Review

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# Recent Advances in the Catalytic Synthesis of the Cyclopentene Core

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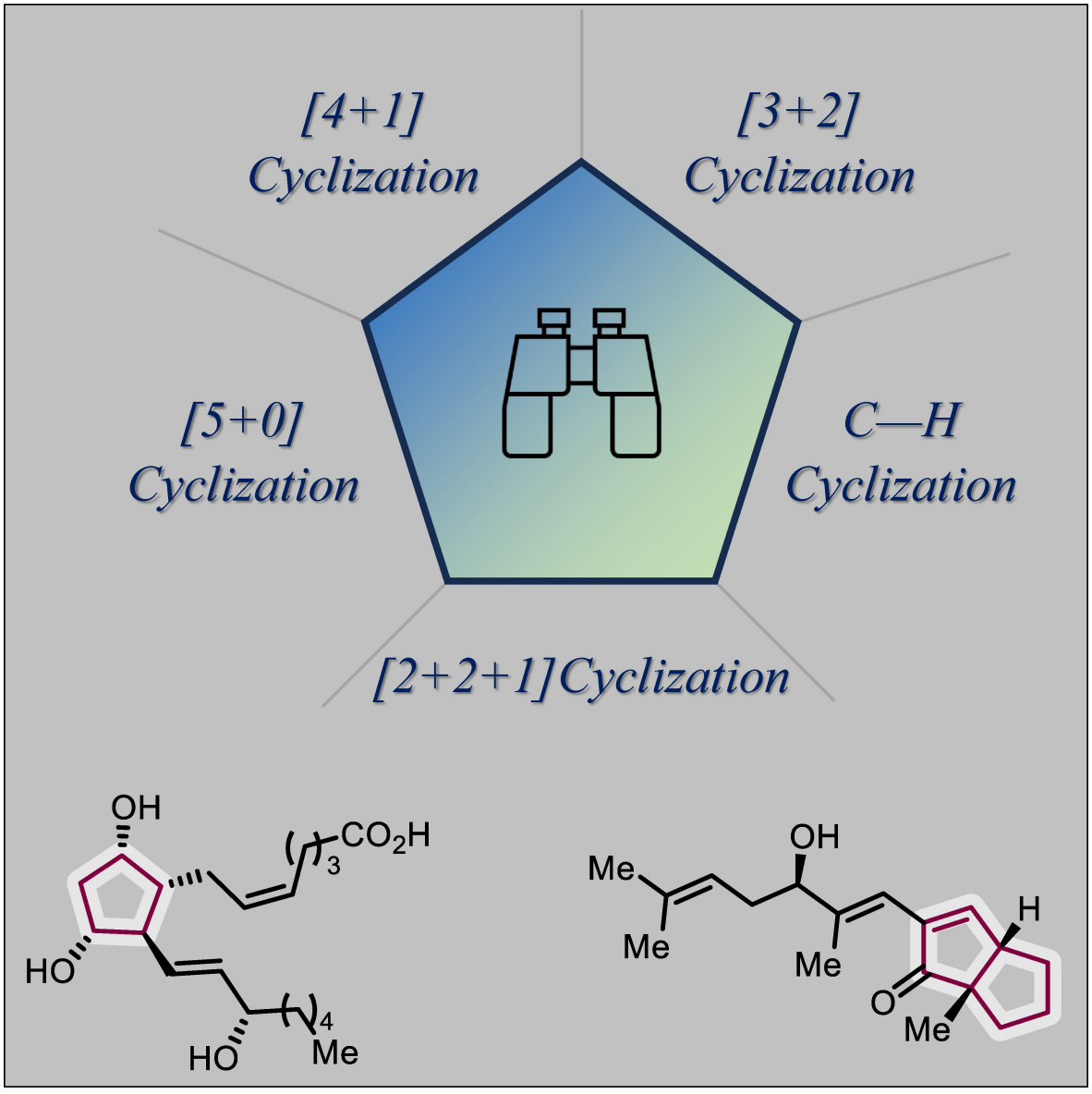
*Dedicated with deep respect and admiration to Prof. Keiji Maruoka on the occasion of his 70th birthday*



**Abstract:** Five-membered carbocycles are ubiquitously found in natural products, pharmaceuticals, and other classes of organic compounds. Within this category, cyclopentenes deserve special attention due to their prevalence as targets and as well as key intermediates for synthesizing more complex molecules. Herein, we offer an overview summarizing some significant recent advances in the catalytic assembly of this structural motif. A great variety of synthetic methodologies and strategies are covered, including transition metal-catalyzed or organocatalyzed processes. Both inter- and intramolecular transformations are documented. On this ground, our expertise in the application of C–H functionalization reactions oriented towards the formation of this ring and its subsequent selective functionalization is embedded.

**Keywords:** Cyclopentene, Catalysis, Cyclopentannulation, Synthetic Methodology, C–H functionalization

Synthetic organic chemists have shown a longstanding interest in the synthesis of the cyclopentane ring due to its prevalence in natural products, pharmaceuticals, and other important classes of organic molecules. Most of the classical methods are based on stoichiometric transformations. Due to the great variety of strategies used for that purpose, their systematization results in a somewhat difficult task. This review is restricted to catalytic methodologies for preparing cyclopentene derivatives, mainly due to their versatility for constructing more complex scaffolds. Several reviews on the synthesis of the cyclopentene core are available in the literature, however, most of them are restricted to the use of a specific transformation (i.e. isomerization of cyclobutanes).[1] Most of the contributions gathered herein fall within the last decade; however, seminal contributions from each section are included in order to provide the reader with an appropriate framework. In this review, the information concerning the different strategies covered is arranged according to the general scheme depicted in Figure 1. The five-membered ring may be assembled by means of [3+2] cyclizations, both by an intermolecular reaction between a 3 C and a 2 C synthons and by the rearrangement of a vinyl cyclopropane, in which the cyclopropane ring acts as 3 C component and the vinyl substituent as 2 C unit. In addition, a [4+1] cyclization between a diene scaffold and an appropriate 1 C synthon may also achieve the formation of cyclopentene derivatives. Furthermore, substrates bearing unsaturations at strategic positions may also undergo intramolecular a [5+0] cyclization towards the cyclopentene core either by means of cycloisomerization or metathesis processes. Finally, within the latter category, we would like to highlight the synthetic potential of C–H functionalization processes that allow the transformation of ubiquitous and generally difficult-to-differentiate C–H bonds into valuable C–C bonds in a selective manner.

Hence, in accordance with the general scheme depicted above, this review will be organized according to the following sections:

## 1. Transition-Metal Catalyzed [3+2] Cyclizations

Transition-metal catalysis lies amongst the most active fields of research within the realm of synthetic organic chemistry. Several recent Nobel Prizes being awarded to Knowles, Noyori, and Sharpless (2001),[2] Chauvin, Grubbs, and Schrock (2005),[3] and Heck, Negishi, and Suzuki (2010) bear witness to such a statement.[4] Transition metal-catalyzed [3+2] cyclizations are very abundant, herein we will only highlight some of the recent trends in the field, always limited to the construction of cyclopentene derivatives

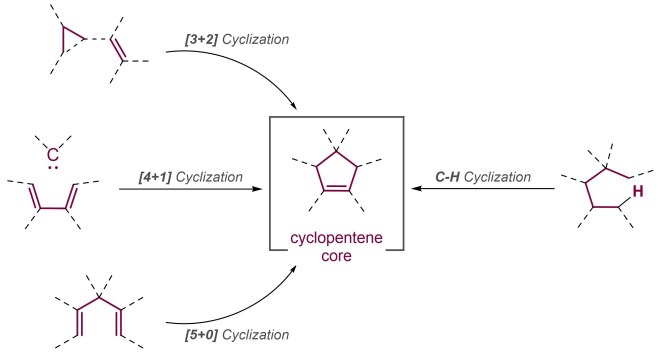



**Figure 1.** Simplified categorization of the different approaches towards the cyclopentene framework.

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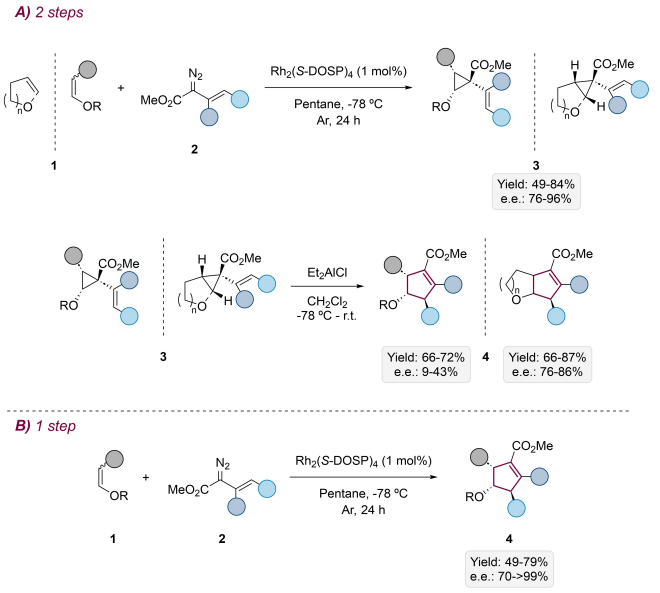
### 1.1. Vinyldiazo Compounds

The decomposition of diazo compounds still represents one of the most common approaches to achieving metal-carbene intermediates.[5] In recent years, vinyldiazo compounds have been added to the synthetic toolbox as very useful reagents.[6] Among their applications, the synthesis of cyclopentene derivatives by means of formal [3+2] cycloadditions is perhaps the most relevant. The development of this transformation is summarized below.

In 1998, an interesting work developed by Davies and coworkers described the use of diazobutenoates **2** and vinyl ethers **1** as reagents and [($Rh_2$(S-DOSP)$_4$] as catalyst providing donor/acceptor-substituted vinylciclopropanes **3** in high diastereo- and enantioselectivity. Then, these vinylcyclopropanes **3** yielded the corresponding cyclopentenes **4** with excellent stereocontrol through a $Et_2AlCl$-mediated rearrangement (Scheme 1).[7] Two years later, Davies and colleagues carried out the same overall transformation employing [($Rh_2$(S-DOSP)$_4$] as catalyst without the requirement of additional Lewis acid. These cyclopentenes were obtained in high yield and better enantioselectivity than before. Moreover, these compounds were further functionalized using different conditions to generate new pentasubstituted cyclopentanes with




**Scheme 1.** a) Synthesis of vinyl cyclopropanes employing rhodium catalysis. b) $Et_2AlCl$-mediated VCP-CP rearrangement.

Rubén Miguélez (1997) studied chemistry at the University of Oviedo where he graduated in 2019. Then, he moved to Valencia starting his master's degree under the supervision of Gonzalo Blay. Later, he started the Doctoral Thesis under the supervision of Pablo Barrio focusing on C($sp^3$)–H functionalization of bromoalkynes with gold (I) catalysis. He is an enthusiast of science, and he really likes playing sports and listening to music, specially hip hop style.

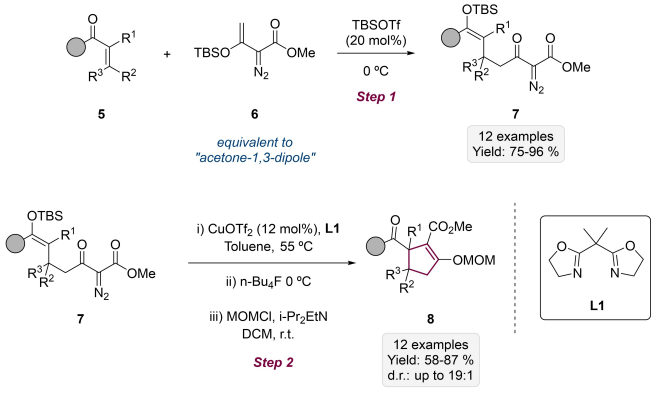
Pablo Barrio completed his Ph.D. at the University of Oviedo in 2007 under the supervision of Prof. Barluenga. After a postdoctoral stay in the group of Prof. Carreira at ETH Zurich, he joined the group of Prof. Fustero in 2009 as a Juan de la Cierva Fellow working for several years in the field of organofluorine chemistry. In 2018 he moved to Oviedo as a Ramón y Cajal Fellow joining the Selective Organic Synthesis group (SOS). His current research interests are focused on gold catalysis.

José M. González graduated in Chemistry and he received his Ph.D. (1988) from the University of Oviedo (Prof. Barluenga, Asensio and Campos). After two years' postdoctoral stay at the University of California, Berkeley, as a Fulbright-MEC fellow (Prof. Vollhardt), in December 1990 he started as assistant professor at the University of Oviedo and in 1993 was promoted to associate professor. In 2007 he became professor. In 2020 he was awarded with the "Felix Serratosa Medal" by the Organic Division of the Spanish Royal Society of Chemistry. He is interested in the discovery of catalytic organic transformations.

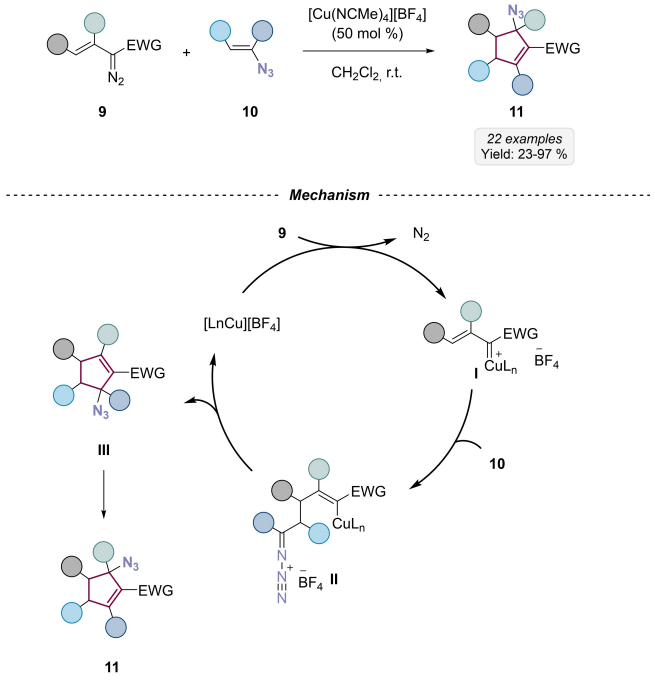
 

full control of the stereochemistry at five contiguous stereocenters.[8]

In 2013, a two-step method for the cyclopentannulation of conjugated enones **5** using methyl 3-(tert-butyldimethylsiloxy)-2-diazo-3-butenoate **6** as a bifunctional reagent was developed by Guerrero and coworkers.[9] The first step consists of the nucleophilic attack from an enol silane to the electrophilic β-carbon of a conjugated enone. In the second step, a formal α,α'-diketone coupling catalyzed by Cu(I) takes place. Cyclopentenes **8** were obtained in excellent yields and good diastereoselectivities (Scheme 2). The implementation of a




**Scheme 2.** Cyclopentannulation of conjugated enones and vinyldiazo compounds.




**Scheme 3.** Cycloadition of vinyldiazo and vinylazides catalysed by copper.

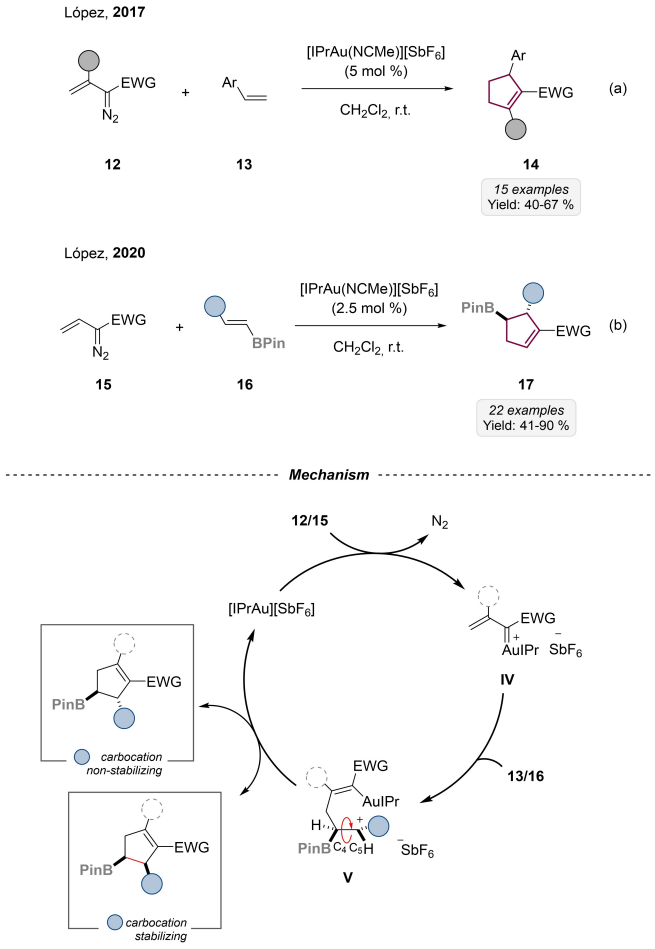
one-pot thermal decarboxylation allows for obtaining cyclopentanones.[10]

Another interesting reaction to obtaining cyclopentenes was developed by López and coworkers in 2017.[11] They developed an efficient copper-mediated [3+2] cycloaddition of vinyl diazocompounds **9** and vinylazides **10** under mild conditions. Noteworthy, the thus obtained densely functionalized cyclopentene derivates **11** contain an azide group, amenable for further transformations (Scheme 3). They proposed a mechanism beginning with the reaction between the vinyldiazo compound and the copper (I) complex affording alkenylcarbene **I**. Then, this species reacts with vinylazide **10**. In this case, the vinylazide behaves as an enamine attacking the vinylogous position of the alkenylcarbene to form intermediate **II**. Subsequent cyclization generates the [3+2] cycloadduct intermediate **III**. Finally, an allylic rearrangement of the azide group affords the observed product **11** (Scheme 3).

Then, López and colleagues described two related formal [3+2] cycloaddition reactions towards the cyclopentene moiety employing gold (I) catalysis.[12,13] First, in 2017, they developed a [3+2] cycloaddition between alkenyldiazo compounds **12** and styrene derivates **13** to obtain the corresponding cyclopentenes **14** in good yields (Scheme 4a).[12] Other compounds such as the vinylcyclopropane corresponding to direct cyclopropanation or a cycloheptene derivative arising from a formal [3+2+2] were also observed in low yields. Then, in 2020, they developed a related transformation replacing the styrene derivates **15** with alkenylboronates **16** affording the corresponding borylated cyclopentene derivatives **17**.[13] This reaction proceeded in high regio- and stereoselectivity. The mechanism proposed in Scheme 4 proceeds as follows: the first step was the generation of a gold vinylcarbene **IV** with dinitrogen release; then, the alkenylboronate **16** attacks at the vinylogous position of the gold carbene generating a cationic intermediate **V** which would then undergo cyclization reaction generating the cyclopentene ring. For most examples, the reaction showed stereospecificity. However, the use of an *E*-alkenylboronate with electron-donating groups, such as c-$C_3H_5$ or 4-$MeOC_6H_4$ afforded the *cis*-configurated [3+2] adduct. In order to rationalize this unexpected outcome, the authors invoke the increased stability of the benzylic carbocation that enables the fast rotation between the $C_4$ and $C_5$ providing the other isomer. Finally, they carried out different further transformations on the boron functional group. One of them was the oxidation with $NaBO_3$ affording the hydroxylated product. Also, a Matteson homologation reaction was carried out in good yield (Scheme 4b).

In 2018, Ferreira and coworkers developed a direct [3+2] cycloaddition between alkenes **19** and vinyl diazo compounds **18** employing chromium- or ruthenium-based metal catalysts and light to produce a variety of cyclopentenes **20** in good yields and diastereoselectivities.[14] As discussed earlier, vinyl

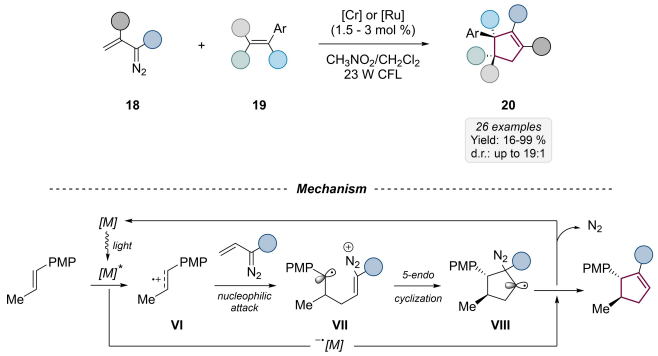
 




**Scheme 4.** [3+2] cycloaddition of alkenyldiazocompounds with styrene derivates (a) and alkenylboronates (b).

diazo compounds usually act as electrophilic reagents. However, the photocatalytic generation of a more reactive electrophilic partner (radical cation) results in an umpolung of the reactivity of the vinyl diazo acting as a nucleophile. The reaction showed broad substituent tolerance in the vinyl diazo and alkene. However, gamma-substitution on the diazo reagent was not tolerated (Scheme 5). This reaction always yielded the trans product regardless of the initial configuration of the alkene used. Finally, the products were diversified employing different organic reactions.

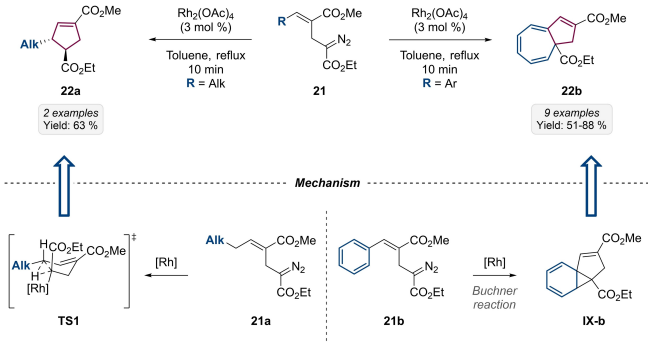
In 2021, Sá and coworkers developed an interesting intramolecular reaction of α-diazo-γ,δ-unsaturated esters **21** employing a rhodium catalyst. [15] The most salient feature of this report would be the selective formation of two different products depending on the reagent and catalyst used. On the one hand, the use of $Rh_2(pfb)_4$ in acetonitrile resulted in a β-hydride migration to give 2*Z*-4*E* dienes (not shown). On the other hand, the use of aryl-diazo compounds **21 b** along with




**Scheme 5.** [3+2] Photo-cycloaddition of alkenyldiazo compounds and styrene derivates.

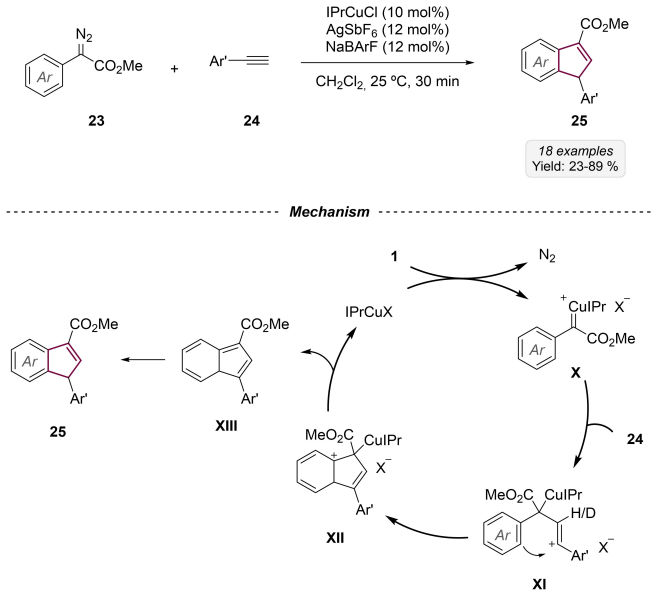
$Rh(OAc)_4$ as catalyst in toluene, afforded 5,7-fused bicyclic tetraenes **22 b** in high yields through a regioselective intramolecular Buchner reaction (Scheme 6). Finally, the alkyl-substituted analogs **21 a** undergo an intramolecular C–H insertion to yield anti-configurated cyclopentenes **22 a**, due to the stereoelectronic factors in the transition state during the insertion of the carbene into the C–H bond (Scheme 6).

Another reaction employing diazocompounds was developed by Chang and coworkers using α-aryldiazoester compounds **23** as precursors of carbenes and terminal alkynes **24** to form the corresponding indenes **25**, using IPrCuCl as the catalyst (Scheme 7).[16] They observed that phenylacetylenes bearing electron-donating groups reacted more readily than the electron-deficient ones. The mechanism started with the nucleophilic attack of the alkyne to the copper carbenoid **X**, affording zwitterionic species **XI**. Then intermediate **XI** is attacked by the aromatic ring to generate intermediate **XII** that, through the release of copper, forms the isoindene **XIII**. Finally, after an isomerization product **25** is formed (Scheme 7).



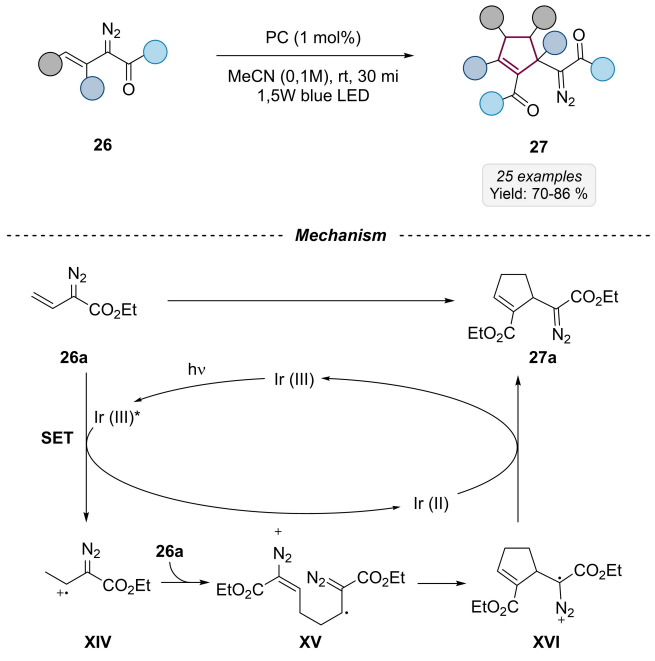

**Scheme 6.** Cyclization through cyclopropanation-retro Buchner and C–H functionalization pathways.




**Scheme 7.** Intermolecular formal [3+2] cycloaddition between terminal alkynes and α-aryldiazoesters.

In 2023, Koenigs and Zhou developed a photoredox dimerization process of vinyldiazo compounds **26** affording cyclpentenyl α-diazocompounds **27**, versatile synthetic intermediates (Scheme 8).[17][18] An in-depth mechanistic study combining experimental and computational data, allowed the authors to suggesting a detailed mechanism. The reaction starts with the excitation of the photocatalyst with visible light followed by single-electron transfer (SET) oxidation of the substrate. The thus obtained radical cation **XIV** would then undergo the nucleophilic attack of a second molecule of vinyldiazo compound. Ring closure with concomitant nitrogen extrusion affords intermediate **XVI** that accepts a single electron from the iridium (II) species affording the final product and regenerating the Ir (III) photocatalyst (Scheme 8). The authors showed the versatility of the obtained scaffolds by subjecting them to a series of transformations affording a number of synthetically useful derivatives.



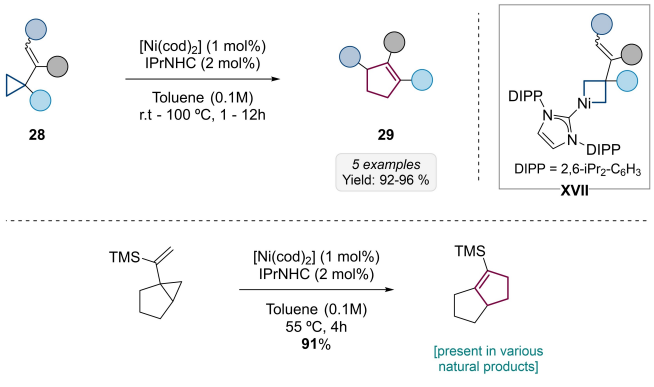

**Scheme 8.** Photoredox dimerization of vinyldiazocompounds.

## 1.2. Vinylcyclopropanes

The vinyl cyclopropane-cyclopentene (VCP-CP) rearrangement was discovered in 1959 and has attracted considerable attention ever since.[19] However, several restrictions related to substrate substitution and harsh reaction conditions somewhat hampered its synthetic applicability. The dawn of the new century witnessed some improvements brought about by transition metal-catalysis (and organocatalysis as well, vide infra). Some significant examples are discussed below.

In 2004, Louie and coworkers developed the isomerization of unactivated vinyl cyclopropanes **28** to cyclopentenes **29** using [Ni(cod)$_2$] as precatalyst and IPr as a NHC ligand being the optimum Ni:IPr ratio 2:1.[20] An important application of this reaction is the synthesis of bicyclic frameworks because of its abundance in natural products (Scheme 9).

In 2018, Uyeda and colleagues described the activation of strained three-membered rings using a dinuclear nickel complex to form the corresponding cyclopentene derivatives.[21] Their initial studies were carried out using stoichiometric quantities of [iPrNDI]Ni$_2$($C_6H_6$) **30** and *N*-tosyl-2-vinylaziridine to form complex **31** as a crystalline solid. Coordinating with the aziridine resulted in the shortening of the Ni–Ni distance as compared to complex **30**, suggesting

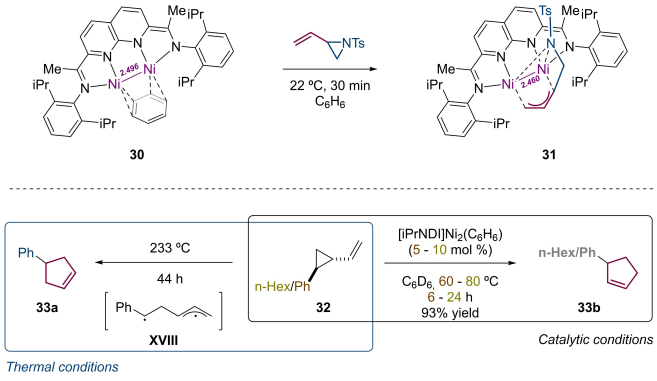



**Scheme 9.** Isomerization of unactivated vinyl cyclopropanes to cyclopentenes.

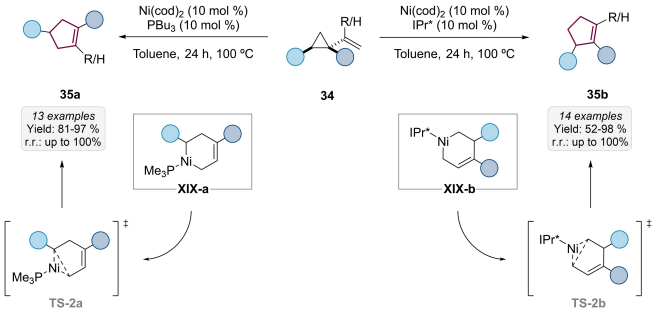
 

that the electron pair required for the two-electron oxidative addition is being provided by the reduced ligand pi-system rather than from the Ni–Ni bond. This conclusion was also supported by DFT calculations. Then, the reaction with vinyl cyclopropanes was studied by variating the catalyst. The aforementioned dinuclear catalyst was found to be the best of all catalysts tried. A computational study showed that when the catalyst is a monoligated Ni species like in Louie's report the C–C oxidative addition is likely rate-determining. In this case, they could obtain neither intermediate. The rearrangement of **32** to generate the cyclopentene **33b** was carried out under catalytic conditions at 80 °C (Scheme 10). This reaction affords a different cyclopentene isomer as compared to the thermal conditions (233 °C) (Scheme 10).

In 2023, Miura and colleagues developed an interesting catalytic vinyl cyclopropane rearrangement towards 1,4- and 1,5-disubstituted cyclopentenes, regiocontrolled by the ligand geometry.[22] The reaction was carried out employing $Ni(cod)_2$ as a pre-catalyst in toluene at 100 °C (Scheme 11). Different ligands were tested, showing that the use of $PBu_3$ yielded 1,4-disubstituted cyclopentenes **35a** in good regiocontrol and excellent yields. However, switching to IPr* as ligand resulted in the formation of 1,5-disubstituted cyclopentenes **35b** (Scheme 10). They carried out mechanistic experiments observing a stereoretentive process, with only a slight erosion of the enantiomeric excess in the product when an enantiomerically enriched vinyl cyclopropane was used. Moreover, DFT calculations were performed observing that when the vinyl cyclopropane **34** reacts under nickel catalyst and $PMe_3$ as a ligand the intermediate **XIXa** arising from cleavage of the C1-C3 bond was formed. This intermediate evolved through the lowest energy transition state **TS-2a** to give the corresponding cyclopentene **35a**. However, when **34** reacts under nickel catalyst and IPr* as a ligand the intermediate **XIXb** arising from cleavage of the C1-C2 bond was formed. Even if intermediate **XIXa** is higher in energy than the corresponding intermediate **XIXb** it can evolve then through a lower energy transition state **TS-2b** explaining the formation of the regioisomeric cyclopentene **35b**. Thus, the product selectivity is controlled by the rate-determining reductive elimination steps. A complete kinetic study of the reaction also supported this mechanistic rationale.




**Scheme 10.** Activation of strained three-membered rings employing a dinuclear complex.

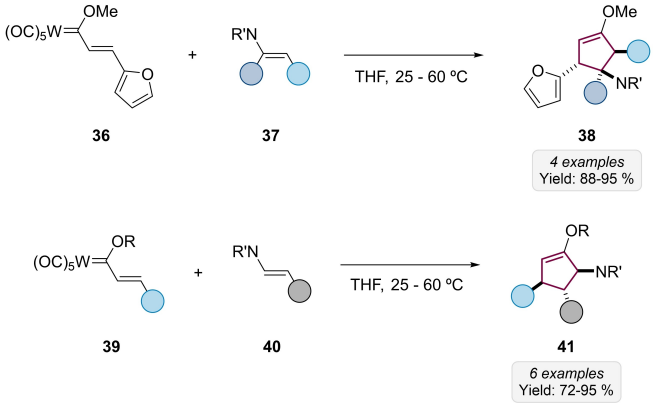



**Scheme 11.** Ni-catalyzed regiodivergent VCP-CP rearrangement.

## 1.3. Fischer Carbene Complexes

Since the seminal report by Fischer and Maasbol in 1964, the chemistry of Fischer carbene complexes has fascinated both organometallic and synthetic organic chemistry due to their incomparable balance between rich reactivity and chemical stability.[23][24] Amongst the innumerable cyclization reactions in which these organometallic entities participate, [3+2] cyclizations hold a prominent position.

In 1999, Barluenga and coworkers described one of the first [3+2] reactions using Fischer carbene complexes.[25] In this work they employed (alkoxyalkenylcarbene)tungsten (0) complexes **36** and tertiary enamines **37** to synthesize cyclopentene derivates **38** with excellent yields, regio- and diastereoselectivities (Scheme 12). Moreover, when enamines derived

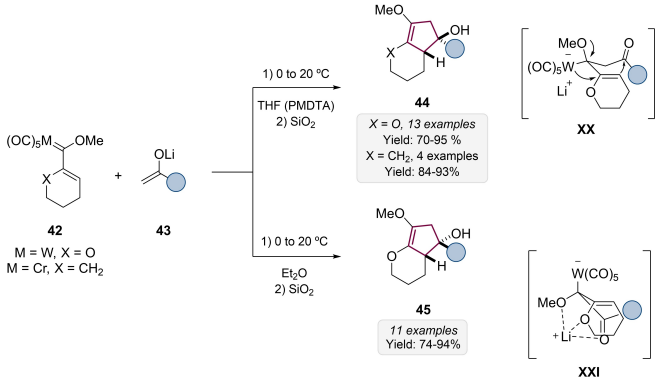



**Scheme 12.** Intermolecular [3+2] cyclization employing tungsten Fischer carbenes and enamines.

from chiral amines were used the corresponding products were obtained in high facial selectivity, delivering enantioenriched cyclopentenones upon hydrolysis of the enol ether and elimination of the amine. Noteworthy, a regioselectivity switch was observed when aldimines **40** were used instead of ketimines **37** (Scheme 12). In this case, the regioselectivity was moderate when a methoxy carbene and an enamine derived from a linear aldehyde were used. Fortunately, they found that the bulkiness of the alkoxy group and the substituent of the enamine played a definitive role in the cyclization, by dictating the regioselectivity of the reaction (Scheme 12). These products were derivatized through hydrolysis with diluted acid, followed by $SmI_2$-mediated reductive C–N bond cleavage, providing the corresponding cyclopentanones.

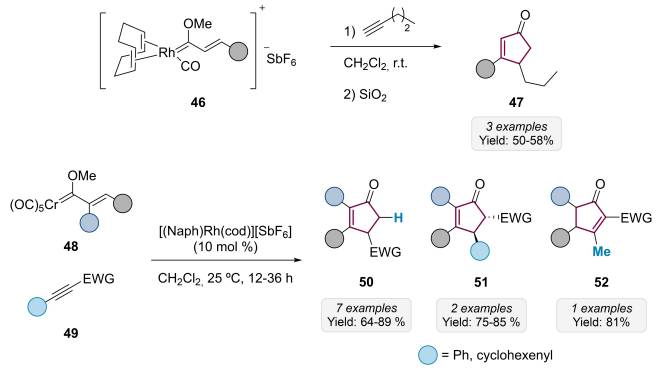
In 2003, Barluenga and coworkers developed a [3+2] cyclization reaction of alkenyl Fischer carbene complexes **42** with lithium enolates **43** derived from methyl ketones forming five-membered ring derivatives **44, 45**.[26] The most interesting feature of this report is the high influence of the solvent on the stereochemical outcome of the process (Scheme 13). When the reaction was carried out in highly coordinating solvents the approach of the allylic carbon atom of the α-allyltungsten moiety to the carbonyl center illustrated by the trajectory depicted for **XX** was favored. However, when the reaction was carried out in a less coordinating solvent the approach was opposite due to the coordination of the three oxygen atoms of the intermediate with the lithium atom as in **XXI** (Scheme 13).



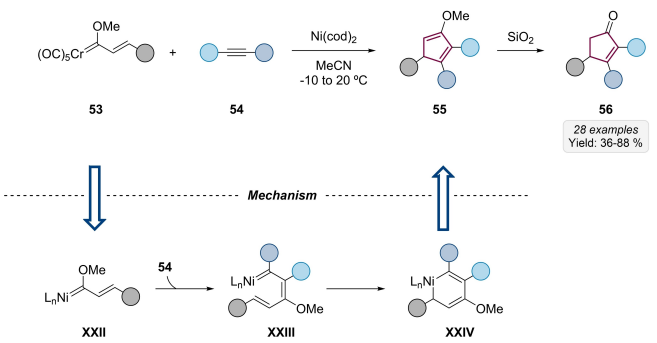

**Scheme 13.** [3+2] cyclization of alkenyl Fischer carbene complexes with lithium enolates.

In 2004, Barluenga and coworkers developed a new reaction to generate cyclopentenones **47** using novel cationic rhodium (I) alkoxycarbene complexes **46**.[27] These complexes were synthesized by transmetalation from chromium alkenylcarbene complexes **48** (Scheme 14).[28] Moreover, the reaction could be carried out from the parent chromium carbene **46** with catalytic amounts of the rhodium complex (Scheme 14). The reaction was limited to the use of electron-poor alkynes **49** (alkynoates and alkynones) and the regio- and the stereochemistry of the process was highly dependent on the substitution at the other carbon of the triple bond (Scheme 14). Hence, while terminal alkynes afford the cyclopentenone derivative with the electron-withdrawing group at the distal position **50** (relative to the carbonyl), internal ones result in the opposite regiochemistry (Scheme 14). Moreover, when the second substituent is a phenyl or a cyclohexenyl ring the reaction proceeds in complete diastereoselectivity (Scheme 14, **51**), while the reaction with a methyl substituent (methyl butynoate as substrate) results in the isomerization of the double bond to the most stable doubly conjugated position **52** (Scheme 14).

In 2007, in a further extension of the transmetallation strategy Barluenga and coworkers described a nickel (0)-mediated [3+2] cyclization of alkenyl carbene complexes **53** and internal alkynes **54** to form substituted cyclopentenones **56**.[29] The reaction worked in good yields and in excellent regioselectivity with electron-donating and with electron withdrawing groups (Scheme 15). This reaction showed a wide functional group tolerance allowing the preparation of boron-




**Scheme 14.** Formation of cyclopentenones employing rhodium carbenes and alkynes.

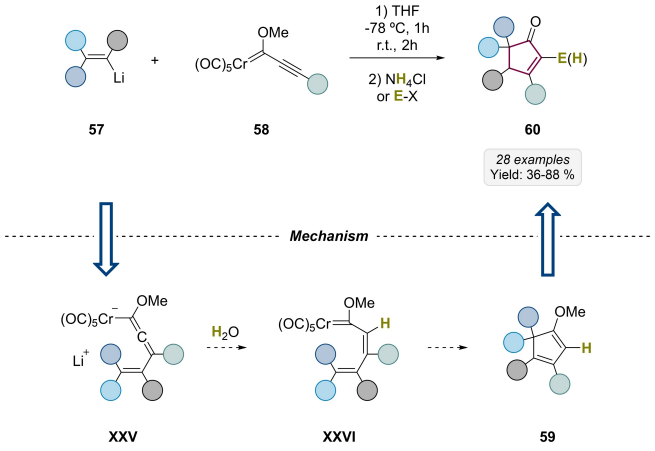



**Scheme 15.** Nickel(0)-mediated [3+2] cyclization of alkenyl Fischer carbene complexes and internal alkynes.

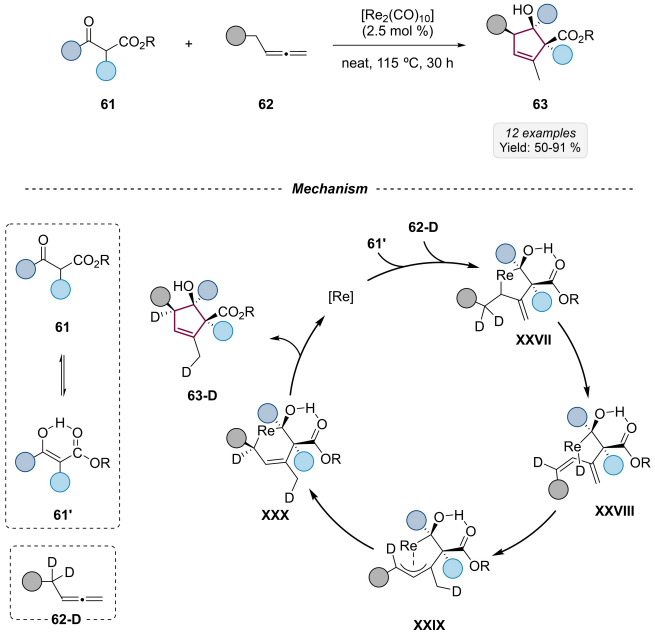
and tin-substituted cyclopentenones amenable for further functionalizations by means of classical palladium-catalyzed C–C cross-coupling processes (Scheme 15).

The last paper in this section was developed by Barluenga and coworkers in 2012. The reaction between a vinyllithium reagent **57** and an alkynyl Fischer carbene complex **58** affords, after hydrolysis polysubstituted cyclopentenones **60** (Scheme 16).[30] The reaction starts with conjugate addition of the organolithium reagent **57**. Protonation of the allenylchromate intermediate **XXV** occurs at the β-position generating a dienyl carbene **XXVI** that evolves to a methoxy-substituted




57 58 60 XXV XXVI 59

**Scheme 16.** [3 + 2] cyclization between alkynyl Fischer carbene complexes and vinyllithium reagents.




61 62 63 61' 63-D XXX XXVII XXVIII XXIX 62-D

**Scheme 17.** Formation of cyclopentenes employing a rhenium catalyst.

cyclopentadiene **59** (Scheme 16). Hydrolysis of the enolether unit affords the observed cyclopentenone **60** (Scheme 16). Interestingly, fully substituted derivatives may be obtained by transmetallation of the allenylchromate intermediate **XXV** with copper and trapping with different electrophiles (Scheme 16).

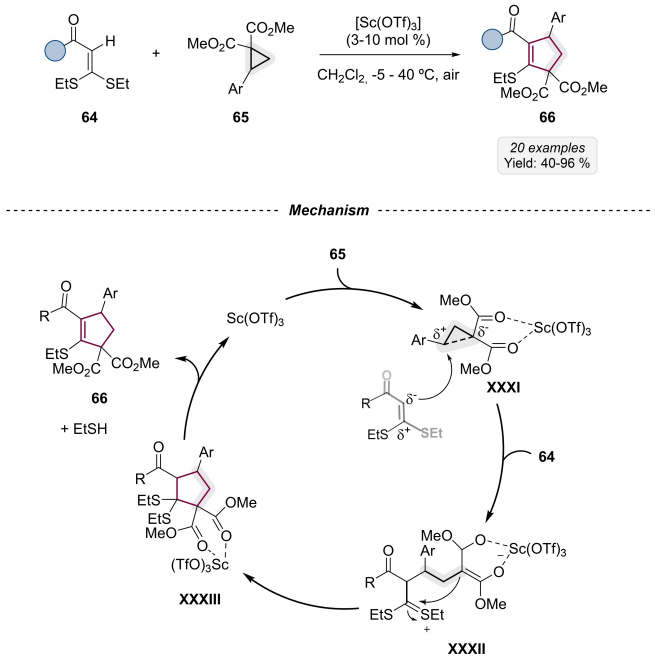
### 1.4. Miscellanea

An elegant synthesis of cyclopentene carbocycles was reported by Takai employing β-ketoesters **61** and allenes **62** as reagents, in 2008.[31] In this publication, the authors described the synthesis of polysubstituted cyclopentenes **63** in good stereoselectivity using rhenium as catalyst (Scheme 17). The corresponding *cis* relationship between the ester and the hydroxy group is explained by a mechanistic proposal supported by deuterium labeling experiments. The first step is the formation of rhenacyclopentane intermediate **XXVII** by an oxidative cyclometallation between the enol form of the ketoester **61'** and the substituted double bond of the allene **62** (Scheme 17). Then, a β-hydride elimination affords the diene intermediate **XXVIII** that undergoes hydrometallation of the *exo* double bond forming a more stable π-allyl rhenium intermediate **XXIX** (Scheme 17). Finally, rearrangement to intermediate **XXX**, followed by reductive elimination would yield the corresponding cyclopentene derivatives (Scheme 17).

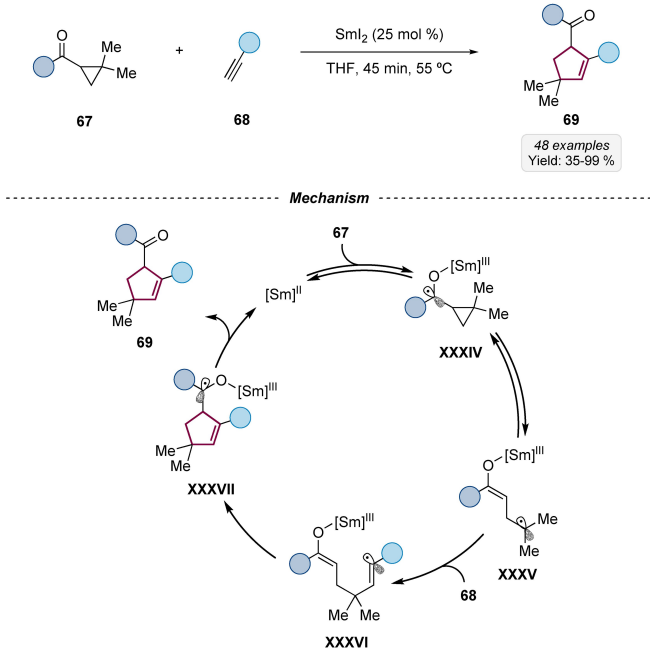
Another interesting reaction was developed by Wang and coworkers in 2020. [32] They report the synthesis of cyclopentenes **66** via ring opening addition and intermolecular nucleophilic vinylic substitution ($S_NV$) reaction between donor-acceptor cyclopropanes **65** and α-oxo ketene dithioacetals **64** employing $Sc(OTf)_3$ as Lewis acid catalyst (Scheme 18). The reaction tolerated a wide range of functional groups. In other to explain the observed regioselectivity, the authors proposed the following mechanism. Activation of cyclopropane **65** with $Sc(OTf)_3$ would trigger the nucleophilic attack of the α-carbon from the ketene dithioacetals **64** to the electrophilic carbon of species **XXXI** affording zwitterionic species **XXXII** (Scheme 18). Then, ring closure would take place by nucleophilic attack of the enolate carbon to the electrophilic carbon of the dithioacetal producing species **XXXIII** (Scheme 18). This intermediate, that may be observed at low temperature, spontaneously eliminates EtSH upon warming to room temperature to yield the corresponding cyclopentene **66** (Scheme 18).

In 2021, Procter and coworkers developed a radical cross-coupling of aryl cyclopropyl ketones **67** and terminal alkynes **68** catalyzed by substoichiometric amounts of $SmI_2$ (Kagan's reagent).[33] The reaction tolerated a broad range of substitution in the (aryl)alkyne **68** and in the (aryl)cyclopropyl ketones **67** giving the corresponding cyclopentenes **69** in excellent yields (Scheme 19). However, functional groups sensitive to




**Scheme 18.** Formation cyclopentenes via Lewis acid-catalyzed ring opening addition / intermolecular $S_NV$ cascade.



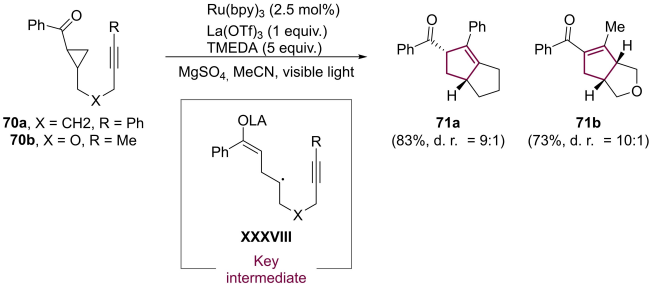

**Scheme 19.** $SmI_2$ mediated radical approach to cyclopentenes.

reduction such as bromo and nitrile were not amenable under the reaction conditions. The presence of the gem-dimethyl unit in the cyclopropyl was crucial to facilitate the reaction due to the formation of a tertiary radical in the carbon attached to those methyl groups. Finally, the proposed mechanism was in line with previous work.[34] The ketone was reduced through a reversible SET from the $SmI_2$ giving radical **XXXIV** which fragmented to give enolate/radical **XXXV**. This intermediate reacted with the alkyne to give radical **XXXVI** which undergoes 5-exo-dig cyclization to form the new ketyl radical **XXXVII**. Regeneration of $SmI_2$ through a back electron transfer yields the corresponding cyclopentene **69**.

The radical ring-opening of cyclopropanes may also be achieved by means of photocatalysis. Cyclopropanes bearing electron-withdrawing groups, i.e. cyclopropyl ketones, are prone to single electron-reduction while electron rich cyclopropanes, i.e. cyclopropyl amines, undergo single electron oxidations.

In 2011, Yoo described a photocatalytic intramolecular [3+2] cycloaddition of cyclopropylketones.[35] In order to lower the reduction potential of the ketone, a Lewis acid additive, namely $La(OTf)_3$, was used in combination with $Ru(bpy)_3Cl_2$ as phorocatalyst and TMEDA as reductive quencher. In most cases, an olefin was the 2 C counterpart; however, in two examples the use of a tethered alkyne **70 a,b** afforded fused bycyclic cyclopentene derivatives **71 a,b** in good yields and diastereoselectivities (Scheme 20).

On the other hand, in a series of publications Zheng described the [3+2] cycloaddition of cyclopropyl amines with olefins, alkynes, diynes and enynes using visible light phtoredox.[36][37][38] The authors studied in detail the scope of the transformation with respect to substitution at the nitrogen atom (only secondary anilines work succesfully), the cyclopropyl unit (substitution at C1 and C2 is tolerated) and the alkyne (terminal aryl and heteroaryl alkynes, propiolates, enynes and diynes, could be engaged in the transformation). When enynes where used chemoselectivity issues arose in some cases. The proposed mechanism is analogous related transformations. The excited photocatalyst is able to oxidize the cyclopropyl amine **72** to the corresponding radical cation **XXXIX** that undergoes ring opening towards distonic radical cation **XL**. Radical addition to the alkyne **73**, followed by ring

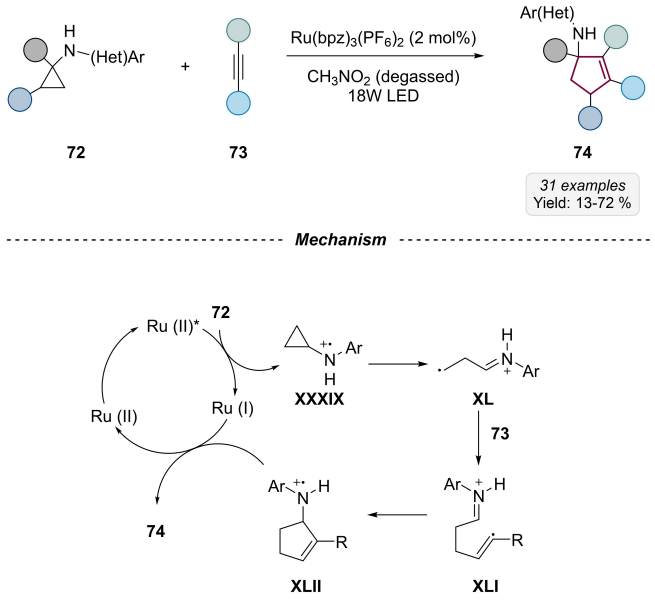



**Scheme 20.** Photocatalyzed intramolecular [3+2] cycloaddition of cyclopropyl ketones with alkynes.

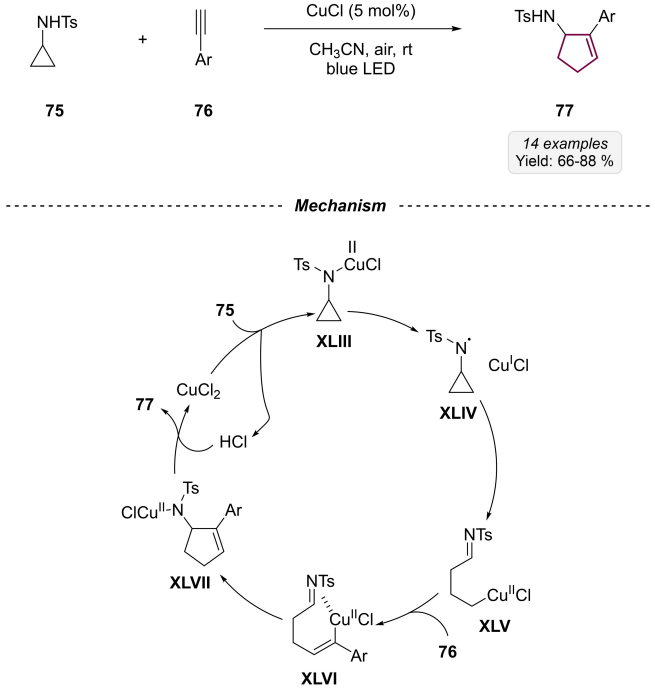
 

closure and reduction of radical cation **XLII**, affords the final product **74** and regenerates the catalyst (Scheme 21).

In 2022, Reiser and Verma described a related copper catalyzed [3+2] cycloaddition between N-tosyl-cyclopropyl amines with alkenes and alkynes, respectively, under blue LED irradiation.[39] The reaction is limited to the use of terminal aryl alkynes **76** and only unsubstituted cyclopropyl rings **75** were tested (Scheme 22). The mechanistic proposal differs substantially from the previous photoredox examples. In this case, the reaction occurs with the intermediacy of organometallic copper species instead of free radicals (Scheme 22).




**Scheme 21.** NHC-catalyzed [3+2] cyclization between enals and chalcone derivatives.




**Scheme 22.** NHC-catalyzed [3+2] cyclization between enals and chalcone derivatives.

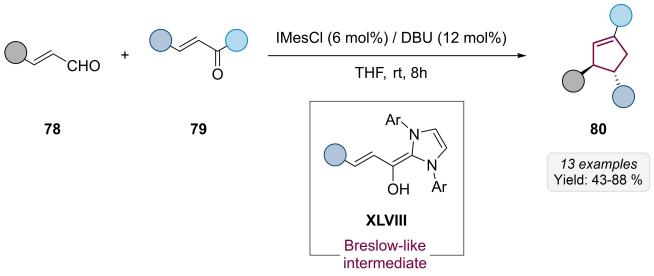
## 2. Organocatalytic [3+2]

During the last two decades, asymmetric organocatalysis has become a fully mature field.[40] This statement finds more than enough ground on the Nobel Prize in Chemistry to be awarded to professors List and MacMillan in 2021 for the development of asymmetric aminocatalysis.[41] In addition to chiral amines, several other kinds of organocatalysts have been developed in recent years. In the following sections, organocatalyzed [3+2] cyclization reactions that allow the construction of the cyclopentene core will be summarized.

### 2.1. NHC-Catalyzed

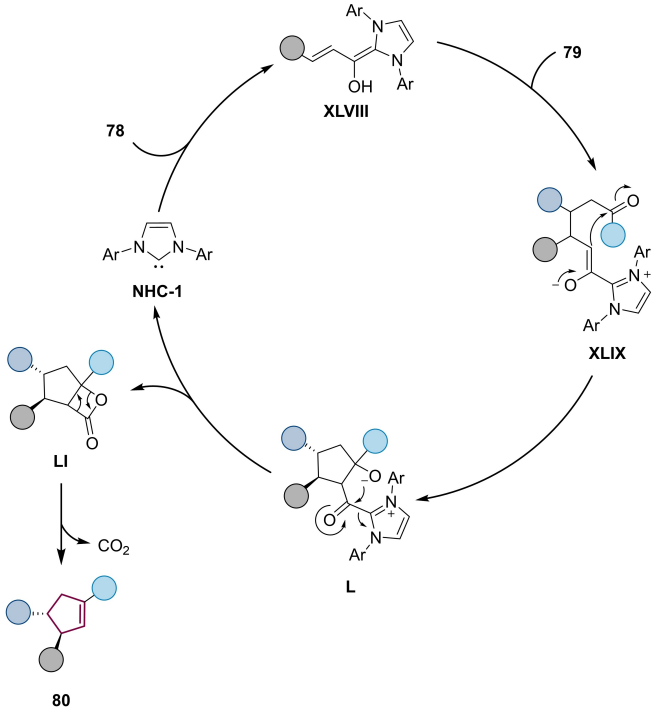
In 2006, Nair described the synthesis of cyclopentenes **80** by means of an *N*-heteocyclic carbene (NHC)-catalyzed reaction between enals **78** and chalcone derivatives **79** (Scheme 23).[42] This new reaction relies on the novel conceptual approach to homoenolate equivalents introduced by Bode and Glorius just two years before.[43] This approach consists of the formation of a Breslow-like intermediate **XLVIII** upon nucleophilic addition of the NHC to the enal **78**, followed by tautomerization. The reaction shows a somewhat limited scope since mostly triaryl-substituted cyclopentenes were obtained, with just two exceptions (Scheme 23).

As indicated above, the proposed mechanism starts with the formation of a Breslow-like intermediate **XLVIII** (Scheme 24). This intermediate behaves as a homoenolate, triggering the nucleophilic addition of the β-carbon of the enal **78** to the β-carbon of the chalcone **79** (Scheme 24). The thus obtained enolate evolves by the nucleophilic addition of the α-

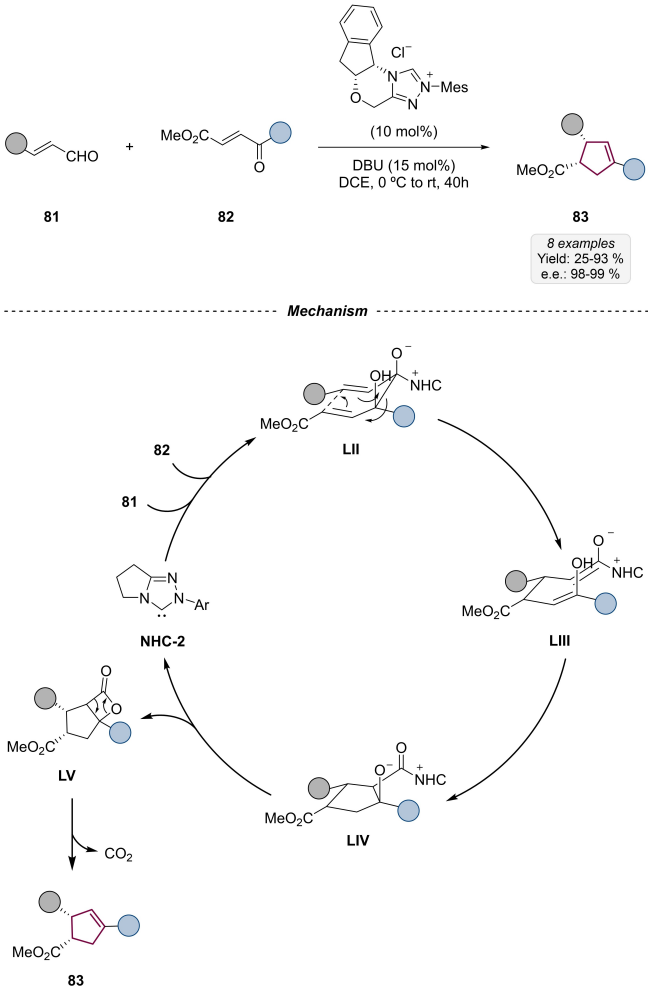



**Scheme 23.** NHC-catalyzed [3+2] cyclization between enals and chalcone derivatives.




**Scheme 24.** Proposed mechanism.



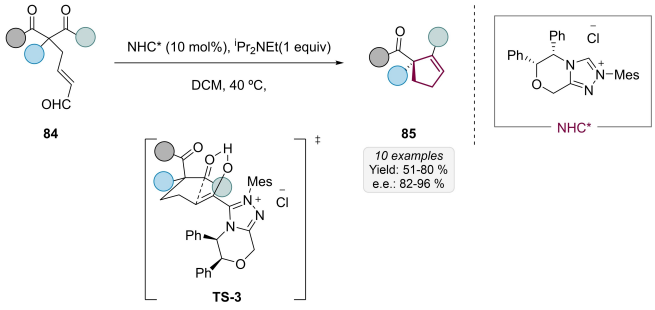

**Scheme 25.** NHC-catalyzed [3+2] cyclization between enals and 4-oxoenoates.

carbon of the enolate **XLIX** to the chalcone carbonyl carbon, forming the five-membered ring **L** (Scheme 24). Finally, the double bond formation occurs with concomitant extrusion of $CO_2$ on β-lactone intermediate **LI**, formed in turn upon intramolecular displacement of the NHC in an addition-elimination process (Scheme 24).

Just one year later, Bode reported a surprising finding, when 4-oxoenoates **82** were used as coupling partners instead of chalcones **79** the corresponding *cis* cyclopentenes **83** were formed (Scheme 25). [44] In addition, the use of a chiral triazonium pre-catalyst afforded the products in very high enantioselectivities (Scheme 25). A series of experiments allowed the authors to explain this discrepancy by suggesting a complementary reaction pathway. According to Bode, the reaction starts with a cross-benzoin condensation followed by an NHC-catalyzed oxy-Cope rearrangement (Scheme 25). The boat-like transition state for the latter step sets the observed *cis*-selectivity. The following steps are similar to Nair's mechanism, intramolecular aldol followed by lactonization regenerates the catalyst. Finally, decarboxylation affords the final product (Scheme 25). The main difference between both mechanisms would be the way in which the $C_\beta$–$C_\beta$ bond is formed, which determines the opposite relative stereochemistry. Bode ascribes the divergent stereochemical outcomes to the preferred reactive conformation of each electrophile. Hence, oxoenoates **82** seem to react predominantly as the s-*cis* conformer, leading to a boat-like transition state, affording *cis*-products **83**. On the other hand, the observed *trans*-selectivity for chalcones **79**, could arise from a different reaction pathway as proposed by Nair, see above, or from an oxy-Cope reaction through the corresponding s-*trans* conformer, leading to a chair-like transition state, affording the *trans*-products **80**.[45] The same conditions applied to chalcones afforded the trans-isomer as the major one but in moderate enantioselectivities.

In the same year, Scheidt envisioned an alternative approach to intermediates analogous to **LII** and **LV**, by means of an intramolecular aldol-type reaction of the Breslow-like intermediate affording the desired transition state **TS-3** (Scheme 26).[46] The evolution through this transition state as above regenerates the catalysts and accounts for the formation of the cyclopentene product **85**. Again, the use of a chiral triazolium NHC-precursor affords the desymmetrization of




**Scheme 26.** NHC-catalyzed intramolecular aldol-type reaction.

1,3-diketones **84** in moderate to good yields and good to excellent enantioselectivities (Scheme 26).

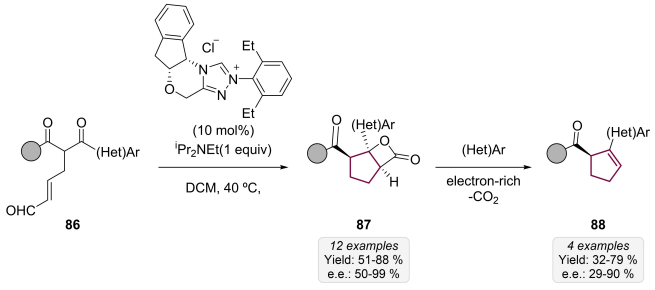
In a further degree of sophistication, Scheidt described the dynamic kinetic resolution of β-ketoesters **86** under very similar reaction conditions (Scheme 27).[47] In this case, only substrates bearing electron-rich aryl rings on the ketone moiety evolved to the corresponding cyclopentenes **88** while other substrates afforded the corresponding β-lactones **87** (Scheme 27).

In 2010, Scheidt overcame the moderate enantioselectivities obtained for chalcones derivatives **90** by using a Lewis acid in combination with the chiral NHC catalyst.[48] Enantioenriched *cis*-cyclopentane derivatives **91** were obtained from enals **89** and chalcones **90** in good yields and excellent enantioselectivities (Scheme 28). Coordination of both carbonyl oxygens to the titanium co-catalyst, pre-organizes the transition state **TS-4** fixing the *s-cis* conformation for the chalcone moiety and hence reversing their inherent *trans*-selectivity.[49]

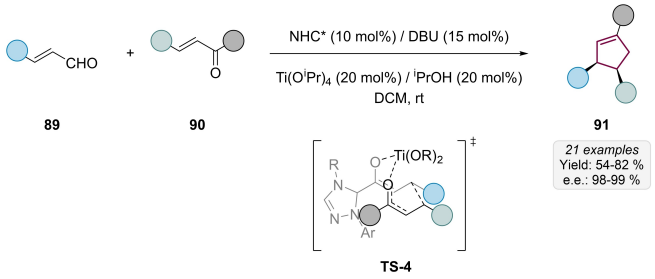
## 2.2. Amine-Catalyzed

As compared to other fields, amine-catalysis has not been very frequently used for assembling the cyclopentene core.[50] The first example, by Wang, relies on a tandem Michael/aldol sequence for the construction of the desired core.[51] Hence, the reaction between an enal **92** and a malonate derive aldehyde **93** using a Jorgensen-Hayashi catalyst **C-1*** afforded the corresponding cyclopentenals **94** in good yields and enantioselectivities (Scheme 29).

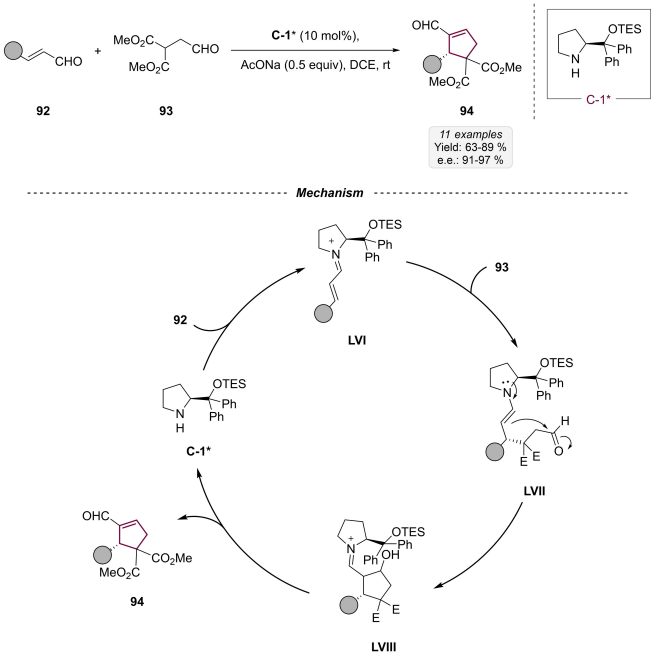
A few years later, Córdova reported a dynamic kinetic asymmetric transformation (DYKAT) by means of a combined amino- / transition-metal catalyzed enantioselective cyclization.[52] In this case, the first C–C bond is formed by a Michael reaction again; however, the reversibility of this step results in a lack of enantioselectivity (Scheme 30). Nevertheless, when the enyne **LIX** formed upon Michael addition is engaged in a subsequent palladium-catalyzed cycloisomerization event, a DYKAT process takes place affording the desired cyclopentenes **97** in high optical purities (Scheme 30). Moreover, the use of a cyanoacetate derivative **96b** allows for




**Scheme 27.** NHC-catalyzed dynamic kinetic resolution of β-ketoesters.

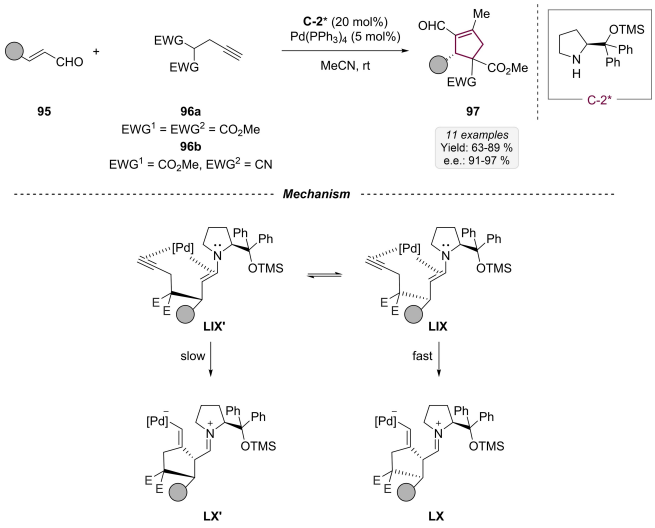



**Scheme 28.** NHC/Ti(O$^i$Pr)$_4$-catalyzed [3+2] cyclization between enals and 4-oxoenoates.

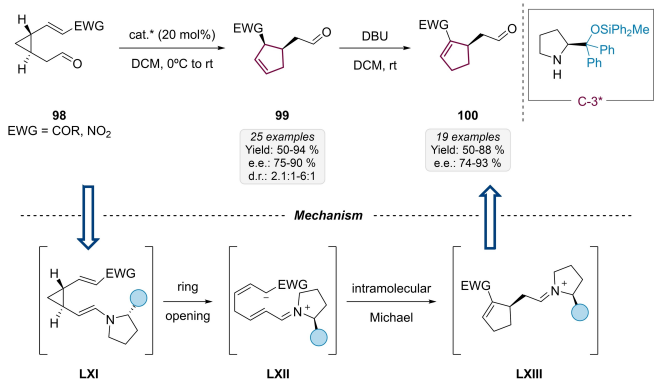



**Scheme 29.** [3+2] cyclization between enals **92** and malonate-derived aldehyde **93**.




**Scheme 30.** Cordova's dynamic kinetic asymmetric version and mechanistic rational.




**Scheme 31.** Chiral amine-catalyzed enantioselective (VCP-CP) rearrangement.

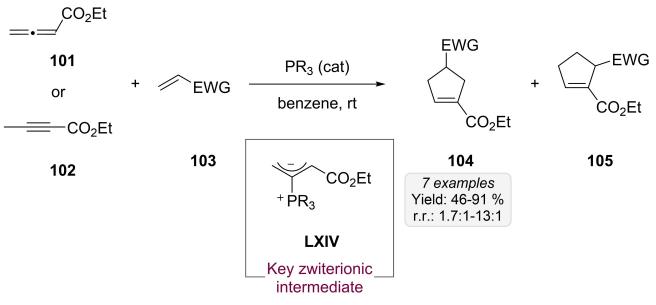
obtaining two-consecutive stereocenters, one of them quaternary, in slightly lower enantioselectivities and variable diastereoselectivities (Scheme 30). In order to rationalize the observed stereochemical outcome, the authors suggest that while the Michael addition itself is racemic due to reversibility, the second step is faster for one of the diastereomeric intermediates, resulting in enantioenriched products (Scheme 30). The in-situ racemization of the intermediate allows affording yields over 50% for dynamic kinetic resolution processes, in contrast with simple kinetic resolutions.

Recently, Reyes and Vicario have reported an organocatalytic enantioselective vinylcyclopropane-cyclopentene (VCP-CP) rearrangement.[53] The key feature for the success of this transformation is the design of the substrate. The introduction of a Michael acceptor and an acetaldehyde moiety in contiguous carbons of substrate **98** affords a donor-acceptor cyclopropane intermediate upon condensation with the organocatalyst (Scheme 27). The push-pull character of key intermediate **LXI** results in the ring-opening of the cyclopropane towards zwitterionic intermediate **LXII** that has lost the stereochemical information of the substrate. This loss of chiral information allows for a DYKAT process since the subsequent intramolecular Michael addition proceeds exclusively under catalyst control. In this way, an array of *cis*-disubstituted cyclopentenes **99** was obtained in good yields and enantioslectivities, although only in moderate diastereoselectivities. To overcome the poor diastereoselectivity observed in most cases, the corresponding products were isomerized under basic conditions to the more stable α,β-unsaturated products **100** bearing a single stereocenter (Scheme 31). DFT calculations confirmed the stereoconvergent nature of the process.

## 2.3. Phosphine-Catalyzed

Despite in general terms amines have found much more applicability than phosphines as organocatalysts,[54] in this specific area (organocatalytic [3+2] cycloadditions leading to cyclopentenes) the scenario is reversed.[55] The seminal publication in this field dates from 1995.[56] In this report, Lu describes the phosphine-catalyzed [3+2] cycloaddition of allenoates **101** and alkynoates **102** with electron-deficient olefins **103** affording cyclopentenes **104,105** (Scheme 32). Upon conjugate addition of the phosphine, both substrates afford an analogous zwitterionic intermediate **LXIV** that undergoes [3+2]-cycloaddition with the electron-deficient olefin affording the final products.

This pioneering work has been followed by numerous improvements, variants, and applications.[57] Herein, only a few relevant variations will be discussed, namely the intramolecular and the enantioselective versions.[58–61] In 2003, Krische described the use of electron-deficient 1,7-enynes




**Scheme 32.** Original conditions described by Lu for the phosphine-catalyzed [3+2] cyclization.

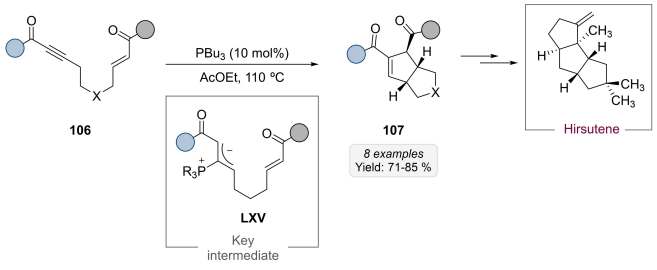
 

**106** as substrates for the phosphine-catalyzed intramolecular [3+2]-cycloaddition affording diquinane derivatives **107** (Scheme 33).[58a] This intramolecular version allows to overcome the regio- and diastereoselectivity issues observed for the intermolecular variant. Quite impressively, on the same year Krische applied this methodology to the formal total synthesis of Hirsutene.[58b]

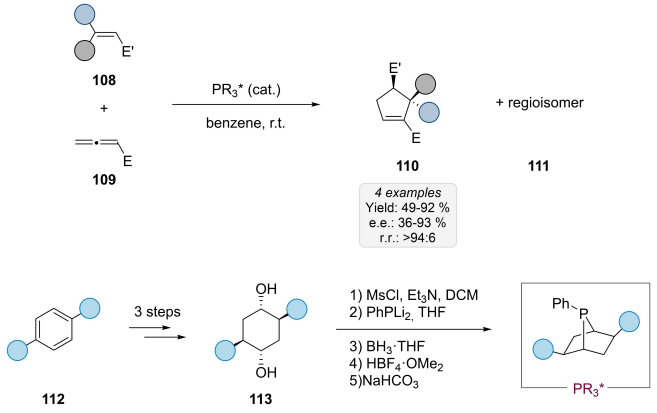
Regarding the enantioselective variant, as soon as in 1997, only two years after Lu's seminal report, Zhang developed the asymmetric variant.[59] In this study, the authors described the use of a new class of chiral phosphines (Scheme 34). Indeed, this transformation, Lu's phosphine-catalyzed [3+2] cycloaddition, has been adopted as a benchmark transformation for testing the asymmetric competence of new phosphines ever since then.[62] The synthesis of the organocatalyst starts with known enantioenriched diol **113**, obtained in three steps from the corresponding 1,4-disubstituted benzene **112**. Mesylation of both hydroxy groups, followed by double nucleophilic displacement and by standard phosphine manipulations afforded the novel chiral bicyclic phosphine **$PR_3$***  (Scheme 34). The authors showed that the new phosphines lead to better results than commonly used ones such as DUPHOS or BINAP in the organocatalyzed [3+2] cycloaddition, both in terms of regio- and enantioselectivity.

In a series of reports, Fu described the use of a phosphepine-derived chiral phosphine as an organocatalyst in this transformation. [60] In the first of these reports, the authors showed a superior reaction scope tolerating substitution at the β-position of the enone **114** for the first time, resulting in highly substituted cyclopentenes **116** (Scheme 35A).[60a] Moreover, a switch in the regiochemistry was observed without affecting the high enantioselectivity (Scheme 35A). In the second of them, the use of a second-generation phosphine containing substituents at the 3,3' positions of the binaphthyl backbone **$PR_3$-B*** allowed the formation of heteroatom-substituted quaternary stereocenters for the first time in this arena (Scheme 35B).[60b] Moreover, a structurally related second-generation phosphine **$PR_3$-C*** also promoted the enantioselective intramolecular variant of this transformation (Scheme 35C).[60c]

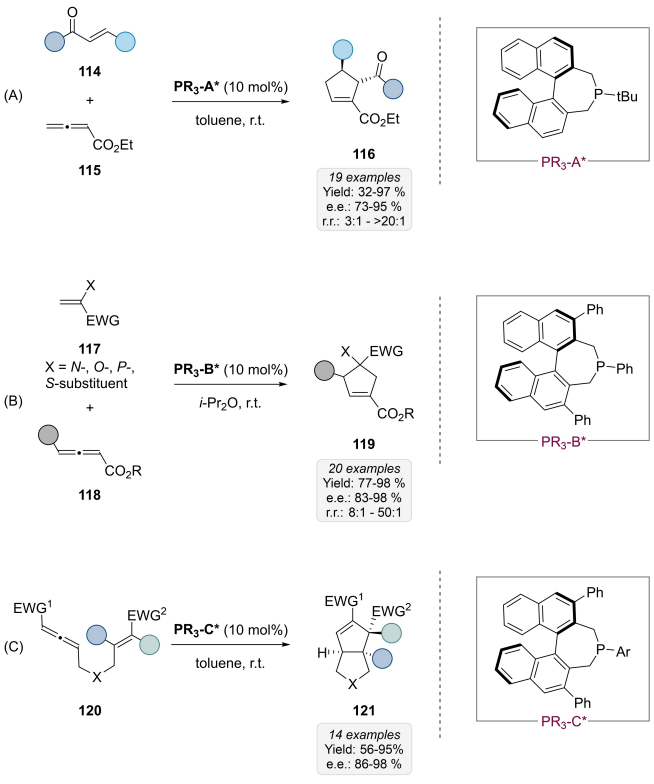
Another interesting addition was provided by Loh who reported the enantioselective [3+2]-cycloaddition reaction using 3-butynoates **123** as substrates, that were isomerized in situ to the corresponding allenes (Scheme 36).[61] In addition, the reaction showed complete regio- and diastereoselectivity (Scheme 36). In this case, a commercially available chiral-at-phosphorous diphosphine **$PR_3$-D*** was the organocatalyst of choice (Scheme 36).




**Scheme 33.** Phosphine-catalyzed intramolecular Lu's reaction.

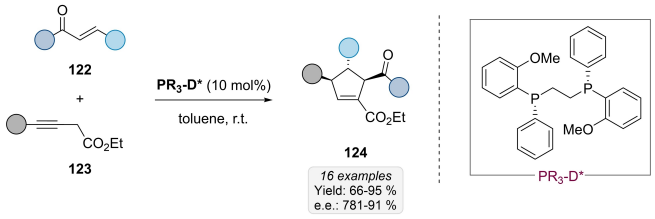



**Scheme 34.** First chiral phosphine-catalyzed enantioselective Lu's reaction.




**Scheme 35.** Achievements with Fu's phosphepine-derived chiral phosphine.




**Scheme 36.** Enantioselective [3+2]-cycloaddition reaction using 3-butynoates.

## 3. [2+2+1] Cyclizations

One of the best-studied transition metal mediated reactions for the formation of five-membered carbocycles is the Pauson-Khand reaction (PKR).[63][64] Although the original conditions used stoichiometric amounts of $Co_2(CO)_8$ both as the transition metal mediator and the CO source, several catalytic variants have been developed since the pioneering work of Rautenstrauch in 1990.[65] The catalytic PKR has been extensively reviewed before and somehow lays beyond the scope of this review since it is intrinsically restricted to the synthesis of cyclopentenones **126**, while this review is devoted to cyclopentenes.[64][66] However, some succinct general considerations on this pivotal transformation are described in this section.

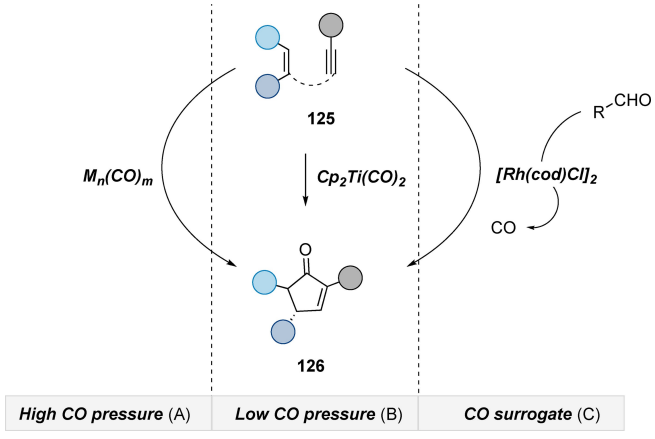
The first examples of catalytic PKR were achieved with metal carbonyl clusters as catalysts and under high pressures of CO to ensure catalyst regeneration (Scheme 37A).[65],[67] An initial improvement was introduced by Buchwald with the use of commercially available titanocene dicarbonyl, allowing the reaction to proceed under lower pressures of CO and with an excellent functional group tolerance (Scheme 37B).[68] Moreover, the use of a chiral titanocene derivative afforded the first catalytic enantioselective PKR.[69] The next key improvement in this field was the use of CO surrogates, which allowed the suppression of the hazards derived from the use of a toxic gas (Scheme 37C).[70] Aldehydes, alcohols and formic acid could be used as surrogates. As it is generally the case for the PKR most of the examples described in these catalytic variants are intramolecular, and hence, they could be described as [4+1] cyclizations.

## 4. [4+1] Cyclizations

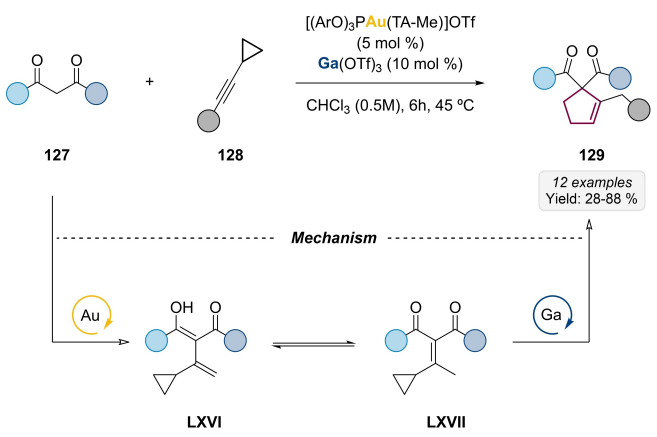
As compared with other cyclization modes, [4+1] cyclizations are relatively rare.[71] Early examples were limited to the carbonylative Mizoroki-Heck reaction of suitable vinyl halides.[72] In this section, a few recent examples leading to the cyclopentene core will be discussed.

In 2012, Shi and coworkers reported a [4+1] tandem cyclization.[73] The cascade sequence starts with the gold-catalyzed Nakamura reaction, followed by a catalytic dienol-enone tautomerization, and a subsequent gallium-catalyzed vinylcyclopropane-cyclopentene (VCP-CP) rearrangement affording the desired cyclopentene products **129**. The reagents used were 1,3-diketones **127** and cyclopropylalkynes **128** both easily accessible from commercial feedstocks. They carried out mechanistic experiments with diastereomerically pure cyclopropanes and they observed the retention of stereochemistry ruling out a [1,3] sigmatropic concerted pathway (Scheme 38).

Another example employing gold (I) catalysis was disclosed by González and coworkers in 2009.[74] In this report, a [4+1] reaction between propargyl tosylates **130** and *N*-tosylaldimines **131** affording cyclopent-2-enimines **132** was described. Noteworthy, a deep reorganization of both substrates was observed (formation of a cyclic structure, methyl migration, cleavage of the carbon-nitrogen bond). The reaction proceeds in short periods of time and under mild conditions. The coordinating effect of the counter anion affected the reaction yield, with the




**Scheme 37.** Different approaches to the catalytic Pauson-Khand reaction.



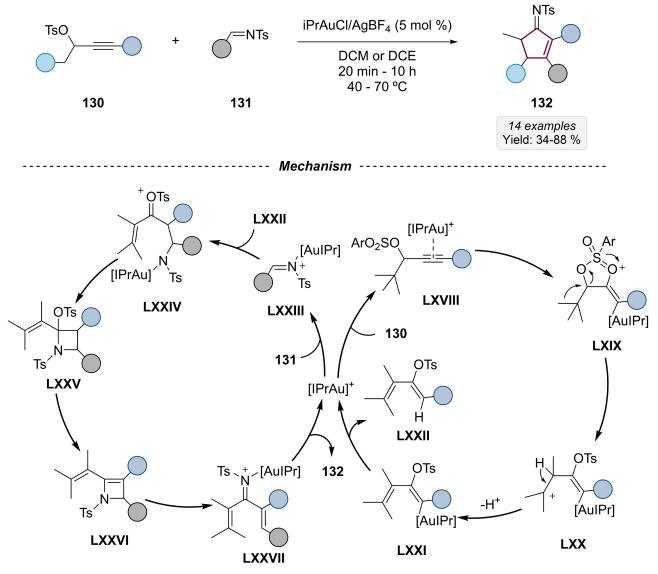

**Scheme 38.** [4+1]-cyclization employing gold and gallium catalysts.

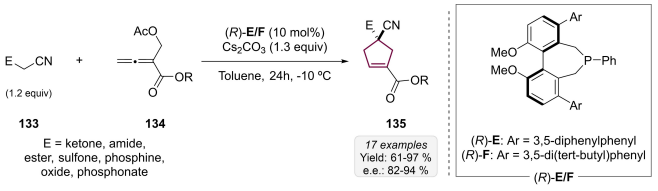
lower coordinating ones such as $BF_4$ affording the best results. The reaction tolerated different groups in the imine and the propargyl tosylate **130**; however, the only substituent tolerated at the imine nitrogen was the *N*-tosyl. They proposed the mechanism depicted in Scheme 39, supported by experimental and computational evidence.[75] The mechanism would consist of two independent catalytic cycles. In the first of them, the activation of the propargyl tosylate **130** by gold would explain the formation of diene **LXXII**. Coordination of catalyst to the alkyne **130** followed by an intramolecular nucleophilic attack of the oxygen of the tosyl group affords intermediate **LXIX** (Scheme 39). Subsequently, a vicinal methyl migration followed by elimination and a protodeauration gave the 1,3-diene skeleton **LXXII** (Scheme 39). Then, diene **LXXII** would enter the second catalytic cycle (Scheme 39, catalytic cycle on the left) attacking the imine activated by the catalyst **LXXIII**. Intramolecular nucleophilic substitution gave azetidine **LXXV** that, through a formal metathesis process, ring-opens to a 1,4-pentadiene **LXXVII**. The final product **132** is formed via an "*imino-Nazarov-like*" reaction mediated by the gold (I) catalyst (Scheme 39). Most importantly, intermediate diene **LXXII** could be isolated in the absence of imine and subsequently reacted with imine **131** under the reaction conditions providing the cyclopentene imine **132**.

A few years later, an interesting stereoselective [4 + 1] reaction towards cyclopentene derivatives **135** was developed by Fu and coworkers employing chiral tertiary phosphines **$PR_3$-E/F***.[76] Under these conditions, the products were obtained in good yields and enantioselectivities (Scheme 40). When ketone, amide or ester groups were present in substrate **133** the best enantioselectivities were obtained employing catalyst **$PR_3$-E***. On the other hand, the presence of sulfone, phosphine oxide and phosphonate groups in **133** required a catalyst switch to **$PR_3$-F*** in order to maintain the high enantioselectivities. To gain insight into the mechanism they determined the order of the reaction experimentally and they observed that the reaction was first-order in catalyst and zero-order in the nucleophile and the electrophile. They also determined by $^{31}P$ NMR that the primary resting state of the phosphine was the phosphonium salt instead of the free phosphine.

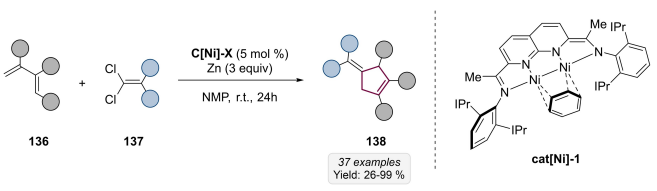
In 2019, a powerful methodology to obtain cyclopentenes was developed by Uyeda and coworkers.[77] They reported that dinickel complexes catalyzed [4 + 1]-cycloaddition reactions between 1,3-dienes **136** and in situ generated vinylidene intermediates as a C1 partner (Scheme 41). The latter were easily accessed from 1,1-dicloroalkenes **137** in the presence of stochiometric zinc. The reaction allowed obtaining the corresponding cycloadducts both in intra- and intermolecular fashions. Moreover, high levels of asymmetric induction were obtained employing a C2-symmetric chiral ligand. This methodology overcame previous attempts to obtain cyclopentenes using carbenes. In that case, the [2 + 1]-cycloaddition is favored due to the excessive closed-shell repulsion between the carbene lone pair and the filled $\Psi_1$ orbital of the diene in the symmetry-allowed transition state geometry. In this case, new alkylidenecyclopentenes **138** with a huge capacity of derivatization to form high-added value compounds were obtained. Finally, they carried out experimental studies and DFT calculations to determine the mechanism of the reaction, observing the role of zinc was as a reductant. For this proposal the most reduced form of the catalyst was synthesized, isolated,




**Scheme 39.** [4 + 1]-cyclization between propargyl tosilates and *N*-tosilaldiminas.

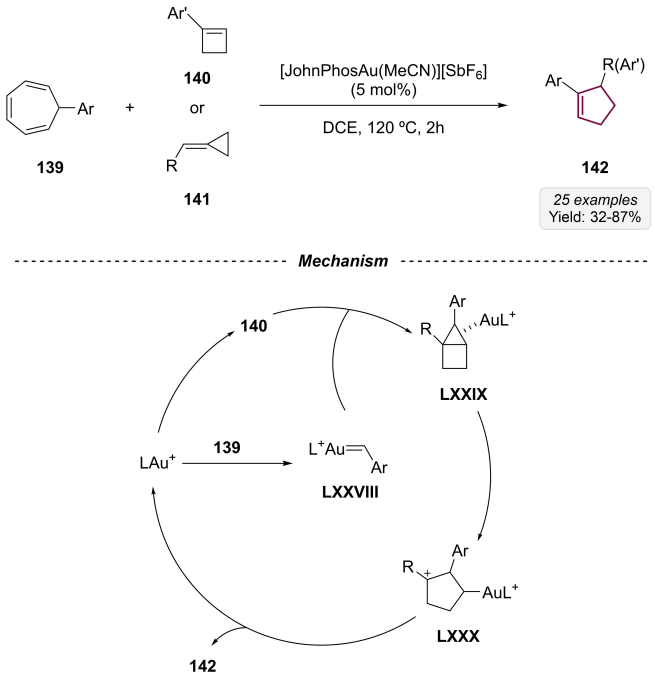



**Scheme 40.** Enantioselective chiral phosphine-catalyzed [4 + 1] cyclization between active methylene compounds and allenoates.

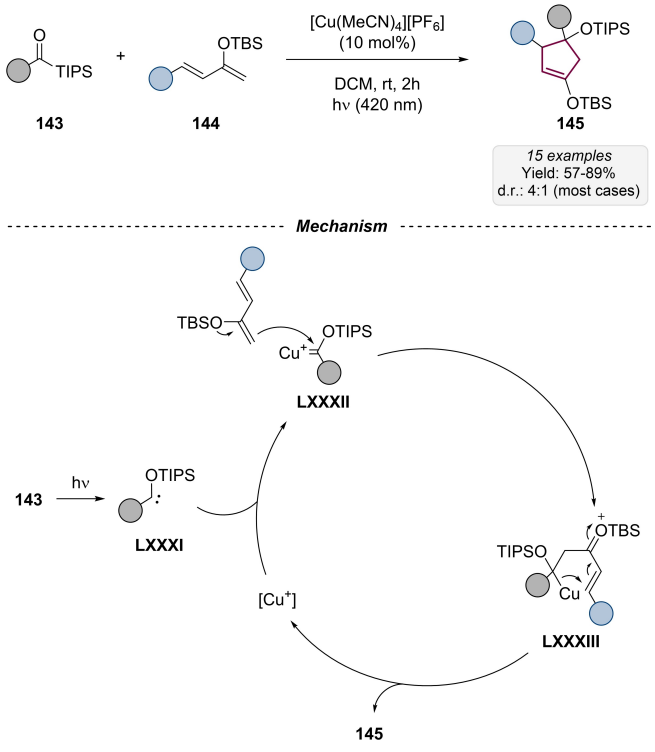



**Scheme 41.** [4 + 1] cycloaddition between dienes and in situ generated vinylidene intermediates.




**Scheme 42.** Gold-catalyzed [4+1] cycloaddition between in-situ generated carbene species and cyclobutenes or vinylcyclopropanes.




**Scheme 43.** Copper-catalyzed [4+1] cycloaddition between acyl silanes, as carbene precursors, and silyloxy dienes.

and added to a solution of 1,1-chloroalkene and 2,3-dimethylbutadiene, obtaining the cycloadduct in moderate yield.

Alternative methods for the catalytic generation of metal carbene species that may participate in a subsequent [4+1] cycloaddition were reported by Echavarren and Kusama, respectively.[78,79]

In 2014, Echavarren disclosed that gold carbene intermediates generated in situ by means of a retro-Buchner reaction on arylsubstituted cycloheptatrienes **139** afforded cyclopentene derivatives **142** when reacted with cyclobutenes **140** or vinylcyclopropanes **141** (Scheme 42).[78],[80] The reaction is restricted to aryl substituents in the cycloheptatriene precursor **139** of the carbene and in the double bond of the cyclobutene **140**, while the vinylcyclopropane **141** also tolerates alkyl substituents at the double bond (Scheme 42). Gold plays several roles in the catalytic cycle: 1) generates the gold carbene from the cycloheptatriene; 2) catalyzes the vinylcyclopropane/cyclobutene isomerization; and 3) catalyzes the formal [4+1] cycloaddition. Herein, only a simplified mechanism will be shown (Scheme 42).

On the other hand, Kusama used a visible light-induced acylsilane/silyloxy carbene rearrangement to catalytically generate copper Fischer carbene intermediates (Scheme 43).[79] The thus obtained intermediates reacted with silyloxy dienes affording substituted cyclopentenes in good yields and moderate diastereoselectivities (Scheme 43). The mechanism suggested by the author consists of the nucleophilic addition of the silyloxi diene to the insitu formed copper carbene intermediate, followed by ring-closure (Scheme 43).

## 5. [5+0] Strategies

Several kinds of difunctionalized substrates are able to undergo intramolecular cyclizations affording cyclopentenes. Perhaps the Nazarov reaction of dienyl ketones is the most emblematic process in this context. In addition, diallyl compounds are known to be amongst the best-suited substrates for ring-closing metathesis (RCM). More recently carbonyl-olefin metathesis has emerged as an appealing alternative for the synthesis of this interesting scaffold. Finally, C–H insertion strategies relying in either carbene (vinylidene) like, radical and vinyl cation like intermediates have recently been developed into powerful synthetic tools in this arena.

### 5.1. Nazarov Reactions

The Nazarov reaction has been studied in depth since the 1940s.[81] This reaction has been used by organic chemists as a powerful synthetic tool to produce five-membered rings. Besides, the stereospecific nature of the cyclization allows the control of the torquoselectivity of the reaction (the preference for conrotatory or disrotatory cyclization). However, this 4π

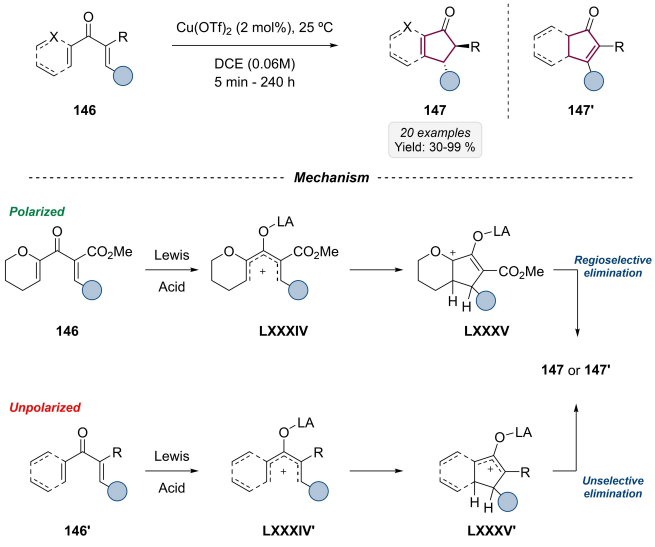
electrocyclic reaction was not carried out in a catalytic fashion until roughly 60 years after. Herein, only pioneering works of the catalytic version will be mentioned.

The first catalytic Nazarov reaction was described by Frontier in 2003.[82] The design of polarized divinyl ketones **146** with a vinyl nucleophile and a vinyl electrophile enabled the reaction to occur under mild Lewis acid activation. Upon activation, pentadienyl cation intermediate **LXXXIV** is produced which further cyclizes towards the corresponding cyclopentenone **147** (Scheme 44). Each cyclopentenone was isolated as a single regio- and stereoisomer. Moreover, when the divinyl ketone was unpolarized the regioselective was affected. In conclusion, the more polarizing the groups on the divinyl ketone the more efficient the cyclization (Scheme 44).

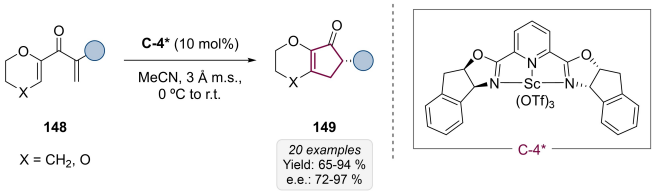
One of the most important limitations associated with the Nazarov reaction is the racemization of the product when the cyclization step proceeds slowly. Due to the importance of stereochemistry in this reaction, Trauner and coworkers developed the first enantioselective Nazarov reaction employing the chiral scandium triflate pybox complex **C-4*** as catalyst.[83] The reaction with disubstituted alkenes gives rise to a mixture of diastereoisomers in low enantioselectivities. However, terminal alkenes **148** afforded high yields and enantioselectivities (Scheme 45). The absolute configuration of cyclopentenone **149** was determined by X-ray crystallography of a (−)-camphanoyl derivative.

In the following years, many original reports and reviews about the Nazarov reaction were published.[84] For example, West and coworkers developed the vinylogous Nazarov reaction with a good wide of cross-conjugated trienes *via* the zwitterionic species **LXXXVI** (Scheme 46A).[85] Another interesting variant was developed by Burnell using allenyl vinyl ketones **151** and TFA or $BF_3{\cdot}OEt_2$ as catalysts affording regioisomeric cyclopentenes depending on the substituent (Scheme 46B).[86] A similar reaction was developed by West using vinylallenes **152** as reagents and TFA as electrophilic source to obtain the corresponding products (Scheme 46C).[87]

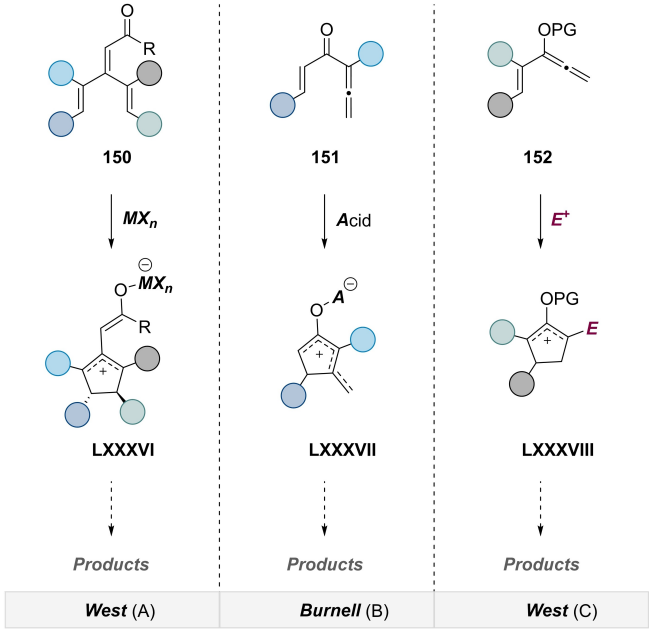
Another addition to the original Nazarov reaction was the development of the corresponding imino-Nazarov variant. The first reaction of this kind was reported by Tius in 2001.[88] A pioneering catalytic variant was already discussed in Section 4 (see Scheme 39, and reference 79). Despite several stoichiometric reports may be found in the literature, catalytic variants are scarcer. The first literature report that claims an imino-Nazarov step in a catalytic reaction was discussed in section 4 (see Scheme 39 and reference 79). A few years later, Hsung reported the gold-catalysed imino-Nazarov reaction using *N*-tosyl-*N*-aryl allenamides **153** as substrates (Scheme 47).[89] The introduction of the tosyl substituent at the nitrogen atom was key for destabilizing the cylopentadienyl cation, one of the




**Scheme 44.** Room temperature Nazarov reaction of polarized divinyl ketones.

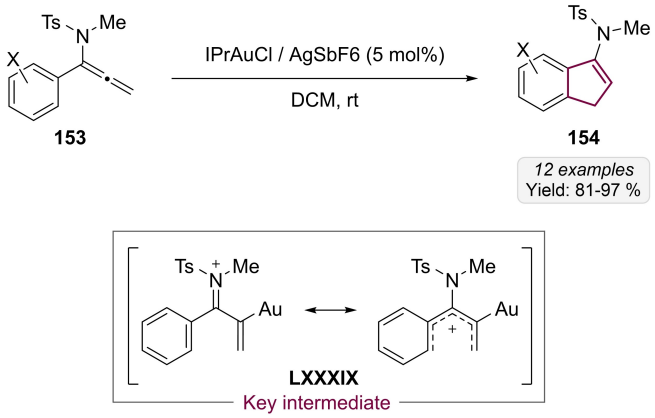



**Scheme 45.** Enantioselective Nazarov reaction.




**Scheme 46.** Variants to the original Nazarov reaction.

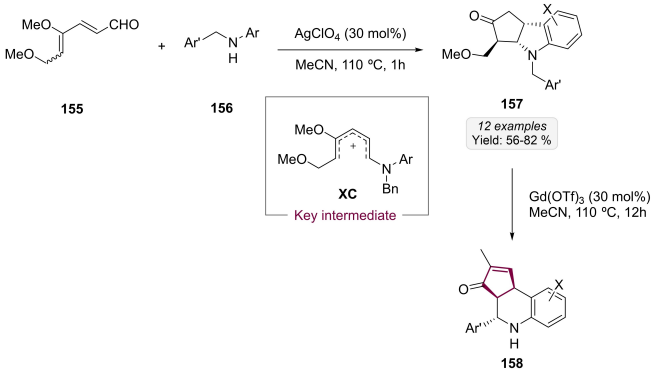



**Scheme 47.** Interrupted imino-Nazarov reaction.

reasons that disfavor the imino-Nazarov reaction with respect to the original oxa-variant.[90]

In 2014, Liu described that understoichiometric amounts of several Lewis acids were able to promote an intramolecular interrupted imino-Nazarov reaction between dienals **155** and secondary amines **156** (Scheme 48). [91] Moreover, divergent products were obtained by using two distinct Lewis acid catalysts; while the reaction with $AgClO_4$ afforded the expected interrupted imino-Nazarov product **157**, the reaction with $Gd(OTf)_3$ gave rise to a different polycyclic skeleton **158** (Scheme 48). The authors could prove that using $Gd(OTf)_3$ the interrupted imino-Nazarov product **157** was initially formed and it evolved towards rearranged product **158** under the reaction conditions (Scheme 48). In a next report, the use *N*-heterocycles as interrupting nucleophiles afforded carbocyclic nucleoside analogs, being the first example of an intramolecular interrupted imino-Nazarov reaction.[92]

Regarding the enantioselective version, in 2015 Toste reported an enantioselective gold(I)-catalyzed dearomative Rautenstrauch rearrangement, containing an imino-Nazarov-

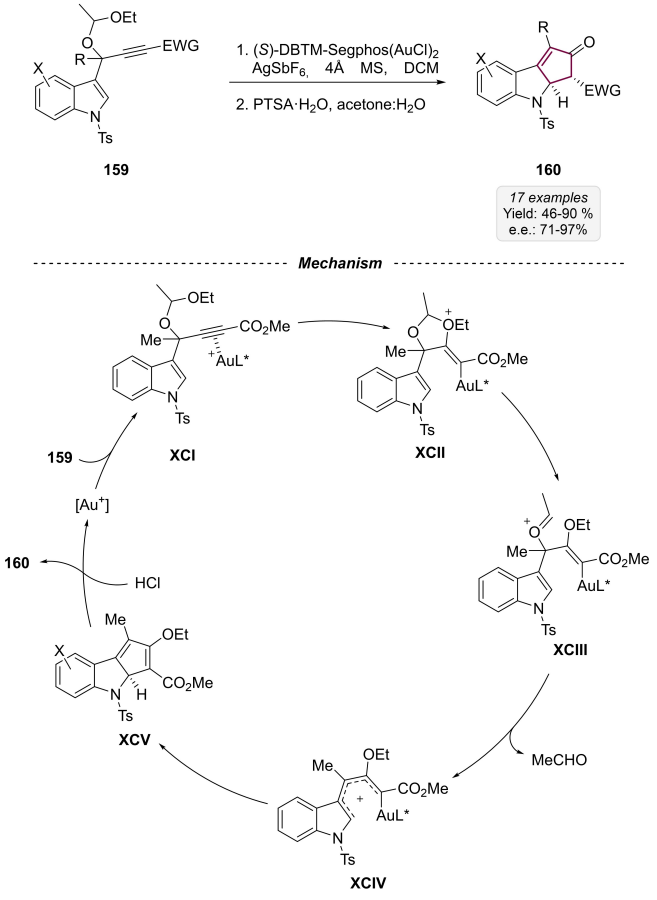



**Scheme 48.** Interrupted imino-Nazarov reaction.

like reaction as the key and enantiodetermining step (Scheme 49).[93] Following a rational design, the authors switched from their initial acetate substrate to the corresponding indolyl propargyl ketal derivative **159** (Scheme 49). This subtle change resulted in a fully planar intermediate, better suited for ligand-controlled enantioselectivity. Under the optimized conditions cyclopenta[b]indoles **160** were obtained in good yields and high enantioselectivities (Scheme 49). The mechanism would start with the gold-catalyzed Rautenstrauch rearrangement affording planar intermediate **XCIV** after acetaldehyde extrusion. Ligand-controlled enantioselective imino-Nazarov reaction would achieve the desired products after decomplexation of gold (Scheme 49).

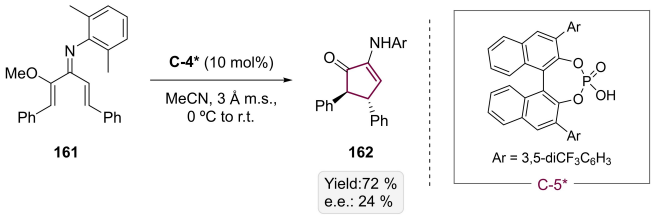
Regarding the enantioselective organocatalyzed variant, Ye, Zhang, and Huang, preliminary studied the chiral Bronsted-acid-catalyzed imino-Nazarov, although with little success (Scheme 50).[94] The study was reported in the context of a one-pot vinylation/4π electrocyclization process.

Finally, in 2020 Schomaker and Fernández studied a rhodium-catalyzed imino-Nazarov reaction inspired in the

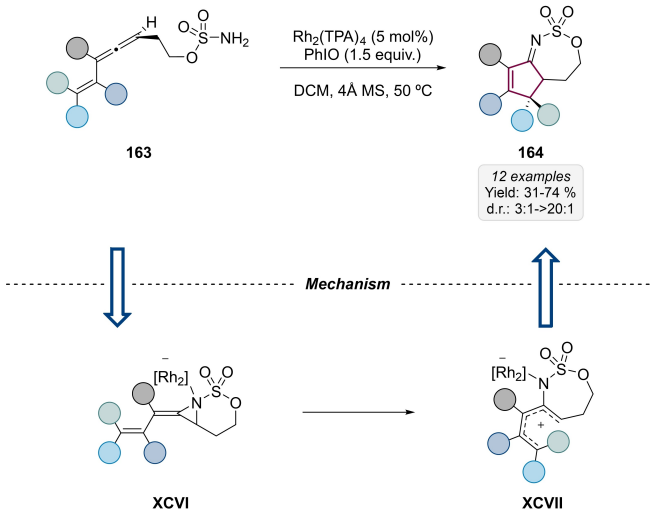



**Scheme 49.** Enantioselective gold(I)-catalyzed dearomative Rautenstrauch rearrangement.

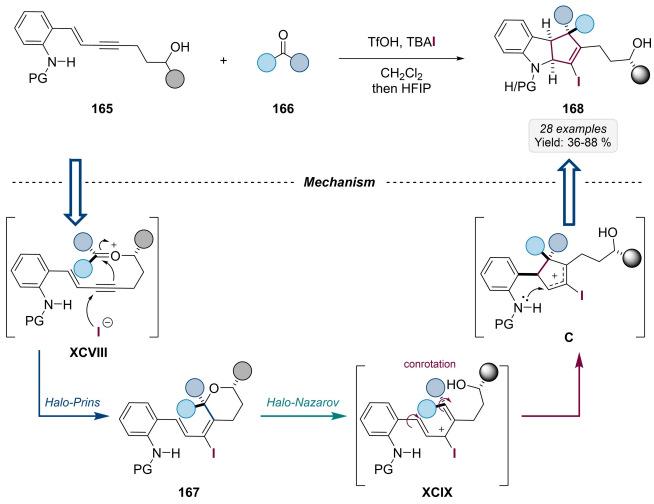
 




**Scheme 50.** enantioselective gold(I)-catalyzed dearomative Rautenstrauch rearrangement.




**Scheme 51.** Biomimetic 2-imino-Nazarov cyclization via eneallene aziridination.




**Scheme 52.** One-pot nitrogen-interrupted halo-Prins/halo-Nazarov coupling cascade.

biosynthesis of the plant prostanoid epi-jasmonic acid, that occurs *via* a 2-oxypentadienyl cation.[95],[96] The authors described that treatment of enallene substrates bearing a sulfamate group as nitrene precursor **163** with PhIO as oxidant and catalytic amounts of $Rh(TPA)_4$ afforded the corresponding methylene aziridines **XCVI** that spontaneously opened up towards the corresponding 2-amidoallyl cation **XCVII** that further evolves towards the observed products **164** by means of a 4π-electrocyclization (imino-Nazarov reaction) (Scheme 51).

In addition to the imino-Nazarov variant, recently, Frontier and coworkers developed a one-pot nitrogen-interrupted halo-Prins/halo-Nazarov coupling cascade as a powerful methodology to synthesize $sp^3$-rich *N*-heterocycles diastereoselectively.[97] The reaction between appropriately designed enynes **165** and carbonyl compounds **166** in the presence of triflic acid and tetrabutylammonium iodide afforded iodinated cyclopenta[b]indole derivatives **168** (Scheme 52). The protective group on the amine was essential to carry out the reaction due to the formation of the corresponding imine when the corresponding unprotected amine was used instead. A broad scope of aldehydes both with aryl and alkyl groups was tolerated. The reaction also employed several ketone derivatives, being an enol ether the most reactive. Finally, the influence of substitution at the aniline aromatic ring was also studied. The mechanism proposed started with a formation of oxycarbenium **XCV** through condensation of the hydroxy group present in aniline **165** with carbonyl compound **166** under acidic conditions. Intermediate **XCVIII** evolves towards the halo-Prins product **167** which could be isolated or can also participate in a cascade reaction by the addition of HFIP. The C–O is broken affording the pentadienyl cation **XCIX** which evolves via a 4π conrotatory electrocyclization to the halo-cyclopentenyl cation **C**. Finally, this cation is trapped by the neighboring nitrogen atom to yield the corresponding *N*-heterocycle **168** (Scheme 52).

In conclusion, an extensive bibliography related to the catalytic Nazarov reaction employing different catalysts such as copper- or palladium-based, Lewis, and Brönsted acids may be found in the literature.[98] Moreover, this methodology has been applied in the total synthesis of natural products due to its versatility and the increase in the structural complexity of the products.[99]

## 5.2. C–H Cyclization

As we mentioned before the formation of the five-membered ring requires a preorganized structure or a structure with specific functional groups to form the specific bonds. For this reason, many research groups have focused their attention on cyclization processes without the need for these requirements.

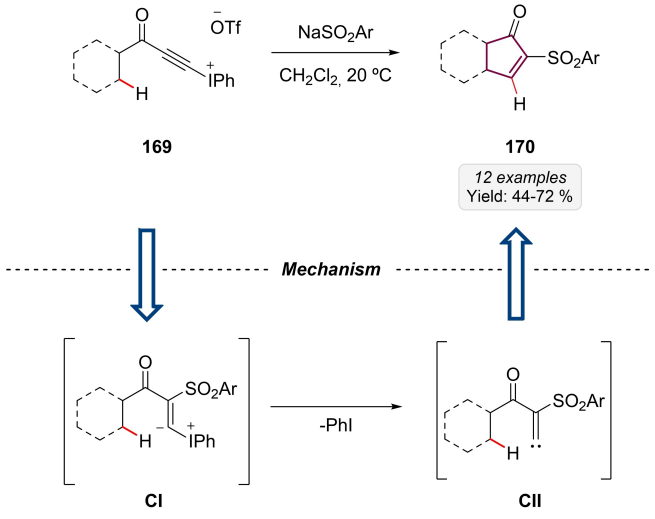
 

Thus, an outstanding chemistry tool has been developed in the last decades, namely C($sp^3$)–H functionalization.[100] This transformation is very challenging due to the relative inertness of these bonds and the similar reactivity of most C($sp^3$)–H bonds within a molecule.[101] Most commonly, the selectivity issue has been tackled by using tailor-made directing groups that, by means of chelation, allow the activation of a specific C–H bond.[102] However, several reactive intermediates are known to react with a [1,5] preference. More specifically, recently carbenes (vinylidene), radicals, and cations (vinyl cations) have been successfully used in the generation of the cyclopentene ring.

### *5.2.1. Vinylidene-Mediated*

Free vinylidenes are elusive highly reactive intermediates and their generation requires harsh conditions. For instance, the formation of the five-membered ring through insertion of a vinylidene into a C($sp^3$)–H bond could be carried out by the gas-phase thermolysis of α-acetylenic ketones at 550–740 °C. However, this methodology with extreme conditions produced low yields and very poor functional group compatibility.[103]

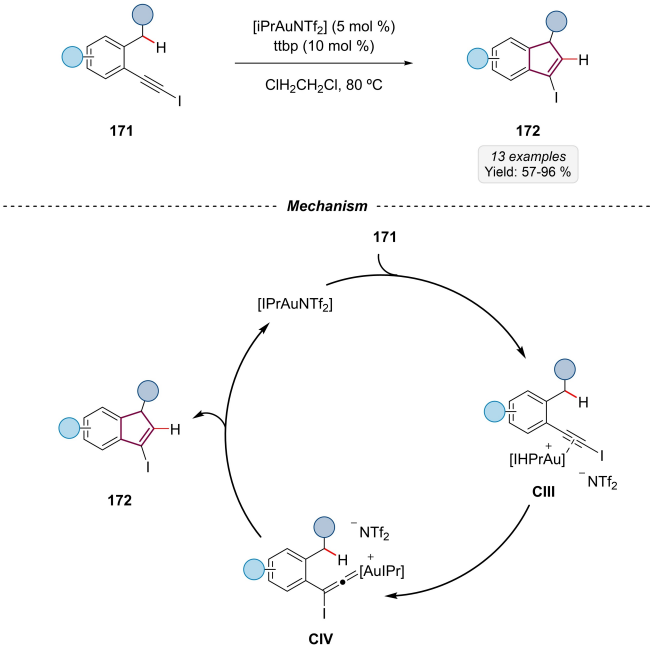
A seminal contribution that allowed to overcome those extreme conditions was developed by Stang and coworkers.[104] They synthesized a variety of 2-cyclopentenones **170** in good yields via 1,5-C–H bond insertion using β-ketoethynyliodonium triflates **169** with different aliphatic chains, carbo-, and heterocycles (Scheme 52). Substrate **169** reacts with sodium p-toluenesulfinate affording intermediate **CI** which evolves to form the vinylidene **CII** releasing iodobenzene (Scheme 53). Finally, an intramolecular 1,5-C($sp^3$)–H insertion yields the corresponding product **170** (Scheme 53).




**Scheme 53.** Annulation of alkynyl(phenyl)iodonium triflates towards cyclopentenones.

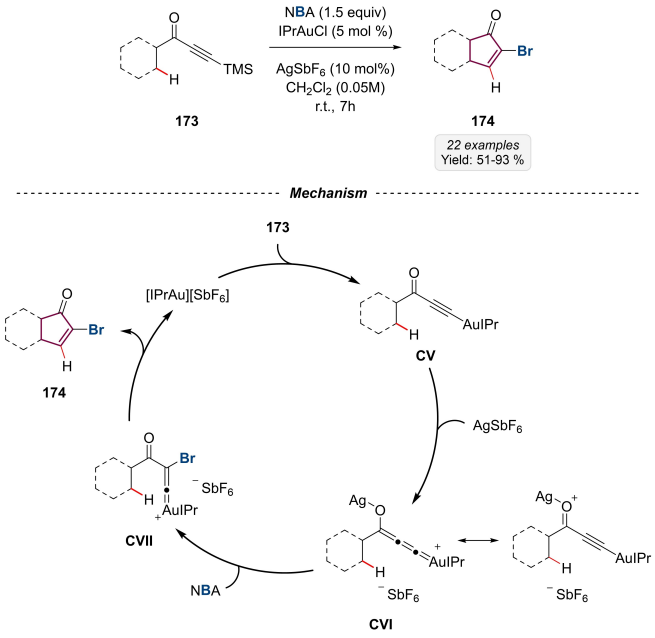
Years later, in 2015, González and coworkers studied the gold-catalyzed intramolecular C–H insertion of iodoalkynes **171**. [105] In this case, the activation of a benzylic C–H bond afforded a broad spectrum of indenes **172** in good yields. They observed a [1,2]-iodine shift, formulating the formation of vinylidene **CIV** as key intermediate. They also showed that the reaction was intramolecular by means of isotopic labeling experiments with deuterium. In addition, the C–H functionalization at a chiral center was also studied, noting that the chiral information was maintained. With all these results, the mechanism depicted in Scheme 54 was proposed. The first step would be the coordination of gold (I) catalyst to the alkyne **171** to form intermediate **CIII** which undergoes a [1,2]-iodine shift to form gold vinylidene **CIV** (Scheme 54). Finally, C–H insertion yielded the corresponding product **172** (Scheme 54).

In 2016, Zhang and coworkers developed an interesting powerful C–H functionalization methodology for the preparation of cyclopentenones using more accesible and safer reagents than the previous repot by Stang.[106] (Trimethylsilyl)ynones **173** afforded a variety of 2-bromocyclopentenones **174** in excellent yields by treatment with an electrophilic bromine source under gold (I) catalysis (Scheme 55). The mechanism proposed begins with the formation of the gold acetylide complex **CV** by treatment of alkynone **173** with a cationic gold species. Then, intermediate **CV** forms allenylidene **CVI** which could react with the electrophile (*N*-bromoacetamide, NBA) to form the vinylidene **CVII** which undergoes C–H

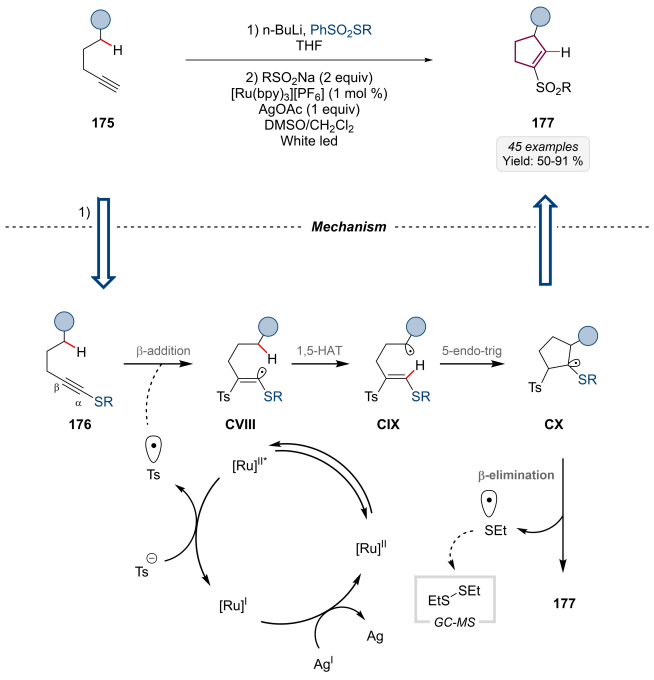



**Scheme 54.** Gold-catalyzed benzylic C($sp^3$)–H insertion of iodoalkynes.




**Scheme 55.** Gold-catalyzed C($sp^3$)–H insertion of (trimethylsilyl)alkynones.




**Scheme 56.** Photocatalytic sulfonylcarbocyclization of alkynes.

insertion at position five giving rise to the corresponding product **174**.

### *5.2.2. Radical-Mediated*

Besides vinylidenes, radicals are also well-known for their intrinsic preference to react through position 5. Thus, 5-exo and 5-endo cyclizations or [1,5]-H abstractions ([1,5]-HAT) are among the most common evolution pathways of radical intermediates.

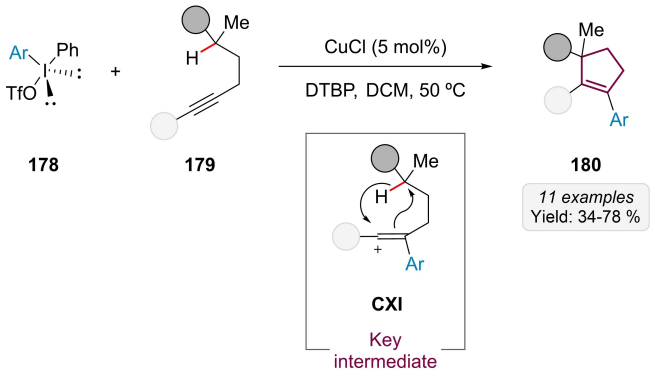
In 2022, an interesting photocatalytic reaction was reported by Zhu.[107] Sulfonylcyclopentenes **177** were achieved by virtue of a photocatalytic cascade pathway comprising a Markovnikov-type sulfonylation, 1,5-hydrogen atom transfer, 5-endo-trig cyclization, and β-elimination (Scheme 56). The reaction tolerated a broad spectrum of functional groups. Moreover, the products were further derivatized using different reaction conditions, showing their great potential. The presence of a radical intermediate was supported by the inhibition of the reaction in the presence of a radical inhibitor (TEMPO). Labelling experiments were also carried out showing a KIE = 3.2 which indicated that the remote C-($sp^3$)–H cleavage may be the rate-determining step of the reaction. Finally, they observed racemization when the reaction proceeded at a chiral centre, validating the radical pathway. With these results they suggested that the first step was a single electron transfer (SET) from the tosyl anion to the photo-excited ruthenium catalyst producing tosyl radical that would then add to the β-position of the thioalkyne **176** to form **CVIII** (Scheme 56). Subsequent 1,5-HAT would afford alkyl radical **CIX** (Scheme 56). Finally, 5-endo-trig radical cyclization achieves radical **CX** which evolves via β-elimination to form the corresponding product **177** (Scheme 56).

### *5.2.3. Vinyl Cation-Mediated*

Carbocations have played a central role in organic chemistry.[108] In recent years, a specific kind of carbocations, namely vinyl cations have received particular attention.[109] Once again, although [1,2]-H shifts are more common in the chemistry of carbocations, [1,5]-H shifts are also commonly found in the literature.

The first report related to the topic of this review came from the group of Gaunt.[110] A vinyl cation intermediate **CXI** formed upon treatment of an alkyne **179** with a diaryliodonium triflate **178** under copper catalysis, evolves by means of an unprecedented [1,5]-H shift / C–C bond-forming cyclopentanulation affording substituted cyclopentenes **180** in moderate to good yields (Scheme 57). This unexpected mechanistic pathway, in addition to its fundamental interest, results in an important synthetic feature, the retention of the stereochemistry when the C–H bond that participates in the insertion belongs to a stereocentre (Scheme 57). A stepwise [1,5]-H shift carbocation interception pathway, as initially proposed by the authors, would have resulted in racemization

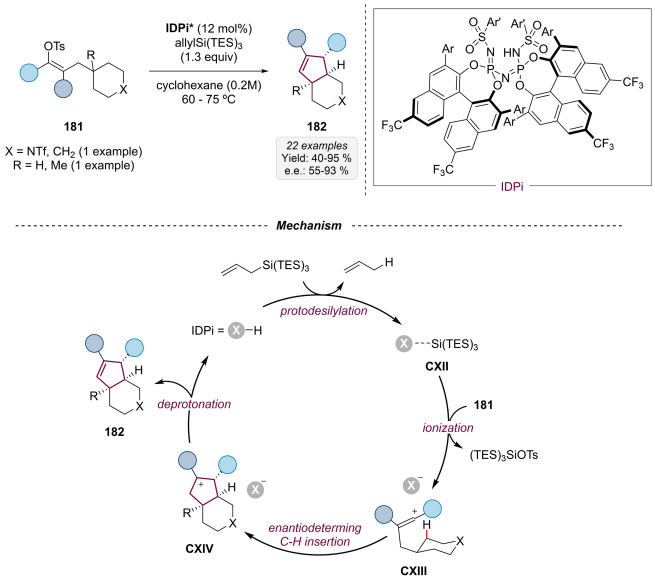
 




**Scheme 57.** In situ generation of a vinyl cation intermediate and subsequent cyclopentannulation by means of C–H insertion.

by virtue of the planar nature of the $sp^3$ carbocation intermediate.

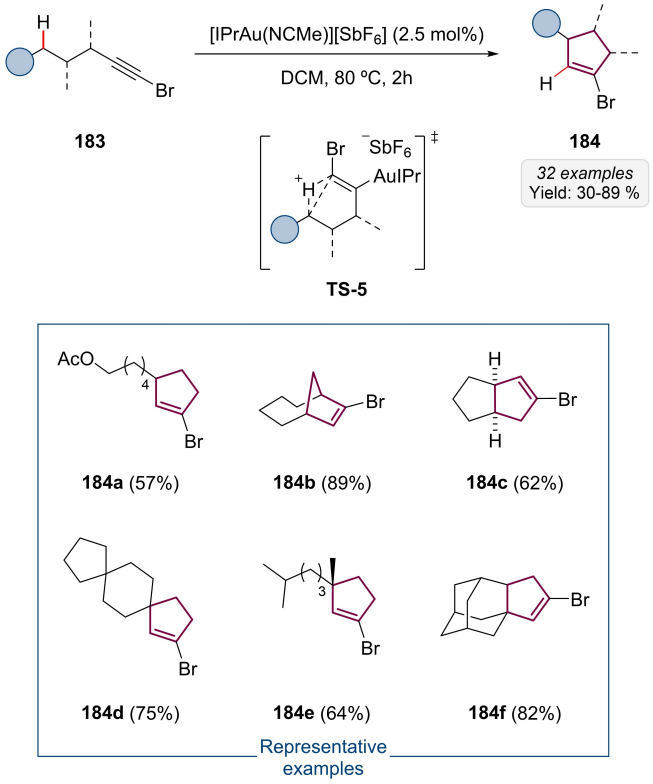
More recently, Nelson has pioneered the use of readily accessible vinyl sulfonates **181** as precursors of vinyl cations.[111] Hence, the asymmetric intramolecular C–H bond insertion of thus generated intermediates afford bicyclic cyclopentenes **182** in moderate to high yields and enantioselectivities (Scheme 58).[112] The chiral environment required for enantiocontrol was supplied by the use of List's imidodiphosphorimidate (IDPi) as strong acid for the ionization of the substrates.[113] The reaction starts with the formation of a silylium cation **CXII** by the reaction of an allylsilane with IDPi.[114] The oxophilicity of this cation would then promote ionization of the substrate affording the key vinyl cation intermediate **CXIII** with a chiral environment provided by the couteranion. Enantiodetermining C–H insertion followed by deprotonation of carbocation **CXIV** would afford the final product while restoring turnover (Scheme 58).




**Scheme 58.** Chiral Brønsted acid-catalyzed enantioselective C–H insertion.

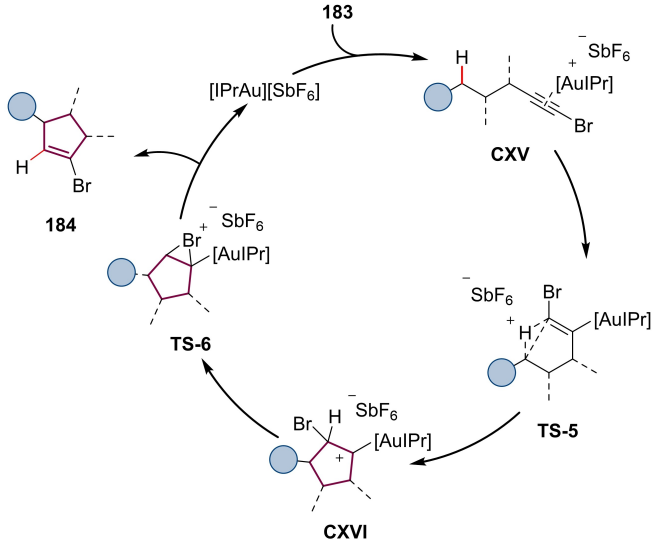
In 2023, Barrio described a gold-catalyzed cycloisomerization reaction of 1-bromoalkynes **183** affording substituted cyclopentenes **184** by virtue of a $C(sp^3)$–H insertion reaction.[115][116] Several features of this transformation are remarkable: the starting materials are easily synthesized from readily available starting materials, the reaction conditions are extremely simple, the products contain an easy-to-functionalize $C(sp^2)$–Br bond and, most importantly, the $C(sp^3)$–H bond that undergoes the insertion is a truly non-activated one (Scheme 59). In addition, a variety of molecular architectures are available depending on the structure of the substrate: simple cyclopentenes, bridged-, fused-, and spiro bicycles (Scheme 59).

Despite the authors initially proposed a gold-vinylidene as the key intermediate, a mechanistic study combining experimental (isotope labeling, KIEs, cross-over experiments) and computational work ruled out this mechanistic pathway (Scheme 60). The calculated energy barrier for the insertion of the gold-vinylidene intermediate was almost negligible




**Scheme 59.** Gold (I)-catalyzed cycloisomerization of 1-bromoalkynes comprising C–H insertion.

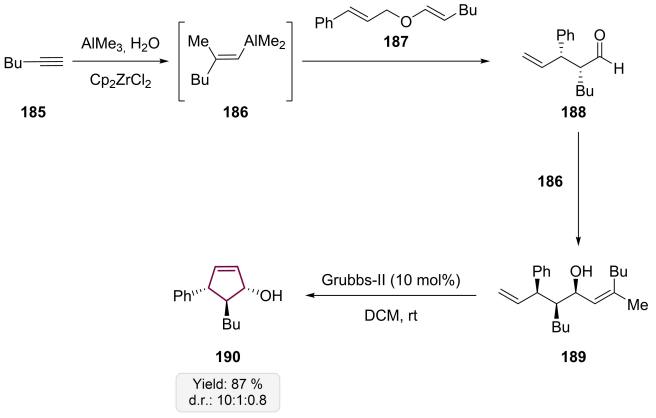



**Scheme 60.** Proposed mechanism featuring a gold-stabilised vinyl cation as key transition state.

(0.3 kcal/mol) in disagreement with the value obtained for the pKIE in the intramolecular competition experiment. The authors, hence, reformulated their mechanistic proposal accordingly featuring now a gold-stabilized vinyl cation key transition state **TS-5** (Scheme 60). It is worth noting that such a mechanistic scenario was unprecedented in gold catalysis.[117]

### 5.3. Miscellanea

In section 5.1 the Nazarov reaction of dienones was described in some detail. However, not only dienones but other bis-unsaturated substrates undergo intramolecular cyclizations towards the cyclopentene core. Perhaps the most obvious transformation of this kind would be the RCM of diallyl substrates.[118] This reaction is so favoured that the RCM of diallyl substrates has commonly been used as a benchmark reaction in the development of new catalysts.[119,120] Herein, only two recent examples that we have found remarkable for the way in which the 1,6-diene unit was assembled will be highlighted. In the first of them, dienes bearing three contiguous stereocenters **190** are obtained in high stereoselectivity by means of a carboalumination-Claisen rearrangement-carbonyl addition cascade reaction (Scheme 61).[121] The reaction starts with the Zr-mediated *syn* carboalumination of a terminal alkyne **185**, affording a vinylaluminum species **186** (Scheme 61). This species plays a double role in the cascade. First, it serves as Lewis acid catalyst for the Claisen rearrangement of an allyl vinyl ether **187** giving rise to a γ,δ-enal **188**. Then, the same species **186** acts as a nucleophile affording the desired 1,6-diene **189** featuring three consecutive stereocenters on the three carbons of the tether between the two olefins

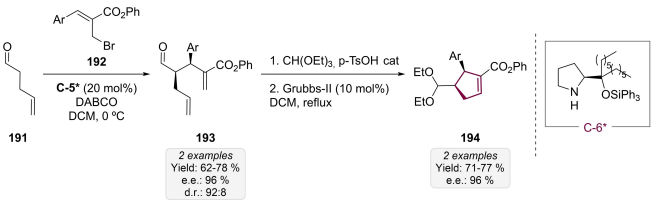



**Scheme 61.** Ring-closing metathesis of stereodefined 1,6-dienes obtained by a stereoselective Claisen rearrangement / nucleophilic addition cascade.

(Scheme 61). Finally, as a possible application, the authors describe the RCM of one of these complex dienes using standard conditions (Grubss' second-generation catalyst in DCM at rt) (Scheme 61).

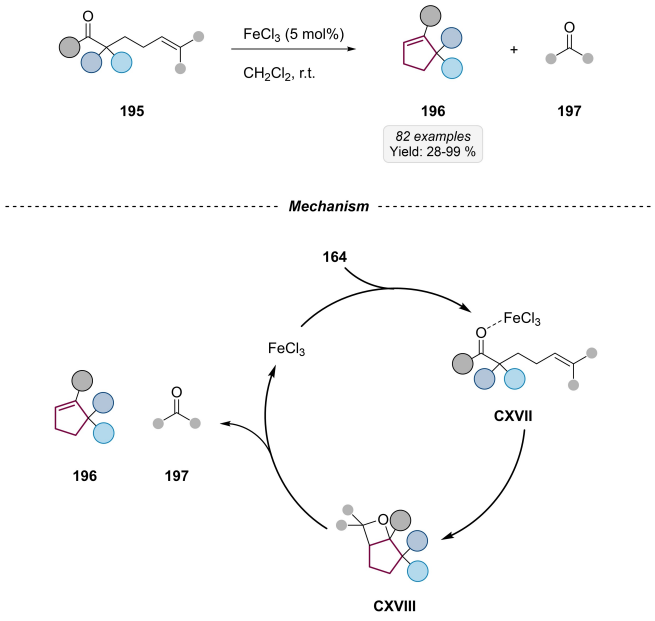
Using an organocatalytic approach, Palomo and co-workers also afforded the synthesis of stereodefined γ,δ-enals featuring several stereocenter in the carbon tether (Scheme 62).[122] More specifically, the authors described the organocatalytic enanio- and diastereoselective α-alkylation of aldehydes using substituted 2-(bromomethyl)acrylates **192** as electrophiles (Scheme 62). In one of these examples, the use of 4-pentenal **191** as substrate affords 1,6-enynes **193** that were in turn engaged in a RCM reaction using standard reaction conditions (Scheme 62). The final cyclopentene products **194** were obtained without erosion of the optical purity (Scheme 62).

Recently, the synthetic potential of a different kind of ring-closing metathesis, namely carbonyl-olefin metathesis has been disclosed by Schindler and co-workers.[123][124] δ- and ε-enones **195** were found to afford cyclopentenes **196** and cyclohexenes (not shown) under $FeCl_3$ catalysis at room temperature (Scheme 63). The synthetic availability of the required substrates and the simple and economic reaction conditions make this strategy a valuable addition added to the toolbox of synthetic organic chemists for synthesizing cyclopentene




**Scheme 62.** Ring-closing metathesis of stereodefined 1,6-dienes obtained by an organocatalyzed enantioselective α-alkylation.

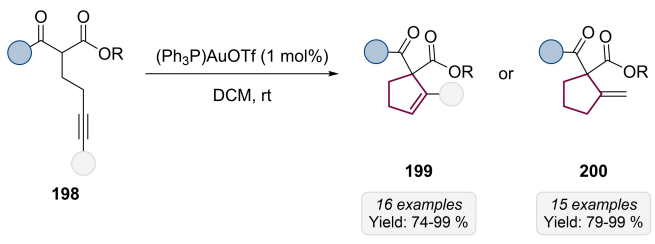



**Scheme 63.** Fe-catalyzed carbonyl-olefin ring-closing metathesis.

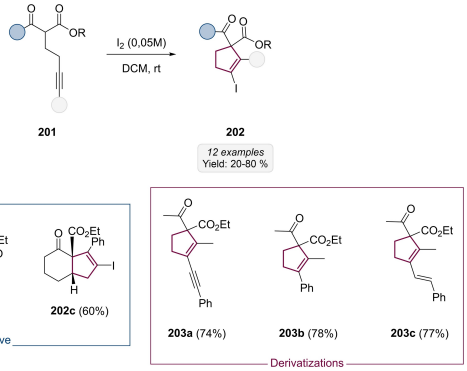
derivatives. First, the reaction was limited to the use of arylketones as substrates, but further studies have allowed to expand the reaction scope to aliphatic ketones (Scheme 63). Regarding the mechanism, an in-depth mechanistic study supports a concerted asynchronous [2 + 2] key elementary step (Scheme 63).

In 2004, Toste and co-workers described the gold-catalyzed intramolecular Conia-ene reaction using acetylenic dicarbonyl compounds **198** as substrates.[125] Depending on the length of the tether and the substitution at the triple bond, alkylidene cyclopentanes **200** or cyclopentenes **199** are obtained by means of 5-exo- or 5-endo-trig cyclization modes, respectively (Scheme 64).

In a related report, Barluenga described the transition metal-free iodocarbocyclization of analogous substrates **201**, using elemental iodine (Scheme 65).[126] The methodology is amenable for the construction of simple iodocyclopentenes **202 a**, along with bridged **202 b** and fused bicycles **202 c**




**Scheme 64.** Gold (I)-catalyzed intramolecular Conia-ene reaction.

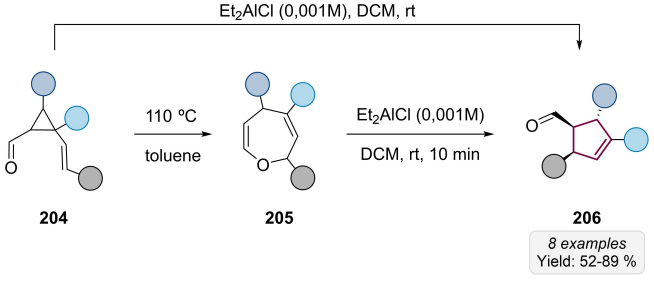



**Scheme 65.** Transition metal-free iodocarbocyclization.

(Scheme 65). The presence of the highly reactive C($sp^2$)–I bond in the final products allows their further functionalization by means of well-stablished palladium-catalyzed cross-coupling chemistry (Sonogashira **203 a**, Suzuki **203 b** and Heck **203 c** products shown on Scheme 65).

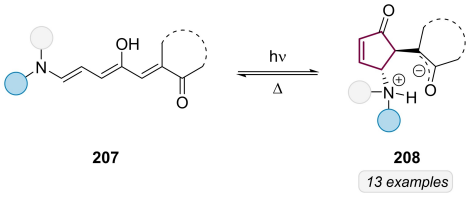
In 2005, Rovis reported an unprecedented ring-contraction strategy for the synthesis of formyl-substituted cycopentenes **206** (Scheme 66).[127] The reaction uses 2,5-dihydrooxepines **205** as starting materials, formed in turn by a retro-Claisen reaction of vinylformylcyclopropanes **204** (Scheme 66). Taken altogether, the reaction sequence would be analogous to a VCP-CP rearrangement described above (see section 1.2). Indeed, the reaction may be carried out from the corresponding vinylformylcyclopropanes **204** without the need to isolate the 2,5-dihydrooxepines **205**. The authors cannot distinguish between the two possible pathways, a stepwise mechanism featuring a 2,5-dihydrooxepine intermediate or the direct VCP-CP rearrangement. The epimerization to the *trans* isomer and the stereoretentive nature of the reaction when using an enantioenriched substrate were also studied, alongside one post-functionalization step (double-bond dihydroxylation).

In a recent publication, the photoswitching behavior of donor-acceptor Stenhouse adducts **208** (DASAs) is studied in detail.[128] As for the scope of this review, we will only note that these adducts, consisting of electron-donating and




**Scheme 66.** Ring-contraction of 2,5-dihydrooxepines **205**.




**Scheme 67.** Photoswitching behavior of donor-acceptor Stenhouse adducts **208** (DASAs).

electron-releasing moieties connected by a triene linker **207**, behave as reverse photochromes, acting as non-linear optical (NLO) switches. Hence, under visible light irradiation, they undergo a series of *trans-cis* isomerizations followed by a 4π-electrocyclization affording cyclopentenone derivatives **208** (Scheme 67). The process may be reverted under thermal conditions.

## 6. Outlook

As has been emphasized in this Review, the synthesis of the cyclopentene core has attracted enormous attention from the synthetic community. The significance of the substructure along with the great variety of approaches amenable for its preparation resulted in a plethora of methodologies, of which some of the most significant, in our opinion, have been highlighted herein. The continuous implementation of modern strategies based on more efficient and sustainable methodologies ensures further developments in the near future. In addition, numerous methodologies for the transformation of simple cyclopentene derivatives into more elaborated frameworks have also been reported in the recent scientific literature.[129] However, herein we have only covered strategies for the assembly of the cyclopentene ring. It would be our wish that this Review may serve both as consulting reference and as a source of inspiration for synthetic organic chemists, especially for those interested in the construction of cyclopentene derivatives.

## *Acknowledgements*

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