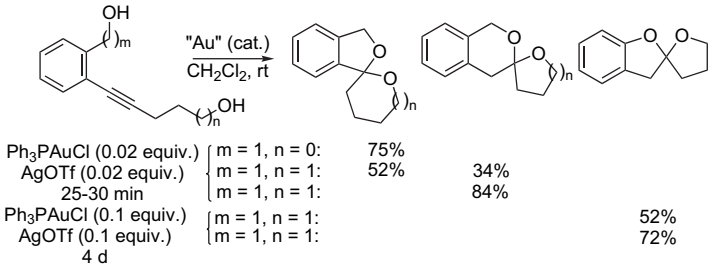
(177)

Liu et al. have obtained a tricyclic compound, namely 2,5-dimethyl-1*H*-cyclopenta[*a*]naphthalene, from the Au-catalysed cyclisation of 4-methyl-1-(2-(prop-1-en-2-yl)phenyl)pent-4-en-2-yn-1-ol (Eq. 178).[152] This cascade reaction would involve the reactive steps already shown in Scheme 19, i.e. a 6-*exo*-*dig* cyclisation followed by dehydroxylation, to afford the carbene **58A** (Scheme 58). This carbene possesses a cationic pentadienyl resonance (**58A'**) that could promote a Nazarov-type cyclisation[153] giving **58B**[154] and, ultimately, the product.

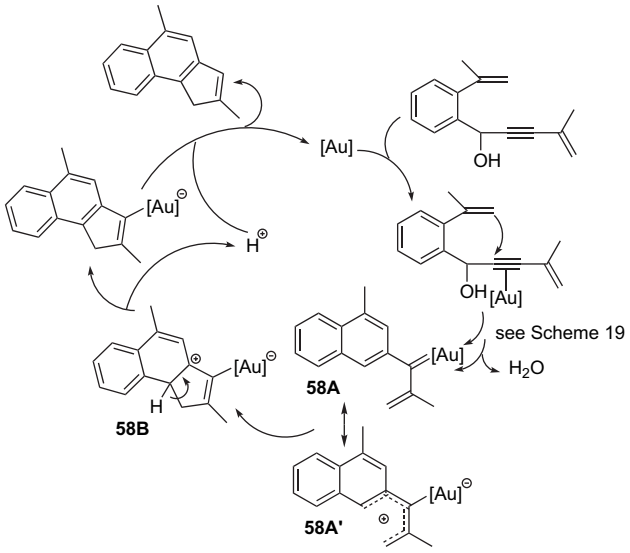


(178)

Xue et al. have synthesised spiroketals via the Au^I-catalysed double intramolecular hydroalkoxylations illustrated in Eq. 179.[155]

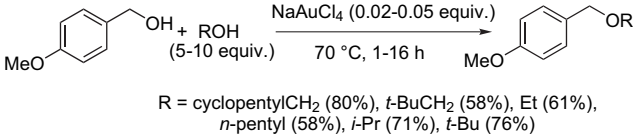


(179)



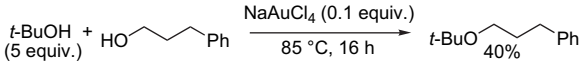
Scheme 58.

Asensio et al. have prepared a panel of unsymmetrical ethers from the reaction, catalysed by $NaAuCl_4$, of benzylic or tertiary alcohols with alkyl alcohols (Eqs. 180 and 181).[156]



R = cyclopentylCH$_2$ (80%), *t*-BuCH$_2$ (58%), Et (61%), *n*-pentyl (58%), *i*-Pr (71%), *t*-Bu (76%)

(180)



(181)

Supported Au nanoparticles have been used by Raffa et al. to catalyse the silylation of alcohols with $HSiR_3$ ($R_3 = Et_3$, Me_2Ph).[157]

A review devoted to the Au-catalysed synthesis of heterocycles and carbocycles has been published by Shen.[158]

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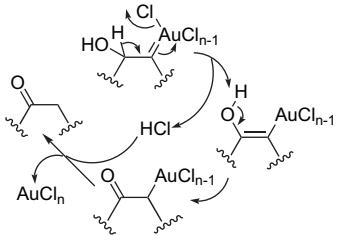

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Biographical sketch

Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Champagne-Ardenne and received his degrees (Doctorat de 3ème cycle—1972, Doctorat d'Etat—1976) for his work with Jean-Pierre Pète on photochemical rearrangements of α,β-epoxyketones and β-diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 as Stagiaire de Recherche and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with Elias J. Corey at Harvard University on natural product synthesis. On his return to Reims, he mainly studied the photoreactivity of η^3-allylpalladium complexes and anionic activation by supported reagents. In 1988, he was promoted to Directeur de Recherche CNRS. His research interests concentrate on transition-metal catalysis with particular emphasis on oxidations, asymmetric reactions, C–H activations and mechanisms. Since a few years, he is also involved in the valorisation of agricultural by-products and in the use of water and molten salts as solvents for Organic Synthesis.