Review

Metal-Catalyzed Intra- and Intermolecular Addition of Carboxylic Acids to Alkynes in Aqueous Media: A Review

Javier Francos and Victorio Cadierno *

Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Centro de Innovación en Química Avanzada (ORFEO-CINQA), Departamento de Química Orgánica e Inorgánica, IUQOEM, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain; francosjavier@uniovi.es

* Correspondence: vcm@uniovi.es; Tel.: +34-985-103453

Abstract: The metal-catalyzed addition of carboxylic acids to alkynes is a very effective tool for the synthesis of carboxylate-functionalized olefinic compounds in an atom-economical manner. Thus, a large variety of synthetically useful lactones and enol-esters can be accessed through the intra- or intermolecular versions of this process. In order to reduce the environmental impact of these reactions, considerable efforts have been devoted in recent years to the development of catalytic systems able to operate in aqueous media, which represent a real challenge taking into account the tendency of alkynes to undergo hydration in the presence of transition metals. Despite this, different Pd, Pt, Au, Cu and Ru catalysts capable of promoting the intra- and intermolecular addition of carboxylic acids to alkynes in a selective manner in aqueous environments have appeared in the literature. In this review article, an overview of this chemistry is provided. The synthesis of β-oxo esters by catalytic addition of carboxylic acids to terminal propargylic alcohols in water is also discussed.

Keywords: aqueous catalysis; alkynes; carboxylic acids; alkynoic acids; hydrocarboxylation reactions; cycloisomerization reactions; enol esters; lactones; β-oxo esters

1. Introduction

The transition metal-catalyzed heterofunctionalization of alkynes by addition of nucleophiles to the C≡C bond has emerged in recent years as a versatile synthetic tool in organic chemistry [1–3]. In particular, the addition of carboxylic acids to alkynes, reaction also referred in the literature as hydro-oxycarbonylation or hydrocarboxylation of alkynes, represents a straightforward way to obtain different types of olefinic esters with atom economy [4–6]. Thus, the intramolecular version of the process, i.e., the cycloisomerization of alkynoic acids, produces unsaturated lactones (Scheme 1) which are common structural motifs found in natural products and biologically active molecules, as well as valuable synthetic intermediates [7–10]. A large variety of transition metal complexes have been used to catalyze these reactions through the π-activation of the carbon-carbon triple bond of the alkynoic acid, the regioselectivity (*exo* or *endo* addition of the carboxylate to the C≡C bond leading to lactones **A** or **B**, respectively) and stereoselectivity of the process being dependent on the metal employed, the length of the hydrocarbon chain connecting the acid and alkyne units, and the terminal or internal nature of the alkyne functionality [1–6]. Among the most commonly employed metals are Pd, Ag, Au and Rh, including examples of heterogeneous systems [11], which have shown a high efficacy for the selective preparation of 5-, 6-, and to a lesser extent, 7-membered ring lactones [1–6].
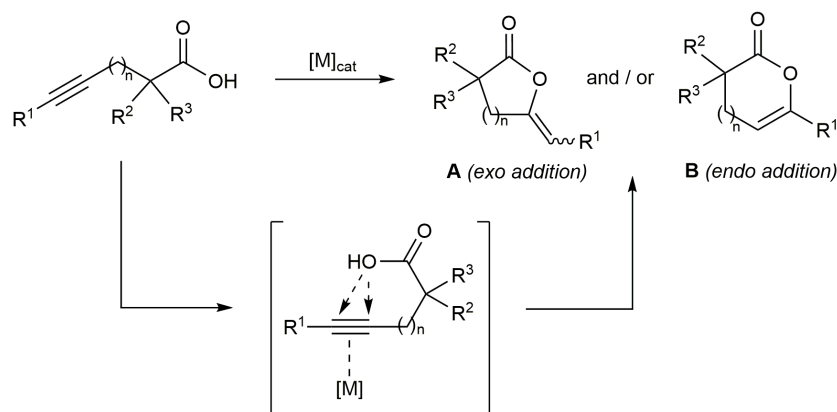
Scheme 1. The catalytic cycloisomerization of alkynoic acids.

The intermolecular addition of carboxylic acids to alkynes also presents enormous interest since the reaction products, i.e., enol esters (**C** or **D** in Scheme 2), are versatile building blocks in organic synthesis and material science. For example, to name just a few of their myriad applications, they are widely employed as mild acylating reagents [12,13], as monomers in diverse polymerization reactions [14–16], as substrates in asymmetric hydrogenation for the generation of enantioenriched alcohols [17–19], or as starting materials for different cross-coupling processes [20–22]. As for the cycloisomerization of alkynoic acids, a huge number of catalytic systems involving late transition metals have been described, with those based on ruthenium playing a prominent role [1–5]. However, for a long time, this reaction was limited to terminal alkynes, since most catalysts failed to enable the hydrocarboxylation of internal alkynes as a consequence of their greater steric hindrance, which disfavours their coordination to the metal catalyst. At this point, it should be noted that a reduced reactivity of internal vs. terminal C≡C bonds is also commonly observed in the cyclization reactions of alkynoic acids, although in this case the problem is not so marked as the intramolecular process is much more favoured from a thermodynamic point of view. Fortunately, recent works focused in the design of increasingly active catalysts have made possible to overcome this limitation and some Ru-, Pd-, Ag- and Au-based systems active with internal alkynes are now available [23].
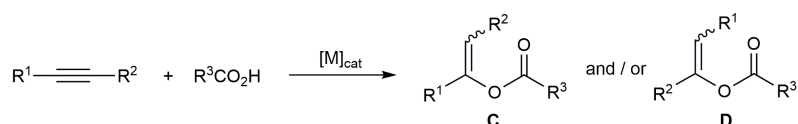
Scheme 2. The intermolecular addition of carboxylic acids to alkynes.

On the other hand, the increasing awareness of environmental concerns has stimulated the development of metal-catalyzed reactions in aqueous media, since water is cheaper, safer and benigner compared to the traditional petroleum-derived organic solvents [24–26]. In addition, the use of water (or aqueous biphasic mixtures) allows in many cases an easy catalyst/product separation, thus allowing the effective recycling of the catalytically active species, which is another key aspect in the Green Chemistry context [27]. However, despite the growing interest in aqueous catalysis, the use of this environmentally benign solvent in the hydrocarboxylation of alkynes been for long time neglected, probably due to the concerns of a competing hydration of the alkyne substrates to form carbonyl compounds, a process that is also catalyzed by transition metals [1–6,28]. In fact, in a general review on the "catalytic reactions of alkynes in water", published by Chen and Li in 2006, no examples of hydrocarboxylation reactions were collected [28]. Catalytic systems able to operate selectively in aqueous environments have only appeared in the literature in recent years, and are the subject of the present review article. Intra- and intermolecular processes are covered, including examples of

sequential transformations of synthetic interest. The access to β-oxo esters by the catalytic addition of carboxylic acids to terminal propargylic alcohols in water is also discussed.

2. Intramolecular Processes

2.1. Cycloisomerization of Preformed or In Situ Generated Alkynoic Acids

The first example of such reactions in an aqueous environment was described by Hidai and co-workers in 1996 employing the mixed-metal cubane-type cluster complex [PdMo$_3$S$_4$(tacn)$_3$Cl][PF$_6$]$_3$ (**1**; tacn = 1,4,7-triazacyclononane) as catalyst [29]. Thus, they found that, in combination with NEt$_3$, **1** was able to transform dipropargylmalonic acid **2** into the enol lactone **3** in water at room temperature (Scheme 3). Unfortunately, although the rate and yield of the reaction were very similar to those observed in acetonitrile, this latter solvent was selected by the authors to study the scope of the process. In this regard, different 5-, 6- and 7-membered ring lactones could be obtained from the corresponding alkynoic acids with complex **1**, which showed an enhanced reactivity in comparison with classical mononuclear Pd(II) sources, such as [PdCl$_2$(PhCN)$_2$] or Na$_2$[PdCl$_4$]. In line with this, despite the presence of three molybdenum atoms in the structure of **1**, the catalytic reactions were assumed to proceed only at the palladium center.
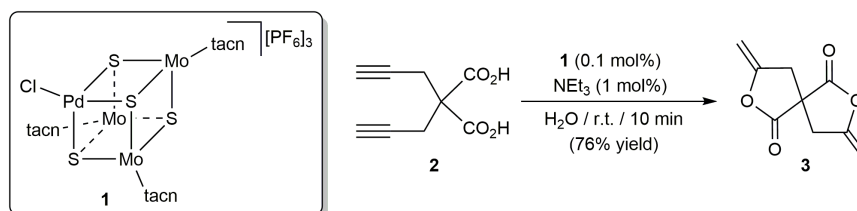
Scheme 3. Cycloisomerization of dipropargylmalonic acid **2** in water using a cluster catalyst.

More recently, other palladium-based catalysts for the cyclization of alkynoic acids in aqueous media have been described. In particular, García-Álvarez and co-workers disclosed that transformation of γ-alkynoic acids into five-membered ring enol-lactones (5-*exo-dig* cyclization) can be conveniently and selectively achieved in pure water, and under aerobic conditions, by using catalytic amounts of the dinuclear Pd(II) derivative *trans*-[PdCl$_2$\{μ^2-*N*,*S*-(PTA)=NP(=S)(OEt)$_2$\}]$_2$ (**4**) (Scheme 4) [30]. This catalyst features a bridging iminophosphorane-type ligand derived from the well-known hydrophilic phosphine PTA (1,3,5-triaza-7-phosphaadamantane) [31,32], which facilitates its solubility in water.
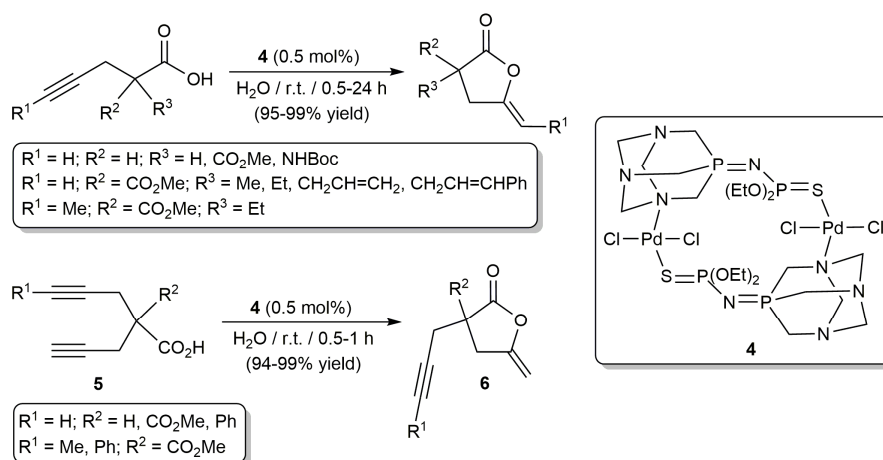
Scheme 4. Cycloisomerization of different γ-alkynoic acids in water catalyzed by a dinuclear Pd(II) complex.

As shown in Scheme 4, the reactions proceeded cleanly at r.t. (room temperature) without formation of any by-product derived from the hydration of the C≡C bond of the substrates or from the hydrolysis of the (Z)-γ-alkylidene butyrolactone products. The process was operative with γ-alkynoic acids containing both terminal and internal C≡C bonds, although for the latter a much longer reaction time was needed (24 instead of 0.5–2 h). It is also worth noting that (*i*) this catalytic system could be recycled up to 10 consecutive runs for the cyclization of the model 4-pentynoic acid (cumulative TON (turnover number) of 982), and (*ii*) it could be applied in the desymmetrization of bispropargylic carboxylic acids **5**, affording enol-lactones **6** containing an intact propargylic side arm in excellent yields.

Although in a limited number of examples (only six substrates were explored), the group of Nakamura also demonstrated the capacity of the NCN-pincer Pd(II) derivative **7** (Figure 1) to promote the high-yield formation of five-membered ring lactones from both γ- and β-alkynoic acids (5-*exo-dig* and 5-*endo-dig* cyclization, respetively) in pure water [33]. Complex **7** easily generates hydrogen-bonding-based supramolecular gels, with well-organized Pd-arrays, in organic solvents. For the catalytic reactions, which were performed at 70 °C and in the presence of Et$_3$N (3 mol %), a water-insoluble xerogel prepared from **7** in toluene was employed (0.5 mol % Pd content). Interestingly, the Pd-gel catalyst could be recovered by filtration and reused three times in the cyclization of 4-pentynoic acid without loss of catalytic activity. However, it should also be mentioned that, contrary to the case of the dinuclear Pd(II) complex **4**, when a bispropargylic carboxylic acid was employed as substrate, partial hydration of propargylic side arm of the enol-lactone product was observed.
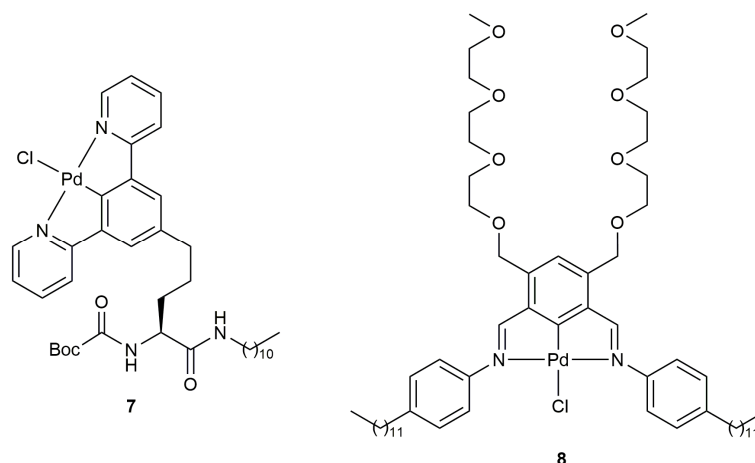

Figure 1. Structure of the pincer palladium(II) complexes **7** and **8**.

Selective 5-*exo-dig* cyclization of pentynoic acids RC≡CCH$_2$CH$_2$CO$_2$H (R = aryl or heteroaryl group) to afford the corresponding (Z)-γ-alkylidene butyrolactones could also be achieved, in water at 50 °C, using the related amphiphilic NCN-pincer Pd(II) complex **8** (2 mol %) (Figure 1) in combination with Et$_3$N (6 mol %) (yields in the range 38–94% after 1–6 h) [34]. Complex **8** self-assembles in aqueous solution forming bilayered vesicles which were found to be essential for the promotion of the catalytic process (markedly lower yields were obtained when the same reactions were performed in organic solvents or employing the amorphous complex **8** in water).

On the other hand, despite the well-known ability of platinum compounds to promote the cycloisomerization of polyunsaturated organic molecules [35,36], this metal has been much less used than palladium to catalyze the cyclization of alkynoic acids [37]. In this regard, the work published by Alemán, Navarro-Ranninger and co-workers merits highlighting [38]. These authors evaluated the catalytic behaviour of a broad family of anticancer platinum(II) and platinum(IV) amino-complexes (**9a–j** and **9k–o**, respectively; see Figure 2) in the cycloisomerization of 4-pentynoic

acid into 5-methylene-dihydrofuran-2-one (5-*exo-dig* cyclization), finding that both the oxidation state of the metal and the stereochemistry of the complex are key factors for the reaction to proceed efficiently. Thus, while the *cis*-platinum(II) derivatives **9a–e** showed a high reactivity in acetone at r.t., their *trans*-platinum(II) counterparts **9f–j** and the Pt(IV) species **9k–o** (regardless of their *cis* or *trans* configuration) turned out to be practically inactive.
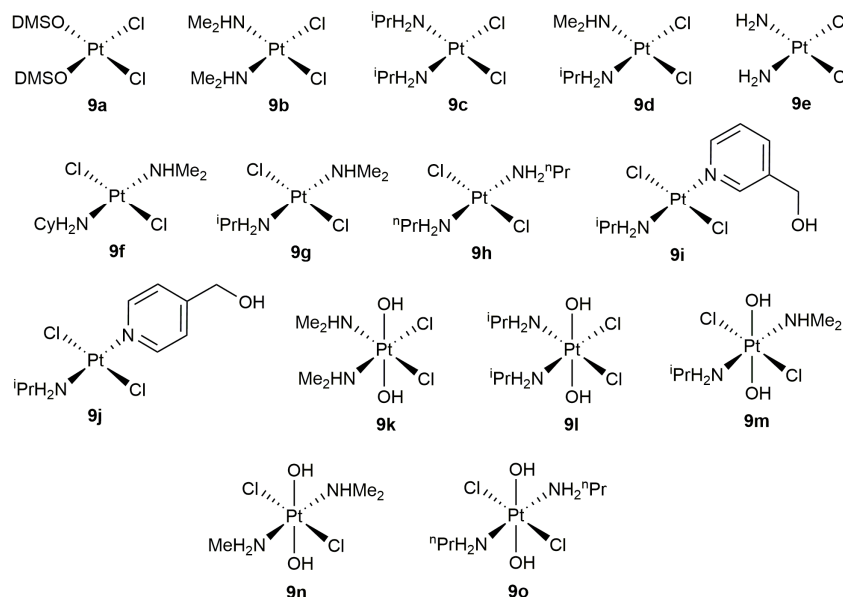

Figure 2. Structure of the platinum complexes **9a–o**.

In addition, they also demonstrated the possibility of using water (or even blood plasma) as solvent. In fact, the scope of the catalytic reaction was explored in water using complexes **9a,b** [38,39]. Thus, as shown in Scheme 5, different 5- and 6-membered ring lactones could be synthesized with these complexes, although mixtures of regioisomers were systematically formed starting from internal alkynes. On the other hand, it is also worth noting that the attempt made to generate a seven-membered ring lactone with this type of catalysts failed.
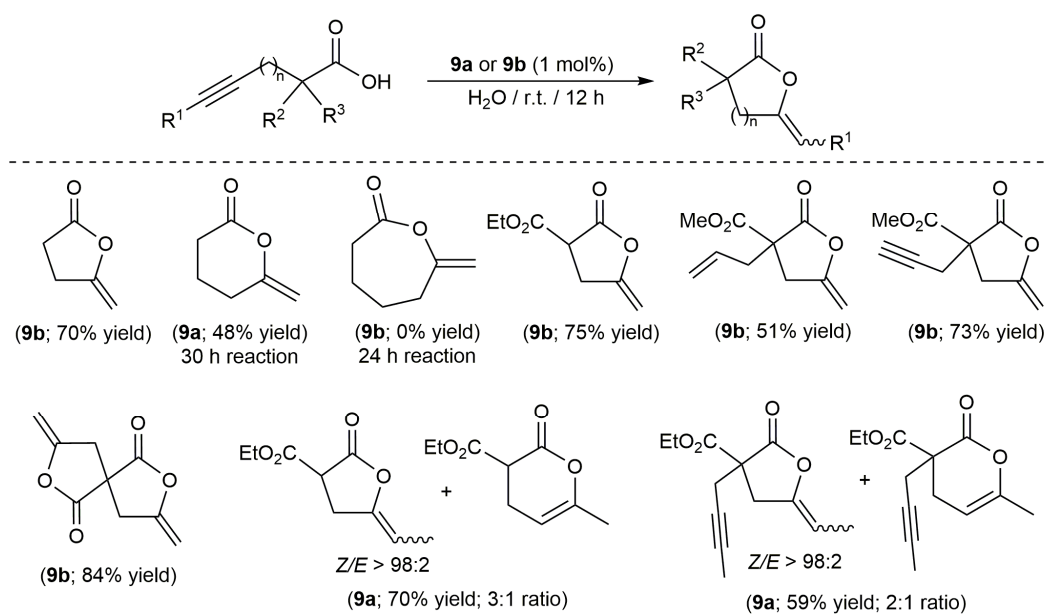
Scheme 5. Cyclization of different alkynoic acids in water using Pt(II) complexes.

Gold compounds are currently recognized as the most effective systems for the electrophilic π-activation of unsaturated carbon–carbon bonds [40,41], and, in 2006, Michelet and co-workers demonstrated for the first time their usefulness in the cycloisomerization of acetylenic acids [42]. The same group was also a pioneer in the use of gold catalysts in aqueous environments. In particular, in 2008, they reported on the tolerance of the heterogeneous system Au_2O_3 towards the presence of water during the cycloisomerization of 2-phenyl-4-pentynoic acid into 5-methylene-3-phenyl-dihydrofuran-2-one (92% yield performing the reaction in MeCN-H_2O (6:1) at r.t. with 2.5 mol % of Au_2O_3 for 3 h; 95% yield when acetonitrile was employed alone under identical reaction conditions) [43]. Since then, a number of gold-based catalysts capable of operating in pure water or in aqueous biphasic mixtures have been described, most involving functionalized *N*-heterocyclic carbenes (NHC) as auxiliary ligands. In this regard, the groups of Michelet, Cadierno and Conejero developed the zwitterionic Au(III)-NHC complex **10b** which proved to be active in the cycloisomerization of a broad range of γ-alkynoic acids under biphasic toluene/water conditions (Scheme 6) [44]. Remarkably, the participation of a silver(I) co-catalyst, usually employed in catalytic gold chemistry to generate vacant coordination sites on the metal through chloride ligands abstraction, was not required. Also of note is the fact that, despite the well-known ability of gold complexes to promote the hydration of alkynes, competitive hydration processes were not observed under the biphasic conditions employed, even during the cycloisomerization of bispropargylic substrates. However, it should be noted that, if pure water is used as solvent, partial hydrolysis of the lactone products takes place, making the use of biphasic conditions more advantageous. In general, the reactions proceeded in air under very mild temperature conditions (r.t.), except with those substrates containing internal C≡C bonds which showed a markedly lower reactivity and required of heating at 80 °C. Concerning the regioselectivity of the process, 5-membered ring enol-lactones were selectively formed when terminal C≡C bonds were involved in the cyclization process. On the other hand, although the 5-*exo-dig* cyclization was also the preferred reaction pathway with internal alkynes, mixtures containing the corresponding 5- and 6-membered ring lactones were in some cases obtained.
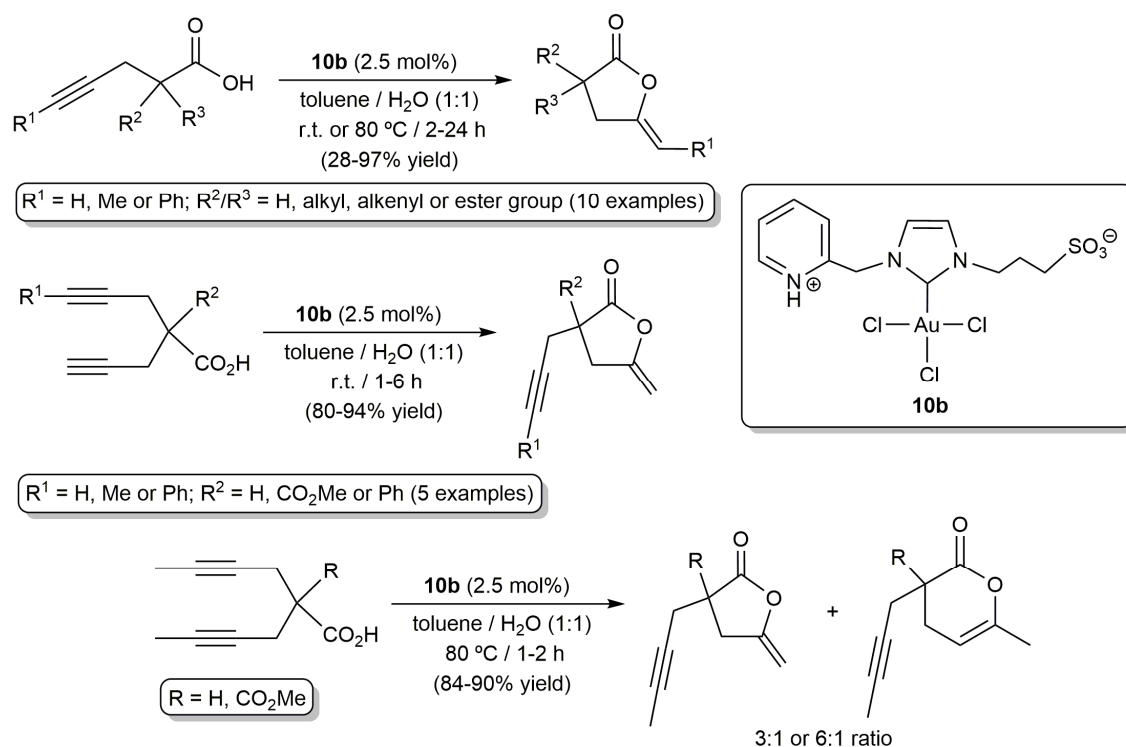
Scheme 6. Cycloisomerization of different γ-alkynoic acids catalyzed by the Au(III)-*N*-heterocyclic carbenes (NHC) complex **10b**.

This initial work with **10b** was subsequently extended to other Au(III) and Au(I) complexes containing related zwitterionic NHC ligands bearing 3-sulfonatopropyl, and 2-pyridyl, 2-pycolyl or pyridylethyl substituents (**10a,c** and **11a–c** in Figure 3) [45]. All of them proved to be catalytically active, even with Au loadings of only 0.1 mol %, showing in general performances similar to that of **10b**. Interestingly, all these gold-carbenes showed a very high recyclability (up to 10 consecutive runs) by simple phase separation (the gold catalyst remained in the aqueous phase while the lactone product was completely dissolved in the toluene one). In this regard, some differences were observed between the Au(I) and Au(III) species, the recyclability of the latter being much more effective due to their higher stability in the aqueous medium (the Au(I) derivatives **11a–c** undergo with time partial decomposition into catalytically inactive Au(0) nanoparticles; a process also observed with **10a–c** but which takes place much more slowly).
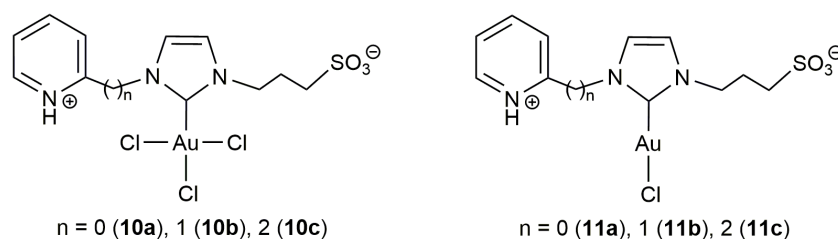

n = 0 (**10a**), 1 (**10b**), 2 (**10c**)   n = 0 (**11a**), 1 (**11b**), 2 (**11c**)

Figure 3. Structure of the zwitterionic Au(III)- and Au(I)-NHC complexes **10,11a–c**.

A good recyclability was also reported by Pleixats and co-workers for the sol-gel immobilized Au(I)-NHC complex **12** (Scheme 7) [46]. This organometallic hybrid silica material proved to be active in the cycloisomerization of different γ-alkynoic acids at room temperature using, as in the previous example, a toluene/water biphasic system and in the absence of silver salts. However, due to the heterogeneous nature of **12**, longer reaction times and a wrist-type shaker stirring (which allows a good mixing of the immiscible layers and the insoluble catalyst) were in this case required to obtain the enol-lactone products in high yields (no reaction was observed using conventional magnetic stirring). Concerning the regioselectivity of the process, five-membered enol-lactones were selectively formed starting from substrates with terminal alkyne units, while a mixture of the 5- and 6-membered ring lactone products was obtained from an internal diyne (Scheme 7).

For its part, the group of Krause described the preparation of the ammonium salt-tagged Au(I)-NHC complexes **13a–f** (Figure 4) and their application in the selective 5-*exo-dig* cyclization of γ-alkynoic acids bearing a terminal alkyne unit in pure water, or in aqueous triethylammonium buffer solution [47]. The catalytic reactions proceeded cleanly at r.t., in short time spans (0.5–6 h), employing 2.5 mol % of these complexes, with yields higher in general when the buffer solution was employed as the reaction medium (partial decomposition of the gold complexes was observed in pure water). Once again, no Ag(I) co-catalysts were needed and the catalysts could be reused after extraction of the lactone product from the aqueous solution with diethyl ether (up to 5 times).
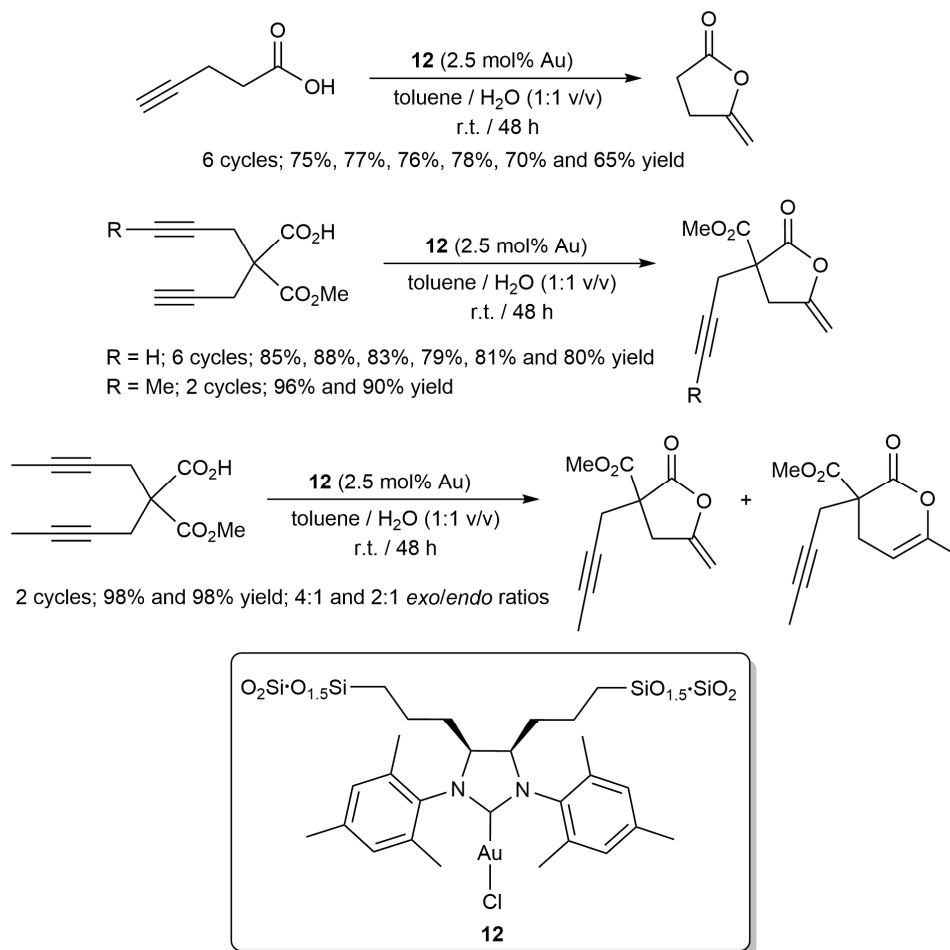
Scheme 7. Cyclosiomerization of γ-alkynoic acids using a sol-gel immobilized Au(I)-NHC complex.
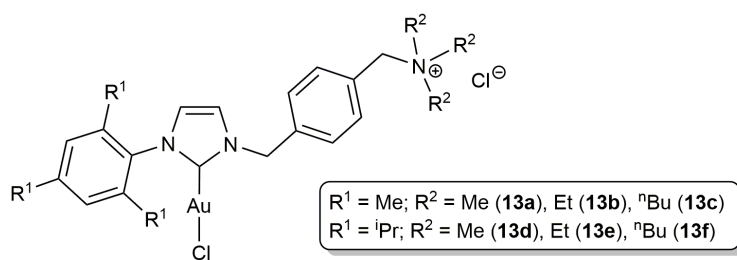

Figure 4. Structure of the water-soluble gold(I)-NHC complexes **13a–f**.

Interestingly, starting from the internal alkynoic acid **14**, a synthetic route to obtain the furanocoumarin-functionalized lactone **15**, an epimer of the natural product clausemarine A, could be developed by Krause and co-workers [47]. As shown in Scheme 8, formation of the lactone ring was successfully achieved by cycloisomerization of **14** with 1 mol % of **13b** in an aqueous triethylammonium buffer solution containing THF (tetrahydrofuran) as co-solvent.
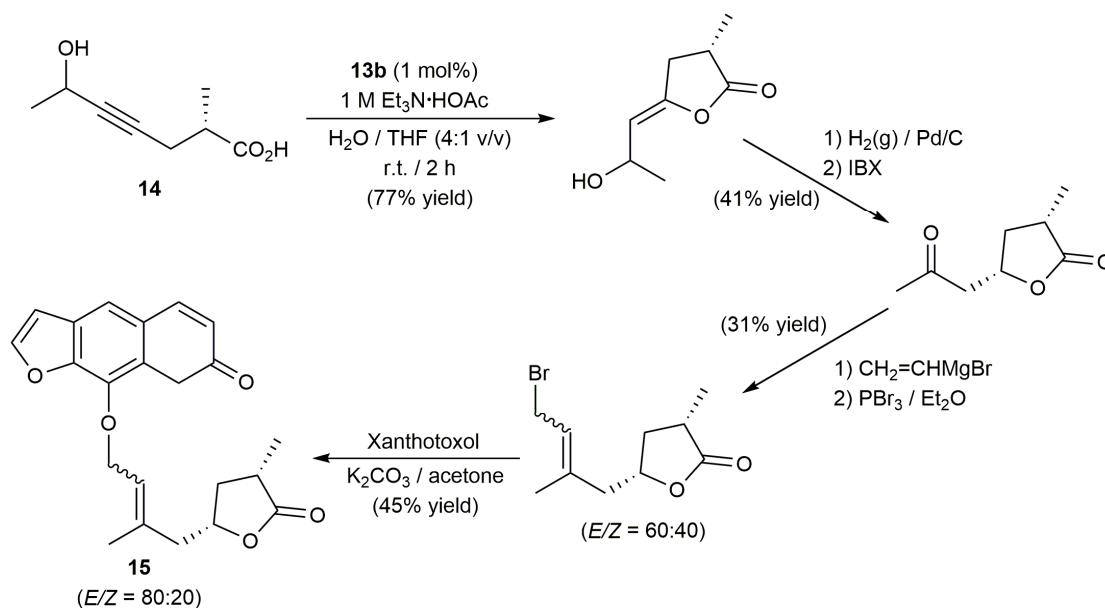
Scheme 8. Synthesis of 2-*epi*-clausemarine A.

Besides the Au-NHC complexes commented above, the PTA-derived iminophosphorane-Au(I) derivative **16** (Figure 5) proved to be also an active and selective catalyst for the 5-*exo-dig* cyclization of 4-pentynoic acid in water (89% yield after 30 min at r.t. with 1 mol % of **16**) [48]. However, this particular catalyst showed a higher reactivity in the eutectic mixture *1ChCl/2Urea* (ChCl = choline chloride; 99% yield after 15 min under identical reaction conditions) and, consequently, its scope was explored only in this alternative and biorenewable reaction medium.
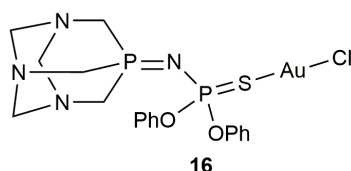

Figure 5. Structure of the iminophosphorane-gold(I) complex **16**.

In addition to palladium, platinum and gold, cheaper copper catalysts have also been used in the cycloisomerization of alkynoic acids in aqueous media. Thus, while studying the CuBr-catalyzed cycloaddition of alkynes with azides in $^tBuOH/H_2O$ mixtures, Mindt and Schibli observed the formation of enol-lactone by-products when employing γ-alkynoic acids as substrates, so they decided to explore separately the cyclization of these compounds [49]. Their results are shown in Scheme 9. Performing the reactions with 10 mol % of CuBr at r.t., different γ-alkynoic acids containing both terminal and internal C≡C units could be efficiently transformed into the corresponding γ-alkylidene butyrolactones. However, in some cases, γ-keto acids were selectively obtained due to the rapid hydrolysis of the lactone products under the aqueous conditions employed. On the other hand, the attempts made to extend the scope of this aqueous protocol to six- and seven-membered ring enol-lactones by cyclization of 5-hexynoic acids and 6-heptynoic acids, respectively, failed. It should be noted, however, that the former could be cyclized by carrying out the reactions in acetonitrile instead of the $^tBuOH/H_2O$ mixture.
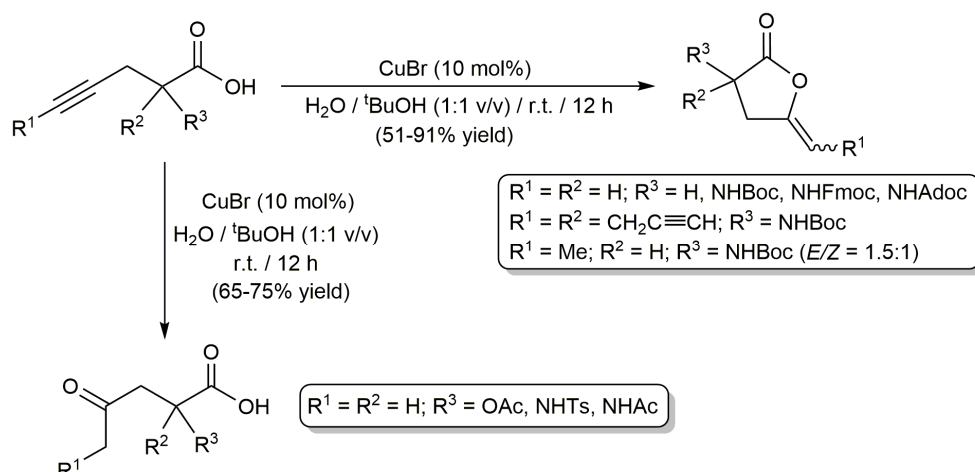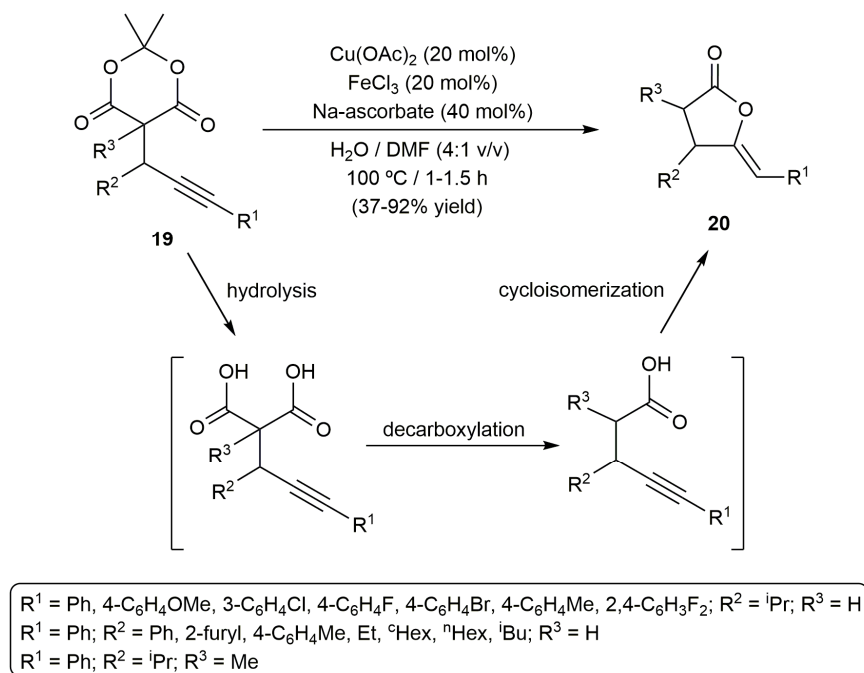
Scheme 9. CuBr-catalyzed transformations of different γ-alkynoic acids in aqueous medium.

More recently, CuBr was also employed to promote the cyclization of a variety of β-hydroxy-γ-alkynoic acids **17** [50]. As shown in Scheme 10, the reactions proceeded cleanly in pure water under microwave (MW) irradiation at 100 °C, leading to the regio- and stereoselective formation of the five membered ring Z-enol-lactones **18** without observing hydrolysis products. In addition, the beneficial effect of water was evidenced by the authors, who obtained markedly lower yields when performing the same reactions in classical organic solvents such as THF or acetonitrile. The same must be said of the use of MW irradiation, since lower yields were also observed when conventional oil-bath heating or ultrasound irradiation was employed. The process was quite general, tolerating a broad range of substitution patterns on the substrate skeleton. However, it should be noted that when an alkynoic acid featuring a hydrogen atom and a phenyl group, as the R^3 and R^4 substituents, was employed in this reaction, the spontaneous dehydration of **18** to form a 5-alkylidene-furan-2-one product took place.
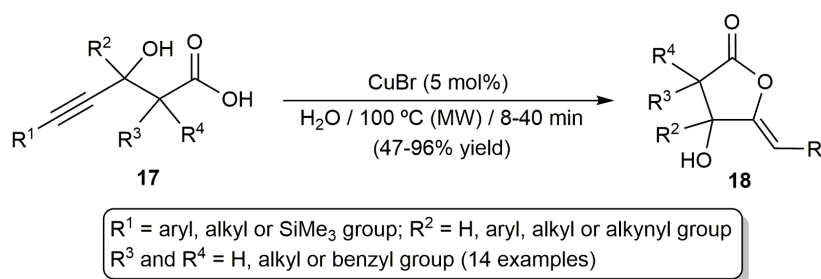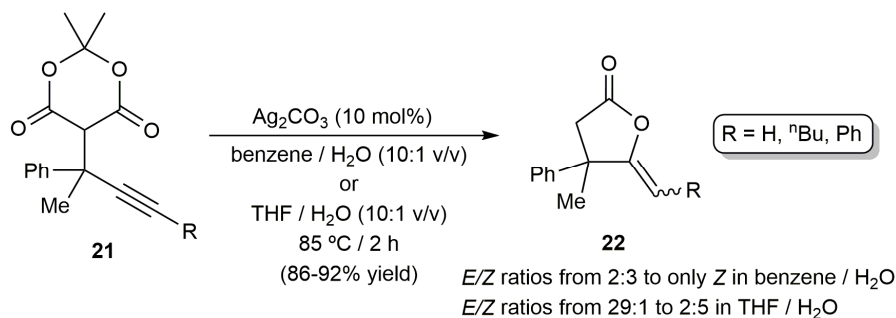

Scheme 10. Cu(I)-catalyzed cyclization of β-hydroxy-γ-alkynoic acids in water under microwave (MW) irradiation.

For its part, the group of Jiao described the cyclization of the propargylic Meldrum´s acids **19** into the (Z)-γ-alkylidene butyrolactones **20**, in a basic aqueous environment, through the combined use of Cu(OAc)$_2$ and FeCl$_3$ (Scheme 11) [51]. A clear cooperative effect of the two metals was observed, the yields decreasing drastically when Cu(OAc)$_2$ or FeCl$_3$ was used as the sole catalyst. The process most probably involves the in situ generation of a γ-alkynoic acid intermediate through a hydrolysis/decarboxylation sequence. On the other hand, although the mechanism could not be unambiguously established, it was assumed that the Cu^{2+} ion is the one responsible for the activation of the alkyne unit during the final cycloisomerization step, with Fe^{3+} probably facilitating the intramolecular nucleophilic addition of the carboxylate on the C≡C bond by coordination to the carbonyl group.

Scheme 11 reaction:

Cu(OAc)$_2$ (20 mol%)
FeCl$_3$ (20 mol%)
Na-ascorbate (40 mol%)

H$_2$O / DMF (4:1 v/v)
100 °C / 1–1.5 h
(37–92% yield)

19 → **20**

hydrolysis → decarboxylation → cycloisomerization

R^1 = Ph, 4-C$_6$H$_4$OMe, 3-C$_6$H$_4$Cl, 4-C$_6$H$_4$F, 4-C$_6$H$_4$Br, 4-C$_6$H$_4$Me, 2,4-C$_6$H$_3$F$_2$; R^2 = ^{i}Pr; R^3 = H
R^1 = Ph; R^2 = Ph, 2-furyl, 4-C$_6$H$_4$Me, Et, ^{c}Hex, ^{n}Hex, ^{i}Bu; R^3 = H
R^1 = Ph; R^2 = ^{i}Pr; R^3 = Me

Scheme 11. Cu/Fe-cocatalyzed synthesis of lactones from propargylic Meldrum's acids.

Further studies by the same group showed that the same catalytic reactions can be more conveniently carried out employing AgNO$_3$ (5 mol %) instead of the Cu/Fe system [52]. The reactions, performed at 100 °C in a H$_2$O/DMF (N,N-dimethylformamide) mixture under air, afforded regio- and stereoselectively the (*Z*)-γ-alkylidene butyrolactone products **20** in 45–87% isolated yields after ca. 1 h. Remarkably, no co-catalysts or bases were in this case needed. On the other hand, transformation of the related Meldrum´s acids **21** into lactones **22**, containing an all-carbon quaternary center at the C-4 position, was also described by Ahmar and Fillion using catalytic amounts of Ag$_2$CO$_3$, and mixtures THF/H$_2$O or toluene/H$_2$O as the reaction media (Scheme 12) [53]. Again, the 5-*exo-dig* cyclization products were exclusively formed and the reactions proceeded cleanly in the absence of base. However, we must note that mixtures of *E/Z* isomers were in most cases obtained starting from those substrates containing an internal C≡C bond.

Scheme 12 reaction:

Ag$_2$CO$_3$ (10 mol%)

benzene / H$_2$O (10:1 v/v)
or
THF / H$_2$O (10:1 v/v)
85 °C / 2 h
(86–92% yield)

21 → **22**

R = H, ^{n}Bu, Ph

E/Z ratios from 2:3 to only *Z* in benzene / H$_2$O
*E/Z* ratios from 29:1 to 2:5 in THF / H$_2$O

Scheme 12. Silver-catalyzed cyclization of the propargylic Meldrum's acids.

2.2. Tandem and Cascade Processes Involving the Cycloisomerization of an Alkynoic Acid

The aminolysis of lactones is a common transformation in organic synthesis which allows their direct conversion into linear amides [54,55]. The combination of this reaction with the cycloisomerization of alkynoic acids has been extensively studied in the last years giving access to a huge number of nitrogen-containing heterocyclic compounds, through different cascade processes, by

appropriate selection of the functionalized amine partner [56–59]. In this context, Liu and co-workers developed an efficient and broad scope gold-catalyzed reaction for the synthesis of fused polycyclic indoles **23** in water, starting from 2-(1*H*-indol-1-yl)alkylamines and alkynoic acids (Scheme 13) [60].
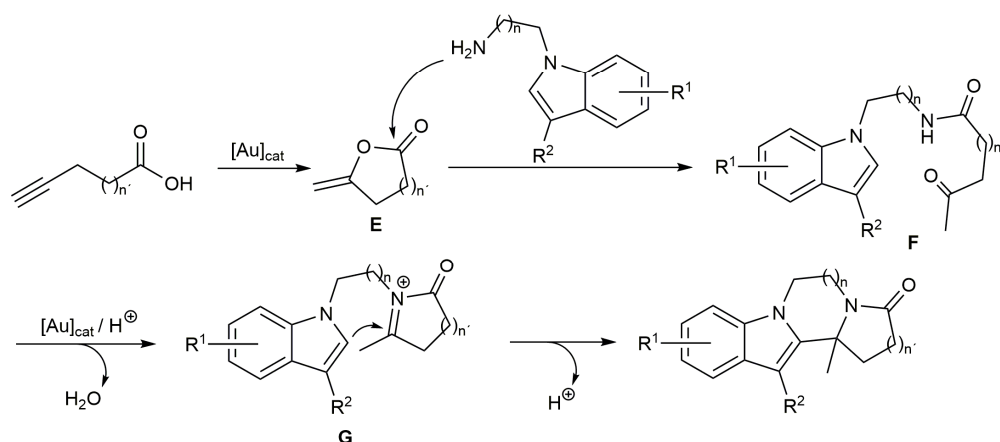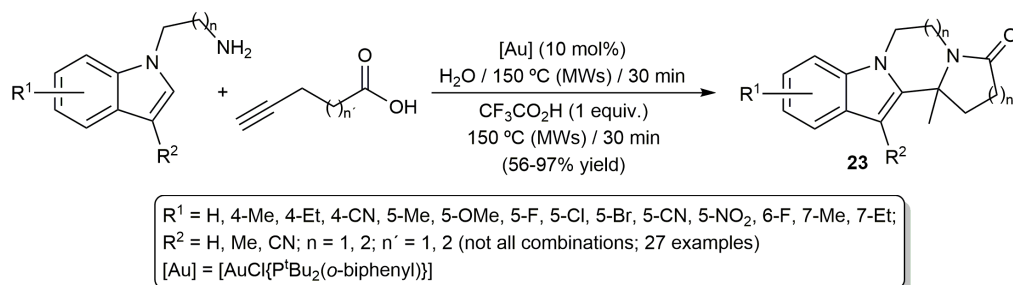
**Scheme 13.** Gold-catalyzed synthesis of fused polycyclic indoles in water.

The process involves the aminolysis of the in situ formed enol-lactones **E** to generate the linear keto-amides **F**, which subsequently evolve into **G** via a gold-catalyzed *N*-acyliminium ion formation/cyclization. Final intramolecular nucleophilic attack of the C-2 carbon of the indolic unit to the iminium carbon yields the products **23**. To facilitate the cyclization step leading to **G**, the addition trifluoroactic acid was in some cases required. As shown in Scheme 13, the reactions proceeded in short times under microwave irradiation, tolerating the presence of different functional groups.

The same group also described the coupling of 4-pentynoic acid with *o*-aminophenylmethanol in water catalyzed by the cationic gold(I) complex [Au{P^{t}Bu$_2$(*o*-biphenyl)}(MeCN)][SbF$_6$] (Scheme 14) [61]. The reaction afforded the pyrrolo[2,1-*b*]benzo[*d*][1,3]oxazin-1-one **24** in 50% yield. However, we must note that this value was much lower to that obtained in THF under identical reaction conditions (91% yield), so it is not surprising that the generality of the process was studied in the latter solvent. As in the precedent case, the reaction is initiated by the cycloisomerization of the alkynoic acid, subsequent aminolysis of the enol lactone intermediate, and final cyclization of the resulting keto amide catalyzed by the gold complex.
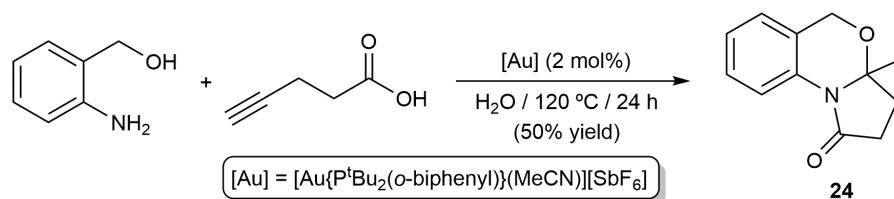

Scheme 14. Gold-catalyzed synthesis of the pyrrolo[2,1-*b*]benzo[*d*][1,3]oxazin-1-one **24** in water.

In another vein, the group of Jiang developed an aqueous protocol for the one-pot synthesis of phthalides **26** from terminal alkynes and *o*-iodobenzoic acid (Scheme 15) [62]. The process, which involves the initial Sonogashira coupling of the substrates and subsequent stereoselective 5-*exo-dig* cyclization of the resulting ethynyl-benzoic acid intermediates **25**, was catalyzed by palladium immobilized on carbon nanotubes (CNTs) in a DMF:H_2O mixture. Unlike previous examples of this tandem reaction, formation of isocoumarin by-products (6-*endo-dig* cyclization) was in this case not observed, and no additives such as phosphine ligands or CuI were needed.

R = Ph, 4-C_6H_4F, 4-C_6H_4Me, CO_2Me, CH_2OH, CH_2CH_2OH, $CH_2(CH_2)_3OH$, $CH(OH)^nPr$, CMe_2OH, $SiMe_3$
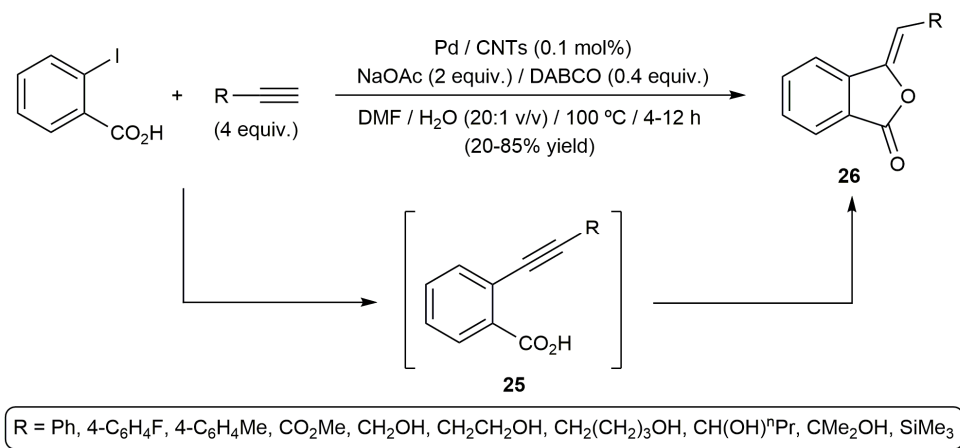
Scheme 15. Catalytic synthesis of phthalides from terminal alkynes and *o*-iodobenzoic acid.

Taking advantage of the ability of the dinuclear iminophosphorane-palladium(II) complex **4** to promote the fast and selective transformation of bispropargylic carboxylic acids **5** into enol-lactones **6** (Scheme 4), García-Álvarez and co-workers could set up an unprecedented one-pot tandem process combining the aforementioned reaction with a copper-catalyzed 1,3-dipolar cycloaddition of azides with the terminal alkyne arm of the enol-lactone products (Scheme 16) [30]. To promote the 1,3-dipolar cycloaddition step the polymeric Cu(I) catalyst $[Cu\{\mu^2\text{-}N,S\text{-}(PTA)=NP(=S)(OEt)_2\}]_x[SbF_6]_x$ (**27**) containing the same hydrophilic iminophosphorane ligand [63], in combination with the 2,6-lutidine base, was employed. The tandem process proceeded in pure water under mild conditions, affording the bicyclic triazol-enol-lactones **28** in excellent yields after a simple extraction with diethyl ether (no chromatographic purification was needed).

R^1 = H, CO_2Me, Ph; R^2 = Bn, CH_2SPh, 1-adamantyl (all combinations)
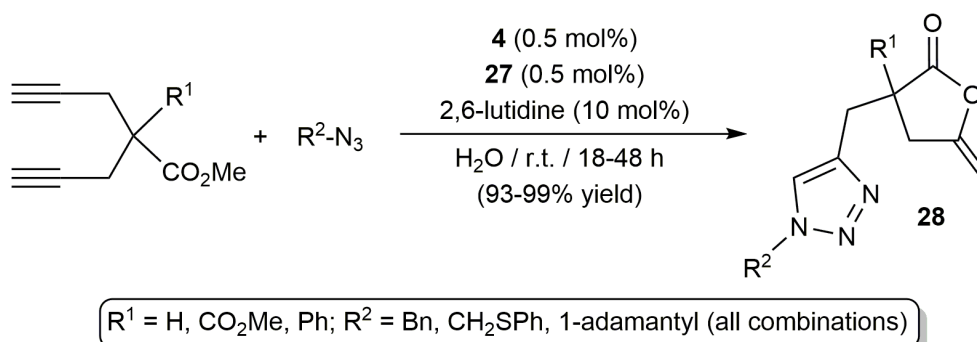
Scheme 16. Access to bicyclic triazol-enol-lactones from of bispropargylic carboxylic acids and azides.

On the other hand, based on the capability of copper salts to promote the conjugate alkynylation of electron-deficient olefins, the (*Z*)-γ-alkylidene butyrolactones **30** could be synthesized in a one-pot manner starting from the corresponding terminal alkynes and the 5-alkylidene-Meldrun's acids **29**, via in situ formation of the corresponding propargylic Meldrun's acids (Scheme 17). The process

was promoted by the Cu(OAc)$_2$/FeCl$_3$ combination discussed above for the cyclization of Meldrun´s acids **19** (Scheme 11) [51].
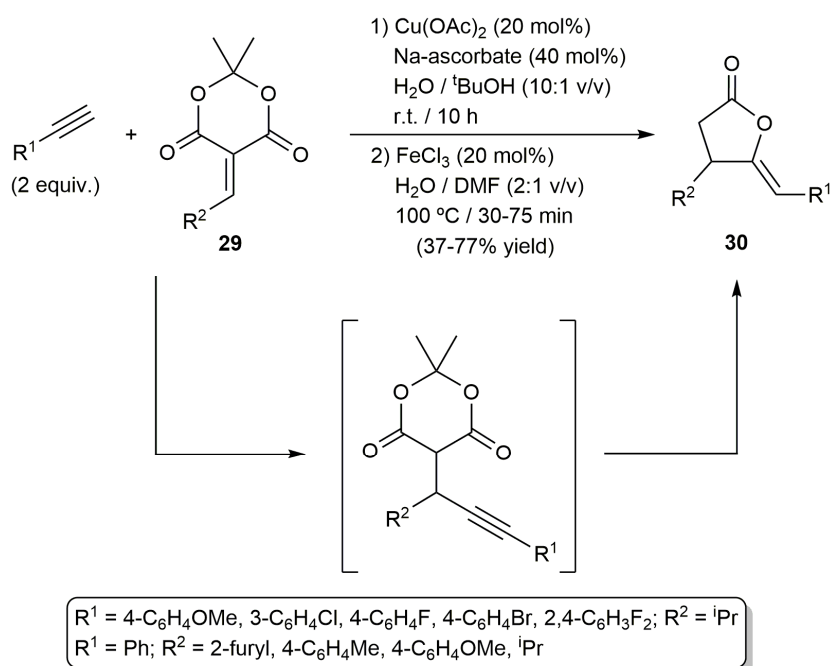
Scheme 17. Cu/Fe-cocatalyzed synthesis of lactones from alkynes and 5-alkylidene-Meldrum's acids.

Finally, the combination of metal catalysis and biocatalysis has emerged in recent years as a powerful tool for developing new synthetic methodologies merging the advantages of both disciplines in terms of reaction scope and selectivity [64–66]. In this context, García-Álvarez, González-Sabín and co-workers described very recently the one-pot conversion of 4-pentynoic acid into enantiopure γ-hydroxyvaleric acid in aqueous medium, through the combined use of KAuCl$_4$ and ketoreductases (KREDs) (Scheme 18) [67]. The process involves the initial gold-catalyzed cycloisomerization of the substrate, concomitant hydrolysis of the lactone to form levulinic acid, and final bioreduction of the keto group of the latter. Remarkably, no isolation or purification steps were required, the reaction medium coming from the metal-catalyzed reaction being directly employed in the enzymatic step. Also of note is the fact that, just by selecting the adequate KRED, both enantiomers of the γ-hydroxyvaleric acid could be obtained with excellent *ee* values.
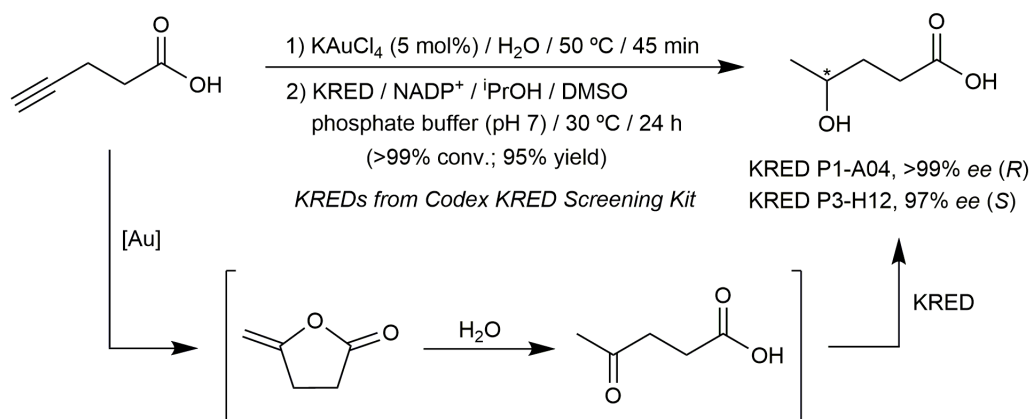
Scheme 18. Chemoenzymatic one-pot conversion of 4-pentynoic acid into enantiopure γ-hydroxyvaleric acid.

3. Intermolecular Processes

3.1. Catalytic Addition of Carboxylic Acids to Terminal and Internal Alkynes

Although the intermolecular hydro-oxycarbonylation of alkynes has been widely studied in organic media [1–6], to date there are very few examples of this catalytic transformation described in water. In this regard, Cadierno, Gimeno and co-workers evaluated in 2011 the catalytic potential of a diverse family of ruthenium(IV) complexes, of general composition *trans*-[RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(L)] (**31a–s** in Figure 6), for the hydro-oxycarbonylation of terminal alkynes in aqueous medium [68].

L = PPh$_3$ (**31a**), TPPMS (**31b**), P(*p*-Tol)$_3$ (**31c**), PPh$_2$Me (**31d**), PPhMe$_2$ (**31e**), PMe$_3$ (**31f**),
P^{i}Pr$_3$ (**31g**), PBn$_3$ (**31h**), P(OMe)$_3$ (**31i**), P(OEt)$_3$ (**31j**), P(O^{i}Pr)$_3$ (**31k**), P(OPh)$_3$ (**31l**),
NCMe (**31m**), NCPh (**31n**), NH$_2$Ph (**31o**), py (**31p**), CO (**31q**), CNBn (**31r**), CNCy (**31s**)
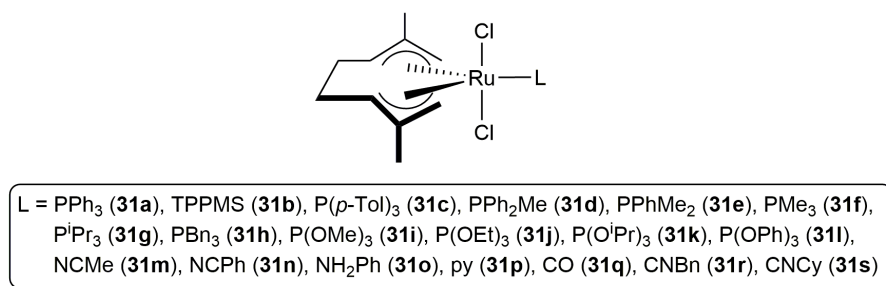
**Figure 6.** Structure of the bis(allyl)-ruthenium(IV) complexes **31a–s**.

All these compounds were found to be active catalysts in the addition of benzoic acid to 1-hexyne in pure water, providing the corresponding enol esters ^{n}BuC(OBz)=CH$_2$ (Markovnikov addition product) and (*E*/*Z*)-^{n}BuCH=CH(OBz) (*anti*-Markovnikov addition products) in moderate to good yields after 3–24 h of heating at 60 °C (with a Ru loading of 2 mol %). A high selectivity towards the Markovnikov addition product was in general observed, except in the case of catalysts **31m–p** containing a labile amine or nitrile ligand which generated preferentially (*E*/*Z*)-^{n}BuCH=CH(OBz), albeit only in moderate yields. The best results in terms of activity and regioselectivity were obtained with [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(PPh$_3$)] (**31a**), which was able to generate the enol ester ^{n}BuC(OBz)=CH$_2$ in 96% yield (by gas chromatography) after only 3 h of heating. However, from the data obtained, no relationships between the steric and/or electronic nature of the auxiliary ligand L and the catalytic activity observed could be drawn. On the other hand, it must be also highlighted that, with the exception of [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(TPPMS)] (**31b**; TPPMS = 3-(diphenylphosphino)benzenesulfonate sodium salt) and [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$){P(OR)$_3$}] (R = Me (**31i**), Et (**31j**), ^{i}Pr (**31k**)), these Ru(IV) complexes are completely insoluble in water. Accordingly, in most of the reactions the catalyst remained dissolved in the organic phase, forming an emulsion with water under stirring. In other words, the reactions proceeded under the so-called "on-water" conditions [69,70]. In addition, when the same reactions were carried out under homogeneous conditions using organic solvents, the results were much worse in terms of yields (the regioselectivity remained unaffected), pointing out the marked positive effect of water in the process. Although to a lesser extent, the beneficial effect of water in the catalytic addition of carboxylic acids to terminal alkynes promoted by tethered arene-ruthenium(II) complexes was also observed by Demonceau and co-workers, who obtained higher yields when performing the reactions in moist vs. dry toluene [71].

The most active catalyst of the series, i.e., [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(PPh$_3$)] (**31a**), showed also a wide scope allowing the preparation of a large variety of enol esters **32** by selective Markovnikov addition of different carboxylic acids to both aliphatic and aromatic terminal alkynes, as well as to 1,3-enynes (Scheme 19) [68,72,73]. As a general trend, the reactions proceeded faster, and with higher yields, when aliphatic terminal alkynes were employed as substrates. Also notable are the high functional group compatibility showed by complex **31a** and the absence of competing processes of hydration of the alkynes.
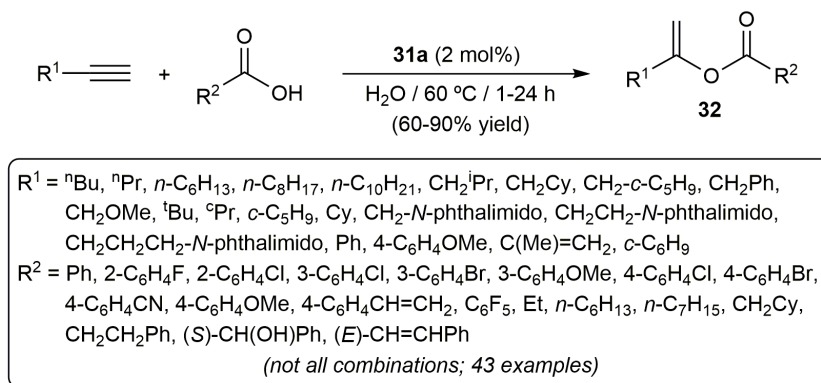
Scheme 19. Ruthenium(IV)-catalyzed Markovnikov addition of carboxylic acids to terminal alkynes.

Further evidence of the versatility of $[RuCl_2(\eta^3{:}\eta^3{-}C_{10}H_{16})(PPh_3)]$ (**31a**) was gained in the reactions of the terminal diynes **33** with benzoic acid. Thus, as shown in Scheme 20, the corresponding enynes **34** or the diesters **35** could be selectively synthesized with **31a** just by adjusting the diyne/benzoic acid ratio employed [68,72,73].
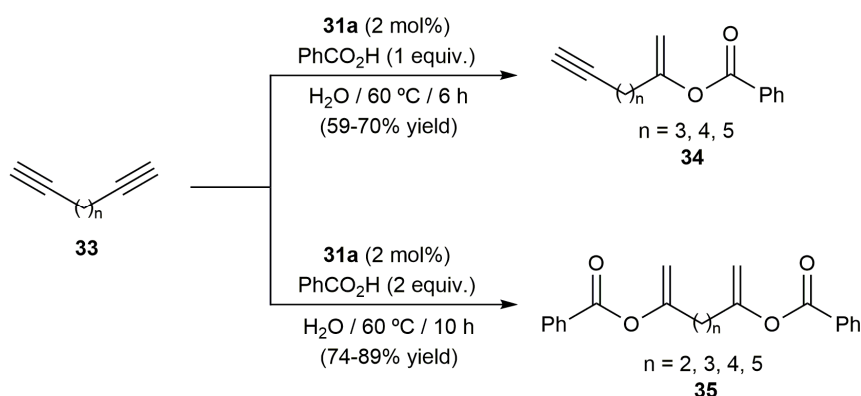

Scheme 20. Ruthenium(IV)-catalyzed Markovnikov addition of benzoic acid to terminal diynes.

The only limitation encountered with the ruthenium catalyst **31a** is that it is completely inactive with internal alkynes; substrates which, as commented in the introduction of this article, show a much lower reactivity in these intermolecular hydrocarboxylation reactions. For this particular class of alkynes, Cadierno, García-Garrido and co-workers developed very recently a protocol in water employing the catalytic system [AuCl(PPh₃)]/AgOAc [74]. Thus, as depicted in Scheme 21, a broad range of trisubstituted enol esters **36** could be synthetized in good yields by addition of different aromatic, aliphatic, heterocyclic and α,β-unsaturated carboxylic acids to internal alkynes symmetrically substituted with aliphatic groups. Concerning the use of aromatic alkynes, they showed only a residual reactivity towards benzoic acid and, when an aliphatic carboxylic acid was employed, a higher temperature and catalyst loading were required to obtain the corresponding products in moderate yields. Interestingly, compounds **36** were obtained in a stereoselective manner (only *Z* isomers) as the result of the exclusive *anti* addition of the O-H bond of the carboxylic acid to the alkyne.
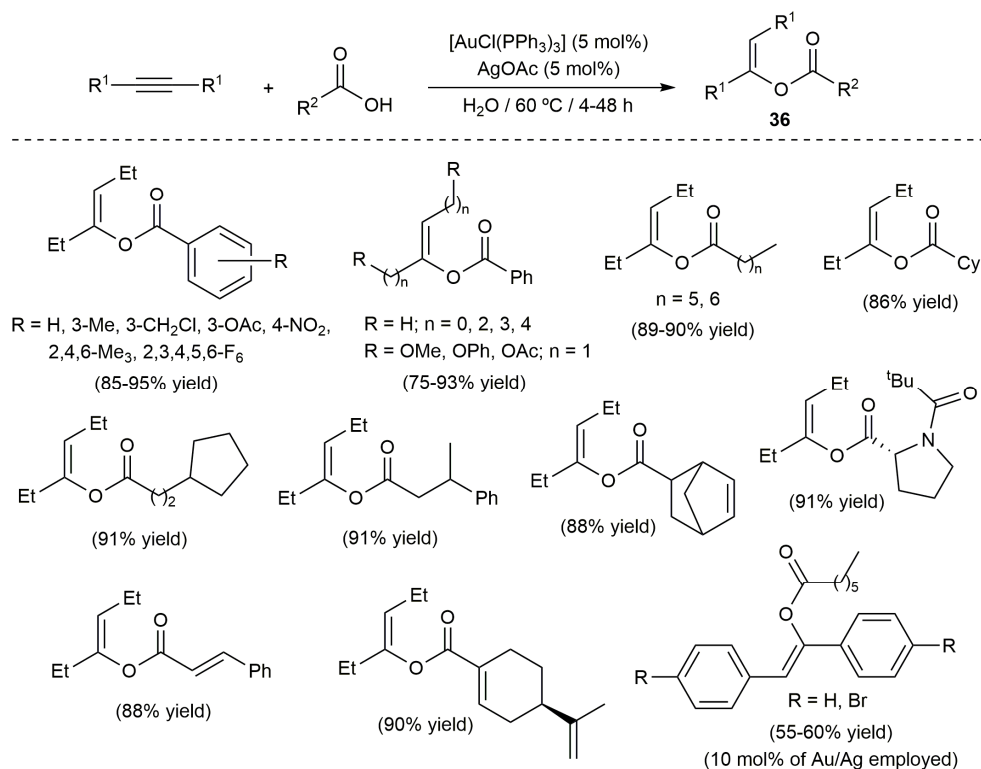
Scheme 21. Gold-catalyzed addition of carboxylic acids to symmetrically substituted internal alkynes.

The reactivity of some unsymmetrically substituted internal alkynes towards benzoic acid in water was also explored using the catalytic system [AuCl(PPh$_3$)]/AgOAc, the reations leading in most of the cases to mixtures of regioisomers derived from the attack of acid to both carbon atoms of the alkyne (complete Z-selectivity was again observed for both regioisomers). Only when the activated internal alkynes **37** and **38** were employed as substrates a complete regioselectivity to enol esters **39** and **40**, respectively, was observed (Scheme 22) [74].
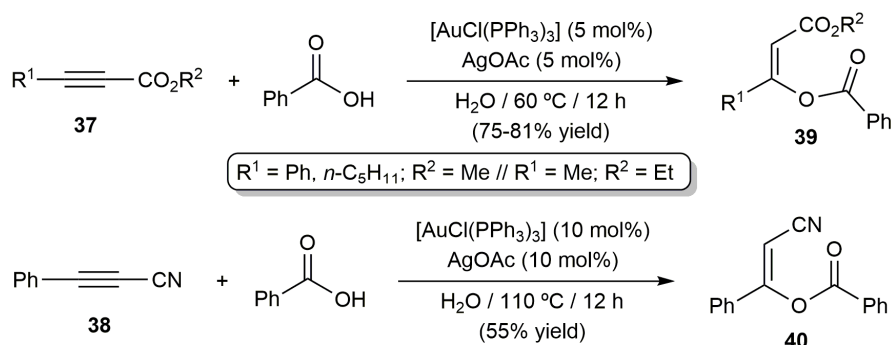

Scheme 22. Regio- and stereoselective addition of benzoic acid to unsymmetrically substituted alkynes.

3.2. Catalytic Addition of Carboxylic Acids to Terminal Propargylic Alcohols

β-Oxo esters are useful intermediates in organic chemistry. For example, they have been employed in the synthesis of different pharmaceuticals [75–77], and can be easily transformed into the corresponding α-hydroxy ketones, which are structural units present in a large variety of biologically active molecules [78,79]. Among the different synthetic approaches to β-oxo esters [80], the ruthenium-catalyzed addition of carboxylic acids to terminal propargylic alcohols has emerged as one of the most straightforward and atom-economical routes (Scheme 23). The process involves

the Markovnikov attack of the carboxylic acid to an initially formed π-alkyne-ruthenium complex **H**, which is followed by the intramolecular transesterification of the resulting intermediate **I** to form an alkenyl derivative **J**. The final protonolysis of **J** releases the β-oxo ester product and regenerates the catalytically active ruthenium species.
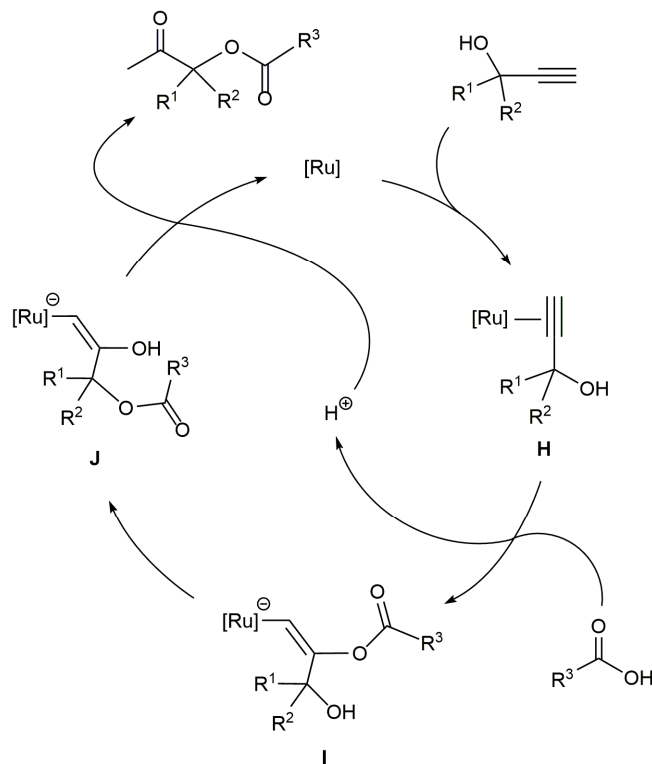
Scheme 23. Mechanism of the Ru-catalyzed β-oxo esters formation reactions.

Since the pioneering work by Mitsudo and Watanabe in 1987 [81], a number of ruthenium catalysts for this transformation have been developed [80,82]. Among them, the bis(allyl)-ruthenium(IV) complex [RuCl$_2$(η^3:η^3-C$_{10}$H$_{16}$)(PPh$_3$)] (**31a**) (Figure 6) proved to be active in water [68]. Thus, as shown in Scheme 24, starting from different propargylic alcohols and benzoic acid, a family of β-oxo esters **41** could be synthetized in moderate to good yields employing identical experimental conditions to those applied in the preparation of the enol esters **32** (Scheme 19). Although the scope of the reaction concerning the carboxylic acid partner was not studied in much detail, the authors showed that it is not restricted to benzoic acid since the addition of 2-chlorobenzoic acid, pentafluorobenzoic acid, heptanoic acid and 3-cyclopentylpropionic acid to 1-phenyl-2-propyn-1-ol also afforded the corresponding β-oxo esters in 47–90% yield.
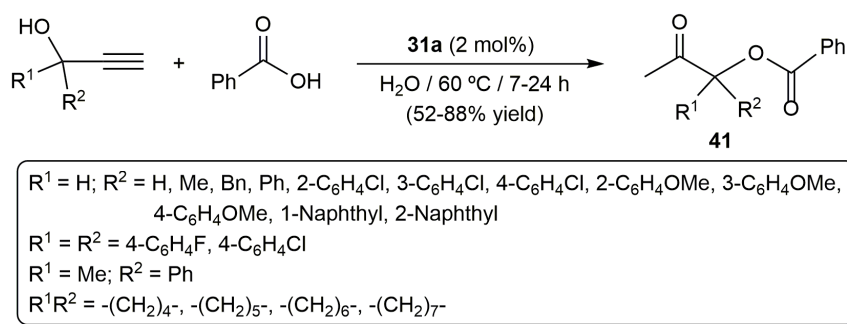
Scheme 24. Synthesis of β-oxo esters in water catalyzed by the ruthenium(IV) complex **31a**.

In an independent work, Cadierno, Gimeno and co-workers also explored the catalytic potential of a series of arene-ruthenium(II) complexes containing different water-soluble phosphine ligands (**42–45a–d** in Figure 7) [83]. All of them proved to the active in the addition of benzoic acid to 1-phenyl-2-propyn-1-ol in pure water, leading to the desired *β*-oxo ester, i.e., 1-phenyl-2-oxopropyl benzoate, as the major reaction product. Among them, best results in terms of activity and selectivity were obtained with the benzene derivative [RuCl$_2$(η^6-C$_6$H$_6$)(TPPMS)] (**45a**) (88% yield of 1-phenyl-2-oxopropyl benzoate after 3 h of heating at 100 °C using a ruthenium loading of 2 mol %). Concerning the scope of this complex, a variety of secondary propargylic alcohols, as well as prop-2-yn-1-ol, could be efficiently transformed. In contrast, tertiary propargylic alcohols resulted to be more challenging substrates and only those featuring low sterically-demanding substituents led to high conversions. On the other hand, **45a** was operative with a large variety of aromatic carboxylic acids, bearing different functional group such as halide, alkoxy, ketone or sulfonamide. The use of heteroaromatic acids, with tetrahydrofuran, pyrrole, thiophene, indole or 2-oxo-2*H*-chromene fragments, as well as aliphatic acids was also tolerated.
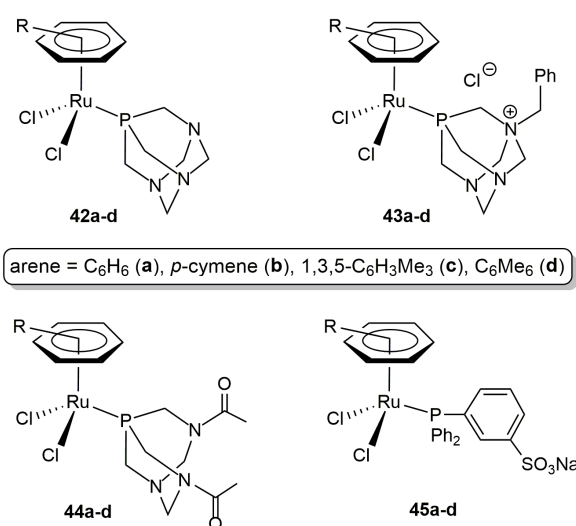

Figure 7. Structure of the water-soluble arene-ruthenium(II) complexes **42–45a–d**.

4. Conclusions

Great attention is currently devoted to synthetic organic chemistry in water and research, particularly in the field of aqueous catalysis, is increasing exponentially since water is the most environmentally benign substitute for the volatile and toxic organic solvents commonly used in laboratories and industries. In this contribution, we have summarized the developments achieved in the field of metal-catalyzed additions of carboxylic acids to alkynes in aqueous media. Such processes now represent powerful tools for the construction of synthetically useful lactones, enol esters and *β*-oxo esters in an atom-economical manner. Throughout this review article, we have presented different catalytic systems based on Pd, Pt, Au, Cu and Ru, capable of promoting selectively these reactions in aqueous environments without observing the competing hydration of the alkyne substrates. The vast majority of the works discussed herein have been published during the last ten years, demonstrating clearly the current interest in this research field, which obviously remains open, with many opportunities for new discoveries.

Author Contributions: Both authors analyzed the data and jointly wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1.　Alonso, F.; Beletskaya, I.P.; Yus, M. Transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes. *Chem. Rev.* **2004**, *104*, 3079–3159. [CrossRef] [PubMed]
2.　Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and anti-Markovnikov functionalization of alkenes and alkynes: Recent developments and trends. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398. [CrossRef] [PubMed]
3.　Patil, N.T.; Kavthe, R.D.; Shinde, V.S. Transition metal-catalyzed addition of C-, N- and O-nucleophiles to unactivated C–C multiple bonds. *Tetrahedron* **2012**, *68*, 8079–8146. [CrossRef]
4.　Hintermann, L. Recent developments in metal-catalyzed additions of oxygen nucleophiles to alkenes and alkynes. *Top. Organomet. Chem.* **2010**, *31*, 123–155.
5.　Bruneau, C. Group 8 metals-catalyzed O–H bond addition to unsaturated molecules. *Top. Organomet. Chem.* **2013**, *43*, 203–230.
6.　Abbiati, G.; Beccalli, E.M.; Rossi, E. Groups 9 and 10 metals-catalyzed O-H bond addition to unsaturated molecules. *Top. Organomet. Chem.* **2013**, *43*, 231–290.
7.　Rao, Y.S. Recent advances in the chemistry of unsaturated lactones. *Chem. Rev.* **1976**, *76*, 625–694. [CrossRef]
8.　Laduwahetty, T. Saturated and unsaturated lactones. *Contemp. Org. Synth.* **1995**, *2*, 133–149. [CrossRef]
9.　Libiszewska, K. Lactones as biologically active compounds. *Biotechnol. Food Sci.* **2011**, *75*, 45–53.
10.　Janecki, T. (Ed.) *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*; Wiley-VCH: Weinheim, Germany, 2013; ISBN 9783527334148.
11.　Neaţu, F.; Toullec, P.Y.; Michelet, V.; Pârvulescu, V.I. Heterogeneous Au and Rh catalysts for the cycloisomerization reactions of γ-acetylenic carboxylic acids. *Pure Appl. Chem.* **2009**, *81*, 2387–2396. [CrossRef]
12.　Bruneau, C.; Neveux, M.; Kabouche, Z.; Ruppin, C.; Dixneuf, P.H. Ruthenium-catalyzed additions to alkynes: Synthesis of activated esters and their use in acylation reactions. *Synlett* **1991**, *11*, 755–763. [CrossRef]
13.　Kumar, M.; Bagchi, S.; Sharma, A. The first vinyl acetate mediated organocatalytic transesterification of phenols: A step towards sustainability. *New J. Chem.* **2015**, *39*, 8329–8336. [CrossRef]
14.　Liu, X.; Coutelier, O.; Harrison, S.; Tassaing, T.; Marty, J.-D.; Destarac, M. Enhanced solubility of polyvinyl esters in scCO$_2$ by means of vinyl trifluorobutyrate monomer. *ACS Macro Lett.* **2015**, *4*, 89–93. [CrossRef]
15.　Foarta, F.; Landis, C.R. Condensation oligomers with sequence control but without coupling reagents and protecting groups via asymmetric hydroformylation and hydroacyloxylation. *J. Org. Chem.* **2016**, *81*, 11250–11255. [CrossRef] [PubMed]
16.　Jena, R.K.; Das, U.K.; Ghorai, A.; Bhattacharjee, M. Ruthenium-catalyzed addition of carboxylic acids to progargylic alcohols: An easy route to *O*-dienyl esters and their tandem atom-transfer radical polymerization. *Eur. J. Org. Chem.* **2016**, 6015–6021. [CrossRef]
17.　Konrad, T.M.; Schmitz, P.; Leitner, W.; Franciò, G. Highly enantioselective Rh-catalysed hydrogenation of 1-alkyl vinyl esters using phosphine-phosphoramidite ligands. *Chem. Eur. J.* **2013**, *19*, 13299–13303. [CrossRef] [PubMed]
18.　González-Liste, P.J.; León, F.; Arribas, I.; Rubio, M.; García-Garrido, S.E.; Cadierno, V.; Pizzano, A. Highly stereoselective synthesis and hydrogenation of (*Z*)-1-alkyl-2-arylvinyl acetates: A wide scope procedure for the preparation of chiral homobenzylic esters. *ACS Catal.* **2016**, *6*, 3056–3060. [CrossRef]
19.　León, F.; González-Liste, P.J.; García-Garrido, S.E.; Arribas, I.; Rubio, M.; Cadierno, V.; Pizzano, A. Broad scope synthesis of ester precursors of nonfunctionalized chiral alcohols based on the asymmetric hydrogenation of α,β-dialkyl-, α,β-diaryl-, and α-alkyl-β-aryl-vinyl esters. *J. Org. Chem.* **2017**, *82*, 5852–5867. [CrossRef] [PubMed]
20.　Takeno, M.; Kikuchi, S.; Morita, S.-I.; Nishiyama, Y.; Ishii, Y. A new coupling reaction of vinyl esters with aldehydes catalyzed by organosamarium compounds. *J. Org. Chem.* **1995**, *60*, 4974–4975. [CrossRef]
21.　Goossen, L.J.; Paetzold, J. Decarbonylative Heck olefination of enol esters: Salt-free and environmentally friendly access to vinyl arenes. *Angew. Chem. Int. Ed.* **2004**, *43*, 1095–1098. [CrossRef] [PubMed]
22.　Geibel, I.; Dierks, A.; Schmidtmann, M.; Christoffers, J. Formation of δ-lactones by cerium-catalyzed, Baeyer-Villiger-type coupling of β-oxoesters, enol acetates, and dioxygen. *J. Org. Chem.* **2016**, *81*, 7790–7798. [CrossRef] [PubMed]

23. González-Liste, P.J.; Francos, J.; García-Garrido, S.E.; Cadierno, V. The intermolecular hydro-oxycarbonylation of internal alkynes: Current state of the art. *Arkivoc* **2018**, *Part II*, 17–39.

24. Cornils, B.; Herrmann, W.A. (Eds.) *Aqueous-Phase Organometallic Catalysis*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; ISBN 3527307125.

25. Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, USA, 2007; ISBN 9780471761297.

26. Dixneuf, P.H.; Cadierno, V. (Eds.) *Metal-Catalyzed Organic Reactions in Water*; Wiley-VCH: Weinheim, Germany, 2013; ISBN 9783527331888.

27. Benaglia, M. (Ed.) *Recoverable and Recyclable Catalysts*; John Wiley & Sons: Chichester, UK, 2009; ISBN 9780470681954.

28. Chen, L.; Li, C.-J. Catalytic reactions of alkynes in water. *Adv. Synth. Catal.* **2006**, *348*, 1459–1484. [CrossRef]

29. Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. A novel catalyst with a cuboidal $PdMo_3S_4$ core for the cyclization of alkynoic acids to enol lactones. *Angew. Chem. Int. Ed.* **1996**, *35*, 2123–2124. [CrossRef]

30. García-Álvarez, J.; Díez, J.; Vidal, C. Pd(II)-catalyzed cycloisomerisation of γ-alkynoic acids and one-pot tandem cycloisomerisation/CuAAC reactions in water. *Green Chem.* **2012**, *14*, 3190–3196. [CrossRef]

31. Phillips, A.D.; Gonsalvi, L.; Romerosa, A.; Vizza, F.; Peruzzini, M. Coordination chemistry of 1,3,5-triaza-7-phosphaadamantane (PTA): Transition metal complexes and related catalytic, medicinal and photoluminescent applications. *Coord. Chem. Rev.* **2004**, *248*, 955–993. [CrossRef]

32. Bravo, J.; Bolaño, S.; Gonsalvi, L.; Peruzzini, M. Coordination chemistry of 1,3,5-triaza-7-phosphaadamantane (PTA) and derivatives. Part II. The quest for tailored ligands, complexes and related applications. *Coord. Chem. Rev.* **2010**, *254*, 555–607. [CrossRef]

33. Ogata, K.; Sasano, D.; Yokoi, T.; Isozaki, K.; Seike, H.; Takaya, H.; Nakamura, M. Pd-complex bound amino acid-based supramolecular gel catalyst for intramolecuar addition-cyclization of alkynoic acids in water. *Chem. Lett.* **2012**, *41*, 498–500. [CrossRef]

34. Hamasaka, G.; Uozumi, Y. Cyclization of alkynoic acids in water in the presence of a vesicular self-assembled amphiphilic pincer palladium complex catalyst. *Green Chem.* **2014**, *50*, 14516–14518. [CrossRef] [PubMed]

35. Michelet, V.; Toullec, P.Y.; Genêt, J.-P. Cycloisomerization of 1,*n*-enynes: Challenging metal-catalyzed rearrangements and mechanistic insights. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315. [CrossRef] [PubMed]

36. Soriano, E.; Marco-Contelles, J. Mechanistic insights on the cycloisomerization of polyunsaturated precursors catalyzed by platinum and gold complexes. *Acc. Chem. Res.* **2009**, *42*, 1026–1036. [CrossRef] [PubMed]

37. Ke, D.; Espinosa, N.A.; Mallet-Ladeira, S.; Monot, J.; Martin-Vaca, B.; Bourissou, D. Efficient synthesis of unsaturated δ- and ε-lactones/lactams by catalytic cycloisomerization: When Pt outperforms Pd. *Adv. Synth. Catal.* **2016**, *358*, 2324–2331, and references therein. [CrossRef]

38. Alemán, J.; del Solar, V.; Navarro-Ranninger, C. Anticancer platinum complexes as non-innocent compounds for catalysis in aqueous media. *Chem. Commun.* **2010**, *46*, 454–456. [CrossRef] [PubMed]

39. Alemán, J.; del Solar, V.; Cubo, L.; Quiroga, A.G.; Navarro-Ranninger, C. New reactions of anticancer-platinum complexes and their intriguing behavior under various experimental conditions. *Dalton Trans.* **2010**, *39*, 10601–10607. [CrossRef] [PubMed]

40. Hashmi, A.S.K.; Toste, F.D. (Eds.) *Modern Gold Catalyzed Synthesis*; Wiley-VCH: Weinheim, Germany, 2012; ISBN 9783527319527.

41. Toste, F.D.; Michelet, V. (Eds.) *Gold Catalysis: An Homogeneous Approach*; Imperial College Press: London, UK, 2014; ISBN 9781848168527.

42. Genin, E.; Toullec, P.Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. Room temperature Au(I)-catalyzed *exo*-selective cycloisomerization of acetylenic acids: An entry to functionalized γ-lactones. *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113. [CrossRef] [PubMed]

43. Toullec, P.Y.; Genin, E.; Antoniotti, S.; Genêt, J.-P.; Michelet, V. Au_2O_3 as a stable and efficient catalyst for the selective cycloisomerization of γ-acetylenic carboxylic acids to γ-alkylidene-γ-butyrolactones. *Synlett* **2008**, 707–711.

44. Tomás-Mendivil, E.; Toullec, P.Y.; Díez, J.; Conejero, S.; Michelet, V.; Cadierno, V. Cycloisomerization versus hydration reactions in aqueous media: A Au(III)-NHC catalyst that makes the difference. *Org. Lett.* **2012**, *14*, 2520–2523. [CrossRef] [PubMed]

45. Tomás-Mendivil, E.; Toullec, P.Y.; Borge, J.; Conejero, S.; Michelet, V.; Cadierno, V. Water-soluble gold(I) and gold(III) complexes with sulfonated *N*-heterocyclic carbene ligands: Synthesis, characterization, and application in the catalytic cycloisomerization of γ-alkynoic acids into enol-lactones. *ACS Catal.* **2013**, *3*, 3086–3098. [CrossRef]

46. Ferré, M.; Cattoën, X.; Wong Chi Man, M.; Pleixats, R. Sol-gel immobilized *N*-heterocyclic carbene gold complex as a recyclable catalyst for the rearrangement of allylic esters and the cycloisomerization of γ-alkynoic acids. *ChemCatChem* **2016**, *8*, 2824–2831. [CrossRef]

47. Belger, K.; Krause, N. Smaller, faster, better: Modular synthesis of unsymmetrical ammonium salt-tagged NHC-gold(I) complexes and their application as recyclable catalysts in water. *Org. Biomol. Chem.* **2015**, *13*, 8556–8560. [CrossRef] [PubMed]

48. Rodríguez-Álvarez, M.J.; Vidal, C.; Díez, J.; García-Álvarez, J. Introducing deep eutectic solvents as biorenewable media for Au(I)-catalysed cycloisomerisation of γ-alkynoic acids: An unprecedented catalytic system. *Chem. Commun.* **2014**, *50*, 12927–12929. [CrossRef] [PubMed]

49. Mindt, T.L.; Schibli, R. Cu(I)-catalyzed intramolecular cyclization of alkynoic acids in aqueous media: A "click side reaction". *J. Org. Chem.* **2007**, *72*, 10247–10250. [CrossRef] [PubMed]

50. López-Reyes, M.E.; Toscano, R.A.; López-Cortés, J.G.; Alvarez-Toledano, C. Fast and efficient synthesis of Z-enol-γ-lactones through a cycloisomerization reaction of β-hydroxy-γ-alkynoic acids catalyzed by copper(I) under microwave heating in water. *Asian J. Org. Chem.* **2015**, *4*, 545–551. [CrossRef]

51. Li, S.; Jia, W.; Jiao, N. Copper/iron-cocatalyzed highly selective tandem reactions: Efficient approaches to Z-γ-alkylidene lactones. *Adv. Synth. Catal.* **2009**, *351*, 569–575. [CrossRef]

52. Jia, W.; Li, S.; Yu, M.; Chen, W.; Jiao, N. AgNO$_3$ catalyzed cyclization of propargyl-Meldrum´s acids in aqueous solvent: Highly selective synthesis of Z-γ-alkylidene lactones. *Tetrahedron Lett.* **2009**, *50*, 5406–5408. [CrossRef]

53. Ahmar, S.; Fillion, E. Expedient synthesis of complex γ-butyrolactones from 5-(1-arylalkylidene) Meldrum´s acids via sequential conjugate alkynylation/Ag(I)-catalyzed lactonization. *Org. Lett.* **2014**, *16*, 5748–5751. [CrossRef] [PubMed]

54. Liu, W.; Xu, D.D.; Repič, O.; Blacklock, T.J. A mild method for ring-opening aminolysis of lactones. *Tetrahedron Lett.* **2001**, *42*, 2439–2441. [CrossRef]

55. Guo, W.; Gómez, J.E.; Martínez-Rodríguez, L.; Bandeira, N.A.G.; Bo, C.; Kleij, A.W. Metal-free synthesis of *N*-aryl amides using organocatalytic ring-opening aminolysis of lactones. *ChemSusChem* **2017**, *10*, 1969–1975. [CrossRef] [PubMed]

56. Yang, T.; Campbell, L.; Dixon, D.J. A Au(I)-catalyzed *N*-acyl iminium ion cyclization cascade. *J. Am. Chem. Soc.* **2007**, *129*, 12070–12071. [CrossRef] [PubMed]

57. Feng, E.; Zhuo, Y.; Zhang, D.; Zhang, L.; Sun, H.; Jiang, H.; Liu, H. Gold(I)-catalyzed tandem transformation: A simple approach for the synthesis of pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones and pyrrolo/pyrido[2,1-*a*]quinazolinones. *J. Org. Chem.* **2010**, *75*, 3274–3282. [CrossRef] [PubMed]

58. Patil, N.T.; Lakshmi, P.G.V.V.; Sridhar, B.; Patra, S.; Bhadra, M.P.; Patra, C.R. New linearly and angularly fused quinazolinones: Synthesis through gold(I)-catalyzed cascade reactions and anticancer activities. *Eur. J. Org. Chem.* **2012**, 1790–1799. [CrossRef]

59. Li, Z.; Li, J.; Yang, N.; Chen, Y.; Zhou, Y.; Ji, X.; Zhang, L.; Wang, J.; Xie, X.; Liu, H. Gold(I)-catalyzed cascade approach for the synthesis of tryptamine-based polycyclic privileged scaffolds as α$_1$-adrenergic receptor antagonists. *J. Org. Chem.* **2013**, *76*, 10802–10811. [CrossRef] [PubMed]

60. Feng, E.; Zhou, Y.; Zhao, F.; Chen, X.; Zheng, L.; Jiang, H.; Liu, H. Gold-catalyzed tandem reaction in water: An efficient and convenient synthesis of fused polycyclic indoles. *Green Chem.* **2012**, *14*, 1888–1895. [CrossRef]

61. Zhuo, Y.; Zhai, Y.; Ji, X.; Liu, G.; Feng, E.; Ye, D.; Zhao, L.; Jiang, H.; Liu, H. Gold(I)-catalyzed one-pot tandem coupling/cyclization: An efficient synthesis of pyrrolo-/pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones. *Adv. Synth. Catal.* **2010**, *352*, 373–378. [CrossRef]

62. Zhou, L.; Jiang, H.-F. Synthesis of phthalides via Pd/CNTs-catalyzed reaction of terminal alkynes and *o*-iodobenzoic acid under copper- and ligand-free conditions. *Tetrahedron Lett.* **2007**, *48*, 8449–8452. [CrossRef]

63. García-Álvarez, J.; Díez, J.; Gimeno, J. A highly efficient copper(I) catalyst for the 1,3-dipolar addition of azides with terminal and 1-iodoalkynes in water: Regioselective synthesis of 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles. *Green Chem.* **2010**, *12*, 2127–2130. [CrossRef]

64. Denard, C.A.; Hartwig, J.F.; Zhao, H. Multistep one-pot reactions combining biocatalysts and chemical catalysts for asymmetric synthesis. *ACS Catal.* **2013**, *3*, 2856–2864. [CrossRef]

65. Gröger, H.; Hummel, W. Combining the 'two worlds' of chemocatalysis and biocatalysis towards multi-step one-pot processes in aqueous media. *Curr. Opin. Chem. Biol.* **2014**, *19*, 171–179. [CrossRef] [PubMed]

66. Wallace, S.; Balskus, E.P. Opportunities for merging chemical and biological synthesis. *Curr. Opin. Biotechnol.* **2014**, *30*, 1–8. [CrossRef] [PubMed]

67. Rodríguez-Álvarez, M.J.; Ríos-Lombardía, N.; Schumacher, S.; Pérez-Iglesias, D.; Morís, F.; Cadierno, V.; García-Álvarez, J.; González-Sabín, J. Combination of metal-catalyzed cycloisomerizations and biocatalysis in aqueous media: Asymmetric construction of chiral alcohols, lactones and γ-hydroxy-carbonyl compounds. *ACS Catal.* **2017**, *7*, 7753–7759. [CrossRef]

68. Cadierno, V.; Francos, J.; Gimeno, J. Ruthenium(IV)-catalyzed Markovnikov addition of carboxylic acids to terminal alkynes in aqueous medium. *Organometallics* **2011**, *30*, 852–862. [CrossRef]

69. Chanda, A.; Fokin, V.V. Organic synthesis "on water". *Chem. Rev.* **2009**, *109*, 725–748. [CrossRef] [PubMed]

70. Butler, R.N.; Coyne, A.G. Water: Nature's reaction enforcer—Comparative effects for organic synthesis "in-water" and "on-water". *Chem. Rev.* **2010**, *110*, 6302–6337. [CrossRef] [PubMed]

71. Nicks, F.; Aznar, R.; Sainz, D.; Muller, G.; Demonceau, A. Novel, highly efficient and selective ruthenium catalysts for the synthesis of vinyl esters from carboxylic acids and alkynes. *Eur. J. Org. Chem.* **2009**, 5020–5027. [CrossRef]

72. Kleman, P.; González-Liste, P.J.; García-Garrido, S.E.; Cadierno, V.; Pizzano, A. Highly enantioselective hydrogenation of 1-alkylvinyl benzoates: A simple, nonenzymatic access to chiral 2-alkanols. *Chem. Eur. J.* **2013**, *19*, 16209–16212. [CrossRef] [PubMed]

73. Kleman, P.; González-Liste, P.J.; García-Garrido, S.E.; Cadierno, V.; Pizzano, A. Asymmetric hydrogenation of 1-alkyl and 1-aryl vinyl benzoates: A broad scope procedure for the highly enantioselective synthesis of 1-substituted ethyl benzoates. *ACS Catal.* **2014**, *4*, 4398–4408. [CrossRef]

74. González-Liste, P.J.; García-Garrido, S.E.; Cadierno, V. Gold(I)-catalyzed addition of carboxylic acids to internal alkynes in aqueous medium. *Org. Biomol. Chem.* **2017**, *15*, 1670–1679. [CrossRef] [PubMed]

75. Scheid, G.; Kuit, W.; Ruijter, E.; Orru, R.V.A.; Henke, E.; Bornscheuer, U.; Wessjohann, L.A. A new route to protected acyloins and their enzymatic resolution with lipases. *Eur. J. Org. Chem.* **2004**, 1063–1074. [CrossRef]

76. Carpino, P.A.; Griffith, D.A.; Sakya, S.; Dow, R.L.; Black, S.C.; Hadcock, J.R.; Iredale, P.A.; Scott, D.O.; Fichtner, M.W.; Rose, C.R.; et al. New bicyclic cannabinoid receptor-1 (CB$_1$-R) antagonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 731–736. [CrossRef] [PubMed]

77. Lu, H.-L.; Wu, Z.-W.; Song, S.-Y.; Liao, X.-D.; Zhu, Y.; Huang, Y.-S. An improved synthesis of nomegestrol acetate. *Org. Process Res. Dev.* **2014**, *18*, 431–436. [CrossRef]

78. Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P.W.; Camphausen, R.T.; Tam, S.; Tsao, D.H.H.; Keith, J.C.; Nickerson-Nutter, C.; Shilling, A.; Young-Sciame, R.; Wang, Q. Synthesis and biological evaluation of quinoline salicylic acids as P-Selectin antagonists. *J. Med. Chem.* **2007**, *50*, 21–39. [CrossRef] [PubMed]

79. Ruiz, J.F.M.; Radics, G.; Windle, H.; Serra, H.O.; Simplício, A.L.; Kedziora, K.; Fallon, P.G.; Kelleher, D.P.; Gilmer, J.F. Design, synthesis, and pharmacological effects of a cyclization-activated steroid prodrug for colon targeting in inflammatory bowel disease. *J. Med. Chem.* **2009**, *52*, 3205–3211. [CrossRef] [PubMed]

80. Jeschke, J.; Korb, M.; Rüffer, T.; Gäbler, C.; Lang, H. Atom economic ruthenium-catalyzed synthesis of bulky β-oxo esters. *Adv. Synth. Catal.* **2015**, *357*, 4069–4081, and references therein. [CrossRef]

81. Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. Ruthenium-catalyzed selective addition of carboxylic acids to alkynes. A new synthesis of enol esters. *J. Org. Chem.* **1987**, *52*, 2230–2239. [CrossRef]

82. Bauer, E. Transition-metal-catalyzed functionalization of propargylic alcohols and their derivatives. *Synthesis* **2012**, *44*, 1131–1151. [CrossRef]

83. Cadierno, V.; Francos, J.; Gimeno, J. Ruthenium-catalyzed synthesis of β-oxo esters in aqueous medium: Scope and limitations. *Green Chem.* **2010**, *12*, 135–143. [CrossRef]