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Review

Gold-Catalyzed Addition of Carboxylic Acids to Alkynes and Allenes: Valuable Tools for Organic Synthesis

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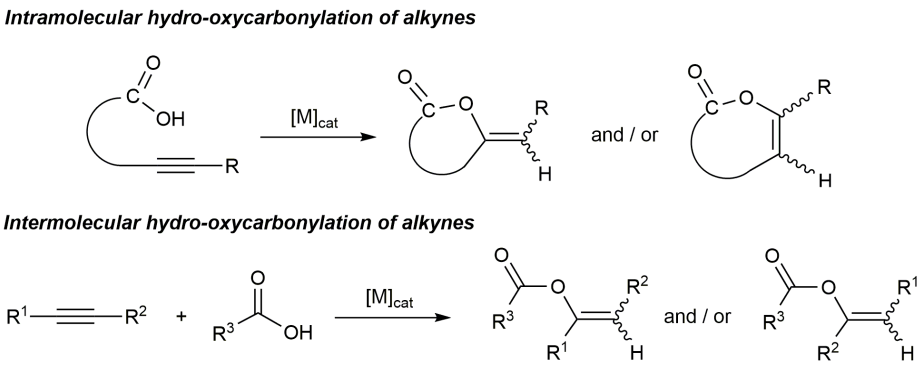
Abstract: In this contribution, the application of gold-based catalysts in the hydrofunctionalization reactions of alkynes and allenes with carboxylic acids is comprehensively reviewed. Both intra- and intermolecular processes, leading respectively to lactones and linear unsaturated esters, are covered. In addition, cascade transformations involving the initial cycloisomerization of an alkynoic acid are also discussed.

Keywords: gold catalysts; addition reactions; hydrofunctionalization; alkynes; allenes; esters; lactones

1. Introduction

The catalytic hydrofunctionalization of alkynes provides convenient routes of access to a wide variety of functionalized olefins that address the current need for atom-economic, green and sustainable processes [1–7]. In this regard, countless catalytic systems capable of promoting the addition of different heteroatom- (e.g., O, N, S, P, B, Se, Si, P or halogens) and carbon-hydrogen bonds to alkyne molecules, with high levels of efficiency and selectivity, can be found in the literature. A relevant example of this type of transformation is the hydro-oxycarbonylation of alkynes with carboxylic acids [2–4,8–13]. Thus, as shown in Scheme 1, the intramolecular version of the process, i.e., the cycloisomerization of alkynoic acids, allows the rapid assembly of unsaturated lactone rings which are structural units present in a huge number of biologically active molecules and natural products [14–16]. Of interest also, are the intermolecular additions of carboxylic acids to alkynes, since the resulting enol ester products are relevant intermediates for synthetic chemistry and polymerization reactions [8,13,17].



Scheme 1. The intra- and intermolecular additions of carboxylic acids to alkynes.

Several transition metals have been employed to promote the hydrofunctionalization of alkynes, among which gold has gained prominence, given its outstanding effectiveness for the π-electrophilic

activation of unsaturated carbon-carbon bonds towards nucleophiles [18–25]. In addition, the fact that the properties of both Au(I) and Au(III) complexes can be easily modulated by the surrounding ligands has been extensively exploited for the fine tuning of the activity and/or selectivity of the catalytic processes in which gold is involved [26]. Regarding the addition reactions of carboxylic acids to alkynes, the use of gold catalysts has made it possible to overcome some of the limitations found with other metals—for example, the hydro-oxycarbonylation of internal alkynes for which ruthenium, one of the most frequently employed metals, is ineffective. The marked preference of π-alkyne-gold complexes to undergo the addition of nucleophiles in an *anti* fashion is also beneficial in these reactions, since it limits the number of isomers that can be formed.

To a lesser extent, gold-based catalysts have also been applied in recent years in the hydrofunctionalization of allenes, molecules of special relevance because their axial chirality can be exploited in asymmetric synthesis. Intramolecular hydroamination and hydroalkoxylation processes are by far the most documented [20,23,27,28], but some examples of both intra- and intermolecular hydro-oxycarbonylation reactions of allenes catalyzed by gold complexes are also known. In addition to the classical chemoselectivity, regioselectivity and stereoselectivity issues, positional selectivity is an extra problem associated to the nucleophilic additions to allenes [29]. In general, the regioselectivity of the addition process, i.e., attack of the heteroatom on the *sp* or the sp^2 carbons, is strongly dependent on the substitution pattern of the substrates, and in the case of intramolecular processes, also on the length of the tether connecting the allenic unit and the nucleophile. In that regard, the exquisite selectivity found in all the gold-catalyzed hydro-oxycarbonylation reactions described to date in the literature is noteworthy.

The aim of the present review article is to provide a comprehensive overview of the developments achieved in this particular research area.

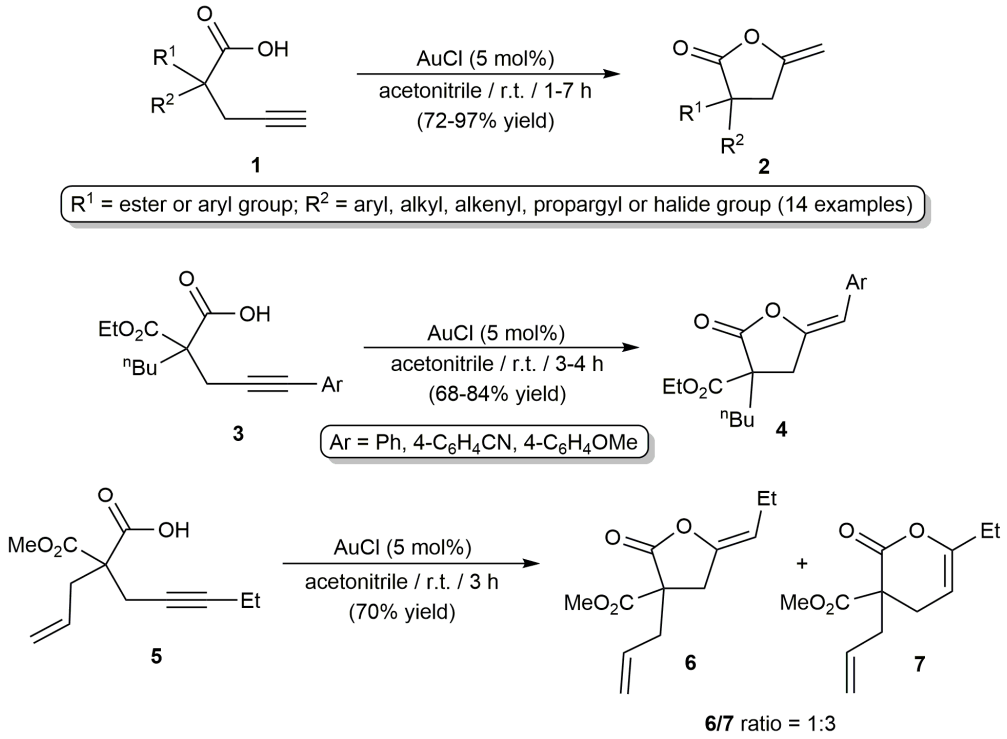
2. Additions of Carboxylic Acids to Alkynes

2.1. Cycloisomerization of Alkynoic Acids

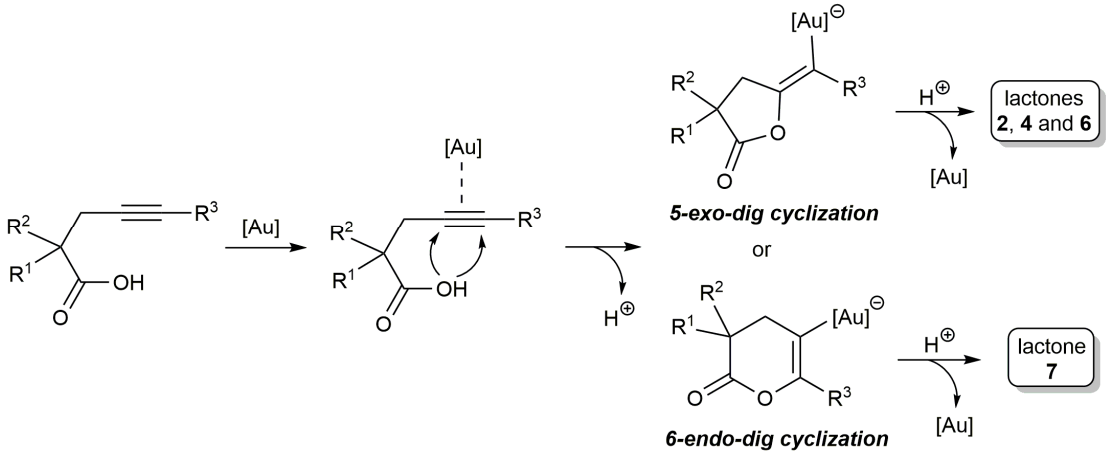
The utility of gold catalysts in the cyclization of acetylenic acids was evidenced for the first time by Michelet and co-workers in 2006 [30]. As shown in Scheme 2, they found that in the presence of catalytic amounts of AuCl (5 mol%), a large variety of terminal γ-alkynoic acids **1** are rapidly converted into the corresponding 5-alkylidene-butyrolactones **2**, in high yields and in a complete regioselective manner, by performing the reactions in acetonitrile at room temperature. The process was also operative with γ-alkynoic acids containing internal alkyne units, such as the aromatic derivatives **3** or the aliphatic one **5** [30,31]. In the case of **3**, regardless of the electronic properties of the aryl substituent, a selective 5-*exo-dig* cyclization was again observed. In addition, the corresponding five-membered ring enol-lactones **4** featured in all the cases (Z) stereochemistry for the exocyclic C=C bond. This last point implies that the reactions proceed through the intramolecular *anti*-addition of the carboxylic acid to the Au(I)-coordinated alkyne moiety (see the mechanistic proposal in Scheme 3). The same stereochemistry was found in the butyrolactone **6** generated from the ethyl-substituted γ-alkynoic acid **5**, although in this case the major reaction product was the 6-membered ring lactone **7** resulting from a *6-endo-dig* cyclization.

Almost simultaneously with Michelet's work, Pale and co-workers reported the AuCl-catalyzed cyclization of different γ, δ and ε-alkynoic acids lacking substituents in α-position with respect to the carboxylic acid group (Scheme 4) [32]. Unlike the previous examples, this type of substrate does not benefit from the Thorpe–Ingold effect and the reactions required of a higher metal loading (10 mol%) and the assistance of a base (K_2CO_3) to facilitate the generation of the nucleophilic carboxylate anion. Regardless of the length of the hydrocarbon chain and the nature of the alkyne terminus, the selective formation of the *exo-dig* cyclization products was observed, with generally high yields (≥ 60%), except for the case of hept-6-ynoic acid—which delivered the corresponding 7-membered ring enol-lactone in only 25% yield after 48 h of stirring in acetonitrile at r.t. (the rest of examples required only two

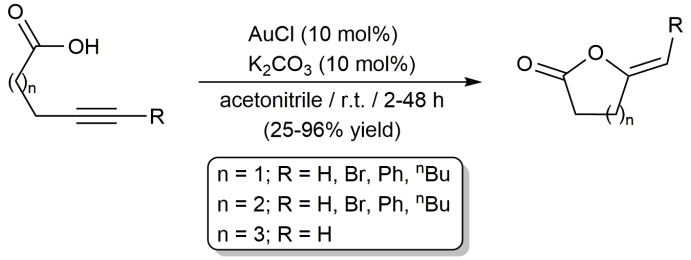
hours of reaction). For those substrates featuring an internal C≡C bond, the *anti*-addition products were again exclusively generated, although in some cases the (*Z*) isomers initially formed partially isomerized in solution into the corresponding (*E*) ones [32,33]. Of note is the fact that the process was completely inoperative when silyl-protected alkynes were employed as substrates due to the strong withdrawing effect of the SiR_3 group, which drastically reduces the electron density of the C≡C bond, thereby making its coordination to the gold center less favorable [32,33].



Scheme 2. AuCl-catalyzed cycloisomerization of γ-alkynoic acids.

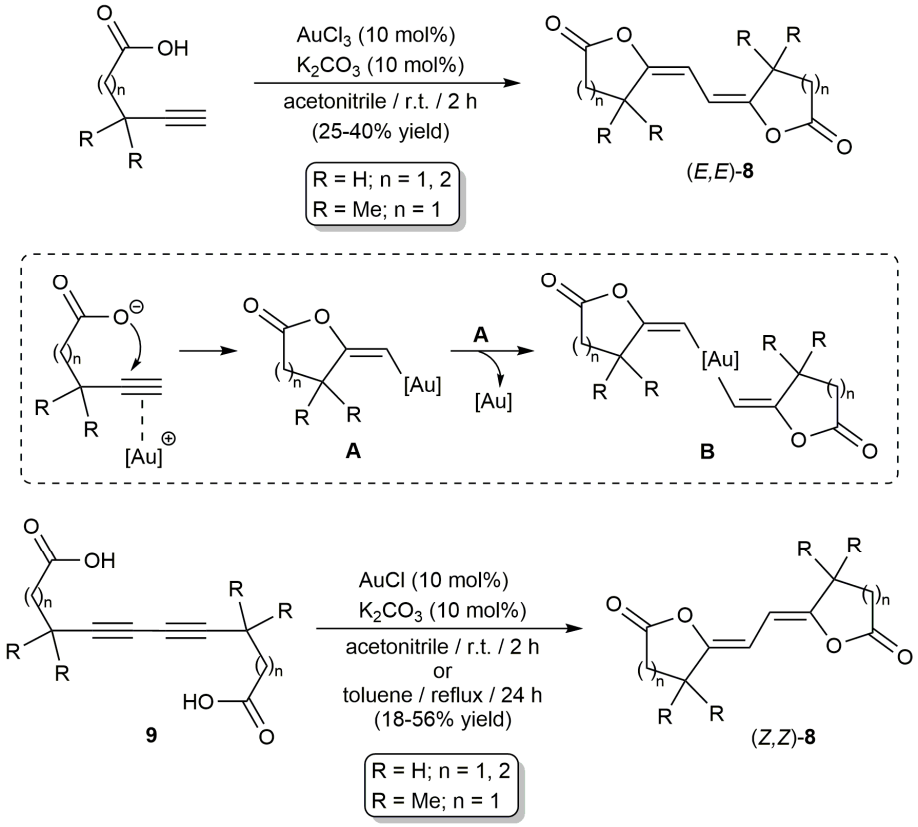


Scheme 3. Proposed mechanism for the AuCl-catalyzed cycloisomerization of γ-alkynoic acids.



Scheme 4. Base-assisted AuCl-catalyzed cycloisomerization of alkynoic acids.

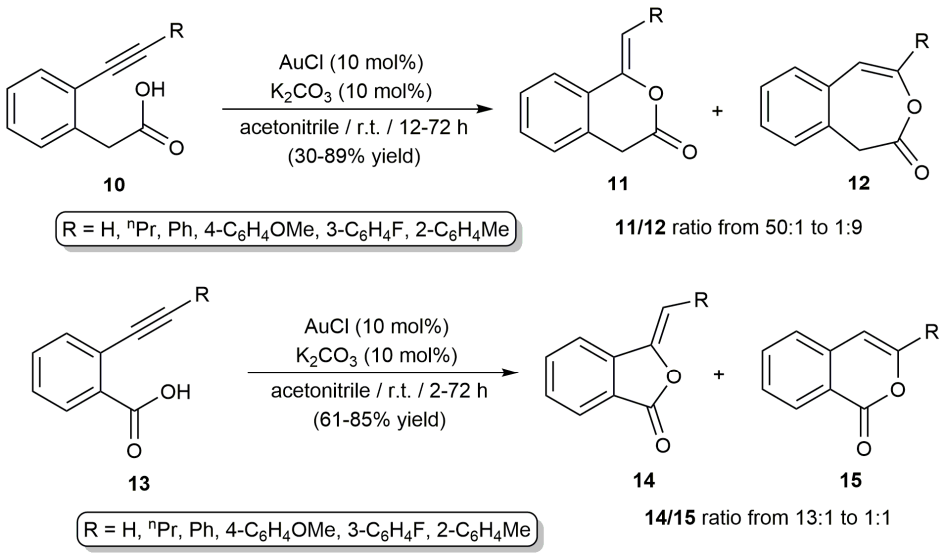
Pale´s group also explored the catalytic behavior of $AuCl_3$ in these cycloisomerization processes, observing for the three model alkynoic acids tested the unexpected formation of the dimeric methylene-lactone derivatives **8** (Scheme 5) [33]. These species were generated in a stereoselective manner as the corresponding (*E*,*E*) isomers, and were isolated in low yields. A reaction pathway involving the homocoupling of the organogold intermediates **A** generated during the *exo* cyclization of the substrates was proposed by the authors to explain the formation of compounds **8**. The reductive elimination of the resulting diorganogold species **B** would give dimers **8** with liberation of Au(I). This last point could be responsible for the low yields observed, since half of the catalyst is consumed. The involvement of the diynyldiacids **9**, which could potentially be generated in the reaction medium through a Glaser-type homocoupling, was totally ruled out, since the gold-catalyzed cyclization of these species leads to the formation of the compounds **8** with an opposite stereochemistry on the two C=C bonds, i.e., as (*Z*,*Z*) isomers (see Scheme 5).



Scheme 5. Gold-catalyzed synthesis of dimeric methylene-lactones from alkynoic acids.

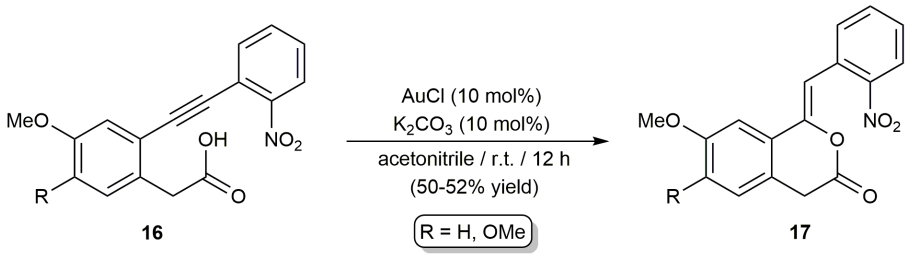
Applying Pale´s conditions, i.e., using the AuCl/K_2CO_3 combination, van de Weghe and co-workers studied the cycloisomerization of the 2-alkynyl-substituted phenylacetic acids **10**, thereby observing the formation of reaction mixtures containing the respective 1-alkylidene-isochroman-3-one **11** (6-*exo*-*dig*

cyclization) and benzo[*d*]oxepin-2(1*H*)-one **12** (7-*endo-dig* cyclization), with the former being the major component in almost all the cases (except for R = ^{n}Pr; see Scheme 6) [34]. Related reactions employing as substrates 2-alkynyl-substituted benzoic acids **13** also afforded mixtures of the regioisomers **14** and **15**; the *exo-dig* mode of cyclization predominated again [34,35].



Scheme 6. AuCl-catalyzed cycloisomerization of 2-alkynyl-substituted phenylacetic and benzoic acids.

Much more selective transformations were described by Estévez and co-workers, starting from the related 2-[(2-nitrophenyl)ethynyl]phenylacetic acids **16,** since lactones **17**, resulting from a regiospecific 6-*exo-dig* cyclization, were exclusively obtained (Scheme 7) [36]. According to the authors, the strong resonance effect of the nitro group was probably behind the exquisite selectivity observed with these particular substrates.

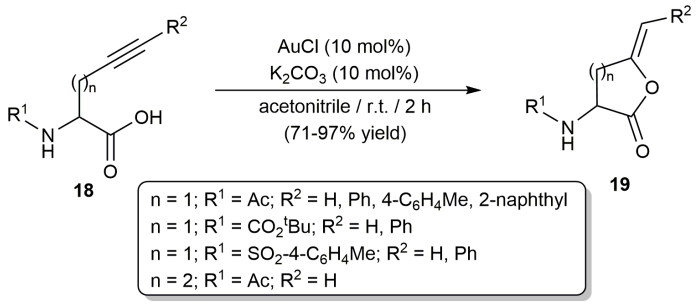


Scheme 7. AuCl-catalyzed cycloisomerization of 2-[(2-nitrophenyl)ethynyl]phenylacetic acids **16**.

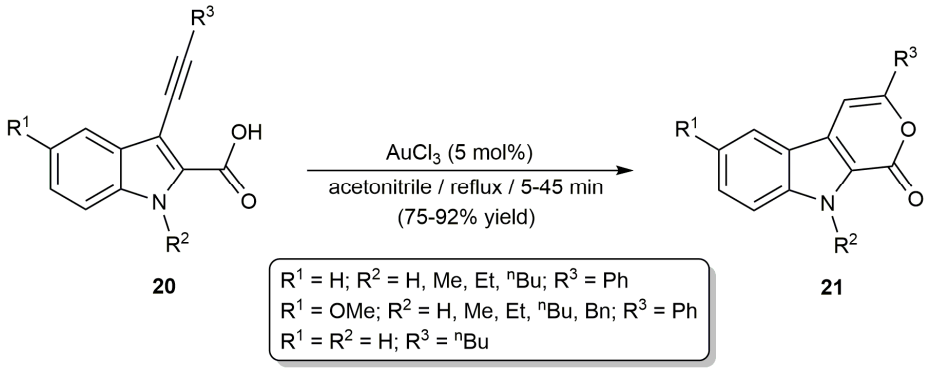
Employing the AuCl/K_2CO_3 combination too, Testero and co-workers reported the regioselective and stereoselective conversion of the amino acid-derived alkynoic acids **18** into the respective enol-lactones **19** (Scheme 8) [37]. Remarkably, secondary products derived from the addition of the N–H unit to the C≡C bond were in no case observed, despite them easily occurring when the CO_2H group was replaced by the ester one CO_2Me.

On the other hand, Perumal and co-workers described the synthesis of several pyrano[3,4-*b*]indol-1(9*H*)-ones **21** by 6-*endo-dig* cyclization of the 3-alkynyl-indole-2-carboxylic acids **20**, using in this case gold(III) chloride as the catalyst (Scheme 9) [38]. The reactions proceeded in high yields and short times in the absence of base, but harsher temperature conditions were needed (refluxing acetonitrile). The excellent regioselectivity observed in these reactions was explained by the authors on the basis of the greater strain associated with the formation of two fused 5-membered rings in the potential 5-*exo-dig* cyclization products. Noteworthily, compounds **21** displayed cytotoxic

activity against human cervix adenocarcinoma (HeLa) cell lines, comparable in some cases to that shown by the standard *cis*-platin drug.

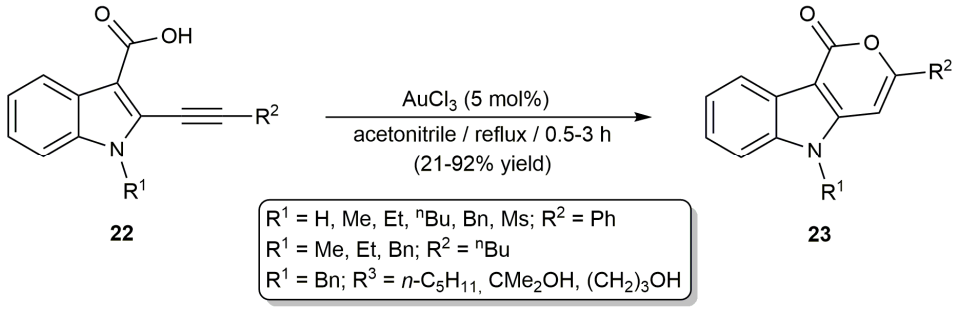


Scheme 8. Catalytic cycloisomerization of alkyne-containing amino acid derivatives.



Scheme 9. $AuCl_3$-catalyzed synthesis of pyrano[3,4-*b*]indol-1(9*H*)-ones.

The same protocol was additionally employed for the preparation of the related pyrano[4,3-*b*]indol-1(5*H*)-one derivatives **23**, which also featured inhibitory activity against HeLa cells, from the corresponding 2-alkynyl-indole-3-carboxylic acids **22** (Scheme 10) [39]. It should be mentioned at this point that the present cyclization process seems to be restricted to substrates containing an internal alkyne unit ($R^2 \neq H$), since a control experiment with a terminal one led, under identical reaction conditions, to the recovery of the starting material—mostly unchanged after 3 h of heating. $AuCl_3$-catalyzed 6-*exo-dig* cyclizations of *N*-propargylpyrrole and indole-2-carboxylic acids have also been described [40].



Scheme 10. $AuCl_3$-catalyzed synthesis of pyrano[4,3-*b*]indol-1(5*H*)-ones.

In addition to the chloride salts AuCl and $AuCl_3$, several molecular gold complexes are known to promote cycloisomerization reactions of alkynoic acids. For example, Hammond, Xu and co-workers reported the use of [AuCl(JohnPhos)] [41,42], and an analogous gold(I)-chloride complex containing the more sterically demanding *o*-biphenyl phosphine **24** (see Figure 1) [43], as catalysts for the *exo* cyclization of the model substrates pent-4-ynoic acid and hex-5-ynoic acid. Both showed remarkable

activity leading to the corresponding alkylidene-lactones in a quantitative manner, and short times (from 5 min to 1 h), while employing metal loadings of only 0.01–0.3 mol%. However, it should be noted that the presence of a chloride abstractor (AgOTf or $AgSbF_6$) was needed to activate the catalysts and generate the required vacant coordination site on the metal for alkyne binding. More elaborated examples include platinum-based nanospheres functionalized with a phosphine-gold(I)-chloride complex [44] and AuCl linked to a resorcinarene cavitand phosphine ligand [45]. These supramolecular systems proved to be active in the of cyclization of linear γ-alkynoic acids, showing differences in reactivity compared to the standard gold(I) chloride salt (lower selectivity towards the *exo* cyclization in the former case or reaction rates strongly dependent on the sizes of the substituents present in the substrates in the latter).

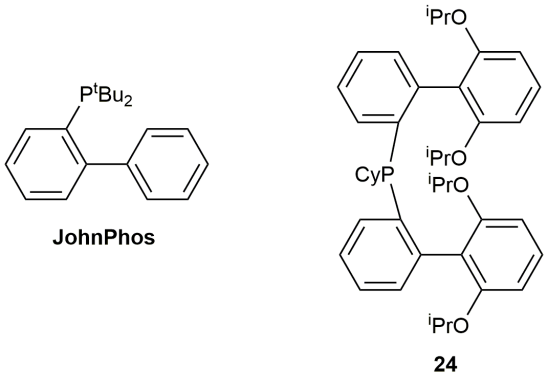


Figure 1. Structure of the *o*-biphenyl phosphine ligands JohnPhos and **24**.

The gold(I) complexes [AuCl(PPh_3)] and [AuCl{P(O-2,4-$C_6H_3{}^tBu_2)_3$}], in combination with $AgSbF_6$, were used by Porcel and co-workers to promote the cyclization of a series of alkynoic acids **25** derived from salicylic acid, reactions that proceeded efficiently in 1,2-dichloroethane at r.t. or 50 °C with catalyst loadings of 5 mol% (Figure 2) [46]. The regioselective formation of the corresponding seven-membered ring lactones **26** was observed for those substrates containing a terminal alkyne unit, while the cycloisomerization of their non-terminal counterparts was not always regioselective, leading to mixtures of the respective exo- and endocyclic enol-lactones **26** (major products) and **27** (minor products). In addition, certain non-terminal alkynoic acids led to the preferential formation of the 2*H*-chromenes **28**, products coming from the hydroarylation of the alkyne group. In a later work, the same group studied the arylative cyclization of compounds **25** with arenediazonium salts employing a stoichiometric amount of [AuCl(SMe_2)] and two equivalents of Li_2CO_3 as the promoters [47]. Regardless of the terminal or internal nature of the alkynes, mixtures of the corresponding lactones **26** and **27** arylated on the C=C bond were systematically generated, thereby revealing a difference in regioselectivity compared to that found in the cycloisomerization reactions just mentioned.

Cyclizations of alkynoic acids with gold complexes containing *N*-heterocyclic carbene (NHC) ligands can also be found in the literature. In this context, the first example was reported by Spenger and Friksdahl with the cycloisomerization of the bispropargylic carboxylic acid **29** employing [AuCl(IMes)] (IMes = 1,3-dimesitylimidazole-2-ylidene) as the catalyst (Scheme 11) [48]. In the presence of K_2CO_3, [AuCl(IMes)] was able to convert selectively **29** into the 5-*exo-dig* cyclization product **30**, while mixtures of **30**, the tetrahydropyranone **31** (6-*endo-dig* cyclization) and the bicyclic species **32** (resulting from the cyclization of **31**) were obtained when the K_2CO_3 co-catalyst was replaced by silver(I) salts ($AgSbF_6$, AgOTf, $AgNTf_2$ or $AgBPh_4$). Similar observations were made when [AuCl(PEt_3)] was employed as the gold source, although the yields were in general lower.

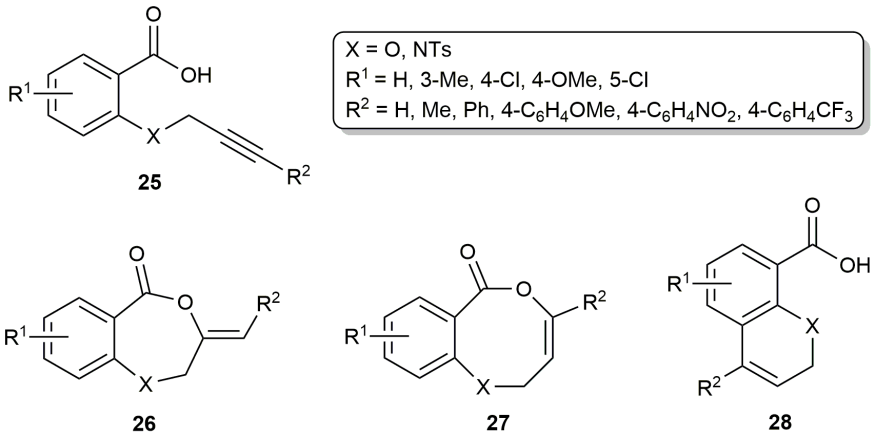
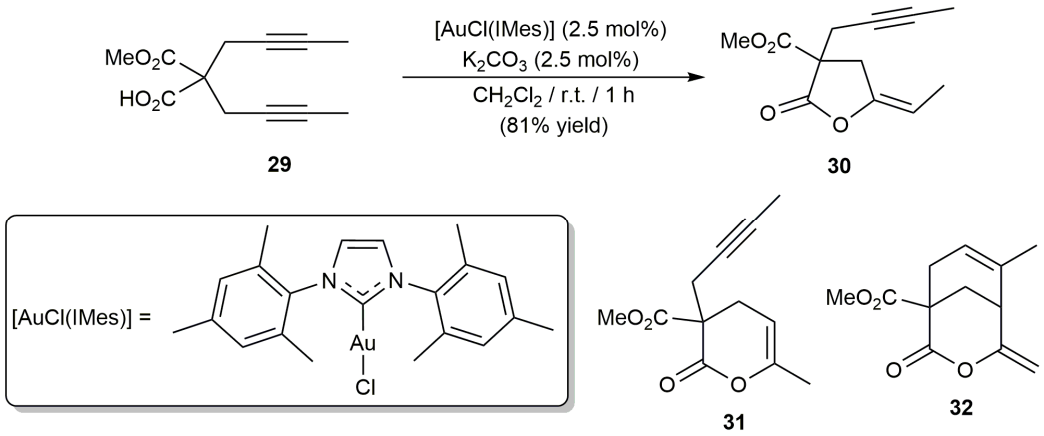


Figure 2. Structure of the alkynoic acids **25** and their cyclization products **26–28**.

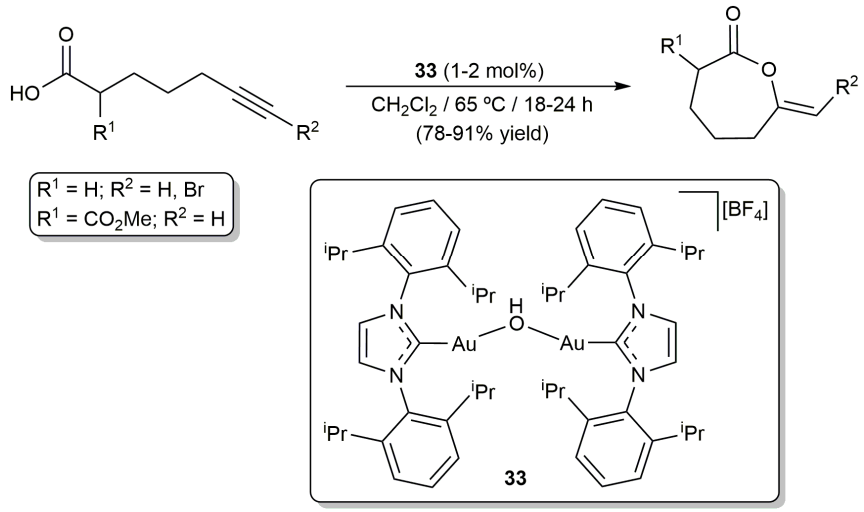


Scheme 11. Cyclization of the bispropargylic carboxylic acid **29** catalyzed by the NHC complex [AuCl(IMes)].

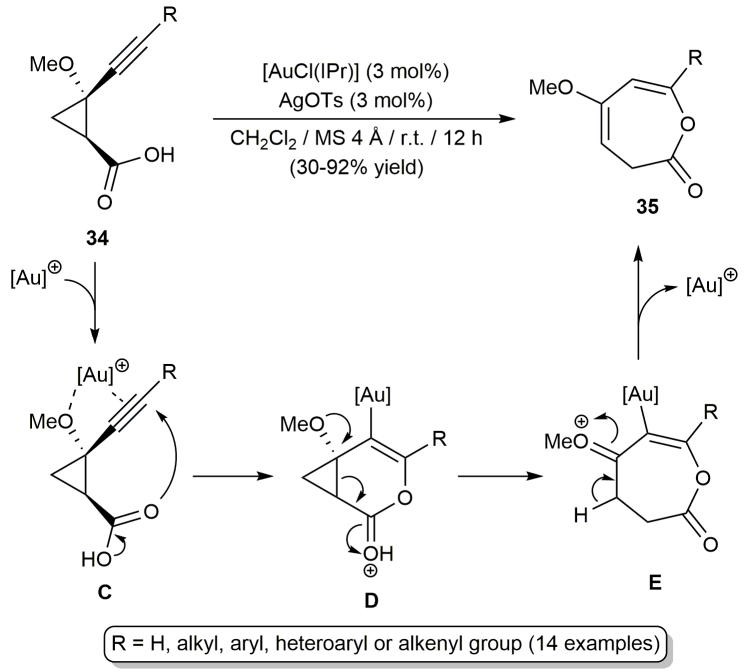
The dinuclear hydroxo-brigded gold(I) complex [{Au(IPr)}$_2$(μ-OH)][BF$_4$] (**33**; IPr = *N,N´*-bis(2,6-di-*iso*-propylphenyl)imidazole-2-ylidene) synthesized by Nolan´s group was particularly effective in the cyclization of linear γ and δ-alkynoic acids of general composition RC≡C(CH$_2$)$_n$CHR´CO$_2$H (n = 1, 2; R = H, Me, Br or aryl group; R´ = H, CO$_2$Me), allowing to perform the reactions at r.t. with remarkably low catalyst loadings (25 ppm-0.1 mol%) [49]. The outstanding activity of **33** is related to its ability to dissociate in solution into the two mononuclear species [Au(IPr)][BF$_4$] and [Au(OH)(IPr)], the former acting as a Lewis acid for the activation of the alkyne bond, and the latter as a Brønsted base capable of generating the more nucleophilic carboxylate anions by deprotonation of the carboxylic acid. An exquisite regioselectivity for the *exo* cyclization was in all the cases observed, except with internal alkynes bearing a methyl substituent, for which mixtures of the *exo* and *endo* addition products were obtained. Of note is the fact that [{Au(IPr)}$_2$(μ-OH)][BF$_4$] (**33**) proved to be also effective in the more challenging cyclization of ε-acetylenic acids, although higher temperatures and catalyst loadings were needed (see Scheme 12).

On the other hand, an interesting approach to challenging oxepin-2-one derivatives **35** was developed by Aguilar and co-workers through the cycloisomerization of the corresponding alkynylcyclopropane carboxylic acids **34** promoted by the in situ generated cation [Au(IPr)]$^+$ (Scheme 13) [50]. The process, which requires strictly anhydrous conditions, involves the regioselective 6-*endo-dig* nucleophilic addition of the carboxylic acid unit to the activated C≡C bond. According to the authors, the 6-*endo-dig* cyclization is favored over the 5-*exo-dig* one by the simultaneous coordination of the C≡C and OMe groups to the gold atom (intermediate **C**). The subsequent cyclopropane ring-opening

in the bicycle **D** thus generated would lead to the seven-membered ring intermediate **E**, which evolves into the final oxepinone product by protodemetalation.

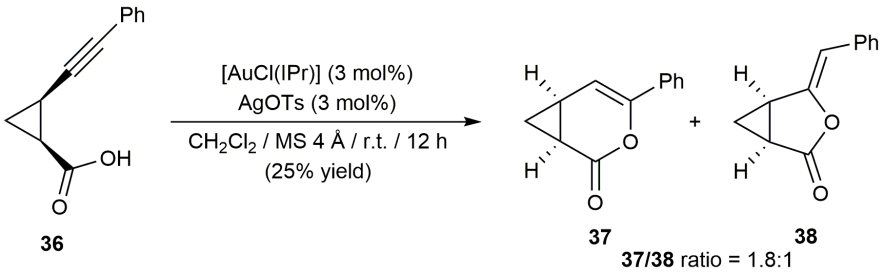


Scheme 12. Cyclization of ε-alkynoic acids catalyzed by the dinuclear complex [{Au(IPr)}$_2$(μ-OH)] [BF_4] (**33**).



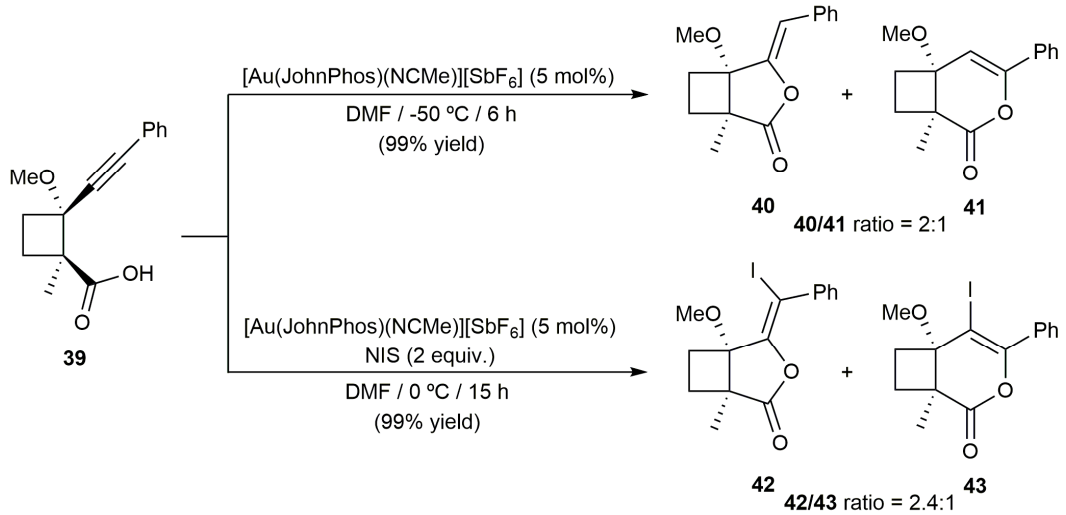
Scheme 13. Gold(I)-catalyzed synthesis of oxepinones by cycloisomerization of the alkynoic acids **34**.

It is important to note that the presence of the donor OMe substituent in the cyclopropane ring is decisive for the formation of the oxepinones to take place. Thus, when the non-substituted derivative **36** was subjected to the action of [AuCl(IPr)]/AgOTs, under identical experimental conditions, a mixture of compounds **37** and **38**, still bearing the cyclopropane ring, was formed in low yield (Scheme 14) [50].



Scheme 14. Gold-catalyzed cyclization of the alkynylcyclopropane carboxylic acid **36**.

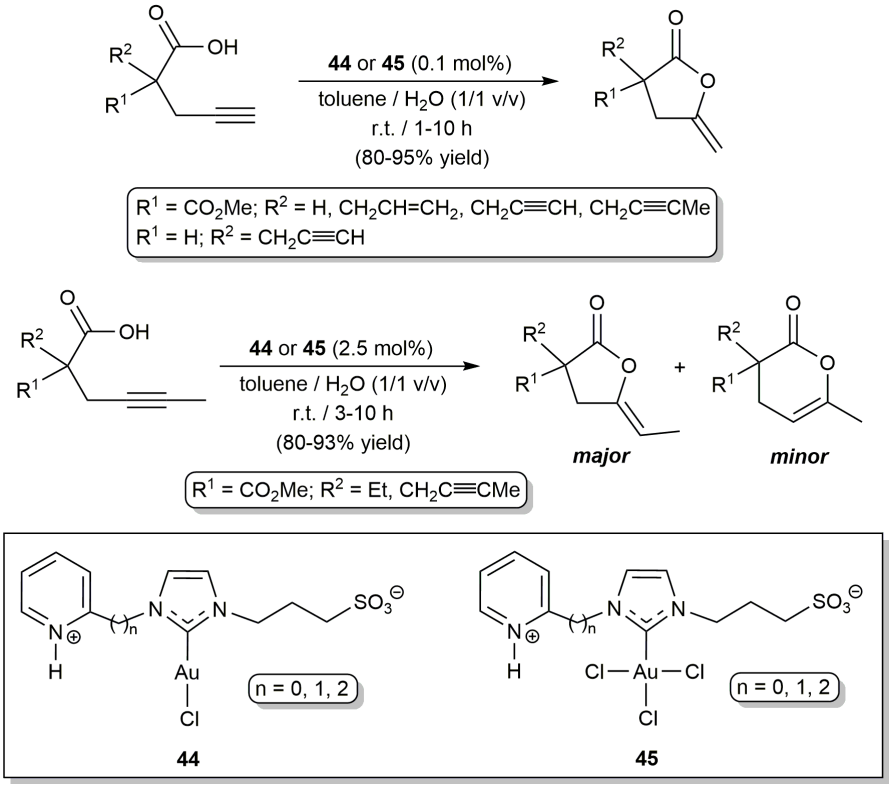
In marked contrast with the behavior of compounds **34**, the cycloisomerization of the related alkynylcyclobutane carboxylic acid **39** catalyzed in this case by the gold(I)-phosphine complex [Au(JohnPhos)(NCMe)][SbF_6] was not accompanied by the cyclobutane ring-opening, and the cyclobutane-fused heterocycles **40** and **41** were obtained in a very high combined yield (Scheme 15) [51]. Moreover, the major product **40** resulted in this case from a 5-*exo-dig* cyclization, thereby pointing out that the ring size plays an important role in the regioselectivity of the cycloisomerization reactions of this particular class of cycloalkane-based alkynoic acids. As shown in Scheme 15, when **39** was treated with the same gold catalyst in the presence of *N*-iodosuccinimide (NIS), the iodinated molecules **42** and **43** could be generated in excellent yield, with the 5-*exo-dig* cyclization product being again the major component of the mixture (an inverted regioselectivity to that observed when the iodocyclization of **39** was performed, employing directly elemental iodine [51]).



Scheme 15. Gold-catalyzed cyclization reactions of the alkynylcyclobutane carboxylic acid **39**.

The groups of Michelet, Cadierno and Conejero reported the preparation of two families of Au(I) and Au(III) complexes containing zwitterionic NHC ligands functionalized with 3-sulfonatopropyl and protonated 2-pyridyl, 2-pycolyl or 2-pyridylethyl groups, i.e., compounds **44** and **45**, capable of catalyzing the cycloisomerization of γ-alkynoic acids under biphasic toluene/water conditions [52,53]. As illustrated with the examples depicted in Scheme 16, the reactions proceeded in air at r.t. and in the absence of silver additives, with all the complexes showing comparable efficiency and selectivity. Regarding this last point, 5-membered ring enol-lactones were exclusively obtained when substrates featuring terminal C≡C bonds were employed, while mixtures of the corresponding 5 and 6-membered ring lactones were formed starting from internal alkynes (an increase in the catalyst loading from 0.1 to 2.5 mol% was also required in these cases). It is noteworthy that in no case was the competitive hydration of the alkyne units observed, even in cases of diynic substrates. Another interesting aspect of these NHC-gold complexes is that their high solubility in water enabled their recycling by simple separation of the organic phase containing the lactone products (up to ten consecutive runs; cumulative

turnover number (TON) = 400). In this regard, the recyclability of the gold(III) derivatives **45** proved to be much more effective due to their higher stability in the aqueous reaction medium (the Au(I) complexes **44** decompose into catalytically inactive Au(0) nanoparticles much faster than **45**).



Scheme 16. Cyclosiomerization of different γ-alkynoic acids in a biphasic medium catalyzed by the water-soluble NHC-gold complexes **44–45**.

Compounds **46** and **47a–f** are additional examples of recyclable NHC-Au(I) complexes able to promote the cycloisomerization of γ-alkynoic acids in aqueous environments under silver-free conditions (Figure 3). As in the examples just discussed, the silica-supported one, **46,** proved to be active at room temperature in a toluene/water biphasic mixture (up to six consecutive runs; cumulative TON = 178), showing an excellent regioselectivity towards the 5-*exo-dig* cyclization products in the case of substrates bearing a terminal C≡C bond [54]. However, similarly to the case of **44–45**, mixtures of the corresponding 5- and 6-membered ring lactones were obtained starting from internal γ-alkynoic acids.

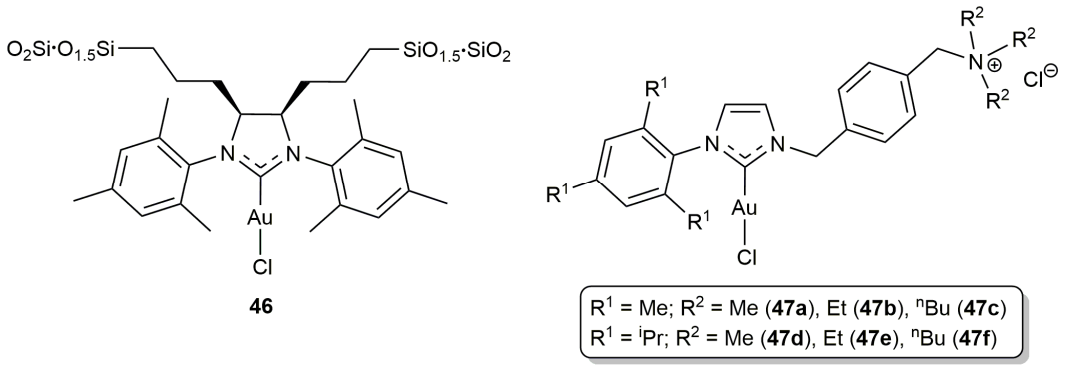
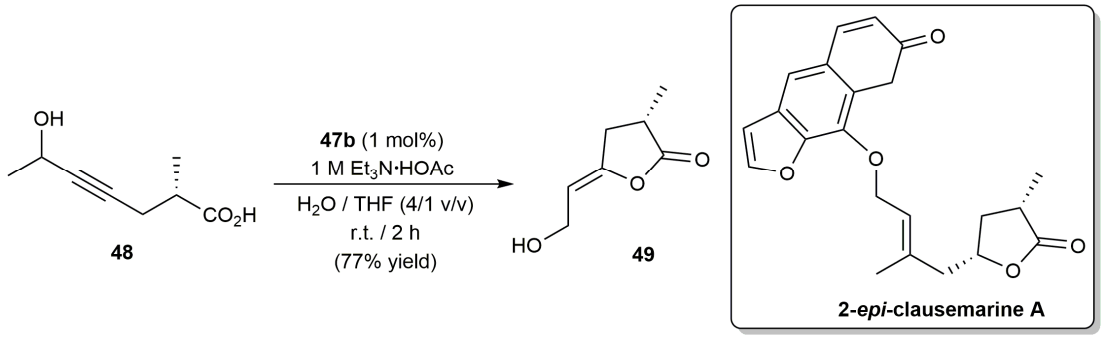


Figure 3. Structure of the NHC-gold(I) complexes **46** and **47a–f**.

Concerning the ammonium salt-tagged Au(I)-NHC complexes **47a–f**, they catalyzed efficiently the 5-*exo-dig* cyclization of different γ-alkynoic acids containing both terminal and internal alkyne units at room temperature (up to 5 consecutive runs; cumulative TON = 198) [55]. The reactions were performed employing pure water or an aqueous triethylammonium buffer solution as the solvent, with yields in general higher in the latter medium since in pure water partial decomposition of the gold complexes takes place. For some particularly hydrophobic substrates, the addition of an organic co-solvent (THF) was needed. This was the case, for example, for the chiral alkynoic acid **48**, whose cycloisomerization into the enol lactone **49** catalyzed by **47b** allowed the authors to develop a synthetic route to 2-*epi*-clausemarine A (Scheme 17), an epimer of the naturally occurring furanocoumarin clausemarine A isolated from *Clausena lansium*. The selective 5-*exo-dig* cyclization of pent-4-ynoic acid in water was additionally described by Krause and co-workers employing a series of water-soluble β-cyclodextrin-tagged NHC-gold(I) complexes [56].



Scheme 17. Au-catalyzed cycloisomerization of the chiral γ-alkynoic acid **48**.

The iminophosphorane-based gold(I)-chloride complex **50** proved to be an active and selective catalyst for the 5-*exo-dig* cyclization of γ-alkynoic acids in water (Figure 4) [57]. However, it was much more effective when using the eutectic mixture *1ChCl/2Urea* (ChCl = choline chloride) as the solvent. Thus, by employing a metal loading of 1 mol%, several 5-membered ring enol lactones could be synthesized in high yields and short times (from 15 min to 3 h) at room temperature, under aerobic conditions and in the absence of co-catalysts, starting from terminal γ-alkynoic acids. In addition, the recyclability of **50** in this alternative and biorenewable reaction medium could also be demonstrated (up to four consecutive runs; cumulative TON = 374). The cyclization of the model substrates $HC{\equiv}CCH_2CR_2CO_2H$ (R = H, Me) into the corresponding 5-membered ring lactones in aqueous solution (buffered at pH 6.0) was additionally studied by employing the phosphine-gold(I) complex [AuCl(tcep)] (tcep = tris(2-carboxyethyl)phosphine) confined in a protein nanoreactor [58]. Interestingly, some of the intermediates involved in the catalytic cycle could be detected by monitoring the changes in the ionic current flow through the protein pores when the reactions were performed under stoichiometric conditions.

Very recently, the 5-*exo-dig* cyclization of several γ-alkynoic acids containing terminal C≡C units in a biphasic water/toluene system was successfully achieved by employing water-soluble gold nanoparticles (NPs) stabilized by the PEG-tagged imidazolium salts **51** and **52** (PEG = polyethylene glycol; see Figure 4) [59]. In terms of both activity and recyclability (up to six consecutive runs; cumulative TON = 560), the PEG-tagged tris-imidazolium bromide **52** provided the best results due to the higher solubility of the Au NPs in the aqueous phase. At this point it should also be mentioned that catalytic systems consisting of Au NPs supported on zeolites [60–62], ultra-small mesoporous silica nanoparticles [63] and thiol-functionalized siliceous mesocellular foams [64] stabilized in interfacially cross-linked reverse micelles (ICRMs) [65] active in organic solvents, have also been described. Most of them showed a superior reactivity to Au_2O_3, which is the simplest gold-based heterogeneous catalyst for the 5-*exo-dig* cyclization of γ-alkynoic acids reported to date in the literature (typically operating at r.t. with a loading of 2.5 mol%) [66]. In this regard, the Au@ICRM systems (see Figure 5)

deserve to be highlighted, since they enabled a drastic reduction of the catalyst loading (up to 100 times lower) [65]. A possible explanation for this enhanced activity is that the ICRM pulls the substrate from the environment towards the catalytic metal, and once converted, the lactone product is rapidly ejected since it prefers the less polar environment rather than the charged ICRM core. An additional heterogeneous catalyst for the cyclization of γ-alkynoic acids in organic media, generated by supporting $[Au(PPh_3)][BF_4]$ on the mesoporous silica SBA-15, can also be found in the literature [67].

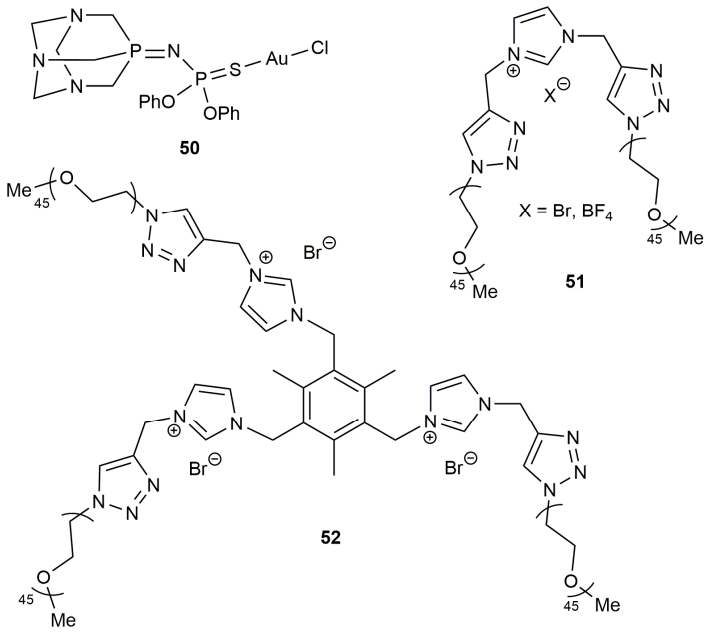


Figure 4. Structures of the gold(I) complex **50** and the PEG-tagged imidazolium salts **51–52**.

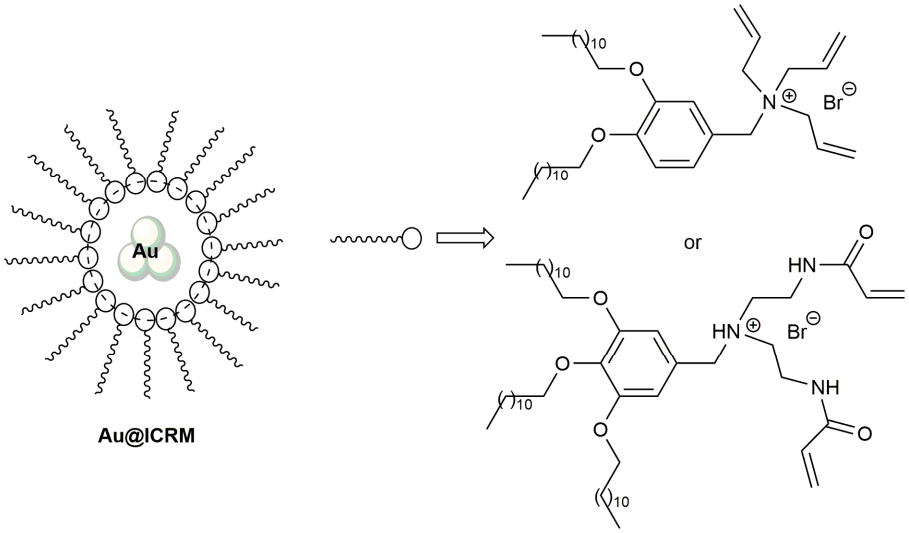
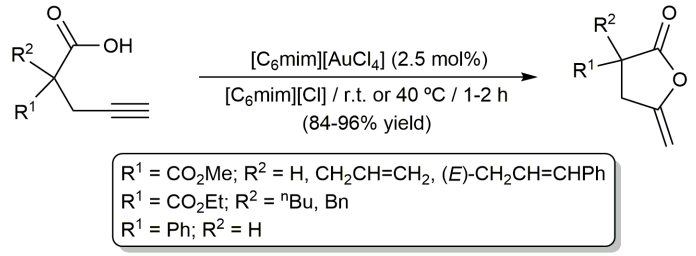


Figure 5. Schematic representation of the Au@ICMR catalysts.

Gold NPs supported on beta zeolite proved to be active in the cycloisomerization of terminal γ-alkynoic acids when employing a range of ionic liquids (ILs) as the reaction media [62]. However, in most cases, the lactone products could not be separated from the ILs at the end of the process. Only $[C_6mim][Cl]$ (C_6mim = 1-hexyl-3-methylimidazolium) was found to separate effectively from Et_2O, and the cycloisomerized products could be selectively extracted with this solvent and isolated in pure form. In the same work, the ability of gold(III) chloride-based ionic liquids of type $[C_nmim][AuCl_4]$ (n = 2, 4, 6, 18) to promote the process was also demonstrated. In particular, using 2.5 mol% of

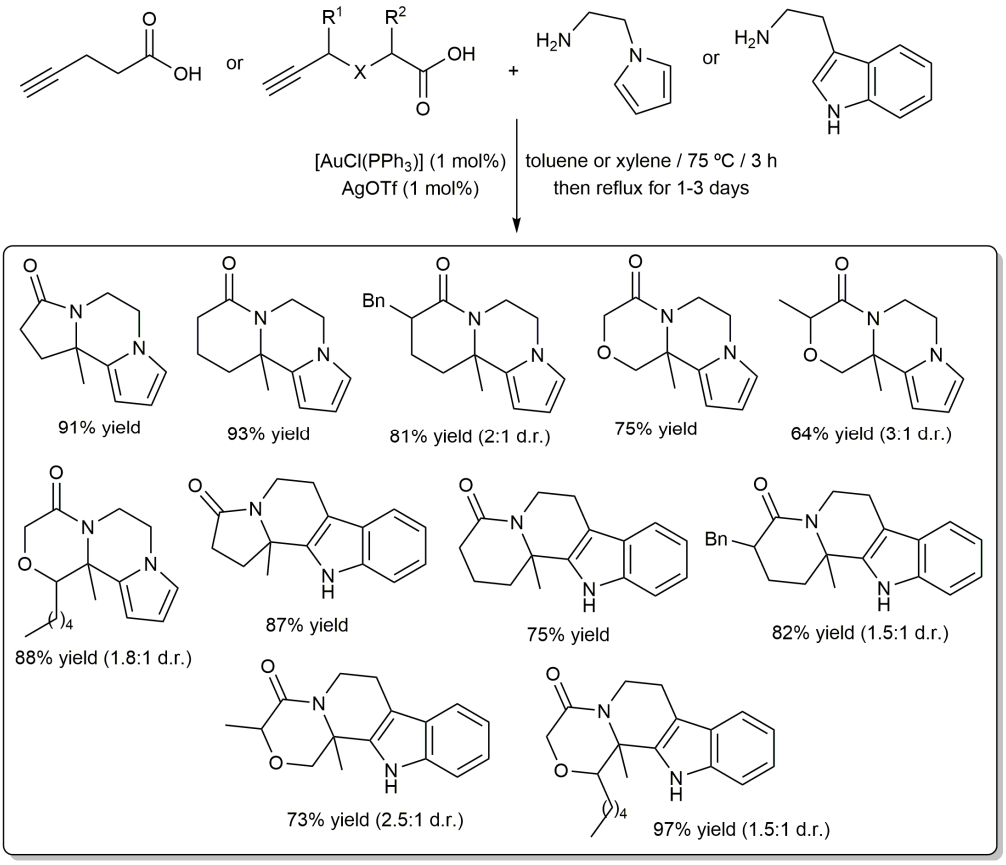
[C_6mim][$AuCl_4$] and [C_6mim][Cl] as the solvent, the selective 5-*exo-dig* cyclization of several hindered and unhindered γ-alkynoic acids was successfully achieved in the absence of base (Scheme 18). The lactone products could be isolated in high yields after extraction with Et_2O and the IL-catalyst recycled three times without loss of activity (cumulative TON = 120). Although no detailed data were provided by the authors, they indicated that [C_2mim][$AuCl_4$], [C_4mim][$AuCl_4$] and [C_{18}mim][$AuCl_4$] show reactivity and recyclability similar to that of [C_6mim][$AuCl_4$].



Scheme 18. Cycloisomerization of γ-alkynoic acids catalyzed by a gold(III) chloride-based IL.

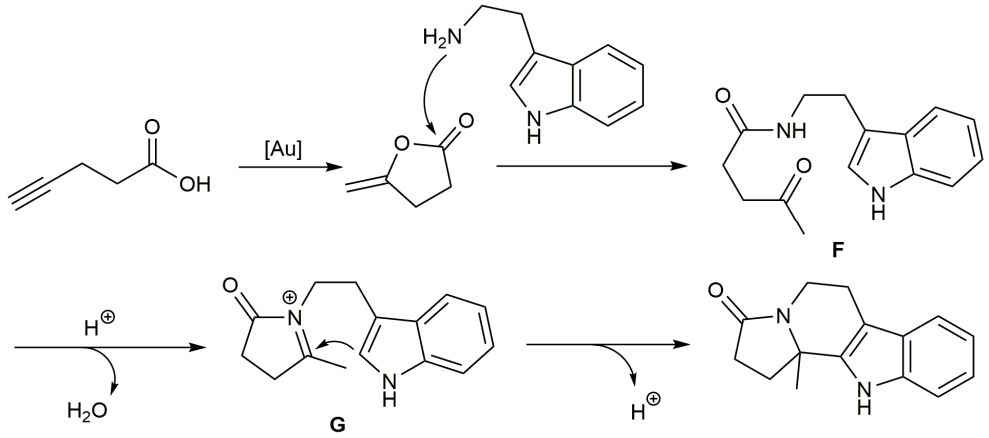
2.2. Cascade Processes Involving the Cycloisomerization of Alkynoic Acids

Taking advantage of the intrinsic reactivity of lactones, a number of cascade processes involving the initial gold-catalyzed cyclization of an alkynoic acid have been developed. The first one was described by Dixon and co-workers in 2007 with the coupling of different linear γ- and δ-alkynoic acids with 2-(2-pyrrolyl)ethylamine or tryptamine to generate fused polycyclic pyrroles and indoles (Scheme 19) [68]. The reactions were catalyzed by the in situ generated cation $[Au(PPh_3)]^+$ and required prolonged heating in toluene or xylene to obtain the products in high yields.



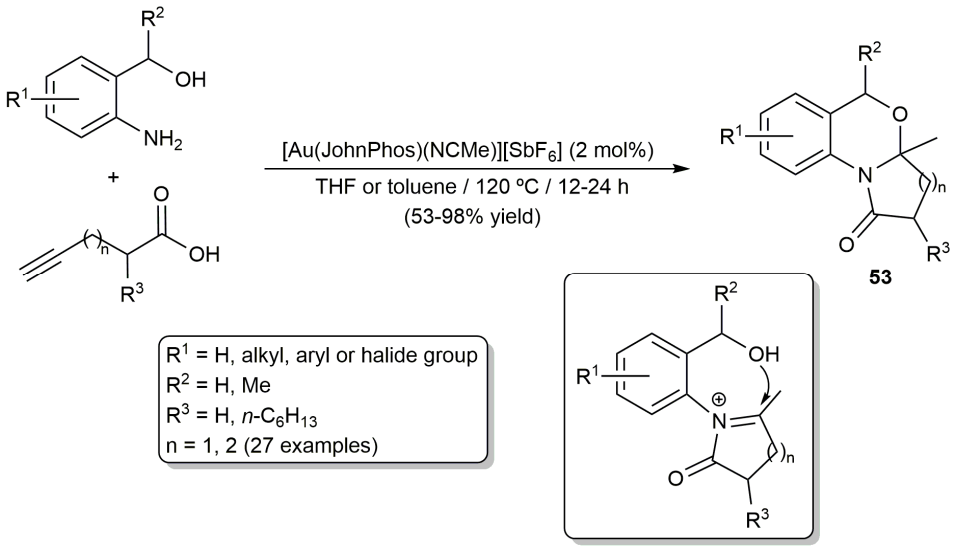
Scheme 19. Gold-catalyzed synthesis of fused polycyclic pyrroles and indoles.

As exemplified with the coupling of pent-4-ynoic acid and tryptamine, the initial step of the process is the generation of the corresponding enol-lactone, which rapidly evolves into the linear keto-amides **F** by aminolysis of the C–O bond (Scheme 20). In a subsequent step, the key one, an *N*-acyliminium ion **G** is formed through an intramolecular reaction probably facilitated by the gold catalyst. The final attack of the nucleophilic C-2 carbon of the indolic unit on the iminium carbon leads to the polycyclic product.



Scheme 20. Proposed mechanism for the gold-catalyzed coupling of pent-4-ynoic acid with tryptamine.

Following this pioneering work, related Au-catalyzed coupling reactions of alkynoic acids with indole- and pyrrole-containing amines were subsequently described in the literature, allowing the rapid construction of a wide variety of nitrogen-containing polycyclic compounds [69–72]. Moreover, the synthetic utility of these cascade processes was fully demonstrated with the use of other functionalized amines [71,72]. For example, starting from 2-aminobenzyl alcohols and different γ- and δ-alkynoic acids, an efficient and general synthesis of pyrrolo- (n = 1) and pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones (n = 2) was described by Liu and co-workers while employing [Au(JohnPhos)(NCMe)][SbF_6] as the catalyst (Scheme 21) [73]. The formation of compounds **53** involves the intramolecular nucleophilic attack of the OH group to the corresponding *N*-acyliminium ion.



Scheme 21. Au(I)-catalyzed coupling of alkynoic acids with 2-aminobenzyl alcohols.

Pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinone **54** [74], pyrrolo/pyrido[2,1-*a*]quinazolinone **55** [74], benzo[4,5]imidazo[1,2-*c*]pyrrolo/pyrido[1,2-*a*]quinazolinone **56** [75], benzo[*e*]indolo[1,2-*a*]

pyrrolo/pyrido[2,1-*c*][1,4]-diazepine-3,9-dione **57** [76] and pyrrolo[1,2-*a*:2´,1´-*c*]-/pyrido[2,1-*c*] pyrrolo[1,2-*a*]quinoxalinone **58** [77] derivatives were also accessed by the same group by employing 2-aminobenzoic acids, 2-aminobenzamides, 2-(1*H*-benzo[*d*]imidazol-2-yl)anilines, (2-aminophenyl)(1*H*-indol-1-yl)methanones and 2-(1*H*-pyrrol-1-yl)anilines, respectively, as the coupling partners (Figure 6). Complex [Au(JohnPhos) (NCMe)][SbF_6] (2–10 mol%) was in all cases used to promote the reactions, which required temperatures in the range 80–120 °C. However, it should be mentioned at this point that, to obtain compounds **56–58** in high yields, the addition of a Brønsted or Lewis acid co-catalyst was needed to facilitate the intramolecular attack of the corresponding nucleophile to the *N*-acyliminium intermediate. On the other hand, it is also worth noting that, in the case of the pyrrolo[1,2-*a*:2´,1´-*c*]-/pyrido[2,1-*c*]pyrrolo[1,2-*a*]quinoxalinones **58**, the reactions could be conveniently carried out in water.

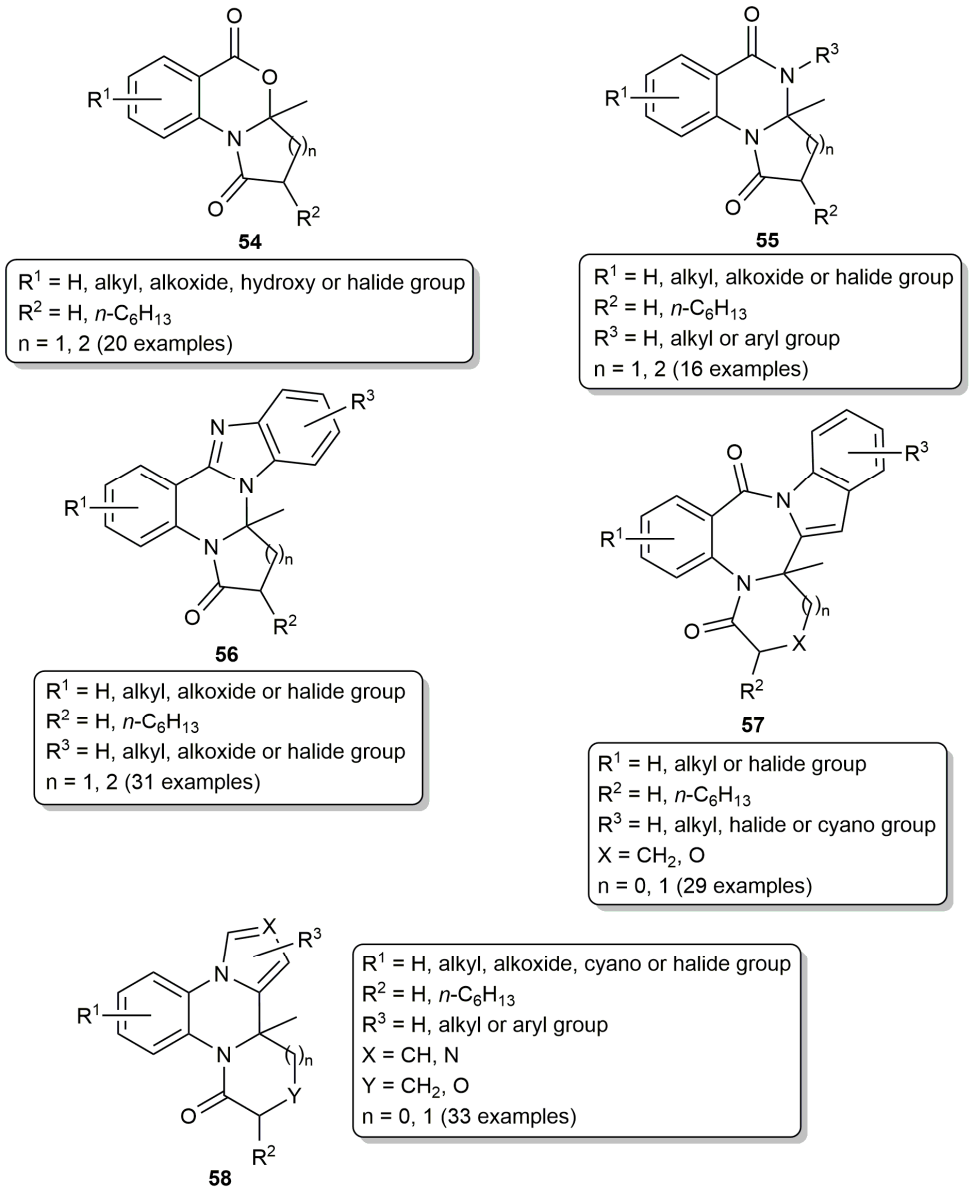
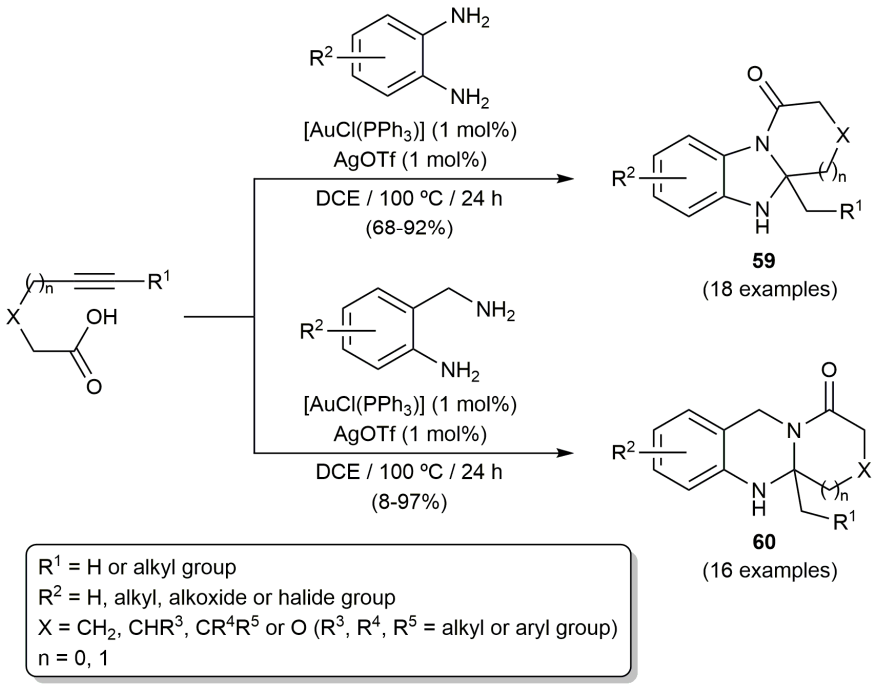


Figure 6. Structures of the fused polycyclic compounds **54–58**.

Related coupling processes employing benzene-1,2-diamines and 2-(aminomethyl)benzenamines as the nucleophiles were reported by Patil and co-workers using the [$AuCl(PPh_3)$]/AgOTf combination as the catalyst [78]. The reactions allowed the regioselective preparation of broad series of fused

dihydrobenzimidazoles **59** and tetrahydroquinazolines **60** starting from both terminal and internal γ- and δ-alkynoic acids (Scheme 22). Interestingly, in the case of α-substituted γ-alkynoic acids (i.e., n = 0 and X = CHR^3 or CR^4R^5), the corresponding products were obtained in high diastereoselectivities as a consequence of the steric interaction between the substituents in this position with the CH_2R^1 unit. By applying the same reaction conditions, the efficient access to different pyrrolo- and indolo-fused quinazolinones, some of them featuring anticancer activities, was possible by reacting γ- and δ-alkynoic acids with 2-aminobenzohydrazides [79]. In addition, Patil´s group also demonstrated the utility of these Au-catalyzed coupling processes for the preparation of a huge variety of multifunctional polyheterocyclic scaffolds, starting from selected alkynoic acids and functionalized amines through the so-called "relay catalytic branching cascade" (RCBC) technique [80]. Cascade reactions involving the cycloaromatization of 2,4-dien-6-yne carboxylic acids [81] and the assembly of fused indeno-pyranones from enediynic carboxylic acids [82] have also been described.

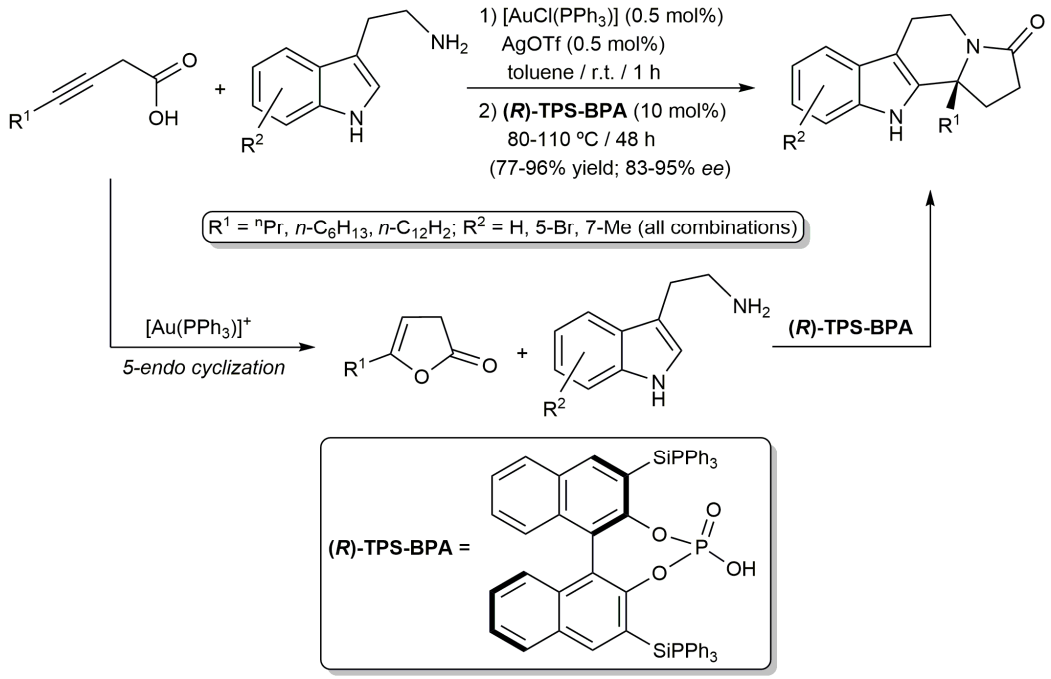


Scheme 22. Gold(I)-catalyzed synthesis of fused dihydrobenzimidazoles and tetrahydroquinazolines.

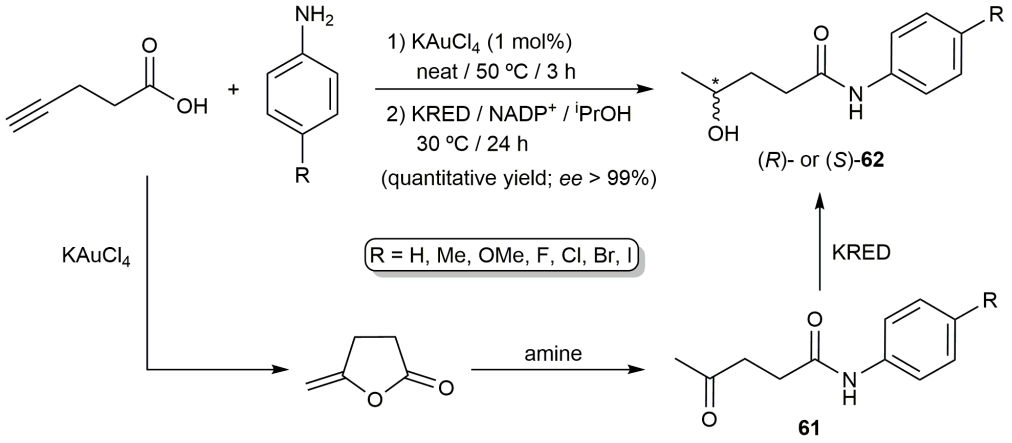
Additional studies by Dixon and co-workers in the field revealed that the coupling of enol-lactones with tryptamine derivatives, via the *N*-acyliminium cyclization cascades just mentioned, can be promoted in an enantioselective manner by chiral Brønsted acids, processes that are compatible with the in situ generation of the enol-lactone through a gold-catalyzed cycloisomerization reaction, as illustrated in Scheme 23 [83].

Within the field of asymmetric synthesis, the work described by García-Álvarez, González-Sabín and co-workers is also noteworthy; they developed a highly enantioselective synthesis of the chiral γ-hydroxy amides **62** starting from pent-4-ynoic acid and secondary aromatic amines through the sequential action of $KAuCl_4$ and a ketoreductase (KRED) enzyme (Scheme 24) [84]. Thus, the initial gold-catalyzed cyclization of the alkynoic acid leads to the corresponding enol-lactone which immediately undergoes aminolysis to generate the linear γ-keto amides **61**. The subsequent addition of the KRED, along with the cofactor $NADP^+$ (nicotinamide adenine dinucleotide phosphate) and the hydrogen source ^{i}PrOH, to the medium, enables the bioreduction of the keto group of **61**. The chiral γ-hydroxy amides **62** were obtained in all cases in almost quantitative yields, and by selecting the appropriate KRED, both enantiomers were accessible with *ee* values ≥ 99%. Similarly, the synthesis of enantiopure (*R*)- and (*S*)-γ-hydroxyvaleric acid could also be achieved in a quantitative manner by

replacing the amine with water, since, at 50 °C, the initially formed enol-lactone is transformed into levulinic acid by hydrolysis.



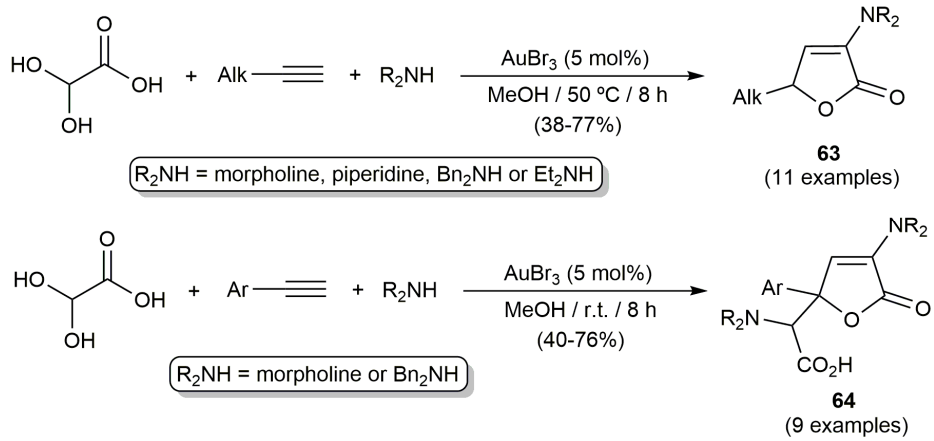
Scheme 23. Enantioselective cyclization cascade of alkynoic acids and trytamine derivatives.



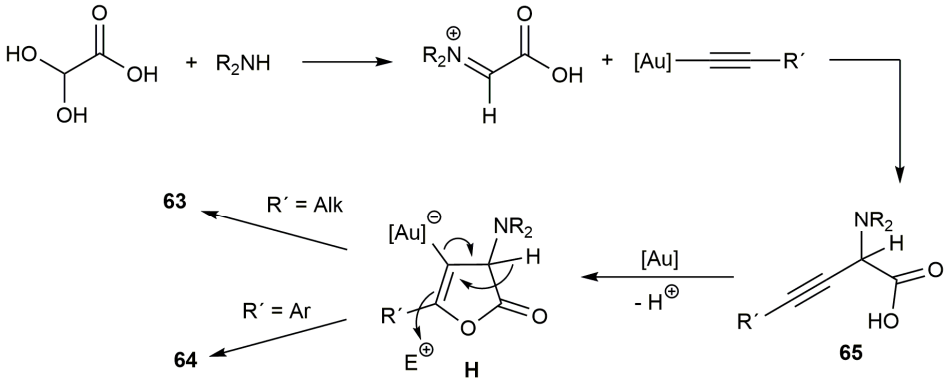
Scheme 24. Synthesis of enantiopure γ-hydroxy amides from pent-4-ynoic acid and anilines.

On the other hand, a synthetically useful approach to butenolide derivatives **63** and **64** was developed by Ji and co-workers through a three-component coupling of terminal alkynes, secondary amines and glyoxylic acid (Scheme 25) [85].

The process, which proceeds under mild conditions in the presence of catalytic amounts of $AuBr_3$, involves the selective 5-*endo-dig* cyclization of the in situ formed α-*N*-substituted β-alkynoic acids **65** (see Scheme 26). These intermediate species are generated through the initial condensation between the amines and glyoxylic acid, and subsequent addition of alkyne to the resulting iminium cation via the corresponding gold-acetylide. Depending on the nature of the alkyne, compounds **63** and **64** were selectively obtained by electrophilic trapping of the metallated intermediate **H** with a proton (aliphatic alkynes) or the iminium cation (aromatic alkynes) along with a 1,2-hydride shift.



Scheme 25. Access to butenolide derivatives though a three-component tandem process.



Scheme 26. Proposed mechanism for the formation of butenolides **63** and **64**.

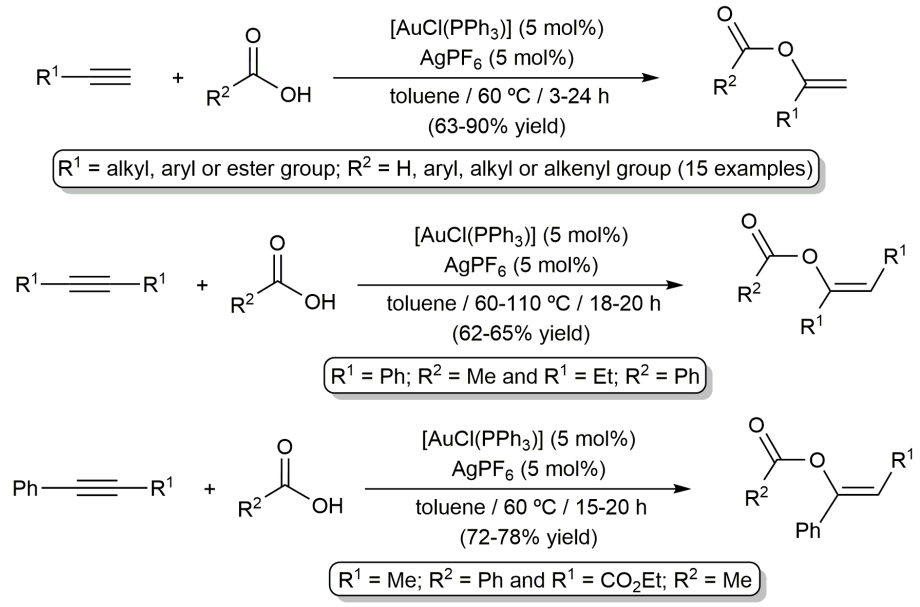
2.3. Intermolecular Addition of Carboxylic Acids to Alkynes

Compared to the cycloisomerization reactions of alkynoic acids, intermolecular additions of carboxylic acids to alkynes have been much less studied with gold-based catalysts. In this context, the first example, reported by Schmidbaur and co-workers in 2004, involved the addition of glacial acetic acid to hex-3-yne catalyzed by the carboxylate-gold(I) complex [Au{OC(O)C_2F_5}(PPh_3)] (0.134 mol%) in the presence of BF_3·Et_2O as a co-catalyst (5.25 mol%) [86]. However, after heating the mixture in THF at 60 °C for 1 h, the desired enol ester hex-3-en-3-yl acetate was generated in only 6% yield together with hexan-3-one (12% yield), resulting from the hydration of the alkyne. A few years later, Chary and Kim reported an efficient and general protocol employing the gold(I) cation $[Au(PPh_3)]^+$ (generated in situ from [AuCl(PPh_3)] and $AgPF_6$) as a catalyst (Scheme 27) [87].

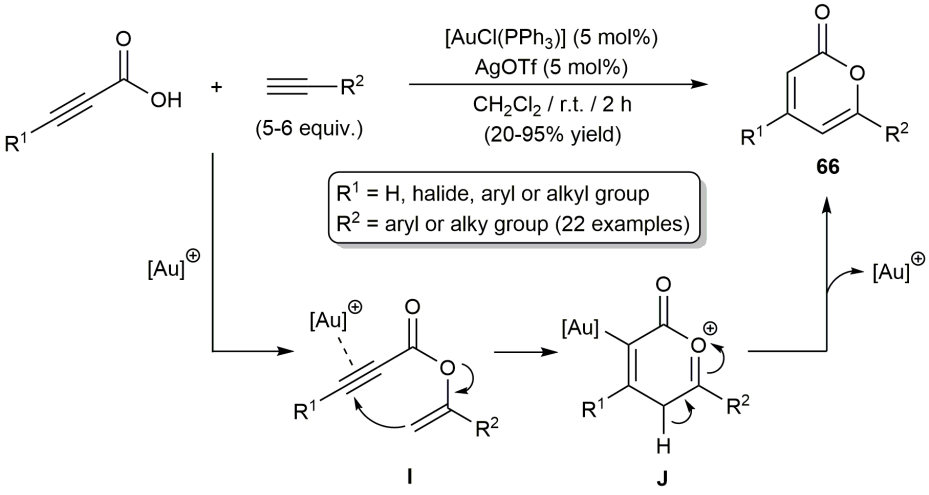
The addition process was operative for both terminal and internal alkynes working in toluene at 60–110 °C with metal loadings of 5 mol%. Starting from terminal alkynes, the corresponding Markovnikov addition products were selectively obtained, and in the case of the internal ones the reactions proceeded with a complete (*Z*) stereoselectivity (*anti*-addition). Moreover, an exquisite regioselectivity was observed when the non-symmetrically substituted internal alkynes 1-propynylbenzene and ethyl 3-phenylpropiolate were employed as substrates. In the same study, Chary and Kim found that enol esters of type $RCH_2C(O_2CR')=CH_2$ easily isomerize into the thermodynamically more stable species $RCH=C(O_2CR')CH_3$, compounds that can be directly accessed by performing the corresponding $[Au(PPh_3)]^+$-catalyzed addition reactions using AgOTf instead of $AgPF_6$.

Complex [AuCl(PPh_3)], in combination with AgOTf, was subsequently employed by Schreiber and co-workers for the preparation of several substituted α-pyrone derivatives by coupling propiolic acids with terminal alkynes (Scheme 28) [88]. The process involves the initial formation of vinyl

propiolate intermediates **I**, resulting from the Au(I)-catalyzed Markovnikov addition of the propiolic acids to the terminal alkynes, which readily evolve into the cyclic oxocarbenium species **J** through a 6-*endo* cyclization (also promoted by the $[Au(PPh_3)]^+$ cation). The α-pyrone products **66** are finally generated from **J** through a deprotonation/protodemetalation sequence.

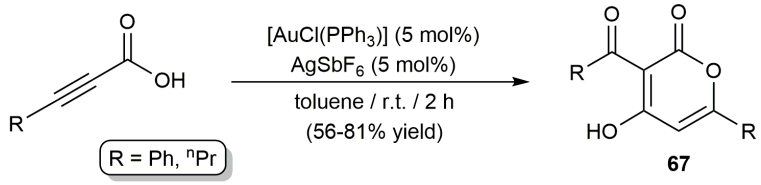


Scheme 27. Intermolecular addition of carboxylic acids to alkynes catalyzed by $[Au(PPh_3)]^+$.



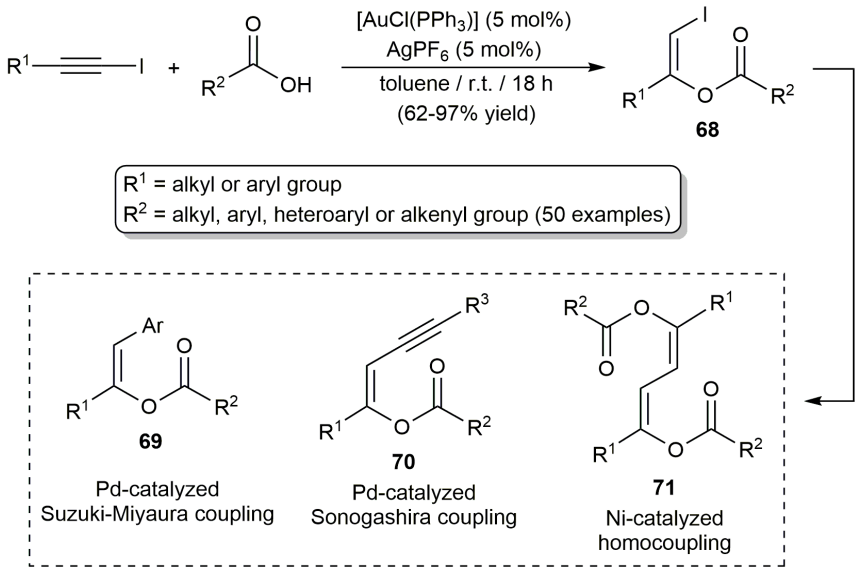
Scheme 28. Au(I)-catalyzed synthesis of α-pyrones from propiolic acids and terminal alkynes.

As shown in Scheme 29 with a couple of representative examples, when the propiolic acids were subjected to the action of $[Au(PPh_3)]^+$ in the absence of the terminal alkyne partner, they dimerized into the 4-hydroxy α-pyrones **67** [88]. The formation of **67** involves the intermolecular addition of the CO_2H unit of one of the propiolic acid molecules to the C≡C bond of the second one and the generation of the corresponding oxocarbenium intermediate, which then evolves into the final products by acyl group migration.



Scheme 29. Au(I)-catalyzed dimerization of propiolic acids into 4-hydroxy α-pyrones.

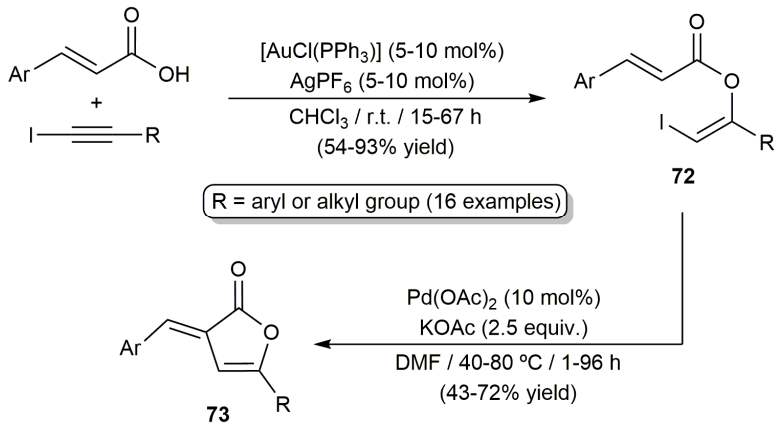
Employing the catalytic [AuCl(PPh$_3$)]/AgPF$_6$ system, a general procedure for the preparation of (*Z*)-β-iodoenol esters **68** by the addition of carboxylic acids to iodoalkynes was developed by Cadierno and co-workers (Scheme 30) [89,90]. The reactions proceeded with high yields, under mild conditions (toluene/r.t.), and in a complete regio- and stereoselective manner (selective *anti*-addition of the carboxylate group to the more electrophilic C-2 carbon of the π-activated iodoalkyne). In addition, the process featured a wide scope and tolerated the presence of different functional groups in both the alkyne and acid partners. It should also be remarked at this point that the (*Z*)-β-iodoenol esters **68** are very useful compounds from a synthetic point of view, as they can participate in Pd-catalyzed Suzuki–Miyaura [89,91] and Sonogashira [90] cross-couplings, and in Ni-catalyzed homocoupling processes [92,93], thereby allowing access to a wide range of stereochemically defined β-aryl-vinyl esters **69**, enynyl esters **70** and buta-1,3-diene-1,4-diyl diesters **71**, respectively.



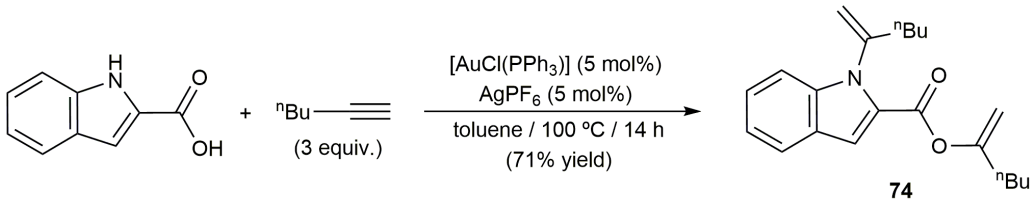
Scheme 30. Au(I)-catalyzed synthesis of (*Z*)-β-iodoenol esters and their derived C–C coupling products.

Based on the [AuCl(PPh$_3$)]/AgPF$_6$-catalyzed addition of β-aryl acrylic acids to iodoalkynes, a synthetic route to (*E*)-3-(arylidene)-5-substituted-2(3*H*)-furanones **73** was subsequently reported by subjecting the resulting (*Z*)-β-iodoenol esters **72** to a palladium-catalyzed Mizoroki–Heck reaction (Scheme 31) [94]. Although the process was routinely performed in two separate steps, the authors demonstrated with a couple of examples the possibility of carrying out both transformations in a one-pot manner, i.e., without the need to isolate the intermediate species **72**, just by replacing the solvent and adding the palladium catalyst and the KOAc base after the initial Au-catalyzed reaction.

Very recently, the catalytic addition of indole-2-carboxylic acid to hex-1-yne was explored with different ruthenium and gold catalysts [95]. As shown in Scheme 32, by employing catalytic amounts of [AuCl(PPh$_3$)]/AgPF$_6$ in toluene at 100 °C, the reaction led to the enol ester **74**, which resulted from the addition of both the acid and NH groups of the indole derivative to hex-1-yne molecules. In the case of ruthenium, the expected monoaddition product of the acid to the alkyne was preferentially formed.



Scheme 31. Synthesis of 2(3*H*)-furanones from iodoalkynes and *β*-aryl acrylic acids.



Scheme 32. Au(I)-catalyzed double addition of indole-2-carboxylic acid to 1-hexyne.

On the other hand, it is also noteworthy that complex [AuCl(PPh$_3$)], associated now with AgOAc, was successfully employed to promote the intermolecular addition of carboxylic acids to non-activated internal alkynes in water, allowing the synthesis of a wide variety of trisubstituted enol esters (37 examples) in moderate to high yields and with complete (*Z*) stereoselectivity (*anti*-addition) [96]. The lower reactivity of the alkyl- and aryl-substituted alkynes employed in this study in comparison to that of the terminal or iodo-substituted ones required the reactions to be carried out in this case at 60 °C instead of room temperature. Related addition reactions in water were more recently described by employing as catalysts the gold(I) chloride complexes **75**, containing hydrophilic ferrocenylphosphino sulfonate ligands (see Figure 7), which allowed the authors to reduce the metal loadings from 5 to 2 mol% [97]. As observed with [AuCl(PPh$_3$)], mixtures of regioisomers were in most cases obtained when non-symmetrically substituted alkynes were used as substrates.

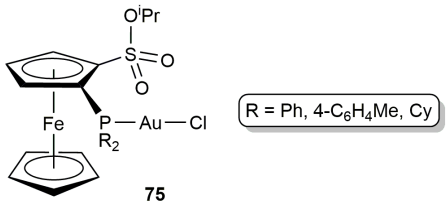
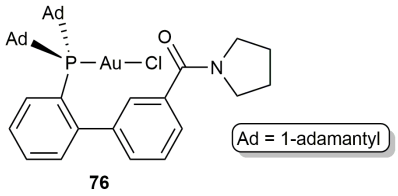


Figure 7. Structure of the water-soluble gold(I) complexes **75**.

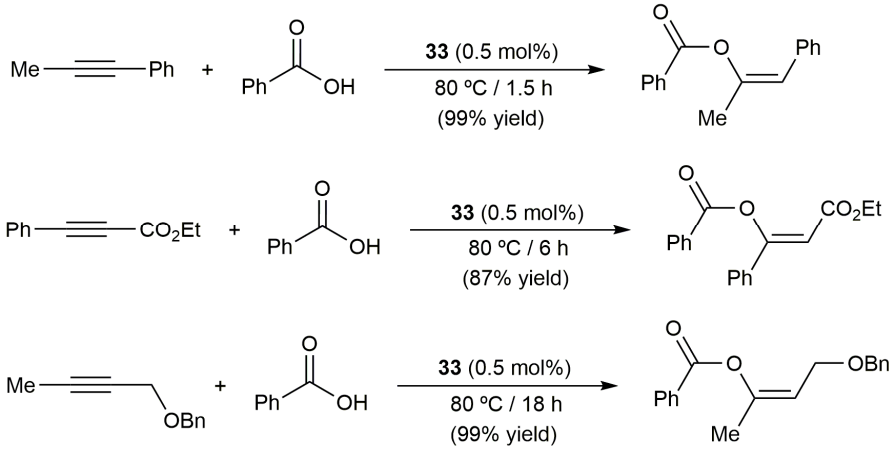
Additional examples of gold-based catalysts able to promote the intermolecular addition of carboxylic acids to alkynes are the dinuclear hydroxo-brigded NHC complex [{Au(IPr)}$_2$(μ-OH)][BF$_4$] (**33** in Scheme 12) [98] and the mononuclear derivative **76** containing an amide-functionalized biphenylphosphine ligand (see Figure 8) [99]. Thus, **33** proved to be highly efficient in the hydrocarboxylation of internal alkynes under solvent-free and silver-free conditions, leading to the enol-ester products in high yields and with complete (*Z*) stereoselectivity by performing the reactions at 80 °C with a catalyst loading of 0.5 mol%. In addition, very good regioselectivity was observed with non-symmetrically substituted alkynes (three representative examples are shown in Scheme 33). Concerning the mononuclear complex **76**, it was employed to promote, in combination

with $AgNTf_2$, the addition of a broad range of aromatic and aliphatic carboxylic acids to both terminal and internal alkynes. Excellent results in terms of activity were achieved while working at 80 °C in fluorobenzene, conditions that allowed them to generate the corresponding *anti*-addition products in excellent yields with remarkably low metal loadings (in the range of 25-150 ppm in most of the cases). The outstanding effectiveness of this catalyst, with which TON values of up to 34,400 were reached, was reasoned in terms of the cooperative effect exerted by the basic amide group present in the ligand. This group would interact with the carboxylic acid, enhancing in this way its nucleophilicity.



76

Figure 8. Structure of the gold(I)-biphenylphosphine complex **76**.

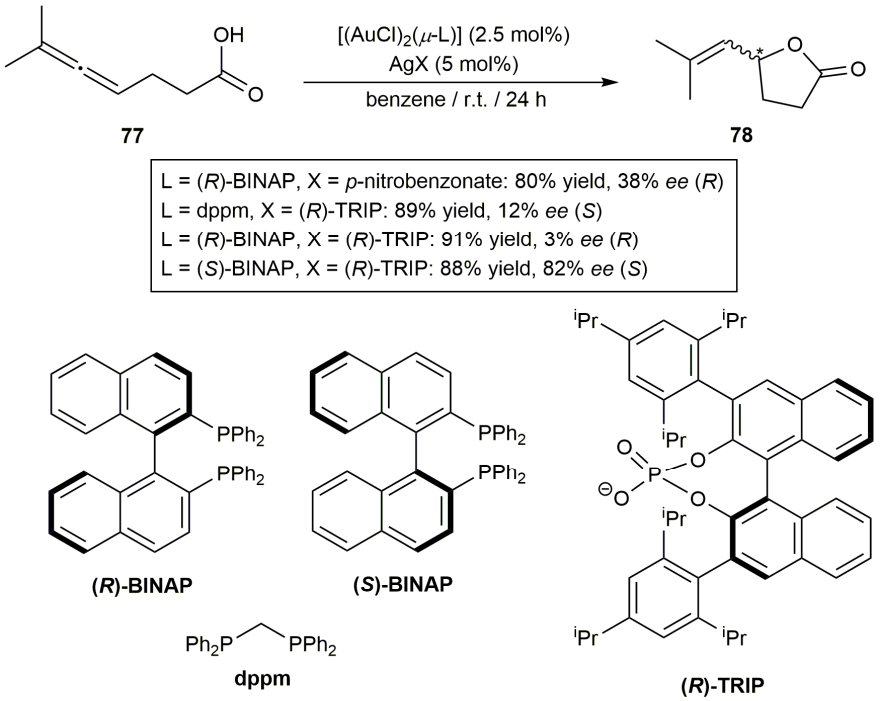


Scheme 33. Regio- and stereoselective addition of benzoic acid to non-symmetrically substituted internal alkynes catalyzed by the dinuclear complex $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ (**33**).

3. Addition of Carboxylic Acids to Allenes

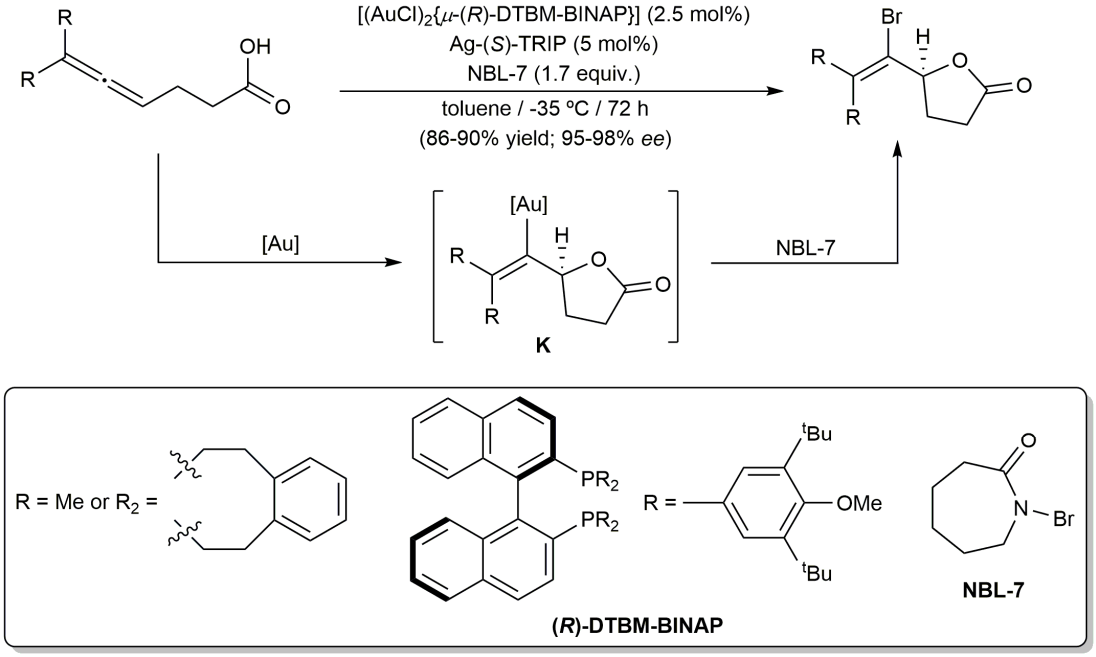
3.1. Cycloisomerization of Allenoic Acids

The first example of this type of cyclization processes catalyzed by gold was described by Toste and co-workers in 2007 [100]. As shown in Scheme 34, they studied the enantioselective cycloisomerization of the trisubstituted γ-allenoic acid **77** with dinuclear Au(I) complexes of general composition $[(AuCl)_2(\mu\text{-L})]$, containing optically pure (*R*)/(*S*)-BINAP or bis(diphenylphosphino)methane (dppm) as bridging L ligands, in combination with a silver(I) salt featuring an achiral or an optically active counteranion (*p*-nitribenzoate or the binaphthol-based phosphate (*R*)-TRIP, respectively). In all cases, the regioselective formation of the five-membered ring lactone **78** was observed, with yields in the range 80–91% after 24 h of stirring in benzene at room temperature. Concerning the enantioselectivity of the process, a maximum enantiomeric excess of 82% was reached when the (*S*)-BINAP diphosphine and the chiral counteranion (*R*)-TRIP made part of the catalytic system.



Scheme 34. Gold-catalyzed enantioselective cyclization of the γ-allenoic acid **77**.

The same group also successfully accomplished the enantioselective bromocyclization of **77** and one of its congeners, through the use of a related dinuclar Au(I) complex associated with Ag-(*S*)-TRIP and a *N*-bromolactam, the latter acting as an electrophilic bromine source able to promote the halodeauration of the corresponding vinylgold intermediate **K** (see Scheme 35) [101].



Scheme 35. Gold-catalyzed enantioselective bromoyclization of γ-allenoic acids.

The high yield synthesis of lactone **78** in racemic form by cyclization of **77** was later reported by Hashmi and co-workers, who employed the achiral mono- and dinuclear gold(I)-phosphine complexes **79–81** depicted in Figure 9 [102,103]. All of them were able to promote the process at room temperature

in C_6D_6 with metal loadings of 0.05–0.5 mol% in the case of **79–80** and 2.5 mol% in the case of **81**, the latter requiring the presence of a silver(I) salt as co-catalyst [103].

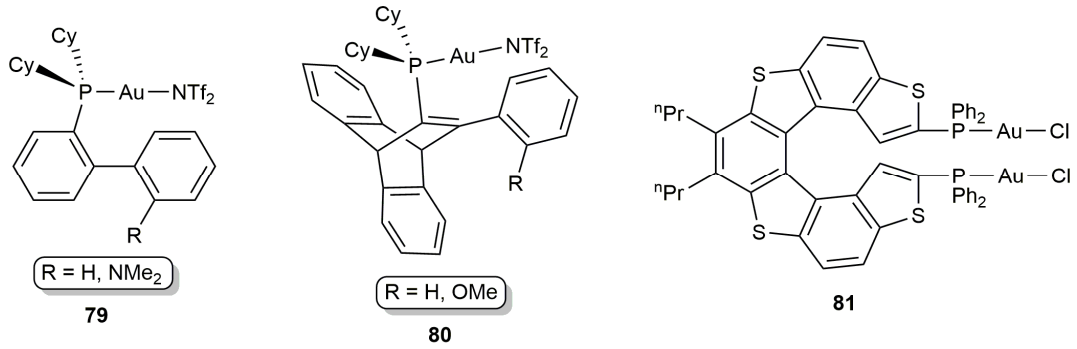
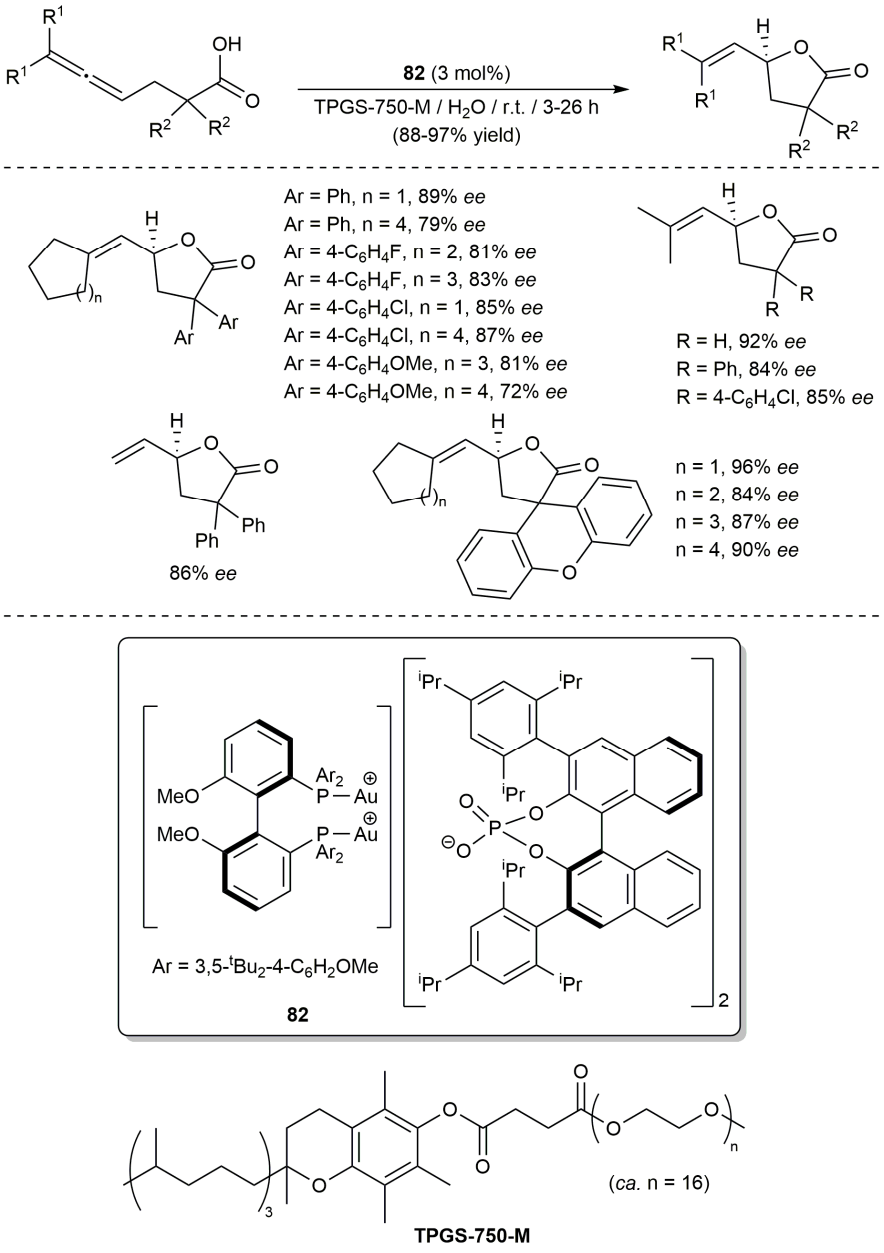


Figure 9. Structure of the gold(I)-phosphine complexes **79–81**.

The group of Lipshutz described the asymmetric cycloisomerization of different γ-allenoic acids in an aqueous micellar medium while employing the ionic dinuclear Au(I) complex **82**, containing (*R*)-MeO-BIPHEP as bridging ligand and the (*R*)-TRIP counteranion, and the surfactant TPGS-750-M (Scheme 36) [104]. The reactions gave high yields under mild conditions (r.t.), leading to the vinyl-lactones with good to excellent *ee*´s (72-96%). The recyclability of the aqueous solution containing **82** was possible after extraction of the lactone products with an ether/hexane mixture—the yields and *ee*´s remained constant throughout six successive reactions. It should be mentioned at this point that Toste and co-workers also developed a recyclable catalytic system for the enantioselective conversion of γ- and δ-allenoic acids into chiral 5- and 6-membered ring vinyl-lactones (*ee*´s in the 81–93% range) by supporting the dinuclear gold(I) complex $[Au_2(\mu\text{-L})][BF_4]_2$ (L = (*R*)-(+)-2,2′-bis[di(3,5-xylyl)phosphino]-6,6′-dimethoxy-1,1′-biphenyl) on the mesoporous silica SBA-15 [67]. In this case, the heterogeneous catalyst was easily recovered from the solution by centrifugation and could be reused for 11 consecutive cycles with no decrease in the activity and enantioselectivity (cumulative TON = 507). In addition, for all the substrates studied, the enantioselectivity reached with the supported catalyst was superior to that obtained with complex $[Au_2(\mu\text{-L})][BF_4]_2$ under homogeneous conditions. The same authors also explored the catalytic behavior of silica-supported Au NPs coated with chiral NHC ligands in the lactonization of two model γ-allenoic acids [105]. Although good results in terms of activity and recyclability (up to five consecutive runs; cumulative TON = 227) were obtained, the enantiomeric excesses did not exceed 16%.

In a subsequent study, Lipshutz and co-workers reported the racemic version of the cyclization reactions depicted in Scheme 36; they employed ppm levels of [AuCl(HandaPhos)]/$AgSbF_6$ (1000 and 2000 ppm, respectively) in an aqueous micellar medium generated with the surfactant Nok (see Figure 10) [106].

On the other hand, Ohfume and co-workers studied the cycloisomerization of different β-allenoic acids containing a silyl group attached to the allenic terminus—for example, the chiral allenylglycine derivatives **83**, employing different Pd, Pt, Hg, Ag and Au-based catalysts. Among them, best results were obtained with the cationic oxo-bridged trinuclear gold(I) complex $[\{(Ph_3P)Au\}_3(\mu\text{-O})][BF_4]$, which allowed the regioselective access to the corresponding 2-amino-4-silylmethylene-substituted γ-butyrolactones **84** resulting from the addition of the carboxylate to the central *sp*-carbon of the allene (Scheme 37) [107]. Regarding the stereoselectivity of the process, it was found to be strongly dependent on the substitution pattern at the C-2 position of the substrates. Thus, while in the case of R = H the product was obtained in an almost diastereomerically pure manner, those substrates featuring a quaternary carbon center (R = Me, Bn) led to the respective γ-butyrolactones **84** as mixtures of diastereoisomers.



Scheme 36. Gold(I)-catalyzed enantioselective lactonization of γ-allenoic acids in aqueous micellar medium.

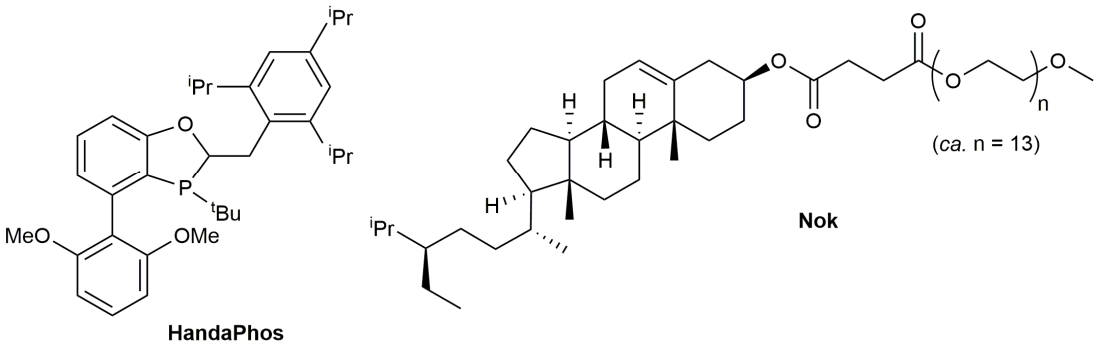
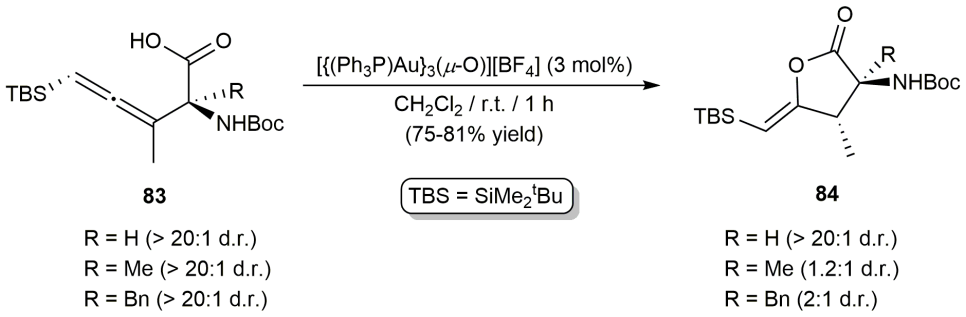
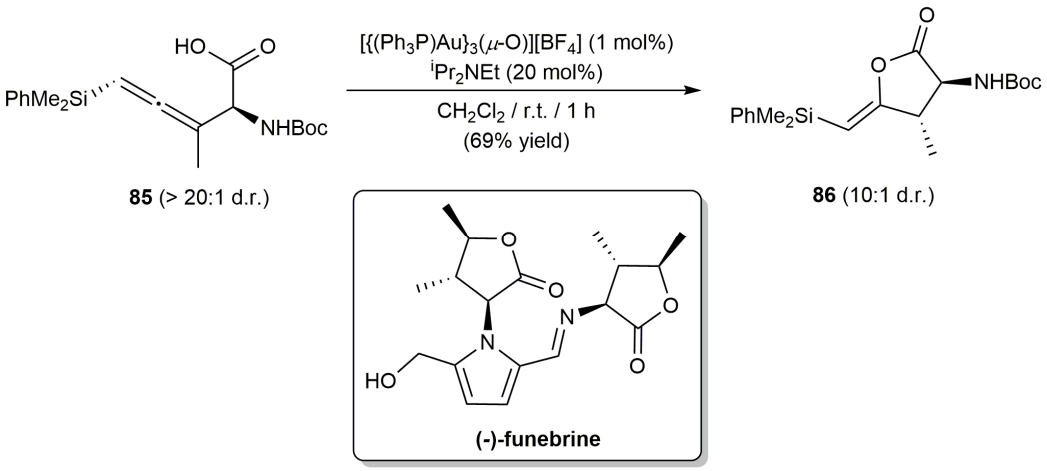


Figure 10. Structures of the phosphine ligand HandaPhos and the surfactant Nok.



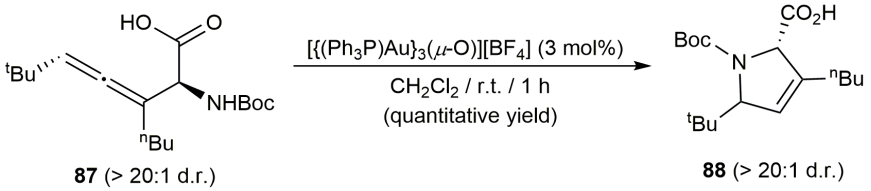
Scheme 37. Au(I)-catalyzed cycloisomerization of the silyl-substituted allenoic acids **83**.

Taking advantage of this initial work, the total synthesis of the natural product (-)-funebrine, in which the two γ-butyrolactone units of the molecule were generated by cycloisomerization of the related allenylsilane **85** into **86**, could be developed (Scheme 38) [108]. Although the use of the dimethylphenylsilyl group instead of the *tert*-butyldimethylsilyl (TBS) one reduced the diasteroselectivity of the cyclization process (diastereomeric ratio d.r. = 10:1 vs. > 20:1), said group was chosen by the authors, since its subsequent removal proceeds under milder conditions, thereby avoiding epimerization at the C-3 carbon. Of note is the fact that, by adding 20 mol% of $^{i}Pr_2NEt$ to the reaction medium, the catalyst loading could be reduced from 3 to 1 mol%.



Scheme 38. γ-Butyrolactonization of the allenylsilane **85** employed in the total synthesis of (-)-funebrine.

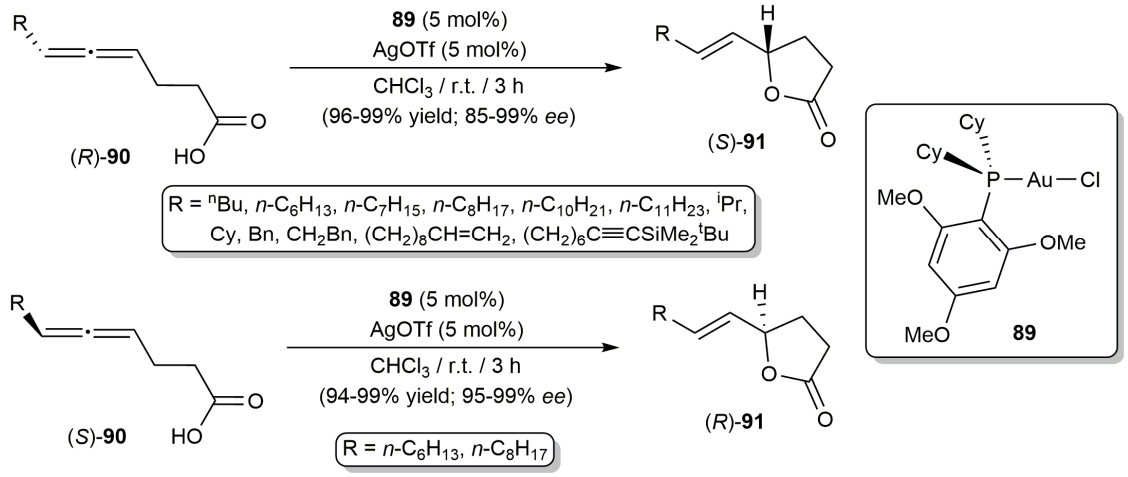
It is also worth noting that the regioselectivity of the cyclization reactions to provide γ-butyrolactones collected in Schemes 37 and 38 seems to be governed by the presence of the silyl group. In fact, when it was replaced by a ^{t}Bu one, such as in compound **87**, hydroamination at the terminal carbon of the allenic unit preferentially occurred to give the pyrrolidine **88** (Scheme 39) [107].



Scheme 39. Cyclization of the allenoic acid **87** catalyzed by [{(Ph$_3$P)Au}$_3$(μ-O)][BF$_4$].

After screening of different gold(I) complexes with phosphine and NHC type ligands, Ma and co-workers identified [AuCl(LB-Phos)] (**89**) as a suitable catalyst for the highly regio- and stereoselective cyclization of optically pure 1,3-disubstituted γ-allenoic acids **90** (Scheme 40) [109]. Thus, using this

complex in combination with AgOTf, the access to a broad range of chiral γ-vinylic γ-butyrolactones **91** could be achieved with an excellent axial-to-central chirality transfer (*ee*´s in the range 85–99%).



Scheme 40. Gold-catalyzed stereoselective cycloisomerization of allenoic acids **90**.

Moreover, they developed a Pd/C-based C–O bond cleavage-free procedure for the hydrogenation of lactones **91**, through which some biologically active molecules of natural origin such as (*R*)/(*S*)-4-tetradecalactone, (*R*)-γ-palmitolactone or (*R*)-4-decalactone could be synthesized (see Figure 11) [109].

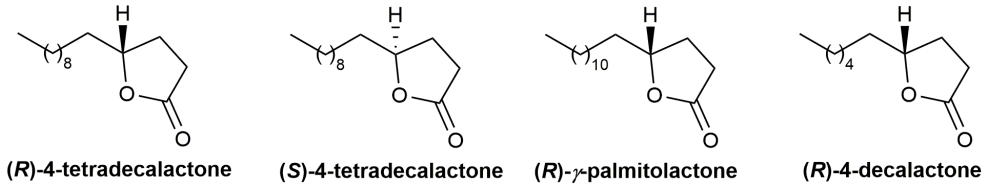


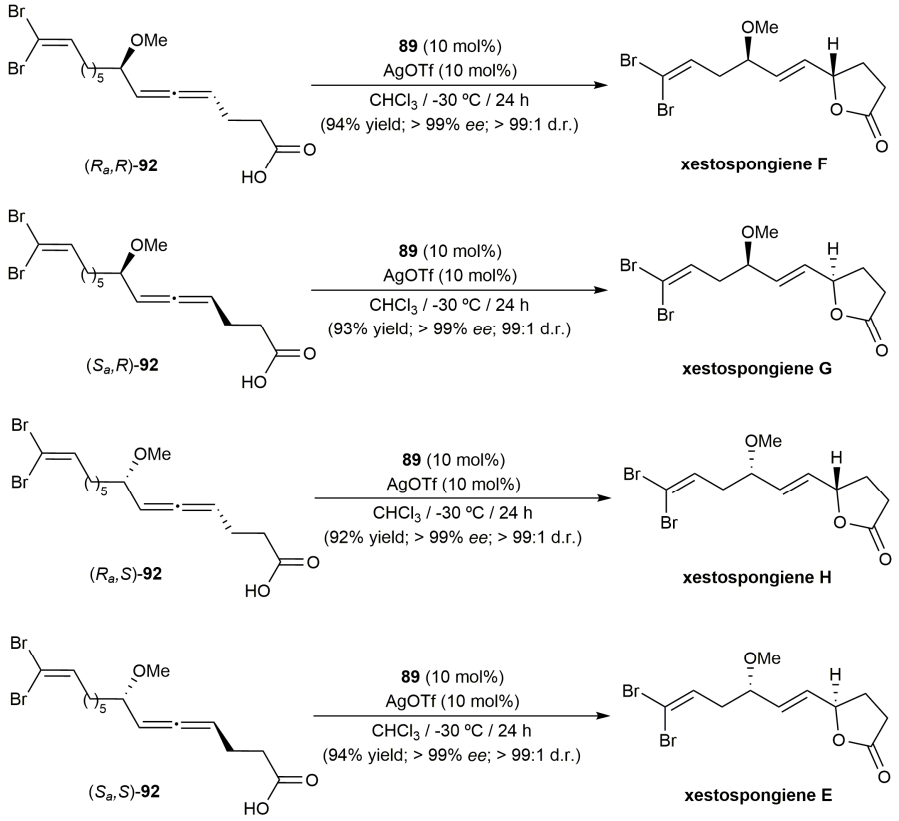
Figure 11. Structure of some naturally occurring γ-alkyl-substituted γ-butyrolactones.

In the same work, the naturally occurring γ-vinyl-substituted γ-butyrolactones xestospongiene F, G, H and E were also conveniently prepared by cycloisomerization of the appropriate stereoisomer of the chiral γ-allenoic acid **92** (Scheme 41) [109].

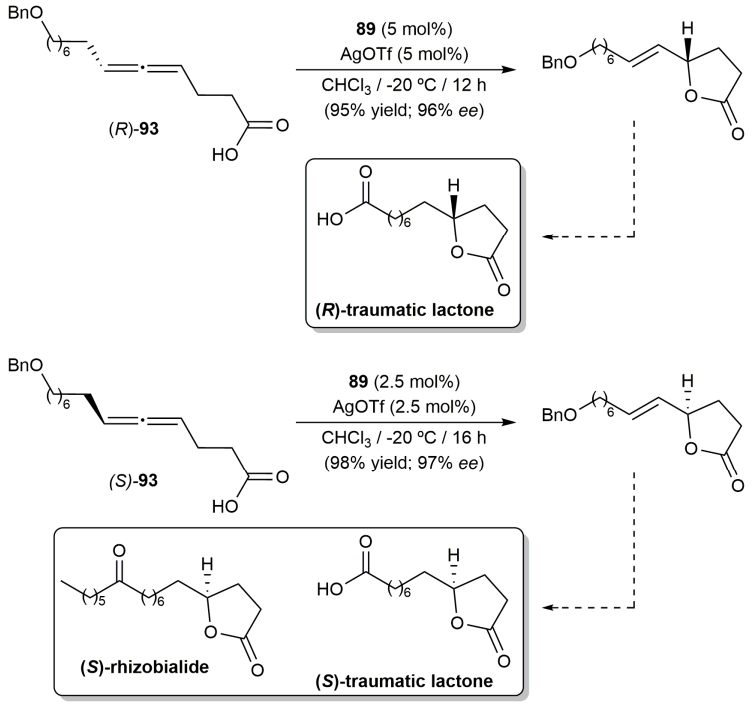
In additional studies, Ma's group accomplished the total synthesis of the natural products (*R*)-traumatic lactone, (*S*)-traumatic lactone and (*S*)-rhizobialide through strategies in which the chiral five-membered ring lactone units of these compounds were generated by means of the [AuCl(LB-Phos)]/AgOTf-catalyzed cyclization of the corresponding enantiomer of the allenoic acid **93** (Scheme 42) [110,111].

On the other hand, the behavior of different mononuclear gold(I)-chloride complexes containing phosphine, phosphite and NHC-type ligands, such as [AuCl(PPh_3)], [AuCl(JohnPhos)], [AuCl{$P(OPh)_3$}], [AuCl(IMes)] or [AuCl(H_2IMes)], in the cyclization of 2,2-diaryl substituted γ-allenoic acids **94**, was explored by Slaughter and co-workers (Scheme 43) [112]. The formation of mixtures of three isomeric products was in most the cases observed—i.e., the expected γ-vinyl-substituted γ-butyrolactones **95**, compounds **96** resulting from the double bond isomerization in **95**, and the tricyclic derivatives **97** which arise from a tandem hydroacyloxylation/hydroarylation process involving **95** as intermediates. However, an in-depth study of the process made it possible to selectively generate lactones **95** and **96** by exploiting Brønsted acid/base and ligand effects. Thus, as shown in Scheme 43, using the phosphite complex [AuCl{$P(OPh)_3$}] in combination with AgOTf, compounds **95** were preferentially formed in the presence of a base, whereas a Brønsted acid oriented the reaction towards

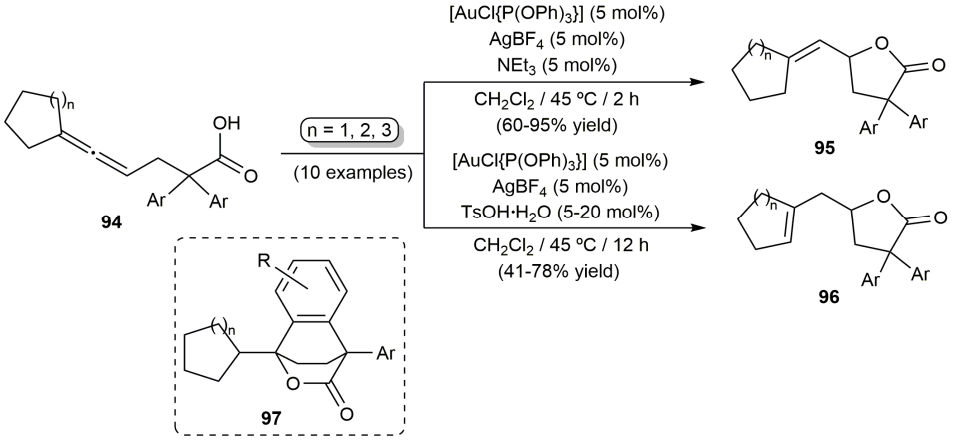
the isomerized products **96**. With a limited substrate scope, the authors also developed protocols to obtain the bridged tricyclic lactones **97** in a selective manner.



Scheme 41. Gold-catalyzed synthesis of some natural xestospongienes.



Scheme 42. Enantioselective cyclizations involved in the total synthesis of some naturally occurring lactones.

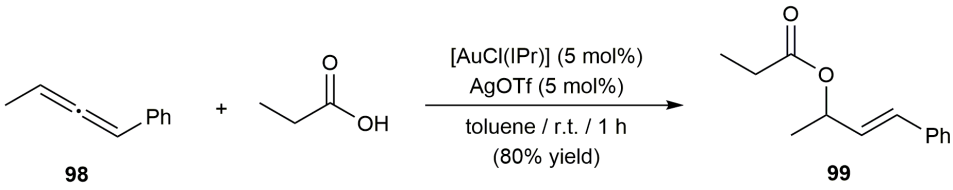


Scheme 43. Gold(I)-catalyzed cyclization of the γ-allenoic acid **94**.

Finally, it should be noted that Reek and co-workers successfully employed a supramolecular platinum-based nanosphere functionalized with a phosphine-gold(I)-chloride complex in the cyclization of the closely related 2,2-diphenylhexa-4,5-dienoic acid into the corresponding five-membered ring vinyl-lactone [44].

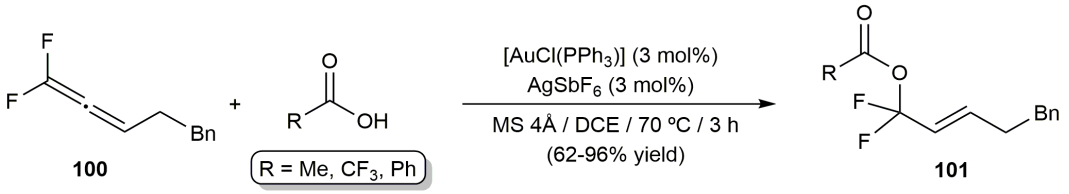
3.2. Intermolecular Addition of Carboxylic Acids to Allenes

Unlike other metals, such as palladium or rhodium, for which various catalytic systems capable of promoting the intermolecular addition of carboxylic acids to allenes have been described [113], the use of gold in this type of transformation has hardly been documented. In fact, only two examples can currently be found in the literature. The first one was described Zhang and Widenhoefer in 2008 and involved the addition of propionic acid to the 1,3-disubstituted allene **98** catalyzed by the carbene-gold(I) complex [AuCl(IPr)] in combination with AgOTf (Scheme 44) [114]. The reaction led to the regio- and stereoselective formation of the allylic ester **99**, which was isolated in 80% yield.



Scheme 44. Gold(I)-catalyzed addition of propionic acid to the 1,3-disubstituted allene **98**.

In a more recent study, the group of Ichikawa reported the synthesis of the fluorinated allyl esters **101** by addition of acetic, trifluoroacetic or benzoic acid to the trisubstituted 1,1-difluoroallene **100** (Scheme 45) [115]. The reactions were promoted by the in situ generated $[Au(PPh_3)]^+$ cation and proceeded again with complete regio- and stereoselectivity. $AuCl_3$ proved to also be active in the process, but led to esters **101** as mixtures of the corresponding (*E*) and (*Z*) isomers.



Scheme 45. Gold(I)-catalyzed intermolecular addition of carboxylic acids to the 1,1-difluoroallene **73**.

4. Summary

In this contribution, the application of gold-based catalysts in the hydrofunctionalization of alkynes and allenes with carboxylic acids has been comprehensively reviewed. The cyclisomerization reactions of alkynoic acids have been the processes most widely studied, and several homogeneous and heterogeneous systems have demonstrated their utility for the regio- and stereoselective construction of different types of enol lactones under mild conditions, even in unconventional reaction media, such as water, ionic liquids or deep eutectic solvents. In addition, a large number of elaborated nitrogen-containing polycyclic compounds have been successfully accessed using readily available alkynoic acids and functionalized amines as starting materials through cascade-type processes. Gold-based catalysts have also demonstrated their utility in the intermolecular addition of carboxylic acids to both terminal and internal alkynes, showing again high regio- and stereoselectivities. Concerning allenes, the most remarkable results concern the preparation of chiral vinyl-lactones with good enentioselectivities by using chiral catalysts or through axial-to-central chirality transfer strategies; the latter found applications in the total synthesis of several natural products. It is hoped that in the near future more attention will be paid to the intermolecular addition of carboxylic acids to allenes, a process for which only two isolated examples are currently known.

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Conflicts of Interest: The author declares no conflict of interest.

References

1. Ananikov, V.P.; Tanaka, M. (Eds.) *Hydrofunctionalization*; Springer: Berlin/Heidelberg, Germany, 2011.
2. Alonso, F.; Beletskaya, I.P.; Yus, M. Transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes. *Chem. Rev.* **2004**, *104*, 3079–3160. [CrossRef]
3. Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and anti-Markovnikov functionalization of alkenes and alkynes: Recent developments and trends. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398. [CrossRef] [PubMed]
4. Patil, N.T.; Kavthe, R.D.; Shinde, V.S. Transition metal-catalyzed addition of C-, N- and O-nucleophiles to unactivated C-C multiple bonds. *Tetrahedron* **2012**, *68*, 8079–8146. [CrossRef]
5. Zeng, X. Recent advances in catalytic sequential reactions involving heteroelement addition to carbon-carbon multiple bonds. *Chem. Rev.* **2013**, *113*, 6864–6900. [CrossRef] [PubMed]
6. Zheng, Y.; Zi, W. Transition-metal catalyzed enantioselective functionalization of alkynes. *Tetrahedron Lett.* **2018**, *59*, 2205–2213. [CrossRef]
7. Cadierno, V. Metal-catalyzed hydrofunctionalization reactions of haloalkynes. *Eur. J. Inorg. Chem.* **2020**, 886–898. [CrossRef]
8. Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P.H. Ruthenium-catalyzed additions to alkynes: Synthesis of activated esters and their use in acylation reactions. *Synlett* **1991**, *1991*, 755–763. [CrossRef]
9. Gooβen, L.J.; Rodríguez, N.; Gooβen, K. Carboxylic acids as substrates in homogeneous catalysis. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120.
10. Hintermann, L. Recent developments in metal-catalyzed additions of oxygen nucleophiles to alkenes and alkynes. *Top. Organomet. Chem.* **2010**, *31*, 123–155.
11. Bruneau, C. Group 8 metals-catalyzed O-H bond addition to unsaturated molecules. *Top. Organomet. Chem.* **2013**, *43*, 203–230.
12. Francos, J.; Cadierno, V. Metal-catalyzed intra- and intermolecular addition of carboxylic acids to alkynes in aqueous media: A review. *Catalysts* **2017**, *7*, 328. [CrossRef]
13. González-Liste, P.J.; Francos, J.; García-Garrido, S.E.; Cadierno, V. The intermolecular hydro-oxycarbonylation of internal alkynes: Current state of the art. *Arkivoc* **2018**, *2*, 17–39.
14. Rao, Y.S. Recent advances in the chemistry of unsaturated lactones. *Chem. Rev.* **1976**, *76*, 625–694. [CrossRef]
15. Libiszewska, K. Lactones as biologically active compounds. *Biotechnol. Food Sci.* **2011**, *75*, 45–53.

16. Janecki, T. (Ed.) *Natural Lactones and Lactams: Synthesis, Ocurrence and Biological Activity*; Wiley-VCH: Weinheim, Germany, 2013.
17. Cadierno, V. Metal-catalyzed synthesis and transformations of β-haloenol esters. *Catalysts* **2020**, *10*, 399. [CrossRef]
18. Hashmi, A.S.K. Gold-catalyzed organic reactions. *Chem. Rev.* **2007**, *107*, 3180–3211. [CrossRef] [PubMed]
19. Corma, A.; Leyva-Pérez, A.; Sabater, M.J. Gold-catalyzed carbon-heteroatom bond-forming reactions. *Chem. Rev.* **2011**, *111*, 1657–1712. [CrossRef]
20. Huang, H.; Zhou, Y.; Liu, H. Recent advances in the gold-catalyzed additions to multiple C-C bonds. *Beilstein J. Org. Chem.* **2011**, *7*, 897–936. [CrossRef]
21. Hashmi, A.S.K.; Toste, F.D. (Eds.) *Modern Gold Catalyzed Synthesis*; Wiley-VCH: Weinheim, Germany, 2012.
22. Toste, F.D.; Michelet, V. (Eds.) *Gold Catalysis: An Homogeneous Approach*; Imperial College Press: London, UK, 2014.
23. Praveen, C. Carbophilic activation of π-systems via gold coordination: Towards regioselective access of intermolecular addition products. *Coord. Chem. Rev.* **2019**, *392*, 1–34. [CrossRef]
24. Alyebyev, S.B.; Beletskaya, I.P. Gold as a catalyst. Part I. Nucleophilic addition to the triple bond. *Russ. Chem. Rev.* **2017**, *86*, 689–749. [CrossRef]
25. Alyebyev, S.B.; Beletskaya, I.P. Gold as a catalyst. Part II. Alkynes in the reactions of carbon-carbon bond formation. *Russ. Chem. Rev.* **2018**, *87*, 984–1047. [CrossRef]
26. Gorin, D.J.; Sherry, B.D.; Toste, F.D. Ligand effects in homogeneous Au catalysis. *Chem. Rev.* **2008**, *108*, 3351–3378. [CrossRef] [PubMed]
27. Krauser, N.; Winter, C. Gold-catalyzed nucleophilic cyclization of functionalized allenes: A powerful access to carbo and heterocycles. *Chem. Rev.* **2011**, *111*, 1994–2009. [CrossRef]
28. Yang, W.; Hashmi, A.S.K. Mechanistic insights into gold chemistry of allenes. *Chem. Soc. Rev.* **2014**, *43*, 2941–2955. [CrossRef]
29. Hashmi, A.S.K. New and selective transition metal catalyzed reactions of allenes. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590–3593. [CrossRef]
30. Genin, E.; Toullec, P.Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. Room temperature Au(I)-catalyzed *exo*-selective cyclosimerization of acetylenic acids: An entry to functionalized γ-lactones. *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113. [CrossRef]
31. Genin, E.; Toullec, P.Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. Gold catalysis in organic synthesis: Efficient intramolecular cyclization of γ-acetylenic carboxylic acids to 5-*exo*-alkylidene-butyrolactones. *Arkivoc* **2007**, 67–78. [CrossRef]
32. Harkat, H.; Weibel, J.-M.; Pale, P. A mild access to γ- or δ-alkylidene lactones through gold catalysis. *Tetrahedron Lett.* **2006**, *47*, 6273–6276. [CrossRef]
33. Harkat, H.; Dembelé, A.Y.; Weibel, J.-M.; Blanc, A.; Pale, P. Cyclization of alkynoic acids with gold catalysts: A surprising dichotomy between Au^{I} and Au^{III}. *Tetrahedron* **2009**, *65*, 1871–1879. [CrossRef]
34. Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; van de Weghe, P. Cycloisomerization of γ- and δ-acetylenic acids catalyzed by gold(I) chloride. *Tetrahedron* **2007**, *63*, 9979–9990. [CrossRef]
35. Feng, Y.; Jiang, X.; De Brabender, J.K. Studies toward the unique pederin family member psymberin: Full structure elucidation, two alternative total syntheses, and analogs. *J. Am. Chem. Soc.* **2012**, *134*, 17083–17093. [CrossRef] [PubMed]
36. Salas, C.O.; Reboredo, F.J.; Estévez, J.C.; Tapia, R.A.; Estévez, R.J. Gold-facilitated "6-*exo-dig*" intramolecular cyclization of 2-[(2-nitrophenyl)ethynyl]phenylacetic acids: General access to 5*H*-benzo[*b*]carbazole-6,11-diones. *Synlett* **2009**, *2009*, 3107–3110. [CrossRef]
37. Medran, N.S.; Villalba, M.; Mata, E.G.; Testero, S.A. Gold-catalyzed cycloisomerization of alkyne-containing amino acids: Controlled tuning of C-N vs. C-O reactivity. *Eur. J. Org. Chem.* **2016**, *2016*, 3757–3764. [CrossRef]
38. Praveen, C.; Ayyanar, A.; Perumal, P.T. Gold(III) chloride catalyzed regioselective synthesis of pyrano[3,4-*b*]indol-1(9*H*)-ones and evaluation of anticancer potential towards human cervix adenocarcinoma. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4170–4173. [CrossRef] [PubMed]
39. Praveen, C.; Ananth, D.B. Design, synthesis and cytotoxicity of pyrano [4,3-*b*]indol-1(5*H*)-ones: A hybrid pharmacophore approach via gold catalyzed cyclization. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2507–2512. [CrossRef]

40. Taskaya, S.; Menges, N.; Balci, M. Gold-catalyzed formation of pyrrolo- and indolo-oxacin-1-one derivatives: The key structure of some marine natural products. *Beilstein J. Org. Chem.* **2015**, *11*, 897–905. [CrossRef]
41. Wang, W.; Kumar, M.; Hammond, G.B.; Xu, B. Enhanced reactivity in homogeneous gold catalysis through hydrogen bonding. *Org. Lett.* **2014**, *16*, 636–639. [CrossRef]
42. Kumar, M.; Hammond, G.B.; Xu, B. Cationic gold catalyst poisoning and reactivation. *Org. Lett.* **2014**, *16*, 3452–3455. [CrossRef] [PubMed]
43. Malhotra, D.; Mashuta, M.S.; Hammond, G.B.; Xu, B. A highly efficient and broadly applicable cationic gold catalyst. *Angew. Chem. Int. Ed.* **2014**, *53*, 4456–4459. [CrossRef] [PubMed]
44. Leenders, S.H.A.M.; Dürr, M.; Ivanović-Burmazović, I.; Reek, J.N.H. Gold functionalized platinum $M_{12}L_{24}$-nanospheres and their application in cyclization reactions. *Adv. Synth. Catal.* **2016**, *345*, 1509–1518. [CrossRef]
45. Ho, T.D.; Schramm, M.P. Au-cavitand catalyzed alkyne-acid cyclizations. *Eur. J. Org. Chem.* **2019**, *2019*, 5678–5684. [CrossRef]
46. Nolla-Saltiel, R.; Robles-Marín, E.; Porcel, S. Silver(I) and gold(I)-promoted synthesis of alkylidene lactones and 2H-chromenes from salicylic and anthranilic acid derivatives. *Tetrahedron Lett.* **2014**, *55*, 4484–4488. [CrossRef]
47. Carrillo-Arcos, U.A.; Porcel, S. Gold promoted arylative cyclization of alkynoic acids with arenediazonium salts. *Org. Biomol. Chem.* **2018**, *16*, 1837–1842. [CrossRef]
48. Sperger, C.A.; Friksdahl, A. Gold-catalyzed tandem cyclizations of 1,6-diynes triggered by internal N- and O-nucleophiles. *J. Org. Chem.* **2010**, *75*, 4542–4553. [CrossRef]
49. Gold(I)-catalysed cyclisation of alkynoic acids: Towards an efficient and eco-friendly synthesis of γ-, δ- and ε-lactones. *Adv. Synth. Catal.* **2016**, *358*, 3857–3862. [CrossRef]
50. Fernández-García, J.M.; García-García, P.; Fernández-Rodríguez, M.A.; Pérez-Anes, A.; Aguilar, E. Regioselective synthesis of oxepinones and azepinones by gold-catalyzed cycloisomerization of functionalized cyclopropyl alkynes. *Chem. Commun.* **2013**, *49*, 11185–11187. [CrossRef] [PubMed]
51. Garre, M.S.; Sucunza, D.; Aguilar, E.; García-García, P.; Vaquero, J.J. Regiodivergent electrophilic cyclizations of alkynylcyclobutanes for the synthesis of cyclobutane-fused O-heterocycles. *J. Org. Chem.* **2019**, *84*, 5712–5725. [CrossRef]
52. Tomás-Mendivil, E.; Toullec, P.Y.; Díez, J.; Conejero, S.; Michelet, V.; Cadierno, V. Cycloisomerization versus hydration reactions in aqueous media: A Au(III)-NHC catalyst that makes the difference. *Org. Lett.* **2012**, *14*, 2520–2523. [CrossRef]
53. Tomás-Mendivil, E.; Toullec, P.Y.; Borge, J.; Conejero, S.; Michelet, V.; Cadierno, V. Water-soluble gold(I) and gold(III) complexes with sulfonated *N*-heterocyclic carbene ligands: Synthesis, characterization, and application in the catalytic cycloisomerization of γ-alkynoic acids into enol-lactones. *ACS Catal.* **2013**, *3*, 3086–3098. [CrossRef]
54. Ferré, M.; Cattoën, X.; Man, M.W.C.; Pleixats, R. Sol-gel immobilized N-heterocyclic carbene gold complex as a recyclable catalyst for the rearrangement of allylic esters and the cycloisomerization of γ-alkynoic acids. *ChemCatChem* **2016**, *8*, 2824–2831. [CrossRef]
55. Belger, K.; Krause, N. Smaller, faster, better: Modular synthesis of unsymmetrical ammonium salt-tagged NHC-gold(I) complexes and their application as recyclable catalysts in water. *Org. Biomol. Chem.* **2015**, *13*, 8556–8560. [CrossRef] [PubMed]
56. Sak, H.; Mawick, M.; Krause, N. Sustainable gold catalysis in water using cyclodextrin-tagged NHC-gold complexes. *ChemCatChem* **2019**, *11*, 5821–5829. [CrossRef]
57. Rodríguez-Álvarez, M.J.; Vidal, C.; Díez, J.; García-Álvarez, J. Introducing deep eutectic solvents as biorenewable media for Au(I)-catalyzed cycloisomerisation of γ-alkynoic acids: An unprecedented catalytic system. *Chem. Commun.* **2014**, *50*, 12927–12929. [CrossRef] [PubMed]
58. Ramsay, W.J.; Bell, N.A.W.; Qing, Y.; Bayley, H. Single-molecule observation of the intermediates in a catalytic cycle. *J. Am. Chem. Soc.* **2018**, *140*, 17538–17546. [CrossRef]
59. Fernández, G.; Bernardo, L.; Villanueva, A.; Pleixats, R. Gold nanoparticles stabilized by PEG-tagged imidazolium salts as recyclable catalysts for the synthesis of propargylamines and the cycloisomerization of γ-alkynoic acids. *New J. Chem.* **2020**, *44*, 6130–6141. [CrossRef]

60. Neaţu, F.; Li, Z.; Richards, R.; Toullec, P.Y.; Genêt, J.-P.; Dumbuya, K.; Gottfried, J.M.; Steinrück, H.-P.; Pârvulescu, V.I.; Michelet, V. Heterogeneous gold catalysts for efficient access to functionalized lactones. *Chem. Eur. J.* **2008**, *14*, 9412–9418. [CrossRef] [PubMed]
61. Neaţu, F.; Toullec, P.Y.; Michelet, V.; Pârvulescu, V.I. Heterogeneous Au and Rh catalysts for cycloisomerization reactions of γ-acetylenic acids. *Pure Appl. Chem.* **2009**, *81*, 2387–2396. [CrossRef]
62. Neaţu, F.; Pârvulescu, V.I.; Michelet, V.; Gênet, J.-P.; Goguet, A.; Hardacre, C. Gold imidazolium-based ionic liquids, efficient catalysts for cycloisomerization of γ-acetylenic carboxylic acids. *New J. Chem.* **2009**, *33*, 102–106. [CrossRef]
63. Verho, O.; Gao, F.; Johnston, E.V.; Wan, W.; Nagendiran, A.; Zheng, H.; Bäckvall, J.-E.; Zou, X. Mesoporous silica nanoparticles applied as a support for Pd and Au nanocatalysts in cycloisomerization reactions. *APL Mater.* **2014**, *2*, 113316. [CrossRef]
64. Eriksson, K.; Verho, O.; Nyholm, L.; Oscarsson, S.; Bäckvall, J.-E. Disperse gold nanoparticles supported in the pores of siliceous mesocellular foam: A catalyst for cyclosiomerization of alkynoic acids to γ-alkylidene lactones. *Eur. J. Org. Chem.* **2015**, *2015*, 2250–2255. [CrossRef]
65. Lee, L.-C.; Zhao, Y. Metalloenzyme-mimicking supramolecular catalyst for highly active and selective intramolecular alkyne carboxylation. *J. Am. Chem. Soc.* **2014**, *136*, 5579–5582. [CrossRef] [PubMed]
66. Toullec, P.Y.; Genin, E.; Antoniotti, S.; Genêt, J.-P.; Michelet, V. Au_2O_3 as a stable and efficient catalyst for the selective cycloisomerization of γ-acetylenic carboxylic acids to γ-alkylidene-γ-butyrolactones. *Synlett* **2008**, *2008*, 707–711.
67. Shu, X.-Z.; Nguyen, S.C.; He, Y.; Oba, F.; Zhang, Q.; Canlas, C.; Somorjai, G.A.; Alivisatos, A.P.; Toste, F.D. Silica-supported cationic gold(I) complexes as heterogeneous catalysts for regio- and enantioselective lactonization reactions. *J. Am. Chem. Soc.* **2015**, *137*, 7083–7086. [CrossRef]
68. Yang, T.; Campbell, L.; Dixon, D.J. A Au(I)-catalyzed *N*-acyl iminium ion cyclization cascade. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071. [CrossRef]
69. Feng, E.; Zhou, Y.; Zhao, F.; Chen, X.; Zhang, L.; Jiang, H.; Liu, H. Gold-catalyzed tandem reaction in water: An efficient and convenient synthesis of fused polycyclic indoles. *Green Chem.* **2012**, *14*, 1888–1895. [CrossRef]
70. Li, Z.; Li, J.; Yang, N.; Chen, Y.; Zhou, Y.; Ji, X.; Zhang, L.; Wang, J.; Xie, X.; Liu, H. Gold(I)-catalyzed cascade approach for the synthesis of tryptamine-based polycyclic scaffolds as α_1-adrenergic receptor antagonists. *J. Org. Chem.* **2013**, *78*, 10802–10811. [CrossRef]
71. Qiao, J.; Jia, X.; Li, P.; Liu, X.; Zhao, J.; Zhou, Y.; Wang, J.; Liu, H.; Zhao, F. Gold-catalyzed rapid construction of nitrogen-containing heterocyclic compound library with scaffold diversity and molecular complexity. *Adv. Synth. Catal.* **2019**, *361*, 1419–1440. [CrossRef]
72. Jia, X.; Li, P.; Liu, X.; Lin, J.; Chu, Y.; Yu, J.; Wang, J.; Liu, H.; Zhao, F. Green and facile assembly of diverse fused *N*-heterocycles using gold-catalyzed cascade reactions in water. *Molecules* **2019**, *24*, 988. [CrossRef] [PubMed]
73. Zhou, Y.; Zhai, Y.; Ji, X.; Liu, G.; Feng, E.; Ye, D.; Zhao, L.; Jiang, H.; Liu, H. Gold(I)-catalyzed one-pot tandem coupling/cyclization: An efficient synthesis of pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones. *Adv. Synth. Catal.* **2010**, *352*, 373–378. [CrossRef]
74. Feng, E.; Zhou, Y.; Zhang, D.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. Gold(I)-catalyzed tandem transformation: A simple approach for the synthesis of pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones and pyrrolo/pyrido[2,1-*a*]quinazolinones. *J. Org. Chem.* **2010**, *75*, 3274–3282. [CrossRef]
75. Ji, X.; Zhou, Y.; Wang, J.; Zhao, L.; Jiang, H.; Liu, H. Au(I)/Ag(I)-catalyzed cascade approach for the synthesis of benzo[4,5]imidazo[1,2-*c*]pyrrolo[1,2-*a*]quinazolinones. *J. Org. Chem.* **2013**, *78*, 4312–4318. [CrossRef] [PubMed]
76. Zhou, Y.; Li, J.; Ji, X.; Zhou, W.; Zhang, X.; Qian, W.; Jiang, H.; Liu, H. Silver- and gold-mediated domino transformation: A strategy for synthesizing benzo[*e*]indolo[1,2-*a*]pyrrolo/pyrido[2,1-*c*][1,4]-diazepine-3,9-diones. *J. Org. Chem.* **2011**, *76*, 1239–1249. [CrossRef] [PubMed]
77. Zhou, Y.; Ji, X.; Liu, G.; Zhang, D.; Zhao, L.; Jiang, H.; Liu, H. Gold(I)-catalyzed cascade for synthesis of pyrrolo[1,2-*a*:2´,1´-*c*]-/pyrido[2,1-*c*]pyrrolo[1,2-*a*]quinoxalinones. *Adv. Synth. Catal.* **2010**, *352*, 1711–1717. [CrossRef]

78. Patil, N.T.; Mutyala, A.K.; Lakshmi, P.G.V.V.; Gajula, B.; Sridhar, B.; Pottireddygari, G.R.; Rao, T.P. Au(I)-catalyzed cascade reaction involving formal doble hydroamination of alkynes bearing tethered carboxylic groups: An easy access to fused dihydrobenzimidazoles and tetrahydroquinazolines. *J. Org. Chem.* **2010**, *75*, 5963–5975. [CrossRef] [PubMed]
79. Patil, N.T.; Lakshmi, P.G.V.V.; Sridhar, B.; Patra, S.; Bhadra, M.P.; Patra, C.R. New linearly and angularly fused quinazolinones: Synthesis through gold(I)-catalyzed cascade reactions and anticancer activities. *Eur. J. Org. Chem.* **2012**, *2012*, 1790–1799. [CrossRef]
80. Patil, N.T.; Shinde, V.S.; Sridhar, B. Relay catalytic branching cascade: A technique to access diverse molecular scaffolds. *Angew. Chem. Int. Ed.* **2013**, *52*, 2251–2255. [CrossRef]
81. García-García, P.; Fernández-Rodríguez, M.A.; Aguilar, E. Gold-catalyzed cycloaromatization of 2,4-dien-6-yne carboxylic acids: Synthesis of 2,3-disubstituted phenols and unsymmetrical bi- and terphenyls. *Angew. Chem. Int. Ed.* **2009**, *48*, 5534–5537. [CrossRef] [PubMed]
82. Huo, Q.; Zhang, Z.; Kong, F.; Wang, S.; Wang, H.; Yao, Z.-J. Assembly of fused indenes via Au(I)-catalyzed C1-C5 cyclization of enediynes bearing an internal nucleophile. *Chem. Commun.* **2013**, *49*, 695–697.
83. Muratore, M.E.; Holloway, C.A.; Pilling, A.W.; Storer, R.I.; Trevitt, G.; Dixon, D.J. Enantioselective Brønsted acid-catalyzed *N*-acyliminium cyclization cascades. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797. [CrossRef]
84. Rodríguez-Álvarez, M.J.; Ríos-Lombardía, N.; Schumacher, S.; Pérez-Iglesias, D.; Morís, F.; Cadierno, V.; García-Álvarez, J.; González-Sabín, J. Combination of metal-catalyzed cycloisomerizations and biocatalysis in aqueous media: Asymmetric construction of chiral alcohols, lactones, and γ-hydroxy-carbonyl compounds. *ACS Catal.* **2017**, *7*, 7753–7759. [CrossRef]
85. Zhang, Q.; Cheng, M.; Hu, X.; Li, B.-G.; Ji, J.-X. Gold-catalyzed three-component tandem process: An efficient and facile assembly of complex butenolides from alkynes, amines and glyoxylic acid. *J. Am. Chem. Soc.* **2010**, *132*, 7256–7257. [CrossRef] [PubMed]
86. Roembke, P.; Schmidbauer, H.; Cronje, S.; Raubenheimer, H. Application of (phosphine)gold(I) carboxylates, sulfonates and related compounds as highly efficient catalysts for the hydration of alkynes. *J. Mol. Catal. A: Chem.* **2004**, *212*, 35–42. [CrossRef]
87. Chary, B.C.; Kim, S. Gold(I)-catalyzed addition of carboxylic acids to alkynes. *J. Org. Chem.* **2010**, *75*, 7928–7931. [CrossRef]
88. Luo, T.; Dai, M.; Zheng, S.-L.; Schreiber, S.L. Synthesis of α-pyrones using gold-catalyzed coupling reactions. *Org. Lett.* **2011**, *13*, 2834–2836. [CrossRef] [PubMed]
89. González-Liste, P.J.; León, F.; Arribas, I.; Rubio, M.; García-Garrido, S.E.; Cadierno, V.; Pizzano, A. Highly stereoselective synthesis and hydrogenation of (*Z*)-1-alkyl-2-arylvinyl acetate: A wide scope procedure for the preparation of chiral homobenzylic esters. *ACS Catal.* **2016**, *6*, 3056–3060. [CrossRef]
90. González-Liste, P.J.; Francos, J.; García-Garrido, S.E.; Cadierno, V. Gold-catalyzed regio- and stereoselective addition of carboxylic acids to iodoalkynes: Access to (*Z*)-β-iodoenol esters and 1,4-disubstituted (*Z*)-enynyl esters. *J. Org. Chem.* **2017**, *82*, 1507–1516. [CrossRef] [PubMed]
91. León, F.; González-Liste, P.J.; García-Garrido, S.E.; Arribas, I.; Rubio, M.; Cadierno, V.; Pizzano, A. Broad scope synthesis of esters precursors of nonfunctionalized chiral alcohols based on the asymmetric hydrogenation of α,β-dialkyl-, α,β-diaryl-, and α-alkyl-β-aryl-vinyl esters. *J. Org. Chem.* **2017**, *82*, 5852–5867. [CrossRef]
92. León, F.; Francos, J.; López-Serrano, J.; García-Garrido, S.E.; Cadierno, V.; Pizzano, A. Double asymmetric hydrogenation of conjugated dienes: A self-breeding chirality route to C_2 symmetric 1,4-diols. *Chem. Commun.* **2019**, *55*, 786–789. [CrossRef]
93. Francos, J.; Cadierno, V. Nickel-catalyzed homocoupling of (*Z*)-β-iodoenol esters: Stereoselective access to (*Z*,*Z*)-buta-1,3-diene-1,4-diyl diesters. *Synthesis* **2019**, *51*, 3117–3126. [CrossRef]
94. Muthusamy, G.; Pansare, S.V. Stereoselective synthesis of *E*-3-(arylmethylidene)-5-(alkyl/aryl)-2(3*H*)-furanones by sequential hydroacyloxylation-Mizoroki-Heck reactions of iodoalkynes. *Org. Biomol. Chem.* **2018**, *16*, 7971–7983. [CrossRef]
95. Francos, J.; Díaz-Álvarez, A.E.; Cadierno, V. Catalytic addition of indole-2-carboxylic acid to 1-hexyne. *Molbank* **2020**, *2020*, M1145. [CrossRef]
96. González-Liste, P.J.; García-Garrido, S.E.; Cadierno, V. Gold(I)-catalyzed addition of carboxylic acids t internal alkynes in aqueous medium. *Org. Biomol. Chem.* **2017**, *15*, 1670–1679. [CrossRef]

97. Francos, J.; Moreno-Narváez, M.E.; Cadierno, V.; Sierra, D.; Ariz, K.; Gómez, J. Gold(I) complexes with ferrocenylphosphino sulfonate ligands: Synthesis and application in the catalytic addition of carboxylic acids to internal alkynes in water. *Catalysts* **2019**, *9*, 955. [CrossRef]
98. Dupuy, S.; Gasperini, D.; Nolan, S.P. Highly efficient gold(I)-catalyzed regio and stereoselective hydrocarboxylation of internal alkynes. *ACS Catal.* **2015**, *5*, 6918–6921. [CrossRef] [PubMed]
99. Wang, Y.; Wang, Z.; Li, Y.; Wu, G.; Cao, Z.; Zhang, L. A general ligand design for gold catalysis allowing ligand-directed anti-nucleophilic attack of alkynes. *Nat. Commun.* **2014**, *5*, 3470. [CrossRef]
100. Hamilton, G.L.; Kang, E.J.; Mba, M.; Toste, F.D. A powerful chiral counterion strategy for asymmetric transition metal catalysis. *Science* **2007**, *317*, 496–499. [CrossRef] [PubMed]
101. Miles, D.H.; Veguillas, M.; Toste, F.D. Gold(I)-catalyzed enantioselective bromocyclization of allenes. *Chem. Sci.* **2013**, *4*, 3427–3431. [CrossRef]
102. Hashmi, A.S.K.; Loos, A.; Littmann, A.; Braun, I.; Knight, J.; Doherty, S.; Rominger, F. Gold(I) complexes of KITPHOS monophosphines: Efficient cycloisomerisation catalysts. *Adv. Synth. Catal.* **2009**, *351*, 576–582. [CrossRef]
103. Cauteruccio, S.; Loos, A.; Bossi, A.; Jaimes, M.C.B.; Dova, D.; Rominger, F.; Prager, S.; Dreuw, A.; Licandro, E.; Hashmi, A.S.K. Gold(I) complexes of tetrathiaheterohelicene phosphanes. *Inorg. Chem.* **2013**, *52*, 7995–8004. [CrossRef]
104. Handa, S.; Lippincott, D.J.; Aue, D.H.; Lipshutz, B.H. Asymmetric gold-catalyzed lactonizations in water at room temperature. *Angew. Chem. Int. Ed.* **2014**, *53*, 10658–10662. [CrossRef]
105. Ye, R.; Zhukhovitskiy, A.V.; Kazantsev, R.V.; Fakra, S.C.; Wickemeyer, B.B.; Toste, F.D.; Somorjai, G.A. Supported Au nanoparticles with *N*-heterocyclic carbene ligands as active and heterogeneous catalysts for lactonization. *J. Am. Chem. Soc.* **2018**, *140*, 4144–4149. [CrossRef] [PubMed]
106. Klumphu, P.; Desfeux, C.; Zhang, Y.; Handa, S.; Gallou, F.; Lipshutz, B.H. Micellar catalysis-enabled sustainable ppm Au-catalyzed reactions at room temperature. *Chem. Sci.* **2017**, *8*, 6354–6358. [CrossRef]
107. Okada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y. Au-catalyzed cyclization of allenylsilanes. Regioselective conversion to 2-amino-4-silylmethylene γ-butyrolactone. *Tetrahedron Lett.* **2011**, *52*, 5740–5743. [CrossRef]
108. Okada, T.; Sakaguchi, K.; Shinada, T.; Ohfume, Y. Total synthesis of (-)-funebrine via Au-catalyzed regio- and stereoselective γ-butyrolactonization of allenylsilane. *Tetrahedron Lett.* **2011**, *52*, 5744–5746. [CrossRef]
109. Zhou, J.; Fu, C.; Ma, S. Gold-catalyzed stereoselective cycloisomerization of allenoic acids for two types of common natural γ-butyrolactones. *Nat. Commun.* **2018**, *9*, 1654. [CrossRef] [PubMed]
110. Song, S.; Zhou, J.; Fu, C.; Ma, S. Catalytic enantioselective construction of axial chirality in 1,3-disubstituted allenes. *Nat. Commun.* **2019**, *10*, 507. [CrossRef] [PubMed]
111. Zhou, J.; Song, S.; Jiang, F.; Fu, C.; Ma, S. Efficient synthesis of traumatic lactone and rhizobialide. *Chem. Eur. J.* **2019**, *25*, 9948–9958. [CrossRef] [PubMed]
112. Handa, S.; Subramanium, S.S.; Ruch, A.A.; Tanski, J.M.; Slaughter, L.M. Ligand- and Brønsted acid/base-switchable reaction pathways in gold(I)-catalyzed cycloisomerizations of allenoic acids. *Org. Biomol. Chem.* **2015**, *13*, 3936–3949. [CrossRef] [PubMed]
113. Muñoz, M.P. Transition metal-catalysed intermolecular reaction of allenes with oxygen nucleophiles: A perspective. *Org. Biomol. Chem.* **2012**, *10*, 3584–3594. [CrossRef] [PubMed]
114. Zhang, Z.; Widenhoefer, R.A. Regio- and stereoselective synthesis of alkyl allylic ethers via gold(I)-catalyzed intermolecular hydroalkoxylation of allenes with alcohols. *Org. Lett.* **2008**, *10*, 2079–2081. [CrossRef]
115. Fuchibe, K.; Abe, M.; Sasaki, M.; Ichikawa, J. Gold-catalyzed electrophilic activation of 1,1-difluoroallenes: α- and γ-selective addition of heteroatom nucleophiles. *J. Fluorine Chem.* **2020**, *232*, 109452. [CrossRef]