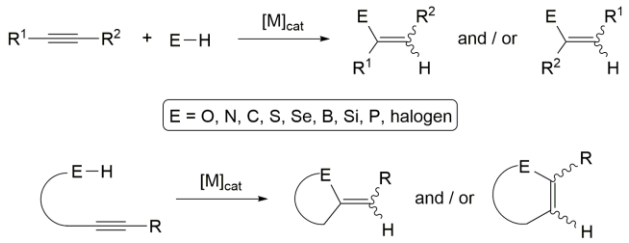
Metal-Catalyzed Hydrofunctionalization Reactions of Haloalkynes

Victorio Cadierno*[a]

Abstract: Metal-catalyzed hydrofunctionalization reactions of alkynes, *i.e.* the addition of E-H units (E = heteroatom or carbon) across the C≡C bond, are of key importance in the modern synthetic chemistry. In recent years, haloalkynes have been successfully involved in these type of transformations, thus opening new atom-economical routes for the generation, among others, of haloalkenes, a pivotal class of compounds for cross-coupling processes. In particular, several catalytic systems able to promote the selective addition of C-H, O-H, N-H, S-H and X-H (X = halide) bonds to haloalkynes have been reported. This chemistry is comprehensively discussed in this Minireview article.

1. Introduction

The alkyne motif is one of the most important and useful building blocks in synthetic organic chemistry. In this regard, the metal-catalyzed hydrofunctionalization of alkynes, *i.e.* the addition of E-H units (E = heteroatom or carbon) across the C≡C bond (see Scheme 1), provides convenient routes for the preparation of a wide array of products with complete atom economy.[1,2] An extensive body of work in the field has been developed in the last decades, consequence of which a large number of efficient catalytic systems able to promote the addition of different heteroelement-hydrogen bonds (O-H, N-H, S-H, Se-H, B-H, Si-H, P-H and halogen-H), as well as C-H bonds, to both terminal and internal alkynes are now available, featuring some of them an exquisite control on the regio-, chemo- and stereoselectivity of the process.[1,2] Furthermore, in its intramolecular version, the catalytic hydrofunctionalization of alkynes represents nowadays one of the best and straightforward ways to obtain heterocyclic and carbocyclic compounds.[1,2]



Scheme 1. Inter- and intramolecular catalytic hydrofunctionalization of alkynes.

Haloalkynes RC≡CX (X = Cl, Br, I), easily accessible through the deprotonation of the corresponding terminal alkynes followed by trapping with a halogenating reagent, are an interesting class of molecules due to their dual functionality, *i.e.* the triple bond and the sp bonded halide. However, their synthetic utility have been for long time mainly restricted to the construction of new carbon-carbon and carbon-heteroatom bonds by coupling of the reactive carbon-halogen motif with appropriate reagents (alkynylation processes).[3] In recent years, the application of metal catalysts has drastically changed this scenario, and several catalytic transformations involving the π-system of these molecules have been developed through the intermediacy of metallic species of type **I**, **II** or **III** (Figure 1).[4]

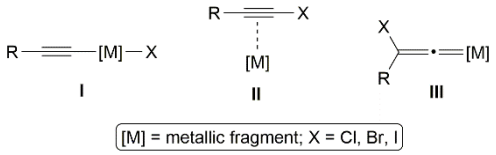


Figure 1. Metallic intermediates commonly proposed in the catalytic transformations of haloalkynes.

In this context, remarkable efforts have been devoted to the development of catalytic systems for the hydrofunctionalization of haloalkynes since this type of reactions would allow a rapid access to haloalkene derivatives, a pivotal class of compounds in

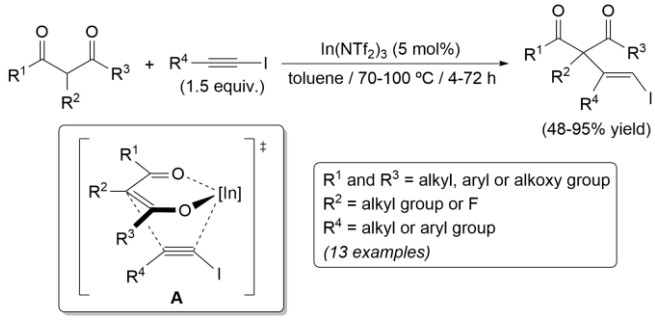
Victorio Cadierno studied chemistry at the University of Oviedo (Spain) and obtained his Ph.D. degree in 1996 from the same institution, working under the supervision of Prof. José Gimeno in the field of metallacumulenes chemistry. He then joined the group of Dr. Jean Pierre Majoral at the LCC-CNRS in Toulouse (France) for a two-year postdoctoral stay, where he worked on the application of group IV organometallics as tools in organophosphorus chemistry. Thereafter he returned to the University of Oviedo, where he is currently Associate Professor of Inorganic Chemistry. In 2002 he was awarded with the Spanish Royal Society of Chemistry (RSEQ) Young Investigator Award, and in 2015 he received the Prize for Excellence in Organometallic Chemistry Research from the Organometallic Chemistry Division (GEQO group) of the RSEQ. His research interests cover the chemistry of organometallic complexes and their catalytic applications, being co-author of around 200 scientific publications.

[a] Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Centro de Innovación en Química Avanzada (ORFEO-CINQA), Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain
E-mail: vcm@uniovi.es
Homepage: http://www.unioviedo.es/comorca

modern chemistry given their increasing use in cross-coupling processes. The aim of the present Minireview article is to provide a comprehensive overview of the developments achieved in this particular research area.

2. C-H bond addition reactions

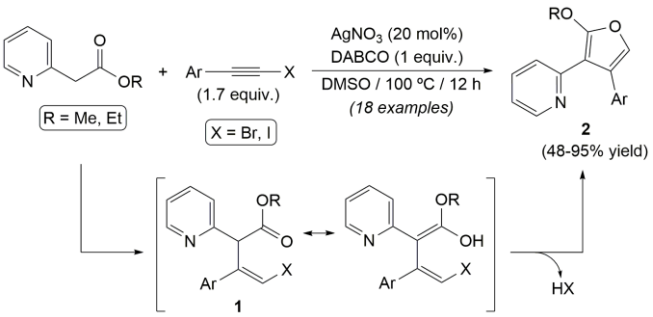
Transition-metal-catalyzed hydrocarbofunctionalization reactions, *i.e.* the addition of C-H bonds to unsaturated molecules, have emerged in recent years as particularly efficient and powerful tools to create new carbon-carbon bonds.[5] However, in spite of its great synthetic potential, the participation of haloalkynes in this type of processes has been scarcely documented to date. In fact, only three works describing the intermolecular addition of C-H bonds to haloalkynes can be currently found in the literature. The first one was reported by Nakamura and co-workers in 2008, who developed a highly stereoselective protocol for the *syn*-addition of 1,3-dicarbonyl compounds to iodoalkynes employing $In(NTf_2)_3$ (NTf_2 = bis(trifluoromethane)sulfonamide) as catalyst (Scheme 2).[6] The cyclic transition state **A** was proposed by the authors to explain the regiochemistry and *E* configuration of the alkene products.



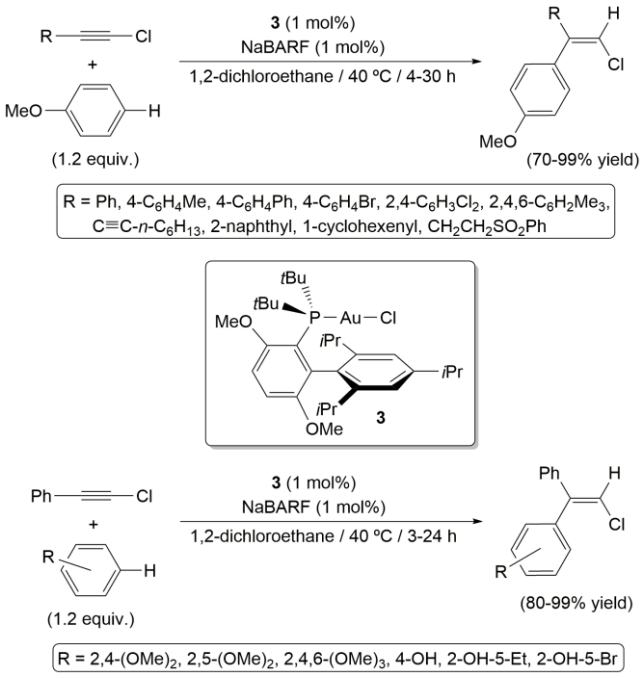
Scheme 2. Catalytic hydroalkylation of iodoalkynes with 1,3-dicarbonyls.

The group of Jiang described the synthesis of a variety of 2,3,4-trisubstituted furans **2** through the intermolecular coupling of methyl or ethyl 2-pyridylacetate with aromatic bromo- and iodoalkynes (Scheme 3).[7] The reactions, promoted by $AgNO_3$ in the presence DABCO (1,4-diazabicyclo[2.2.2]octane), involve an initial Ag-catalyzed hydroalkylation of the haloalkyne to generate the corresponding haloalkene intermediate **1**, which undergoes a base-promoted cyclization.

Very recently, highly efficient intermolecular hydroarylation reactions of chloroalkynes with electron rich arenes were described, making use of a catalytic system composed of the gold(I)-phosphine complex [AuCl(*t*BuBrettPhos)] (**3**) and the chloride abstractor NaBARF (sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)borate).[8] Selected examples are shown in Scheme 4. The resulting (*Z*)-styryl chloride products were obtained in a complete regio- and stereoselective manner, as the result of the *anti* addition of the C-H bond of the arenes to the C≡C bond of the alkyne, which is activated by π-coordination to the cationic gold(I) fragment [Au(*t*BuBrettPhos)]$^+$.



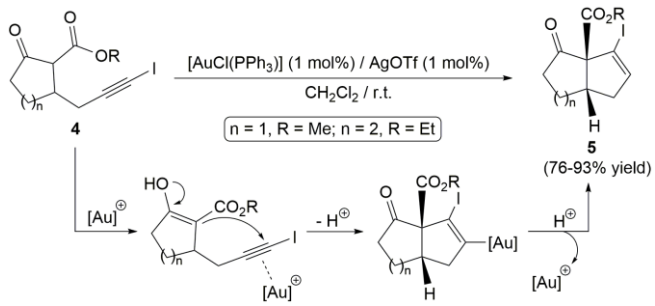
Scheme 3. Synthesis of 2,3,4-trisubstituted furans from haloalkynes.



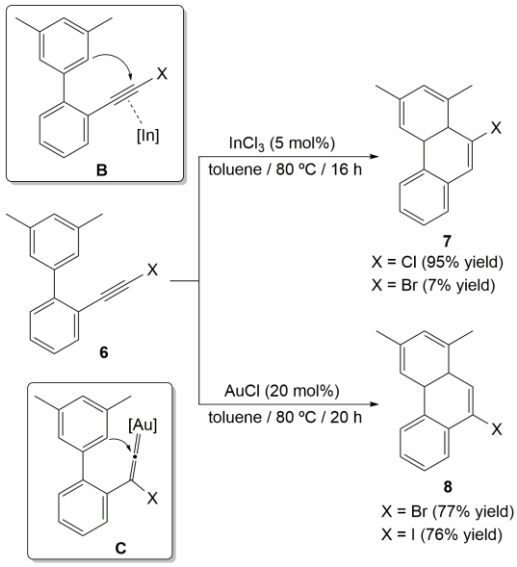
Scheme 4. Gold-catalyzed intermolecular hydroarylations of chloroalkynes.

Intramolecular C-H bond additions across the C≡C bond of haloalkynes are also known. In particular, Toste and co-workers reported in 2004 the diastereoselective preparation of the bicyclic compounds **5** through a gold(I)-catalyzed 5-*endo*-dig carbocyclization of the iodoalkynes **4** (Scheme 5).[9] Almost at the same time, the group of Fürstner studied cycloisomerization reactions of biphenyl derivatives containing an haloalkyne unit at one of their *ortho*-positions. As illustrated with compounds **6**, depending on the metal catalyst employed, two different products were selectively obtained (Scheme 6).[10] Thus, with $InCl_3$, the 10-halophenanthrenes **7** were isolated as the result of a 6-*endo*-dig cyclization, in which the addition of the aromatic C(sp^2)-H bond

takes place on the corresponding π-activated alkyne **B**. Conversely, the use of AuCl as catalyst led to the isomeric 9-halophenanthrenes **8**. According to the authors, the formation of **8** stems from the addition of the C(sp^2)-H bond on a gold-vinylidene intermediate **C**, generated from the corresponding π-alkyne complex by 1,2-halide shift.[11]

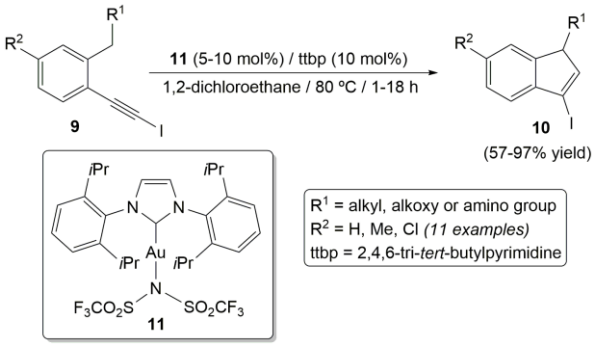


Scheme 5. Gold-catalyzed cyclization of the iodoalkynes **4**.

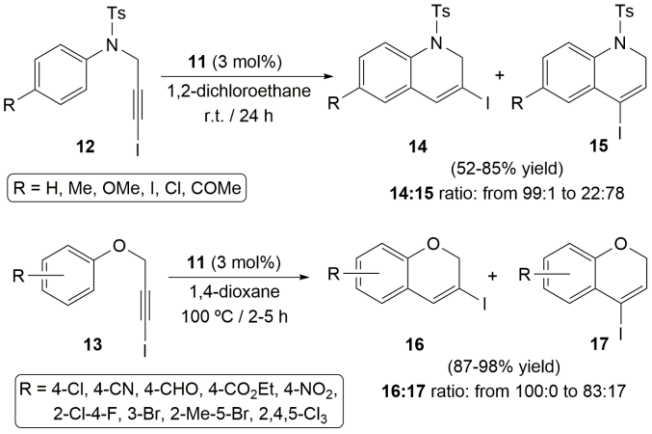


Scheme 6. Cycloisomerization reactions of the biphenyl derivatives **6**.

Related vinylidene intermediates were proposed by González and co-workers to explain the formation of the indene derivatives **10** from the iodoalkynes **9**, a reaction catalyzed by the *N*-heterocyclic carbene-gold(I) complex [Au(NTf_2)(IPr)] (**11**) in combination with the 2,4,6-tri-*tert*-butylpyrimidine base (Scheme 7).[12,13] The same group also described cyclization processes of the functionalized iodoalkynes **12** and **13** catalyzed by [Au(NTf_2)(IPr)] (**11**) (Scheme 8).[14,15] The intramolecular hydroarylation of these compounds proceeded in high yields, delivering isomeric mixtures of the corresponding 1,2-dihydroquinolines **14**/**15** and chromenes **16**/**17**, respectively. While the formation of **14** and **16** seems to involve again the intermediacy of vinylidene-type species, compounds **15** and **17** are the result of the direct 6-*endo*-dig cyclization of the substrates (*via* a classical gold(I)-π-alkyne intermediate).



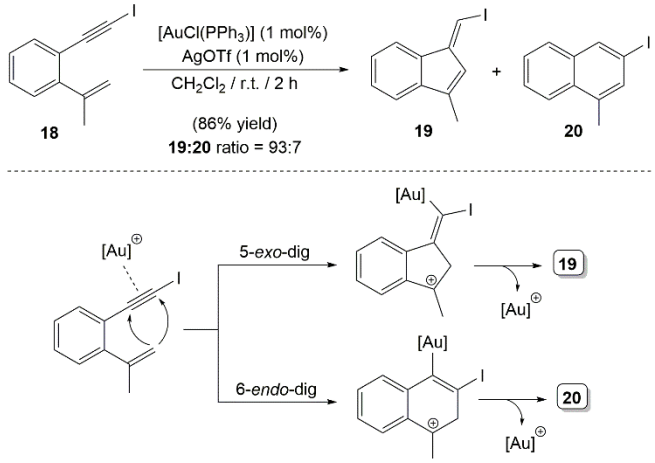
Scheme 7. Access to indene derivatives by cyclization of the iodoalkynes **9**.



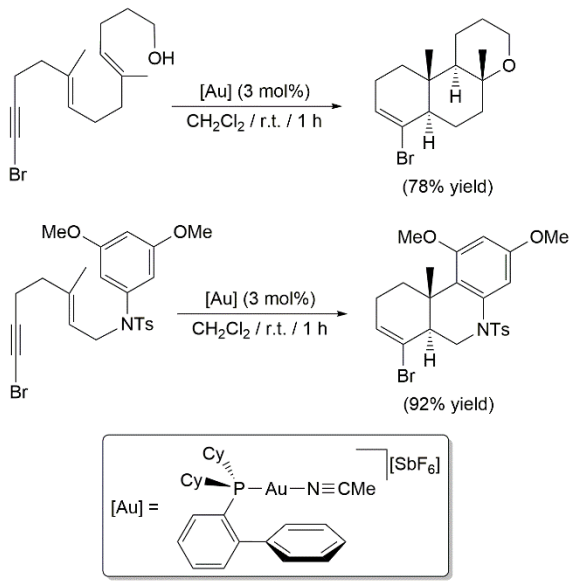
Scheme 8. Cycloisomerization reactions of compounds **12** and **13**.

The cycloisomerization of the iodo-substituted 1,5-enyne **18** by the cationic gold(I) complex $[Au(PPh_3)]^+$, generated *in situ* from [AuCl(PPh_3)] and silver triflate, was described by Shibata and co-workers (Scheme 9).[16] The reaction led to the major formation of the 1-iodomethylene-1*H*-indene **19**, as the result of a 5-*exo*-dig-type cyclization. However, the process was not completely regioselective and minor amounts of the 2-iodonaphthalene derivative **20**, arising from a competing 6-*endo*-dig cyclization, were also obtained. The outcome of this transformation contrast with that observed for related substrates bearing aromatic or aliphatic substituents on their alkyne terminus, where the 6-*endo*-dig cyclization process was largely favoured.

More elaborated 1-bromo-1,5-enyne derivatives were found to undergo gold-catalyzed polycyclization reactions leading to the selective formation of steroid-like molecules under mild conditions.[17] A couple of representative examples are shown in Scheme 10.

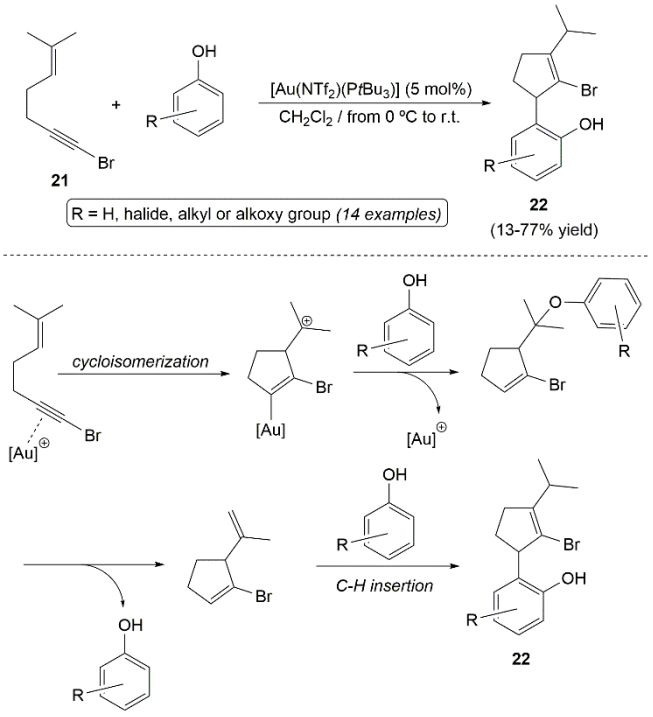


Scheme 9. Gold-catalyzed cycloisomerization of enyne **18**.



Scheme 10. Gold-catalyzed polycyclization of 1-bromo-1,5-enyne derivatives.

In the same context, employing [Au(NTf$_2$)(P*t*Bu$_3$)] as catalyst, several (2-bromocyclopent-2-en-1-yl)phenols **22** could be accessed by coupling the 1-bromo-1,5-enyne derivative **21** with different phenols (Scheme 11).[18] The reaction is initiated by a gold-catalyzed enyne-cycloisomerization process, followed by a phenol addition/elimination sequence, and a final C-H insertion step.



Scheme 11. Catalytic access to (2-bromocyclopent-2-en-1-yl)phenols.

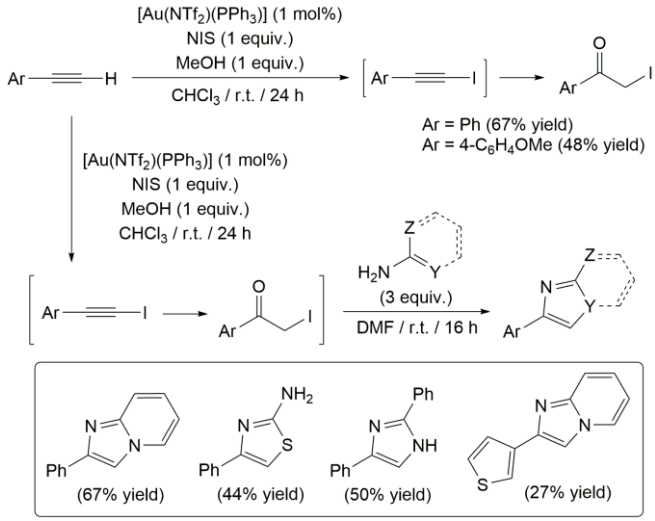
3. O-H bond addition reactions

3.1. Hydration reactions

The catalytic addition of water to alkynes is one of the most straightforward methods currently available for the synthesis of carbonyl compounds, the reactions involving the tautomerization of initially formed enol-type species.[19] In particular, the hydration of haloalkynes provides a simple entry to α-halomethyl ketones, which are valuable and versatile building blocks in synthetic organic chemistry.[20] Although the process can be promoted by simple Brønsted acids,[21] most of the examples that can be found in the literature involve the use of metal-based catalysts. The first one was reported by Sheppard and co-workers in 2012 while studying the electrophilic halogenation of terminal alkynes catalyzed by gold(I) complexes.[22] Thus, they found that the treatment of aromatic alkynes with 1 equiv. of *N*-iodosuccinimide (NIS) and methanol, at r.t. and in the presence of 1 mol% of [Au(NTf$_2$)(PPh$_3$)], leads to the formation of the corresponding α-iodomethyl ketones in moderate yields, *via* hydration of *in situ* formed iodoalkyne intermediates by adventitious water (Scheme 12).[23] In addition, they also demonstrated that the process can be combined, in a *one-pot* manner, with a subsequent annulation reaction to form thiazole, imidazole or azaindoline derivatives with no requirement to purify any intermediate (Scheme 12).

Shortly after this work, Xiang, He and co-workers screened different Au(I) complexes of general composition [Au(NTf$_2$)(L)] (L = phosphine, phosphite or *N*-heterocyclic carbene (NHC)) as catalysts for the hydration of 1-bromo-2-phenylacetylene, obtaining the best results with the bulky ligands shown in Figure

2.[24] In particular, complexes [Au(NTf$_2$)(XPhos)] and [Au(NTf$_2$)(BrettPhos)] showed the highest, and almost identical, reactivities. Employing the former, the scope of the reaction was studied in depth. Thus, as shown in Scheme 13, a large variety of aromatic and aliphatic bromo- and chloroalkynes could be transformed under mild conditions into the corresponding α-halomethyl ketones, in excellent yields, and with a wide functional group tolerance. In contrast, when iodoalkynes were employed as substrates, very poor results were obtained with conversions of up to 20%. The higher steric hindrance of the iodo- *vs* bromo/chloro-alkynes was assumed by the authors to be behind this lower reactivity. Due also to steric constraints, [Au(NTf$_2$)(XPhos)] proved ineffective in the hydration of *ortho*-substituted aromatic bromoalkynes.[25]



Scheme 12. Gold-catalyzed direct conversion of terminal alkynes into α-iodomethyl ketones and five-membered aromatic heterocycles.

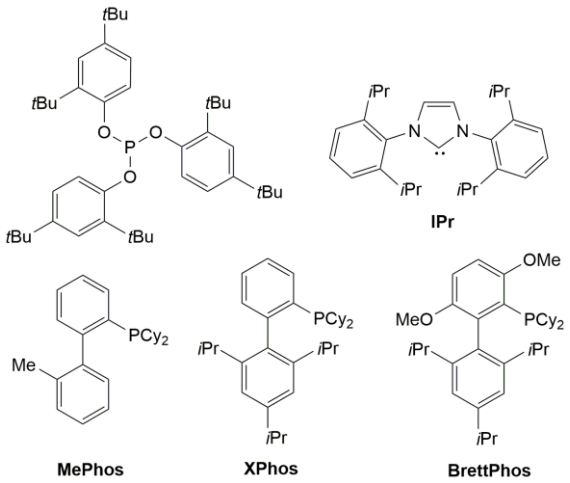
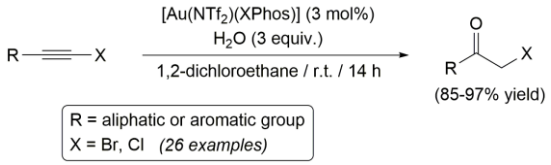
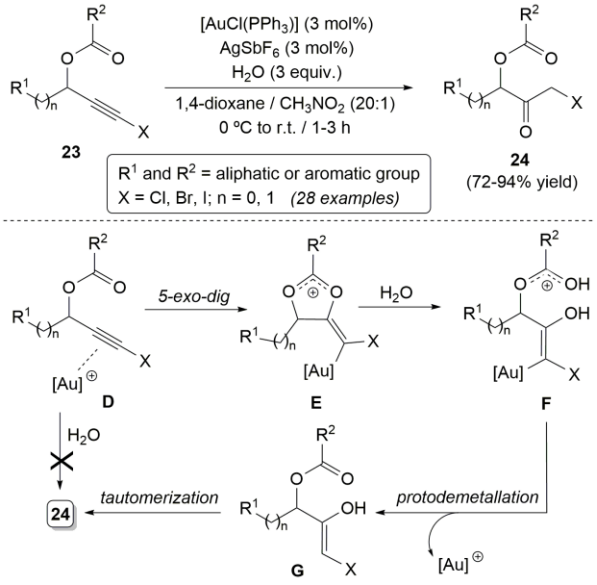


Figure 2. Structure of some ligands employed in gold-catalyzed hydration of haloalkynes.



Scheme 13. Catalytic hydration of haloalkynes by complex [Au(NTf$_2$)(XPhos)].

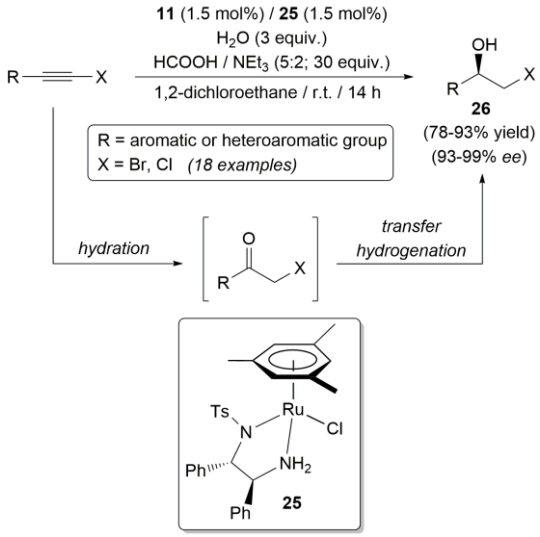
Making use of a catalytic system composed of [AuCl(PPh$_3$)] and the chloride abstractor AgSbF$_6$, Sahoo and co-workers developed an efficient and wide scope protocol for the regioselective hydration of halo-substituted propargyl carboxylates **23** (Scheme 14).[26] The reactions proceeded cleanly at r.t. in a 1,4-dioxane/nitromethane mixture, affording the corresponding α-acyloxy α'-halomethyl ketones **24** in good to excellent yields.[27] As confirmed later with the aid of density functional theory (DFT) calculations, the formation of compounds **23** does not proceed through the direct addition of water to the π-activated alkyne (**D** in Scheme 14), as in the examples presented above.[28] Instead, an *anti* type 5-*exo*-dig cyclization initially takes place leading to the intermediate species **E**, which readily evolve into **F** by hydrolysis. Subsequent protodemetallation of **F** generates the halo-enol **G**, which tautomerizes into the final α-acyloxy α'-halomethyl ketone product.



Scheme 14. Gold-catalyzed hydration of halo-substituted propargyl carboxylates and its mechanism.

On the other hand, by combining the NHC-gold(I) complex [Au(NTf$_2$)(IPr)] (**11** in Scheme 7) with the arene-ruthenium(II) derivative **25**, a variety of chiral aromatic and heteroaromatic halohydrins **26** could be synthesized in high yields, and with enantiomeric excesses in the range 93-97%, through a *one-pot* cascade process involving the initial gold-catalyzed hydration of

the haloakynes and a subsequent ruthenium-catalyzed asymmetric transfer hydrogenation (ATH) of the resulting α-halomethyl ketones (Scheme 15).[29] Both bromo- and chloroalkynes participated in the reaction and several functional groups were tolerated.



Scheme 15. *One-pot* hydration/ATH of haloalkynes.

In addition, this cascade hydration/ATH process could be combined with a further amination reaction of the halohydrin products.[29] In this way, the β-andrenergic receptor blockers (*R*)-difluoroisoproterenol, (*R*)-pronethalol and (*R*)-nifenalol (see Figure 3) were accessible in *one-pot* from the corresponding bromoalkyne and isopropylamine (71-86% yield and 99% *ee* in all the cases).

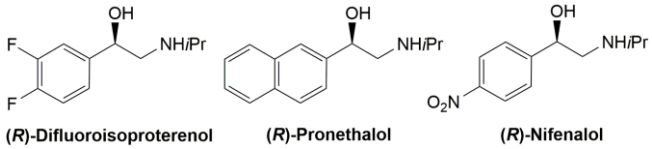


Figure 3. Structure of β-andrenergic receptor blockers.

In a subsequent study, related hydration/ATH reactions of bromo- and chloroalkynes were studied employing a bifunctional heterogeneous catalyst generated by anchoring the cationic NHC-gold(I) complex [Au(IPr)][BF_4], *via* H-bonding of the tetraflouroborate anion to surface silanols, and a chiral ruthenium-diamine derivative, *via* covalent-bonding of the diamine ligand, on the large-pore mesoporous silica FDU-12 (**27** in Figure 4).[30] The activities and enantioselectivities reached with this heterogeneous system were comparable to those observed with the **11**/**25** combination under homogeneous conditions (Scheme 15). In addition, **27** could be easily recovered by a simple filtration at the end of the reactions and reused up to seven consecutive times, without erosion of its activity and enantioselectivity. In this context, it should also be mentioned that the MCM-41-supported phosphine-gold(I) complex **28** (Figure 4) was recently employed as an effective and recyclable catalyst for the hydration of different chloro-, bromo- and iodoalkynes (yields of the α-halomethyl ketone products ≥ 85% after 14 h at r.t. in 1,2-dichloroethane, employing an Au loading of 3 mol%; up to 8 recycling cycles without loss of activity).[31]

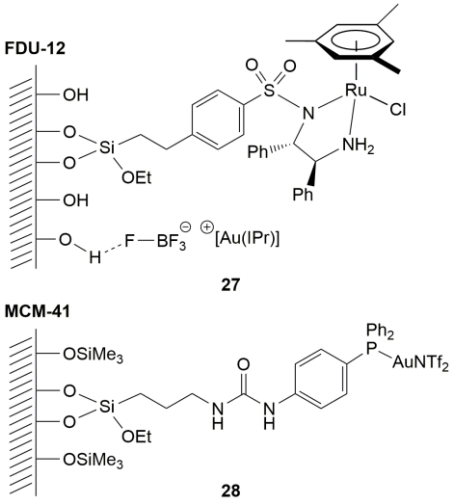
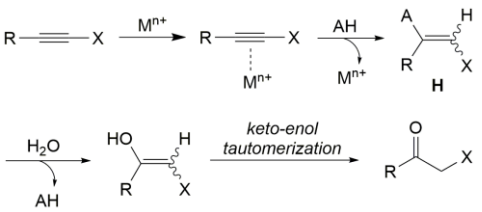


Figure 4. Structure of the silica-supported catalysts **27** and **28**.

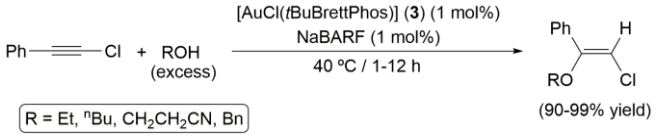
In addition to the gold-based catalysts just discussed, other protocols for the hydration of haloalkynes involving the use of a metallic salt in combination with a Brønsted acid, *i.e.* AgF/TFA,[32] $In(OTf)_3$/AcOH,[33] $FeCl_2 \cdot 4H_2O$/MsOH,[34] $FeCl_3 \cdot 6H_2O$/MsOH,[35] $Cu(OAc)_2$/TFA[36] and $Ce(SO_4)_2/H_2SO_4$,[37] have been described. As a general trend, these systems operate at higher temperatures (40-100 ºC), and require higher metal loadings (5-10 mol%) to generate the α-halomethyl ketone products in good yields. Also of note is the fact that, from a mechanistic point of view, the reactions seem to proceed through the initial addition of the acid (AH) to the metal-activated C≡C bond of the substrates to generate a vinylic intermediate **H** (Scheme 16).[33,34] Further hydrolysis of **H** leads to the ketone product.



Scheme 16. Proposed reaction pathway for the acid-assisted metal-catalyzed hydrations of haloalkynes.

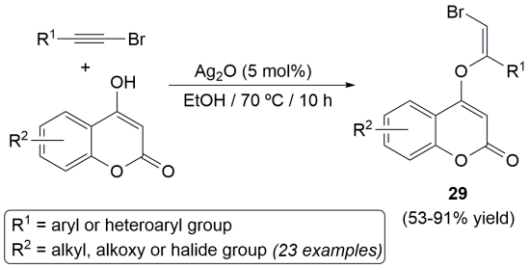
3.2. Hydroalkoxylation reactions

The addition of alcohols to haloalkynes is a reaction that can be promoted by simple bases.[38] However, most of the examples quoted in the literature make use of metal catalysts. In this regard, the catalytic system [AuCl(*t*BuBrettPhos)] (**3**)/NaBARF discussed above (see Scheme 4) proved useful for the intermolecular hydroalkoxylation of (chloroethynyl)benzene with different aliphatic alcohols (Scheme 17).[8] It should be noted at this point that the use of phenol derivatives led, on the contrary, to the exclusive formation of the corresponding hydroarylated products (see Scheme 4).



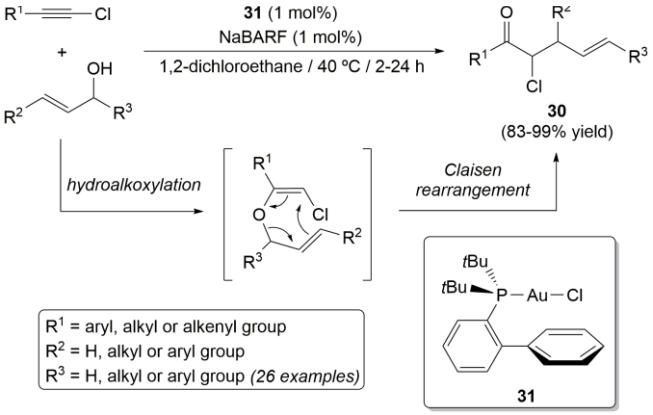
Scheme 17. Gold-catalyzed intermolecular hydroalkoxylation of (chloroethynyl)benzene.

The selective *anti* addition of a series of hydroxycoumarin derivatives to aromatic and heteroaromatic bromoalkynes was also successfully achieved employing silver(I) oxide as catalyst, the reactions leading to the corresponding (*Z*)-β-bromoenol ethers **29** in moderate to excellent yields (Scheme 18).[39] Chloroalkynes also undergo the addition process, but not iodoalkynes for which the silver-promoted cleavage of the C-I bond was exclusively observed.



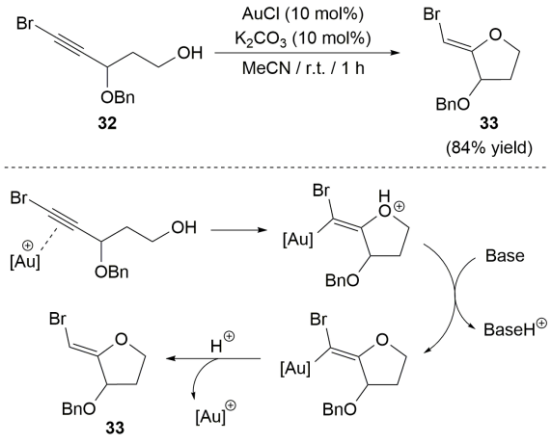
Scheme 18. Silver-catalyzed addition of 4-hydroxycoumarins to bromoalkynes.

Very recently, a highly efficient and broad scope protocol for the synthesis of γ,δ-unsaturated α-chloroketones **30**, through a tandem intermolecular hydroalkoxylation/Claisen rearrangement reaction between chloroalkynes and allylic alcohols, has been described (Scheme 19).[40] The process was found to be catalyzed by different gold(I)-phosphine complexes, among which [AuCl(JohnPhos)] (**31**), in combination with NaBARF, provided the best results.



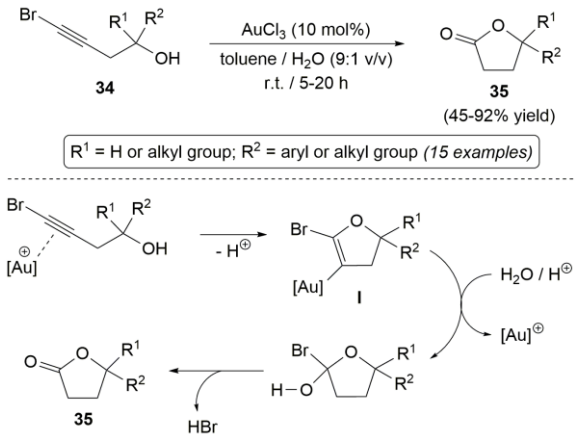
Scheme 19. Tandem hydroalkoxylation/Claisen rearrangement between chloroalkynes and allylic alcohols.

On the other hand, despite the fact that cycloisomerization reactions of acetylenic alcohols have been widely studied for the assembly of oxygen-containing heterocycles during the last decades,[41] examples involving haloalkynes are till now very scarce. In this context, Pale and co-workers reported the selective 5-*exo*-dig cyclization of the 5-bromopent-4-yn-1-ol derivative **32** into the α-alkylidene tetrahydrofuran **33** catalyzed by AuCl under basic conditions (Scheme 20).[42]



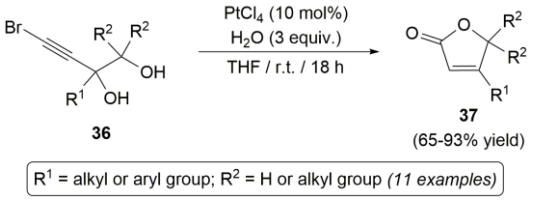
Scheme 20. Gold-catalyzed cycloisomerization of the acetylenic alcohol **32**.

Reddy's group described an efficient protocol for the synthesis of γ-butyrolactones **35** through the $AuCl_3$-catalyzed cyclization of 4-bromo-3-yn-1-ol derivatives **34** in wet toluene (Scheme 21).[43] A reaction pathway involving the initial intramolecular hydroalkoxylation of the bromoalkyne (5-*endo*-dig cyclization), followed by hydrolysis of the metallated intermediate **I** was proposed by the authors. The same transformations were also described employing a catalytic system composed of $Hg(OTf)_2$/AgOTf.[43]



Scheme 21. Au-catalyzed synthesis of γ-butyrolactones from 4-bromo-3-yn-1-ols.

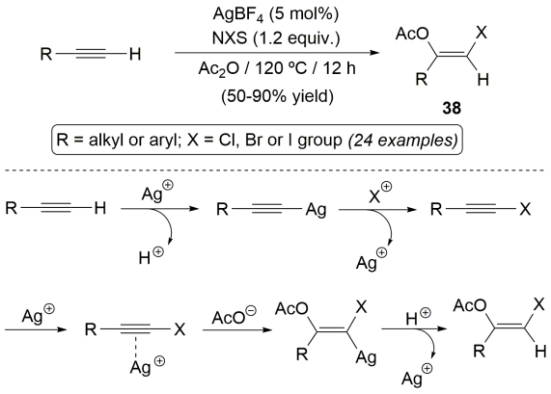
Related α,β-unsaturated γ-butyrolactones **37** could also be accessed in high yields from 4-bromo-3-yn-1,2-diols **36** employing in this case $PtCl_4$ as catalyst (Scheme 22).[44] A reaction pathway similar to that depicted in Scheme 21 was proposed by the authors, with an additional dehydration step of the initially formed 4-hydroxy-γ-butyrolactones.



Scheme 22. Pt-catalyzed synthesis of α,β-unsaturated γ-butyrolactones from 4-bromo-3-yn-1,2-diols.

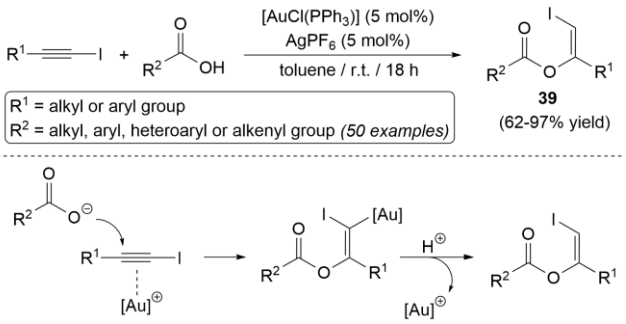
3.3. Hydro-oxycarbonylation reactions

The addition of carboxylic acids to alkynes catalyzed by transition metals provides one of the most efficient and atom-economical methods of preparing enol esters,[45] versatile building blocks in organic chemistry that can be used as intermediates in polymerization,[46] asymmetric hydrogenation,[47] and cross-coupling reactions,[48] to name a few. In 2010, Jiang and co-workers developed an efficient protocol for the synthesis of (*Z*)-β-haloenol acetates **38** through a $AgBF_4$-catalyzed difunctionalization reaction of terminal alkynes, in which *in situ* formed haloalkynes undergo the formal addition of acetic acid (Scheme 23).[49] In the process, which was performed in acetic anhydride at 120 ºC with 5 mol% of $AgBF_4$, the silver(I) cation participates first as a σ-activator allowing the halogenation of the terminal alkyne by the corresponding *N*-halosuccinimide (NXS) reagent, and later as a π-activator facilitating the nucleophilic attack of the acetate anion to the C≡C bond of the resulting haloalkyne. Compounds **38** were obtained in almost all the cases with exquisite regio- and stereoselectivity.



Scheme 23. Silver(I)-catalyzed synthesis of (*Z*)-β-haloenol acetates **38**.

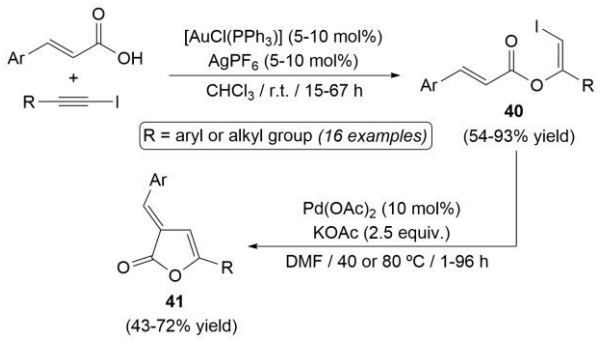
Related (*Z*)-β-iodoenol esters **39** could be accessed in high yields, and in a complete regio- and stereoselective manner, by the direct intermolecular *anti* addition of carboxylic acids to iodoalkynes employing a catalytic system composed of [AuCl(PPh_3)] and the chloride abstractor $AgPF_6$ (Scheme 24).[50] The process featured a wide scope and tolerated the presence of different functional groups in both the iodoalkyne and carboxylic acid partners. On the other hand, as demonstrated with the addition of acetic acid to 1-(chloroethynyl)-4-methylbenzene and 1-bromooct-1-yne, which led to the corresponding (*Z*)-β-haloenol acetates in 73 and 69% yield, respectively, under identical experimental conditions, this gold-catalyzed hydro-oxycarbonylation reaction is not restricted to iodoalkynes.[50b] Also of note is the fact that compounds **39** proved to be useful starting materials for the preparation of a wide variety of stereochemically defined β-aryl-vinyl esters and enynyl esters through Suzuki[50a,c] and Sonogashira[50b] cross-couplings, as well as buta-1,3-diene-1,4-diyl diesters by homocoupling.[50d,e]



Scheme 24. Au(I)-catalyzed intermolecular addition of carboxylic acids to iodoalkynes.

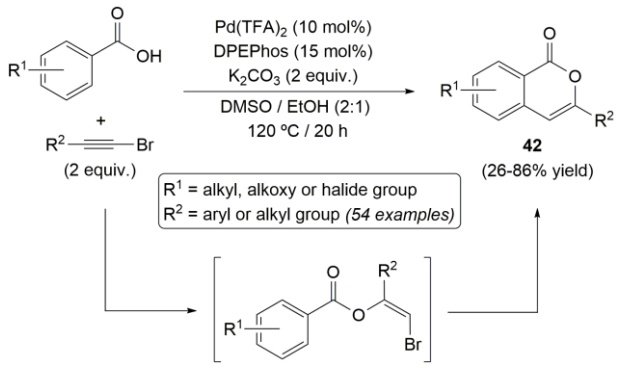
In an independent study, the addition of β-aryl acrylic acids to iodoalkynes catalyzed by [AuCl(PPh_3)]/$AgPF_6$ was combined with

a palladium-catalyzed Mizoroki-Heck reaction on the resulting (*Z*)-β-iodoenol esters **40** (Scheme 25).[51] In this way, a variety of (*E*)-3-(arylidene)-5-substituted-2(3*H*)-furanones **41** could be accessed in moderate yields. With a couple of examples, the authors demonstrated the possibility of carrying out both transformations in a *one-pot* manner, without the need to isolate **40**, by vacuum concentration and solvent replacement after the initial Au-catalyzed reaction.



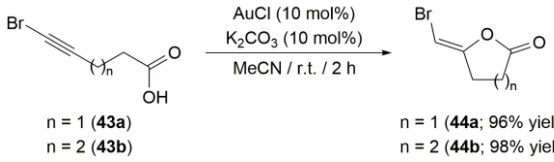
Scheme 25. Access to 2(3*H*)-furanones from iodoalkynes and β-aryl acrylic acids.

The intermolecular addition of benzoic acid derivatives to bromoalkynes was proposed by Jiang and co-workers as the first step in the synthesis of the isocoumarins **42** depicted in Scheme 26, in which the β-bromoenol esters formed readily undergo an oxidative annulation.[52] The catalytic system employed for this transformation, which featured a wide scope, was composed of palladium(II) trifluoroacetate, the diphosphine ligand DPEPhos (bis[2-(diphenylphosphino)phenyl] ether) and K_2CO_3.



Scheme 26. Pd-catalyzed synthesis of isocoumarins from bromoalkynes and benzoic acid derivatives.

Intramolecular examples of hydro-oxycarbonylation reactions of haloalkynes are also known. Thus, Pale and co-workers described the selective *exo*-dig cyclization of the bromo-substituted alkynoic acids **43a,b** into the corresponding alkylidene-lactones **44a,b** using AuCl as catalyst under basic conditions (Scheme 27).[53]



Scheme 27. AuCl-catalyzed cycloisomerization of the alkynoic acids **43a,b**.

The selective cycloisomerization of **43b** into **44b** was alternatively achieved, in high yield and under neutral conditions, employing catalytic amounts of the dinuclear NHC-gold(I) complex **45** (0.1 mol% at r.t.)[54] or the pincer-type palladium(II) derivatives **46** and **47** (5 mol% at 90 ºC)[55] (Figure 5). Remarkably, complex **45** was also able to convert 7-bromohept-6-ynoic acid **43c** into the ε-alkylidene-lactone **44c**, a more challenging process that required of heating and of a higher metal loading to proceed satisfactorily (Scheme 28).[54] At this point it should be noted that the use of these gold and palladium catalysts is an appealing alternative to previous protocols described in the literature based on the use of highly toxic mercury salts as promoters.[56]

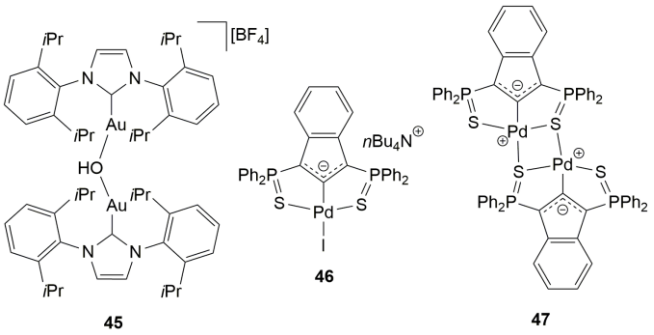
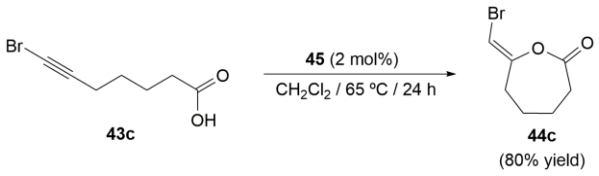
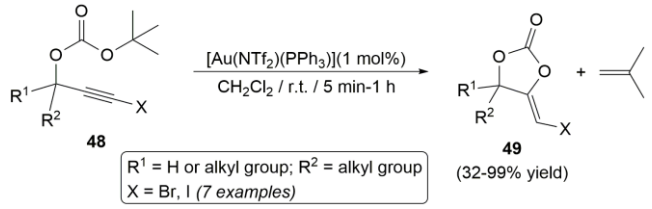


Figure 5. Structure of the gold and palladium complexes **45-47**.



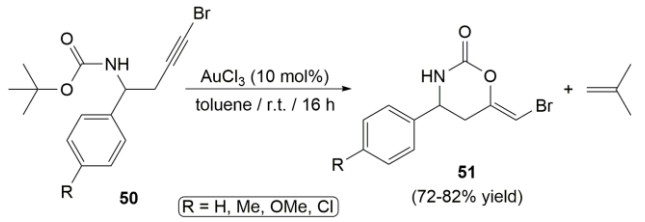
Scheme 28. Catalytic synthesis of the ε-lactone **44c**.

On the other hand, in the context of their studies on the gold-catalyzed rearrangement of propargylic *tert*-butyl carbonates, Gagosz and co-workers reported the preparation of a series of 4-(*Z*-halomethylene)-1,3-dioxolan-2-ones **49** from haloalkynes **48**, *via* formal 5-*exo*-dig cyclization of the deprotected acid (Scheme 29).[57]



Scheme 29. Gold-catalyzed cyclization of the *tert*-butyl carbonates **48**.

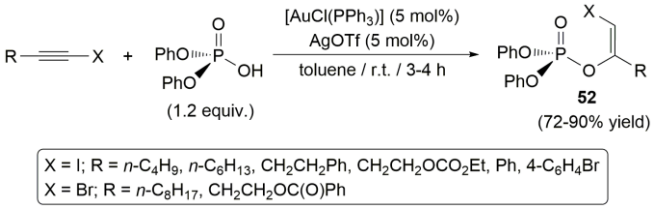
In the same context, oxazinones **51** were also accessible by $AuCl_3$-catalyzed 6-*exo*-dig cyclization of bromoalkynes **50** (Scheme 30).[44]



Scheme 30. Gold-catalyzed synthesis of oxazinones from bromoalkynes.

3.4. Hydrophosphoryloxylation reactions

Only one work dealing with this type of transformations can be currently found in the literature, in which the addition of diphenyl phosphate to different bromo- and iodoalkynes was successfully achieved by using catalytic amounts of the cationic species $[Au(PPh_3)]^+$, generated *in situ* from the chloride complex $[AuCl(PPh_3)]$ and silver triflate (Scheme 31).[58] The resulting alkenyl-halophosphate products **52** were generated with complete regio- and *Z*-stereoselectivity as the result of the expected *anti* addition of O-H bond of $(PhO)_2P(=O)OH$ to the gold-π-complexed alkyne. The utility of **52** as coupling partners in palladium catalyzed Sonogashira, Kumada-Corriu, Suzuki and Stille reactions was also demonstrated by the authors.

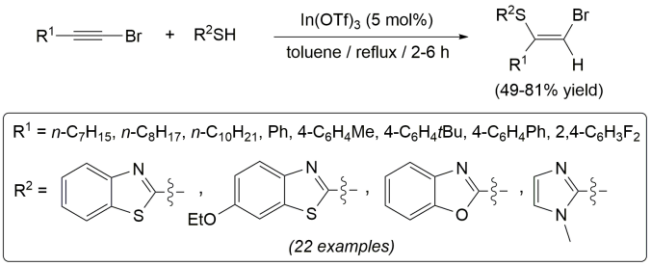


Scheme 31. Synthesis of the (*Z*)-alkenyl-halophosphates **52**.

4. S-H bond addition reactions

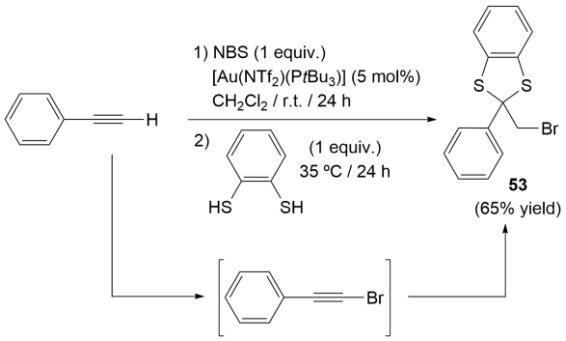
4.1. Hydrothiolation reactions

The addition of thiols across the carbon-carbon triple bond of alkynes has been widely studied in the last two decades, since it represents the most efficient and atom-economical process to construct vinyl sulfides, which are significant structural motifs found in natural products, biologically active compounds and functional materials.[59] However, haloalkynes have been rarely employed as substrates in these reactions.[60] In fact, only three examples involving metal catalysts have been reported to date. In one of them, indium(III) trifluoromethanesulfonate was found to catalyze the regioselective *anti* addition of different heterocyclic thiols to aromatic and aliphatic bromoalkynes, generating the corresponding (*Z*)-β-bromo vinyl sulfides in good yields (Scheme 32).[61] Attempts to add aromatic and aliphatic thiols failed, and only the formation of disulfide products *via* homocoupling of the thiols was in these cases observed.



Scheme 32. $In(OTf)_3$-catalyzed addition of heterocyclic thiols to bromoalkynes.

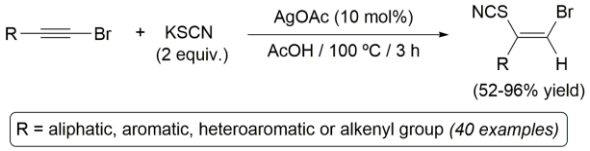
In the other two examples, gold(I)-phosphine complexes, *i.e.* [AuCl(*t*BuBrettPhos)] (**3** in Scheme 4) and $[Au(NTf_2)(PtBu_3)]$, were employed as catalysts. The former, in combination with NaBARF, catalyzed the addition of thiophenol and naphthalene-2-thiol to (chloroethynyl)benzene, affording selectively the corresponding (*Z*)-β-chloro vinyl sulfides.[8] Complex $[Au(NTf_2)(PtBu_3)]$ was used in the preparation of the cyclic dithioacetal **53** from phenylacetylene through a *one-pot* cascade reaction (Scheme 33), in which it first acts as a σ-activator facilitating the bromination of the terminal alkyne with *N*-bromosuccinimide (NBS), and later as a π-activator allowing the double hydrothiolation of the carbon-carbon triple bond of PhC≡CBr by benzene-1,2-dithiol.[62]



Scheme 33. Synthesis of the cyclic dithioacetal **53** from phenylacetylene.

4.2. Hydrothiocyanation reactions

The catalytic hydrothiocyanation of alkynes has emerged in recent years as a powerful tool for the preparation of vinyl thiocyanates.[63] In this context, Jiang, Wu and co-workers reported in 2017 the first hydrothiocyanation reactions of haloalkynes, employing KSCN in acetic acid, and silver(I) acetate as the catalyst.[64] As shown in Scheme 34, performing the reactions at 100 ºC with 10 mol% of AgOAc, a large number of bromoalkynes were converted into the corresponding vinyl thiocyanates in high yields and with exclusive *Z*-type configuration (*anti* addition). Competing Br/SCN substitution processes were not observed and the functional group compatibility was very high. On the other hand, under identical reaction conditions, PhC≡CX (X = Cl, I) could also be transformed into (*Z*)-PhC(SCN)=CHX, albeit in much lower yields (21-49%).



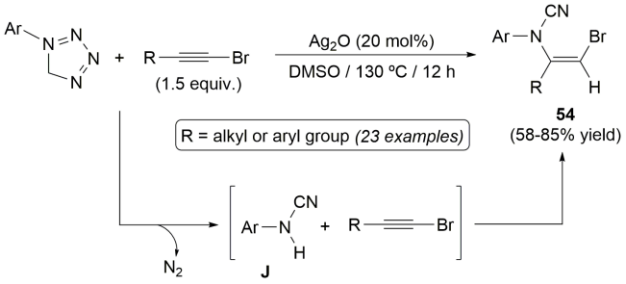
Scheme 34. Silver-catalyzed hydrothiocyanation of bromoalkynes.

Very recently, related hydrothiocyanation of both bromo- and chloroalkynes have been described employing homogeneous and heterogeneous gold-based catalysts, *i.e.* AuCl·SMe_2 and TiO_2-supported Au nanoparticles, respectively.[65] The reactions proceeded cleanly in acetic acid at 70 ºC, with NH_4SCN as the thiocyanate anion source, leading again to the halovinyl products with complete *Z* stereoselectivity.

5. N-H bond addition reactions

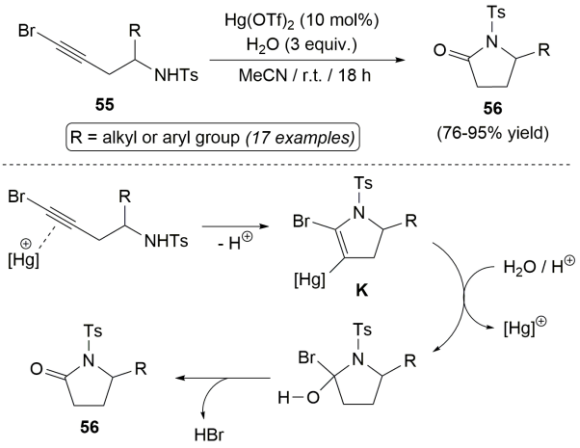
Despite the reactivity of N-H nucleophiles towards haloalkynes has been extensively investigated,[66] examples leading to the N-H addition across the C≡C bond are relatively rare.[67] In most of the cases ynamide products resulting from the hydrodehalogenative C-N coupling of the reactants are exclusively formed.[68]

An interesting transformation involving a N-H bond addition step was described by Wang and co-workers while studying the reactivity of aryl-tetrazoles towards bromoalkynes.[69] As shown in Scheme 35, performing the reactions at high temperature (130 ºC) and in the presence of catalytic amounts of silver(I) oxide, (*Z*)-*N*-(2-bromo-1-vinyl)-*N*-arylcyanamides **54** could be isolated in moderate to good yields. Formation of **54** involves the initial decomposition of the tetrazoles into the corresponding cyanamides **J** which are subsequently added, in an *anti* fashion, to the bromoalkynes. The silver catalyst seems to play a dual role in the reaction, facilitating not only the decomposition of the tetrazoles but also the activation of the π-bond.



Scheme 35. Silver-catalyzed addition of tetrazoles to bromoalkynes.

An additional example of the addition of a N-H bond to an haloalkyne was described by Reddy and co-workers in the cyclization of 4-bromo homopropargyl amides **55** into γ-butyrolactams **56**, a reaction catalyzed by $Hg(OTf)_2$ in wet acetonitrile (Scheme 36).[44] The process involves the initial 5-*endo*-dig cyclization of the substrates, followed by hydrolysis of the metallated intermediate **K**.

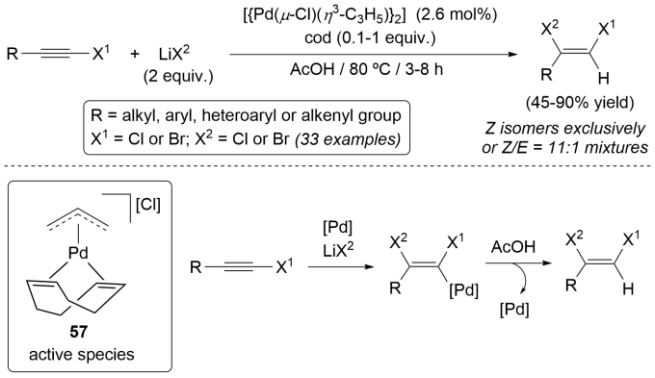


Scheme 36. Hg-catalyzed synthesis of γ-butyrolactams from 4-bromo homopropargyl amides.

6. Hydrohalogenation reactions

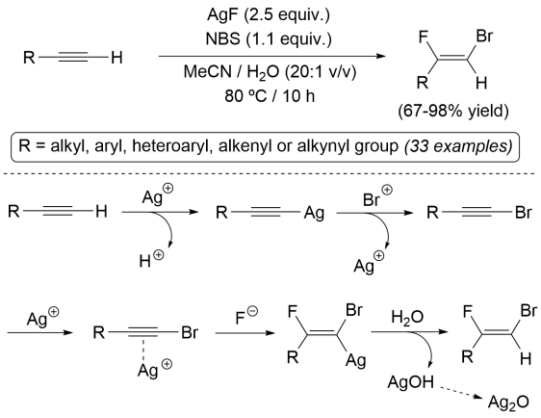
Dihaloalkenes are valuable starting materials in organic chemistry, especially for transition metal-catalyzed cross-coupling reactions. The hydrohalogenation of haloalkynes offers a convenient entry to 1,2-dihaloalkenes, for which traditional methods of synthesis suffer from poor selectivity and difficult separation.[70] In 2012, Zhu and co-workers reported an efficient and highly stereoselective palladium-catalyzed procedure for the hydrohalogenation of haloalkynes with the corresponding lithium halide salt LiX in acetic acid (Scheme 37).[71,72] The catalytic system was composed of the allylpalladium chloride dimer [{Pd(μ-Cl)(η^3-C_3H_5)}$_2$] and 1,5-cyclooctadiene (cod), from which the catalytically active cationic species [Pd(η^3-C_3H_5)(η^4-cod)][Cl] (**57**) is generated *in situ*. A reaction pathway involving the initial *trans*-halopalladation of the alkyne to give an alkenyl-palladium intermediate, which evolves

into the final product by protonolysis, was proposed by the authors. The process proved to be effective for the preparation of a variety of (*Z*)-1,2-dichloroalkenes, (*Z*)-1-bromo-2-chloroalkenes and (*Z*)-1,2-dibromoalkenes through the hydrochlorination or hydrobromination of both chloro- and bromoalkynes, but resulted inoperative for the hydrochlorination of iodoalkynes and the hydroiodination of chloroalkynes.[71]



Scheme 37. Palladium-catalyzed hydrohalogenation reactions of haloalkynes.

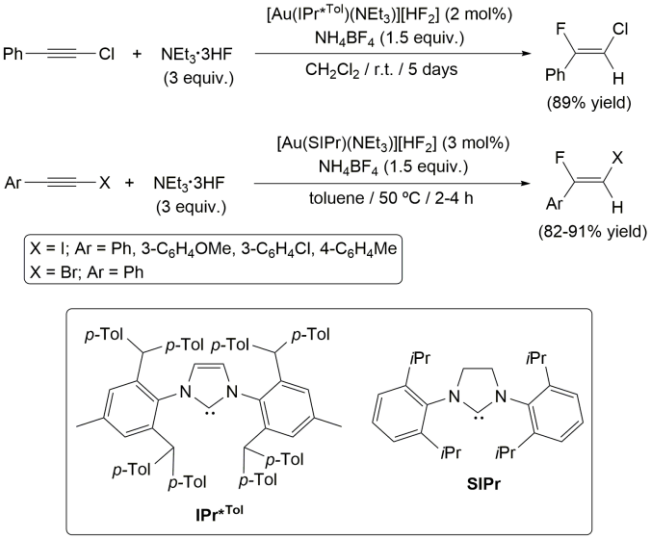
Almost simultaneously, a *one-pot* bromofluorination reaction of terminal alkynes employing NBS and silver(I) fluoride as the halogen sources was described by the group of Jiang (Scheme 38).[73] In the process, which leads to the formation of (*Z*)-1-fluoro-2-bromoalkenes with a very high stereoselectivity (*Z*/*E* ratios from 77:23 to > 95:5), the silver(I) cation acts again as a σ/π-activator promoting the bromination of the terminal alkyne by NBS and the addition of the fluoride anion to the resulting bromoalkyne. Control experiments performed by the authors also indicated that AgF can be employed as a reagent for the direct fluorination of isolated haloalkynes.



Scheme 38. Silver(I)-assisted bromofluorination reactions of terminal alkynes.

More recently, hydrochlorination reactions of chloroalkynes and bromoalkynes related to those depicted in Scheme 37, *i.e.* with LiCl (5 equiv.) in AcOH, have been described employing [AuCl(JohnPhos)] (5 mol%) (**31** in Scheme 19) as catalyst.[74] The reactions proceeded cleanly at 80 (for bromoalkynes) or 100 ºC (for chloroalkynes), and in the absence of any additive, delivering the *anti*-addition (*Z*)-1,2-dichloroalkene and (*Z*)-1-bromo-2-chloroalkene products in high yields.

Finally, works by Nolan and co-workers demonstrated the utility of the NHC-gold(I) bifluoride complexes [Au(IPr*^{Tol})(NEt$_3$)][HF$_2$] and [Au(SIPr)(NEt$_3$)][HF$_2$] as catalysts for the hydrofluorination of aromatic chloro-, bromo- and iodoalkynes with NEt$_3$·3HF (Scheme 39).[75,76] As expected, the addition of the HF molecule across the C≡C bond of the substrates proceeded in a complete regio- and stereoselective manner (*anti* addition). On the other hand, given the ability of [Au(SIPr)(NEt$_3$)][HF$_2$] to promote the iodination of terminal alkynes by means of NIS, an efficient protocol for the direct conversion of arylacetylenes into the corresponding 2-fluoro-1-iodoalkenes, through a *one-pot* two-steps iodination/hydrofluorination sequence, could also be developed.[76]



Scheme 39. Gold-catalyzed hydrofluoration of haloalkynes.

7. Conclusion

In this Minireview article we have highlighted the current state of the art on the catalytic hydrofunctionalization of haloalkynes, a research field in which the most significant advances have been reached in the last ten years, and that have been mainly associated with the application of gold catalysts. Along the article, examples of highly regio- and stereoselective additions of C-H, O-H, N-H, S-H and X-H (X = halide) bonds to these fascinating molecules, allowing the access to novel organic compounds that contains useful sites for further functionalization, have been given. Although there is already a body of work in this area, it is clear that further advances can be expected in the near future. In this context, the development of catalytic systems for hydrosilylation,

hydrophosphination or hydroboration reactions, untouched to date, would deserve to be considered. It is hoped that the reading of this article will help to stimulate research in this direction.

Acknowledgments

Financial support by the Spanish MINECO (project CTQ2016-75986-P) and the University of Oviedo (PAPI-19-GR-2011-0032) is gratefully acknowledged.

Keywords: catalysis • hydrofunctionalization • chloroalkynes • bromoalkynes • iodoalkynes

[1] *Hydrofunctionalization* (Eds.: V. P. Ananikov, M. Tanaka), Springer-Verlag, Berlin, **2011**.

[2] For selected review articles covering catalytic hydrofunctionalization reactions of alkynes, see: a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079-3159; b) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.* **2004**, *43*, 3368-3398; *Angew. Chem.* **2004**, *116*, 3448-3479; c) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167-182; d) C. Bruneau, P. H. Dixneuf, *Angew. Chem. Int. Ed.* **2006**, *45*, 2176-2203; *Angew. Chem.* **2006**, *118*, 2232-2260; e) I. P. Belestskaya, V. P. Ananikov, *Pure Appl. Chem.* **2007**, *70*, 1041-1056; f) N. T. Patil, R. D. Kavthe, V. S. Shinde, *Tetrahedron* **2012**, *68*, 8079-8146; g) X. Zheng, *Chem. Rev.* **2013**, *113*, 6864-6900; h) Y. Zheng, W. Zi, *Tetrahedron Lett.* **2018**, *59*, 2205-2213.

[3] a) W. Wu, H. Jiang, *Acc. Chem. Res.* **2014**, *47*, 2483-2504; b) H. Jiang, C. Zhu, W. Wu in *Haloalkyne Chemistry*, Springer-Verlag, Berlin, **2016**.

[4] During the preparation of this manuscript a general review covering the transition metal-catalyzed reactions of alkynyl halides has appeared: D. Petko, S. Koh, W. Tam, *Curr. Org. Synth.* **2019**, *16*, 546-582.

[5] For selected reviews covering this topic, see: a) G. Yan, X. Wu, M. Yang, *Org. Biomol. Chem.* **2013**, *11*, 5558-5578; b) X.-S. Zhang, K. Chen, Z.-J. Shi, *Chem. Sci.* **2014**, *5*, 2146-2159; c) L. Yang, H. Huang, *Chem. Rev.* **2015**, *115*, 3468-3517; d) J. R. Hummel, J. A. Boerth, J. A. Ellman, *Chem. Rev.* **2017**, *117*, 9163-9227.

[6] H. Tsuji, T. Fujimoto, K. Endo, M. Nakamura, E. Nakamura, *Org. Lett.* **2008**, *10*, 1219-1221.

[7] W. Zeng, W. Wu, H. Jiang, Y. Sun, Z. Chen, *Tetrahedron Lett.* **2013**, *54*, 4605-4609.

[8] C. Liu, Y. Xue, L. Ding, H. Zhang, F. Yang, *Eur. J. Org. Chem.* **2018**, 6537-6540.

[9] S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem. Int. Ed.* **2004**, *43*, 5350-5352; *Angew. Chem.* **2004**, *116*, 5464-5466.

[10] a) A. Fürstner, V. Mamane, *Chem. Commun.* **2003**, 2112-2113; b) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556-4575.

[11] We must point out that theoretical DFT calculations have called into question the real involvement of these vinylidene-gold intermediates in the process, suggesting that, as in the case of $InCl_3$, a 6-*endo*-dig cyclization *via* a gold-π-alkyne complex also takes place, with concomitant migration of the halide: a) E. Soriano, J. Marco-Contelles, *Organometallics* **2006**, *25*, 4542-4553; b) G. Huang, B. Cheng, L. Xu, Y. Li, Y. Xia, *Chem. Eur. J.* **2012**, *18*, 5401-5415.

[12] P. Morán-Poladura, E. Rubio, J. M. González, *Angew. Chem. Int. Ed.* **2015**, *54*, 3052-3055; *Angew. Chem.* **2015**, *127*, 3095-3098.

[13] The generation of iodinated tungsten vinylidene complexes from iodoalkynes, and their involvement as intermediates in cyclization processes, has also been described: a) T. Miura, N. Iwasawa, *J. Am. Chem. Soc.* **2002**, *124*, 518-519; b) N. Iwasawa, T. Miura, K. Kiyota, H. Kusama, K. Lee, P. H. Lee, *Org. Lett.* **2002**, *4*, 4463-4466.

[14] P. Morán-Poladura, S. Suárez-Pantiga, M. Piedrafita, E. Rubio, J. M. González, *J. Organomet. Chem.* **2011**, *696*, 12-15.

[15] P. Morán-Poladura, E. Rubio, J. M. González, *Beilstein J. Org. Chem.* **2013**, *9*, 2120-2128.

[16] T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, 411-414.

[17] Z. Rong, A. M. Echavarren, *Org. Biomol. Chem.* **2017**, *15*, 2163-2167.

[18] K. Speck, K. Karaghiosoff, T. Magauer, *Org. Lett.* **2015**, *17*, 1982-1985.

[19] For a review on this topic, see: L. Hintermann, A. Labonne, *Synthesis* **2007**, 1121-1150.

[20] For selected reviews covering the chemistry of α-halomethyl ketones, see: a) I. K. Moiseev, N. V. Makarova, M. N. Zemtsova, *Russ. J. Org. Chem.* **2003**, *39*, 1685-1701; b) A. W. Erian, S. M. Sherif, H. M. Gaber, *Molecules* **2003**, *8*, 793-865; c) R. H. Vekariya, H. D. Patel, *Tetrahedron* **2014**, *70*, 3949-3961; d) V. Fülöpová, M. Soural, *Synthesis* **2016**, *48*, 3684-3695.

[21] See, for example: M. Ye, Y. Wen, H. Li, Y. Fu, Q. Wang, *Tetrahedron Lett.* **2016**, *57*, 4983-4986.

[22] P. Starkov, F. Rota, J. M. D´Oyley, T. D. Sheppard, *Adv. Synth. Catal.* **2012**, *354*, 3217-3224.

[23] The utility of this protocol was demonstrated later in a multi-step asymmetric synthesis of carbocyclic propellanes: L. M. Schneider, V. M. Schmiedel, T. Pecchioli, D. Lentz, C. Merten, M. Christmann, *Org. Lett.* **2017**, *19*, 2310-2313.

[24] L. Xie, Y. Wu, W. Yi, L. Zhu, J. Xiang, W. He, *J. Org. Chem.* **2013**, *78*, 9190-9195.

[25] In an independent study, the hydration of several aromatic and aliphatic bromo- and chloroalkynes using complex [Au(NTf_2)(BrettPhos)] as catalyst was reported, with results almost identical to those obtained by Xiang, He and co-workers employing [Au(NTf_2)(XPhos)]: K. Liu, *Chem. J. Chinese U.* **2014**, *35*, 1236-1240.

[26] N. Ghosh, S. Nayak, B. Prabagar, A. K. Sahoo, *J. Org. Chem.* **2014**, *79*, 2453-2462.

[27] It should be noted that formation of trace amounts of compounds **24** had been previously observed by Zhang and co-workers while studying the rearrangement of propargylic carboxylates **23** employing complex [Au(NTf_2)(PPh_3)] as catalyst: Y. Wang, B. Lu, L. Zhang, *Chem. Commun.* **2010**, *46*, 9179-9181.

[28] L. Jin, Y. Wu, X. Zhao, *RSC Adv.* **2016**, *6*, 89836-89846.

[29] Q. Ye, T. Cheng, Y. Zhao, J. Zhao, R. Jin, G. Liu, *ChemCatChem* **2015**, *7*, 1801-1805.

[30] X. Xia, J. Meng, H. Wu, T. Cheng, G. Liu, *Chem. Commun.* **2017**, *53*, 1638-1641.

[31] S. Hu, D. Liu, C. Yan, M. Cai, *Synth. Commun.* **2018**, *48*, 2983-2991.

[32] Z.-W. Chen, D.-N. Ye, M. Ye, Z.-G. Zhou, S.-H. Li, L.-X. Liu, *Tetrahedron Lett.* **2014**, *55*, 1373-1375.

[33] M. Zeng, R.-X. Huang, W.-Y. Li, X.-W. Liu, F.-L. He, Y.-Y. Zhang, F. Xiao, *Tetrahedron* **2016**, *72*, 3818-3822.

[34] J. Park, J. Yeon, P. H. Lee, K. Lee, *Tetrahedron Lett.* **2013**, *54*, 4414-4417.

[35] W. Yi, D. Yan, C. Wu, L. Lan, *Chem. J. Chinese U.* **2014**, *35*, 2563-2566.

[36] H. Zou, W. He, Q. Dong, R. Wang, N. Yi, J. Jiang, D. Pen, W. He, *Eur. J. Org. Chem.* **2016**, 116-121.

[37] H. Zou, J. Jiang, N. Yi, W. Fu, W. Deng, J. Xiang, *Chin. J. Chem.* **2016**, *34*, 1251-1254.

[38] See, for example: S. Wang, P. Li, L. Yu, L. Wang, *Org. Lett.* **2011**, *13*, 5968-5971.

[39] X. Hong, F. Ma, D. Zha, H. Li, *Asian J. Org. Chem.* **2018**, *7*, 2552-2556.

[40] G. Liu, J. Xu, L. Ding, H. Zhang, Y. Xue, F. Yang, *Org. Biomol. Chem.* **2019**, *17*, 4435-4439.

[41] For selected review articles covering this topic, see: a) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395-3442; b) K. C. Majumdar, P. Debnath, B. Roy, *Heterocycles* **2009**, *20*, 152-189; c) N. T. Patil, R. D. Kauthe, Y. Yamamoto, *Adv. Heterocycl. Chem.* **2010**, *101*, 75-95; d) B. Alcaide, P. Almendros, J. M. Alonso, *Org. Biomol. Chem.* **2011**, *9*, 4405-4416; e) J. A. Varela, C. Saá, *Synthesis* **2016**, *48*, 3470-3478.

[42] H. Harkat, J.-M. Weibel, P. Pale, *Tetrahedron Lett.* **2007**, *48*, 1439-1442.

[43] S. M. Reddy, Y. K. Kumar, N. Thirupathi, *Org. Lett.* **2012**, *14*, 824-827.

[44] Y. K. Kumar, G. R. Kumar, M. S. Reddy, *Org. Biomol. Chem.* **2016**, *14*, 1252-1260.

[45] For review articles covering this topic, see: a) L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100-3120; *Angew. Chem.* **2008**, *120*, 3144-3164; b) L. Hintermann, *Top. Organomet. Chem.* **2010**, *31*, 123-155; c) C. Bruneau, *Top. Organomet. Chem.* **2013**, *43*, 203-230; d) J. Francos, V. Cadierno, *Catalysts* **2017**, *7*, 328/1-328/23; e) P. J. González-Liste, J. Francos, S. E. García-Garrido, V. Cadierno, *Arkivoc* **2018**, *ii*, 17-39.

[46] See, for example: a) C. E. Lipscomb, M. K. Mahanthappa, *Macromolecules* **2009**, *42*, 4571-4579; b) X. Liu, O. Coutelier, S. Harrisson, T. Tassaing, J.-D. Marty, M. Destarac, *ACS Macro Lett.* **2015**, *4*, 89-93; c) F. Foarta, C. R. Landis, *J. Org. Chem.* **2016**, *81*, 11250-11255; d) R. K. Jena, U. K. Das, A. Ghorai, M. Bhattacharjee, *Eur. J. Org. Chem.* **2016**, 6015-6021; e) J. Hwang, H.-C. Lee, M. Antonietti, B. V. K. J. Schmidt, *Polym. Chem.* **2017**, *8*, 6204-6208.

[47] See, for example: a) T. M. Konrad, P. Schmitz, W. Leitner, G. Franciò, *Chem. Eur. J.* **2013**, *19*, 13299-13303; b) P. Kleman, P. J. González-Liste, S. E. García-Garrido, V. Cadierno, A. Pizzano, *Chem. Eur. J.* **2013**, *19*, 16209-16212; c) P. Kleman, P. J. González-Liste, S. E. García-Garrido, V. Cadierno, A. Pizzano, *ACS Catal.* **2014**, *4*, 4398-4408; d) C. Liu, J. Yuan, J. Zhang, Z. Wang, Z. Zhang, W. Zhang, *Org. Lett.* **2018**, *20*, 108-111; e) J. Jia, D. Fan, J. Zhang, Z. Zhang, W. Zhang, *Adv. Synth. Catal.* **2018**, *360*, 3793-3800.

[48] See, for example: a) L. J. Gooßen, J. Paetzold, *Angew. Chem. Int. Ed.* **2004**, *43*, 1095-1098; *Angew. Chem.* **2004**, *116*, 1115-1118; b) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486-1495; c) I. Geibel, J. Christoffers, *Eur. J. Org. Chem.* **2016**, 918-920; d) I. Geibel, A. Dierks, M. Schmidtmann, J. Christoffers, *J. Org. Chem.* **2016**, *81*, 7790-7798.

[49] Z. Chen, J. Li, H. Jiang, S. Zhu, Y. Li, C. Qi, *Org. Lett.* **2010**, *12*, 3262-3265.

[50] a) P. J. González-Liste, F. León, I. Arribas, M. Rubio, S. E. García-Garrido, V. Cadierno, A. Pizzano, *ACS Catal.* **2016**, *6*, 3056-3060; b) P. J. González-Liste, J. Francos, S. E. García-Garrido, V. Cadierno, *J. Org. Chem.* **2017**, *82*, 1507-1516; c) F. León, P. J. González-Liste, S. E. García-Garrido, I. Arribas, M. Rubio, V. Cadierno, A. Pizzano, *J. Org. Chem.* **2017**, *82*, 5852-5867; d) F. León, J. Francos, J. López-Serrano, S. E. García-Garrido, V. Cadierno, A. Pizzano, *Chem. Commun.* **2019**, *55*, 786-789; e) J. Francos, V. Cadierno, *Synthesis* **2019**, *51*, 3117-3126.

[51] G. Muthusamy, S. V. Pansare, *Org. Biomol. Chem.* **2018**, *16*, 7971-7983.

[52] G. Jiang, J. Li, C. Zhu, W. Wu, H. Jiang, *Org. Lett.* **2017**, *19*, 4440-4443.

[53] a) H. Harkat, J.-M. Weibel, P. Pale, *Tetrahedron Lett.* **2006**, *47*, 6273-6276; b) H. Harkat, A. Y. Dembelé, J.-M. Weibel, A. Blanc, P. Pale, *Tetrahedron* **2009**, *65*, 1871-1879.

[54] D. Gasperini, L. Maggi, S. Dupuy, R. M. P. Veenboer, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Adv. Synth. Catal.* **2016**, *358*, 3857-3862.

[55] N. Á. Espinosa-Jalapa, D. Ke, N. Nebra, L. Le Goanvic, S. Mallet-Ladeira, J. Monot, B. Martín-Vaca, D. Bourissou, *ACS Catal.* **2014**, *4*, 3605-3611.

[56] a) G. A. Krafft, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1981**, *103*, 5459-5466; b) R. W. Spencer, T. F. Tam, E. Thomas, V. J. Robinson, A. Krantz, *J. Am. Chem. Soc.* **1986**, *108*, 5589-5597; c) W. Dai, J. A. Katzenellenbogen, *J. Org. Chem.* **1991**, *56*, 6893-6896.

[57] A. K. Buzas, F. M. Istrate, F. Gagosz, *Tetrahedron* **2009**, *65*, 1889-1901.

[58] B. C. Chary, S. Kim, D. Shin, P. H. Lee, *Chem. Commun.* **2011**, *47*, 7851-7853.

[59] For review articles covering this topic, see: a) A. Ogawa, *Top. Organomet. Chem.* **2013**, *43*, 325-360; b) R. Castarlenas, A. Di Giuseppe, J. J. Pérez-Torrente, L. A. Oro, *Angew. Chem. Int. Ed.* **2013**, *52*, 211-222; *Angew. Chem.* **2013**, *125*, 223-234; c) A. Dondoni, A. Marra, *Eur. J. Org. Chem.* **2014**, 3955-3969; d) N. V. Orlov, *ChemistryOpen* **2015**, *4*, 682-697.

[60] a) H. Xu, S. Gu, W. Chen, D. Li, J. Dou, *J. Org. Chem.* **2011**, *76*, 2448-2458; b) G. Liu, L. Kong, J. Shen, G. Zhu, *Org. Biomol. Chem.* **2014**, *12*, 2310-2321.

[61] N. Rajesh, D. Prajapati, *RSC Adv.* **2014**, *4*, 32108-32112.

[62] a) A. Leyva-Pérez, P. Rubio-Marqués, S. S. Al-Deyab, S. I. Al-Resayes, A. Corma, *ACS Catal.* **2011**, *1*, 601-606; b) In the same work, related transformations involving alcohols and amines as the nucleophiles were also described.

[63] C. Wu, L.-H. Lu, A.-Z. Peng, G.-K. Jia, C. Peng, Z. Cao, Z. Tang, W.-M. He, X. Xu, *Green Chem.* **2018**, *20*, 3683-3688 and references therein.

[64] G. Jiang, C. Zhu, J. Li, W. Wu, H. Jiang, *Adv. Synth. Catal.* **2017**, *359*, 1208-1212.

[65] X. Zeng, B. Chen, Z. Lu, G. B. Hammond, B. Xu, *Org. Lett.* **2019**, *21*, 2772-2776.

[66] For representative examples, see: a) M. O. Frederick, J. A. Mulder, M. A. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* **2003**, *125*, 2368-2369; b) J. R. Dunetz, R. L. Danheiser, *Org. Lett.* **2003**, *5*, 4011-4014; c) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151-1154; d) S. Hirano, Y. Fukudome, R. Tanaka, F. Sato, H. Urabe, *Tetrahedron* **2006**, *62*, 3896-3916; e) C. Laroche, J. Li, M. W. Freyer, S. M. Kerwin, *J. Org. Chem.* **2008**, *73*, 6462-6465; f) B. Yao, Z. Liang, T. Niu, Y. Zhang, *J. Org. Chem.* **2009**, *74*, 4630-4633; g) G. A. Burley, D. L. Davies, G. A. Griffith, M. Lee, K. Singh, *J. Org. Chem.* **2010**, *75*, 980-983; h) K. A. DeKorver, M. C. Walton, T. D. North, R. P. Hsung, *Org. Lett.* **2011**, *13*, 4862-4865; i) H. Harkat, S. Borghèse, M. De Nigris, S. Kiselev, V. Bénéteau, P. Pale, *Adv. Synth. Catal.* **2014**, *356*, 3842-3848.

[67] For examples not involving metal catalysts, see: a) M. Yamagishi, K, Nishigai, T. Hata, H. Urabe, *Org. Lett.* **2011**, *13*, 4873-4875; b) M. Yamagishi, J. Okazaki, K, Nishigai, T. Hata, H. Urabe, *Org. Lett.* **2012**, *14*, 34-37.

[68] In some copper-catalyzed reactions the formation of minor amounts of the corresponding olefinic addition products was observed. See references 66e,g,i.

[69] J. Zhang, L.-G. Meng, P. Li, L. Wang, *RSC Adv.* **2013**, *3*, 6807-6812.

[70] Z. Chen, H. Jiang, Y. Li, C. Qi, *Chem. Commun.* **2010**, *46*, 8049-8051 and references therein.

[71] G. Zhu, D. Chen, Y. Wang, R. Zheng, *Chem. Commun.* **2012**, *48*, 5796-5798.

[72] The utility of this protocol was demonstrated later in the multi-step syntheses of different analogs of the natural product meiogynin A: C. Remeur, S. Desrat, V. Gandan, F. Roussi, *Eur. J. Org. Chem.* **2018**, 5869-5877.

[73] Y. Li, X. Liu, D. Ma, B. Liu, H. Jiang, *Adv. Synth. Catal.* **2012**, *354*, 2683-2688.

[74] X. Zeng, S. Liu, G. B. Hammond, B. Xu, *ACS Catal.* **2018**, *8*, 904-909.

[75] F. Nahra, S. R. Patrick, D. Bello, M. Brill, A. Obled, D. B. Cordes, A. M. Z. Slawin, D. O´Hagan, S. P. Nolan, *ChemCatChem* **2015**, *7*, 240-244.

[76] A. Gómez-Herrera, F. Nahra, M. Brill, S. P. Nolan, C. S. J. Cazin, *ChemCatChem* **2016**, *8*, 3381-3388.