Journal Name

ARTICLE

Synthetic Applications of Vinyl Cyclopropane Opening

Marta Meazza,[a] Hao Guo[b*] and Ramon Rios[a]*

Received 00th January 20xx,
Accepted 00th January 20xx

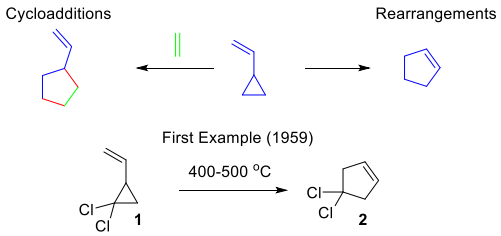
DOI: 10.1039/x0xx00000x

www.rsc.org/

Vinyl cyclopropanes are amongst the most usefuls building blocks in organic synthesis. Their easy opening and capacity to generate dipoles have been exploited for the synthesis of cyclopentanes with good yields and sometimes excellent stereoselectivities. In this review we give an overview of their applications, focusing on the present century.

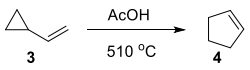
1 Introduction

Vinyl cyclopropanes have attracted much attention due to their versatility and chemical utility. Vinyl cyclopropanes are well known to undergo rearrangement reactions, as donor acceptor cyclopropanes,[1] leading to the synthesis of cyclopentenes, and opening reactions to generate a dipole that can be used in a range of cycloaddition reactions. The first rearrangement of vinyl cyclopropanes was developed by Norman P. Neureiter when he was a research chemist at Humble Oil and Refining. Pyrolysis of 1,1-dichloro-2-vinylcyclopropane **1** rendered 1,1-dichlorocyclopent-3-ene **2** and 2-chorocyclopentane.[2,3]



Scheme 1

This was the start of a huge interest of the organic chemistry community in this scaffold. One year later Vogel,[4] Overberger and Borchert[5] independently reported the thermal rearrangement of vinyl cyclopropanes **3** to obtain cyclopentanes **4**. This last reaction was studied by Flowers, Frey[6] and Wellington[7] some years later.



[a] School of Chemistry. University of Southampton. Highfield Campus, SO17 1BJ, Southampton, UK. Email:rrt1f11@soton.ac.uk.
[b] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai, 200433, Fudan, People's Republic of China.

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Scheme 2

The interest of this type of rearrangement is clearly based on the possibility to synthesize 5-membered rings. Opposite to their brother cyclohexanes, few synthetic methods were reported. Moreover, the interest for the synthesis of triquinane terpenes which contain this scaffold, made vinyl cyclopropanes a common subject of study and a creative platform for the development of new methodologies leading to cyclopentanes and other carbocycles.

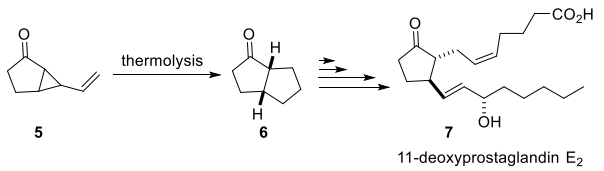
Moreover, the metal catalyzed ring opening of vinyl cyclopropanes has attracted attention thanks to the possibility to use the generated dipoles in several cycloaddition reactions.

In this review, we aim to cover the last methodologies reported in the opening of vinyl cyclopropanes with special focus in the last ten years.

2 Vinyl cyclopropane rearrangements[8]

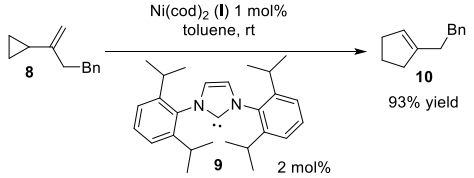
Despite not being the main focus of this review, vinyl cyclopropanes rearrangements have a huge importance in the development of cycloaddition reactions. As stated in the introduction, the rearrangement of vinyl cyclopropanes led to the synthesis of cyclopentanes. Opposite to 6-membered carbocycles that can be easily accessed by Diels Alder or by hydrogenation of benzene rings, 5-membered all carbon rings are difficult to synthesize. The normal [3+2] cyclization requires the use of dipoles that contain at least 1 heteroatom, leading to the synthesis of pyrroles or furanes. For these reasons vinyl cyclopropanes have become one of the most popular starting materials for the synthesis of cyclopentanes.
Probably, one of the earliest examples of the use of vinyl cyclopropanes in total synthesis leading to the formation of cyclopentanes was reported by E. J. Corey in 1975.[9] In their approach to the synthesis of prostenoids **7**, they reported a

thermolysis of vinyl cyclopropane **5** to generate the bicyclic ketone **6** (Scheme 3).



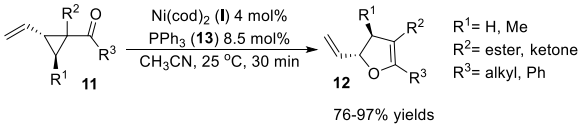
Scheme 3

One of the first examples of vinyl cyclopropane rearrangement leading to cyclopentenes, catalyzed by metal, was reported by Louie using nickel complexes as catalysts.[10] In this work, vinyl cyclopropanes **8** reacted with $Ni(cod)_2$ **I** using NHC carbenes **9** as ligands. The final cyclopentanes **10** were obtained in excellent yields 92-96% (Scheme 4).



Scheme 4

Johnson and coworkers, in 2006, reported a rearrangement of 1-acyl vinyl cyclopropanes **11** to form dihydrofuranes **12** using Ni(0) **I** as catalyst.[11] The reaction starting from stereodefined vinyl cyclopropanes proceeds in good yields and with retention of the configuration (Scheme 5).

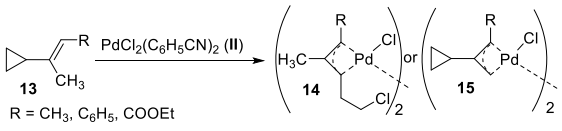


Scheme 5

3 Vinyl cyclopropane cycloadditions

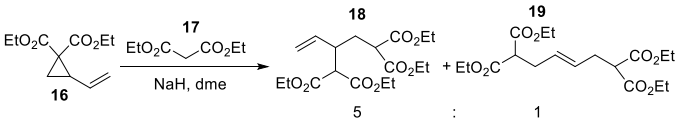
3.1 Pd catalyzed reactions

The opening of vinyl cyclopropanes to form dipoles was initially studied by Oda and coworkers in the formation of π-allyllic palladium complexes from vinyl cyclopropane derivatives.[12] In this work Oda shows that vinyl cyclopropanes **13** can be easily opened by Pd(II) **II**, forming allylic Pd complexes and adding a chloro atom at the same time (Scheme 6). The importance of this work relies on the fact that, for the first time, it is clearly showed the potential of vinyl cyclopropanes as synthetic precursors of dipoles.



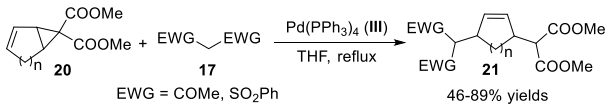
Scheme 6

Despite the potentiality of this preliminary report, organic chemists did not study the opening of vinyl cyclopropanes with Pd to generate dipoles until long time after. A synthetic application of vinyl cyclopropanes was reported by Danishefsky in 1972.[13] Vinyl cyclopropane **16** reacts with diethyl malonate sodium salt **17** leading, after quenching, to a two component mixture (5:1, **18**:**19**) of the primary products of the homo-conjugate addition (Scheme 7).



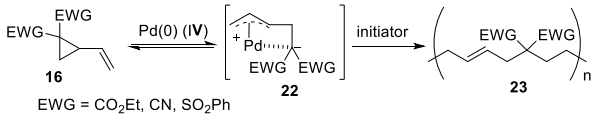
Scheme 7

Several other groups reported radical openings of vinyl cyclopropanes. Should be highlighted the [3+2] cycloaddition, reported by Feldman, between vinyl cyclopropanes and alkenes using phenyldisulfide, AIBN and trimethylaluminium as catalysts.[14] Burgess reported the opening of vinyl cyclopropanes bearing two electron-withdrawing groups **20**, using Pd(0) **III** as catalyst.[15] Malonates, ketosulfones or disulfones **17** were used as nucleophiles obtaining a mixture of monomer and dimer **21** as products with good yields (Scheme 8).



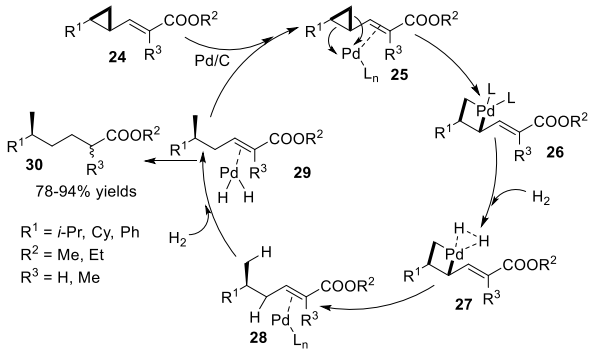
Scheme 8

In 1993, Suzuki and coworkers reported a ring opening polymerization of vinyl cyclopropanes using Pd(0) as catalyst.[16] The vinyl cyclopropane was decorated with two electron-withdrawing substituents **16**, showing clearly the formation of the dipole, which then polymerizes **23**. The key intermediate is the π-allylpalladium complex **22**, which is generated by oxidative addition of Pd(0) to the monomer (Scheme 9).



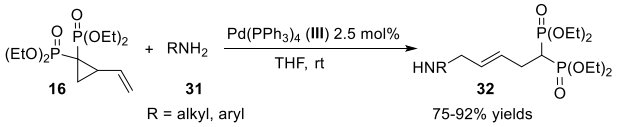
Scheme 9

Some years later, Barrett and coworkers proposed the regioselective ring opening of vinyl cyclopropanes by hydrogenation with Palladium on activated carbon.[17] The reaction follows a similar mechanism of the previous ones. At first coordination of the double bond to palladium **25**, followed by insertion into the less hindered bond of the cyclopropane, leads to the formation of the palladacyclobutane **26**. Next, the addition of H_2 to the palladium **27** and the reductive cleavage of the palladacycle, renders **28** that, after hydrogenation of the double bond, gives the observed product **30** (Scheme 10).



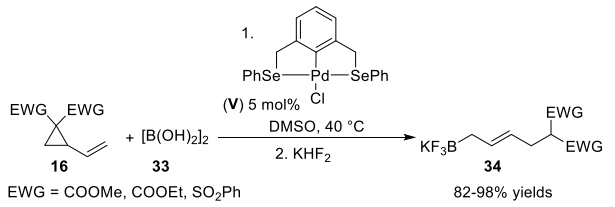
Scheme 10

In 2004, Maffei and coworkers reported an interesting Pd catalyzed vinyl cyclopropane opening with amines.[18] In this work vinyl cyclopropanes, decorated with bisphosphonate unit **16**, reacted with several amines **31** rendering the final compounds **32** in excellent yields (Scheme 11).



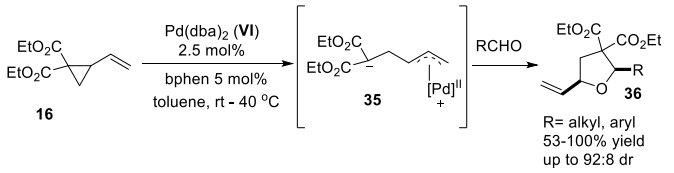
Scheme 11

Szabó and coworkers reported a vinyl cyclopropane opening using Pd pincer complexes.[19] The vinyl cyclopropanes **16** react with tetrahydroxydiboron **33** to form triflouroboron compound (after treatment with KHF_2) **34** in excellent yields and regioselectivities (Scheme 12). Soon after, they combined this reaction with a coupling of the corresponding boron compounds acid with iodobenzenes with excellent results.[20]



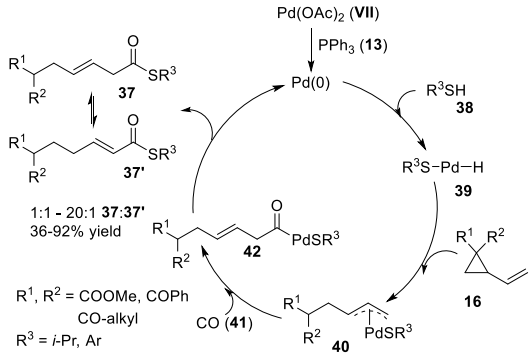
Scheme 12

Johnson and coworkers, following their rearrangements with Ni(0), reported a [3+2] cycloaddition, between vinyl cyclopropanes and aldehydes. This reaction is catalyzed by Pd(0) complexes **VI**, to afford tetrahydrofuran derivatives **36** in excellent yields and diastereoselectivities.[21] As shown in Scheme 13, the reaction consists on the formation of π-allyl palladium zwitterion **35** that reacts with the aldehyde in an aldol type mechanism, followed by the intramolecular ring closure between the alcoxide and the allyl palladium complex.[22] A similar reaction was reported by Shi, Xu and Wei where the vinyl cyclopropanes react with isatins. The use of chiral imidazoline-phosphine ligands is crucial to get excellent yields and enantioselectivities.



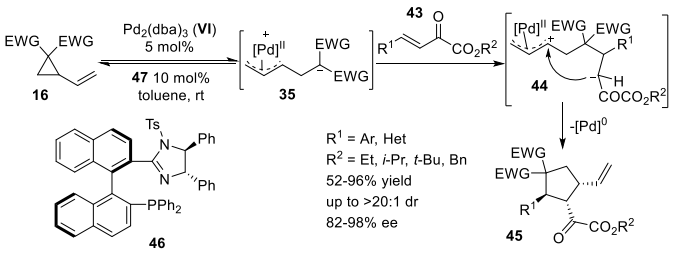
Scheme 13

In 2009 Alper and Xiao reported a new Pd catalyzed vinyl cyclopropanes ring opening.[23] The palladium catalyzed opening of vinyl cyclopropanes **16** is followed by a carbonylation **42** and later thiol addition to get the thiocarbonylated product **37**, as shown in Scheme 14. The reaction requires high temperatures and CO pressure, under $Pd(OAc)_2$ **VII**/PPh_3 **13** catalysis and rendered the final compounds in good yields and with good group tolerance (Scheme 14).



Scheme 14

An enantioselective palladium catalyzed [3+2] cycloaddition of vinyl cyclopropanes **16** with β,γ-unsaturated α-keto esters **43** was reported by Shi in 2012.[24] In this reaction, Pd(0) complexes **VI** reacted with the vinyl cyclopropanes, forming the zwitterion **35** that reacts with the unsaturated ketoester **43** to form the corresponding cyclopentane **45**. Chiral imidazoline-phosphines **46** were used as ligands, achieving the final products with good yields and stereoselectivities (Scheme 15).

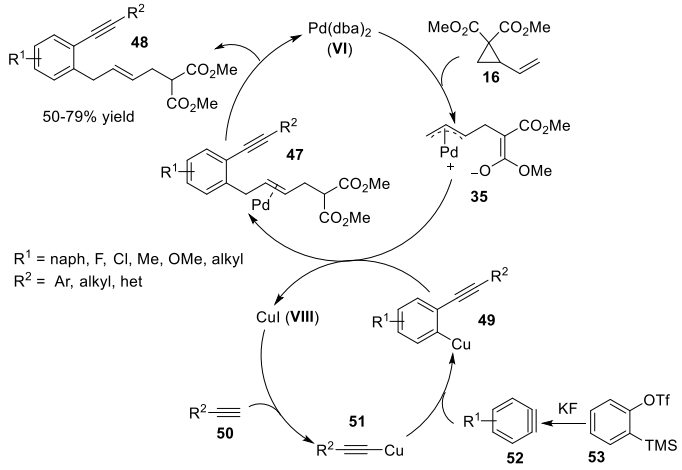


Scheme 15

Years later, Shi reported a novel cycloaddition between vinyl cyclopropanes and diazo oxindoles.[25] The reaction was efficiently catalyzed by Pd(0) complexes, using chiral imidazoline-phosphines as ligand. The reaction afforded the corresponding oxindole-fused spiropyrazoline in good yields and enantioselectivities. Moreover, they designed a one-pot

cascade reaction adding maleimides. The maleimide reacts with the recent formed dipole to furnish the final multicyclic products, bearing 4 stereocenters, in good yields and stereoselectivities. Later on, the same research group reported a similar reaction using with 2-vinyl-spiroindanones.[26] Again, chiral imidazoline-phosphines were the best ligands, achieving the spiro indanone derivatives in excellent yields but only moderate enantioselectivities.

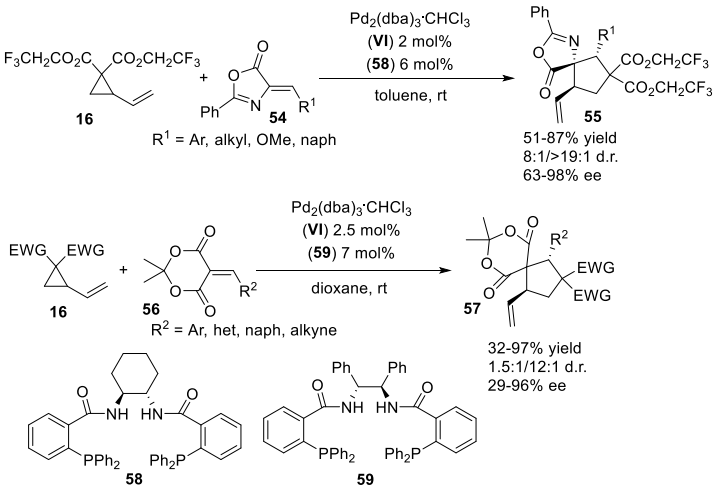
A three component coupling between terminal alkynes **50**, arynes **52** and vinyl cyclopropanes **16** was reported by Werz in 2015.[27] Initially copper acetylide **51** is generated by deprotonation of the terminal alkyne **50**, then it undergoes a nucleophilic attack to the benzyne **52**, which was generated "in situ" by treatment of **53** with KF, affording the highly nucleophilic intermediate **49**. Simultaneously, the vinyl cyclopropane **16** reacts with Pd(0) **VI** to form the zwitterionic π-allyl palladium complex **35**. The allyl complex reacts with the nucleophilic intermediate **49** by the less hindered carbon, forming the desired product **48** and releasing the Pd(0) catalyst **VI**. The reaction gave the final alkynes products in good yields (Scheme 16).



Scheme 16

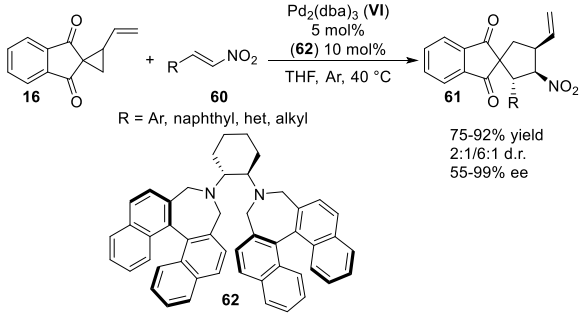
Trost and coworkers reported a formal [3+2] cycloaddition between benzylidene azalactones **54** and racemic vinyl cyclopropanes **16**.[28] The reaction was catalyzed by Pd_2dba_3 **VI**, using chiral phosphine ligands **58** to induce enantioselectivity. Interestingly, a key aspect to obtain reactivity was the type of substituents in the malonate moiety of the vinyl cyclopropane **16**. The authors proposed that the use of trifluoroethylester increases the half-life of the intermediate dipole formed, without losing reactivity. The reaction rendered the spiro azalactone derivatives **55** with good yields and excellent stereoselectivities (Scheme 17, top).

Later, the same research group expanded the scope of the reaction using alkylidene meldrum's acid **56**.[29] DPPBA biphosphine ligands **59** were used, achieving the final spiro cyclopentanes **57** in good yields and excellent stereoselectivities (Scheme 17, bottom).



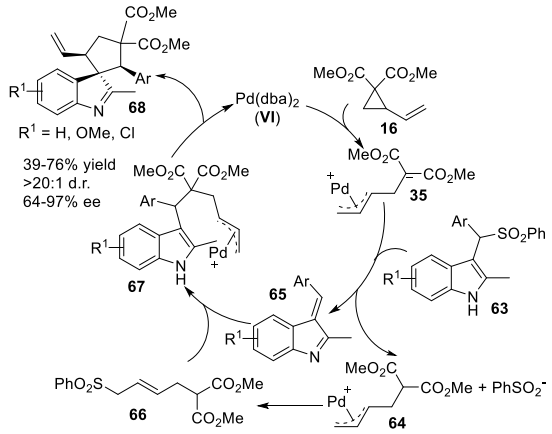
Scheme 17

In 2015 two different groups reported the reaction between vinyl cyclopropanes and nitrostyrenes. In the first paper, vinyl cyclopropanes derived from malonates or malononitriles, react with nitrostyrenes, catalyzed by $Pd_2(dba)_3$ using chiral diphosphine ligands.[30] The resulting nitrocyclopentanes were obtained in good yields and enantioselectivities, albeit with low diastereoselectivities. In the second paper, vinyl cyclopropanes derived from 1,3-indanone **16** react with nitrostyrene **60**, catalyzed by $Pd_2(dba)_3$ **VI**, using diamine ligands **62**.[31] This time the nitrocyclopentanes **61** were obtained in good yields and stereoselectivities (Scheme 18).



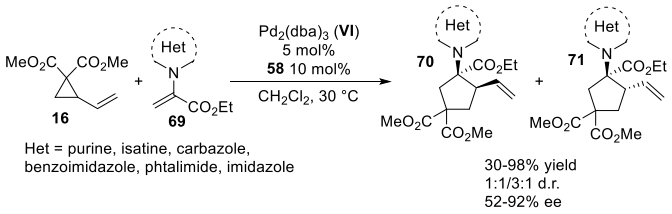
Scheme 18

A palladium catalyzed cycloaddition of vinyl cyclopropanes with "*in situ*" formed imines was reported by Liu in 2015.[32] In this paper arenesulfonyl indoles **63** react with the zwitterion **35** formed by the ring opening of the vinyl cyclopropane **16** by Pd **VI**, forming the conjugate imine **65**. Next, conjugate addition of malonate **66** and subsequent palladium catalyzed allylation, afforded the spiroindolines **68** in good yields and stereoselectivities, using phosphoramidites as ligands (Scheme 19).



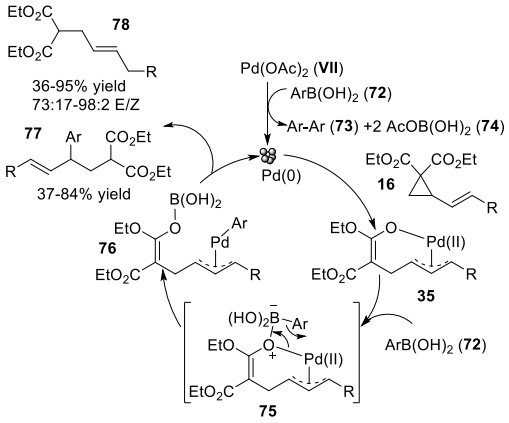
Scheme 19

A similar reaction was reported by Li and Guo regarding the synthesis of carbocyclic nucleosides.[33] Acrylate derivative **69** reacts with vinyl cyclopropanes **16** under Pd(0) catalysis, using Trost ligand **58** as catalyst. The reaction affords the chiral carbocyclic nucleoside analogues **70**,**71** in good yields and moderate to good enantioselectivities (Scheme 20).



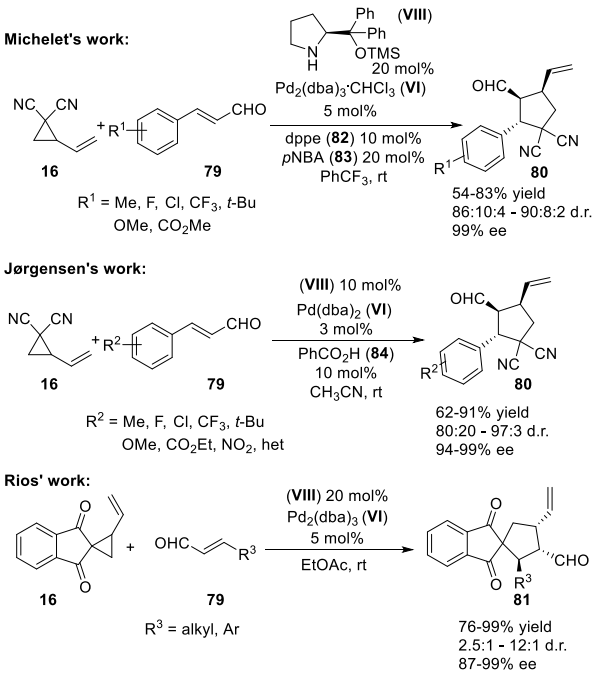
Scheme 20

A new palladium catalyzed vinyl cyclopropane opening was reported by Hyland in 2015.[34] In this example, vinyl cyclopropanes **16** react with boronic acids **72** in water under Pd(II) catalysis without the need of ligands. In the proposed reaction mechanism, the authors claim that first Pd(II) **VII** reacts with the boronic acid **72** to generate Pd(0) nanoparticles. Oxidative addition of the vinyl cyclopropane **16** to the "*in situ*" generated Pd(0), followed by transmetallation with the boronic acid and reductive elimination, generates the final compounds **78** and **77** in good yields, regio and diastereoselectivities, using mild reaction conditions (Scheme 21).



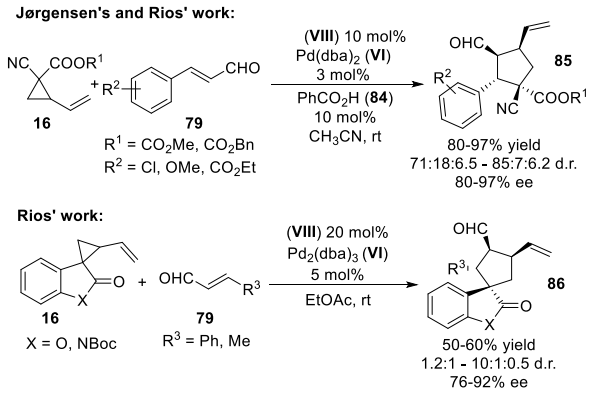
Scheme 21

In 2016 Michelet,[35] Jørgensen[36] and Rios[37] reported, almost at the same time, the formal [3+2] cycloaddition between vinyl cyclopropanes **16** and enals **79**. The vinyl cyclopropanes **16** are opened by Pd(0), while the enal **79** is activated by the secondary amine catalyst **VIII** in a synergistic fashion. The final cyclopentanes **80** and **81**, bearing three new stereocenters, were obtained in excellent stereoselectivities (Scheme 22).



Scheme 22

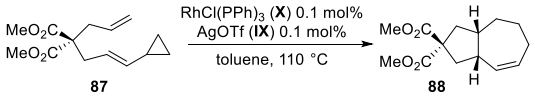
Rios[38] and Jørgensen[36] also expanded the scope of this reaction, obtaining the final cyclopentanes **85** and **86** with four new stereocenters while maintaining the excellent control of the stereoselectivity (Scheme 23).



Scheme 23

3.2 Rh catalyzed reactions

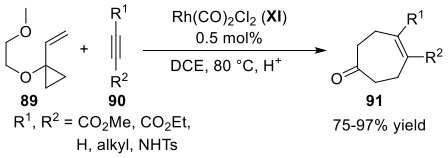
Wender and coworkers demonstrated the utility of vinyl cyclopropanes by developing an intramolecular [5+2] cycloaddition with alkenes.[39-41] The cycloaddition was efficiently catalyzed by Rh(I) **X** salts in combination of Ag(I) **IX** affording the *cis* fused bicycles **88** in good yields (Scheme 24).



Scheme 24

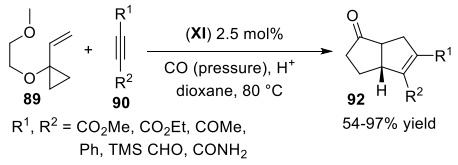
In 1999 they reported that, with a careful choice of the substituents in the cyclopropyl moiety and/or through catalyst modifications, an excellent control over the regiochemical outcome of the reaction can be achieved. Concretely, the configuration of the cyclopropyl substituents (*cis*/*trans*) determines the final configuration of the cycloheptenes.[42]

One year later, the same group expanded this concept to intermolecular reactions.[43] This time vinyl cyclopropane **89** reacted with alkynes **90** to furnish cycloheptenones **91** in excellent yields. The reaction is catalyzed by Rh(I) salts **XI** as it is shown in Scheme 25.



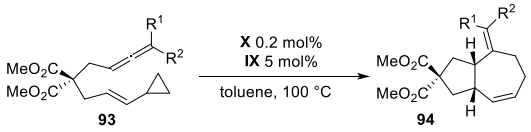
Scheme 25

Working further on this concept, Wender developed a multicomponent version of this last reaction.[44,45] The Rh catalyzed **XI** reaction between alkynes **90**, vinyl cyclopropanes **89** and CO, through an overall [5+2+1] cycloaddition, rendered the final bicyclic octenone derivatives **92** in excellent yields (Scheme 26). Years later the same group expanded the scope of the reaction based on computational calculations.[46]



Scheme 26

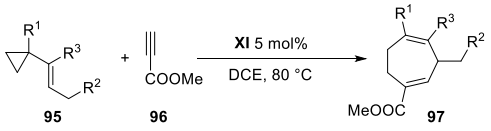
Wender also developed a closely related reaction consisting in the [5+2] intramolecular cycloaddition between vinyl cyclopropanes and allenes **93**, catalyzed by rhodium **X**.[47,48] The reaction favors the formation of fused rings with a *cis* fused configuration **94**. Importantly, when chiral allenes are used, the asymmetric information is preserved in the course of the cycloaddition (Scheme 27).



Scheme 27

The same year, Wender and coworkers reported the use of this cycloaddition as a key step for the total synthesis of (+)-Dictamnol[49] and (+)-Aphanamol.[50] Moreover, in 2003 they developed the same reaction but using water as the solvent.[51]

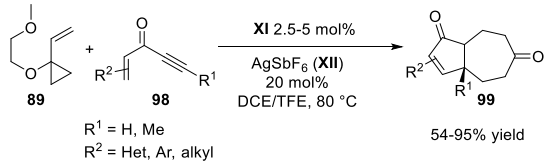
In 2001, Wender and coworkers reported the first intermolecular [5+2] cycloaddition of vinyl cyclopropanes with alkynes.[52-54] For the first time, unactivated vinyl cyclopropanes **95** reacted intermolecularly with alkynes **96** using Rh complexes **XI** as catalysts. The substitution at the position 1 of the vinyl cyclopropane resulted to be the key to accelerate the reaction, correlating the steric bulkiness of the substituents with the degree of rate enhancement. As it is shown in Scheme 28, good to moderate yields were obtained and with high degree of selectivity when terminal alkynes were used.



Scheme 28

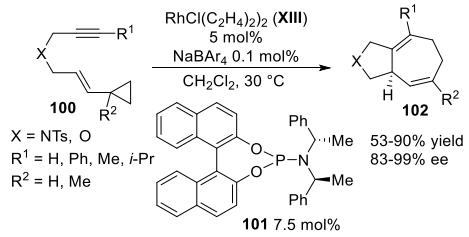
Years later, Wender described the first enantioselective [5+2] intramolecular cycloaddition between vinyl cyclopropanes and alkenes.[55,56] Chiral diphosphines (BINAP derivatives) were used as Rh ligands affording the final compounds in excellent yields and enantioselectivities. Later on, the same group expanded the scope developing a cascade reaction consisting in an intermolecular [5+2] cycloaddition, followed by a Nazarov cyclization.[57, 58] Vinyl cyclopropanes **89** reacted with enynones **98** furnishing, in the first instance, a dienone that renders, through a Nazarov cyclization, the bicyclic product **99**. The [5+2]

cycloaddition reaction is catalyzed by Rh(I) catalysts **XI**, while the Nazarov reaction is catalyzed by Ag(I) **XII**, affording the final bicyclic products **99** in good yields and moderate to excellent diastereoselectivities (Scheme 29).



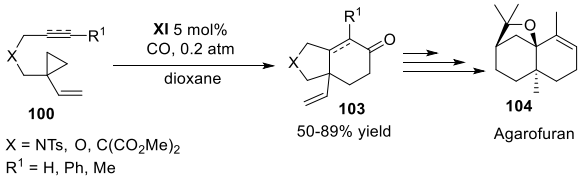
Scheme 29

In 2009, Shintani and Hayashi reported an intramolecular enantioselective [5+2] cycloaddition between alkyne and vinyl cyclopropane **100**, catalyzed by Rh(I) **XIII** complexes.[59] The use of phosphoramidites **101** as ligands rendered the cycloaddition adducts **102** in excellent yields and enantioselectivities (Scheme 30).



Scheme 30

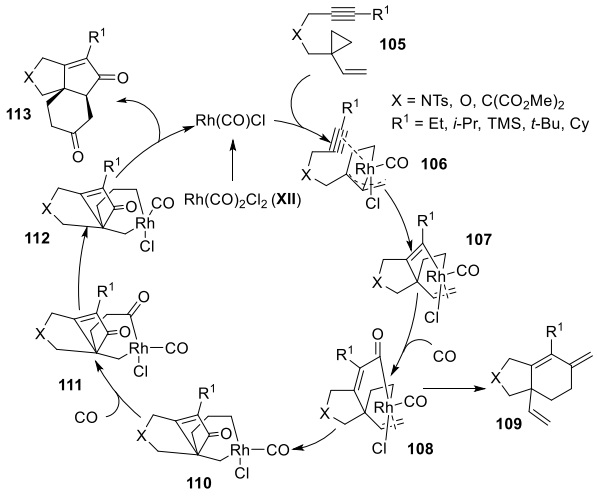
Later, Yu and coworkers reported a similar intramolecular [3+2] cycloaddition between vinyl cyclopropanes and alkenes **100** catalyzed by Rh(I) salts **XII**, with excellent results.[60,61] The same group also expanded the reaction by using CO.[62] They reported a homologous Pauson-Khand reaction, based on a Rh(I) **XII** catalyzed [3+2+1] cycloaddition. As it is shown in Scheme 31, the reaction renders the final products **103** in excellent yields and regioselelectivities. Moreover, they demonstrated the value of this methodology by using it as a key step for the synthesis of α-Agarofuran **104**. Later on they reported a similar strategy for the formal synthesis of Gracilamine.[63]



Scheme 31

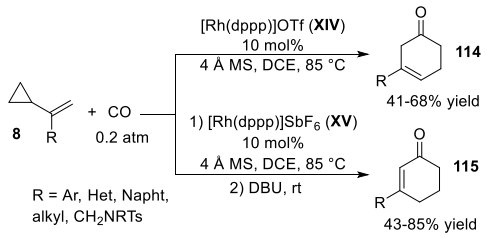
Chung and coworkers developed a Rh catalyzed intramolecular [5+2] cycloadditions with vinyl cyclopropanes.[64] NHC carbenes were used as ligands for the first time in this type of reactions. The reactions are extremely fast (10 min) and render the final products in excellent yields (91-98%).

Yu and coworkers described a formal [5+1]/[2+2+1] of 1-yne-vinylcyclopropanes **105** catalyzed by Rh(I) **XI**.[65] This methodology allows the construction of multifunctional angular tricyclic 5/5/6 scaffolds **113** in a single step. The authors proposed the following mechanism: 1-yne-vinyl cyclopropane **105** and Rh **XI** generate the intermediate **106** by complexation, cyclopropane cleavage and alkyne insertion. Migratory insertion of CO into the Rh-C bond **107** and addition of CO render intermediate **108**. Next, insertion of the alkene into the Rh-COR bond takes place, forming a tricyclic intermediate **110**. This, after another CO insertion **111** and reductive elimination **112**, affords the final tricyclic products **113** in good yields (Scheme 32).



Scheme 32

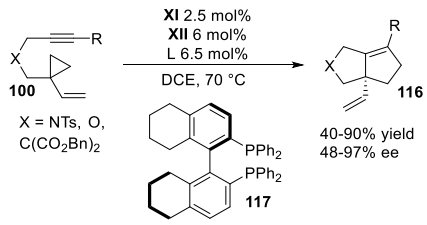
A Rh(I) catalyzed [5+1] cycloaddition of vinyl cyclopropanes was reported by Yu.[66] Vinyl cyclopropanes **8** reacted with CO to furnish cyclohexenones in good yields. Careful choice of the Rh catalysts and the reaction conditions, led to the selective formation of α,β-unsaturated cyclohexenones **115** (when [Rh(dppp)]SbF_6 **XV** was used as catalyst and the product was then treated with DBU, Scheme 33 bottom) or to the formation of the β,γ-cyclohexenone **114** as major isomer (when [Rh(dppp)]OTf **XIV** was used, Scheme 33 top). In 2016 the same research group reported a similar reaction using $Fe_2(CO)_9$ as mediator for the synthesis of cyclohexenones.[67]



Scheme 33

The same research group reported an enantioselective intramolecular [3+2] cycloaddition of 1-yne-vinyl cyclopropanes catalyzed by Rh(I).[68] The reaction affords the bicycle compounds **116** with a chiral quaternary center in excellent yields and stereoselectivities when H_8-BINAP **117** was used as a ligand

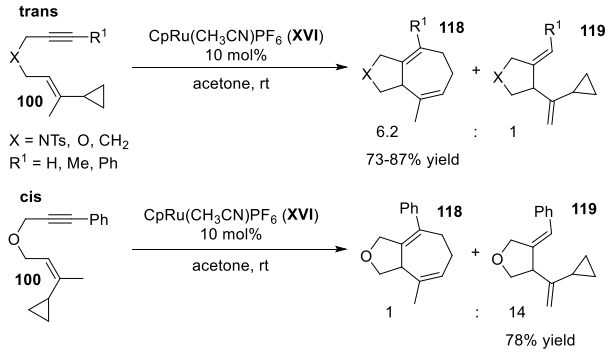
(Scheme 34). The authors also studied the reaction mechanism by DFT calculations.



Scheme 34

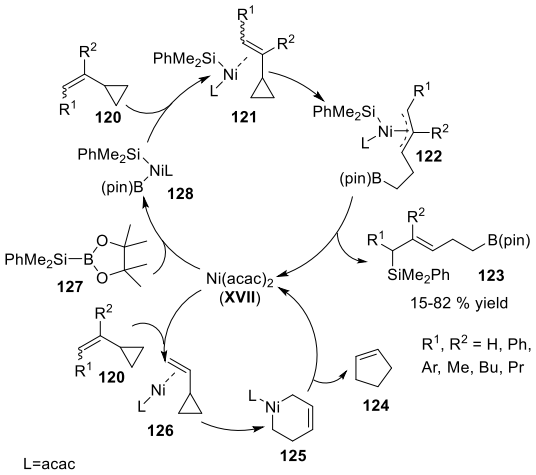
3.3 Other metals catalyzed reactions

Trost and coworkers reported a similar intramolecular [5+2] cycloaddition between vinyl cyclopropanes and alkynes **100**, this time catalyzed by cationic Ruthenium catalysts **XVI**.[69,70] The main characteristics are the mild conditions required (rt, acetone), the excellent chemoselectivity and the high group tolerance. As before, the regioselectivity can be controlled by the choice of substituents and the reaction furnished the products **118** and **119** with complete diastereoselectivity (Scheme 35).



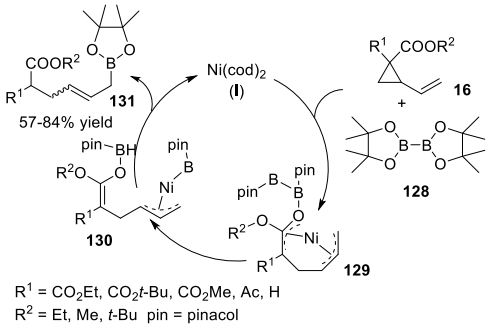
Scheme 35

Suginome reported the silaboration of vinyl cyclopropanes **120** catalyzed by nickel **XVII**.[71] The reaction consists in the cleavage of the vinyl cyclopropane, resulting in the highly regio- and stereoselective formation of 2-borylalkyl-allylsilanes **123**. The proposed mechanism consists in the formation of a (silyl)(boryl)Ni(II) intermediate **128** *via* an oxidative addition of Ni to silanoborane. Next, coordination of the Ni complex to the vinyl cyclopropane **120**, followed by migratory B-C insertion with cleavage of the C-C bond, renders the allyl nickel species **122**. Reductive elimination of the Si-C bond proceeds at the allylic carbon *cis* group, leading to the high regioselectivity of the final products **123** (Scheme 36).



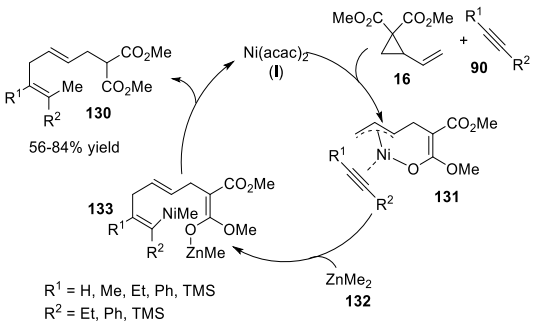
Scheme 36

Oshima in 2008, developed a ring opening of vinyl cyclopropanes **16** catalyzed by Ni(0) **I** with bis(pinacolato)diboron **128** to yield allylic boronates **131**.[72] The mechanism of the reaction (Scheme 37) is based on the activation of the cyclopropane **16** by the boron compound **128**, followed by an oxidative addition of the nickel complex to afford the π-alkyl(oxa-π-allyl)nickel intermediate **129**. Transmetalation and reductive elimination provide the final allyl boronate compounds **131** in good yields.



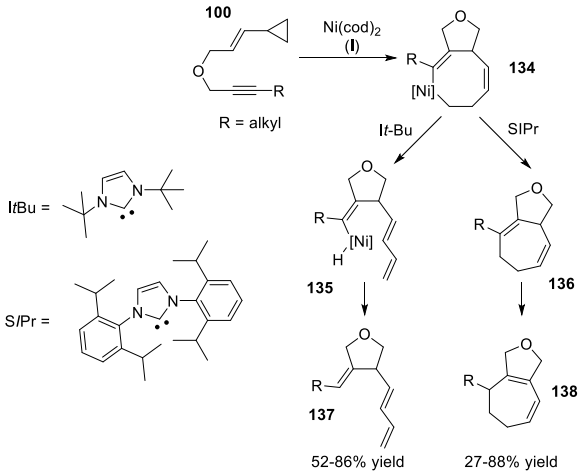
Scheme 37

A nickel catalyzed reaction with vinyl cyclopropanes was reported by Kimura.[73] Vinyl cyclopropanes **16** reacted with alkynes **90** and alkyl zinc **132** to generate the final addition products **130** in good yields and stereoselectivities. The reaction starts with the formation of the nickelocene **131** by ring cleavage of the vinyl cyclopropane **16**. Next, $ZnMe_2$ **132** addition and alkyne insertion in the terminal position of the allyl, lead exclusively to the (*E*)-vinyl-nickel **133**, that undergoes reductive elimination to form the *trans*-alkene **130** (Scheme 38).



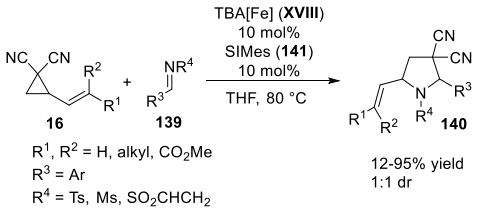
Scheme 38

A nickel catalyzed reaction with vinyl cyclopropanes was reported by Louie in 2005.[74] In this paper vinyl cyclopropanes **100** react intramolecularly with the triple bond to form, depending of the nature of the NHC ligand, the 5+2 cycloadduct **138** or the cyclopentane product **137**. Remarkably, when bulkier NHC ligands were used, the major product was **137**. The authors proposed that a common intermediate **134** is formed in the reaction and, depending of the size of the NHC ligand, reductive elimination or β-hydride elimination take place, to afford the respective final products in good yields (Scheme 39). Years later, Houk and coworkers studied the reaction performing DFT calculations.[75]



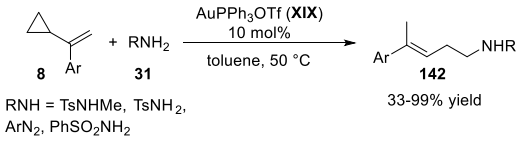
Scheme 39

Another reaction catalyzed by $Ni(cod)_2$ was reported by Matsubara and Kurahashi.[76] Vinyl cyclopropanes **16** react with imines **139**, in a [3+2]-cycloaddition, to furnish highly substituted pyrrolidines **140** in good to moderate yields and good to excellent diastereoselectivities. The authors explored the use of chiral phosphines to develop an asymmetric version with moderate enantioselectivities. A slightly different version was reported by Plietker.[77] The main difference relies in the catalyst: nucleophilic iron complexes are used, rendering the final pyrrolidines **140** in good yields albeit in very low diastereoselectivities (Scheme 40).



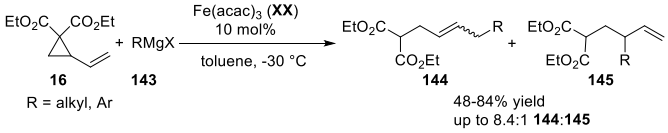
Scheme 40

Togni reported the vinyl cyclopropane **8** opening with sulphonamides **31**, catalyzed by Au(I) **XIX** complex with good yields.[78] The reaction works with unactivated cyclopropanes affording the formal hydroaminated products **142** (Scheme 41).



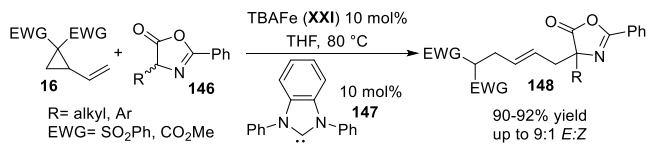
Scheme 41

Fuerstner reported an iron catalyzed addition of Grignard reagents **143**.[79] This is the first example of the use of a hard organometallic nucleophile. The cheap and benign $Fe(acac)_3$ **XX**, catalyzed the conjugate Grignard addition. Primary Grignard reagents rendered as the major product the 1,7-addition **144** in good yields and, in the case of secondary Grignard reagents, with increased regioselectivities (Scheme 42).



Scheme 42

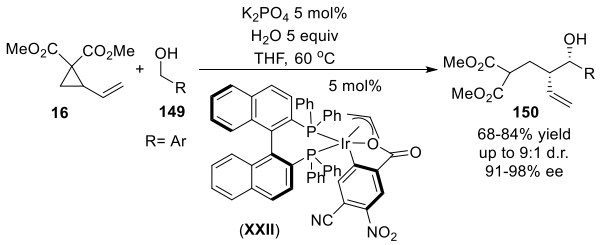
Another interesting reaction, catalyzed by iron, was reported by Plietker.[80,81] The combination of the NHC ligand **147** and electron rich ferrate TBAFe **XXI** is a powerful electron-transfer catalyst that reacts with vinyl cyclopropanes **16** to form allylic substituted products (**148**) or undergoes a [3+2] cycloaddition depending on the starting materials. The addition of pronucleophiles like cyano ketones, azalactones or cyanoesters took place on the terminal position (Scheme 43) with excellent control of the diastereoselectivity and very good yields. On the other hand, when the same vinyl cyclopropanes reacted with Michael acceptors, the 5 member rings were furnished in excellent yields, albeit with very low diastereoselectivities.



Scheme 43

Krishe and Johnson reported an umpolung reaction with vinyl cyclopropanes.[82] In this work, after the cleavage by the Ir

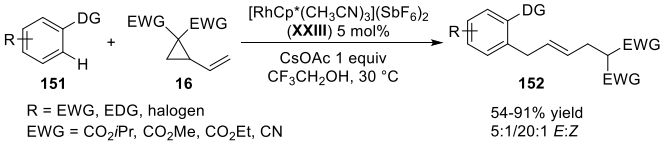
catalyst, the nucleophilic allylmetal species reacted with aldehydes in an enantioselective fashion. Moreover, they coupled this vinyl cyclopropane **16** ring opening with an iridium **XXII** catalyzed oxidation of alcohols **149** to form the aldehyde "*in situ*". The products **150** were obtained in good yields and diastereoselectivities and excellent enantioselectivities (Scheme 44).



Scheme 44

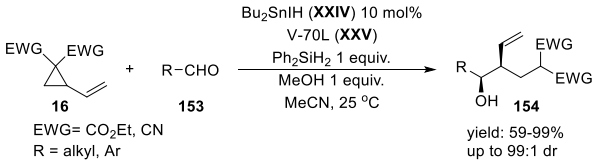
An intermolecular [5+2] cycloaddition between vinyl cyclopropanes and alkynes, catalyzed by Ir(I) complexes, was reported by Strand in 2015.[83] In a fashion similar to the previously reported ones, Ir catalyzes the [5+2] intermolecular cycloaddition and the reaction renders the cycloheptene derivatives in excellent yields. The main advantage to use Ir instead of Rh is the lower cost of the catalyst and the fact that Ir shows catalytic rates 50 times higher.

In 2015 Wang and Huang reported a Rh(III) catalyzed C-H/C-C sequence between aryl rings **151** and vinyl cyclopropanes **16**.[84] In this reaction Rh **XXIII** has a dual function: first it activates the aryl group by coordination with a directing group, second it coordinates the vinyl cyclopropane **16**, followed by the alkene insertion and β-carbon elimination to cleave the C-C bond of the cyclopropane. The corresponding compounds **152** were obtained in good yields and diastereoselectivities (Scheme 45).



Scheme 45

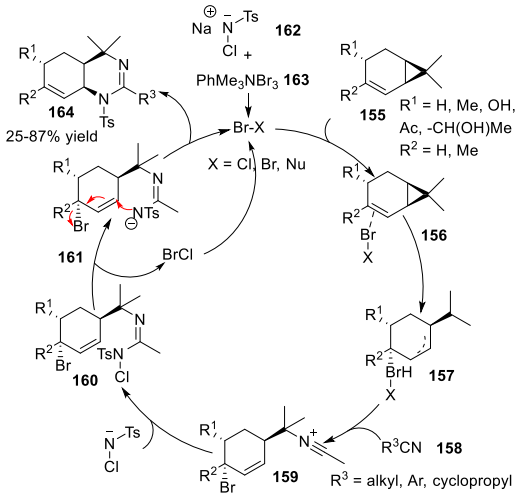
Shibata reported a transition metal free coupling reaction of vinyl cyclopropanes **16** with aldehydes **153**, catalyzed by tin hydride **XXIV**.[85] The proposed mechanism consists first in the addition of the tin radical to the vinyl cyclopropane **16**, to form an intermediate radical which undergoes ring opening and reacts with tin hydride. Next, the organotin reacts with an aldehyde **153** in an aldol fashion to generate alcohol **154** in good yields and moderate to excellent diastereoselectivities (Scheme 46).



Scheme 46

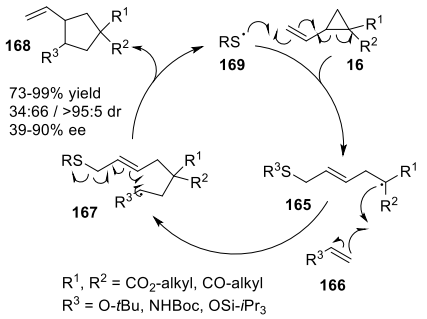
3.4 Metal-free reactions

A metal free ring opening/cyclization of vinyl cyclopropanes, catalyzed by bromine, was reported by Chandrasekaran.[86,87] Vinyl cyclopropanes **155** reacted with Chloramine-T **162** in the presence of a catalytic amount of PTAB **163**, affording bicyclic amidines **164**. The vinyl cyclopropane **155** undergoes a Ritter-type reaction. First, bromine reacts with the alkene forming the bromonium ion **156**, followed by opening of the cyclopropane ring to form the more stable cation **157**. Addition of acetonitrile **158** forms the intermediate **159**, that reacts with Chloramine-T to form **160**. Intramolecular addition of the tosyl amine, through a S_N2, renders the final product **164** and regenerates the bromine. Remarkably, the reaction occurs with retention of the configuration of the cyclopropane in excellent yields.



Scheme 47

An organocatalytic enantioselective ring opening of vinyl cyclopropanes was reported by Maruoka in 2014.[88] The reaction consists in an enantioselective radical [3+2] cycloaddition between vinyl cyclopropanes **16** and vinyl ethers **166**, catalyzed by thiyl radicals **169** derived from binol. The reaction proceeds *via* addition of the thiyl radical to the vinyl cyclopropane, forming radical **165** by ring opening of the cyclopropane. Next, the radical reacts with the vinyl ether to form intermediate **167**, that undergoes intramolecular ring closing to form the cyclopentane adduct **168** and regenerate the thiyl radical (Scheme 48). After an impressing catalyst optimization, the products were obtained in good to excellent and excellent stereoselectivities.



Scheme 48

Conclusions

Vinyl cyclopropanes have been a useful building block for the development of new synthetic methodologies. The possibility to easily generate dipoles makes these substrates appealing for the development of [3+2] or higher order cycloadditions. In this review we summarized the most recent developments in the field. Organometallic approaches, racemic and enantioselective, have been reported with excellent results. Very recently, synergistic approaches based on the use of organometallic complexes and secondary amine catalysis have proved to be excellent platform to obtain chiral cyclopentanes. In the future, we expect a huge increase of new enantioselective methodologies for the opening of vinyl cyclopropanes. Probably in the next years we will see an explosion of new cycloaddition reactions based on these concepts.

Acknowledgements

M.M. and R.R acknowledge the European Regional Development Fund (ERDF) for co-financing the AI-CHEM-Chem project (No. 4061) through the INTERREG IV A France (Channel) - England cross-border cooperation Programme. M.M. and R.R. are grateful for the EPSRC Core Capability Funding (EP/K039466/1). H.G. and R.R. acknowledge International Science & Technology Cooperation Program of China (2014DFE40130) for financial Support.

Notes and references

1 H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151-1196; F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano and J. Waser, Chem. Commun., 2014, **50**, 10912-19028; T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem. Int. Ed.*, 2014, **53**, 5504-5523.
2 N. P. Neureiter, *J. Org. Chem.* 1959, **24**, 2044-2046.
3 N. P. Neureiter, U.S. Patent 2 951 878, 1960; N. P. Neureiter, U.S. Patent 2 981 756, 1960.
4 E. Vogel, *Angew. Chem.*, 1960, **72**, 4.
5 C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc.*, 1960, **82**, 1007; C. G. Overberger and A. E. Borchert, *J. Am. Chem. Soc*., 1960, **82**, 4896-4899.
6 M. C. Flowers and H. M. Frey, *J. Chem. Soc*., 1961, **83**, 3547-3551.
7 C. A. Wellington, *J. Phys. Chem*., 1962, **66**, 1671-1674.
8 For an excellent review regarding vinyl cyclopropane rearrangement and their use in the synthesis of natural products, see: T. Hudlicky and J. W. Reed, *Angew. Chem. Int. Ed*., 2010, **49**, 4864-4876.
9 E. J. Corey and R. H. Wollenberg, *J. Org. Chem.,* 1975, **40**, 2265-2266.
10 G. Zuo and J. Louie, *Angew. Chem. Int. Ed.*, 2004, **43**, 2277-2279.
11 R. K. Bowman and J. S. Johnson, *Org. Lett.*, 2006, **8**, 573-576.
12 T. Shono, T. Yoshimura, Y. Matsumura and R. Oda, *J. Org. Chem.*, 1968, **33**, 876-877.
13 S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 1972, 820-821.
14 K. S. Feldman, A. L. Romanelli, R. E. Ruckle Jr. and R. F. Miller, *J. Am. Chem. Soc.*, 1988, **110**, 3300-3302.
15 K. Burgess, *J. Org. Chem.*, 1987, **52**, 2046-2051.
16 M. Suzuki, S. Sawada, S. Yoshida, A. Eberhardt and T. Saegusa, *Macromolecules*, 1993, **26**, 4748-4750.
17 A. G. M. Barrett and W. Tam, *J. Org. Chem.*, 1997, **62**, 7673-7678.
18 P. Moreau and M. Maffei, *Tetrahedron Lett.*, 2004, **45**, 743-746.
19 S. Sebelius, V. J. Olsson and K. J. Szabó, *J. Am. Chem. Soc.*, 2005, **127**, 10478-10479.
20 S. Sebelius, V. J. Olsson, O. A. Wallner and K. J. Szabó, *J. Am. Chem. Soc.*, 2006, **128**, 8150-8151.
21 A. T. Parsons, M. J. Campbell and J. S. Johnson, *Org. Lett.*, 2008, **10**, 2541-2544.
22 L.-Y. Mei, Y. Wei, Q. Xu and M. Shi, *Organometallics*, 2013, **32**, 3544-3556.
23 C.-F. Li, W.-J. Xiao and H. Alper, *J. Org. Chem.*, 2009, **74**, 888-890.
24 L.-Y. Mei, Y. Wei, Q. Xu and M. Shi, *Organometallics*, 2012, **31**, 7591-7599.
25 L.-Y. Mei, X.-Y. Tang and M. Shi *Chem. - Eur. J.*, 2014, **20**, 13136-13142.
26 B. Cao, L.-Y. Mei, X.-G. Li and M. Shi, *RSC Adv.*, 2015, **5**, 92545-92548
27 L. K. B. Garve and D. B. Werz, *Org. Lett.*, 2015, **17**, 596-599.
28 B. M. Trost and P. J. Morris, *Angew. Chem. Int. Ed.*, 2011, **50**, 6167-6170.
29 B. M. Trost, P. J. Morris and S. J. Sprague, *J. Am. Chem. Soc.*, 2012, **134**, 17823-17831.
30 W.-K. Li, Z.-S. Liu, L. He, T.-R. Kang and Q.-Z. Liu, *Asian J. Org. Chem.*, 2015, **4**, 28-32.
31 F. Wei, C.-L. Ren, D. Wang and L. Liu, *Chem. - Eur. J.*, 2015, **21**, 2335-2338.
32 Z.-S. Liu, W.-K. Li, T.-R. Kang, L. He and Q.-Z. Liu, *Org. Lett.*, 2015, **17**, 150-153.
33 M.-S. Xie, Y. Wang, J.-P. Li, C. Du, Y.-Y. Zhang, E.-J. Hao, Y.-M. Zhang, G.-R. Qu and H.-M. Guo, *Chem. Commun.*, 2015, **51**, 12451-12454.
34 J. X. Yin and C. J. T. Hyland, *J. Org. Chem.*, 2015, **80**, 6529-6536.
35 M. Laugeois, S. Ponra, V. Ratovelomanana-Vidal, V. Michelet and M. R. Vitale, *Chem. Commun.*, 2016, **52**, 5332-5335.
36 K. H. Halskov, L. Næsborg, F. Tur and K. A. Jørgensen, *Org. Lett.*, 2016, **18**, 2220-2223.
37 M. Meazza and R. Rios, *Chem. Eur. J.*, 2016, **22**, 9923-9928.
38 K. Zhang, M. Meazza, A. Izaga, C. Contamine, M. C. Gimeno, R. P. Herrera and R. Rios, 2016, *DOI: 10.1055/s-0036-1588347*.
39 P. A. Wender, H. Takahashi and B. Witulski, *J. Am. Chem. Soc.*, 1995, **117**, 4720-4721.
40 P. A. Wender, C. O. Husfeld, E. Langkopf and J. A. Love, *J. Am. Chem. Soc.*, 1998, **120**, 1940-1941.
41 Z.-X. Yu, P. A. Wender and K. N. Houk, *J. Am. Chem. Soc.*, 2004, **126**, 9154-9155.
42 P. A. Wender and A. J. Dyckman, *Org. Lett.*, 1999, **1**, 2089-2092.

43 P. A. Wender, A. J. Dyckman, C. O. Husfeld and M. J. C. Scanio, *Org. Lett.*, 2000, **2**, 1609-1611.
44 P. A. Wender, G. G. Gamber, R. D. Hubbard and L. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 2876-2877.
45 Y. Wang and Z.-X. Yu, *Acc. Chem. Res.*, 2015, **48**, 2288-2296.
46 Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 10060-10061.
47 P. A. Wender, F. Glorius, C. O. Husfeld, E. Langkopf and J. A. Love, *J. Am. Chem. Soc.*, 1999, **121**, 5348-5349.
48 Z.-X. Yu, P. H.-Y. Cheong, P. Liu, C. Y. Legault, P. A. Wender and K. N. Houk, *J. Am. Chem. Soc.*, 2008, **130**, 2378-2379.
49 P. A. Wender, M. Fuji, C. O. Husfeld and J. A. Love, *Org. Lett.*, 1999, **1**, 137-139.
50 P. A. Wender and L. Zhang, *Org. Lett.*, 2000, **2**, 2323-2326.
51 P. A. Wender, J. A. Love and T. J. Williams, *Synlett*, 2003, 1295-1298.
52 P. A. Wender, C. M. Barzilay and A. J. Dyckman, *J. Am. Chem. Soc.*, 2001, **123**, 179-180.
53 P. Liu, L. E. Sirois, P. H.-Y. Cheong, Z.-X. Yu, I. V. Hartung, H. Rieck, P. A. Wender and K. N. Houk, *J. Am. Chem. Soc.*, 2010, **132**, 10127-10135.
54 X. Hong, M. C. Stevens, P. Liu, P. A. Wender and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 17273-17283.
55 P. A. Wender, L. O. Haustedt, J. Lim, J. A. Love, T. J. Williams and J.-Y. Yoon, *J. Am. Chem. Soc.*, 2006, **128**, 6302-630
56 P. Liu, P. H.-Y. Cheong, Z.-X. Yu, P. A. Wender and K. N. Houk, *Angew. Chem. Int. Ed.*, 2008, **47**, 3939-3941.
57 P. A. Wender, R. T. Stemmler and L. E. Sirois, *J. Am. Chem. Soc.*, 2010, **132**, 2532-2533.
58 X. Xu, P. Liu, A. Lesser, L. E. Sirois, P. A. Wender and K. N. Houk, *J. Am. Chem. Soc.*, 2012, **134**, 11012-11025.
59 R. Shintani, H. Nakatsu, K. Takatsu and T. Hayashi, *Chem. - Eur. J.*, 2009, **15**, 8692-8694.
60 L. Jiao, M. Lin and Z.-X. Yu, *Chem. Commun.*, 2010, **46**, 1059-1061.
61 Q. Li, G.-J. Jiang, L. Jiao and Z.-X. Yu, *Org. Lett.*, 2010, **12**, 1332-1335.
62 L. Jiao, M. Lin, L.-G. Zhuo and Z.-X. Yu, *Org. Lett.*, 2010, **12**, 2528-2531.
63 S. Bose, J. Yang and Z.-X. Yu, *J. Org. Chem.*, 2016, **81**, 6757-6765.
64 S. I. Lee, S. Y. Park, J. H. Park, I. G. Jung, S. Y. Choi, Y. K. Chung and B. Y. Lee, *J. Org. Chem.*, 2006, **71**, 91-96.
65 M. Lin, F. Li, L. Jiao and Z.-X. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 1690-1693.
66 G.-J. Jiang, X.-F. Fu, Q. Li and Z.-X. Yu, *Org. Lett.*, 2012, **14**, 692-695.
67 C.-H. Liu, Z. Zhuang, S. Bose and Z.-X. Yu, *Tetrahedron*, 2016, **72**, 2752-2755.
68 M. Lin, G.-Y. Kang, Y.-A. Guo and Z.-X. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 398-405
69 B. M. Trost, F. D. Toste and H. Shen, *J. Am. Chem. Soc.*, 2000, **122**, 2379-2380.
70 X. Hong, B. M. Trost and K. N. Houk, *J. Am. Chem. Soc.*, 2013, **135**, 6588-6600.
71 M. Suginome, T. Matsuda, T. Yoshimoto and Y. Ito, *Organometallics*, 2002, **21**, 1537-1539.
72 Y. Sumida, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2008, **10**, 4677-4679.
73 T. Mori, T. Nakamura and M. Kimura, *Org. Lett.*, 2011, **13**, 2266-2269.
74 G. Zuo and J. Louie, *J. Am. Chem. Soc.*, 2005, **127**, 5798-5799.
75 X. Hong, P. Liu and K. N. Houk, *J. Am. Chem. Soc.*, 2013, **135**, 1456-1462.
76 R. Tombe, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2013, **15**, 1791-1793.
77 D. Pursely and B. Plietker, *Synlett*, 2014, **25**, 2316-2318.
78 W.-J. Shi, Y. Liu, P. Butti and A. Togni, *Adv. Synth. Catal.*, 2007, **349**, 1619-1623.
79 B. D. Sherry and A. Fuerstner, *Chem. Commun.*, 2009, 7116-7118.
80 A. P. Dieskau, M. S. Holzwarth and B. Plietker, *J. Am. Chem. Soc.*, 2012, **134**, 5048-5051.
81 C.-H. Lin, D. Pursley, J. E. M. N. Klein, J. Teske, J. A. Allen, F. Rami, A. Koehn and B. Plietker, *Chem. Sci.*, 2015, **6**, 7034-7043.
82 J. Moran, A. G. Smith, R. M. Carris, J. S. Johnson and M. J. Krische, *J. Am. Chem. Soc.*, 2011, **133**, 18618-18621.
83 M.-C. Melcher, H. von Wachenfeldt, A. Sundin and D. Strand, *Chem. - Eur. J.*, 2015, **21**, 531-535.
84 J.-Q. Wu, Z.-P. Qiu, S.-S. Zhang, J.-G. Liu, Y.-X. Lao, L.-Q. Gu, Z.-S. Huang, J. Li and H. Wang, *Chem. Commun.*, 2015, **51**, 77-80.
85 R. Ieki, Y. Kani, S. Tsunoi and I. Shibata, *Chem. - Eur. J.*, 2015, **21**, 6295-6300.
86 V. Ganesh, D. Sureshkumar and S. Chandrasekaran, *Angew. Chem. Int. Ed.*, 2011, **50**, 5878-5881.
87 V. Ganesh, D. Sureshkumar, D. Chanda and S. Chandrasekaran, *Chem. - Eur. J.*, 2012, **18**, 12498-12511,
88 T. Hashimoto, Y. Kawamata and K. Maruoka, *Nat. Chem.*, 2014, **6**, 702-705.