Recent Advances in the Transition Metal Catalyzed Addition of Carboxylic Acids to Alkynes

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Abstract: Recent advances in the metal-catalyzed hydrofunctionalization of alkynes with carboxylic acids are comprehensively reviewed. Both inter- and intramolecular processes, leading respectively to enol esters and lactones, are discussed, as well as the involvement of these transformations in the synthesis of natural products and biologically active molecules, and the assembly of elaborated heterocyclic compounds though cascade processes. Literature published since 2011 is covered.

Keywords: Enol esters, lactones, alkynes, hydro-oxycarbonylation reactions, cycloisomerization reactions, metal-catalyzed transformations.

Short running title: Catalytic hydro-oxycarbonylation of alkynes.

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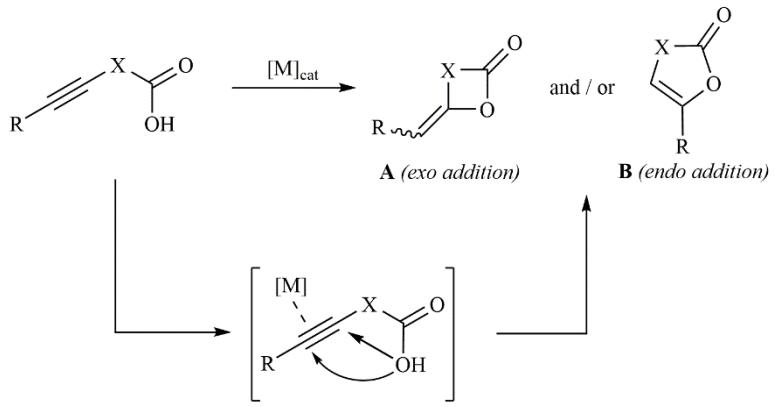
1. INTRODUCTION

Alkyne is one of the fundamental functional groups in organic chemistry. Electrophilic activation of alkynes by transition metals has attracted enormous attention for decades, becoming a mainstay in the toolbox of synthetic chemists, biochemists, and materials scientists [1-3]. In this context, the catalytic hydrofunctionalization of alkynes, *i.e.* the addition of E-H units (E = heteroatom or carbon) across the C≡C bond, provides a direct access to multisubstituted functionalized alkenes in an atom-economical manner [4-10]. A relevant example of this type of transformations is the hydro-oxycarbonylation of alkynes with carboxylic acids. Thus, the intramolecular version of the process, *i.e.* the cycloisomerization of alkynoic acids, allows the easy assembly of unsaturated lactones (Scheme **1**) which are key structural units in a huge number of natural products and bioactive molecules, as well as valuable synthetic intermediates [11-14].

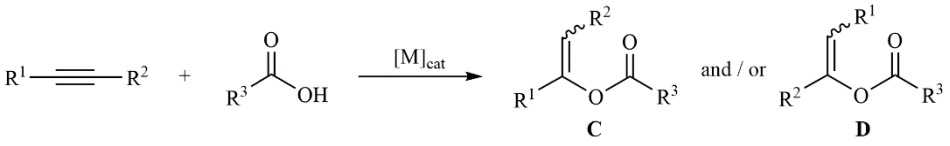


Scheme 1. The metal-catalyzed cycloisomerization of alkynoic acids.

After seminal works in the 70-80s with toxic mercury salts [15-18], a wide range of transition metal compounds have been subsequently employed to promote these reactions by π-activation of the C≡C bond of the substrates towards the carboxylate attack. Formation of the exo- **A** or endocyclic **B** enol lactone products, as well as the

stereoselectivity of the process (*syn* or *anti* type addition), are strongly dependent on the metal employed, the reaction conditions (solvent and temperature), the spacer unit X connecting the acid and alkyne functionalities, and the terminal or internal nature of the alkyne group, being a priori difficult to predict.

On the other hand, the intermolecular hydro-oxycarbonylation of alkynes represents the simplest and "greenest" approach currently known to obtain enol esters (**C** or **D** in Scheme **2**), which are versatile building blocks in organic chemistry commonly employed as monomers for polymerization [19], as mild acylating agents [20], as substrates in asymmetric hydrogenation [21] and hydroformylation processes [22], and in different cross-coupling reactions [23-26]. Although some metal-free protocols can be found in the literature [27-30], they usually feature a restricted substrate scope compared to those methodologies that make use of a transition metal to active the alkyne (and in some cases also the carboxylic acid partner).



Scheme 2. The metal-catalyzed intermolecular addition of carboxylic acids to alkynes.

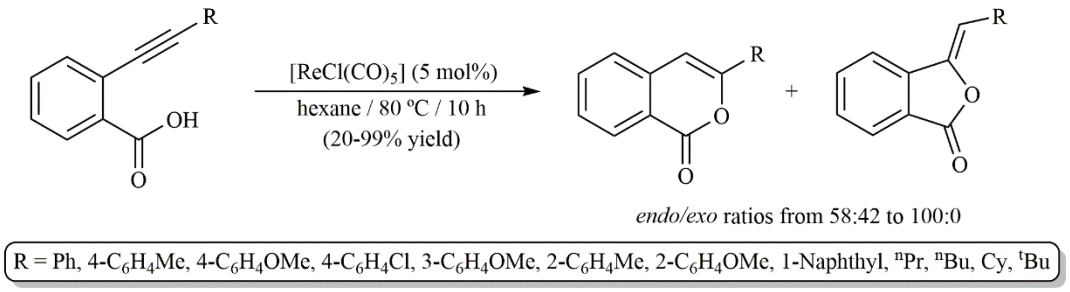
Two comprehensive and general review articles covering intra- and intramolecular hydro-oxycarbonylation reactions of alkynes were published in 2004 [5] and 2012 [7], the latter summarizing the works published up to April 2011. In this contribution, a coverage of the literature during the period 2011-2020 is given. However, mentions to previous studies have been in some cases included to contextualize the reports under discussion. We advise the reader that oxidative annulation reactions of benzoic acids with alkynes to afford isocoumarin derivatives, and related annulation processes

involving C-H bond activation, are considered out of the scope of this review since the field has an updated literature coverage [31-37]. Similarly, inter- and intramolecular additions of carbamate and carbonate derivatives to alkynes are also excluded. In most cases, these reactions involve the *in situ* generation of the carbamate and carbonate nucleophiles by CO_2 fixation, a field that has been extensively reviewed [38-43].

2. GROUP 7 METAL CATALYSTS

2.1. Rhenium

Rhenium derivatives are the only examples of Group 7 catalysts for the addition of carboxylic acids to alkynes described so far in the literature, although their use is quite rare [44]. In this sense, the only work published during the period covered in this review is that shown in Scheme **3**, where several 2-ethynylbenzoic acids were subjected to the action of the carbonyl-rhenium(I) complex [$ReCl(CO)_5$] [45]. The reactions, conducted in hexane at 80 ºC, led in most of the cases to mixtures of the corresponding isocoumarin (6-*endo-dig* cyclization) and phthalide (5-*exo-dig* cyclization) products, with marked preference toward the former (selectivity > 88% in most of the cases). Other rhenium species tested, such as [$ReBr(CO)_5$], $Re_2(CO)_{10}$, $ReCl_5$ or [$ReCp(CO)_3$] (Cp = η^5-cyclopentadienyl), proved to be also active but much less effective.

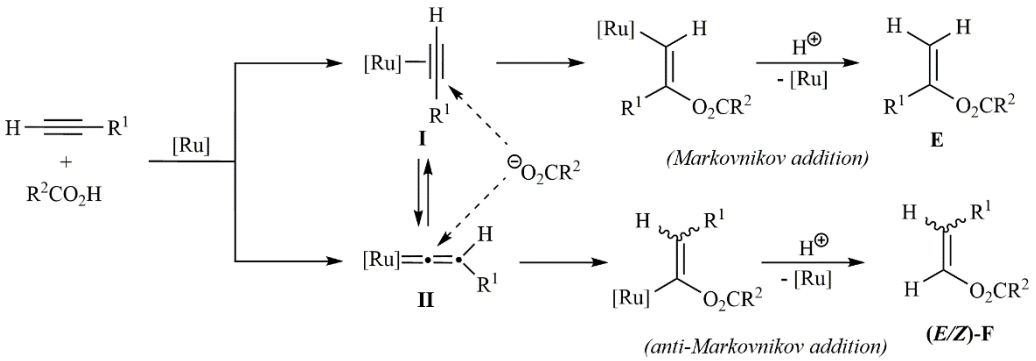


Scheme 3. Cyclization of 2-ethynylbenzoic acids catalyzed by [$ReCl(CO)_5$].

3. GROUP 8 METAL CATALYSTS

3.1. Ruthenium

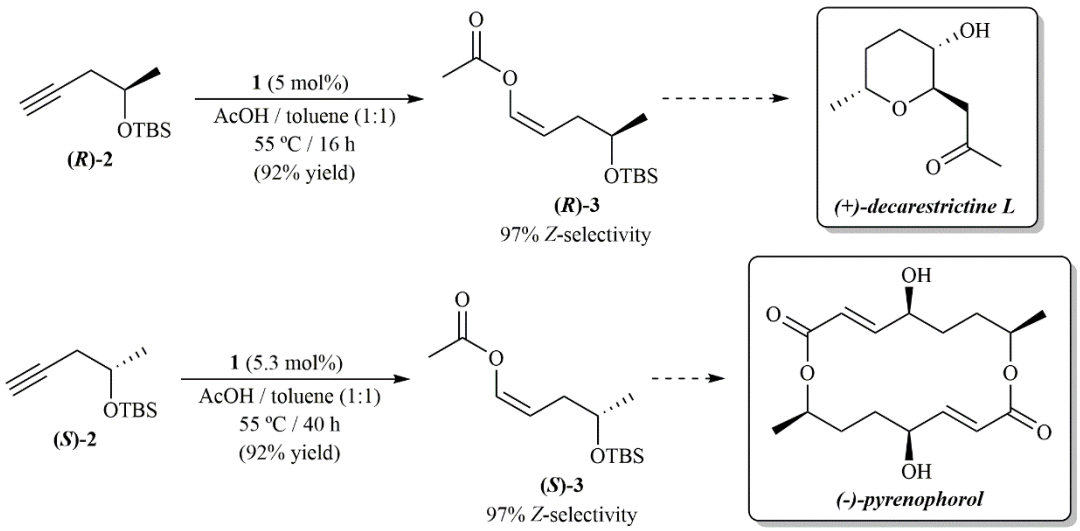
Following the first report by Roten and Shvo in 1983 [46], ruthenium-based catalysts have been the most widely employed to promote the intermolecular addition of carboxylic acids to terminal alkynes due to their high efficiency and tolerance to functional groups [5, 7, 47]. In addition, some of them allow the control of the regioselectivity of this transformation, leading preferentially to the Markovnikov **E** or the *anti*-Markovnikov **F** addition products, an aspect closely related to the ability of ruthenium fragments to direct the π-alkyne-vinylidene equilibrium (Scheme **4**). Thus, while the addition of the carboxylate anion on the corresponding π-alkyne intermediate **I** generates the Markovnikov product **E**, the carboxylate attack to the vinylidene-ruthenium isomer **II** leads to the *anti*-Markovnikov ones **F**.



Scheme 4. Reaction pathways for the ruthenium-catalyzed addition of carboxylic acids to terminal alkynes.

Recent Density Functional Theory (DFT) calculations by Koley and co-workers on the addition of benzoic acid to 1-hexyne catalyzed by bis(allyl)-ruthenium(II) complexes of general composition [Ru(η^3-2-methylallyl)$_2$(P^P)] (P^P = diphosphine ligand) fully agree with the reaction pathways depicted in Scheme **4** [48]. This family of catalysts was originally developed by Dixneuf and co-workers in the 90´s, who showed

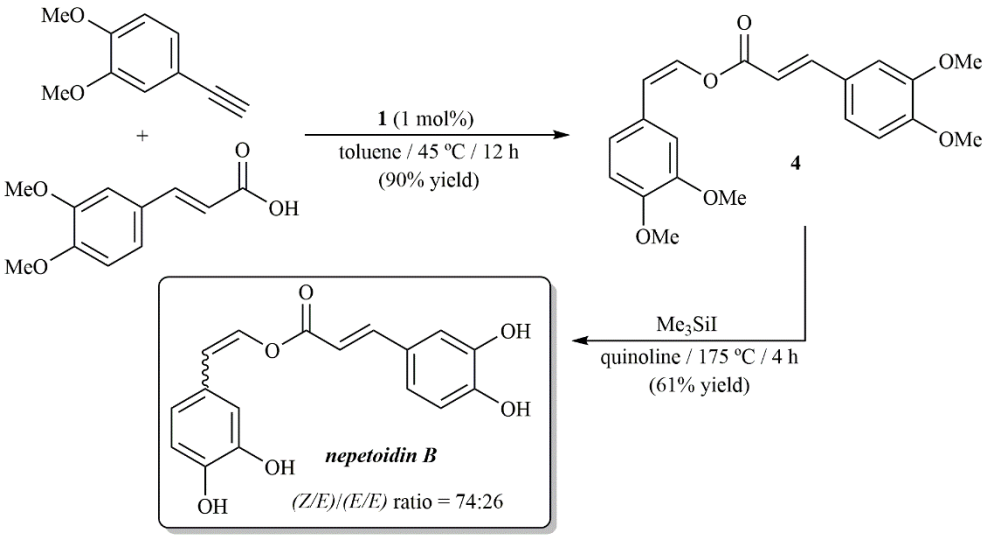
the marked effect that the chelating diphosphine ligand exerts on the regioselectivity of the addition process [49]. Thus, while [Ru(η^3-2-methylallyl)$_2$(dppm)] (dppm = bis(diphenylphosphino)methane) generates predominantly the Markovnikov addition products, [Ru(η^3-2-methylallyl)$_2$(dppb)] (**1**; dppb = 1,4-bis(diphenylphosphino)butane) orients the addition towards the regio- and stereoselective formation of the corresponding (*Z*)-*anti*-Markovnikov adducts. In this context, recent works have exploited the synthetic utility of complex [Ru(η^3-2-methylallyl)$_2$(dppb)] (**1**). For example, starting from enantiomeric (*R*)- and (*S*)-4-(*tert*-butyldemethylsiloxy)-1-pentyne **2**, Burke and co-workers synthesized the optically pure (*Z*)-enol esters (*R*)-**3** and (*S*)-**3** by addition of acetic acid, from which the natural products (+)-decarestrictine L and (-)-pyrenophorol, respectively, could be accessed (Scheme **5**) [50].



Scheme 5. Ru-catalyzed *anti*-Markovnikov addition of AcOH to the (*R*) and (*S*) enantiomers of alkyne **2**.

The *Z*-selective *anti*-Markovnikov addition of 3,4-dimethoxycinnamic acid to 4-ethynyl-1,2-dimethoxybenzene catalyzed by complex **1** was reported by Xiong and co-workers (Scheme **6**) [51]. Demethylation of the resulting enol ester **4** by means of the

iodotrimethylsilane/quinoline system afforded naturally occurring nepetoidin B as a mixture of the corresponding *Z/E* and *E/E* isomers.

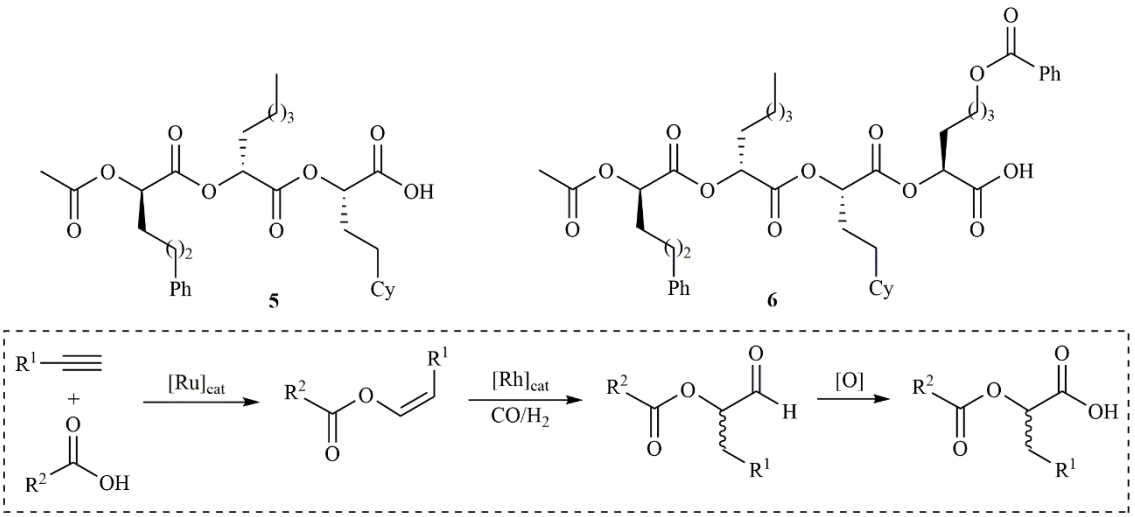


Scheme 6. Total synthesis of nepetoidin B involving a Ru-catalyzed hydro-oxycarbonylation reaction.

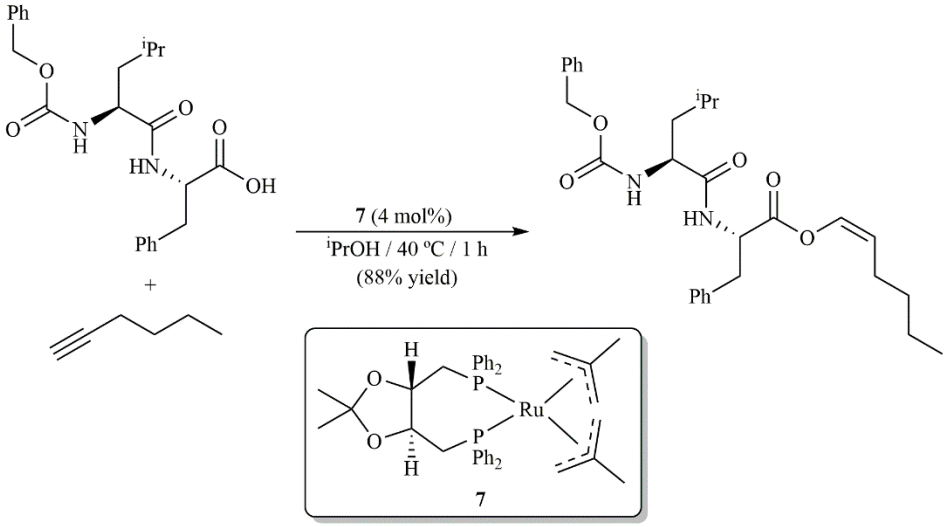
Additionally, Foarta and Landis developed an iterative process for the assembly of oligo(2-hydroxyacid)s, such as compounds **5** and **6**, through the combination of a hydro-oxycarbonylation reaction catalyzed by complex **1** with a Rh-catalyzed asymmetric hydroformylation/oxidation sequence (Scheme **7**) [52]. The side chains present in **5-6** were tailored by reacting a different terminal alkyne in each iterative step with the carboxylic acid generated in the previous one.

It should be noted at this point that, employing the related bis(allyl)-ruthenium(II) complex [Ru(η^3-2-methylallyl)$_2${(*S*,*S*)-DIOP}] (**7**; DIOP = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane) as catalyst, the *Z*-selective *anti*-Markovnikov addition of a series of oligopeptides to terminal alkynes could be successfully achieved without observing racemization at the *C*-terminal amino acid position (an illustrative example is given in Scheme **8**) [53]. Complex [Ru(η^3-2-

methylallyl)$_2$(dppb)] (**1**) also catalyzes these reactions, but longer reaction times were in general needed.



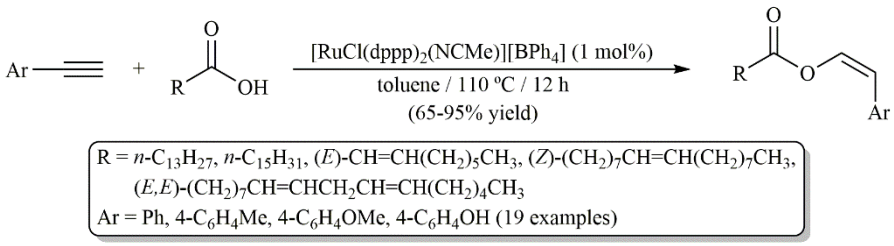
Scheme 7. Structure of **5** and **6** and the iterative sequence employed in their synthesis.



Scheme 8. Ru-catalyzed *anti*-Markovnikov addition of a dipeptide to 1-hexyne.

Novel ruthenium-based catalysts for the *anti*-Markovnikov hydro-oxycarbonylation of terminal alkynes have also seen the light in the last years. One of them is the octahedral derivative [RuCl(dppe)$_2$(NCMe)][BPh$_4$] (dppe = 1,2-bis(diphenylphosphino)ethane) described by Das and Bhattacharjee, which is compatible

with both aromatic and aliphatic alkynes, as well as with a broad range of carboxylic acids [54]. However, compared to the examples discussed above, this catalyst is somewhat less stereoselective since it led in all the cases to the enol ester products as mixtures of the corresponding *E* and *Z* isomers (*E/Z* ratios from 35:65 to 5:95). In a subsequent study, complete *Z*-selectivity was achieved by changing the diphosphine ligand dppe by dppp (dppp = 1,3-bis(diphenylphosphino)propane) [55]. However, we must note that only aromatic alkynes were in this case tolerated and only long-chain fatty acids were screened (see Scheme **9**). High preference for the *anti*-Markovnikov addition was also observed by Şehitoğlu and co-workers employing a recyclable ammonium tagged Hoveyda-Grubbs-type ruthenium carbene supported on silica-coated ferrite nanoparticles [56]. Isomeric mixtures were systematically obtained regardless of the nature of the alkyne and carboxylic acid employed, with the *E* isomers being in this case predominant.



Scheme 9. Ru(II)-catalyzed *Z*-selective *anti*-Markovnikov addition of fatty acids to aromatic alkynes.

Additional examples of ruthenium catalysts for *anti*-Markovnikov hydro-oxycarbonylation reactions are shown in Fig. **1**. The half-sandwich Ru(II) complexes **8** and **9**, featuring 2,2-dipyridylamino-type ligands, were employed by Wong and co-workers to promote the addition of aliphatic carboxylic acids to phenylacetylene [57]. Interestingly, while the dinuclear derivative **8** led to the corresponding enol esters with a high *E*-selectivity (*E/Z* ratios up to 11:1), a slight preference for the *Z* isomers was observed with the mononuclear species **9**. These results were explained in terms of the

different orientation adopted by the phenyl-vinylidene intermediates in the case of **8** as the result of the steric constrains imposed by the rigid anthracene spacer. Concerning the octahedral Ru(III) complex **10**, and related bis-*N*-heterocyclic carbene derivatives developed by Bera´s group, it shows a marked preference for the formation of (*Z*)-enol esters regardless of the nature of the alkynes and carboxylic acids employed (*Z*-selectivity in the range 60-100%) [58].

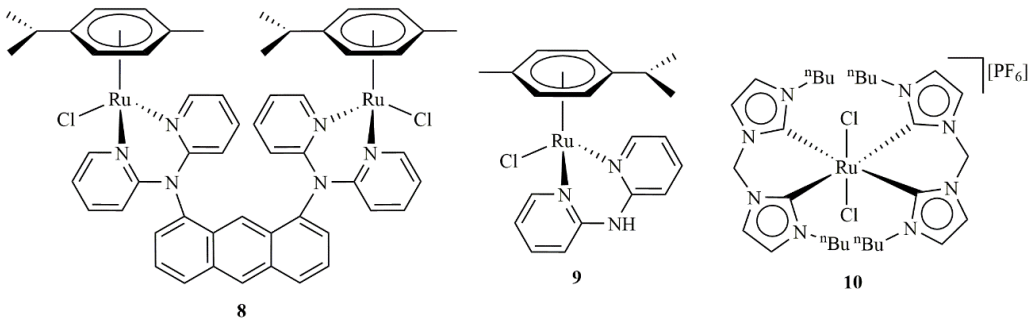
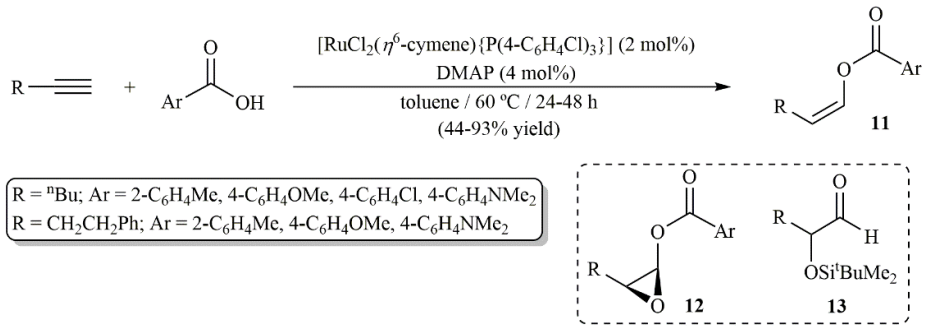


Fig. 1. Structure of the ruthenium complexes **8**-**10**.

In 2003, Gooßen and co-workers discovered that the activity of arene-ruthenium(II) complexes $[RuCl_2(\eta^6\text{-cymene})(PR_3)]$, commonly employed for the intermolecular addition of carboxylic acids to terminal alkynes [5, 7, 47], can be drastically enhanced by the addition of a base, and that its nature drastically influences the regioselectivity of the process [59]. In this way, they identified the $[RuCl_2(\eta^6\text{-cymene})\{P(4\text{-}C_6H_4Cl)_3\}]$/DMAP (DMAP = 4-dimethylaminopyridine) and $[RuCl_2(\eta^6\text{-}p\text{-cymene})(PFur)_3]/Na_2CO_3$ (Fur = 2-furyl) combinations as efficient systems for the selective generation of the corresponding *Z-anti*-Markovnikov and Markovnikov products, respectively. These results were later exploited by Friestad´s group to access a series of epoxides **12** and synthetically useful α-silyloxyaldehydes **13** starting from the

enol esters **11**, which were selectively generated using the [$RuCl_2(\eta^6$-cymene){P(4-$C_6H_4Cl)_3$}]/DMAP catalytic system (Scheme **10**) [60].



Scheme 10. Synthesis of enol esters **11** and their synthetic utility.

On their side, Czarnocki and co-workers successfully applied the [$RuCl_2(\eta^6$-*p*-cymene)$(PFur)_3$]/Na_2CO_3 combination in the synthesis of a series of chiral enol esters by addition of optically pure *N*-protected amino acids to 1-butyne and phenylacetylene (representative examples are depicted in Fig. **2**) [61]. Markovnikov addition of indole-2-carboxylic acid to 1-hexyne employing [$RuCl_2(\eta^6$-*p*-cymene)$(PPh)_3$] under base-free conditions has also been described [62].

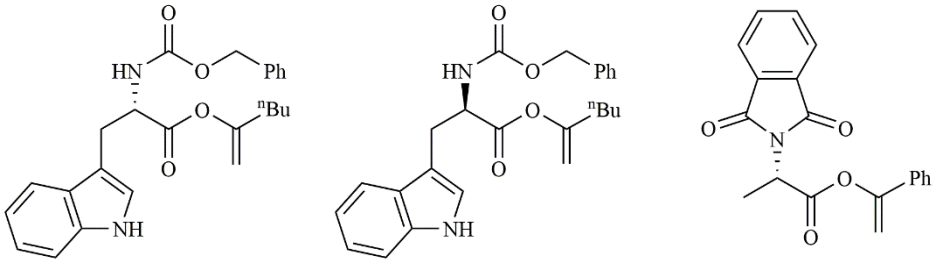
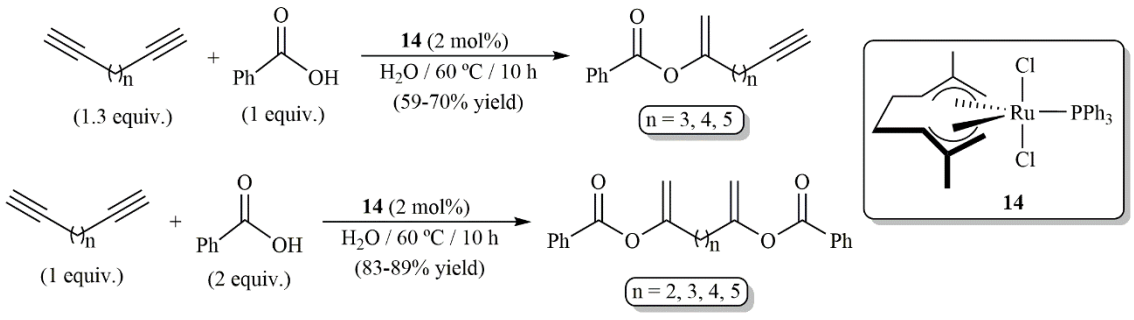


Fig. 2. Chiral enol esters generated by addition of *N*-protected amino acids to terminal alkynes.

A marked effect of phosphine ligands in the selectivity of the heterogeneous catalyst Ru/CeO_2 was observed by Wada and co-workers. Thus, while Ru/CeO_2 by itself orients the addition reactions towards the formation of the *E*-isomers of the *anti*-

Markovnikov adducts [63], the *Z*-isomers or the Markovnikov products can be obtained with up to 100% selectivity by modifying the Ru(0) species supported on ceria with dppb and trioctylphosphine, respectively [64]. All these systems showed a broad scope and could be reused repeatedly without significant loss of activity after separation of the reaction products by simple filtration.

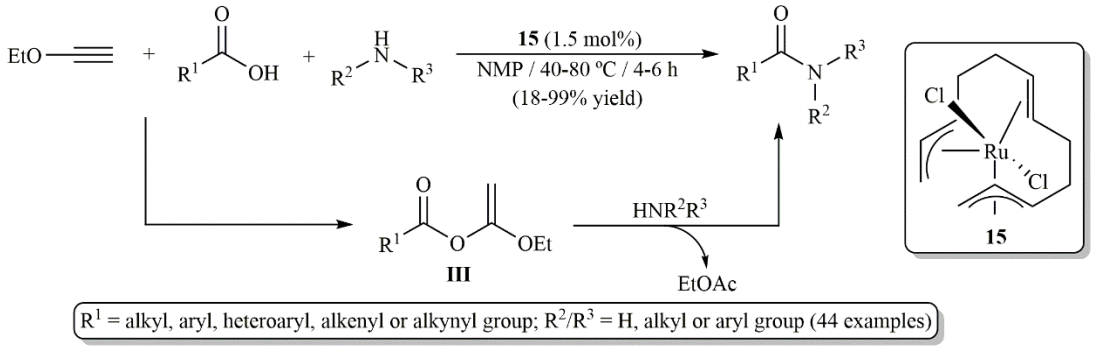
Employing the bis(allyl)-ruthenium(IV) complex [$RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})(PPh_3)$] (**14**; $C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) as catalyst, the selective Markovnikov addition of a wide range of aromatic and aliphatic carboxylic acids to terminal alkynes and 1,3-enynes was successfully accomplished in water by Cadierno and co-workers [65-67]. The reactions proceeded cleanly at 60 ºC, without observing the formation of byproducts resulting from the C≡C bond hydration, and did not require additives. In addition, **14** proved effective in adding benzoic acid to diynes, generating with high selectivity the corresponding mono- and di-addition products depending on the stoichiometry employed (Scheme **11**). It should be remarked at this point that intermolecular hydro-oxycarboxylation processes in aqueous media have been rarely documented [68].



Scheme 11. Ru(IV)-catalyzed addition of benzoic acid to diynes in water.

On the other hand, the related bis(allyl)-ruthenium(IV) complex **15** was employed by Gooßen and co-workers to develop an efficient and broad scope protocol for the

amidation of carboxylic acids activated *in situ* with ethoxyacetylene (Scheme **12**) [69]. The process involves the initial generation of the corresponding enol ester intermediates **III**, which act as acylating agents for the amines (primary or secondary). Acetylene instead of ethoxyacetylene can alternatively be used in these reactions, but it leads to the final amide products in lower yields.



Scheme 12. Ru(IV)-catalyzed amidation of carboxylic acids with ethoxyacetylene as activating agent.

The octahedral complexes **16** [70] and **17** [71], and the half-sandwich derivatives **18** and **19** [72] (see Fig. **3**), are additional examples of ruthenium catalysts capable to promote the Markovnikov addition of carboxylic acids to terminal alkynes. All of them operate in toluene at 60-85 ºC with low metal loadings (0.8-1 mol%) and feature a broad scope. However, it should be noted that in the case of **16** and **18-19** the addition of a co-catalyst to the reaction medium, AgOTf or Na_2CO_3, respectively, was needed to attain optimal activities. Delaude and co-workers also explored the behavior of the ruthenium-arene complexes **20** bearing thiocarboxylate ligands in the hydro-oxycarbonylation of 1-hexyne with 4-acetoxybenzoic acid (see Fig. **3**) [73]. They catalyzed the process in toluene at 60 ºC when combined with a base (Na_2CO_3), but all showed a low regioselectivity.

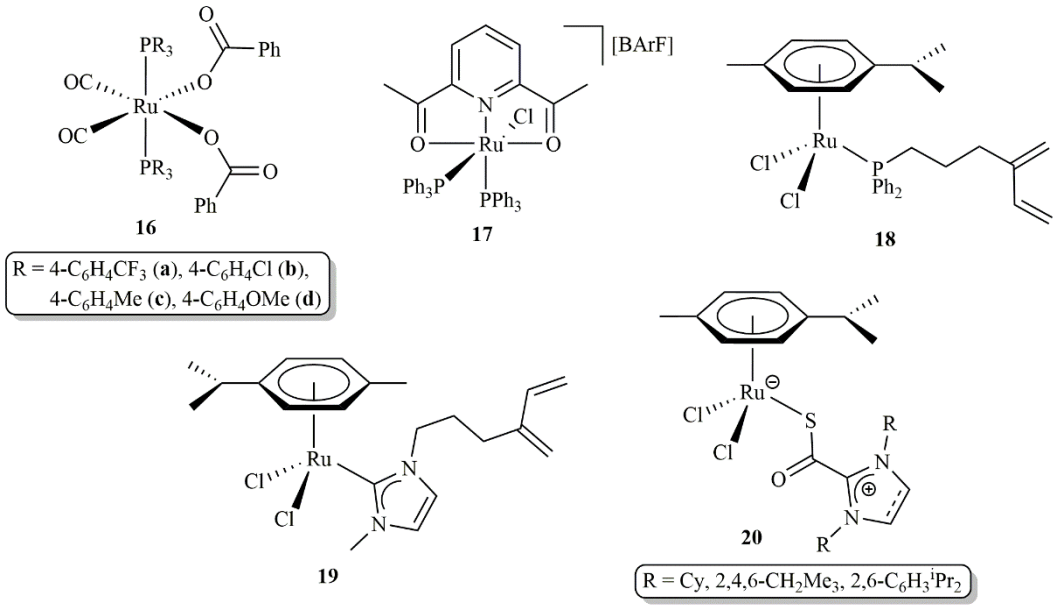
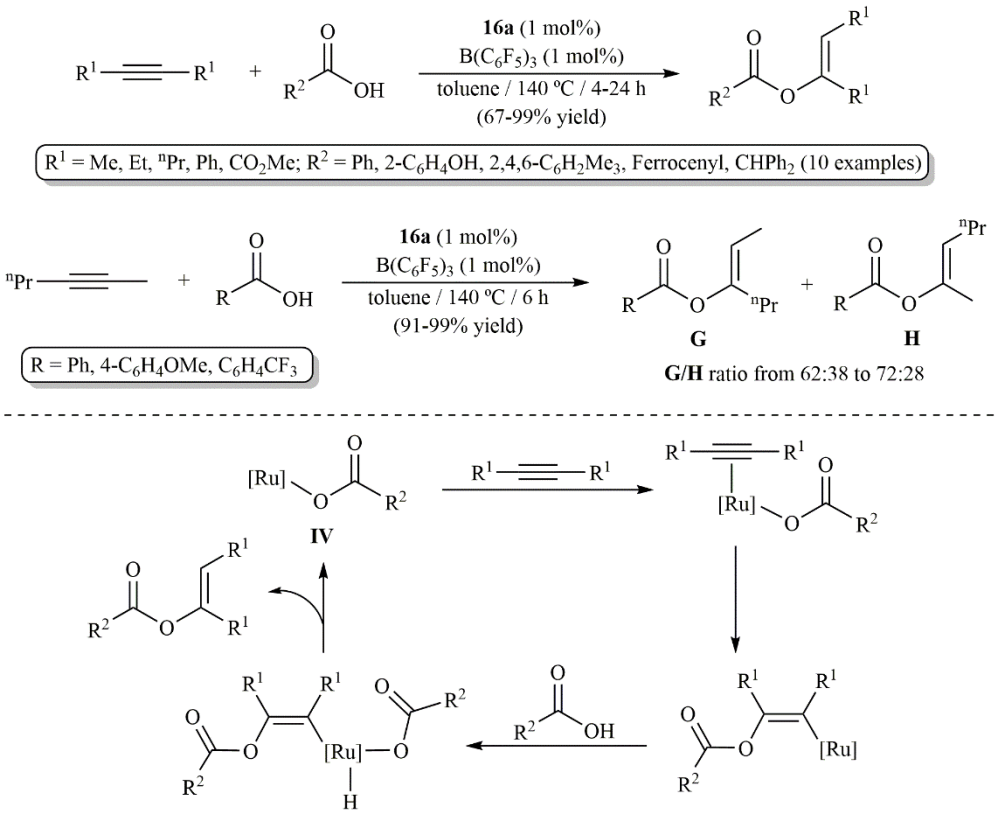


Fig. 3. Structure of the ruthenium(II) complexes **16-20**.

Remarkably, the octahedral complex *cis,cis,trans*-[Ru(κ^1-O_2CPh)$_2$(CO)$_2${P(4-$C_6H_4CF_3$}$_2$] (**16a**; see Fig. **3**), in combination with $B(C_6F_5)_3$, turned out to be effective in the hydro-oxycarbonylation of internal alkynes [74], much less reactive substrates compared to the terminal ones for which most ruthenium catalysts are inoperative [75]. The resulting trisubstituted enol esters were in all the cases obtained with complete (*E*)-configuration as the result of a *syn* type addition (Scheme **13**). However, it should be noted that the regioselectivity observed with non-symmetrically substituted alkynes, such as 2-hexyne, was very low. A carboxylate complex **IV**, generated from the reaction of **16a** with the corresponding carboxylic acid, was proposed by the authors as the active species. Subsequent π-coordination of the alkyne and insertion into the Ru-O bond explain the *syn*-selectivity found. According to the authors, the Lewis acid $B(C_6F_5)_3$ helps in the reaction activating the carboxylic acid by carbonyl oxygen coordination.

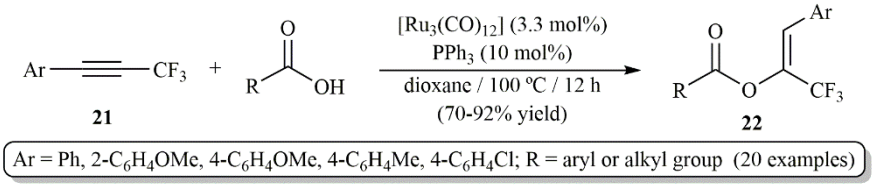


Scheme 13. Ru-catalyzed addition of carboxylic acids to internal alkynes.

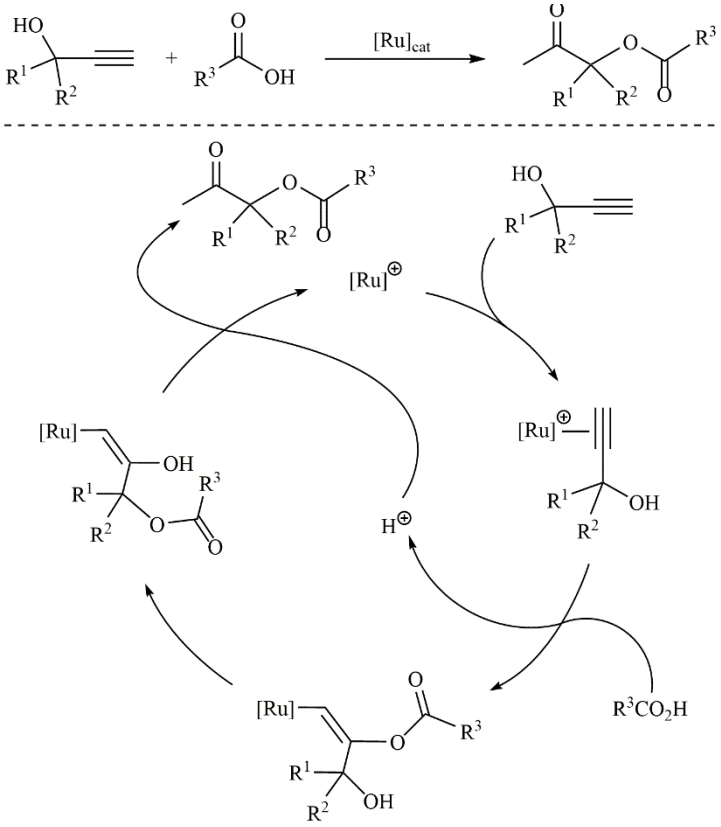
More regioselective transformations were described by Itoh and co-workers with the activated non-symmetric alkynes **21** bearing aryl and trifluoromethyl group substituents. The reactions, catalyzed by the $[Ru_3(CO)_{12}]/PPh_3$ system in refluxing dioxane, afforded exclusively the trifluoromethyl group-substituted (*E*)-enol esters **22** (Scheme **14**) [76]. A mechanism analogous to that depicted in Scheme **13** was proposed. Related reactions have also been described, with identical regio- and stereoselectivity levels, employing a catalytic system composed of dimer $[\{RuCl(\mu\text{-}Cl)(\eta^6\text{-}p\text{-cymene})\}_2]$, $AgSbF_6$ and $Cu(OAc)_2 \cdot H_2O$ [77].

On the other hand, since the pioneering works of Watanabe [78] and Dixneuf [79] in the 1980s, the addition of carboxylic acids to terminal propargylic alcohols catalyzed by ruthenium complexes has emerged as a powerful tool for the atom economical access to synthetically useful α-acyloxy ketones (also referred to as β-oxo esters) [80]. From a

mechanistic point of view, the formation of these products can be explained through a selective ruthenium-mediated Markovnikov addition of the acid to the alkynol followed by an intramolecular transesterification step (Scheme **15**).



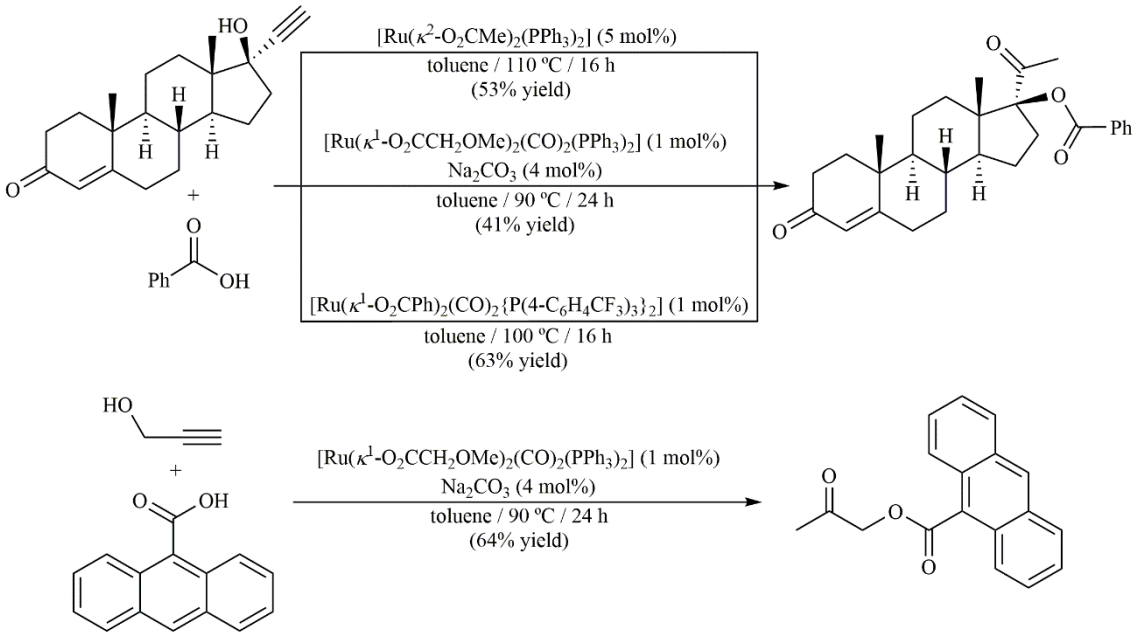
Scheme 14. Ru-catalyzed addition of carboxylic acids to CF_3-substituted unsymmetrical internal alkynes.



Scheme 15. α-Acyloxy ketones from Ru-catalyzed addition of carboxylic acids to propargylic alcohols.

Arene-ruthenium(II) complexes $[RuCl_2(\eta^6\text{-arene})(PR_3)]$ and dimeric carboxylate derivatives of type $[\{Ru(\mu\text{-}O_2CR)(CO)_2(PR_3)\}_2]$ are the catalysts most commonly employed in these transformations [5, 7, 47]. In this context, during the period covered in

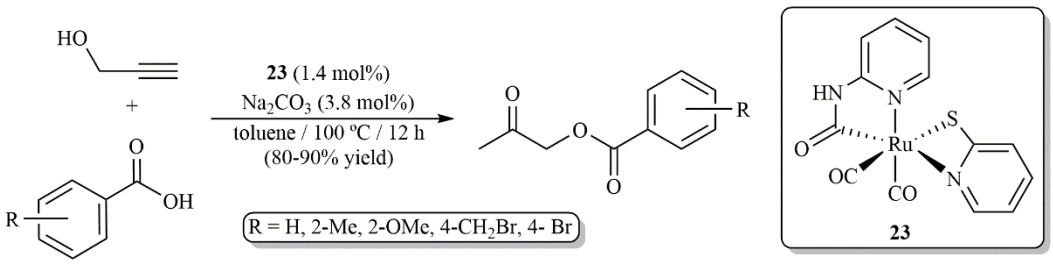
this review, the use of a series of (η^6-*p*-cymene)-Ru(II) complexes containing different ferrocenyl phosphines [81, 82], as well as the cage-like aminophosphine ligand 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA) [83], for the addition of benzoic acid to HC≡CCH$_2$OH has been described. In broader substrate scope studies, the utility of mononuclear ruthenium(II) carboxylate complexes *cis*-[Ru(κ^2-O$_2$CMe)$_2$(PPh$_3$)$_2$] [84] and *cis,cis,trans*-[Ru(κ^1-O$_2$CR)$_2$(CO)$_2$(PR$_3$)$_2$] (R = aryl or alkyl group; PR$_3$ = trialkyl or triarylphosphine; among them compounds **16** in Fig. **3**) [85, 86] was also demonstrated. In this sense, it is noteworthy that, unlike previously described catalytic systems, these compounds proved to be effective with sterically hindered substrates such as the hormonal steroid ethisterone or 9-anthracenecarboxylic acid (see Scheme **16**).



Scheme 16. Examples of Ru-catalyzed addition reactions of carboxylic acids to propargylic alcohols.

The addition of benzoic acids to propargyl alcohol in organic media was additionally described employing catalytic amounts of the octahedral carbamoyl ruthenium(II) complex [Ru{2-NHC(=O)C$_5$H$_4$N}(2-SC$_5$H$_4$N)(CO)$_2$] (**23**) in combination

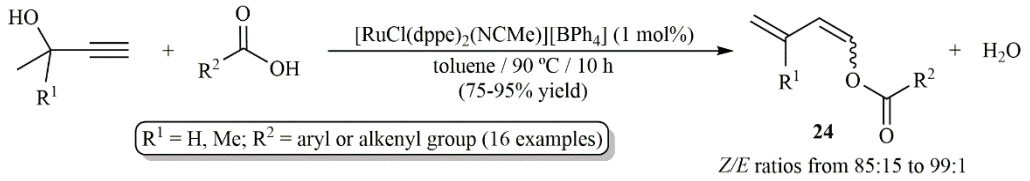
with sodium carbonate (Scheme **17**) [87]. The corresponding β-oxo esters were selectively obtained in high yields by performing the reactions at 100 ºC. On the other hand, the bis(allyl)-ruthenium(IV) derivative [$RuCl_2(\eta^3:\eta^3\text{-}C_{10}H_{16})(PPh_3)$] (**14** in Scheme **11**) was also able to promote the addition of aromatic and aliphatic carboxylic acids to a variety of propargylic alcohols in water at 60 ºC, affording the corresponding α-acyloxy ketones in moderate to good yields even when challenging aromatic alkynols of type $HC{\equiv}CC(OH)Ar_2$ were used as substrates [65]. Previous studies with this particular type of propargylic alcohols using the hydrophilic arene-ruthenium(II) complex [$RuCl_2(\eta^6$-benzene)(TPPMS)] (TPPMS = 3-(diphenylphosphino)benzenesulfonic acid sodium salt) in aqueous medium had revealed their preference to form alkene products $H_2C{=}CAr_2$ *via* hydrolysis of highly reactive allenylidene intermediates $[Ru]{=}C{=}C{=}CAr_2$ generated by dehydration of the substrates on the Ru coordination sphere [88].



Scheme 17. Addition of benzoic acids to propargyl alcohol catalyzed by the octahedral Ru(II) complex **23**.

Although to a much lesser extent, ruthenium-based catalysts for the *anti*-Markovnikov addition of carboxylic acids to terminal propargylic alcohols can also be found in the literature [89, 90]. In this context, Bhattacharjee and co-workers reported a synthesis of buta-1,3-dienyl esters **24** catalyzed by the octahedral Ru(II) complex $[RuCl(dppp)_2(NCMe)][BPh_4]$ in which the *anti*-addition of the carboxylic acid to the C≡C bond of but-3-yn-2-ol and 2-methylbut-3-yn-2-ol is accompanied by a spontaneous

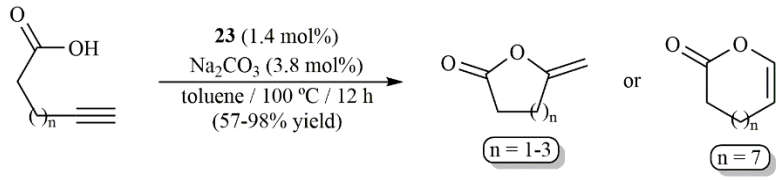
dehydration process (Scheme **18**) [91]. In addition, by performing the reactions in the presence of an initiator, the one-pot atom-transfer radical polymerization (ATRP) of compounds **24** catalyzed by complex $[RuCl(dppp)_2(NCMe)][BPh_4]$ could be successfully accomplished. Regarding the scope of the addition process, it was restricted to aromatic and α,β-unsaturated carboxylic acids since no reaction was observed when using aliphatic ones. In a subsequent study, this limitation was overcome with the use of the half-sandwich derivative $[RuCl(\eta^6\text{-}p\text{-cymene})(dppp)][PF_6]$, which showed a good performance even with long chain fatty acids such as oleic acid [92]. It should also be noted that one of the products obtained in this last study, namely octadec-9-enoic acid 3-methyl-buta-1,3-dienyl ester featured a potent anticancer activity. As in the case of $[RuCl(dppp)_2(NCMe)][BPh_4]$, the addition process was completely regioselective and the buta-1,3-dienyl esters were generated with a very high (*Z*)-stereoselectivity.



Scheme 18. Ru-catalyzed synthesis of dienyl esters by addition of carboxylic acids to propargylic alcohols.

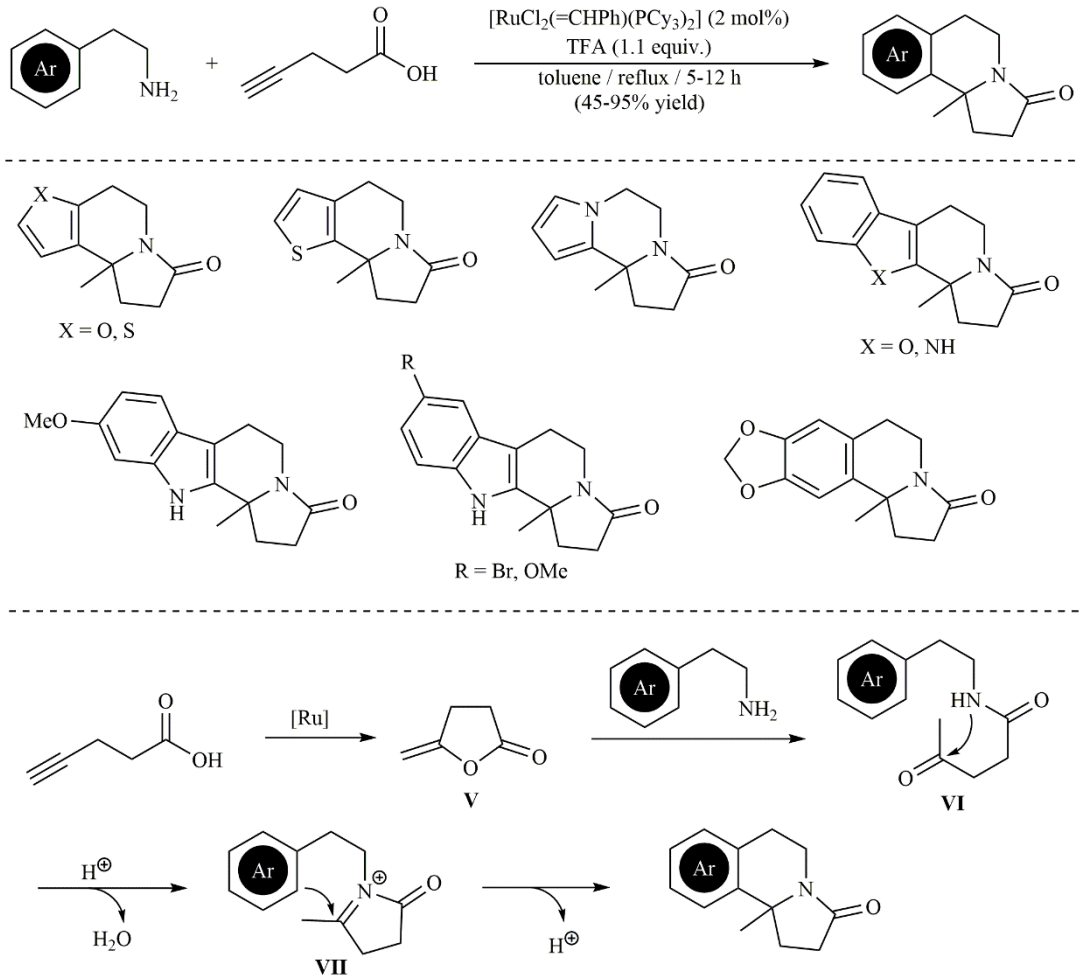
In marked contrast to the intermolecular processes, the participation of ruthenium-based catalysts in cyclization reactions of alkynoic acids has rarely been documented [93]. In fact, during the period covered in this review, only two studies have been published. In the first one, Leong and co-workers employed the octahedral carbamoyl ruthenium(II) complex $[Ru\{2\text{-}NHC(=O)C_5H_4N\}(2\text{-}SC_5H_4N)(CO)_2]$ (**23**; see Scheme **17**) to promote, in combination with Na_2CO_3, the cycloisomerization of linear alkynoic acids of type $HC{\equiv}C(CH_2)_nCH_2CO_2H$ [87]. As shown in Scheme **19**, depending on the chain length of

the substrates, the corresponding exo- (n = 1-3) or endocyclic (n = 7) enol lactones were selectively obtained in moderate to good yields.



Scheme 19. Cycloisomerization of alkynoic acids catalyzed by the octahedral Ru(II) complex **23**.

In the second study, published in 2020 by Lei and co-workers, a large variety of fused polyheterocyclic compounds were assembled by coupling alkynoic acids with functionalized amines employing the first-generation Grubbs catalyst [$RuCl_2$(=CHPh)(PCy_3)$_2$] in conjunction with trifluoroacetic acid (TFA) [94]. Reactions starting from 4-pentynoic acid and a series of (hetero)arylethylamines are shown in Scheme **20**. The process involves the initial 5-*exo*-*dig* cyclization of the alkynoic acid into enol-lactone **V**, which undergoes an aminolysis reaction to generate the linear keto-amides **VI**. A subsequent acid-catalyzed intramolecular condensation leads to the *N*-acyliminium intermediates **VII**, which evolve into the final products by nucleophilic attack of the aromatic ring to the iminium carbon. The scope of the process was very high and different alkynoic acids could be employed. In addition, amines tagged with various N- and O-nucleophilic groups, capable to trap the corresponding *N*-acyliminium intermediates, were also tolerated thus expanding the structural diversity of the heterocyclic products formed (representative examples are collected in Fig. **4**).



Scheme 20. Ru/TFA-catalyzed coupling of 4-pentynoic acid and (hetero)arylethylamines.

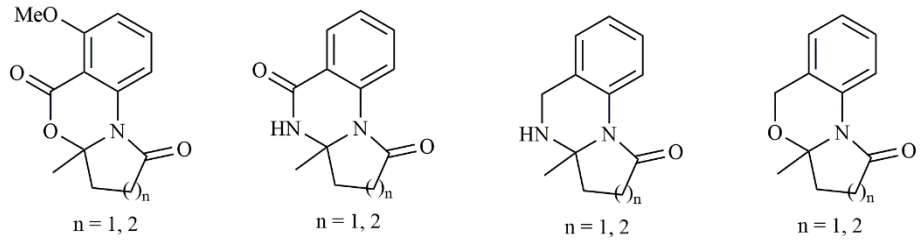


Fig. 4. Heterocyclic compounds generated by Ru/TFA-catalyzed coupling of alkynoic acids and functionalized anilines.

3.2. Osmium

The use of osmium in hydro-oxycarbonylation processes has been described for the first time very recently by Leong and co-workers [87]. In particular, they synthesized

the osmium(II) complex [Os{2-NHC(=O)C_5H_4N}(2-SC_5H_4N)$(CO)_2$], with a structure analogous to that of **23** (see Scheme **17**), which in the presence of Na_2CO_3 also catalyzed the cyclization reactions depicted in Scheme **19** with identical regioselectivity but in lower yields.

4. GROUP 9 METAL CATALYSTS

4.1. Cobalt

Catalytic systems based this earth-abundant metal are yet extremely rare and have only shed to light in 2018. In particular, Leconte and co-workers successfully applied the diradical cobalt(III) complex **25** (Fig. **5**) in the cycloisomerization of different γ- and δ-alkynoic acids [95]. This catalyst was able to operate under mild conditions (CH_2Cl_2/r.t. with metal loadings in the range 0.5-5 mol%) and showed a complete *exo* selectivity with substrates containing a terminal C≡C bond, whereas mixtures of the corresponding *exo* and *endo* cyclization products were systematically obtained with internal alkynes. The authors also explored the catalytic behavior of the related chloride derivative **26**, which showed an activity comparable to that of **25** only when NaOAc was added to the reaction medium. The effectiveness of **26** was negligible in the absence of NaOAc, thus suggesting that the axial acetate ligand in complex **25** acts as an internal base during catalysis facilitating the generation of the more nucleophilic carboxylate anion.

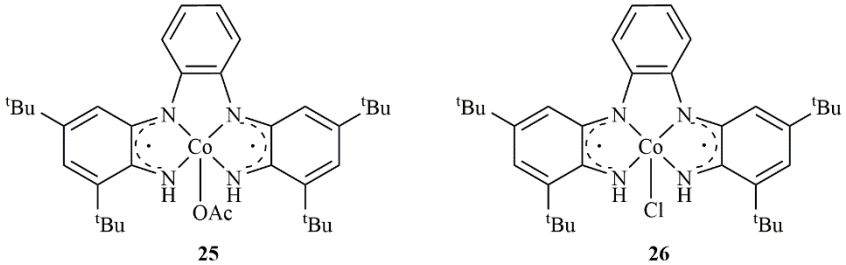
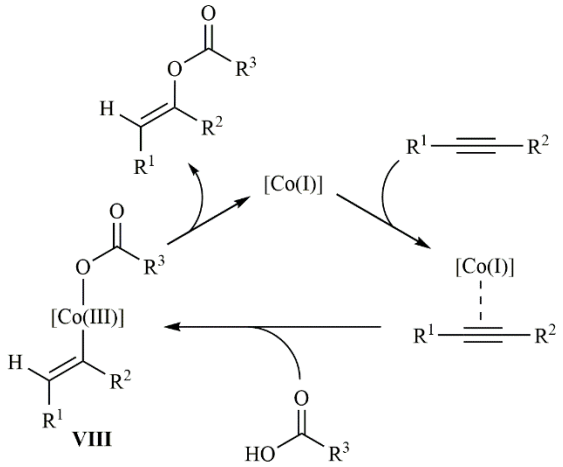


Fig. 5. Structure of the diradical cobalt(III) complexes **25** and **26**.

A broad scope procedure for intermolecular addition of carboxylic acids to alkynes was also described by Chen and Li in 2018 employing $Co(BF_4)_2$ in combination with the tridentate phosphine ligand $PhP(CH_2CH_2PPh_2)_2$ and Zn dust [96]. The process was operative with both terminal and internal alkynes and proceeded efficiently in acetonitrile at r.t. or 80 ºC, respectively, with a cobalt loading of 5 mol%. The corresponding Markovnikov addition products were selectively obtained starting from terminal alkynes and a complete *E*-selectivity was observed for internal substrates (*syn* addition). With regard to the latter, mixtures of regioisomers were in most of the cases obtained from non-symmetrically substituted alkynes. A reaction pathway involving Co(I) species, generated *in situ* by Zn-mediated reduction of the Co(II) precursor, was proposed by the authors. Thus, after the initial π-coordination of the alkyne to this Co(I) species, an oxidative addition of the carboxylic acid would occur to generate the vinyl-Co(III)-carboxylate intermediates **VIII**, from which the enol ester products are released by reductive elimination (Scheme **21**).



Scheme 21. Proposed reaction pathway for the cobalt-catalyzed intermolecular addition of carboxylic acids to alkynes.

4.2. Rhodium

Since the seminal work by Chan and Marder in 1987 [97], many examples of rhodium catalysts for the cyclization of alkynoic acids into enol lactones have appeared in the literature [5, 7, 98]. In this context, extending previous studies with cationic Rh(I) complexes bearing bidentate *N*-donor ligands [99], Messerle and co-workers explored the catalytic behavior of compounds **27-30** in the cycloisomerization of the model substrates 4-pentynoic and 5-hexynoic acid (Fig. **6**) [100]. All of them were able to promote the selective *exo* cyclization of both alkynoic acids in C_6D_6 at 70-80 ºC without the help of any additive, with complex **27** lacking extra coordinating groups in the ligand backbone showing the best performances (full conversion after 0.3-13.3 h with metal loadings of 1-2 mol%).

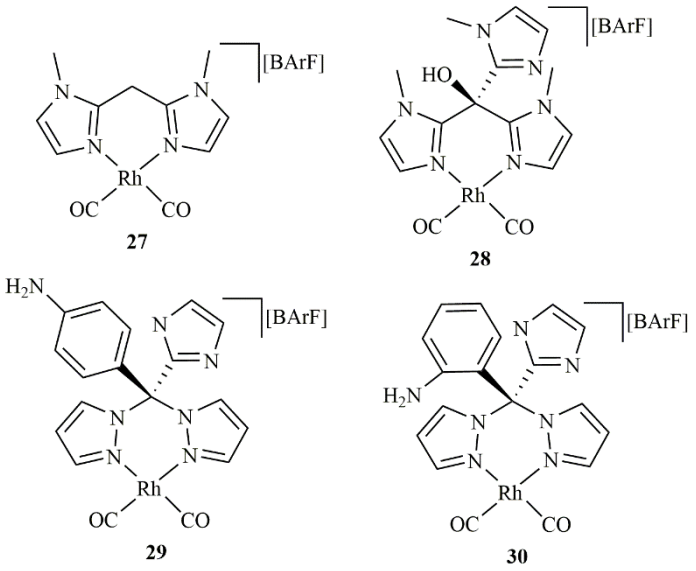
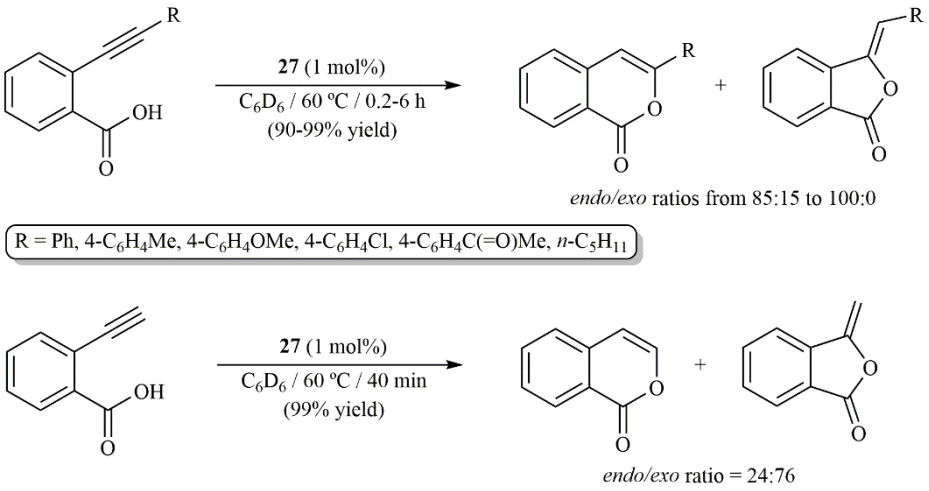


Fig. 6. Structure of the rhodium(I) complexes **27-30**.

The same complexes were subsequently applied in the cyclization of 2-alkynylbenzoic acids, with the regioselectivity of the reaction being strongly dependent on the terminal or internal nature of the alkyne unit [101]. As exemplified with complex

27, which was again the most active of the series, while the 6-*endo* cyclization was largely favored with internal substrates, the corresponding phthalide was the major product when 2-ethynylbenzoic acid was employed (Scheme **22**).



Scheme 22. Cyclization of 2-alkynylbenzoic acids catalyzed by the rhodium(I) complex **27**.

In an independent study, Meserle and co-workers evaluated the catalytic behavior of the mono- and dinuclear Rh(I) complexes **31-34**, containing bidentate imidazolyl-imine ligands (see Fig. **7**), in the cyclization of 4-pentynoic acid (reactions performed in C_6D_6 at 60 ºC with a Rh loading of 2 mol%) [102]. Of them, only the *ortho*-phenylene- and ethylene-linked dinuclear derivatives **33** and **34** were active in the process, with the former being by far the most effective (full conversion after 2.5 h; the 5-*exo*-*dig* cyclization product was exclusively formed). The results obtained were explained in terms of a cooperative bimetallic effect that would be particularly enhanced in complex **33** since it features the shorter intermetallic Rh···Rh distance due to the conformational restrictions imposed by the *ortho*-phenylene linker. The same group also reported the 5-*exo*-*dig* cyclization of 4-pentynoic acid employing different Rh(I) derivatives with bi- and

tridentate *N*-heterocyclic carbene (NHC) ligands functionalized with pyrazole wingtips, systems that were less effective than those just commented [103].

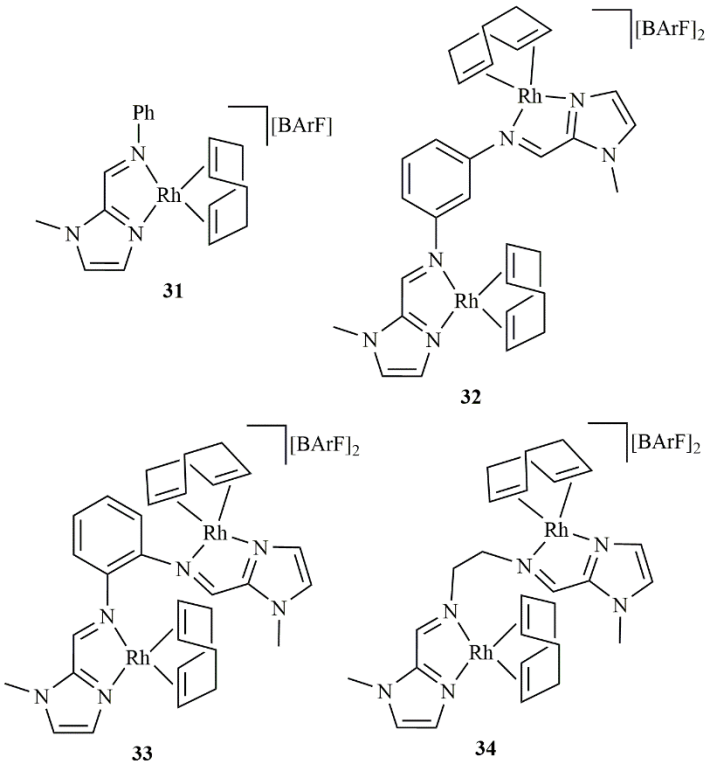


Fig. 7. Structure of the mono- and dinuclear rhodium(I) complexes **31**-**34**.

Additionally, the mono- and tetranuclear NHC-Rh(I) complexes **35** and **36** (Fig. **8**) were tested by Poyatos and co-workers in the cycloisomerization of 4-pentynoic and 5-hexynoic acid [104]. Both promoted selectively the *exo* cyclization of the substrates at 80 ºC, featuring a high efficiency at low metal loadings (0.1-1 mol%).

Concerning intermolecular processes, the group of Breit developed in 2010 an efficient and general catalytic system for the *Z*-selective *anti*-Markovnikov addition of carboxylic acids to terminal alkynes by combining the Rh(I) dimer [{Rh(μ-Cl)(COD)}] (COD = 1,5-cyclooctadiene) with the bidentate *P*,*N*-donor ligand 2-[(diphenylphosphino)methyl]pyridine (Ph_2PCH_2-2-Py) [105]. The synthetic utility of this protocol was further evidenced by Burke and co-workers with the preparation of the chiral

(*Z*)-enol ester **38** by addition of acetic acid to (2*R*)-8-nonyl-2-ol (**37**) (Scheme **23**), from which the total synthesis of the natural product (+)-patulolide C could be accomplished through an asymmetric hydroformylation/macrocyclization sequence [50, 106].

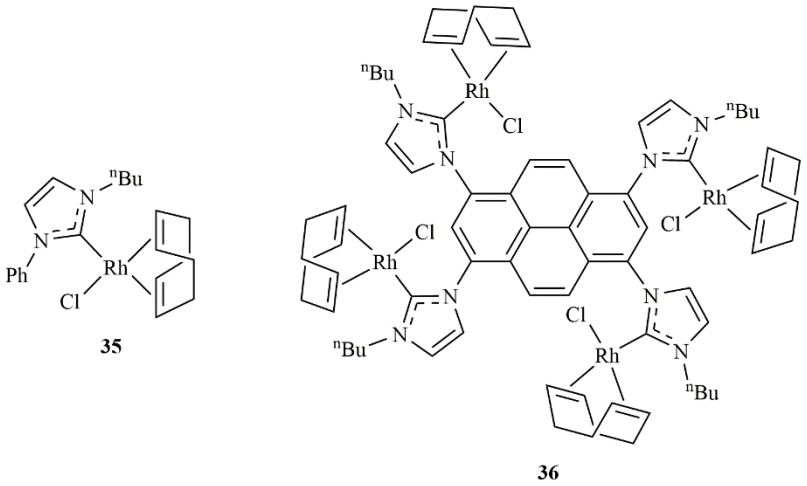
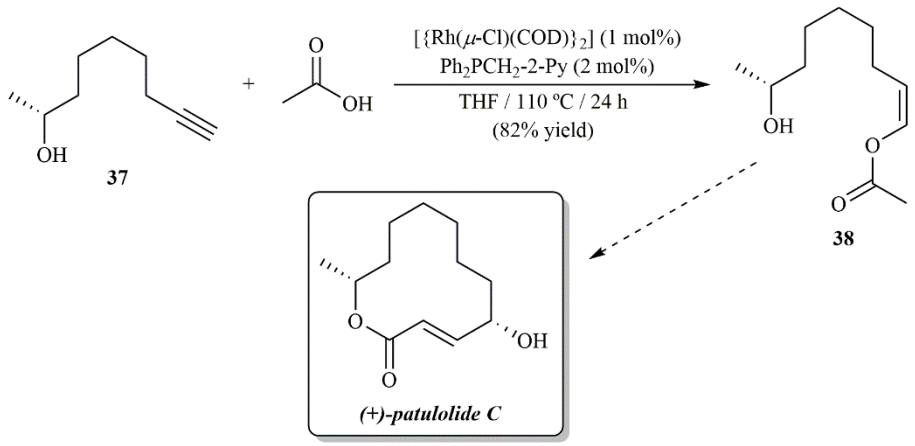


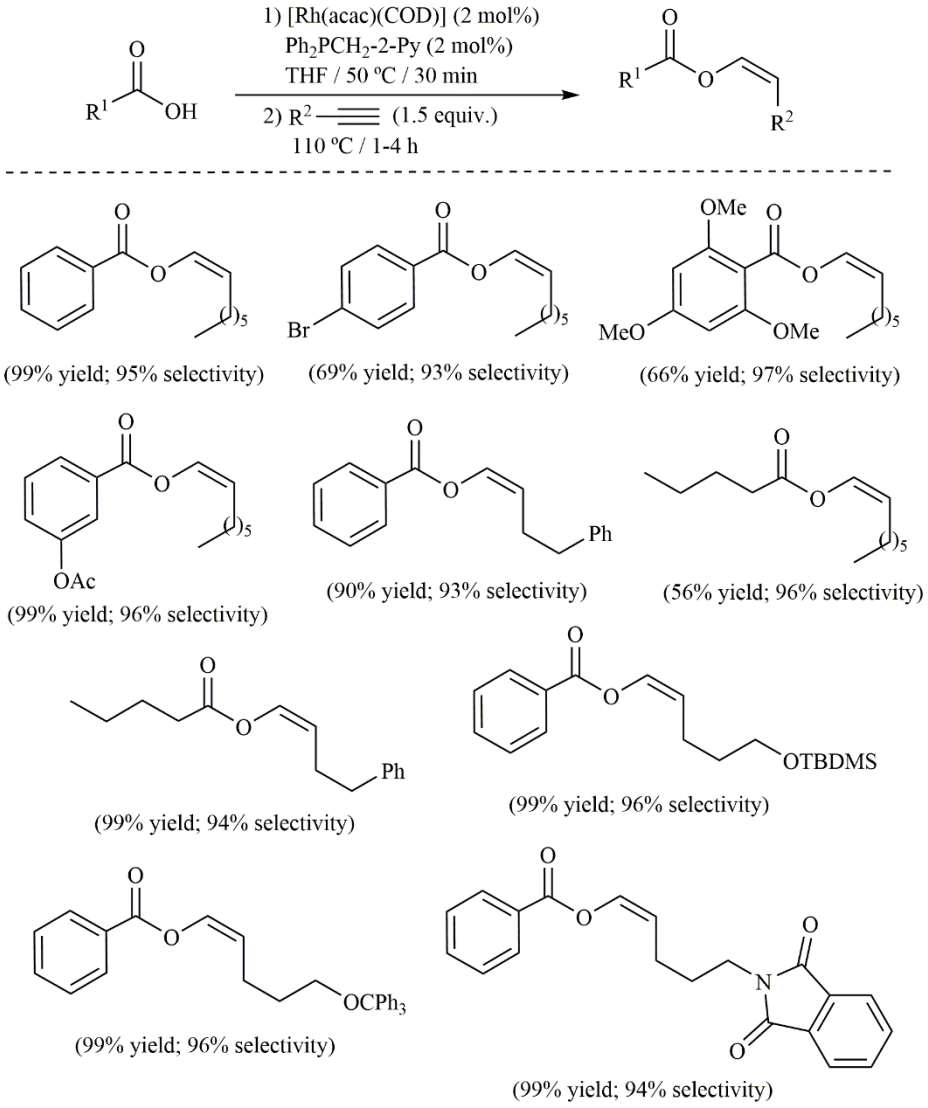
Fig. 8. Structure of the NHC-rhodium(I) complexes **35** and **36**.



Scheme 23. Rh(I)-catalyzed *anti*-Markovnikov addition of acetic acid to the chiral alkyne **37**.

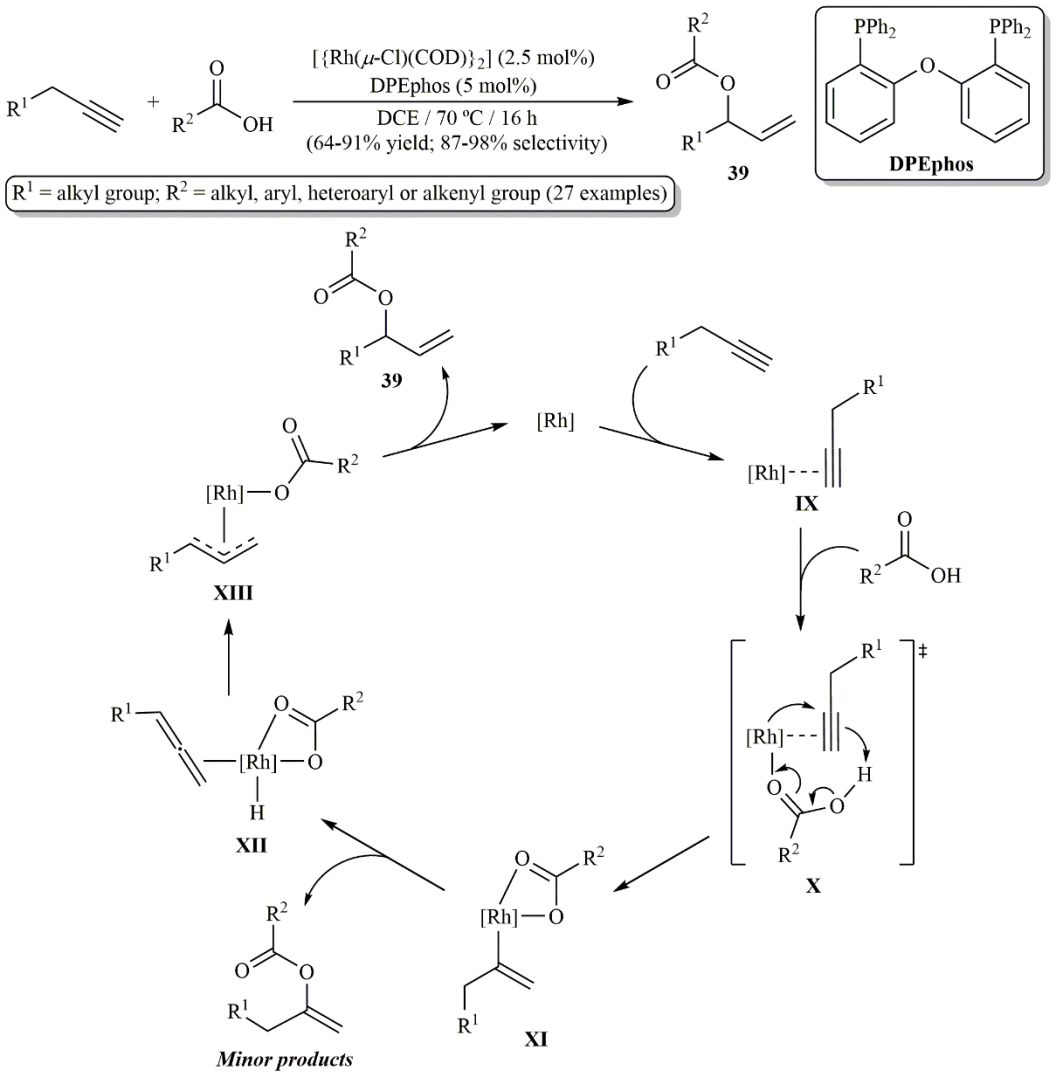
Breit and co-workers conducted additional studies on these *Z*-selective intermolecular hydro-oxycarbonylation reactions that allowed to identify an improved catalytic system [107, 108]. Thus, they found that the combined use of two rhodium species, namely $[Rh(Ph_2PCH_2\text{-}2\text{-}Py)_2][H(carboxylate)_2]$ and [{Rh(*μ*-

carboxylate)(COD)}$_2$], allows to reduce significantly the reaction times (from 16-24 to 1-4 h) without erosion of selectivities and yields. In addition, this new catalytic system, which is generated *in situ* by treating [Rh(acac)(COD)] (acac = acetylacetonate) with Ph_2PCH_2-2-Py and the corresponding carboxylic acid in THF at 50 ºC prior to the addition of the terminal alkyne, enabled the use of substrates previously incompatible such as 4-bromobenzoic acid (see Scheme **24**).



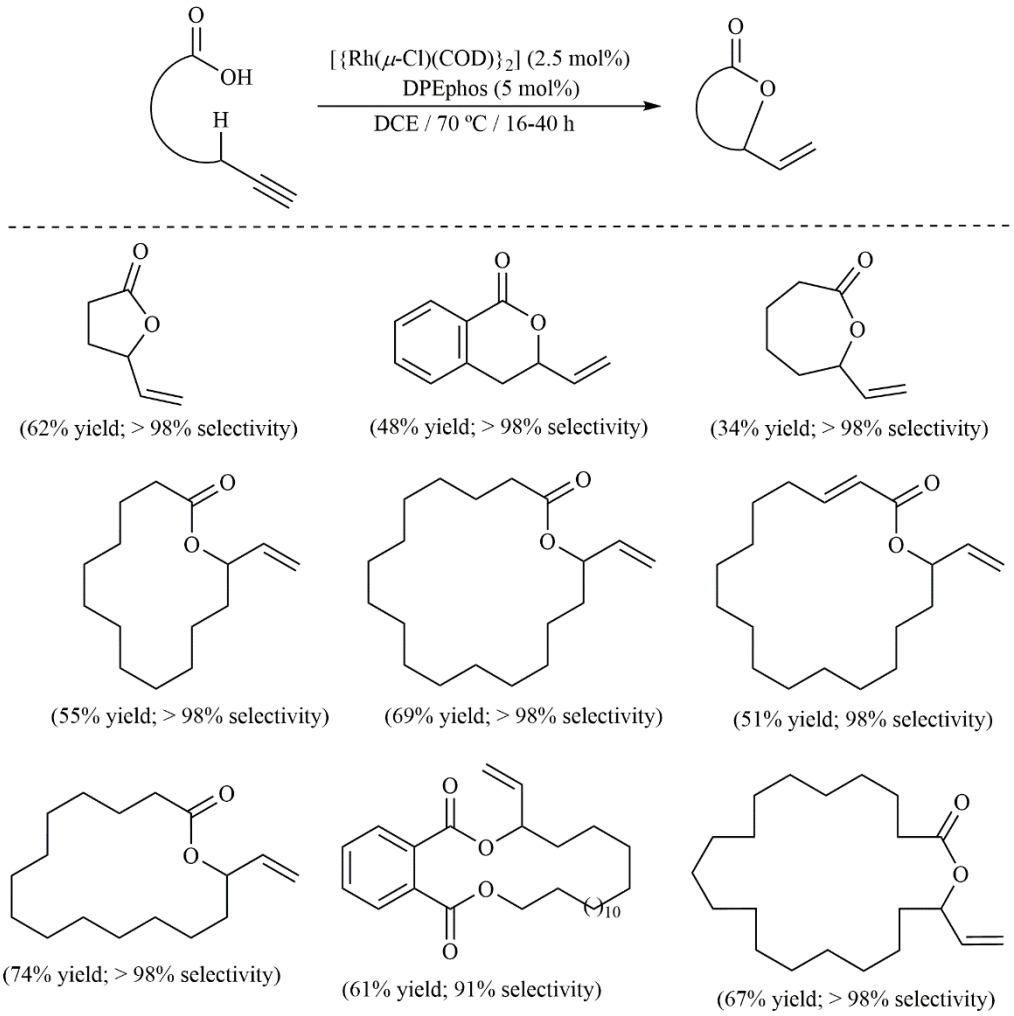
Scheme 24. Rh(I)-catalyzed *Z*-selective *anti*-Markovnikov addition of carboxylic acids to terminal alkynes.

Remarkably, when the Rh(I) dimer [{Rh(μ-Cl)(COD)}] was combined with the wider bite angle diphosphine ligand DPEphos, the addition process took place with a completely different chemoselectivity leading to the branched allylic esters **39** instead of the expected *anti*-Markovnikov addition products (Scheme **25**) [109]. Compounds **39** are the result of a redox-neutral activation of the propargylic C-H bond of the terminal alkynes and were generated with high selectivity (only the formation of minor amounts of the corresponding Markovnikov addition products was observed in the crudes).



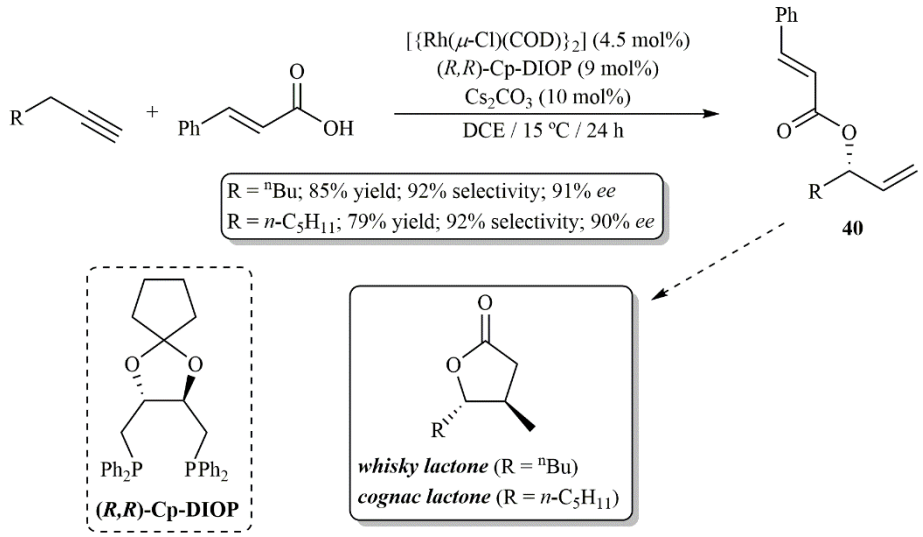
Scheme 25. Rh(I)-catalyzed coupling of terminal alkynes with carboxylic acids *via* propargylic C-H activation.

Detailed mechanistic investigations indicated that the reactions proceed through the initial π-coordination of the alkyne to a monomeric rhodium(I) complex (intermediate **IX**), which evolves into the vinyl-rhodium(III) species **XI** upon coordination of the carboxylic acid through a transition state of type **X** (Scheme **25**) [110]. Intermediate **XI** can either undergo reductive elimination leading to the Markovnikov addition byproducts or through a β-hydride elimination to generate the hydride derivative **XII** (preferred path). Subsequent insertion of the resulting allene into the Rh-H would generate the Rh(III)-π-allyl species **XIII**, which releases the branched allylic ester product **39** by reductive elimination. In full accord with this mechanistic proposal, compounds **39** could be alternatively obtained using the corresponding allenes instead of the alkynes as starting materials [109, 110]. Also of note is the fact that this rhodium-catalyzed coupling reaction can be performed in an intramolecular manner allowing a rapid and atom-economic access to a wide range of allylic lactones and macrolactones (ring sizes ranging from 5 to 23 members) with high selectivities (the only byproducts observed in this case were the enol lactones derived from the *exo* addition of the carboxylic acid to the C≡C bond) [111]. Some representative examples are given in Scheme **26**.



Scheme 26. Rh(I)-catalyzed synthesis of different allylic lactones from alkynoic acids.

Furthermore, an enantioselective variant of the process was successfully developed employing the chiral diphosphine ligand (*R*,*R*)-Cp-DIOP [112]. An illustrative example is given in Scheme **27** where the preparation of the branched allylic esters **40**, which proved to be useful intermediates in the total synthesis of the naturally occurring *γ*-butyrolactones *trans*-cognac lactone and *trans*-whisky lactone through a RCM/Michael addition-based strategy, is shown.



Scheme 27. Rh(I)-catalyzed enantioselective synthesis of the branched allylic esters **40**.

4.3. Iridium

Compared to rhodium, iridium-based catalysts for hydroxycarbonylation reactions are less common due probably to the general guess that, as a third row metal, its reactivity would be too low to achieve high activities. Studies carried out by Messerle with the NHC complexes **41a,b** (Fig. **9**) in the cycloisomerization of 4-pentynoic acid seem to confirm this assumption since the activity of **41a** far exceeded that of **41b** (full *vs* 50% conversion after 18 h at 80 ºC with a metal loading of 5 mol%) [103]. We must note, however, that Poyatos and co-workers found similar activities between the tetranuclear NHC-Ir(I) complex **42** (Fig. **9**) and its rhodium counterpart **36** (see Fig. **8**) in the cycloisomerization of the model 4-pentynoic and 5-hexynoic acids [104]. In all the cases, a 5-*exo-dig* cyclization pathway was observed.

In addition to the comparative studies just commented, Dong and co-workers developed a catalytic system, consisting of the combination of dimer [{Ir(μ-Cl)(COD)}$_2$] with the chiral diphosphine (*S*,*S*)-Ph-BPE, capable to promote successfully the selective *exo* cyclization of various alkynoic acids in TFE (2,2,2-trifluoroethanol) to generate five-

, six-, and specially challenging seven-membered ring unsaturated lactones (see Scheme **28**) [113].

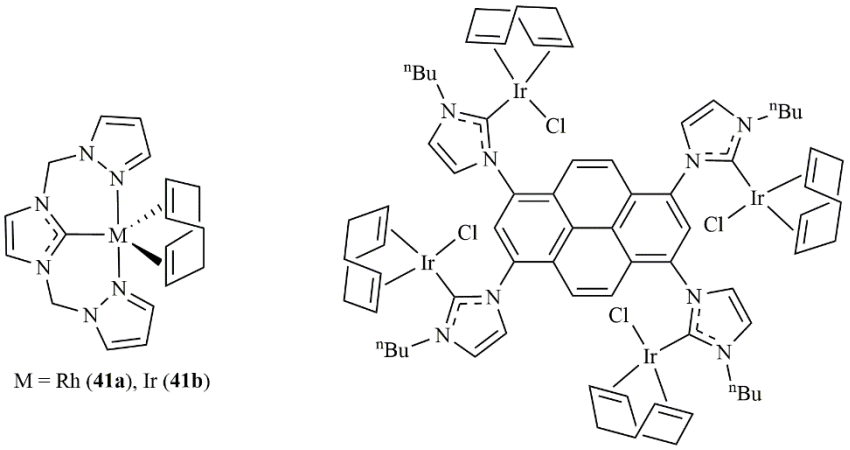
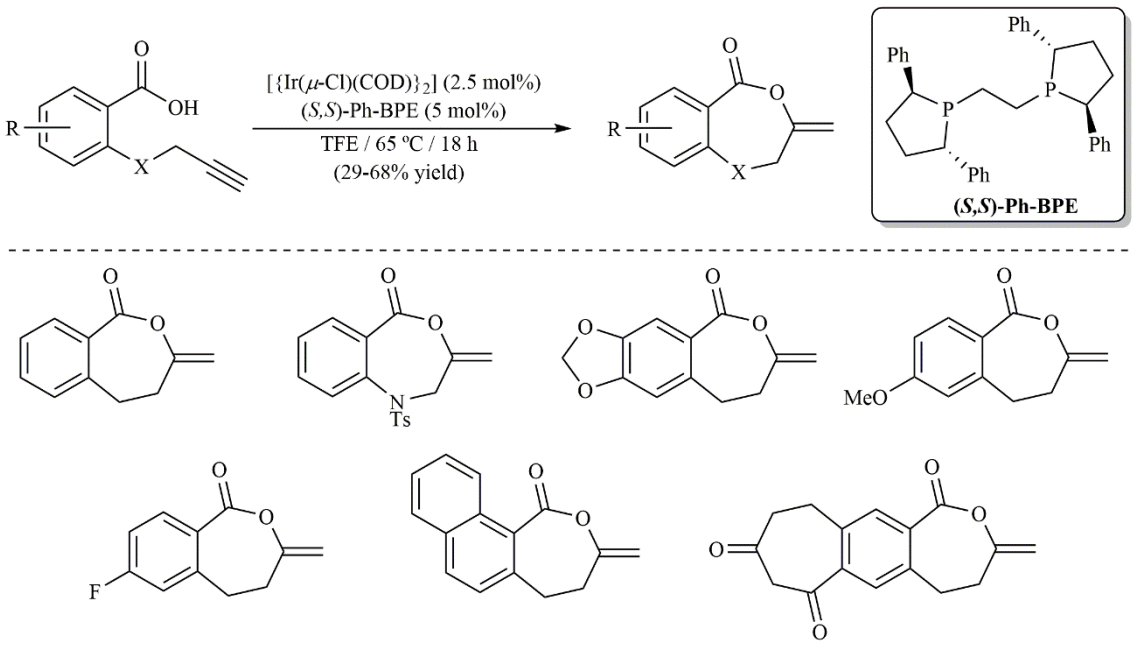


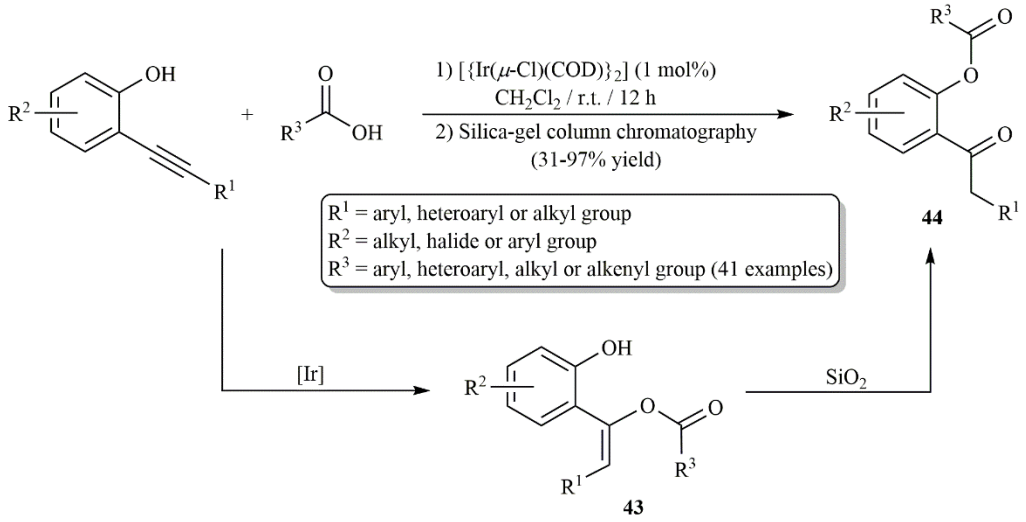
Fig. 9. Structure of NHC complexes **41a,b** and **42**.



Scheme 28. Ir(I)-catalyzed synthesis of seven-membered ring enol lactones.

Additionally, dimer [{Ir(μ-Cl)(COD)}$_2$] was recently employed by Cui and co-workers to promote the intermolecular addition of a broad range of carboxylic acids to 2-

alkynylphenols. The reactions proceeded under mild conditions in the absence of additives or ligands and, as shown in Scheme **29**, furnished the aromatic *ortho*-acyloxyketones **44** after chromatographic work-up on silica gel [114]. Compounds **44** result from the SiO_2-mediated rearrangement, *via* acyl group migration, of the initially formed enol esters **43**. Changing the purification method of the products from silica gel column chromatography to recrystallization allowed to isolate the enol esters **43** in a complete regio- and stereoselective manner (*syn* type addition).



Scheme 29. Ir(I)-catalyzed addition of carboxylic acids to 2-alkynylphenols.

The intermolecular addition of benzoic acid to phenylacetylene using the Ir(III) complex $[IrHCl(\kappa^1\text{-}O_2CPh)(PMe_3)_3]$ as catalyst has also been described [115]. The reaction, performed in C_6D_6 at 120 ºC, led mainly to the dimerization of the alkyne and only minor amounts of the Markovnikov addition product were formed.

5. GROUP 10 METAL CATALYSTS

Although early studies involving nickel-based catalysts can be found in the literature [5, 7, 98], during the period covered in this review only examples involving palladium and platinum have been described.

5.1. Palladium

The effectiveness of palladium derivatives as catalysts for cycloisomerization reactions of alkynoic acids has been amply demonstrated [5, 7, 98] and continuous efforts have been devoted to the design of new catalytic systems. In this context, the works carried out by Martin-Vaca, Bourissou and co-workers with the indenediide palladium(II) pincer complexes **45-47** deserve to be highlighted (Fig. **10**) [116-118]. These compounds proved to be competent toward a broad range of terminal and internal γ-, δ- and ε-alkynoic acids, allowing the access to 5-, 6- and 7-membered ring lactones in high yields, under mild reaction conditions (at r.t. in most cases), and without requiring the addition of a base to the reaction medium (a common requirement with other palladium-based systems). In addition, all of them showed an exquisite *exo* selectivity in the cyclization of terminal substrates, but furnished mixtures of the corresponding *exo* and *endo* cyclization products starting from internal alkynes.

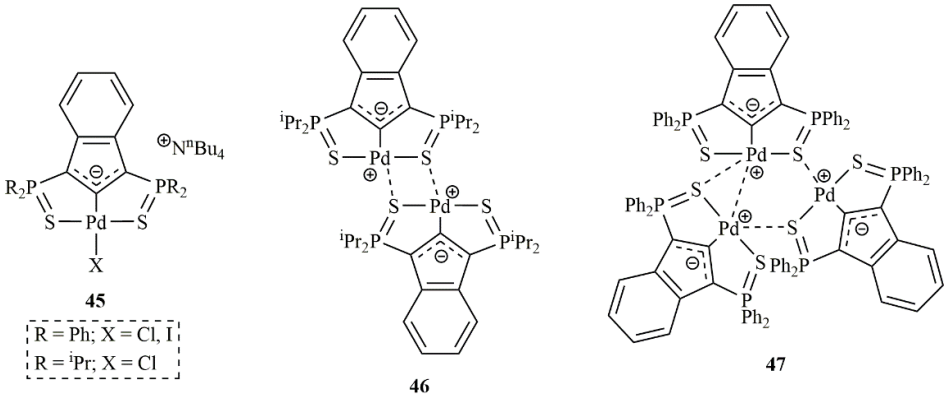
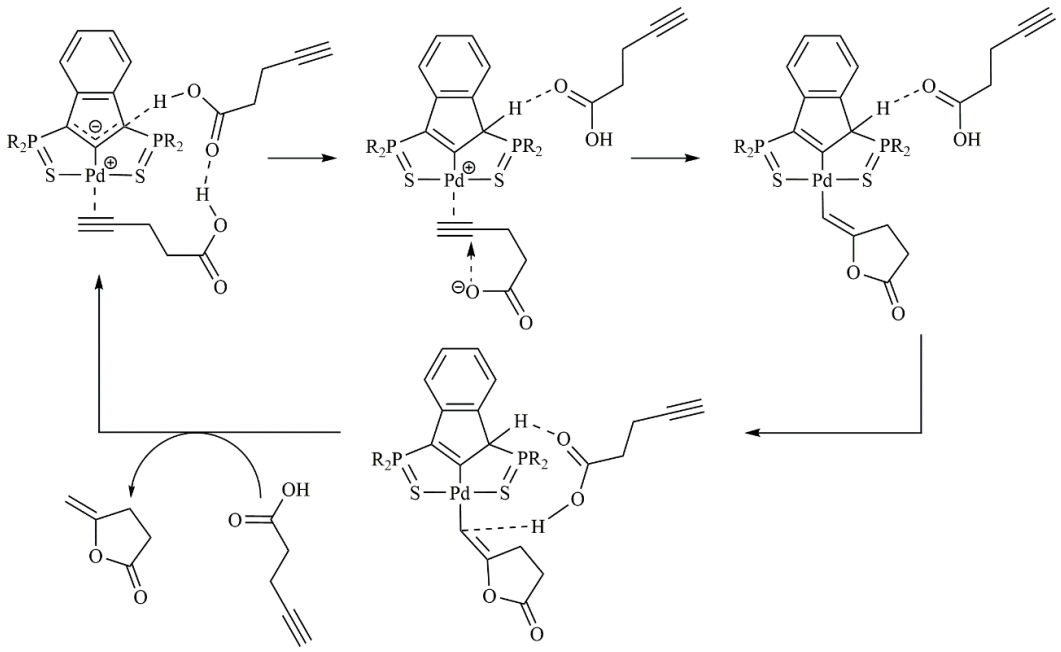


Fig. 10. Structure of the indenediide palladium pincer complexes **45-47**.

The mode of action of complexes **45-47** was investigated computationally using DFT theory and the calculations suggested the active participation of the indenediide motif during catalysis [118]. Thus, this group would act as an internal base deprotonating the carboxylic acid and generating the more nucleophilic carboxylate anion, a process in which a second molecule of the substrate participates as a proton shuttle *via* H-bonding (see Scheme **30**). After the selective *anti* addition of the carboxylate to the coordinated C≡C bond, the second molecule of the substrate is again in charge of transferring the proton necessary for the final demetallation step.

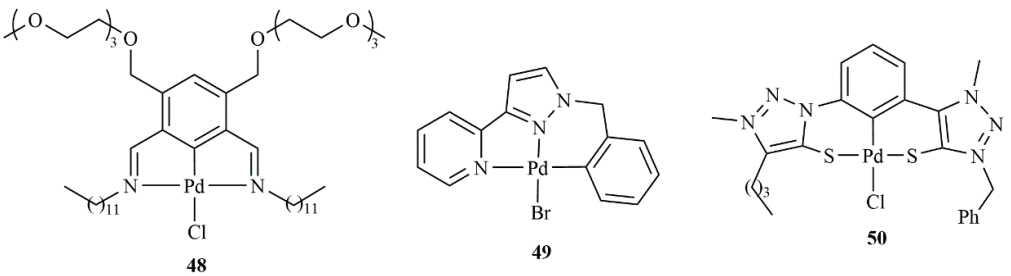


Scheme 30. Computed mechanism for the cyclization of 4-pentynoic acid catalyzed by complexes **45-47**.

Based on these theoretical findings, it was possible to improve the catalytic activity of complexes **45-47** by introducing in the reaction medium H-bond donor additives capable of carrying out the proton transfer processes in a more effective way than the second substrate molecule. In particular, in the presence of catechol derivatives, up to 60-fold increase in reactivity could be achieved along with a higher preference

towards the *endo* cyclization when internal alkynoic acids were employed as substrates [118].

Complexes **48-50** are additional examples of Pd(II) pincer complexes capable to promote the cycloisomerization of alkynoic acids that can be found the literature (Fig. **11**). Unlike the indenediide derivatives **45-47**, all of the them required the assistance of a base as co-catalyst. Thus, concerning complex **48**, in combination with Et_3N it proved to be effective in the 5-*exo*-*dig* cyclization of γ-alkynoic acids of type $ArC{\equiv}CCH_2CH_2CO_2H$ in water at 50 ºC [119]. Associated also with Et_3N, complex **49** showed a remarkable reactivity towards both terminal and internal γ- and δ-alkynoic acids, allowing to perform the reactions at 50 ºC in chloroform with a palladium loading of only 0.0001 mol% [120]. The *exo*-*dig* cyclization products were again selectively obtained and an exquisite (*Z*)-stereochemistry was observed with internal substrates (*anti*-addition). Identical experimental conditions were employed to evaluate the behavior of complex **50**, which catalyzed efficiently the 5-*exo*-*dig* cyclization of terminal γ-alkynoic acids but resulted inoperative in the construction of 6-membered enol lactones even when the temperature was increased to 90 ºC [121].

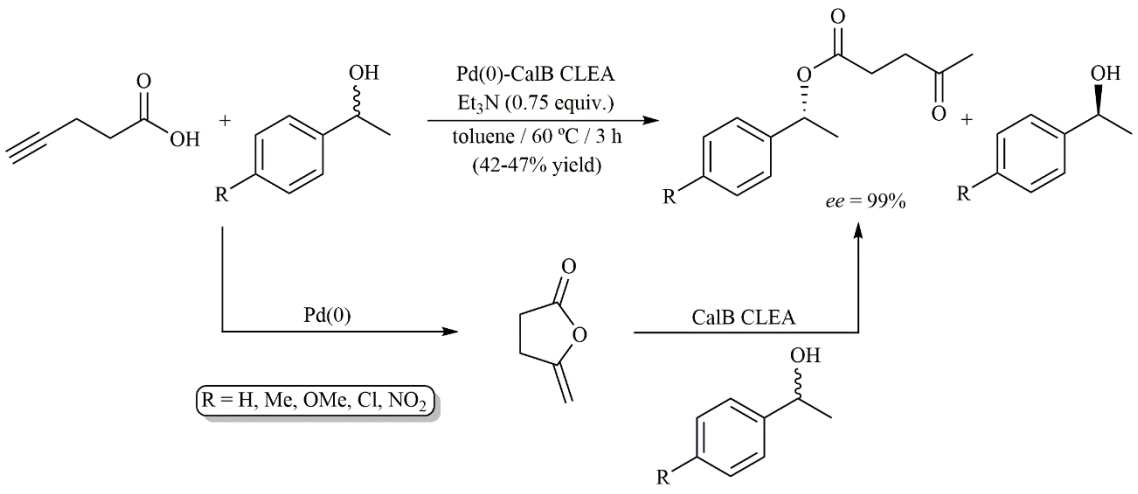


48 **49** **50**

Fig. 11. Structure of the palladium(II) complexes **48-50** containing pincer-type ligands.

Cycloisomerization reactions of linear γ- and δ-alkynoic acids into alkylidene-lactones (*exo* cyclizations) with Pd-based heterogeneous catalysts have also been

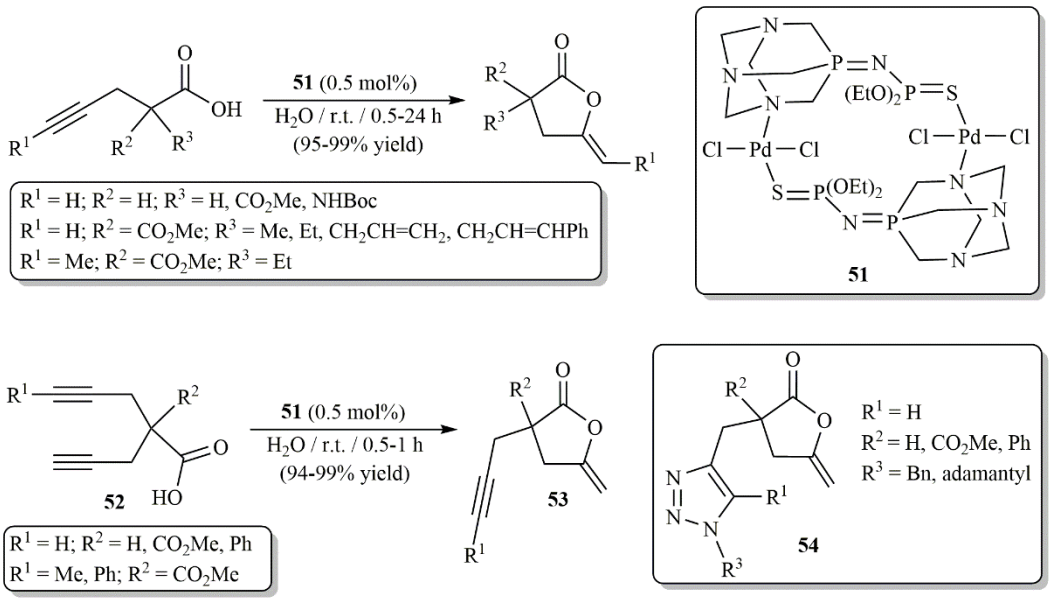
described, including examples of Pd(0) nanoparticles (NPs) supported on mesoporous silica nanoparticles [122], PdO impregnated on magnetite [123] and Pd(II) complexes encapsulated in polyamine dendrimers [124], supported on an amino-functionalized siliceous mesocellular foam [125] or bound to an amino acid-based supramolecular gel [126]. Some of them proved to be active in water [123, 126] and in most cases their recyclability could be demonstrated [122, 123, 125, 126]. In this context, it is noteworthy the design by Bäckvall and co-workers of a biohybrid catalyst consisting of Pd(0) NPs supported on a cross-linked network of aggregated lipase B enzyme of *Candida antarctica* (CalB CLEA) capable to promote efficiently a one-pot reaction for the kinetic resolution of 1-phenylethanol derivatives with 4-pentynoic acid, in which the *in situ* formed enol-lactone acts as an acyl donor (Scheme **31**) [127]. The catalyst displayed an excellent enantioselectivity (99% *ee*) and a good recyclability (up to 6 consecutive catalytic cycles without loss of activity or selectivity).



Scheme 31. Kinetic resolution of 1-phenylethanol derivatives using a Pd(0)-CalB CLEA biohybrid catalyst.

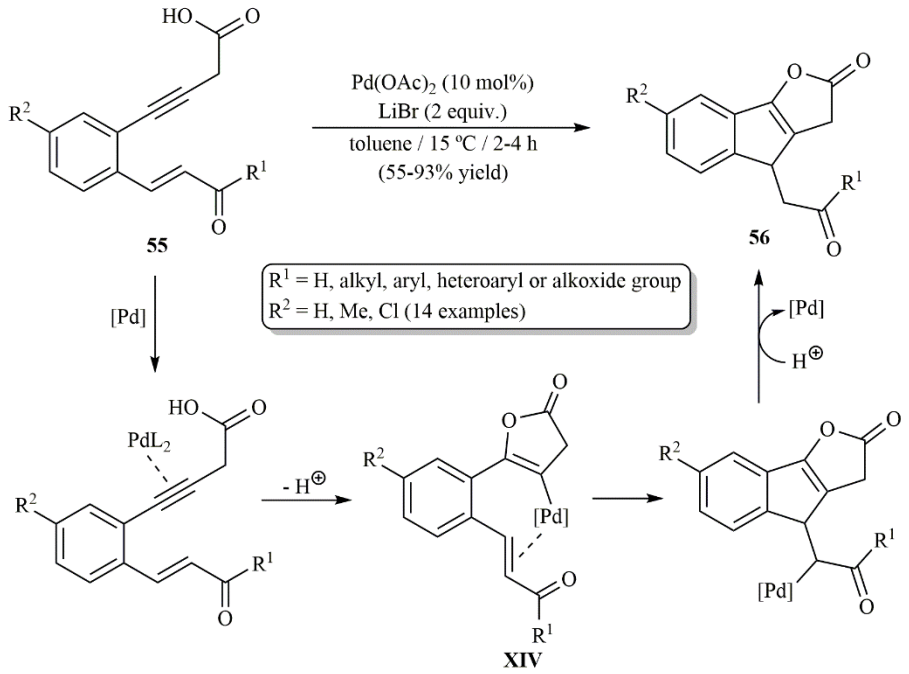
The selective transformation of *γ*-alkynoic acids into (*Z*)-*γ*-alkylidene butyrolactones in water was successfully achieved using the dinuclear Pd(II) derivative

trans-[$PdCl_2\{\mu^2$-N,S-(PTA)=NP(=S)$(OEt)_2\}]_2$ (**51** in Scheme **32**) [128]. This catalyst features a bridging iminophosphorane-type ligand derived from the well-known hydrophilic phosphine PTA, which facilitates its solubility in water. The reactions proceeded cleanly at room temperature, under base-free conditions, and without formation of any by-product derived from the hydration of the C≡C bond of the substrates or from the hydrolysis of the products. Remarkably, complex **51** could be recycled up to 10 consecutive times for the cyclization of the model 4-pentynoic acid (cumulative turnover number of 982) and it could be applied in the desymmetrization of bispropargylic carboxylic acids **52**. In addition, in combination with a Cu(I) source, it allowed the one pot access to a series of bicyclic triazol-enol-lactones **54** from bispropargylic carboxylic acids **52** and azides, *via* 1,3-dipolar cycloaddition of the latter with the C≡C unit of the *in situ* generated enol-lactones **53**. It should also be mentioned at this point that the asymmetric desymmetrization of bispropargylic carboxylic acids related to **52** has been reported using $Pd(OAc)_2$, associated to a chiral diphosphine ligand, in chloroform (enantioselectivities up to 71%) [129].



Scheme 32. Cyclization of alkynoic acids in water catalyzed by a PTA-based Pd(II) catalyst.

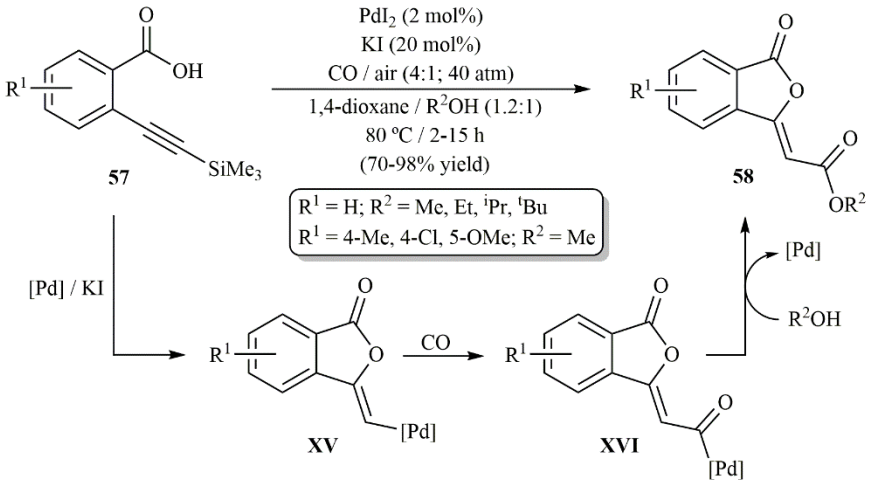
On the other hand, an atom economical route to indeno[1,2-*b*]furan-2-ones **56** from aryl alkynoic acids **55**, bearing a tethered enone partner, was described by Sridharan and co-workers using catalytic amounts of $Pd(OAc)_2$ in combination with lithium bromide (Scheme **33**) [130]. A 5-*endo-dig* cyclization of the substrates, accompanied by the intramolecular olefin insertion in the corresponding vinyl-palladium intermediate **XIV**, was proposed by the authors as a plausible mechanism for this domino reaction. Lithium bromide was responsible for the high selectivity observed in the process since it avoids the competitive β-hydride elimination during the final protodemetallation step.



Scheme 33. Palladium-catalyzed synthesis of indeno[1,2-*b*]furan-2-ones **56** from alkynoic acids **55**.

Under the action of PdI_2 in conjunction with KI, different 2-[(trimethylsilyl)ethynyl]benzoic acids **57** could be regio- and stereoselectively converted into the phthalides **58**, incorporating an alkyl ester functionality on the exocyclic C=C bond, by performing the cyclization reactions under CO/air atmosphere with a solvent

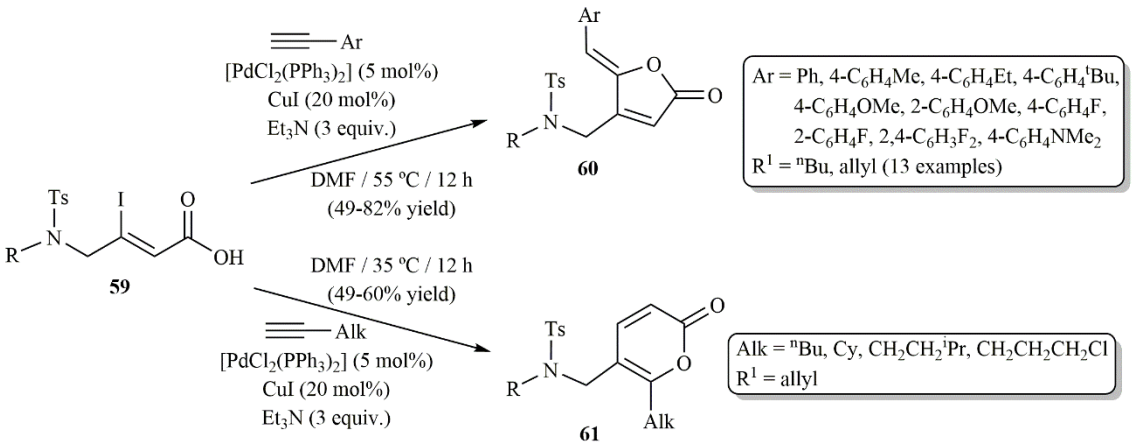
system composed of 1,4-dioxane and the corresponding aliphatic alcohol (Scheme **34**) [131]. The authors proposed that, after 5-*exo-dig* cyclization of the desilylated alkyne, carbon monoxide inserts into the palladium-vinyl bond of intermediate **XV** to generate the acyl-palladium species **XVI**, which evolves into the final product by alcoholysis.



Scheme 34. Palladium-catalyzed cyclization-alkoxycarbonylation of alkynoic acids **57**.

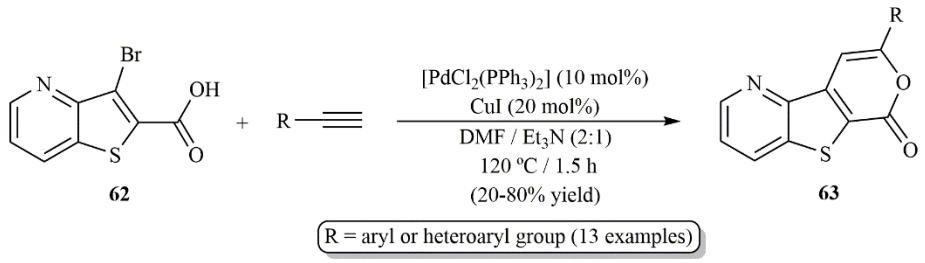
Metal-catalyzed tandem coupling/cyclization reactions of halo-substituted carboxylic acids and terminal alkynes have been for long time applied for the assembly of functionalized lactones [5, 7, 98]. In this context, Thibonnet and co-workers studied the palladium-catalyzed Sonogashira coupling/oxacyclization of the 3-iodovinylic acids **59**, the reactions leading to the selective formation of the five- or six-membered ring unsaturated lactones **60** and **61**, respectively, depending on the aromatic or aliphatic nature of the terminal alkyne employed (Scheme **35**) [132]. Additionally, to obtain the 6-*endo-dig* cyclization products **61** in a pure manner, the reactions had to be carried out at a slightly lower temperature (35 *vs* 55 ºC). Otherwise, significant amounts of the corresponding phthalides (5-*endo-dig* cyclization) are also formed. DFT calculations revealed a direct relationship between the regioselectivity of the cyclization step and the

differences in local charge on the alkyne carbon atoms of the corresponding intermediate Sonogashira coupling products.



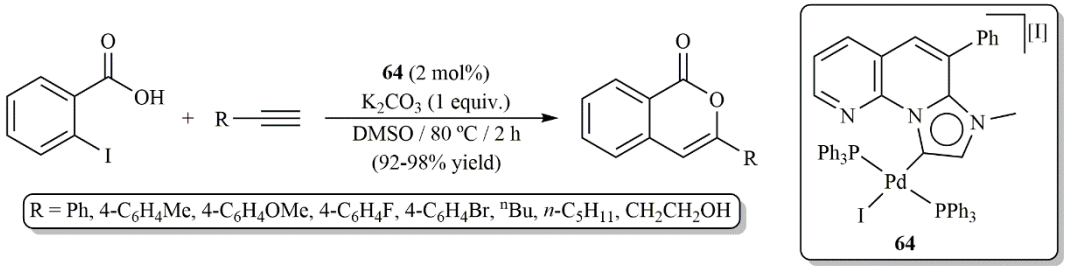
Scheme 35. Tandem Sonogashira coupling/cyclization of 3-iodovinylic acids **59** and terminal alkynes.

Applying similar reaction conditions, a series of 6*H*-pyrano[4´,3´:4,5]thieno[3,2-*b*]pyridines **63** substituted at the C-8 position were synthesized in one-pot manner starting from 3-bromothieno[3,2-*b*]pyridine-2-carboxylic acid **62** and different aromatic and heteroaromatic terminal alkynes (Scheme **36**) [133]. The selective 6-*endo-dig* lactonization of the intermediate Sonogashira coupling products took place in this case as it leads to less stressed polycyclic derivatives in comparison to those resulting from a potential 5-*exo-dig* cyclization.



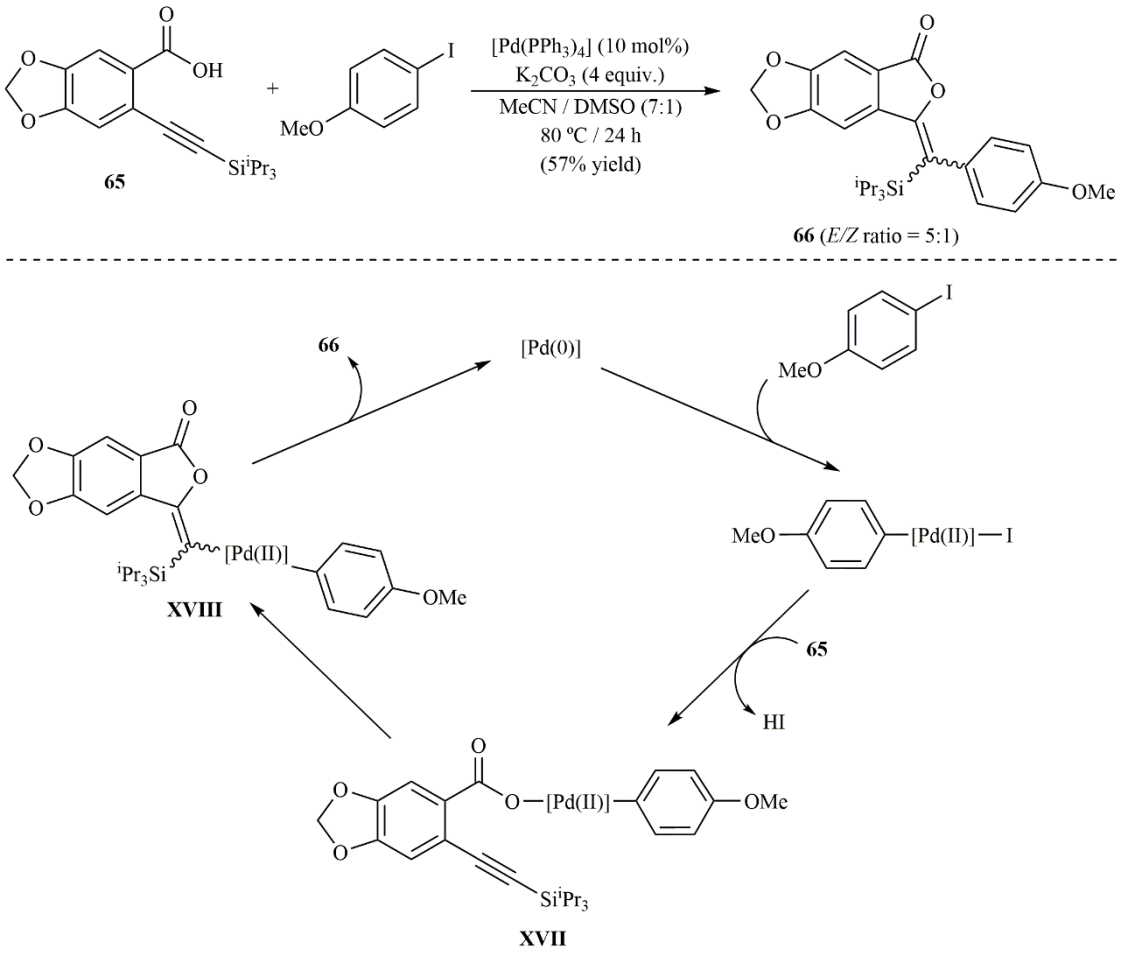
Scheme 36. Palladium-catalyzed synthesis of substituted 6*H*-pyrano[4´,3´:4,5]thieno[3,2-*b*]pyridines.

Very recently, a copper-free sequential Sonogashira coupling/cyclization reaction of terminal alkynes with 2-iodobenzoic acid to afford isocoumarin derivatives was described employing the Pd(II) complex **64**, containing a mesoionic carbene ligand, as catalyst (Scheme **37**) [134]. In addition, tandem Sonogashira coupling/cyclization reactions were also employed to construct silica-based hollow microporous organic networks bearing isocoumarin moieties with application in nitrophenol sensing [135].



Scheme 37. Palladium-catalyzed synthesis of isocoumarins from 2-iodobenzoic acid and terminal alkynes.

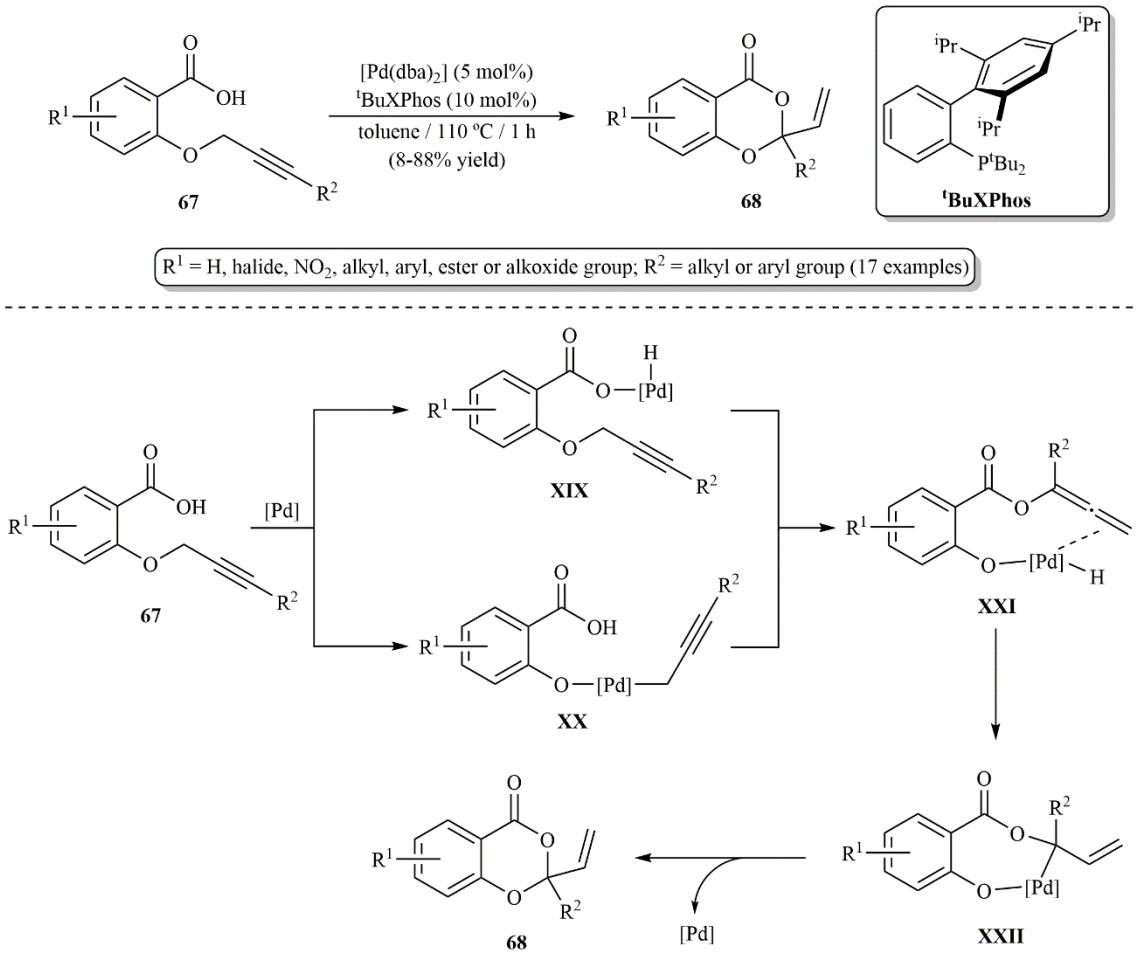
On the other hand, extending previous studies by Rossi and co-workers [136], the palladium-catalyzed tandem cyclization/coupling reaction of the silylated 2-ethynylbenzoic acid **65** with 4-iodoanisole was explored in 2018 by Pelkey´s group [137]. As shown in Scheme **38**, using $[Pd(PPh_3)_4]/K_2CO_3$ as the catalytic system, a stereoisomeric mixture of the phthalide **66** was obtained in moderate yield, with the major isomer resulting from the unexpected *syn* addition of the aryl group and the carboxylic acid across the alkyne. A reaction mechanism involving the initial oxidative addition of the iodoarene to palladium was proposed by the authors. Subsequent iodide/carboxylate metathesis generates the intermediate **XVII**, which evolves into **XVIII** by insertion of the alkyne into the palladium-oxygen bond. In the final step, a reductive elimination liberates the product and regenerates the Pd(0) catalyst.



Scheme 38. Pd-catalyzed synthesis of phthalide **65** through a tandem cyclization/C-C coupling reaction.

The Pd(0) complex [Pd(dba)$_2$] (dba = dibenzylideneacetone), in combination with the bulky biaryl phosphine ligand ^{t}BuXPhos, was used by Sakai and co-workers to promote the cyclization of a series of alkynoic acids **67** derived from salicyclic acids (Scheme **39**) [138]. The unexpected formation of the vinyl dioxanone derivatives **68** was observed, products that could be isolated in variable yields depending on the substituents present in the aromatic ring. Mechanistic studies employing deuterium-labelled substrates suggested the involvement of allenes **XXI** in the reactions. These intermediates could be generated from the palladium-carboxylate **XIX** through a carboxy-palladation/β-aryloxy substitution sequence or, alternatively, by cyclization of species of type **XX** resulting from the oxidative addition of the propargylic C-O bond to palladium. Once the allenyl

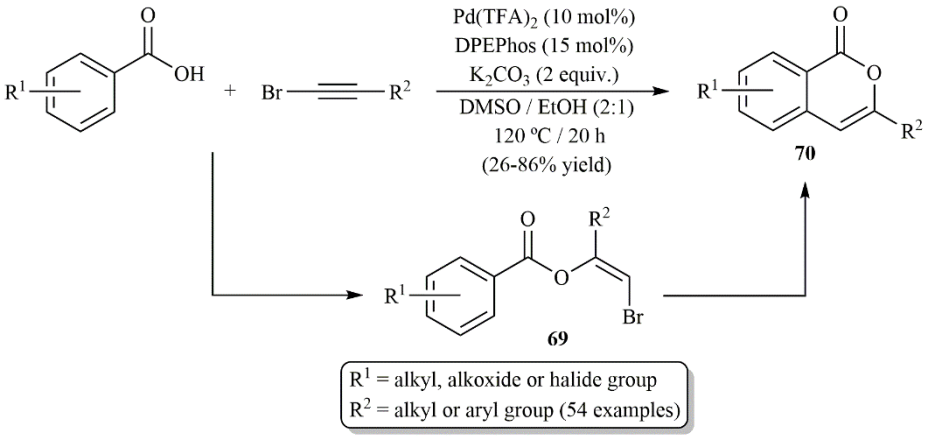
carboxylates **XXI** are formed, they evolve into **XXII** by insertion of the allene into the Pd(II)-H bond, which finally undergo reductive elimination liberating the products **68** and regenerating the catalytically active Pd(0) species.



Scheme 39. Pd(0)-catalyzed cyclization of alkynoic acids **67**.

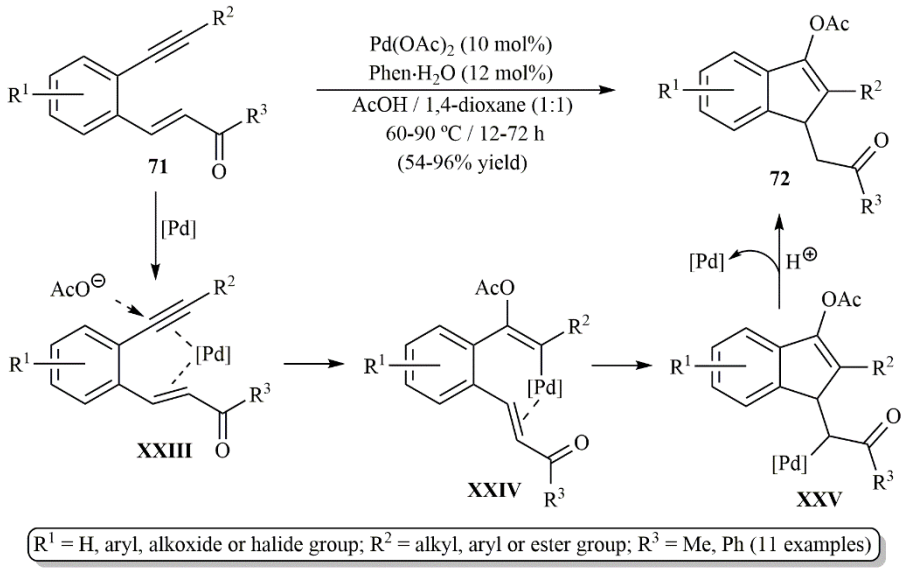
With regard to intermolecular addition processes, Wu, Jiang and co-workers developed a broad scope procedure for the synthesis of 3-substituted isocoumarins **70** by coupling of bromoalkynes with benzoic acids (Scheme **40**) [139]. The reactions, which are catalyzed by palladium(II) trifluoroacetate in combination with the diphosphine ligand DPEPhos (bis[2-(diphenylphosphino)phenyl] ether) and K_2CO_3, involve the initial

anti addition of the acid to the alkyne and subsequent oxidative annulation of the resulting *β*-bromoenol benzoates **69**.



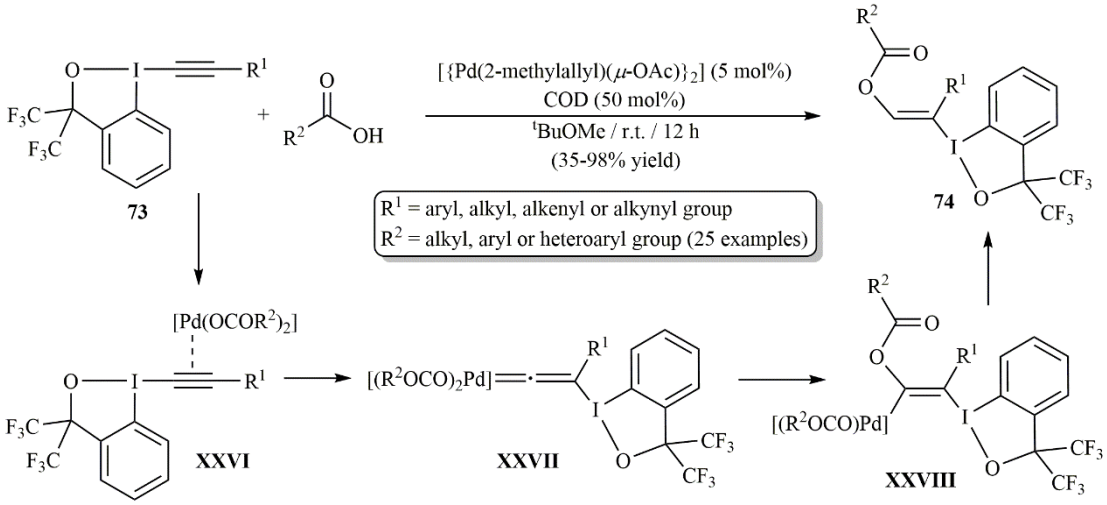
Scheme 40. Palladium-catalyzed synthesis of isocoumarins from bromoalkynes and benzoic acids.

Lu and co-workers reported the preparation of a series of 3-acetoxy indene derivatives **72** through the palladium-catalyzed addition of acetic acid to *o*-alkynylbenzylidene ketones **71** (Scheme **41**) [140]. Thus, activation of the substrate by *π*-coordination of both the C≡C and C=C bonds to Pd(II) species generated from $Pd(OAc)_2$ and 1,10-phenanthroline (Phen) enables the attack of the acetate anion to the alkyne unit (**XXIII**), affording the vinyl-palladium intermediate **XXIV**. Subsequent insertion of the olefin into the Pd-C bond generates **XXV** which evolves into the final product by protonolysis.



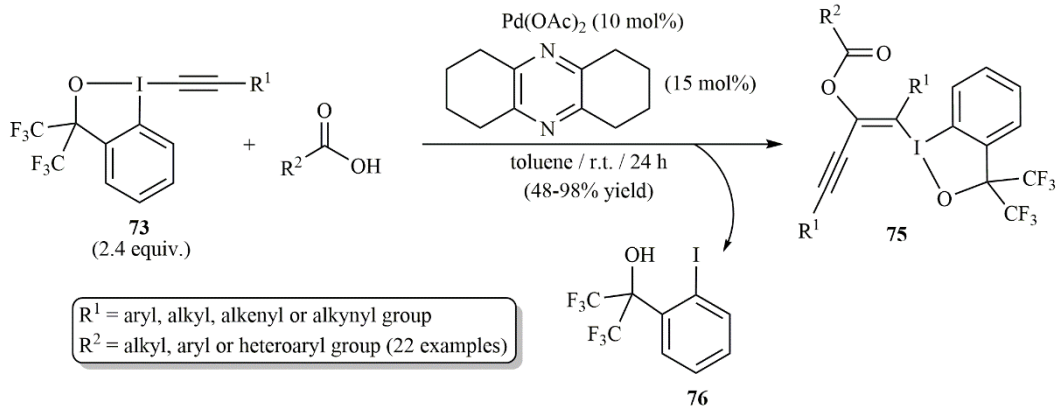
Scheme 41. Palladium-catalyzed synthesis of 3-acetoxy indenes from *o*-alkynylbenzylidene ketones.

Following previous studies on multicomponent coupling reactions of alkynylbenziodoxoles **73** [141], Hirao, Yoshikai and co-workers reported the catalytic addition of carboxylic acids to these compounds employing a catalytic system composed of [{Pd(2-methylallyl)(μ-OAc)}$_2$] and the 1,5-cyclooctadiene ligand [142]. As shown in Scheme **42**, the reactions proceeded under mild conditions and led to the stereoselective formation of the alkenylbenziodoxoles **74**, which were isolated in moderate to excellent yields. Palladium-carboxylate complexes were proposed to act as the active species with DFT calculations supporting the involvement of metal-vinylidenes **XXVII**, generated from the corresponding π-alkyne complex **XXVI** by 1,2-shift of the benziodoxole moiety, as key intermediates in the catalytic cycle. A subsequent migratory insertion of the vinylidene unit into one of the Pd-carboxylate bonds, followed by protonation of the resulting palladium-alkenyl derivative **XXVIII**, would explain the formation compounds **74**.



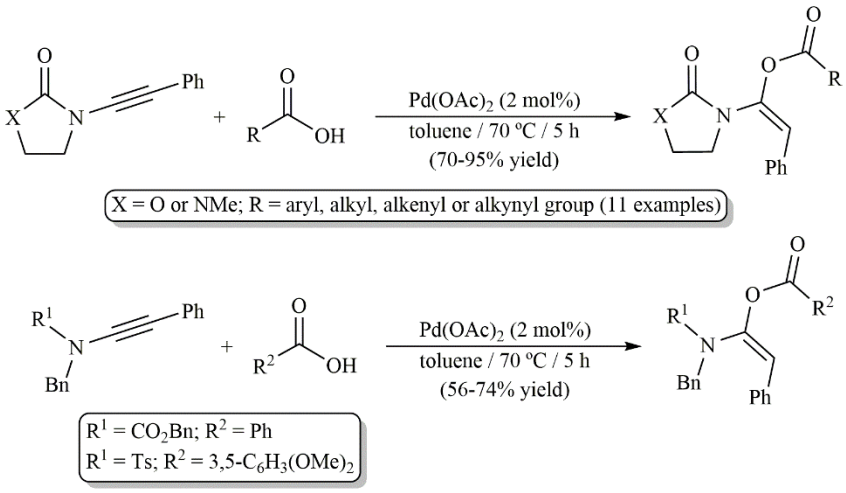
Scheme 42. Palladium-catalyzed addition of carboxylic acids to alkynylbenziodoxoles **73**.

The same group also described the preparation of different (alk-1-en-3-ynyl)benziodoxoles **75** through a 2:1 coupling reaction of alkynylbenziodoxoles **73** with carboxylic acids (Scheme **43**) [143]. $Pd(OAc)_2$ was in this case employed as the metal source and 1,2,3,4,6,7,8,9-octahydrophenazine as the ligand. According to the authors, coordination of this particular ligand to the metal enables the alkynylation of the vinyl-palladium intermediates of type **XXVIII** by a second molecule of the alkynylbenziodoxole substrate, with concomitant release of 1,1,1,3,3,3-hexafluoro-2-(2-iodophenyl)propan-2-ol **76**.



Scheme 43. Palladium-catalyzed 2:1 coupling of alkynylbenziodoxoles **73** and carboxylic acids.

On the other hand, a general palladium-catalyzed protocol for the intermolecular addition of carboxylic acids to ynamides, leading to α-acyloxyenamide derivatives in a regio- and stereoselective manner (*syn* addition), has also been described (representative examples are shown in Scheme **44**) [144]. However, we must note that subsequent studies demonstrated that hydro-oxycarbonylation reactions to this particular class of activated alkynes also takes place, with similar levels of efficiency and selectivity, in the absence of metal catalysts [145-147].

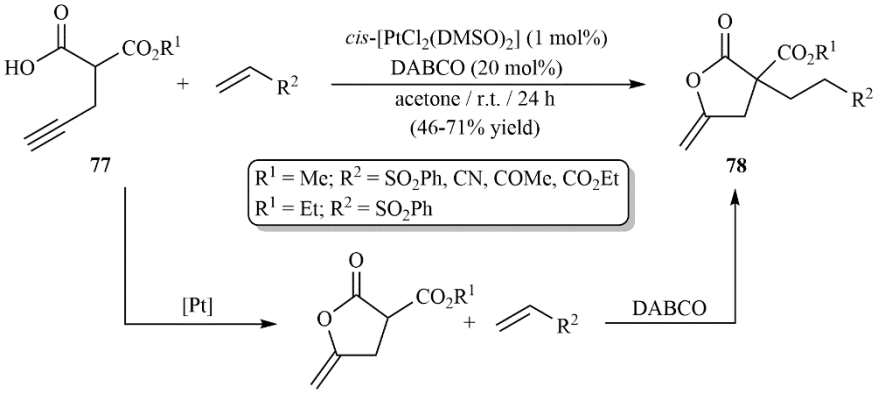


Scheme 44. Pd-catalyzed intermolecular addition of carboxylic acids to ynamides.

5.2. Platinum

Despite the well-known ability of platinum compounds to activate carbon-carbon multiple bonds [148, 149], their application in hydro-oxycarbonylation reactions of alkynes has been scarcely investigated [5, 7, 98]. In fact, during the period covered in this review, only three works have been published. In the first one, Alemán and co-workers employed the Pt(II) complex *cis*-$[PtCl_2(DMSO)_2]$, whose utility in the cyclization of

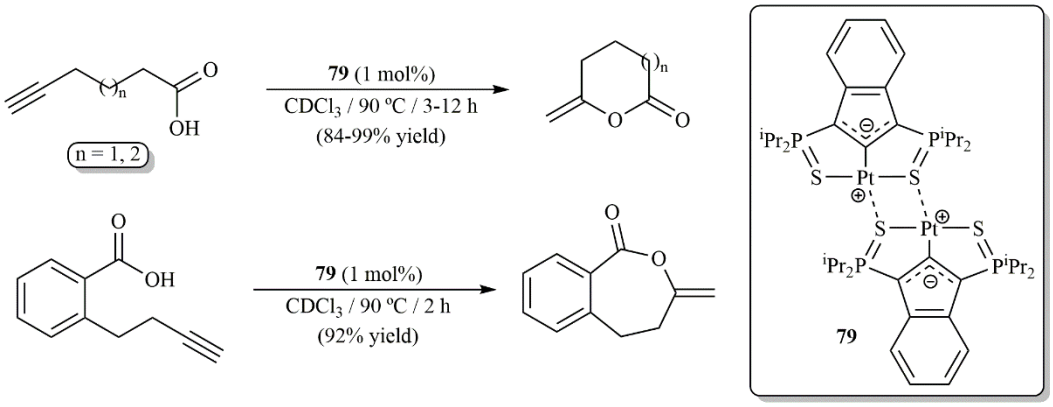
alkynoic acids had been previously demonstrated [150, 151], and 1,4-diazabicyclo[2.2.2]octane (DABCO) to develop a synthetic route to alkylidene lactones **78**, featuring a quaternary center at C-3, by coupling the γ-alkynoic acids **77** with activated olefins through a tandem 5-*exo*-*dig* cyclization/Michael addition reaction (Scheme **45**) [152]. In the process, which nicely illustrates the enormous potential of the metal- and organocatalysis combination, DABCO deprotonates the acidic C-3 position of the alkylidene lactone generated in the initial Pt-catalyzed cyclization step, thus favoring its addition to the alkene. Related δ-alkynoic acids, as well as trisubtituted olefins, also participated in these coupling reactions but they led in general to substantially lower yields.



Scheme 45. Tandem cyclization/Michael reaction catalyzed by a Pt(II) in combination with DABCO.

As an extension of their studies with the indenediide palladium(II) pincer complexes **45-47** (see Fig. **10**), Martin-Vaca, Bourissou and co-workers synthesized related Pt(II) derivatives and studied the catalytic behavior of the dinuclear derivative **79** [153]. This complex was also catalytically active in the cycloisomerization of a diverse family of alkynoic acids, resulting particularly useful for the generation of 6- and 7-membered ring lactones (illustrative examples are given in Scheme **46**). Furthermore, the effectiveness of **79** turned out to be

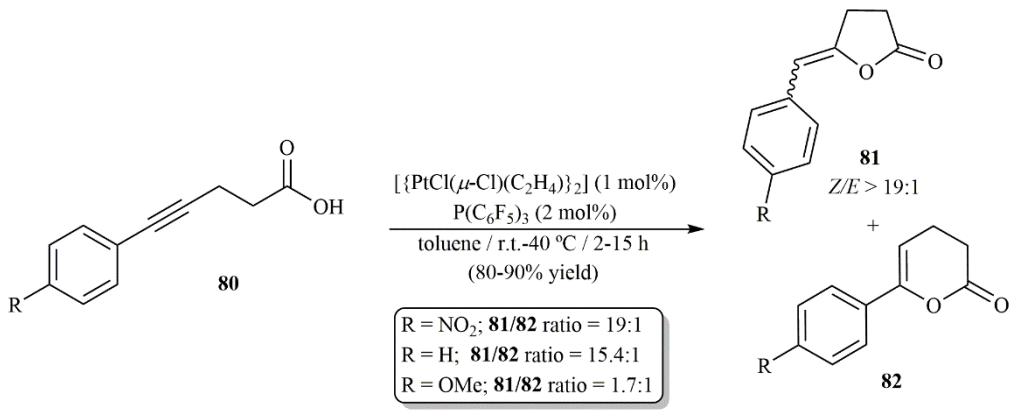
superior to that previously described for its palladium analog **46**. As an example, while the quantitative cyclization of 5-hexynoic acid could be achieved at 90 ºC employing only 1 mol% of **79**, a higher catalyst loading (5 mol%) was required in the case of **46** to attain the same result.



Scheme 46. Representative cycloisomerization reactions catalyzed by the platinum(II) complex **79**.

The last example was described by Costello and Ferreira in 2019 in the context of a general study aimed at determining how the electronic and steric properties of substrates influence regioselectivity in platinum-catalyzed intramolecular O-H and N-H addition reactions [154]. They concluded that the main influence arises from the electronic effect of the alkyne substituent, which induces the polarization of the C≡C bond and conditions the preferential heteroatom attack at the more electron-deficient carbon. This was evidenced in the cyclization of the aryl-substituted *γ*-alkynoic acids **80** catalyzed by the ethylene complex [{PtCl(μ-Cl)(C_2H_4)}$_2$] in combination $P(C_6F_5)_3$. As shown in Scheme **47**, although a preference for the 5-*exo-dig* cyclization products **81** *vs* the 6-*endo-dig* ones **82** was in all the cases observed, the electronic nature of the substituents present in the

aromatic ring impacted the ratios in which they are formed, with the electron-withdrawing nitro group largely favoring the *exo* addition.



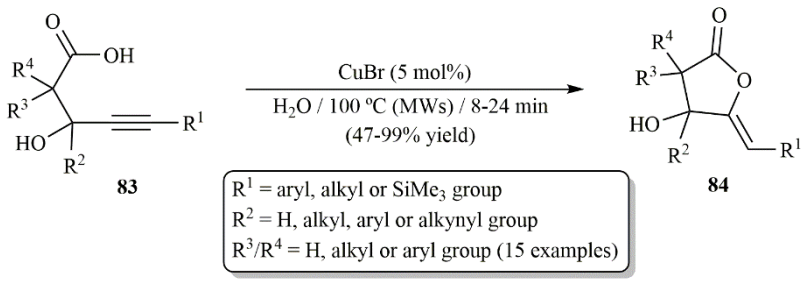
Scheme 47. Pt(II)-catalyzed cycloisomerization of γ-alkynoic acids **80**.

6. GROUP 11 METAL CATALYSTS

6.1. Copper

The ability of copper compounds to catalyze the cycloisomerization of alkynoic acids has been known for long time [5, 7]. In this context, copper(I) bromide was employed by Álvarez-Toledano and co-workers to promote the regio- and stereoselective synthesis of the *Z*-enol lactones **84**, functionalized with a hydroxyl group at C-4, by cyclization of the corresponding β-hydroxy-γ-alkynoic acids **83** (Scheme **48**) [155]. The reactions were conveniently conducted in water at 100 ºC under microwave (MW) heating and delivered the products in moderate to excellent yields after short irradiation periods. The selective *exo-dig* cycloisomerization of 4-pentynoic and 5-hexynoic acids under MW irradiation (100 ºC) was equally described by Westcott and co-workers using as catalysts the phosphino-copper(I) complexes $[Cu(PPh_3)_3(NCMe)][B(O_2C_6H_4\text{-}4\text{-}R)_2]$ (R = H, Me, NO_2) featuring weakly coordinating arylspiroborate counteranions (full conversions in $CDCl_3$ after 0.2-4 h) [156]. It should be noted at that point that

[$CuCl(PPh_3)_3$] is completely ineffective in these reactions and that attempts to cyclize 6-heptynoic acid with compounds [$Cu(PPh_3)_3(NCMe)][B(O_2C_6H_4\text{-}4\text{-}R)_2$] failed.



Scheme 48. Cu(I)-catalyzed cycloisomerization of β-hydroxy-γ-alkynoic acids in water.

A series of camphor derived Cu(I) coordination polymers [157], as well as the mononuclear derivative [Cu(OAc)Xantphos] (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) [158], have also been explored in the cyclization of 4-pentynoic acid. Regarding the coordination polymers, the reactions led in most of the cases to mixtures containing the expected 5-*exo*-*dig* lactone 5-methylenedihydrofuran-2(3*H*)-one and 2-methyl-5-oxotetrahydrofuran-2-yl pent-4-ynoate, the latter resulting from the addition of a second substrate molecule to the exocyclic C=C bond of the former (compound **130** in Scheme **70**, see below). Complex [Cu(OAc)Xantphos] was much more selective towards the formation of the 5-alkylidene lactone and allowed the cyclization process to proceed at room temperature, although the addition of a base to the reaction medium was in this case necessary. In the same work, the authors also showed that the reaction can be drastically accelerated by encapsulation of [Cu(OAc)Xantphos] in guanidinium-based Pd and Pt nanospheres [158]. The reaction rate improvement is related with the high local concentration of copper inside the nanospheres which favor the dual activation of the substrate (see Fig. **12**).

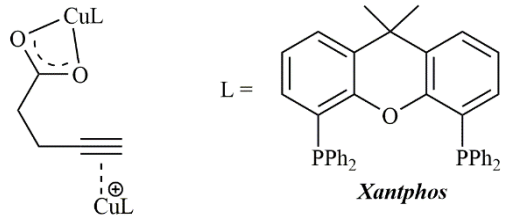
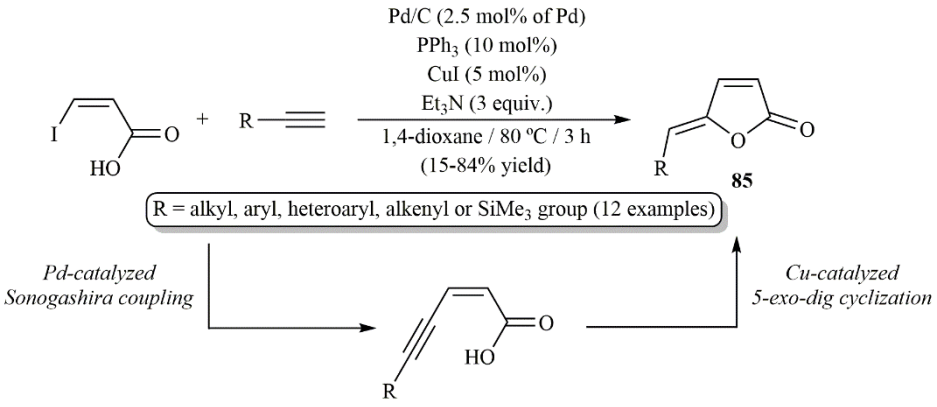


Fig. 12. Activation mode of 4-pentynoic acid in the [Cu(OAc)Xantphos]-catalyzed cyclization.

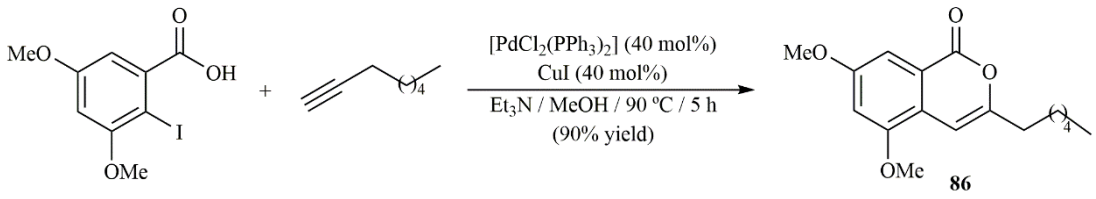
Pal, Rao and co-workers developed a one-pot procedure for the preparation of γ-ylidenebutenolides **85** by coupling (*Z*)-3-iodocarylic acid with terminal alkynes using a catalytic system composed of Pd/C, CuI, PPh_3 and Et_3N (Scheme **49**) [159]. According to the authors, a palladium-catalyzed Sonogashira coupling between the reactants initially occurs to generate the corresponding (Z)-pent-2-en-4-ynoic acid intermediate, which subsequently undergoes a copper-catalyzed regioselective 5-*exo-dig* cyclization. Compounds **85** featured in all the cases a (*Z*)-stereochemistry on the exocyclic C=C bond, thus indicating that the addition of the carboxylic acid to the copper-activated C≡C bond takes place in an *anti* fashion.



Scheme 49. Access to γ-ylidenebutenolides though a one-pot tandem Sonogashira/cyclization sequence.

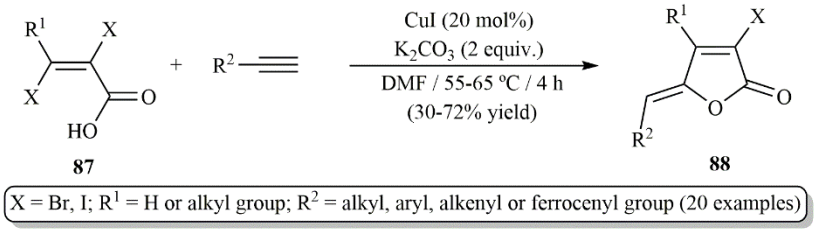
A related one-pot palladium-catalyzed Sonogashira coupling/CuI-catalyzed intramolecular annulation allowed the high yield preparation of the genotoxic

isocoumarin **86** (Scheme **50**) [160]. Complex $[PdCl_2(PPh_3)_2]$ was in this case employed as the palladium source and a mixture MeOH/NEt_3 as the solvent system. Contrary to the previous example, the cyclization step proceeded through a 6-*endo* addition.



Scheme 50. Access to an isocoumarin though a one-pot tandem Sonogashira/cyclization sequence.

Taking advantage of the ability of Cu(I) to promote by itself Sonogashira-type coupling reactions, related palladium-free copper-catalyzed tandem coupling-cyclization processes have also been described. For example, extending previous studies in the field, Ngi, Thibonnet and co-workers reported a straightforward access to (*Z*)-configured 3-halo-substituted γ-ylidenebutenolides **88** from α,β-dihaloalkenoic acids **87** and terminal alkynes using CuI as catalyst (Scheme **51**) [161].



Scheme 49. Access to butenolide derivatives through a CuI-catalyzed tandem coupling/cyclization process.

The utility of this copper-catalyzed reaction was fully demonstrated with the total synthesis of the natural products nostoclide I, nostoclide II and enhygrolide A (see Fig. **13**), as well as some unnatural analogs, which were accessed from the corresponding (*Z*)-

3-bromo-5-ylidene-butenolides through a Pd-catalyzed Suzuki-Miyaura coupling with the corresponding potassium benzyltrifluoroboronate [162, 163].

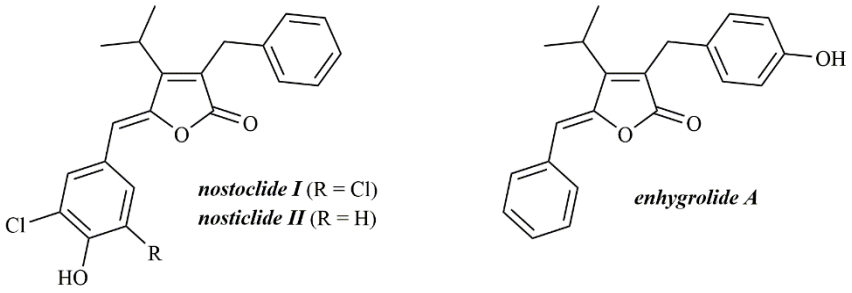
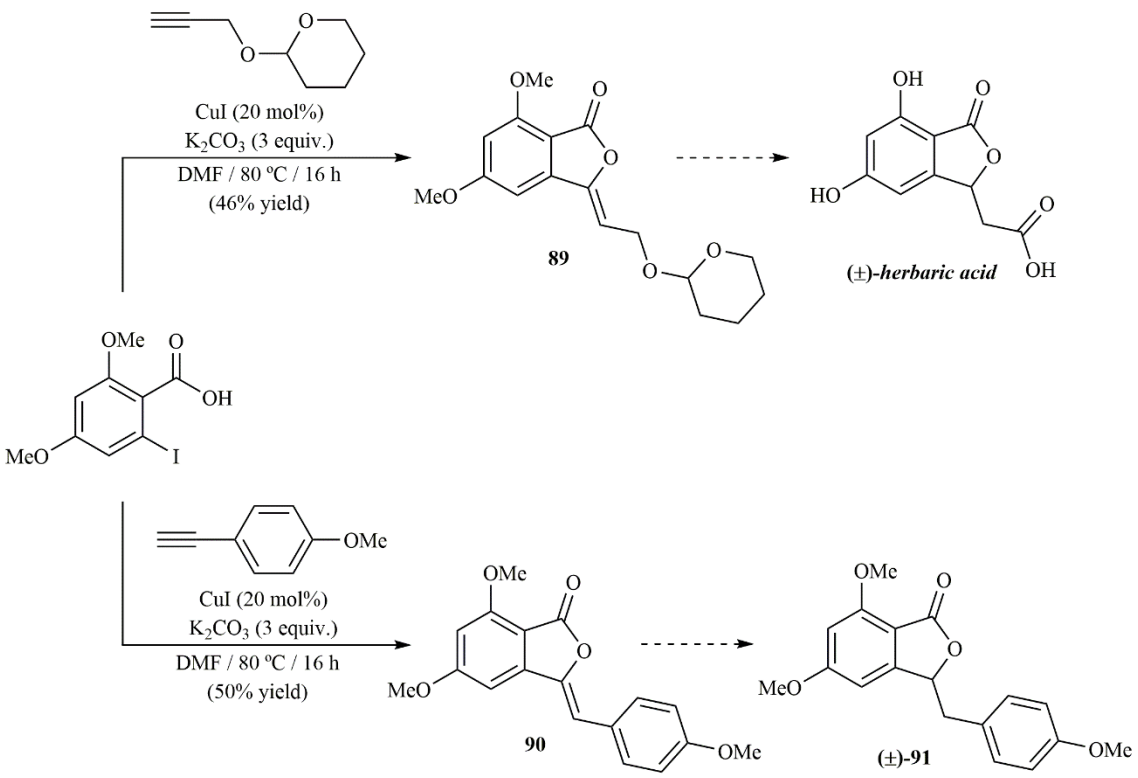


Fig. 13. Structure of the natural products nostoclide I, nostoclide II and enhygrolide A.

Starting from 2-iodo-4,6-dimethoxybenzoic acid, Thibonnet and co-workers also developed synthetic routes to a couple of natural phthalides, *i.e.* (±)-herbaric acid and (±)-**91**, in which the bicyclic skeletons were generated through the same copper-catalyzed tandem C-C cross-coupling/oxacyclization sequence (Scheme **52**) [164]. Although the intermediate species **89** and **90** were generated only in a moderate yield, it is noteworthy the high regioselectivity observed since previous studies by the same group indicated that, starting from 2-iodobenzoic acids, mixtures of the corresponding 5-*exo-dig* (phthalides) and 6-*endo-dig* (isocoumarins) cyclization products are usually obtained [165]. Complete selectivity towards the formation of phthalide derivatives was additionally reported by Ray and co-workers in the coupling of 2-bromobenzoic acids and terminal alkynes catalyzed by CuI/Et_3N [166].

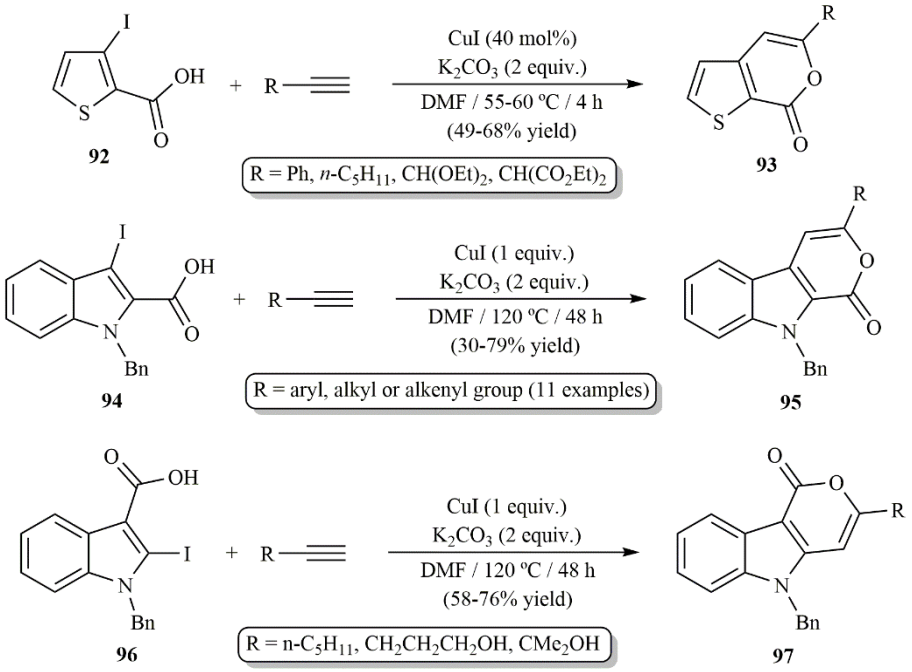


Scheme 52. Tandem coupling-cyclization processes used in the preparation of two natural phthalides.

The works just commented, together with the result depicted in Scheme **50**, are clear examples that the outcome of these cyclization processes is difficult to predict and is strongly influenced by the nature of the substrates, catalysts and solvents employed. In this regard, a study carried out by Lee and co-workers employing CuI/Cs_2CO_3 showed a dependence of regioselectivity with temperature in the coupling of 2-iodobenzoic acids with terminal alkynes [167]. Thus, while isocoumarins were exclusively formed at 100 ºC, mixtures of isocoumarins and phthalides were generated at room temperature with the latter being the major products. Related coupling-cyclization processes were performed at room temperature using CuI/K_2CO_3 in polyethylene glycol 400 (PEG 400), under ultrasonic irradiation, with remarkable regioselectivity in this case towards the isocoumarin products [168]. The cycloisomerization of preformed 2-alkynylbenzoic acids catalyzed by $CuCl_2$ in ionic liquids (ILs) has also been described, with the 5-*exo-dig*/6-*endo-dig* selectivity being strongly dependent on the nature of IL employed [169].

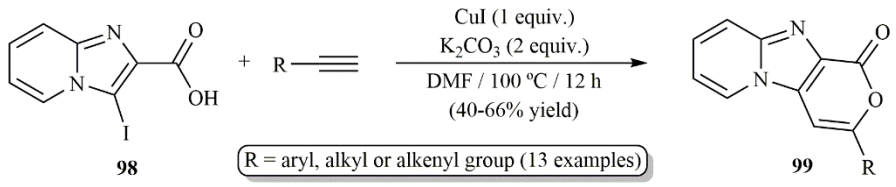
According to DFT calculations, the sterical interactions between the IL anion and the 2-alkynylbenzoic acid substrate are key to orient the reaction in one direction or the other.

A valuable synthetic extension of these Cu(I)-catalyzed one-pot tandem reactions was described by Thibonnet with the preparation of a series of thieno[2,3-*c*]pyrane-7-one **93**, indolo[2,3-*c*]pyrane-1-one **95** and indolo[3,2-*c*]pyrane-1-one **97** derivatives starting from 3-iodothiophene-2-carboxylic acid **92**, 1-benzyl-3-iodo-indole-2-carboxylic acid **94** or 1-benzyl-2-iodo-indole-3-carboxylic acid **96**, respectively, and different terminal alkynes (Scheme **53**) [170]. The excellent regioselectivity observed in these particular reactions, in which the 6-*endo-dig* cyclization products are exclusively formed, was explained by the authors on the basis of the greater strain associated with the generation of two fused 5-membered rings in the potential 5-*exo-dig* cyclization.



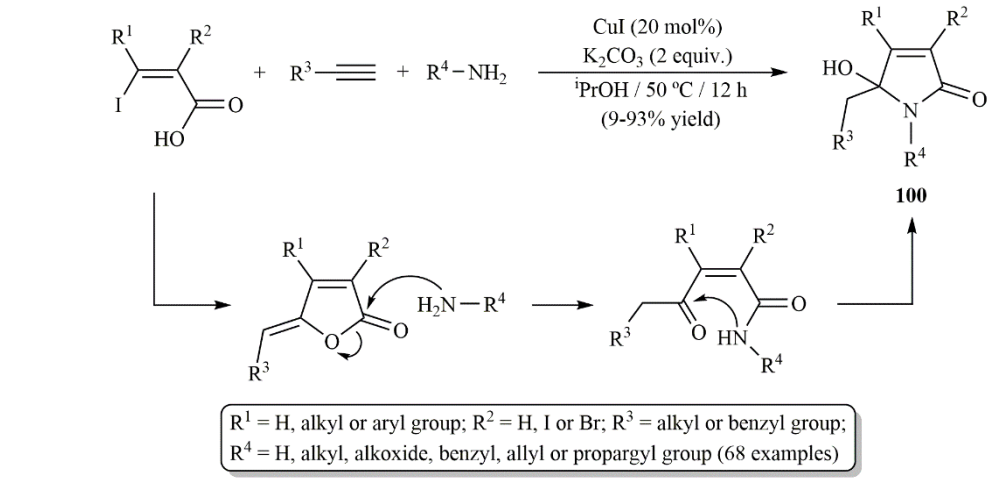
Scheme 53. Copper(I)-catalyzed tandem coupling/cyclization of heteroaromatic *β*-iodo-substituted carboxylic acids with terminal alkynes.

Similarly, a regiospecific 6-*endo-dig* cyclization was also observed starting from 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylic acid **98**, its copper-mediated cross-coupling/heteroannulation reactions with different terminal alkynes leading to the pyrano[3´,4´:4,5]imidazo[1,2-*a*]pyridin-1-one derivatives **99** (Scheme **54**) [171]. As in some of the precedent examples, the use of a stoichiometric amount of CuI and a high temperature were needed to obtain compounds **99** with acceptable yields.

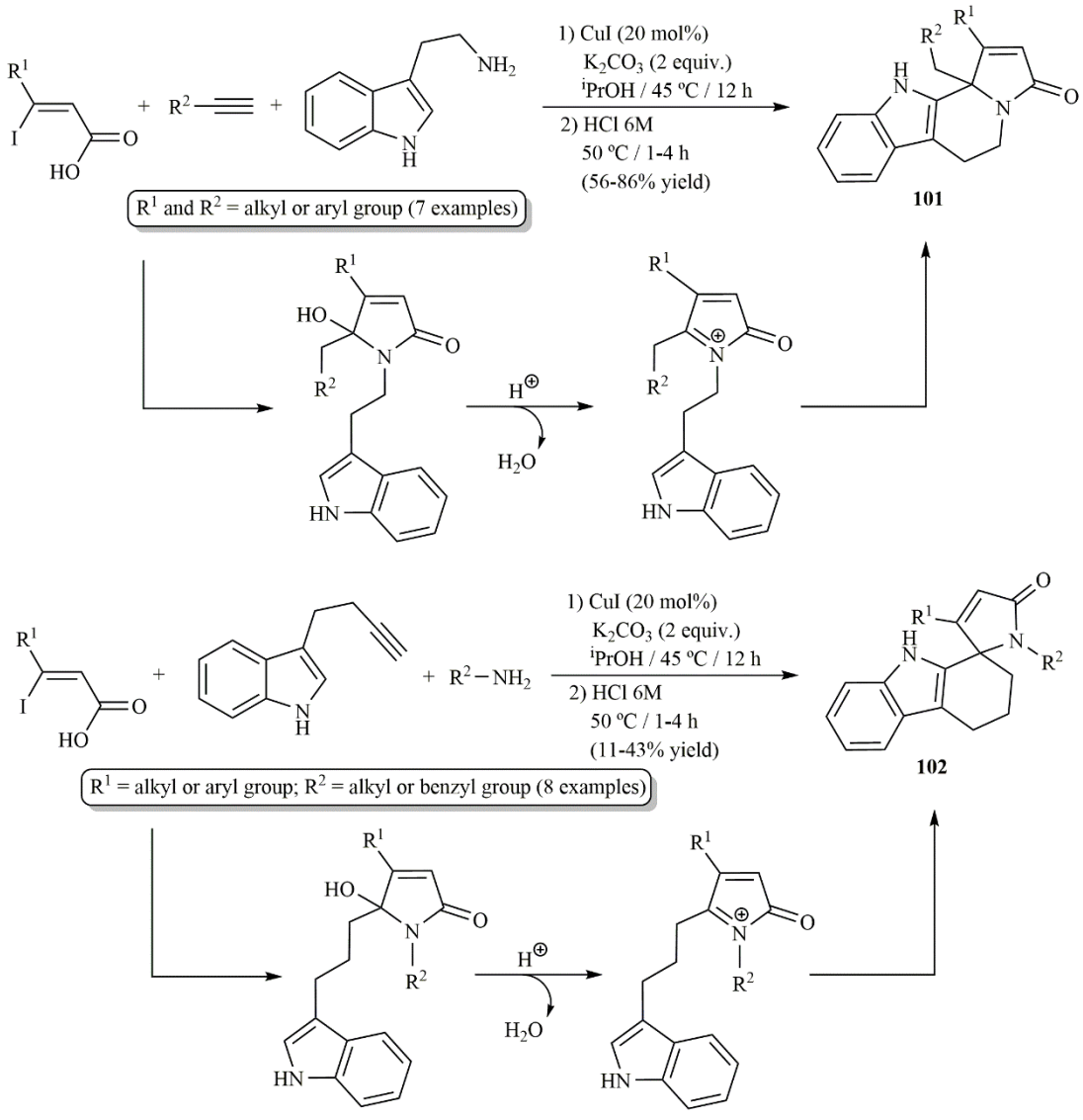


Scheme 54. Copper(I)-catalyzed access to pyrano[3´,4´:4,5]imidazo[1,2-*a*]pyridin-1-ones **99**.

On the other hand, taking advantage of these tandem coupling-cyclization processes and the intrinsic reactivity of *γ*-alkylidenebutenolides, a broad scope procedure to synthesize biologically relevant *γ*-hydroxy-*γ*-butyrolactams **100** through a copper-catalyzed three component reaction between (*Z*)-3-iodoacrylic acids, terminal alkynes and primary amines was developed by Parrain, Commeiras and co-workers, in which the *in situ* formed *γ*-alkylidenebutenolides undergo aminolytic ring opening followed by intramolecular cyclization of the resulting *α,β*-unsaturated-*γ*-ketoamide (Scheme **55**) [172, 173]. As shown in Scheme **56**, the same group also reported the access to polycyclic derivatives containing indole/lactam scaffolds, *i.e*. compounds **101** and **102**, through a two-step sequence in which the protonation of the corresponding *γ*-hydroxy-*γ*-butyrolactams allows an intramolecular C-C coupling reaction by nucleophilic attack of the indole C-2 carbon to the resulting *N*-acyliminium cation [173, 174].

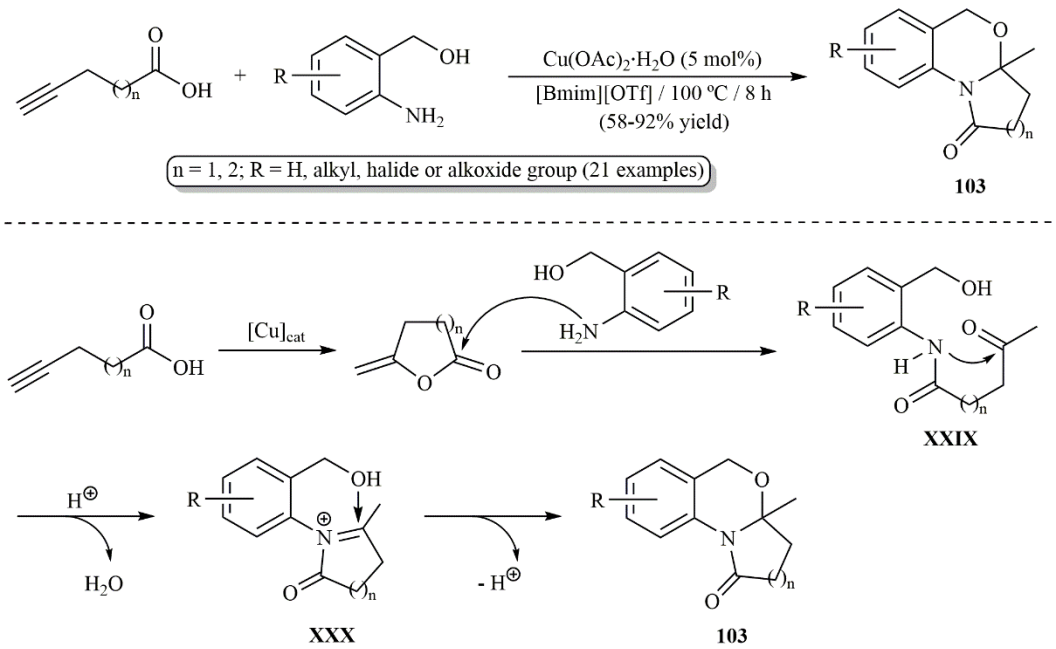


Scheme 55. Copper(I)-catalyzed multicomponent synthesis of γ-hydroxy-γ-butyrolactams.



Scheme 56. Copper(I)-catalyzed multicomponent synthesis of polycyclic indole/lactam derivatives.

Cascade processes involving the initial copper-catalyzed cyclization of an alkynoic acid have also been developed. This is the case of the reactions depicted in Scheme **57**, in which a series of pyrrolo- and pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-one derivatives **103** were synthesized through the coupling of 4-pentynoic acid and 5-hexynoic acid, respectively, with 2-aminobenzyl alcohols [175]. The reactions were catalyzed by $Cu(OAc)_2 \cdot H_2O$ at 100 ºC, employing the IL 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([Bmim][OTf]) as the reaction medium, and cleanly delivered the tricyclic compounds **103** in moderate to high yields. The process involves the initial *exo-dig* cyclization of the alkynoic acids into the corersponding enol-lactones, which undergo an aminolysis reaction to generate the linear keto-amides **XXIX**. A subsequent proton-catalyzed intramolecular condensation leads to the *N*-acyliminium intermediates **XXX**, which evolve into the final products **103** by nucleophilic attack of the OH group to the iminium carbon.



Scheme 57. Copper-catalyzed synthesis of pyrrolo- and pyrido[2,1-*b*]benzo[*d*][1,3]oxazin-1-ones.

Related one-pot tandem coupling reactions of 4-pentynoic acid with 2-aminobenzoic acids and *N*-monosubstituted 2-aminobenzamides, catalyzed by $Cu(OAc)_2 \cdot H_2O$ in the ionic liquid [Bmim][BF_4], have also been described allowing the access to a variety of pyrrolo[2,1-*a*][1,3]benzoxazinones **104** and pyrrolo[2,1-*a*]quinozalinones **105**, respectively (Fig. **14**) [176]. As in the precedent case, both the catalyst and IL could be recycled 5 times without loss of activity.

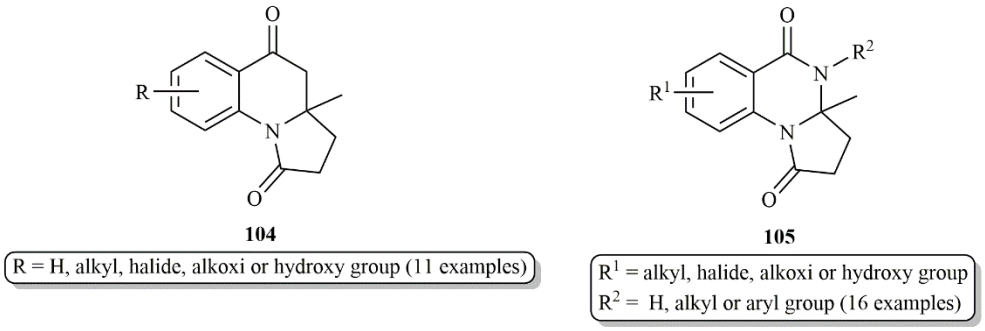
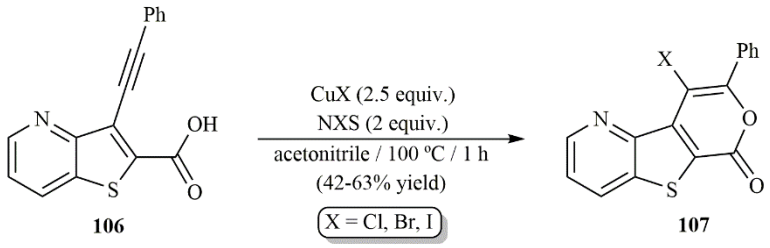


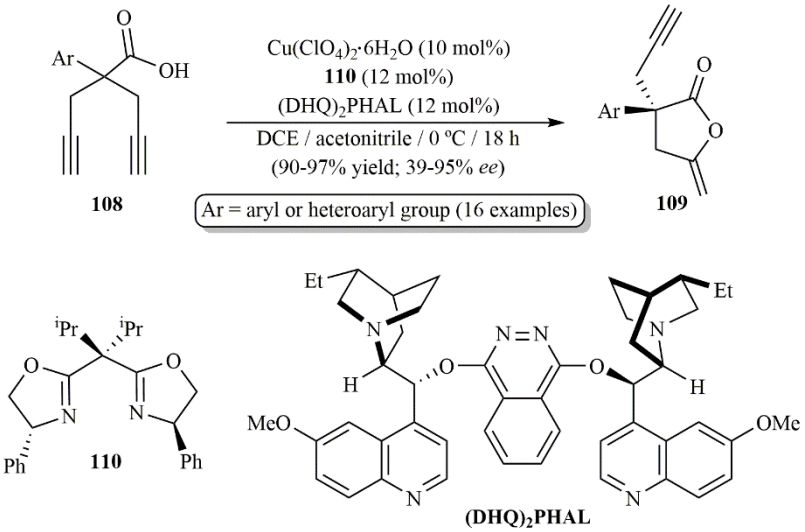
Fig. 14. Structure of the nitrogen-containing heterocyclic compounds **104** and **105**.

On the other hand, halolactonization reactions of 3-(phenylethynyl)thieno[3,2-*b*]pyridine-2-carboxylic acid **106** to afford the halogenated tricyclic lactones **107** were described employing a combination of the corresponding copper(I) halide and *N*-halosuccinimide reagent (Scheme **58**) [133]. CuX_2 salts can be alternatively used and lead to similar results.



Scheme 58. CuX/NXS-mediated halolactonization of alkynoic acid **106**.

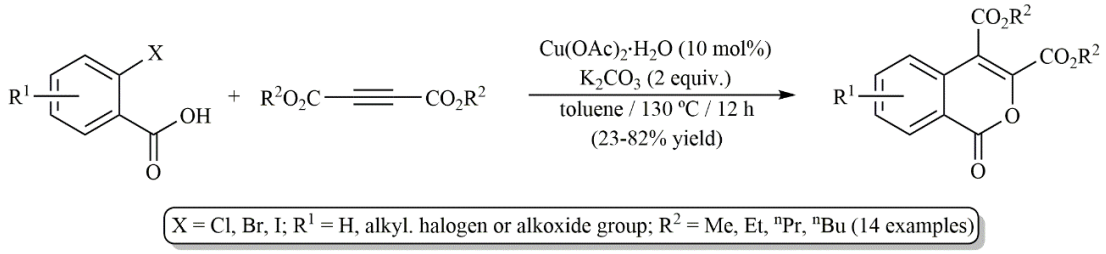
Very recently, the enantioselective access to five-membered ring lactones **109** was successfully achieved (up to 95% *ee*) by desymmetrization of the prochiral bispropargylic carboxylic acids **108** employing a catalytic system composed of copper perchlorate hexahydrate, the bisoxazoline ligand **110** and the chiral base $(DHQ)_2$-PHAL (Scheme **59**) [177]. The presence of common functional groups on the aromatic substituent was tolerated and the reactions could be conducted in gram scale.



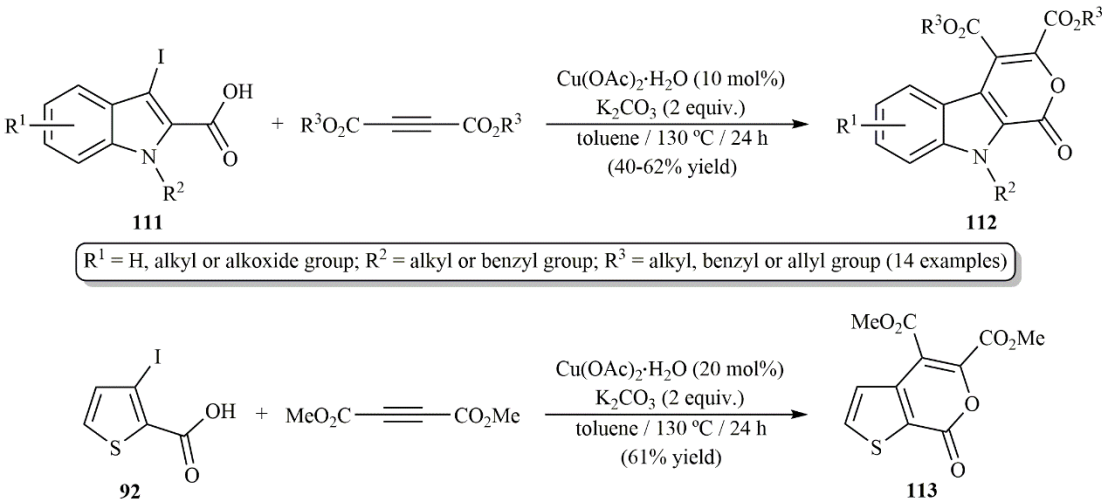
Scheme 59. Copper-catalyzed asymmetric lactonization of bispropargylic carboxylic acids.

Guo developed a synthetic route to isocoumarin derivatives by addition of *ortho*-halobenzoic acids to internal alkynes catalyzed by $CuCl_2$ in combination with K_2CO_3 (Scheme **60**) [178]. Both chloro-, bromo- and iodo-benzoic acids can be employed, but the process was found to be operative only with strongly activated alkynes, *i.e.* acetylenedicarboxylate esters. Although no mechanistic details were given, it was suggested that dimeric Cu(II)-carboxylate species generated by bridging coordination of the corresponding *ortho*-halobenzoates may be involved in the reaction. Applying the same protocol, a variety of indolo[2,3-*c*]pyrane-1-ones **112** and the thieno[2,3-*c*]pyrane-

7-one **113** were also accessed in moderate yield by annulation of different acetylenedicarboxylate esters with 3-iodo-indole-2-carboxylic acids **111** and 3-iodothiophene-2-carboxylic acid **92**, respectively (Scheme **61**) [179].



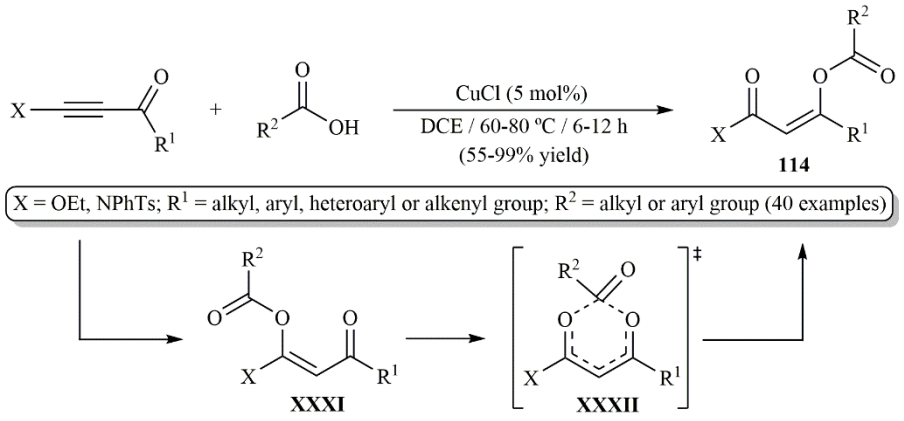
Scheme 60. Cu(II)-catalyzed synthesis of isocoumarins from *o*-halobenzoic acids and internal alkynes.



Scheme 61. Cu(II)-catalyzed annulation reactions of heteroaromatic *β*-halo-carboxylic acids with alkynes.

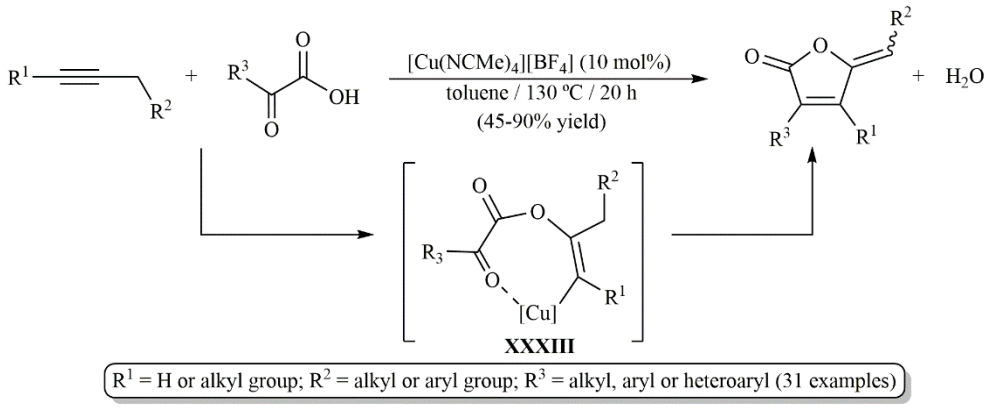
Zhu and co-workers reported an efficient and stereoselective access to (*Z*)-enol esters **114** by reacting ethoxy- and sulfonamide-substituted alkynones with carboxylic acids in the presence of catalytic amounts of CuCl (Scheme **62**), a reaction outcome that contrasts with the conventional 1,3-*O*-transposition, *i.e.* the formation of compounds $R^1C{\equiv}CC(=O)X$, usually observed when this particular class of alkynes are faced to transition metal catalysts [180]. According to DFT calculations, enol esters **XXXI** are

initially generated as the result of a Cu-catalyzed *anti*-addition of the acids to the C≡C bond of the alkynone substrates, evolving into the final reaction products **114** by acyl group transposition *via* the cyclic transition state **XXXII** [181].



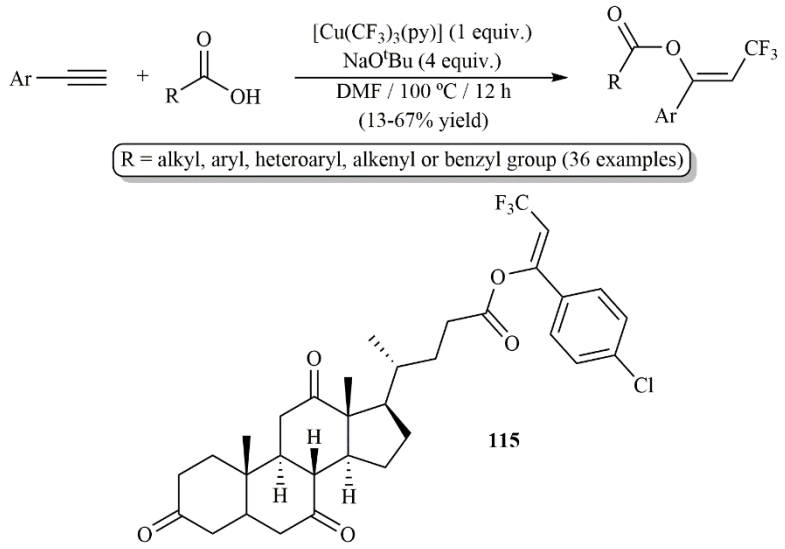
Scheme 62. Cu(I)-catalyzed addition of carboxylic acids to alkynones.

Seo and Willis studied the intermolecular addition of α-ketoacids to different terminal and internal aliphatic alkynes catalyzed by the cationic Cu(I) complex $[Cu(NCMe)_4][BF_4]$ (Scheme **63**) [182]. The reactions, which were performed in toluene at 130 ºC, opened a new synthetic pathway to γ-ylidenebutenolides since the addition process is accompanied by the dehydrative cyclization of the metallated intermediate **XXXIII**. The process featured a good substrate scope and delivered the cyclized products with a high stereoselectivity (in most of the cases as the corresponding (*Z*)-isomers).



Scheme 63. Access to *γ*-ylidenebutenolides through a Cu(I)-catalyzed addition/annulation reaction.

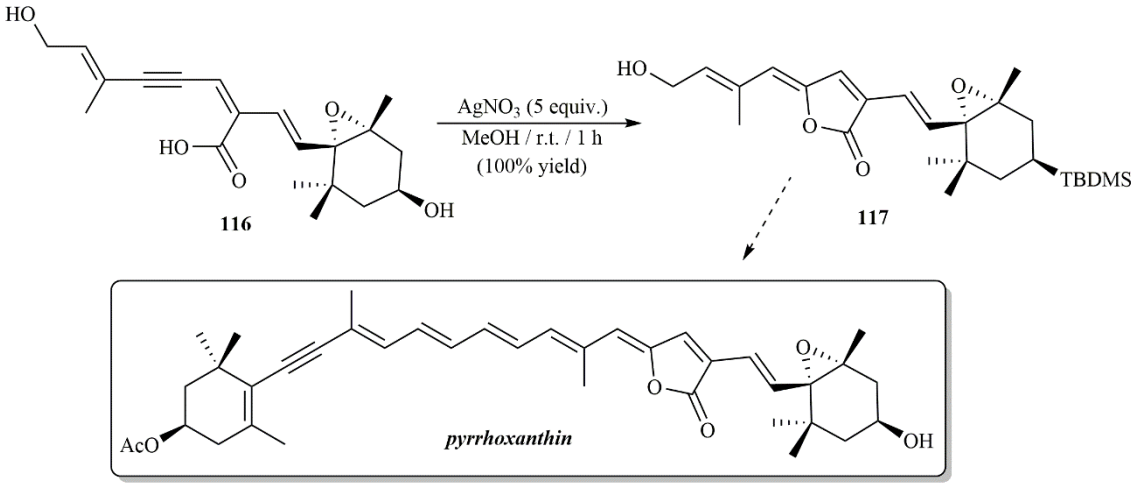
Recently, a synthetic route to trifluoromethyl group-substituted (*Z*)-enol esters by selective *syn*-difunctionalization of aromatic terminal alkynes with the Cu(III) complex $[Cu(CF_3)_3(py)]$ and carboxylic acids was described by Zhang and co-workers (Scheme **64**) [183]. The process involves the initial generation of the corresponding trifluoromethylated alkynes $ArC{\equiv}CCF_3$, which subsequently undergo a copper-mediated *anti*-addition of the carboxylic acid. Compound **115**, generated from dehydrocholic acid and 1-chloro-4-ethynylbenzene, illustrates the broad applicability and potential of this synthetic methodology. It is worth mentioning at this point that access to related trifluoromethyl group-substituted enol esters (*E*)-$RC(OCOAr)=CHCF_3$ (R = aryl or $SiMe_3$; Ar = 2-C_6H_4I), through a CuI-catalyzed electrophilic addition of the CF_3-transfer reagent 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (Togni´s reagent II) to terminal alkynes, has also been reported [184].



Scheme 64. Cu(III)-mediated difunctionalization of alkynes to access CF_3-substituted (*Z*)-enol esters.

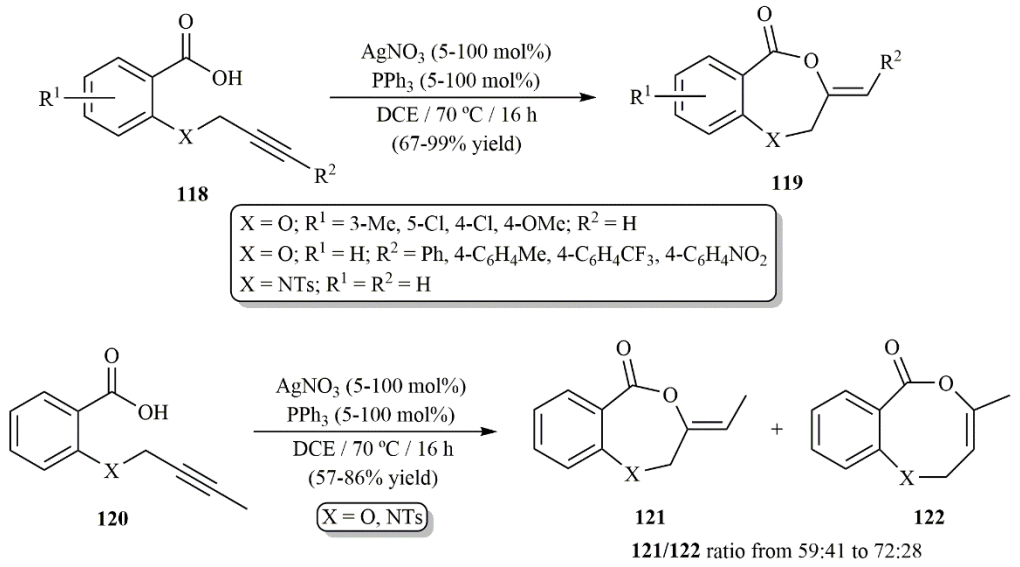
6.2. Silver

Due to their superior alkynophilicity silver(I) salts have been widely employed as catalysts for alkyne-based organic reactions [185], including hydro-oxycarbonylation processes [5, 7]. The synthetic potential of this metal was evidenced by Vaz, de Lera and co-workers in 2013 with a total synthesis of the natural C_{37}-norcarotenoid pyrrhoxanthin in which the 4-alkylidenebutenolide unit was generated through a silver-mediated lactonization of the pent-2-en-4-ynoic acid derivative **116** (Scheme **65**) [186]. Thus, employing an excess of $AgNO_3$, the 5-*exo*-*dig* cyclization of **116** proceeded in a complete regio- and stereoselective manner (*anti*-addition), affording the desired *γ*-ylidenebutenolide derivative **117** in quantitative yield and under remarkably mild conditions.



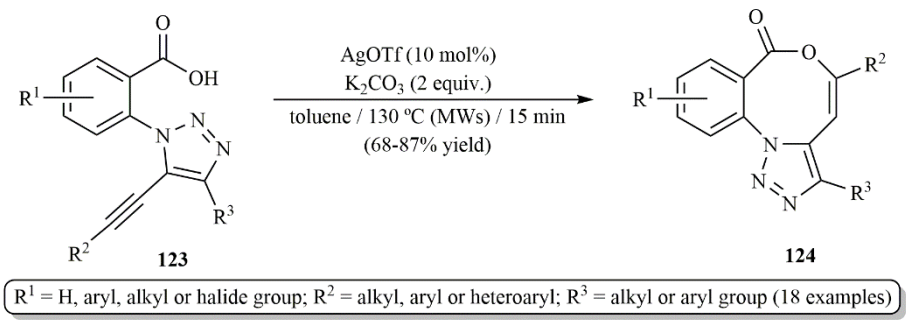
Scheme 65. Construction of the γ-alkylidenebutenolide unit of pyrrhoxanthin.

Silver nitrate, in combination with triphenylphosphine, was used by Porcel and co-workers to promote the cyclization of a series of alkynoic acids derived from salicylic acid (Scheme **66**) [187]. The reactions were conducted in 1,2-dichloroethane at 70 ºC with catalyst loadings of 5 mol%, although in some cases stoichiometric amounts of both $AgNO_3$ and PPh_3 were required to obtain good conversions (mainly with internal alkynes). As exemplified with compounds **118**, seven-membered ring lactones **119** were exclusively formed with those substrates featuring a terminal or an aryl-substituted alkyne moiety (7-*exo*-*dig* cyclization; when $R^2 \neq H$ the corresponding products were generated with (*Z*)-configuration of the C=C bond (*anti*-addition)). Conversely, the cycloisomerization of their methyl-substituted counterparts **120** was not regioselective, leading to mixtures of the respective exo- and endocyclic enol-lactones **121** (major products) and **122** (minor products).



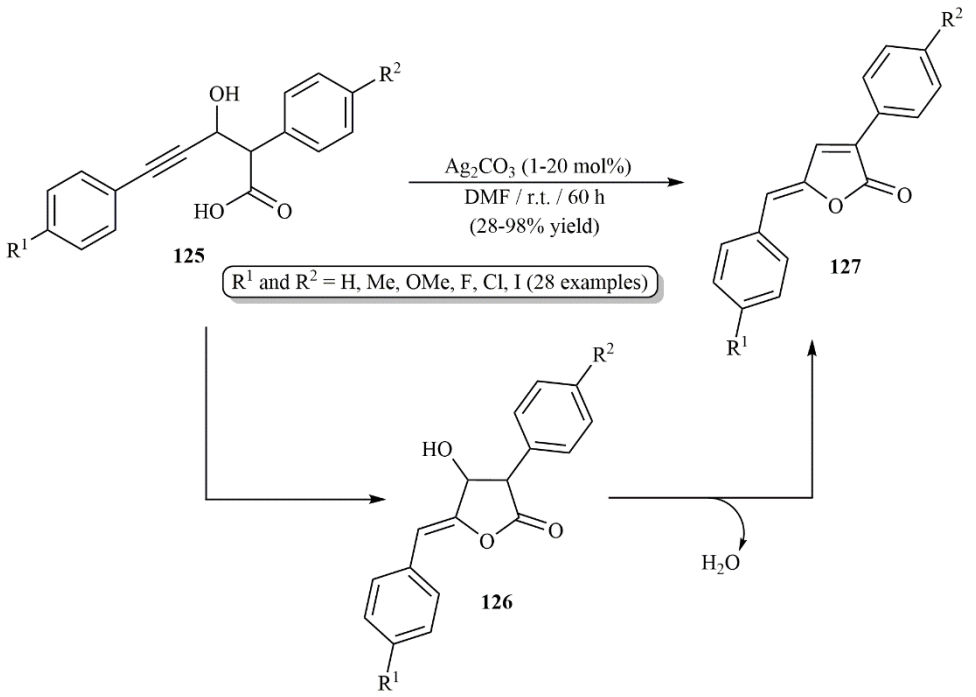
Scheme 66. Silver(I)-promoted cycloisomerization alkynoic acids derived from salicylic acid.

The regioselective synthesis of 8-membered ring systems was successfully achieved by Sun and co-workers starting from the benzoic acids **123** substituted in *ortho* position with 5-ethynyltriazol-1-yl units, whose cyclization led to the 1,2,3-triazole-fused-1,5-benzoxazocinones **124** (Scheme **67**) [188]. The exquisite selectivity towards the 8-*endo-dig* cyclization mode observed in these reactions, which were carried out in toluene at 130 ºC under MW irradiation employing catalytic amounts of AgOTf in combination with K_2CO_3, was rationalized by the authors in terms of the polarization effect exerted by the triazole unit that enhances the electrophilicity of the external carbon atom of the alkyne.



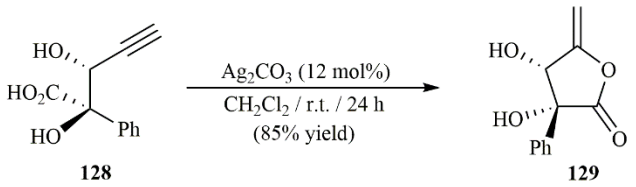
Scheme 67. Silver-catalyzed synthesis of 1,2,3-triazole-fused-1,5-benzoxazocinones.

Brückner and co-workers reported the synthesis of a series of (*Z*)-3-aryl-5-(arylmethylidene)butenolide derivatives **127** through the regio- and stereoselective (*anti*-addition) silver(I)-catalyzed 5-*exo*-*dig* cyclization of the 3-hydroxy-2,5-diarylpent-4-ynoic acids **125**, process that is accompanied by the spontaneous dehydration of the resulting 3-hydroxy-γ-butyrolactones **126** (Scheme **68**) [189]. The cyclization of related *tert*-butyl 2,5-diaryl-3-oxopent-4-ynoate compounds were also described by the same group [190].



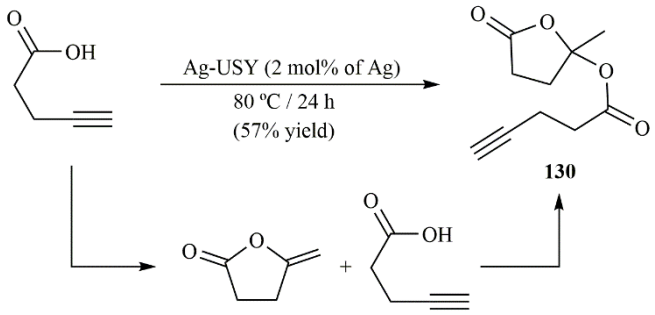
Scheme 68. Silver-catalyzed stereoselective synthesis of (*Z*)-3-aryl-5-(arylmethylidene)butenolides **127**.

Interestingly, in marked contrast with the behavior of compounds **125**, no dehydration was observed during the Ag_2CO_3-catalyzed cyclization of the diastereomerically pure α,β-dihydroxy-substituted γ-alkynoic acid **128**, the reaction leading to the high yield formation of enol-lactone **129** (Scheme **69**) [191].



Scheme 69. Silver-catalyzed lactonization of the *γ*-alkynoic acid **128**.

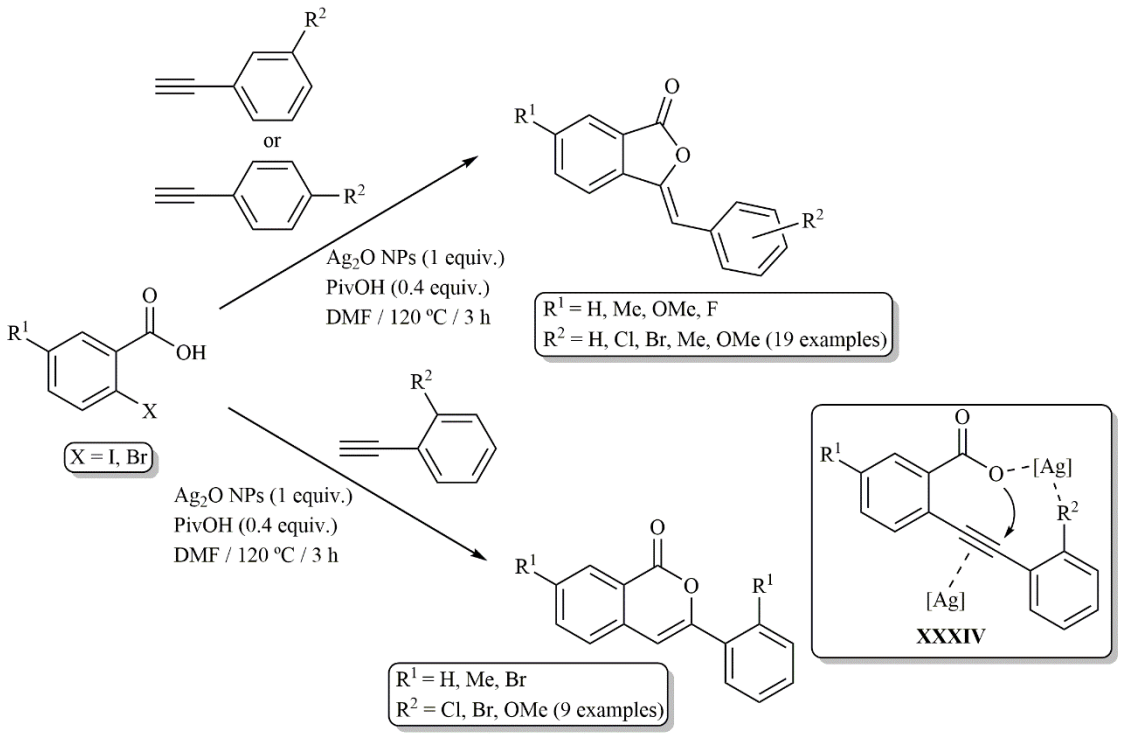
On the other hand, in the context of a broad study on the utility of Ag-zeolites as catalysts for cyclization reactions of alkynol derivatives, Pale and co-workers observed the formation of the ketal-type compound **130** when 4-pentynoic was subjected to the action of Ag-USY (USY = ultra-stable Y faujasite) at 80 ºC under solvent-free conditions (Scheme **70**) [192]. Compound **130** results from the hydro-oxycarbonylation of the exocyclic C=C bond of the expected 5-membered ring enol-lactone by a second molecule of the substrate.



Scheme 70. Formation of the ketal derivative **130** from 4-pentynoic acid catalyzed by a silver-zeolite.

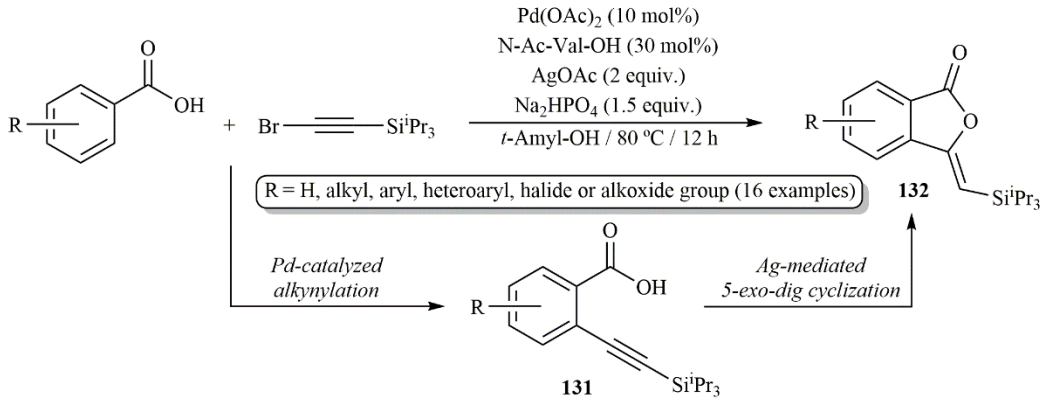
One-pot coupling/annulation reactions of 2-halobenzoic acids with phenylacetylene derivatives mediated by Ag_2O NPs were described by Chaudhary and co-workers (Scheme **71**) [193]. An interesting control of regioselectivity by the alkyne substrate was observed. Thus, while phthalides were selectively obtained from *meta*- and *para*-substituted phenylacetylenes, as the result of a 5-*exo*-*dig* cyclization of the

corresponding 2-alkynylbenzoic acid intermediates, the use of *ortho*-substituted phenylacetylenes led to the regioselective formation of isocoumarins. According to the authors, interaction between the lone pairs of the substituents in *ortho* position with silver in the putative bimetallic intermediate **XXXIV** was responsible from the selectivity switch observed, orienting such interaction the reaction towards the 6-*endo*-*dig* cyclization.



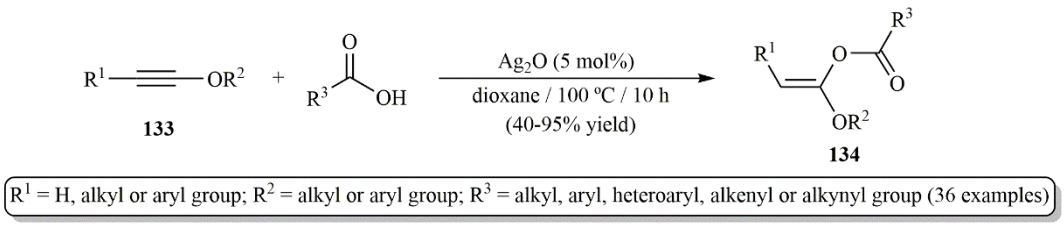
Scheme 71. Ag_2O NPs-catalyzed regioselective access to 3-ylidenephthalides and isocoumarins.

Regioselective one-pot access to phthalides **132** from benzoic acids and the silylated bromoalkyne $BrC{\equiv}CSi^iPr_3$ was also described (Scheme **72**) [194]. The intermediate 2-alkynylbenzoic acids **131** were in this case generated through a palladium-catalyzed C-H alkynylation reaction and evolved into **132** by action of AgOAc.



Scheme 72. Access to phthalides from benzoic acids and a bromoalkyne.

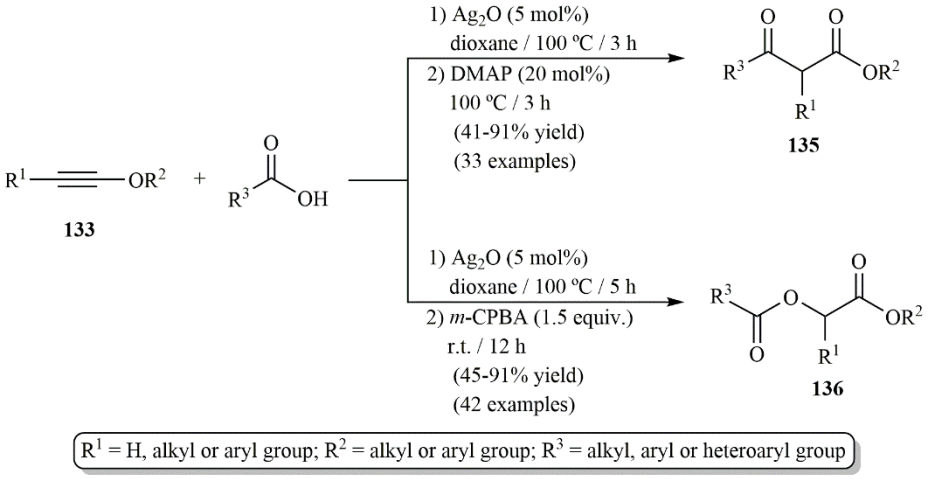
Concerning intermolecular addition processes, Zhu and co-workers reported in 2014 a broad scope procedure for the addition of carboxylic acids to both terminal and internal ynol ethers **133** employing Ag_2O as catalyst (Scheme **73**) [195]. The reactions, which were carried out in dioxane at 100 °C, afforded the corresponding (*Z*)-α-alkoxy-enol esters **134** in a complete regio- and stereoselective manner (*anti* addition). Other Ag(I) salts, as well as different Ru(0), Cu(I), Cu(II), Zn(II) and Au(I) compounds, tested in the process showed an efficacy much lower than that of Ag_2O.



Scheme 73. Ag_2O-catalyzed addition of carboxylic acids to ynol ethers.

Based on this work, Cui's group subsequently developed two efficient and general *one-pot* protocols to obtain β-keto esters **135** and α-carbonyloxy esters **136** from ynol ethers **133** and carboxylic acids involving a DMAP-catalyzed rearrangement (DMAP = 4-(dimethylamino)pyridine) [196] or a *m*-CPBA-mediated oxidation (*m*-CPBA = *meta*-

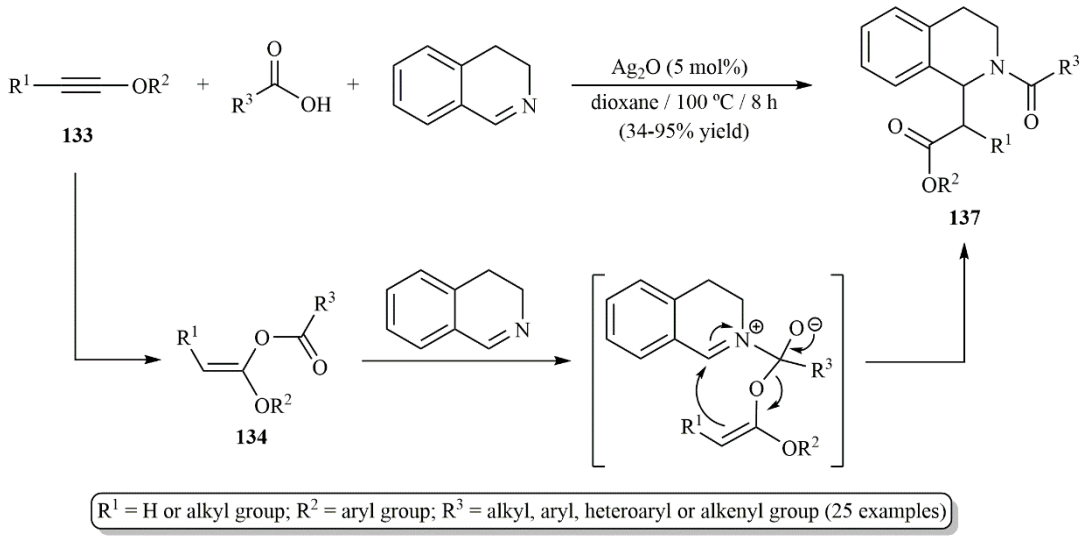
chloroperbenzoic acid) [197], respectively, of the *in situ* formed (*Z*)-α-alkoxy-enol esters **134** (Scheme **74**).



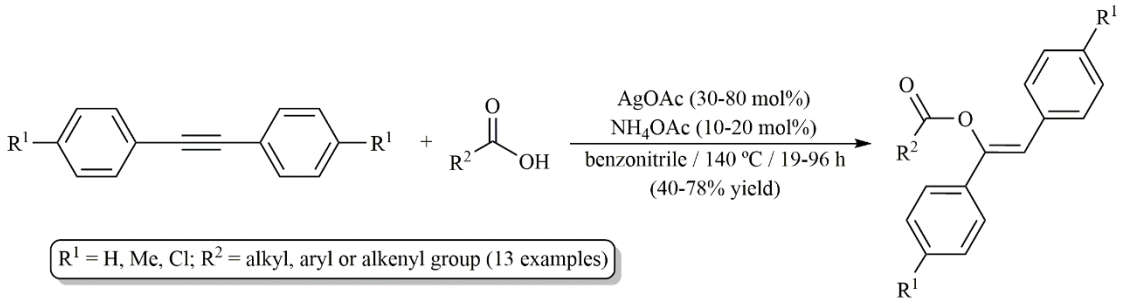
Scheme 74. Access to β-keto esters and α-carbonyloxy esters from ynol ethers and carboxylic acids.

In a further study, Cui and co-workers reported the preparation of a diverse family of 1-substituted *N*-acyl-1,2,3,4-tetrahydroisoquinolines **137** through the Ag_2O-catalyzed three component coupling of ynol ethers **133**, carboxylic acids and 3,4-dihydroisoquinoline (Scheme **75**) [198]. Compounds **137** result from the addition of the 3,4-dihydroisoquinoline to the carbonyl group of the initially formed (*Z*)-α-alkoxy-enol esters **134** and subsequent intramolecular rearrangement.

On the other hand, Satoh and co-workers achieved the selective *anti*-addition of carboxylic acids to diarylacetylenes, substrates that generally show a low reactivity in hydrofunctionalization processes, employing a combination of AgOAc and ammonium acetate (Scheme **76**) [199]. However, it should be noted that to obtain the (*Z*)-enol ester products with acceptable yields, very high metal loadings (30-80 mol%), a high temperature (140 ºC), a large excess of the acid (8 equiv.), and long reaction times (40-78%) were required.



Scheme 75. Multicomponent synthesis of the functionalized tetrahydroisoquinolines **137**.

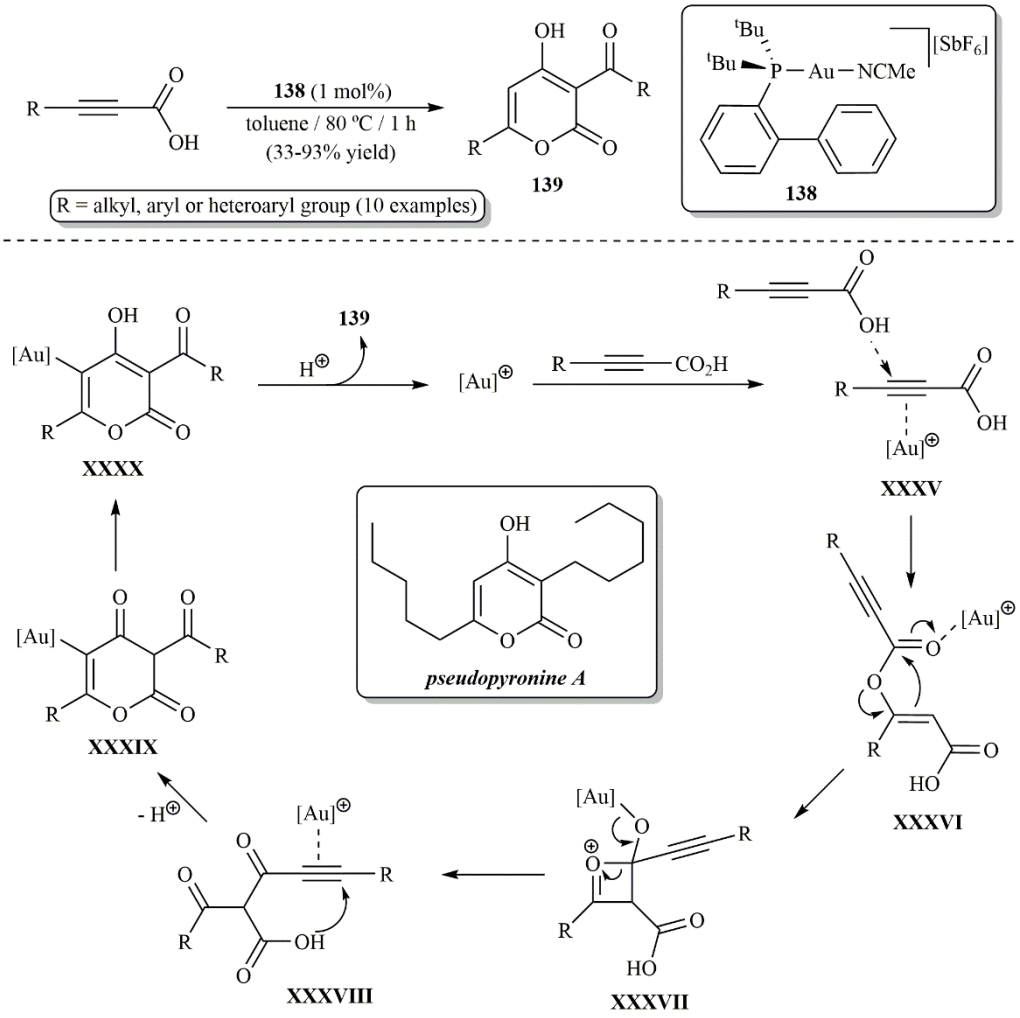


Scheme 76. Silver-catalyzed addition of carboxylic acids to diarylacetylenes.

6.3. Gold

Among the different metals employed to promote the hydrofunctionalization of alkynes, gold has gained an increasing prominence given its outstanding effectiveness for the π-electrophilic activation of unsaturated carbon-carbon bonds [200, 201]. In relation with the topic covered in the present review article, we note that the application of gold-based catalysts in inter- and intramolecular hydro-oxycarbonylation reactions of alkynes has been comprehensively summarized in 2020 [202]. Therefore, to avoid unnecessary duplication of information, those readers interested in the field are referred to that review.

Not included works published later are: (i) the use of Au(I) complexes encapsulated on NHC-capped cyclodextrins as catalysts for the 5-*exo-dig* cycloisomerization of linear γ-alkynoic acids in aqueous medium [203], and (ii) the access to 4-hydroxy 2*H*-pyrones **139** by homocoupling of propiolic acids catalyzed by [Au(JohnPhos)(NCMe][SbF_6] (**138**) (Scheme **77**) [204].



Scheme 77. Gold-catalyzed synthesis of 4-hydroxy 2*H*-pyrones from propiolic acids.

Formation of **139** involves the initial generation of intermediates **XXXVI**, resulting from the Markovnikov addition of one molecule of the propiolic acid to the C≡C bond a second one activated by π-coordination to the Au(I) cation **XXXV**, which evolves

into **XXXVIII** through the transient 4-membered oxacyclic species **XXXVII**. Subsequent 6-*endo-dig* cyclization of **XXXVIII** generates **XXXIX** which isomerizes into **XXXX**, from which products **139** are released by protodeauration. The synthetic utility of the process was demonstrated with the synthesis of naturally occurring pseudopyronine A by reduction of the C=O group of the corresponding 4-hydroxy 2*H*-pyrone (R = *n*-C_5H_{12}).

7. CONCLUSIONS

In this review, a comprehensive literature survey regarding intra- and intermolecular hydro-oxycarbonylation reactions of alkynes covering the period 2011-2020 has been presented. Efforts made by many research groups around the world to apply this hydrofunctionalization reactions in total syntheses of natural products, biologically active molecules and elaborated heterocyclic compounds are remarkable. It is also worth mentioning the large number of new catalytic systems that have seen the light in recent years, allowing some of them to overcome some limitations of those already known. However, there are still some unsolved challenges in the field such as the control of regioselectivity when non-symmetrically substituted internal alkynes are employed as substrates or the development of catalytic systems for the *E*-selective *anti*-Markovnikov addition of carboxylic acids to terminal alkynes. Taking into account the enormous synthetic potential of enol esters and lactones we are confident that new catalysts, reactions and applications will appear soon in this field.

8. CONSENT FOR PUBLICATION

Not applicable.

9. FUNDING

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10. CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

11. ACKNOWLEDGEMENTS

Declared none.

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GRAPHICAL ABSTRACT & CAPTION

Recent advances in the metal-catalyzed inter- and intramolecular addition of carboxylic acids to alkynes are reviewed. Literature published since 2011 is covered.

AUTHOR´S PHOTOGRAPH

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