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Review

Metal-Catalyzed Synthesis and Transformations of β-Haloenol Esters

Victorio Cadierno

Laboratorio de Compuestos Organometálicos y Catálisis (Unidad Asociada al CSIC), Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, Julián Clavería 8, E-33006 Oviedo, Spain; vcm@uniovi.es; Tel.: +34-985-103453

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Abstract: In the last years there has been an increasing interest in the search for protocols to obtain β-haloenol esters in an efficient and selective manner as they are versatile building blocks in synthetic organic chemistry. In this article, metal-catalyzed transformations allowing the access to both acyclic and cyclic (i.e., haloenol lactones) β-haloenol esters are reviewed. Metal-catalyzed reactions in which these molecules participate as substrates are also discussed.

Keywords: haloenol esters; haloenol lactones; enol esters; enol lactones; haloalkenes; haloalkynes; C–C coupling reactions

1. Introduction

Alkenyl halides (haloalkenes) are a pivotal class of compounds in organic synthesis that can be used in a variety of carbon–carbon and carbon–heteroatom bond-forming reactions. For example, alkenyl halides are widely used as substrates in transition metal-catalyzed cross-coupling reactions [1,2] and can be easily converted, through a metal–halogen exchange, into nucleophiles for 1,2-additions to carbonyl compounds [3]. Enol esters are also relevant olefinic derivatives with multitude of applications in modern organic chemistry [4–6]. The introduction of a halogen atom on the C=C bond of the latter leads to functionalized molecules, i.e., α-and β-haloenol esters (Figure 1), in which the reactivities of the haloalkene and enol ester functionalities can be combined and potentially exploited in numerous synthetic ways.

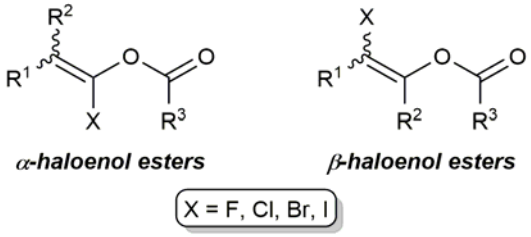
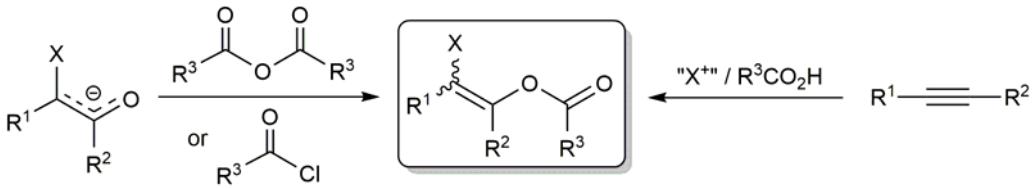


Figure 1. Generic structures of α- and β-haloenol esters.

In this context, while the utility of α-haloenol esters remains almost unexplored due to the lack of efficient and general synthetic methods [7–10], more accessible β-haloenol esters have gained significance in recent years as coupling partners in diverse chemical transformations. Several methodologies can be employed for the preparation β-haloenol esters, the most classical ones involving the acylation of haloenolate anions [11–15] or the haloacyloxylation of alkynes employing the elemental halogens [16–20], bis(pyridine)iodonium tetrafluoroborate (IPy_2BF_4) [21–25],

N-halosuccinimides (NXS; X = Cl, Br, I) [26–28], $PhI(OAc)_2$ [29–31], trihaloisocyanuric acids [32] or *N*,*N*-dibromo-*p*-toluenesulfonamide ($TsNBr_2$) [33] as the electrophilic halogen source (Scheme 1).



Scheme 1. Synthetic routes commonly employed in the preparation of *β*-haloenol esters.

Haloenol lactones of type **A** and **B** (see Figure 2) are also a relevant class of compounds due to their biological activity as enzymes inhibitors [34–38], and also because they are a common structural motif in many natural products [39].

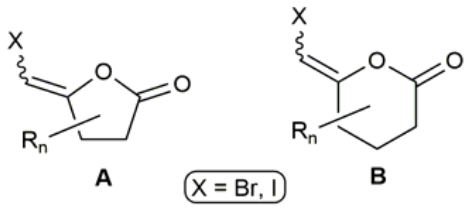
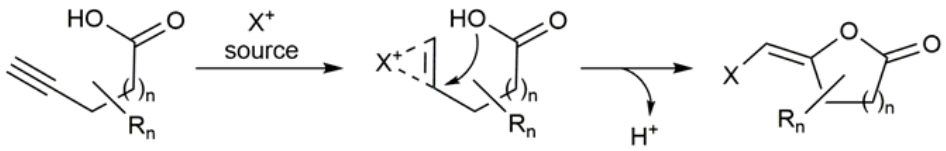


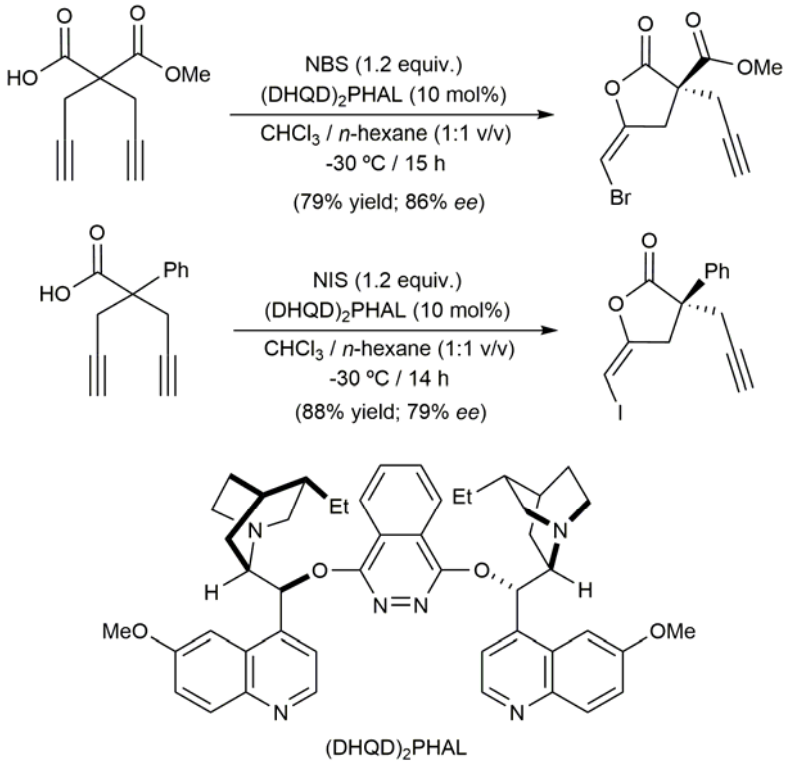
Figure 2. Generic structures of haloenol lactones featuring biological activity.

Access to these molecules is usually achieved by halolactonization of the corresponding alkynoic acid using I_2, NBS, NIS or related halogenating agents, reactions that deliver the haloenol lactone products as the *E* isomers exclusively (Scheme 2) [34–38,40,41]. We would like also to highlight here that asymmetric versions of these halolactonization processes have been recently described employing cinchona alkaloid-based organocatalysts [42–44]. A couple of illustrative examples are given in Scheme 3. Mechanistic investigations indicated a bifunctional behavior of the organocatalysts, activating simultaneously the halogenating agent and the carboxylic acid unit.



Scheme 2. The *E*-halolactonization of alkynoic acids.

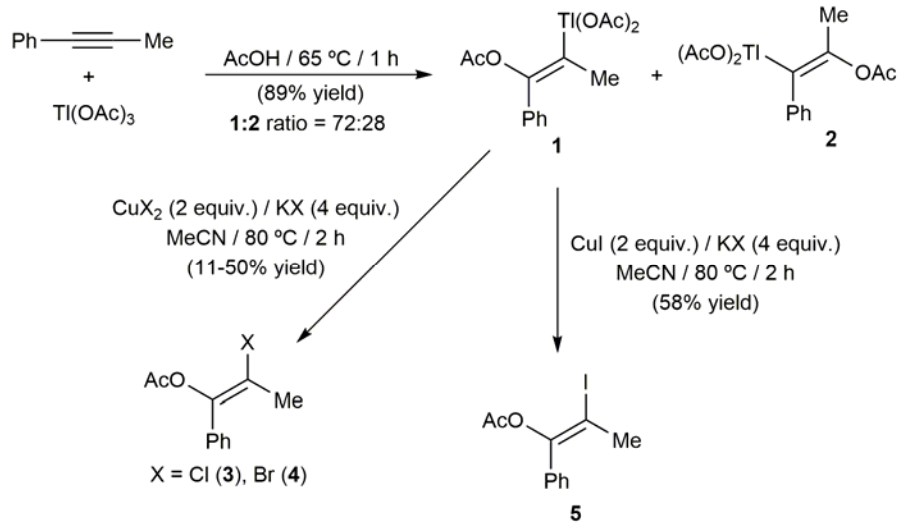
Synthetic approaches to both acyclic and cyclic *β*-haloenol esters have been expanded in the most recent years by the aid of metal catalysts, employing in most of the cases in situ generated or preformed haloalkynes [45–47] as starting materials, and are the subject of the present review article. Thus, the catalytic synthesis of *β*-haloenol esters will be discussed, as well as the participation of these molecules in metal-catalyzed cross-coupling processes.



Scheme 3. Enantioselective halolactonization of alkynoic acids employing an organocatalyst.

2. Metal-Catalyzed Synthesis of *β*-Haloenol Esters

The first metal-mediated route to access *β*-haloenol esters was described by Ichikawa and co-workers in 1974 (Scheme 4) [48]. They found that 1-propynylbenzene readily undergoes a *trans*-acetoxythallation, upon treatment of with $Tl(OAc)_3$ in acetic acid, to give a separable mixture of the two isomeric vinylthallium(III) compounds **1** and **2**. Subsequent reaction of the major isomer **1** with the corresponding copper(I) or copper(II) halide salt in acetonitrile resulted in the formation of the (*E*)-*β*-haloenol acetates **3**–**5**, which were isolated in low yield (11–58%). The halogenodethallation step proceeded in all the cases with complete retention of the C=C configuration.

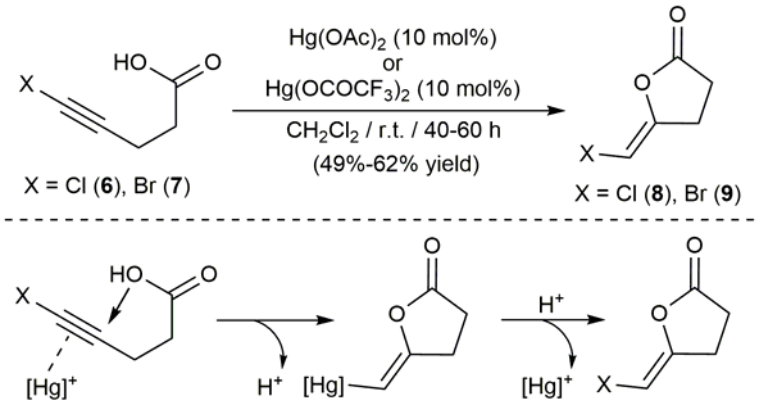


Scheme 4. Thallium-mediated synthesis of the (*E*)-*β*-haloenol acetates **3**–**5** from 1-propynylbenzene.

After this seminal work, more general methodologies based on the use of Hg, Ag, Au and Pd metals have been described.

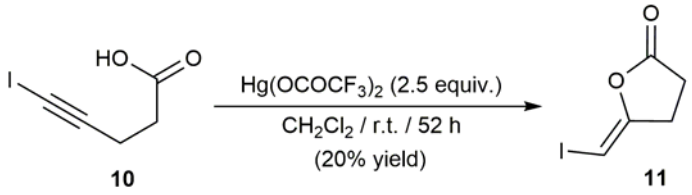
2.1. Hg-Catalyzed Synthesis of β-Haloenol Esters

Extending previous studies with non-halogenated molecules [49], Krafft and Katzenellenbogen described in 1981 a synthetic route to haloenol lactones through the mercury-catalyzed cyclization of halogen-substituted alkynoic acids [50]. In particular, they were able to generate compounds **8** and **9** in moderate yield (40–69%) by treatment of dichloromethane solutions of 5-chloro-4-pentynoic acid (**6**) and 5-bromo-4-pentynoic acid (**7**), respectively, with 10 mol % of $Hg(OAc)_2$ or $Hg(OCOCF_3)_2$ (Scheme 5). The reactions proceed through the anti addition of the carboxylate group to the C≡C bond activated by π-coordination to mercury and, contrary to the halolactonization methods commented above (see Scheme 2), they delivered the haloenol lactone products as the *Z* isomers exclusively.



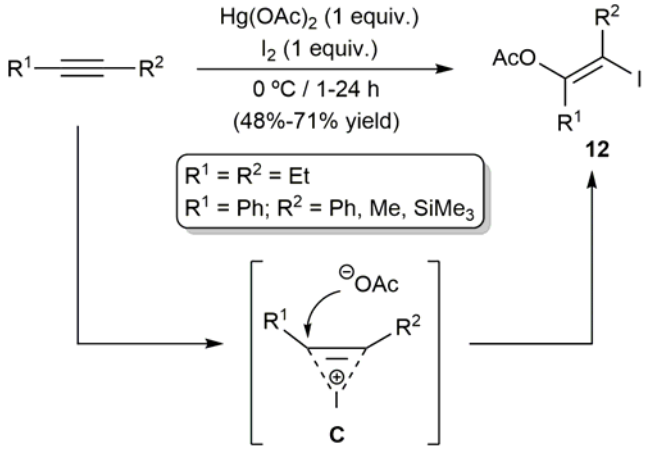
Scheme 5. Mercury-catalyzed cyclization of the alkynoic acids **6** and **7**.

In an independent study, Krantz and co-workers extended this cyclization reaction to 5-iodo-4-pentynoic acid (**10**). However, the use of an excess of mercury(II) trifluoroacetate was in this case needed, and the (*Z*)-iodoenol lactone **11** could only be obtained in low yield (Scheme 6) [51].



Scheme 6. Mercury-mediated cyclization of 5-iodo-4-pentynoic acid.

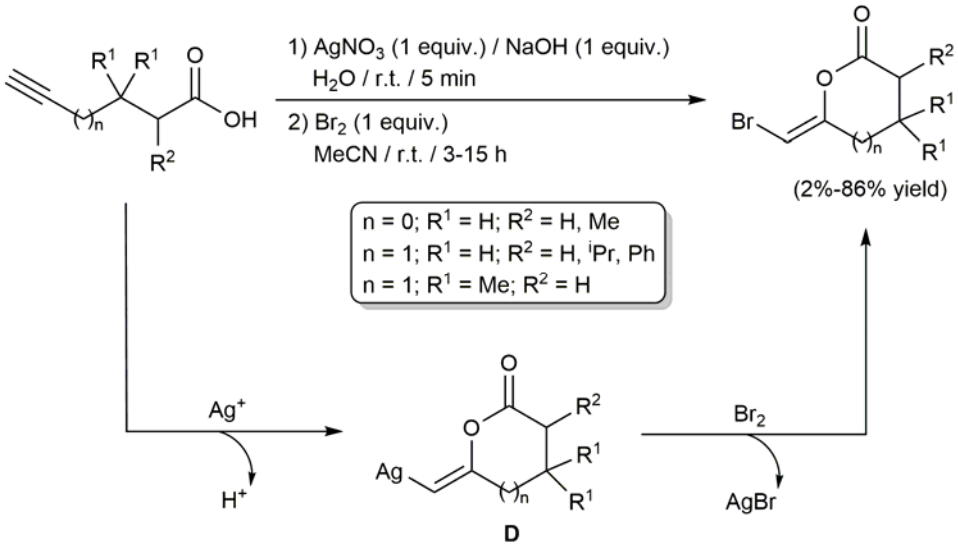
Barluenga and co-workers achieved also the stereoselective synthesis of the acyclic (Z)-β-iodoenol acetates **12** through a difunctionalization reaction of the corresponding internal alkynes by means of the $Hg(OAc)_2/I_2$ combination (Scheme 7) [52]. The formation of a cationic intermediate of type **C**, which undergoes the attack of the acetate anion, was proposed by the authors as the most likely reaction pathway.



Scheme 7. Synthesis of acyclic (*E*)-*β*-iodoenol acetates by bifunctionalization of internal alkynes.

2.2. Ag-Catalyzed Synthesis of β-Haloenol Esters

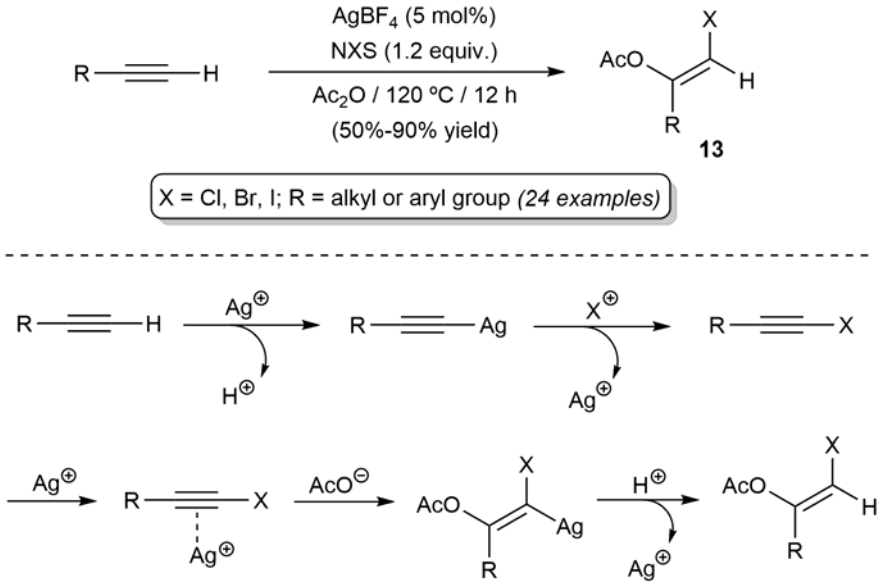
In 1991, the group of Katzenellenbogen described a two-steps protocol for the selective *Z*-bromoenol lactonization of akynoic acids employing stoichiometric amounts of $AgNO_3$ and Br_2 (Scheme 8) [53]. The process involves the initial silver-mediated cyclization of the substrates to generate the metallated lactones **D**, which subsequently undergo an Ag/Br exchange upon treatment with Br_2. Both 5- and 6-membered ring lactones could be synthesized employing this methodology, whose efficiency was found to be conditioned by the substitution pattern of the starting alkynoic acids. In particular, the presence of substituents in α and β position with respect to the carboxylate group (R^1 and R^2) was key to obtain the products in high yields, those substrates unsubstituted in these positions leading to very poor results (2–5% yield). Additionally, of note is the fact that the lactonization process resulted ineffective with akynoic acids featuring an internal C≡C bond or when I_2 was employed as the electrophile.



Scheme 8. Silver-mediated *Z*-bromoenol lactonization of alkynoic acids.

The first general and truly catalytic protocol to obtain acyclic *β*-haloenol esters came to light only in 2010 and it was developed by Jiang's group [54]. As shown in Scheme 9, they were able to synthesize a large variety of (*Z*)-haloenol acetates **13** through an $AgBF_4$-catalyzed difunctionalization reaction of terminal alkynes with *N*-halosuccinimides (NXS) and acetic anhydride. In the reactions, which were performed at 120 °C with 5 mol % of $AgBF_4$ and employing directly Ac_2O as the

solvent, the silver(I) cation plays a dual role. Thus, it first acts a σ-activator allowing the in situ generation of the corresponding haloalkynes RC≡CX, and subsequently as a π-activator facilitating the nucleophilic attack of the acetate anion to the C≡C bond. The process featured an exquisite regio- and stereoselectivity, and tolerated the presence of common functional groups in the alkyne substrates.

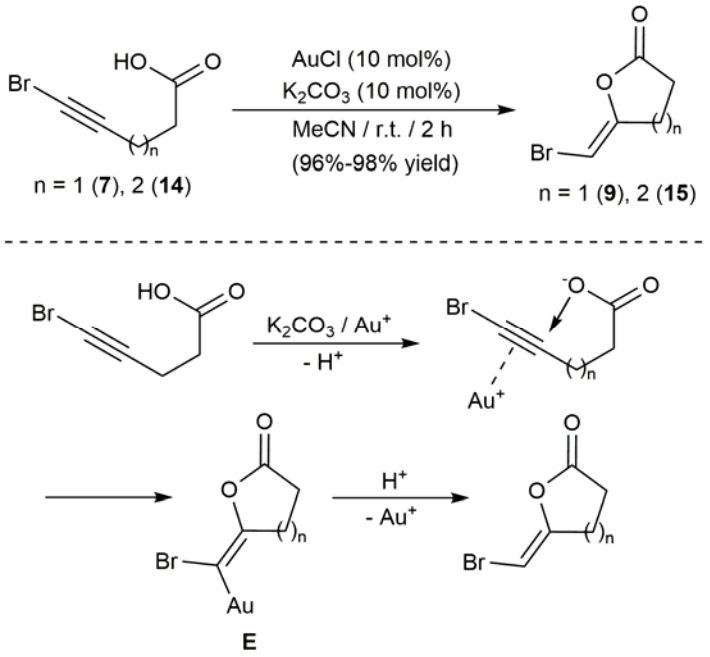


Scheme 9. Silver-catalyzed synthesis of (*Z*)-β-haloenol acetates from terminal alkynes.

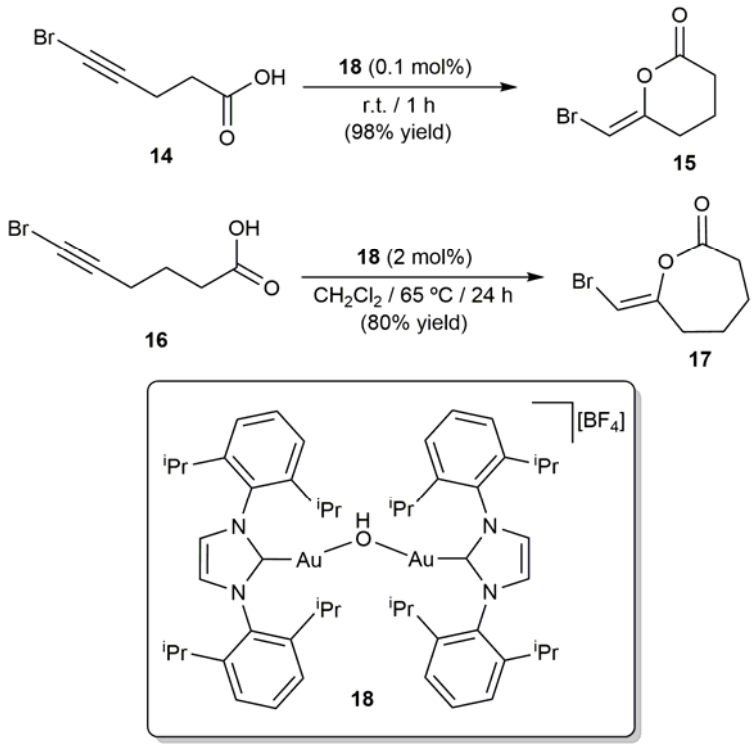
2.3. Au-Catalyzed Synthesis of β-Haloenol Esters

In 2006, and almost simultaneously, the groups of Michelet and Pale demonstrated that both terminal and internal alkynoic acids could be efficiently cyclized under mild conditions employing AuCl as a catalyst [55,56]. 5-Bromo-4-pentynoic acid (**7**) and 6-bromo-5-hexynoic acid (**14**) made part of the substrates studied by Pale and, from them, the *Z*-bromoenol lactones **9** and **15**, respectively, could be synthesized in excellent yield (Scheme 10) [56,57]. The cycloisomerization reactions, which were performed at room temperature with 10 mol % of AuCl in combination with K_2CO_3 (10 mol %), involve the intramolecular exo-dig anti-addition of the carboxylate anion generated by deprotonation with the K_2CO_3 base to the C≡C bond, which is activated by π-coordination to the Au^+ cation. Final protonolysis of the gold-carbon bond in the metallated intermediate **E** liberates the enol-lactone products.

More recently, Nolan and coworkers reported the regio- and stereoselective cyclization of 6-bromo-5-hexynoic acid (**14**) and 7-bromo-6-heptynoic acid (**16**) into lactones **15** and **17** employing catalytic amounts of the hydroxo-bridged dinuclear gold(I) complex [{Au(IPr)}$_2$(μ-OH)][BF_4] (**18**; IPr = *N*,*N*′-bis(2,6-di-*iso*-propylphenyl)imidazole-2-ylidene) (Scheme 11) [58]. The addition of an external base was in this case not needed, the bridging OH ligand facilitating the generation of the carboxylate anion. It is also worthy of note that, while the conversion of **14** into **15** proceeded rapidly at r.t. with only 0.1 mol % of **18**, the generation of the ε-alkylidene-lactone **17** from **16** resulted in being more demanding and an increase of the Au loading, temperature and reaction time was required.



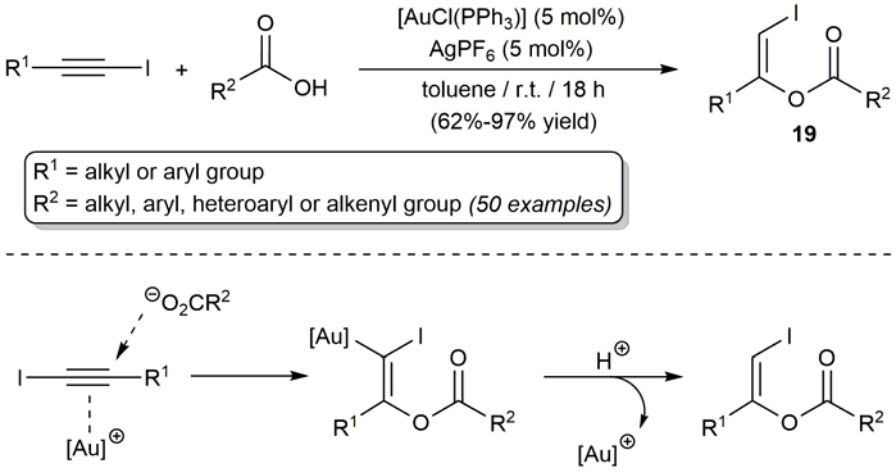
Scheme 10. AuCl-catalyzed cycloisomerization of bromo-substituted alkynoic acids.



Scheme 11. Cycloisomerization of alkynoic acids **14** and **16** catalyzed by [{Au(IPr)}$_2$(μ-OH)][BF$_4$] (**18**).

Making use of a catalytic system composed of the gold(I) complex [AuCl(PPh$_3$)] and the chloride abstractor AgPF$_6$, a broad scope procedure for the preparation of acyclic (*Z*)-β-iodoenol esters was also recently developed by Cadierno and co-workers (Scheme 12) [59–61]. The process, which proceeds under mild conditions and tolerates the presence of several functional groups in the substrates, involves the intermolecular addition of carboxylic acids to iodoalkynes, the latter being activated towards the carboxylate anion attack by π-coordination to the in situ generated gold(I) cation [Au(PPh$_3$)]$^+$. As expected, the carboxylate anion adds selectively to the more electrophilic C-2 carbon of the

iodoalkyne [45–47] and, as usually observed in the chemistry of π-alkyne-gold complexes [62], the addition takes places in an anti fashion, thus affording the olefinic products **19** in a complete regio- and stereoselective manner. With a couple of representative examples, i.e., the addition of acetic acid to 1-(chloroethynyl)-4-methylbenzene and 1-bromooct-1-yne, the authors also demonstrated the applicability of this procedure for the synthesis of related (*Z*)-*β*-chloroenol and (*Z*)-*β*-bromoenol esters [60].



Scheme 12. Gold-catalyzed intermolecular addition of carboxylic acids to iodoalkynes.

Following the same gold-catalyzed protocol, Muthusamy and Pansare synthesized later a large family of (Z)-*β*-iodoenol cinnamates **20** starting from the corresponding aromatic or aliphatic iodoalkyne and cinnamic acid (Figure 3) [63].

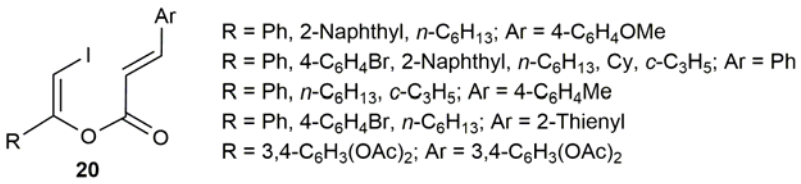
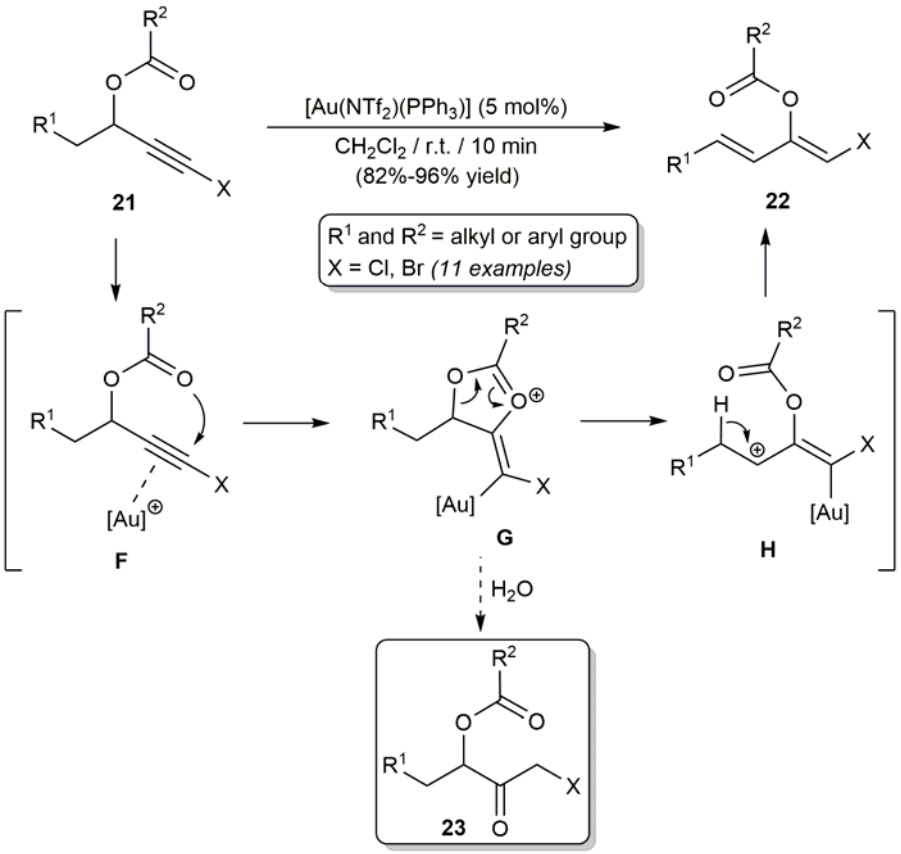


Figure 3. Structure of the (Z)-*β*-iodoenol cinnamates **20**.

On the other hand, Zhang and coworkers reported the efficient synthesis of different *β*-haloenol esters of type **22** by rearrangement of the corresponding halo-substituted propargylic carboxylates **21** (Scheme 13) [64]. The process, which is catalyzed by the gold(I) complex [Au(NTf_2)(PPh_3)] (NTf_2 = bis(trifluoromethane)sulfonamide) under mild conditions (r.t.), involves the initial activation of the C≡C bond of the substrates by the cationic gold species $[Au(PPh_3)]^+$ (intermediate **F**), followed by 1,2-migration of the carboxylate group via the cyclic intermediate **G** [64,65]. The allyl cation **H** thus generated evolves into the final products **22** by deprotonation and protodeauration. It is important to note that the use of rigorously anhydrous conditions is mandatory for the rearrangement process to proceed selectively since, in the presence of water, hydrolysis of intermediate **G** readily takes place leading to the corresponding *α*-halomethyl ketones **23** [64,66,67]. In line with this, we would like to mention that efficient protocols for the hydration of haloalkynes RC≡CX into *α*-halomethyl ketones $RC(=O)CH_2X$ employing catalytic systems composed of AgF/CF_3CO_2H [68], $In(OTf)_3/CH_3CO_2H$ [69] and $Cu(OAc)_2{\cdot}H_2O/CF_3CO_2H$ [70] have been described, in which hydrolysis of a *β*-haloenol acetate or trifluoroacetate intermediate ($RC(O_2CR')=CHX$; R′ = CH_3 or CF_3) has been proposed as the most likely reaction pathway.

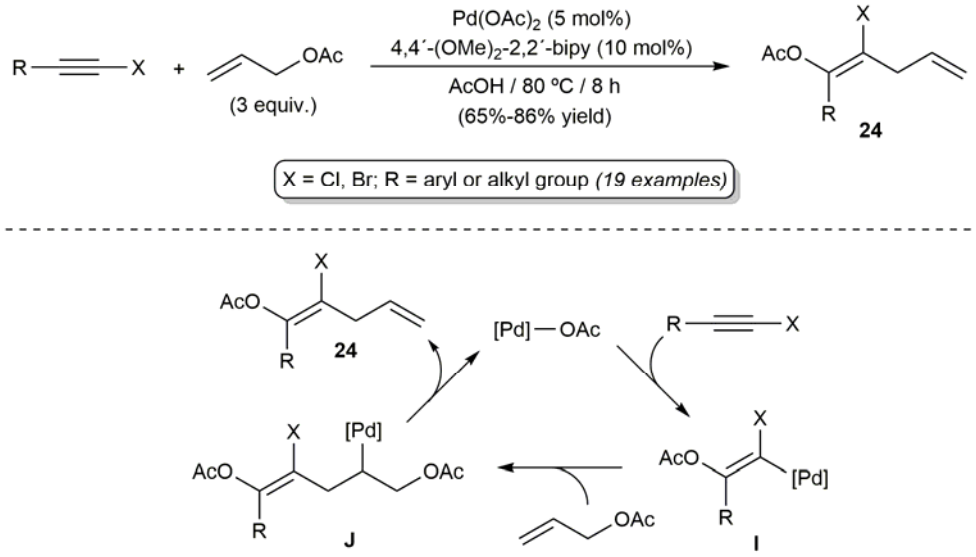


Scheme 13. Gold(I)-catalyzed rearrangement of halo-substituted propargylic carboxylates.

2.4. Pd-Catalyzed Synthesis of β-Haloenol Esters

In 2011, an efficient approach to (Z)-*β*-haloenol acetates **24** was developed by Zhu and coworkers by coupling haloalkynes with allyl acetate, employing a catalytic system composed of $Pd(OAc)_2$ and the bidentate ligand 4,4′-dimethoxy-2,2′-bipyridine (Scheme 14) [71]. The regio- and stereoselectivity of the process was exquisite, the formation of byproducts being in no case observed. A reaction pathway involving the initial acetoxypalladation of the alkyne, followed by insertion of the allyl acetate molecule into the Pd-C bond of the resulting alkenyl-palladium intermediate **I**, was proposed by the authors. A final *β*-elimination step in the alkyl-palladium species **J** furnished the (Z)-*β*-haloenol acetate products **24**. Both chloro- and bromoalkynes participated in the reaction, but the process resulted inoperative with iodoalkynes due to their decomposition under the reaction conditions employed. Negative results were also obtained when substituted allyl acetates, such as 1-phenylallyl acetate, 2-methylallyl acetate or cinnamyl acetate, were used as the olefinic coupling partners.

On the other hand, in the context of their studies on the cycloisomerization of alkynoic acids with indenediide-based palladium pincer catalysts, the group of Martin-Vaca and Bourissou also reported the efficient and selective conversion of 6-bromo-5-hexynoic acid (**14**) into the corresponding lactone **15** (see Scheme 11) employing complexes **25** and **26** (5 mol % of Pd at 90 °C; see Figure 4) [72,73]. Analogously to the case of hydroxo-gold complex $[\{Au(IPr)\}_2(\mu\text{-}OH)][BF_4]$ (**18**), a reaction mechanism involving the intramolecular exo-dig anti-addition of the carboxylate anion on the *π*-activated C≡C bond of substrate was proposed, with the electron-rich indenediide ligand being in this case responsible for the deprotonation of the carboxylic acid unit.



Scheme 14. Palladium-catalyzed coupling of haloalkynes with allyl acetate.

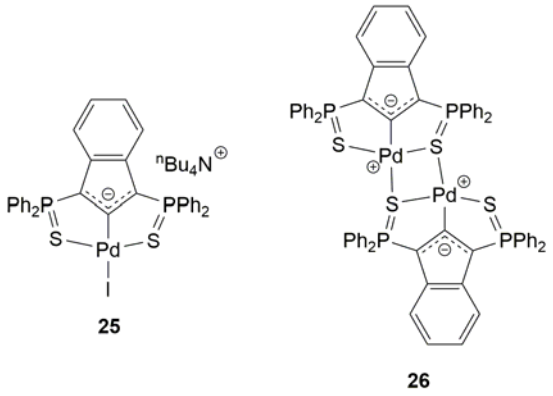


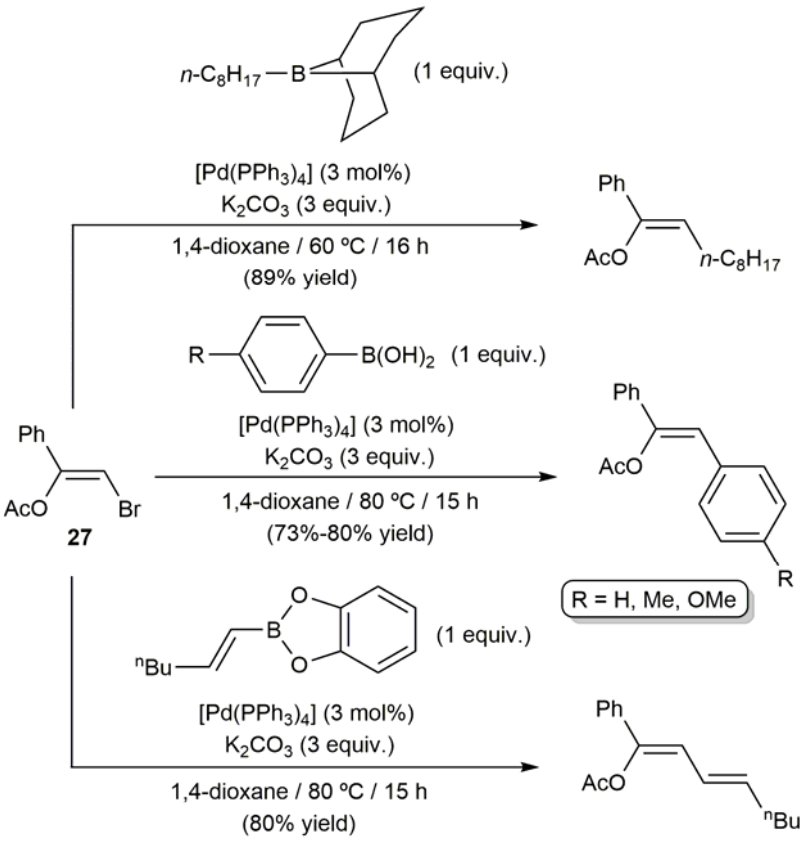
Figure 4. Structure of the palladium(II) pincer complexes **25** and **26**.

3. Metal-Catalyzed Transformations of β-Haloenol Esters

As commented in the introduction of this article, haloalkenes are widely employed in synthetic organic chemistry for the construction of polysubstituted olefins through transition-metal catalyzed cross-coupling reactions [1,2]. In this section, the participation of β-haloenol esters in metal-catalyzed transformations is discussed.

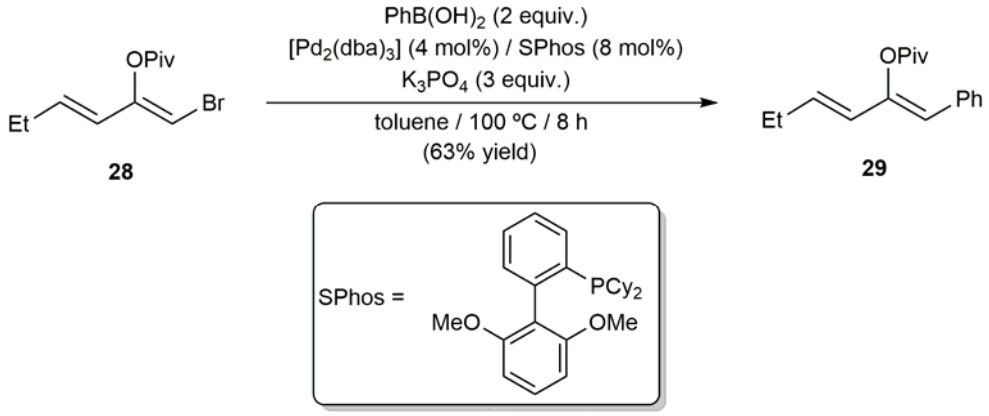
3.1. Acyclic β-Haloenol Esters

In the context of their studies on the palladium-catalyzed coupling of haloalkenes with organoboron compounds, Suzuki and Miyaura reported in 1992 the first cross-coupling reactions involving a β-haloenol ester [74]. Thus, as shown in Scheme 15, the treatment of the bromoenol acetate **27** with different alkyl-, aryl- and alkenyl-boron reagents in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ and a base cleanly afforded the corresponding trisubstituted olefins, which were isolated in high yields (73–89%) and with complete retention of the stereochemistry of the starting C=C bond.



Scheme 15. Pd-catalyzed coupling of (*Z*)-*β*-bromoenol acetate **27** with organoboron compounds.

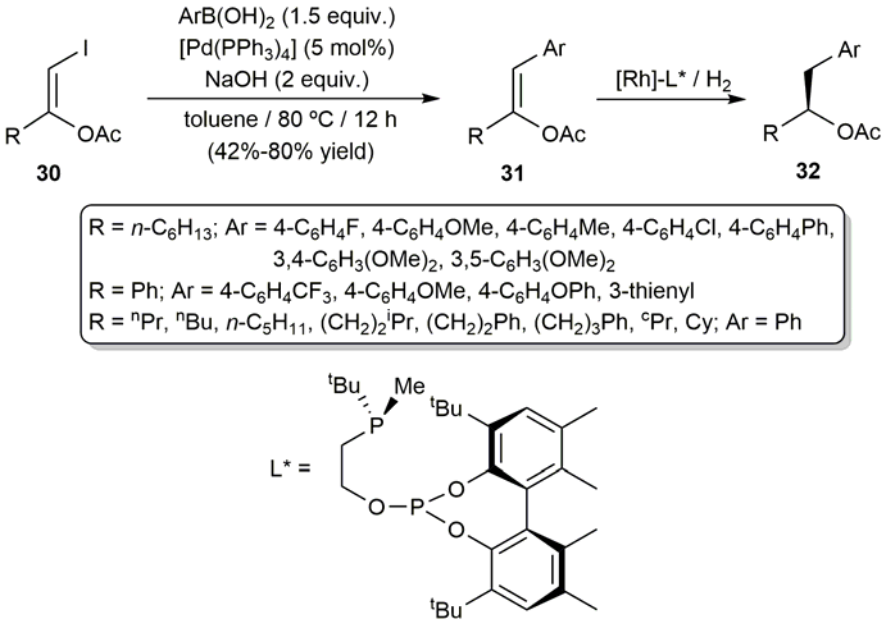
After this seminal contribution, several works reporting the use of *β*-haloenol esters as substrates in Suzuki–Miyaura type reactions have appeared in the literature. For example, Zhang and coworkers described the preparation of the aryldiene **29** through the cross-coupling of **28** with phenylboronic acid catalyzed by the $[Pd_2(dba)_3]$/SPhos system (dba = dibenzylideneacetone; see Scheme 16) [64].



Scheme 16. Synthesis of the aryldiene **29** through Suzuki–Miyaura coupling of **28** with $PhB(OH)_2$.

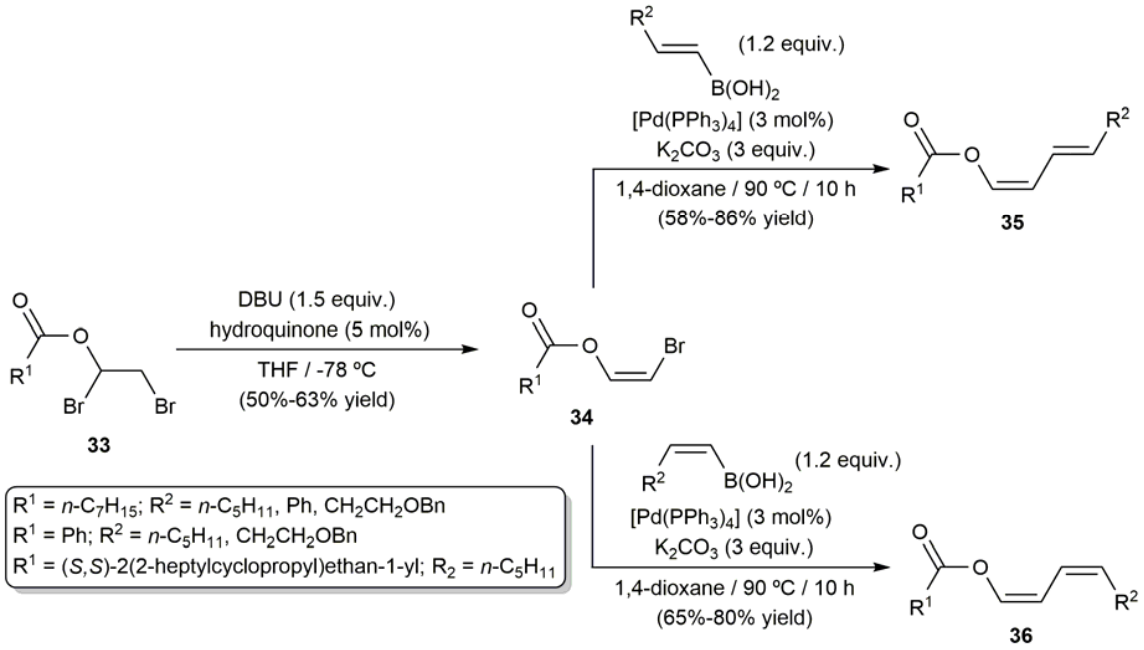
In a wider scope study, Cadierno, Pizzano and coworkers employed the (*Z*)-*β*-iodoenol acetates **30** as starting materials for the synthesis of several (*Z*)-1-substituted-2-arylvinyl acetates **31**, via $[Pd(PPh_3)_4]$-catalyzed coupling of **30** with aromatic boronic acids (Scheme 17) [59,61]. Remarkably, the asymmetric hydrogenation of compounds **31** to afford the corresponding chiral homobenzylic esters **32**, of interest as precursors of synthetically useful chiral alcohols by deacylation, could be successfully

accomplished by the same authors employing rhodium(I) catalysts containing optically pure bidentate phosphine-phosphite ligands (*ee* up to 98%) [59,61].



Scheme 17. (*Z*)-*β*-Iodoenol acetates as starting materials for the preparation of chiral homobenzylic esters.

As shown in Scheme 18, the Suzuki–Miyaura coupling of (*Z*)-2-bromovinyl esters **34**, generated by stereocontrolled dehydrobromination of 1,2-dibromoethyl esters **33** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and a catalytic amount of hydroquinone, with stereodefined alkenylboronic acids provided also an efficient route for the selective construction of (*Z*,*E*)- and (*Z*,*Z*)-conjugated dienyl esters (**35** and **36**, respectively), molecules of enormous interest since they can be employed as precursors for the preparation of several natural products through Diels–Alder reactions [75].



Scheme 18. Stereoselective synthesis of conjugated dienyl esters through Suzuki–Miyaura-type cross-coupling reactions.

In addition, the tetrasubstituted olefins **37**–**40** (see Figure 5) were also synthesized in high yields (72–99%) by Suzuki–Miyaura coupling of the corresponding β-haloenol acetates with boronic acids (the C–C bond formed is highlighted in bold) [28,31,71].

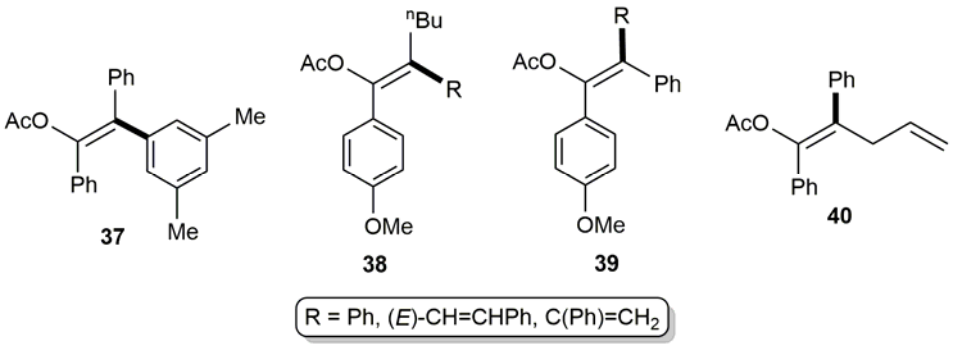
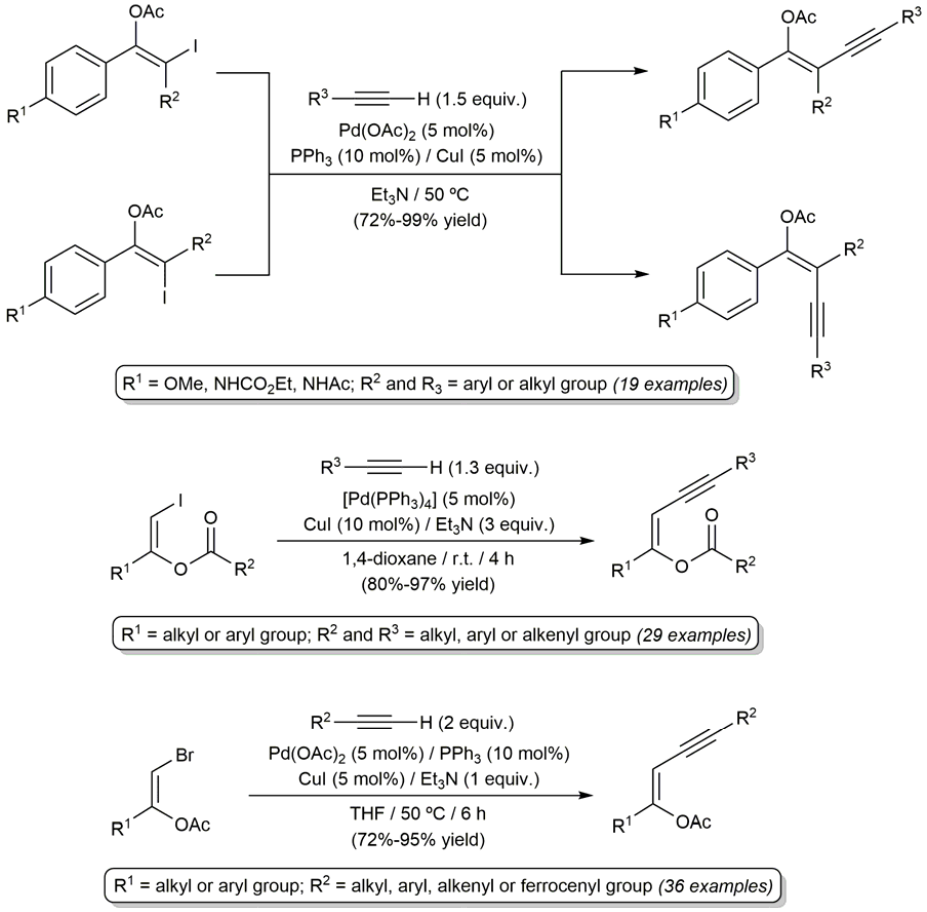


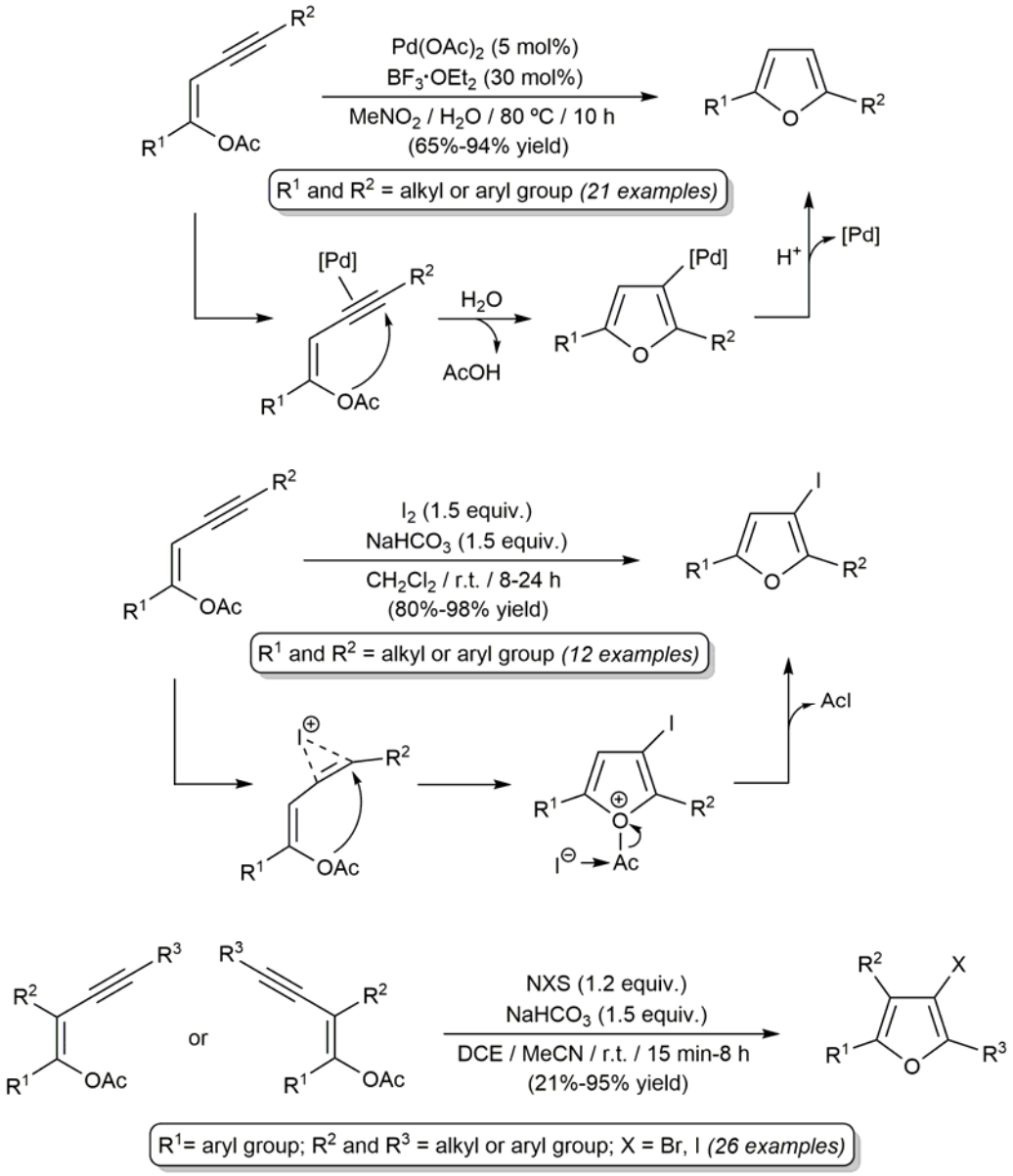
Figure 5. Structure of the tetrasubstituted olefins **37**–**40**.

Probably, the reactions of β-haloenol esters most widely studied to date are the palladium-catalyzed Sonogashira-type couplings with terminal alkynes [30,54,60,71,76–78]. In this regard, a large number of (*Z*)- and (*E*)-β-haloenol esters (both chlorides, bromides and iodides) have been successfully coupled with alipahic and aromatic alkynes, 1,3-enynes or propargylic alcohols to generate the corresponding enynyl ester products in high yields and with complete preservation of the C=C bond stereochemistry of the starting olefins (the results obtained in references [60,76,77] are depicted in Scheme 19).



Scheme 19. Sonogashira-type coupling reactions of β-haloenol esters.

The main interest in these Sonogashira-type reactions is that the enynyl ester products can be employed as starting materials for the generation of polysubstituted furans via metal-catalyzed [76,77] or halogen-induced electrophilic cyclization reactions [30,79–81]. Illustrative examples are shown in Scheme 20.

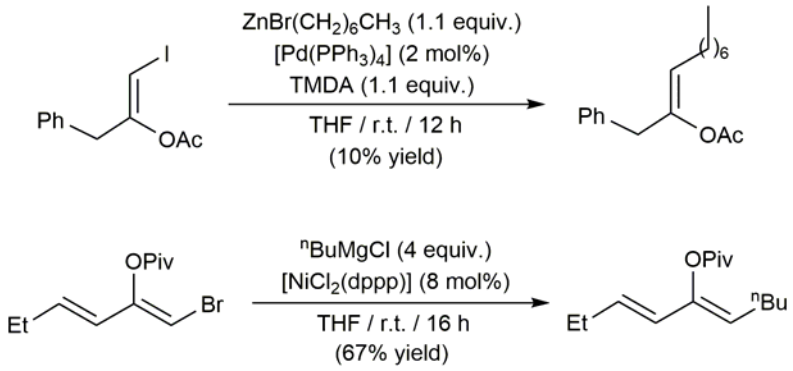


Scheme 20. Some furan-ring formation reactions employing enynyl acetates as precursors.

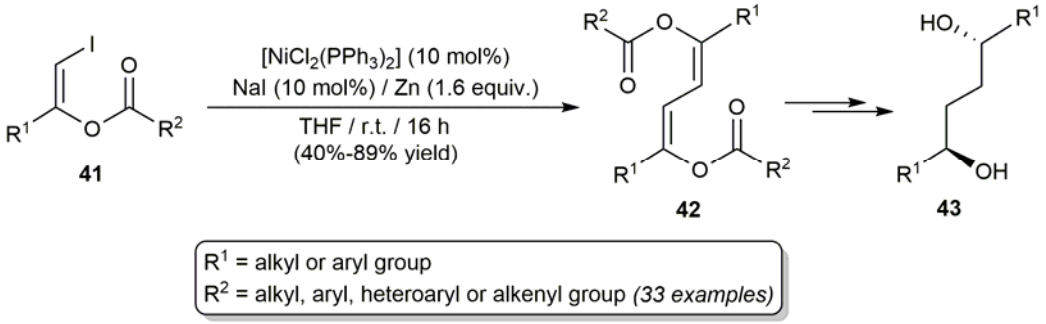
Contrary to the case of the Suzuki-Miyaura and Sonogashira reactions, the participation of *β*-haloenol esters in Negishi- and Kumada-Corriu-type cross-coupling processes remains almost unexplored. In fact, only the examples depicted in Scheme 21 can be currently found in the literature [61,64].

On the other hand, homocoupling reactions of alkenyl halides have been extensively studied during the last decades since they provide a straightforward access to conjugated 1,3-dienes and polyenes [82]. In this context, taking advantage of previous works by Takagi and coworkers with non-functionalized alkenyl halides [83–85], an efficient and broad scope protocol for the homocoupling of (*Z*)-*β*-iodoenol esters **41** was developed by Francos and Cadierno (Scheme 22) [86]. The process, which is catalyzed by nickel(0) species generated in situ by combining $[NiCl_2(PPh_3)_2]$ with NaI and Zn dust, afforded the buta-1,3-diene-1,4-diyl diester products **42** as the corresponding ZZ-isomers exclusively. It is also

worth noting that 1,3-dienes **42** proved to be useful precursors for the preparation of synthetically relevant C_2 symmetric 1,4-diols **43**, through a rhodium-catalyzed asymmetric hydrogenation of the two C=C bonds of **42** and a subsequent base-promoted deacylation reaction [87].

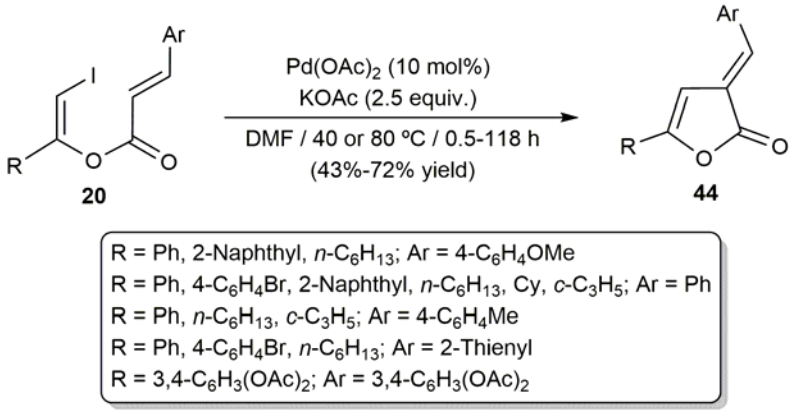


Scheme 21. Negishi- and Kumada-Corriu cross-coupling reactions involving β-haloenol esters.



Scheme 22. Ni-catalyzed homocoupling of (Z)-β-iodoenol esters.

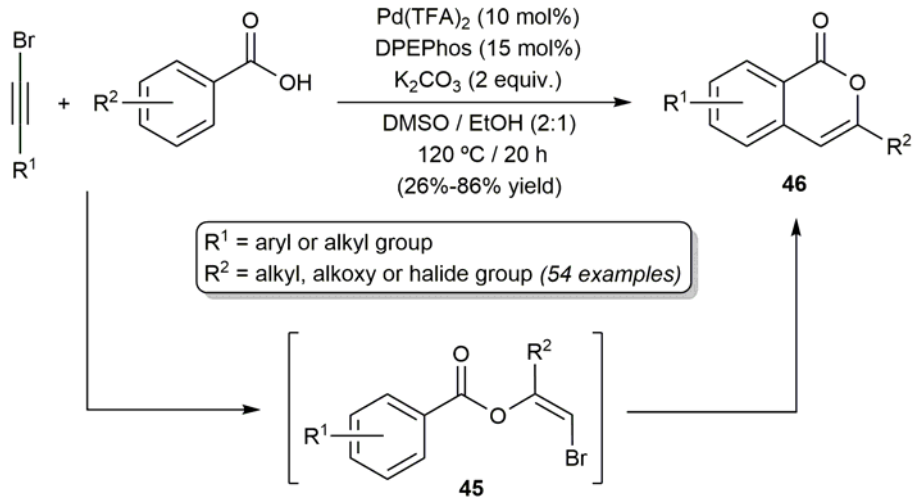
Acyclic β-haloenol esters have also been employed as starting materials for the generation of heterocyclic systems. In this context, the intramolecular palladium-catalyzed Mizoroki–Heck coupling of the (Z)-β-iodoenol cinnamates **20** allowed the preparation of furanones **44** in moderate to high yields (Scheme 23) [63].



Scheme 23. Intramolecular Mizoroki–Heck coupling of (Z)-β-iodoenol cinnamates.

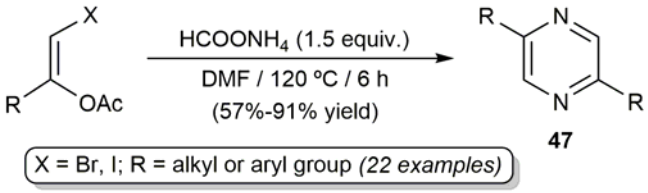
A broad scope protocol for the synthesis of 3-substituted isocoumarins **46** by coupling of bromoalkynes with benzoic acids, catalyzed by palladium(II) trifluoroacetate in combination with the diphosphine ligand DPEPhos (bis[2-(diphenylphosphino)phenyl] ether) and K_2CO_3, was described by Wu, Jiang and co-workers (Scheme 24) [88]. A reaction pathway involving the initial anti addition of

the acid to the alkyne, and subsequent oxidative annulation of the resulting β-bromoenol benzoates **45**, was proposed by the authors.



Scheme 24. Catalytic synthesis of isocoumarins from bromoalkynes and benzoic acids.

(Z)-β-Halenol acetates proved to be also useful starting materials for the preparation of symmetrical 2,5-disubstituted pyrazines **47** (Scheme 25) [89]. Although the formation of compounds **47** was initially observed in the reactions of the haloenol acetates with an ammonia solution under palladium/copper-catalyzed conditions, a more detailed investigation showed that no metal sources are really needed for the reaction to proceed, and that any source of ammonia can be employed. In this regard, employing ammonium formate, and performing the reaction in DMF at 120 °C, a wide range of 2,5-disubstituted pyrazines could be accessed in moderate to excellent yields starting from both aromatic and aliphatic (Z)-β-iodoenol or (Z)-β-bromoenol acetates (Scheme 25). The regioselectivity of the process was excellent, the formation of the corresponding 2,6-disubtituted regioisomers being not observed under these optimized conditions. According to the authors, α-halomethyl ketones could be involved as intermediates.



Scheme 25. Synthesis of 2,5-disubstituted pyrazines from (Z)-β-haloenol acetates.

3.2. Cyclic β-Haloenol Esters

Although to a much lesser extent, the participation of haloenol lactones in metal-catalyzed cross-coupling reactions has also been described. In this regard, several 5- and 6-membered ring ynenol lactones, including some optically pure representatives, could be accessed from the corresponding iodoenol lactones via classical Pd-catalyzed Sonogashira coupling reactions (Figure 6) [41,44,90,91]. Interestingly, these compounds featured biological activity as enzymes inhibitors [44,90,91].

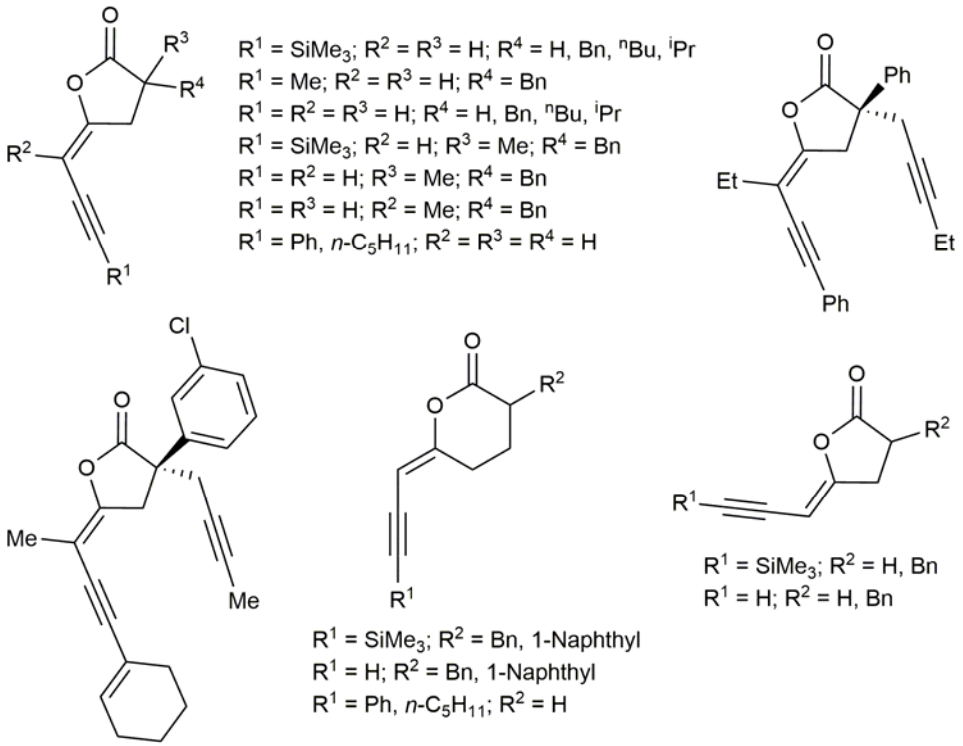
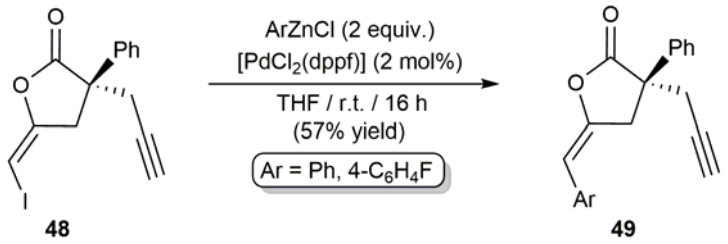


Figure 6. Ynenol lactones synthesized by Sonogashira coupling of the respective iodoenol lactones with terminal alkynes.

Additionally, Hennecke and coworkers reported the synthesis of the arylenol lactones **49** by Negishi coupling of the iodoenol derivative **48** with the corresponding arylzinc chloride catalyzed by [$PdCl_2$(dppf)] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) (Scheme 26) [44]. The use of [$PdCl_2$(dppf)] as catalyst proved to be crucial, since other palladium sources, i.e., PEPPSI-type catalysts or the [$Pd_2(dba)_3$]/trisfurylphosphine combination, led to the extensive dehalogenation of **48**. Additionally, of note is the fact that attempts to generate compounds **49** through Pd-catalyzed Suzuki–Miyaura coupling of **48** with aryl boronic acids failed, due to the incompatibility of the iodoenol moiety with the basic conditions required in this particular cross-coupling process [44].



Scheme 26. Access to arylenol lactones by Negishi coupling.

4. Conclusions

In this contribution we summarized the catalytic protocols currently known for the preparation of *β*-haloenol esters and haloenol lactones, a particular class of haloalkenes, which are gaining significance as coupling partners in diverse chemical transformations of synthetic interest. Metal-catalyzed reactions in which these functionalized olefins participate as substrates, mainly palladium-catalyzed C–C cross-coupling processes, were also discussed. Most of the works herein presented have been published during the last decade, demonstrating the current interest on the use of these molecules as building blocks in organic synthesis. Although there is already a body of work in the field, it still

remains open and new synthetic approaches to these compounds and applications can be expected in the near future.

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

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