Radical addition reactions to cyclopropenes

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Dedicated to Prof. Samir Zard, on the occasion of his emeritus, with the greatest admiration and friendship

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Abstract

This review focuses on the reactivity of cyclopropenes in addition reactions of carbon- or heteroatom-centered radicals, generated through classical initiating systems or photocatalysis. These addition reactions lead to cyclopropyl radicals as intermediates which can undergo subsequent atom transfer (inter- or intramolecular) or be involved in cyclization reactions. In some cases, depending on the structure of the added radical, the cyclopropyl radical intermediate can evolve by ring-opening and elimination reactions leading to open-chain unsaturated products or heterocyclic compounds. This review discusses the contributions that have been made in this field and highlights the scope and mechanisms of the different transformations.

Keywords: Cyclopropenes, radicals, addition reactions, cyclopropanes, regioselectivity, stereoselectivity.
Table of Contents

1. Introduction
2. Radical Addition Reactions Leading to Substituted Cyclopropanes
   2.1. Hydrostannylation of cyclopropanes
   2.2. Addition of carbon-centered radicals to cyclopropanes
      2.2.1. Addition of xanthates
      2.2.2. Trichloromethylation
      2.2.3. Carbocyanation
      2.2.4. Cascade processes initiated by radical trifluoromethylation
      2.2.5. Photocatalyzed carboarylation
      2.2.6. Photocatalyzed (3+2) annulation with cyclopropyl anilines
   2.3. Addition of sulfur-centered radicals to cyclopropanes
      2.3.1. Addition of pentafluorosulfanyl chloride
      2.3.2. Addition of arylsulfonyl iodides
3. Radical Addition Reactions Accompanied by Ring-opening of the Three-membered Ring
   3.1. Addition of the azide radical
   3.2. Addition of α-iodo carbon-centered radicals
4. Conclusions

1. Introduction

The highly strained cyclopropanes possess an extremely rich and versatile reactivity.\textsuperscript{1–11} Within the broad repertoire of transformations involving these substrates, two main categories can be distinguished depending whether the three-membered ring is retained or broken in the final product(s).\textsuperscript{1–11} In particular, addition reactions across the strained C=C bond of cyclopropanes constitute an appealing class of transformations to access substituted cyclopropanes, which are ranked into the top ten of the most encountered ring systems in marketed drugs\textsuperscript{12,13} and are important fragments in drug design.\textsuperscript{14} Whereas the addition of nucleophiles (organometallic species or pronucleophiles in the presence of transition metal catalysts) to cyclopropanes has been widely investigated as a route to stereodefined highly substituted cyclopropanes, radical addition reactions to cyclopropanes remain much less explored comparatively although their feasibility was first demonstrated 30 years ago.\textsuperscript{1–11} In this review, the various contributions that have been reported in the field of radical addition reactions to cyclopropanes will be presented, with a discussion on the scope and mechanism of each transformation.

Cyclopropanes share more similarity with alkynes than with alkenes in terms of reactivity because of the increased $p$ character of the cyclopropene carbon-carbon bonds (and conversely an increased $s$ character of the orbitals used by the “vinylcic carbons” of cyclopropanes to make bonds).\textsuperscript{15,16} Addition of a radical to a cyclopropene benefits from a considerable relief of ring strain\textsuperscript{17} and generates a cyclopropyl radical intermediate which has a strong $\sigma$ character and a pyramidal geometry.\textsuperscript{18} The cyclopropyl radical is less stable than any alkyl radical including the methyl one.\textsuperscript{19} Cyclopropyl radicals are also configurationally labile and readily undergo inversion.\textsuperscript{18,20–22}

When substituted cyclopropanes are involved in radical addition reactions, regioselectivity and stereoselectivity issues have to be considered. For the sake of simplicity, we shall consider cyclopropanes A
bearing a single substituent on the C=C bond, which correspond to the great majority of substrates considered in the different investigations. For cyclopropenes A, radical addition occurs preferentially on the less-substituted carbon, designated as C1 by convention throughout the course of the review, and generates a substituted cyclopropyl radical B at C2 as the major regioisomer, most often exclusively. Cyclopropenes lacking any stereocenter at C3 (R₃ = R'₃) or bearing a single substituent at that carbon atom (R'₃ = H) have also been classically used as substrates. For those latter cyclopropenes A1, the radical addition at C1 proceeds with a high diastereoselectivity, preferentially trans to the most sterically hindered substituent (R₃) at C3 to generate the rapidly interconverting cyclopropyl radicals C and C’. Both radical intermediates C and C’ suffer from a steric interaction, between the R² and R or alternatively the R² and R³ substituents, respectively. In most cases, those cyclopropyl radicals C and C’ subsequently will evolve by atom transfer to deliver cyclopropanes D and D’, respectively, which are epimers at C2. In the transition states of the reactions leading to diastereomers D and D’, steric interactions will develop between the atom transfer reagent (R-X) and the substituent located on the same face of the three-membered ring, with R³ for C and R for C’, respectively. Hence, stereocontrol at C2 results from a typical Curtin-Hammett scenario and depends on the rates of the atom transfer process (k₁ and k₂), but in most cases mixtures of diastereomers D and D’ are produced (Scheme 1).

Scheme 1. Radical addition to cyclopropenes leading to substituted cyclopropanes.

Depending on the substituents present on the cyclopropane products D and D’, ring-opening reactions can subsequently occur but cleavage of the three-membered ring is not triggered by a radical species. Those radical addition reactions leading to substituted cyclopropanes as primary products will be presented in the next section (Section 2) of the present review.

Cyclopropyl radicals do not usually undergo ring-opening to the allyl radical, eventhough the energetic barrier for this transformation has been calculated to 20.7 kcal/mol. However, in this review (Section 3), we shall see examples of radical addition reactions to cyclopropenes accompanied by cleavage of the three-membered ring. This particular mode of reactivity and fragmentation of the initially formed cyclopropyl radicals of the type E has been reported for two types of added radicals so far, namely the azide radical or α-iodo C-centered radicals which both incorporate a leaving group (LG) (dinitrogen or iodine atom, respectively) (Scheme 2).
2. Radical Addition Reactions Leading to Substituted Cyclopropanes

The different contributions are presented according to the type of radicals added to the three-membered ring (tin-, carbon- and sulfur centered radicals) which corresponds more or less to the chronological order in which the articles were published.

2.1. Hydrostannylation of cyclopropenes

In 1994, Nakamura et al. reported the first examples of radical addition reactions to cyclopropenes.\textsuperscript{24} Hydrostannylation of cyclopropanone acetal 1a with Ph₃SnH was efficiently accomplished in toluene either by heating at 60 °C in the presence of AIBN, by initiation with n-Bu₃B at room temperature or activation by ultrasound irradiation to afford cyclopropylstannane 2a in high yields (83-100%) (Scheme 3).\textsuperscript{24} By comparison, hydrostannylation of 1a with n-Bu₃SnH proceeded at a slower rate than with Ph₃SnH and led to the corresponding adduct in moderate yield (64%).

![Scheme 3](image_url)

Scheme 3. Hydrostannylation of cyclopropanone acetal 1a.

The scope of the radical hydrostannylation was examined with diversely substituted cyclopropanone acetals 1b-1g. High regioselectivities were observed in almost all cases in favor of the addition of the tin-centered radical at the terminal position (C1), except for the less hindered methyl-substituted substrate 1b which afforded a mixture of regioisomeric cyclopropylstannanes 2b and 3b in a 70:30 ratio. The cis cyclopropylstannanes (2b-2g) were preferentially formed with moderate to excellent diastereoccontrol. It is also worth noting that for substrates 1e and 1f incorporating a disubstituted (E)- and (Z)-alkene, respectively, no isomerization of the double bond was observed in the cyclopropylstannanes 2e and 2f (Scheme 4).\textsuperscript{24}
Scheme 4. Scope of the hydrostannylation of cyclopropenone acetals.

The preferential formation of the cis cyclopropylstannanes 2 indicates that the cyclopropyl radical intermediate preferentially abstracts a hydrogen atom to Ph₃SnH from the less hindered face of the three-membered ring, through configuration 4 (trans to the R and SnPh₃ groups) (Scheme 5).

Scheme 5. Diastereoselectivity of the hydrostannylation of cyclopropenone acetals.

An intermolecular competition experiment revealed that cyclopropenone acetal 1a is three times more reactive than 1-hexyne towards Ph₃SnH (Et₃B cat., toluene, 0 °C). Also a disubstituted alkyne (1-trimethylsilyl-1-hexyne) failed to undergo hydrostannylation in competition with 1a. However, hydrostannylation of substrate 1h, possessing an appropriately located disubstituted alkyne, delivered two new spirocyclic products 5 (49%) and 6 (24%). Cyclopropylstannane 5 results from the addition of the tin-centered radical to the cyclopropene followed by 5-exo-dig cyclization of the resulting cyclopropyl radical 7. Formation of compound 6 demonstrates that the (reversible) addition of the triphenyltin radical across the triple bond of the disubstituted alkyne in substrate 1h can occur competitively, but in this case the resulting vinylic radical 8 underwent an irreversible 5-exo-trig cyclization to the cyclopropene double bond (Scheme 6).
Scheme 6. Hydrostannylation of cyclopropene-yne 1h.

Only cyclopropenone acetals were considered as substrates in this seminal study\textsuperscript{24} but it was later reported by Gevorgyan \textit{et al.} that the hydrostannylation of a wide variety of substituted cyclopropenes can be conveniently achieved in the presence of a palladium catalyst and an enantioselective rhodium-catalyzed process was also developed.\textsuperscript{40,41}

The radical hydrostannylation of \textit{gem}-difluorocyclopropenes 9 was reported by Konno \textit{et al.} in 2015.\textsuperscript{25} It should be mentioned that the palladium-catalyzed hydrostannylation fails for this particular class of substrates and hence radical conditions represent a valuable alternative. Mono-substituted difluorocyclopropenes 9a-9c were hydrostannylated with high regioselectivity (addition of the tin-centered radical at C1) using Et$_3$B as initiator (toluene, 80 °C) but subsequent hydrogen atom transfer at C2 proceeded with moderate or no diastereoecontrol thereby leading to mixtures of cyclopropylstannanes 10a/10'a-10c/10'c.

Difluorocyclopropenes 9d-9g possessing a disubstituted C=C bond were also viable substrates and a \textit{trans} hydrostannylation was observed predominantly. High regiocontrol was observed in the case of the unsymmetrical substrates 9f and 9g bearing a phenyl group at C2 which can be explained by the preferential formation of a benzylic cyclopropyl radical intermediate (Scheme 7).\textsuperscript{25}

Scheme 7. Radical hydrostannylation of \textit{gem}-difluorocyclopropenes.
The authors investigated the feasibility of a tin-lithium exchange on the (difluorocyclopropyl)stannane 10d by treatment with MeLi (1.5 equiv) (THF, -78 °C). After quenching with acid, the β-fluoroallylic alcohol 11 was obtained as a single (Z) geometric isomer (51%). Attempts to intercept the putative intermediate organolithium 12 by quenching with PhCHO was unsuccessful. In the proposed mechanism, organolithium 12 would undergo β-elimination of fluoride and generate fluorocyclopropene 13, which would evolve by electrocyclic ring-opening to the allylic carbene species 14 (stabilized by the phenyl groups). Addition of water to 14 would explain the formation of the β-fluoroallylic alcohol 11. The observation of an equimolar mixture of monodeuterated fluoroallylic alcohols [D]-11 and [D]-11', at the allylic and vinylic positions respectively, upon quenching with D₂O supports the proposed mechanism. Additionally, quenching with other protic derivatives such as tert-butanol, acetic acid or p-toluenesulfonamide resulted in the formation of the corresponding substituted β-fluoroallylic derivatives 15a-15c (54-60%) (Scheme 8).

**Scheme 8.** Reactivity of (gem-difluorocyclopropyl)stannane 10d.

### 2.2. Addition of carbon-centered radicals to cyclopropenes

#### 2.2.1. Addition of xanthates

The addition of C-centered radicals to cyclopropenes was disclosed in two publications in 2000.²⁶,²⁷ In the first article, Saičić et al. showed that electron-deficient electrophilic radicals generated upon irradiation of xanthates 16a and 16b with a sunlamp (C₆H₆, 15 °C) underwent addition to cyclopropenone ketal 1a. The corresponding adducts 17a/17’a and 17b/17’b were isolated in modest yield (37-46%) as diastereomeric mixtures (trans/cis = 68:32 and 77:23, respectively) (Scheme 9, Eq. 1).²⁶ Addition of the malonyl radical generated from 16c afforded 17c/17’c (44%, dr = 77:23) but the presence of a methyl or an allyl group at the α position of the sulfur atom in xanthates 16d and 16e hampered the radical addition (Scheme 9, Eq. 2).²⁶
Scheme 9. Radical addition of xanthates to cyclopropenone acetal 1a.

Kinetic studies indicated that allyl cyanide and cyclopropenone acetal 1a underwent addition of the tert-butoxycarbonyl radical at similar rates (relative rates 1 and 0.95, respectively) thereby suggesting no influence of the ring-strain on the reactivity of cyclopropene 1a.\(^{26}\)

The second article, published by Zard and co-workers in 2000, further expanded the scope of radical additions to strained olefins.\(^{27}\) Cyclopropene gem-dicarboxylate 18 was used as substrate and the radical chain addition of xanthates 19 and 20 was achieved in the presence of diilauroyl peroxide in refluxing 1,2-dichloroethane. The corresponding cyclopropyl xanthate adducts 21/21' and 22/22', respectively, were isolated in modest yields (30-35%). The trans diastereomers (21 and 22) were formed predominantly as a result of a preferential transfer of the xanthate moiety at C2 trans to the substituent at C1 (Scheme 10).\(^{27}\)

Scheme 10. Radical addition of xanthates to cyclopropene 18.

These pioneering examples demonstrated the feasibility of C-centered radical addition reactions to cyclopropenes\(^{26,27}\) but further derivatization of the cyclopropyl xanthates arising from those reactions were not reported.

Recently, in the context of their work on the modular synthesis of substituted cyclobutylboronates by consecutive radical additions, Zard and co-workers reported another example of xanthate addition to cyclopropenylboronate 23 aimed at evaluating the effect of the ring-size on the reactivity.\(^{28}\) Thus, reaction of
cyclopropenyl(pinacolato)boronate 23 with xanthate 24 in the presence of dilauroyl peroxide afforded adduct 25 (71%) with high diastereoselectivity. Attempt to further functionalize cyclopropyl xanthate 25 by peroxide-mediated radical addition to an olefinic partner (but-3-enyl acetate) failed. Indeed, cyclopropyl radical 26 (generated at C2 from 25) is much less stable than the secondary alkyl radical that would arise from addition of 26 to a terminal olefin (but-3-enyl acetate) thereby preventing a radical chain process.\textsuperscript{19,28} However, radical reduction of cyclopropyl xanthate 25 was efficiently accomplished with tris(trimethylsilyl)silane and led to cyclopropylboronate 27 (71%) functionalized by an aminomethyl group. The observed high 1,2-cis diastereoselectivity is consistent with the approach of the sterically demanding silane on the less hindered face of the radical intermediate 26 (Scheme 11).\textsuperscript{28}

**Scheme 11.** Radical addition of xanthate 24 to cyclopropenylboronate 23.

### 2.2.2. Trichloromethylation

In 2015, Miyata \textit{et al.} reported the addition of the trichloromethyl radical generated from chloroform to substituted cyclopropene-3-carboxylates 28 using Et\textsubscript{3}B as initiator.\textsuperscript{29} A stoichiometric quantity of the latter reagent was required in order to get good yields of trichloromethylated cyclopropanes 29/29', formed as mixtures of diastereomers at C2. Indeed, whereas cyclopropene 28b possessing a n-butyl group at C2 led to cyclopropanes 29b/29'b (dr = 82:18, 77%), the yield dropped to 24% in the presence of a lower quantity (0.5 equiv) of Et\textsubscript{3}B.\textsuperscript{29} Addition of the trichloromethyl radical occurs regioselectively (at C1) and diastereoselectively (trans to the ester moiety at C3). However, subsequent hydrogen atom transfer at C2 proceeded with low to moderate stereocontrol (dr = 54:46–82:18) in the case of cyclopropene carboxylates 28a-28i bearing a primary or a secondary (cyclopentyl) alkyl group at C2. Cyclopropanes 29a-29i possessing a trans relationship between the CC\textsubscript{3} group (at C1) and the R substituent (at C2) were the major diastereomers formed. High diastereoselectivities were observed only in the synthesis of the trisubstituted (trichloromethyl)-cyclopropanes 29j and 29k, possessing a sterically hindered substituent at C2 (Scheme 12).\textsuperscript{29}
Scheme 12. Addition of the trichloromethyl radical to cyclopropenecarboxylates 28 mediated by Et₃B.

Additional experiments revealed that no deuterium incorporation took place at C2 when CDCl₃ was used as the solvent, thereby indicating that chloroform does not act as hydrogen donor in a radical chain mechanism.²⁹ The authors suggested that the H atom at C2 could arise from a water-Et₃B complex⁴² or from Et₃B itself,⁴³ thereby explaining why at least a stoichiometric quantity of this reagent is required. The ester moiety at C3 does not exert any particular role since it could be replaced by an (acetoxy)methyl group without any adverse effect on the efficiency of the addition process.²⁹

The authors also investigated the use of Me₂Zn as radical mediator and a different reactivity profile was observed since the reaction led to the ring-opened gem-dichloroolefins 30 (59–74%) (Scheme 13).²⁹

Scheme 13. Reaction of cyclopropenecarboxylates 28 with chloroform mediated by Me₂Zn.

Deuterium labeled substrate [D₂]-28b provided the vicinally deuterated olefin [D₂]-30b (38%) which indicated the occurrence of a 1,2-hydrogen shift in the mechanism (Scheme 14, Eq. 1). From cyclopropene 28j possessing a tert-butyl substituent, migration of one methyl group was observed to afford 31 (Scheme 14, Eq. 2). Additionally, for substrate 28i bearing a cyclopentyl group, a ring-expansion took place to afford product 32 incorporating a cyclohexene (Scheme 14, Eq. 3).²⁹ On the basis of these experiments, the authors proposed a mechanism that involves addition of the trichloromethyl radical across the C=C bond of the cyclopropene 28 and the resulting cyclopropyl radical 33 would then be trapped by Me₂Zn to generate the
organozinc reagent 34 as the initial adduct.\textsuperscript{44,45} The organometallic species 34 would trigger a 1,2-hydride shift, cleavage of the three-membered ring and subsequent elimination of a chloride ion to deliver the gem-dichlororoelfin 30 (Scheme 14).

![Scheme 14. Additional experiments and proposed mechanism for the formation of gem-dichlororoelphins 30.]

In 2016, the authors subsequently reported regiodivergent ring-opening reactions of trichloromethyl-cyclopropanecarboxylates 29 to illustrate the interest of these products.\textsuperscript{46} A reductive ring-opening process of the epimeric (trichloromethyl)cyclopropanes 29b (or 29'b) was described in the presence of AgOAc (THF, 100 °C) which afforded the gem-dichlororoelfin 35 (82%). The authors suggested that some in situ generated Ag(0) would promote chlorine atom abstraction and generate radical 36 which would trigger regioselective ring-opening of the three-membered ring leading to 37. Subsequent hydrogen atom abstraction from the solvent by radical 37 would explain the formation of dichlororoelfin 35 (Scheme 15).\textsuperscript{46}

![Scheme 15. Radical ring-opening of (trichloromethyl)cyclopropanecarboxylates 29b/29'b.]

Ring-opening reactions of (trichloromethyl)cyclopropanes 29 with fluoride were also reported using both AgBF\(_4\) and n-Bu\(_4\)NBF\(_4\) (CH\(_2\)Cl\(_2\), –10 °C). Abstraction of a chloride by the silver cation would result in the development of a positive charge adjacent to the cyclopropane and hence trigger regioselective ring-opening (C1–C2 cleavage) with concomittant nucleophilic attack of a fluoride ion at C2. That a stereospecific process is
involved in this reaction was evidenced by the formation of the diasteomeric ring-opening products \(38\) and \(38'\) from epimeric cyclopropanes \(29\) and \(29'\) (Scheme 16).\(^{46}\)

Scheme 16. Ring-opening/fluorination of (trichloromethyl)cyclopropanecarboxylates \(29\) and \(29'\).

2.2.3. Carbocyanation. In 2016, Landais et al. reported the first examples of a radical addition of two carbon fragments to cyclopropenes.\(^{30}\) The carbocyanation of diversely substituted cyclopropenecarboxylates was achieved by addition of radicals generated from iodides of the type \(39\), possessing an adjacent electron-withdrawing group (EWG), and \(p\)-tosyl cyanide (TsCN) was used as a cyanating reagent. The reaction was carried out in the presence of hexamethylditin as a chain carrier and di(tert-butyl) hyponitrite as initiator (slowly added with TsCN over 5 h, \(C_6H_6\), 65 °C). Under these conditions, the generated trimethyltin radical triggers a iodine atom abstraction from iodide \(39\) and the resulting electrophilic radical adds regio- and stereoselectively to the cyclopropene-3-carboxylate substrate. Subsequent cyanation of the cyclopropyl radical intermediate at C2 proceeded with moderate stereocontrol and delivered an epimeric mixture of cyclopropyl nitriles \(40\) and \(40'\) (Scheme 17).\(^{30}\)

Scheme 17. Radical carbocyanation of cyclopropenecarboxylates.

\(^{a}\) dr = Diastereomeric ratio \(40/40'\) (major diastereomers are drawn).
Analysis of the scope of the carbocyanation reaction reveals that various \( n \)-alkyl substituents, possibly containing another functional group (a mesylate, an acetoxy group or a chlorine atom), could be present at C2 in the cyclopropene-3-carboxylate substrates. The electron-withdrawing group (EWG) in the starting iodides of the type 39 could be an ethyl ester, a phenyl ester, a phenyl thioester or a cyano group but the former gives the best results, as judged by comparing the yields of the corresponding products 40a/40’a-40d/40’d. The ethyl ester at C3 could be replaced by a tert-buty1 ester without any adverse effect on the efficiency of the reaction which led to 40e/40’e (dr = 75:25, 61%). Secondary alkyl groups were tolerated at C2 although the yields of the corresponding products (40k/40’k and 40l/40’l) were lower than in the other cases and no diastereocntrol at C2 was observed (Scheme 17).

After regioselective and stereoselective addition of the electrophilic radical 41 to cyclopropene 28a (addition at C1 and \( \text{trans} \) to the ester at C3), the resulting interconverting cyclopropyl radical 42a/42’a could potentially evolve by an iodine atom transfer process (Kharasch type process) and deliver iodocyclopropanes 43a/43’a, or undergo cyanation with tosyl cyanide to produce cyclopropyl nitriles 40a/40’a. However, abstraction of the iodine atom in 43a/43’a by the tin radical can regenerate the cyclopropyl radical intermediates 42a/42’a and hence eventually favor the formation of the carbocyanation products 40a/40’a.

For steric reasons, this latter step proceeds more efficiently with the less hindered trimethyltin rather than the tributyltin radical (Scheme 18).

**Scheme 18.** Mechanism of the radical carbocyanation of cyclopropene 28a.

In agreement with the proposed mechanism, the authors achieved the carboiodation of cyclopropene 28a with ethyl iodoacetate in the presence of a substoichiometric quantity of hexabutylditin and obtained a diastereomeric mixture of cyclopropyl iodides 43a/43’a (87%, dr = 88:12). Subjection of iodides 43a/43’a to the radical carbocyanation conditions afforded an epimeric mixture of cyclopropyl nitriles 40a/40’a (65%, dr = 70:30) (Scheme 19).
Scheme 19. Sequential radical carboniodation and cyanation reactions from cyclopropene 28a.

Cleavage of the three-membered ring in the cyanocyclopropanes of the type 40 can be subsequently achieved to generate α,β-unsaturated esters possessing a quaternary stereocenter at the γ position. Cyclopropene (S)-28a (accessible by an enantioselective rhodium-catalyzed cyclopropanation of 1-pentyne) was involved in the radical carbocyanation and afforded the optically enriched cyclopropyl nitriles 40a* and 40’a*, which were separated by flash chromatography. Under soft enolization conditions (MgBr₂•OEt₂, iPr₂NEt), regioselective ring-opening of 40a* and 40’a* took place (with preferential anionic cleavage of the C1–C3 bond) and led to the enantiomeric (E)-enoates (R)-44 and (S)-44, respectively, both possessing the same enantiomeric purity than the starting substrate (ee = 88%) (Scheme 20).[30]

Scheme 20. Ring-opening of optically enriched cyanocyclopropanes 40a* and 40’a*.

Interestingly, in the case of cyclopropene 28m bearing an n-pentyl chain, the diastereomeric cyanocyclopropanes 40m/40’m arising from the carbocyanation process were isolated in low yield (14%). In this case, Landais et al. observed that the major products were cyclopropanes 45/45’ (70:30 mixture of two diastereomers of unassigned relative stereochemistry) possessing a cyano group at a remote position of the three-membered ring. Indeed, the cyclopropyl radical intermediate 46 could evolve by a 1,5-hydrogen atom transfer (1,5-HAT) and hence generate the more stable secondary alkyl radical 47. Reaction of the latter radical species with tosyl cyanide accounted for the formation of 45/45’ (Scheme 21).[30]
Scheme 21. 1,5-Hydrogen atom transfer in the case of substrate 28m.

The ability of a cyclopropyl radical to trigger a 1,5-HAT on an alkyl chain was exploited very recently in the development of cascade radical processes initiated by the addition of a trifluoromethyl radical.

2.2.4. Cascade radical processes initiated by radical trifluoromethylation. In 2023, Wu, Zhu and co-workers reported the trifluoromethylation of cyclopropene 28m (used in excess, 3 equiv) using Togni’s reagent 49 and Fe(acac)₃ as the catalyst to generate trifluoromethyl radicals. The reaction was conducted in the presence of a quinoxalinone 48 as a radical trap to achieve an heteroarylation of the secondary alkyl radical generated after the 1,5-HAT triggered by the cyclopropyl radical intermediate 50. The resulting (trifluoromethyl)cyclopropane 51a-51f were all obtained as mixtures of diastereomers (Scheme 22).³¹

Scheme 22. Radical trifluoromethylation/1,5-HAT/heteroarylation cascade process from cyclopropene 28m.
The broad scope of the transformation was illustrated with more than 25 examples of quinoxalinones and only a few of them have been selected in this review. It is noteworthy that the quinoxalinones of type 48 can incorporate frameworks of bioactive compounds as shown with the formation of products 51e (derived from ibuprofen) and 51f (derived from oestrone) (Scheme 22). The diastereomeric ratios were only indicated in the experimental section of the manuscript, without details on the determination of the actual number of stereoisomers formed.

The authors also illustrated the broad scope of substituted cyclopropenes amenable in this latter radical trifluoromethylation/1,5-HAT/heteroarylation cascade process. The substituent at C3 can be a phenyl ester, a phenyl ketone or a nitrile as shown with the formation of CF3-substituted cyclopropanes 52a-52c. The aliphatic chain at C2 on which the 1,5-HAT operates can incorporate a functional group such as an ester (product 52d) or a phosphate (product 52e). The activated C–H bond can be located at the α position of an oxygen atom (product 52f), on a cycloalkyl substituent (product 52g) or at a methine position (products 52h and 52i). Disubstitution at C3 on the cyclopropene ring is also tolerated, as illustrated in the case of the α-methyl ester 52j, the gem-diester 52k and the gem-difluorocyclopropane 52l, although the yield of the latter product is quite low (23%) (Scheme 23).

Scheme 23. Scope of the radical trifluoromethylation/1,5-HAT/heteroarylation cascade process.

DFT calculations revealed that the 1,5-HAT process of the cyclopropyl radical intermediate 50 (see Scheme 22) has an activation barrier of only 11.1 kcal/mol and that it leads to a more stable secondary alkyl radical (ΔG = −8.2 kcal/mol). These computational studies also highlight the unique reactivity of a cyclopropyl radical.
radical compared to a cyclobutyl radical or a cyclopentyl radical for which 1,5-HAT reactions display higher activation barriers (16.7 and 18.7 kcal/mol, respectively) and are either slightly exothermic (−0.3 kcal/mol) or endothermic (+2.9 kcal/mol), respectively.\(^{31}\)

### 2.2.5. Photocatalyzed carboarylation

In 2017, Landais \textit{et al.} reported the visible-light mediated reaction of cyclopropene-3-carboxylates with phenacyl bromides of the type 53 in the presence of K\(_2\)CO\(_3\), LiBr and the iridium photocatalyst \(\text{fac-Ir(ppy)}_3\) under irradiation with blue LEDs (DMF, 20 °C). This transformation led to naphthoquinone-type products 54a-54o resulting from an intramolecular carboarylation/ring-opening sequence (involving cleavage of the C1–C3 bond).\(^{32}\) The irradiation time was limited to 12 h to avoid decomposition of the products formed at this stage and the ring-opening was completed by raising the temperature to 60 °C without irradiation. As illustrated with products 54a-54d, the phenacyl bromides can be substituted at the para position of the aromatic ring by a halogen atom or a methoxy group. When a cyano group was present, formation of 54e was not observed and only competitive dehalogenation of the \(\alpha\)-bromo carbonyl substrate took place. In the case of a \textit{meta}-substituted phenacyl bromide, a mixture of the corresponding regioisomeric carboarylation products (54f/54f') was formed. As shown with the other examples (products 54g-54n), the reaction accommodates different alkyl groups on the cyclopropene although a branched substituent generally led to a lower yield (product 54h). A variety of substituents could be present on the chain at C2 (halide, silyl ether, ester, phenyl group). Interestingly, compounds 54m and 54n possessing a bromoalkyl group were obtained from cyclopropene substrates incorporating a mesylate which was displaced \textit{in situ} by a bromide. Heteroaryl \(\alpha\)-bromo ketones were tested as reaction partners and whereas a benzofuran or a \(N\)-methyl pyrrole moiety led the heterocyclic adducts 54o (16%) and 54p (24%) in low yields, 54q incorporating a thiophene was obtained with a yield (37%) comparable to those attained with the other phenacyl bromides (Scheme 24).\(^{32}\)

\[\text{CO}_2\text{Et} + \text{Br}^- \xrightarrow{\text{EtO}_2\text{C}} \text{R}_1 \text{R}_2 \xrightarrow{\text{fac-Ir(ppy)}_3 (2 \text{ mol \%})} \text{Br}^- \xrightarrow{\text{LiBr (2 \text{ equiv})} \xrightarrow{\text{K}_2\text{CO}_3 (2 \text{ equiv})} \xrightarrow{\text{blue LEDs, DMF, 20 °C, 12 h}} \text{aromatic ring}} \xrightarrow{\text{no LEDs, 60 °C, 24 h}} \text{54a-54q} \]

\[\text{54a, R'} = \text{H (44%)} \quad \text{54b, R'} = \text{Br (37%)} \quad \text{54c, R'} = \text{Cl (31%)} \quad \text{54d, R'} = \text{OMe (34%)} \quad \text{54e, R'} = \text{CN (0%)} \quad \text{(2 equiv) 53} \]

\[\text{54f (40%, 54f'/54f' = 70:30)} \quad \text{54g, R = n-Pent (40%)} \quad \text{54h, R = c-Pent (32%)} \quad \text{54i, R = (CH}_2\text{)}_3\text{Cl (41%)} \quad \text{54j, R = (CH}_2\text{)}_3\text{OTBS (51%)} \quad \text{54k, R = (CH}_2\text{)}_3\text{OAc (42%)} \quad \text{54l, R = (CH}_2\text{)}_3\text{Ph (35%)} \quad \text{54m, R = (CH}_2\text{)}_3\text{Br (41%)}^a \quad \text{54n, R = (CH}_2\text{)}_3\text{Br (32%)}^a \]

\[^a\] The starting cyclopropenes contain a mesylate which is displaced \textit{in situ} by a bromide.

\textbf{Scheme 24.} Visible-light mediated reaction of cyclopropene-3-carboxylates with phenacyl bromides.
The proposed mechanism starts with the reduction of the phenacyl bromide, by the photoexcited state of the iridium catalyst, to generate the electrophilic radical 55 which adds to cyclopropene 28a in a regio- and diastereoselective manner. The resulting cyclopropyl radical 56 would subsequently undergo intramolecular addition to the arene moiety leading to cyclohexadienyl radical 57. Oxidation of 57 to cyclohexadienyl cation 58 by the Ir(IV) species [Ir(ppy)$_3$]$^{+}$, followed by reaction with the base (K$_2$CO$_3$), would explain the formation of the heterolytic aromatic substitution product 59. Subsequent ring-opening of 59 to naphthalenone 54a does not require irradiation and simply involves deprotonation by the base at the α position of the ketone which triggers a regioselective anionic ring-opening of the three-membered ring (with C1–C3 bond cleavage and generation of an ester enolate intermediate) (Scheme 25). When enantio-enriched cyclopropene (S)-28a (ee = 90%) was used as substrate, the corresponding naphthalenone 54a was obtained with the same optical purity (ee = 90%). In agreement with the proposed mechanism, the stereogenic center at C3 in 28a controls the configuration of C1 in 56 (radical addition trans to the ester at C3) and formation of a cis ring fusion between the three- and six-membered ring dictates the configuration at C2 in the tricyclic compound 59. Ring-opening of 59 eventually deletes the C1 and C3 asymmetric carbons but does not affect the quaternary C2 stereocenter (Scheme 25).

Naphthalenones 54 can be engaged in post-functionalization reactions. From 54k, cleavage of the acetate (by transesterification) induced an intramolecular diastereoselective oxa-Michael reaction leading to pyran 60 (76%) (Scheme 26, Eq. 1). Naphthalenone 54n was subjected to halogen exchange and the resulting iodide was involved in a 5-exo trig radical cyclization to produce the tricyclic compound 61 (70%, two steps from 54n) (Scheme 26, Eq. 2).\(^{32}\)

![Scheme 26. Post-functionalization reactions of naphthoquinones 54k and 54n.](attachment:image)

### 2.2.6. Photocatalyzed (3+2) annulation with cyclopropylanilines

In 2019, Waser et al. disclosed a new (3+2) annulation between cyclopropenes and cyclopropyl anilines leading to bicyclo[3.1.0]hexanes 62 substituted by an amino group.\(^{33}\) The reaction was conducted in the presence of the organic dye 4DPAIPN as the photocatalyst and under irradiation with blue LEDs (MeNO\(_2\), 18 h). Various 3,3-disubstituted cyclopropenes bearing either two esters, cyano groups, fluorine atoms, as well as a phenyl substituent on the C=C bond were used as substrates, as shown by the isolation of bicyclic compounds 62a-62d (76-88%) obtained as mixtures of diastereomers at the amino-substituted carbon. A high diastereoselectivity was observed in the case of a cyclopropenone acetal although the yield of 62e is modest (45%). The substituent at C2 on the cyclopropene can be an aromatic group, a hydrogen atom or a trimethylsilyl group (corresponding products 62f-62i) but not an alkyl (n-butyl) group since only traces of 62j were detected. The aromatic group on the three-membered ring in 3,3-difluorocyclopropenes could also be varied, as illustrated with products 62k (89%) and 62l (68%). Various aryl or heteroaryl substituents could be present on the nitrogen atom of the cyclopropyl aniline as shown with bicyclo[3.1.0]hexanes 62m-62q (74-89%). Interestingly, an increase of diastereoselectivity was noted when N-(2,6-dimethyl-4-methoxy)-cyclopropyl amine was used as reaction partner albeit at the expense of a reduced yield for adduct 62r (26%) (Scheme 27).\(^{33}\)
The reaction likely involves oxidation of the aminocyclopropane by the excited photocatalyst (PC*) leading to radical-cation 63, which undergoes ring-opening to generate the radical-iminium species 64. Regioselective addition of radical 64 to the cyclopropene would result in the formation of the cyclopropyl radical intermediate 65, which would then cyclize onto the iminium to generate the nitrogen-centered radical cation 66. Subsequent electron transfer from the reduced photocatalyst (PC•–) would complete the photocatalytic cycle and explain the formation of the diastereomeric bicyclic products 62/62' (Scheme 28).33

Scheme 27. Photocatalyzed (3+2) annulation of cyclopropenes with cyclopropyl anilines.

Scheme 28. Mechanism of the photocatalyzed (3+2) annulation.
The relative stereochemistry of the diastereomeric bicyclo[3.1.0]hexane products 62a/62’a was found to impact their reactivity in a reported post-functionalization. Thus, treatment of 62a with LiHMDS resulted in an intramolecular addition of the lithium amide to the ester located on the same concave face of the bicyclic system and afforded amide 67 (87%) (Scheme 29, Eq. 1). Under similar conditions, epimer 62’a produced the bicyclic aziridine 68 (95%) by intramolecular nucleophilic addition to the cyclopropane with the malonate moiety acting as leaving group (Scheme 29, Eq. 2).  


Having observed an increase of diastereoselectivity in the case of a cyclopropyl aniline bearing an aryl group substituted at both ortho positions on the nitrogen atom, Waser et al. specifically reinvestigated the (3+2) cycloaddition of aminocyclopropane 69 with aryl 3,3-difluorocyclopropenes. Compared to the previous conditions, a larger excess of cyclopropyl aniline was used (2.5 equiv) and the organic dye 4DPAIPN was replaced by the less-oxidizing iridium(III) photocatalyst [Ir(dtbbpy)(ppy)2](PF6). Cycloadducts 70a-70i were obtained in moderate to good yields (41-83%) and with high diastereoselectivities (rd ≥ 91:9) (Scheme 30).  

Scheme 30. Ir(III)-photocatalyzed (3+2) annulation between 3,3-difluorocyclopropenes and cyclopropylaniline 69.
The gem-difluorobicyclo[3.1.0]hexanes 70, armed with an amino group, are building blocks of potential interest in medicinal chemistry.\textsuperscript{47-49} It is worth mentioning that the feasibility of the oxidative cleavage of the 2,6-dimethyl-4-methoxy group by treatment with CAN was demonstrated for products of the type 70.\textsuperscript{33}

2.3. Addition of sulfur-centered radicals to cyclopropanes

2.3.1. Addition of pentafluorosulfanyl chloride. As already pointed just above, cyclopropanes incorporating fluorine atoms or fluorinated groups are attracting significant interest in the design of bioactive compounds.\textsuperscript{49,50} Until recently, cyclopropanes substituted by the pentafluorosulfanyl (SF\textsubscript{5}) group, which belongs to the so-called “emerging fluorinated motifs”,\textsuperscript{51,52} were unknown compounds. Since the radical addition of gaseous SF\textsubscript{5}Cl to alkenes and alkynes initiated by the Et\textsubscript{3}B/O\textsubscript{2} system affords a convenient entry to aliphatic pentafluorosulfanyl compounds,\textsuperscript{53,54} the reactivity of cyclopropanes was investigated.\textsuperscript{34} Initial attempts to achieve the radical addition of SF\textsubscript{5}Cl to cyclopropene gem-dicarboxylate 18 were unsuccessful and adduct 71 was not detected (Scheme 31, Eq. 1). Addition effectively took place for substrate 72 bearing an alkyl chain at C2, although a large excess of SF\textsubscript{5}Cl was required to observe complete conversion. Under these forcing conditions, adduct 73 was isolated in only 26% yield, as a single detectable diastereomer. Concomitant cleavage of the tert-butylidiphenylsilyl ether (TBDPS) took place, presumably by a fluoride source arising from the decomposition of a SF\textsubscript{5}Cl derivative (S\textsubscript{2}F\textsubscript{10} was likely formed during the reaction), and the primary alcohol 74 was also isolated (15%) (Scheme 31, Eq; 2). Because of the strong electrophilic character of the SF\textsubscript{5} radical, cyclopropene 75 bearing a more electron-rich C=C bond than 18 was tested as substrate. The radical addition of SF\textsubscript{5}Cl to the gem-(diacetoxyethyl)-cyclopropene 75 proceeded efficiently and after cleavage of the acetyl groups by reduction with DIBAL-H, the SF\textsubscript{5}-cyclopropane 77 was isolated in good overall yield (55%) (Scheme 31, Eq. 3). Addition of SF\textsubscript{5}Cl was also successful on cyclopropanes 78a-78c substituted at C2 by an alkyl chain incorporating a TBDPS ether and afforded SF\textsubscript{5}-cyclopropanes 79a-79c (53–77%, dr > 95:5) (Scheme 31, Eq. 4). Thus, addition of the SF\textsubscript{5} radical (generated by abstraction of a chlorine atom from SF\textsubscript{5}Cl by the ethyl radical) occurs on the less substituted terminus (C1) and subsequent chlorine atom transfer at C2, which ensures propagation of the radical chain mechanism, occurs preferentially trans to the sterically demanding SF\textsubscript{5} group (Scheme 31, Eqs. 3 and 4).\textsuperscript{34}
Scheme 31. Radical addition of SF₅Cl to 3,3-disubstituted cyclopropenes.

The addition of SF₅Cl to cyclopropenes bearing a single substituent at C3 was also investigated. The presence of an ester (an ethyl or a benzyl ester) moiety at C3 allows for an efficient radical addition of SF₅Cl, as illustrated with the formation of adducts 80a/80'a (78%) and 80b/80'b (74%) as mixtures of epimers at C2. Although a TBDPS ether was a suitable protecting group for the alcohol of the 2-hydroxyethyl chain at C2, a benzyl ether could not be used and adduct 80c was isolated in low yield (< 10%). In this latter case, the intermediate cyclopropyl radical also induces a 1,5-HAT at the benzylic position and side-products were generated. By contrast, a benzoate was used successfully (products 80d/80'd, 83% yield). The chain length could be increased or shortened by one methylene unit and the corresponding adducts 80e/80'e (66%) and 80f/80'f (45%) were isolated. The lower yield for 80f/80'f may be explained by the presence of the sterically demanding TBDPS ether which may retard chlorine atom transfer at C2 and hence the chain mechanism efficiency. Indeed, the less hindered benzyl ether afforded adducts 80g/80'g in a better yield (60%). The primary aliphatic chain at C2 could incorporate a chlorine atom, as shown with products 80h/80'h (72%). When an n-pentyl group was present, the chlorine atom transfer at C2 could potentially compete with a 1,5-HAT process, as observed in the carbocyanation reaction,³⁰ but 80i/80'i were the only products detected. The addition of SF₅Cl could not be achieved efficiently to a substrate possessing a sterically demanding protected tertiary alcohol at C2 [R² = CMe₂(OTBS)] and this constitutes one limitation of the method (not illustrated). The ester at C3 could be replaced by an acetoxyethyl group, as illustrated with the formation of adducts 80j/80'j (57%) and 80k/80'k (72%) (Scheme 32).³⁴
Scheme 32. Radical addition of SF$_5$Cl to cyclopropenes bearing a single substituent at C3.

As observed in other radical reactions involving similar substrates, addition of the SF$_5$ radical proceeds regioselectively (at the less hindered C1 atom) and diastereoselectively (trans to the substituent at C3). The rates of chlorine atom transfer from SF$_5$Cl to the rapidly equilibrating cyclopropyl radical intermediates 81 and 81' eventually control the proportion of the epimers at C2. The observed stereochemical outcome could be explained by a preferential chlorine atom abstraction from SF$_5$Cl trans to the sterically demanding SF$_5$ group (at C1) in cyclopropyl radical 81 (Scheme 33).$^{34}$

Scheme 33. Diastereoselectivity of the radical addition of SF$_5$Cl to cyclopropenes.

When an equimolar mixture of a cyclopropene-3-carboxylate, a terminal alkene and a terminal alkyne all possessing the same substituent on the unsaturation [(CH$_2$)$_2$OTBDPS group] were involved in the radical addition of SF$_5$Cl (1 equiv), conversions were respectively 8%, 12% and 80%. This indicated the greater reactivity of the terminal alkyne whereas a cyclopropene-3-carboxylate and a terminal alkene display similar reactivity toward the SF$_5$ radical, with little influence of the ring strain.$^{34}$
The C–Cl bond in adducts 80/80' could be cleaved by radical reduction with tris(trimethylsilyl)silane and AIBN under standard conditions. As illustrated with 80e/80'e, radical reduction afforded a mixture of the diastereomeric SF₅-cyclopropanes 82e/82'e (dr = 60:40), which were separated by flash chromatography on silica gel (Scheme 34, Eq. 1). Starting from adduct 80j, the acetate was cleaved by reduction with DIBAL-H and the resulting alcohol was involved in a conjugate addition to ethyl propiolate. Treatment of the resulting compound 83 with tris(trimethylsilyl)silane in the presence of AIBN enabled the 5-exo-trig cyclization of the cyclopropyl radical at C2 onto the acrylate moiety and after treatment with fluoride, the oxabicyclic compound 84 was formed as a single detectable diastereomer (49%) (Scheme 34, Eq. 2).

Scheme 34. Post-functionalization reactions leading to diversely substituted (pentafluorosulfanyl)-cyclopropanes.

It is worth mentioning that an alternative route to SF₅-cyclopropanes was reported recently by Charette, Paquin et al. using an intramolecular cyclopropanation of diazoesters derived from SF₅-subsitituted allylic alcohols.

2.3.2. Addition of arylsulfonyl iodides. Another transformation exploiting the addition of sulfur-centered radicals to cyclopropenes was disclosed by Cao et al. in 2023. The iodosulfonylation of cyclopropene gem-dicarboxylates was achieved by heating with various sulfonyl iodides in water at 120 °C to provide β-iodocyclopropyl sulfoxes 85a-85n. The scope is restricted to cyclopropene gem-dicarboxylates bearing an aryl group at C2. The two carboalkoxy groups at C3 could also not be replaced by two cyano or two phenyl groups. Otherwise, as judged by the yields of adducts 85a-85n, the efficiency of the reaction does not seem to be sensitive to the aryl substituent at C2 on the cyclopropene, which can be substituted at the para, meta or ortho positions by electron-releasing or electron-withdrawing groups. Various aryl groups (p-Tolyl, phenyl, p-chloro or p-bromophenyl) were also accommodated on the sulfone. A single diastereomer was formed in most cases, except for 85e and 85j for which minor epimers were quantified, otherwise the diastereoselectivity was always high (Scheme 35).
Scheme 35. Iodosulfonylation of cyclopropene gem-dicarboxylates.

A radical mechanism was proposed by the authors, starting with the homolytic cleavage of the sulfonyl iodide which would generate a sulfonyl radical and an iodine atom. Addition of the sulfonyl radical (at C1) across the C=C bond of the cyclopropene would deliver a cyclopropyl benzylic radical which would undergo iodine atom transfer (from either molecular iodine or from the starting sulfonyl iodide to ensure propagation of a chain mechanism). This iodine atom transfer would preferentially occur through the more stable configuration 86 in which the aryl group at C2 and the arylsulfonyl group at C1 are trans, thereby leading to a cis-iodosulfonylation process forming 85 as the major diastereomer (Scheme 36).  

Scheme 36. Stereochemical outcome of the idosulfonylation of cyclopropene gem-dicarboxylates.

Subsequent deiodination of the β-iodocyclopropyl sulfone 85a was accomplished by reduction with Hantzsch ester in the presence of Mn₂(CO)₁₀ under irradiation with blue LEDs, to afford a diastereomeric mixture of cyclopropyl sulfoones 87a and 87'a (dr = 71:29, 98%) (Scheme 37).
Scheme 37. Reductive deiodination of β-iodocyclopropyl sulfone 85a.

In all the reactions examined so far, the primary products arising from the radical addition to a cyclopropene were substituted cyclopropanes, eventhough subsequent ring-opening of the three-membered ring was observed in some cases. In the following section, we shall examine examples of radical addition reactions which are accompanied by cleavage of the three-membered ring.

3. Radical Addition Reactions Accompanied by Ring-opening of the Three-membered Ring

3.1. Addition of the azide radical

In 2021, Muriel and Waser disclosed the first examples of addition of a nitrogen-centered radical to cyclopropenes. During the course of studies initially aimed at developing a radical azidation of cyclopropenes under mild photoredox-catalyzed conditions, the authors discovered that treatment of 2-aryl cyclopropene-gem-dicarboxylates with PhI(OAc)₂ and Me₃SiN₃ in the presence of a catalytic amount of CuCl₂ (MeCN, rt, 0.5 h) led to tetrasubstituted alkenyl nitriles 88a–88h (72–95%). The reaction, which is accompanied by cleavage of the three-membered ring and loss of dinitrogen, is compatible with different types of esters at C3 (methyl, benzyl or 2,2,2-trifluoroethyl) and accommodates various aryl groups at C2. However, the presence of an aryl group at C2 is mandatory as only traces of alkenyl nitriles 88i–88k were isolated from substrates bearing a hydrogen atom, a trimethylsilyl group or a n-butyl chain at C2 (Scheme 38).³⁷

Scheme 38. Addition of the azide radical to cyclopropene gem-dicarboxylates leading to alkenyl nitriles.

Replacement of one ester at C3 by a phenyl group did not hamper the reaction for substrate 89a but the corresponding alkenyl nitrile 90a was obtained as a mixture of geometric isomers (84%). Interestingly,
oxidative cyclization of 90a was subsequently accomplished by irradiation with UV light in the presence of DDQ and delivered the disubstituted functionalized phenanthrene 91a (74%) (Scheme 39).\textsuperscript{37}

\[
\text{Phl(OAc)}_2 (1.8 \text{ equiv}) \quad \text{Me}_2\text{SiN}_3 (1.8 \text{ equiv}) \quad \text{CuCl}_2 (5 \text{ mol }\%)
\]

\[
\text{MeCN, rt, 0.5 h} \quad \text{84%}
\]

\[
\text{90a (Z/E = 46:54)} \quad \text{DDQ (1.1 equiv)} \quad \text{UV light (365 nm)} \quad \text{MeCN, rt, 20 h} \quad \text{74%}
\]

\[
\text{91a}
\]

\textbf{Scheme 39.} Addition of the azide radical to cyclopropene 89a and oxidative photocyclization of 90a.

The scope of the sequential radical amination/oxidative photocyclization was then extended to a variety of cyclopropenes 89a-89m bearing an electron-withdrawing group at C3 and aromatic groups (phenyl or naphthyl groups) at both C2 and C3. Further optimization led to the achievement of the sequence in a one-pot manner. The electron-withdrawing group at C3 can be a methyl ester, a tert-butyl ester, an ethyl ketone or a trifluoromethyl substituent, as illustrated with the formation of phenanthrenes 91a-91d (51-80%). Variation of the substituents on the aromatic rings at C2 and C3 led to diversely substituted phenanthrenes 91e-91h (70-76%) and replacement of one phenyl by a 2-naphthyl group resulted in the formation of the [4]helicenes 91i (74%) and 92j (70%). An appropriate choice of the aromatic systems at C2 and at C3 enabled access to various polyaromatic hydrocarbons, including chrysene 91k (66%), benzochrysene 91l (72%) and picene 91m (54%) (Scheme 40).\textsuperscript{37}

\textbf{Scheme 40.} Scope of the one-pot sequential radical amination and oxidative photocyclization.
The precise role of the copper(II) salt in the radical amination has not been fully elucidated, but in its absence, the formation of nitrile 90a is still observed (30%) along with quinoline 92a (34%). Addition of the azide radical, generated by decomposition of PhI(N₃)₂ or PhI(OAc)N₃ to cyclopropene 89a would produce cyclopropyl radical 93. In this particular case, the electrocyclic ring-opening of the cyclopropyl radical to the corresponding allyl radical³⁶ may become favorable because it is accompanied by the release of dinitrogen gas. This would result in the formation of an iminyl radical 94 which would be oxidized (likely by a hypervalent iodine species) to the corresponding alkanyl nitrile 90a. An alternative evolution for the iminyl radical 94 would be the cyclization onto the aromatic ring at C3 and an heterolytic aromatic substitution process would explain the account for the formation of quinoline 92a. Thus, the presence of the copper salt seems to influence the fate of the iminyl radical 94 and favor its oxidation into nitrile 90a, at the expense of its cyclization onto the aromatic ring leading to 92a (Scheme 41).

Scheme 41. Speculative mechanism for the reaction of the azide radical with cyclopropene 89a.

The opportunity to access diversely substituted quinolines from 3-arylcyclopropenes of the type 89 was further explored by Waser et al.³⁸ A visible-light mediated process was initially devised wherein azidobenziodazolone (ABZ) served as a source of azide radicals but during the optimization studies, the authors found that a photocatalyst was not required and that the presence of iodine(III) impurities in some ABZ batches could act as an initiator. This observation led them to consider BIOAc as a catalyst and the addition of pyridine further improved the yields of the expected quinolones. When a phenyl group was present at C2 and at C3, the other group at C3 can be an ester (methyl, tert-butyl or benzyl) as illustrated with the formation of quinolines 92a, 92b and 92n. 3,3-Disubstituted cyclopropenes (R² = H) are viable substrates in this transformation as judged by the successful formation of quinolines 92o-92q. The authors particularly focus on the synthesis of 4-trifluoromethylquinolines (R³ = CF₃) and were able to synthesize quinolines 92d, 92r-92v in which the substituent at C2 can be a phenyl group, an alkyl chain (although the yield of 92u is modest) or a thiophene (Scheme 42).³⁸
Scheme 4.2. Scope of the amination of cyclopropenes via azide radicals leading to substituted quinolines.

Remarkably, cyclopropenes bearing a 1,2-disubstituted double bond were viable substrates provided that at least one of the substituents is an aryl group. Thus, from cyclopropenes 93a and 93b, the 4-trifluoromethyl quinolines 94a (70%) and 94b (45%) were obtained, respectively. Worthy of note is the regioselectivity observed for the azide radical addition (at C1 preferentially) in the case of the unsymmetrical substrate 93b which indicates that the reaction favors the formation of a benzylic cyclopropyl radical at C2 (Scheme 43). 38

Scheme 43. Radical amination of cyclopropenes 93a and 93b possessing a 1,2-disubstituted double bond.

Those latter transformations highlight the synthetic potential of the addition of azide radicals to cyclopropenes to access nitrogen heterocycles with substitution patterns not so easily attained by other strategies.

3.2. Addition of α-iodo carbon-centered radicals

Recently, Hu et al. reported the addition of α-iodo carbon-centered radicals to cyclopropene gem-dicarboxylates. 39 The method involved in the generation of those latter radical species relies on an earlier report by Shi and Li et al. describing the iodine-catalyzed diazo activation for the generation of gem-diiodides and the use of photoredox catalysis. 57 Thus, irradiation of a mixture of a cyclopropene gem-dicarboxylate and a stabilized diazo compound (substituted by an electron-withdrawing group) in the presence of iodine (2 x 0.25 equiv), AcONa, and [Ir(dtbppy)(ppy)]2(PF6) (2 mol %) as photocatalyst under irradiation with blue LEDs (MeCN, rt) led to dienes 95. The scope of the transformation is limited to cyclopropenes bearing an aryl...
group at C2 but several variations are possible for the substituents. Hence, the reaction can be applied to different esters at C3 on the cyclopropene (methyl, ethyl, benzyl, 2,2,2-trifluoroethyl and tert-butyl) as shown with the isolation of 95a-95e (46-70%) formed from ethyl diazoacetate as reaction partner. The phenyl group at C2 can also be substituted at the para, meta or ortho positions with little variations in the yields of the corresponding dienes 95f-95j (63-75%). Various diazoacetates were used successfully as partners, as shown with products 95k-95q incorporating a bromine atom, an isopropyl group and also the sterically demanding adamantly substituent (Ad). The reaction is not limited to α-diazo esters since α-diazo acetamides, p-toluenesulfonyl diazomethane, and 2,2,2-trifluorodiazooethane were successfully involved in this transformation to provide dienes 95r-95u (Scheme 4).

Scheme 44. Synthesis of substituted 1,3-dienes from cyclopropene gem-dicarboxylates and diazo compounds.

In the proposed mechanism, the gem-diiodide 96 would be formed by reaction of the diazo reagent with iodine. The stabilized α-iodo C-centered radical 97 would be generated by electron transfer from the excited state of the iridium photocatalyst. Addition of 97 to the cyclopropene would generate the corresponding cyclopropyl radical 98. By analogy with the ring-opening process reported in the preceding section after the addition of azide radical, cyclopropyl radical 98 would undergo a favorable electrocyclic ring-opening coupled with the elimination of a iodine atom to form diene 95. A redox process with the Ir(IV) species would enable the regeneration of iodine and completion of the photocatalytic cycle (Scheme 45).

Scheme 45. Proposed mechanism for the formation of dienes 95.
Some dienes of the type 95 were found to exhibit antiproliferative activity against HCT116 human colon cancer cells.

Conclusions

The different contributions on radical addition reactions to cyclopropenes have been presented in this review, gathering results disseminated in fifteen articles published since 1994. Many different classes of cyclopropenes have become available but some particular families of those strained substrates have classically been involved so far in radical additions, including those synthesized by transition metal-catalyzed cyclopropenation of alkynes with diazo reagents, gem-difluorocyclopropenes and cyclopropenone acetals. During the last decades, thanks to advances in the development of new radical precursors, photoredox catalysis and dual catalytic processes, radical reactions are now clearly lying at the forefront in organic synthesis and among the most powerful chemoselective synthetic tools. In light of the continuing growing interest for the chemistry of strained rings, addition of other new classes of radicals to cyclopropenes should allow for a chemoselective access to diversely functionalized cyclopropanes, complementary to those exclusively relying on polar reagents. We hope that this review may stimulate efforts in this research area.

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**Authors’ Biographies**

**Gauthier Lefebvre** graduated as engineer from the Ecole Supérieure de Physique et Chimie Industrielles de la ville de Paris (ESPCI Paris-PSL) in 2017. During his studies, he had the opportunity to accomplish a six-months industrial placement at UCB Pharma (Belgium). He obtained an M. Sc. in molecular chemistry from Sorbonne University in 2018 and started a PhD thesis under the supervision of Dr. Christophe Meyer at ESPCI Paris–PSL. His research work focused on the synthesis of new classes of organic compounds incorporating a pentafluorosulfanyl group. Since the defense of his PhD thesis in 2021, he has been working as a postdoctoral researcher associate at ORIL (Bolbec, France) in collaboration with the COBRA laboratory (IRCOF, Rouen, France).
Olivier Charron graduated as engineer from the Ecole Supérieure de Physique et Chimie Industrielles de la ville de Paris (ESPCI Paris-PSL) in 2021. During his studies, he had the opportunity to accomplish a six-months industrial placement at Syngenta (Stein, Switzerland). He obtained an M. Sc. in molecular chemistry from Sorbonne University in 2022 and started a PhD thesis under the supervision of Dr. Christophe Meyer at ESPCI Paris–PSL. He is currently working on the development of catalytic enantioselective reactions enabling access to diversely substituted strained carbo-and heterocycles of potential interest in medicinal chemistry.

Christophe Meyer graduated from the Ecole Nationale Superieure de Chimie de Paris in 1991 and received his PhD from Université Pierre et Marie Curie in 1994 under the supervision of the late Prof. Jean-François Normant and Dr. Ilan Marek. After working as a research assistant (military duties) with Dr. Laurent Elkaim (ENSTA, Paris) and a postdoctoral stay (Lavoisier fellowship) in the group of Prof. Mark Lautens (University of Toronto, Canada), he obtained a CNRS researcher position in 1996 at ESPCI Paris in the team of Prof. Janine Cossy. He was promoted to CNRS Director of Research in 2008. His research activity, within the Molecular, Macromolecular Chemistry and Materials research unit at ESPCI Paris–PSL, focuses on the development of selective synthetic methods with a particular interest in strained rings, transition metal-catalyzed reactions, sigmatropic rearrangements, and their application to the synthesis of bioactive compounds or scaffolds of potential interest in medicinal chemistry.

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