A Platinum Open Access Journal
for Organic Chemistry

Review

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (2) 202312099

Radical addition reactions to cyclopropenes

Gauthier Lefebvre, Olivier Charron and Christophe Meyer*

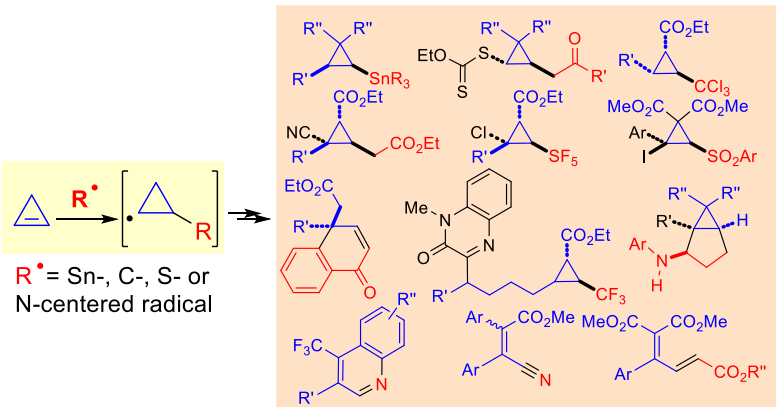
Molecular, Macromolecular Chemistry, and Materials
ESPCI Paris-PSL, CNRS, 10 rue Vauquelin 75005 Paris, France
Email: christophe.meyer@espci.fr

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

Received 09-29-2023 **Accepted** 11-09-2023 **Published on line** 11-26-2023

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

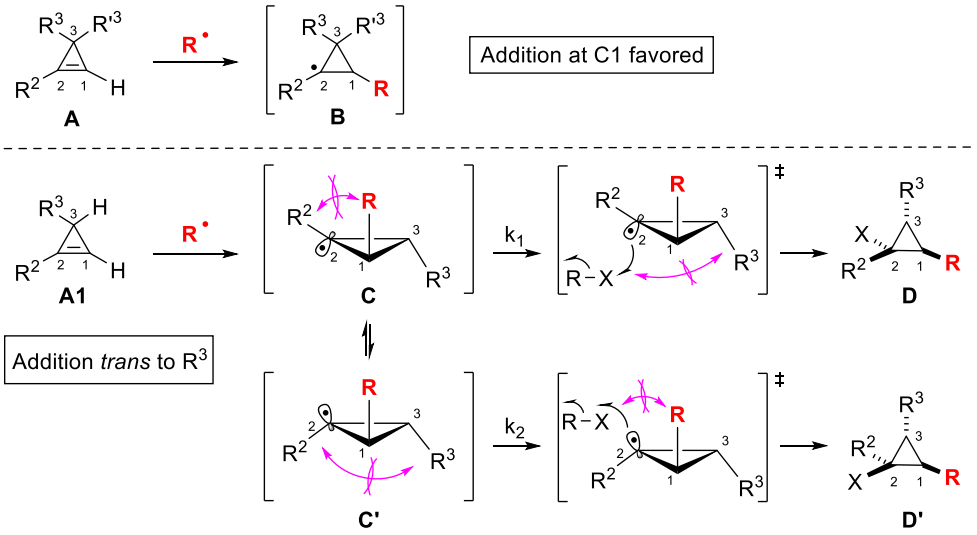
1. Introduction

The highly strained cyclopropenes possess an extremely rich and versatile reactivity.[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).[1–11] In particular, addition reactions across the strained C=C bond of cyclopropenes 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[12,13] and are important fragments in drug design.[14] Whereas the addition of nucleophiles (organometallic species or pronucleophiles in the presence of transition metal catalysts) to cyclopropenes has been widely investigated as a route to stereodefined highly substituted cyclopropanes, radical addition reactions to cyclopropenes remain much less explored comparatively although their feasibility was first demonstrated 30 years ago.[1–11] In this review, the various contributions that have been reported in the field of radical addition reactions to cyclopropenes will be presented, with a discussion on the scope and mechanism of each transformation.

Cyclopropenes 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 “vinylic carbons” of cyclopropenes to make bonds).[15,16] Addition of a radical to a cyclopropene benefits from a considerable relief of ring strain[17] and generates a cyclopropyl radical intermediate which has a strong σ character and a pyramidal geometry.[18] The cyclopropyl radical is less stable than any alkyl radical including the methyl one.[19] Cyclopropyl radicals are also configurationally labile and readily undergo inversion.[18,20–22]

When substituted cyclopropenes are involved in radical addition reactions, regioselectivity and stereoselectivity issues have to be considered. For the sake of simplicity, we shall consider cyclopropenes **A**

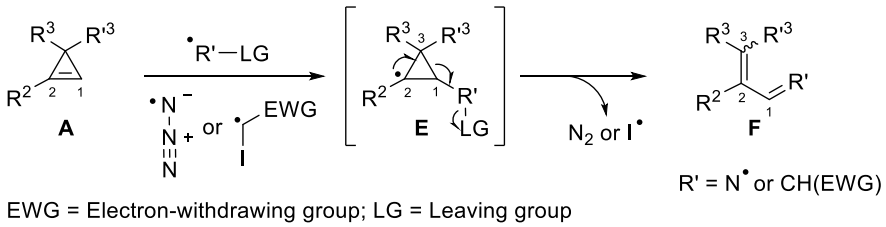
bearing a single substituent on the C=C bond, which correspond to the great majority of substrates considered in the different investigations. For cyclopropenes **A**, radical addition occurs preferentially on the less-substituted carbon, designated as C1 by convention throughout the course of the review, and generates a substituted cyclopropyl radical **B** at C2 as the major regioisomer, most often exclusively. Cyclopropenes lacking any stereocenter at C3 ($R^3 = R'^3$) 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 (R^3) 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 R^2 and R or alternatively the R^2 and R^3 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 R^3 for **C** and R for **C'**, respectively. Hence, stereocontrol at C2 results from a typical Curtin-Hammett scenario[23] and depends on the rates of the atom transfer process (k_1 and k_2), 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[24–35] 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.[36] 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[37,38] or α-iodo C-centered radicals[39] which both incorporate a leaving group (LG) (dinitrogen or iodine atom, respectively) (Scheme 2).



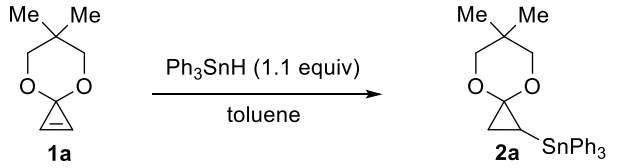
Scheme 2. Radical addition to cyclopropenes accompanied by cleavage of the three-membered ring.

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

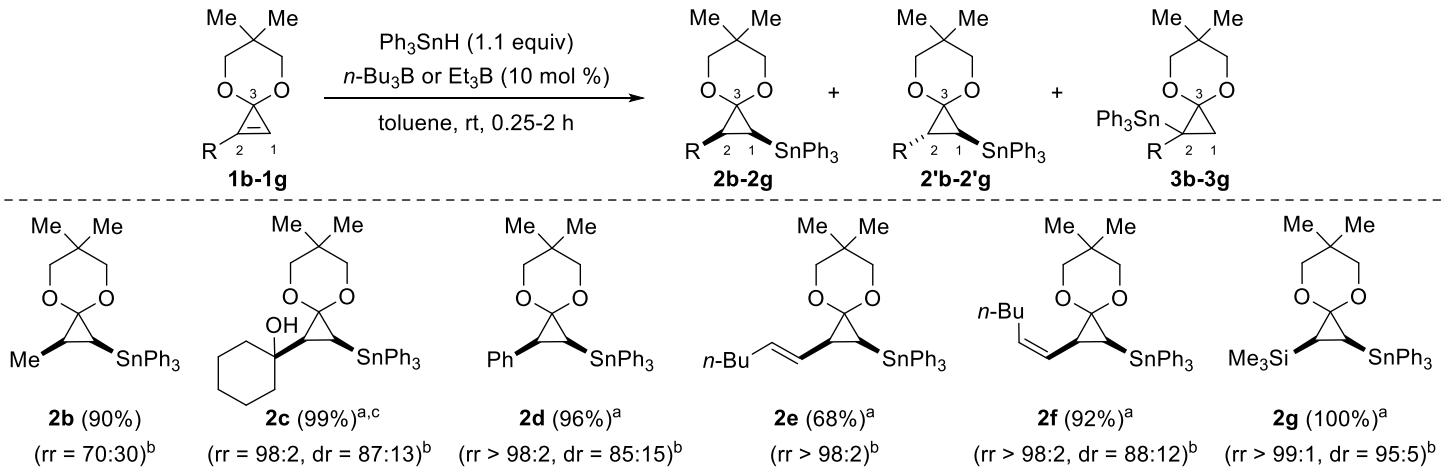
In 1994, Nakamura *et al.* reported the first examples of radical addition reactions to cyclopropenes.[24] Hydrostannylation of cyclopropenone acetal **1a** with Ph_3SnH was efficiently accomplished in toluene either by heating at 60 °C in the presence of AIBN, by initiation with *n*-Bu_3B at room temperature or activation by ultrasound irradiation to afford cyclopropylstannane **2a** in high yields (83-100%) (Scheme 3).[24] By comparison, hydrostannylation of **1a** with *n*-Bu_3SnH proceeded at a slower rate than with Ph_3SnH and led to the corresponding adduct in moderate yield (64%).



reaction conditions	yield (**2a**)
AIBN (10 mol %), 60 °C, 1.1 h	99%
n-Bu_3B (10 mol %), rt, 1.4 h	100%
ultrasound irradiation, 7 °C, 2 h	83%

Scheme 3. Hydrostannylation of cyclopropenone acetal **1a**.

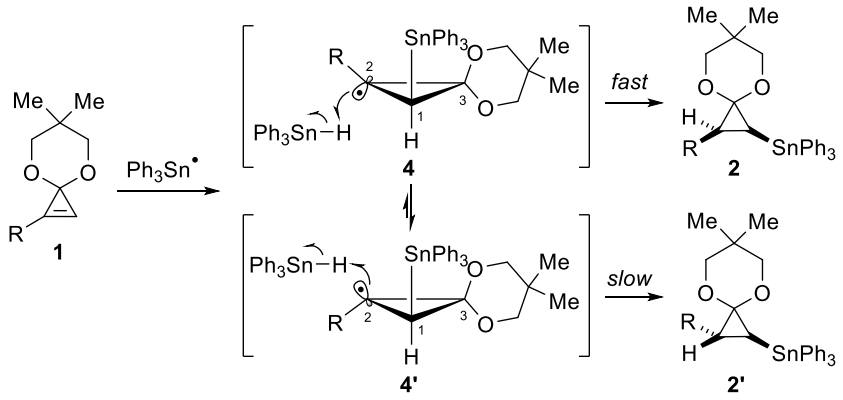
The scope of the radical hydrostannylation was examined with diversely substituted cyclopropenone acetals **1b**-**1g**. High regioselectivities were observed in almost all cases in favor of the addition of the tin-centered radical at the terminal position (C1), except for the less hindered methyl-substituted 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 diastereocontrol. It is also worth noting that for substrates **1e** and **1f** incorporating a disusbtituted (*E*)- and (*Z*)-alkene, respectively, no isomerization of the double bond was observed in the cyclopropylstannanes **2e** and **2f** (Scheme 4).[24]



[a] Isolated yields (major regioisomer/stereoisomer drawn). [b] rr = Regioisomeric ratio (**2**+**2'**)/**3**; dr = diastereomeric ratio (**2**/**2'**) (indicated when mentioned in the publication). [c] Reaction run at 0 °C.

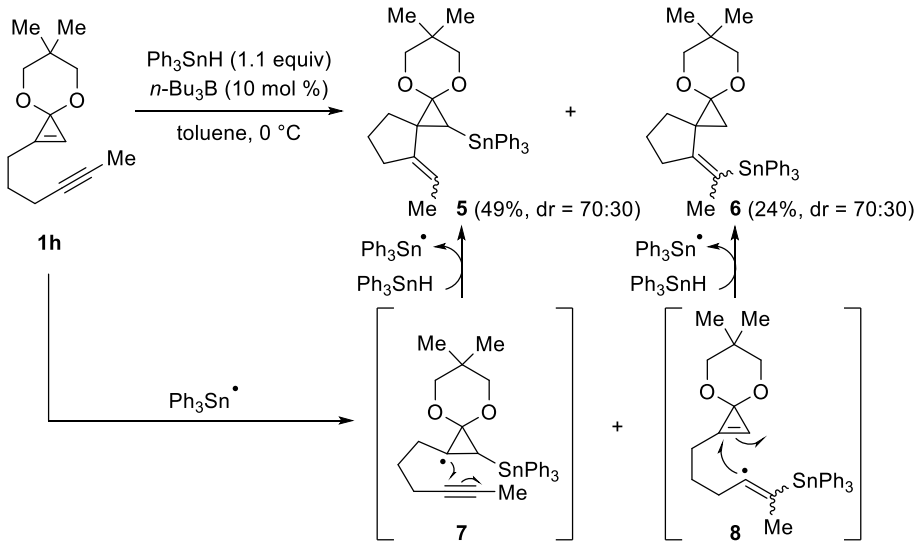
Scheme 4. Scope of the hydrostannylation of cyclopropenone acetals.

The preferential formation of the *cis* cyclopropylstannanes **2** indicates that the cyclopropyl radical intermediate preferentially abstracts a hydrogen atom to Ph_3SnH from the less hindered face of the three-membered ring, through configuration **4** (*trans* to the R and $SnPh_3$ groups) (Scheme 5).[24]



Scheme 5. Diastereoselectivity of the hydrostannylation of cyclopropenone acetals.

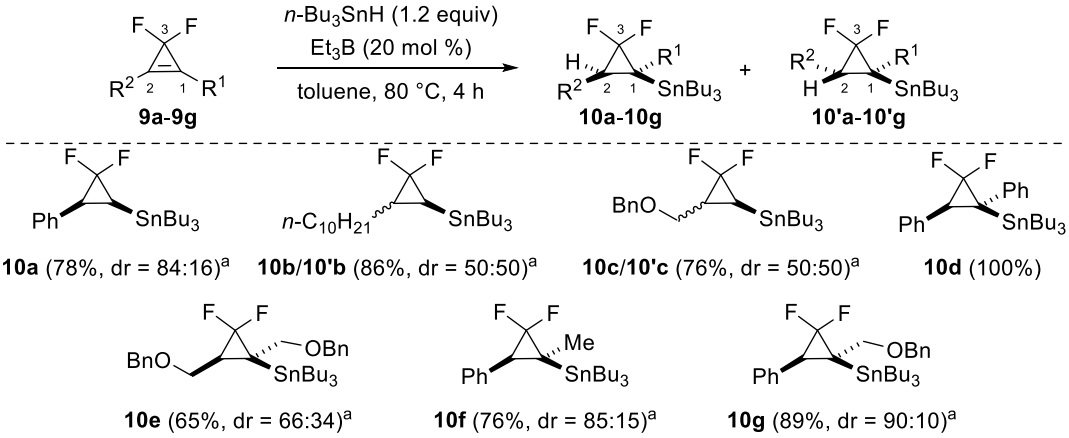
An intermolecular competition experiment revealed that cyclopropenone acetal **1a** is three times more reactive than 1-hexyne towards Ph_3SnH (Et_3B cat., toluene, 0 °C). Also a disubstituted alkyne (1-trimethylsilyl-1-hexyne) failed to undergo hydrostannylation in competition with **1a**.[24] However, 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).[24]



Scheme 6. Hydrostannylation of cyclopropene-yne **1h**.

Only cyclopropenone acetals were considered as substrates in this seminal study[24] but it was later reported by Gevorgyan *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.[40,41]

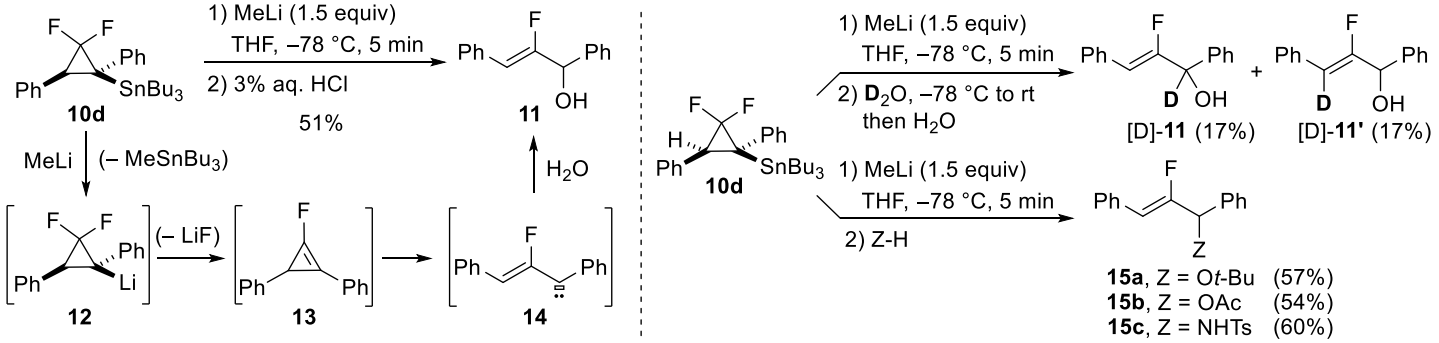
The radical hydrostannylation of *gem*-difluorocyclopropenes **9** was reported by Konno *et al.* in 2015.[25] It should be mentioned that the palladium-catalyzed hydrostannylation fails for this particular class of substrates and hence radical conditions represent a valuable alternative. Mono-substituted difluorocyclopropenes **9a**-**9c** were hydrostannylated with high regioselectivity (addition of the tin-centered radical at C1) using Et_3B as initiator (toluene, 80 °C) but subsequent hydrogen atom transfer at C2 proceeded with moderate or no diastereocontrol 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 *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).[25]



[a] dr = Diastereomeric ratio **10**/**10'** (major diastereomers are drawn).

Scheme 7. Radical hydrostannylation of *gem*-difluorocyclopropenes.

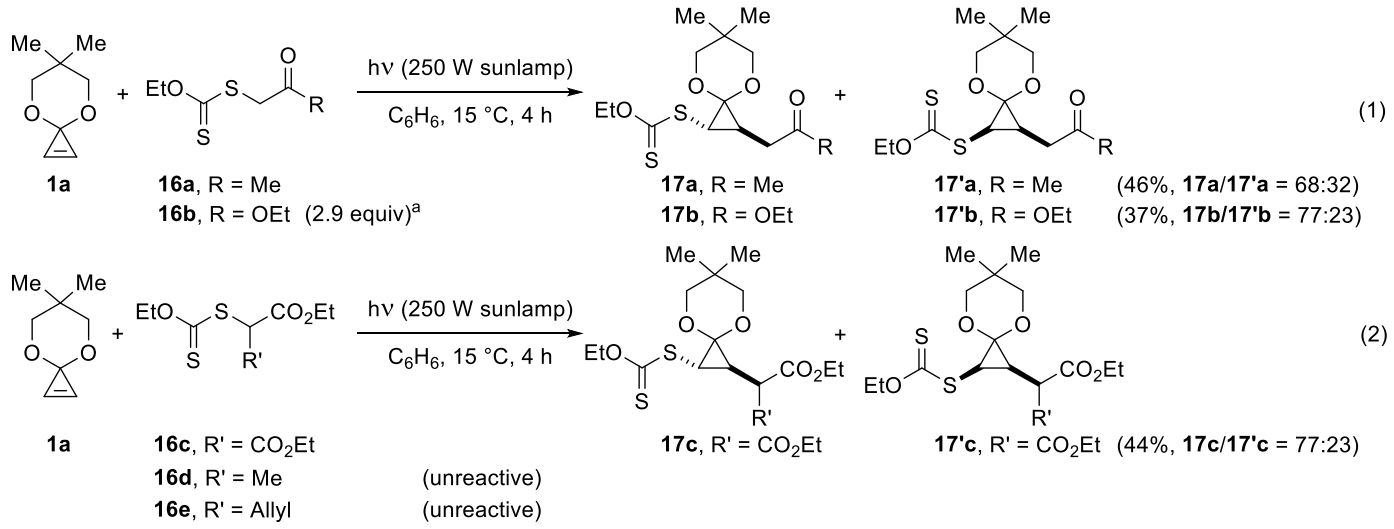
The authors investigated the feasilibity of a tin-lithium exchange on the (difluorocyclopropyl)stannane **10d** by treatment with MeLi (1.5 equiv) (THF, –78 °C). After quenching with acid, the β-fluoroallylic alcohol **11** was obtained as a single (*Z*) geometric isomer (51%). Attempts to intercept 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 D_2O 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).[25]



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 (C_6H_6, 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]

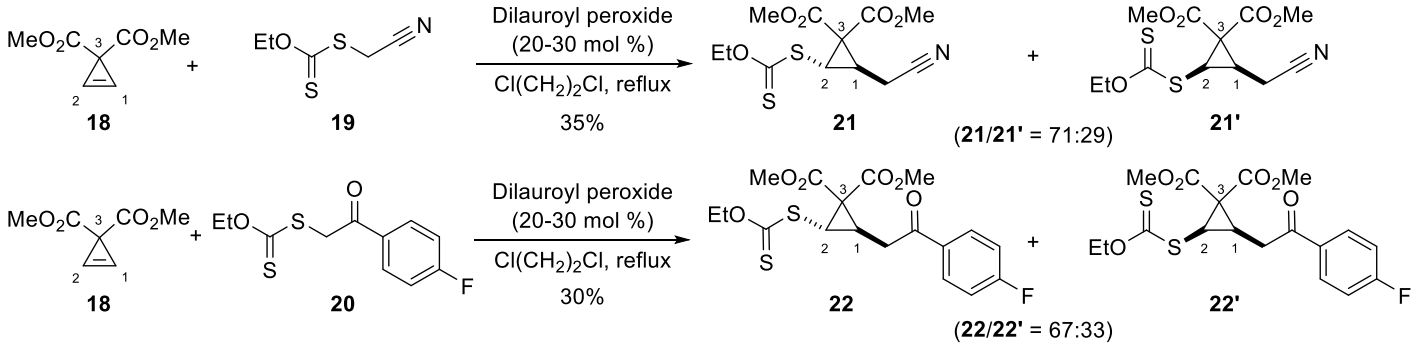


[a] The stoichiometry was only indicated for this particular example (representative procedure).

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 dilauroyl 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]

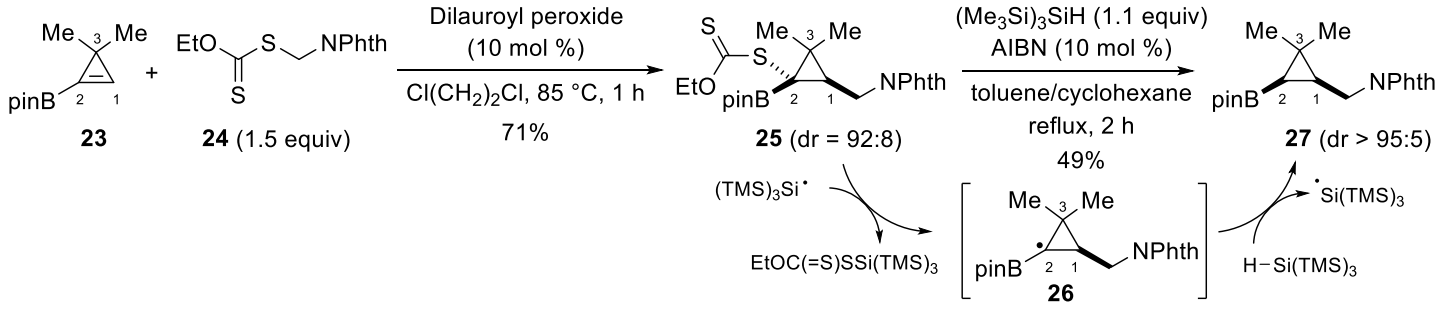


Scheme 10. Radical addition of xanthates to cyclopropene **18**.

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.

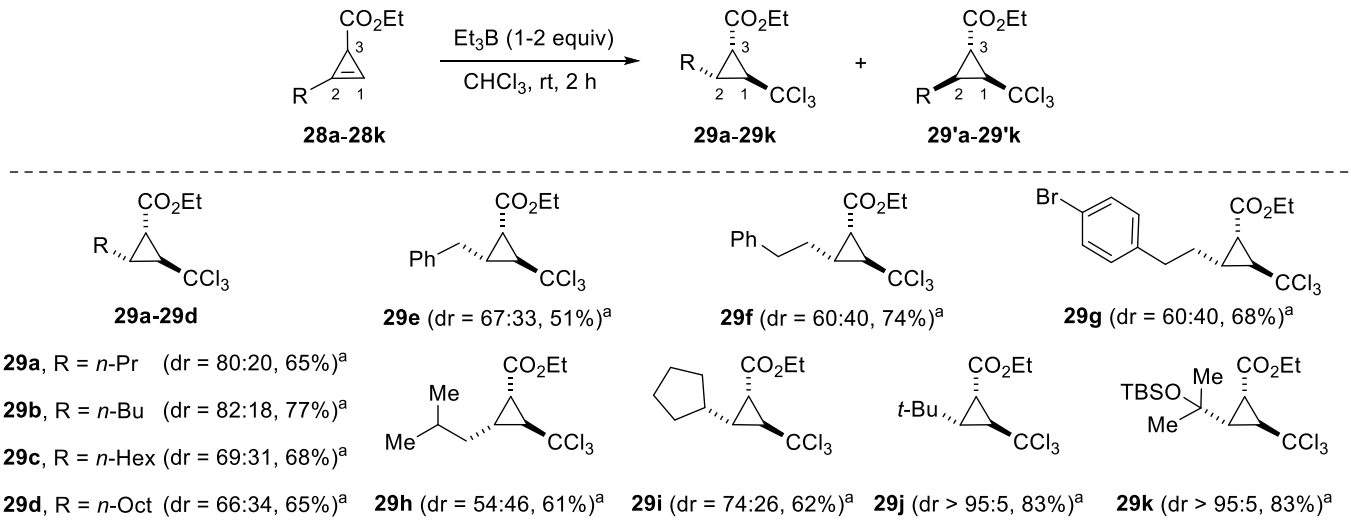
Recently, in the context of their work on the modular synthesis of substituted cyclobutylboronates by consecutive radical additions, Zard and co-workers reported another example of xanthate addition to cyclopropenylboronate **23** aimed at evaluating the effect of the ring-size on the reactivity.[28] 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.[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).[28]



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

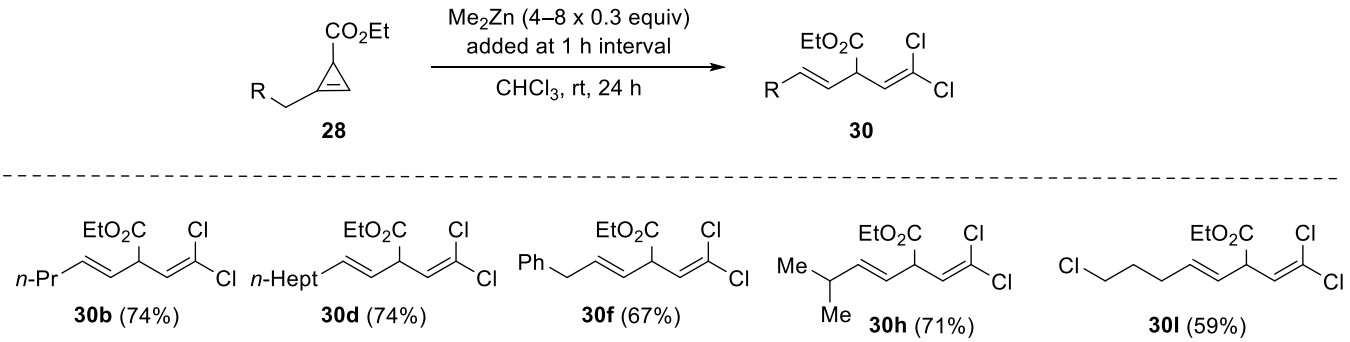
2.2.2. Trichloromethylation. In 2015, Miyata *et al.* reported the addition of the trichloromethyl radical generated from chloroform to substituted cyclopropene-3-carboxylates **28** using Et_3B as initiator.[29] A stoichiometric quantity of the latter reagent was required in order to get good yields 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_3B.[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 cyclopropenecarboxylates **28a**-**28i** bearing a primary or a secondary (cyclopentyl) alkyl group at C2. Cyclopropanes **29a**-**29i** possessing a *trans* relationship between the CCl_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).[29]



Scheme 12. Addition of the trichloromethyl radical to cyclopropenecarboxylates **28** mediated by Et_3B.

Additional experiments revealed that no deuterium incorporation took place at C2 when $CDCl_3$ 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-Et_3B complex[42] or from Et_3B 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 adeverse effect on the efficiency of the addition process.[29]

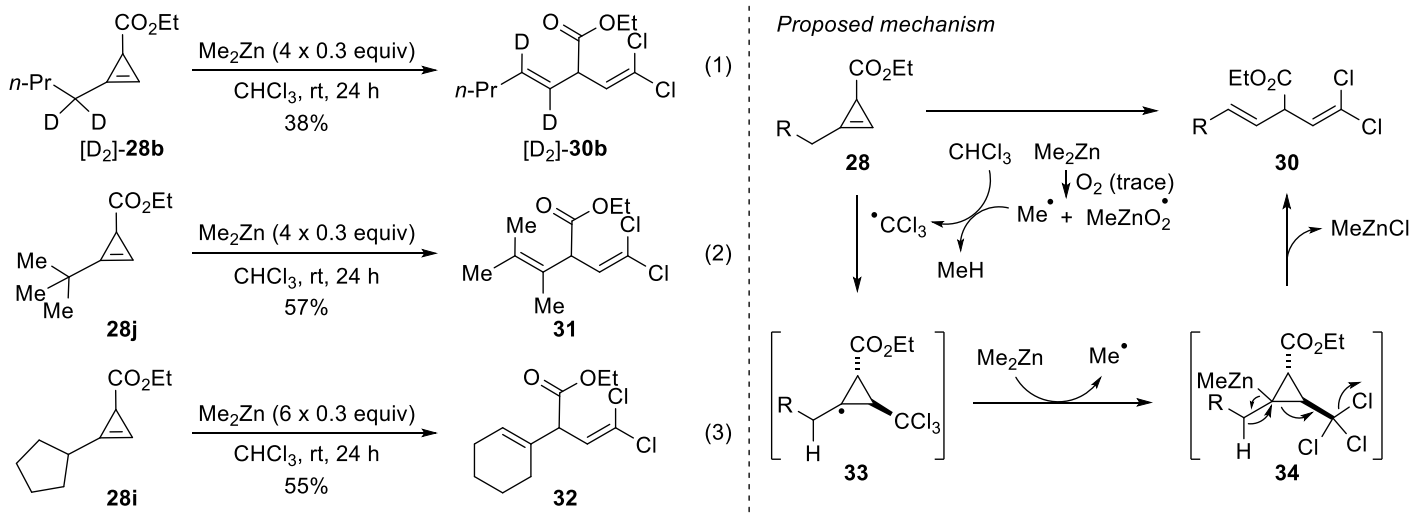
The authors also investigated the use of Me_2Zn as radical mediator and a different reactivity profile was observed since the reaction led to the ring-opened *gem*-dichloroolefins **30** (59–74%) (Scheme 13).[29]



Scheme 13. Reaction of cyclopropenecarboxylates **28** with chloroform mediated by Me_2Zn.

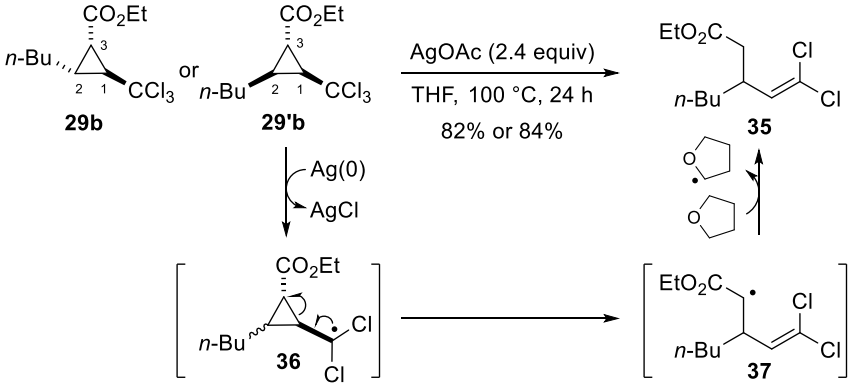
Deuterium labeled substrate [D_2]-**28b** provided the vicinally deuterated olefin [D_2]-**30b** (38%) which indicated the occurrence of a 1,2-hydrogen shift in the mechanism (Scheme 14, Eq. 1). From cyclopropene **28j** possessing a *tert*-butyl substituent, migration of one methyl group was observed 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 Me_2Zn to generate the

organozinc reagent **34** as the initial adduct.[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*-dichloroolefin **30** (Scheme 14).



Scheme 14. Additional experiments and proposed mechanism for the formation of *gem*-dicholoroolefins **30**.

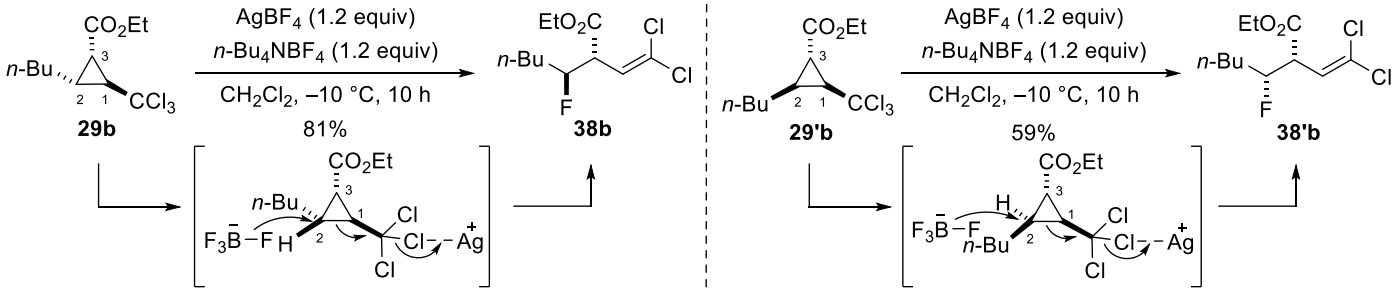
In 2016, the authors subsequently reported regiodivergent ring-opening reactions of trichloromethyl-cyclopropanecarboxylates **29** to illustrate the interest of these products.[46] A reductive ring-opening process of the epimeric (trichloromethyl)cyclopropanes **29b** (or **29'b**) was described in the presence of AgOAc (THF, 100 °C) which afforded the *gem*-dichloroolefin **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 dichloroolefin **35** (Scheme 15).[46]



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

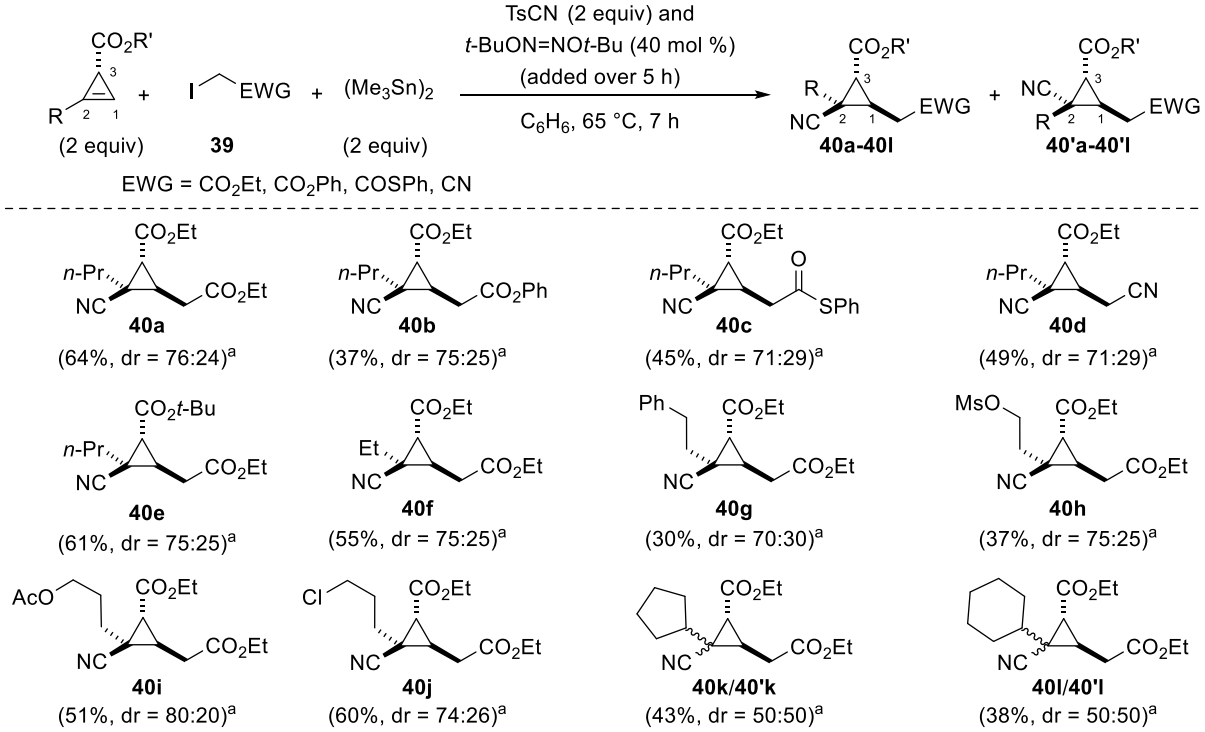
Ring-opening reactions of (trichloromethyl)cyclopropanes **29** with fluoride were also reported using both $AgBF_4$ and *n*-Bu_4NBF_4 (CH_2Cl_2, –10 °C). Abstraction of a chloride by the silver cation would result in the development of a positive charge adjacent to the cyclopropane and hence trigger 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 **38b** and **38'b** from epimeric cyclopropanes **29b** and **29'b** (Scheme 16).[46]



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

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]

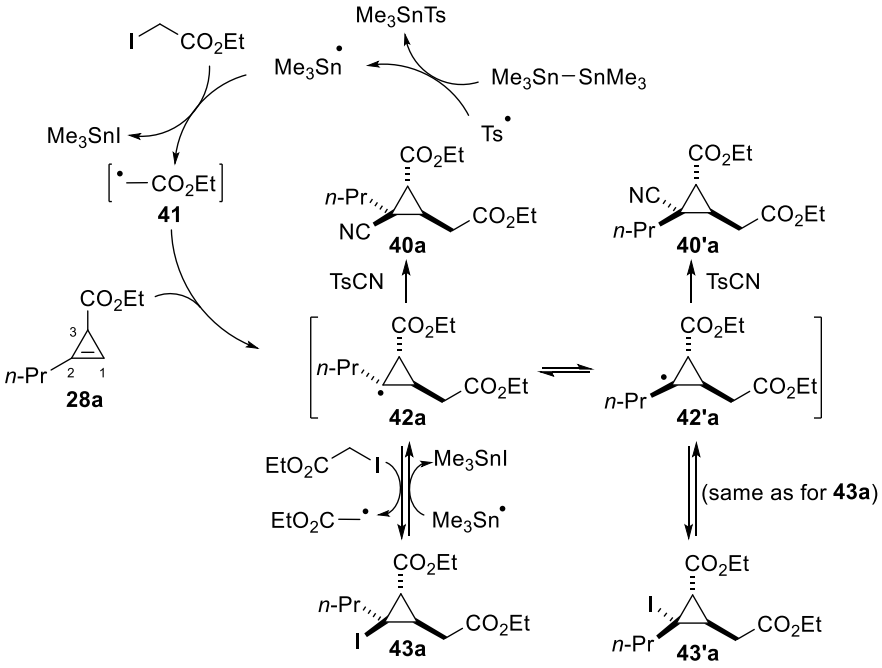


[a] dr = Diastereomeric ratio **40**/**40'** (major diastereomers are drawn).

Scheme 17. Radical carbocyanation of cyclopropenecarboxylates.

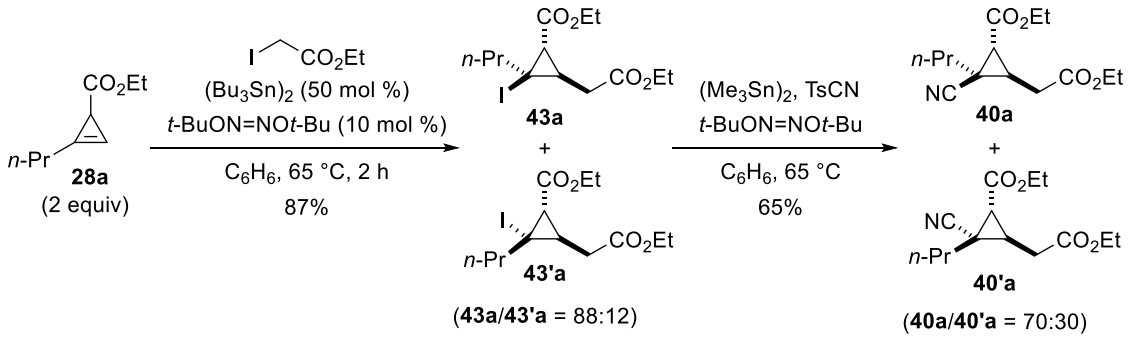
Analysis of the scope of the carbocyanation reaction reveals that various *n*-alkyl substituents, possibly containing another functional group (a mesylate, an acetoxy group or a chlorine atom), could be present at C2 in the cyclopropene-3-carboxylate substrates. The electron-withdrawing group (EWG) in 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*-buyl 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 diastereocontrol at C2 was observed (Scheme 17).[30]

After regioselective and stereoselective addition of the electrophilic radical **41** to cyclopropene **28a** (addition at C1 and *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).[30]



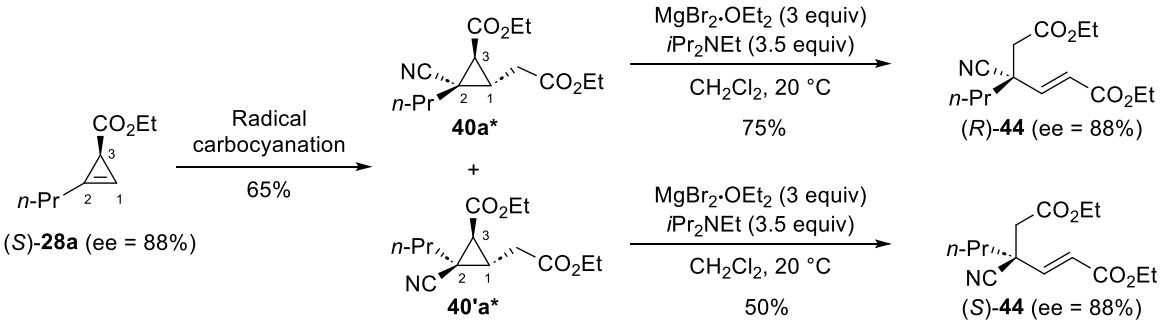
Scheme 18. Mechanism of the radical carbocyanation of cyclopropene **28a**.

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).[30]



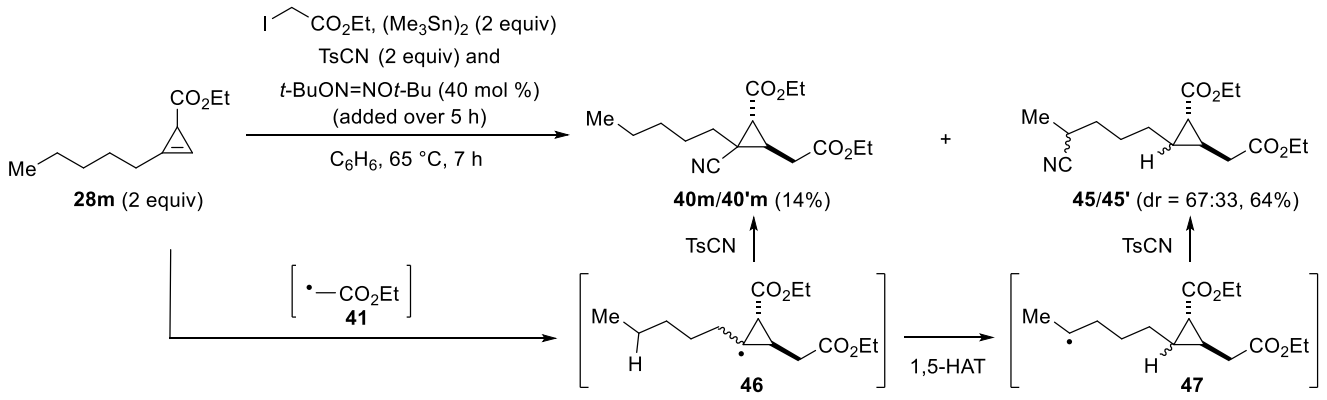
Scheme 19. Sequential radical carboiodation and cyanation reactions from cyclopropene **28a**.

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 ($MgBr_2$•OEt_2, *i*Pr_2NEt), 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***.

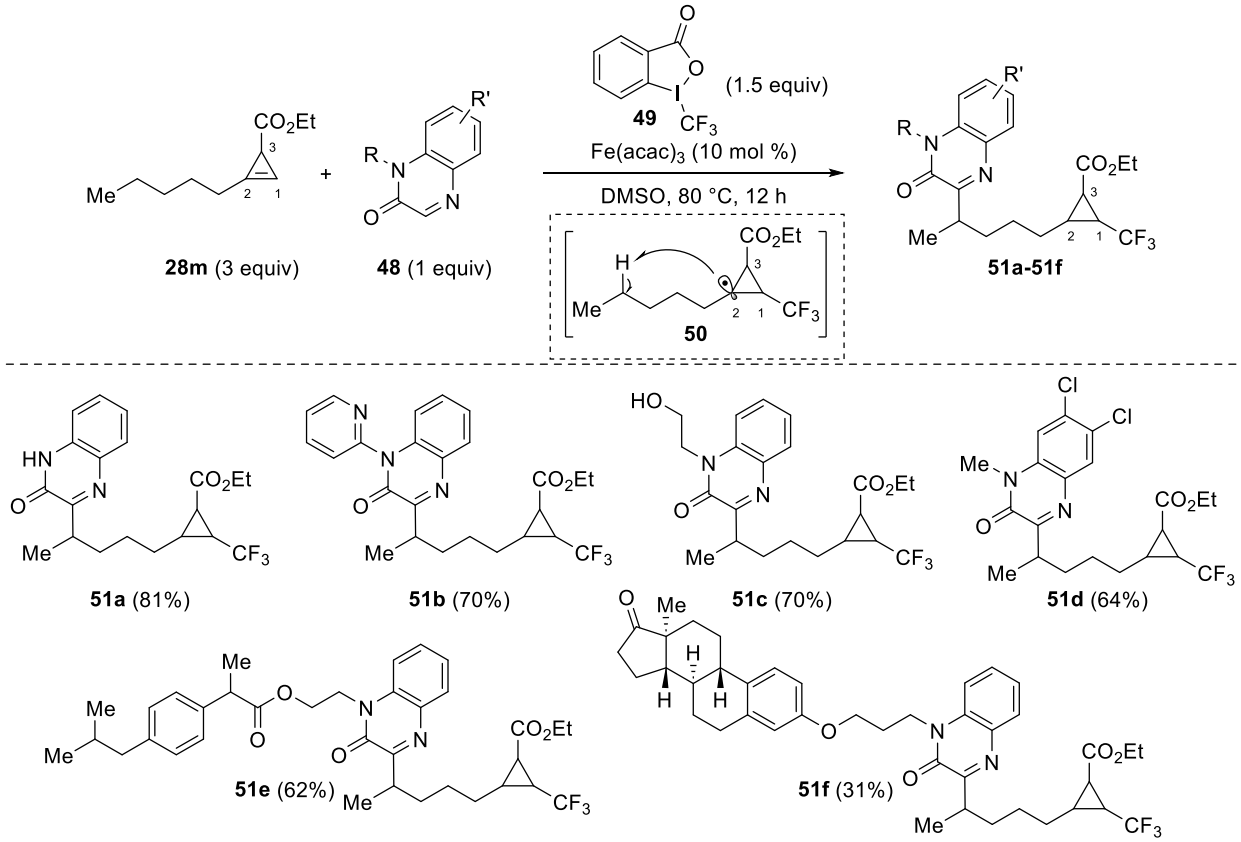
Interestingly, in the case of cyclopropene **28m** bearing an *n*-pentyl chain, the diastereomeric cyanocyclopropanes **40m**/**40'm** arising from the carbocyanation process were isolated in low yield (14%). In this case, Landais *et al.* observed that the major products were cyclopropanes **45**/**45'** (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 tranfer (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.

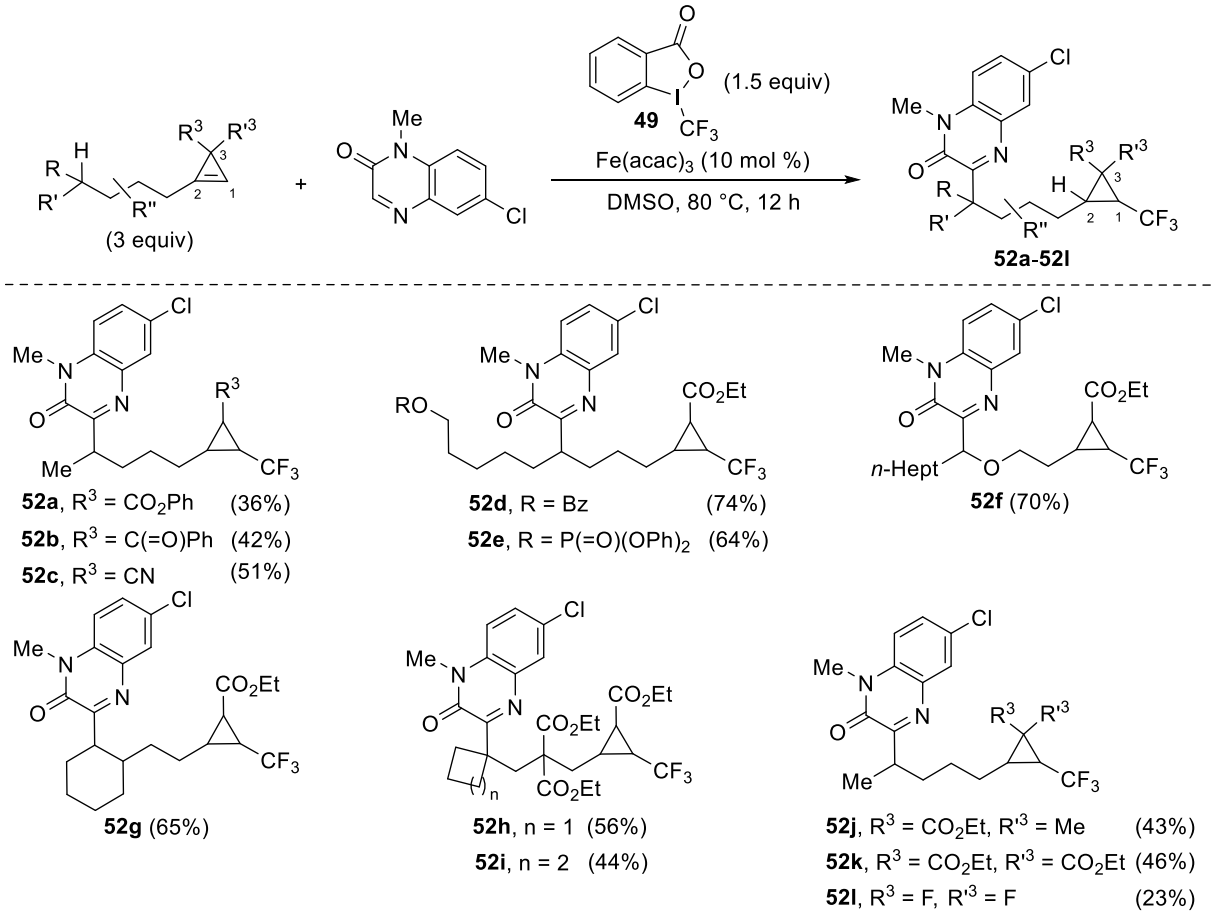
2.2.4. Cascade radical processes initiated by radical trifluoromethylation. In 2023, Wu, Zhu and co-workers reported the trifluoromethylation of cyclopropene **28m** (used in excess, 3 equiv) using Togni's reagent **49** and $Fe(acac)_3$ as the catalyst to generate trifluoromethyl radicals. The reaction 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 triggerred 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.[31]

The authors also illustrated the broad scope of substituted cyclopropenes amenable in this latter radical trifluoromethylation/1,5-hydrogen atom transfer/heteroarylation cascade process. The substituent at C3 can be a phenyl ester, a phenyl ketone or a nitrile as shown with the formation of CF_3-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 substitutent (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).[31]

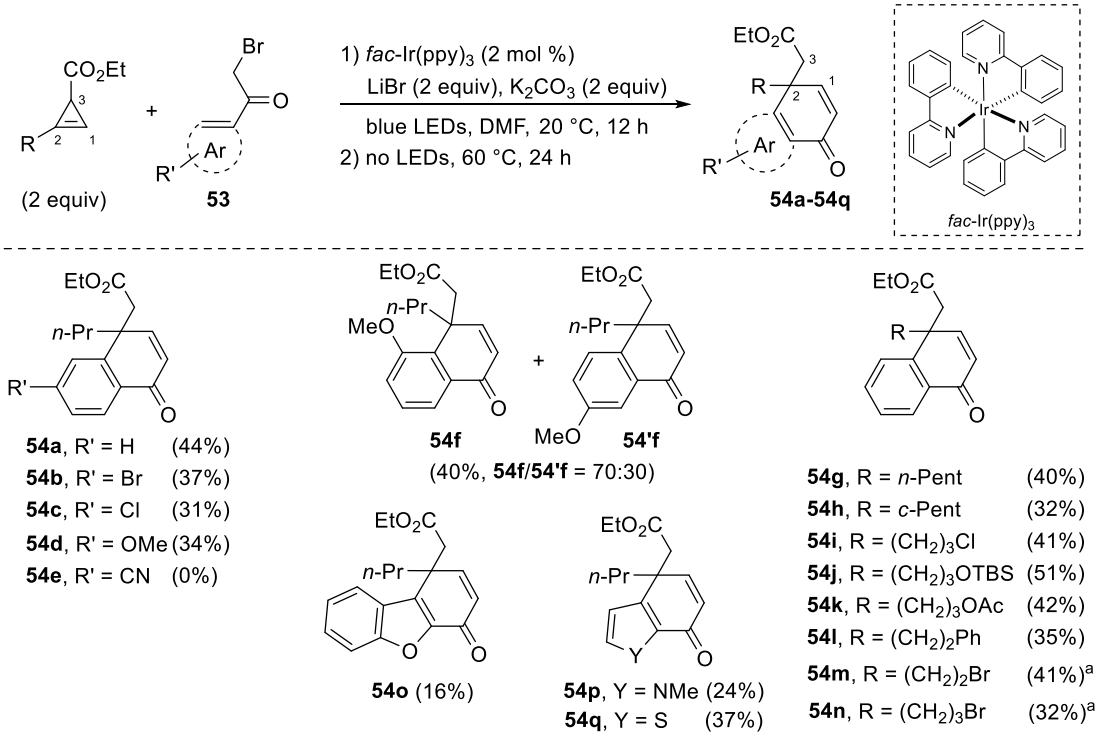


Scheme 23. Scope of the radical trifluoromethylation/1,5-HAT/heteroarylation cascade process.

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 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]

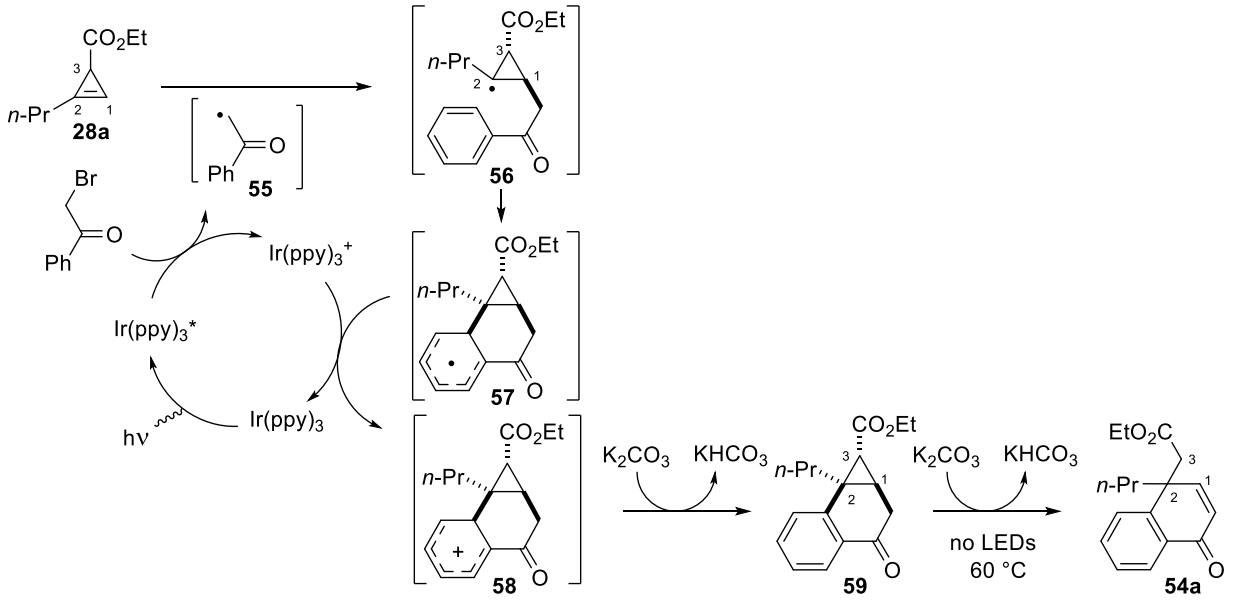
2.2.5. Photocatalyzed carboarylation. In 2017, Landais *et al.* reported the visible-light mediated reaction of cyclopropene-3-carboxylates with phenacyl bromides of the type **53** in the presence of K_2CO_3, LiBr and the iridium photocatalyst *fac*-Ir(ppy)$_3$ under irradiation with blue LEDs (DMF, 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 α-bromo carbonyl substrate took place. In the case of a *meta*-substituted phenacyl bromide, a mixture of the corresponding regioisomeric carboarylation products (**54f**/**54'f**) 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 *in situ* by a bromide. Heteroaryl α-bromo ketones were tested as reaction partners and whereas a benzofurane 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]



[a] The starting cyclopropenes contain a mesylate which is displaced *in situ* by a bromide.

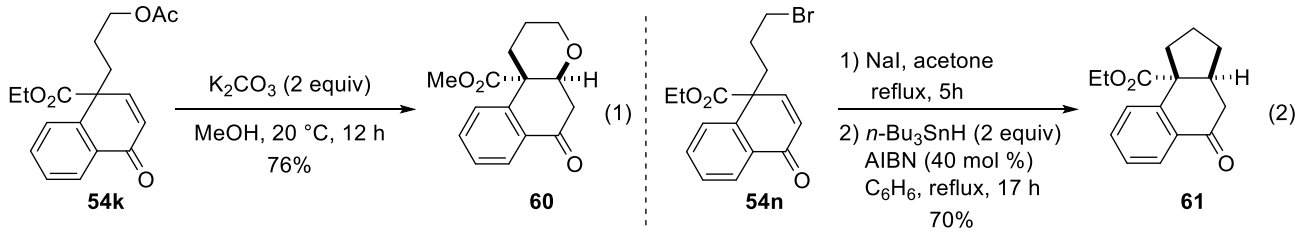
Scheme 24. Visible-light mediated reaction of cyclopropene-3-carboxylates with phenacyl bromides.

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_2CO_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).[32] 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).



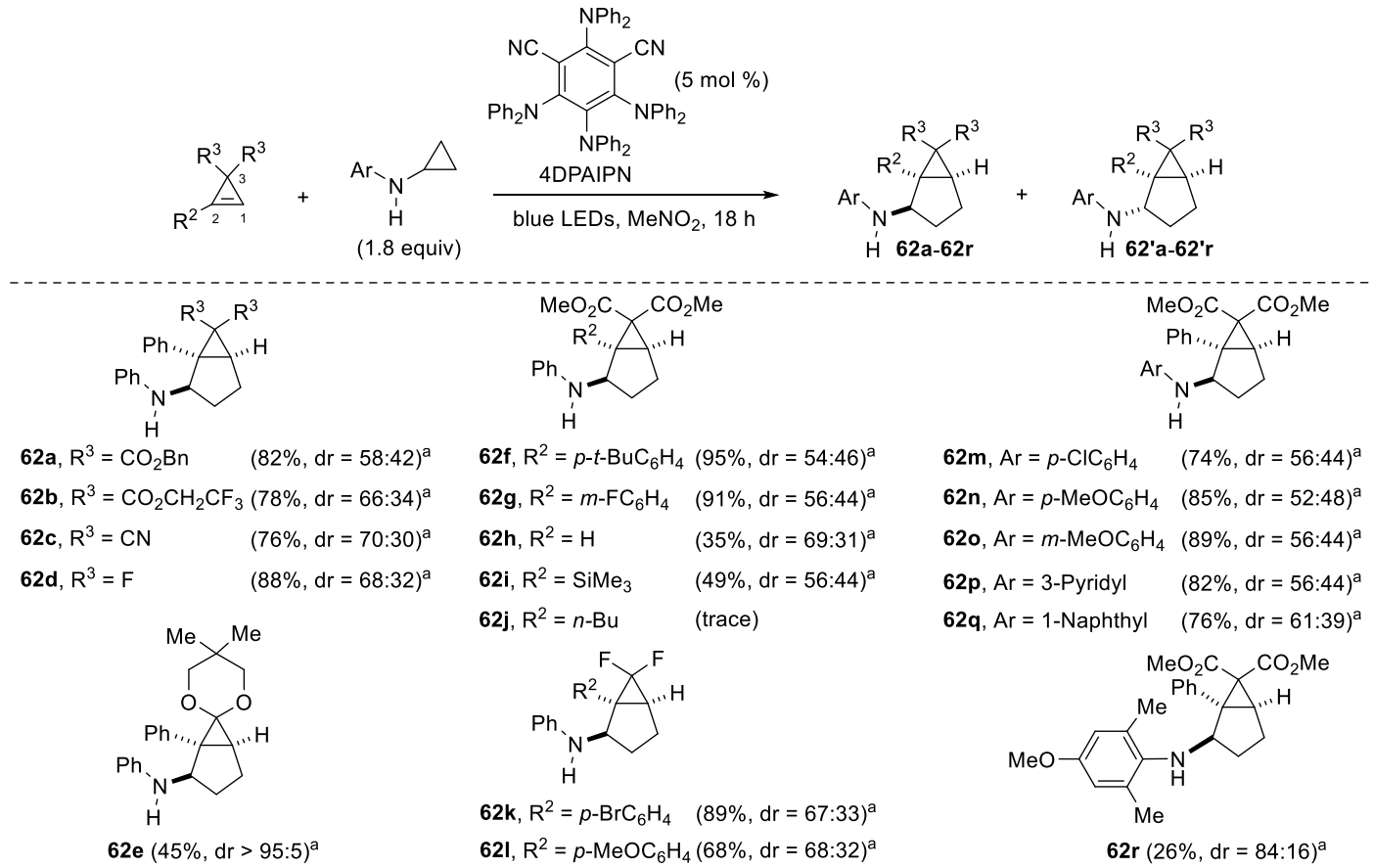
Scheme 25. Visible-light mediated addition of phenacyl bromides to cyclopropenecarboxylates.

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**.

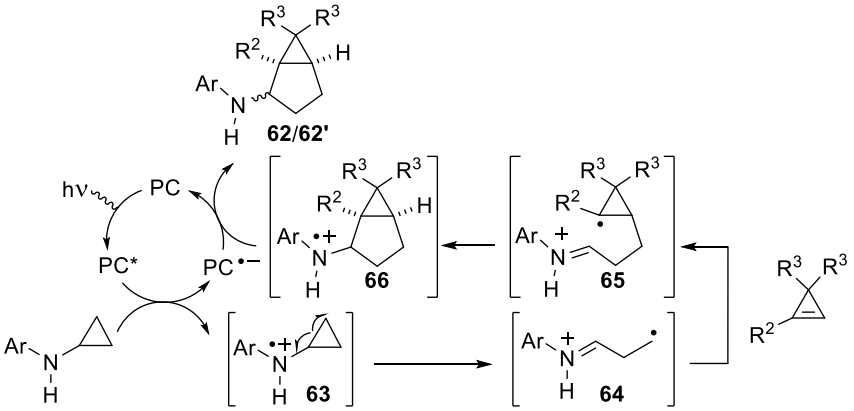
2.2.6. Photocatalyzed (3+2) annulation with cyclopropylanilines. In 2019, Waser *et al.* disclosed a new (3+2) annulation between cyclopropenes and cyclopropyl anilines leading to bicyclo[3.1.0]hexanes **62** substituted by an amino group.[33] The reaction was conducted in the presence of the organic 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]



[a] dr = Diastereomeric ratio **62**/**62'** (major diastereomers are drawn).

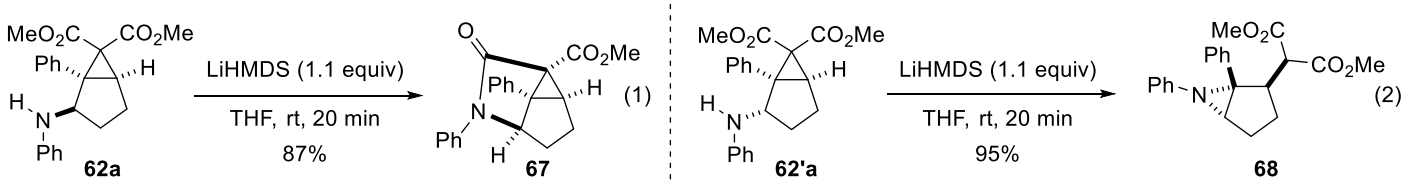
Scheme 27. Photocatalyzed (3+2) annulation of cyclopropenes with cyclopropyl anilines.

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 ($PC^{\bullet -}$) would complete the photocatalytic cycle and explain the formation of the diastereomeric bicyclic products **62**/**62'** (Scheme 28).[33]



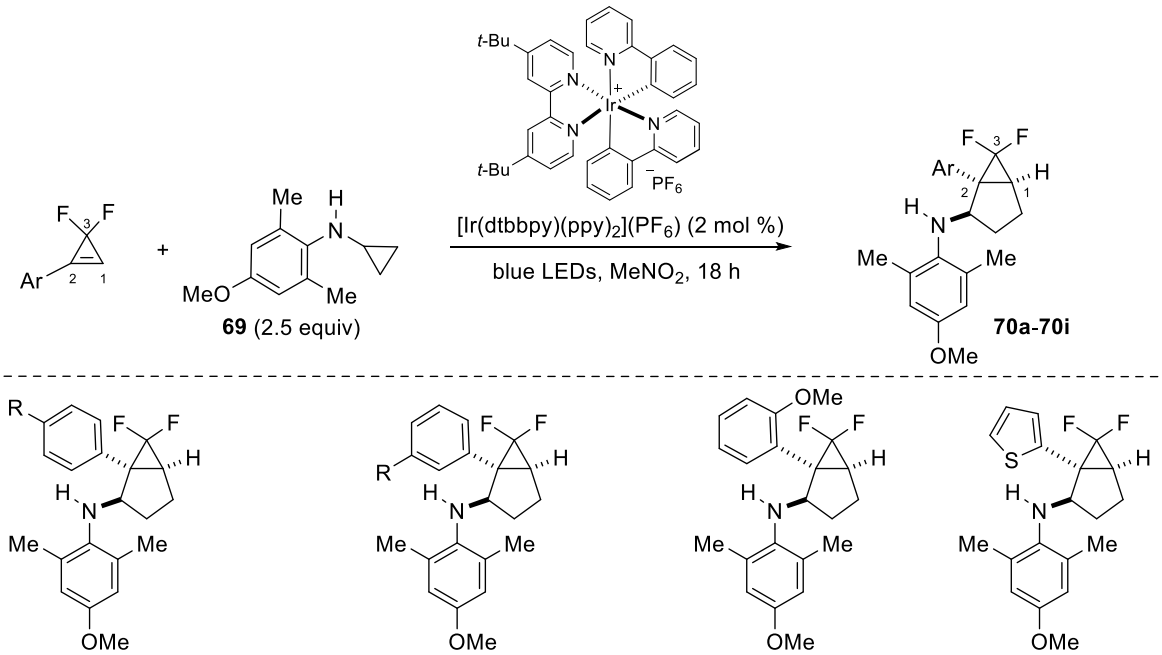
Scheme 28. Mechanism of the photocatalyzed (3+2) annulation.

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 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).[33]



Scheme 29. Post functionalization reactions of the epimeric aminobicyclo[3.1.0]hexanes **62a** and **62'a**.

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(dtbby)(ppy)$_2$](PF$_6$). Cycloadducts **70a**-**70i** were obtained in moderate to good yields (41-83%) and with high diastereoselectivities (rd ≥ 91:9) (Scheme 30).[33]



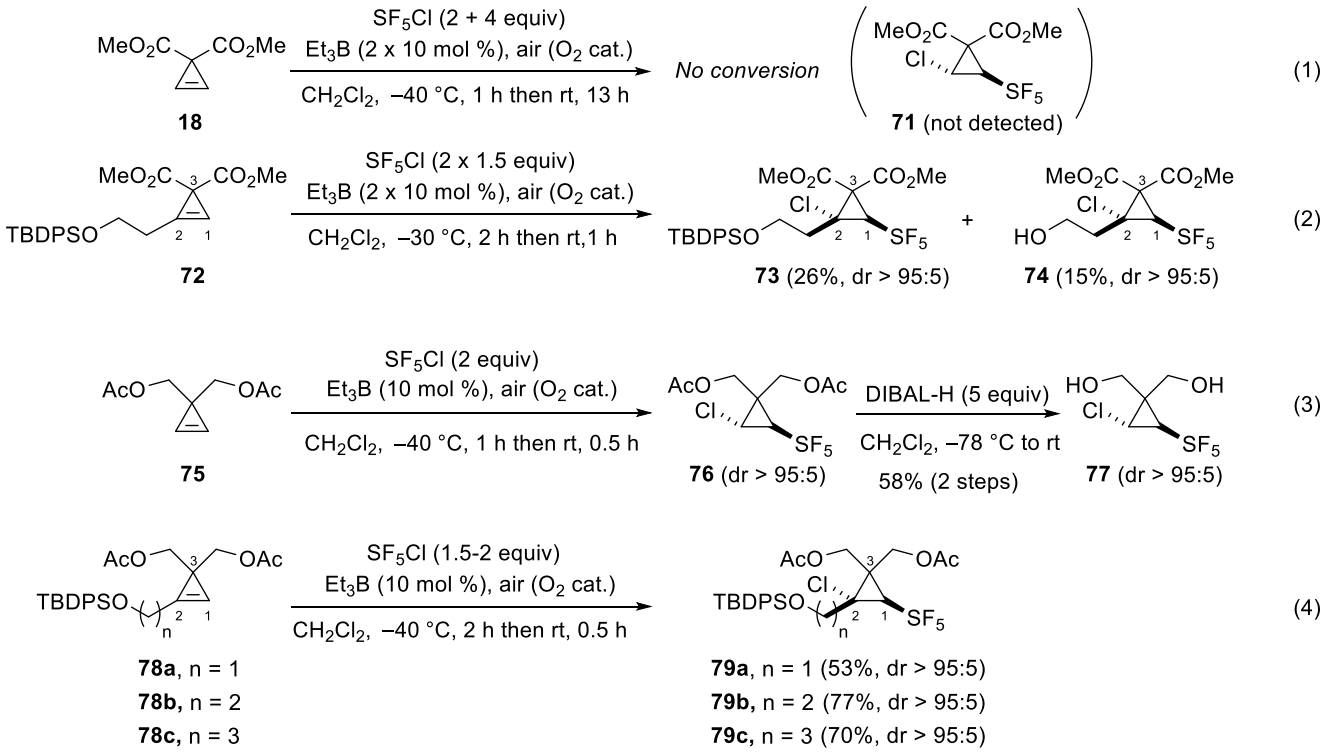
70a, R = OMe (61%, dr = 93:7)
70b, R = CF_3 (77%, dr = 93:7)
70c, R = Br (79%, dr = 93:7)
70d, R = Me (79%, dr = 93:7)
70e, R = NO_2 (75%, dr = 91:9)
70f, R = Cl (83%, dr = 92:8)
70g, R = Me (75%, dr = 94:6)
70h (74%, dr = 94:6)
70i (41%, dr = 95:5)

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.[47-49] It is worth mentionning 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**.[33]

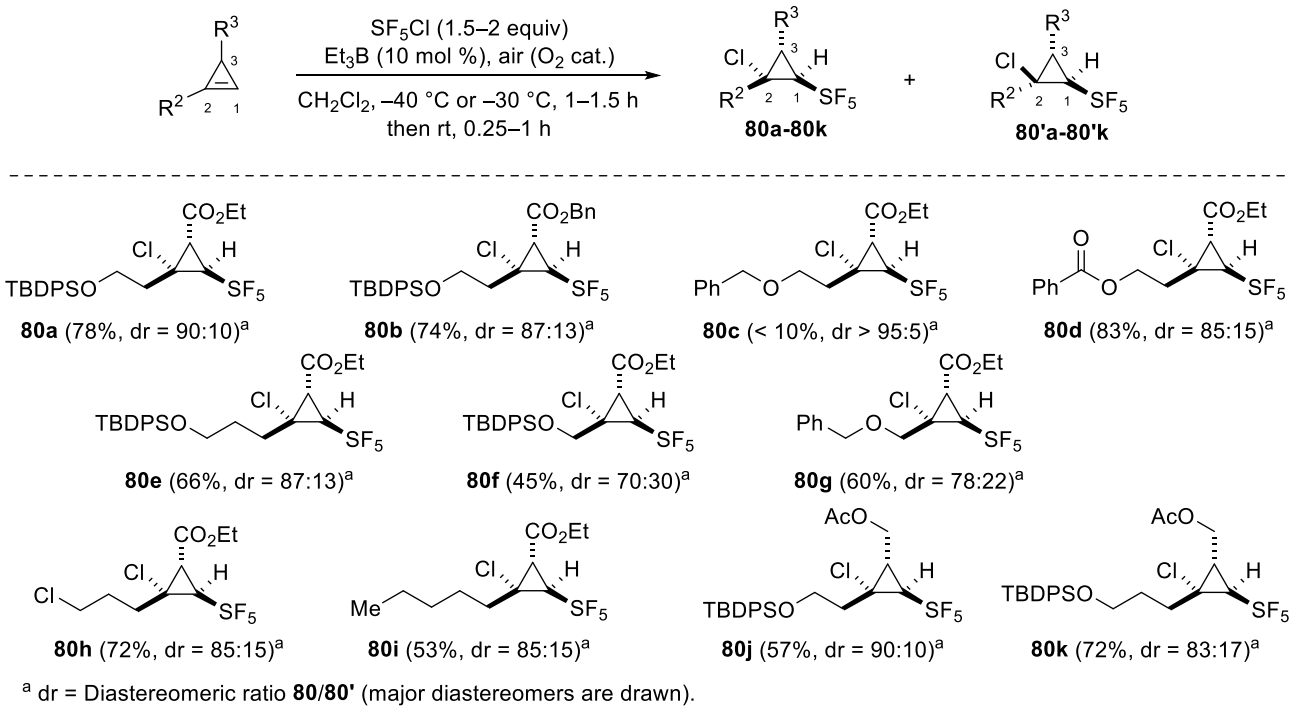
2.3. Addition of sulfur-centered radicals to cyclopropenes

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.[49,50] Until recently, cyclopropanes substituted by the pentafluorosulfanyl (SF_5) group, which belongs to the so-called "emerging fluorinated motifs",[51,52] were unknown compounds. Since the radical addition of gaseous SF_5Cl to alkenes and alkynes initiated by the Et_3B/O_2 system affords a convenient entry to aliphatic pentafluorosulfanyl compounds,[53,54] the reactivity of cyclopropenes was investigated.[34] Initial attempts to achieve the radical addition of SF_5Cl 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_5Cl was required to observe complete conversion. Under these forcing conditions, adduct **73** was isolated in only 26% yield, as a single detectable diastereomer. Concomittant cleavage of the *tert*-butyldiphenylsilyl ether (TBDPS) took place, presumably by a fluoride source arising from the decomposition of a SF_5Cl derivative (S_2F_{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_5 radical, cyclopropene **75** bearing a more electron-rich C=C bond than **18** was tested as substrate. The radical addition of SF_5Cl to the *gem*-(diacetoxymethyl)-cyclopropene **75** proceeded efficiently and after cleavage of the acetyl groups by reduction with DIBAL-H, the SF_5-cyclopropane **77** was isolated in good overall yield (55%) (Scheme 31, Eq. 3). Addition of SF_5Cl was also successful on cyclopropenes **78a**-**78c** substituted at C2 by an alkyl chain incorporating a TBDPS ether and afforded SF_5-cyclopropanes **79a**-**79c** (53–77%, dr > 95:5) (Scheme 31, Eq. 4). Thus, addition of the SF_5 radical (generated by abstraction of a chlorine atom from SF_5Cl 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_5 group (Scheme 31, Eqs. 3 and 4).[34]



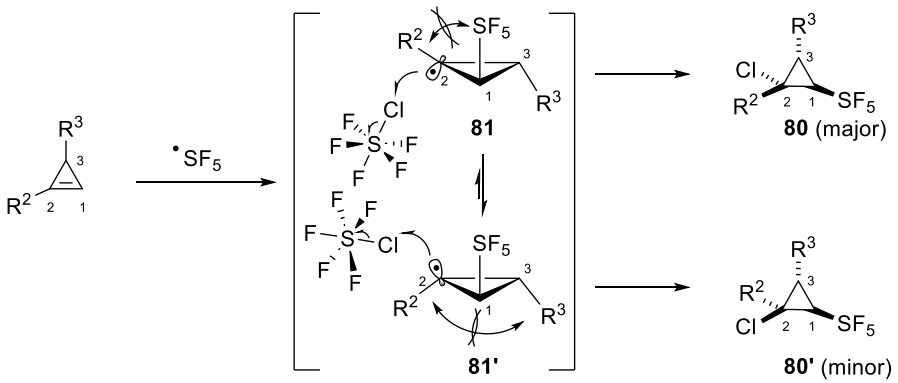
Scheme 31. Radical addition of SF_5Cl to 3,3-disubstituted cyclopropenes.

The addition of SF_5Cl 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 SF_5Cl, 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 SF_5Cl could not be achieved efficiently to a substrate possessing a sterically demanding protected tertiary alcohol at C2 [R^2 = CMe_2(OTBS)] and this constitutes one limitation of the method (not illustrated). The ester at C3 could be replaced by an acetoxymethyl 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_5Cl to cyclopropenes bearing a single substituent at C3.

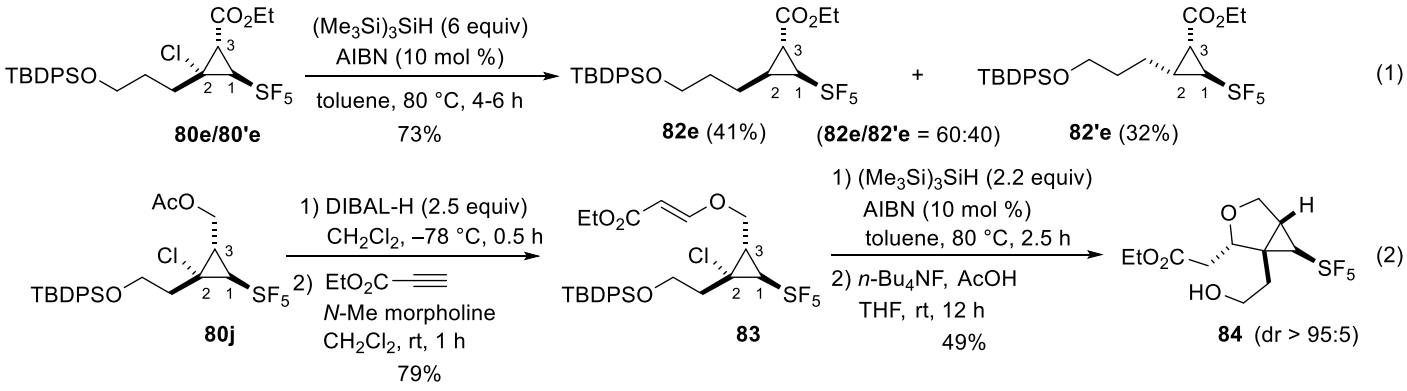
As observed in other radical reactions involving similar substrates, addition of the SF_5 radical proceeds regioselectively (at the less hindered C1 atom) and diastereoselectively (*trans* to the substituent at C3). The rates of chlorine atom transfer from SF_5Cl to the rapidly equilibrating cyclopropyl 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_5Cl *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_5Cl 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_5Cl (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]

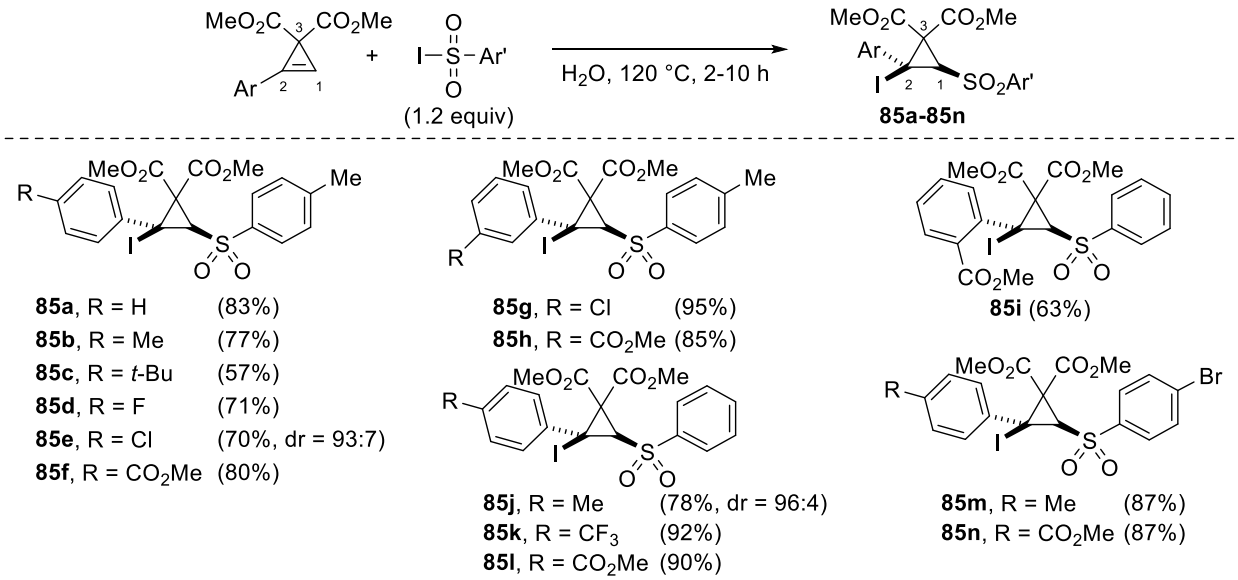
The C–Cl bond in adducts **80**/**80'** could be cleaved by radical reduction with tris(trimethylsilyl)silane and AIBN under standard conditions. As illustrated with **80e**/**80'e**, radical reduction afforded a mixture of the diastereomeric SF_5-cyclopropanes **82e**/**82'e** (dr = 60:40), which were 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).[34]



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

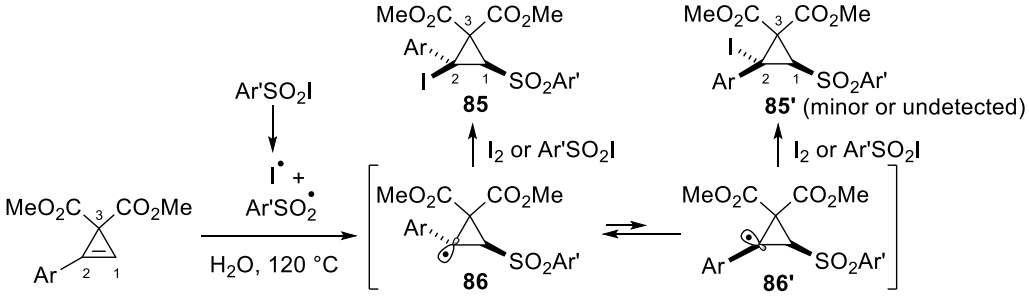
It is worth mentioning that an alternative route to SF_5-cyclopropanes was reported recently by Charette, Paquin *et al.* using an intramolecular cyclopropanation of diazoesters derived from SF_5-susbtituted allylic alcohols.[55]

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 sulfones **85a**-**85n**.[35] 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 accomodated 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).[35]



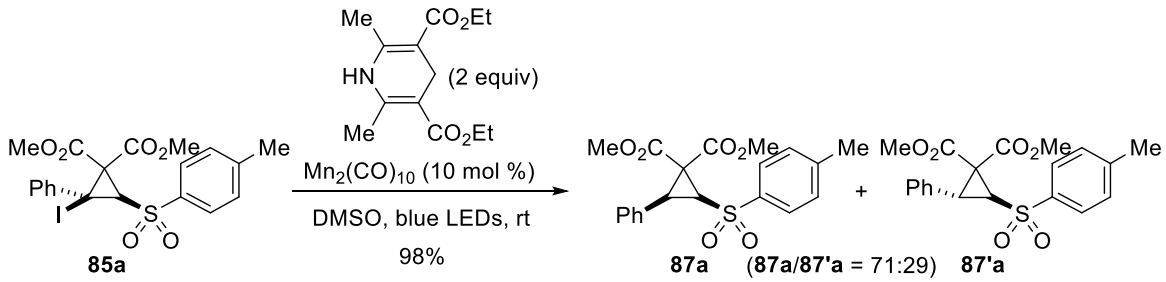
Scheme 35. Iodosulfonylation of cyclopropene *gem*-dicarboxylates.

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).[35]



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 $Mn_2(CO)_{10}$ under irradiation with blue LEDs,[56] to afford a diastereomeric mixture of cyclopropyl sulfones **87a** and **87'a** (dr = 71:29, 98%) (Scheme 37).[35]



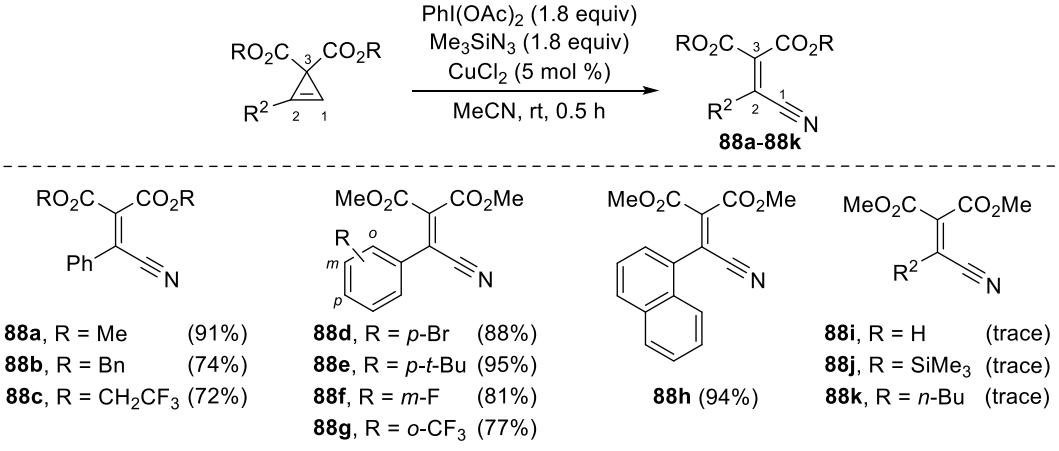
Scheme 37. Reductive deiodination of β-iodocyclopropyl sulfone **85a**.

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

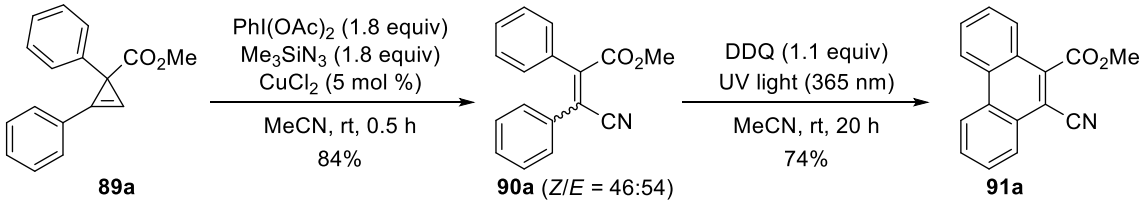
In 2021, Muriel and Waser disclosed the first examples of addition of a nitrogen-centered radical to cyclopropenes.[37] During the course of studies initially aimed at developing a radical azidation of cyclopropenes under mild photoredox-catalyzed conditions, the authors discovered that treatment of 2-aryl cyclopropene-*gem*-dicarboxylates with $PhI(OAc)_2$ and Me_3SiN_3 in the presence of a catalytic amount of $CuCl_2$ (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 trimethysilyl 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,

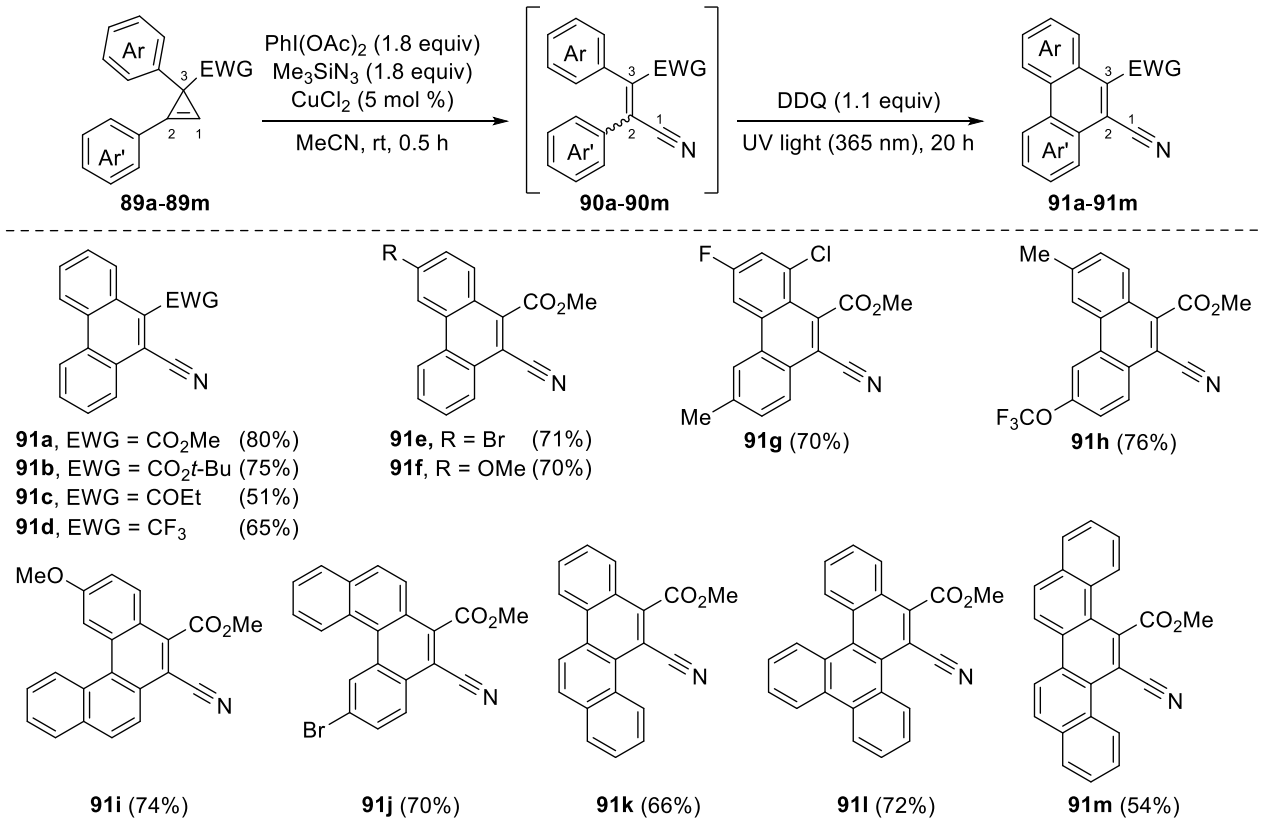
oxidative cyclization of **90a** was subsequently accomplished by irradiation with UV light in the presence of DDQ and delivered the disubstituted functionalized phenanthrene **91a** (74%) (Scheme 39).[37]



89a **90a** (*Z*/*E* = 46:54) **91a**

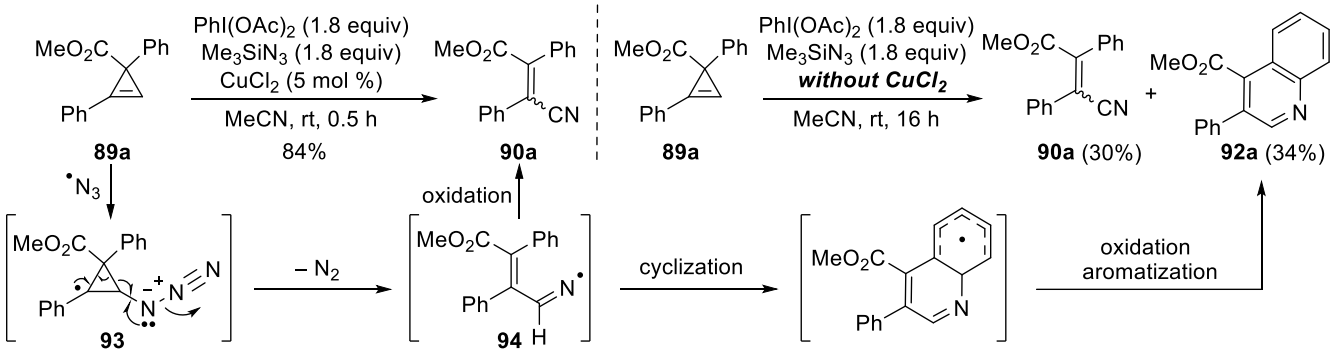
Scheme 39. Addition of the azide radical to cyclopropene **89a** and oxidative photocyclization of **90a**.

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).[37]



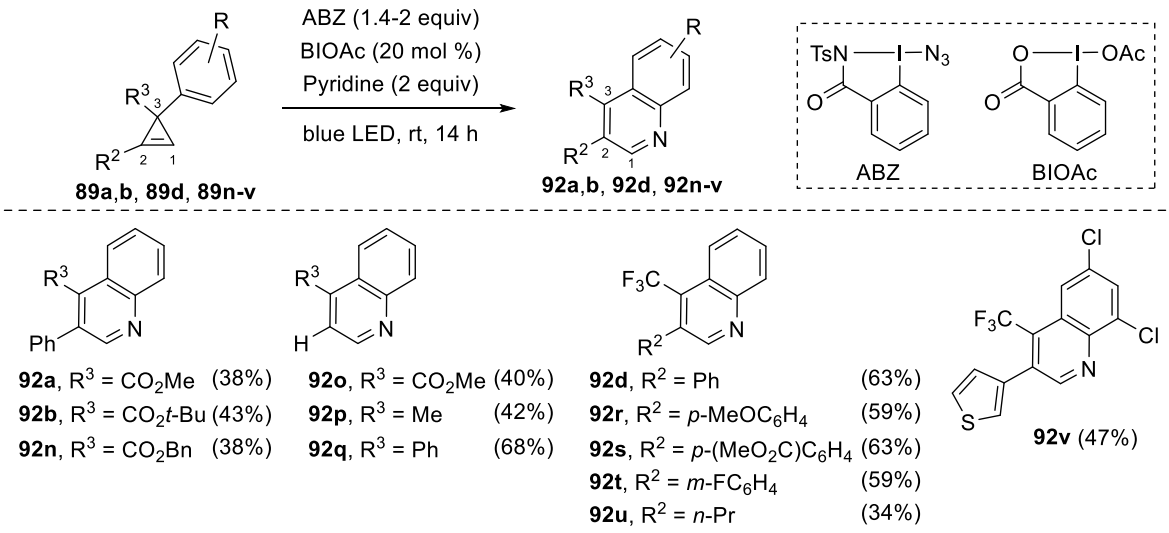
Scheme 40. Scope of the one-pot sequential radical amination and oxidative photocyclization.

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 $PhI(N_3)_2$ or $PhI(OAc)N_3$, to cyclopropene **89a** would produce cyclopropyl radical **93**. In this particular case, the electrocyclic ring-opening of the cyclopropyl radical to the corresponding allyl radical[36] 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 alkenyl 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).[37]



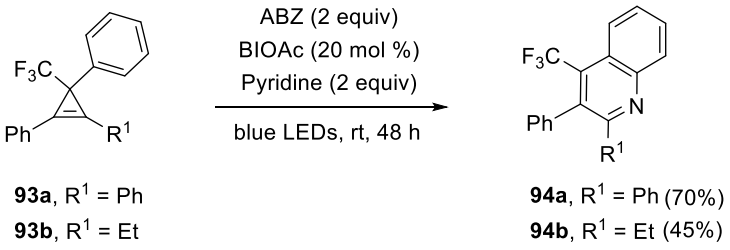
Scheme 41. Speculative mechanism for the reaction of the azide radical with cyclopropene **89a**.

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 (R^2 = H) are viable substrates in this transformation as judged by the successful formation of quinolines **92o**-**92q**. The authors particulary focus on the synthesis of 4-trifluoromethylquinolines ($R^3 = CF_3$) 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 42. 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]



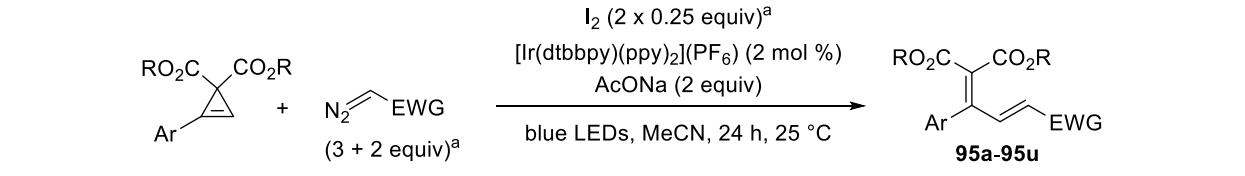
Scheme 43. Radical amination of cyclopropenes **93a** and **93b** possessing a 1,2-disubstituted double bond.

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 $[Ir(dtbbpy)(ppy)_2](PF_6)$ (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-trifluorodiazoethane were successfully involved in this transformation to provide dienes **95r**-**95u** (Scheme 44).[39]



95a, R = Me (70%)
95b, R = Et (68%)
95c, R = Bn (57%)
95d, R = CH_2CF_3 (46%)
95e, R = *t*-Bu (61%)

95f, R = *p*-Et (68%)
95g, R = *p*-Br (63%)
95h, R = *p*-Ph (75%)
95i, R = *m*-F (66%)
95j, R = *o*-Cl (72%)

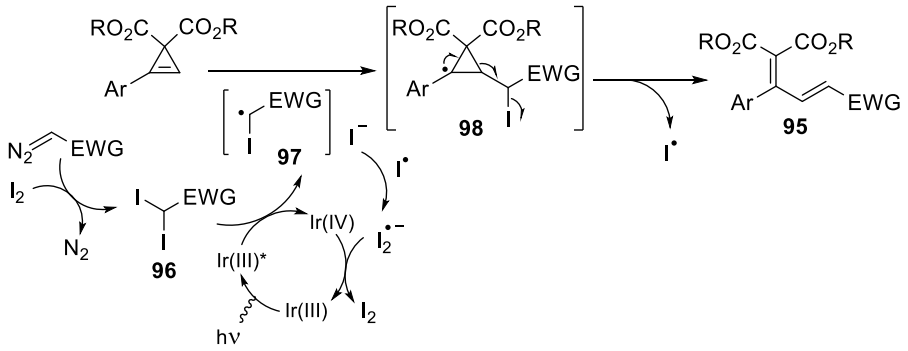
95k, R = Bn (65%)
95l, R = Ph (60%)
95m, R = $(CH_2)_2OMe$ (73%)
95n, R = $(CH_2)_3Br$ (66%)
95o, R = *i*Pr (65%)
95q, R = Ad (63%)

95r, EWG = $CONEt_2$ (59%)
95s, EWG = CONHTol (64%)
95t, EWG = SO_2Tol (47%)
95u, EWG = CF_3 (41%)

[a] Additional quantities were introduced after 12 h.

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.[57] 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).[39]



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.

Acknowledgements

Financial support from the ANR (DEFIS project**,** ANR-17-CE07-0008) is gratefully acknowledged for the development of the radical chloropentafluorosulfanylation of cyclopropenes.

References

1. Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719–732. https://doi.org/10.2174/1385272053765006
2. Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221–1245. https://doi.org/10.1055/s-2006-926404
3. Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. https://doi.org/10.1021/cr050988l
4. Zhu, Z.-B.; Wei Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534–5563. https://doi.org/10.1039/C1CS15074J
5. Vicente, R. *Synthesis* **2016**, *48*, 2343–2360. https://doi.org/10.1055/s-0035-1561644
6. Dian, L.; Marek, I. *Chem. Rev.* **2018**, *118*, 8415–9434. https://doi.org/10.1021/acs.chemrev.8b00304
7. Li, P.; Zhang, X.; Shi, M. *Chem. Commun.* **2020**, *56*, 5457–5471. https://doi.org/10.1039/D0CC01612H
8. Raiguru, B. P.; Nayak, S.; Mishra, D. R.; Das, T.; Mohapatra, S.; Mishra, N. P. *Asian J. Org. Chem.* **2020**, *9*, 1088–1132. https://doi.org/10.1002/ajoc.202000193

9. Vicente, R. *Chem. Rev.* **2021**, *121*, 162–226. https://doi.org/10.1021/acs.chemrev.0c00151
10. Cohen, Y.; Marek, I. *Acc. Chem. Res.* **2022**, *55*, 2848–2868. https://doi.org/10.1021/acs.accounts.2c00424
11. Huo, H.; Gong, Y. *Org. Biomol. Chem.* **2022**, *20*, 3847–3869. https://doi.org/10.1039/D1OB02450G
12. Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845‑5859. https://doi.org/10.1021/jm4017625
13. Shearer J.; Castro, J. L.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. D. *J. Med. Chem.* **2022**, *65*, 8699–8712. https://doi.org/10.1021/acs.jmedchem.2c00473
14. Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712−8756. https://doi.org/10.1021/acs.jmedchem.6b00472
15. Allen, F. H. *Tetrahedron* **1982**, *38*, 645– 655. https://doi.org/10.1016/0040-4020(82)80206-8
16. Fattahi, A.; McCarthy, R. E.; Ahmad, M. R.; Kass, S. R. *J. Am. Chem. Soc.* **2003**, *125*, 11746–11750. https://doi.org/10.1021/ja035725s
17. Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444–4452. https://doi.org/10.1021/ja036309a
18. Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625−1651. https://doi.org/10.1016/S0040-4020(01)98924-0
19. Coote, M. L.; Lin, C. Y.; Zavitsas, A. A. *Phys. Chem. Chem. Phys.* **2014**, *16*, 8686–8696. https://doi.org/10.1039/c4cp00537f
20. Johnston, L. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1986**, *108*, 2343–2348. https://doi.org/10.1021/ja00269a034
21. Zerbetto, F.; Zgierski, M. Z.; Siebrand, W. *J. Am. Chem. Soc.* **1989**, *111*, 2799–2802. https://doi.org/10.1021/ja00190a009
22. Yamaguchi, K.; Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 9255–9262. https://doi.org/10.1021/jo0302206
23. Seeman, J. I. *J. Chem. Rev.* **1983**, *83*, 83–134. https://doi.org/10.1021/cr00054a001
24. Yamago, S.; Ejiri, S.; Nakamura, E. *Chem. Lett.* **1994**, 1889−1892. https://doi.org/10.1246/cl.1994.1889
25. Nihei, T.; Hoshino, T.; Konno, T. *Org. Biomol. Chem.* **2015**, *13*, 3721–3731. https://doi.org/10.1039/C5OB00046G
26. Ferjančić, Z.; Čeković, Ž.; Saičić, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979−2982. https://doi.org/10.1016/S0040-4039(00)00286-0
27. Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815−9818. https://doi.org/10.1016/S0040-4039(00)01777-9
28. Michalland, J.; Casaretto, N.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2022**, *61*, e202113333. https://doi.org/10.1002/anie.202113333
29. Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Commun.* **2015**, *51*, 4204−4207. https://doi.org/10.1039/C4CC09649E
30. Dange, N. S.; Robert, F.; Landais, Y. *Org. Lett.* **2016**, *18*, 6156−6159.

https://doi.org/10.1021/acs.orglett.6b03163
31. Liu, C.; Feng, T.; Wu, X.; Zhu, C. *ACS Catal.* **2023**, *13*, 8394–8401. https://doi.org/10.1021/acscatal.3c01342
32. Dange, N. S.; Jatoi, A. H.; Robert, F.; Landais, Y. *Org. Lett.* **2017**, *19*, 3652−3655. https://doi.org/10.1021/acs.orglett.7b01651
33. Muriel, B.; Gagnebin, A.; Waser, J. *Chem. Sci.* **2019**, *10*, 10716–10722. https://doi.org/10.1039/C9SC03790J
34. Lefebvre, G.; Charron, O.; Cossy, J.; Meyer, C. *Org. Lett.* **2021**, *23*, 5491–5495. https://doi.org/10.1021/acs.orglett.1c01840
35. Peng, C.; Gu, F.; Lin, X.; Ding, N.; Zhan, Q.; Cao, P.; Cao, T. *Green Chem.* **2023**, *25*, 671–677. https://doi.org/10.1039/D2GC04296G
36. Genossar, N.; Changala, P. B.; Gans, B.; Loison, J.-C.; Hartweg, S.; Martin-Drumel, M.-A.; Garcia, G. A.; Stanton, J. F.; Ruscic, B.; Baraban, J. H. *J. Am. Chem. Soc.* **2022**, *144*, 18518–18525. https://doi.org/10.1021/jacs.2c07740
37. Muriel, B.; Waser, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 4075–4079. https://doi.org/10.1002/anie.202013516
38. Smyrnov, V.; Muriel, B.; Waser, J. *Org. Lett.* **2021**, *23*, 5435–5439. https://doi.org/10.1021/acs.orglett.1c01775
39. Liu, G.–X.; Jie, X.-T.; Li, X.-I., Yang, L.–S.; Qiu, H.; Hu, W.-H. *ACS Catal.* **2023**, *13*, 5307–5314. https://doi.org/10.1021/acscatal.3c00619
40. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566–11567. https://doi.org/10.1021/ja027095k
41. Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688–3689. https://doi.org/10.1021/ja0496928
42. Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515. https://doi.org/10.1021/ja052185l
43. Walton, J. C.; McCarroll, A. J.; Chen, Q.; Carboni, B.; Nziengui, R. *J. Am. Chem. Soc.* **2000**, *122*, 5455–5463. https://doi.org/10.1021/ja9944812
44. Bazin, S.; Feray, L.; Bertrand, M. *Chimia* **2006**, *60*, 260–265. https://doi.org/10.2533/000942906777674679
45. Pérez-Luna, A.; Bothua, C.; Ferreira, F.; Chemla, F. *Chem. Eur. J.* **2018**, *14*, 8784–8788. https://doi.org/10.1002/chem.200801451
46. Doi, N.; Takeda, N.; Miyata, O.; Ueda, M. *J. Org. Chem.* **2016**, *81*, 7855−7861. https://doi.org/10.1021/acs.joc.6b01508
47. Itoh, T. in *Fluorine in Bioorganic and Medicinal Chemistry*; Ojima, I., Ed.; Wiley-Blackwell, 2009; pp. 313–334. https://doi.org/10.1002/9781444312096.ch12
48. Volochnyuk, D. M.; Grygorenko, O. O. In *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*; Cahard, D.; Ma, J.-A., Eds.; Wiley-VCH, 2020; pp. 135–190. https://doi.org/10.1002/9783527824342.ch5
49. Inoue, M.; Sumii, Y.; Shibata, N. *ACS Omega* **2020**, *5*, 10633–10640. https://doi.org/10.1021/acsomega.0c00830
50. Decaens, J.; Couve-Bonnaire, S.; Charette, A. B.; Poisson, T.; Jubault, P. *Chem. Eur. J.* **2021**, *27,* 2935‑2962.

https://doi.org/10.1002/chem.202003822
51. Savoie, P. R.; Welch, J. T. *Chem. Rev.* **2015**, *115*, 1130−1190. https://doi.org/10.1021/cr500336u
52. Cahard, D., Ma, J.-A., Eds. *Emerging Fluorinated Motifs: Synthesis, Properties and Applications*; Wiley-VCH, 2020. https://doi.org/10.1002/9783527824342
53. Aït-Mohand, S.; Dolbier, W. R., Jr. *Org. Lett.* **2002**, *4*, 3013−3015. https://doi.org/10.1021/ol026483o
54. Gilbert, A.; Paquin, J.-F. *J. Fluorine Chem.* **2019**, *221*, 70‑74. https://doi.org/10.1016/j.jfluchem.2019.04.003
55. Peyrical, L. C.; Ouellet-Du Berger, M.-R.; Boucher, M.; Birepinte, M.; Paquin, J.-F.; Charette, A. B. *Org. Lett.* **2023**, *25*, 2487–2491. https://doi.org/10.1021/acs.orglett.3c00642
56. Herrick, R. S.; Herrinton, T. R.; Walker, H. W.; Brown, T. L. *Organometallics* **1985**, *4*, 42–45. https://doi.org/10.1021/om00120a008
57. Li, P.; Zhao, J.; Shi, L.; Wang, J.; Shi, X.; Li, F. *Nat. Commun.* **2018**, *9*, 1972. https://doi.org/10.1038/s41467-018-04331-4

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.