1,3-Dien-5-ynes: Versatile Building Blocks for the Synthesis of Carbo- and Heterocycles

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ABSTRACT:

1,3-Dien-5-ynes have been extensively used as starting materials for the synthesis of a wide number of different carbo- and heterocycles. The aim of this review is to give an overview of their utility in organic synthesis, highlighting the variety of compounds that can be directly accessed from single reactions over these systems. Thus, cycloaromatization processes are initially commented, followed by reactions directed towards the syntheses of five-membered rings, other carbocycles and, finally, heterocycles. The diverse methodologies that have been developed for the synthesis of each of these types of compounds from 1,3-dien-5-ynes are presented, emphasizing the influence of the reaction conditions and the use of additional reagents in the outcome of the transformations.

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1. INTRODUCTION

1,3-Dien-5-ynes are highly versatile conjugated dienynes that show a rich reactivity. Therefore, they have been broadly used as starting materials for the synthesis of a wide variety of carbo- and heterocycles. Thus, 1,3-dien-5-ynes have been traditionally utilized as precursors of aromatic rings through cycloaromatization reactions. However, the reactivity of 1,3-dien-5-ynes is not in the least limited to cycloaromatizations, and they have recently emerged as useful substrates for the synthesis of diverse five-membered carbocycles and also for the construction of heterocyclic rings. The outcome of the transformations of 1,3-dien-5-ynes can be tuned mainly by the use of appropriate catalysts and additional reagents, as well as by the nature and location of the substituents of the dienyne skeleton.

This review extensively covers all types of diverse transformations that are possible employing 1,3-dien-5-ynes as starting materials published up to 2015, and is organized based on the different structures that can be accessed (Figure 1).

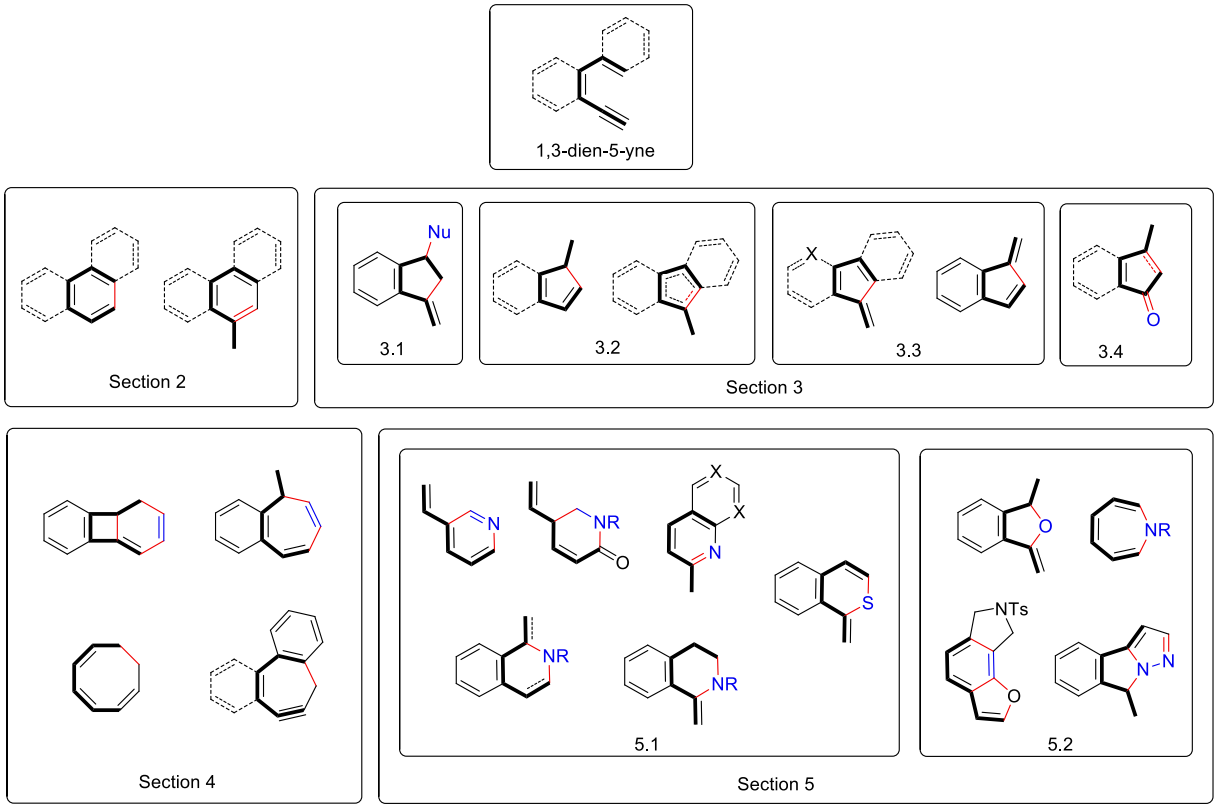


FIGURE 1. Main types of structures accessed by reactions of 1,3-dien-5-ynes

Only reactions involving the entire dienyne skeleton in a single operational step are considered. Thus, transformations in which the triple bond is not participating or, conversely, those in which only the alkyne is reacting are not covered. Moreover, reactions which modify the entire dienyne skeleton after several steps implying different reaction conditions are also out of the scope of this revision. Furthermore, the review focuses in the synthetic applications of 1,3-dien-5-ynes and, consequently, reactions where the yield is not reported or is very low, and those that represent single examples or are only used as mechanistic evidence are not covered unless their usefulness for discussion is guaranteed. Likewise, reactions in which 1,3-dien-5-ynes are only proposed as intermediates are not discussed.

Although the cycloaromatization of 1,3-dien-5-ynes has been the subject of previous reviews,[1,2] in our aim of giving a complete overview of the usefulness of 1,3-dien-5-ynes as precursors of carbo- and heterocycles, the cycloaromatization is also covered in this review. Nonetheless the classical cycloaromatization reactions are only briefly commented, whereas more emphasis is focused on those transformations that afford access to alternative structures or substitution patterns.

For the sake of coherence, the dienyne system is numbered along the review starting in the alkene unit, regardless of the nature of the substituents in each position. Moreover, the dienyne skeleton has been highlighted with bold bonds and the new bonds in the products in red to allow the reader to easily understand at first sight the role of the dienyne in each transformation, except for 1,6-cycloaromatizations in which it becomes obvious. With the same purpose external components that are incorporated in the final product are shown in blue, whereas green color indicates either groups present in the starting dienyne that are loss in the final product or additional reagents.

2. SYNTHESIS OF SIX-MEMBERED CARBOCYCLES: BENZENE DERIVATIVES

The synthesis of six-membered rings from 1,3-dien-5-ynes is basically focused in the construction of new benzene rings via cycloaromatization processes, a transformation that has attracted enormous interest among

organic chemists. For a better understanding, the numerous cycloaromatization reactions have been classified in this review according to Figure 2. Thus, the classical 1,6-cycloaromatizations in which the new bond is created between the terminal carbon of the external alkene (labeled as 1) and the terminal carbon of the alkyne (labeled as 6), and all the substituents remain bonded in the final product to the same carbon that they were bonded in the starting material, are discussed first. Then, cycloaromatizations that also follow a 1,6-topology but in which additional transformations, such as incorporation of new moieties or migration of an existing group, take place are considered. Finally, cycloaromatizations that do not follow a 1,6-topology, that is, those in which the six carbon atoms of the new benzene ring are not the six carbon atoms of the dienyne skeleton of the starting material, are covered.

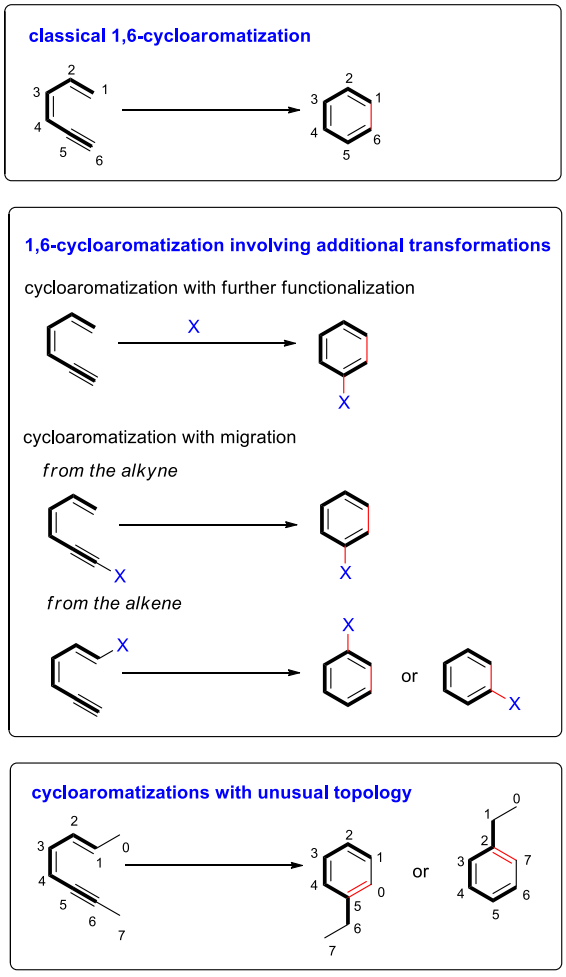


FIGURE 2. Classification of cycloaromatizations

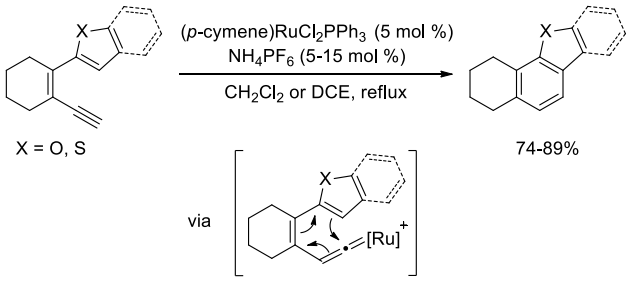
2.1. Classical 1,6-cycloaromatizations

From the groups depicted in Figure 2, the classical 1,6-cycloaromatization is by far the section including a higher number of contributions. In the 1960s the first thermal[3] and photochemical[4] cycloaromatizations of 1,3-dien-5-ynes were reported. Although the thermal cycloaromatization of 1,3-dien-5-ynes has found remarkable applications in the synthesis of diverse polycyclic aromatic hydrocarbons (PAHs), this methodology suffers from the serious limitation of the harsh conditions employed: temperatures over 200 ºC, and frequently over 500 ºC, are required. Moreover both thermal and photochemical cycloaromatizations are typically limited in scope, secondary products are frequently formed and low yields of the cycloaromatized product are usually obtained. Those limitations make these methodologies generally not useful from a synthetic point of view and, therefore, they are not covered in this review.

2.1.1. Metal-catalyzed cycloaromatizations. Noteworthy, during the last twenty years catalysis with transition metal complexes has allowed cycloaromatizations of 1,3-dien-5-ynes to take place under mild conditions and with excellent yields, making these transformations of high synthetic usefulness.

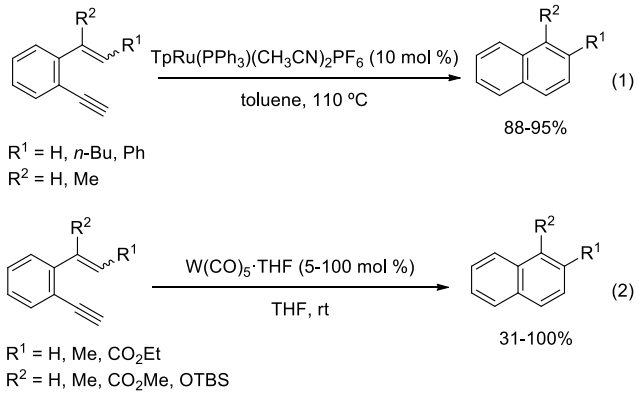
The first metal-catalyzed cycloaromatization of a 1,3-dien-5-yne was reported by Merlic in 1996 (Scheme 1).[5] The reaction, catalyzed by a ruthenium complex, implies the activation of the triple bond through the formation of a vinylidene intermediate and a subsequent 6π-electrocyclization. Therefore, it is limited to dienynes having a terminal alkyne. This transformation is highly efficient for those substrates where the external olefin of the dienyne is forming part of a heterocyclic ring, thus forming benzofused heteroaromatics, but low yields are obtained otherwise.

SCHEME 1. Cycloaromatization of 1,3-dien-5-ynes having terminal alkynes via vinylidene intermediates: proof of concept



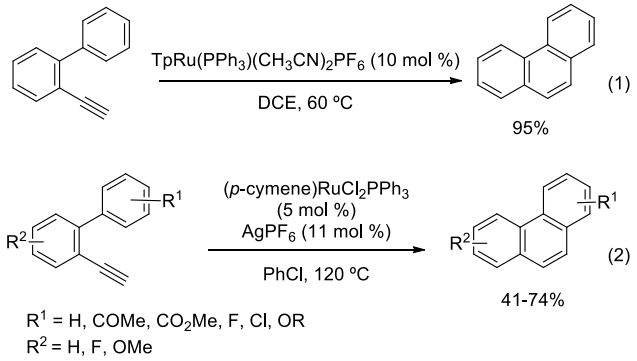
Similarly, Liu has described a ruthenium-catalyzed cycloaromatization of *o*-(ethynyl)styrenes leading to naphthalenes (Scheme 2, eq. 1),[6] although for some particular substituents at the terminal position of the olefin a migration step accompanies the cyclization event (see Schemes 37 and 38). Moreover, Iwasawa has reported a related synthesis of naphthalenes from *o*-(ethynyl)styrenes using $W(CO)_5 \cdot THF$ as catalyst (Scheme 2, eq. 2).[7,8]

SCHEME 2. Cycloaromatization of *o*-(ethynyl)styrenes



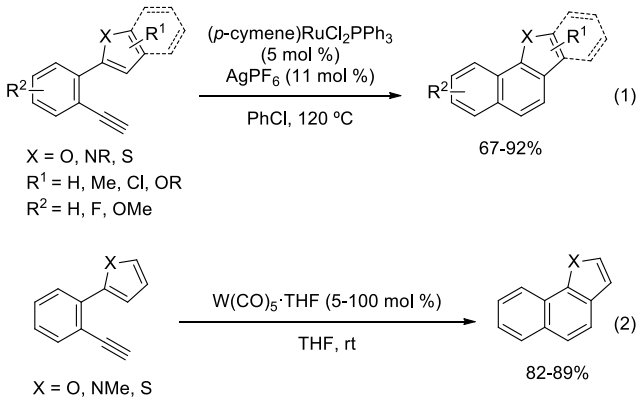
The cycloaromatization via vinylidene complexes can also be extended to the synthesis of phenanthrenes from *o*-(alkynyl)biphenyls under ruthenium catalysis (Scheme 3, eq. 1, 2).[9,10] As in the previous examples, the reaction is still limited to terminal triple bonds, although in this case the intermediacy of vinylidene species is not clear, as computational studies support a cyclization involving a π-alkyne complex.

SCHEME 3. Cycloaromatization of *o*-(ethynyl)biaryls



Moreover, both ruthenium and tungsten complexes are able to efficiently catalyze the cycloaromatization of *o*-(ethynyl)heterobiaryls (Scheme 4, eq. 1, 2).[8,10]

SCHEME 4. Cycloaromatization of *o*-(ethynyl)heterobiaryls

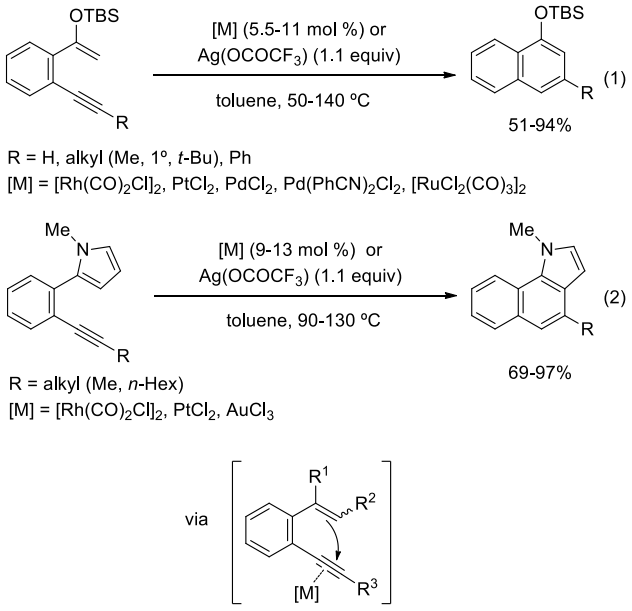


The cycloaromatization of 1,3-dien-5-ynes with terminal alkynes has been applied in the synthesis of diverse polycyclic aromatic compounds including coronene derivatives,[9,11] as well as benzothiophene and benzofuran annelated estranes.[12] Moreover, the syntheses of ethene-bridged *p*-phenylene oligomers[13,14] and luminescent boron-containing PAHs[15] have been recently accomplished using a ruthenium-catalyzed cycloaromatization as key step.

Despite the great potential of the metal-catalyzed cycloaromatizations via vinilydene intermediates described above, they are intrinsically limited by the nature of the intermediate to 1,3-dien-5-ynes having a terminal alkyne. Metal-catalyzed cycloaromatizations of 1,3-dien-5-ynes possesing an internal alkyne, that proceed via 6-*endo* nucleophilic attack of the olefin over the triple bond activated by coordination of the metal

complex, were first reported by Dankwardt in 2001.[16,17] Heating of *o*-(alkynyl)styrenes in which the olefin is forming part either of a silyl enol ether or of a pyrrol in the presence of different complexes of platinum, rhodium, palladium, ruthenium, silver or gold, efficiently leads to the corresponding cycloaromatized products (Scheme 5, eq. 1, 2).

SCHEME 5. Cycloaromatization of *o*-(alkynyl)styrenes via alkyne-metal complexes: proof of concept

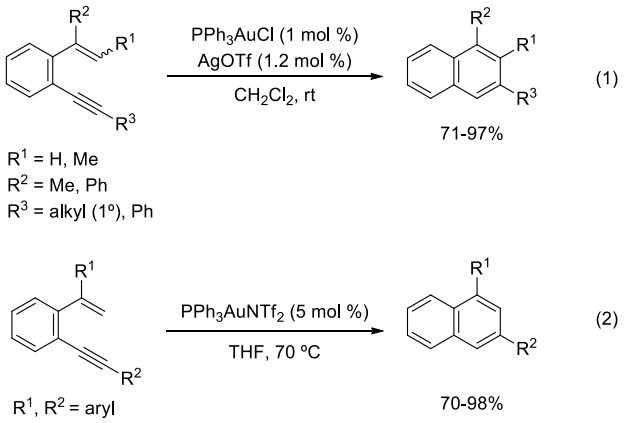


Later, Shibata described the use of a cationic gold catalyst which allows the cycloaromatization of *o*-(alkynyl)styrenes to take place at room temperature and with increased substrate scope (Scheme 6, eq. 1), although in some cases competition of a 5-*exo* mode of cyclization is observed as a minor pathway, that becomes the main one when terminal or iodo-substituted alkynes are used.[18] More recently, the selectivity in the cycloisomerization of *o*-alkynyl-(1-arylvinyl)benzenes has been evaluated in the presence of different metal complexes, and it has been found that a high selectivity towards the 6-*endo* cyclization is achieved in the presence of a gold catalyst (Scheme 6, eq. 2), whereas the use of a palladium complex exclusively leads to benzofulvenes coming from a 5-*exo* cyclization (see Scheme 76, eq. 2).[19] Moreover, a significant influence of the substitution patern of the olefin in the 6-*endo*/5-*endo* selectivity has been observed, with β,β-disubstituted olefins favouring the formation of products coming from a formal 5-*endo* cyclization pathway

(see Section 3.2).

Interestingly, metal-catalyzed cycloaromatizations of *o*-(alkynyl)styrenes with internal alkynes have been applied to the synthesis of acridines,[20,21] and chiral biaryls.[22,23,24]

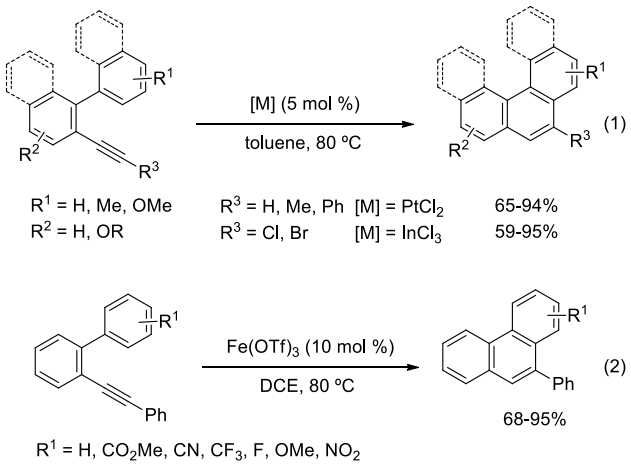
SCHEME 6. Gold-catalyzed cycloaromatization of *o*-(alkynyl)styrenes



In 2002 Fürstner reported a related $PtCl_2$-catalyzed synthesis of phenanthrenes by cycloaromatization of *o*-(alkynyl)biphenyls either with terminal or internal acetylenes, observing generally very high selectivity for the expected 6-*endo* cyclization over the possible competing 5-*exo* cyclization mode (Scheme 7, eq. 1).[25,26] For internal acetylenes, the *endo*-*exo* selectivity seems to be influenced by the nature of the substituent at the triple bond, as a substrate having an electron-rich arene at this position gives a mixture of both isomers whereas that with an ester group affords mainly the *exo* adduct. Other metal complexes such as $GaCl_3$ and $AuCl_3$ are also effective catalysts for this 6-*endo* cyclization.[27,28] The $PtCl_2$-catalyzed synthesis of phenanthrenes by cycloaromatization of *o*-(alkynyl)biphenyls has demonstrated to be very useful and has found multiple applications in the preparation of diverse natural and synthetic products with biological activity, including alkaloids,[26,29,30,31] and HIV-1 integrase inhibitors,[32] but mainly in the synthesis of polyaromatic compounds[33] with interesting optoelectronic and structural properties such as chrysenes[34,35] pyrenes,[34,36,37,38,39] coronenes,[40,41] helicenes[42,43,44,45,46,47] and other PAHs.[13,14,48,49,50,51,52,53,54,55,56] However, in the cycloaromatization of *o*-(alkynyl)biphenyls with a halogen substituent in the triple bond, $InCl_3$ has proved to be a better catalyst in terms of selectivity (Scheme 7, eq. 1), and this methodology has been

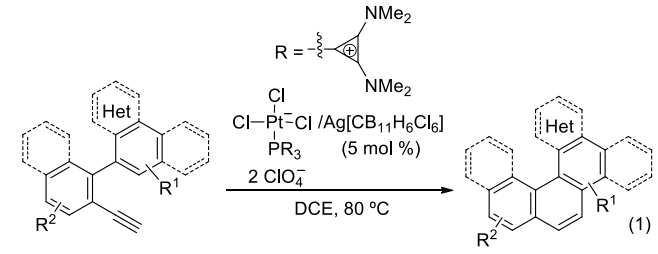
applied to the synthesis of an alkaloid from the aporphine family.[25,57] $InCl_3$ is also the catalyst of choice in the synthesis of ullazine derivatives from 1-(2,6-dialkynylphenyl)-1*H*-pyrroles.[58] The suitability of $Fe(OTf)_3$ as catalyst for the cycloaromatization of *o*-(alkynyl)biphenyls has also been reported and compatibility with different functional groups in the nucleophilic aryl group has been demonstrated, although only enynes with a phenyl substituent in the triple bond have been used as starting materials (Scheme 7, eq. 2).[59]

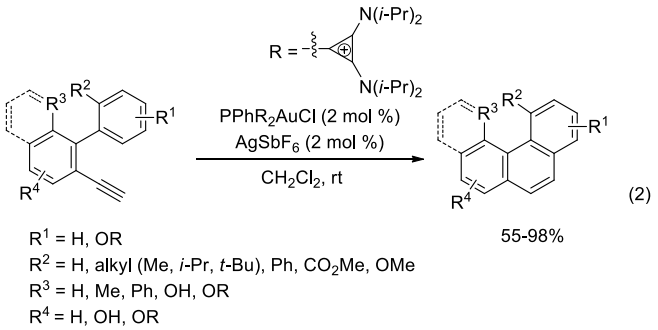
SCHEME 7. Cycloaromatization of *o*-(alkynyl)biphenyls: synthesis of phenanthrenes



Alcarazo has developed improved highly π-acidic catalytic systems for the cycloaromatization of *o*-(ethynyl)biphenyls. Thus, a platinum complex having a P_1-centered trication as ligand has been shown to both accelerate the transformation and extend its scope, showing a broad functional group tolerance and a high 6-*endo vs* 5-*exo* selectivity (Scheme 8, eq. 1).[60] A related platinum catalyst has been applied in the synthesis of chrysotoxene and epimedoicarisoside A.[61] Moreover, a gold catalyst with a dicationic phosphine as ligand has allowed the efficient synthesis of sterically hindered 4,5-disubstituted phenanthrenes (Scheme 8, eq. 2). Thus, the naturally occurring products bulbophyllantrin, marylaurencinol A, ochrolide and coeleginin, have been easily accessed using the reported methodology.[62]

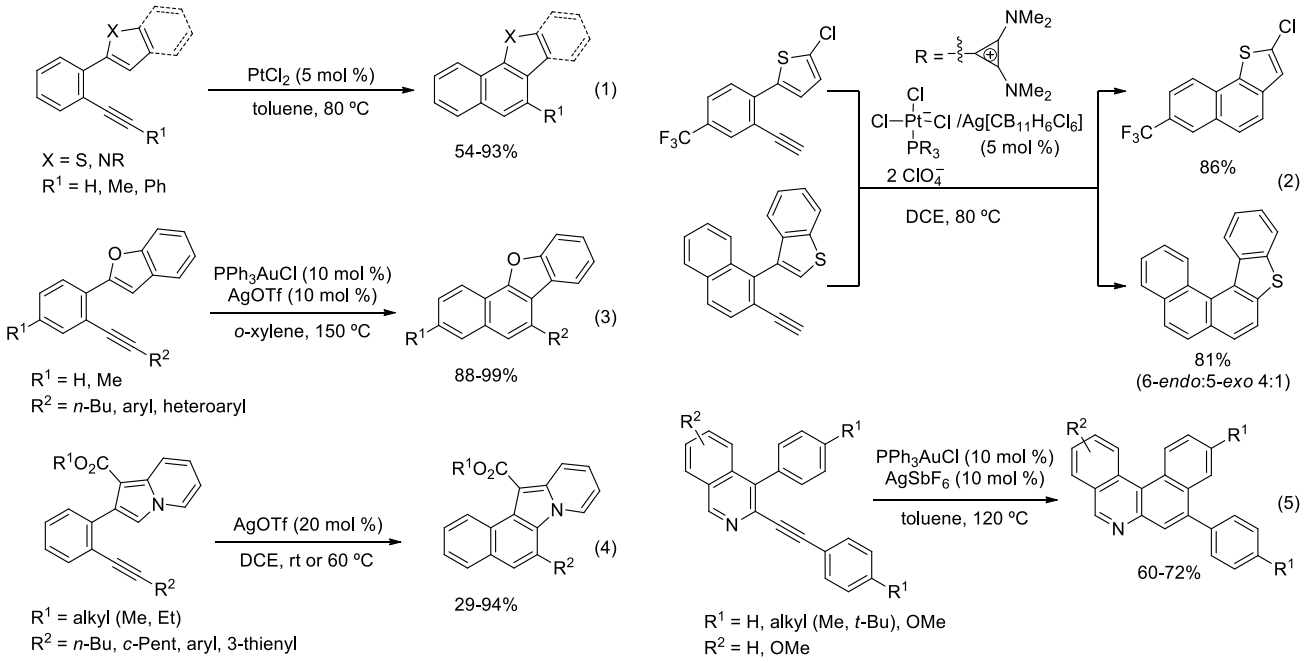
SCHEME 8. Cycloaromatization of *o*-(ethynyl)biphenyls with highly π-acidic-metal complexes





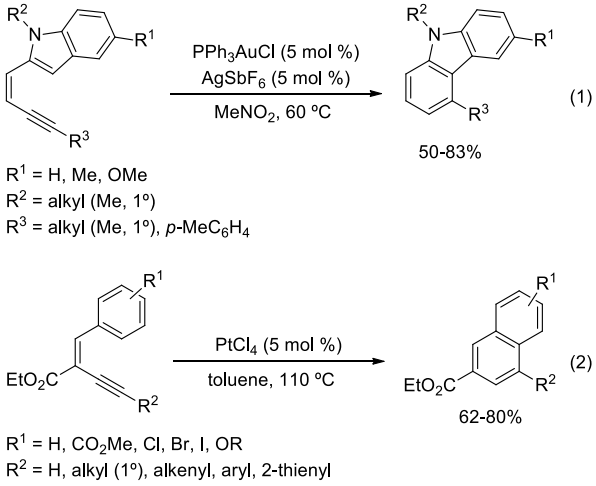
As pointed out in the pioneer work of Dankwardt and further demonstrated in the reports by Fürstner,[25,26] Alcarazo,[60] and, more recently, Alabugin[63] and Kim,[64] 1,3-dien-5-ynes where the terminal double bond is forming part of a heteroaromatic ring are also efficiently cycloaromatized, either under platinum, gold or silver catalysis, leading to polycyclic heteroaromatic compounds (Scheme 9, eq. 1-4). In these reactions the cycloaromatized isomer is generally obtained with total or very high selectivity, although in some particular cases minor amounts of the corresponding 5-*exo* adduct are also formed. Moreover, a related gold-catalyzed cycloaromatization of 1,3-dien-5-ynes where the central double bond is included in an isoquinoline moiety allows the synthesis of benzo[*a*]phenanthridines in good yields (Scheme 9, eq. 5).[65]

SCHEME 9. Cycloaromatization of *o*-(alkynyl)heterobiaryls



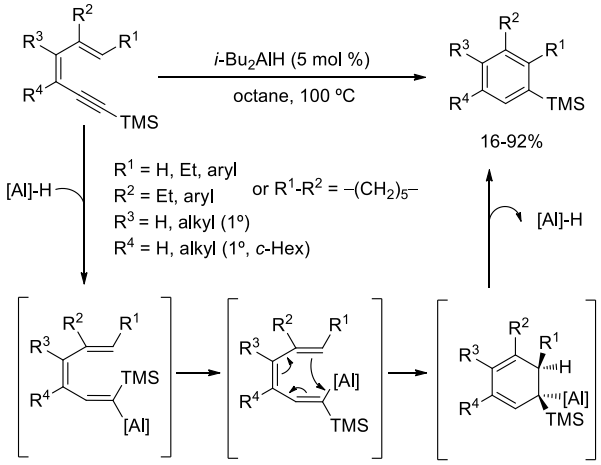
Additionally, 1,3-dien-5-ynes in which the central double bond is not forming part of an aromatic ring are also suitable substrates for cycloaromatizations via π-coordination of the alkyne to the metal complex.[66] Thus, 1,3-dien-5-ynes in which the terminal olefin belongs to an indole ring have been used as substrates in an efficient route for the synthesis of carbazoles under gold-catalysis (Scheme 10, eq. 1).[67] Moreover, naphthalene formation by $PtCl_4$-catalyzed cycloaromatization of aryl-enynes has been described (Scheme 10, eq. 2).[68]

SCHEME 10. Cycloaromatization of 1-[(hetero)aryl]-1-en-3-ynes



Following a completely different mechanism to those reported so far, Miura has recently reported an aluminum promoted cycloaromatization of 1,3-dien-5-ynes with a trimethylsilyl substituent in the triple bond (Scheme 11).[69] The cyclization, that is initiated by hydroalumination of the triple bond and proceeds by a 6π-electrocyclization, gives rise regioselectively to benzenes with up to five different substituents, although in variable yields and with high dependence on the substitution pattern. For some particular substrates different reaction pathways including loss or rearrangements of certain groups are observed.

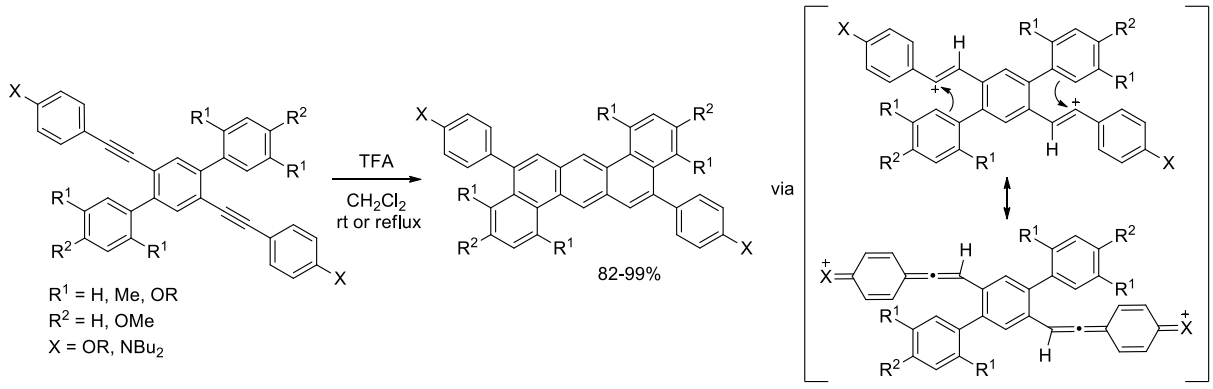
SCHEME 11. DIBAL-H promoted cycloaromatization of silylated 1,3-dien-5-ynes



2.1.2. Acid and base promoted/catalyzed cycloaromatizations. Although catalysis with metal complexes has been, as shown above, the most widely used approach for promoting the cycloaromatization of 1,3-dien-5-ynes under useful reaction conditions and with high efficiencies, some metal free procedures

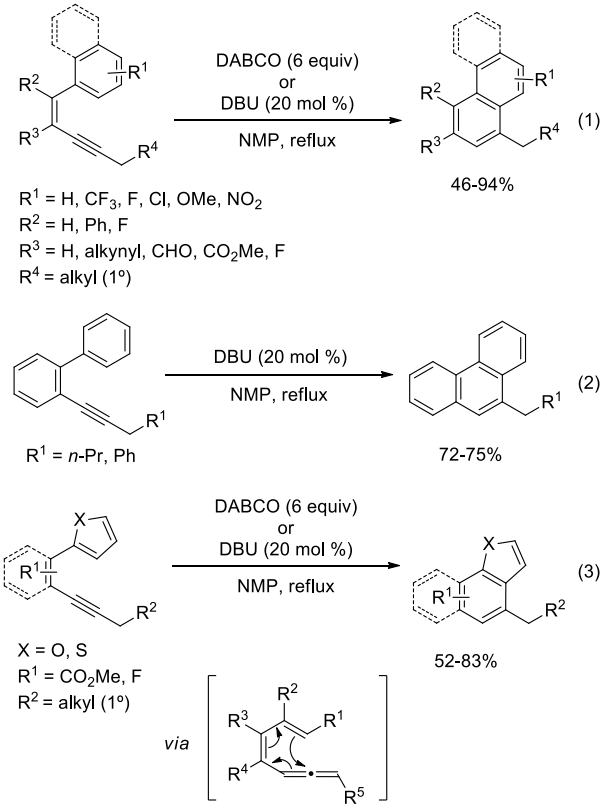
based on activation either under acidic or basic conditions have also been reported. Thus, Swager has developed a convenient TFA-promoted cycloaromatization that has been applied for the synthesis of fused polycyclic aromatic systems.[70,71,72,73,74] The transformation is proposed to be triggered by alkyne protonation, and is therefore limited to substrates having electron-rich aryl groups as substituents in the triple bond, able to stabilize by resonance the positive charge generated upon protonation (Scheme 12).

SCHEME 12. Acid-promoted cycloaromatization of *o*-(alkynyl)biaryls



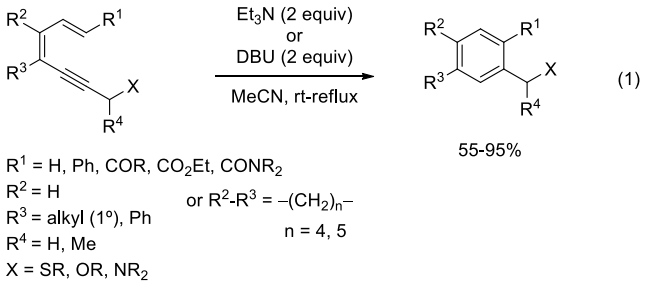
On the other hand, base-promoted cycloaromatizations are essentially based on alkyne to allene isomerization under basic conditions of 1,3-dien-5-ynes having a CH_2R group at the triple bond, and subsequent 6π-electrocyclization of the generated allene-diene (Scheme 13). Thus, Burton reported in 2006 the DABCO-promoted or DBU-catalyzed synthesis of diverse naphthalenes, including fluoro- and alkoxycarbonyl-substituted ones, from the corresponding 1-aryl-1-en-3-ynes (Scheme 13, eq. 1).[75,76,77] He has also extended this methodology to the synthesis of phenanthrenes by cycloaromatization of *o*-(alkynyl)biphenyls[77] (Scheme 13, eq. 2) and of benzo[*b*]furanes and benzo[*b*]thiophenes from 1-heteroaryl-1-en-3-ynes (Scheme 13, eq. 3).[78] Although high yields are usually obtained in these reactions, quite harsh conditions are required. The base-mediated cycloaromatization has been applied to the synthesis of the alkaloid tylophorine,[79] coronene derivatives acting as telomerase inhibitors,[80] angular-shaped anthradiselenophenes[81] and naphthodithiophenes[82] with promising optoelectronic applications, thienoacenes[53] and ethene-bridged terthiophenes.[83]

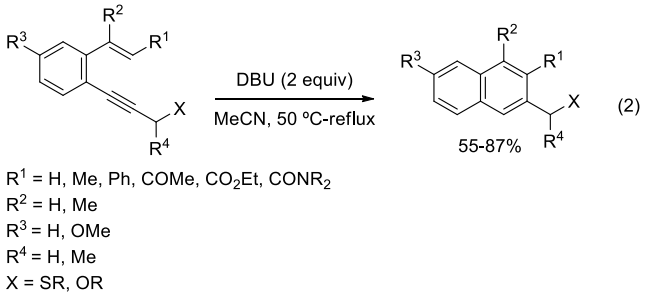
SCHEME 13. Base-mediated cycloaromatization of various 1,3-dien-5-ynes



More recently, Zhou has described a base-promoted cycloaromatization under milder reaction conditions, by using as starting materials 1,3-dien-5-ynes that have a heteroatom at the propargylic position, which favors the alkyne-allene cycloisomerization (Scheme 14, eq. 1, 2). Either sulfur,[84,85] oxygen[85] or nitrogen[85] substituents are suitable for promoting this transformation.

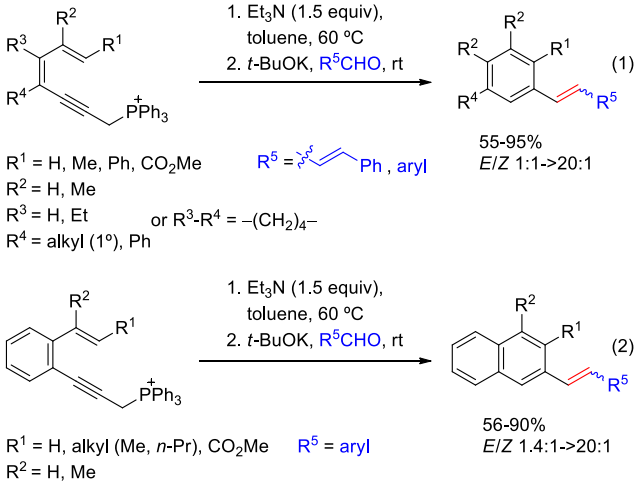
SCHEME 14. Base-promoted cycloaromatization of activated 1,3-dien-5-ynes





Moreover, the use of 1,3-dien-5-ynes with a phosphonium salt as substituent of the triple bond allows both for the activation of the substrate for the base-promoted cyclization and for further functionalization of the cyclized products by a *one-pot* Wittig reaction (Scheme 15).[86]

SCHEME 15. Base-promoted *one-pot* synthesis of vinylbenzenes and vinylnaphthalenes from dienynyl phosphonium salts



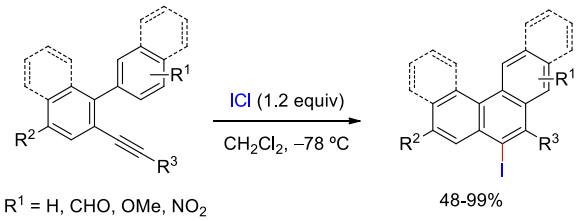
2.2. 1,6-Cycloaromatizations involving additional transformations

This section includes those reactions where a cycloaromatization involving all the six carbon atoms of the dienyne backbone takes place, as in the previous section, but in which additional transformations, such as

incorporation of new moieties or migration or loss of existing groups occur with the cyclization event. Therefore, the structure of the final product differs from this that would come from a "conventional" cycloaromatization in the number and/or in the position of the substituents.

2.2.1. Cycloaromatizations accompanied by further functionalization. ***Halocycloaromatizations.*** One of the most relevant transformations falling in this section are halocycloaromatizations, which are based on the activation of the triple bond by coordination of a halogen atom. This resambles what has been commented above about metal-catalyzed transformations, but differs in the fact that the halogen atom is finally incorporated in the cyclized product, contrary to the metal moiety that is used in a catalytic amount, as protodemetalation yields the final product and regenerates the catalytic species. In this sense, Swager, in his previously commented reports about acid-promoted cycloaromatizations,[70,71,72,73] also reported the use of Barluenga's reagent, IPy_2BF_4, as promoter of the corresponding iodocycloaromatizations. However, as in the case of the acid-promoted reaction, the scope of this transformation is limited to substrates having electron-rich aryl groups directly linked the triple bond. In 2004 Larock first reported an efficient iodocycloaromatization of *o*-(alkynyl)biaryls using ICl as promoter (Scheme 16).[87,88] These reactions take place with good yields and broad substrate scope including substituents of different electronic nature at the triple bond. Nevertheless, direct iodochlorination of the acetylene occurs as secondary reaction in particular examples, and this pathway is the only one observed for alkyl or TMS substituted alkynes. In addition, other sources of electrophile, such as $I_2/NaHCO_3$, NBS in the presence of silica gel or *p*-$O_2NC_6H_4SCl$ can also be used for the cycloaromatization.

SCHEME 16. Iodocycloaromatizations of *o*-(alkynyl)biaryls

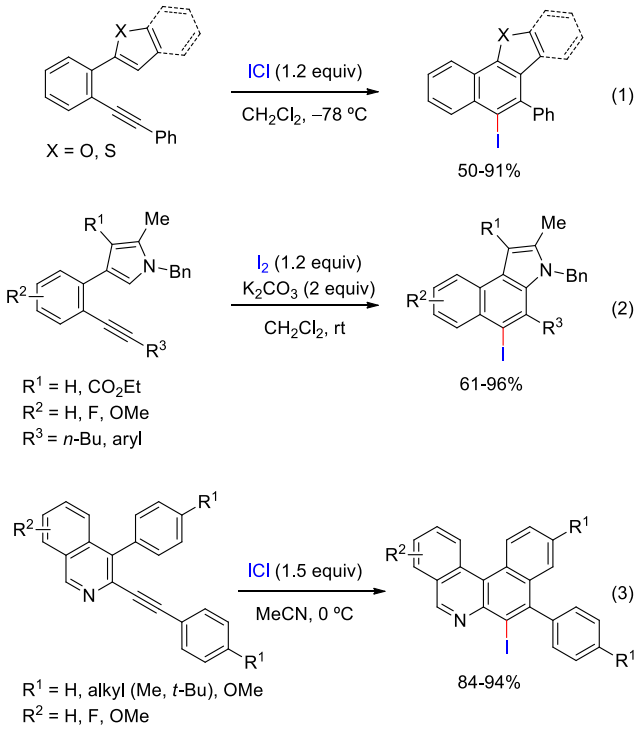


48-99%

R^1 = H, CHO, OMe, NO_2
R^2 = H, NO_2
R^3 = CH_2TMS, alkenyl, aryl, heteroaryl

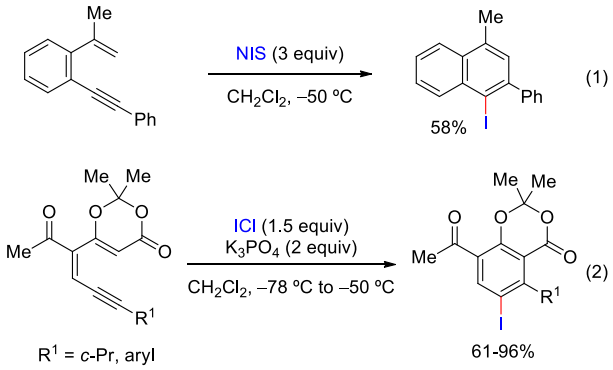
This methodology can also be applied for the iodocycloaromatization of *o*-(alkynyl)heterobiaryls (Scheme 17, eq. 1). In the same way, 3*H*-benzo[*e*]indoles have been synthesized by I_2-promoted iodocyclization of 4-(2-alkynylaryl)pyrroles (Scheme 17, eq. 2),[89] and 7-iodo-8-aryl-benzo[*a*]phenanthridines have been prepared by ICl-promoted cycloaromatization of 4-aryl-3-alkynylisoquinolines (Scheme 17, eq. 3).[65]

SCHEME 17. Iodocycloaromatizations of *o*-(alkynyl)heterobiaryls



Moreover, Kirsch has described a single example of a NIS triggered iodocycloaromatization of an *o*-(alkynyl)styrene (Scheme 18, eq. 1),[90] and Barrett has reported a related procedure for the synthesis of 4*H*-1,3-benzodioxin-4-ones from a particular type of 1,3-dien-5-ynes employing ICl (Scheme 18, eq. 2).[91] The scope of this iodobenzannulation is limited, as reactions fail with substrates bearing at the triple bond alkyl, silyl and electron-deficient or *ortho*-substituted aryl groups whereas the iodoarene obtained from a dienyne with a thienyl group at the acetylene was also iodinated at the heterocycle.

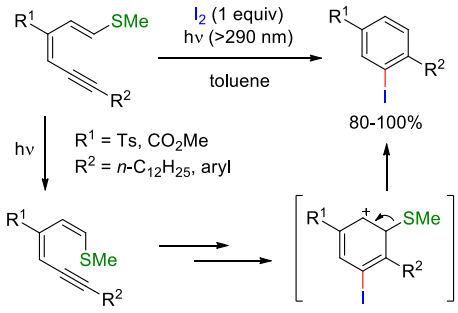
SCHEME 18. Iodocycloaromatizations of α-methyl-*o*-(phenylethynyl)styrene and other particular 1,3-dien-5-ynes



Notably, as in the case of metal-catalyzed cycloaromatizations, the iodocycloaromatization of 1,3-dien-5-ynes has been widely applied, mainly in the synthesis of PAHs.[92,93,94,95,96,97,98,99]

A particular case of iodocycloaromatization is the one of 1-(methylthio)-1,3-dien-5-ynes described by Ogura.[100] These substrates experiment a cycloaromatization with incorporation of iodine and concomitant loss of SMe group (Scheme 19). The reaction is accelerated by UV irradiation, which induces an initial *trans* to *cis* isomerization yielding a more reactive dienyne for the iodine promoted cyclization step. Finally, after the cyclization takes places by attack of the olefin over the iodine-coordinated alkyne, the aromatization is achieved by loss of the methylthio group, instead of the proton that would lead to a typical iodocycloaromatization product. Iodobenzenes are obtained in high yields with this methodology, although a narrow scope is described.

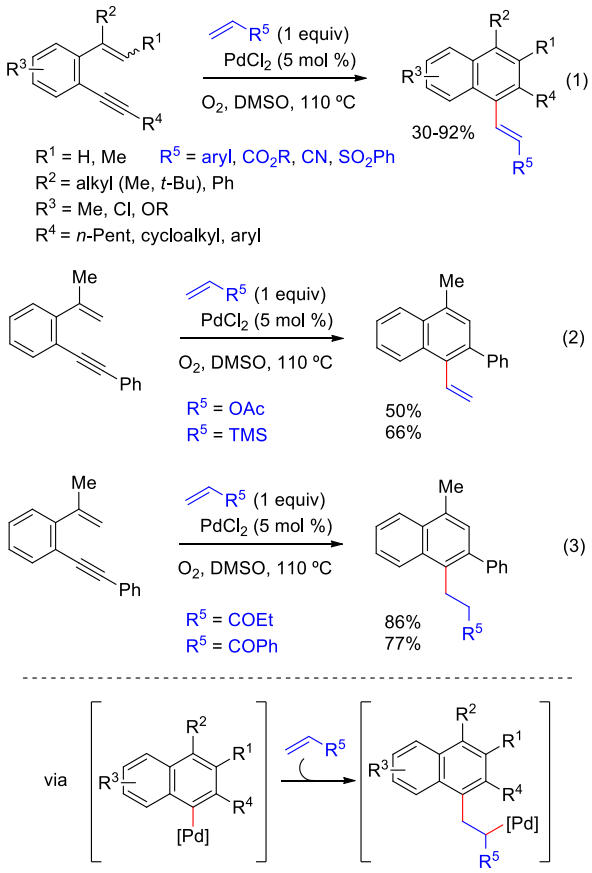
SCHEME 19. Iodocycloaromatizations of 1-(methylthio)-1,3-dien-5-ynes



Functionalization of aryl-metal/halo intermediates. The aryl-metal complexes generated as

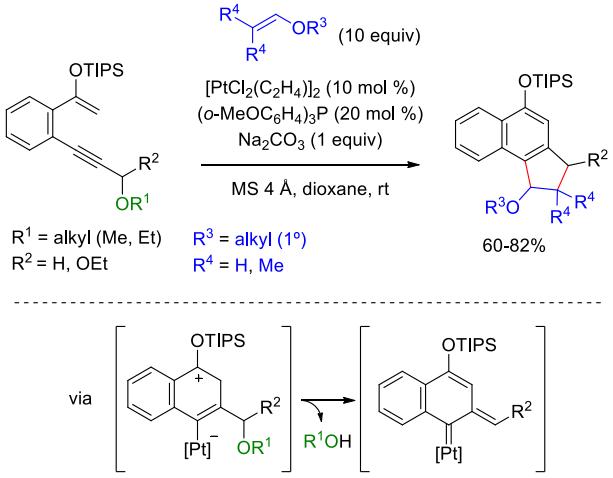
intermediates in conventional metal-catalyzed cycloaromatizations can be trapped *in situ* with different reagents instead of experimenting a protodemetalation as in the examples commented so far. In this way a door is opened for the preparation of highly functionalized aromatic rings. Thus, Loh, has described the synthesis of (alkenyl)naphthalenes by cycloaromatization of *o*-(alkynyl)styrenes in the presence of an olefin and catalytic amounts of $PdCl_2$ under an oxygen atmosphere (Scheme 20, eq. 1).[101] The authors suggest a mechanism initiated by nucleophilic attack of the olefin onto the Pd-coordinated triple bond, as proposed for metal-catalyzed "conventional" cycloaromatizations. However, now this intermediate, instead of protodemetalation, experiences olefin insertion followed by β-hydride elimination, generating the final (alkenyl)naphthalene product and Pd(0), which is reoxidized to the catalytically active Pd(II) species by molecular oxygen. The reaction displays a wide scope both at the dienyne moiety and the external olefin, which encompasses styrenes of varied electronic nature and acrylates and related compounds, although the reaction with vinyl phenyl sulfone provides low yield. An exception to this quite general behavior is found in the use of olefins with a TMS or OAc substituent which lead to vinyl substituted naphthalenes (Scheme 20, eq. 2), and vinyl ketones, which generate naphthalenes with an alkyl instead of an alkenyl group (Scheme 20, eq. 3).

SCHEME 20. Synthesis of (alkenyl)naphthalenes by palladium-catalyzed cycloaromatization of *o*-(alkynyl)styrenes in the presence of olefins



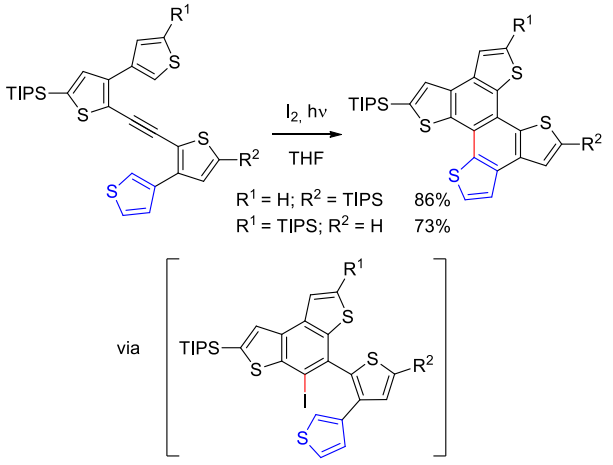
Moreover, cycloisomerization in the presence of a platinum catalyst of *o*-(alkynyl)styrenes in which the olefin is forming part of a silyl enol ether and the triple bond has an (alkoxy)methyl substituent leads, via the usual nucleophilic attack of the alkene to the metal-coordinated alkyne, followed by metal-assisted elimination of alcohol, to α,β-unsaturated carbene complexes (Scheme 21). These intermediates can be trapped *in situ* by [3+2] cycloaddition with vinyl ethers, thus leading to the efficient synthesis of naphthol derivatives fused to a five-membered ring.[102] Narrow scope has been described for this transformation, which is included in a more general study of [3+2] cycloadditions of platinum carbenes generated from different propargylic ethers with vinyl ethers.

SCHEME 21. Synthesis of five-membered-ring-fused naphthalenes by platinum-catalyzed cycloaromatization of *o*-(alkynyl)styrenes in the presence of sylyl enol ethers



On the other hand, two particular compounds with a tetrathienonaphthalene core have been synthesized by a double cyclization of bis(bithienyl)acetylenes under photoirradiation in the presence of iodine (Scheme 22).[103] The authors propose an initial conventional halocyclization followed by a second electrocyclization promoted by the photoirradiation with concomitant loss of HI.

SCHEME 22. Synthesis of tetrathienonaphthalenes by iodine-promoted double cyclization

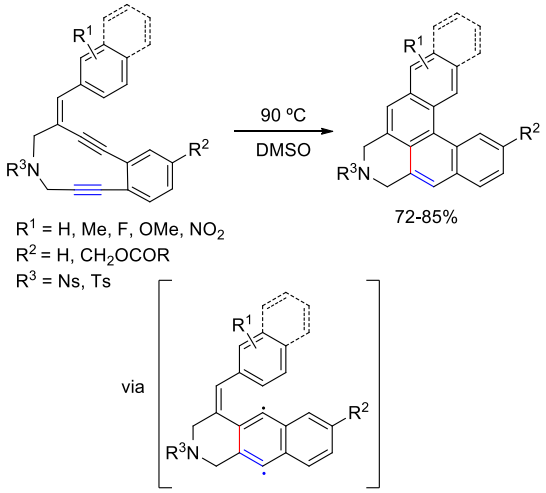


Reactions initiated by transformations over the alkyne or the alkene. The reactions commented so far in the present section have in common the fact that they are initiated by nucleophilic attack of the olefin on the alkyne activated by coordination of an electrophilic moiety, either a halogen or a metal. However, other

activation modes are also possible, in which either the alkyne or the alkene moiety of the dienyne are transformed before the cyclization takes place.

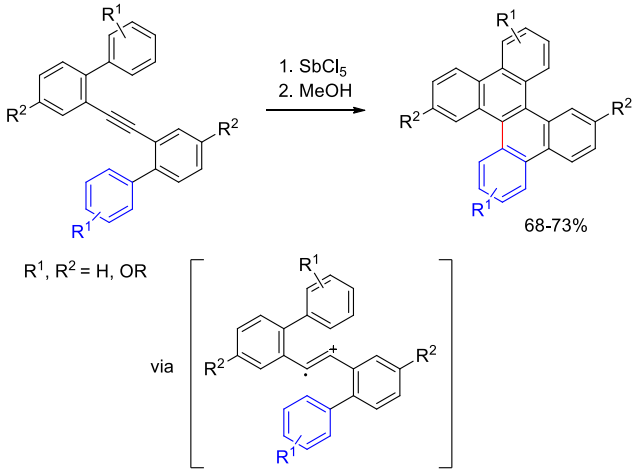
For example, Basak has described a polycyclization initiated by a Bergman cyclization of an enediyne moiety, which includes the alkyne of the 1,3-dien-5-yne, leading to a diradical that then cyclizes with the external aromatic ring of the initial 1-aryl-1-en-3-yne. In this way, heating of the substrates at 90 ºC in DMSO allows the synthesis of helicenes in high yields with a varied substitution at the external aromatic rings (Scheme 23).[104,105]

SCHEME 23. Synthesis of helicenes initiated by Bergman cyclization



Also based on the formation of radical intermediates, in 2001 Swager demonstrated with a few examples the viability of using $SbCl_5$ as an oxidant for promoting a double cyclization in bis(biaryl)alkynes.[106] The transformation is proposed to be initiated by a one-electron oxidation of the triple bond, generating a cation radical that suffers subsequent electrophilic and radical cyclizations leading to two new hexasubstituted benzene rings (Scheme 24). The global outcome of the reaction is analogous to that shown in Scheme 22.

SCHEME 24. Oxidative double-cyclization of bis(biaryl)alkynes



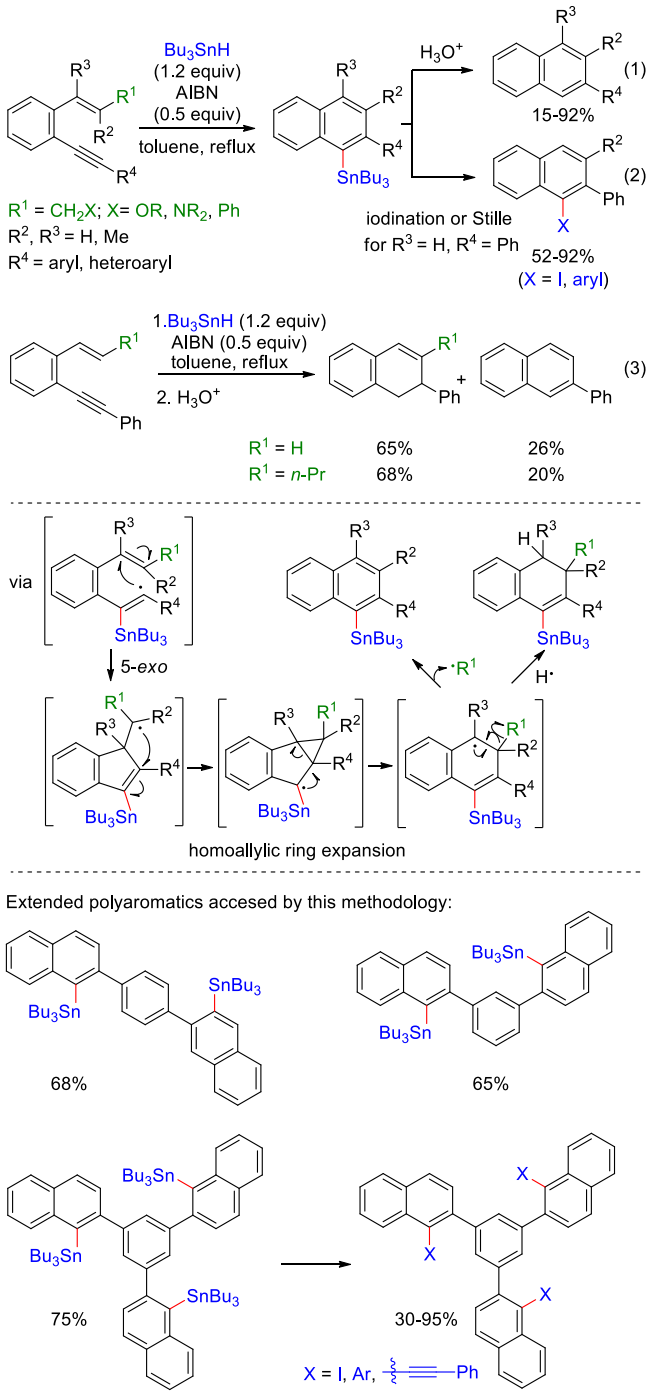
It is worth to note that in these last transformations the additional substituent is introduced intramolecularly. Other particular examples of cycloaromatizations initiated by intramolecular reactions over the alkyne, other than nucleophilic attack of the olefin, have also been described.[107,108] Nevertheless, transformations initiated by intermolecular reactions over the alkyne are more common.

For example, and also in the field of radical mediated processes, Alabugin has developed a synthesis of tin-substituted naphthalenes by Bu_3Sn-mediated radical cyclization/C–C fragmentation of *o*-(alkynyl)styrenes having a CH_2X (X= OR, NR_2 or Ph) substituent at the alkene terminus (Scheme 25, eq. 1, 2).[109,110,111] Interestingly, a critical influence of the olefin substitution in the outcome of the cyclization is observed, as the presence of radical-stabilizing groups leads to indene adducts (see Scheme 68), whereas a terminal alkene or one substituted with a simple alkyl, such as propyl, affords dihydronaphthalenes as major products (Scheme 25, eq. 3).

The authors propose that the naphthalene formation is initiated by addition of the stannyl radical to the internal carbon atom of the alkyne. Noteworthy, considering all possible additions to the alkyne or alkene moieties this one provides the least stable radical, but is the only one that evolves through a productive pathway. Then, a selective 5-*exo*-*trig* cyclization occurs followed by homoallylic ring expansion. Although the intermediate generated by this sequence is analogous to the one that would be directly generated by a formal initial 6-*endo* cyclization, experimental and theoretical investigations support the 5-*exo*

cyclization/homoallylic rearrangement pathway over the direct 6-*endo* cyclization pathway. The radical cascade leading to naphthalenes is concluded by a β-C–C bond scission. In the case of H or *n*-Pr substituents at the alkene this last fragmentation is less favoured, due to the lower stability of the radical leaving group, and H abstraction becomes the major pathway for the termination of the reaction giving rise to dihydronaphthalenes. On the other hand, for olefins with radical-stabilizing groups H abstraction ocurrs directly over the intermediate generated in the 5-*exo* cyclization step leading to indene derivatives (See Scheme 68). Besides the requisite of a CH_2X group in the olefin, the efficiency of the naphthalene synthesis is restricted to substrates with aryl groups of limited bulkiness at the acetylene, as simple reduction of the triple bond without cyclization occurs for *n*-butyl and 1-naphthyl substituted substrates. Interestingly, the obtained arylstannanes are usually hydrolyzed to yield the corresponding aromatic compounds in good yields (Scheme 25, eq. 1), but further functionalization of the tin moiety allows the synthesis of highly functionalized naphthalenes (Scheme 25, eq. 2). Moreover, the use of appropriate starting materials containing several 1,3-dien-5-yne moieties in their structure provides a method for the preparation of extended polyaromatics.

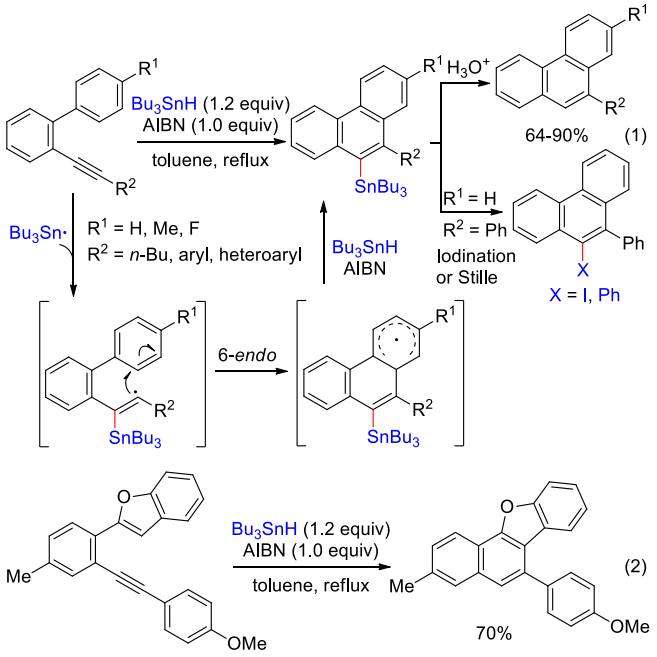
SCHEME 25. Synthesis of naphthalenes from β-alkyl-substituted *o*-(alkynyl)styrenes by radical cascade 5-*exo*-trig cyclization/homoallyl ring expansion/C–C bond scission



In a parallel study, the same authors have described that the combination Bu_3SnH/AIBN in stoichiometric amounts promote the oxidative radical cyclization of *o*-(alkynyl)biphenyls to produce phenanthrenes (Scheme 26, eq. 1).[112] These reactions occur with total selection displaying good yields and broad scope that also

includes the preparation of fused-heterocyclic adducts (Scheme 26, eq. 2). A mechanism for this transformation, supported by theoretical calculations, suggests again an initial regioselective alkenyl radical formation followed in this case by a 6-*endo* cyclization to build the new ring. Then, an aromatization triggered by a second Bu_3Sn radical would provide the final products. As in the case of the naphthalene synthesis depicted in Scheme 25, the intermediate arylstannanes are usually hydrolyzed to the corresponding aromatic compounds but can also be subjected to further functionalization, although yields are not reported for these transformations.

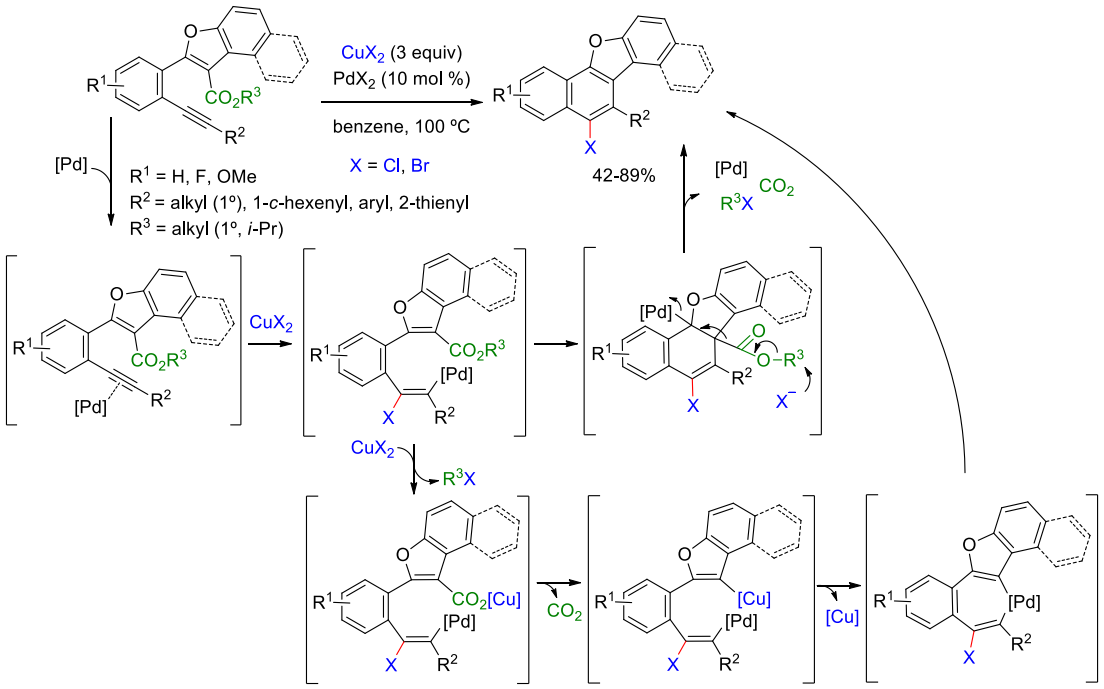
SCHEME 26. Synthesis of phenathrenes from *o*-(alkynyl)byphenyls by regioselective oxidative radical cyclization



Considering non-radical reactions, Li has described a formal halocyclization/decarboxylation of 2-(*o*-alkynylphenyl)-3-(alkoxycarbonyl)benzofurans initiated by addition of an halide, coming from a CuX_2 species, to the triple bond activated by coordination of a Pd complex (Scheme 27).[113] Then, an intramolecular Heck-like reaction followed by decarboxylative β-carbo-elimination gives rise to the corresponding 5-halo-benzo[*b*]naphtho[2,1-*d*]furans. Alternatively, hydrolysis of the ester group of the initial intermediate followed by decarboxylation, intramolecular transmetallation and reductive elimination could also explain the formation

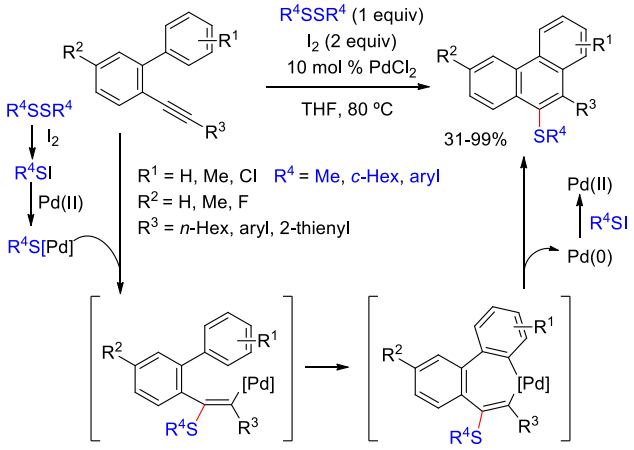
of the final products. The reaction tolerates a wide range of substituents at both the arene and the acetylene of the starting dienyne, affording the polyheterocyclic adducts in moderate to good yields. In this sense, lower yields are obtained for substrates bearing electron-defficient arenes, alkyl or alkenyl groups at the triple bond.

SCHEME 27. Synthesis of 5-halo-benzo[*b*]naphtho[2,1-*d*]furans by palladium-catalyzed cycloaromatization with concomitant decarboxylation and halogen incorporation



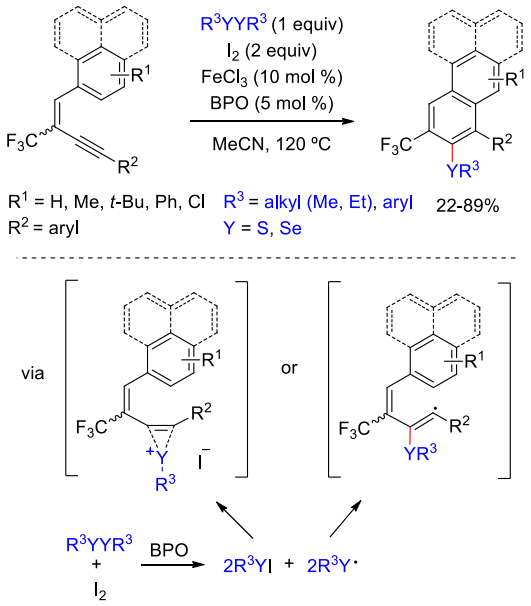
Also initiated by a palladium-catalyzed addition over the alkyne is the high-yielding synthesis of 9-sulfenyl phenanthrenes by cycloaromatization of *o*-(alkynyl)biphenyls in the presence of aromatic or aliphatic disulfides (Scheme 28).[114] Only reactions with dicyclohexyldisulfide or with dienynes possessing electron-deficient substituents either at the external arene or at the triple bond afford the polycyclic adducts in moderate yields. The reaction is mediated by iodine, and the use of a palladium-catalyst has proved to be necessary for an efficient transformation. It is proposed that RSI is generated from interaction of iodine and disulfide, and this active species reacts with $PdCl_2$ affording RSPdX. Alkyne insertion generates an alkenylpalladium intermediate, which upon C–H insertion into the aryl group and further reductive elimination yields the sulfenyl phenanthrene and regenerates the catalytic species. The intermediacy of an iodo-cycloaromatized product in the process is ruled out based on experimental observations.

SCHEME 28. Synthesis of 9-sulfenyl phenanthrenes by palladium-catalyzed iodine-promoted reaction of *o*-(alkynyl)biaryls and disulfides



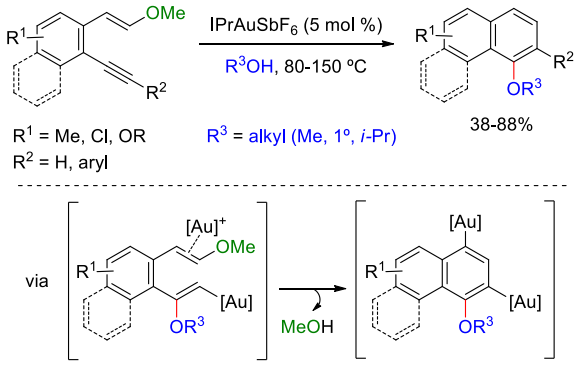
Later, the same authors reported an analogous global transformation for the synthesis of polysubstituted naphthalenes (Scheme 29).[115] In this case, the conditions previously reported for the cycloaromatization of *o*-(alkynyl)biphenyls in the presence of disulfides lead to low yields, but a screening of different catalysts and additives allowed the finding of an efficient method using an iron catalyst and benzoyl peroxide (BPO) as a radical initiator in catalytic amounts. As in their previous report, inferior yields are observed in reactions where electron-withdrawing groups are located either at the disulfide or at the arene or the acetylene of the substrate. Based on experimental observations, a different mechanism is proposed to operate under these conditions. The reaction would be initiated by addition to the triple bond of a RSI species, generated in situ by reaction of the disulfide with iodine in the presence of BPO. Then, an iron catalyzed cyclization occurs, leading to the final product after deprotonation. On the other hand, a free radical pathway starting with the addition of RS· to the alkyne can not be ruled out. Moreover, this methodology can also be extended to the use of diselenides as electrophiles.

SCHEME 29. Synthesis of polysubstitued naphthalenes by iron/BPO-catalyzed cycloaromatization of 1-aryl-1-en-3-ynes in the presence of disulfides/diselenides



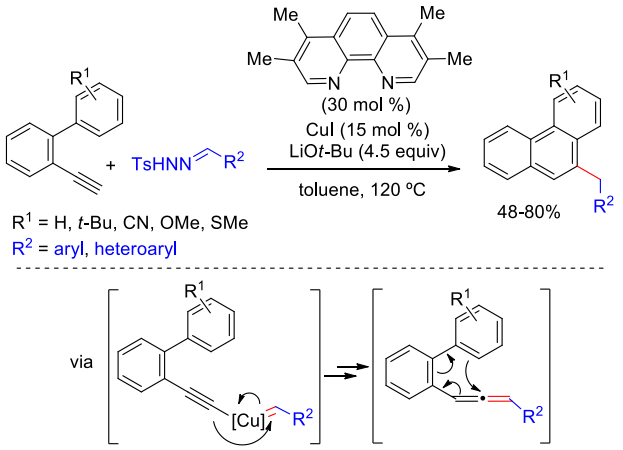
Liu and Cheng have described a cycloaromatization initiated by intermolecular addition of an alcohol, also used as solvent, to the triple bond of *o*-(alkynyl)styrenes with the double bond forming part of a methyl enol ether. The authors propose a mechanism for substrates having a terminal alkyne in which addition of the alcohol leads to a dienolether intermediate, which experiments a cyclization with concomitant elimination of methanol, finally giving rise to alkoxy naphthalenes in good yields although with limited scope (Scheme 30).[116] For example, no reaction occurs with *t*-butyl, benzyl or allyl substituted alcohols, or with *o*-(alkynyl)styrenes having strong electron-withdrawing substituents, such as NO_2 or F, in the aryl ring. Interestingly, a different reaction pathway is observed when only two equivalents of MeOH in toluene as solvent are used; in this case, an indene derivative coming from direct attack of the olefin to the alkyne is obtained.

SCHEME 30. Synthesis of (alkoxy)naphthalenes by gold(I)-catalyzed reaction of β-OMe-*o*-(alkynyl)styrenes and alcohols



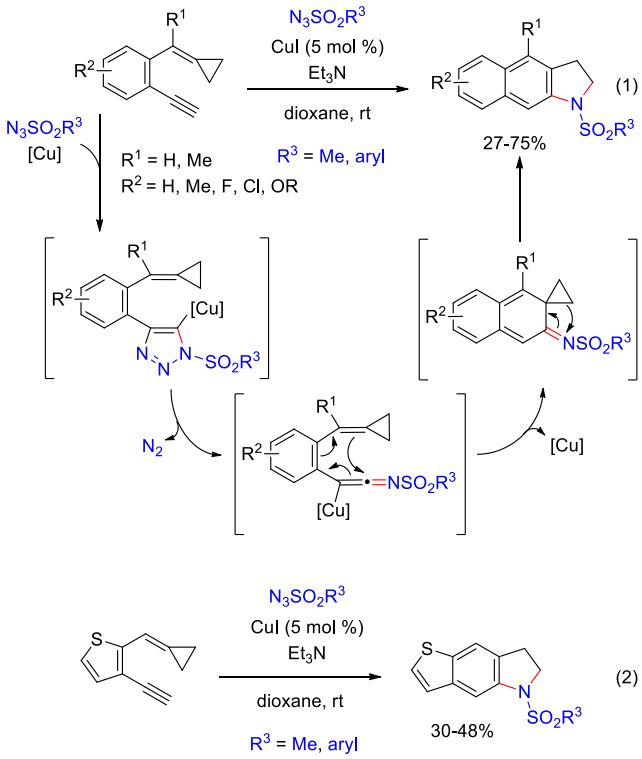
Moreover, phenanthrenes can be synthesized by copper-catalyzed reaction between aromatic *N*-tosylhydrazones and *o*-(ethynyl)biaryls (Scheme 31).[117] The transformation starts with the reaction between the hydrazone and the alkyne moiety to generate an *o*-(allenyl)biaryl species *via* a copper carbene. This intermediate evolves through a 6π-electrocyclization followed by isomerization to form the corresponding phenanthrenes in good yields and very broad scope. The *N*-tosylhydrazone can either be preformed or generated in situ in a *one-pot* protocol, and no influence of the substitution or electronic nature of its arene ring is observed, whereas reactions with aliphatic hydrazones mainly afford non-cyclized allene derivatives accompanied with other products. Moreover, a wide range of groups are tolerated at the external arene moiety and, notably, completely selective cyclizations through the sterically favored position are observed for unsymmetrically substituted biphenyls.

SCHEME 31. Synthesis of phenanthrenes by copper-catalyzed reaction of *o*-(alkynyl)biaryls in the presence of hydrazones



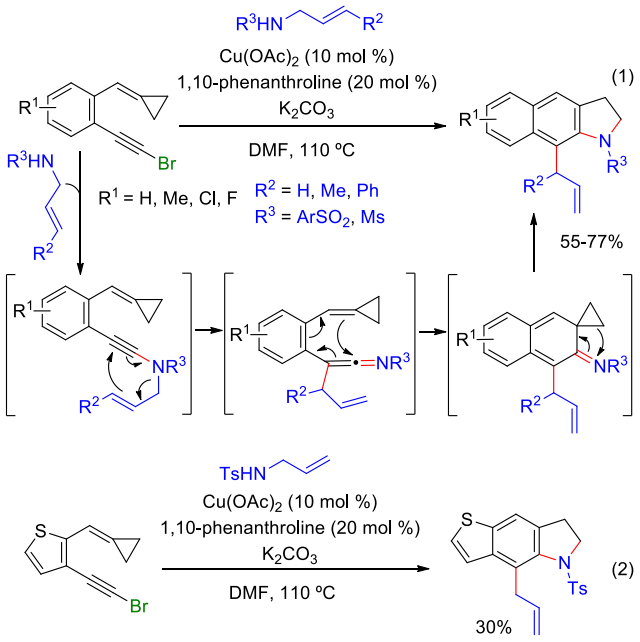
On the other hand, Wu has reported a couple of transformations initiated by pericyclic reactions on the alkyne. Thus, the copper-catalyzed reaction of particular *o*-(ethynyl)styrenes, in which the external double bond belongs to a methylenecyclopropane moiety, with sulfonyl azides is proposed to be initiated by copper-catalyzed [3+2] cycloaddition of the alkyne and the azide affording a triazol intermediate (Scheme 32, eq. 1). This triazol would evolve by nitrogen extrusion generating a metalated ketenimine that experiences a 6π-electrocyclization and leads, after a rearrangement involving cyclopropane ring expansion, to the final fused indoline derivatives. These tricyclic adducts are obtained generally in good yields that slightly drop in reactions involving electron-deficient azides or dienynes having halogens at the benzene ring.[118] Related tiophene derivatives also experience this transformation, although low yields are obtained (Scheme 32, eq. 2). Moreover, only trace amounts of cycloaromatized product are observed in the reactions of the corresponding pyridine or quinoline derivatives.

SCHEME 32. Synthesis of indolines by copper-catalyzed reaction of 1-(cyclopropylidenemethyl)-2-ethynylbenzenes and azides



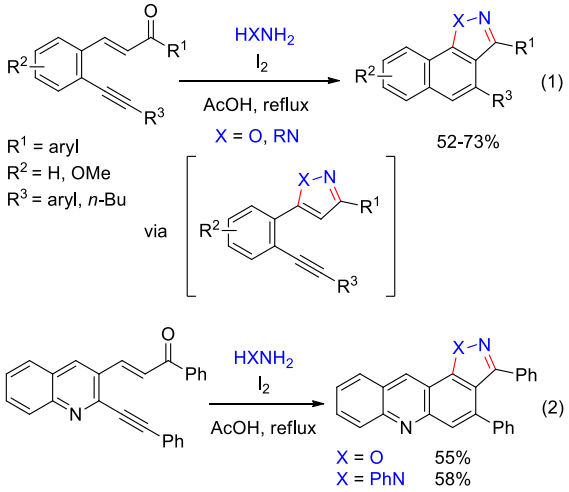
The same authors have described a related synthesis of 7-allyl indoline derivatives also based on a 6π−electrocyclization of a ketenimine intermediate, although now this intermediate is generated in a different way that allows for additional functionalization at position 7 of the final indoline structure (Scheme 33, eq. 1). Starting from *o*-(alkynyl)styrenes structurally similar to the previous ones, but with a bromine-substituted triple bond, the authors propose an initial copper-catalyzed coupling with an allylamine generating *in situ* a new *o*-(alkynyl)styrene. Aza-Claisen rearrangement would then lead to the ketenimine intermediate over which the cyclization takes place.[119] Broad scope at the arene and the allylamine is observed and, as in the previous report, a thiophene derivative reacts in the same fashion although with reduced yield (Scheme 33, eq. 2). Low yield is also achieved with *N*-allyl-*P*,*P*-diphenylphosphinic amide and, moreover, no reaction occurs when an electron-defficient sulfonyl allyl amine or *N*-allylbenzamide are employed as coupling partners.

SCHEME 33. Synthesis of 7-allyl indolines by copper-catalyzed reaction of 1-(cyclopropylidenemethyl)-2-(bromoethynyl)benzenes and amines



Cyclizations triggered by transformations over the terminal alkene of the dienyne have also been reported. Thus, the reaction of *o*-(alkynyl)chalcones with hydrazine derivatives or hydroxylamine in the presence of iodine in AcOH is proposed to start by oxidative cyclocondensation of the α,β-unsaturated ketone with the hydrazine or hydroxylamine. This initial transformation would lead to an *o*-(alkynyl)heterobiaryl adduct which cyclizes to give the final tricyclic products in moderate to good yields (Scheme 34, eq. 1).[120] The conversion of the intermediate into the final products represents a "conventional" acid catalyzed cycloaromatization. However, the overall transformation yielding naphtho[2,1-*d*]isoxazoles that occurs in *one-pot* from the starting *o*-(alkynyl)styrenes exemplifies a cycloaromatization with concomitant incorporation of an additional moiety. Regarding the scope, only reactions with a chalcone possessing a strong electron-defficient aryl ring at R^1 fail and, in addition, the analogous quinoline-fused indazole and benzoisoxazole can also be synthesized under the same reaction conditions starting with the appropriate dienyne (Scheme 34, eq. 2).

SCHEME 34. Synthesis of 1*H*-benzo[*g*]indazoles and naphtho[2,1-*d*]isoxazoles by iodine-promoted reaction of *o*-(alkynyl)chalcones and hydrazine derivatives

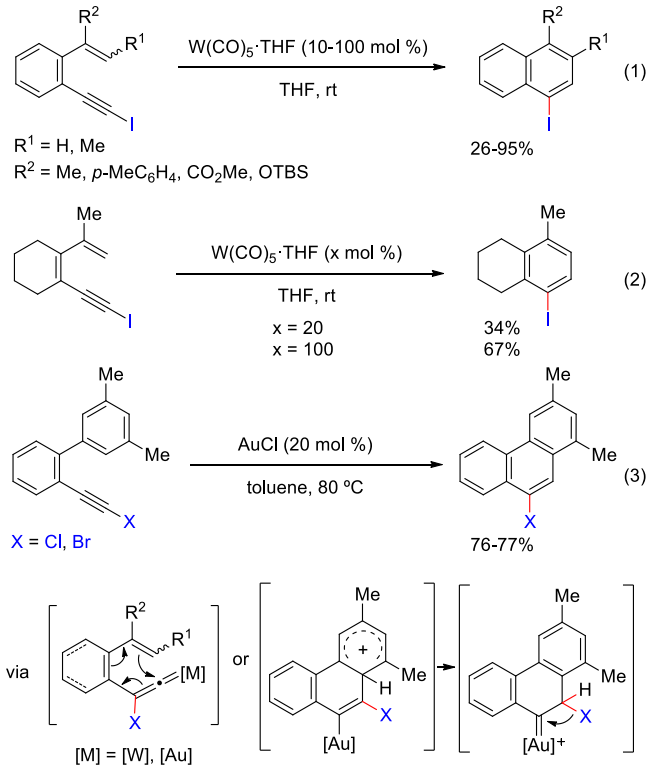


2.2.2. Cycloaromatizations accompanied by migration or loss of a substituent. Other transformations that can be taken out from the "conventional" cycloaromatization group are those which imply a migration step and therefore the position of the substituents in the final cycloaromatized product differs from the one that would be expected. The migrating group can be either a substituent of the triple bond or of the alkene. Moreover, loss of a subtituent of the dienyne system during the cycloaromatization event has also been observed in particular cases.

Migration of a substituent of the alkyne. Iwasawa described in 2002 that the reaction of 1,3-dien-5-ynes with an iodine substituent in the triple bond in the presence of $W(CO)_5 \cdot THF$ leads to cycloaromatization with concomitant formal 1,2-migration of the iodine atom (Scheme 35, eq. 1, 2).[121,122] As in the case of the $W(CO)_5 \cdot THF$ promoted cycloaromatization of *o*-(ethynyl)styrenes previously described by Iwasawa (see Scheme 2, eq. 2), the reaction is proposed to proceed via a vinylidene intermediate, that is now obtained by migration of the iodine atom. Good yields of the corresponding iodo-naphthalenes are obtained for certain α-substituted *o*-(iodoethynyl)styrenes as starting materials using catalytic amounts of the metal complex, whereas stoichiometric amounts are necessary in other cases to provide useful yields. During his studies about the metal-catalyzed synthesis of phenanthrenes by cycloaromatization of *o*-(alkynyl)biphenyls, Fürstner has

also observed a concomitant migration of chlorine or bromine for alkynes substituted with these halogen atoms when gold chloride is used as catalyst (Scheme 35, eq. 3).[26,123] The authors also propose a vinylidene intermediate for this transformation, which was initially supported by a teorethical analysis.[28] Nevertheless, later computational studies have demonstrated that a mechanism consisting in a 6-*endo* cyclization followed by consecutive 1,2-H/1,2-halo migrations cannot be ruled out.[124] As commented above, the cycloaromatization of these same substrates under In(III) catalysis efficiently leads to the products coming from a "conventional" cycloaromatization (see Scheme 7, eq. 1), which evidences the extreme influence that the catalytic species can exert in the outcome of the reaction.

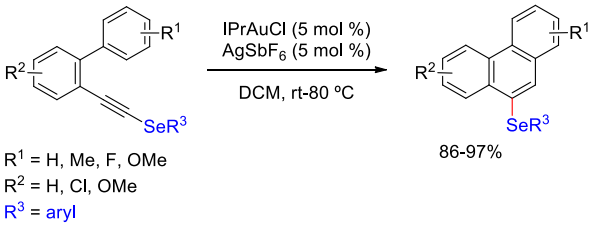
SCHEME 35. Cycloaromatization accompanied of halogen migration of 1,3-dien-5-ynes with halogen-substituted alkynes



Moreover, a cycloaromatization accompanied by migration of a selenyl group has been described.[125] As previously observed by Fürstner for the related *o*-(haloethynyl)biphenyls (Scheme 7, eq. 1), the cycloaromatization of *o*-(selenylethynyl)biphenyls proceeds through a conventional pathway, via cyclization over an alkyne-metal complex, when $In(OTf)_3$ is used as the catalyst.[125] However, under gold catalysis a

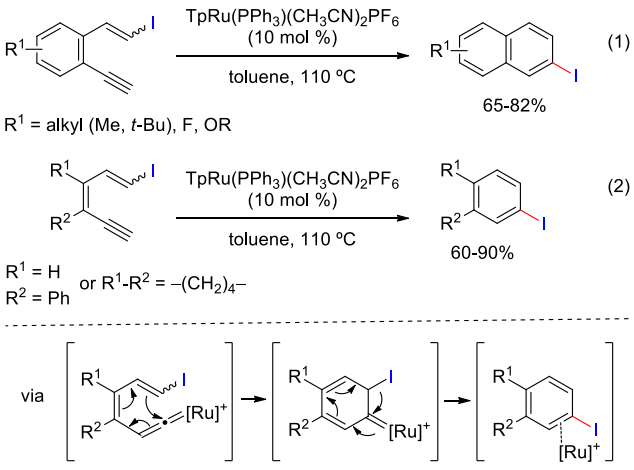
concomitant selenyl group migration takes place during the cycloaromatization event, presumably involving a vinylidene intermediate. In this way, selenylphenanthrenes with varied substitution at the external arene rings can be synthesized in high yields (Scheme 36).

SCHEME 36. Cycloaromatization accompanied of selenyl group migration of *o*-(selenylalkynyl)biphenyls



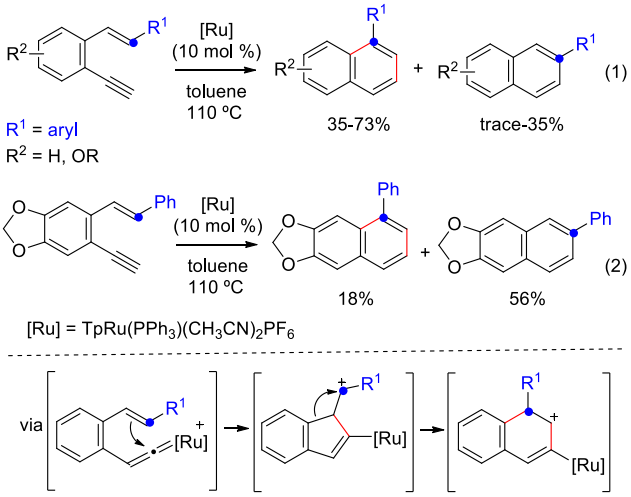
Migration of a substituent of the alkene. Liu reported in 2003 the ruthenium-catalyzed cyclization of 1,3-dien-5-ynes having a terminal acetylene and a β-iodo substituted olefin, which proceeds with a 1,2-migration of the halogen atom (Scheme 37, eq. 1, 2).[6] The reaction is proposed to start with a 6-*endo*-cyclization over a vinylidene intermediate, as usual in the ruthenium-catalyzed cycloaromatization of 1,3-dien-5-ynes having a terminal acetylene. However, in this case, a 1,2-iodo shift takes place in the generated carbene intermediate, instead of the common proton elimination. The same behavior is observed for β-bromo-derivatives, although low yields are obtained in this case.

SCHEME 37. Ruthenium-catalyzed cycloaromatization of 1,3-dien-5-ynes accompanied of iodo migration from the olefin



Moreover, the same authors have reported that certain β-aryl substituted *o*-(ethynyl)styrenes experiment a ruthenium-catalyzed cycloaromatization-1,2-aryl shift, although in this case the aryl group migrates to a different position than that observed for halogen atoms (Scheme 38, eq. 1, 2).[6] Nevertheless, this transformation is not selective, and significant amounts of products coming from a "conventional" cycloaromatization are also obtained, particularly for less electron-rich aryl substituents. The authors propose that the formal aryl-shift can be explained by an initial 5-*endo*-cyclization over the usual vinylidene intermediate, followed by a 1,2-C–C-bond-shift. This mechanism is supported by isotopic labelling of the carbon bearing the aryl group, which is found to be the one bearing the aryl group in the product as well.

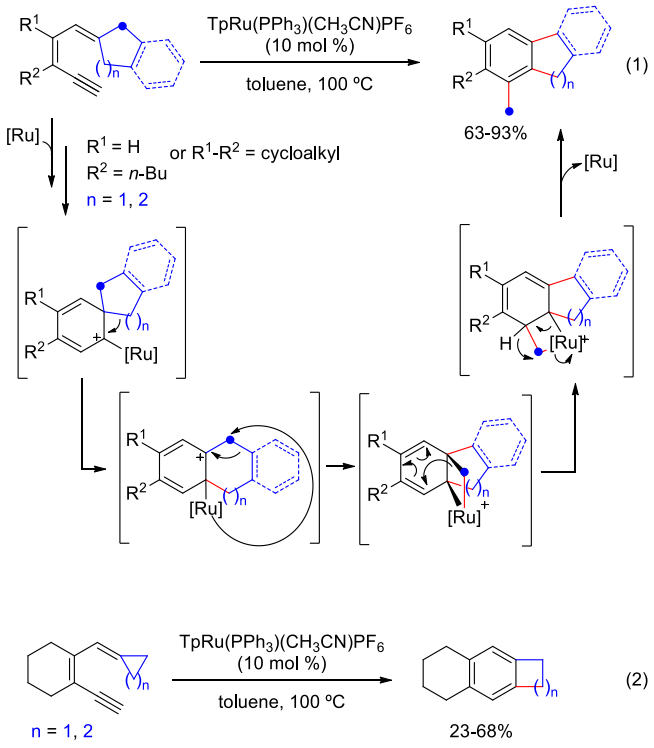
SCHEME 38. Ruthenium-catalyzed cycloaromatization of *o*-(ethynyl)styrenes accompanied of aryl migration from the olefin



Continuing with the studies on ruthenium-catalyzed cycloaromatizations of 1,3-dien-5-ynes, Liu has also described the use as starting materials of 1,3-dien-5-ynes with a cyclopentylidenyl or cyclohexylidenyl substituent at the terminal olefin.[126] The reaction yields benzene rings where a new C–C bond is apparently created between one of the α atoms of the cycloalkylidene and the internal carbon of the acetylene (Scheme 39, eq. 1). However a detailed mechanistic survey, supported by isotopic labelling, reveals that the transformation is in fact a common 1,6-cycloaromatization, but accompanied by migration of a methylene group from the cycloalkylidene moiety. The mechanism proposed by the authors starts with an

electrocyclization of an initially formed vinylidene intermediate, as usually proposed in the ruthenium-catalyzed cycloaromatization of 1,3-dien-5-ynes having terminal acetylenes. However, direct aromatization of the generated intermediate is not possible, due to the disubstitution in the terminal carbon of the olefin of the starting material and, therefore, this intermediate evolves by a 1,2-alkyl shift. Then, several rearrangements take place finally leading to the observed cycloaromatized products. Interestingly, the products coming from direct demetalation of the intermediate obtained after the initial 1,2-alkyl shift are formed when a smaller ring, such as cyclopropylidene or cyclobutylidene, is present in the starting materials, thus leading to final products where a cycloaromatization accompanied by ring expansion has taken place (Scheme 39, eq. 2).

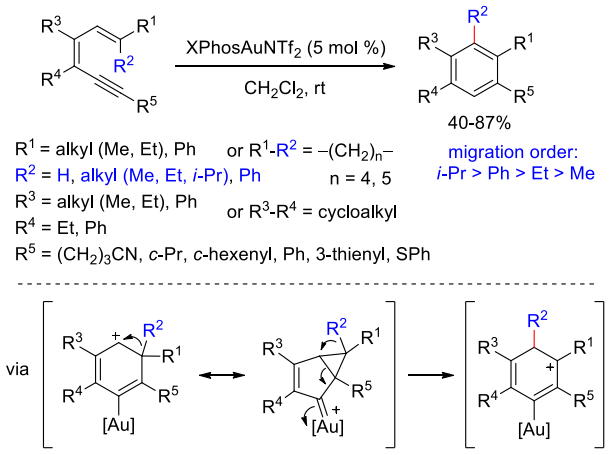
SCHEME 39. Ruthenium-catalyzed cycloaromatization of 1,3-dien-5-ynes with cycloalkylidene moieties



Moreover, Sanz has described that 1,3-dien-5-ynes having β,β-disubstituted olefins evolve in the presence of catalytic amounts of a cationic gold complex by a cycloaromatization with 1,2-migration of one of the substituents of the double bond.[127] Notably, when both substituents at β position of the double bond are different a completely regioselective shift takes place, being the groups with a higher ability to stabilize positive

charge those which preferentially migrate. This methodology allows the regioselective synthesis of highly substituted benzene rings in good yields with a variety of groups located at the five points of diversity (Scheme 40). The reaction starts with nucleophilic attack of the olefin to the gold-coordinated triple bond, yielding an intermediate that can be represented either as a carbocation or as a cyclopropyl gold-carbenoid. Considering the carbocation intermediate, migration of R^2 implies the transformation of a secondary carbocation into a more stable tertiary one. It is worth to note that for these 1,3-dien-5-ynes a "conventional" cycloaromatization is not possible, as the usual aromatization of the intermediate by simple proton elimination cannot take place due to the disubstitution in one of the C-atoms.

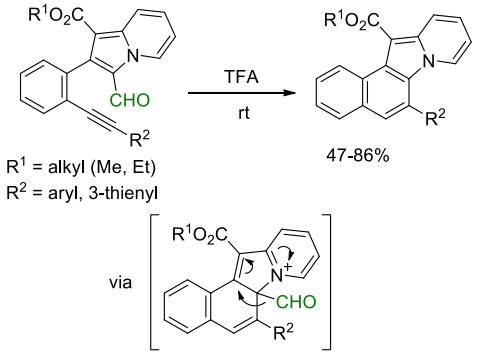
SCHEME 40. Gold-catalyzed cycloaromatization of 1,3-dien-5-ynes accompanied by selective migration from the olefin



Loss of a substituent of the alkene. Besides the examples described in Schemes 19, 21, 25, 27, 30 and 33, in which both incorporation of a new moiety and loss of a substituent of the dienyne occur, Kim has recently described a cycloaromatization of 2-[*o*-(alkynyl)phenyl]indolizine-3-carbaldehydes that takes place with concomitant deformylation.[64] The reaction is promoted by TFA at room temperature and yields benzo[*e*]pyrido[1,2-*a*]indoles in moderate to good yields although it is limited to substrates bearing an (hetero)aromatic group at the triple bond. The authors propose that the deformylation takes place to recover aromaticity after the initial attack of the heteroaryl group to the alkyne. Noteworthy the same products can be obtained from analogous starting materials lacking the formyl group under silver catalysis through a

conventional cycloaromatization process (See Scheme 9, eq. 4).

SCHEME 41. Deformylative cycloaromatization of *o*-(alkynyl)heterobiaryls



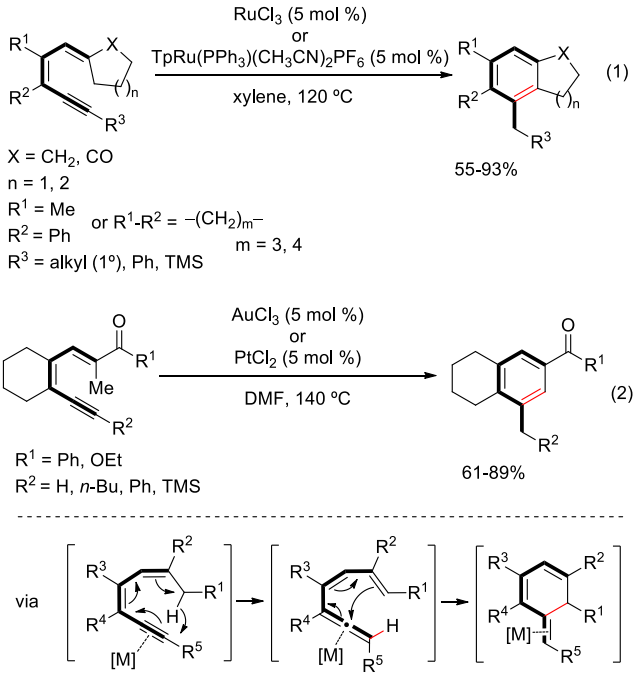
2.3. Cycloaromatizations with unusual topology

As already shown, most of the cycloaromatizations of 1,3-dien-5-ynes encompass a 1,6-topology, that is, the new aromatic ring formed contains all the six carbon atoms of the dienyne system. However, scarce examples of other topologies have been reported, being the 0,5 (See Figure 2), that is the connection of a carbon atom bonded to the terminal position of the olefin with the internal position of the alkyne, the most common among them.

In this regard, Liu has described the metal-catalyzed cycloaromatization of 1,3-dien-5-ynes bearing internal alkynes and having substituents at the olefin with protons in the α-position. In the final products, selectively obtained in good yields, a new bond is formed between the α-C of one of the substituents on the olefin and the internal C atom of the alkyne, whereas the terminal C of the alkyne is not forming part of the new benzene ring (Scheme 42, eq. 1, 2).[128] This outcome is in principle formally similar to that observed by the same author for terminal alkynes (see Scheme 39), but now a different mechanism operates which implies a cycloaromatization following a non 1,6-topology, via an initial [1,7]-hydrogen shift followed by a 6π-electrocyclization and a subsequent [1,3]-hydrogen shift. $RuCl_3$ and $TpRu(PPh_3)(CH_3CN)_2PF_6$ are appropriate catalysts for the reaction of 1,3-dien-5-ynes having cyclic groups in the terminal olefin (Scheme 42, eq. 1), whereas the use of $PtCl_2$ and $AuCl_3$ is demonstrated to be efficient for 1,3-dien-5-ynes bearing

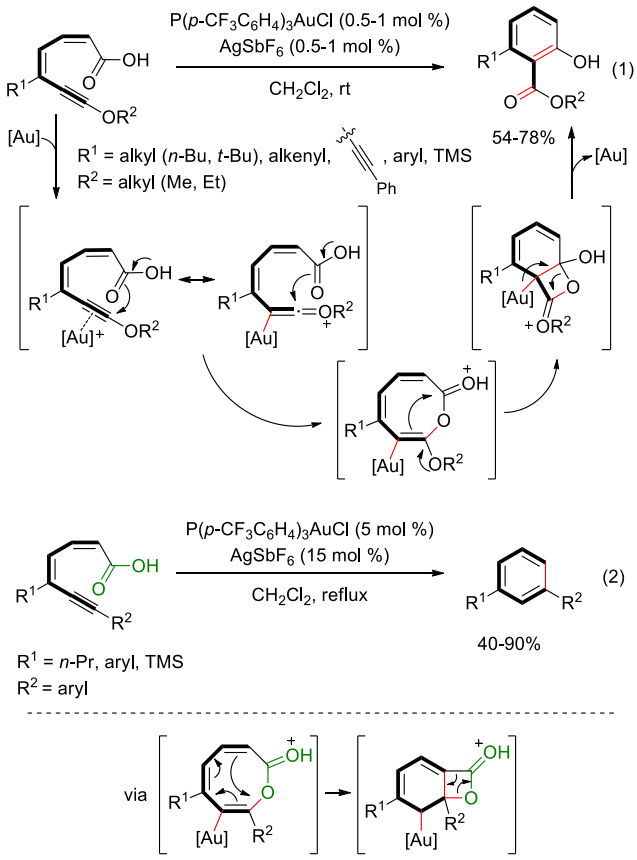
acyclic substituents at that position (Scheme 42, eq. 2). The thermal cycloaromatization of both kind of substrates is also possible, although generally low efficiencies are achieved.

SCHEME 42. Cycloaromatization of 1,3-dien-5-ynes triggered by [1,7]-hydrogen shift



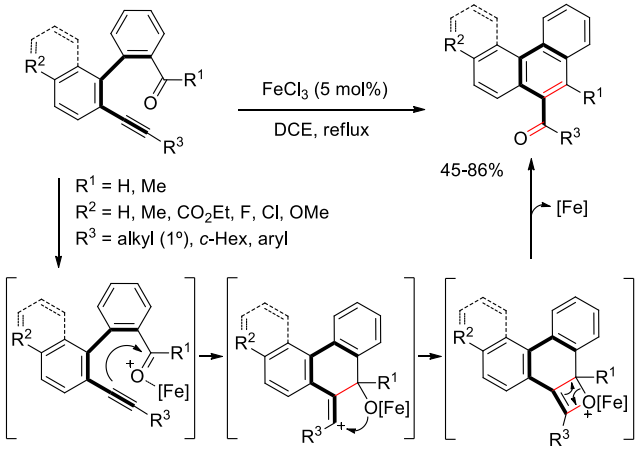
Moreover, Aguilar has described the synthesis of salicylic acid derivatives by gold-catalyzed cycloaromatization of push-pull 1,3-dien-5-ynes that bear a carboxylic acid in the alkene terminus and an alkoxy group as substituent of the alkyne (Scheme 43, eq. 1).[129] The reaction, that proceeds with remarkably low catalyst loadings, is proposed to be initiated with a nucleophilic attack of the carboxylic acid to the gold-coordinated triple bond, giving rise to an eight-membered-ring intermediate. Then, an alkoxy-group promoted intramolecular attack to the activated carbonyl group leads to a bicyclic intermediate that yields the final product after ring opening of the four-membered ring with concomitant aromatization. The decisive role of the electron rich alkyne in the outcome of the reaction is demonstrated: substrates bearing an aryl-substituted triple bond lead to 1,3-disubstituted benzene derivatives trough a 1,6-cycloaromatization/decarboxylation process, and harsher conditions are necessary to achieve an efficient transformation (Scheme 43, eq. 2). This differential behavior is explained based on the different evolution experimented by the common eight-membered-ring intermediate bearing or not bearing an alkoxy group.

SCHEME 43. Gold-catalyzed cycloaromatization of push-pull 1,3-dien-5-ynes



Several further examples of cycloaromatization of 1,3-dien-5-ynes with a non conventional topology have been reported following a common activation mode that implies coordination of the catalyst to the carbonyl group rather than to the alkyne. In this regard, Jana has described a synthesis of phenanthrene derivatives by iron-catalyzed cycloisomerization of *o*-alkynylbiphenyls with an acyl substituent in the *ortho* position of the external aryl ring (Scheme 44).[130] Altough the transformation is formally analogous to the one depicted in Scheme 43, as it implies a formal intramolecular alkyne-carbonyl metathesis, a different mechanism is proposed. Thus, it is suggested to start with a nucleophilic attack of the alkyne over the iron-coordinated carbonyl group, leading to an alkenylic carbocation which subsequently generates an oxetene by intramolecular trapping with the oxygen. Finally, a [2+2] cycloreversion gives rise to the final product and regenerates the catalytic species. The reaction tolerates a wide number of substituents in the starting biphenyl moiety, including electron-donating and electron-withdrawing ones. In addition, it is compatible with aryl and alkyl groups in the triple bond, whereas terminal alkynes do not undergo this transformation.

SCHEME 44. Iron-catalyzed cycloaromatization of *o*-alkynylbiphenyls with an acyl substituent



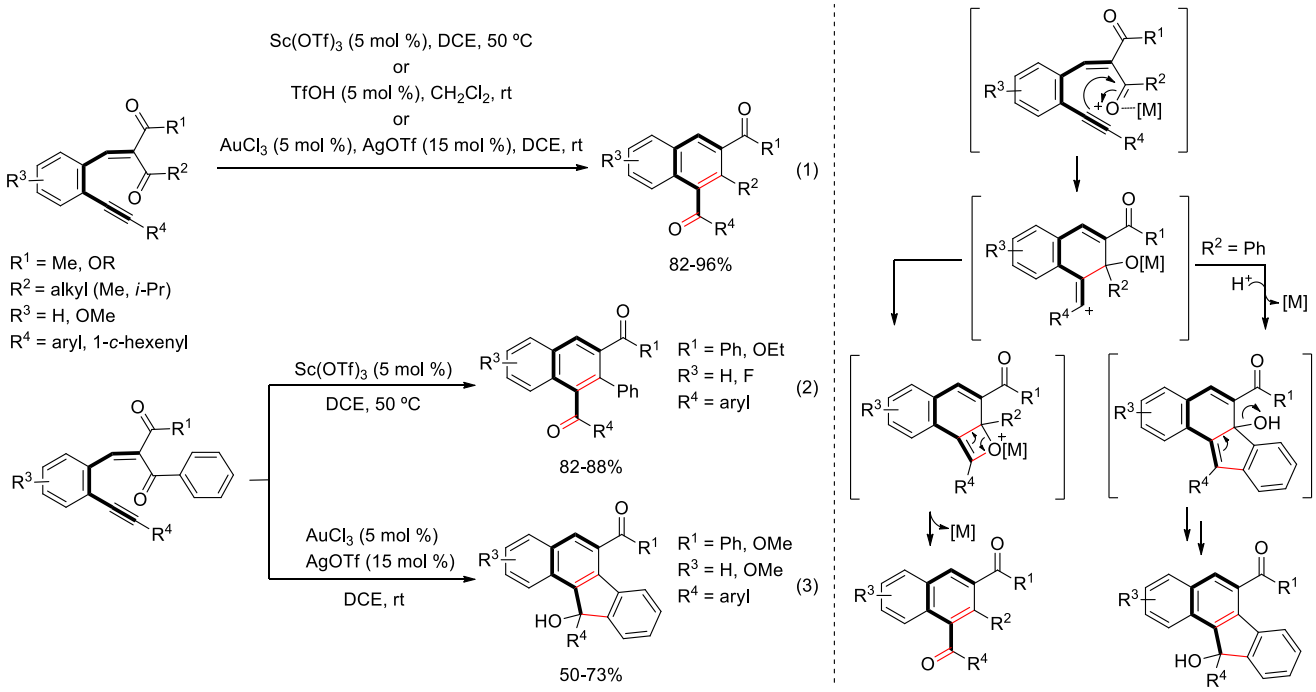
Moreover Zhang has studied the cycloaromatization of *o*-(alkynyl)styrenes with two carbonyl substituents in the terminal position of the external olefin. Different outcomes are observed for this particular type of 1,3-dien-5-ynes depending on the substituents of the substrate and/or the metal complex employed as catalyst.

Thus, this kind of substrates lead to acyl substituted naphthalenes when $Sc(OTf)_3$ is used as the catalyst (Scheme 45, eq. 1, 2). TfOH has also been shown to act as an efficient catalyst, although lower yields than for $Sc(OTf)_3$ are generally obtained.[131] More recently, $Au(OTf)_3$ has been reported as a useful catalyst for this transformation, and the cycloaromatization of a related 1,3-dien-5-yne in which the central double bond is not forming part of an aromatic ring is also achieved in this case, although with a moderate yield.[132] The authors propose a mechanism similar to the one previously depicted in Scheme 44, in which a nucleophilic attack of the alkyne over the activated carbonyl group takes place generating an alkenyl cation, which is intramolecularly trapped by the nucleophilic O[M] moiety. Finally, a retro-[2+2] cycloaddition gives rise to the observed naphthalene derivatives. Noteworthy, the synthetic usefulness of this reaction seems to be limited to aryl and alkenyl substituted acetylenes, as the use of *n*-butyl substituted starting materials leads to mixtures of (alkynyl)naphthalenes, obtained as major products, and the expected acyl substituted naphthalenes.

Morover, in the particular case of *o*-(alkynyl)styrenes in which one of the carbonyl substituents is a phenyl ketone, minor amounts of benzo[*a*]fluorenol derivatives are formed when these substrates are treated with

$Sc(OTf)_3$, although the acyl substituted naphthalenes are still obtained in good yields (Scheme 45, eq. 2).[131] Interestingly, these benzo[*a*]-fluorenol derivatives are isolated in moderate to good yields from the same kind of starting materials in the presence of catalytic amounts of $Au(OTf)_3$, although a narrow substrate scope has been described (Scheme 45, eq. 3).[133] In addition, the use of TfOH as catalyst leads to variable mixtures of the corresponding acyl substituted naphthalenes and benzo[*a*]fluorenols, being the latter the major ones.[131] This alternative pathway is explained by a Friedel-Crafts type cyclization of the intermediate alkenyl cation, generated as proposed above, followed by protodemetalation and double bond isomerization.

SCHEME 45. Cycloaromatization of *o*-(alkynyl)styrenes with carbonyl-substituted olefins

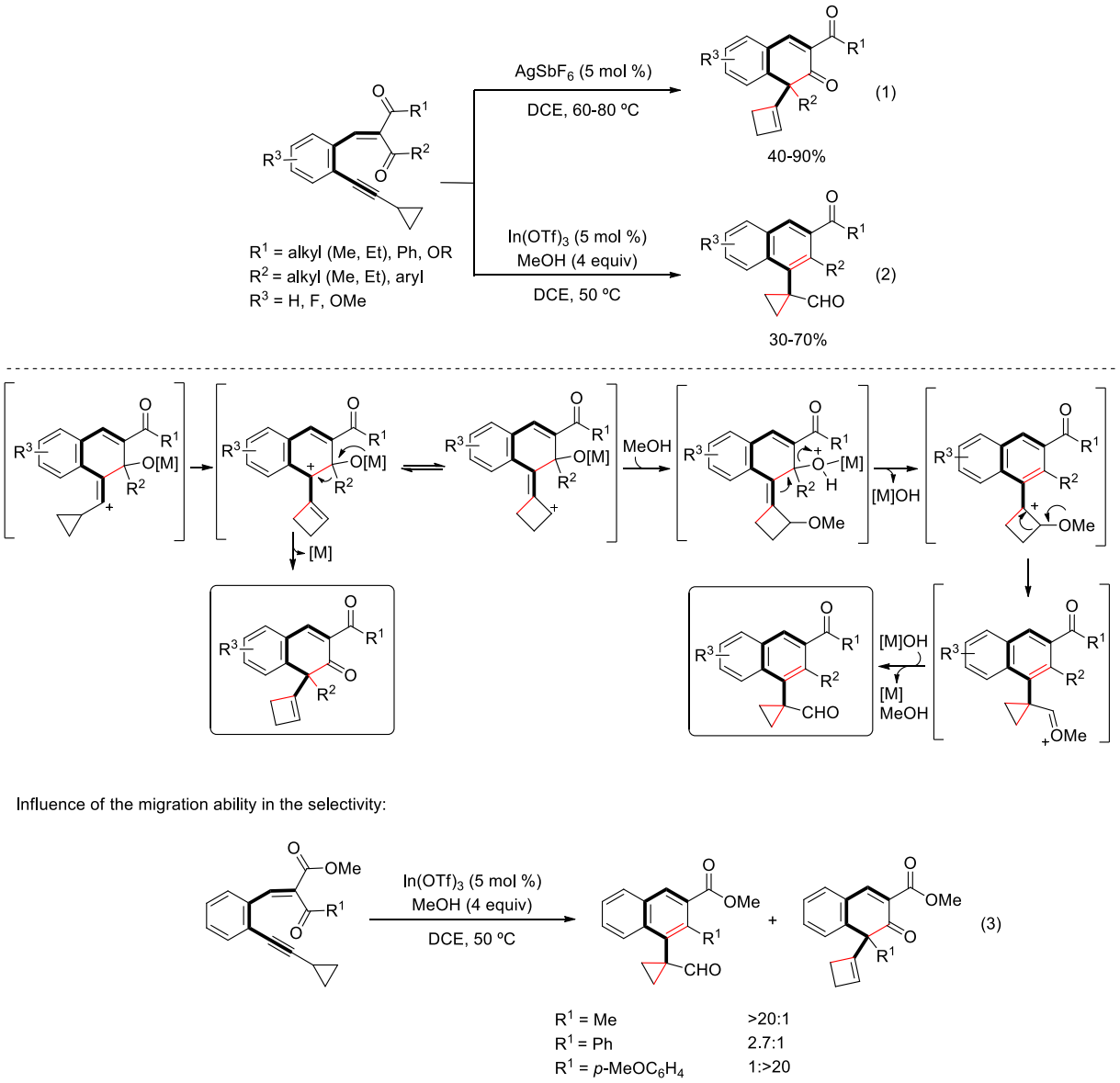


Furthermore, when analogous *o*-(alkynyl)styrenes having a cyclopropyl group linked to the triple bond are used as starting materials a different evolution of the intermediate formed after the nucleophilic attack of the alkyne to the carbonyl group is observed, which depends on the reaction conditions.[133] Thus, when employing $AgSbF_6$ as catalyst cyclobutenyl naphthalenones are obtained by ring expansion followed by pinacol rearrangement (Scheme 46, eq. 1), whereas the use of $In(OTf)_3$ in the presence of MeOH leads to cyclopropyl naphthalenes (Scheme 46, eq. 2). In this latter case the carbocation generated after ring expansion is trapped by the MeOH and, after aromatization with loss of [In]OH, a pinacol rearrangement

generates an oxonium intermediate which is finally trapped by the [In]OH giving rise to the final products.

High selectivities towards cyclobutenyl naphthalenones are achieved when using $AgSbF_6$ as catalyst, as long as the substituent initially placed in the carbonyl group has a good migrating ability. This factor also has a significant influence in the selectivity of the $In(OTf)_3$ catalyzed process (Scheme 46, eq. 3): moderate selectivities are usually obtained, whereas a poor migrating group, such as methyl, leads to a completely selective reaction, and a very good migrating group, such as *p*-methoxyphenyl gives rise only to the corresponding cyclobutenyl naphthalenone, even under these conditions. Moreover, substrates with a substituted cyclopropane lead to cyclobutenyl naphthalenones independently of the conditions used.

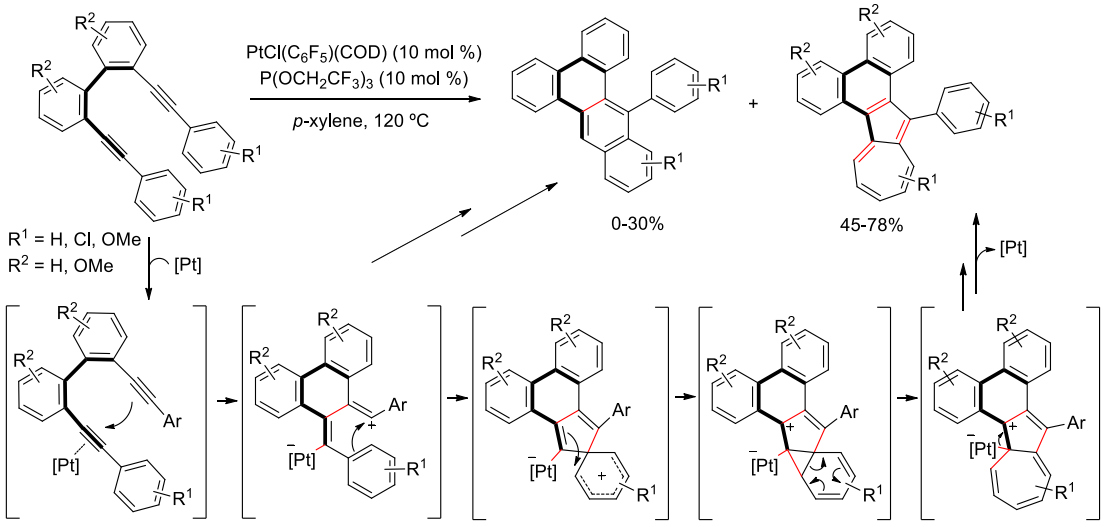
SCHEME 46. Cycloaromatization of *o*-(alkynyl)styrenes with a carbonyl-substituted olefin and a cyclopropyl alkyne



On the other hand, Matsuda and Murakami have reported a synthesis of azulenophenanthrenes based on a cycloaromatization initiated by the intramolecular reaction of an alkyne with the acetylene moiety of a dienyne system (Scheme 47).[134] Thus, nucleophilic attack of the alkyne over the platinum-coordinated acetylene gives rise to an alkenyl cation intermediate, which is then attacked in a Friedel-Crafts type cyclization by the *ipso*-C of an aryl group initially bonded to the triple bond of the 1,3-dien-5-yne. The formed spyrocyclic intermediate reorganizes, including a ring-expansion step, finally leading to the azulenophenanthrene derivatives in moderate

to good yields. Alternatively, the attack of the aryl group over the alkenyl cation intermediate can occur through the *ortho*-C, giving rise to benzo[*f*]tetraphene derivatives that are observed as minor products in some cases. Interestingly, the benzo[*f*]tetraphene becomes the major product when a substrate having a particularly activated *ortho* position, that is with a *m*-methoxyphenyl as substituent of the triple bond, is used. Moreover, the starting material is recovered when a 2,2'-di(alkynyl)biphenyl having a strong electron-deficient aryl ring in both acetylenes is treated under the optimal reaction conditions, whereas the use of unsymmetrical 2,2'-di(alkynyl)biphenyls leads to complex mixtures.

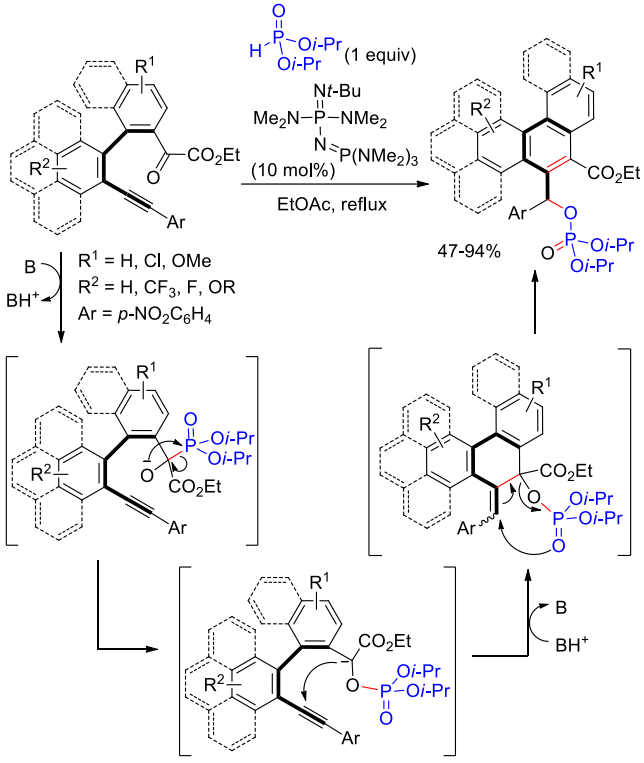
SCHEME 47. Synthesis of azulenophenanthrenes by platinum-catalyzed cycloisomerization of 2,2'-di(alkynyl)biphenyls



Other reagents can also be incorporated into the final products during the course of cycloaromatizations with topology different from 1,6. For example, the synthesis of phenanthrene derivatives from *o*-(alkynyl)styrenes having an α-ketoester at the *ortho* position of the external aryl ring in the presence of a dialkylphosphite has been described (Scheme 48).[135] The phosphite promotes the cyclization by an initial base-catalyzed attack to the ketoester moiety. Then, a [1,2]-phospha-Brook rearrangement occurs and the generated enolate attacks the alkyne leading to a cyclized intermediate that gives rise to the final product after a [3,3] rearrangement of the allyl phosphate group. The reaction is limited to *o*-(alkynyl)styrenes having a *p*-nitrophenyl group as substituent in the alkyne; substrates having aryl groups with less electron donating

groups, such as ester or CF_3 lead to low yields. Nevertheless, a wide range of substituents can be present in the biaryl moiety, affording the corresponding phenanthrene derivatives in good yields. Moreover, fused aryl rings are also well tolerated, thus allowing the synthesis of diverse isomeric tetracyclic compounds.

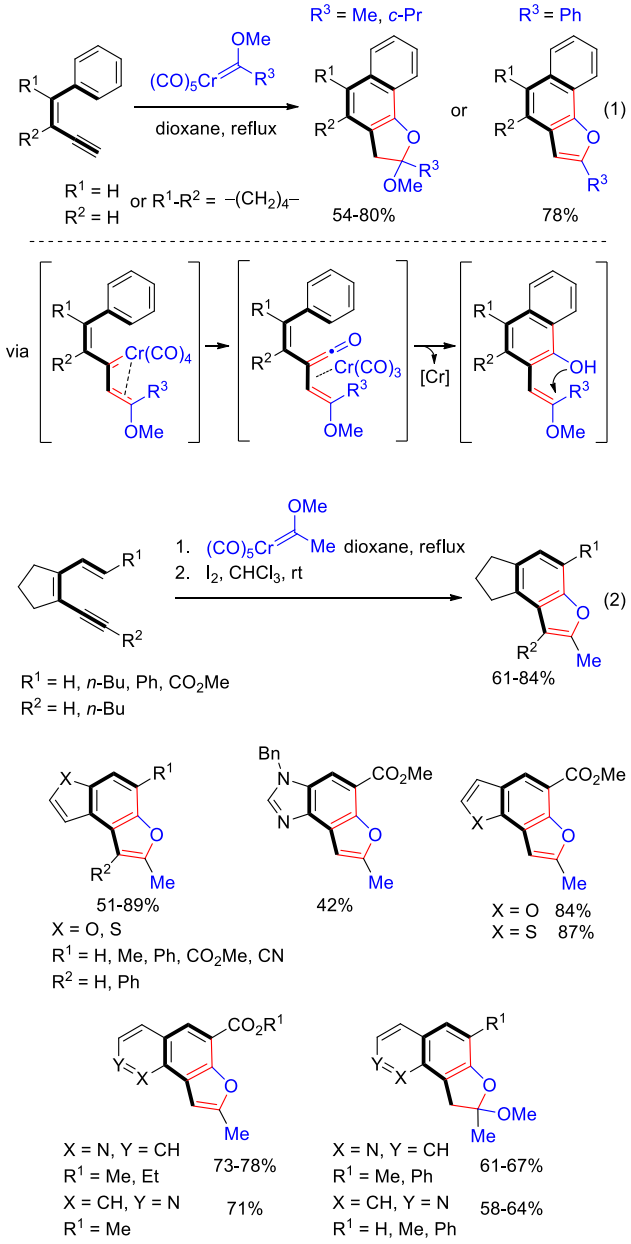
SCHEME 48. Synthesis of phenanthrene derivatives by cycloaromatization of *o*-(alkynyl)biaryls with a ketoester moiety in the presence of a dialkylphosphites



In addition, several examples have been reported involving 1,3-dien-5-ynes in combination with Fischer carbene complexes, leading to transformations which encompass both a non 1,6-cycloaromatization and incorporation of new moieties to the final product. Thus, Herndon initially reported in 1995 the reaction of Fischer carbene-chromium complexes with 1-phenyl-1-en-3-ynes, yielding benzofuran derivatives (Scheme 49, eq. 1).[136] In this case the six carbon atoms of the created aromatic ring include five coming from the dienyne skeleton and one coming from one of the carbonyl ligands of the Fischer carbene-chromium complex. The mechanism proposed for these transformations is related with that of the Dötz benzannulation and starts with the insertion of the alkyne into the Cr–C bond of the carbene complex. Then, CO insertion leads to a vinylketene intermediate that experiences a 6π-electrocyclization giving rise to a naphthol derivative which

cyclizes to the observed benzofuran derivative. This reaction is limited to substrates having terminal alkynes, as the product coming from an internal acetylene turns out to be unstable. This methodology has later been expanded to 1,3-dien-5-ynes where the terminal double bond is not forming part of a phenyl ring and, in this case, internal aliphatic alkynes are also suitable starting materials (Scheme 49, eq. 2).[137] Moreover, 1,3-dien-5-ynes in which the central double bond is forming part of a heterocyclic ring can indeed be used as precursors of the corresponding heterocycle-fused benzofurans.[138,139] In the latter reactions an additional treatment with iodine or acid is necessary to convert a complex crude reaction mixture containing arene-chromium complexes into the final tricyclic compounds. However, *o*-(alkynyl)styrenes and *o*-(alkynyl)biphenyls are not useful as starting materials, as they yield mixtures of products.[140] Only in the case of *o*-(alkynyl)styrenes having a terminal or TMS substituted triple bond selective processes are observed, but furnishing five-membered rings instead of products of cycloaromatization (See Scheme 71).

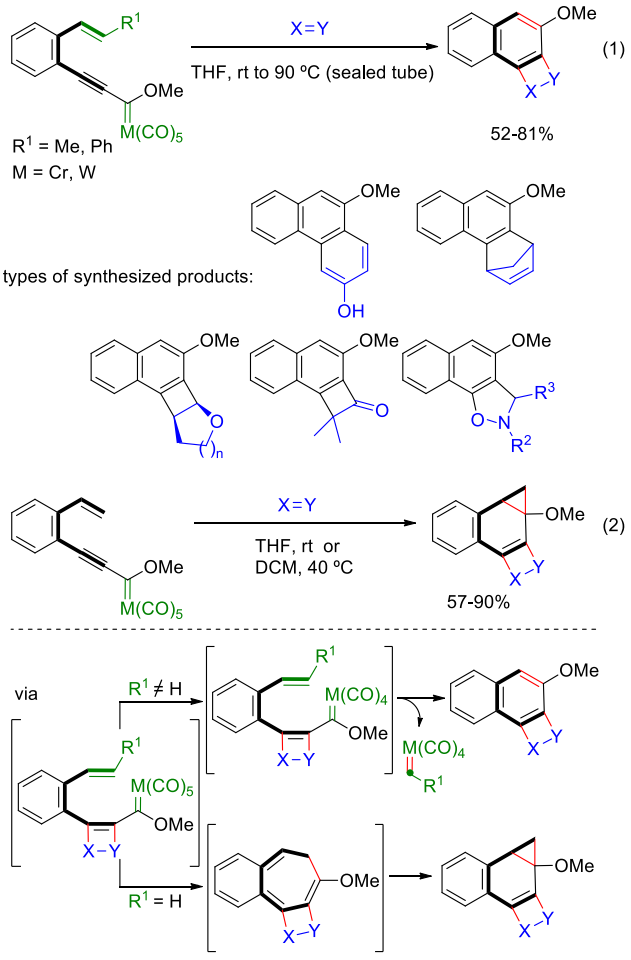
SCHEME 49. Cycloaromatization of 1,3-dien-5-ynes involving Fischer carbene complexes



Also using Fischer carbene complexes, but in an intramolecular fashion by bonding to the alkyne moiety, Barluenga has described a synthesis of naphthalenes fused to diverse carbo- and heterocycles, in a process that encompasses a 2,7-topology, as the new aromatic ring includes both carbon atoms of the alkyne, and leaves out the terminal carbon of the olefin (Scheme 50, eq. 1 and 2).[141] The mentioned substrates react with enol ethers, nitrones or dienes giving rise initially to the products coming from regioselective [2+2], [3+2] or [4+2] cycloadditions, respectively, over the alkyne. When the terminal position of the olefin is substituted,

these intermediates lead, after heating, to the naphthalene derivatives through a metathesis process that is initiated by an irreversible carbonyl ligand dissociation (Scheme 50, eq. 1). However, if the olefin is unsubstituted a cascade process is observed where the initially formed tetraene intermediate spontaneously evolves at room temperature to a cyclopropane-fused dihydronaphthalene derivative (Scheme 50, eq. 2), which is formed by consecutive 8π- and 6π-electrocyclizations. This difference in reactivity between terminal and substituted olefins is attributed to the steric repulsion between the substituent in the olefin and the metal fragment, which disfavors the 8π-electrocyclization.

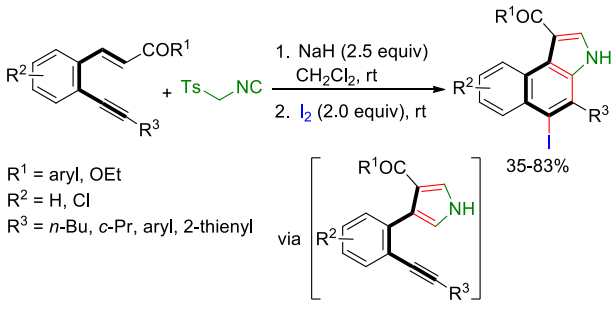
SCHEME 50. Synthesis of carbo- and heterocycle-fused naphthalenes from dienyne-tethered Fischer carbene complexes



On the other hand, an expedient synthesis of benzo[*e*]indoles by iodocycloaromatization of *in situ*-generated *o*-(alkynyl)heterobiaryls has been reported, also following a global 2,7-topology (Scheme 51).[142]

The nucleophilic pyrrol moiety is formed by reaction of an *o*-(alkynyl)cinnamate or chalcone with TosMIC in dichloromethane. Whereas the conversion of the intermediate in the final products represents a conventional iodocycloaromatization of an *o*-(alkynyl)heterobiaryl, the global transformation from the dienyne is an example of a cycloaromatization with unsual topology, as one of the carbons finally forming part of the aromatic ring is not coming from the initial dienyne moiety, but from an external reagent. The cycloaddition tolerates *o*-(alkynyl)chalcones/cinnamates with varied substitution at the acetylene and also the presence of a chlorine atom at the central arene ring. Interestingly, the outcome of the reaction is controlled by the solvent, and spiro[indene-1,3'-pyrroles] are obtained if the global reaction sequence is performed in THF (see Scheme 65, eq. 2).

SCHEME 51. Synthesis of 5-iodo-3*H*-benzo[*e*]indoles by iodo-cycloaromatization of *in-situ* generated *o*-(alkynyl)heterobiaryls



3. SYNTHESIS OF FIVE-MEMBERED RINGS

As pointed out in the previous lines, 1,3-dien-5-ynes have been extensively used as valuable precursors of benzene derivatives through cycloaromatization processes. However, in recent years the versatility of these substrates has been expanded to the preparation of other carbocyclic frameworks. In this section the synthesis of five-membered rings from 1,3-dien-5-ynes is discussed and classified attending to the skeleton formed: 1-methyleneindanes, cyclopentadienes, fulvenes and cyclopentenones, as well as their benzofused analogues.

3.1. 1-Methyleneindanes

A common strategy to efficiently access functionalized 1-methyleneindanes from *o*-(alkynyl)benzylidenemalonates and related keto-ester derivatives has been described by different authors in the last years. These processes comprise the creation of two new bonds in a tandem fashion: one between carbons 1 and 5 of the dienyne system by a formal 5-*exo* cyclization and the other one through a Michael inter- or intramolecular nucleophilic addition to the position 2 of the dienyne (Figure 3). Interestingly, this kind of 1,3-dien-5-ynes functionalized with carbonyl groups have also been shown as useful starting materials in cycloaromatization processes (See Schemes 45 and 46), which again highlights the importance of the substitution pattern and the reaction conditions in the outcome of the transformations of 1,3-dien-5-ynes.

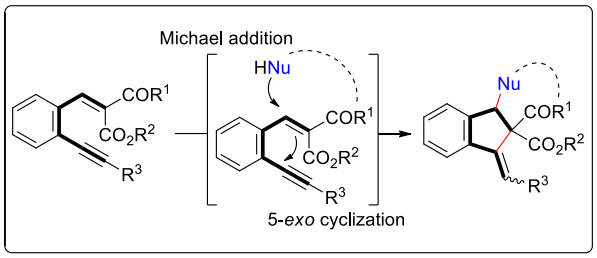
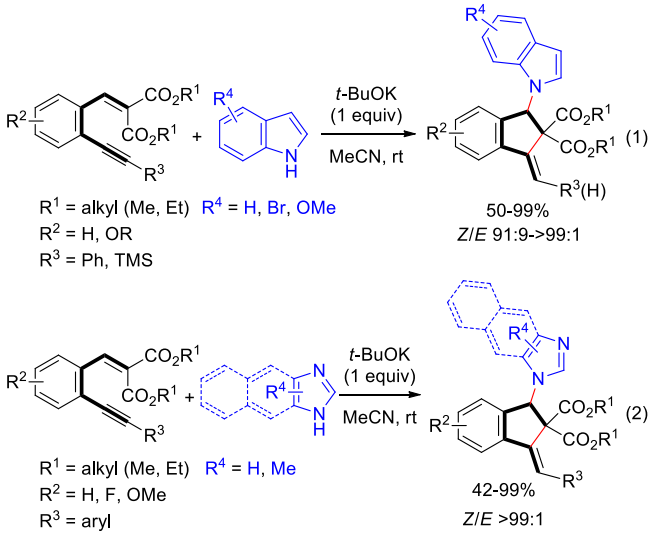


FIGURE 3. Tandem approach to the 1-methyleneindane skeleton from 1,3-dien-5-ynes

This approach to 1-methyleneindanes from *o*-(alkynyl)benzylidenemalonates was first reported by Wu using indoles as external nucleophiles in the presence of stoichiometric amounts of *t*-BuOK (Scheme 52, eq. 1).[143] The corresponding cycloadducts are usually formed with high *Z*/*E* selectivity and isolated in excellent yields for a variety of electron-rich or neutral indoles, whereas an indole with reduced nucleophilicity (R^4 = Br) leads to the 1-methyleneindane product in moderate yield. However, the scope of the process is limited to dienynes bearing a phenyl substituent at the triple bond and no cyclization is detected with substrates bearing in that position an alkyl group. Moreover, a methyleneindane unsubstituted at the olefin is obtained from a TMS substituted dienyne as a result of a complete desylilation. In addition, other nucleophiles tested such as pyrrol, disopropylamine, *p*-anisidine, phenylacetylene and acetylacetone lead to no reaction or complex mixtures. Nevertheless, the methodology can be extended to the use of imidazoles as nucleophiles

(Scheme 52, eq. 2).[144] The transformation is again limited to the use of *o*-(alkynyl)benzylidenemalonates with aryl substituted triple bonds, and ocurrs with complete *Z* selectivity, leading to the corresponding products in high yields except for 1,3-dien-5-ynes with OMe substituents in the central aryl ring, which afford only moderate yields.

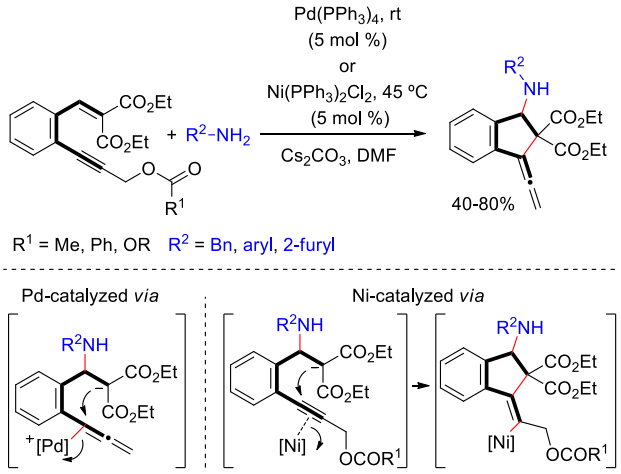
SCHEME 52. Synthesis of 1-methyleneindanes by base-promoted tandem reaction of *o*-(alkynyl)benzylidenemalonates with indoles or imidazoles



The effective use of primary amines as nitrogen nucleophiles in a related transformation has been reported by Liang.[145] In this case the conjugated malonates bear a good leaving group at the propargylic position that, in the presence of a base and a metal catalyst, triggers the formation of 1-vinylidenindanes (Scheme 53). These products are obtained in moderate to good yields with benzylamine and a wide range of anilines irrespective of the electronic nature of their substituents. However, reactions with phenol and diethyl malonate as nucleophiles lead to no conversion under the developed conditions or to complex mixtures by forcing the reaction conditions. Two alternative protocols have been developed which mainly diverge in the metal employed, palladium or nickel, and a different mechanism is proposed for each metal. On the one hand, in the presence of palladium, after the initial Michael-nucleophilic addition of the primary amine, a decarboxylation occurs to form an allenyl intermediate that evolves to the final product by a regioselective intramolecular nucleophilic attack. On the other hand, nickel activates the triple bond of the intermediate generated after the

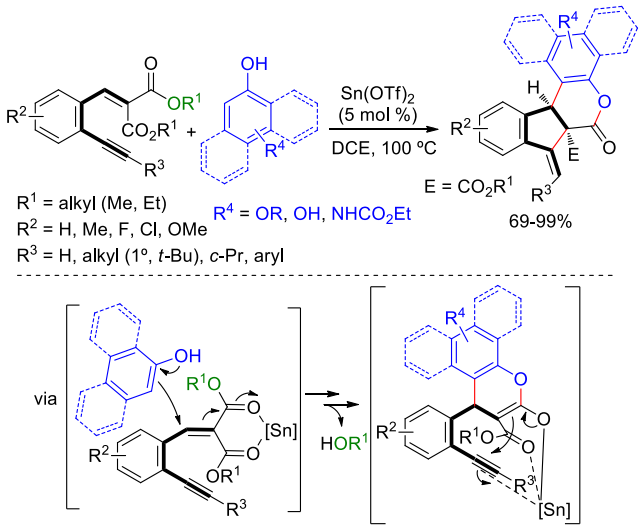
Michael addition towards an analogous regioselective nucleophilic attack that builds the indane core. Then, α-heteroatom elimination renders the observed vinylidenindane.

SCHEME 53. Synthesis of 1-vinylidenindanes by palladium- or nickel-catalyzed reaction of *o*-(alkynyl)benzylidenemalonates with primary amines



Moreover, Youn and Joo have described the use of phenols as nucleophiles with *o*-(alkynyl)benzylidenemalonates for the synthesis of 3,4-dihydrocoumarin-fused 1-methyleneindanes by a tandem reaction catalyzed by $Sn(OTf)_2$ (Scheme 54).[146] The reaction is proposed to proceed by initial arylation of the activated electron-deficient olefin followed by intramolecular lactonization that furnishes the coumarin ring. Then, the indane skeleton is formed by intramolecular nucleophilic addition of a tin-enolate onto the alkyne, activated by the Lewis acid as well. A subsequent proto-destannylation gives the observed tetracyclic compounds. This tandem process displays broad scope at both the aromatic ring and the acetylene of the dienyne system and furnishes the corresponding cycloadducts in good yields and exclusively as *E* isomers, except for substrates bearing an electron-rich substituent at the phenyl ring or an alkyl group at the alkyne where the *E* selectivity is low. The reaction is limited to highly electron-rich phenols or naphthols as nucleophiles and, on the other hand, to diethyl or dimethyl malonates. In this sense, the replacement of a carboxylate by a nitrile, a hydrogen or a ketone leads to moderate yields, no reaction or other adducts respectively.

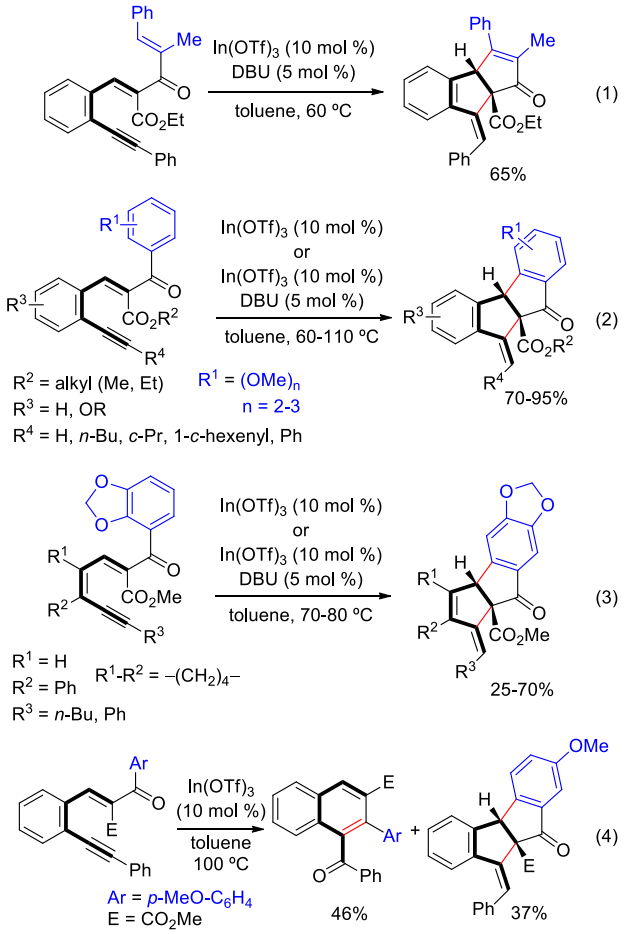
SCHEME 54. Synthesis of 3,4-dihydrocoumarin-fused 1-methyleneindanes by tandem $Sn(OTf)_2$-catalyzed reaction of *o*-(alkynyl)benzylidenemalonates with phenols



In addition, Zhang has developed an intramolecular version of these useful methodologies for the synthesis of diverse fused-polycyclic compounds containing the methyleneindane skeleton by linking a vinyl or aryl nucleophilic counterpart to the external olefin of the 1,3-dien-5-yne system.[132,147] Thus, in the presence of catalytic amounts of $In(OTf)_3$, and DBU in some examples, reactions under thermal conditions of *o*-alkynylcinnamates with an additional cynammyl or benzoyl group at the terminal position of the external olefin occurr in good yields to afford tetracyclic adducts bearing a quaternary stereocenter (Scheme 55, eq. 1, 2). Moreover, the reaction with dienynes in which the internal double bond is not forming part of a benzene ring also produces the corresponding polycyclic compounds in variable yields (Scheme 55, eq. 3). The two new fused five-membered rings are formed in a selective *cis* configuration and the *exo* double bond usually displays complete *E* selectivity. Except for terminal acetylenes, the scope of the process is limited to substrates having two or more electron-rich substitutents at the nucleophilic arene. Therefore, a dienyne with a *p*-methoxybenzoyl moiety gives an almost equimolecular mixture of the corresponding tetracycle, formed following the general process depicted in Figure 3, and a naphthalene (Scheme 55, eq. 4) obtained by an initial cycloaromatization (see Scheme 45). Furthermore, the reaction of a substrate possesing an indole ring as the vinyl nucleophile stops at the Nazarov adduct and does not give any of the desired pentacycle probably

due to the strain of polycyclic fused compounds containing five-membered rings.

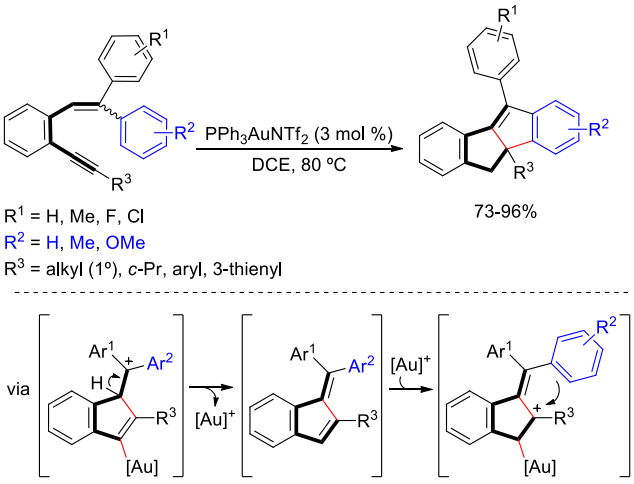
SCHEME 55. Tandem In(OTf)$_3$-catalyzed synthesis of polycyclic compounds containing the methyleneindane core from functionalized 1,3-dien-5-ynes



Besides this general methodology, particular examples of syntheses of methyleneindanes from *o*-(alkynyl)styrenes involving alternative topologies have been reported. For example, β,β-diaryl-substituted-*o*-(alkynyl)styrenes cycloisomerize when heated at 80 ºC in the presence of a gold catalyst through a formal [4+1] cycloaddition between the double bond, one of the aryl rings, and the terminal carbon of the acetylene, giving rise to dihydroindeno[2,1-*a*]indenes (Scheme 56).[148] The reaction would start with a formal 5-*endo* attack of the olefin to the gold activated triple bond followed by elimination of the only proton available and protodemetalation to yield a benzofulvene derivative. In fact, these benzofulvene derivatives have been isolated when the reaction is performed at 0 ºC (Scheme 92), and it has been demonstrated that they convert into the corresponding dihydroindeno[2,1-*a*]indenes when heated in the presence of the gold catalyst or other

Brønsted or Lewis acids. This final transformation could be explained by coordination of the gold catalyst to the diene moiety of the benzofulvene generating an allylic carbocation that is intramolecularly trapped by one of the aryl groups. As a result dihydroindeno[2,1-*a*]indenes with a quaternary stereocenter are obtained in good yields and, moreover, with high selectivity when starting materials having two different aryl groups are used. One example of a formal [4+1] cycloaddition of a β-alkyl-β-aryl substituted *o*-(alkynyl)styrene is also reported, although addition of an excess of Brønsted acid to the reaction media is required to promote the final cyclization step, and the reaction is overall less efficient. However, *o*-(alkynyl)styrenes with other substitution patterns at the olefin follow different reaction pathways, mainly leading to indene derivatives (see Section 3.2.)

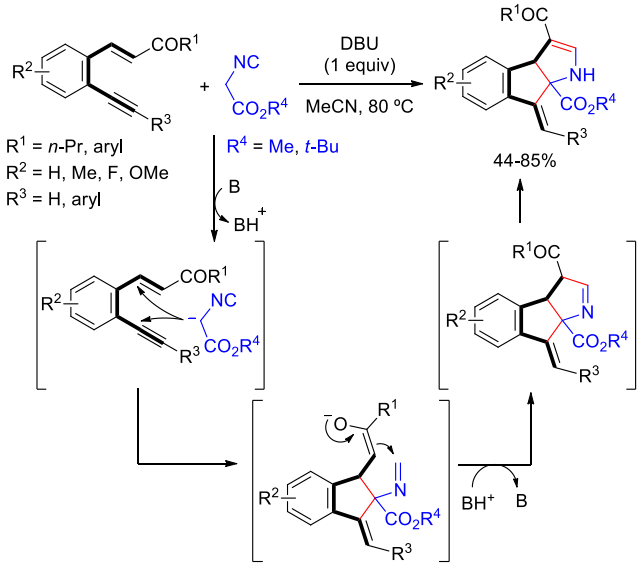
SCHEME 56. Synthesis of dihydroindeno[2,1-*a*]indenes by gold-catalyzed cycloisomerization of β,β-diaryl-*o*-(alkynyl)styrenes



On the other hand, dihydropyrrol-fused 1-methyleneindanes can be obtained from *o*-(alkynyl)chalcones and 2-isocyanates in a base-promoted cascade process (Scheme 57).[149] To explain the formation of these tricyclic compounds, the authors propose the creation of the methyleneindane unit by an intermolecular nucleophilic addition of the stabilized anion derived from isocyanoacetate to the alkynylchalcone, followed by the construction of the fused heterocycle by an intramolecular reaction of the generated enolate. Then a 1,3-H shift gives the observed dihydropyrrol-fused 1-methyleneindanes. This cascade reaction produces the

corresponding cycloadducts in moderate to good yields provided that a hydrogen or an aryl group is attached to the triple bond of the substrate, whereas complex mixtures are obtained with alkyl-substituted dienynes at that position.

SCHEME 57. Synthesis of dihydropyrrol-fused 1-methyleneindanes by base promoted cascade reaction of *o*-(alkynyl)chalcones with 2-isocyanoacetates



3.2. Cyclopentadienes and benzofused analogues

The preparation of valuable synthetic intermediates such as cyclopentadienes and their benzofused derivatives from 1,3-dien-5-ynes has also been described in the last decade. Attending to the topology of the cycloisomerization, the new five-membered ring can be formed by connecting carbons 2 and 6 or, alternatively, C1 and C5 of the dienyne system (Figure 4).

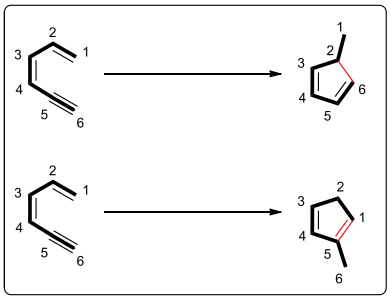


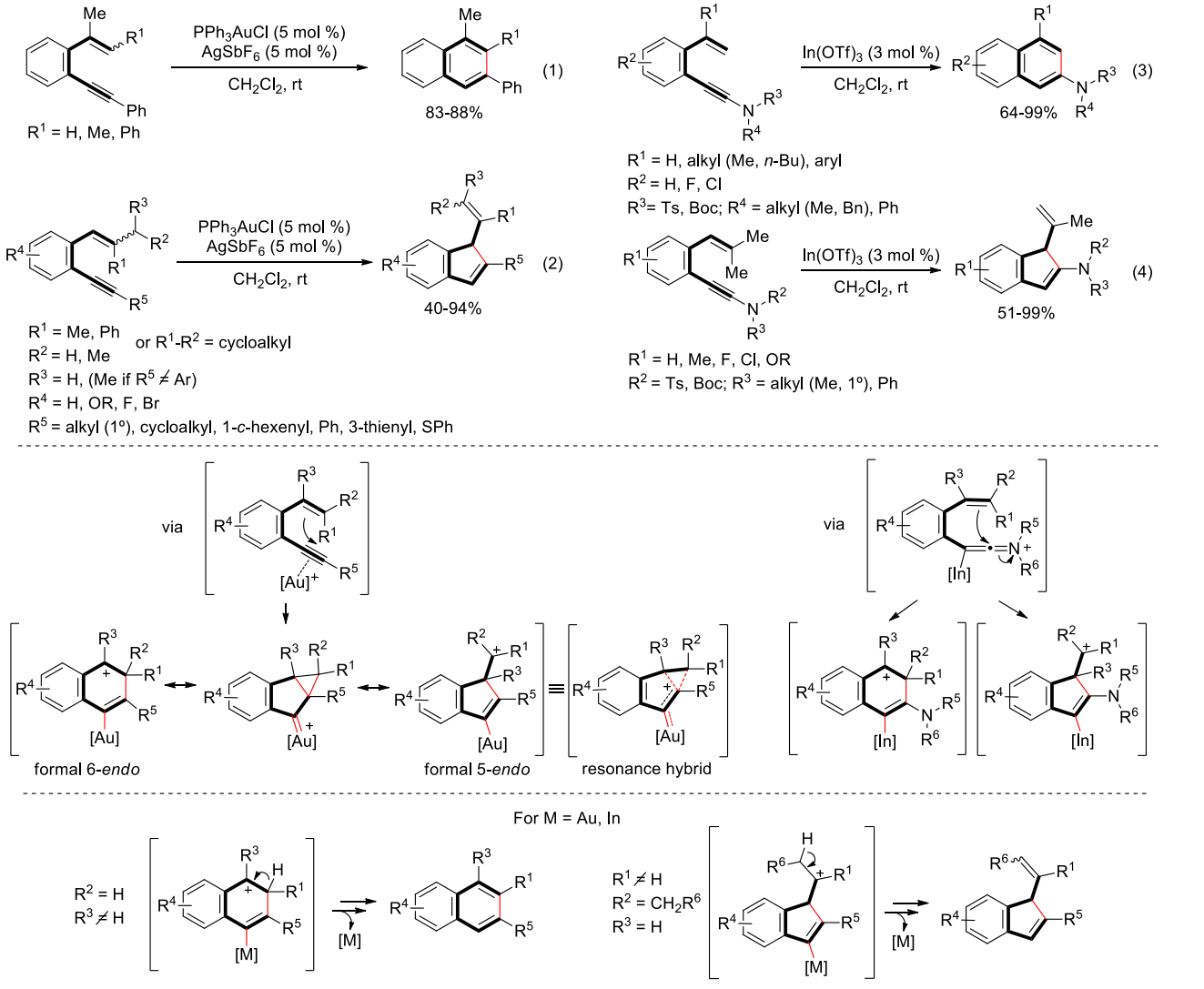
FIGURE 4. Possible topologies for the cycloisomerization of 1,3-dien-5-ynes to cyclopentadienes and related derivatives

3.2.1. Reactions with formation of a new bond between C2 and C6. Sanz and coworkers have thoroughly examined the cycloisomerization of *o*-(alkynyl)styrenes under gold catalysis. This study revealed that the substitution pattern at the olefin moiety of the dienyne controlls the outcome of the rearrangement. Besides the synthesis of methyleneindanes from β,β-diaryl-*o*-(alkynyl)styrenes previously commented (see Scheme 56), they have observed that β-mono or unsubstituted-α-methyl-*o*-(phenylethynyl)styrenes cleanly give the corresponding 6-*endo* adducts (Scheme 58, eq. 1), as it had been previously reported for that kind of dienynes with different metal catalysts including gold (see Section 2.1.1.). On the contrary, under the same reaction conditions, β,β-disubstituted-*o*-(alkynyl)styrenes exclusively evolve through an unprecedented formal 5-*endo*-cyclization (Scheme 58, eq. 2).[150,151] This novel methodology is general and allows the regioselective synthesis in high yields of 1*H*-indenes with varied substitution at C1, C2 and at the arene ring. This substitution encompasses alkyl and aryl groups at the olefin, electron-donating and electron-withdrawing groups at the arene and almost all type of substituents at the acetylene, as only substrates with H, I or TMS at that position lead to decomposition products. The same tendency in 5-*endo vs* 6-*endo* cyclization has been later observed by Yeh in the indium-catalyzed cycloisomerization of *o*-(aminoethynyl)styrenes.[152] Thus, a series of 2-aminonaphthalenes can be efficiently obtained from α-substituted-β-unsubstituted *o*-(alkynyl)styrenes (Scheme 58, eq. 3), whereas starting materials disubstituted at the terminal position of the olefin selectively lead to 2-amino-1*H*-indenes in generally excellent yields (Scheme 58, eq. 4). Moreover, analogous *o*-(vinyl)thiophenylinamides are also efficiently cyclized under indium catalysis, observing the same selectivity pattern.

Regarding the proposed mechanisms, in the case of the gold-catalyzed cycloisomerization the nucleophilic addition of the olefin moiety over the gold-coordinated triple bond would provide, as proposed for 1,3-dien-5-ynes depicted in Scheme 40, a cyclopropyl carbene intermediate that can also be represented as limit resonance structures accounting for formal 6-*endo* or 5-*endo* cyclizations. This intermediate is more accurately shown as a hybrid compiling all the possible resonance structures, with higher or lower

contributions from one or another depending on the different substituents. For the indium-catalyzed process an initial formation of a ketiminium ion is proposed, which can also experience formal 6-*endo* or 5-*endo* cyclizations. In any case, the observed selectivity is explained on the basis of the stability of the intermediate carbocations generated after the intramolecular nucleophilic addition of the olefin. Thus, for α-substituted-β-unsubstituted (or monosubstituted)-*o*-(alkynyl)styrenes the tertiary-benzylic carbocation generated from a formal 6-*endo* cyclization is more stable, and proton elimination from this species accounts for the formed naphthalenes. On the other hand, for α-unsubstituted-β,β-disubstituted-*o*-(alkynyl)styrenes the tertiary carbocation coming from a formal 5-*endo* pathway becomes the most favorable species, and proton elimination and protodemetalation from this intermediate explains the formation of indene derivatives.

SCHEME 58. 5-*endo* *vs* 6-*endo* selectivity in the cycloisomerization of *o*-(alkynyl)styrenes

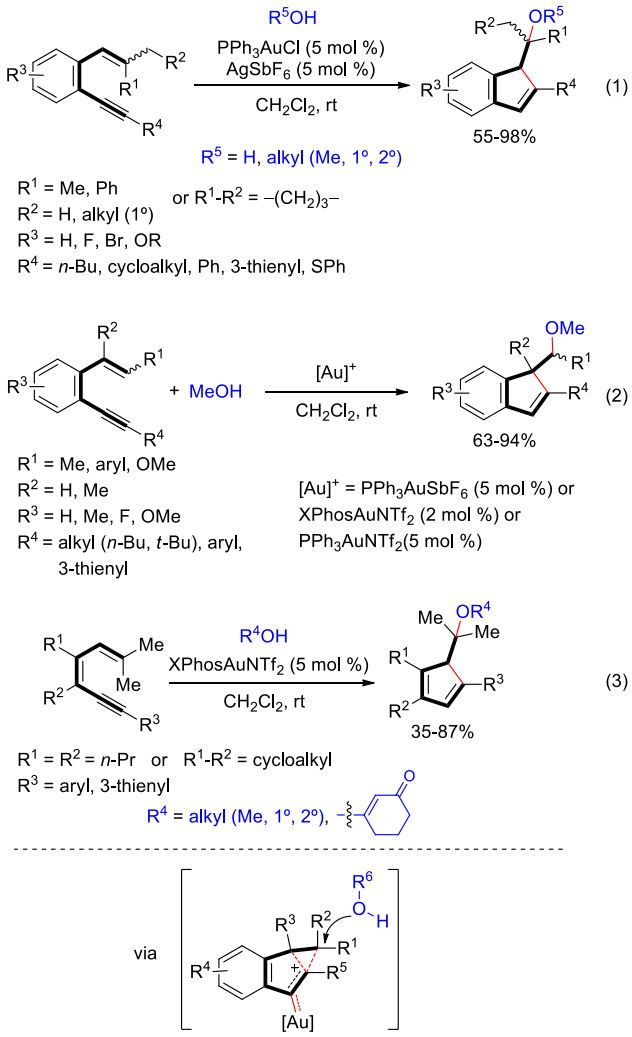


Moreover, gold-catalyzed reactions of β,β-disubstituted-*o*-(alkynyl)styrenes in the presence of oxygen-centered nucleophiles, such as water or primary or secondary alcohols, selectively give the corresponding oxygen-functionalized indenes also in high yields and very broad scope at the dienyne system (Scheme 59, eq. 1).[150,151] The methoxycyclization is also efficient with β-monosubstituted-*o*-(alkynyl)styrenes, whose reactions under gold catalysis in the absence of methanol lead to complex mixtures (Scheme 59, eq. 2, R^2 = H).[151,153] In addition, the synthesis of oxygen-functionalized 1*H*-indenes having a quaternary centre at C1 is also possible from α-methyl-β-aryl-*o*-(alkynyl)styrenes (Scheme 59, eq. 2, R^2 = Me). Notably, the latter reactions reveal a crucial role of methanol to promote a complete switch on the selectivity of the dienyne rearrangement from 6-*endo* to 5-*endo* (Scheme 58, eq. 1 *vs* Scheme 59, eq. 2).

An analogous alcohol induced switch in the selectivity of a cyclization has been also observed by the same authors with related β,β-disubstituted-1,3-dien-5-ynes in the presence of catalytic amounts of a cationic gold complex. In this case, functionalized cyclopentadienes are obtained in good yields and with complete regioselection as a result of a formal 5-*endo* cyclization (Scheme 59, eq. 3),[154] whereas in the absence of the oxygen nucleophile a tandem 6-*endo* cycloisomerization/1,2-migration occurs to exclusively afford polysubstituted benzene derivatives (See Scheme 40).

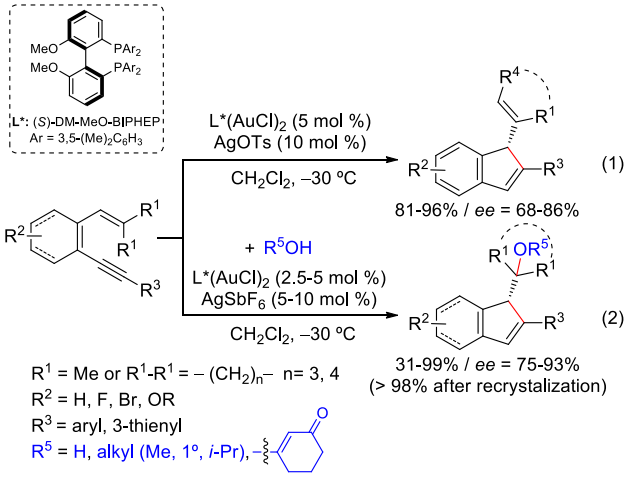
All of these results are explained by intermolecular trapping of the intermediate generated by formal 5-*endo* cyclization with the external nucleophile present in the reaction media. It is worth to note that in the presence of an oxygen-centered nucleophile, and on the contrary to that observed in the absence of external nucleophile, this is the preferred pathway regardless of the dienyne substitution.

SCHEME 59. Gold-catalyzed alkoxycyclization of *o*-(alkynyl)styrenes and 1,3-dien-5-ynes



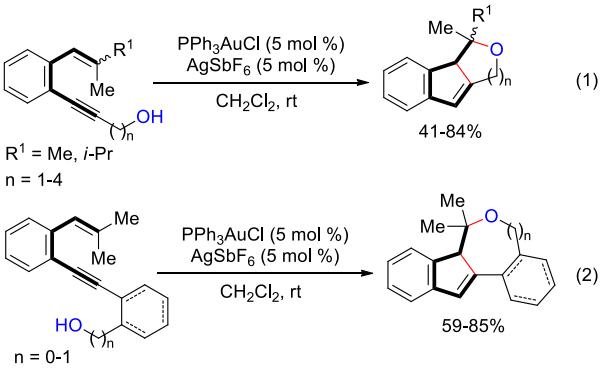
In addition, using a gold catalyst derived from a BIPHEP ligand, the asymmetric version of these rearrangements has been developed allowing access to elusive enantioenriched chiral 1*H*-indenes and cyclopentadienes.[150,151,154] Good to excellent yields and high enantioselectivities up to 93%, that can be improved to >98% by recrystallization, are obtained provided that the conjugated dienyne bears an (hetero)aromatic group attached to the alkyne and the central double bond is included in a carbocycle (Scheme 60). Otherwise, high yields but low to moderate enantioselectivities are achieved.

SCHEME 60. Gold-catalyzed enantioselective synthesis of 1*H*-indenes and cyclopentadienes from 1,3-dien-5-ynes



On the other hand, diverse heterocycle-fused indenes can be prepared by gold-catalyzed intramolecular alkoxycyclization of *o*-(alkynyl)styrenes possessing a hydroxy group in their structure (Scheme 61, eq. 1, 2).[151] Thus, indenes fused to five-, six or seven-membered oxygen-containing heterocycles are selectively obtained in good yields although low stereoselectivity is observed when two diastereomers can be formed, as for the intermolecular version.

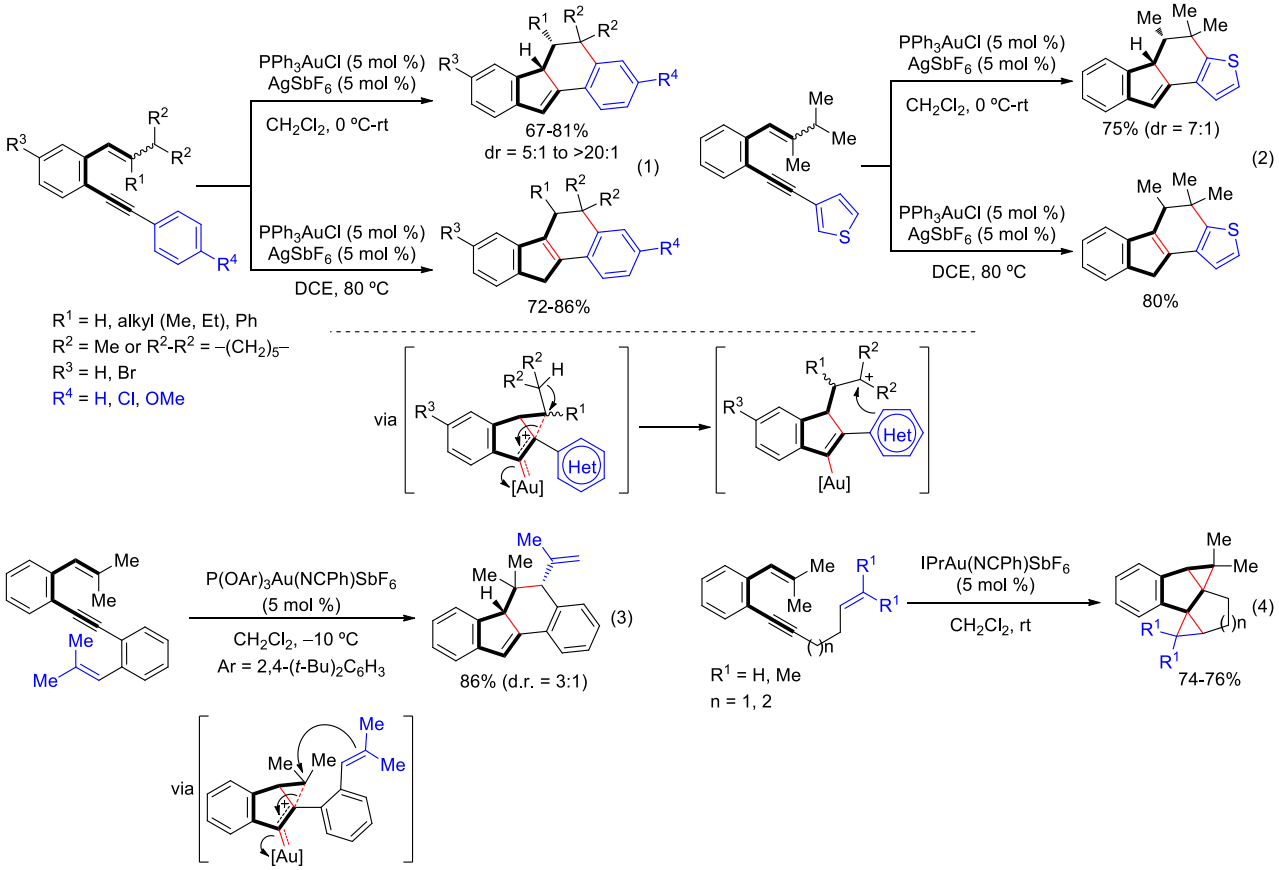
SCHEME 61. Synthesis of heterocycle-fused indenes by gold-catalyzed cycloisomerization of functionalized *o*-(alkynyl)styrenes



Moreover, suitable substituted *o*-(alkynyl)styrenes are also valuable precursors of indene derived tetracarbocyclic compounds under gold catalysis. In this sense, dihydrobenzo[*a*]fluorenes can be selectively synthesized in a formal [3+3] cycloaddition from substrates bearing a secondary alkyl group at the β-position

of the styrene unit and an aromatic group at the acetylene (Scheme 62, eq. 1).[155] The reaction is proposed to proceed through a tandem 5-*endo* cycloisomerization/1,2-hydride migration, instead of the common proton elimination of related substrates (see Scheme 58). The new carbocation generated by this way would experience a Friedel-Crafts-type alkylation reaction followed by a protodemetalation to finally afford the tetracyclic adducts. Two isomeric dihydrobenzo[*a*]fluorenes with varied substitution patterns can be selectively obtained in high yields and diastereoselectivities by simply controlling the reaction conditions. Moreover, tetracyclic thieno-fused derivatives are also accessible by this methodology from a dienyne bearing a thienyl group linked to the triple bond (Scheme 62, eq. 2). Furthermore, a single example of dihydrobenzo[*a*]fluorene preparation from a symmetric 1,3,7,9-tetraen-5-yne in the presence of a phosphite-derived cationic gold catalyst has also been reported.[156] The cycloadduct is obtained in high yield and moderate diastereoselection and it is proposed to be formed by an intramolecular nucleophilic addition of the extra olefin to the 5-*endo* intermediate (Scheme 62, eq. 3). In contrast, reactions of related *o*-(alkynyl)styrenes with the extra olefin linked to the triple bond by an alkyl chain exclusively produce pentacyclic compounds, probably by intramolecular cyclopropanation at the *N*-heterocyclic derived gold carbene intermediate (Scheme 62, eq. 4).

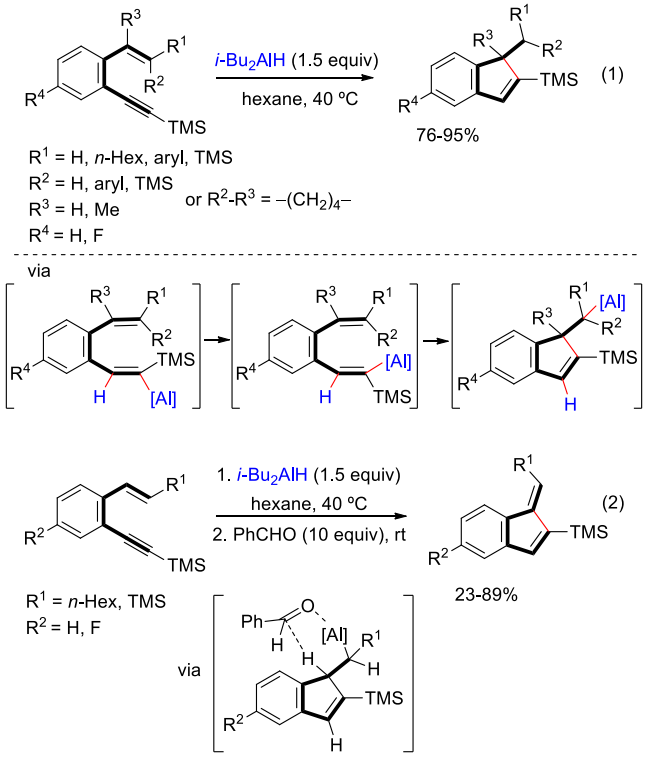
SCHEME 62. Synthesis of polycarbocyclic compounds containing an indene moiety by gold-catalyzed cycloisomerization of functionalized *o*-(alkynyl)styrenes



Although, as shown above, gold-catalysis has been a fundamental tool in the synthesis of indenes from *o*-(alkynyl)styrenes, other complementary approaches have been reported. Thus, Miura has described a synthesis of 2-trimethylsilyl-1*H*-indenes by DIBAL-H-promoted cyclization of *o*-(trimethylsilylethynyl)styrenes (Scheme 63, eq. 1).[157] The reaction encompasses a regioselective hydroalumination of the triple bond followed by an intramolecular carboalumination. Noteworthy, the trienic intermediate generated after the initial hydroalumination of the acetylene evolves by an alternative 6π-electrocyclization when the central double bond is not forming part of an aryl group (see Scheme 11). Both *E* and *Z* monosubstituted styrenes cyclize efficiently under the reported conditions, although aliphatic substituents are not well tolerated for *Z* olefins. Non-substituted, α-substituted and α,β-disubstituted styrenes also yield the corresponding indenes, whereas a β,β-disubstituted substrate does not lead to the

expected product. Moreover, in an effort for trapping the aluminated intermediate obtained after the cyclization, the reaction has been performed in the presence of benzaldehyde. However, the expected electrophilic trapping is not observed and a benzofulvene derivative is formed instead, which can be explained by a dehydroalumination through a 6-membered transition state (Scheme 63, eq. 2). Nevertheless, this process appears to be quite limited in scope and good yields are only shown for a couple of examples having a TMS group as substituent of the olefin.

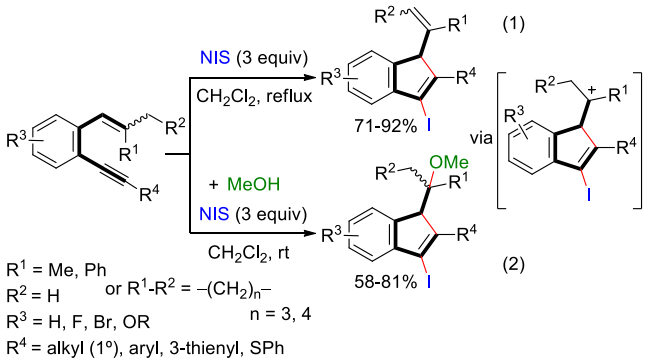
SCHEME 63. Synthesis of 2-trimethylsilyl-1*H*-indenes by DIBAL-H-promoted cyclization of *o*-(trimethylsilylethynyl)styrenes



On the other hand, indenes functionalized at C3 can be obtained by using different strategies encompassing the use of additional reagents. For example, although less fruitful than analogous halocycloaromatizations, direct halogen activation of the alkyne towards a formal 5-*endo* nucleophilic attack of the terminal alkene of the dienyne has been reported. In this sense, the iodocyclization of β,β-disubstituted *o*-(alkynyl)styrenes provides an efficient access to 3-iodo-1*H*-indenes (Scheme 64, eq. 1).[158] As in the related gold-catalyzed cyclizations reported above, the disubstitution at the β-position of the external olefin seems to be crucial for

the 5-*endo* ring closure (a 6-*endo* cyclization is observed for the corresponding α-methyl styrene substrate, see Scheme 18, eq. 1), probably through the key formation of a stabilized tertiary carbocation intermediate. These reactions occurr with broad scope, high yields and total regioselectivity using NIS as electrophilic reagent. Molecular iodine as well as NBS can also be used as halogen sources although lower yields and selectivities are achieved. In addition, further functionalization of the indenes is possible by adding an excess of an external nucleophile to the reaction media such as methanol (Scheme 64, eq. 2) or through palladium-catalyzed cross-coupling reactions with the halogen.

SCHEME 64. Synthesis of 3-iodo-1*H*-indenes by iodocyclyzation and methoxyiodocyclization of *o*-(alkynyl)styrenes

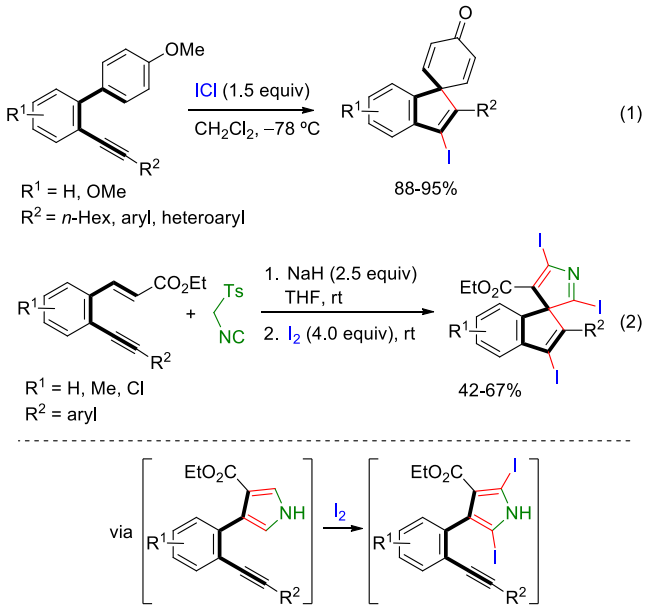


Moreover, ICl promoted reaction of 4'-methoxy-2-ethynylbiphenyls gives spirocyclic iodoindenes in excellent yields via a 5-*endo* cyclization through the *ipso* C of the *p*-methoxyphenyl group (Scheme 65, eq. 1).[159] The reaction is general at the alkyne but the *ipso* selectivity is limited to substrates bearing the *p*-methoxy arene as nucleophile, while substrates with other aromatic groups lead to iodophenantrenes through a conventional iodo-cycloaromatization (see Scheme 16). In this sense, the spirocyclic derivatives can also be rearranged to the corresponding phenantrenes by treating them with sulfuric acid in mixed CH_2Cl_2/MeOH.

A related *ipso*-5-*endo* iodine-promoted cyclization of 3-(2-ethynylphenyl)-1*H*-pyrroles, generated *in situ* from *o*-(alkynyl)cinnamates and TosMIC in the presence of NaH, allows the synthesis of spiro-2-aryl-3-iodo-indenes through a 3-(*o*-alkynylphenyl)pyrrol intermediate (Scheme 65, eq. 2).[142] These reactions, conducted in THF by a sequential *one-pot* protocol, afford the spiro-3-iodo-indene derivatives diiodinated at

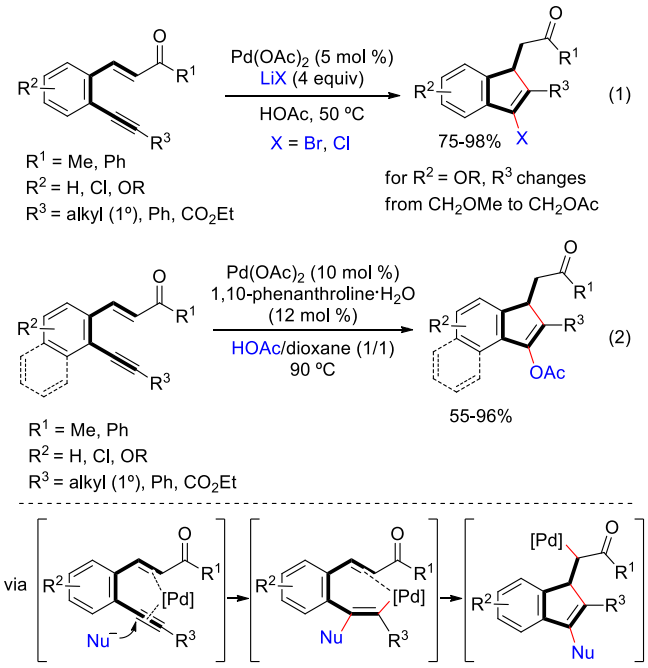
the pyrrol unit in moderate yields referred to the starting cinnamates, as a result of the initial periodination of the heterocyclic unit followed by the 5-*endo* cyclization. Interestingly, the tandem reaction is solvent dependent, and a conventional cycloaromatization of the intermediate *o*-(alkynyl)biaryl selectively occurs in dichloromethane to give benzo[*e*]indoles (See Scheme 51).

SCHEME 65. Synthesis of spirocyclo-3-iodo-1*H*-indenes by iodine-promoted iodocyclization of particular 1,3-dien-5-ynes



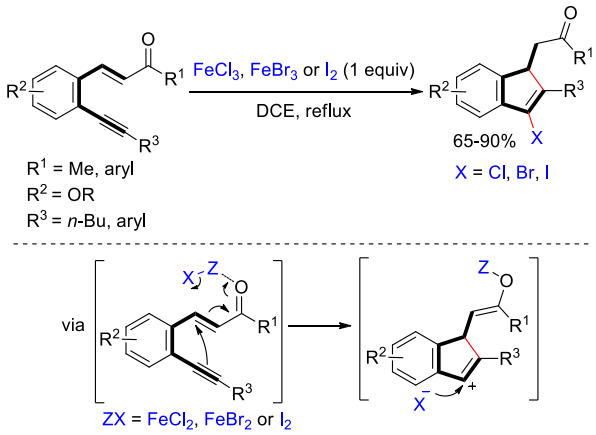
On the other hand, *o*-(alkynyl)benzylideneketones have demonstrated to be valuable precursors of 3-haloindenes by metal-mediated reactions in the presence of a nucleophilic halogen source. For example, Lu has reported that the intermediate generated by intermolecular addition of a halogen coming from a LiX species to the palladium-activated triple bond undergoes an olefin insertion followed by protonolysis of the carbon-palladium bond to afford the corresponding 3-haloindenes (Scheme 66, eq. 1). Moreover, 3-acetoxyindenes can be synthesized in a similar way by performing the reaction in HOAc and in the absence of LiX species (Scheme 66, eq. 2). Both 3-functionalized indenes are obtained in good yields.[160]

SCHEME 66. Palladium-catalyzed synthesis of 3-halo- and 3-acetoxy-1*H*-indenes from *o*-(alkynyl)benzylideneketones



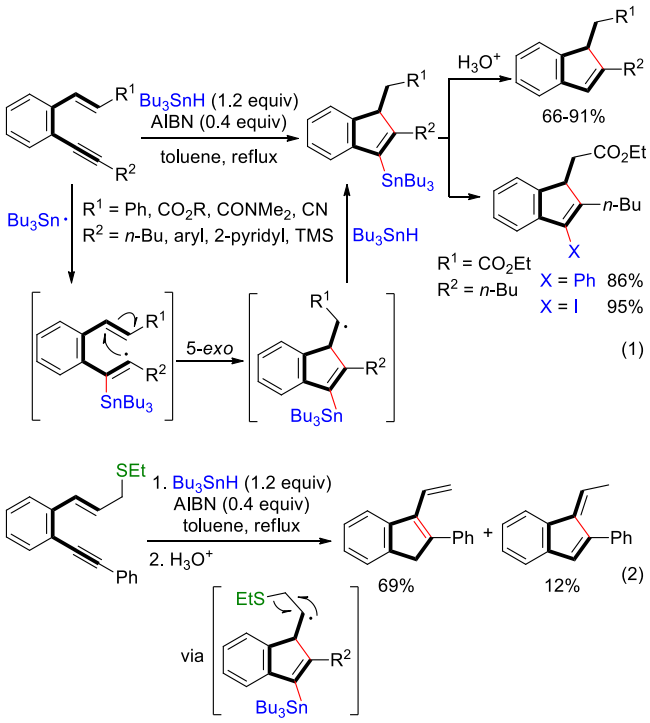
An analogous synthetic strategy has been employed by Srinivasan using stoichiometric amounts of FeX_3 or I_2 as reaction promoter and halogen source.[161] These reactions occur with good yields although the scope is limited to *o*-(alkynyl)benzylideneketones having an electron-rich arene (Scheme 67). The mechanism proposed by the authors differs from the palladium-catalyzed transformation previously depicted. In this case, the Lewis acid would activate the α,β-unsaturated ketone towards an intramolecular conjugated addition of the acetylene. A vinyl cationic intermediate would be thus generated and intermolecularly trapped by a halide ion to produce an enolate that, in the presence of water, would render the observed haloindenes.

SCHEME 67. Lewis acid-promoted synthesis of 3-halo-1*H*-indenes from *o*-(alkynyl)benzylideneketones



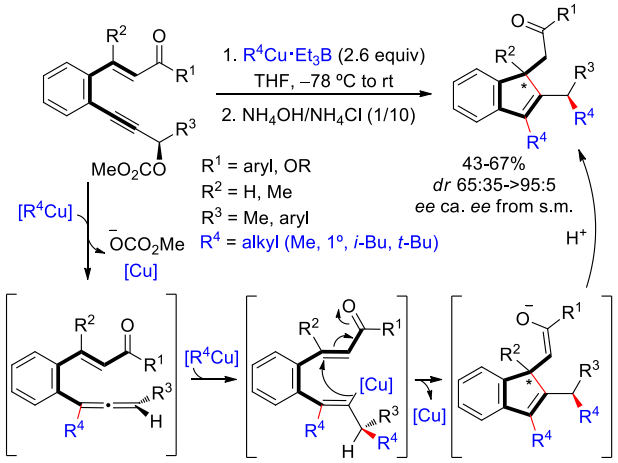
Moreover, indenes having a organotin substituent at C3 can be accesed by cycloaromatization of *o*-(alkynyl)styrenes in the presence of tributyltin hydride and a radical initiator. As pointed out in Section 2.2.1, the outcome of this radical cascade reaction of *o*-(alkynyl)styrenes is determined by the substitution at β-position of the styrene unit. In fact, whereas alkyl groups lead to naphthalene derivatives (see Scheme 25), a radical-stabilizing substituent, such as ester, amide, cyano or phenyl, at that position completely switches the selectivity of the cyclization to the exclusive formation of indene derivatives (Scheme 68, eq. 1). The reaction is proposed to proceed through a 5-*exo*-*trig* cyclization of the least stable radical intermediate to form an indene species that, rather than evolving through a ring expansion as observed for *o*-(alkynyl)styrenes bearing H or alkyl groups at the alkene terminus (see Scheme 25), undergoes a H abstraction to give, after a hydrolysis step or alternatively by further functionalization, the corresponding 2-substituted and 2,3-disubstituted indenes in high yields and wide scope.[109,110,162] Moreover, indene derivatives with an additional double bond are obtained from a thioether substrate through β-C–S scission at the indene radical intermediate, which is also an experimental evidence for the proposed mechanism (Scheme 68, eq. 2).

SCHEME 68. Radical-mediated synthesis of indenes from *o*-(alkynyl)styrenes



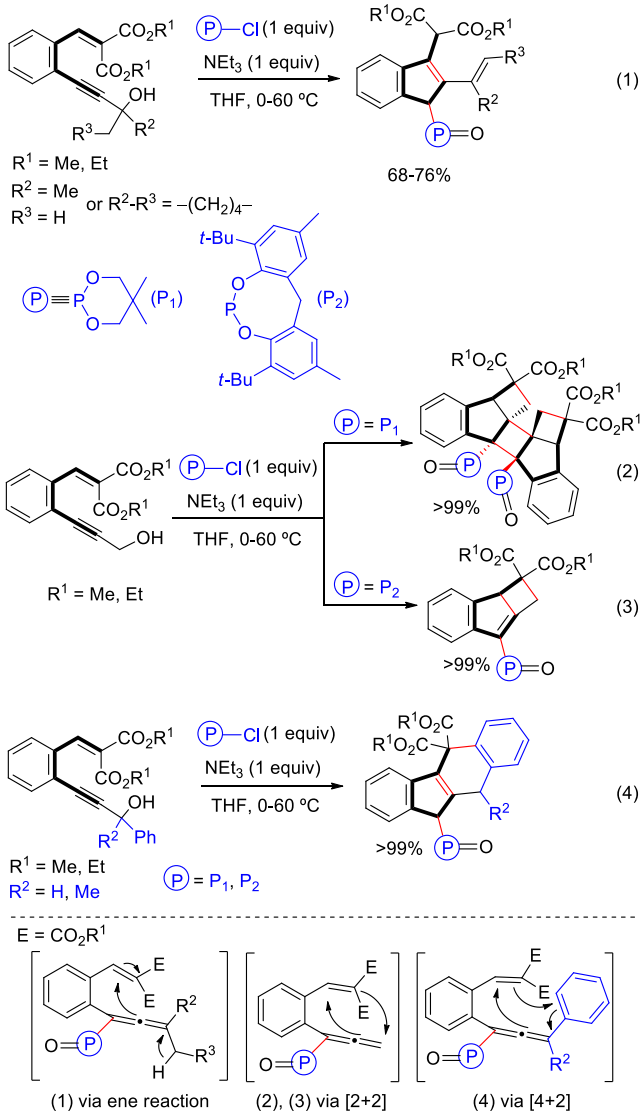
Bertrand and Nechab have made use of an organocopper-triggered cyclization to access chiral 3-alkyl indenes with high enantiomeric exceses and moderate to good yields and diastereoselectivities (Scheme 69).[163] The reaction takes place with chirality transfer from enantiomerically enriched *o*-(alkynyl)chalcones with a propargylic carbonate moiety. The mechanism that accounts for this transformation begins with selective addition of an organocopper reagent to the propargylic carbonate in a S_N2' fashion, generating an allene intermediate in a process that occurs with central-to-axial chirality transfer. Then, carbocupration of the allene with a second equivalent of the organocopper reagent occurs, in a step that implies another chirality transfer, in this case axial to central. Finally, diastereoselective intramolecular 1,4 addition and hydrolysis gives rise to the chiral indene derivatives. Interestingly, almost complete chirality transfer from the starting material to both formed diastereoisomers is observed in all the cases studied, and indenes bearing a cuaternary stereocenter can be obtained with high enatiomeric excesses by this methodology.

SCHEME 69. Synthesis of 3-alkylindenes by organocopper-triggered cyclization of *o*-(alkynyl)chalcones with a propargylic carbonate moiety



Indenes having a phosphorous substituent in C1 can also be synthesized from appropriate *o*-(alkynyl)benzylidenemalonates and phosphorochloridites in the presence of a base (Scheme 70). This approach is based on the cyclization of *in situ* generated styryl substituted allenyl phosphonates. The nature of the substituents at the terminal carbon of the allene unit, i.e. the propargylic carbon in the starting material, determines the outcome of the reaction. Thus, dialkyl-substituted propargyl derivatives produce in good yields phosphono-indenes that would be formed by an intramolecular ene reaction at the allene intermediate and subsequent isomerization (Scheme 70, eq. 1).[164] However, the corresponding terminal allenes generated from alcohols unsubstituted at the propargylic position evolve through a [2+2] cyclization to selectively afford in quantitative yields phosphorous-functionalized cyclobutane-fused indenes or their [2+2] dimeric adducts depending on the bulkiness of the P(III) reagent (Scheme 70, eq. 2, 3).[165] Moreover, quantitative formation of benzo[*b*]fluorenes occurs with substrates possessing a phenyl group at the propargylic position (Scheme 70, eq. 4). In this case, the extra aryl group partakes in a formal [4+2] cycloaddition that would afford the observed tetracycles by rearomatization.

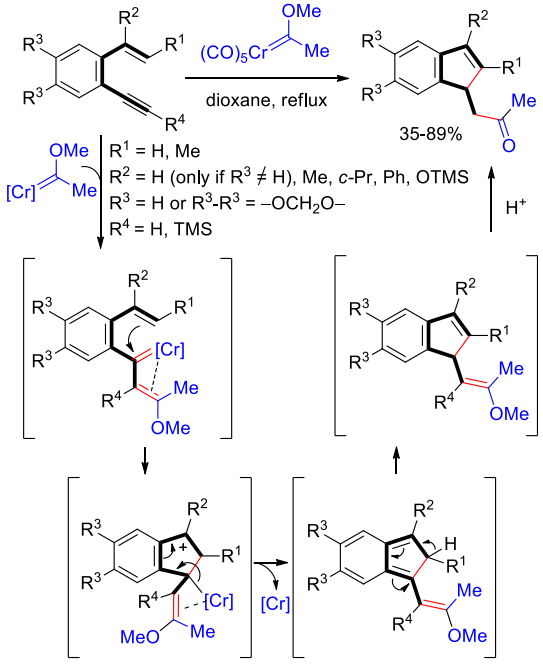
SCHEME 70. Synthesis of 1-phosphono-indenes and related polycyclic compounds by reaction of *o*-(3-hydroxyprop-1-yn-1-yl)benzylidenemalonates with phosphorochloridites



3.2.2. Reactions with formation of a new bond between C1 and C5. Early examples of indene synthesis by creating a new bond between C1 and C5 of an *o*-(alkynyl)styrene system were reported by Herndon during his studies on the reactivity between 1,3-dien-5-ynes and Fischer carbene complexes.[166] Thus, he found that indene derivatives can be selectively obtained in good yields from selected *o*-(alkynyl)styrenes with terminal or TMS substituted triple bonds and electron-donating groups either in the α-position of the olefin or in the aryl moiety (Scheme 71). In some cases double-bond isomers are also obtained as minor products. The process starts with the insertion of the alkyne in the Cr–C bond of the carbene complex, as proposed for

the benzannulation reactions previously reported (see Scheme 49). However, now a nucleophilic attack of the alkene to the carbene carbon, favoured by the presence of electron-donating groups, occurs instead of the expected CO insertion, thus finally leading to indene derivatives after loss of the metal, isomerization and hydrolysis. On the other hand, *o*-(alkynyl)styrenes with unsubstituted or β-Me-substituted olefins lead to significant amounts of cycloaromatized products together with the indene derivatives and/or their isomers.

SCHEME 71. Synthesis of indenes from *o*-(alkynyl)styrenes and Fischer carbene complexes

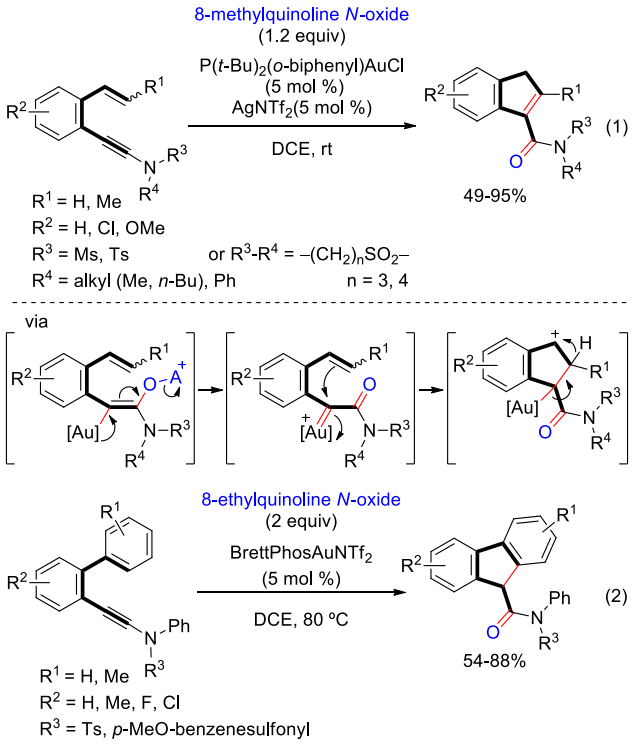


A modern strategy for the construction of the indene skeleton by connecting C1 and C5 of the starting 1,3-dien-5-ynes is based on a gold-catalyzed oxidative cyclization. Liu initially described this approach in the reaction of 8-methylquinoline *N*-oxide with *o*-(aminoethynyl)styrenes in the presence of a cationic gold complex (Scheme 72, eq. 1). These reactions afford 3-aminocarbonyl-substituted indenes in high yields and with complete selectivity when the external olefin of the dienyne is unsubstituted; otherwise, moderate yields are obtained due to the formation of appreciable amounts of acyclic adducts.[167] Moreover, this reaction is restricted to aminoethynyl styrenes, as substrates unsubstituted or alkyl-substituted at the alkyne exclusively produce benzocyclopentenones (see Scheme 94, eq. 1, 3). The reaction is proposed to proceed through the formation of an α-amido gold carbenoid intermediate generated by a regioselective oxidation at the terminal

carbon of the acetylene of the starting dienyne and subsequent rearrangement. Then, carbocyclization would occur followed by a 1,2-H shift that finally gives the observed 3-(aminocarbonyl)indenes. The latter proton shift is experimentally supported by deuterium-labelling experiments.

The same strategy has been later employed by Ye for the synthesis of 9-(aminocarbonyl)fluorenes from appropriate *o*-(aminoethynyl)biaryls (Scheme 72, eq. 2).[168] The functionalized tricyclic compounds are obtained in moderate to good yields although with narrow scope at the external aryl of the conjugated system, that should be unsubstituded or alkyl substituted. In this sense, halogen substitution at that benzene ring leads to <10 % of the desired fluorene and, on the other hand, a substrate with a methoxy group at this arene efficiently furnishes an spirocyclic indene as a result of direct cycloisomerization without oxidation.

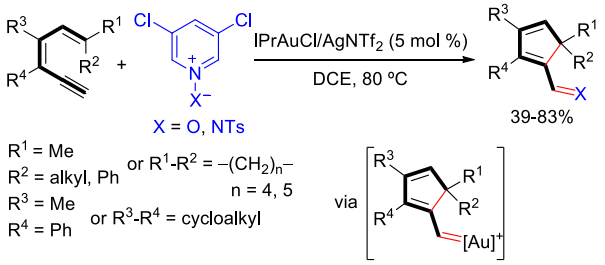
SCHEME 72. Synthesis of 3-(aminocarbonyl)indenes and 9-(aminocarbonyl)fluorenes by gold-catalyzed oxidative cyclization of *o*-(aminoethynyl)styrenes



An interesting oxidant-dependent chemoselectivity has been reported in the analogous gold-catalyzed oxidative cycloisomerization of substituted 1,3-dien-5-ynes having a terminal alkyne.[169] Thus, whereas reaction with 8-methylquinoline *N*-oxide gives cyclopentenones (see Scheme 94, eq. 2), the reaction with less

nucleophilic 3,5-dichloropyridine *N*-oxide exclusively produces cyclopentadienyl aldehydes under same gold-catalyzed conditions (Scheme 73). These reactions occur with moderate to good yields provided that a tetrasubstituted substrate is employed as starting material. The favored formation of these cyclopentadienes over the cyclopentenones is attributed to an exchange in the order of the cyclization and oxidation steps along the reaction mechanism. Moreover, a related iminocylization allows the synthesis of the corresponding cyclopentadienyl imines with similar yields and scope. Furthermore, this chemoselectivity switch is not observed for related β,β-disubstituted *o*-(alkynyl)styrenes that exclusively afford the expected cyclopentanones even when 3,5-dichloropyridine *N*-oxide is used as oxidant (Scheme 94, eq. 3).

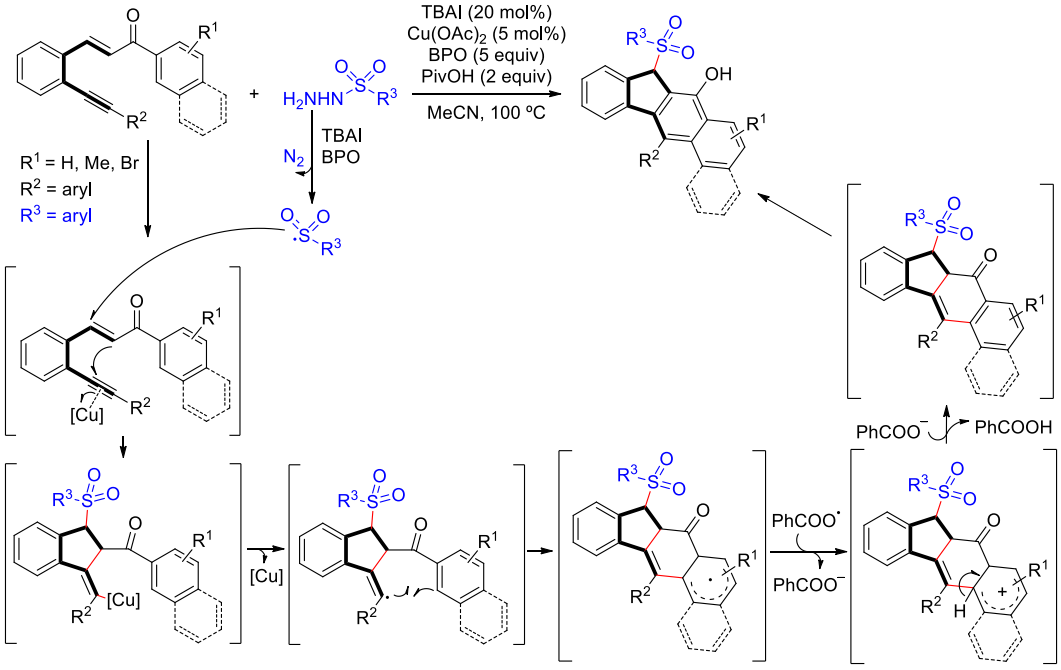
SCHEME 73. Synthesis of cyclopentadienyl aldehydes or imines by gold-catalyzed oxidative cyclization of 1,3-dien-5-ynes



Moreover, Jiang, Tu and Liu have described a straightforward synthesis of 11-sulfonyl-11*H*-benzo[*b*]fluorenes based on a catalytic arylsulfonyl radical-triggered bicyclization of *o*-(alkynyl)chalcones in the presence of a copper catalyst (Scheme 74).[170] Noteworhty, both a five-membered ring and an aromatic ring are built in a single step in this transformation. The reaction starts with the addition of a sulfonyl radical, generated *in situ* from the corresponding sulfonyl hydrazide in the presence of BPO and TBAI, to the internal carbon of the olefin of the *o*-(alkynyl)chalcone, followed by a 5-*exo* cyclization over the copper-coordinated triple bond. Then, homolytic cleavage of the copper-carbon bond occurs, forming a vinyl radical intermediate that cyclizes to form the new six-membered ring. Subsequent single electron transfer oxidation, deprotonation and final tautomerization lead to the final products. In this way 5-aryl-11-arylsulfonyl-11*H*-benzo[*b*]fluorenes can be synthesized in moderate to high yields. Moreover both electron-withdrawing and electron-donating

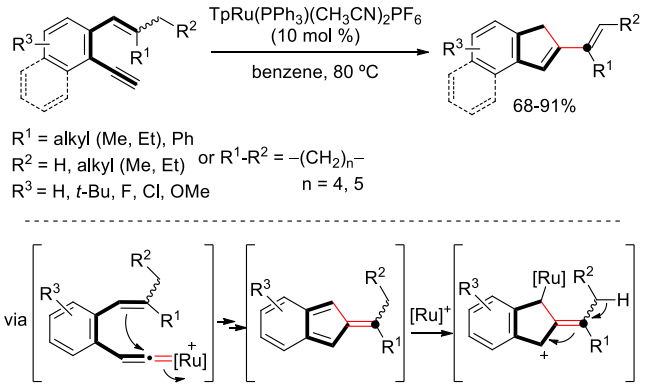
groups are well tolerated as substituents of the aryl group which participates in the cyclization.

SCHEME 74. Synthesis of 11-sulfonyl-11*H*-benzo[*b*]fluorenes by arylsulfonyl radical-triggered bicyclization of *o*-(alkynyl)chalcones



3.2.3. Reactions involving a migration of a carbon atom of the alkene. As part of his studies on ruthenium-catalyzed cycloisomerizations of 1,3-dien-5-ynes (see Schemes 37-39), Liu has described that β,β-disubstituted *o*-(ethynyl)styrenes produce 2-alkenyl-1*H*-indenes usually in high yields (Scheme 75).[171] However, this transformation is not completely selective, and variable amounts of isomeric naphthalenes, coming from a formal 6-*endo* cyclization, are also formed depending on the position and electronic nature of the substituents at the central aromatic ring and on the substitution at the alkene terminus. Based on deuterium- and ^{13}C-labelling experiments the authors propose a plausible mechanism for the indene formation. Thus, the reaction is initiated by a 5-*endo*-cyclization over a ruthenium-vinylidene intermediate that, after different rearrangements, gives a isobenzofulvene intermediate where cleavage of the original C–C double bond of the dienyne has occurred. Further evolution of the isobenzofulvene adduct catalyzed by the cationic ruthenium complex through a benzyl cation intermediate accounts for the formation of the observed 2-alkenyl-1*H*-indenes.

SCHEME 75. Ruthenium-catalyzed synthesis of 2-alkenyl-1*H*-indenes from *o*-(ethynyl)styrenes



3.3. Fulvenes and benzofused analogues

Most of the syntheses of fulvenes, benzofulvenes and methylenefluorenes from 1,3-dien-5-ynes imply the formation of a new bond between carbons 1 and 5. However, diverse transformations following different mechanisms can lead to this topology. Moreover, scarce examples following other topologies have been reported.

3.3.1. Reactions with formation of a new bond between C1 and C5. One of the more general strategies for the synthesis of fulvenes from 1,3-dien-5-ynes is depicted in Figure 5. It consists on the initial activation of the alkene moiety, either by direct C–H activation or via oxidative addition of a C–halogen bond to a metal catalyst. Then, a regioselective intramolecular carbometalation of the alkyne occurs, and the vinylmetal intermediate can evolve by a protodemetalation or experience further functionalization.

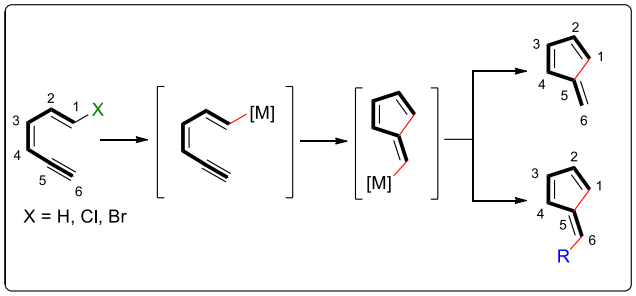


FIGURE 5. Main strategy for the synthesis of fulvenes from 1,3-dien-5-ynes with formation of a new bond between C1 and C5

In the following lines, reactions initiated by C–H activation are first considered, followed by those starting

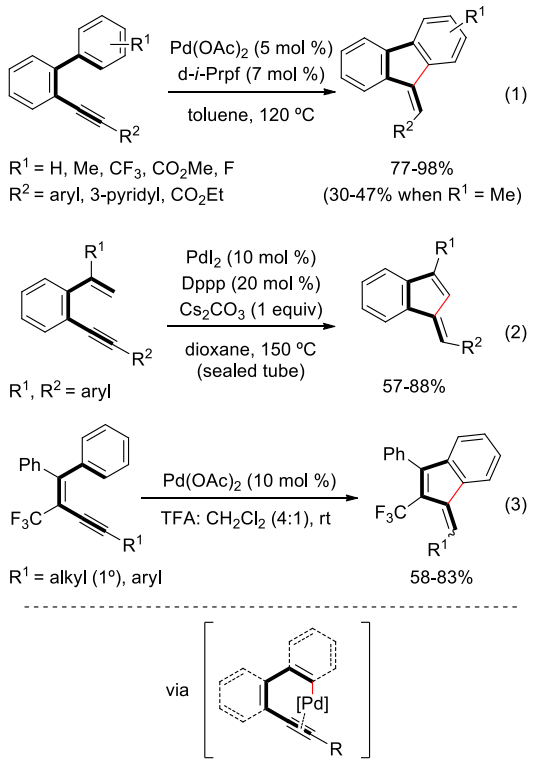
with an oxidative addition.

We have previously discussed how *o*-(alkynyl)biphenyls can serve as efficient precursors for the synthesis of phenanthrene derivatives under different metal catalysis by formal 6-*endo* cyclizations (see Section 2.1.1.). However, under certain conditions these substrates can lead to methylenefluorenes via a formal 5-*exo* cyclization. In this sense, Gevorgyan has reported an efficient synthesis of methylenefluorenes from *o*-(alkynyl)biaryls using a palladium catalyst (Scheme 76, eq. 1).[172,173] Noteworthy, the reaction is completely *cis* selective in all cases. Moreover, biaryls containing electron-defficient groups react faster than those with neutral ones, whereas reactions of substrates with electron-donating substituents are sluggish, which supports a C–H activation pathway rather than an electrophilic activation of the alkyne. Kinetic isotope effect studies also are in better agreement with the suggested C–H activation.

More recently, Hamze and Alami have studied the selectivity in the metal-catalyzed cyclization of *o*-alkynyl-(1-arylvinyl)benzenes, and they have found, in line with the previous observations of Gevorgyan for *o*-(alkynyl)biphenyls, that a selective synthesis of benzofulvenes via a formal 5-*exo* cyclization takes place when using a palladium catalyst (Scheme 76, eq. 2), whereas cycloaromatization occurs in the presence of a gold catalyst (see Scheme 6, eq. 2).[19] With this methodology, benzofulvenes can be synthesized in good yields and, in contrast with the formation of fluorenes reported by Gevorgyan, with total *trans*-stereoselectivity. Either electron-withdrawing or electron-donating substituents are well tolerated in both of the aryl groups whereas alkyl substituents do not lead to the cyclized products. Computational studies also support a C–H activation pathway for this transformation.

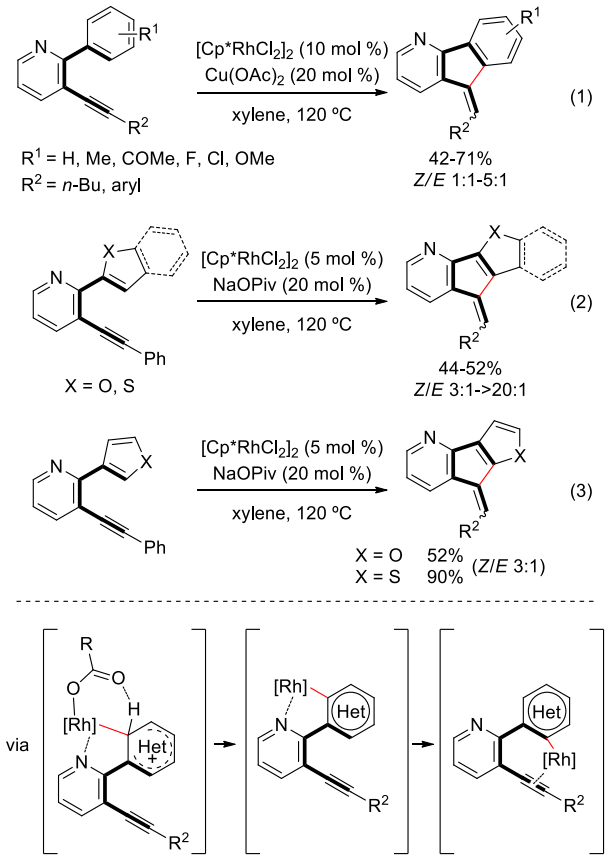
A related methodology based on the use of palladium catalysis has been used by Jeong for the synthesis of trifluoromethyl-substituted benzofulvenes from 2-trifluoromethyl-1,1-diphenyl-1,3-enynes, although a narrow scope is surveyed and the products are in this case obtained as a mixture of isomers (Scheme 76, eq. 3).[174]

SCHEME 76. Synthesis of methylenefluorenes and benzofulvenes by palladium catalyzed cyclization of 1,3-dien-5-ynes



Although palladium complexes have been the most commonly used catalysts for the synthesis of fulvene derivatives via C–H activation of the alkene/arene moiety, a rhodium-catalyzed protocol has also been reported by Shibata.[175] Thus, cyclization of 3-alkynyl-2-arylpyridines in the presence of catalytic amounts of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ leads to 4-azamethylenefluorene derivatives in moderate to good yields and generally low diastereoselectivities (Scheme 77, eq. 1). The proposed mechanism for this transformation starts with a pyridine-directed C–H activation, facilitated by the acetate. Then a "rollover" occurs giving an intermediate in which the metal is coordinated to the alkyne, similar to the one proposed in the palladium catalyzed reactions discussed above. The directing role of the pyridine in the C–H activation is confirmed by the lack of reactivity of substrates missing the N at this position. Analogously, 3-alkynyl-2-heteroarylpyridines can also be cyclized using this methodology, although in this case the use of NaOPiv leads generally to better results than $Cu(OAc)_2$ (Scheme 77, eq. 2, 3).[176]

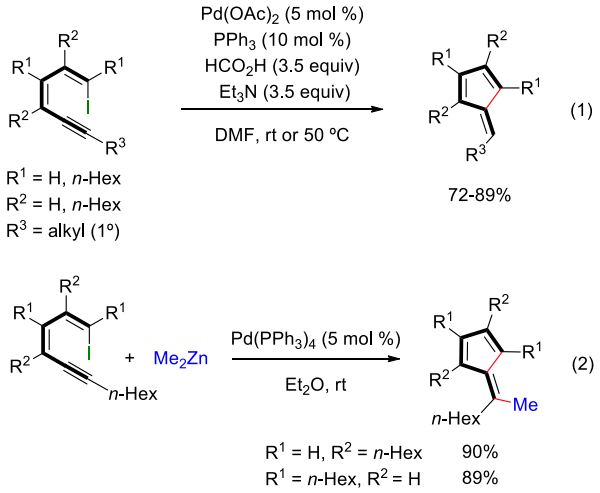
SCHEME 77. Synthesis of 4-azamethylenefluorenes and other related heterocycles by rhodium catalyzed cyclization of 3-alkynyl-2-(hetero)arylpyridines



As previously pointed out, activation via oxidative addition to a metal complex of a halo-alkene or halo-arene moiety is also a common approach for the synthesis of fulvene derivatives from 1,3-dien-5-ynes, being palladium the metal of choice.

For example, Sato has used this strategy for the synthesis of a few fulvenes from 1-iodo-1,3-dien-5-ynes.[177] The reaction is catalyzed by $Pd(OAc)_2$ in the presence of PPh_3, and provides fulvenes in good yields and as single *E*/*Z* isomers, which allows the selective synthesis of both the *E* and *Z* isomers by proper election of the substituents of the starting dienyne (Scheme 78, eq. 1). Moreover, when the cyclization is carried out in the presence of Me_2Zn the methyl group is incorporated into the final product, thus yielding fulvenes with a tetrasubstituted olefin unit in excellent yields (Scheme 78, eq. 2).

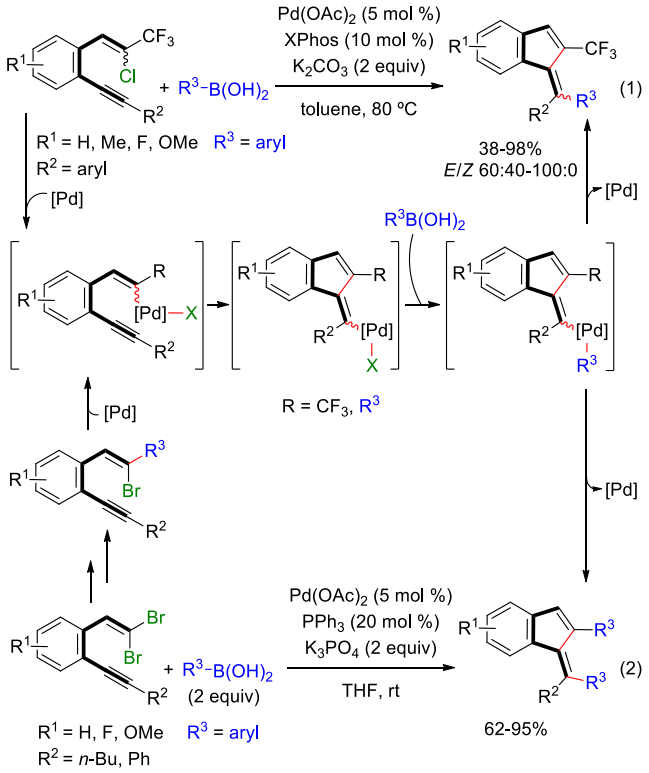
SCHEME 78. Synthesis of fulvenes by palladium-catalyzed cyclization of 1-iodo-1,3-dien-5-ynes



Using an analogous approach Zhang has reported a synthesis of trifluoromethyl-substituted fulvenes from *o*-(alkynyl)styrenes which have CF_3 and Cl as substituents at the terminal position of the olefin and boronic acids in the presence of a palladium catalyst (Scheme 79, eq. 1).[178] A broad substrate scope is demonstrated and the corresponding benzofulvenes are generally obtained in good yields and variable stereoselectivities. Only the use of boronic acids with electron-withdrawing groups leads to decreased yields. The reaction proceeds through an initial oxidative addition, followed by carbopalladation of the triple bond. Then, transmetallation with the boronic acid and subsequent reductive elimination generate the final products.

In a similar fashion, Wu has described the synthesis of benzofulvenes with a tetrasubstituted olefin by a palladium-catalyzed reaction of *o*-(alkynyl)styrenes with a dibromo-substituted olefin and two equivalents of a boronic acid (Scheme 79, eq. 2).[179] In this case the products are obtained with excellent stereoselectivity. The process is proposed to start with an initial Suzuki reaction involving one of the C–Br bonds. Then, the reaction would proceed through a mechanism analogous to that discussed above for the synthesis of trifluoromethyl-substituted fulvenes.

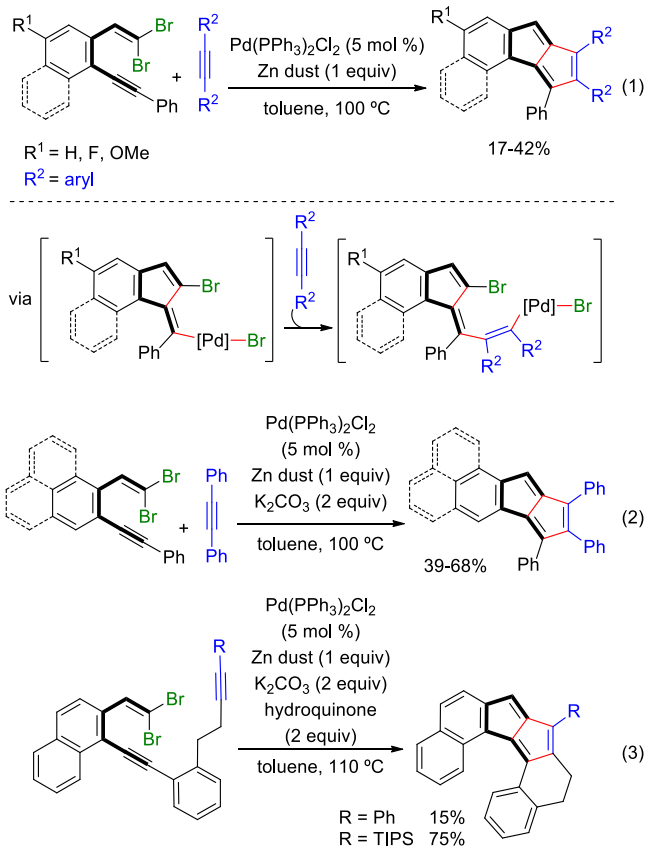
SCHEME 79. Synthesis of benzofulvenes by palladium catalyzed reaction of *o*-(alkynyl)styrenes and boronic acids



The intermediate vinylpalladium species generated by intramolecular carbopalladation of the triple bond in 1,3-dien-5-ynes can also be trapped by reaction with an alkyne in the presence of Zn, leading to benzopentalenes. Thus, Diederich has reported a synthesis of a variety of benzopentalenes by reaction between internal acetylenes and β,β-dibromo-*o*-(alkynyl)styrenes (Scheme 80, eq. 1), analogous to the ones used by Wu in his synthesis of benzofulvenes. The first steps of this transformation are again oxidative addition followed by intramolecular carbopalladation. Then, the generated vinylpalladium species experiences an intermolecular carbopalladation with the alkyne, leading to a new vinylpalladium intermediate whose evolution to the final product could be explained by different mechanisms, all of them involving the participation of Zn as reducing reagent. Although very low yields were generally obtained in their first reported aproach,[180] they later found the beneficial effect of adding 2 equivalents of K_2CO_3 to the reaction media (Scheme 80, eq. 2, 3).[181] The use of this additive leads to enhanced yields, and this improved protocol has been applied for the synthesis of novel naphthopentalenes, via both inter- and intramolecular procceses. This methodology

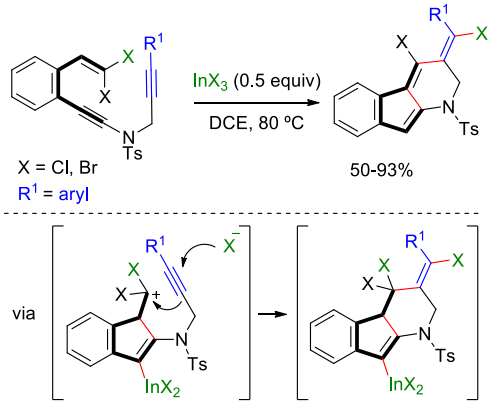
provides access to a kind of compounds that are otherwise inaccessible or difficult to prepare, and has for example been applied to the synthesis of interesting bispentalenes.[182]

SCHEME 80. Synthesis of benzopentalenes by palladium catalyzed reaction of β,β-dibromo-*o*-(alkynyl)styrenes and acetylenes.



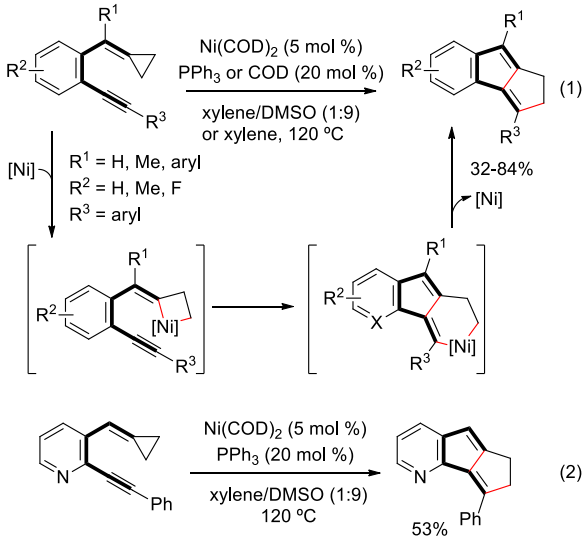
On the other hand, Yeh has also reported an intramolecular trapping of an alkyne moiety for the synthesis of benzofulvene derivatives from β,β-dihalo-*o*-(alkynyl)styrenes, although through a completely different mechanism (Scheme 81).[152] In this case a carbocationic alkenylindium intermediate is generated by addition of the dihaloolefin unit to the triple bond activated by coordination to an indium-catalyst, in an analogous way to what was proposed for the synthesis of indenes from similar substrates (see Scheme 58). Then, intramolecular addition of the pendant alkyne to the carbocation occurs with simultaneous *anti*-addition of a halide to the triple bond. Finally, loss of HX and protodemetalation lead to 2,3-dihydro-1*H*-indeno[2,1-*b*]pyridines in good yields for a series of starting materials having an aryl substituent in the pendant triple bond.

SCHEME 81. Synthesis of 2,3-dihydro-1*H*-indeno[2,1-*b*]pyridines by indium-catalyzed cycloisomerization of *o*-(alkynyl)styrenes with a pendant triple bond



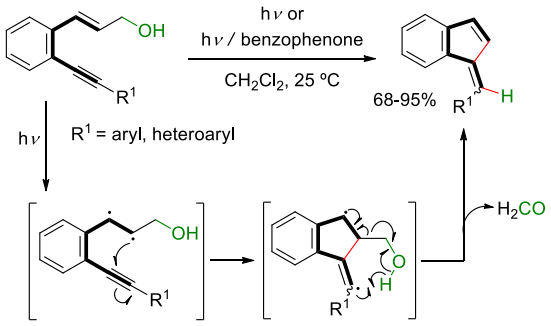
Complementing the reactions triggered by C–H or C–X activation of the olefin/arene moiety of the 1,3-dien-5-ynes mentioned so far, Zhang has reported a transformation implying C–C activation.[183] Using *o*-(alkynyl)styrenes in which the olefin is forming part of a methylenecyclopropane moiety as starting materials, cyclopenta[*a*]indene derivatives can be obtained in moderate to good yields through a nickel catalyzed process (Scheme 82, eq. 1). The reaction is proposed to be initiated by an oxidative addition of the proximal C–C bond of the cyclopropane to the nickel complex generating a nickelacyclobutane intermediate. Then, intramolecular addition to the triple bond occurs, followed by reductive elimination leading to the corresponding cyclopenta[*a*]indene derivatives. This methodology is restricted to substrates having aryl substituted alkynes; both electron-withdrawing and electron-donating groups are well tolerated either in *meta* or *para* positions, whereas *o*-substitution leads to lower yields. The use of PPh_3 as ligand and a mixture of xylene and DMSO as solvent are the conditions of choice for substrates with $R^1 = H$, while better results are obtained using COD as ligand in pure xylene as solvent for those 1,3-dien-5-ynes with $R^1 \neq H$. Moreover, a single example of the cyclization of a dienyne containing a pyridine ring is also reported (Scheme 82, eq. 2).

SCHEME 82. Synthesis of cyclopenta[*a*]indene derivatives by nickel-catalyzed cyclization of *o*-(alkynyl)styrenes with a methylenecyclopropane moiety



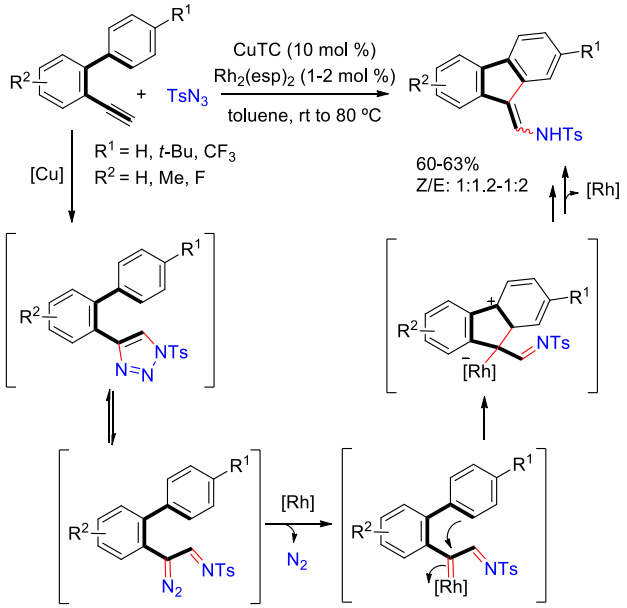
In addition, Ottosson and Alabugin have reported an efficient synthesis of benzofulvenes via the elusive C1−C5 photochemical cyclization of *o*-(alkynyl)styrenes (Scheme 83).[184] The process is initiated in this case by photochemical activation of the olefin followed by cyclization. The authors envisioned that the diradical species formed during the desired C1−C5 photochemical cyclization could be efficiently trapped through a concerted carbon−carbon fragmentation/H abstraction process with a CH_2OH group located at the terminal position of the olefin. Therefore, reactions of such substrates having as well an (hetero)aryl substituent at the triple bond give the corresponding benzofulvenes in good to excellent yields and complete selectivity. Interestingly, for some dienynes the addition of benzophenone, a recognized triplet sensitizer, to the reaction media is needed to suppress the formation of C1−C6 cyclized naphtalenes, thus suggesting a triplet excited state cyclization/fragmentation mechanism for the benzofulvene formation.

SCHEME 83. Synthesis of benzofulvenes by C1-C5 photochemical cyclization of *o*-(alkynyl)styrenes



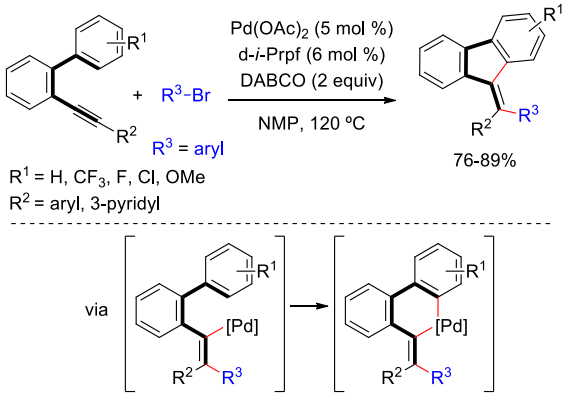
The transformations discussed up to now in this section are initiated by activation of the olefin moiety of the dienyne. However, some reactions starting with addition of external reagents to the alkyne, without implication of the olefin, have also been reported. In this sense, Lee has described a synthesis of fluorene derivatives with an enamine group at C9 by reaction of *o*-(ethynyl)biaryls and tosylazide in the presence of both a copper and a rhodium catalyst (Scheme 84).[185] The transformation starts with a copper-catalyzed [3+2] cycloaddition between the azide and the triple bond, leading to a triazol that tautomerizes to a diazo compound that, in the presence of the rhodium complex, generates an α-imino rhodium carbenoid. This intermediate experiences a cyclization by intramolecular attack of the terminal aryl group. Finally, rearomatization and protodemetalation yields the methylenefluorene derivatives as mixtures of isomers at the enamine double bond. Although for selected examples it has been demonstrated that the transformation can be efficiently performed as explained in *one-pot*, starting from the *o*-(ethynyl)biaryls and the azides and adding both the copper and the rhodium catalysts at the beginning of the reaction, most of the reported examples use a preformed triazol.

SCHEME 84. Synthesis of fluorene derivatives with an enamine substituent at C9 from *o*-(ethynyl)biaryls and azides



Moreover, Gevorgyan has described a cascade transformation closely related to the one depicted in Scheme 76, eq. 1, but involving as external reagent an aryl halide, which allows the synthesis of highly substituted methylenefluorene derivatives in high yields (Scheme 85).[173] C–H activation is also a key step in this reaction, although it is proposed to be initiated by the carbopalladation of the alkyne with participation of the aryl halide derivative.

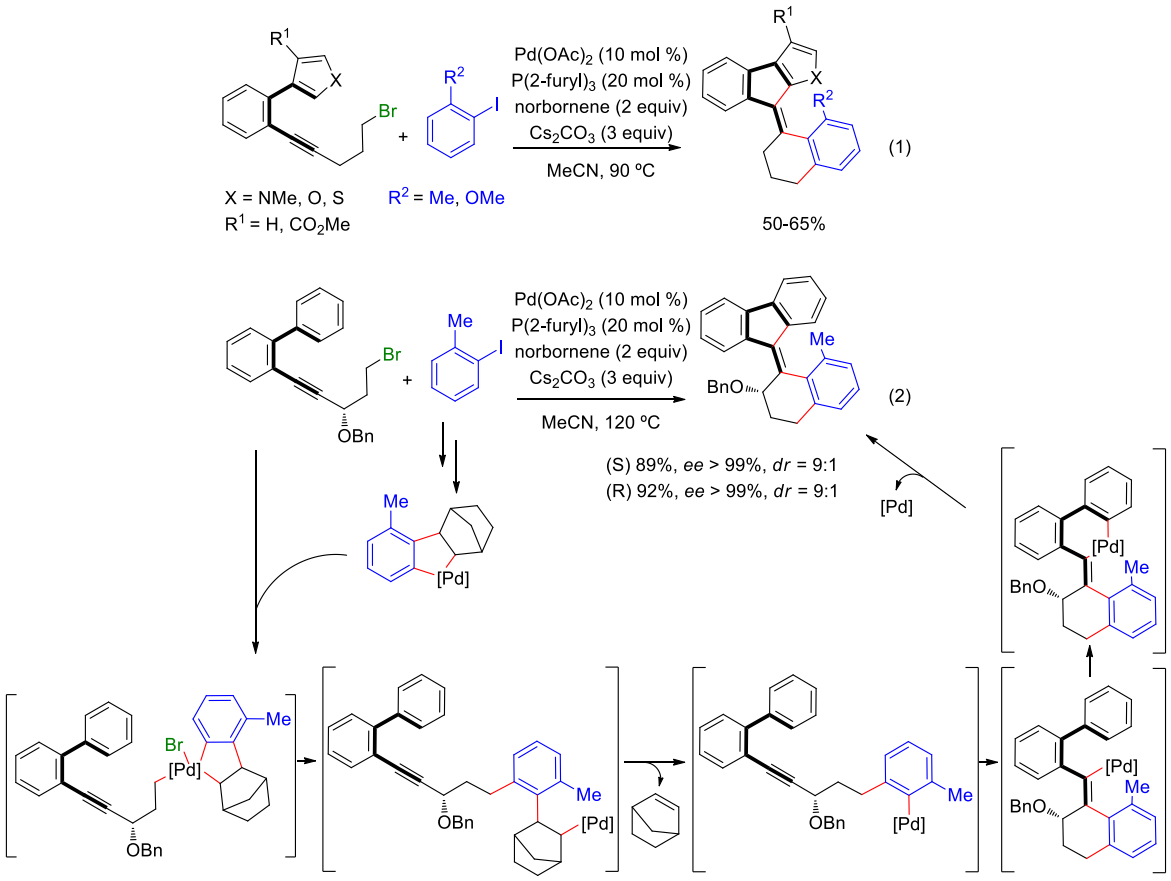
SCHEME 85. Synthesis of methylenefluorene derivatives by palladium-catalyzed cyclization of *o*-(alkynyl)biaryls in the presence of aryl halides



Furthermore, a synthesis of compounds with tetrasubstituted helical olefins containing a benzofulvene in

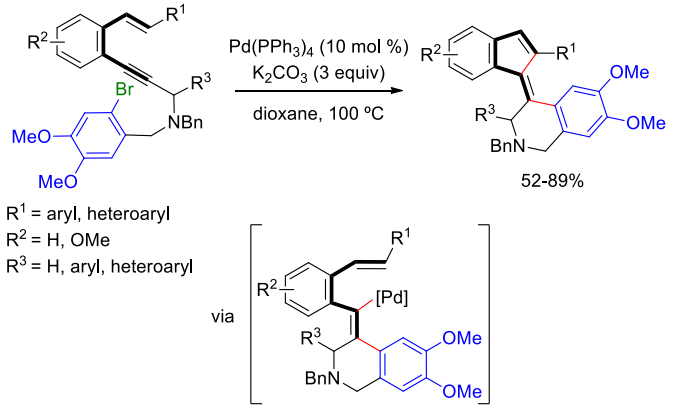
their structure has been reported using functionalized *o*-(alkynyl)bi(hetero)aryls and iodobenzene derivatives as starting materials in the presence of norbornene and a palladium catalyst (Scheme 86, eq. 1).[186] The obtained compounds could have interesting potential applications in the field of light-driven molecular devices. The initial steps of the proposed mechanism involve a Catellani reaction. Thus, a carbopalladacycle is formed from the iodobenzene derivative and norbornene. This palladacycle experiences an oxidative addition with an alkyl bromide present in the structure of the conjugated dienyne, followed by a reductive elimination leading, after retrocarbopalladation of norbornene, to an arylpalladium intermediate. Then, the first transformation over the dienyne system occurs, that is, as in the previous example, carbopalladation of the alkyne to generate an alkenylpalladium species which induces a C−H functionalization on the (hetero)aryl ring giving rise, after reductive elimination, to the final products. Noteworthy, the use of enantiomerically pure 1,3-dien-5-ynes allows the synthesis of chiral helical alkenes with good stereoselectivity (Scheme 86, eq. 2).

SCHEME 86. Synthesis of benzofulvene-containing compounds with a tetrasubstituted helical olefin from appropriately functionalized *o*-(alkynyl)bi(hetero)aryls and iodobenzene derivatives



A closely related transformation has been later reported by Perumal.[187] In this case, the arylpalladium intermediate is directly generated by oxidative addition into a pendant bromoaryl moiety and the C–H functionalization occurs over an alkene rather than an aryl group (Scheme 87). The rest of the mechanism is analogous to the one previously discussed and also leads to tetrasubstituted olefins containing a benzofulvene in their structure in moderate to good yields.

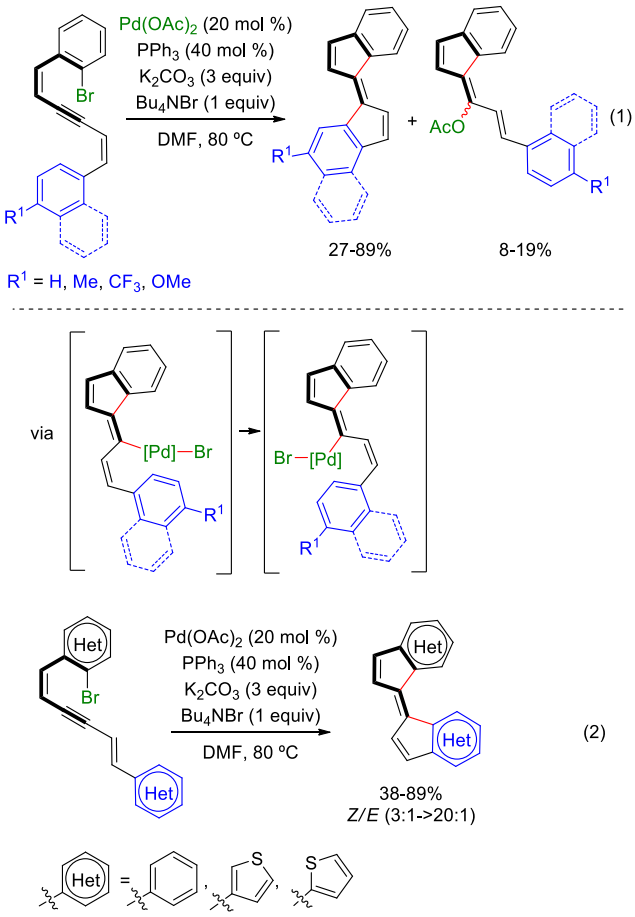
SCHEME 87. Synthesis of benzofulvene-containing compounds with a tetrasubstituted olefin from appropriately functionalized *o*-(alkynyl)styrenes



On the other hand, several examples of double cyclizations of 1,3,7,9-tetraene-5-ynes for the synthesis of biindenylidenes or benzofused analogues have been reported, following different approaches.

Thus, according to the general strategy depicted in Figure 5, Tobe has described the intramolecular trapping of an intermediate alkenylpalladium species with an aryl group via a cyclization involving C–H activation, in a process that ultimately leads to biindenylidene derivatives from 1,6-diaryl-1,5-dien-3-ynes (Scheme 88, eq. 1).[188] Low to moderate yields are obtained and minor amounts of methyleneindenes coming from the trapping of the intermediate alkenylpalladium species by an acetate ligand, instead of experimenting the cyclization, are formed. Varied substitution is tolerated at the non-halogenated arene of the substrate including electron-neutral, deficient and rich groups, although a compound with a cyano substituent only produces the undesired acetylated adduct. Interestingly, complete *E* selectivity is observed, which is explained by isomerization of the alkenylpalladium intermediate prompted by the steric hindrance of the *Z* isomer. This methodology has also been applied to the synthesis of bridged phenylthienylethenes and dithienylethenes, in yields that range from moderate for substrates having 3-thienyl substituents to high for the rest of compounds examinated (Scheme 88, eq. 2).[189] In contrast to the synthesis of biindenylidene derivatives, a lower steric repulsion leads to mixtures of *Z* and *E* isomers in this case, being the *Z* isomer the major one.

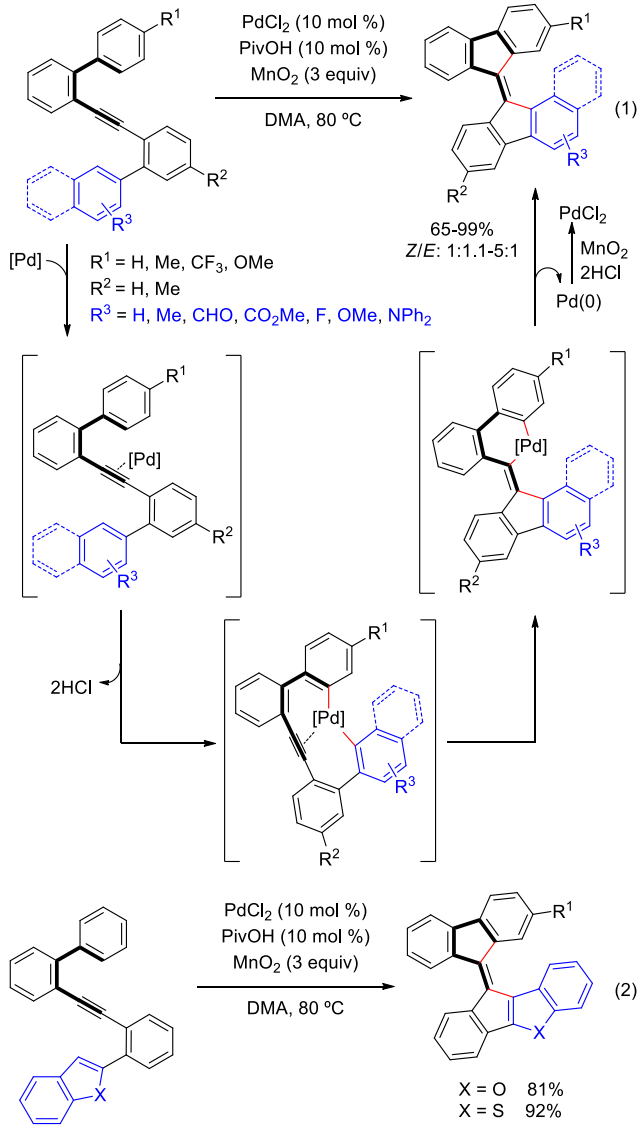
SCHEME 88. Synthesis of biindenylidene derivatives and related heterocyclic compounds by palladium catalyzed double-cyclization of 1,6-diaryl-1,5-dien-3-ynes



On the other hand, related 9,9-bifluorenylidene derivatives have been prepared by a palladium-catalyzed double cyclization of bis-biaryl acetylenes (Scheme 89, eq. 1, 2).[190] On the basis of experimental evidences, the authors propose an unusual mechanism based on a dual C–H activation. Thus, the reaction would start by coordination of the palladium catalyst to the triple bond followed by a double *ortho*-C–H bond insertion assisted by PivOH, added to the reaction media as cocatalyst. The double *ortho* C–H bond insertion can occur either stepwise or simultaneously. Then, intramolecular alkyne carbopalladation takes place followed by reductive elimination to give the final products and release Pd(0), which is oxidized to the catalytically active Pd(II) species with MnO_2. The combination of $PdCl_2$ as catalyst and MnO_2 as oxidant turns out to be crucial for a satisfactory outcome of the reaction. Under these conditions a series of bis-bi(hetero)aryl alkynes bearing different functional groups, including electron-donating and electron-withdrawing substituents, are

efficiently cyclized, although a mixture of *cis* and *trans* isomers is formed for substrates having substituents in both external aryl rings. Noteworthy, analogous bis-biaryl-acetylenes double-cyclize through a formal 6-*endo* pathway in the presence of $SbCl_5$ as oxidant (see Scheme 24).

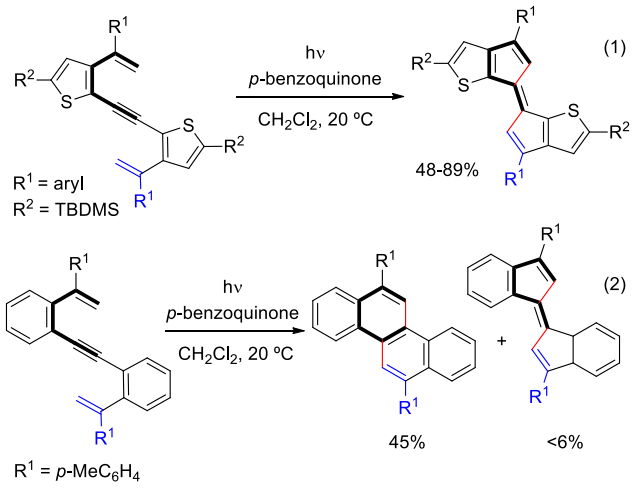
SCHEME 89. Synthesis of 9,9-bifluorenylidene derivatives by palladium-catalyzed double cyclization of bis-biaryl-acetylenes



Moreover, Fukazawa, Irle and Yamaguchi have described an efficient synthesis of dithienofulvalenes that show a great potential for the preparation of organic dyes and electron-transporting materials. The reaction proceeds also via double cyclization of the appropriately substituted 1,3-dien-5-ynes, but in this case under photochemical conditions in the presence of *p*-benzoquinone as oxidant (Scheme 90, eq. 1).[191] Noteworthy,

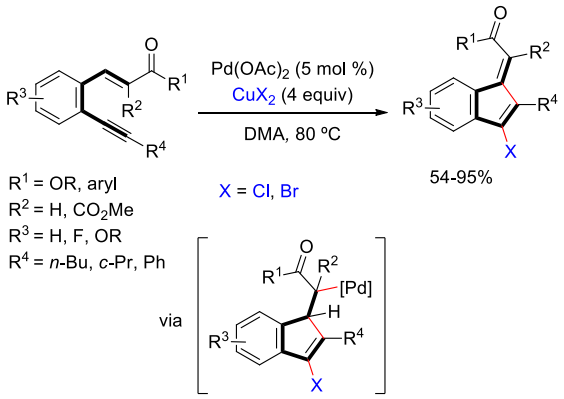
both the olefin and the alkyne participate simultaneously in the cyclization event, and the reaction is completely selective towards the formal double 5-*exo* cyclization when the central double bond of the 1,3-dien-5-ynes is part of a thiophene ring, whereas an analogous *o*-(alkynyl)styrene selectively leads to a chrysene derivative by a formal double 6-*endo* cycloaromatization (Scheme 90, eq. 2).

SCHEME 90. Synthesis of dithienofulvalenes by photochemical double 5-*exo* cyclization



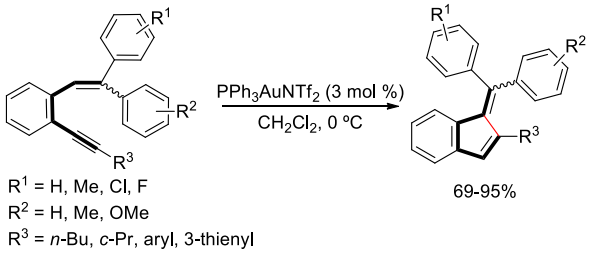
3.3.2. Reactions with other topology. Synthesis of fulvene derivatives from 1,3-dien-5-ynes with formation of a new bond between C2 and C6 is less common than the previously described approaches with generation of the new bond between C1 and C5. In this sense, Wu has reported a synthesis of 3-halobenzofulvenes by palladium-catalyzed cyclization of *o*-(alkynyl)cinnamates in the presence of an excess of CuX_2 (Scheme 91).[192] The transformation follows a mechanism similar to that proposed for the synthesis of indenes in Scheme 66. However, the intermediate obtained after the insertion of the double bond experiences a β-hydrogen elimination rather that a protodemetalation, thus leading to benzofulvenes instead of indenes. The corresponding acyl-functionalized benzofulvenes, alkyl or phenyl substituted at C2 and possessing groups of varied electronic nature at the arene ring, are obtained in moderate to good yields and both Cl and Br can be efficiently introduced in position 3.

SCHEME 91. Synthesis of 3-halobenzofulvenes by palladium-catalyzed reaction between *o*-(alkynyl)styrenes and CuX_2



Moreover, Sanz has described a gold-catalyzed cycloisomerization of β,β-diaryl-*o*-(alkynyl)styrenes that also leads to benzofulvenes following a C2-C6 topology (Scheme 92).[148] The reaction would occur by a formal 5-*endo* attack of the olefin to the gold coordinated acetylene and subsequent elimination of the only proton available, as proposed in Scheme 56. It is worth to note that the corresponding benzofulvenes are obtained selectively when the reaction is performed at 0 ºC, whereas further cyclization to yield dihydroindeno[2,1-*a*]indenes occurs at 80 ºC (see Scheme 56). Substrates with an alkyl, aryl or heteroaryl substituted triple bond are well tolerated, leading to the corresponding benzofulvenes in high yields, although ca. 1:1 mixtures of geometrical isomers are formed when *o*-(alkynyl)styrenes having two different aryl groups in the olefin are used.

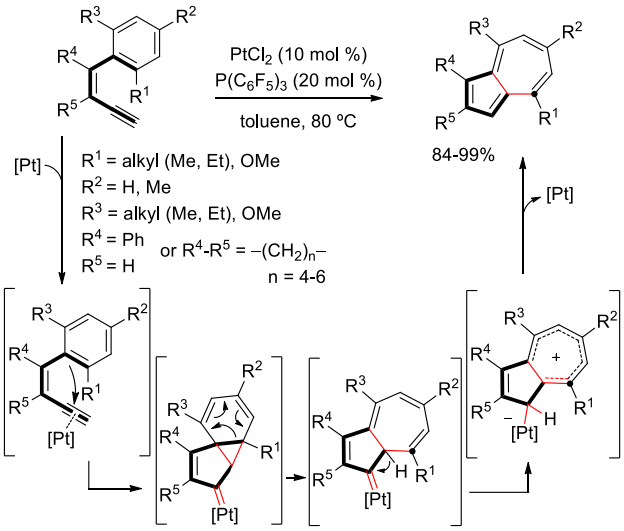
SCHEME 92. Synthesis of benzofulvenes by gold-catalyzed cycloisomerization of β,β-diaryl-*o*-(alkynyl)styrenes



On the other hand, an efficient synthesis of azulenes, a particular example of compounds including a fulvene moiety in their structure, has been described by Usui and Suemune via a platinum-catalyzed cyclization/ring

expansion sequence from 1-aryl-1-en-3-ynes (Scheme 93).[193] The reaction starts with an *ipso* cyclization of the aromatic ring over the platinum-coordinated triple bond, generating a cyclopropyl platinum carbene intermediate that experiences a Büchner ring expansion to a seven-membered ring. Then, 1,2-hydrogen shift and loss of the metal fragment gives rise to the corresponding azulene derivatives, which are obtained in excellent yields. Noteworthy, the central bond of the dienyne can be included in a six-, seven-, or eight-membered ring, whereas the reaction is not efficient for substrates having a five-membered ring, which is attributed to the increased angle between the triple bond and the aryl ring.

SCHEME 93. Synthesis of azulenes by platinum-catalyzed cyclization/ring expansion of 1,3-dien-5-ynes



3.4. Cyclopentenones and indanones

The syntheses of cyclopentenone derivatives from 1,3-dien-5-ynes generally follow the topology outlined in Figure 6, which encompasses the oxidation of the internal carbon atom of the alkyne (carbon 5) and the creation of a new bond between carbons 2 and 6. However, diverse methodologies have been developed, which allow for the synthesis of various particular structures by using different reagents and conditions.

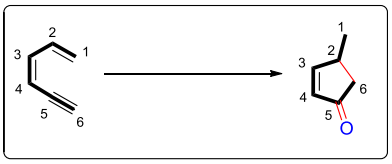
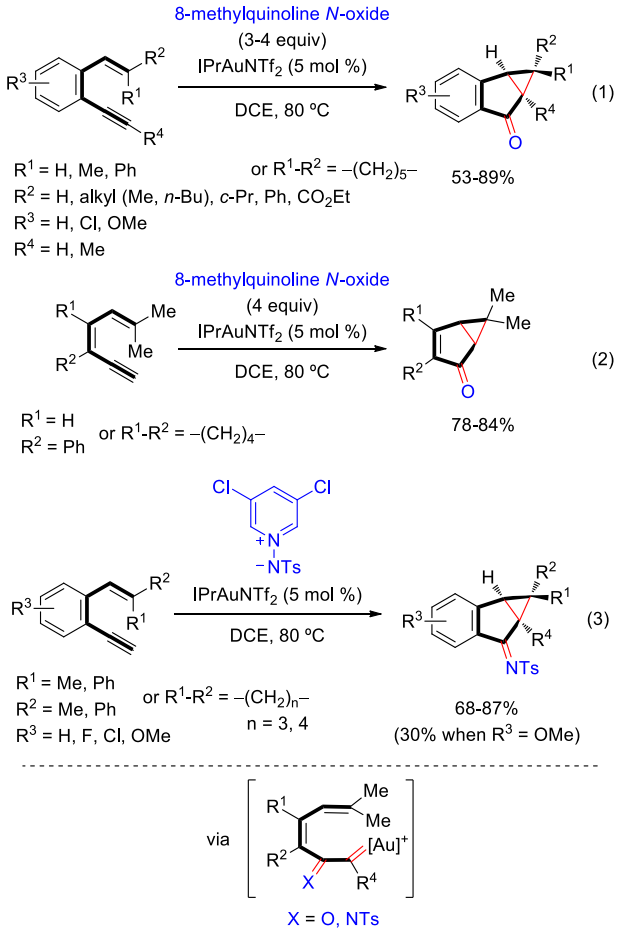


Figure 6. General outline of the synthesis of cyclopentenones from 1,3-dien-5-ynes

The synthesis of several cyclopentenone derivatives has been achieved using a strategy based on a gold-catalyzed oxidative cyclization of 1,3-dien-5-ynes, an approach that was first reported by Liu in 2011. Thus, cyclopropane-fused cyclopentenones are obtained in good yields by treatment of diverse 1,3-dien-5-ynes with an excess of 8-methylquinoline *N*-oxide in the presence of catalytic amounts of $IPrAuNTf_2$ (Scheme 94).[167] The reaction, that is stereospecific, starts with the oxidation of the alkyne giving an α-oxo carbene intermediate which evolves by an intramolecular cyclopropanation yielding the final product. This mechanism has been experimentally supported demonstrating the intermediacy of the α-oxo carbene species. Both *o*-(alkynyl)styrenes (Scheme 94, eq. 1) and other 1,3-dien-5-ynes (Scheme 94, eq. 2) are appropriate starting materials for this transformation and, although most of the tested substrates contain terminal alkynes, a dienyne with a methyl-substituted acetylene can also be converted into the corresponding cyclopentenone derivative in good yield.

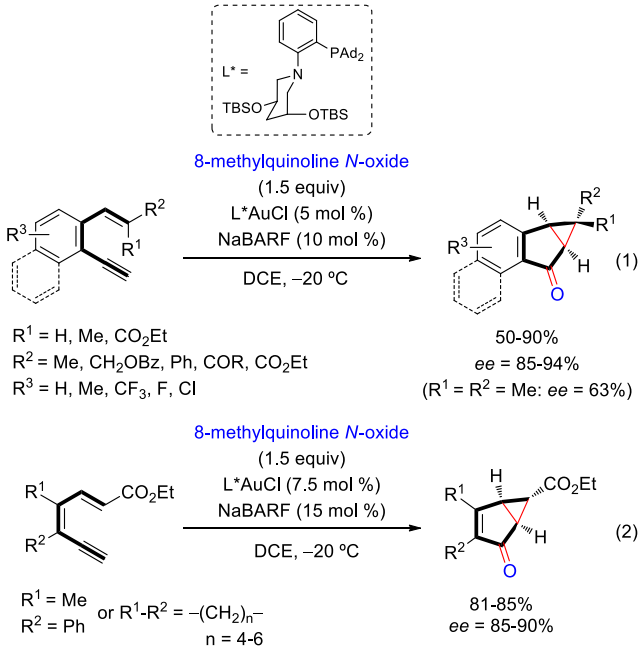
The same author has reported an analogous synthesis of cyclopropyl-indanimines using a *N*-iminopyridinium ylide as oxidant. A narrow substrate scope is surveyed for this reaction, including only *o*-(ethynyl)styrenes, and reduced yield is obtained for a substrate with an electron-donating group in the benzene ring (Scheme 94, eq. 3).[194] It is worth to note that the gold-catalyzed oxidative cyclization of *o*-(aminoethynyl)styrenes leads to a completely different outcome, giving rise to indene derivatives (See Scheme 72).

SCHEME 94. Synthesis of cyclopropane-fused cyclopentenones and indanimines by gold-catalyzed oxidative cyclization of 1,3-dien-5-ynes



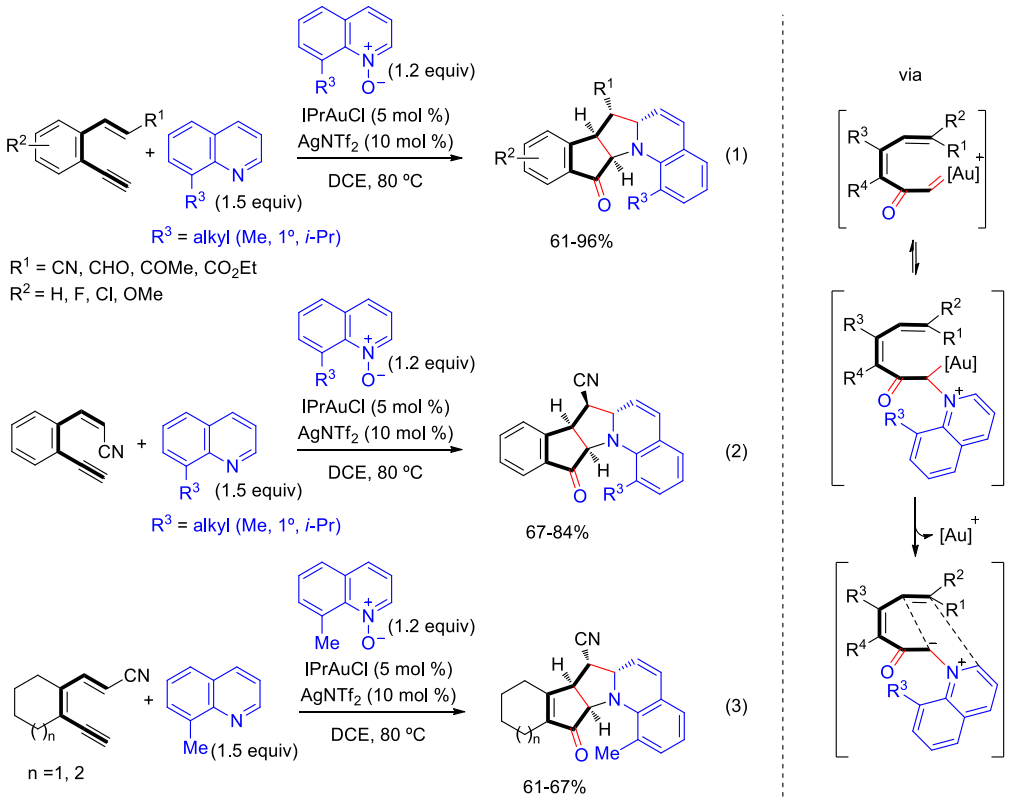
Notably, Zhang later developed an enantioselective version of the above reported methodology by using a gold complex with a P,N-bidentate ligand (Scheme 95, eq. 1, 2).[195] Thus, several cyclopropane-fused cyclopentenones are synthesized with good yields and high enantioselectivities, and only in the cyclization of a β,β-dimethyl-*o*-(alkynyl)styrene a significant decrease in the enantiomeric excess is observed.

SCHEME 95. Enantioselective synthesis of cyclopropane-fused cyclopentenones by gold-catalyzed oxidative cyclization of 1,3-dien-5-ynes



α-Oxo gold carbenes can also be trapped by other means than cyclopropanation. For example, Liu has reported the reaction of 1,3-dien-5-ynes with 8-alkylquinoline *N*-oxides in the presence of 8-alkylquinolines.[196] In this case, the initially generated α-oxo gold carbene is proposed to be reversibly trapped by the quinoline and, after dissociation of the gold fragment, the quinolinium ylide formed undergoes a concerted [3+2] cycloaddition with the alkene moiety of the initial *o*-(alkynyl)styrene, finally leading to tetracyclic indolizine derivatives containing a cyclopentenone in their structure (Scheme 96, eq. 1-3). The final products are obtained in good yields as single diastereoisomers, and the reaction, which proceeds in a stereospecific fashion, is compatible with diverse 1,3-dien-5-ynes having a terminal alkyne and various quinoline derivatives. Nevertheless, electron deficient pyridines and unsubstituted quinoline do not lead to the corresponding indolizine products. Interestingly, the addition of the quinoline derivative to the reaction media preventes the formation of the products coming from the intramolecular cyclopropanation of the alkene with the intermediate carbene (see Scheme 94), and only in the case of a conjugated dienyne with an olefin having an ester substituent this compound is isolated as a minor product.

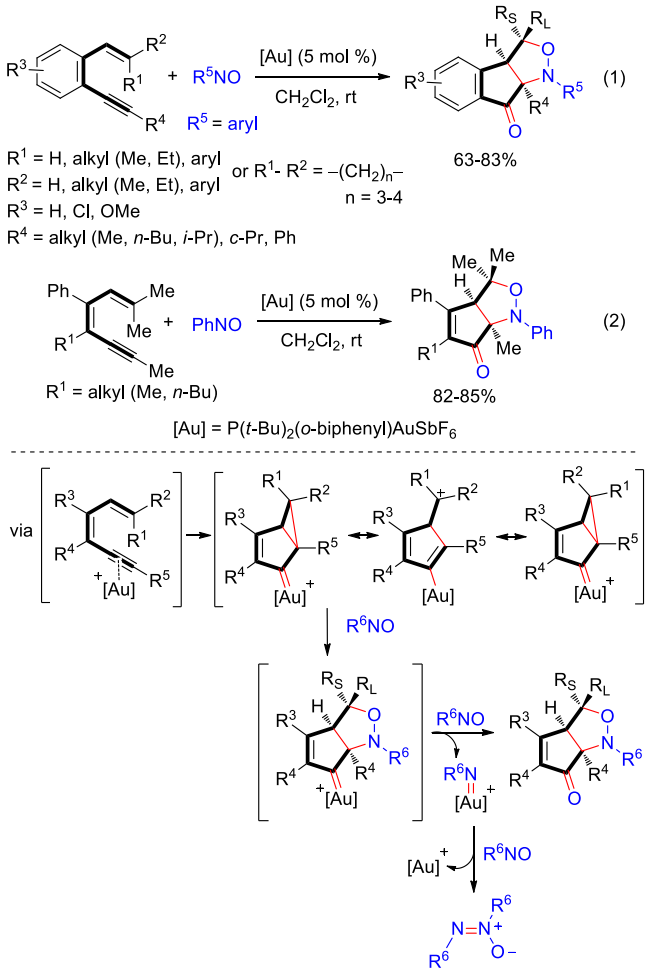
SCHEME 96. Synthesis of polycyclic derivatives containing a cyclopentenone by gold-catalyzed oxidative cyclization of 1,3-dien-5-ynes in the presence of quinoline derivatives



Moreover, 1,3-dien-5-ynes with a β,β-disubstituted olefin react in the presence of nitrosobenzenes and a gold catalyst through an oxidative cyclization/[3+2] cycloaddition sequence in which the nitrosobenzene acts both as counterpart for the cycloaddition and as oxidant (Scheme 97).[197] This transformation, that leads to isoxazolidine-fused cyclopentenones, is mechanistically distinct from those reported above, and does not proceed through an α-oxo carbene intermediate. Instead, the reaction is proposed to be initiated by nucleophilic addition of the olefin to the gold-coordinated triple bond, leading to an intermediate that can be represented either as a cyclopropyl carbene or as an alkenyl gold carbocation, as already discussed in Section 3.2. for analogous substrates. This intermediate reacts via [3+2] cycloaddition with the nitroso benzene derivative giving rise to a new carbene intermediate that is thought to be oxidized by another molecule of nitroso benzene yielding the final product. In addition, this last step generates a nitrene species that reacts further with nitrosobenzene to regenerate the gold catalyst. The reaction affords isoxazolidine-

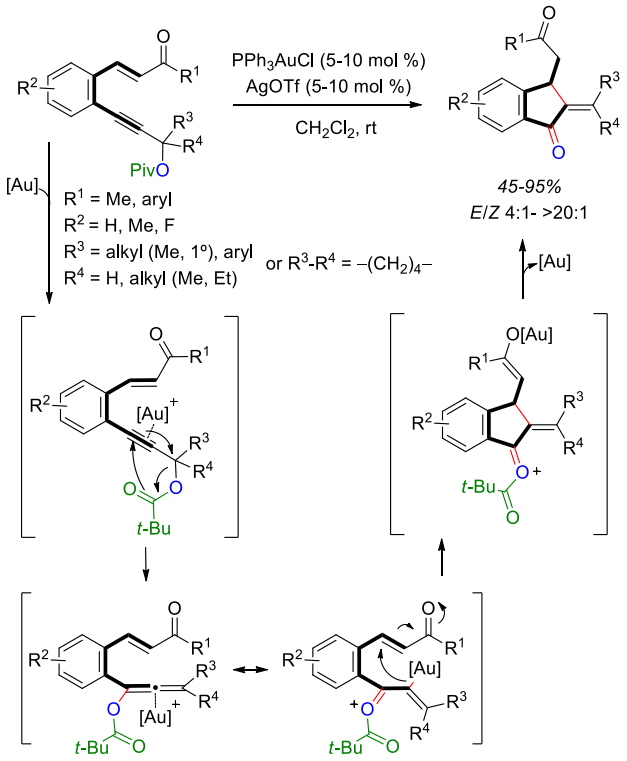
fused cyclopentenones in good yields, although indenes coming from a formal 5-*endo* cycloisomerization without incorporation of nitrosobenzene (see Scheme 58, eq. 2) are generally also formed in minor amounts (up to 11 % yield). Interestingly, the indene derivative becomes the major product when an *o*-(alkynyl)styrene with a methoxy substituent at the *para* position with respect to the alkyne is used. The oxidative cyclization/[3+2] cycloaddition is not stereospecific, and the product having the less sterically demanding substituent (R_S) placed in the same side than the neighboring hydrogen atom is always formed, regardless the configuration of the olefin in the starting dienyne. This can be explained by the interconversion between the intermediate gold carbenes coming from both configurations through the open carbocation structure, and the further cyclization taking place only over the one leading to a more favorable transition state.

SCHEME 97. Synthesis of isoxazolidine-fused cyclopentenones by gold-catalyzed oxidative cyclization of 1,3-dien-5-ynes in the presence of nitrosobenzenes



On the other hand, Liang has described a synthesis of 2-methyleneindanones by gold-catalyzed cycloisomerization of *o*-(alkynyl)benzylidene ketones with a pivaloxy substituent at the propargylic position (Scheme 98).[198] Unlike the above commented gold-catalyzed syntheses of cyclopentenones, in this case the oxygen of the generated cyclopentenone is not coming from an external oxidant, but from the pivaloxy substituent of the starting material. The reaction is initiated by the well documented 1,3-migration of the pivaloxy group over the gold-coordinated alkyne. Then, a Michael addition occurs leading, after hydrolysis, to the final products. Following this methodology a variety of 2-methyleneindanones are obtained in good yields and high diastereoselectivity, being the *E* isomer the major one. The carbonyl group bonded to the alkene in the initial *o*-(alkynyl)styrene can be either a methyl or an aryl ketone, although the use of aryl ketones leads to somewhat lower yields. Moreover, *o*-(alkynyl)styrenes with a tetrasubstituted propargylic position also afford efficiently the corresponding indanones, although a higher catalyst loading is required.

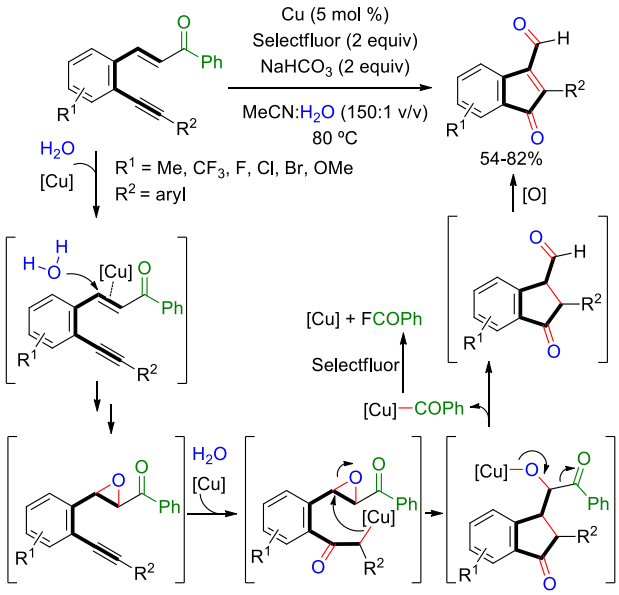
SCHEME 98. Synthesis of 2-methyleneindanones by gold-catalyzed cycloisomerization of *o*-(alkynyl)benzylidene ketones bearing a pivaloxy substituent at the propargylic position



A copper-catalyzed oxidative cyclization of 1,3-dien-5-ynes has also been described. Thus, *o*-

(alkynyl)chalcones react in the presence of catalytic amounts of Cu(0), with Selectfluor as oxidant and water as oxygen source, leading to 3-formyl-1-indenone derivatives in moderate to good yields (Scheme 99).[199] This methodology is limited to 1,3-dien-5-ynes with an electron deficient or moderately electron-rich aryl substituent in the triple bond, as dienynes with an alkyl- or a *p*-(alkoxy)aryl substituted acetylene fail to give the corresponding indenone derivative. The mechanism of this transformation has been studied in detail, mainly by means of isotopic labelling that revealed that both of the carbonyl oxygen atoms proceed from water. Thus, the reaction is proposed to be initiated by coordination of the double bond to the active copper species, generated *in situ* by a redox reaction between copper powder and Selectfluor. Then, nucleophilic attack of water takes place, finally leading to epoxidation of the olefin through a series of rearrangements. The generated intermediate experiences an oxycupration of the triple bond, followed by opening of the epoxide ring by intramolecular nucleophilic attack. Finally, an alkoxyde-based C-elimination and oxidative aromatization give rise to the corresponding 3-formyl-1-indenone derivatives. Nevertheless, other alternative pathways are not completely discarded.

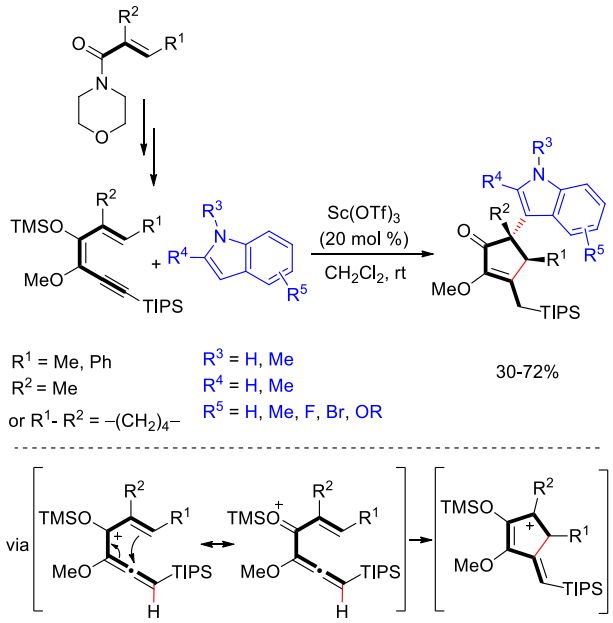
SCHEME 99. Synthesis of 3-formyl-1-indenone derivatives by copper-catalyzed oxidative cyclization of *o*-(alkynyl)chalcones



Following a topology different from that shown in Figure 6, Tius has reported a synthesis of indolyl-

substituted cyclopentenones from 1,3-dien-5-ynes containing a trimethylsilyl enol ether moiety in their structure and indole derivatives, through an interrupted Nazarov cyclization in the presence of catalytic amounts of $Sc(OTf)_3$ (Scheme 100).[200] The transformation proceeds via the initial formation of a pentadienyl cation intermediate, that cyclizes generating a carbocation that is trapped by the indole as nucleophile. The reaction is proposed to be catalyzed by a proton, and the role of $Sc(OTf)_3$ is thought to be the activation of trace water. Despite the interest of the transformation, its synthetic utility is restricted: limited variations in the dienyne structure are allowed, and electron-rich indoles without substituents in the C2 position are required for an efficient process. Although the 1,3-dien-5-ynes are isolated before treatment with $Sc(OTf)_3$, the yields are provided for a three-step process starting from an enamide precursor.

SCHEME 100. Synthesis of indolyl-substituted cyclopentenones from 1,3-dien-5-ynes containing a trimethylsilyl enol ether moiety in their structure and indole derivatives



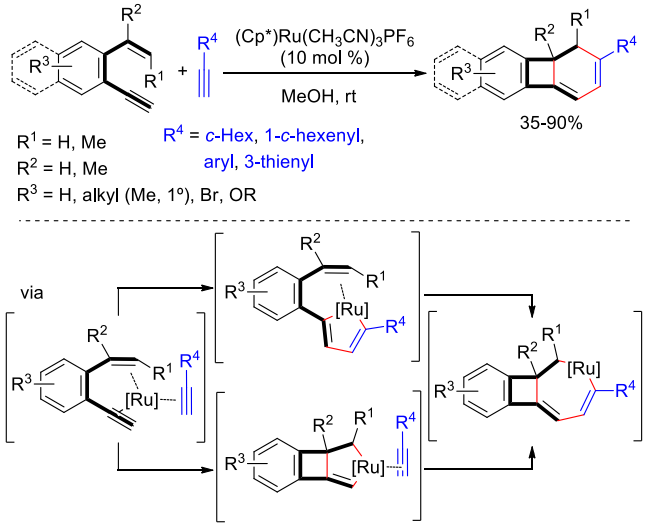
4. SYNTHESIS OF FOUR-, SEVEN- AND EIGHT-MEMBERED RINGS

Most of the synthetic applications of 1,3-dien-5-ynes are based on the construction of either benzene derivatives or diverse five-membered carbocycles, as shown above. However, scarce examples of their use in the synthesis of other-size rings have been reported.

In this regard, Esteruelas and Saá have described a ruthenium-catalyzed [2+2+2] cyclization of *o*-

(ethynyl)styrenes and terminal acetylenes leading to dihydrobiphenylenes in moderate to good yields (Scheme 101).[201] The authors propose a mechanism, supported by deuterium-labelling experiments, in which both the alkene and the alkyne of the conjugated dienyne and the external acetylene are initially coordinated to the metal center. Then, an oxidative coupling, either between the two alkyne moieties or between the alkene and the alkyne from the *o*-(ethynyl)styrene, takes place. In any case, a further insertion into a Ru–C bond generates a seven-membered metallacycle intermediate that, after reductive coupling, yields the corresponding dihydrobiphenylenes. The reaction is limited to *o*-(ethynyl)styrenes, as starting material is recovered when an *o*-(alkynyl)styrene with an internal acetylene is used. Moreover, a 1,3-dien-5-yne in which the central double bond is not forming part of an aromatic ring is not a suitable substrate for this transformation, and only the corresponding classical cycloaromatized product is formed, albeit in low yield, when it is subjected to the optimized reaction conditions.

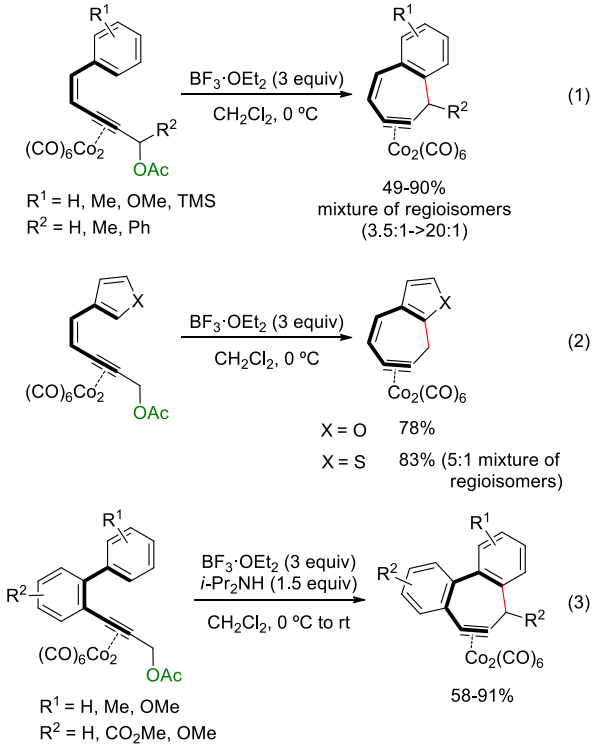
SCHEME 101. Synthesis of dihydrobiphenylenes by ruthenium-catalyzed [2+2+2] cyclization of *o*-(alkynyl)styrenes and acetylenes



Regarding seven-membered rings, Green has reported the synthesis of benzocycloheptynes complexed to a dicobalt moiety through an intramolecular Lewis-acid-mediated Nicholas reaction of 1-aryl-1-en-3-ynes with an acetate group at the propargylic position (Scheme 102, eq. 1, 2). Both neutral and electron-rich arenes, including heteroaryls, are cyclized under the reaction conditions in moderate to good yields, but mixtures of

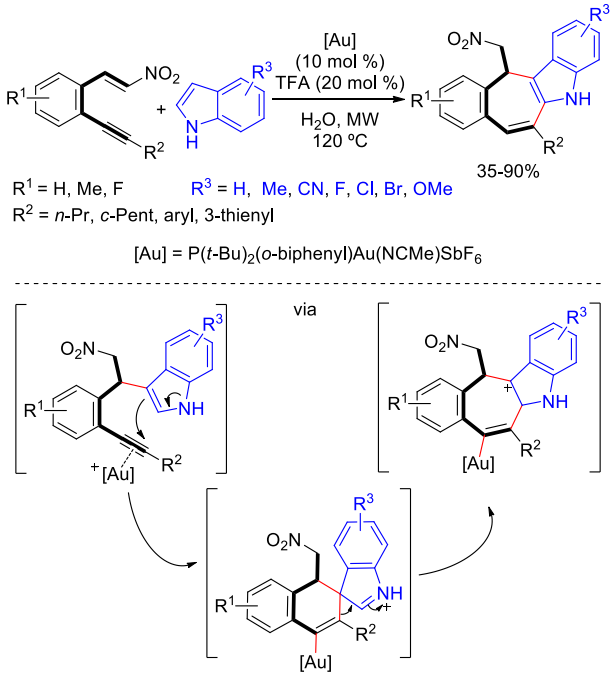
regioisomers are obtained for arenes having non-equivalent nucleophilic positions.[202] This methodology has been later extended to the cyclization of *o*-(alkynyl)biphenyls, (Scheme 102, eq. 3), and applied to the synthesis of diverse allocolchicine derivatives.[203,204] The use of a basic additive to scavenge the acid liberated during the reaction proved to be in this case beneficial for the product yields.

SCHEME 102. Synthesis of cobalt-coordinated benzocycloheptynes by intramolecular Nicholas reaction



Moreover, β-nitro-*o*-(alkynyl)styrenes have been used as precursors for the synthesis of tetracyclic indole derivatives containing a seven-membered ring (Scheme 103).[205,206] Thus, reaction of these substrates with indoles in the presence of a gold catalyst and TFA in water under microwave irradiation affords the corresponding tetracyclic compounds in good yields, and with broad scope. The reaction proceeds via an initial Michael addition of the indole to the nitroalkene moiety followed by a cyclization over the gold-coordinated triple bond. It is worth to note that only five of the six carbon atoms of the dienyne moiety are forming part of the final seven-membered ring, that is generated by a formal [5+2] cycloaddition.

SCHEME 103. Synthesis of tetracyclic indole derivatives with a seven-membered ring by gold-catalyzed reaction of β-nitro-*o*-(alkynyl)styrenes and indoles

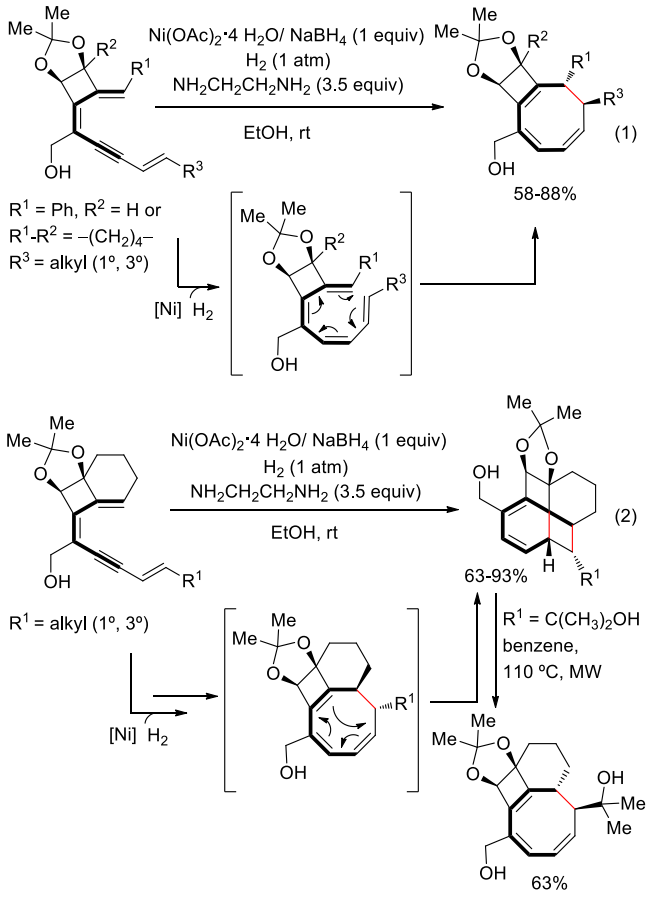


Finally, eight-membered rings can also be prepared from appropriate 1,3-dien-5-ynes. Thus, Schreiner, Muller and Suffert have reported a synthesis of complex tricyclic compounds containing a cyclooctatriene ring from 1,3,7-trien-5-ynes through a hydrogenation/8π-electrocyclization cascade process.[207,208] By using a nickel-catalyst in the presence of H_2 the corresponding products are formed in high yields and with complete stereoselectvity in most of the cases (Scheme 104, eq. 1).

Interestingly, analogous substrates having the terminal bond of the dienyne system included in a cyclohexene moiety react at room temperature to yield a bicyclo[4.2.0]octane instead of the eight-membered ring, thus obtaining final products with fenestradiene structure (Scheme 104, eq. 2).[207,209] This result can be explained by a further 6π-electrocyclization of the initially formed cyclooctatriene. Noteworthy, it has been demonstrated for a single example that the reaction at 70 ºC gives rise to the corresponding cyclooctatriene derivative also for this kind of substrates, with analogous stereoselectivity to that obtained for other 1,3,7-trien-5-ynes, which is opposed to that observed in the fenestradiene derivatives. Moreover, the isolated fenestradiene furnishes the cyclooctatriene under microwave irradiation, which suggest a series of selective

electrocyclizations-retro electrocyclizations occurring in the reaction media. DFT calculations have been perfomed to account for the observed products and stereoselectivities in each case.

SCHEME 104. Synthesis of cyclooctatrienes and fenestradienes by nickel-catalyzed reductive cyclization of 1,3,7-trien-5-ynes



5. SYNTHESIS OF HETEROCYCLES

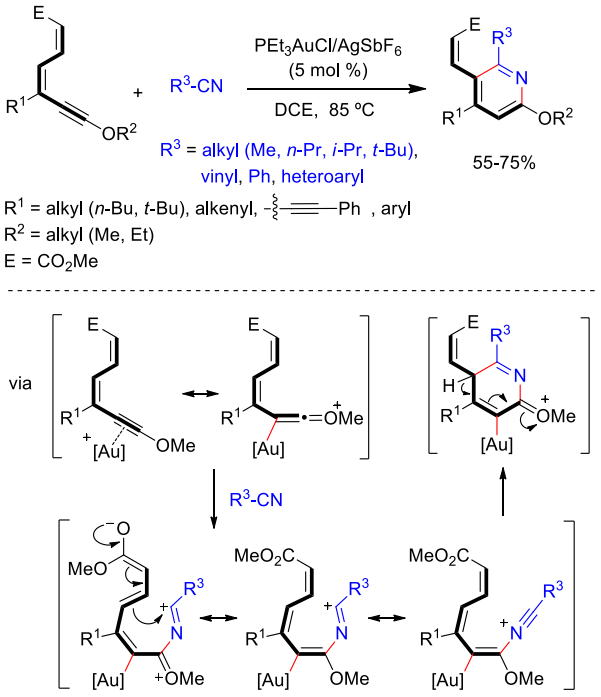
5.1. Six-membered rings

The synthesis of six-membered heterocyclic rings from 1,3-dien-5-ynes implies that not all carbon atoms of the conjugated system will be included into the newly formed ring in the final product. However, among all the possibilities, only examples of formal [5+1] or [4+2] cycloadditions, involving five or four carbon atoms of the conjugated system, have been reported so far.

5.1.1. Six-membered *N*-heterocycles. Push-pull 1,3-dien-5-ynes have proved to be appropriate substrates for the synthesis of heterocycles by metal-catalyzed transformations. Thus, tetrasubstituted

pyridines are regioselectively prepared when these dienynes are treated with nitriles in DCE at 85 ºC in the presence of catalytic amounts of a cationic gold-complex (Scheme 105).[210] Overall, the formal [4+2] cycloaddition can be considered as a hetero-dehydro-Diels-Alder-reaction. It works perfectly for non-activated nitriles and, regarding the conjugated dienyne, a variety of substituents at position 3 are allowed: aryl (bearing electron-donating or electron-withdrawing groups), alkyl (1º, 2º, 3º), and alkenyl groups. Alkynyl groups are also tolerated and, in fact, alkynyl-substituted dienynes bearing two triple bonds of different electronic nature provide some insights about dienyne electronic requirements for the reaction to occur, as only the electron-rich triple bond takes part in the cycloaddition reaction yielding 4-alkynylpyridines: the presence of the donating group is crucial for the reaction outcome. The proposed mechanism would start by an initial coordination of the alkyne moiety of the dienyne to the gold catalyst to form a complex, which presents a highly-contributing resonance structure due to electron-donating methoxy group linked to the triple bond. Then, a regioselective nucleophilic attack from nitrile would take place, facilitated by the push-pull substitution on the dienyne, leading to a metallated intermediate, which cyclizes to form a dihydropyridine species. Finally, a proto-deauration step would render the observed pyridines and allow the incorporation of the catalytic species into a new cycle.

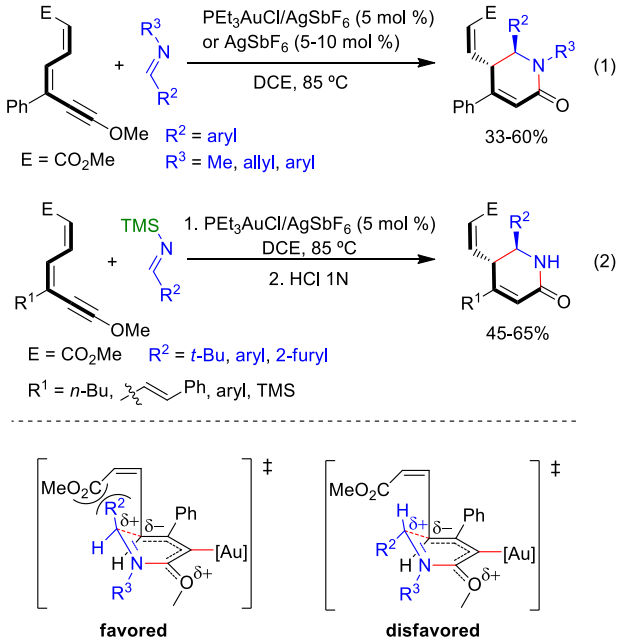
SCHEME 105. Gold-catalyzed intermolecular hetero-dehydro-Diels-Alder between push-pull dienynes and nitriles



This type of reactivity has been extended to the employment of other unsaturated *N*-nucleophiles such as aldimines (Scheme 106).[211] On one hand, *N*-substituted 5,6-dihydropyridin-2-ones are synthesized in moderate yields and in a regio- and diastereoselective manner by mixing push-pull 1,3-dien-5-ynes with aldimines under the same reaction conditions employed in their reaction with nitriles (Scheme 106, eq. 1). In all cases, only the *trans*-diastereoisomer is observed. Moreover, $AgSbF_6$ may itself catalyze this transformation although slightly lower yields are reached. The process works nicely for electron-withdrawing or electron-donating substituted aryl aldimines, being the substitution pattern at the N atom of wider scope. On the other hand, *N*-unsubstituted 5,6-dihydropyridin-2-ones are prepared in moderate yields when *N*-silylaldimines are used under gold-catalysis conditions (Scheme 106, eq. 2). This cycloaddition reaction requires an additional hydrolysis step to reach the reported yields; it is also completely regio-, diastereoselective and of wide scope regarding both the dienyne and the *N*-silylaldimine. Thus, several aryl groups bearing different substitution patterns and/or electronic properties, as well as heteroaryl and tertiary alkyl groups are placed at position 6 of dihydropiridones while the dienyne substituent can either be aromatic,

alkyl, alkenyl or a silyl group. The suggested mechanism is similar to the one proposed for the reaction with nitriles (see Scheme 105) and a favored transition state (preferred due to steric reasons) has been invoked to account for the diastereoselectivity found.

SCHEME 106. Intermolecular hetero-dehydro-Diels-Alder reaction between push-pull dienynes and aldimines



In the reactions depicted so far in this section, the dienyne moiety behaves as a 4C component, reacting through positions 3 and 6 while the remaining double bond is formally inert. However, simpler enyne substrates, bearing different electronic properties, are not suitable substrates for these hetero-dehydro-Diels-Alder transformations. Therefore, the use of a 1,3-dien-5-yne as starting material is a requisite for the reaction to proceed, which seems to indicate that the remaining olefin of the dienyne also plays some role in the reaction outcome.

Unlike in the previous transformations, in the next examples the dienyne moiety behaves as a 5C component and it reacts through positions 2 and 6 of the conjugated system. In this sense, the dihydroisoquinoline skeleton is accessed from *o*-(ethynyl)styrene derivatives by employing ketenimine chemistry. For example, Bolm and Chang have reported a *one-pot* three-component coupling between 1-

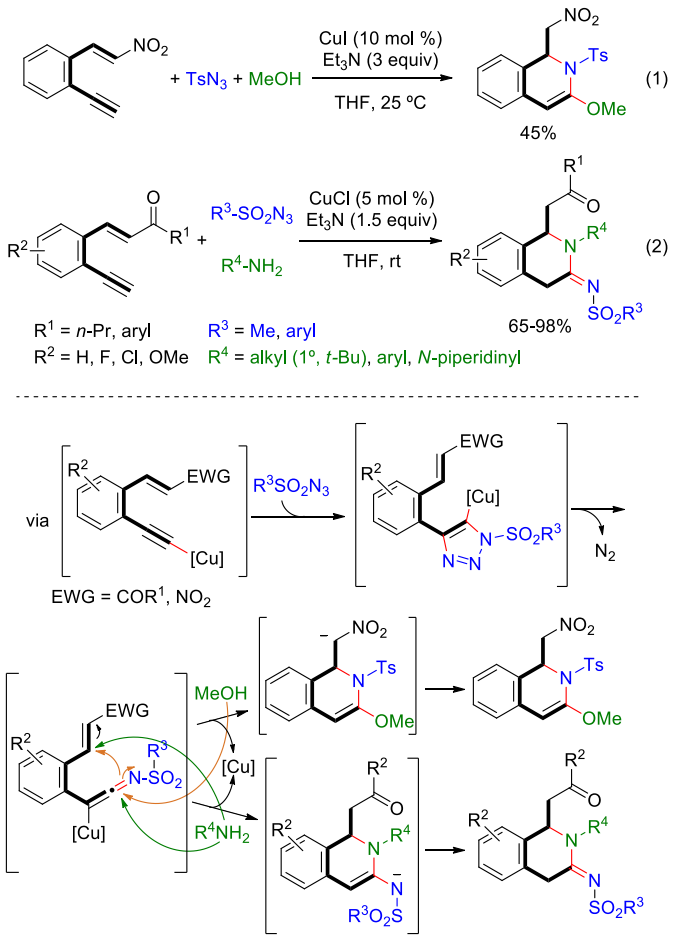
ethynyl-2-(2-nitroethenyl)benzene, tosyl azide and methanol in the presence of Et_3N and catalytic amounts of CuI to yield a 1,2-dihydroisoquinoline adduct in a moderate 45% yield (Scheme 107, eq. 1).[212] This example is the only case reported in the manuscript involving a 1,3-dien-5-yne, as it represents an intramolecular version of a more general four-component (terminal acetylene, nitroalkene, tosyl azide and methanol) coupling, which leads to functionalized imidates.

In a very similar transformation, Wu has prepared 1,2-dihydroisoquinolin-3(4*H*)-imines by a copper-catalyzed three-component cycloaddition involving *o*-(ethynyl)benzylidene ketones, sulfonyl azides and primary amines (Scheme 107, eq. 2). CuCl is the most efficient catalyst in this case and the amounts of catalyst and base required are lower than for the previous example. Four points of diversity (R^1 to R^4, two of them in the chalcone derivative, one in the sulfonyl azide and one in the amine) can be introduced into the reaction products, which are isolated in good to almost quantitative yields. Moreover, several functional groups such as halogens (in chalcone or in amine), nitro (in all components) or ester (in amine) are tolerated, and even hydrazines show satisfactory reactivity under the standard conditions.[213]

The mechanism proposed to account for the formation of these dihydroisoquinoline derivatives involves the commonly accepted formation of a copper acetylide by combination of the copper salt, the base and the terminal acetylene. This species then would undergo a [3+2]-cycloaddition with tosyl azide to form a metallated triazole, which would evolve to a ketenimine intermediate by extruding N_2. These first steps are analogous to that proposed by the same author for the cycloaromatization of related *o*-(alkynyl)styrenes in the presence of azides, a base and a copper catalyst (see Scheme 32). However, in the current example the presence of an external nucleophile favours the evolution of the ketenimine intermediate by a nucleophilic addition instead of the previously reported 6π-electrocyclization. Thus, on one hand, methanol attack to ketenimine central carbon (Scheme 107, green arrows) would be followed by a Michael-type addition to the nitroalkene moiety leading, after a final protonation, to the methoxy-functionalized observed dihydroisoquinolines. On the other hand, a double nucleophilic attack by the amine both to the ketenimine

central carbon and to the β position of the benzylidene ketone moiety (Scheme 107, brown arrows) followed by protonation would give 1,2-dihydroisoquinolin-3(4*H*)-imines.

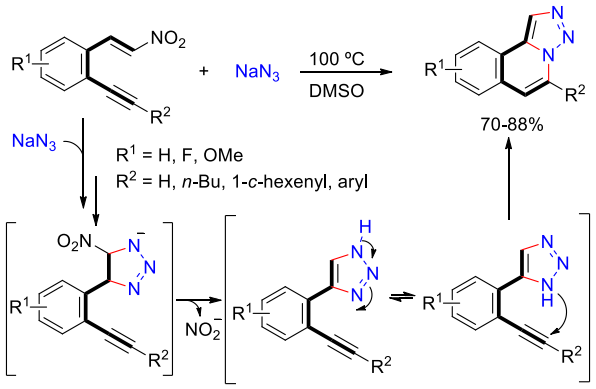
SCHEME 107. Copper-catalyzed multicomponent synthesis of dihydroisoquinoline derivatives



In a metal-free transformation employing closely related starting materials, the 1,3-dien-5-yne system partakes in the formation of two fused cycles: a six-membered one by reacting through positions 2 and 6, and a triazole involving positions 1 and 2. Thus, the treatment of *o*-alkynylaryl nitro olefins with sodium azide leads to formation of triazolo isoquinolines in high yields (Scheme 108).[214] The scope of the reaction, involving two points of diversity, has been determined: R^1 in the aromatic ring may have either electron-donating or electron-withdrawing properties, while the alkyne may be terminal or have aromatic, alkenyl or aliphatic substituents. However, formation of the expected triazolo isoquinoline is not observed when a relatively strong electron-withdrawing group, such as cyano, is present in R^2. Mechanistically, the reaction would be initiated by an aza-Michael addition of sodium azide to the nitroolefin moiety to give an azide-attached intermediate,

which would evolve to a dihydrotriazole intermediate. This one would undergo extrusion of nitrous acid to afford an N-H triazole containing species, which upon tautomerization followed by an intramolecular 6-*endo*-*dig* cyclization would lead to the observed triazolo isoquinolines.

SCHEME 108. Transition-metal free synthesis of triazolo isoquinolines

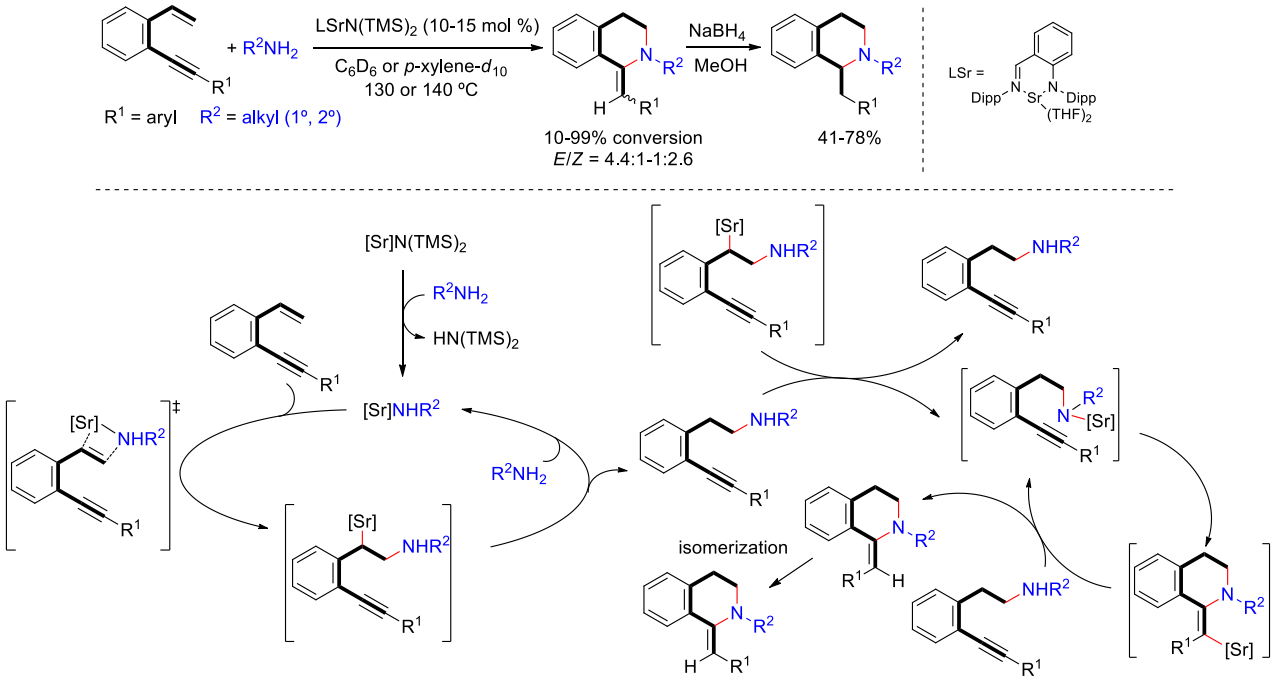


A synthesis of tetrahydroisoquinoline frameworks in a chemo- and regioselective manner from *o*-(alkynyl)styrene derivatives has been reported by Barrett, Hill and coworkers employing an heteroleptic anilido-imine supported alkaline earth catalysts (Scheme 109).[215] After screening, a strontium complex was selected as optimal to explore the reaction scope due to its acceptable high activity and greater ease of synthesis than its barium analogue, even though the latter one provides higher activity. In this transformation, starting dienynes undergo heterofunctionalization at positions 1 and 5 of the conjugated system by sequential hydroamination steps. The reaction is limited to dienynes bearing an aromatic group at the acetylene, tolerates a variety or primary and particular secondary amines and the cycloadducts are obtained as mixtures of *Z* and *E* isomers in conversions that fluctuate from very low to excellent. Nevertheless, increasing the temperature to 140 ºC is required to obtain good yields for bulky amines, and for substituted benzyl amines the catalytic turnover depends on the position of the aromatic substitution. Hydrolytically sensitive arylmethylidene tetrahydroisoquinolines have to be reduced to their corresponding saturated derivatives to allow characterization and purification.

The mechanism suggested by the authors involves two catalytic cycles. Indeed, it may be considered a case of self-relay or auto-tandem catalysis. An amine-ligand exchange would initially occur to form an amino-

strontium species, which enters in the first catalytic cycle giving rise to the hydroamination of the double bond, presumably through a four-membered metalla-heterocyclic transition state, and a final protonolysis step. This protonolysis can be effected either by the starting amine or, as the reaction proceeds, by the homobenzylic amine generated in this first catalytic cycle. In the latter case, a strontium amide species is formed, that enters in the second catalytic cycle. Then, a cyclization occurs followed by another protonolysis step that releases the *Z*-stilbene tetrahydroisoquinoline product, which may isomerize to its *E*-isomer under the reaction conditions.

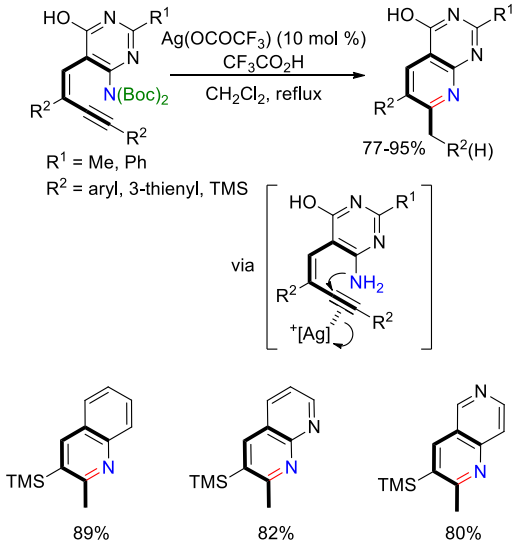
SCHEME 109. Strontium-catalyzed synthesis of tetrahydroisoquinolines by reaction of *o*-(alkynyl)styrenes and amines



Moreover, pyrido[2,3-*d*]pyrimidines have been synthesized by silver trifluoroacetate catalyzed cyclization of 6-*N,N*-di-Boc-amino-5-(but-3'-yn-1'-enyl)-2-methylpyrimidin-4-ol derivatives in good to excellent yields (Scheme 110). The Boc protecting group has a relevant role in guiding this tandem reaction. In the ring-closing reaction, the Boc group is removed in the presence of TFA and a 6-*exo* cyclization takes place by nucleophilic attack of the free amino group to the silver activated triple bond. Then, an aromatization step would account for the formation of pyrido[2,3-*d*]pyrimidines. When R^2 = TMS, desilylation at the alkyne

terminal position under the cyclization reaction conditions leads to 2-methyl-3-trimethylsilyl-pyridine fused aromatic compounds. Besides pyrimidines, the scope of this transformation includes also benzene and pyridine derivatives.[216]

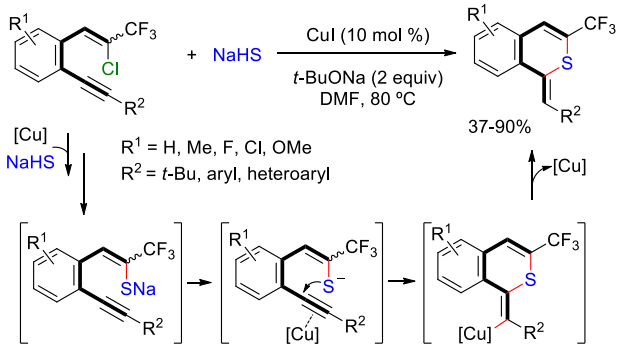
SCHEME 110. Synthesis of functionalized pyrido[2,3-*d*]pyrimidines and related compounds by cyclization of pyrimidine enynes



5.1.2. Other six-membered heterocycles. A copper-catalyzed thiolation/cyclization protocol has been developed to stereoselectively prepare trifluoromethyl-containing 1*H*-isothiochromenes in moderate to very high yields by addition of sodium hydrosulfide to β-chloro-β-trifluoromethyl-*o*-(alkynyl)styrenes (Scheme 111).[217] A wide range of aromatic and heteroaromatic groups as well as *t*-butyl can be located as substituents onto the triple bond and a variety of substitution patterns are tolerated in the benzene ring. The employment of two equivalents of base (*t*-BuONa) enhances the reaction yields.

A plausible mechanism for this transformation implies an initial copper-catalyzed coupling between the thiolate and the vinyl chloride moiety. Then, copper iodide would act as a π-acid by complexing to the alkyne moiety and activating it towards the intramolecular attack of the sulfur nucleophile by a stereoselective 6-*exo* cyclization leading to a bicyclic intermediate. Then a protodemetallation step would afford (*Z*)-1-methylene-3-trifluoromethyl-1*H*-isothiochromenes and regenerate again the catalyst species.

SCHEME 111. Copper-catalyzed synthesis of CF_3-containing 1*H*-isothiochromenes

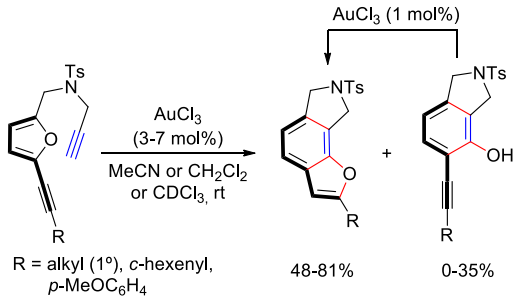


5.2. Five- and seven-membered rings

Reports regarding the formation of five- and seven-membered heterocycles from 1,3-dien-5-ynes are scarce in the literature.

One of the few examples is the synthesis of benzofurans fused to an *N*-heterocycle by gold(III)-catalyzed cycloisomerization of alkynylfurans with a pendant triple bond described by Hashmi (Scheme 112).[218] This transformation is initiated by the phenol synthesis previously described by the same author.[219] This well stablished reaction gives in this particular case an *o*-(alkynyl)phenol that cyclizes *in situ* in the presence of the gold-catalyst to yield the corresponding benzofurans in moderate to good yields. Intermediate *o*-(alkynyl)phenols are observed as minor products in these reactions, which is attributed to the deactivation of the catalyst before the cyclization is completed. In fact, it was demonstrated that further addition of catalyst to the reaction mixture provides complete conversion to the corresponding benzofurans. It is worth to note that in the overall transformation both a five-membered heterocycle and a benzene ring are formed along the dienyne skeleton. However, the synthesis of the phenol occurs in the first step without participation of the alkyne from the dienyne system. The reported scope for this transformation is quite limited, as only variations in the substituent of the triple bond of the alkynylfuran moiety are performed. Moroever, substrates having in this position a trimethylsilyl group or alkyl chains with pendant hydroxy groups, as well as terminal alkynes, failed to give the benzofuran products in significant amounts.

SCHEME 112. Gold-catalyzed synthesis of benzofurans



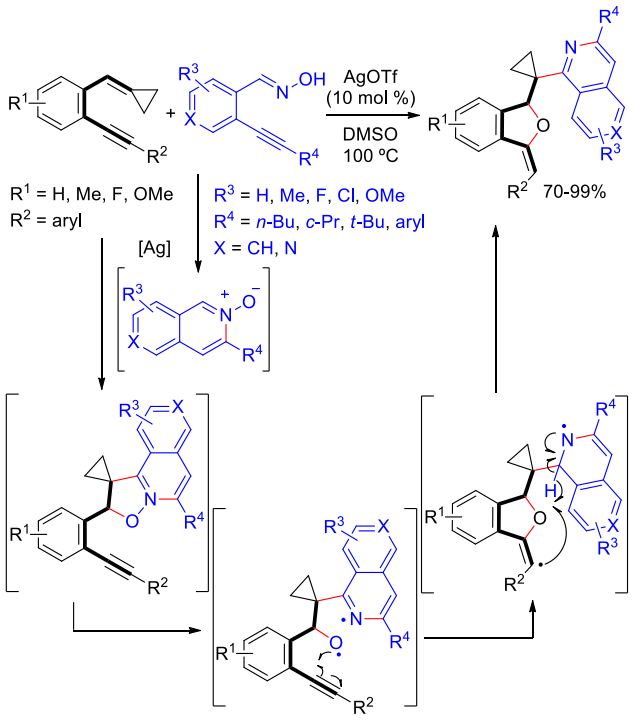
Furthermore, a silver triflate-catalyzed reaction between *o*-(alkynyl)styrenes in which the olefin belongs to a methylenecyclopropane moiety and *o*-(alkynyl)benzaldoxime derivatives leads to the formation of 1-[(1,3-dihydroisobenzofuran-1-yl)methyl]isoquinolines in good to excellent yields by a cascade reaction sequence (Scheme 113).[220] This transformation, as in previous examples using this kind of 1,3-dien-5-ynes (see Schemes 32, 33 and 82), takes advantage of the highly active sites of the conjugated system, that is, the alkynyl moiety and the methylenecyclopropane. Moreover, in this case the ease of *o*-(alkynyl)benzaldoxime to undergo 6-*endo-dig* cyclization in the presence of an electrophile or a catalytic amount of a Lewis acid is fundamental for the reaction to proceed.

In the overall transformation four new bonds are formed involving three carbons of the conjugated dienynic system. Thus, positions 2 and 5 are oxygenated while a new C–C bond is formed at position 1. The reaction is proposed to be initiated with the creation of a C–N bond by a silver triflate-catalyzed 6-*endo* cyclization to produce an isoquinoline *N*-oxide, which then undergoes a regioselective [3+2]-cycloaddition with the highly reactive methylenecylopropane moiety to form a dihydroisoxazole adduct. Then, a homolytic cleavage of the N–O bond would take place to generate a di-radical species, which would evolve by regioselective intramolecular 5-*exo* radical addition of the oxygen atom to the triple bond to furnish, after a final radical migration, the isoquinoline reaction products.

The scope of the reaction has been established: a variety of substitutions in the *o*-(alkynylaryl) methylenecyclopropane as well as functional groups such as fluoro, chloro, methoxy and ester as substitutents in the *o*-(alkynyl)benzaldoxime component are all compatible with the reaction conditions, and even a

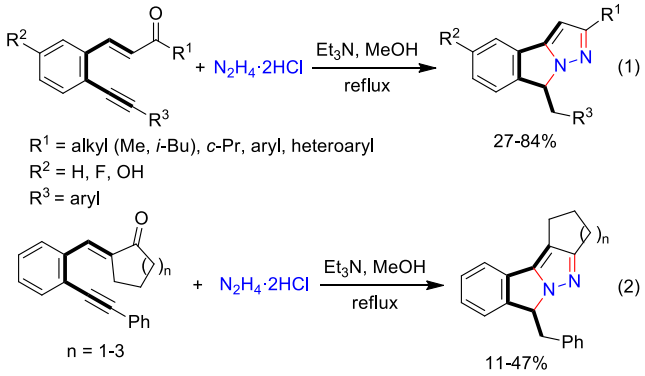
pyridinyl-substituted oxime leads to the corresponding 6-azaisoquinoline derivative. Additionally, not only aryl but also primary, secondary or tertiary alkyl groups can be attached onto the triple bond of benzaldoxime component.

SCHEME 113. Synthesis of 1-[(1,3-dihydroisobenzofuran-1-yl)methyl]isoquinolines



On the other hand, the classical pyrazole synthesis by treating α,β-unsaturated carbonyl compounds with hydrazine hydrochloride has been applied to prepare fused pyrazoles by employing *o*-(alkynyl)chalcones as α,β-unsaturated carbonyl compounds (Scheme 114, eq. 1). The use of triethylamine as base in refluxing methanol proved to be the best reaction conditions. The nature of the substituent R^1 in the *o*-(alkynyl)chalcone is determinant for the reaction yield: alkyl and electron-rich aromatic substituents provide good yields of fused pyrazoles, while only moderate yields are reached for heteroaromatic substituents. The reaction has been extended to cyclic *o*-(alkynyl)chalcones, although low yields of polycyclic pyrazoles are generally obtained (Scheme 114, eq. 2).[221]

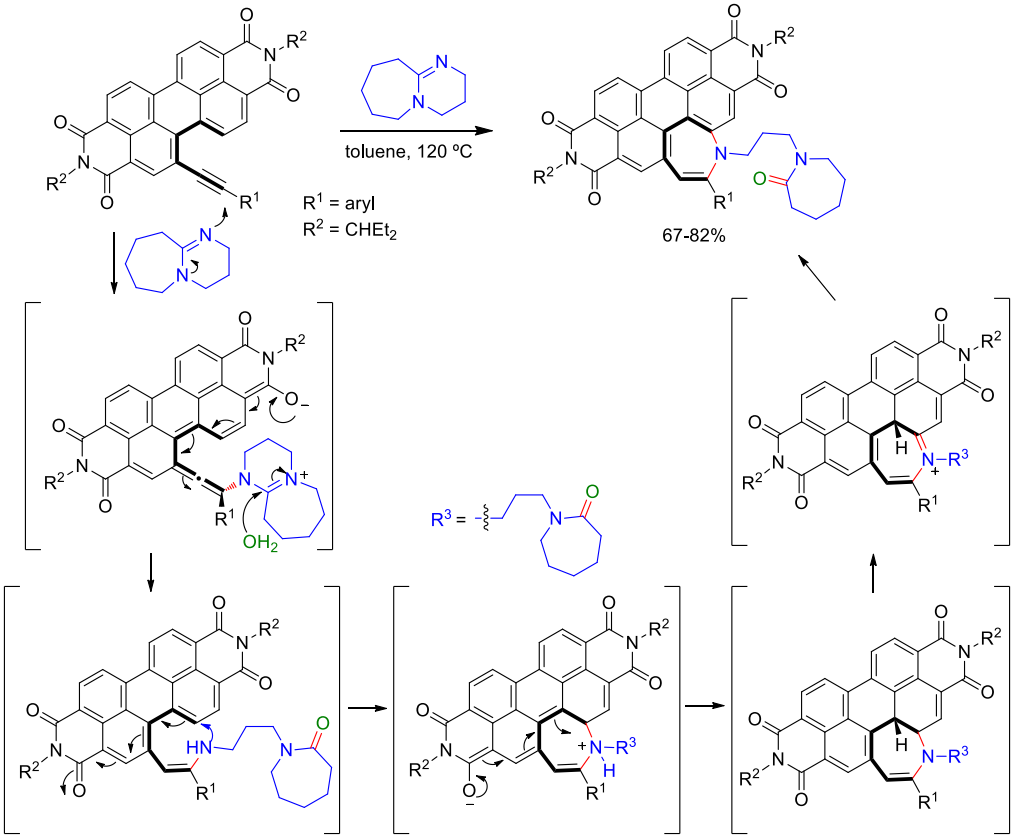
SCHEME 114. Synthesis of fused pyrazoles by cyclization of *o*-(alkynyl)chalcones with hydrazine



Regarding the formation of seven-membered heterocyclic rings, a straightforward and amenable method for the construction of azepino-perilenebisimides without the use of any metals has been developed by Sankar and coworkers (Scheme 115).[222] The most important features of this formal [6+1] cyclization rely in the reaction products due to the properties they exhibited, as they are panchromatic absorbing chromophores with exceptional photophysical characteristics and promising dyes. Such properties can be electronically modulated as starting alkynyl-perylenebisimides tolerate different aryl substituents onto the triple bond, giving rise to the final products in yields that range from moderate to good.

The azepine-perylenebisimides would be formed by an initial nucleophilic attack of DBU 8-nitrogen via a formal 1,10-conjugate addition onto the alkyne moiety, placed in a sterically congested bay position of the highly electron-deficient peylenebisimide core. Then, ring opening of DBU due to the attack of a water molecule occurs, and a second C−N bond is created by a formal intramolecular 1,8-conjugate addition of the nitrogen of the secondary amine. Finally, single electron transfer would lead to the formation of an iminium ion intermediate, which aromatizes to the final products by an iminium-enamine tautomerization. Therefore, the complete carbonated skeleton of the 1,3-dien-5-yne is included into the new ring and new bonds are created between N and positions 1 and 6 of the conjugated system.

SCHEME 115. Synthesis of azepino-perylenebisimides



6. CONCLUSIONS

The work compiled in this review highlights the great potential of 1,3-dien-5-ynes in organic synthesis, as precursors of a wide number of different carbo- and heterocycles.

Early contributions mainly focused in cycloaromatizations, and this field has notably advanced from low-yielding photochemical or thermal processes performed under harsh conditions and with limited scope to highly efficient metal-catalyzed reactions carried out under mild conditions. Noteworthy, the metal-catalyzed cycloaromatization of 1,3-dien-5-ynes has found numerous applications in the preparation of PAHs, which is a clear indicator of the advantages that this methodology provides over other aromatic ring forming strategies. These advantages encompass the ease of synthesis of the precursors of the cyclization, which are usually prepared in few steps from commercially available substrates through classical transformations such as Wittig reactions, Sonogashira or Suzuki couplings and aldol condensations, as well as the mildness of the conditions

used and the high yields generally obtained. Moreover, it is worth to note that the regioselective synthesis of polysubstituted aromatic rings is a challenging task in organic synthesis. In this sense, the cycloaromatization of 1,3-dien-5-ynes in the presence of additional appropriate reagents provides a usefull tool for preparing aromatic rings with a wide number of substitution patterns not easily accesible through other methodologies.

Nevertheless, the cycloaromatization of 1,3-dien-5-ynes is an already mature area and, although significant contributions have been recently made and are still expected, the area that has attracted a higher number of contributions in the last years is the use of 1,3-dien-5-ynes in the synthesis of five-membered rings. Mainly based on metal-catalyzed processes, different methodologies have been developed for the efficient and selective synthesis of indene, cyclopentenone and fulvene derivatives, among others. The possibility of accesing a number of different substitution patterns through the judicious selection of the precursors and the use of appropriate additional reagents, together with the previously commented ease of synthesis of 1,3-dien-5-ynes and the mildness of the conditions makes the cyclization of 1,3-dien-5-ynes an appealing alternative for the synthesis of five membered-rings.

Although less explored, some examples describing the use of 1,3-dien-5-ynes in the synthesis of other-size carbocycles and diverse heterocycles have also started to appear in the last years.

The already demonstrated versatility of 1,3-dien-5-ynes and the vast amount of related literature that has appeared during the last few years make us foresee that significant contributions in the field are still to come. Thus, PAHs are very relevant molecules for the design of new materials, and cycloaromatization of 1,3-dien-5-ynes will continue to be a method of choice in their synthesis. In this regard, although the state of the art in the cycloaromatization of 1,3-dien-5-ynes is quite advanced, the development of new methodologies that employ cheaper catalysts or lower catalyst loadings would be highly desirable from a practical point of view. Particularly appealing would be the development of a metal-free method that could overcome the narrow scope so far described for the acid-catalyzed procedure. Moreover, the use of 1,3-dien-5-ynes for the synthesis of 7- and 8-membered rings and heterocycles is clearly underdeveloped compared to their

utilization in the preparation of 5- and 6- membered rings, despite its potential has already been demostrated. Thus, it is expected that in the next years a thoughtful choice of appropriate 1,3-dien-5-ynes and additional reagents would allow a blooming of new methodologies for the regioselective synthesis of higher rings and heterocycles with various substitution patterns.

ACKNOWLEDGMENTS

We are grateful to the Ministerio de Economía y Competitividad (MINECO) and FEDER (CTQ2013-41336-P, CTQ2013-48937-C2-1-P, CTQ2014-52488-R), Universidad de Alcalá (CCG2015/EXP-003) and Junta de Castilla y León (BU237U13) for financial support. P. G.-G. thanks MINECO for a "Ramón y Cajal" contract.

ABREVIATIONS LIST

AIBN	azobisisobutyronitrile
BARF	$[B[3,5\text{-}(CF_3)_2C_6H_3]_4]^-$
BIPHEP	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
BPO	benzoyl peroxide
BrettPhos	2-(dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl
COD	1,5-cyclooctadiene
Cp*	pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DIBAL-H	diisobutylaluminum hydride
Dipp	2,6-diisopropylphenyl
d-*i*-Prpf	1,1'-bis(diisopropylphosphino)ferrocene
Dppp	1,3-bis(diphenylphosphino)propane
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid

Hex	hexyl
IPr	*N*,*N*'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
Ms	methanesulfonyl
MS	molecular sieve
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl-2-pyrrolidone
Ns	*p*-nitrobenzenesulfonyl
PAHs	polycyclic aromatic hydrocarbons
Piv	trimethylacetyl
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TC	thiophene-2-carboxylate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TosMIC	*p*-toluenesulfonylmethyl isocyanide
Tp	trispyrazolylborate
Ts	*p*-toluenesulfonyl
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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BIOGRAPHIES

Enrique Aguilar received his PhD in Organic Chemistry from the Universidad de Oviedo (under the direction of Prof. J. Barluenga and Prof. Santos Fustero) in 1991. He underwent postdoctoral research with the late Prof. A. I. Meyers at Colorado State University (1991–1994) working in natural product synthesis. He then returned to Universidad de Oviedo as Researcher, being promoted to Assistant Professor in 1996, and to Associate Professor in 2002. He has been a Visiting Scientist at the University of Colorado (1996, with Prof. Gary A. Molander). His research work is centered in the development of synthetic organic methodology, new asymmetric reactions, homogeneous catalysis and organometallic chemistry

Roberto Sanz received his Ph.D. degree from the Universidad de Oviedo (Spain) in 1997 under the supervision of Prof. J. Barluenga and Prof. F. J. Fañanás, working on the design of new carbometallation reactions. In 1997 he took an Assistant Professor position at Universidad de Burgos, where he became Associate Professor in 2003 starting his independent career. He has been a Visiting Scientist at ETH Zürich (Switzerland, 2000) with Prof. E. M. Carreira. Since 2010 he is a Full Professor in Organic Chemistry. His research interests are focused on the development of new methods in organic synthesis in the fields of homogeneous catalysis (including the use of gold and dioxomolybdenum complexes as well as Brønsted acids) and organolithium chemistry for the synthesis of functionalized heterocycles.

Manuel Ángel Fernández-Rodríguez obtained his PhD in Organic Chemistry from the Universidad de Oviedo in 2003 under the supervision of Prof. J. Barluenga and Prof. E. Aguilar developing new processes involving Fischer carbene complexes. In 2004 he moved to Yale University, where he stayed two years for a postdoctoral position as a MEC/Fullbrigth fellow, working on cross-coupling reactions with Prof. J. F. Hartwig. Then he worked as a "Juan de la Cierva" researcher in the CSIC (2006–2008) and as a "Ramón y Cajal" researcher (2009-2013) in the Universidad de Burgos where he became Associate Profesor in 2013. His current investigation is focused on organometallic chemistry and homogeneous catalysis.

Patricia García-García received her Ph.D. from the Universidad de Oviedo in 2007 under the supervision of Prof. J. Barluenga and Prof. E. Aguilar working on the development of new reactions of Fischer carbene complexes. Then she moved to Germany as a postdoctoral researcher where she worked in the field of organocatalysis with Prof. B. List in the Max-Planck Institut für Kohlenforschung (2007–2009). After that, she joined the group of Prof. R. Sanz at the Universidad de Burgos as a "Juan de la Cierva" fellow (2009-2013) and in 2014 she moved to the Universidad de Alcalá as a "Ramón y Cajal" researcher. Her current research interests cover metal catalysis and its application to the synthesis of new materials.

TOC