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Recent developments in the reactivity of methylene- and alkylidenecyclopropane derivatives

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Abbreviations: Ac, acetyl; AIBN, 2,2′-azobisisobutyronitrile; Ar, aryl; Atm, atmosphere; BARF, tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; Bn, benzyl; bpy, 2,2′-bipyridine; Bu, butyl; Bz, benzoyl; c, *cyclo*; CAN, ceric ammonium nitrate; cod, cyclooctadiene; Cp, cyclopentadienyl; Cy, cyclohexyl; Dba, (*E*,*E*)-dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; de, diastereomeric excess; DEAD, diethyl azodicarboxylate; DIAD, diisopropyl azodicarboxylate; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; DPE, 1,2-bis(diphenylphosphino)ethane; E, electrophile; ee, enantiomeric excess; Et, ethyl; fod, 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate; Fu, furyl; Hept, heptyl; Hex, hexyl; HMPA, hexamethylphosphoramide; L, ligand; LDA, lithium diisopropylamide; M, metal; MAD, methylaluminum bis(2,6-*tert*-butyl-4-methylphenoxide); Me, methyl; Ms, mesyl; Naph, naphthyl; NBS, *N*-bromosuccinimide; NFSI, *N*-fluorobenzenesulfonimide; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; NMP, *N*-methyl-2-pyrrolidinone; Non, nonyl; Ns, nosyl; Nu, nucleophile; Oct, octyl; Pa, pascal; Pent, pentyl; Ph, phenyl; Piv, pivalate; PMB, *p*-methoxybenzoyl; Pr, propyl; Py, pyridyl; Sc, supercritical; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyldimethylsilyl; TEA, triethylamine; TEBAC, triethylbenzylammonium chloride; Tedicyp, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane; Tf, trifluoromethanesulfonyl; THF, tetrahydrofuran; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; Tol, tolyl; Ts, 4-toluenesulfonyl (tosyl).

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1. Introduction

The importance of strained carbocycles such as three-membered rings has long been recognised in organic chemistry.[1] Indeed, organic chemists have always been fascinated by the cyclopropane subunit,[2] which has played and continues to play a prominent role in organic chemistry. Its strained structure, interesting bonding characteristics and value as an internal mechanistic probe have attracted the attention of the physical organic community. Due to the limited degrees of freedom in the system, these conformationally constrained molecules have very pronounced steric, stereoelectronic and directing effects, which make them versatile probes for the study of regio-, diastereo- and enantioselectivity.[3] Furthermore, a diverse reactivity pattern resulting from the significant strain energy accounts for the use of small carbocycles as convenient models for the investigation of organic and organometallic reaction mechanisms. Among the class of cyclopropanes, methylenecyclopropane and alkylidenecyclopropane derivatives have been well documented as useful synthetic intermediates in organic chemistry over the past few decades. Arguably, the chemistry of these compounds is the most rapidly developing among all small-ring compounds. Indeed, alkylidenecyclopropanes and methylenecyclopropanes are highly interesting compounds. Surprisingly, in spite of their highly strained structure (40 kcal mol^{-1}), they usually exist as stable compounds at room temperature, allowing their use in many synthetic applications with an otherwise unattainable chemical reactivity. Because of this strained nature, associated with a large structural differentiation available, methylene- and alkylidenecyclopropanes show various reactivities and have long been widely used in organic synthesis for their enormous potential. It must be noted that numerous efficient and straightforward syntheses of different types of methylene- and alkylidenecyclopropanes have appeared in the literature.[4] The goal of the present review is to cover the recent advances in the reactivity of methylene- and alkylidenecyclopropane derivatives, focussing on those published since 2003. This area was previously reviewed by Brandi et al. in 2003, focussing on the synthesis of heterocycles starting from alkylidenecyclopropanes,[5] and by Yamamoto et al. in 2002, focussing on the transition metal-catalysed reactions[6] of methylene- and alkylidenecyclopropanes.[7] In a more general context, it must be noted that Rubin et al. reported the transition metal chemistry of cyclopropenes and cyclopropanes, in 2007.[8] This review is subdivided into six sections, according to the different types of reactions, such as ring-opening reactions, cycloaddition reactions, rearrangements, radical reactions, polymerisation reactions and miscellaneous reactions including addition reactions with ring conservation and Heck reactions. It must be noted that the transformations of one methylene- or alkylidenecyclopropane into another through a simple functionalisation of the methylene- or alkylidenecyclopropane moiety have not been included in this review, but have been reported in a very recent review dealing with the synthesis of methylene- and alkylidenecyclopropane derivatives.[4f]

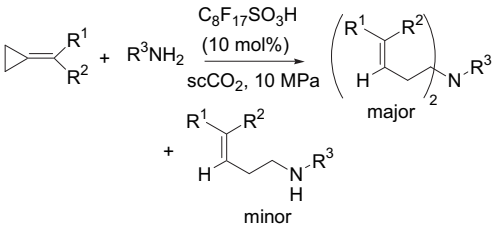
2. Ring-opening reactions

Methylene- and alkylidenecyclopropanes undergo a variety of ring-opening reactions because the relief of ring strain provides a potent thermodynamic driving force. These reactions can be achieved by using transition metal catalysts, Lewis acids and also Brønsted acids. Transition metal-catalysed ring-opening reactions of alkylidenecyclopropanes have been widely explored over the past decades.[5,7] On the contrary, less attention has been paid to the Lewis acid- or Brønsted acid-mediated reactions of alkylidenecyclopropanes.[9] Ring-opening reactions of methylene- and alkylidenecyclopropanes can be completed with various nucleophiles, such as amines, alcohols, water, carboxylic acids, thiols, sulfonamides, metal halides, etc. An attractive, but also troublesome, feature of methylene- and alkylidenecyclopropanes is their diverse reactivities that may lead to the formation of a variety of products through the addition to a C=C double bond and cleavage of proximal or distal bonds of the three-membered ring. Moreover, for the reactions with unsymmetrical alkylidenecyclopropanes, the regiochemistry generally affords different possible products. Indeed, the regioselectivity of the ring-opening reaction is one of the attractive issues in exploring this field of chemistry, and the selectivity is controlled by the selection of the metal reagents or catalysts and/or the structure of the cyclopropane substrates. So far, the crucial factor to determine the mode of ring opening of alkylidenecyclopropanes is not clear.

2.1. Ring-opening reactions by amine derivatives

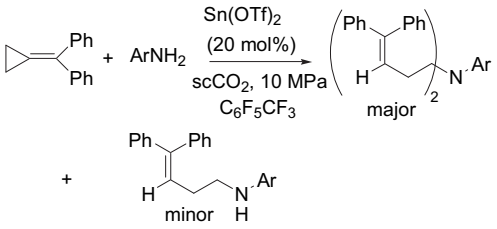
The formation of carbon–nitrogen bonds is one of the most important processes in organic synthesis. In particular, the addition of the nitrogen–hydrogen bond of amines to carbon–carbon multiple bonds (hydroamination) is an ideal and challenging method for this purpose, offering an efficient synthetic route to amines, enamines and imines.[10] In 2003, Shi et al. showed that the ring-opening reaction of alkylidenecyclopropanes with aromatic amines could be performed in an environmentally benign solvent, such as supercritical carbon dioxide at 10 MPa, in the presence of heptadecafluorooctanesulfonic acid as the catalyst, providing an access to the formation of homoallylic amines.[11] Therefore, the reaction proceeded smoothly to give the corresponding dialkylated derivative as the major product along with the corresponding monoalkylated compound, as shown in Scheme 1. The best yields of up to 95% were obtained with aromatic amines bearing an electron-withdrawing group on the benzene ring. Moreover, apart from aromatic amines, this methodology could be applied to sulfonamides, as shown in Scheme 1.

These authors have demonstrated that the ring-opening reaction of diphenylmethylenecyclopropane with aromatic amines in supercritical carbon dioxide could also be catalysed by a Lewis acid, such as $Sn(OTf)_2$, in the presence of an additive, such as perfluorotoluene.[12] As shown in Scheme 2, the reaction led to a mixture of the corresponding mono- and dialkylated amine products in



$R^1 = R^2 = R^3$ = Ph: 42% + 18%
$R^1 = R^2$ = Ph, R^3 = 3,5-$Cl_2C_6H_3$: 95% + 0%
$R^1 = R^2$ = Ph, R^3 = *p*-FC_6H_4: 65% + 21%
$R^1 = R^2$ = Ph, R^3 = *p*-$EtOC_6H_4$: 37% + 20%
$R^1 = R^2$ = *p*-Tol, R^3 = *m*-$CF_3C_6H_4$: 72% + 19%
$R^1 = R^2$ = Ph, R^3 = *p*-Ts: 48% + 41%

Scheme 1. Ring-opening reaction of alkylidenecyclopropanes with aromatic amines and sulfonamide catalysed by $C_8F_{17}SO_3H$ in $scCO_2$.

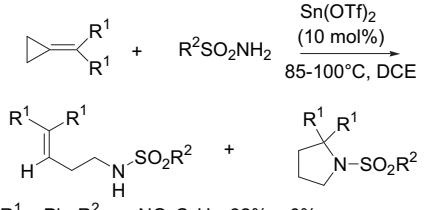


Ar = *m*-FC_6H_4: 61% + 21%
Ar = 2,6-$Cl_2C_6H_3$: 93% + 0%
Ar = 2,6-$Br_2C_6H_3$: 81% + 0%
Ar = *m*-$CF_3C_6H_4$: 56% + 18%

Scheme 2. Ring-opening reaction of diphenylmethylenecyclopropane with aromatic amines catalysed by $Sn(OTf)_2$ in $scCO_2$ with perfluorotoluene.

good yields. In some cases, the dialkylated compound was obtained as the single product in high yield.

On the other hand, the same authors have shown that the reaction of aromatic alkylidenecyclopropanes with sulfonamides catalysed by $Sn(OTf)_2$ in dichloroethane at 85 °C produced preferentially the corresponding *N*-monoalkylated homoallylic sulfonamides in good yields, as shown in Scheme 3.[13] In contrast, the reaction of the less reactive aliphatic alkylidenecyclopropanes with sulfonamides needed a higher temperature (100 °C) to produce the corresponding pyrrolidine compounds derived from the intramolecular nucleophilic attack of the formed corresponding *N*-monoalkylated sulfonamide products on the double bond, which should be a fast reaction process at 100 °C (Scheme 3). In almost all cases of alkylidenecyclopropanes, either aromatic or aliphatic, none of the corresponding *N*,*N*-dialkylated products were formed, even if

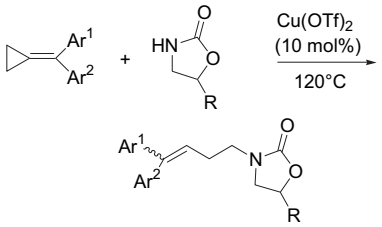


R^1 = Ph, R^2 = *p*-$NO_2C_6H_4$: 62% + 0%
R^1 = Ph, R^2 = *m*-$NO_2C_6H_4$: 54% + 0%
R^1,R^1 = $(CH_2)_5$, R^2 = *p*-Tol: 0% + 46%
R^1 = *n*-Bu, R^2 = *p*-Tol: 0% + 44%
R^1,R^1 = $(CH_2)_2$-CH(Ph)-$(CH_2)_2$, R^2 = *p*-Tol: 0% + 51%

Scheme 3. $Sn(OTf)_2$-catalysed ring-opening reaction of alkylidenecyclopropanes with sulfonamides.

the reaction time was extended, with the exception of aromatic alkylidenecyclopropanes bearing an electron-withdrawing group, such as a fluoro or a chloro atom, which required prolonged reaction times (several days), yielding a mixture of the corresponding *N*-monoalkylated and *N*,*N*-dialkylated homoallylic sulfonamides.

The synthesis of homoallylic oxazolidinones has been of great interest for organic chemists, since the structural framework of homoallylic amines is often found in biologically important natural products and the synthetic intermediates leading to them. In this context, Yamamoto et al. have developed the Cu-catalysed reaction of arylidenecyclopropanes with 2-oxazolidinones, which yielded the corresponding *gem*-aryl disubstituted homoallylic oxazolidinones in good-to-high yields.[14] As shown in Scheme 4, these products were isolated in up to 89% yield when the reaction was performed in the presence of 10 mol % of $Cu(OTf)_2$ without solvent at 120 °C.

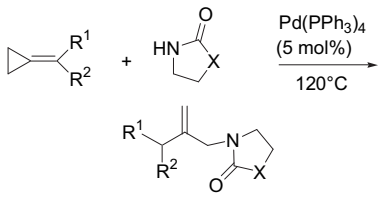


$Ar^1 = Ar^2$ = Ph, R = H: 89%
$Ar^1 = Ar^2$ = *p*-Tol, R = H: 80%
$Ar^1 = Ar^2$ = 2-Naph, R = H: 47%
$Ar^1 = Ar^2$ = *p*-$MeOC_6H_4$, R = H: 58%
Ar^1 = Ph, Ar^2 = 2-Naph, R = H: 63% (*Z*/*E*)
$Ar^1 = Ar^2$ = Ph, R = CH_2Cl: 52%
$Ar^1 = Ar^2$ = Ph, R = Bn: 58%
$Ar^1 = Ar^2$ = R = Ph: 60%

Scheme 4. $Cu(OTf)_2$-catalysed ring-opening reaction of arylidenecyclopropanes with 2-oxazolidinones.

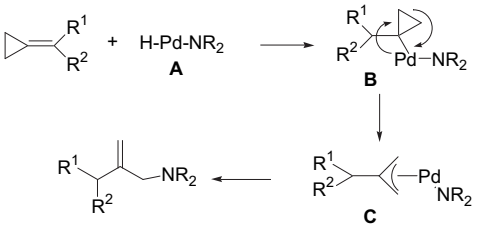
On the other hand, the Pd-catalysed hydroamination of alkylidenecyclopropanes was investigated by Yamamoto et al.[15] In this work, it was demonstrated that cyclic amides reacted with alkylidenecyclopropanes in good-to-excellent yields to provide the corresponding allylamines derived from ring opening of the alkylidenecyclopropanes at the distal position of the cyclopropane ring. The best results, collected in Scheme 5, were obtained by using $Pd(PPh_3)_4$ as the catalyst, which allowed a series of monoalkylated products to be regioselectively produced, starting from lactams, oxazolidinones and ureas. These authors have proposed the mechanism depicted in Scheme 5, which begins with the oxidative addition of a Pd(0) species to the N–H bond of the nitrogen pronucleophile to give a Pd(II) hydride species **A**. The latter reacts with the alkylidenecyclopropane through hydropalladation in which Pd is linked to a C2 carbon, leading to the cyclopropylpalladium **B**. The distal cleavage of **B** affords the π-allylpalladium intermediate **C**, leading to the final product and Pd (0) upon reductive coupling. A similar selectivity in the reactions of diphenylmethylenecyclopropane with sulfonamides was also observed by Shi et al.[16] Indeed, the corresponding ring-opened products were regioselectively formed in the presence of catalytic amounts of $Pd(PPh_3)_4$ and $Pd(OAc)_2$ in high yields (60–91%).

The scope of this methodology could be extended to the intramolecular hydroamination of alkylidenecyclopropanes, providing an efficient route to tetrahydroquinolines.[15] As shown in Scheme 6, upon treatment with $Pd(PPh_3)_4$ combined with P(O)*n*-Bu_3, a series of aniline-tethered alkylidenecyclopropanes underwent a facile and regioselective cyclisation to provide the corresponding six-membered exomethylene nitrogen heterocycles in high yields. In addition, 1,2-dimethylindolizine could be synthesised in 57%

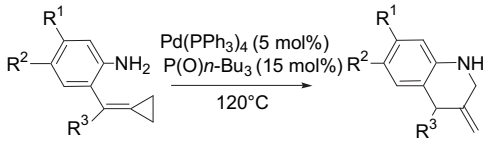


R^1 = R^2 = Ph, X = CH_2: 91%
R^1 = *n*-Oct, R^2 = H, X = CH_2: 82%
R^1 = *n*-Hept, R^2 = H, X = CH_2: 68%
R^1 = R^2 = *n*-Hex, X = CH_2: 64%
R^1 = $BnNH(CH_2)_2$, R^2 = H, X = CH_2: 72%
R^1 = R^2 = Ph, X = O: 96%
R^1 = R^2 = Ph, X = $CHCH_2Cl$: 79%
R^1 = R^2 = Ph, X = NH: 84%

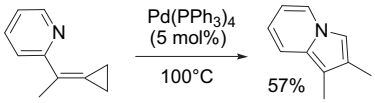
proposed mechanism:



Scheme 5. Pd-catalysed ring-opening reaction of alkylidenecyclopropanes with cyclic amides.



R^1 = R^2 = H, R^3 = Me: 74%
R^1 = H, R^2 = Cl, R^3 = Ph: 71%
R^1 = Me, R^2 = H, R^3 = Ph: 86%
R^1 = R^2 = H, R^3 = Ph: 86%



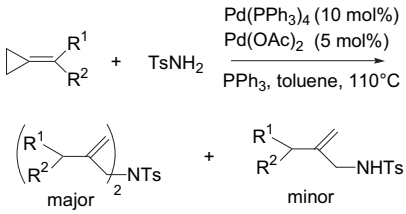
Scheme 6. Intramolecular Pd-catalysed hydroaminations of alkylidenecyclopropanes.

yield by the application of similar conditions to the corresponding alkylidenecyclopropane (Scheme 6).

In 2003, Shi et al. reported the ring opening of alkylidenecyclopropanes by sulfonamides unprecedently cocatalysed by Pd(0) and Pd(II) catalysts to give high yields of the corresponding ring-opened products (Scheme 7).[16] In almost all cases of substrates, the *N*,*N*-dialkylated compound was obtained as the major product.

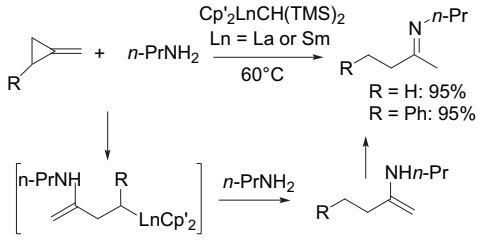
On the other hand, Marks et al. have demonstrated that the hydroamination of methylenecyclopropanes could be successfully catalysed by organolanthanides.[17] The organolanthanide complex, $Cp'_2LnCH(TMS)_2$ (Ln=La or Sm), mediated the intermolecular hydroamination of a methylenecyclopropane to the corresponding enamine, which underwent a subsequent tautomerisation to the more stable imine. As shown in Scheme 8, this process gave excellent regioselectivities in the case of *n*-propylamine hydroamination.

In the same area, Eisen et al. have found that a novel octahedral titanium catalyst, such as $Ti(Ph_2PNpy)_2(NEt_2)_2$, was an efficient catalyst for the hydroamination of methylene- and



R^1 = Ph, R^2 = *o*-ClC_6H_4: 71% + 27%
R^1 = R^2 = *p*-$MeOC_6H_4$: 100% + 0%
R^1 = Me, R^2 = *n*-Hept: 100% + 0%
R^1,R^2 = $(CH_2)_5$: 85% + 0%
R^1,R^2 = $(CH_2)_2CH(Ph)(CH_2)_2$: 62% + 14%

Scheme 7. Pd(II)- and Pd(0)-cocatalysed ring-opening reaction of alkylidenecyclopropanes with sulfonamide.

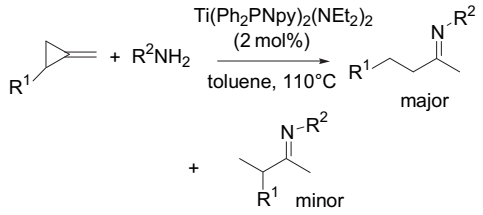


Scheme 8. Ln-catalysed ring-opening reaction of methylenecyclopropanes with amine.

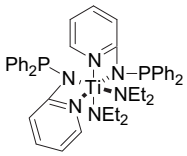
alkylidenecyclopropanes with either aromatic or aliphatic amines.[18] In almost all of the substrates, the corresponding linear imine was obtained as a single product in high yield, as shown in Scheme 9. The authors have proposed that this reaction was catalysed by the imidotitanium species **D** produced upon reaction of the octahedral titanium complex with a primary amine (Scheme 9). The 1,2-insertion of **D** into the double bond of the methylene- or alkylidenecyclopropane affords the azatitanacyclobutane complex **E**, which undergoes a skeletal rearrangement via two different pathways to produce five-membered cyclic complexes **F** and **H**. The rearrangement involving the cleavage of a more substituted proximal bond of the cyclopropane (pathway A) in **E** leads to the intermediate **F**, in which titanium is attached to a secondary benzylic carbon. Alternatively, the pathway B presumes the cleavage of a less substituted proximal bond and formation of the intermediate **H** with titanium attached to a primary carbon. The protolytic cleavage of the Ti–C bond in complexes **F** and **H** with another molecule of amine leads to the bis-amido complexes **G** and **I**, respectively. The latter, upon 1,2-elimination, regenerates the catalytically active imidotitanium species **D** and, after tautomerisation, produces the final imines. Overall, the formation of a more stable species **F** versus **H** makes pathway A favourable, leading to the linear imine as the major product.

In order to study the role of the metal centre in the methylene- or alkylidenecyclopropane hydroamination reactions, these authors have tested how replacement of the titanium metal centre with zirconium could affect the activity and regioselectivity of the catalysts. The most important finding, when using a zirconium complex such as $Zr(NMe_2)_4$, was that the main products obtained for those reactions were the branched imines, in contrast to the results obtained when the titanium analogue was employed.[18b] The best results are collected in Scheme 10.

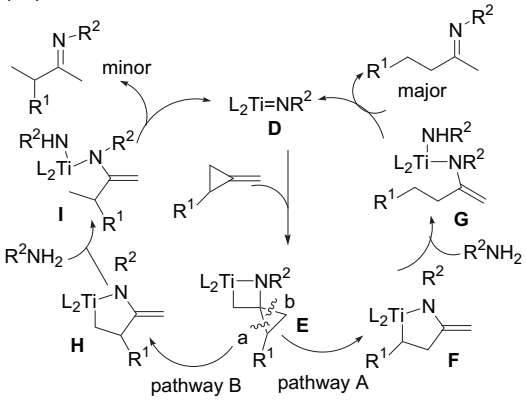
In 2006, Shi et al. reported a domino version of gold(I)-catalysed hydroamination of alkylidenecyclopropanes, allowing a facile synthetic route to various pyrrolidine derivatives to be achieved.[19] Therefore, in the presence of catalytic amounts of $Au(PPh_3)Cl$ and AgOTf, alkylidenecyclopropanes reacted with sulfonamides through a domino ring-opening, ring-closing hydroamination in good yields, as shown in Scheme 11.



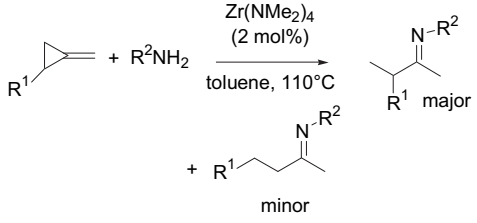
R^1 = Ph, R^2 = Et: 95% + 0%
R^1 = R^2 = Ph: 83% + 10%
R^1 = Ph, R^2 = *n*-Bu: 90% + 0%
R^1 = Ph, R^2 = *i*-Pr: 63% + 8%
R^1 = Ph, R^2 = 2,6-(*i*-Pr)$_2$C$_6$H$_3$: 97% + 0%
R^1 = H, R^2 = Ph: 90% + 0%
R^1 = H, R^2 = Et: 90% + 0%
R^1 = H, R^2 = *n*-Bu: 56% + 0%
R^1 = H, R^2 = *i*-Pr: 76% + 0%



proposed mechanism:



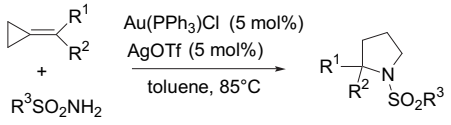
Scheme 9. Ti-catalysed ring-opening reaction of methylene- and alkylidenecyclopropanes with amines.



R^1 = H, R^2 = 2,6-(Me)$_2$C$_6$H$_3$: 91% + 0%
R^1 = H, R^2 = 2,6-(*i*-Pr)$_2$C$_6$H$_3$: 92% + 0%
R^1 = H, R^2 = 2,4,6-(Me)$_3$C$_6$H$_2$: 89% + 0%
R^1 = Ph, R^2 = 2,6-(Me)$_2$C$_6$H$_3$: 83% + 9%
R^1 = Ph, R^2 = 2,6-(*i*-Pr)$_2$C$_6$H$_3$: 71% + 29%
R^1 = Ph, R^2 = 2,4,6-(Me)$_3$C$_6$H$_2$: 82% + 7%

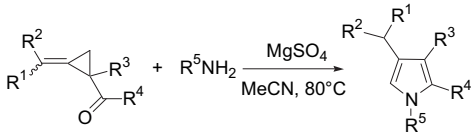
Scheme 10. Zr-catalysed ring-opening reaction of methylene- and alkylidenecyclopropanes with amines.

Another domino reaction based on the ring opening of alkylidenecyclopropanes with amines was reported by Ma et al., in 2006.[20] This work dealt with an efficient approach to 2,3,4-trisubstituted pyrroles via the intermolecular cyclisation of alkylidenecyclopropyl ketones with amines through distal cleavage of the carbon–carbon bond of the three-membered ring. Good-to-high yields were obtained when the reactions were performed in the presence of an additive, such as $MgSO_4$, which would be able to remove the in situ-formed water (Scheme 12). A rationale for this



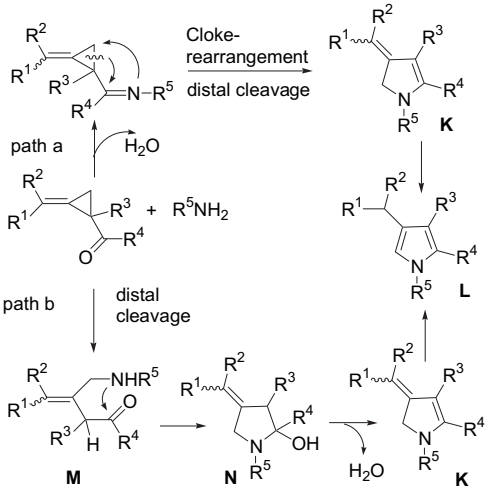
R^1 = *o*-Tol, R^2 = H, R^3 = *p*-Tol: 68%
R^1 = *m*-Tol, R^2 = H, R^3 = *p*-Tol: 76%
R^1 = R^3 = *p*-Tol, R^2 = H: 70%
R^1 = Ph, R^2 = Me, R^3 = *p*-Tol: 68%
R^1 = R^3 = *p*-Tol, R^2 = Me: 72%
R^1 = *p*-EtOC$_6$H$_4$, R^2 = Me, R^3 = *p*-Tol: 71%
R^1 = R^2 = *n*-Bu, R^3 = *p*-Tol: 70%
R^1 = *n*-Hept, R^2 = Me, R^3 = *p*-Tol: 64%
R^1 = R^3 = Ph, R^2 = H: 79%
R^1 = Ph, R^2 = H, R^3 = *m*-NO$_2$C$_6$H$_4$: 69%
R^1 = Ph, R^2 = H, R^3 = *p*-NO$_2$C$_6$H$_4$: 74%

Scheme 11. Au-catalysed domino ring-opening, ring-closing hydroamination of alkylidenecyclopropanes with sulfonamides.



R^1 = *n*-Hept, R^2 = H, R^3 = CO_2Et, R^4 = Me, R^5 = Bn: 78%
R^1 = *n*-Bu, R^2 = H, R^3 = CO_2Et, R^4 = Me, R^5 = Bn: 78%
R^1 = R^5 = Bn, R^2 = H, R^3 = CO_2Et, R^4 = Me: 75%
R^1 = *n*-Hept, R^2 = H, R^3 = SO_2Ph, R^4 = Me, R^5 = Bn: 75%
R^1 = *n*-Bu, R^2 = H, R^3 = SO_2Ph, R^4 = Me, R^5 = Bn: 82%
R^1 = *n*-Hept, R^2 = H, R^3 = CO_2Et, R^4 = Me
R^5 = *p*-MeOC$_6$H$_4$CH$_2$: 86%
R^1 = Bn, R^2 = H, R^3 = CO_2Et, R^4 = Me
R^5 = *p*-MeOC$_6$H$_4$CH$_2$: 77%
R^1 = *n*-Hept, R^2 = H, R^3 = Ac, R^4 = Me, R^5 = Bn: 64%

proposed mechanism:



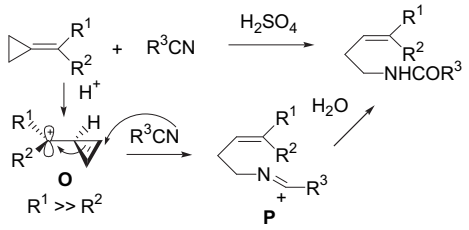
Scheme 12. Ring-opening reaction of alkylidenecyclopropyl ketones with amines.

reaction is depicted in the scheme, starting from the intermolecular reaction of the alkylidenecyclopropyl ketone with the amine to afford the cyclopropylimine intermediate **J** with the release of one molecule of H_2O (path a). A Cloke-type rearrangement of the intermediate **J** would easily lead to ring expansion via the subsequent nucleophilic attack of the nitrogen atom at the less sterically hindered carbon atom in the cyclopropane ring, which would cause the distal cleavage to form the intermediate **K**. The subsequent

aromatisation would afford the final pyrrole **L**. Another possible route starts from the nucleophilic attack of the amine at the less sterically hindered carbon atom of the three-membered ring to afford the intermediate **M** via distal cleavage (path b). The nucleophilic nitrogen would then attack the carbonyl group, leading to a 3-alkylidene-5-hydroxy tetrahydropyrrole intermediate **N**. The subsequent dehydration and aromatisation of **N** would generate the final pyrrole **L** together with H_2O.

In addition, Xiao et al. have reported the ring-opening reactions of a difluoro(methylene)cyclopropane with primary or secondary alkylamines, occurring with proximal bond cleavage to give the corresponding monofluorinated butadiene derivative, *N*-alkyl-3-fluoro-4-methyl-1-tosylpenta-1,3-dien-2-amine, as the sole product of the reaction in low-to-good yield (0–83%).[21]

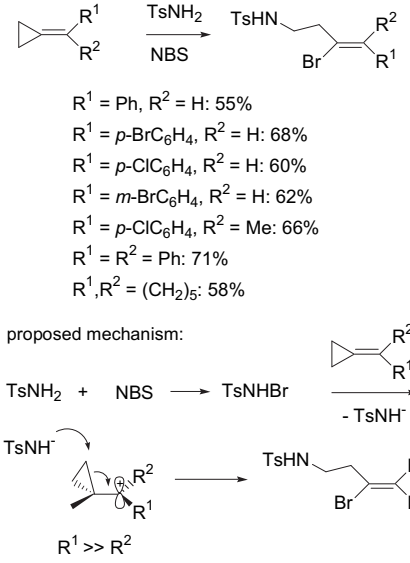
In 2004, Huang et al. reported the first one-pot, ring-opening reaction of alkylidenecyclopropanes with nitriles performed under acidic conditions in which *N*-[(*E*)-homocinnamyl]amides were stereoselectively prepared in moderate yields (Scheme 13).[22] A plausible mechanism for this reaction promoted by H_2SO_4 is depicted in Scheme 13. Firstly, the regioselective protonation with H^+ at the C2 position of the double bond produces a cyclopropylcarbinyl cation **O**, since the protonation at the C1 position would lead to a less stable cyclopropyl cation. Ring opening of the cyclopropyl group and concomitant bond migration would then give intermediate **P** stereoselectively, which would produce the final homocinnamyl amide after hydrolysis. In contrast, Shi et al. have obtained very different results for the TfOH-mediated reactions of 2-(arylmethylene)cyclopropylcarbinols with acetonitrile, since the corresponding ring-enlarged *N*-(3-arylmethylidenecyclobutyl)acetamides were produced in moderate-to-high yields (33–76%) under mild conditions.[23]



$R^1 = R^2 = Ph$, $R^3 = Me$: 55%
$R^1 = Ph$, $R^2 = H$, $R^3 = Me$: 51%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = H$, $R^3 = Me$: 48%
$R^1 = R^2 = Ph$, $R^3 = Bn$: 60%
$R^1 = R^2 = Ph$, $R^3 = n\text{-}Pr$: 49%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = H$, $R^3 = n\text{-}Pr$: 53%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = H$, $R^3 = n\text{-}Pr$: 50%

Scheme 13. Ring-opening reaction of alkylidenecyclopropanes with nitriles.

Even if a number of hydroaminations of alkylidenecyclopropanes have been successfully developed under various conditions, much fewer studies have been dedicated to the aminohalogenation of these compounds. The first example, described by Huang et al., dealt with the aminobromination of alkylidenecyclopropanes performed in the presence of *p*-toluenesulfonamide and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources, respectively.[24] This process allowed a simple access to γ-bromohomoallylic sulfonamides, which were obtained in moderate yields, as shown in Scheme 14. The authors have proposed a mechanism, depicted in Scheme 14, which begins with the formation of TsNHBr by the reaction between $TsNH_2$ and NBS. The interaction between TsNHBr and the alkylidenecyclopropane leads to a cyclopropylcarbinyl cation, which is stabilised by the cyclopropyl and aryl rings. In this intermediate, if R^1 is sterically bulkier than R^2, the smallest group Br is located most probably on the R^1 side and the cyclopropyl

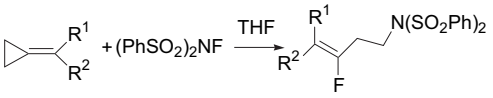


$R^1 = Ph$, $R^2 = H$: 55%
$R^1 = p\text{-}BrC_6H_4$, $R^2 = H$: 68%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = H$: 60%
$R^1 = m\text{-}BrC_6H_4$, $R^2 = H$: 62%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Me$: 66%
$R^1 = R^2 = Ph$: 71%
$R^1, R^2 = (CH_2)_5$: 58%

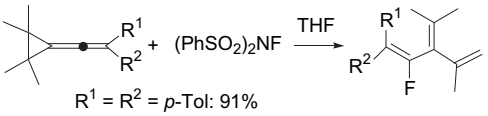
Scheme 14. Aminobromination of alkylidenecyclopropanes.

group is on the R^2 side. Subsequently, this cation is attacked by the corresponding anion $TsNH^-$ to give the final product.

The specific properties of fluorine as a substituent in organic compounds have resulted in a steadily growing interest in organofluorine chemistry, which has proved to be a research area with numerous applications in agrochemistry and pharmaceutical chemistry.[25] In this context, Shi et al. have recently disclosed the ring-opening reaction of alkylidenecyclopropanes with *N*-fluorodibenzenesulfonimide (NFSI) to give the corresponding fluorinated derivatives in good-to-excellent yields, as shown in Scheme 15.[26] For unsymmetrical alkylidenecyclopropanes, the corresponding products were obtained as mixtures of *E*- and *Z*-isomers. The same conditions were applied to vinylidenecyclopropanes, which yielded the corresponding fluorinated derivatives in high yields (76–95%), as shown in Scheme 15.



$R^1 = R^2 = p\text{-}Tol$: 86%
$R^1 = R^2 = p\text{-}MeOC_6H_4$: 91%
$R^1 = R^2 = p\text{-}ClC_6H_4$: 62%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$: 78% (13:7)
$R^1 = 3,4\text{-}(MeO)_2C_6H_3$, $R^2 = H$: 90% (>99:1)
$R^1 = p\text{-}Tol$, $R^2 = H$: 84% (4:1)

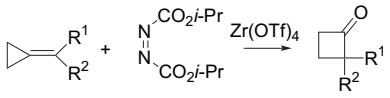


$R^1 = R^2 = p\text{-}Tol$: 91%
$R^1 = R^2 = p\text{-}MeOC_6H_4$: 95%
$R^1 = R^2 = p\text{-}ClC_6H_4$: 76%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$: 79% (17:3)
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = Ph$: 94% (1:1)

Scheme 15. Aminofluorinations of alkylidene- and vinylidenecyclopropanes.

Another example of the reactivity of alkylidenecyclopropanes with amine derivatives was reported by Shi et al., in 2004.[27] Indeed, these authors showed that alkylidenecyclopropanes with diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD) in acetonitrile under mild conditions in the presence of $Zr(OTf)_4$

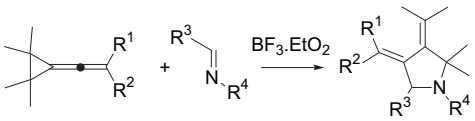
underwent ring-expansion reactions to give the corresponding cyclobutanones in good-to-high yields (57–99%). The best results are collected in Scheme 16.



R^1 = *p*-$MeOC_6H_4$, R^2 = Ph: 99%
R^1 = R^2 = *p*-$MeOC_6H_4$: 53%
R^1 = R^2 = *p*-ClC_6H_4: 91%
R^1 = R^2 =*p*-Tol: 92%
R^1 = R^2 = *p*-FC_6H_4: 78%
R^1 = 3,4-$(OCH_2CH_2O)C_6H_3$, R^2 = Me: 91%

Scheme 16. Zr-catalysed ring expansion of alkylidenecyclopropanes with DIAD.

Finally, Shi et al.[28] and Kostikov et al.[29] have independently studied the reactivity of arylvinylidenecyclopropanes with aromatic imines in the presence of $BF_3{\cdot}Et_2O$. A number of pyrrolidine derivatives could be prepared selectively in moderate-to-good yields on the basis of these reactions, which were highly dependent on the electronic nature of the aryl substituents of both the arylimine and the arylvinylidenecyclopropane. As an example, the pyrrolidine product was formed exclusively when the *N*-aryl substituent of the arylimine was an electron-poor aromatic group, while electron-rich aromatic groups had to be avoided as substituents of the vinylidene. The best results are collected in Scheme 17.



R^1 = R^2 = R^3 = Ph, R^4 = Ts: 92%
R^1 = R^2 = Ph, R^3 = *p*-BrC_6H_4, R^4 = Ts: 98%
R^1 = R^2 = *p*-ClC_6H_4, R^3 = CO_2Et, R^4 = *p*-BrC_6H_4: 85%
R^1 = Ph, R^2 = *p*-ClC_6H_4, R^3 = CO_2Et, R^4 = *p*-BrC_6H_4: 86%
R^1 = R^2 = Ph, R^3 = CO_2Et, R^4 = *p*-BrC_6H_4: 89%
R^1 = R^2 = Ph, R^3 = CO_2Et, R^4 = *o*-$CF_3C_6H_4$: 99%
R^1 = R^2 = Ph, R^3 = CO_2Et, R^4 = *p*-ClC_6H_4: 81%

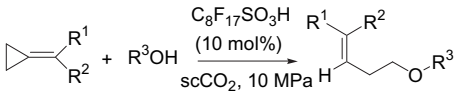
Scheme 17. $BF_3{\cdot}Et_2O$-catalysed reaction of arylvinylidenecyclopropanes with arylimines.

2.2. Ring-opening reactions by oxygen derivatives

In recent years, several groups have developed ring-opening reactions of alkylidenecyclopropanes with alcohols and their derivatives as the nucleophiles. As an example, Shi et al. have shown that these reactions could be catalysed by heptadecafluorooctanesulfonic acid in an environmentally benign solvent such as supercritical carbon dioxide at 10 MPa.[11] In all cases of alkylidenecyclopropanes and alcohols, the corresponding homoallylic ethers were isolated in almost quantitative yields, as shown in Scheme 18.

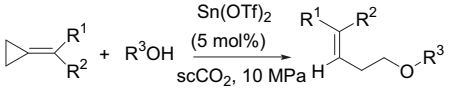
These authors have demonstrated that the ring-opening reaction of alkylidenecyclopropanes with alcohols in supercritical carbon dioxide could also be catalysed by a Lewis acid, such as Sn $(OTf)_2$, to provide the corresponding homoallylic ethers in excellent yields (Scheme 19).[12] In contrast with the reactions with amines as nucleophiles performed under similar conditions, these reactions with alcohols proceeded very well without any perfluorocarbon additive, because the alcohol itself could modify $scCO_2$ fluid to solvate the Lewis acid.

In 2003, Yamamoto et al. reported the ring-opening reaction of a series of arylidenecyclopropanes with water performed in



R^1 = R^2 = Ph, R^3 = Et: 95%
R^1 = R^2 = *p*-ClC_6H_4, R^3 = Et: 93%
R^1 = R^2 = *p*-Tol, R^3 = Et: 98%
R^1 = *n*-Hept, R^2 = Me, R^3 = Et: 97%
R^1 = R^2 = Ph, R^3 = *n*-Bu: 92%
R^1 = R^2 = Ph, R^3 = *i*-Pr: 93%

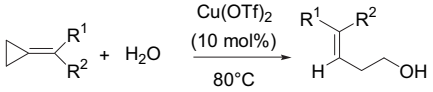
Scheme 18. Ring-opening reaction of alkylidenecyclopropanes with alcohols catalysed by $C_8F_{17}SO_3H$ in $scCO_2$.



R^1 = R^2 = Ph, R^3 = Et: 95%
R^1 = R^2 = Ph, R^3 = *i*-Pr: 99%
R^1 = R^2 = Ph, R^3 = *i*-Bu: 93%
R^1 = R^2 = *p*-$MeOC_6H_4$, R^3 = Et: 96%
R^1 = *o*-ClC_6H_4, R^2 = Ph, R^3 = Et: 90% (*E*/*Z* = 5.6:1)
R^1 = Me, R^2 = *n*-Hept, R^3 = Et: 96% (*E*/*Z* = 3.2:1)

Scheme 19. Ring-opening reaction of alkylidenecyclopropanes with alcohols catalysed by $Sn(OTf)_2$ in $scCO_2$.

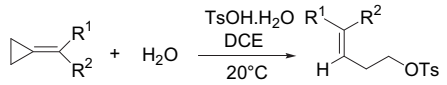
the presence of a catalytic amount of $Cu(OTf)_2$.[30] As shown in Scheme 20, the corresponding *gem*-aryl disubstituted homoallylic alcohols were produced in good-to-excellent yields at 80 °C.



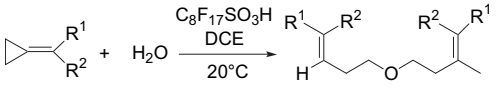
R^1 = R^2 = Ph: 86%
R^1 = R^2 = *p*-Tol: 87%
R^1 = *p*-Tol, R^2 = Ph: 81%
R^1 = 2-Naph, R^2 = Ph: 85%
R^1 = R^2 = *p*-$MeOC_6H_4$: 92%
R^1 = Ph, R^2 = *p*-ClC_6H_4: 72%

Scheme 20. Cu-catalysed ring-opening reaction of arylidenecyclopropanes with water.

In the same area, excellent results were also reported by Shi et al. by performing the ring-opening reaction of alkylidenecyclopropanes with water in the presence of TsOH as the catalyst (Scheme 21).[31] On the other hand, when the reaction was carried out in the presence of heptadecafluorooctane-1-sulfonic acid as the catalyst, the ring opening of the alkylidenecyclopropanes by water was followed by etherification, which yielded the corresponding homoallylic ethers in moderate-to-high yields (Scheme 21).[31] This difference of reactivity was explained by the authors by the dramatic effect of the anion of the employed Brønsted acid on the ring-opening mode of the alkylidenecyclopropane. Therefore, the cyclopropyl ring of the alkylidenecyclopropane could be opened by water when the corresponding anion was a weak nucleophile, such as heptadecafluorooctane-1-sulfonic acid as the Brønsted acid mediator, providing the corresponding homoallylic alcohol, which subsequently ring opened another equivalent of alkylidenecyclopropane to give the final corresponding homoallylic ether. On the other hand, the cyclopropyl ring of the alkylidenecyclopropane could also be opened by the corresponding anion of a strong nucleophile, such as TsOH as the Brønsted acid mediator, to furnish the final homoallylic tosylate.



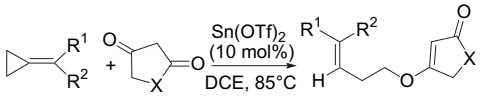
$R^1 = R^2$ = Ph: 98%
$R^1 = R^2 = p$-$MeOC_6H_4$: 96%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph: 99% (*E*/*Z* = 1:1)
$R^1 = p$-$MeOC_6H_4$, $R^2 = p$-Tol: 77%
$R^1 = o$-ClC_6H_4, R^2 = Ph: 93% (*E*/*Z* = 7.8:1)
$R^1 = R^2 = p$-FC_6H_4: 96%
$R^1 = p$-$EtOC_6H_4$, R^2 = Me: 97% (*E*/*Z* = 2.5:1)



$R^1 = R^2 = p$-$MeOC_6H_4$: 52%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph: 60%
$R^1 = R^2 = p$-Tol: 56%
$R^1 = o$-ClC_6H_4, R^2 = Ph: 63%
$R^1 = R^2 = p$-FC_6H_4: 94%

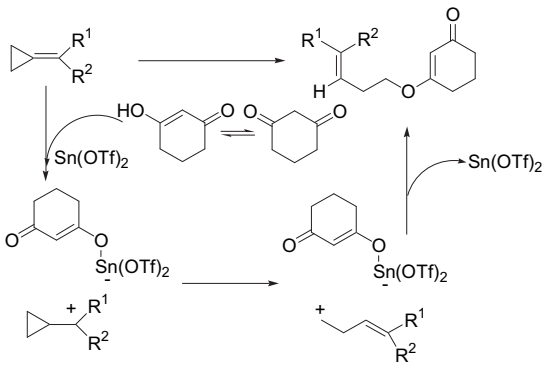
Scheme 21. Brønsted acid-catalysed ring-opening reactions of alkylidenecyclopropanes with water.

An interesting ring-opening reaction of alkylidenecyclopropanes with 1,3-cyclodiones, reacting as their isomerised corresponding enols, was reported by Shi et al., in 2007.[32] As shown in Scheme 22, this novel process mediated by $Sn(OTf)_2$ upon heating at 85 °C allowed the corresponding homoallylic alcohol derivatives to be formed in good-to-high yields. A plausible mechanism involving an ionic reaction pathway is depicted in Scheme 22. The enol derived from the 1,3-cyclodione first protonates the double bond of the alkylidenecyclopropane in the presence of the Lewis



$R^1 = R^2$ = Ph, X = $(CH_2)_2$: 80%
$R^1 = R^2 = p$-ClC_6H_4, X = $(CH_2)_2$: 62%
$R^1 = R^2 = p$-$MeOC_6H_4$, X = $(CH_2)_2$: 93%
$R^1 = R^2 = p$-FC_6H_4, X = $(CH_2)_2$: 80%
$R^1 = R^2$ = Ph, X = CH_2: 87%
$R^1 = R^2 = p$-$MeOC_6H_4$, X = CH_2: 93%
$R^1 = R^2$ = Ph, X = $CH_2C(Me)_2$: 95%
$R^1 = R^2 = p$-$MeOC_6H_4$, X = $CH_2C(Me)_2$: 96%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph, X = $CH_2C(Me)_2$: 82%

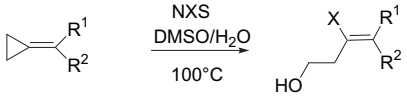
plausible mechanism:



Scheme 22. $Sn(OTf)_2$-catalysed ring-opening reaction of alkylidenecyclopropanes with 1,3-cyclodiones.

acid to give the corresponding zwitterionic intermediate, which immediately rearranges to another zwitterionic intermediate. The subsequent nucleophilic attack affords the final product.

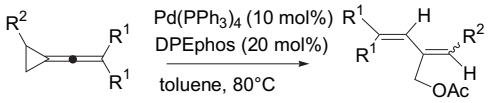
In 2005, Huang et al. developed the synthesis of 3-butenyl ethyl phosphites on the basis of the ring opening of a series of alkylidenecyclopropanes with diethyl phosphite in the presence of water with moderate yields (44–63%).[33] In another context, the same authors have developed the iodohydroxylation of alkylidenecyclopropanes performed in the presence of iodine in aqueous DMSO.[34] A series of iodine-substituted allylic alcohols could be isolated in high yields of up to 95% through this novel process. In order to enlarge this application and overcome some of its inherent limitations, such as inconvenience in use and environmental toxicity, these authors have explored the use of *N*-halosuccinimides (NXS) as more convenient, mild, and variable sources of electrophilic halogen.[35] As shown in Scheme 23, a variety of 3-halo-but-3-en-1-ol derivatives could be obtained in good-to-high yields by treating alkylidenecyclopropanes with various *N*-halosuccinimides as the halogen sources in aqueous DMSO at 100 °C.



$R^1 = R^2$ = Ph, X = Br: 93%
$R^1 = R^2 = p$-ClC_6H_4, X = Br: 75%
$R^1 = R^2 = p$-FC_6H_4, X = Br: 65%
$R^1 = R^2 = p$-Tol, X = Br: 72%
$R^1 = R^2 = p$-*i*-$BuOC_6H_4$, X = Br: 89%
$R^1 = R^2 = p$-*i*-$PrOC_6H_4$, X = Br: 94%
$R^1 = R^2 = p$-ClC_6H_4, X = I: 68%
$R^1 = R^2 = p$-*i*-$BuOC_6H_4$, X = I: 85%

Scheme 23. Halohydroxylation of alkylidenecyclopropanes.

Finally, the first example of palladium(0)-catalysed ring-opening reactions of vinylidenecyclopropanes with acetic acid was reported by Shi et al., in 2006.[36] In this process, performed at 80 °C in toluene in the presence of $Pd(PPh_3)_4$ combined with DPEphos ligand, the corresponding acetylated dienes were formed as mixtures of *E*- and *Z*-isomers in moderate-to-good yields (36–78%), as shown in Scheme 24.



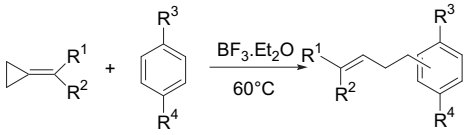
R^1 = Ph, $R^2 = p$-Tol: 67% (8:1)
R^1 = Ph, $R^2 = p$-ClC_6H_4: 67% (7:1)
R^1 = Ph, $R^2 = p$-$MeOC_6H_4$: 78% (19:1)
$R^1 = p$-Tol, R^2 = Ph: 75% (8:1)
$R^1 = p$-$MeOC_6H$, R^2 = Ph: 70% (14:1)

Scheme 24. Pd-catalysed reaction of vinylidenecyclopropanes with acetic acid.

2.3. Ring-opening reactions through alkylation or acylation

In 2003, Shi et al. reported the Friedel–Crafts reaction of alkylidenecyclopropanes with arenes catalysed by $BF_3 \cdot Et_2O$.[37] This novel process could be applied to a wide range of substrates with good-to-excellent yields, as shown in Scheme 25. When unsymmetrical alkylidenecyclopropanes were employed, the Friedel–Crafts products were obtained as mixtures of *E*- and *Z*-isomers along with *ortho*/*para*-isomers.

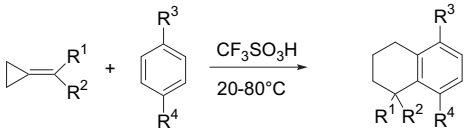
These authors have demonstrated, however, that the use of triflic acid as the catalyst combined with a prolonged reaction time



$R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = OMe$: 100% *o:p* = 1:1
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$, $R^3 = H$, $R^4 = Me$: 67%
o:p = 2:1 *E/Z* = 1:1
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$, $R^3 = R^4 = Me$: 73% *E/Z* = 1:1
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$, $R^3 = H$, $R^4 = OMe$: 93%
o:p = 1.3:1 *E/Z* = 1:1
$R^1 = R^2 = p\text{-}ClC_6H_4$, $R^3 = R^4 = Me$: 88%
$R^1 = R^2 = p\text{-}ClC_6H_4$, $R^2 = Ph$, $R^3 = H$, $R^4 = OMe$: 90% *o:p* = 1:1
$R^1 = R^2 = p\text{-}Tol$, $R^2 = Ph$, $R^3 = H$, $R^4 = OMe$: 91% *o:p* = 1:0.9

Scheme 25. $BF_3{\cdot}Et_2O$-catalysed Friedel–Crafts reaction of alkylidenecyclopropanes with arenes.

modified the outcome of the reaction between alkylidenecyclopropanes and arenes.[38] Indeed, in these conditions, a double Friedel–Crafts reaction occurred, providing the corresponding naphthalene derivatives in moderate-to-good yields, as shown in Scheme 26.



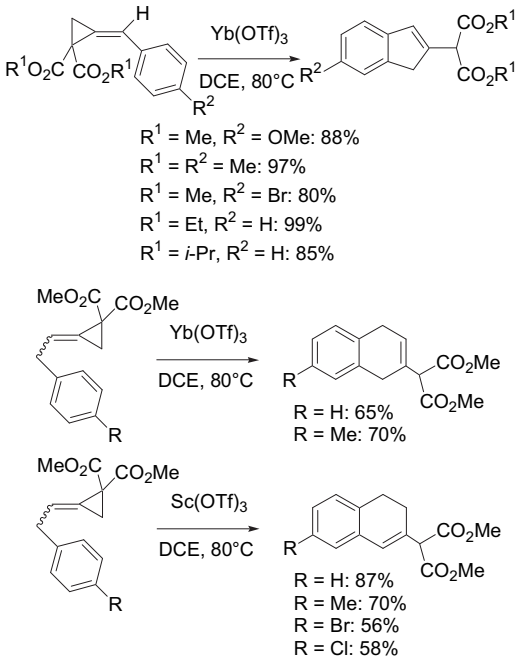
$R^1 = R^2 = Ph$, $R^3 = R^4 = H$: 70%
$R^1 = R^2 = p\text{-}ClC_6H_4$, $R^3 = R^4 = H$: 81%
$R^1 = R^2 = Ph$, $R^3 = R^4 = Me$: 81%
$R^1 = R^2 = p\text{-}FC_6H_4$, $R^3 = R^4 = Me$: 88%
$R^1 = R^2 = p\text{-}ClC_6H_4$, $R^3 = R^4 = Me$: 81%
$R^1 = p\text{-}ClC_6H_4$, $R^2 = Ph$, $R^3 = R^4 = Me$: 80%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = Ph$, $R^3 = R^4 = Me$: 50%

Scheme 26. Double Friedel–Crafts reaction of alkylidenecyclopropanes with arenes.

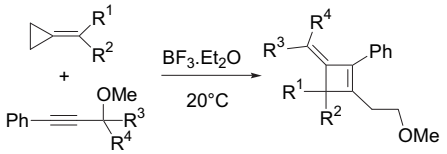
In addition, Wang et al. have developed the first Friedel–Crafts reaction initiated by the direct generation of a carbocation at the C3 position of an alkylidenecyclopropane-1,1-diester through distal bond cleavage.[39] This novel synthetic strategy allowed indene and hydronaphthalene derivatives to be prepared in moderate-to-excellent yields under mild conditions. Therefore, upon treatment with a catalytic amount of $Yb(OTf)_3$, a variety of C4-phenyl-substituted methylenecyclopropane 1,1-diesters provided the corresponding indene derivatives in high yields (Scheme 27), while C4-benzyl-substituted methyleneyclopropane 1,1-diesters led in the same conditions to the corresponding 1,4-dihydronaphthalenes in moderate yields (Scheme 27). It was noted that the use of $Sc(OTf)_3$ as catalyst instead of $Yb(OTf)_3$ led to the formation of the corresponding 1,2-dihydronaphthalenes in comparable yields (Scheme 27).

In 2007, an interesting procedure was reported by Shi et al. in which disubstituted arylidenecyclopropanes reacted with 3-methoxy-1,3,3-triarylprop-1-ynes in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ to provide the corresponding functionalised methylenecyclobutene derivatives bearing an allenic moiety in moderate-to-good yields (Scheme 28).[40]

In addition, Shi et al. have disclosed the reactions of alkylidenecyclopropanes with aldehydes, imines[41] and acetals to give the



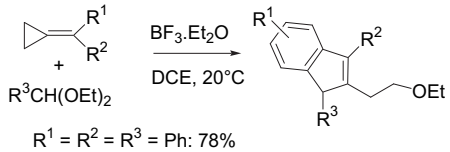
Scheme 27. Intramolecular Friedel–Crafts reactions of alkylidenecyclopropanes.



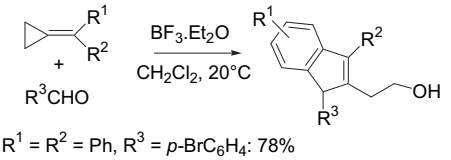
$R^1 = p\text{-}ClC_6H_4$, $R^2 = R^3 = R^4 = Ph$: 55%
$R^1 = R^2 = p\text{-}FC_6H_4$, $R^3 = R^4 = Ph$: 59%
$R^1 = R^2 = p\text{-}Tol$, $R^3 = R^4 = Ph$: 56%
$R^1 = R^2 = Ph$, $R^3 = R^4 = p\text{-}MeOC_6H_4$: 65%
$R^1 = R^2 = Ph$, $R^3 = R^4 = p\text{-}Tol$: 63%

Scheme 28. Reaction of arylidenecyclopropanes with 3-methoxy-1,3,3-triarylprop-1-ynes.

corresponding indene derivatives in the presence of $BF_3{\cdot}Et_2O$.[42] The best results dealing with acetals are shown in Scheme 29. Yamamoto et al. have demonstrated that these reactions could also be catalysed by ytterbium, involving a carboalkoxylation/



$R^1 = R^2 = R^3 = Ph$: 78%
$R^1 = R^2 = Ph$, $R^3 = p\text{-}ClC_6H_4$: 70%
$R^1 = R^2 = R^3 = p\text{-}ClC_6H_4$: 74%
$R^1 = R^2 = p\text{-}ClC_6H_4$, $R^3 = p\text{-}NO_2C_6H_4$: 84%

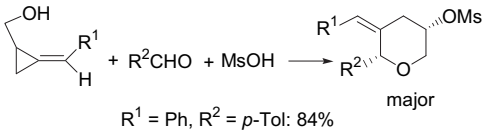


$R^1 = R^2 = Ph$, $R^3 = p\text{-}BrC_6H_4$: 78%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}Tol$, $R^3 = p\text{-}BrC_6H_4$: 91%
$R^1 = p\text{-}MeOC_6H_4$, $R^2 = p\text{-}Tol$, $R^3 = p\text{-}ClC_6H_4$: 95%

Scheme 29. Reactions of alkylidenecyclopropanes with acetals and aldehydes.

Friedel–Crafts reaction mechanism and providing moderate-to-good yields (42–85%).[43]

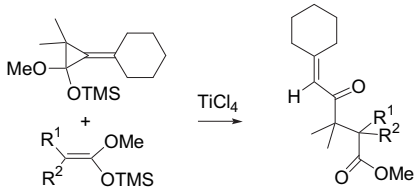
In 2003, Kilburn et al. reported the intermolecular addition of silylated methylenecyclopropanes to aldehydes mediated by $BF_3{\cdot}Et_2O$ to give mixtures of the corresponding simple tetrahydrofurans and furofurans in moderate yields.[44] Moreover, these authors have studied the cyclisations of both silylated methylenecyclopropyl hydrazones[45] and silylated methylenecyclopropyl imines[46] upon treatment with $BF_3{\cdot}Et_2O$. While the reactions of silylated methylenecyclopropyl hydrazones led to the formation of various products resulting from a series of rearrangements, the reactions of silylated methylenecyclopropyl imines yielded stereoselectively the corresponding indolizidine products, albeit in low yields. On the other hand, Shi et al. have disclosed an interesting procedure in which 2-(arylmethylene)cyclopropylcarbinols reacted with aldehydes to provide stereo- and regioselectively the corresponding tetrahydropyrans in good yields (Scheme 30).[47] A Prins-type reaction mechanism was proposed for these reactions mediated by a Brønsted acid such as MsOH.



R^1 = Ph, R^2 = *p*-Tol: 84%
R^1 = *p*-ClC_6H_4, R^2 = Ph: 86%
R^1 = *p*-BrC_6H_4, R^2 = Ph: 82%
R^1 = *p*-FC_6H_4, R^2 = Ph: 89%

Scheme 30. Reaction of 2-(arylmethylene)cyclopropylcarbinols with aldehydes.

In addition, Fujita et al. have demonstrated that the alkylideneallyl cation, generated from the Lewis acid-mediated ring-opening reaction of the corresponding alkylidenecyclopropanone acetal, could react with siloxyalkenes to give the corresponding acyclic addition products resulting from the nucleophilic addition to the sp^2 centre of the alkylideneallyl cation (Scheme 31).[48] In contrast, when furan was employed as the nucleophilic partner, the reaction with an alkylidenecyclopropanone acetal under acidic conditions led to the formation of the corresponding formal [3+2] and [4+3] cycloadducts, as well as electrophilic substitution products.[49]

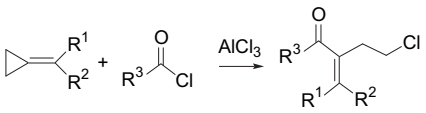


R^1 = R^2 = Me: 90%
R^1 = Me, R^2 = H: 81%

Scheme 31. Reaction of alkylidenecyclopropanone acetal with ketene silyl acetals.

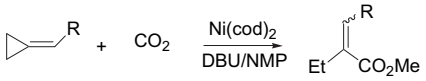
In 2007, Huang et al. reported the acylation of alkylidenecyclopropanes mediated by a stoichiometric amount of $AlCl_3$, allowing the synthesis of a variety of α,β-unsaturated ketone derivatives with high stereoselectivity to be achieved.[50] This process could be applied to a number of acyl chlorides and alkylidenecyclopropanes, and the best results are collected in Scheme 32.

In 2006, Murakami et al. demonstrated that alkylidenecyclopropanes could be carboxylated with gaseous carbon dioxide in the presence of a stoichiometric amount of a nickel complex and an amine.[51] When DBU was used as the amine in a solvent such as *N*-methyl-2-pyrrolidinone (NMP), the reaction afforded the corresponding branched α,β-unsaturated ester in quantitative yield as a mixture of *Z*/*E*-isomers (Scheme 33).



R^1 = R^2 = Ph, R^3 = *p*-$MeOC_6H_4$: 92%
R^1 = R^2 = *p*-Tol, R^3 = Me: 92%
R^1 = R^2 = *p*-ClC_6H_4, R^3 = Ph: 79%
R^1 = R^2 = *p*-$MeOC_6H_4$, R^3 = Ph: 76%

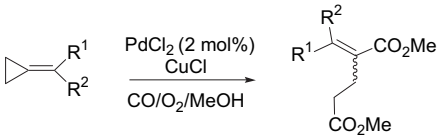
Scheme 32. Acylation of alkylidenecyclopropanes.



R = *p*-Tol: 99% (*E*/*Z*= 93:7)
R = *o*-Tol: 99% (*E*/*Z*= 97:3)
R = *p*-$MeOC_6H_4$: 99% (*E*/*Z*= 91:9)
R = *p*-FC_6H_4: 99% (*E*/*Z* = 97:3)

Scheme 33. Ni-catalysed carboxylation of alkylidenecyclopropanes.

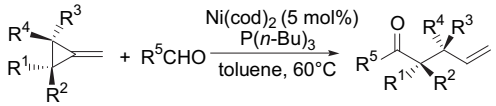
In 2009, a ring-opening bis(alkoxycarbonylation) reaction of alkylidenecyclopropanes was developed by Inamota et al.[52] This novel process was catalysed by palladium in the presence of a copper salt under normal pressure of carbon monoxide and oxygen to give the corresponding α-methyleneglutarates, as shown in Scheme 34. It was noteworthy that the (*E*)-products were selectively produced by the reaction of mono-aromatic-substituted alkylidenecyclopropanes, whereas the (*Z*)-products were obtained from tetrasubstituted olefinic substrates.



R^1 = Ph, R^2 = H: 68% (*E*/*Z* = 93:7)
R^1 = *p*-$NO_2C_6H_4$, R^2 = H: 94% (*E*/*Z* = 80:20)
R^1 = *p*-$MeOC_6H_4$, R^2 = H: 80% (*E*/*Z* = 89:11)
R^1 = Ph, R^2 = Me: 88% (*E*/*Z* = 17:83)
R^1 = 2-Naph, R^2 = Me: 91% (*E*/*Z* = 17:83)
R^1 = *n*-Hex, R^2 = Me: 91% (*E*/*Z* = 16:84)

Scheme 34. Pd-catalysed bis(alkoxycarboxylation) reaction of alkylidenecyclopropanes.

In 2009, Suginome et al. established an efficient method for the conversion of aldehydes into γ,δ-unsaturated ketones on the basis of the Ni-catalysed ring-opening hydroacylation of methylenecyclopropanes.[53] As shown in Scheme 35, the reaction was

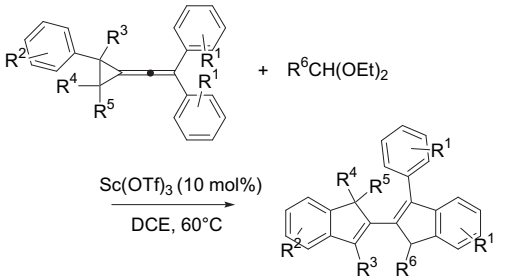


R^1 = R^3 = Ph, R^2,R^4 = $(CH_2)_4$, R^5 = *p*-FC_6H_4: 96%
R^1 = R^3 = Ph, R^2,R^4 = $(CH_2)_4$, R^5 = *p*-$MeOC_6H_4$: 94%
R^1 = R^3 = Ph, R^2,R^4 = $(CH_2)_4$, R^5 = *p*-$NMe_2C_6H_4$: 95%
R^1 = R^3 = Ph, R^2,R^4 = $(CH_2)_4$, R^5 = *p*-Tol: 84%
R^1 = R^3 = Ph, R^2,R^4 = $(CH_2)_4$, R^5 = 2-Thienyl: 84%
R^1 = R^4 = *n*-Pr, R^2 = R^3 = H, R^5 = Ph: 88%
R^1 = R^2 = R^3 = R^4 = Me, R^5 = Ph: 83%
R^1 = R^2 = H, R^3 = Me, R^4 = R^5 = Ph: 72%

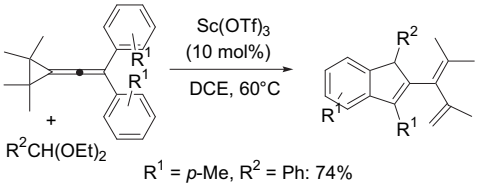
Scheme 35. Ni-catalysed hydroacylation of alkylidenecyclopropanes.

applicable to a wide range of aldehydes and proceeded with both high stereospecificity and regioselectivity for the cleavage of the cyclopropane ring, providing high yields.

Finally, a wide range of studies have been undertaken by Shi et al. dealing with the ring opening of vinylidenecyclopropanes. As an example, a number of highly substituted indene derivatives could be prepared in moderate-to-good yields (37–95%) through the reactions of arylvinylidenecyclopropanes with acetals in the presence of a Lewis acid such as $Sc(OTf)_3$, as shown in Scheme 36.[54] Interestingly, it was found that the reactions of arylvinylidenecyclopropanes bearing four methyl groups on the cyclopropane ring afforded selectively another type of indene derivative in good-to-high yields (60–99%), as shown in Scheme 36. The reactions were believed to proceed via the regioselective addition of oxonium intermediates to arylvinylidenecyclopropanes and a subsequent intramolecular Friedel–Crafts reaction.



R^1 = *p*-Me, R^2 = R^3 = R^6 = Ph, R^4 = R^5 = H: 89%
R^1 = *p*-FC_6H_4, R^2 = R^3 = R^6 = Ph, R^4 = R^5 = H: 90%
R^1 = R^6 = Ph, R^2 = R^3 = *p*-Tol, R^4 = R^5 = H: 93%
R^1 = R^2 = R^3 = R^6 = Ph, R^4 = Me, R^5 = H: 95%
R^1 = R^2 = R^3 = Ph, R^4 = R^5 = H, R^6 = *p*-ClC_6H_4: 94%

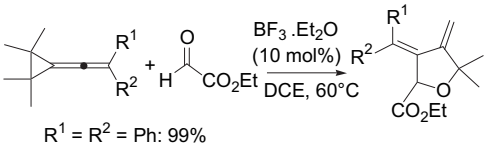


R^1 = *p*-Me, R^2 = Ph: 74%
R^1 = *p*-ClC_6H_4, R^2 = Ph: 93%
R^1 = Ph, R^2 = *p*-ClC_6H_4: 99%
R^1 = Ph, R^2 = *p*-Tol: 84%

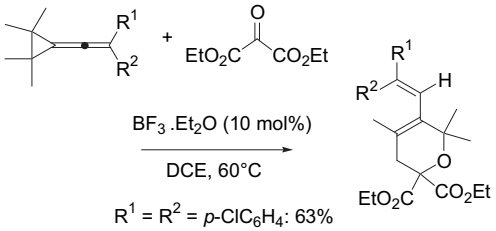
Scheme 36. Reactions of arylvinylidenecyclopropanes with acetals.

These authors have extended their investigation on the reactivity of arylvinylidenecyclopropanes by examining their reactions with activated carbonyl compounds, such as ethyl glyoxylate and diethyl ketomalonate.[55] Interestingly, the reactions, which were induced by a Lewis acid such as $BF_3 \cdot Et_2O$, provided different products according to the nature of the starting carbonyl compounds. As shown in Scheme 37, the reactions of ethyl glyoxylate with arylvinylidenecyclopropanes afforded the corresponding tetrahydrofuran derivatives in high yields (77–99%), while those involving diethyl ketomalonate yielded the corresponding 3,6-tetrahydropyran derivatives in moderate yields (30–66%). This difference of reactivity could be caused by the electronic nature and electronic effect of the carbonyl compound.

A difference of reactivity due to the nature of the substituents borne by the cyclopropane ring was observed in the reactions of arylvinylidenecyclopropanes with 1,1,3-triarylprop-2-yn-1-ols or their methyl ethers.[56] Therefore, these reactions selectively produced, in the presence of $Zr(OTf)_4$ or $Sc(OTf)_3$ as the Lewis acid, respectively, the corresponding 4-dihydro-1*H*-cyclopenta[*b*]-naphthalene derivatives or 1,2,3,8-tetrahydrocyclopenta[*a*]indene



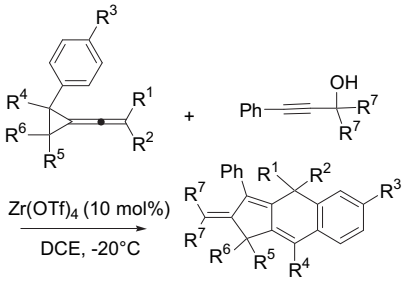
R^1 = R^2 = Ph: 99%
R^1 = R^2 = *p*-ClC_6H_4: 94%
R^1 = R^2 = *p*-FC_6H_4: 97%
R^1 = *p*-ClC_6H_4, R^2 = Ph: 99% (*E*/*Z* = 1.5:1)
R^1 = R^2 = *p*-Tol: 98%



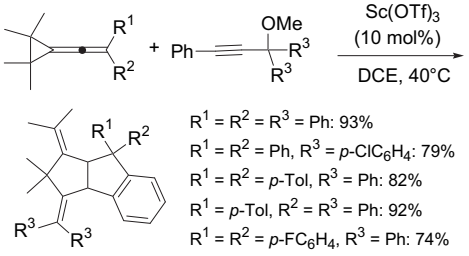
R^1 = R^2 = *p*-ClC_6H_4: 63%
R^1 = R^2 = *p*-FC_6H_4: 66%
R^1 = *p*-Tol, R^2 = Ph: 62%
R^1 = R^2 = *p*-Tol: 62%

Scheme 37. Reactions of arylvinylidenecyclopropanes with activated carbonyl compounds.

derivatives, depending on the substituents on the cyclopropane ring. As shown in Scheme 38, moderate-to-high yields of 30–91 and 25–95%, respectively, were obtained under mild conditions.



R^1 = R^2 = R^3 = R^4 = R^7 = Ph, R^5 = Me, R^6 = H: 80%
R^1 = R^2 = R^7 = Ph, R^3 = R^4 = *p*-FC_6H_4, R^5 = R^6 = H: 80%
R^1 = R^2 = R^7 = Ph, R^3 = R^4 = *p*-Tol, R^5 = R^6 = H: 80%
R^1 = R^2 = *p*-FC_6H_4, R^3 = R^4 = R^7 = Ph, R^5 = R^6 = H: 91%
R^1 = *p*-ClC_6H_4, R^2 = R^3 = R^4 = R^7 = Ph, R^5 = R^6 = H: 88%

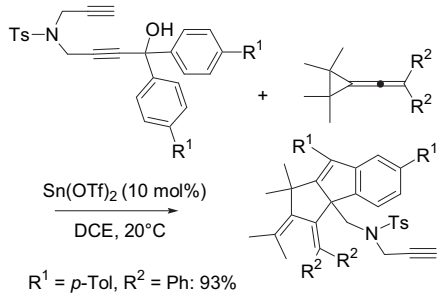


R^1 = R^2 = R^3 = Ph: 93%
R^1 = R^2 = Ph, R^3 = *p*-ClC_6H_4: 79%
R^1 = R^2 = *p*-Tol, R^3 = Ph: 82%
R^1 = *p*-Tol, R^2 = R^3 = Ph: 92%
R^1 = R^2 = *p*-FC_6H_4, R^3 = Ph: 74%

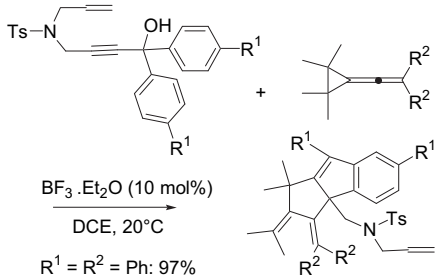
Scheme 38. Reactions of arylvinylidenecyclopropanes with 1,1,3-triarylprop-2-yn-1-ols and their methyl ethers.

In addition, the reactions of arylvinylidenecyclopropanes with 1,6-diynes and 1,6-enynes were investigated by the same authors.[57] While the reactions of vinylidenecyclopropanes with 1,6-diynes were catalysed by $Sn(OTf)_2$, those with 1,6-enynes were performed in the presence of $BF_3 \cdot Et_2O$ as the catalyst. These reactions

selectively produced the corresponding polycyclic compounds in good-to-high yields (70–99 and 50–97%, respectively), as shown in Scheme 39.



R^1 = *p*-Tol, R^2 = Ph: 93%
R^1 = *p*-FC_6H_4, R^2 = Ph: 95%
R^1 = R^2 = *p*-FC_6H_4: 91%
R^1 = Ph, R^2 = *p*-Tol: 99%
R^1 = Ph, R^2 = *p*-ClC_6H_4: 94%

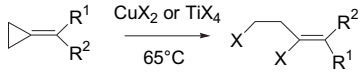


R^1 = R^2 = Ph: 97%
R^1 = Ph, R^2 = *p*-Tol: 90%
R^1 = *p*-Tol, R^2 = Ph: 88%

Scheme 39. Reactions of arylvinylidenecyclopropanes with 1,6-diynes and 1,6-enynes.

2.4. Ring-opening reactions through dihalogenation

In 2003, Huang et al. reported that the CuX_2-mediated halogenation of alkylidenecyclopropanes constituted a highly efficient and stereoselective method for the preparation of *Z*-2,4-dihalobutenes.[58] As shown in Scheme 40, the ring-opened dihalogenated products were obtained in excellent yields in all cases of substrates.



with CuX_2:

R^1 = *p*-ClC_6H_4, R^2 = H, X = Cl: 89%
R^1 = *p*-BrC_6H_4, R^2 = H, X = Br: 82%
R^1 = *p*-BrC_6H_4, R^2 = H, X = I: 91%
R^1 = Ph, R^2 = Me, X = I: 89%
R^1 = R^2 = Ph, X = Cl: 93%
R^1 = R^2 = Ph, X = Br: 90%
R^1 = R^2 = Ph, X = I: 94%

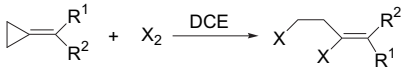
with TiX_4, DEAD/DCE:

R^1 = R^2 = Ph, X = Br: 82%
R^1 = R^2 = *p*-Tol, X = Br: 71%
R^1 = R^2 = *p*-ClC_6H_4, X = Br: 83%
R^1 = R^2 = Ph, X = I: 98%
R^1 = R^2 = *p*-Tol, X = I: 99%
R^1 = R^2 = *p*-ClC_6H_4, X = I: 99%

Scheme 40. Metal-mediated halogenation of alkylidenecyclopropanes.

Similar dihalogenations were also performed by Shi et al. in the presence of TiX_4 combined with DEAD in DCE, providing comparable excellent results, as shown in Scheme 40.[59]

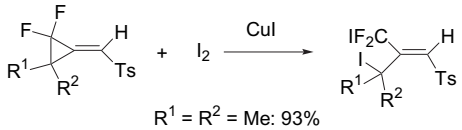
Moreover, these authors have disclosed that the dihalogenated ring-opened products could be also generated by the reaction of alkylidenecyclopropanes with free halogens, such as bromine and iodine, in good yields. These reactions were performed in DCE and provided, under mild conditions, good-to-excellent yields, as shown in Scheme 41.[59,60]



R^1 = R^2 = *p*-ClC_6H_4, X = Br: 83%
R^1 = R^2 = *p*-Tol, X = Br: 93%
R^1 = *p*-$EtOC_6H_4$, R^2 = Me, X = I: 91%
R^1 = R^2 = Ph, X = I: 88%
R^1 = R^2 = *p*-Tol, X = I: 90%
R^1 = R^2 = *p*-ClC_6H_4, X = I: 92%
R^1 = R^2 = *p*-$MeOC_6H_4$, X = I: 90%

Scheme 41. Halogenation of alkylidenecyclopropanes with free halogens.

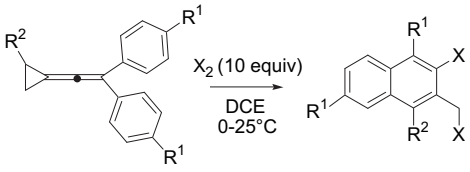
In 2006, Chen et al. reported the ring opening of difluoro(methylene)cyclopropanes with iodine in the presence of CuI, which provided the corresponding tetrahalogenated derivatives.[61] It must be noted that the reactions were significantly affected by the substituents on the cyclopropane ring. Therefore, no reaction occurred with difluoro(methylene)cyclopropanes bearing bulky or aromatic substituents on their cyclopropane rings, while, with other difluoro(methylene)cyclopropanes, the ring-opened products were obtained in good-to-excellent yields (80–95%), as shown in Scheme 42.



R^1 = R^2 = Me: 93%
R^1 = Et, R^2 = Me: 80%
R^1,R^2 = $(CH_2)_5$: 95%

Scheme 42. Cu-catalysed iodination of difluoro(methylene)cyclopropanes.

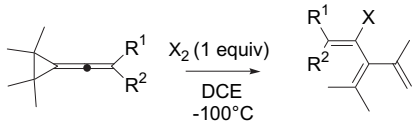
Finally, Shi et al. have investigated the ring-opening reactions of arylvinylidenecyclopropanes by iodine or bromine in various conditions. In the presence of an excess of iodine or bromine at 0–25 °C in DCE, arylvinylidenecyclopropanes underwent a novel ring-opening cascade reaction to give the corresponding iodinated or brominated naphthalene derivatives in good-to-high yields, as shown in Scheme 43.[62]



R^1 = *p*-Tol, R^2 = Ph, X = I: 85%
R^1 = *p*-$MeOC_6H_4$, R^2 = Ph, X = I: 84%
R^1 = Ph, R^2 = *p*-$MeOC_6H_4$, X = Br: 61%
R^1 = R^2 = Ph, X = I: 95%
R^1 = R^2 = Ph, X = Br: 78%

Scheme 43. Reaction of arylvinylidenecyclopropanes with iodine or bromine in excess at 0–25 °C.

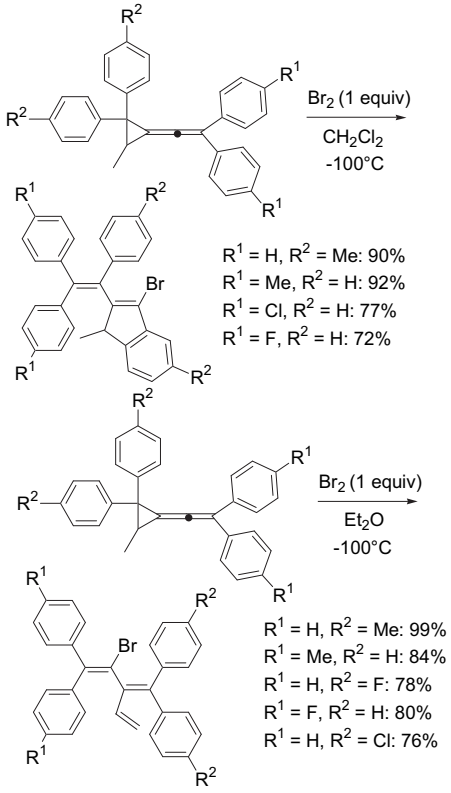
On the other hand, these authors have demonstrated that arylvinylidenecyclopropanes reacted in a different manner with an equimolar amount of bromine or iodine at low temperature (−100 °C) to produce in generally high yields (80–95%) the corresponding opened halogenated products, as depicted in Scheme 44.[63]



$R^1 = R^2$ = Ph, X = Br: 88%
$R^1 = R^2$ = Ph, X = I: 80%
$R^1 = R^2$ = *p*-$MeOC_6H_4$, X = Br: 87%
$R^1 = R^2$ = *p*-$MeOC_6H_4$, X = I: 89%
$R^1 = R^2$ = *p*-FC_6H_4, X = Br: 95%
$R^1 = R^2$ = *p*-FC_6H_4, X = I: 79%
$R^1 = R^2$ = *p*-Tol, X = Br: 78%
$R^1 = R^2$ = *p*-Tol, X = I: 80%

Scheme 44. Reaction of arylvinylidenecyclopropanes with equimolar amount of bromine or iodine at −100 °C.

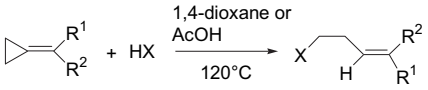
Moreover, these authors have found that arylvinylidenecyclopropanes, bearing two aromatic groups at the C1 position and one methyl group at the C2 position of the cyclopropyl ring, reacted differently compared to other compounds of this type.[64] Thus, these particular arylvinylidenecyclopropanes produced, in the presence of an equimolar amount of bromine at −100 °C, either the corresponding brominated indene derivatives when dichloromethane was used as the solvent, or the corresponding brominated conjugated triene derivatives when Et_2O was employed as the solvent, as shown in Scheme 45. Indeed, the reaction afforded these two types of products depending on the employed solvents, providing, in each case, good-to-high yields of 66–92 and 65–99%, respectively.



Scheme 45. Reactions of arylvinylidenecyclopropanes with bromine at −100 °C.

2.5. Ring-opening reactions by hydrogen halides

The ring-opening reaction of alkylidenecyclopropanes with HCl or HBr proceeded very smoothly at 120 °C to produce the corresponding homoallylic halides stereoselectively in excellent yields (Scheme 46).[65] The hydrochlorination was performed in 1,4-dioxane, whereas the hydrobromination was carried out in acetic acid. In addition, Okuyama et al. have studied the ring-opening reactions of 2-cyclohexylidene-3,3-dimethylcyclopropanone acetal with HCl in various solvents.[66] This study has demonstrated that the bond cleavage took place at the C1–C2 or C2–C3 bond, and the ratio of C1–C2/C2–C3 cleavages changed from >99/1 to 1/99, depending on the solvent. The two modes of bond cleavage were initiated by protonation at the carbon–carbon double bond and the acetal oxygen. The regioselectivity could be rationalised by the rate-determining protonation at carbon and the equilibrium protonation at oxygen.



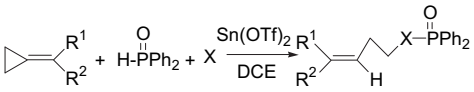
$R^1 = R^2$ = Ph, X = Cl: 99%
$R^1 = R^2$ = *n*-Bu, X = Cl: 96%
$R^1 = R^2$ = *n*-Hex, X = Cl: 94%
$R^1 = R^2$ = Cy, X = Cl: 89%
R^1 = *n*-Hept, R^2 = H, X = Cl: 87%
$R^1 = BnCH_2$, R^2 = H, X = Cl: 86%
$R^1 = R^2$ = *n*-Bu, X = Br: 95%

Scheme 46. Addition of hydrogen halides to alkylidenecyclopropanes.

2.6. Ring-opening reactions by sulfur and selenium reagents

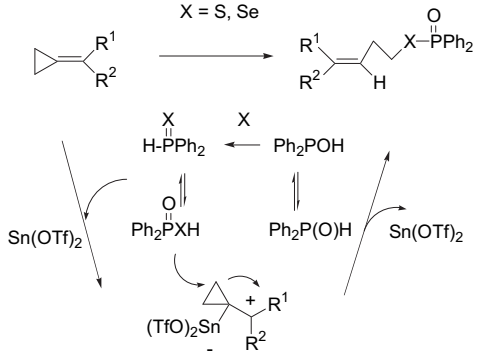
An interesting Lewis acid-catalysed ring-opening reaction of alkylidenecyclopropanes with diphenylphosphine oxide in the presence of sulfur or selenium upon heating at 85 °C in DCE was reported by Shi et al., in 2007.[67] This novel process allowed the formation of the corresponding homoallylic thiol or selenol derivatives in good-to-high yields, as shown in Scheme 47. The proposed mechanism involved the preliminary reaction of sulfur or selenium with Ph_2POH to produce the corresponding $Ph_2P(X)OH$ species, which was in equilibrium with $Ph_2P(O)XH$. The reaction of $Ph_2P(O)XH$ or $Ph_2P(X)OH$ with the $Sn(OTf)_2$-activated alkylidenecyclopropane produced the final product and regenerated $Sn(OTf)_2$ (Scheme 47). On the other hand, the same authors have studied the reaction of arylidenecyclopropanes with phenylsulfenyl chloride and phenylselenyl chloride performed in dichloromethane at 0 °C.[68] The reaction of diphenylmethylenecyclopropane with phenylsulfenyl chloride or phenylselenyl chloride gave (cyclobut-1-enylsulfanyl)benzene or (cyclobut-1-enylselanyl)benzene along with the corresponding ring-opened product in good yields, whereas the reaction of arylidenecyclopropanes bearing an electron-donating group (*p*-MeO or *p*-Me) on the benzene ring produced the ring-opened compounds as major products in 69–80% yields. Moreover, these authors have investigated the reaction of *gem*-aryl disubstituted methylenecyclopropanes with diaryl diselenide in the presence of $PhI(OAc)_2$.[69] This process led to the formation of the corresponding ring-opened products, 1,2-bis(arylselanyl)-3,3-diarylcyclobut-1-enes, in moderate-to-high yields (37–66%).

In 2009, Yu et al. studied the additions of 1,2-diphenyldiselane or 1,2-di-*p*-tolyldisulfane to a series of alkylidenecyclopropanes in the presence of a catalytic amount of $TiCl_4$.[70] In these conditions, the corresponding substituted cyclobutane-1,1-diylbis(phenylselane) derivatives or cyclobutane-1,1-diylbis(*p*-tolylsulfane) derivatives were obtained in moderate-to-high yields of 10–73 and 54–88%, respectively (Scheme 48).

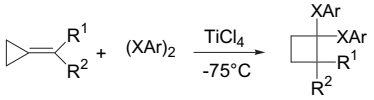


$R^1 = R^2 = p$-Tol, X = S: 71%
$R^1 = R^2 = p$-ClC_6H_4, X = S: 81%
$R^1 = R^2 = p$-$MeOC_6H_4$, X = S: 80%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph, X = S: 78% (*E*/*Z* = 1:1)
R^1 = Ph, R^2 = H, X = S: 73%
$R^1 = R^2 = p$-Tol, X = Se: 82%
$R^1 = R^2 = p$-ClC_6H_4, X = Se: 66%
R^1 = Ph, R^2 = H, X = Se: 71%

proposed mechanism:



Scheme 47. Ring-opening reaction of alkylidenecyclopropanes with diphenylphosphine oxide in presence of sulfur or selenium.



with XAr = SePh:
$R^1 = p$-BrC_6H_4, R^2 = H: 62%
$R^1 = n$-Hept, R^2 = H: 73%
$R^1 = n$-Non, R^2 = H: 68%
R^1,R^2 = $(CH_2)_2CH(Ph)(CH_2)_2$: 71%
with XAr = S(*p*-Tol):
$R^1 = p$-BrC_6H_4, R^2 = H: 75%
$R^1 = n$-Hept, R^2 = H: 72%
$R^1 = n$-Non, R^2 = H: 88%
R^1,R^2 = $(CH_2)_2CH(Ph)(CH_2)_2$: 70%

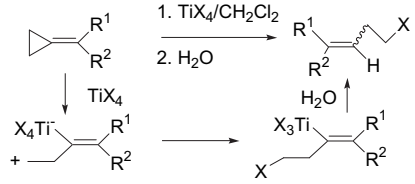
Scheme 48. Ti-catalysed reactions of alkylidenecyclopropanes with 1,2-diphenyldiselane and 1,2-di-*p*-tolyldisulfane.

2.7. Ring-opening reactions by metal halides

Shi et al. have disclosed the ring-opening reactions of alkylidenecyclopropanes promoted by metal halides, such as TiX_4 (X=Cl, Br) or $BiCl_3$, under mild conditions in which homoallylic chlorides and bromides could be obtained in high yields after subsequent quenching by water (Scheme 49).[71] Moreover, the corresponding homoallylic iodides could be synthesised in comparable yields by using the $TiCl_4$/*n*-Bu_4NI system, as shown in Scheme 49.

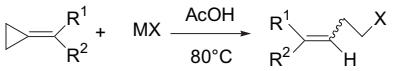
These products could also be synthesised in almost quantitative yields by the same authors through treatment of alkylidenecyclopropanes with LiCl, LiBr or NaI in acetic acid, as shown in Scheme 50.[72]

In 2004, Huang et al. reported a facile and efficient CuX_2 catalysis-mediated cyclisation reaction of cyclopropylideneacetic esters and cyclopropylideneacetonitriles, providing the corresponding 4-halo-



$R^1 = R^2$ = Ph, X = Cl: 82%
$R^1 = R^2 = p$-ClC_6H_4, X = Cl: 84%
$R^1 = R^2 = p$-$MeOC_6H_4$, X = Cl: 93%
$R^1 = R^2$ = Ph, X = Br: 80%
R^1 = Ph, $R^2 = p$-ClC_6H_4, X = Br: 89%
$R^1 = R^2 = p$-ClC_6H_4, X = Br: 84%
with *n*-Bu_4NI:
$R^1 = R^2$ = Ph, X = I: 80%
$R^1 = R^2 = p$-ClC_6H_4, X = I: 75%
$R^1 = R^2 = p$-$MeOC_6H_4$, X = I: 75%

Scheme 49. Ring-opening reaction of alkylidenecyclopropanes with TiX_4.



$R^1 = R^2$ = Ph, MX = LiCl: 96%
$R^1 = R^2$ = Ph, MX = LiBr: 98%
$R^1 = R^2$ = Ph, MX = NaI: 100%
$R^1 = R^2 = p$-$MeOC_6H_4$, MX = LiCl: 99%
$R^1 = R^2 = p$-$MeOC_6H_4$, MX = LiBr: 100%
$R^1 = R^2 = p$-$MeOC_6H_4$, MX = NaI: 100%
$R^1 = R^2 = p$-Tol, MX = LiCl: 98%
$R^1 = R^2 = p$-Tol, MX = LiBr: 96%
$R^1 = R^2 = p$-Tol, MX = NaI: 96%
$R^1 = R^2 = p$-FC_6H_4, MX = LiCl: 97%
$R^1 = R^2 = p$-FC_6H_4, MX = LiBr: 92%
$R^1 = R^2 = p$-FC_6H_4, MX = NaI: 95%
$R^1 = R^2 = n$-Bu, MX = LiCl: 89%
$R^1 = R^2 = n$-Bu, MX = LiBr: 80%
$R^1 = R^2 = n$-Bu, MX = NaI: 73%

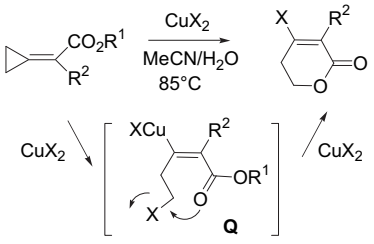
Scheme 50. Ring-opening reaction of alkylidenecyclopropanes with MX.

5,6-dihydro-2*H*-pyran-2-ones and 4-halo-5,6-dihydro-2(1*H*)-pyridinones in moderate-to-good yields, respectively (Scheme 51).[73] In order to explain the formation of these products, the authors have proposed a mechanism involving the ring opening of the alkylidenecyclopropane with CuX_2, which generated the corresponding vinylic copper intermediate **Q**. The subsequent oxidative cleavage of **Q** with CuX_2 afforded the final 4-halo-5,6-dihydro-2*H*-pyran-2-one (Scheme 51).

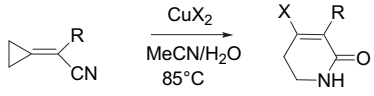
Another type of reaction initiated by the halometallation of alkylidenecyclopropanes was reported by Ma et al., in 2003.[74] As shown in Scheme 52, a series of 4*H*-pyran derivatives could be obtained in good-to-high yields by the treatment of 2-alkylidenecyclopropanyl ketones with a catalytic amount of $PdCl_2(MeCN)_2$.

Further studies indicated that in the presence of a catalytic amount of NaI in refluxing acetone, the distal C–C bond of the three-membered ring could be cleaved highly selectively to afford the corresponding 3-alkylidene-2,3-dihydrofuran in moderate-to-good yield (Scheme 53).[75]

In 2003, Lautens et al. reported the MgI_2-mediated alkylative ring expansion of secondary methylenecyclopropyl amides performed in the presence of aryl aldimines or aldehydes as the alkylating agents.[76] This process afforded the corresponding highly functionalised

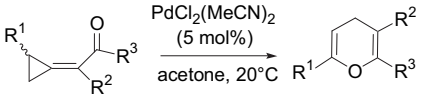


R^1 = H, R^2 = Me, X = Br: 79%
R^1 = H, R^2 = Me, X = I: 73%
R^1 = Et, R^2 = Me, X = Br: 81%
R^1 = Et, R^2 = Me, X = I: 71%
R^1 = R^2 = Et, X = Br: 83%
R^1 = R^2 = Et, X = I: 77%
R^1 = Et, R^2 = *n*-Pr, X = Br: 80%
R^1 = Et, R^2 = *n*-Pr, X = I: 76%



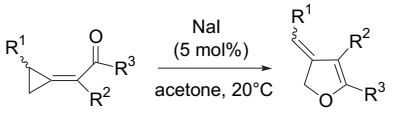
R = Bn, X = Br: 57%
R = Bn, X = I: 54%
R = Et, X = Br: 60%
R = Me, X = Br: 52%

Scheme 51. CuX_2 catalysis-mediated cyclisation reactions of cyclopropylideneacetic esters and cyclopropylideneacetonitriles.



R^1 = *n*-Hept, R^2 = CO_2Et, R^3 = Me: 80%
R^1 = *n*-Bu, R^2 = CO_2Et, R^3 = Me: 75%
R^1 = $TBS(CH_2)_3$, R^2 = CO_2Et, R^3 = Me: 85%
R^1 = *n*-Bu, R^2 = SO_2Ph, R^3 = Me: 91%
R^1 = *n*-Oct, R^2 = H, R^3 = Ph: 70%

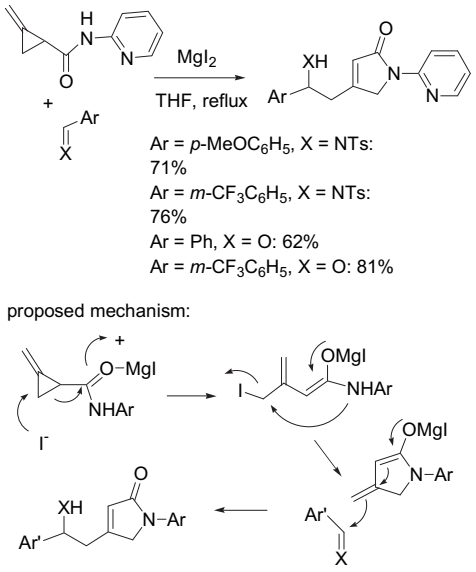
Scheme 52. Pd catalysis-mediated cyclisation reaction of 2-alkylidenecyclopropanyl ketones.



R^1 = *n*-Bu, R^2 = CO_2Et, R^3 = Me: 92%
R^1 = Bn, R^2 = CO_2Et, R^3 = Me: 92%
R^1 = $TBS(CH_2)_3$, R^2 = CO_2Et, R^3 = Me: 80%
R^1 = *n*-Hept, R^2 = SO_2Ph, R^3 = Me: 94%
R^1 = R^2 = H, R^3 = Ph: 90%
R^1 = R^2 = H, R^3 = 1-Naph: 98%
R^1 = R^2 = H, R^3 = 2-Fu: 78%

Scheme 53. NaI catalysis-mediated cyclisation reaction of 2-alkylidenecyclopropanyl ketones.

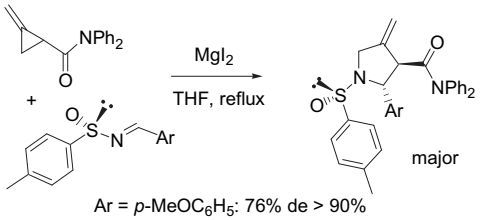
γ′-amino- or γ′-hydroxy-alkylated five-membered lactams in moderate-to-good yields (29–82%) by using a stoichiometric amount of MgI_2, as shown in Scheme 54. The authors have proposed that the mechanism initially involved the activation of the amide functionality followed by iodide attack to give a vinylogous enolate intermediate. Then, either this vinylogous enolate arising from ring opening of the substrate, or the corresponding cyclic enolate arising from ring closing of the acyclic enolate, attacked the aryl aldimine or aldehyde to yield the final product (Scheme 54).



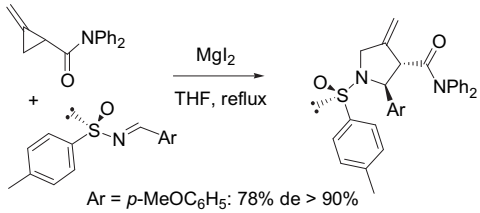
Ar = *p*-$MeOC_6H_5$, X = NTs: 71%
Ar = *m*-$CF_3C_6H_5$, X = NTs: 76%
Ar = Ph, X = O: 62%
Ar = *m*-$CF_3C_6H_5$, X = O: 81%

Scheme 54. MgI_2-mediated alkylative ring expansion of secondary methylenecyclopropyl amides.

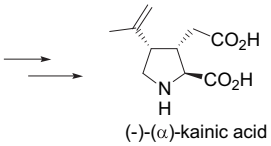
In contrast, when these conditions were applied to tertiary methylenecyclopropyl amides, the vinylogous enolate did not cyclise and directly attacked the aldimine. The addition of the electrophile occurred exclusively at the α-position of the vinylogous enolate. In the final part of the mechanism, ring closure occurred to give the *anti* 2,3,4-trisubstituted pyrrolidine. As an example, a highly diastereoselective MgI_2-mediated ring expansion of *N*,*N*-diphenylmethylenecyclopropyl amide to the corresponding pyrrolidines has been developed by using chiral aromatic sulfinimines.[77] As shown in Scheme 55, a series of 2,3,4-trisubstituted pyrrolidines were obtained in good-to-excellent yields (65–94%) combined with excellent diastereoselectivities of up to 90% de. This



Ar = *p*-$MeOC_6H_5$: 76% de > 90%
Ar = Ph: 90% de > 90%
Ar = *p*-Tol: 85% de > 90%
Ar = *p*-$CF_3C_6H_5$: 94% de > 90%
Ar = 3-py: 82% de > 90%
Ar = 4-py: 76% de > 90%
Ar = 3-Fu: 85% de > 90%
Ar = 2-Fu: 82% de > 90%



Ar = *p*-$MeOC_6H_5$: 78% de > 90%

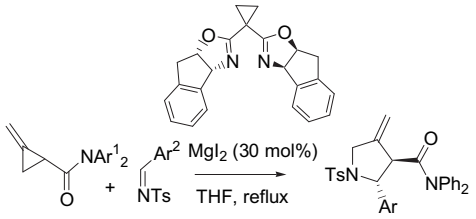


(-)-(α)-kainic acid

Scheme 55. MgI_2-mediated reactions of *N*,*N*-diphenylmethylenecyclopropyl amide with chiral aromatic sulfinimines.

methodology constituted the key step of a total synthesis of the neurological active agent, (−)-(α)-kainic acid, reported by these authors, in 2005 (Scheme 55).[78]

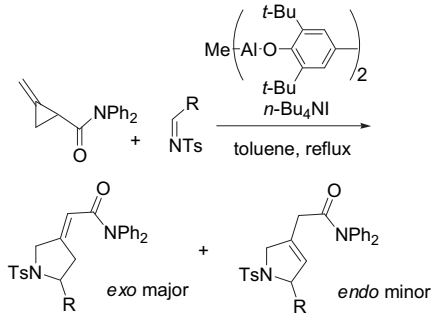
In 2007, a catalytic enantioselective version of the reaction of methylenecyclopropyl amides with *N*-tosyl aldimines was successfully developed by using a chiral bis(oxazoline) ligand.[79] As shown in Scheme 56, a variety of aromatic and heteroaromatic aldimines by reaction with methylenecyclopropyl amides provided the corresponding *trans*-C2,C3-disubstituted methylenepyrrolidines in moderate-to-good yields (52–92%) combined with enantioselectivities of up to 86% ee.



Ar^1 = Ph, Ar^2 = *o*-$CF_3C_6H_5$: 64% ee = 86%
Ar^1 = Ph, Ar^2 = *p*-$CF_3C_6H_5$: 52% ee = 83%
Ar^1 = Ph, Ar^2 = 2,4-$Cl_2C_6H_4$: 60% ee = 78%
Ar^1 = Ph, Ar^2 = 2-Fu: 66% ee = 72%
Ar^1 = 2-py, Ar^2 = Ph: 92% ee = 78%

Scheme 56. Enantioselective MgI_2-catalysed reaction of methylenecyclopropyl amides with *N*-tosyl aldimines.

Finally, these authors have shown that the use of a sterically demanding Lewis acid, such as methylaluminum bis(2,6-*tert*-butyl-4-methylphenoxide) (MAD), directed the reaction to the γ-position of the intermediate vinylogous enolate.[80] Indeed, when mediated by MAD in the presence of *n*-Bu_4NI, the reaction between *N*,*N*-diphenylmethylenecyclopropyl amide and *N*-tosyl aldimines afforded the corresponding alkylidene pyrrolidines in moderate-to-good yields (35–92%), as shown in Scheme 57. The substrate scope of the process was found to be broad for a variety of aldimines and symmetrical as well as unsymmetrical methylenecyclopropyl amides.

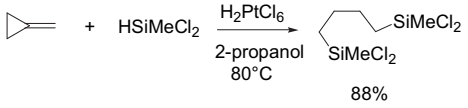


R = 2-Naph: 92% *exo/endo* > 20:1
R = 2-Fu: 86% *exo/endo* > 20:1
R = CH=CHPh: 81% *exo/endo* > 20:1
R = *p*-$MeOC_6H_5$: 64% *exo/endo* = 13:1
R = *i*-Bu: 59% *exo/endo* > 20:1
R = *i*-Bu: 35% *exo/endo* > 20:1

Scheme 57. MAD-mediated reaction of *N*,*N*-diphenylmethylenecyclopropyl amide with *N*-tosyl aldimines.

2.8. Ring-opening reactions by metal hydrides

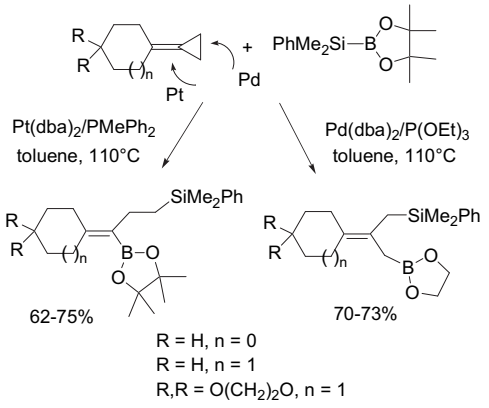
In 2004, Voronkov et al. studied the reaction of unsubstituted methylenecyclopropane with an excess of methyldichlorosilane in the presence of H_2PtCl_6 as catalyst.[81] This process afforded 1,4-bis-silylbutane as the major product in 78% yield, as shown in Scheme 58. The authors explained its formation by the initial formation of 4-silyl-1-butene followed by a second hydrosilylation of the resulting olefin. On the other hand, the synthesis of novel complexes of rhodium and iridium was achieved by Osakada et al. based on the reactions of 2,2-bis(2-phenylethyl)-1-methylenecyclopropane with hydride complexes of Rh(I) and Ir(I), respectively.[82] Therefore, the 3-butenyl-rhodium complex, Rh{η^1:η^2-$CH_2C(CH_2CH_2Ph)_2CH{=}CH_2$}(CO)($PPh_3$)$_3$, and the 3-butenyl-iridium complex, Ir{η^1:η^2-$CH_2C(CH_2CH_2Ph)_2CH{=}CH_2$}(CO)($PPh_3$)$_3$, were obtained from the reactions with RhH(CO)(PPh_3)$_3$ and IrH(CO)(PPh_3)$_3$ at 70 °C in 89 and 92% yields, respectively.



Scheme 58. Hydrosilylation of methylenecyclopropane.

2.9. Ring-opening reactions through bismetallation

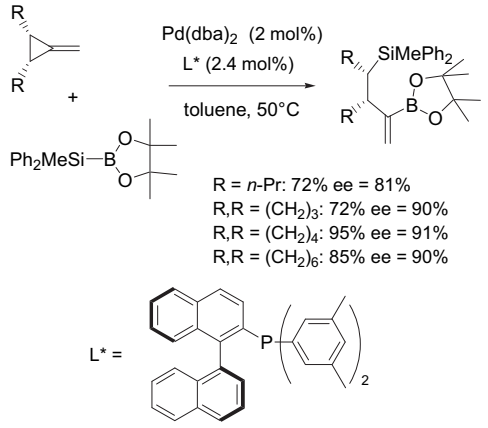
Catalytic bismetallation is of current interest because this process is an attractive methodology to introduce two metal atoms into a carbon framework by addition to carbon–carbon multiple bonds directly.[83] In 2003, Suginome et al. found that the silaboration of alkylidenecyclopropanes could be catalysed by palladium and platinum complexes.[84] It was remarkable that the silaboration of alkylidenecyclopropanes could take two distinct reaction pathways by complementary use of the palladium and platinum catalysts (Scheme 59). Thus, the reaction of cycloalkylidenecyclopropanes in the presence of $Pd(dba)_2$/$P(OEt)_3$ as the catalyst provided 2-(borylmethyl)allylsilanes exclusively via cleavage of the distal C–C bond in the cyclopropane ring, while the corresponding platinum-catalysed reaction afforded the alkenylborane products exclusively via the proximal C–C bond cleavage.



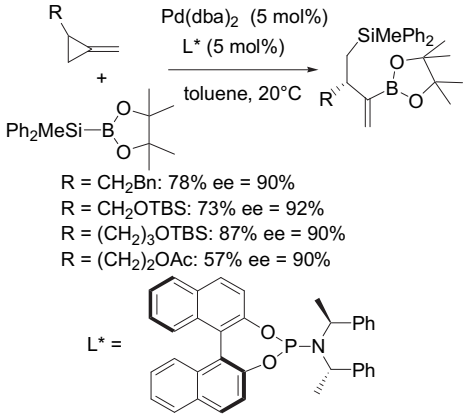
Scheme 59. Pd- and Pt-catalysed silaborations of cycloalkylidenecyclopropanes.

An asymmetric version of the Pd-catalysed silaboration of alkylidenecyclopropanes was developed by these authors, based on the involvement of a chiral monodentate phosphorus ligand depicted in Scheme 60.[85] Thus, the Pd-catalysed asymmetric silaboration C–C cleavage of *meso*-methylenecyclopropanes afforded the corresponding 2-boryl-4-silyl-1-butene derivatives with high enantioselectivities of up to 91% ee combined with high yields.

In 2009, this methodology was extended to the kinetic resolution of racemic 1-alkyl-2-methylenecyclopropanes, which provided the corresponding highly enantioenriched alkenylboronic acid derivatives (up to 92% ee) when the reaction was performed in the presence of a chiral phosphoramidite as the palladium ligand (Scheme 61).[86]



Scheme 60. Asymmetric Pd-catalysed silaboration of *meso*-methylenecyclopropanes.



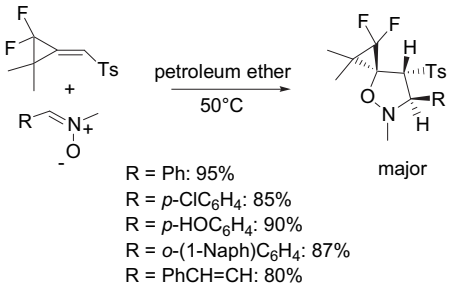
Scheme 61. Asymmetric Pd-catalysed silaboration of 1-alkyl-2-methylenecyclopropanes.

Finally, Yus et al. have reported the reaction of diphenylmethylenecyclopropane with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (4 mol %) in THF at −78 °C, leading to the formation of the corresponding 2-substituted 1,3-dilithiopropane by reductive opening of the cyclopropane ring.[87] This dianion could be subsequently trapped with a variety of electrophiles, especially carbonyl compounds, affording interesting 1,5-diols in moderate-to-good yields.

3. Cycloaddition reactions

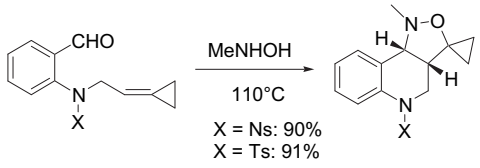
3.1. 1,3-Dipolar cycloadditions

One of the most typical reactivities of alkylidenecyclopropanes is their involvement in concerted cycloaddition reactions.[4a,88] As an example, the cycloaddition of a nitrone to an alkylidenecyclopropane is able to produce a spirocyclopropaneisoxazolidine heterocycle in a regio- and stereoselective manner. The rich chemistry associated with this kind of heterocyclic ring, originating from the easy cleavage of the N–O bond followed by further chemical transformations, makes these reactions among the most studied of this class. Excellent results were reported by Xiao et al. for the 1,3-dipolar cycloaddition of sulfonyl difluoro(methylene)cyclopropane with various nitrones.[89] The reaction was performed in petroleum ether at 50 °C and afforded in high yields the corresponding difluoro-substituted spirocyclopropaneisoxazolidines with good regio- and stereoselectivity, as shown in Scheme 62. The latter could be further rearranged into a series of 3,3-difluorinated tetrahydropyridinols.



Scheme 62. 1,3-Dipolar cycloaddition of sulfonyl difluoro(methylene)cyclopropane with nitrones.

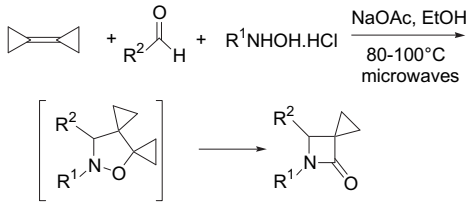
Brandi et al. have investigated the 1,3-dipolar cycloadditions of methylenecyclopropane and (alkoxycarbonyl)methylenecyclopropanes with various nitrones, providing the corresponding spirocyclopropane-1,5-isoxazolidines in moderate yields. Low regioselectivities were generally observed by using methylenecyclopropane, while (alkokycarbonyl)methylenecyclopropanes provided the corresponding 4-oxa-5-azaspiro[2.4]heptanes as single regioisomers, albeit as mixtures of cis- and trans-diastereomers with generally low diastereoselectivities.[90] This methodology was successfully applied to the synthesis of structurally diverse dihydro- and tetrahydropyridones through a two-step, metal-catalysed overall transformation of the spirocyclopropane-1,5-isoxazolidines prepared via 1,3-dipolar cycloadditions.[91] On the other hand, these authors have reported a complete control of both the regio- and stereoselectivity for the intramolecular 1,3-dipolar cycloaddition of an alkylidenecyclopropane bearing an aldehyde (Scheme 63).[92] When treated with *N*-methylhydroxylamine, this aldehyde was in situ converted into the corresponding nitrone, which underwent the intramolecular cycloaddition to give the corresponding *cis*-fused cycloadduct in high yield (Scheme 63).



Scheme 63. Intramolecular 1,3-dipolar cycloaddition of alkylidenecyclopropanes bearing nitrone functionality.

In 2006, de Meijere et al. involved the bicyclopropylidene unit[93] in intramolecular 1,3-dipolar cycloadditions. Therefore, the intramolecular cycloadditions of various nitrone functionalities with different substituents at the nitrogen atom tethered to a bicyclopropylidene unit through a two-carbon chain led to *cis*-fused tricyclic isoxazolidines (3-alkyl-3,3a,4,5,5a,6-hexahydrocyclopropa[2,3]cyclopenta[1,2-*c*]isoxazolespiro[1,1′]cyclopropanes) in moderate yields (42–58%) with complete regio- and diastereoselectivity.[94] The subsequent thermal rearrangement of the cycloadducts afforded the corresponding tricyclic tetrahydropyridones.[95] Moreover, the involvement of bicyclopropylidene in a new three-component cascade reaction yielding 3-spirocyclopropanated β-lactams was reported by the same authors. As shown in Scheme 64, the reaction of bicyclopropylidene with a nitrone, in situ generated from the reaction of formaldehyde or an alkyl glyoxylate with an alkylhydroxylamine hydrochloride, furnished the corresponding 3-spirocyclopropanated 2-azetidinones upon microwave heating in the presence of NaOAc. These products, arising from the further rearrangement of the intermediate spirocyclopropane-1,5-isoxazolidine cycloadducts, were isolated in moderate-to-good yields.

In 2009, Molchanov et al. showed that the 1,3-dipolar cycloaddition of C-aryl-*N*-aryl- or *N*-methylnitrones with esters of Feist's acid

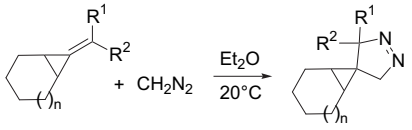


R^1 = Bn, R^2 = H: 68%
R^1 = *t*-Bu, R^2 = H: 73%
R^1 = Bn, R^2 = CO_2Et: 72%
R^1 = PMB, R^2 = CO_2Me: 78%

Scheme 64. Three-component 1,3-dipolar cycloaddition of bicyclopropylidene.

(3-methylenecyclopropane-*trans*-1,2-dicarboxylic acid) occurred with the formation of the corresponding spirocyclopropane-1,4-isoxazolidines as single isomers with low-to-moderate yields (17–59%).[96] In this case, the reaction proceeded with an inverse regiochemical outcome, compared to cycloadditions with unsubstituted methylenecyclopropanes such as diethyl cyclopropylidenemalonate, leading to spirocyclopropane-1,5-isoxazolidines.[97]

In addition to nitrones, diazoalkanes can react with methylene- or alkylidenecyclopropanes to provide the corresponding 1,3-dipolar cycloadducts, according to either inter-[98] or intramolecular processes. As an example, de Meijere et al. have shown that the carbonyl ylide 1,3-dipole generated by dirhodium tetraacetate-catalysed decomposition from 1-diazo-5-phenylpentane-2,5-dione cycloadded to bicyclopropylidene to give the corresponding dispirocyclopropanated 8-oxabicyclo[3.2.1]octan-2-one in 57% yield as the sole isomer.[99] Almost quantitative yields have been reported by Tokuda et al. for the reactions of bicyclo[*n*.1.0]alkylidene derivatives with diazomethane, yielding regioselectively the corresponding spiropyrazolines (Scheme 65).[100] The latter were further submitted to thermal decomposition, resulting in ring enlargement, which afforded the corresponding bicyclo[*n*.2.0]alkylidene derivatives in high yields.

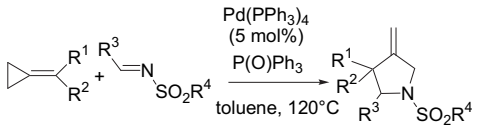


R^1 = H, R^2 = CO_2Me, n= 1: 98%
R^1 = H, R^2 = CO_2Et, n= 1: 97%
R^1 = Me, R^2 = CO_2Me, n= 1: 99%
R^1 = $CH_2CH{=}CH_2$, R^2 = CO_2Me, n= 1: 97%
R^1 = H, R^2 = CO_2Me, n= 2: 99%
R^1 = H, R^2 = CO_2Et, n= 2: 98%
R^1 = Me, R^2 = CO_2Me, n= 2: 99%
R^1 = $CH_2CH{=}CH_2$, R^2 = CO_2Me, n= 2: 95%

Scheme 65. 1,3-Dipolar cycloaddition of ring-fused alkylidenecyclopropanes with diazomethane.

On the other hand, Pd-catalysed formal [3+2] cycloaddition reactions of alkylidenecyclopropanes with 1,2-diazines were reported by Yamamoto et al., in 2004.[101] These reactions afforded the corresponding 5-azaindolizine derivatives in low-to-good yields (6–61%) in the presence of a catalytic amount of $Pd(PPh_3)_4$. Better yields were obtained by these authors for the Pd-catalysed formal [3+2] cycloaddition reactions of alkylidenecyclopropanes with imines, which allowed a series of 3-methylenepyrrolidines to be produced in good-to-excellent yields (71–97%), as shown in Scheme 66.[102]

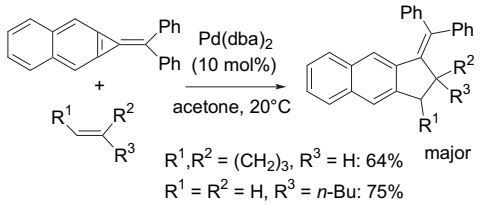
In 2008, Huang et al. reported the first Pd-catalysed highly regioselective [3+2] cycloaddition reactions of alkylidenecyclopropa[*b*]naphthalenes with alkenes or alkynes, providing an



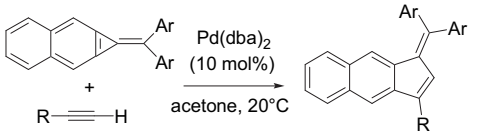
R^1 = R^2 = *n*-Bu, R_3 = 2-Fu, R^4 = *p*-Tol: 89%
R^1 = R^2 = *n*-Bu, R_3 = *p*-$MeOC_6H_4$, R^4 = *p*-Tol: 94%
R^1 = R^2 = *n*-Bu, R_3 = *p*-$CF_3C_6H_4$, R^4 = *p*-Tol: 88%
R^1 = R^2 = *n*-Bu, R_3 = R^4 = *p*-Tol: 91%
R^1 = R^2 = *n*-Bu, R_3 = Ph, R^4 = Me: 97%
R^1 = R^2 = *n*-Hex, R_3 = 2-Fu, R^4 = *p*-Tol: 88%
R^1 = $BnCH_2$, R^2 = Me, R_3 = 2-Fu, R^4 = *p*-Tol: 91%

Scheme 66. Pd-catalysed formal [3+2] cycloaddition of alkylidenecyclopropanes with imines.

efficient method for the synthesis of 1(3)-alkylidene-2,3-dihydro-1*H*-benzo[*f*]indenes or 1-alkylidene-1*H*-benzo[*f*]indenes under mild conditions.[103] Moderate-to-high yields of up to 93% were obtained by using $Pd(dba)_2$ as the catalyst, as shown in Scheme 67.



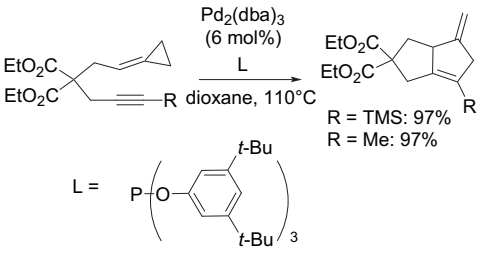
R^1,R^2 = $(CH_2)_3$, R^3 = H: 64% major
R^1 = R^2 = H, R^3 = *n*-Bu: 75%



R = *p*-FC_6H_4CO, Ar = Ph: 71%
R = Ar = Ph: 54%
R = *p*-TolCO, Ar = Ph: 68%
R = *n*-Bu, Ar = Ph: 85%
R = *p*-Bu, Ar = *p*-TolCO: 79%
R = Ar = *p*-TolCO: 52%

Scheme 67. Pd-catalysed [3+2] cycloadditions of alkylidenecyclopropa[*b*]naphthalenes with alkenes or alkynes.

Intramolecular Pd-catalysed [3+2] cycloadditions of alk-5-ynylidenecyclopropanes have been successfully developed by Mascarenas et al., providing a rapid, practical and highly efficient approach to a range of bicyclo[3.3.0]octenes in excellent yields (Scheme 68). It was demonstrated that the use of a bulky phosphite ligand allowed low catalyst loadings and facilitated the otherwise sluggish cycloaddition.[104] Moreover, these authors showed that similar reactions could be catalysed with ruthenium catalysts, such as Grubbs carbene complex, albeit in generally lower yields compared to those obtained by using palladium catalysts.[105]



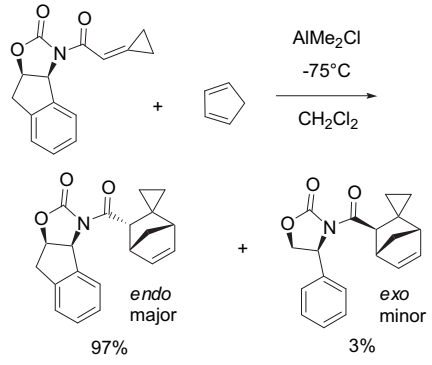
R = TMS: 97%
R = Me: 97%

Scheme 68. Pd-catalysed [3+2] intramolecular cycloaddition of alk-5-ynylidenecyclopropanes.

The scope of this methodology could be extended by these authors to Pd-catalysed [3+2] intramolecular cycloadditions of alk-5-enylidenecyclopropanes, which yielded stereoselectively the corresponding *cis*-fused bicyclo[3.3.0]octanes in moderate-to-high yields (30–96%).[106] In this case, the ligand of $Pd_2(dba)_3$ was $P(Oi\text{-}Pr)_3$. In addition, the authors showed that allenes were also useful two-carbon partners in Pd-catalysed [3+2] intramolecular cycloadditions with alkylidenecyclopropanes, enabling the preparation of the corresponding dienyl bicyclo[3.3.0]octane adducts with moderate-to-good yields (29–99%) and moderate diastereoselectivity (up to 50% de in favour of the *cis*-fused bicyclic product).[107]

3.2. [4+2] Cycloadditions

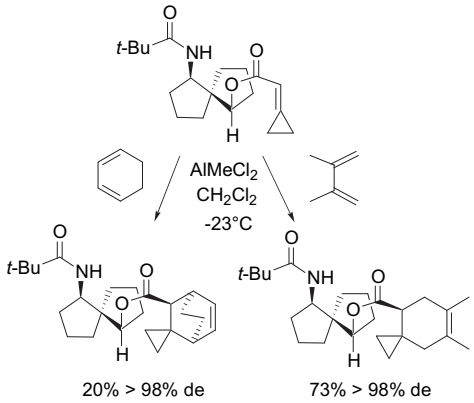
Despite the large body of Diels–Alder cycloadditions in organic synthesis, alkylidenecyclopropanes are still underestimated as valuable partners in these reactions.[88b] Alkylidenecyclopropanes can behave as dienophiles or, when properly substituted, as dienes to afford the cycloadducts. In recent years, several groups have involved various alkylidenecyclopropanes as dienophiles in Diels–Alder or hetero-Diels–Alder reactions. As an example, de Meijere et al. have developed the Diels–Alder reactions of ethyl cyclopropylidenepyruvate with cyclopentadiene, 2,3-dimethylbuta-1,3-diene and furan to give at 25 °C the corresponding Diels–Alder cycloadducts in 65, 82 and 65% yields, respectively.[1c] A complete regioselectivity, and a high *endo*-stereoselectivity of up to 98% de combined with excellent yields (75–99%) were observed for the Diels–Alder reactions of difluoro(methylene)cyclopropanes with various cyclic dienes, such as furan and cyclopentadiene.[108] An asymmetric Diels–Alder reaction between a chiral cyclopropylidene imide and cyclopentadiene was reported by Kuethe et al., in 2006.[109] As shown in Scheme 69, the cycloaddition performed at −75 °C in the presence of Me_2AlCl provided a mixture of the *endo*- and *exo*-cycloadducts as the exclusive products in a 97:3 ratio and in quantitative yield.



Scheme 69. Asymmetric Diels–Alder reaction of chiral cyclopropylidene imide.

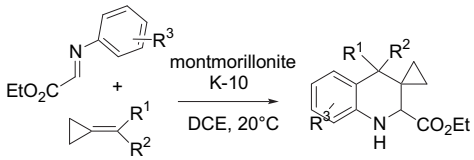
In the same area, Keay et al. have applied a novel cyclopropenyl-containing 1,3-spiroaminoalcohol as chiral dienophile to the asymmetric Diels–Alder reaction with various dienes.[110] The corresponding *endo*-cycloadducts were obtained in moderate-to-high yields (20–88%) with diastereomeric ratios ranging from 2:1 to 99:1. Some of the best results are collected in Scheme 70.

On the other hand, high-pressure-induced, inverse-electron-demand hetero-Diels–Alder reactions of ethyl *trans*-4-ethoxy-2-oxo-3-butenoate and methyl *trans*-4-benzyloxy-2-oxo-3-butenoate with benzyl (cyclopropylidenemethyl) ether have been developed by de Meijere et al.[111] These novel reactions led with moderate diastereoselectivity to mixtures of the two corresponding diastereomeric *cis*- and *trans*-esters in 64 and 80% yields, respectively.



Scheme 70. Asymmetric Diels–Alder reactions of chiral cyclopropenyl-containing 1,3-spiroaminoalcohol.

In 2003, Shi et al. reported aza-Diels–Alder reactions of alkylidenecyclopropanes with imines derived from aromatic amines and arylaldehydes.[112] These reactions catalysed by $Sc(OTf)_3$ provided a novel and highly efficient route to the synthesis of the corresponding tetrahydroquinoline derivatives bearing a spirocyclopropyl ring in good-to-excellent yields (65–100%). More recently, these reactions were also performed by Wu et al. in the presence of a catalytic amount of $FeCl_3$, providing a series of aza-Diels–Alder cycloadducts in good-to-excellent yields (80–99%).[113] Moreover, Shi et al. demonstrated that these cycloadducts could also be synthesised through one-pot, three-component aza-Diels–Alder reactions of arenecarbaldehydes, arylamines and alkylidenecyclopropanes using a heterogeneous solid acid catalyst, such as montmorillonite K-10, under mild conditions and with moderate-to-quantitative yields (32–100%).[114] In 2009, the scope of this methodology was extended to the aza-Diels–Alder reactions of alkylidenecyclopropanes with a wide range of ethyl (arylimino)acetates.[115] Some selected results are collected in Scheme 71. It was shown that these reactions could also be induced by a Brønsted acid, such as TfOH, albeit in generally lower yields.



$R^1 = R^2 = p$-Tol, $R^3 = p$-Br: 91%
$R^1 = R^2 = p$-$MeOC_6H_4$, $R^3 = p$-Br: 95%
$R^1 = R^2 = p$-FC_6H_4, $R^3 = p$-Br: 97%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph, $R^3 = p$-Br: 99% (1:1)
$R^1 = R^2 = p$-ClC_6H_4, $R^3 = p$-Br: 99%
$R^1 = p$-ClC_6H_4, R^2 = Ph, $R^3 = p$-Br: 99% (1:1)
$R^1 = R^2 = p$-$MeOC_6H_4$, $R^3 = p$-MeO: 99%
$R^1 = R^2 = p$-$MeOC_6H_4$, $R^3 = p$-Cl: 99%
$R^1 = R^2 = p$-$MeOC_6H_4$, R^3 = H: 92%
$R^1 = R^2 = p$-$MeOC_6H_4$, $R^3 = o$-Cl: 82%

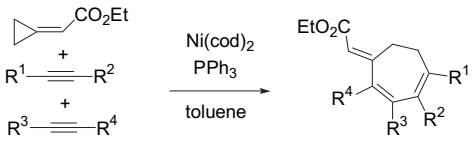
Scheme 71. Aza-Diels–Alder reaction of alkylidenecyclopropanes with ethyl (arylimino)acetates catalysed by montmorillonite K-10.

On the other hand, novel (1′-arylallylidene)cyclopropanes have been implicated as dienes in Pd-catalysed Diels–Alder reactions with various carbonyl, azo and nitroso heterodienophiles, such as trichloroacetaldehyde, diethyl mesoxalate, indane-1,2,3-trione, pyrimidine-2,4,5,6-tetrone, *N*-phenyltriazolinedione, diisopropyl azodicarboxylate and various nitrosoarenes.[116] Whereas carbonyl compounds had to be activated to react and mostly required a mild

Lewis acid catalyst ($Eu(fod)_3$), azo compounds and nitrosoarenes underwent cycloadditions at ambient temperature and pressure. A wide variety of spirocyclopropanated heterocycles could be synthesised by application of this novel methodology in moderate-to-almost quantitative yields (22–99%).

3.3. [3+2+2] Cycloadditions

Compared to the rich chemistry of the cycloaddition reactions available for the synthesis of six-membered carbocycles, fewer cycloaddition reactions are available for the synthesis of seven-membered carbocycles. In this context, Ni-catalysed intermolecular [3+2+2] cycloadditions of ethyl cyclopropylideneacetate with alkynes have been reported by Saito et al., providing a wide range of multisubstituted cycloheptadienes with moderate-to-high yields, as shown in Scheme 72.[117] This methodology could also be applied to the reaction of ethyl cyclopropylideneacetate with 1,7-diynes or 1,6-diynes, which yielded in similar conditions the corresponding 7,6- and 7,5-fused bicyclic compounds in moderate-to-good yields (1–73%).[118]

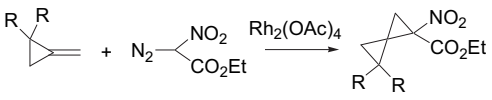


$R^1 = R^2 = t$-Bu, $R^3 = R^4$ = H: 89%
R^1 = TMS, $R^2 = R^4$ = H, R^3 = Ph: 72%
R^1 = TMS, $R^2 = R^4$ = H, $R^3 = p$-$CF_3C_6H_4$: 74%
$R^1 = R^3$ = TMS, $R^2 = R^4$ = H: 70%

Scheme 72. Ni-catalysed [3+2+2] cycloaddition of ethyl cyclopropylideneacetate with alkynes.

3.4. [1+2] Cycloadditions

A convenient synthesis of novel polyspirocyclic cyclopropane amino acids was reported by Kuznetsova et al., in 2006.[119] This process was based on the Rh-catalysed [1+2] cycloaddition of ethyl nitrodiazoacetate to a series of methylenecyclopropanes, followed by reduction of nitrocarbethoxy adducts and subsequent hydrolysis. As shown in Scheme 73, a series of ethyl nitrospiro[2.2]pentane carboxylates were produced in good yields through this [1+2] cycloaddition. In 2009, these authors also reported the synthesis of a series of novel bromofluorospiropentanes in moderate-to-good yields (35–92%) by the [1+2] cycloaddition of bromofluorocarbene, in situ generated from $CHBr_2F$, to the corresponding methylenecyclopropanes in the presence of 50% NaOH and TEBAC.[120]

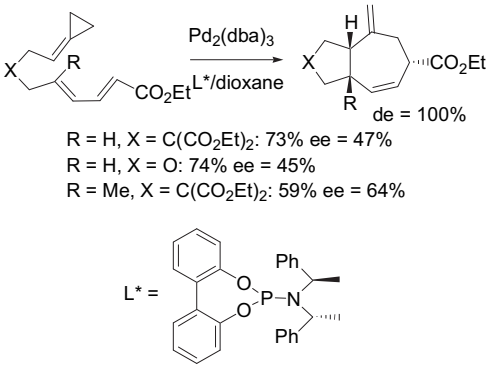


R = H: 85%
R,R = $(CH_2)_2$: 85% (3:1)
R,R = $(CH_2)_3$: 85% (3:1)
R,R = $(CH_2)_6$: 70%

Scheme 73. Rh-catalysed [1+2] cycloaddition of methylenecyclopropanes with ethyl nitrodiazoacetate.

3.5. [4+3] Cycloadditions

Only a few examples of [4+3] cycloadditions of alkylidenecyclopropanes have been reported to date. In 2007, Saito et al. described the Ni-catalysed [4+3] cycloaddition reactions of ethyl cyclopropylideneacetate with 1,3-dienes, which provided the corresponding cycloheptene derivatives in moderate yields.[121] The reaction was performed in the presence of $Ni(cod)_2$ combined with tri-*o*-biphenylyl phosphate as ligand. With symmetrical 2,3-disubstituted 1,3-butadienes, the corresponding cycloheptenes were formed as single products in 38–70% yields, whereas the reaction of 2-substituted 1,3-butadienes led to the formation of the corresponding cycloheptenes as mixtures of two regioisomers in 0–68% yields, according to the nature of the substituents. In addition, a new type of Pd-catalysed [4+3] cycloaddition was reported by Mascarenas et al., in 2007.[122] This work dealt with the first enantioselective intramolecular [4+3] cycloaddition of various dienylidenecyclopropanes performed in the presence of a palladium catalyst combined with a chiral phosphoramidite ligand, providing in both moderate yields and enantioselectivities (up to 64% ee) the corresponding 5,7-bicarbocyclic cycloadducts as single diastereomers, as shown in Scheme 74.

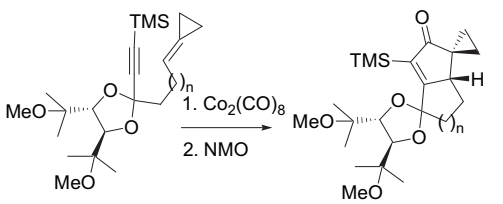


R = H, X = $C(CO_2Et)_2$: 73% ee = 47%
R = H, X = O: 74% ee = 45%
R = Me, X = $C(CO_2Et)_2$: 59% ee = 64%

Scheme 74. Enantioselective Pd-catalysed [4+3] intramolecular cycloaddition of dienylidenecyclopropanes.

3.6. [2+2+1] Cycloadditions

The Pauson–Khand reaction is the Co-mediated cocyclisation of an alkyne and an alkene with carbonyl insertion which yields a cyclopentenone. De Meijere et al. have demonstrated that alkylidenecyclopropanes and even bicyclopropylidene moieties included in 1,6- and 1,7-enynes did favour the intramolecular Pauson–Khand reactions in the presence of $Co_2(CO)_8$ to furnish the corresponding spirocyclopropanated and/or cyclopropane-annelated bicyclo[3.3.0]octanones or bicyclo[4.3.0]nonanones in moderate-to-good yields (0–65%) after a subsequent treatment with *N*-methylmorpholine *N*-oxide (NMO).[123] Moreover, an asymmetric version of this methodology was developed by these authors by incorporating a chiral C_2-symmetric acetal moiety adjacent to the triple bond in the starting material, which allowed the formation of the corresponding spirocyclopropanated cycloadduct with a diastereoselectivity of up to 78% de. In 2003, higher levels of diastereoselection of up to 100% de were achieved by Krafft et al. in the asymmetric Pauson–Khand reaction of closely related 1,6- and 1,7-cyclopropylidenynones bearing more sterically demanding substituents on the tartrate-derived auxiliary, as depicted in Scheme 75.[124]

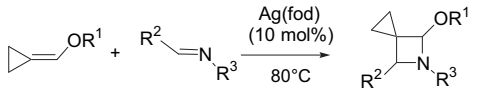


n = 1: 68% de = 90%
n = 2: 94% de = 100%

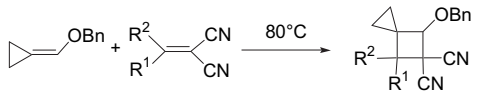
Scheme 75. Asymmetric Pauson–Khand reaction of chiral 1,6-cyclopropylidenynone.

3.7. [2+2] Cycloadditions

Only few examples of [2+2] cycloadditions of methylene- and alkylidenecyclopropanes have been developed so far, one of which was reported by de Meijere et al., who developed thermally induced and Ag-catalysed [2+2] cycloadditions of (alkoxymethylene) cyclopropanes with imines.[125] The corresponding readily available 2-alkoxyazetidines were obtained in high yields with a high level of cis/trans diastereoselectivity of up to 96% de, as shown in Scheme 76. Moreover, the thermally induced [2+2] cycloaddition of (benzyloxymethylene)cyclopropane with a range of alkylidenemalononitriles was also successfully achieved by these authors, providing the corresponding cyclobutane derivatives in good-to-high yields combined with moderate cis/trans diastereoselectivity (≤54% de), as shown in Scheme 76.[126]



R^1 = Bn, R^2 = Ph, R^3 = Ts: 97% *cis/trans* = 51:1
R^1 = Bn, R^2 = *p*-$MeOC_6H_4$, R^3 = Ts: 82% *cis/trans* = 24:1
R^1 = Bn, R^2 = *p*-$CF_3C_6H_4$, R^3 = Ts: 91% *cis/trans* = 18:1
R^1 = Bn, R^2 = *t*-Bu, R^3 = Ts: 80% *cis/trans* = 29:1
R^1 = Bn, R^2 = Ph, R^3 = Ns: 92% *cis/trans* = 28:1
R^1 = *n*-Bu, R^2 = Ph, R^3 = Ts: 80% *cis/trans* = 8:1



R^1 = Ph, R^2 = H: 96% *trans/cis* = 1.5:1
R^1 = *p*-$NO_2C_6H_4$, R^2 = H: 93% *trans/cis* = 2.0:1
R^1 = *p*-$MeOC_6H_4$, R^2 = H: 91% *trans/cis* = 1.3:1
R^1 = 2-Naph, R^2 = H: 96% *trans/cis* = 1.8:1
R^1 = R^2 = Me: 54%

Scheme 76. Thermally induced [2+2] cycloadditions of (alkoxymethylene)cyclopropanes with imines and alkylidenemalononitriles.

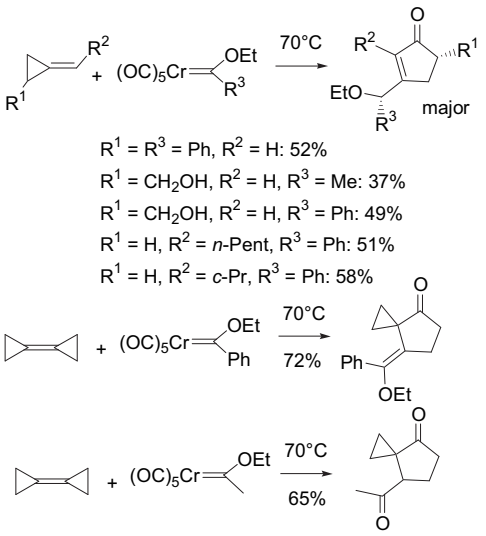
In order to explain the formation of formal [3+2] cycloadducts having a tetrahydrofuran skeleton through the $Yb(OTf)_3$-catalysed reactions of activated aldehydes (or ketones) with alkylidenecyclopropanes, Shi et al. have proposed a stepwise process involving the Lewis acid-catalysed [2+2] cycloaddition of ketenes with aldehydes as the first step, rather than a concerted process.[127] The intermediate [2+2] cycloadducts were subsequently rearranged in the presence of the Lewis acid into the final five-membered products.

3.8. [4+1] Cycloadditions

Since 2003, a single example of a [4+1] cycloaddition has been reported by de Meijere et al.[128] This work dealt with the reaction of Fischer carbenechromium complexes with alkylidenecyclopropanes and bicyclopropylidene in an unprecedented manner. Indeed, all four carbon atoms of the alkylidenecyclopropane moiety along with carbon monoxide were incorporated with the formation of three new C–C σ-bonds to give the corresponding cyclopentenone derivatives in moderate (33–58% for alkylidenecyclopropanes)-to-good yields (65–72% for bicyclopropylidene) as shown in Scheme 77.

3.9. [3+1+1] Cycloadditions

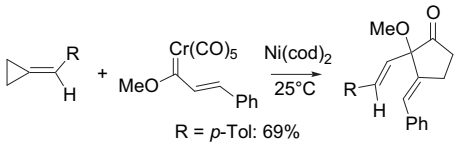
A rare example of a [3+1+1] cycloaddition was reported by Kamikawa et al., in 2006.[129] In this study, the synthesis of various methylenecyclopentenones was achieved through the Ni-catalysed



R^1 = R^3 = Ph, R^2 = H: 52%
R^1 = CH_2OH, R^2 = H, R^3 = Me: 37%
R^1 = CH_2OH, R^2 = H, R^3 = Ph: 49%
R^1 = H, R^2 = *n*-Pent, R^3 = Ph: 51%
R^1 = H, R^2 = *c*-Pr, R^3 = Ph: 58%

Scheme 77. [4+1] Cocyclisations of alkylidenecyclopropanes and bicyclopropylidene with Fischer carbenechromium complexes.

[3+1+1] cycloaddition reaction of alkenyl Fischer carbene complexes with alkylidenecyclopropanes, occurring with moderate-to-good yields (40–71%), as shown in Scheme 78.

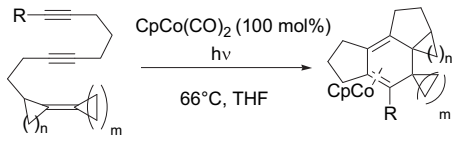


R = *p*-Tol: 69%
R = *p*-$MeOC_6H_4$: 71%
R = *p*-ClC_6H_4: 51%
R = *p*-$CF_3C_6H_4$: 43%

Scheme 78. Ni-catalysed [3+1+1] cycloaddition of alkylidenecyclopropanes with alkenyl Fischer carbene complexes.

3.10. [2+2+2] Cycloadditions

In 2005, Malacria et al. reported the Co-catalysed [2+2+2] cocyclisations of (methylenecyclopropyl)diynes as an easy access to various cyclopropanated oligocycles.[130] Therefore, it was found that methylenecyclopropyldiynes bearing an electron-withdrawing substituent at the acetylenic terminus were suitable substrates for Co-mediated intramolecular [2+2+2] cocylisations to provide the corresponding cyclopropane-fused and spirocyclopropanated tricyclic skeletons in moderate-to-excellent yields as mixtures of diastereomers. As shown in Scheme 79, the process was performed upon irradiation in boiling THF in the presence of a stoichiometric amount of $CpCo(CO)_2$.



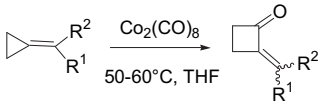
R = $P(O)Ph_2$, n = m = 1: 94% (1.5:1)
R = $P(O)Ph_2$, n = 1, m = 0: 85% (2.1:1)
R = CO_2Me, n = 0, m = 1: 47% (1:0)
R = $P(O)Ph_2$, n = 0, m = 1: 91% (1.8:1)

Scheme 79. Co-mediated [3+1+1] cocyclisation of methylenecyclopropyldiynes.

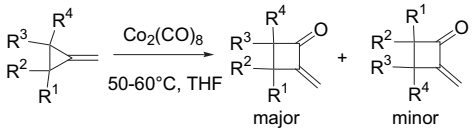
3.11. [1+3] Cycloadditions

A novel Co-mediated [3+1] cocyclisation of alkylidenecyclopropanes with carbon monoxide was developed by de Meijere

et al., providing the corresponding 2-alkylidenecyclobutanones under mild conditions in low-to-high yields (5–90%), as summarised in Scheme 80.[131] With monosubstituted methylenecyclopropanes, the corresponding cyclobutanones were obtained as trans/cis-mixtures of diastereomers with up to 96% de in favour of the trans-isomer, while the reactions of 2- and 2,3-substituted methylenecyclopropanes led to mixtures of the two corresponding regioisomers, 3- and 4-substituted 2-methylenecyclobutanones. In all cases, the 3-substituted 2-methylenecyclobutanone regioisomers predominated.



R^1 = *n*-Hex, R^2 = H: 88% *trans/cis* = 71:29
R^1 = Ph, R^2 = H: 80% *trans/cis* = 98:2

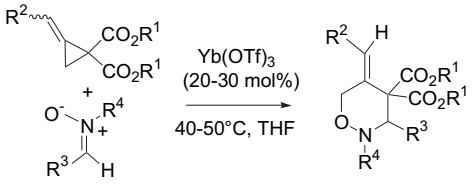


R^1 = *n*-Hex, R^2 = R^3 = R^4 = H: 90% major/minor = 85:15
R^1 = Ph, R^2 = Me, R^3 = R^4 = H: 67% major/minor = 89:11
R^1 = R^2 = R^3 = R^4 = Me: 81%

Scheme 80. Co-mediated [3+1] cocyclisations of alkylidenecyclopropanes with carbon monoxide.

3.12. [3+3] Cycloadditions

Finally, a new type of Lewis acid-promoted distal [3+3] cycloaddition of alkylidenecyclopropane-1,1-diesters with C,*N*-diaryl nitrones was recently disclosed by Wang et al.[132] As shown in Scheme 81, this process occurred in the presence of a catalytic amount of $Yb(OTf)_3$ with high site-, regio- and stereoselectivity, yielding exclusively the corresponding distal [3+3] cycloaddition products in high yields.

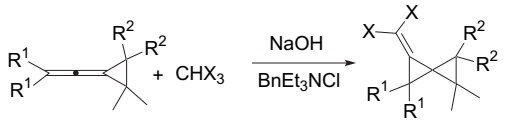


R^1 = Me, R^2 = R^3 = R^4 = Ph: 98%
R^1 = Me, R^2 = *p*-Tol, R^3 = R^4 = Ph: 93%
R^1 = Me, R^2 = $BnCH_2$, R^3 = R^4 = Ph: 94%
R^1 = Me, R^2 = $Ph(CH_2)_2$, R^3 = R^4 = Ph: 89%
R^1 = Et, R^2 = R^3 = R^4 = Ph: 98%
R^1 = Me, R^2 = R^3 = Ph, R^4 = *p*-ClC_6H_4: 90%
R^1 = Me, R^2 = Ph, R^3 = *p*-$MeOC_6H_4$, R^4 = *p*-ClC_6H_4: 94%
R^1 = Me, R^2 = Ph, R^3 = *m*-$MeOC_6H_4$, R^4 = *p*-ClC_6H_4: 98%
R^1 = Me, R^2 = Ph, R^3 = *p*-$MeOC_6H_4$, R^4 = *p*-BrC_6H_4: 93%
R^1 = Me, R^2 = Ph, R^3 = 2-Fu, R^4 = *m*-ClC_6H_4: 81%

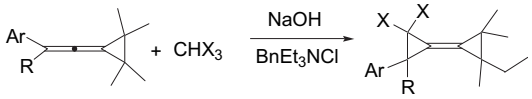
Scheme 81. Yb-catalysed [3+3] cycloaddition of alkylidenecyclopropane-1,1-diesters with nitrones.

3.13. [2+1] Cycloadditions

In 2003, Mizuno et al. investigated the cyclopropanation of arylvinylidenecyclopropanes by dihalocarbenes.[133] It was found that the reaction of diarylvinylidenecyclopropanes with dibromocarbenes or dichlorocarbenes exclusively produced the corresponding 1-(dihalomethylene)spiropentanes in generally high yields, as shown in Scheme 82. On the other hand, a different reactivity was observed in the case of monoarylvinylidenecyclopropanes, which provided the corresponding cyclopropylidenecyclopropanes as the major products (Scheme 82).



R^1 = Ph, R^2 = Me, X = Br: 73%
R^1 = *p*-ClC_6H_4, R^2 = Me, X = Br: 77%
R^1 = *p*-$MeOC_6H_4$, R^2 = Me, X = Br: 78%
R^1 = Ph, R^2 = Me, X = Cl: 99%
R^1 = R^2 = Ph, X = Br: 84%

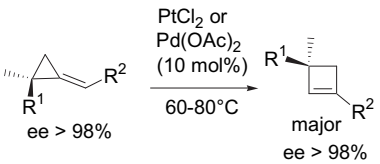


Ar = 1-Naph, R = Me, X = Br: 68%
Ar = 1-Naph, R = Me, X = Cl: 79%
Ar = Ph, R = Cy, X = Br: 48%
Ar = Ph, R = Me, X = Br: 40%
Ar = *p*-ClC_6H_4, R = Me, X = Br: 69%
Ar = 2-Naph, R = Me, X = Br: 65%

Scheme 82. Cyclopropanations of arylvinylidenecyclopropanes with dihalocarbenes.

4. Rearrangements

In addition to thermal[134] and photochemical[135] rearrangements of alkylidenecyclopropanes into cyclobutenes, an efficient synthesis of cyclobutenes via transition metal-catalysed rearrangements of alkylidenecyclopropanes was independently developed by Fürstner and Aïssa[136] and Shi et al., in 2006.[137] It was demonstrated that in the presence of catalytic amounts of $Pd(OAc)_2$ combined with $CuBr_2$,[137] or $PtCl_2$,[136] a range of non-substituted alkylidenecyclopropanes were converted into the corresponding non-substituted cyclobutenes in moderate-to-high yields (41–93%). Moreover, Shi et al. have found that 3-methylenecyclopropylmethyl sulfonates could be easily isomerised into the corresponding 3-methylenecyclobutyl analogues by simple silica gel chromatography in moderate-to-good yields (30–77%).[138] In addition, a new access to cyclobutenes possessing quaternary stereocentres was recently developed by Marek et al. on the basis of the Pd(II)- and Pt(II)-catalysed rearrangements of enantiomerically pure alkylidenecyclopropanes with the complete preservation of the stereogenic centre.[139] As shown in Scheme 83,

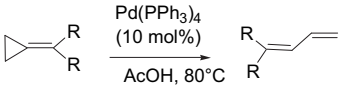


with $PtCl_2$:
R^1 = Et, R^2 = Ph: 70% de > 98%
R^1 = Et, R^2 = *p*-Tol: 74% de > 98%
R^1 = Et, R^2 = *p*-$MeOC_6H_4$: 82% de > 98%
with $Pd(OAc)_2$:
R^1 = *n*-Bu, R^2 = Ph: 55% de > 98%
R^1 = Et, R^2 = *p*-$BnOC_6H_4$: 85% de > 98%

Scheme 83. Pd- and Pt-catalysed rearrangements of chiral alkylidenecyclopropanes into cyclobutenes.

in almost all of the substrates studied, the cyclobutene was obtained as a single enantiopure regioisomer in good yield.

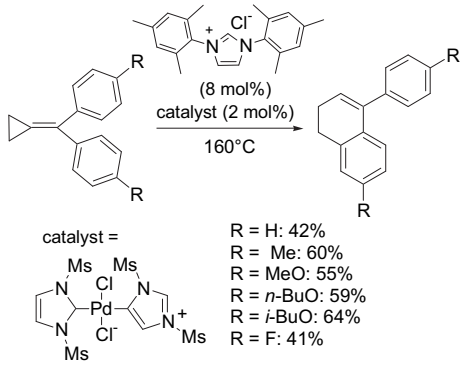
On the other hand, Pd-catalysed ring-opening isomerisations of alkylidenecyclopropanes proceeded smoothly in acetic acid at 80 °C to give the corresponding 1,1-disubstituted dienes in good-to-excellent yields under mild conditions, as shown in Scheme 84.[140] In addition, Osakada et al. have reported that 2-phenyl-1-methylenecyclopropane was isomerised into 2-phenyl-1,3-butadiene at room temperature in the presence of $RhH(CO)(PPh_3)_3$ as catalyst in 86% yield.[141]



R = Ph: 96%
R = *p*-FC_6H_4: 97%
R = *p*-Tol: 98%
R = *p*-$MeOC_6H_4$: 77%
R = *n*-Bu: 90%

Scheme 84. Pd-catalysed ring-opening isomerisations of alkylidenecyclopropanes into 1,1-disubstituted dienes.

In 2008, Huang et al. developed the *N*-heterocyclic carbene Pd-catalysed cycloisomerisation of aryl-substituted alkylidenecyclopropanes to the corresponding 1-aryl dihydronaphthalenes.[142] The best results for this cascade C–C bond cleavage/C–H activation/C–C bond formation are shown in Scheme 85.



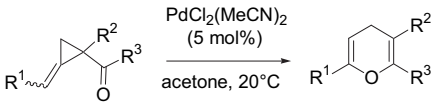
R = H: 42%
R = Me: 60%
R = MeO: 55%
R = *n*-BuO: 59%
R = *i*-BuO: 64%
R = F: 41%

Scheme 85. Pd-catalysed cycloisomerisation of aryl-substituted alkylidenecyclopropanes.

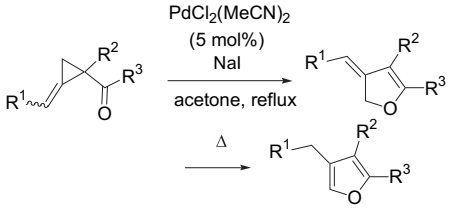
Ma et al. have reported that acyl-substituted alkylidenecyclopropanes underwent smooth cycloisomerisation into the corresponding 4*H*-pyrans in good yields (56–96%) in the presence of catalytic amounts of Pd(II), as shown in Scheme 86.[75a,143] Interestingly, in the presence of NaI in refluxing acetone, the same palladium catalyst triggered a different cycloisomerisation, affording alkylidenedihydrofurans, which after prolonged heating isomerised into the corresponding furans (Scheme 86) in good yields (66–89%).

In 2007, Lautens et al. reported a highly efficient and selective route to cyclic diazadienes through the ring expansion of methylenecyclopropyl hydrazones.[144] The best results, shown in Scheme 87, were obtained by performing the reaction at 120 °C in DME in the presence of a Lewis acid such as $MgCl_2$ and TMEDA as an additive, which allowed up to 91% yield to be reached.

In the same context, these authors have reported the rearrangement of secondary methylenecyclopropyl amides into the corresponding β,γ-unsaturated lactams by treatment with MgI_2 at high dilution.[145] This ring expansion provided moderate-to-good yields (55–100%), as shown in Scheme 88, and could be extended to secondary alkylidenecyclopropyl amides, albeit in generally lower

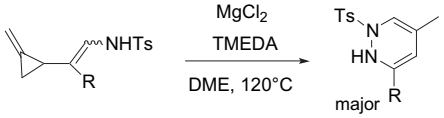


R^1 = *n*-Hept, R^2 = CO_2Et, R^3 = Me: 80%
R^1 = Bn, R^2 = CO_2Et, R^3 = Me: 80%
R^1 = *n*-Bu, R^2 = SO_2Ph, R^3 = Me: 91%
R^1 = *n*-Hept, R^2 = CO_2Et, R^3 = Ph: 96%



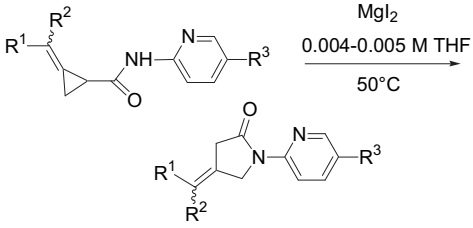
R^1 = Bn, R^2 = CO_2Et, R^3 = Me: 78%
R^1 = *n*-Hept, R^2 = SO_2Ph, R^3 = Me: 89%
R^1 = *n*-Hept, R^2 = CO_2Et, R^3 = Ph: 88%
R^1 = R^2 = H, R^3 = 1-Naph: 83%

Scheme 86. Pd-catalysed cycloisomerisations of acyl-substituted alkylidenecyclopropanes.



R = Me: 86%
R = Et: 77%
R = Bn: 70%
R = *n*-Bu: 91%
R = $CH_2CH{=}CH_2$: 87%
R = *n*-Bu: 91%
R = $(CH_2)_3OTBS$: 81%
R = 2-Fu: 81%

Scheme 87. Rearrangement of methylenecyclopropyl hydrazones.

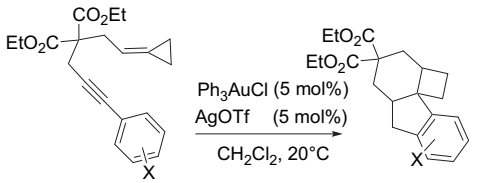


R^1 = R^2 = H, R^3 = Me: 99%
R^1 = R^2 = H, R^3 = NO_2: 100%
R^1 = Me, R^2 = R^3 = H: 63%
R^1 = Bn, R^2 = R^3 = H: 64%
R^1 = Cy, R^2 = R^3 = H: 75%

Scheme 88. Rearrangement of secondary methylene- and alkylidenecyclopropyl amides.

yields (39–75%) than those obtained with secondary methylenecyclopropyl amides.

In the course of developing a total synthesis of the angular triquinane, ventricosene, Toste et al. have disclosed a novel cycloisomerisation of ynilidenecyclopropanes catalysed by a gold catalyst.[146] Thus, upon treatment with catalytic amounts of Ph_3AuCl and AgOTf, these enynes, containing an embedded cyclopropane unit, led selectively to the formation of the corresponding tetracycles as single diastereomers in moderate-to-high yields (35–91%), as shown in Scheme 89. An enantioselective version of

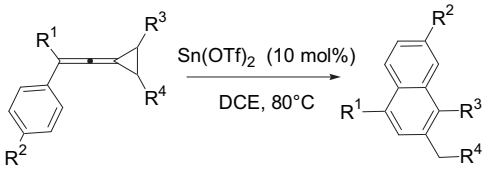


X = H: 75%
X = 2-Me: 75%
X = 2-I: 91%
X = 3,5-Me: 44%
X = 3,5-Cl: 86%

Scheme 89. Au-catalysed cycloisomerisation of ynilidenecyclopropanes.

the reaction was developed in the case of the sterically hindered *o*-iodo substrate, which was the most efficient substrate. An enantioselectivity of 82% ee was obtained for the corresponding tetracycle in the presence of a chiral biphosphine ligand.

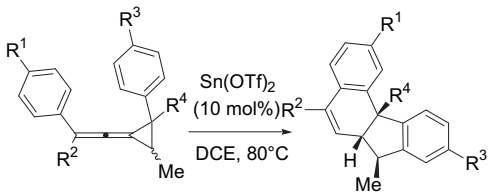
Shi et al. have studied the rearrangements of a wide number of arylvinylidenecyclopropanes, providing different types of products depending on the substituents at their cyclopropyl ring. Thus, it was found that aryl-monosubstituted or aryl-disubstituted vinylidenecyclopropanes underwent interesting rearrangements in the presence of Lewis acids such as $Sn(OTf)_2$ to give the corresponding naphthalene derivatives in good-to-high yields, as shown in Scheme 90.[147] In 2007, similar results were obtained for these reactions by using a heterogeneous solid acid catalyst, such as montmorillonite K-10.[148]



R^1= R^4 = H, R^2 = Ph, R^3 = *p*-Tol: 80%
R^1= R^4 = H, R^2 = Ph, R^3 = *p*-$MeOC_6H_4$: 61%
R^1= Me, R^2 = *p*-Tol, R^3 = Ph, R^4 = H: 91%
R^1= MeO, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph, R^4 = H: 70%
R^1= F, R^2 = *p*-FC_6H_4, R^2 = Ph, R^4 = H: 80%
R^1= H, R^2 = R^3 = Ph, R^4 = Me: 85%

Scheme 90. Rearrangement of aryl-monosubstituted and aryl-disubstituted vinylidenecyclopropanes.

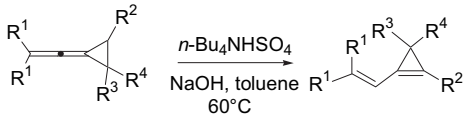
On the other hand, these authors have found that arylvinylidenecyclopropanes bearing three substituents at the cyclopropyl ring rearranged upon treatment with $Sn(OTf)_2$ into the corresponding phenyl-1*H*-indene derivatives in good-to-high yields, as shown in Scheme 91.[149]



R^1= H, R^2 = Ph, R^3 = Cl, R^4 = Me: 91%
R^1= H, R^2 = Ph, R^3 = Br, R^4 = Me: 97%
R^1= H, R^2 = Ph, R^3 = R^4 = Me: 84%
R^1= H, R^2 = Ph, R^3 = OMe, R^4 = Me: 82%
R^1= F, R^2 = *p*-FC_6H_4, R^3 = H, R^4 = Me: 97%
R^1= R^3 = H, R^2 = Ph, R^4 = Et: 96%

Scheme 91. Rearrangement of trisubstituted arylvinylidenecyclopropanes.

Finally, Shi et al. have shown that vinylidenecyclopropanes underwent a simple isomerisation into the corresponding vinylcyclopropenes when submitted to basic conditions.[150] As shown in Scheme 92, a series of vinylcyclopropenes could be prepared in good-to-high yields (61–93%) through this rearrangement.



R^1= R^2 = Ph, R^3 = R^4 = Me: 92%
R^1= *p*-FC_6H_4, R^2 = Ph, R^3 = R^4 = Me: 63%
R^1= *p*-ClC_6H_4, R^2 = Ph, R^3 = R^4 = Me: 81%
R^1= Ph, R^2 = *p*-ClC_6H_4, R^3 = R^4 = Me: 93%
R^1= Ph, R^2 = *p*-BrC_6H_4, R^3 = R^4 = Me: 93%
R^1= R^2 = Ph, R^3 = R^4 = H: 68%

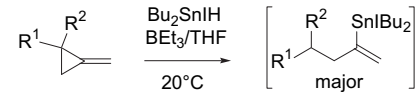
Scheme 92. Rearrangement of trisubstituted arylvinylidenecyclopropanes.

5. Radical reactions

The *exo* C=C double bond of alkylidenecyclopropanes has also been reacted with radical species in a number of recent works. The initial attack is often followed by the cyclopropane ring opening, but this is not the rule. The radical species derived from the initial reaction then give the final products by hydrogen capture or evolve into other species through a radical cascade sequence. In 2004, Shi et al. reported the heat-promoted free radical reaction of arylidenecyclopropanes with diphenylselenide, which provided the corresponding 1,1-diaryl-2,4-diphenylselenyl-1-butenes in good yields (59–89%).[151] This process required a high temperature (150 °C), however, which could limit its application in organic synthesis. In this context, Huang et al. have successfully developed similar reactions under visible-light irradiation, which allowed a range of 1,1-dialkyl-2,4-diphenylselenyl-1-butenes and 1,1-diaryl-2,4-diphenylselenyl-1-butenes to be produced in good yields (71–90%), starting from the corresponding (dialkylmethylene)cyclopropanes and (diarylmethylene)cyclopropanes, respectively.[152] In addition, these authors have investigated these reactions in the presence of copper(II) acetate.[153] They found that copper(II) acetate did mediate the reactions of (diarylmethylene)cyclopropanes with diphenyl diselenide or diphenyl disulfide, providing different products under different conditions. Thus, under visible irradiation, the corresponding 2-phenylselenyl-3,3-diarylcyclobutenes were generated in moderate yields (50–65%), while, under heating conditions (110 °C), 2-phenylselenyl- or 2-phenylsulfanyl-1,1-diaryl-1,3-butadienes were obtained in moderate yields (40–68 and 48–63%, respectively).

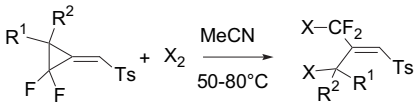
In 2008, Baba et al. reported the hydrostannation of methylenecyclopropanes using Bu_2SnIH to prepare α-substituted vinyltins with unprecedented regioselectivity.[154] These vinyltins could be applied to a one-pot, Pd-catalysed coupling reaction with 4-iodonitrobenzene, providing the corresponding disubstituted alkenes in high yields, as shown in Scheme 93.

In 2007, Huang et al. reported the synthesis of a series of 1,1-diaryl-2,4-dibromobutenes in high yields (76–84%) through the reaction of (diarylmethylene)cyclopropanes with KBr in AcOH in the presence of dibenzoyl peroxide, providing an environmentally friendly method, which avoided the employment of transition metals, for the synthesis of 2,4-dibromobutenes.[155] The thermal ring opening of difluoro(methylene)cyclopropanes with halogens, such as Br_2 or I_2, was shown to provide the corresponding tetrahalogenated products arising from the cleavage of the distal bond under radical conditions.[21] The best results are collected in Scheme 94.



R^1 = Ph, R^2 = H: 92%
R^1 = R^2 = Ph: 75%
R^1,R^2 = $(CH_2)_5$: 98%

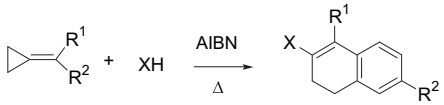
Scheme 93. Bu_2SnIH-promoted hydrostannation-Pd-catalysed coupling domino reaction of methylenecyclopropanes.



R^1 = R^2 = Me, X = Br: 50%
R^1 = R^2 = Me, X = I: 61%
R^1 = Me, R^2 = Et, X = Br: 63%
R^1 = Me, R^2 = Et, X = I: 85%
R^1,R^2 = $(CH_2)_5$, X = Br: 49%
R^1,R^2 = $(CH_2)_5$, X = I: 80%

Scheme 94. Thermal ring opening of difluoro(methylene)cyclopropanes with halogens.

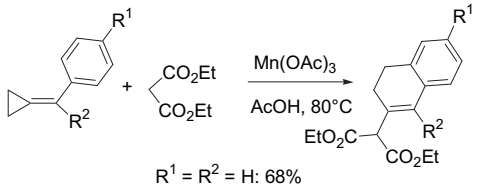
On the other hand, Huang et al. have reported the reaction of alkylidenecyclopropanes with benzenethiol in the presence of 2,2′-azobisisobutyronitrile (AIBN), which gave selectively the corresponding 3-phenylsulfanyl-1,2-dihydronaphthalenes in moderate-to-good yields (51–74%), as shown in Scheme 95.[33] In the same area, the AIBN-mediated reaction of alkylidenecyclopropanes with diethyl phosphite produced the corresponding diethyl 3,4-dihydro-2-naphthylphosphonates in moderate yields (65–75%), as shown in Scheme 95.[156]



with XH = PhSH:
R^1 = Ph, R^2 = H: 74%
R^1 = p-FC_6H_4, R^2 = F: 65%
R^1 = p-ClC_6H_4, R^2 = Cl: 69%
R^1 = p-Tol, R^2 = F: 70%
R^1 = p-$MeOC_6H_4$, R^2 = MeO: 74%
R^1 = H, R^2 = Br: 53%
with XH = $H(O)P(OEt)_2$:
R^1 = Ph, R^2 = H: 75%
R^1 = p-FC_6H_4, R^2 = F: 65%
R^1 = p-ClC_6H_4, R^2 = Cl: 70%
R^1 = p-Tol, R^2 = Me: 74%

Scheme 95. AIBN-mediated reactions of alkylidenecyclopropanes with benzenethiol and diethyl phosphite.

In 2004, Huang et al. reported a tandem cyclisation reaction of alkylidenecyclopropanes with malonic acid diethyl ester mediated by $Mn(OAc)_3$, providing highly regioselectively the corresponding 2-(3,4-dihydronaphthalen-2-yl)malonic esters in moderate-to-good yields (59–72%).[157] The best results are shown in Scheme 96. The scope of this methodology was extended to the reaction of alkylidenecyclopropanes with methyl-substituted dicarbonyl

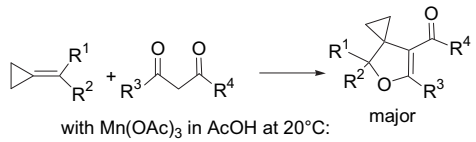


R^1 = R^2 = H: 68%
R^1 = Me, R^2 = H: 70%
R^1 = H, R^2 = Ph: 72%
R^1 = OMe, R^2 = H: 64%
R^1 = Br, R^2 = H: 67%

Scheme 96. $Mn(OAc)_3$-mediated reaction of alkylidenecyclopropanes with malonic acid diethyl ester.

compounds, such as 3-methyl-2,4-pentanedione or ethyl 2-methylacetoacetate, which gave the corresponding dihydronaphthalene derivatives in 52–67 and 47–67% yields, respectively.[158]

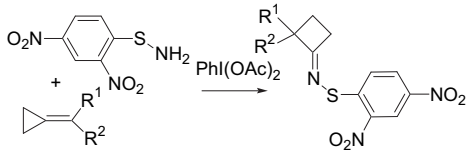
These results were totally different from those obtained by Shi et al. in similar conditions by using more enolisable β-dicarbonyl compounds, such as 1,3-diketones, as the reactants.[159] Indeed, the reaction of a series of alkylidenecyclopropanes with either cyclic or acyclic 1,3-diketones led selectively to the formation of the corresponding 4,5-dihydrofurans in moderate-to-high yields (30–87%), as shown in Scheme 97. Even better results were independently obtained by Huang and Nair by inducing these reactions with cerium(IV) ammonium nitrate (CAN) instead of $Mn(OAc)_3$.[160–162] Moreover, the scope of this methodology was extended to a wide range of alkylidenes, including unsymmetrical alkylidenes, and to other 1,3-dicarbonyl compounds, such as β-ketoesters, in high yields, as shown in Scheme 97.



with $Mn(OAc)_3$ in AcOH at 20°C:
R^1 = R^2 = p-Tol, R^3 = R^4 = Me: 72%
R^1 = R^2 = p-$MeOC_6H_4$, R^3 = R^4 = Me: 53%
R^1 = R^2 = p-FC_6H_4, R^3 = R^4 = Me: 77%
R^1 = R^2 = Ph, R^3,R^4 = $(CH_2)_3$: 79%
R^1 = R^2 = p-Tol, R^3,R^4 = $(CH_2)_3$: 72%
R^1 = R^2 = p-ClC_6H_4, R^3,R^4 = $(CH_2)_3$: 87%
R^1 = R^2 = p-FC_6H_4, R^3,R^4 = $(CH_2)_3$: 71%
with CAN in MeOH at 0°C:
R^1 = Ph, R^2 = p-Tol, R^3,R^4 = $(CH_2)_3$: 85%
R^1 = R^2 = Ph, R^3 = Me, R^4 = OEt: 77%
R^1 = R^2 = R^3 = Ph, R^4 = OEt: 84%
R^1 = R^2 = R^3 = R^4 = Ph: 85%
R^1 = R^2 = p-Tol, R^3 = Me, R^4 = OEt: 85%
R^1 = R^2 = p-Tol, R^3 = R^4 = Ph: 93%

Scheme 97. $Mn(OAc)_3$- and CAN-mediated reactions of alkylidenecyclopropanes with 1,3-dicarbonyl compounds.

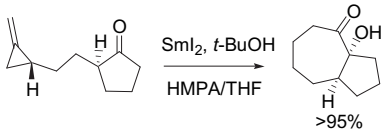
On the other hand, an interesting and stereoselective addition of a nitrene, derived from $PhI(OAc)_2$ and 2,4-dinitrophenylsulfenamide, to alkylidenecyclopropanes was found to produce the corresponding ring-enlargement products.[163] As shown in Scheme 98, a variety of (cyclobutylidene)amide derivatives were obtained in moderate-to-excellent yields under mild conditions. In addition, ring expansions also occurred when alkylidenecyclopropanes were reacted with a nitrenoid species generated from *N*-aminophthalimide and $PhI(OAc)_2$.[164] A series of aryl-substituted cyclobutylidenes could be prepared under these conditions in moderate-to-high yields (45–98%).



$R^1 = R^2 = p$-Tol: 99%
$R^1 = R^2 = p$-$MeOC_6H_4$: 96%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph: 99%
$R^1 = R^2 = p$-FC_6H_4: 84%
R^1 = Ph, R^2 = Me: 67%
$R^1 = p$-ClC_6H_4, R^2 = Ph: 69%

Scheme 98. $PhI(OAc)_2$-mediated reaction of alkylidenecyclopropanes with 1,3-dinitrophenylsulfenamide.

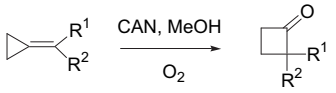
Kilburn et al. have developed SmI_2-mediated 6-*exo* cyclisations of methylenecyclopropyl ketones, through the generation of methylenecycloheptanyl radicals.[165] The efficiency of these cyclisations to synthesise cycloheptane derivatives was found, however, to be highly dependent on the stereochemistry of the cyclisation precursor. While mixtures of products were often obtained, the reaction of a methylenecyclopropane bearing a cyclopentanone led to the formation of the corresponding *cis*-fused bicyclic alcohol as a single product in excellent yield, as shown in Scheme 99.



>95%

Scheme 99. SmI_2-mediated 6-*exo* cyclisation of methylenecyclopropyl ketone.

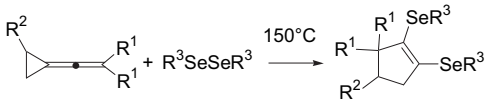
A convenient synthesis of 2,2-diarylcyclobutanones was developed by Nair et al. on the basis of the oxidative ring expansion of alkylidenecyclopropanes.[166] This process was mediated by cerium ammonium nitrate under an oxygen atmosphere and provided the expected butanones in good yields, as shown in Scheme 100.



$R^1 = R^2$ = Ph: 75%
R^1 = Ph, $R^2 = o$-Tol: 62%
R^1 = Ph, $R^2 = p$-Tol: 82%
R^1 = Ph, R^2 = 1-Naph: 73%
R^1 = Ph, R^2 = 2-Naph: 78%
$R^1 = p$-$MeOC_6H_4$, R^2 = Ph: 48%
$R^1 = R^2 = p$-ClC_6H_4: 57%

Scheme 100. CAN-mediated oxidative ring expansion of alkylidenecyclopropanes.

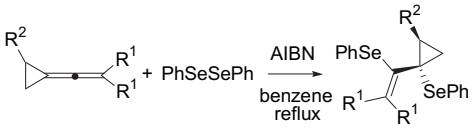
On the other hand, Tokuda et al. have investigated the electrochemical carboxylation of ring-fused alkylidenecyclopropanes in a suitable aprotic solvent, using a one-compartment electrochemical cell equipped with a platinum plate cathode and a zinc plate anode under an atmospheric pressure of carbon dioxide.[167] This process afforded either the corresponding mono- or dicarboxylic acids in moderate-to-good yields. Finally, Shi et al. have studied the sulfinatodehalogenation reactions of *gem*-aryl disubstituted methylenecyclopropanes with perfluoroiodoalkanes.[168] This novel process led to mixtures of the corresponding ring-opened products, rearranged products and addition products in moderate yields in the presence of sodium dithionite. In addition, Shi et al. have disclosed a novel radical ring-opening reaction of arylvinylidenecyclopropanes with diaryl diselenides upon heating at 150 °C to produce in good-to-high yields (61–89%) the corresponding 1,2-diarylselenocyclopentene derivatives, as shown in Scheme 101.[169]



$R^1 = p$-Tol, $R^2 = R^3$ = Ph: 78%
$R^1 = p$-FC_6H_4, $R^2 = R^3$ = Ph: 86%
$R^1 = R^3$ = Ph, $R^2 = p$-ClC_6H_4: 89%
$R^1 = R^2$ = Ph, $R^3 = p$-Tol: 79%

Scheme 101. Ring-opening reaction of arylvinylidenecyclopropanes with diaryl diselenides.

On the other hand, when the reactions of arylvinylidenecyclopropanes with diphenyl diselenide were performed in the presence of AIBN, they led to the formation of the corresponding cyclopropanated addition products in moderate-to-high yields (48–92%) under mild conditions, as shown in Scheme 102.[170]

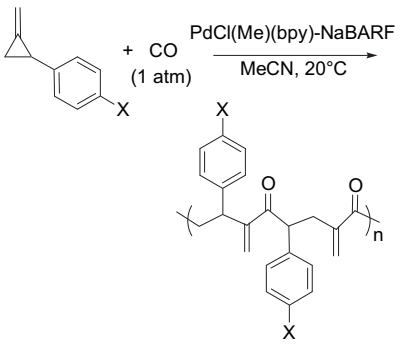


$R^1 = R^2$ = Ph: 92%
$R^1 = p$-Tol, R^2 = Ph: 88%
$R^1 = p$-FC_6H_4, R^2 = Ph: 79%
R^1 = Ph, $R^2 = p$-Tol: 83%

Scheme 102. AIBN-induced reaction of arylvinylidenecyclopropanes with diphenyl diselenide.

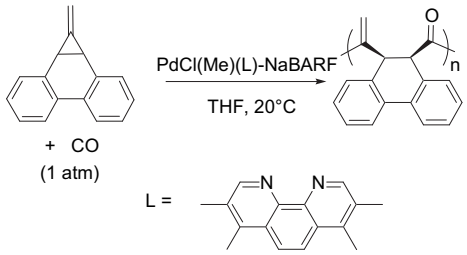
6. Polymerisation reactions

In recent years, progress in the polymerisation and copolymerisation of methylenecyclopropanes has been achieved by using the late transition metal complexes as promoters.[171] While the Pd-catalysed co- and terpolymerisations of methylenecyclopropanes with CO proceeded with partial ring opening to afford polyketones containing both cyclic and ring-opened exomethylene units in the chain,[172] Osakada et al. have demonstrated that the copolymerisation of 2-aryl-1-methylenecyclopropanes with CO in the presence of PdCl(Me)(bpy) and NaBARF afforded the corresponding polyketones composed of ring-opened structural units exclusively (Scheme 103).[173]



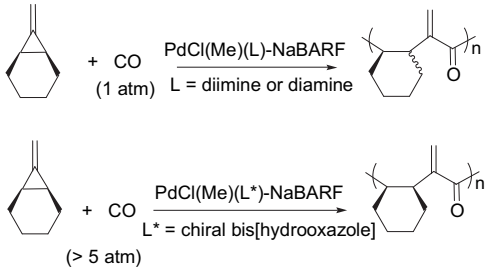
Scheme 103. Pd-catalysed copolymerisation of 2-aryl-1-methylenecyclopropanes with CO.

In 2006, these authors reported the Pd-catalysed alternating copolymerisation of 7-methylenedibenzo[*a*,*c*]bicyclo[4.1.0]heptane with CO to produce the corresponding ketone (Scheme 104).[174] The use of palladium complexes with substituted 1,10-phenanthroline ligands produced the polymer with a narrow molecular weight distribution. An asymmetric version of this process was developed by using a chiral bisoxazoline ligand to afford the corresponding optically active polymer with narrow polydispersity.



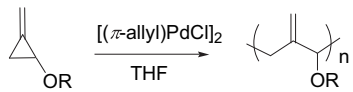
Scheme 104. Pd-catalysed copolymerisation of 7-methylenedibenzo[*a*,*c*]bicyclo[4.1.0]heptane with CO.

Analogously, the ring-opening copolymerisation of 7-methylenebicyclo[4.1.0]heptane with CO in the presence of palladium diamine complexes combined with NaBARF proceeded readily to produce the corresponding regulated polyketone (Scheme 105) with cyclohexane rings incorporated in the polymer chain.[175] It was shown that the cis/trans stereoselectivity of the 1,2-cyclohexyl units as well as the tacticity of the polyketone was strongly dependent on the palladium ligands and the solvent used. The observed partial epimerisation of one of the centres leading to the formation of a thermodynamically more favourable trans-isomer was rationalised via the reversible β-hydride elimination of palladium during polymer growth.[176] The scope of this methodology was successfully extended to the asymmetric copolymerisation of 7-methylenebicyclo[4.1.0]heptane with CO performed in the presence of chiral palladium complexes, bearing optically active bis[dihydrooxazole]-type ligands, to produce the corresponding optically active polyketone.[177] The reaction was carried out under an increased CO pressure (>5 atm), affording a chiral polymer, which contained monomer units bearing the *cis*-cyclohexane-1,2-diyl group almost exclusively.



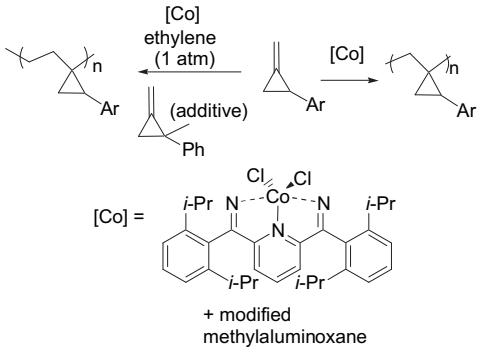
Scheme 105. Pd-catalysed copolymerisations of 7-methylenebicyclo[4.1.0]heptane with CO.

In 2008, these authors reported the polymerisation of a series of 2-alkoxy-1-methylenecyclopropanes initiated by dinuclear π-allylpalladium complexes, which furnished the corresponding polymers having the vinylidene and alkoxy groups for every three-carbon atom unit (Scheme 106).[178] In addition, the use of a cyclic dinuclear (π-allyl)palladium complex as the initiator in the presence of pyridine has allowed the synthesis of cyclic polymers with narrow molecular weight to be performed.[179]



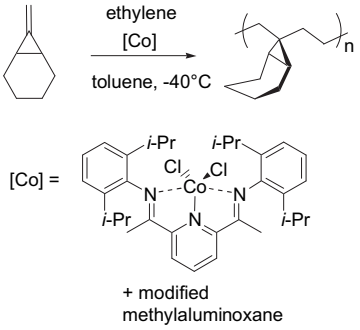
Scheme 106. Pd-catalysed polymerisations of 2-alkoxy-1-methylenecyclopropanes.

In 2004, Osakada et al. demonstrated that Co-catalysed polymerisation of 2-aryl-1-methylenecyclopropanes could proceed with preservation of the three-membered ring to yield a well-regulated polymer with head-to-tail linkage of the monomer units (Scheme 107).[180] It was shown that the molecular weight of the polymer increased with the introduction of electron-withdrawing substituents in the aryl ring of the monomer. The cobalt catalyst, depicted in Scheme 107, in combination with modified methylaluminoxane enabled alternating copolymerisation of methylenecyclopropane with ethylene to cleanly produce the corresponding regulated copolymer, consisting of two alternating monomer units with no homopolymers or random copolymer units. The employment of an additive, such as 2-methyl-2-phenyl-1-methylidenecyclopropane, to suppress ethylene homopolymerisation was found to be necessary to obtain the regulated copolymer structure.



Scheme 107. Co-catalysed polymerisation and copolymerisation of 2-aryl-1-methylenecyclopropanes with ethylene.

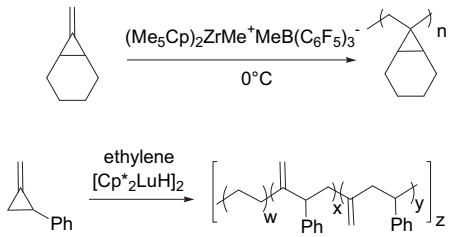
The scope of this methodology could be extended to the copolymerisation of 7-methylenebicyclo[4.1.0]heptane with ethylene, affording the corresponding alternating copolymer, as shown in Scheme 108.[181] In this case, the reaction was initiated by a cobalt complex with a bis(1-iminoalkyl)pyridine ligand combined with modified methylaluminoxane as the cocatalyst.



Scheme 108. Co-catalysed copolymerisation of 7-methylenebicyclo[4.1.0]heptane with ethylene.

On the other hand, metallocene complexes of early transition metal complexes, such as zirconium and lutetium, have been reported to promote selective ring-opening polymerisation and copolymerisation with ethylene of methylenecyclopropanes.[182] Therefore, while a variety of metallocene catalysts were curiously ineffective in the polymerisation of 2-phenyl-1-methylenecyclopropane, a variety of catalysts, such as $[Cp^*_2LuH]_2$, were competent to achieve random copolymerisation of this compound with ethylene (Scheme 109). On the other hand, the copolymerisation of 7-methylenebicyclo[4.1.0]heptane with ethylene resulted in the formation of two different

polymers, depending on the nature of the catalyst used, whereas the polymerisation of this compound led to the formation of the expected polymer in the presence of $(Me_5Cp)_2ZrMe^+MeB(C_6F_5)_3^-$, as shown in Scheme 109.

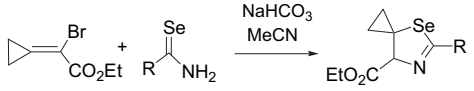


Scheme 109. Zr-catalysed polymerisation of 7-methylenebicyclo[4.1.0]heptane and Lu-catalysed copolymerisation of 2-phenyl-1-methylenecyclopropane with ethylene.

7. Miscellaneous reactions

7.1. Addition reactions with ring conservation

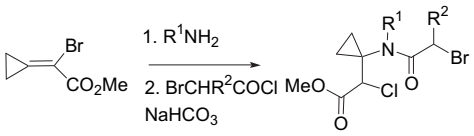
Chloro- or bromocyclopropylidene acetates are much better Michael acceptors than any other 3,3-disubstituted acrylates.[183] This is partly due to the strain release on increasing the p character of hybridisation upon nucleophilic addition, but is also related to the presence of the α-chloro or α-bromo substituent.[184] Furthermore, the multifunctionality of these compounds makes them versatile tools in organic synthesis, as was demonstrated by the synthesis of 5-spirocyclopropane-annulated selenazoline-4-carboxylates developed by Huang et al.[185] As shown in Scheme 110, these compounds were generated in good yields through the Michael addition of the corresponding selenoamides to ethyl 2-bromo-2-cyclopropylideneacetate followed by an intramolecular substitution in the presence of $NaHCO_3$ as base.



R = Ph: 85%
R = *p*-ClC_6CH_4: 83%
R = *m*-BrC_6CH_4: 83%
R = *p*-Tol: 79%
R = *m*-Tol: 88%
R = *p*-FC_6CH_4: 84%

Scheme 110. Michael addition of selenoamides to ethyl 2-bromo-2-cyclopropylideneacetate.

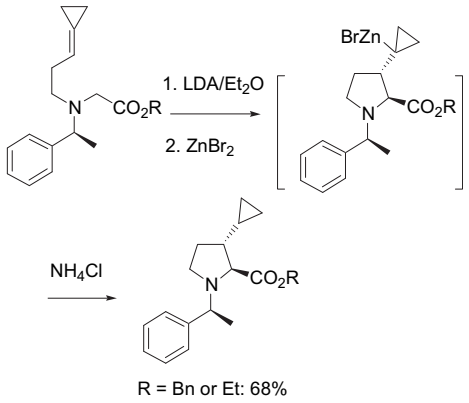
Several reactions of this type have also been reported by de Meijere et al.[97,186] As an example, these authors developed the Michael addition of a primary aliphatic or aromatic amine onto methyl 2-bromo-2-cyclopropylideneacetate, which was followed by acylation of the Michael adduct with an α-bromo acid chloride under modified Schotten–Baumann conditions to give the corresponding bishalide in high yield (72–91%), as shown in Scheme 111.



$R^1 = BnO(CH_2)_3$, R^2 = H: 91%
$R^1 = MeO(CH_2)_2$, R^2 = H: 66%
$R^1 = MeO_2CCH_2$, R^2 = Ph: 86%
R^1 = *p*-$CF_3C_6CH_4CH_2$, R^2 = Ph: 80%

Scheme 111. Michael addition of amines to methyl 2-bromo-2-cyclopropylideneacetate.

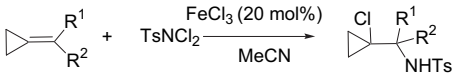
In addition, the treatment of phenylsulfonylmethylenecyclopropane with sodium ethoxide in ethanol led to the retrieval of the corresponding Michael product in 81% yield.[187] Another nucleophilic addition to alkylidenecyclopropane, described by Karoyan et al., dealt with the amino–zinc–enolate carbometallation cyclisation of a hindered alkylidenecyclopropane, which provided after subsequent hydrolysis the corresponding proline derivative in good yield as a single diastereoisomer (Scheme 112).[188] In 2005, de Meijere et al. reported the synthesis of spirocyclopropanated analogues of biologically active demethoxyfumitremorgine C and tadalafil.[189] The first step of these syntheses was the conjugated addition of indole to methyl 2-chloro-2-cyclopropylideneacetate mediated by $EtAlCl_2$ in dichloromethane at 0 °C, which furnished the Michael adduct in 85% yield.



R = Bn or Et: 68%

Scheme 112. Amino–zinc–enolate carbometallation cyclisation of alkylidenecyclopropanes.

On the other hand, Shi et al. have developed Fe-catalysed aminohalogenation of arylidenecyclopropanes, providing the corresponding aminochlorinated products in moderate-to-high yields (44–99%), as shown in Scheme 113.[190]

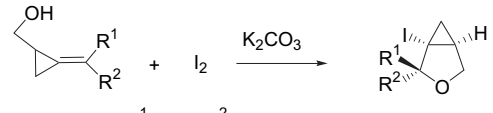


R^1 = H, R^2 = Ph: 48%
R^1 = H, R^2 = *p*-$MeOC_6CH_4$: 77%
$R^1 = R^2$ = *p*-$MeOC_6CH_4$: 99%
R^1 = H, R^2 = *p*-Tol: 75%

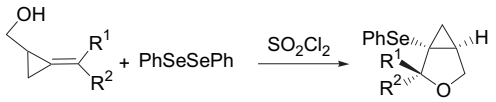
Scheme 113. Fe-catalysed aminohalogenation of arylidenecyclopropanes.

A variety of iodocyclopropylmethanols could be readily prepared in moderate-to-excellent yields (36–96%) via the simple iodohydroxylation reaction of the corresponding alkylidenecyclopropanes with I_2 and water. In order to enlarge this methodology and avoid the use of iodine, these authors have developed more general halohydroxylations of alkylidenecyclopropanes by using *N*-halosuccinimides as the halogen source.[34,35] In this context, a wide range of 3-halobut-3-en-1-ol derivatives could be synthesised under mild conditions in moderate-to-excellent yields (31–93%). In a same area, Shi et al. have shown that the reaction of arylmethylenecyclopropylcarbinols with iodine in the presence of K_2CO_3, or diphenyl diselenide in the presence of sulfuryl chloride, stereoselectively gave the corresponding ring-closure product, 1-iodo-2-aryl-3-oxabicyclo[3.1.0]hexane, or 1-phenylselenenyl-2-aryl-3-oxabicyclo[3.1.0]hexane, respectively, in good-to-high yields at room temperature (Scheme 114).[191]

In the same area, a highly stereoselective iodolactonisation reaction of alkylidenecyclopropyl esters with iodine or *N*-iodosuccinimide (NIS) under aqueous conditions was reported by Ma



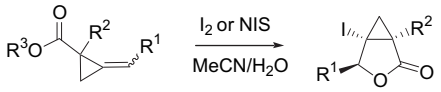
R^1 = Ph, R^2 = H: 91%
R^1 = *p*-FC_6CH_4, R^2 = H: 96%
R^1 = *p*-ClC_6CH_4, R^2 = H: 94%
R^1 = *p*-Tol, R^2 = H: 92%
R^1 = *p*-$MeOC_6CH_4$, R^2 = H: 95%
R^1 = H, R^2 = *p*-BrC_6CH_4: 86%



R^1 = Ph, R^2 = H: 84%
R^1 = *p*-FC_6CH_4, R^2 = H: 74%
R^1 = *p*-ClC_6CH_4, R^2 = H: 80%%
R^1 = *p*-$MeOC_6CH_4$, R^2 = H: 61%

Scheme 114. Reactions of arylmethylenecyclopropylcarbinols with iodine and diphenyl diselenide.

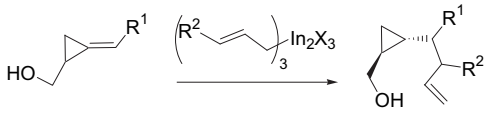
et al., leading to the formation of the corresponding 4,5-*trans*-1,5-*cis*-3-oxabicyclo[3.1.0]hexan-2-ones in moderate-to-good yields (40–96%), as shown in Scheme 115.[192]



with I_2:
R^1 = *n*-Hept, R^2 = Ph, R^3 = Bn: 96%
R^1 = *n*-Hept, R^2 = Ph, R^3 = Me: 85%
with NIS:
R^1 = *n*-Hept, R^2 = CO_2Me, R^3 = Me: 91%
R^1 = Bn, R^2 = CO_2Me, R^3 = Me: 77%
R^1 = *n*-Hept, R^2 = CO_2Et, R^3 = Et: 84%
R^1 = *n*-Hept, R^2 = Ph, R^3 = Me: 87%

Scheme 115. Iodolactonisation reaction of alkylidenecyclopropyl esters.

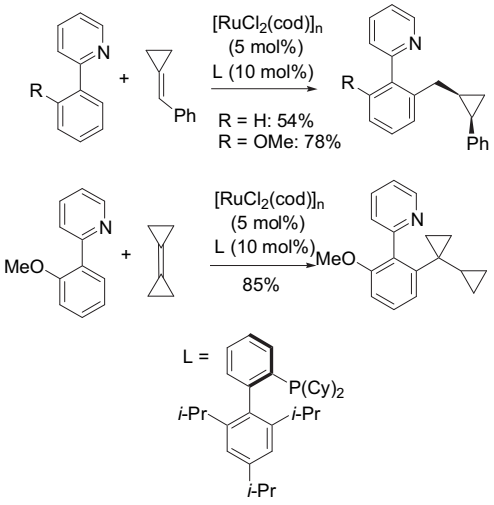
In 2008, Hirashita et al. investigated the allylation of alkylidenecyclopropanes with allylindium reagents.[193] It was shown that alkylidenecyclopropanes bearing a hydroxymethyl group at the ring underwent a stereoselective allylindation with allylindium sesquiiodide to afford the corresponding allylated products, in which the allyl group was delivered at the external sp^2 carbon via cyclopropylindium intermediates. The best results were obtained by performing the reaction in refluxing THF or DMF as the solvent (Scheme 116).



R^1 = R^2 = H, X = I: 89%
R^1 = H, R^2 = Ph, X = Br: 30%
R^1 = Ph, R^2 = H, X = I: 52%

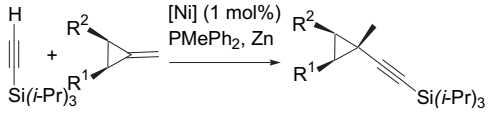
Scheme 116. Allylation of alkylidenecyclopropanes.

The ring conservation was also observed in the first catalytic intermolecular hydroarylation of alkylidenecyclopropanes via C–H bond functionalisation.[194] Indeed, the Ru-catalysed *anti*-Markovnikov addition of an arene to an alkylidenecyclopropane, employing a monophosphine biphenyl ligand, occurred highly selectively with complete conservation of the three-membered ring to yield the corresponding *cis* cyclopropane derivative in moderate-to-good yield (Scheme 117). Surprisingly, the more challenging hydroarylation of bicyclopropylidene led to the corresponding product with up to 85% yield.



Scheme 117. Ru-catalysed hydroarylations of alkylidenecyclopropanes.

In 2009, Suginome et al. reported the Ni-catalysed regio- and stereoselective hydroalkynylation of methylenecyclopropanes, in which the alkynyl group was selectively introduced to the internal carbon atom to give the corresponding alkynylcyclopropane derivatives in excellent yields and as single stereoisomers.[195] As shown in Scheme 118, the reactions were performed with triisopropylsilylacetylene in the presence of $NiCl_2$(DME) or Ni(cod)$_2$ combined with $PMePh_2$ as a ligand and Zn powder as a reductant (in the case of $NiCl_2$(DME) as catalyst). It must be noted that the use of less sterically hindered alkynes, such as 1-hexyne and phenylacetylene, resulted in their oligomerisation.

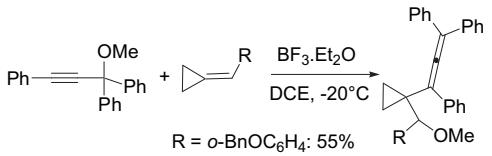


with [Ni] = $NiCl_2$(DME)/Zn:
R^1 = CH_2Bn, R^2 = H: 84%
R^1 = $(CH_2)_2OTBS$, R^2 = H: 92%
R^1 = $(CH_2)_4OTBS$, R^2 = H: 89%
R^1 = $(CH_2)_4OBn$, R^2 = H: 78%
R^1 = $(CH_2)_4OPiv$, R^2 = H: 94%
R^1 = Ph, R^2 = H: 89%
R^1 = *p*-$MeOC_6H_4$, R^2 = H: 87%
With [Ni] = Ni(cod)$_2$:
R^1,R^2 = $(CH_2)_4$: 85%
R^1,R^2 = $(CH_2)_5$: 84%

Scheme 118. Ni-catalysed hydroalkynylation of methylenecyclopropanes.

On the other hand, Shi et al. have shown that 3-methoxy-1,3,3-triphenylprop-1-yne reacted with arylidenecyclopropanes in the presence of $BF_3{\cdot}Et_2O$ at −20 °C to provide the corresponding cyclopropane derivatives bearing an allenic moiety in moderate yields (30–55%) (Scheme 119), while the corresponding alkylidenecyclobutene and cyclobutane derivatives were obtained when performing the reaction at higher temperature.[40]

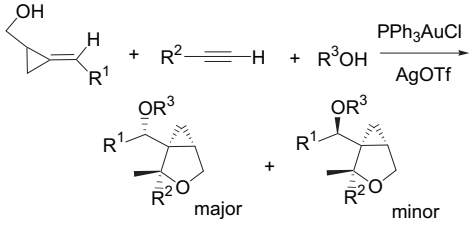
An efficient three-component addition reaction between 2-(arylmethylene)cyclopropylcarbinols, terminal alkynes and alcohols was developed by Shi et al., in 2007.[196] This process, catalysed by



R = *o*-BnOC$_6$H$_4$: 55%
R = *o*-MeOC$_6$H$_4$: 40%
R = *p*-MeOC$_6$H$_4$: 30%

Scheme 119. Reaction of 3-methoxy-1,3,3-triphenylprop-1-yne with arylidenecyclopropanes.

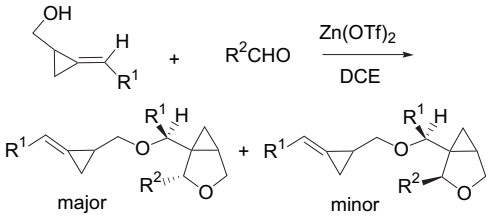
gold(I), furnished the corresponding 3-oxabicyclo-[3.1.0]hexanes straightforwardly under mild conditions and in good-to-high yields (59–95%), as shown in Scheme 120. The authors have proposed a mechanism involving an intermolecular tandem hydroalkoxylation/Prins-type reaction.



R^1 = R^2 = Ph, R^3 = CH$_2$Bn: 92% (1.8:1)
R^1 = Ph, R^2 = *p*-Tol, R^3 = CH$_2$Bn: 95% (2:1)
R^1 = Ph, R^2 = *p*-BrC$_6$CH$_4$, R^3 = CH$_2$Bn: 90% (2.1:1)
R^1 = Ph, R^2 = *p*-MeOC$_6$CH$_4$, R^3 = Me: 93% (2.3:1)
R^1 = Ph, R^2 = *p*-MeOC$_6$CH$_4$, R^3 = CH$_2$Bn: 90% (2.7:1)
R^1 = Ph, R^2 = *p*-MeOC$_6$CH$_4$, R^3 = CH$_2$CH=CH$_2$: 92% (2:1)

Scheme 120. Au-catalysed reaction of 2-(arylmethylene)cyclopropylcarbinols with alkynes and alcohols.

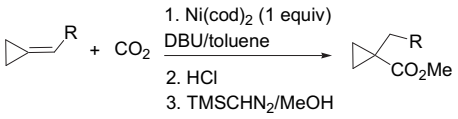
On the other hand, 2-(arylmethylene)cyclopropylcarbinols reacted with aldehydes in the presence of Zn(OTf)$_2$ to give the corresponding 3-oxa-bicyclo[3.1.0]hexanes as mixtures of two diastereoisomers via a 5-*exo* Prins-type cyclisation in good-to-high yields (Scheme 121).[197] Moreover, the scope of this methodology could be extended to the reaction of these alkylidenecyclopropanes with aldimines, providing the same products.



R^1 = Ph, R^2 = *p*-ClC$_6$CH$_4$: 67% + 30%
R^1 = Ph, R^2 = *p*-Tol: 59% + 19%
R^1 = Ph, R^2 = *m*-Tol: 57% + 24%
R^1 = *p*-Tol, R^2 = *p*-ClC$_6$CH$_4$: 61% + 26%
R^1 = R^2 = *p*-Tol: 58% + 22%

Scheme 121. Zn-catalysed reaction of 2-(arylmethylene)cyclopropylcarbinols with aldehydes.

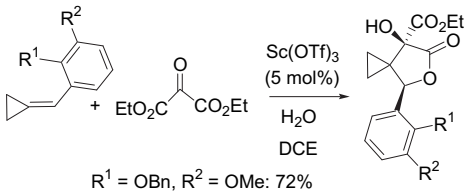
In 2006, Murakami et al. demonstrated that it was possible to carboxylate alkylidenecyclopropanes with gaseous carbon dioxide in the presence of a stoichiometric amount of a nickel complex and an amine.[51] According to the nature of the solvent and the amine, the reaction led to different products. When the reaction was carried out in toluene as the solvent and DBU as the base, it provided the corresponding cyclopropane derivatives in moderate-to-high yield (20–93%), as shown in Scheme 122.



R = Ph: 93%
R = *p*-Tol: 78%
R = *o*-Tol: 92%
R = *p*-ClC$_6$H$_4$: 93%
R = *p*-FC$_6$H$_4$: 89%

Scheme 122. Ni-catalysed carboxylation of alkylidenecyclopropanes.

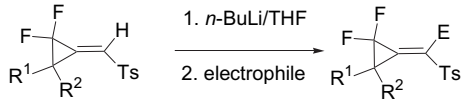
In 2007, Shi et al. reported the synthesis of 7-hydroxy-5-oxa-spiro[2,4]heptan-6-one derivatives based on the Sc(OTf)$_3$-catalysed reaction of monosubstituted arylidenecyclopropanes with diethyl ketomalonate in the presence of water.[198] As shown in Scheme 123, the tetrahydrofuran derivatives were obtained in moderate yields as single diastereoisomers.



R^1 = OBn, R^2 = OMe: 72%
R^1 = OCH$_2$-*o*-Tol, R^2 = H: 75%
R^1 = OCH$_2$-*o*-Tol, R^2 = OMe: 56%

Scheme 123. Sc(OTf)$_3$-catalysed reaction of arylidenecyclopropanes with diethyl ketomalonate.

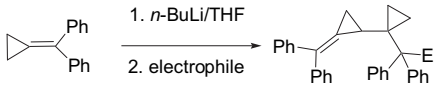
In addition, Chen et al. have condensed the lithiated intermediates prepared in situ from the treatment of (difluoro)alkylidenecyclopropanes with *n*-BuLi onto a variety of electrophiles, such as aldehydes, methyl iodide or iodine.[61] As shown in Scheme 124, the corresponding alkylated or iodinated products were obtained in moderate yields.



with electrophile = PhCHO:
R^1 = R^2 = Me, E = CH(OH)Ph: 75%
R^1 = *t*-Bu, R^2 = Me, E = CH(OH)Ph: 70%
R^1,R^2 = (CH$_2$)$_5$, E = CH(OH)Ph: 61%
with electrophile = MeI:
R^1 = R^2 = Me, E = Me: 60%
with electrophile = I$_2$:
R^1 = R^2 = Me, E = I: 57%

Scheme 124. Reaction of (difluoro)alkylidenecyclopropanes with electrophiles.

Another carbolithiation of alkylidenecyclopropanes was reported by Shi et al., in 2005.[199] In this study, *gem*-aryl disubstituted methylenecyclopropanes, such as diphenylmethylenecyclopropane, reacted with a variety of electrophiles, such as aldehydes, α,β-unsaturated ketones, CO$_2$ or epoxides, in the presence of *n*-BuLi to give in moderate-to-excellent yields the corresponding dicyclopropanated addition products, as shown in Scheme 125. Actually, this cascade reaction proceeded through a self-carbolithiation of

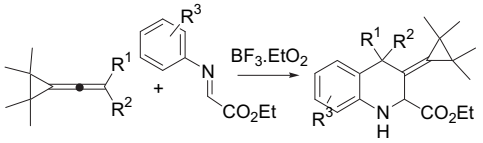


with electrophile = RCHO:
R = Ph: 92%
R = p-$MeOC_6H_4$: 99%
R = p-ClC_6H_4: 94%
R = p-FC_6H_4: 70%
R = p-Tol: 77%
with electrophile = CO_2: 96%
with electrophile = CH_2=CHAc: 95%
with electrophile = n-Bu-CH(O)CH_2: 42%

Scheme 125. Reaction of diphenylmethylenecyclopropane with electrophiles.

the arylidenecyclopropane followed by quenching with an electrophile.

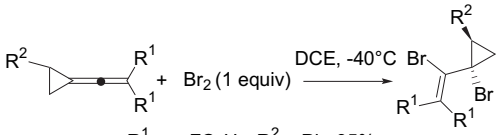
In addition, a ring conservation was observed by Shi et al. for the reaction of arylvinylidenecyclopropanes with ethyl (arylimino)acetates in the presence of $BF_3{\cdot}Et_2O$.[28] Indeed, the corresponding 1,2,3,4-tetrahydroquinoline derivatives could be prepared selectively in moderate yields, on the basis of these reactions, which were highly dependent on the electronic nature of the *N*-aryl substituent of the arylimine, which had to be an electron-rich aromatic group. The best results are collected in Scheme 126.



$R^1 = R^2 = p\text{-}ClC_6H_4$, $R^3 = m$-Me: 70%
$R^1 = R^2 = p\text{-}FC_6H_4$, $R^3 = m$-Me: 70%
$R^1 = R^2 = p$-Tol, $R^3 = m$-Me: 70%
$R^1 = R^2 = p\text{-}MeOC_6H_4$, $R^3 = m$-Me: 66%
$R^1 = R^2$ = Ph, $R^3 = p$-Me: 75%
$R^1 = R^2$ = Ph, R^3 = H: 50%

Scheme 126. $BF_3{\cdot}Et_2O$-catalysed reaction of arylvinylidenecyclopropanes with ethyl (arylimino)acetates.

Moreover, the reaction of arylvinylidenecyclopropanes with an equimolar amount of bromine at low temperature (−40 °C) in DCE produced the corresponding dibrominated cyclopropane products in moderate-to-good yields, as shown in Scheme 127.[63]

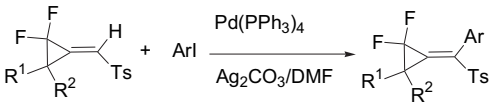


$R^1 = p\text{-}FC_6H_4$, R^2 = Ph: 85%
R^1 = Ph, $R^2 = p$-Tol: 61%
$R^1 = p\text{-}ClC_6H_4$, R^2 = Ph: 81%
R^1 = Ph, $R^2 = p\text{-}MeOC_6H_4$: 53%

Scheme 127. Reaction of arylvinylidenecyclopropanes with bromine.

7.2. Heck reactions

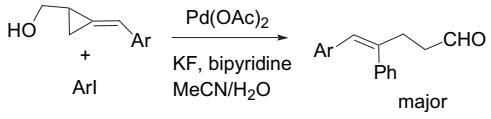
These authors have also investigated the Heck reaction of (difluoro)alkylidenecyclopropanes with aryl iodides, providing the corresponding cyclopropanated Heck products in moderate-to-good yields (25–74%), as shown in Scheme 128.[61] In comparison with their non-fluorinated analogues, the (difluoro)alkylidenecyclopropanes did not yield the corresponding ring-opened products.



$R^1 = R^2$ = Me, Ar = $p\text{-}MeOC_6H_4$: 74%
$R^1 = R^2$ = Me, Ar = p-Tol: 60%
$R^1 = R^2$ = Me, Ar = Ph: 55%
R^1 = Et, R^2 = Me, Ar = $p\text{-}MeOC_6H_4$: 57%
$R^1 = t$-Bu, R^2 = Me, Ar = $p\text{-}MeOC_6H_4$: 60%
R^1,$R^2 = (CH_2)_5$, Ar = $p\text{-}MeOC_6H_4$: 66%

Scheme 128. Heck reaction of (difluoro)alkylidenecyclopropanes.

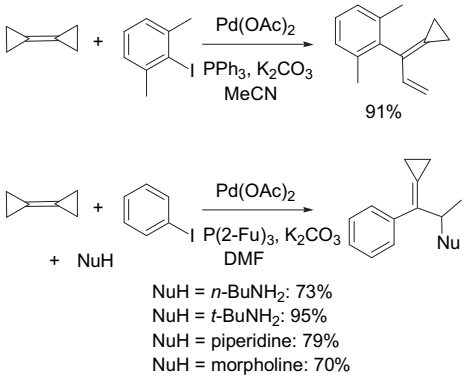
On the other hand, the ring-opened Heck products were achieved from the reaction between 2-(arylmethylene)cyclopropylcarbinols and iodobenzene.[200] Indeed, the corresponding 4,5-arylphenylpent-4-enals were formed as major products in moderate-to-good yields (21–70%) in the presence of $Pd(OAc)_2$ as the catalyst, 2,2′-bipyridine as the ligand, and KF as the base in acetonitrile–water as the solvent, as shown in Scheme 129.



Ar = Ph: 70%
Ar = $p\text{-}FC_6H_4$: 50%
Ar = p-Tol: 47%
Ar = $p\text{-}ClC_6H_4$: 52%

Scheme 129. Heck reaction of 2-(arylmethylene)cyclopropylcarbinols.

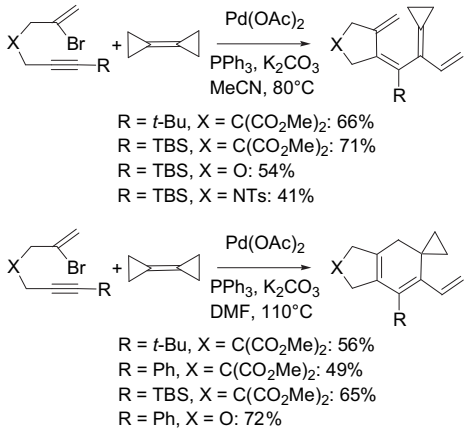
In 2003, de Meijere et al. reported the Heck reaction of bicyclopropylidene with a sterically encumbered iodide, such as 2,6-dimethyliodobenzene, to give the corresponding diene in 91% yield, as shown in Scheme 130.[201] It was shown that the reaction of bicyclopropylidene with phenyl iodide carried out in the presence of tris-(2-furyl)phosphine instead of triphenylphosphine did not lead to the corresponding phenyl-substituted diene but to a σ-allyl-/π-allylpalladium complex, which could quite efficiently be trapped with various nucleophiles. The best yields for the allyl substitution products (41–95%) were obtained with amine nucleophiles, as shown in Scheme 130.



NuH = n-$BuNH_2$: 73%
NuH = t-$BuNH_2$: 95%
NuH = piperidine: 79%
NuH = morpholine: 70%

Scheme 130. Heck reactions of bicyclopropylidene.

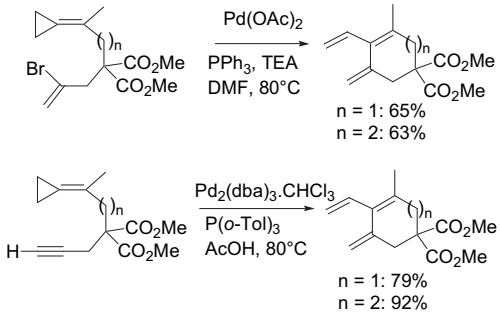
Moreover, acyclic 2-bromo-1,6-enynes bearing bulky substituents at the acetylenic terminus were co-cyclised with bicyclopropylidene under Heck conditions at 80 °C to give the corresponding cross-conjugated tetraenes in moderate-to-good yields (34–71%), as shown in Scheme 131.[202] At higher temperature (110 °C), these tetraenes underwent 6π-electrocyclisation to give



Scheme 131. Heck reactions of bicyclopropylidene with 2-bromo-1,6-enynes.

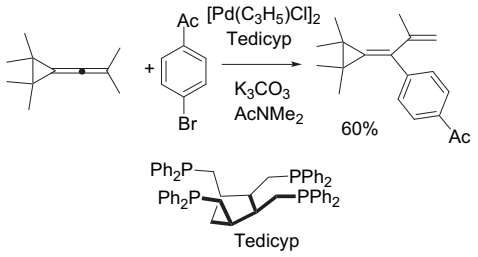
the corresponding spiro[cyclopropane-1,4′-bicyclo[4.3.0]-1(6),2-] dienes according to a one-pot process (Scheme 131) in moderate-to-good yields (32–72%).

As an extension of this methodology, these authors have developed the intramolecular Heck reactions of 2-bromo-1,6-dienes and 2-bromo-1,7-dienes bearing tetrasubstituted methylenecyclopropane end groups.[203] Under Heck conditions, these processes produced in good yields (63–65%) the corresponding cross-conjugated trienes depicted in Scheme 132, which are substituted monocyclic [3]dendralenes. In addition, the same cross-conjugated trienes were isolated in good-to-excellent yields (79–92%) from the corresponding 1,6- and 1,7-enynes by a more economic, palladium-catalysed cycloisomerisation, as shown in Scheme 132.



Scheme 132. Heck reactions of 2-bromo-1,6- and -1,7-dienes and 1,6- and 1,7-enynes.

Finally, Santelli et al. have developed Heck reactions of alkenylvinylidenecyclopropanes.[204] Therefore, the palladium-catalysed arylationof an alkylidenecyclopropane afforded the corresponding 1-aryl-2-methyl-1-(2,2,3,3-tetramethylcyclopropylidene)propene in moderate yield, as shown in Scheme 133. The reaction was performed in the presence of $[Pd(C_3H_5)Cl]_2$ combined with a Tedicyp ligand.



Scheme 133. Heck reaction of alkenylvinylidenecyclopropane.

8. Conclusions

Organic chemists have always been fascinated by the cyclopropane subunit, which plays a prominent role in organic chemistry. Among the class of cyclopropanes, methylene- and alkylidenecyclopropanes have been well documented as useful synthetic intermediates in organic chemistry over the past few decades. In spite of their highly strained structure, these atypical compounds usually exist as stable compounds, allowing their use in many synthetic applications with an otherwise unattainable chemical reactivity. Indeed, because of this significantly strained nature, associated with a large structural differentiation available, these compounds show a peculiar and diverse reactivity pattern that would be achievable from other starting materials only with difficulty. This review, which updates the recent developments in the reactivity of methylene- and alkylidenecyclopropanes covering the literature from 2003, clearly demonstrates the diversity and power of the reactions of these compounds in the field of synthetic organic chemistry, such as the synthesis of a large number of heterocyclic compounds, which constitute almost two-thirds of all the known organic compounds. An impressive number of very different products have recently been prepared through diverse reactions, such as ring-opening reactions catalysed by transition metals as well as Lewis and Brønsted acids, cycloaddition reactions, rearrangements, radical reactions, polymerisation reactions and miscellaneous reactions including addition reactions with ring conservation and Heck reactions. The great variety of products obtained from these reactions is directly related to the high versatility of this chemistry and, for example, dramatic differences in the chemoselectivity, regioselectivity and stereoselectivity of these reactions, such as ring-opening reactions, are often observed according to the nature of the substrates used and the catalysts along with the reaction conditions (solvent, temperature). The crucial factor that determines the mode of ring opening of the cyclopropane moiety is still not clear. On the other hand, it must be noted that efforts remain to be undertaken on the development of enantioselective versions in almost all reaction types, since, in the last seven years, relatively few studies have been reported dealing with asymmetric reactions of methylene- and alkylidenecyclopropanes. Among these, some reactions were based on the use of chiral auxiliaries, such as the reactions of *N*,*N*-diphenylmethylenecyclopropyl amides with chiral aromatic sulfinimines leading to 2,3,4-trisubstituted pyrrolidines in up to 90% de, and Diels–Alder cycloadditions of chiral cyclopropenyl-containing 1,3-spiroaminoalcohols with various dienes performed with up to 98% de. Moreover, a diastereoselectivity of up to 100% de was reported for asymmetric Pauson–Khand reactions of 1,6- and 1,7-cyclopropylidenynones. In addition, a new access to chiral cyclobutenes was developed on the basis of palladium-catalysed rearrangements of chiral alkylidenecyclopropanes. More interestingly, chirality has also been induced in reactions of methylene- and alkylidenecyclopropanes by using chiral catalysts. Thus, an enantioselective reaction of methylenecyclopropyl amides with *N*-tosyl aldimines was developed by using a chiral bis(oxazoline) ligand, providing chiral *trans*-C2,C3-disubstituted methylenepyrrolidines with enantioselectivity of up to 86% ee. Better enantioselectivities of up to 92% ee were recently reported for the enantioselective palladium-catalysed silaboration of *meso*-methylenecyclopropanes and for the kinetic resolution of 1-alkyl-2-methylenecyclopropanes in the presence of chiral phosphorus ligands. The first enantioselective intramolecular [4+3] cycloaddition of diphenylidenecyclopropanes was performed with a moderate enantioselectivity of up to 64% ee. In addition, chiral copolymers derived from 7-methylenebicyclo[4.1.0]heptane and CO could be prepared in the presence of chiral palladium complexes.

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Biographical sketch

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