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PERSPECTIVE

Gold catalyzed oxycyclizations of alkynols and alkyndiols

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Alkynols and alkyndiols represent excellent building blocks for oxycyclization reactions, leading to a large number of different cyclic structures in one single step. Recently, the use of gold salts and gold complexes has been introduced as an alternative to the traditional methods, providing mild reaction conditions and high group compatibility. This overview focuses on the most recent achievements on gold-catalyzed oxycyclizations, both from alkynols and alkyndiols, and their use in different cascade processes and total synthesis.

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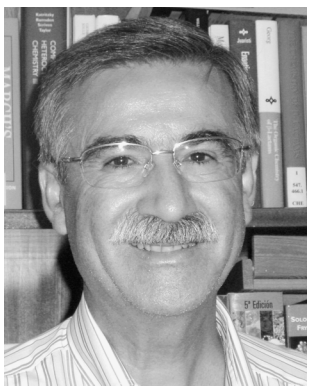
1. Introduction

During the last decade, the number of reactions catalyzed by gold complexes has experienced a dramatic growth.[1] Due to the powerful soft Lewis acidic nature of these catalysts and their exceptional alkynophilicity, that allow surprisingly mild reaction conditions, gold-oxycyclization of alkynols and alkyndiols have concretely become a hot topic in current organic chemistry.



Benito Alcaide

Benito Alcaide was born in Aldea del Rey, Ciudad Real, Spain, in 1950. He received his B.S. degree (1972) and Ph.D. degree (1978) from the Universidad Complutense de Madrid (UCM) under the supervision of Professor Franco Fernández. After a 4-year period working on the chemistry of α-iminoketones and related compounds, he began working on β-lactam chemistry. In 1984 he assumed a position of Associate Professor of Organic Chemistry and in 1990 was promoted to Full Professor at the UCM. His current recent interests include β-lactam chemistry, asymmetric synthesis of compounds of biological interest, free radicals, cycloaddition reactions, allenes, metal-promoted cyclizations, C–C coupling reactions, and organocatalysis.

Pedro Almendros

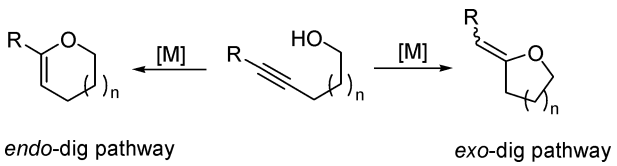
Pedro Almendros was born in Albacete (Spain) in 1966. He received his B. S. degree (1989) and his Ph. D. degree (1994) from the Universidad de Murcia under the supervision of Profs. Molina and Fresneda. After three years (1995–1998) postdoctoral work with Prof. Eric J. Thomas (University of Manchester), supported by two postdoctoral grants (Spanish MEC and European Marie Curie), he joined the research group of Prof. Benito Alcaide (UCM, Madrid) in 1998 as Associate Researcher (Contrato de Reincorporación de Doctores y Tecnólogos). Subsequent appointments have included Assistant Professor at the UCM (2000–2002), and Científico Titular (Tenured Scientist) at the Instituto de Química Orgánica General, CSIC, Madrid. In 2007 he was promoted to Investigador Científico (Research Scientist) at the IQOG, CSIC, Madrid. He has co-authored over 120 research publications and 12 book chapters. Pedro has a Hirsch's index h = 30. His research interest includes β-lactam chemistry, allene chemistry, asymmetric synthesis, metal-promoted heterocyclizations, and C–C coupling reactions.

In most cases, the initial step is the activation of the alkyne by the metal catalyst, followed by the nucleophilic attack of the hydroxylic group. Thus, a wide range of interesting structures can be achieved by this methodology, such as furans,[2] dihydrofurans,[3] pyrans,[4] furanones[5] or ketals,[6] among many other heterocyclic systems and naturally occurring structures.

2. Gold-catalyzed oxycyclization in alkynols

2.1. Single cycloisomerization processes

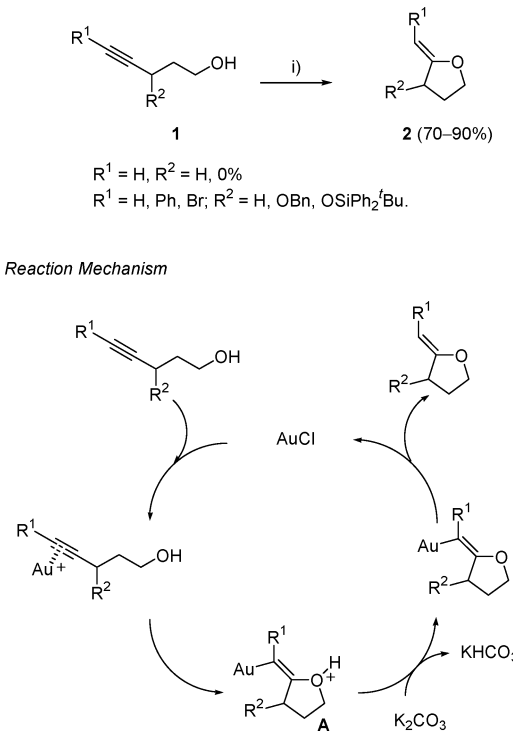
Tetrahydrofurans[7] and pyrans represent a crucial target in organic chemistry because of their recurring presence in several natural structures. A large number of methodologies have been described for their synthesis, and among them, metal based cycloisomerization of alkynols is one of the most convenient. High efficiency, atom economy and mild reaction conditions are just a few reasons to follow this strategy, and the obtention of products resulting through an *exo*-dig and/or *endo*-dig process has been widely reported (Scheme 1).



Scheme 1 Synthesis of dihydrofurans, pyrans and analogs through an *endo*-dig rearrangement, and tetrahydrofurans, tetrahydropyrans and related systems through an *exo*-dig process.

After the earlier versions using different transition metal catalysts, such as palladium, silver, chromium or tungsten,[8] gold salts and gold complexes have emerged as effective catalysts for this kind of cycloisomerization.

After studying the electronic effects on silver-catalyzed cycloisomerization,[9] Pale and coworkers reported the change of catalyst to gold salts, trying to achieve a general and more effective methodology for the synthesis of methylene oxolanes from simple terminal alkynols **1**.[10] Although the first described examples with unsubstituted acetylenic alcohols failed, they found that the use of AuCl together with K_2CO_3 worked efficiently at least on activated systems. More interestingly, a complete selectivity was reported for the 5-*exo*-dig adducts **2**, which was explained through the reaction mechanism noted below (Scheme 2). The observed regio- and stereoselectivity was rationalized through first a coordination of the alkyne motif by the gold(I) ion, followed by a nucleophilic addition of the hydroxylic group in an *anti* auration process, generating intermediates **A**.[11] Deprotonation promoted by K_2CO_3, and C–Au bond hydrolysis would finally lead to the observed final tetrahydrofurans **2**.



Scheme 2 $AuCl/K_2CO_3$ catalyzed cycloisomerization of alkynols and proposed reaction mechanism. i) AuCl (0.1 eq), K_2CO_3 (0.1 eq), MeCN, rt, 1–3 h.

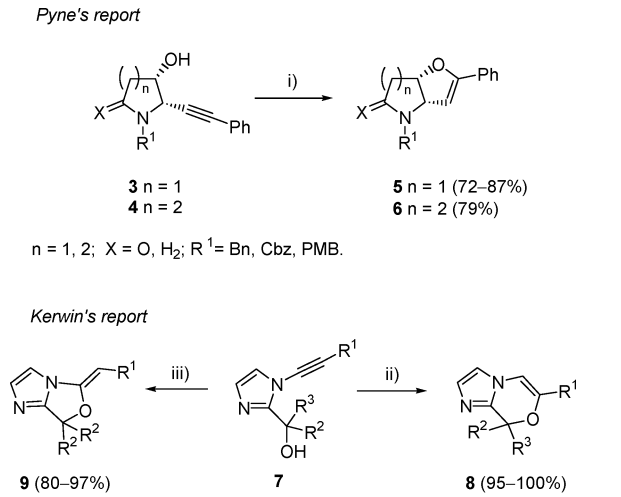
The scope of the process was also extended giving one example of a 6-membered oxane. Despite the lack of generality from a structural point of view, the selective obtention of *Z* isomers and *exo*-dig adducts through a very simple experimental procedure is the more remarkable feature of the work.

Recently, an identical methodology has been applied by Manzo and coworkers for the synthesis of substituted benzoxazines.[12] Starting from 2-(prop-2-yn-1-ylamino)phenols and employing the same dual catalyst system ($AuCl/K_2CO_3$), an interesting family of this fused six-membered heterocycle was obtained, exhibiting a complete *exo*-selectivity, but a less effective *Z*/*E* ratio.

Pyne *et al.* also tested gold salts among different catalysts for the synthesis of furo[3,2-*a*]pyrroles **5** and furo[3,2-*b*]pyridines **6**.[13] Starting from *cis*-4-hydroxy-5-alkynylpyrrolidinones and *cis*-5-hydroxy-6-alkynyl-piperidinones **3** and **4**, cycloisomerization occurred in high yields in most experiments (Scheme 3). In this case, a Au(I) catalyst did not provide any advantage compared to

José Miguel Alonso

José Miguel Alonso was born in Madrid (Spain) in 1975. He received his B. S. degree (1998) and his Ph. D. degree (2003) from the Universidad Complutense de Madrid, under the supervision of Prof. Benito Alcaide and Dr Pedro Almendros. After several years working for the industry, he joined the research group of Prof. Enrique Guitián at Universidade de Santiago de Compostela (Spain, 2009), and later he rejoined Benito Alcaide's research group where he is currently working as researcher (2010, Contrato de Apoyo a la Investigación de la Comunidad de Madrid). His research interests includes β*-lactam chemistry, allene chemistry, asymmetric synthesis and metal-promoted heterocyclizations.*

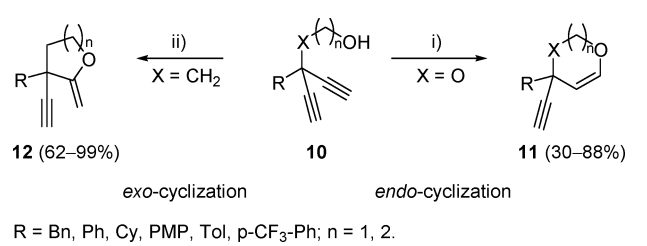


Scheme 3 Cycloisomerization reactions to yield fused bicyclic heterocycles. i) $Au(PPh_3)Cl$ (17–30% mol), EtOH, 65–70 °C, 8 h–5 days. ii) $AuCl_3$ (2% mol), CH_3CN, reflux, 14 h. iii) K_3PO_4 (5% mol), CH_3CN, reflux, 14 h.

Ag(I) or Pd(II)/Cu(I) salts, which made the reaction faster and the conversion higher. Nevertheless, it is worthy to note how cycloisomerization took place selectively, yielding dihydrofuran systems in every case.

More interestingly, other similar fused bicyclic heteroatomic structures were obtained by Kerwin *et al.* under Au-catalysis as the best reaction conditions.[14] Employing only 2 mol% of metal salt, compared to even 30 mol% for Pyne's substrates, they got access to imidazo[1,2-*c*]-oxazoles **8** in excellent yields. Moreover, a dual behaviour for 1-alkynylimidazoles **7** was reported. These hydroxyacetylenic systems reacted in a regiospecific manner through a 6-*endo*-dig pathway in the presence of metal catalyst, and through a 5-*exo*-dig pathway under basic conditions yielding structures **9** (Scheme 3).

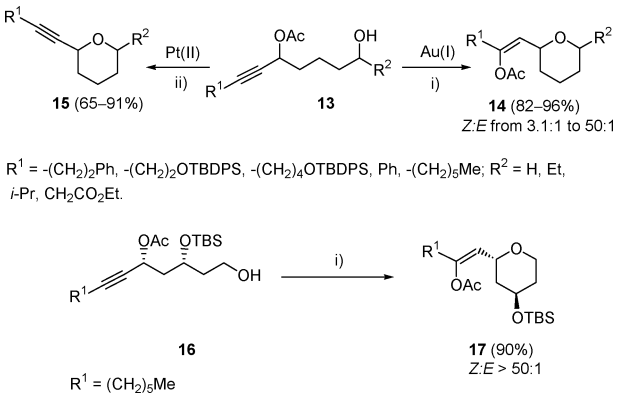
Czekelius and coworkers recently described an example where the competition between *exo* and *endo* cyclization could be totally controlled, obtaining selectively both of the two possibilities.[15] Starting from 3,3-disubstituted 1,4-diynes **10** they found that only one isomer was obtained, *exo* or *endo*, depending on the experimental procedure (Scheme 4). After going through different reaction conditions, checking several solvents and catalysts, they concluded that the nature of the group at the C3 position of diynes **10** was responsible for this selectivity. Thus, when an alkoxy group was located at this position, only *endo*-isomers **11** were obtained. On the contrary, when an aliphatic chain was present at the C3



Scheme 4 *exo vs. endo* Cycloisomerization in 1,4-diynols. i) $(Ph_3P)AuCl$ (5 mol%), $AgBF_4$ (4 mol%), THF, rt, 1–2 h. ii) $(Cy_3P)AuCl$, $AgBF_4$, toluene, rt, 1–2 h.

position of the corresponding 1,4-diynes, only *exo*-isomers **12** were obtained. The same complete selectivity was observed even when changing the length of the hydroxylic substituent. Czekelius *et al.* also reported a mechanistic proposal for this divergent behaviour, suggesting a possible coordination between the oxygen at the C3 position and the gold catalyst, as the main factor to set a different reaction pathway.

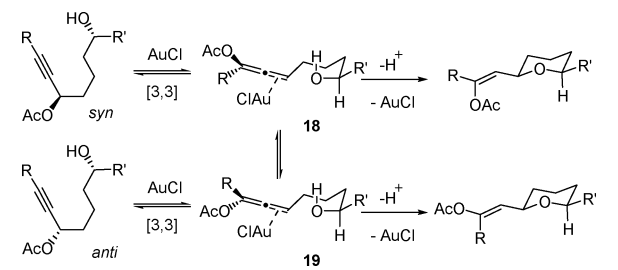
Gold salts can also catalyze a different kind of cycloisomerization, apart from the most commonly studied *endo*-dig and *exo*-dig rearrangements. De Brabander and coworkers reported the cycloetherification of ω-hydroxy propargylic acetates **13**, and their different reactivity depending on the nature of the metal catalyst.[16] Thus, when AuCl was employed oxacyclic enol acetates **14** were formed, while the change to Pt(II) complex surprisingly led to compound **15** through an unprecedented S_N2 allenic substitution (Scheme 5).



Scheme 5 Cycloetherification process catalyzed by Au(I) and Pt(II). i) AuCl (5% mol), THF, rt, 30 min. ii) $[Cl_2Pt(CH_2CH_2)]_2$ (2.5 mol%), THF (0.1 M), rt, 30 min.

Paying attention first to the gold experiments, we can enjoy a general methodology for the obtention of oxygen containing heterocycles, with 5 mol% AuCl as the optimal catalyst reported for this transformation. Moreover, going through a wide range of starting hydroxy propargylic esters, a good *Z*-selectivity on the final alkenes, interesting protecting group compatibility, and retention of the configuration of diastereomerically pure substrates, such as ω-hydroxyproparylic acetate **16**, can be stated.

Scheme 6 shows the proposed mechanism explaining the *Z*-selectivity through the less hindered intermediate **18** in the Au(I) catalyzed process.

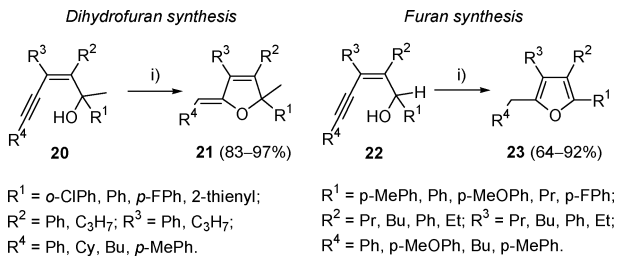


Scheme 6 Cycloetherification mechanism of the gold-catalyzed process.

A related mild and efficient approach to the preparation of cyclic ethers bearing an alkyl ketone side chain, in which

homopropargylic ethers serve as latent electrophiles through a sequence of alkyne hydration, β-alkoxy group elimination, and 1,4-addition has been described.[17] Diastereoselectivity in these transformations can be predicted on the basis of product stability, in accord with studies that products equilibrate under the reaction conditions. Au(III) and cationic Au(I) catalysts effectively promote these reactions, with the cationic Au(I) catalyst showing superior reactivity.

The high activity of gold salts and complexes for C–O bond formation has also been used on enynols for the synthesis of furans. After the first brief example appeared in literature,[18] Liu *et al.* developed a general methodology to yield both dihydrofuran and furan skeletons **21** and **23**.[19] Starting from *Z*-enynols **20** exhibiting a tertiary alcohol group, a wide range of highly substituted dihydrofurans were obtained. Moreover, different gold species and reaction conditions were tested, concluding that the use of extremely small amounts of catalyst ($AuCl_3$ 0.1 mol%), or even open air experiments provided the desired compounds with high yields. More interestingly, when moving to secondary alcohols **22** the same versatility was observed for the synthesis of different furan structures (Scheme 7).



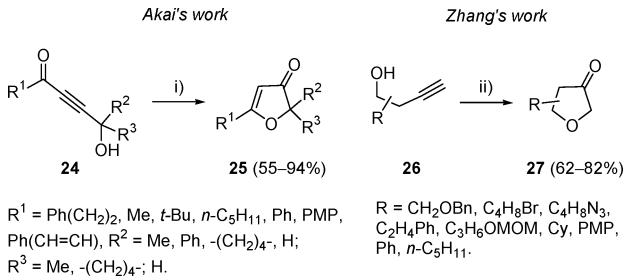
Scheme 7 Synthesis of furans and dihydrofurans from *Z*-enynols. i) $AuCl_3$ (1 mol%) or $Au(PPh_3)Cl/AgOTf$ (1 mol%) in DCM, rt, 1–4 h.

Every *Z*-enynol was prepared from commercially available chemicals, by a cross coupling Zr-catalyzed procedure. The authors also reported the addition of $AuCl_3$ to this reaction media, getting the desired final furan systems, with a notable yield decrease (up to 12%), but in just one step.

Hashmi *et al.* have also recently reported another way to afford furan structures from enynols. Various 2-alkynylallyl alcohols were synthesized by a generally applicable Sonogashira coupling protocol. Subsequent gold-catalyzed transformations were investigated. The use of Au(I) catalysts bearing carbene ligands, of either the N-heterocyclic carbene or nitrogen acyclic carbene type, delivered the desired products with low catalyst loadings and under very mild reaction conditions.[20] A broad array of substrates was tested, including alkyl-, alkenyl-, and aryl-substituted alkynes, as well as substrates with two alkynyl moieties. The methodology turned out to have a broad scope. Secondary allyl alcohols were also tolerated, and the resulting trisubstituted furans could be isolated in high yields. The transformation of even bifunctional substrates to the corresponding bisfurans opens interesting aspects for synthetic chemistry.

These results clearly show the benefits of gold catalysis on oxycycloisomerization reactions. Enynol cyclizations have been carried out before in the presence of strong base promotors,[21] which was not possible on base-sensitive systems, under Ru-catalysis,[22] only for terminal alkynes, or by Pd-catalyzed experiments,[23] where temperatures up to 100 °C were needed. Thus, compared to previously reported works, Au-mediated processes provide higher versatility, functional group compatibility, and milder conditions.

The 3-furanone moiety is also a synthetic target of special interest.[24] Again, opposite to the traditional preparation procedures which usually need harsh conditions and provide low yields,[25] Au-catalyzed methodology emerges as an effective and easy way to obtain these recurring structures. Akai *et al.* recently developed the gold mediated cyclization of γ-hydroxyalkynones **24**.[26] Although they described successful experiments with single catalysts, such as $(PPh_3)AuNTf_2$ or $[(PPh_3)Au]_3O^+BF_4^-$, the best results were observed employing $(p\text{-}CF_3C_6H_4)_3PAuCl$ together with AgOTf as additive. Thus, many 3(*2H*)-furanone systems **25** were prepared in good to high yields as shown in Scheme 8.



Scheme 8 Synthesis of 3-furanones and dihydrofuranones. i) $(p\text{-}CF_3C_6H_4)_3PAuCl/AgOTf$ (5 mol%), toluene, rt, 1–3.5 h. ii) $(PPh_3)AuNTf_2$ (5 mol%), 3,5-dichloropyridine (2 eq.), MsOH (1.2 eq), DCE, rt, 2.5 h.

The only disadvantage derived from this methodology is the preparation of the starting materials. Although it is well stated and doesn't take more than two steps, Zhang and coworkers sorted this inconvenience on related compounds by adding an external oxidant (pyridine *N*-oxides) to the cyclization experiments of readily available alkynols **26** (Scheme 8).[27]

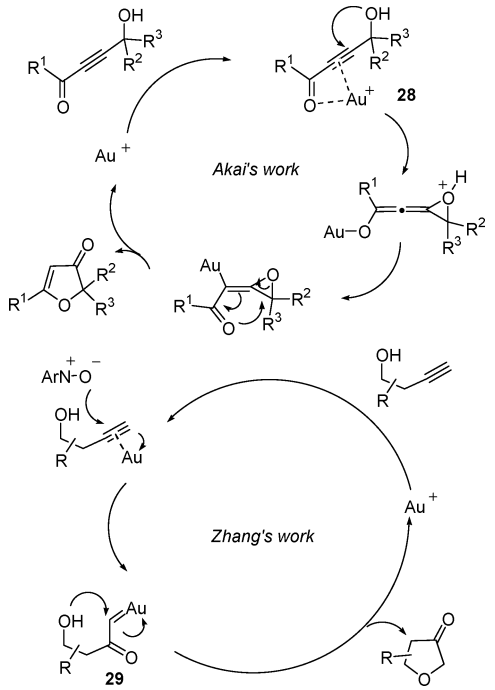
From the mechanistic point of view, this strategy allowed the synthesis of different dihydrofuran-3-ones through a proposed gold carbene intermediate **29**, in spite of the π-activated gold complex **28** proposed for the γ-hydroxyalkynone cyclization (Scheme 9).

Although this procedure could be more assimilable to a cascade process than to a single cycloisomerization example, we found it interesting to be included at this stage as a clear comparison between both furanone synthetic methods.

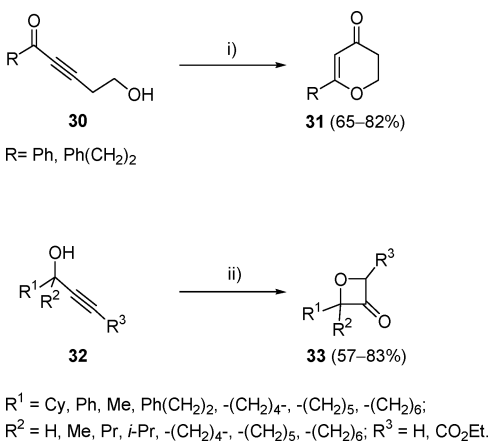
The scope of both processes was extended. On the one hand, some examples for the synthesis of pyranones **31** by enlarging the hydroxylic chain have been reported.[25] On the other hand, Zhang *et al.* studied the use of the cascade methodology for the synthesis of the more ring strained oxetan-3-ones **33** (Scheme 10).[28]

2.2 Cascade processes involving gold-catalyzed oxycyclization

Cascade processes represent a useful access to complex organic structures from quite simple reactants.[29] Due to the ability of gold species to catalyze unusual reactions, many examples have appeared incorporating gold-mediated strategies for the synthesis of different heterocyclic systems. Concretely, Au-oxycyclization tandem reactions are present in many recent reports.[30]



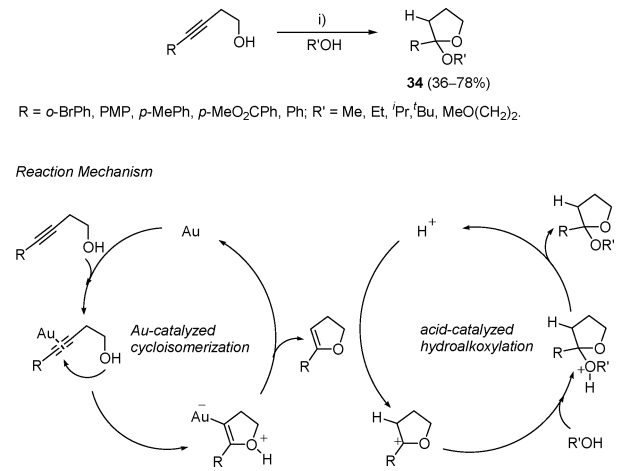
Scheme 9 Proposed reaction mechanisms for both γ-hydroxyalkynone cyclization and gold-carbene mediated alkynol oxidation/cycloisomerization cascade.



Scheme 10 Gold-catalyzed pyranone and oxetan-3-one syntheses. i) (p-$CF_3C_6H_4)_3$PAuCl/AgOTf (5% mol), toluene, rt, 1–3.5 h. ii) (2-Biphenyl)Cy_2AuNTf_2 or ^{i}PrAuNTf$_2$ (5 mol%), 3,5-dichloropyridine (2 eq.), Tf_2NH (1.2 eq), DCE, rt, 2.5 h.

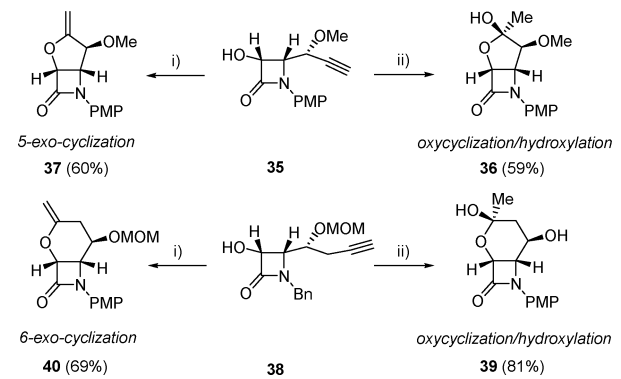
Tandem cycloisomerization/hydroalkoxylation of homopropargylic alcohols is one of the most simple and efficient examples. This methodology leads to tetrahydrofuranyl ethers, important building blocks and naturally occurring skeletons with diverse biological activities.[31] Krause *et al.* reported a methodology consisting of a dual catalyst system, including a gold complex for the first cyclization and a Brønsted acid for the hydroalkoxylation step (Scheme 11).[32] Thus, a family of tetrahydrofuranyl ethers **34** was obtained.

A similar idea was recently applied to β-lactam structures **35** and **38**.[33] It was found that the use of gold catalysis selectively led to a tandem cycloisomerization/hydroxylation, affording structures **36** and **39**, while the use of silver-based systems yielded



Scheme 11 Tandem cycloisomerization/hydroxyalkoxylation and reaction mechanism. i) $Ph_3PAuCl/AgBF_4$ (2 mol%), p-TsOH (10 mol%), R′OH (normally as solvent), rt, 45 min–3 h.

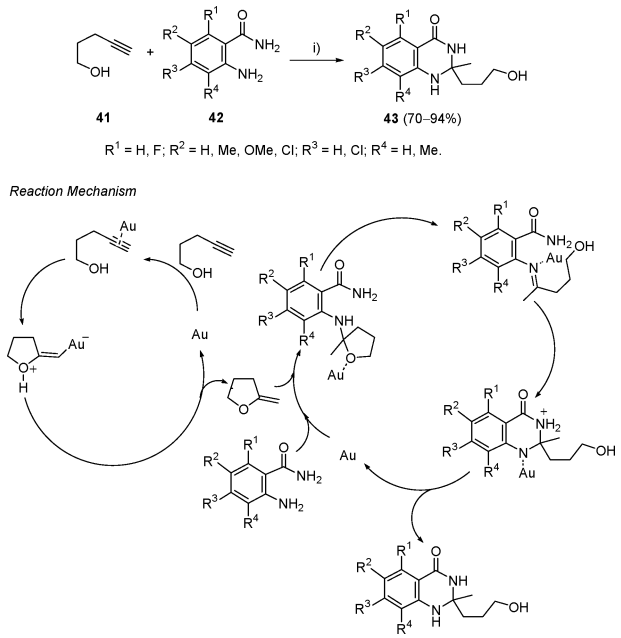
the corresponding *exo*-dig cycloadducts **37** and **40** respectively (Scheme 12). Thus, gold catalysis provides an easy route for tetrahydrofuran- and pyran-based β-lactams, structures of interest but with relatively few methods of obtention.[34]



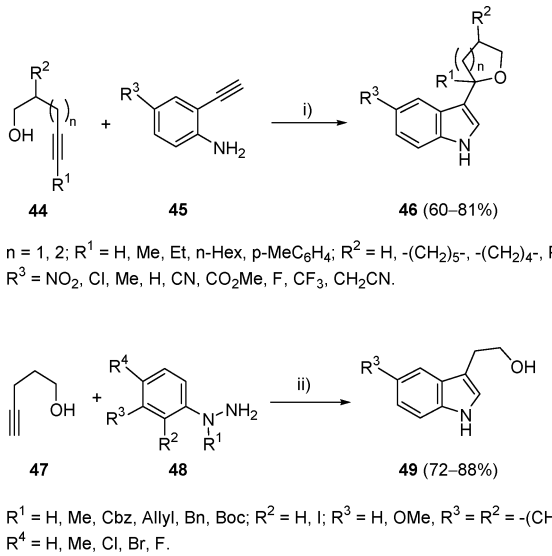
Scheme 12 Tandem Au-catalyzed cycloisomerization/hydroxylation *vs.* Ag-promoted cycloisomerization of β-lactam alkynols. i) AgOAc, Et_3N, acetone, rt, 96 h. ii) $AuCl_3$ (5 mol%), PTSA (10 mol%), DCM, rt, 6 h.

Patil and coworkers have deeply studied the cycloisomerization based tandem reactions of alkynols. Looking through many of their recent works we can find several examples of interest. One of them established the first double hydroamination of alkynes.[35] Starting from 2-aminobenzamides **42** and different alkynols, a gold-catalyzed formal Markovnikov process was reported (Scheme 13). $PtBr_4$ was also tested as catalyst for this procedure, providing similar results as the ones for gold.

Two related examples of cascade gold-mediated cycloisomerizations have been reported.[36] In both of them the extremely high activity of gold complexes is used to catalyze the methylene tetrahydrofuran formation from alkynols **44** and **47**, the indole synthesis from 2-propargylanilines **45** or phenylhydrazines **48**, and even the coupling reaction between both species in the first case. Thus, an interesting family of substituted indoles **46** and **49** was easily accessible through a one pot gold-mediated procedure. Moreover, several catalysts were tested, and the best results were found for the pair $Ph_3PAuCl/AgOTf$ (Scheme 14).

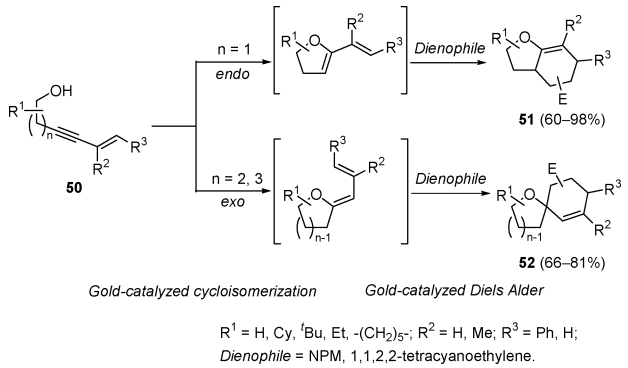


Scheme 13 Double hydroamination of alkynols catalyzed by gold and reaction mechanism. i) Alkynol : 2-aminobenzamide (1 : 1), $Au(PPh_3)Cl$ (5 mol%), MeOH, 80 °C, 12–30 h.



Scheme 14 One pot synthesis of substituted indoles. i) Propargylaniline/alkynol (1 : 1.1), $Ph_3PAuCl/AgOTf$ (5 mol%), DCE, 60 °C, 12–18 h. ii) Phenylhydrazine/alkynol (1 : 1.2), $Ph_3PAuNTf_2$ (2 mol%), pTSA (1 eq), toluene, 100 °C, 2 h.

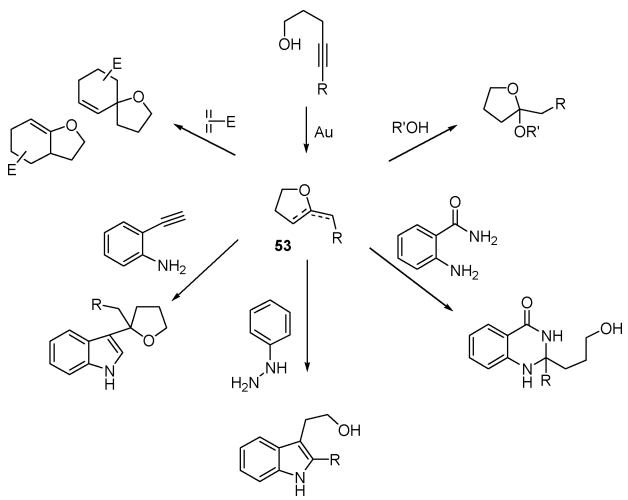
Barluenga *et al.* have employed the gold-catalyzed oxycyclization in enynols, to develop a cascade cycloisomerization/Diels–Alder reaction.[37] Starting from different enynols **50**, an interesting selectivity was observed. When homopropargylic alcohols were employed, the first step went specifically through an *endo*-cycloisomerization pathway, finally yielding fused heterocyclic systems **51**. On the other hand, when the alcohol chain was enlarged, the process went through an *exo*-cycloisomerization pathway, consequently yielding spiro systems **52** as the only final products (Scheme 15). A double use of the gold catalyst was encountered, in as much as the Diels–Alder step was observed



Scheme 15 Cascade cycloisomerization/Diels–Alder of enynols. Reaction conditions: $AuCl_3$ (3 mol%), DCM, rt for n = 1 or DCE, reflux for n = 2, 3.

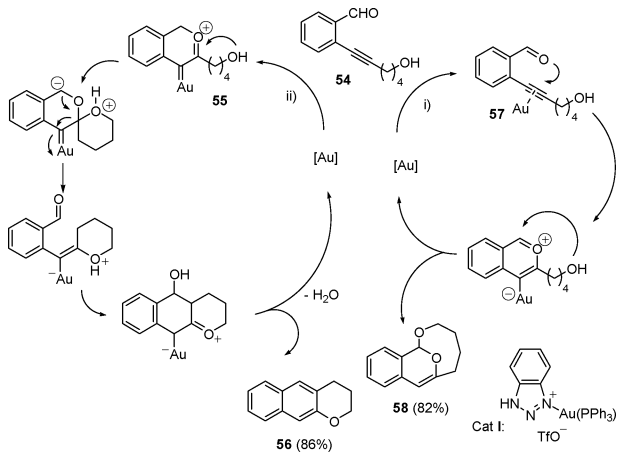
to occur much more slowly and only at higher temperatures in the absence of the metal salt. Moreover, among many other catalysts reported in this work, such as Pt or Ir species, $AuCl_3$ provided the best conversion, and the easiest handling.

According to the results summarized above, there is therefore a promising rising number of applications starting from methylene tetrahydrofuran **53** as a formal building block. Thus, as is shown in Scheme 16, tetrahydrofuranyl ethers, substituted indoles, different fused- and spiro-oxacyclic systems and hydroaminated alkynes could be achieved from quite simple alkynols, in a single step.



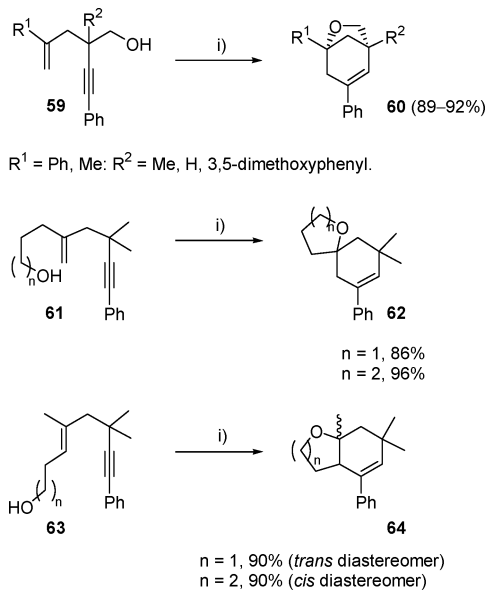
Scheme 16 Methylene tetrahydrofuran as building block in gold-catalyzed reactions of alkynols.

Different cascade processes, which do not involve the most common methylene tetrahydrofuran intermediates, have also been reported. In one of them, Hammond and coworkers recently proved the versatility of gold catalysis in promoting unexpected reactions.[38] They found that the use of two different gold salts interestingly changed the course of 2-(ynol)aryl aldehyde **54** oxycyclization reactions. Thus, $AuCl_3$ favored the formation of the carbene intermediate **55** which yielded benzochromane **56**, while the use of a gold-triazole catalyst allowed the synthesis of benzobicycloacetal **58**, through a gold-alkyne π-complex **57**. Both structures were obtained with high yields, setting a facile synthetic route to complex heterocyclic systems (Scheme 17).



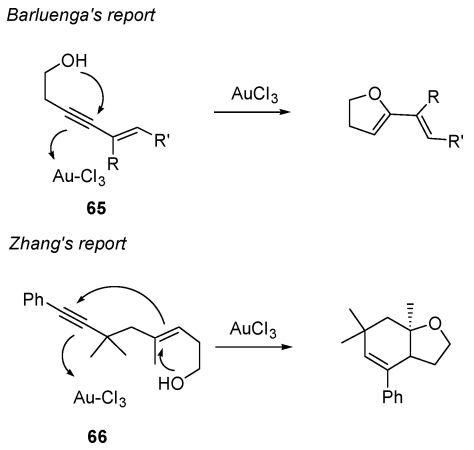
Scheme 17 Gold catalyzed cascade annulations of 2-(ynol)aryl aldehydes. i) Cat **I** (5 mol%), DCM, rt, 12 h. ii) $AuCl_3$ (5 mol%), DCM, rt, 12 h.

A different cascade process has been reported, starting in this case from enynols, and yielding different types of heterobicycles, as bridged, spiro or fused compounds, **60**, **62** or **64**, respectively.[39] A detailed study of different catalysts, mechanistic considerations, and several starting substrates was carried out (Scheme 18).



Scheme 18 Gold catalyzed formation of heterobicyclic systems. i) $AuCl_3$ or $[Au(PPh_3)]ClO_4$ (5 mol%), DCM or MeCN, rt, 1 h.

Compared to Barluenga's previously described work (Scheme 15), we can show how a slight difference in the enynol structure changes dramatically the course of the reaction. Using the same reaction conditions (3–5 mol% of $AuCl_3$, DCM), the nucleophilic hydroxy group starts the process by attacking the alkene or the gold-activated alkyne, depending on the structural conformation of the starting materials **65** and **66**. Thus, both studies represent a proof of alkynol versatility and open a door to learn more of its unexpected behaviour (Scheme 19).

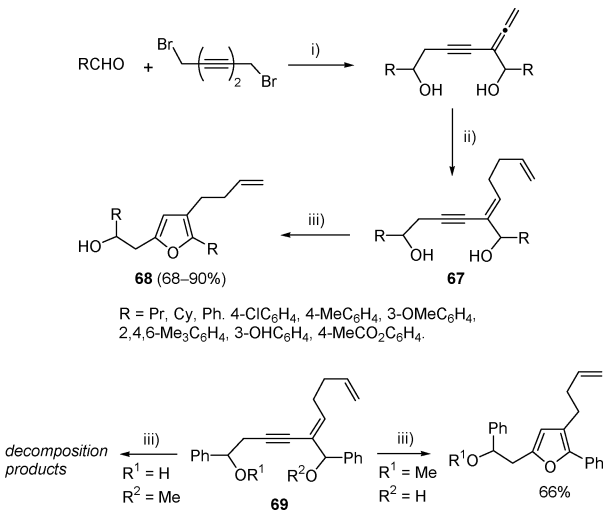


Scheme 19 Enynol reactivity divergency under $AuCl_3$ catalyzed cycloisomerization processes.

3. Gold-catalyzed oxycyclization in alkyndiols

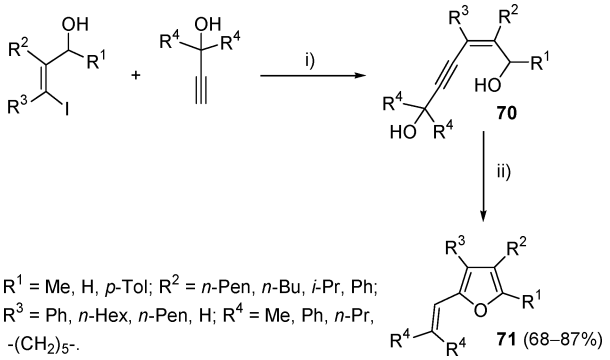
Alkyndiols have also been tested in gold-catalyzed cycloisomerization reactions. Even though their reactivity follows the same pattern as the one observed for alkynols, it is in the final compounds where we find the main interest. This fact has encouraged us to dedicate special attention to some of the recent papers dealing with this item.

Highly substituted furans have been accessible from easily prepared enyne-1,6-diols through a selective gold-catalyzed cyclization of alkyndiols **67**.[40] Many catalysts were tested, finding with Au-based salts and complexes the best results, while other transition metals like Ag failed. The scope of different substituents was also studied, and in every case the authors observed a complete selectivity for the furan structures **68**, resulting from the attack of the activated hydroxy group, while the second one stayed inert. This regioselectivity appears as the main interest of the work. Two additional experiments on *O*-protected substrates **69** demonstrated that cyclization from OH at C6 position is not accessible (Scheme 20).



Scheme 20 Synthesis of furans from enyne-1,6-diols. i) In, LiI, THF, rt. ii) In, allyl bromide, THF, rt. iii) $Ph_3PAuCl/AgOTf$ (5 mol%), DCM, rt, 5–10 min.

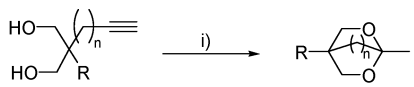
Ma *et al.* recently reported another example using enyne-1,6-diols to afford substituted furans.[41] In this case, the elimination of H_2O from the cyclic product became the promoter of the ring aromatization, opposite to previous related works, where the furan ring is created by double bond isomerization. Many substituents were tested, and among several catalysts, gold ones appeared as the most convenient. While different palladium complexes or silver salts afforded furan structures **71** with only 15% yield in the best cases, PPh_3AuCl provided more than 80% conversion employing much more milder reaction conditions (Scheme 21).



Scheme 21 Synthesis of furans from enyne-1,6-diols. i) Alkene/alkyne (1 : 2), CuI (2 mol%), $Pd(PPh_3)_2Cl_2$ (3 mol%), DMSO, Et_3N. ii) $Au(PPh_3)Cl/AgOTf$ (2 mol%), DCM, rt, 2 h.

More interestingly, some reports have appeared describing the simultaneous nucleophilic attack of both hydroxylic groups to gold-activated alkynes. Thus, starting from alkyndiols, an easy route to complex structures such as bicyclic ketals, spiroketals or even cage-like structures was accessible.

Genêt *et al.* pioneered a bicyclic ketal synthesis through gold catalyzed alkyndiol cycloisomerization.[42] An interesting family of strained ketals **73**, present in many natural structures,[43] was therefore accessible by using both AuCl and $AuCl_3$ in excellent yields. Moreover, the process was compatible with different functional groups, and no trace of methanol addition was observed when the reaction took place in this solvent (Scheme 22).

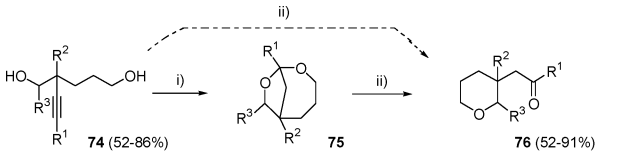


R = Bn, Ph, *n*-Bu, cinnamyl, allyl, cyclohex-2-enyl, 3-methylbut-2-enyl; n = 1, 2.

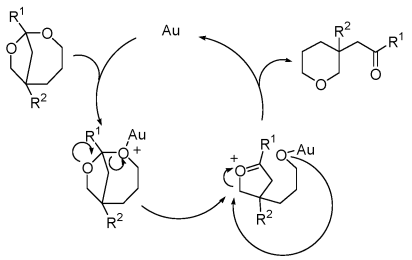
Scheme 22 Synthesis of strained bicyclic ketals. i) AuCl or $AuCl_3$, (2 mol%), MeOH, rt, 30–50 min.

Starting from alkyne-1,5-diols **74**, it was found that together with the expected ketals **75**, traces of substituted tetrahydropyran systems **76** came out,[44] especially when the reaction time was prolonged, or the catalyst loading increased. After going through numerous reaction conditions, the process was optimized, with the finding that gold salts promoted both transformations, while another metal catalysts or Brønsted acids failed (Scheme 23).

An unusual gold complex was found that increased the selectivity on oxycyclization of unactivated internal alkynes. After an exhaustive screening of catalysts, it was observed

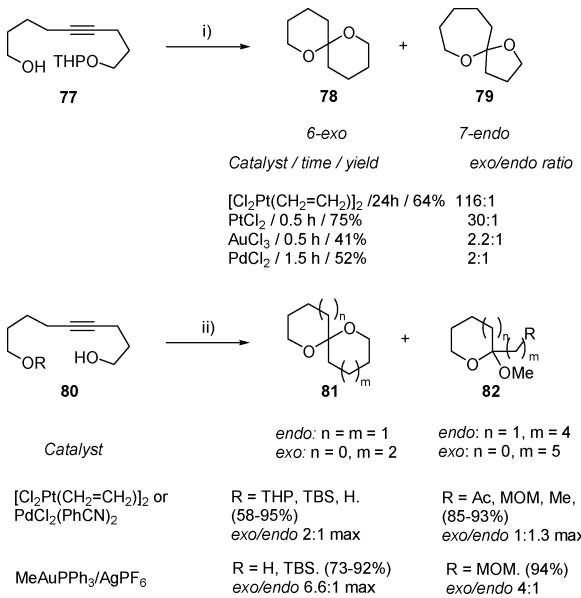


Reaction mechanism for the ketal-tetrahydropyran interconversion



Scheme 23 Synthesis of bicyclic ketals and tetrahydropyrans from alkyne-1,5-diols. i) AuCl (2 mol%), DCM, rt, 2–10 min. ii) AuCl (6 mol%), DCM (5 mL $mmol^{-1}$), rt, 6–24 h.

that $[Cl_2Pt(CH_2{=}CH_2)]_2$ or $PtCl_2$ improved the 6-*exo*/7-*endo* selectivity up to 116 : 1 on system **77**.[45] Nevertheless, when the 5-*exo*/6-*endo* selectivity was studied on 4-alkynols **80**, results were more disappointing. Only when the reaction took place under $MeAuPPh_3/AgPF_6$ as catalyst the selectivity for the *exo* structure rose to 6.6 : 1. On the other hand, depending on the *O*-protecting group in use, ketal systems **82** were also obtained (Scheme 24).

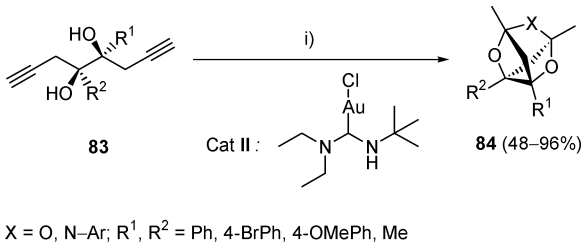


Scheme 24 Ketal synthesis using gold catalyzed oxycyclization of alkyne-diols. i) cat (1–5 mol%), Et_2O, rt, 0.5–1 h. ii) cat (1–5 mol%), Et_2O, PPTS, $HC(OMe)_3$, rt, 3–13 h.

A new mode of reactivity of propargyl alcohols has been reported that enables a facile preparation of substituted 5- and 6-membered ring spiroketals from propargylic triols by action of the cationic gold(I) complex generated from Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl and AgOTf. The reactions are rapid and generally

high yielding, providing a concise synthesis of useful building blocks in short order.[46]

Starting from bis(homopropargylic) diols **83**, interesting tricyclic cage-like systems **84** were obtained.[47] For that purpose, different diyne-diols composed of two terminal homopropargylic alcohol groups were tested, in the presence of an external nucleophile such as water or aromatic amines. Gold and platinum catalysts were employed, yielding the desired structures in reasonable yields. Thus, a multistep process consisting on a selective hydroalkoxylation and hydration or hydroamination allowed the formation of eight new bonds in one single reaction step (Scheme 25).



X = O, N–Ar; R^1, R^2 = Ph, 4-BrPh, 4-OMePh, Me

Scheme 25 Cage-like structure synthesis from diyne-diols. i) Cat. **II** (2 mol%), $AgNTf_2$ (2 mol%), DCM sat. with H_2O, rt, 16 h for X = O; CH_3CN, $ArNH_2$ (3 eq.), rt, 16 h–6 d for X = N–Ar.

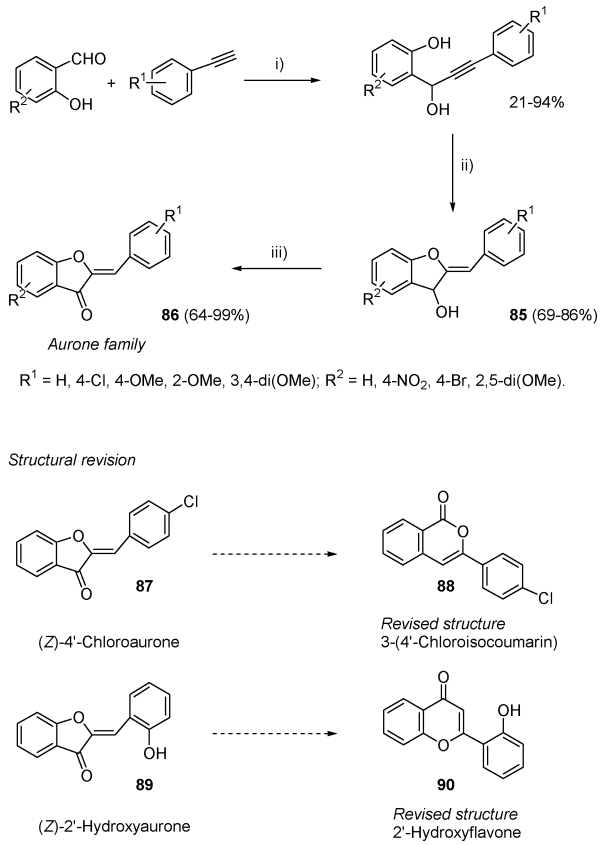
The intramolecular cyclizations of 3-alkyne-1,2-diols and 1-amino-3-alkyn-2-ols with a low catalyst loading (0.05–0.5 mol%) of the combination of $(Ph_3P)AuCl$ with either $AgNTf_2$ or AgOTf proceeded at room temperature to provide a variety of substituted furans and pyrroles in excellent yields (85–98% yields),[48] involving coordination of the acetylene bond to a cationic Au species, 5-*endo* cyclization of the homopropargylic hydroxyl or amino group, and dehydration.

A method for the construction of the bisbenzannelated 5,6-spiroketal core of rubromycins starting from alkyndiphenols has been developed, which allows for the synthesis of various substituted 5,6-aromatic spiroketal skeletons under the catalysis of gold reagents.[49]

4. Gold-catalyzed oxycyclization in total synthesis

The extremely high versatility of gold catalyzed oxycyclization of alkynols was proved by its use in total synthesis. For this reason, it appears interesting to us to collect some examples where the gold-catalyzed rearrangement appears as one of the key steps of the synthetic route.

The synthesis of aurone skeletons, natural flavonoids,[50] by an easy three step sequence has recently been reported. Aurones exhibit many interesting biological activities,[51] and its importance had led to several groups to develop convenient synthetic routes.[52] Among them, gold-catalyzed oxycyclization provided the best results, as milder reaction conditions and excellent selectivities, avoiding the formation of flavones as byproducts, were achieved (Scheme 26).[53] Moreover, the present methodology was used for the structural revision of two natural products, such as (*Z*)-4′-chloroaurone **87**,[54] and (*Z*)-2′-hydroxyaurone **89**,[55] proving that the assumed structure was not the correct one. Thus, flavonoid systems **87** and **89** could be prepared by the above three step strategy, finding that their spectral data did not match with



Scheme 26 Aurone synthesis and structural revision. i) *n*-BuLi (1 eq), THF, −78 °C to −40 °C, 4 h. ii) AuCl (10 mol%), K_2CO_3 (10 mol%), MeCN, rt, 30 h. iii) MnO_2 (10 eq), DCM, rt, 1 h.

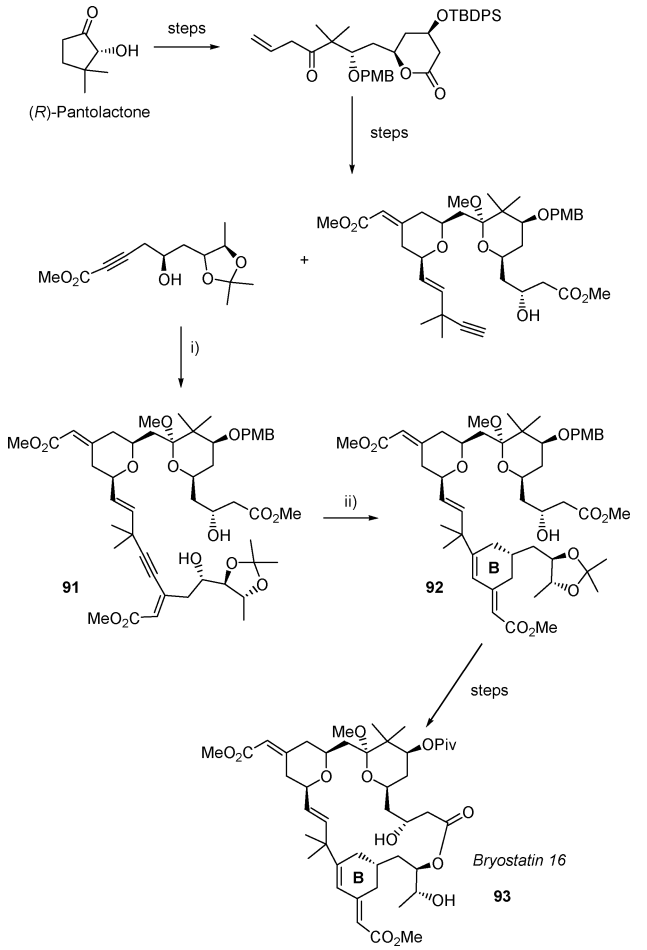
the natural isolated ones, previously reported. Therefore, the isocumarine **88** and the flavone **90** were prepared as the real structures for these natural products (Scheme 26).

Trost *et al.* recently completed the total synthesis of bryostatin 16,[56,57] a structurally complex macrolide which exhibits a wide range of biological activities.[58] Along the proposed 26 step sequence (in the longest linear sequence, and 39 steps as the total), the gold-catalyzed 6-*endo*-dig oxycyclization of alkynol **91** to generate the inner dihydropyran cycle **B** in macrocyclic precursor **92** in 65% yield deserves special mention (Scheme 27).

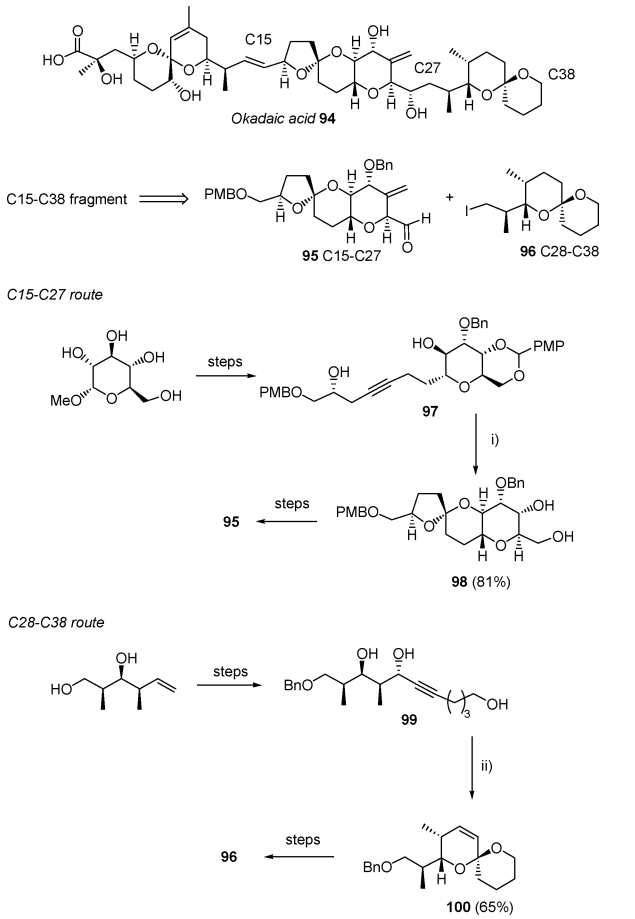
Okadaic acid **94** is a complex natural structure isolated from marine sponges.[59] Its biological activities,[60] together with its attractive chemical structure have focused much interest among organic chemists. In particular, the presence of several spiroketal motifs in this structure makes it a real challenge from the retrosynthetic point of view. Forsyth and coworkers have reported an efficient synthesis of the C15–C38 fragment, based on the high activity and selectivity of AuCl for the synthesis of spiroketals **98** and **100**, starting from alkynediols **97** and **99** respectively.[61] (Scheme 28).

A simple, efficient, and enantiocontrolled synthesis of a near-structural mimic of platensimycin has been accomplished.[62] This route uses the $AuCl_3$-catalyzed acetalization of a diol, affording the tricyclic core of the natural product in 85% yield and >98% ee after one crystallization from EtOAc–hexanes.

A synthesis of the trioxadispiroketal-containing A–D rings of the natural product azaspiracid has been developed. It features two



Scheme 27 Total synthesis of bryostatin 16. i) $Pd(OAc)_2$ (10 mol%), TDMPP (10 mol%), benzene, rt. ii) $AuCl(PPh_3)$ (10 mol%), $AgSbF_6$ (10 mol%), DCM/MeCN (4 : 1), $NaHCO_3$, 0 °C to rt.



Scheme 28 Synthesis of the C15–C38 fragment of okadaic acid. i) AuCl (19 mol%), rt, DCM, then $TsOH{\cdot}H_2O$, MeOH. ii) AuCl (10 mol%), 4 Å MS, THF, 0 °C.

different catalytic intramolecular oxametalations to assemble the A–D polyether from acyclic precursors. First, a cobalt-catalyzed oxaetherification was used to form the 2,5-*trans*-fused trisubstituted tetrahydrofuran D ring. Thereafter, a gold(I)-catalyzed bis-spiroketal formation was accomplished using a bridging alkyne as a surrogate for the C10 ketal. This method provided the thermodynamically favored establishment of both of the newly formed spiroketal centers.[63]

5. Conclusions

In this overview we have collected the most recent advances in gold-catalyzed oxycyclization of alkynols and alkyndiols. This type of reactivity has been shown as an established methodology to access to a large number of oxacyclic structures containing different sized skeletons. Furan, pyrans, and different ketals and spiroketal systems are therefore accessible through this strategy. The reactions discussed herein demonstrate the high synthetic potential of alkynols and alkyndiols undergoing gold catalyzed cyclization. The extremely high reactivity of gold salts and gold complexes has also been documented in this work, allowing mild reaction conditions and great functional group compatibility, especially compared to related thermal or basic rearrangements. In addition, the unexpected behaviour of this metal-based catalysis promoting new processes will certainly provide more promising results and new routes for organic chemists. Thus, it is believed that the continued and renewed investigation on oxycyclization reactions of alkynols and alkyndiols will discover new patterns of reactivity, enabling new synthetic strategies.

Acknowledgements

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