Sigmatropic rearrangements of cyclopropenylcarbinol derivatives. Access to diversely substituted alkylidenecyclopropanes

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Abstract
Cyclopropenes constitute useful precursors of other classes of compounds incorporating a three-membered ring. Although the transformation of substituted cyclopropenes into alkylidenecyclopropanes can be accomplished through different strategies, this review is focusing specifically on the use of [2,3]- and [3,3]-sigmatropic rearrangements involving cyclopropenylcarbinol derivatives as substrates. These sigmatropic rearrangements, which have been developed in recent years, allow a remarkably efficient and stereoselective access to a wide variety of heterosubstituted and/or functionalized alkylidenecyclopropanes which would not be readily accessible by other strategies. The different [2,3]- and [3,3]-sigmatropic rearrangements of cyclopropenylcarbinol derivatives disclosed to date, as well as the analysis of their substrate scope and some applications of the products arising from those reactions, are presented in this review.

Introduction
Among the ever expanding diversity of chemical transformations involving cyclopropenes, which are largely dominated by ring-cleavage processes to access functionalized acyclic compounds or to construct new carbocycles or heterocycles, those reactions that preserve the three-membered ring and enable access to diversely substituted cyclopropanes or alkylidenecyclopropanes are also synthetically useful [1-6]. The importance of this latter class of transformations is obviously related to the widespread occurrence of cyclopropanes in natural and/or bioactive compounds [7,8] and the great interest of the cyclo-
propyl core in new drugs development [9]. Alkylidene cyclopropanes also constitute another important class of strained carbocycles displaying a versatile chemistry owing to their multiple reactive sites (the exocyclic olefin and the proximal and distal bonds on the ring) [10-15]. Although the synthesis of alkylidene cyclopropanes can be achieved by many different routes, controlling the configuration of the exocyclic olefin as well as that of stereocenters on and adjacent to the three-membered ring remains a challenging task [15]. In this context, cyclopropenes can serve as useful precursors of substituted and functionalized alkylidene cyclopropanes. The transformation of cyclopropenes into alkylidene cyclopropanes has been achieved through different strategies (Scheme 1). The first one relies on the isomerization of the olefin in alkylcyclopropanes \( \text{A} \) from the endocyclic to the exocyclic position (Scheme 1, reaction 1) [16-18]. Owing to the relief of ring-strain, the formation of the alkylidene cyclopropane \( \text{B} \) is generally thermodynamically favored [19,20]. However, in the particular case of \( \text{gem-difluorocyclopropane} \ (\text{A}' , R = \text{Ph}) \) which possesses a cyclopropenium (aromatic) character, the position of the equilibrium depends on the substituent at \( C1 \). Whereas conjugation with the phenyl group (\( R = \text{Ph} \)) provides the driving force for the base-promoted isomerization of 1-benzyl-3,3-difluorocyclopropane (\( \text{A}' , R = \text{Ph} \)) into the corresponding benzylidene(\( \text{gem-difluorocyclopropane} \) (\( \text{B}' \)) [18], methylene(\( \text{gem-difluorocyclopropane} \) (\( \text{B}'' \), \( R = \text{H} \)) is isomerized into 1-methyl-3,3-difluorocyclopropane (\( \text{A}'' \)) [21] (Scheme 1, reaction 1). Another approach relies on the reaction of cyclopropenylmethyl organometallic species \( \text{C} \) with electrophiles through an \( \text{S}_{2}^{\prime} \) process leading to substituted alkylidene cyclopropanes \( \text{D} \) (Scheme 1, reaction 2). Examples of those transformations include the carbonylation of a (trimethylsilylmethyl)cyclopropane in the presence of a fluoride promoter [22], and also the addition of electrophiles to (lithiomethyl)cyclopropanes generated by lithiation of the corresponding methylcyclopropenylsulfone [23] or -sulfoxide [24]. More recently, the addition of cyclopropenylmethylboronates to aldehydes was also reported [25]. A complementary strategy involves the addition of nucleophiles, in particular organometallic reagents, to cyclopropenylcarbinols or their derivatives \( \text{E} \), which leads to alkylidene cyclopropanes \( \text{F} \) through a formal \( \text{S}_{2}^{\prime} \) process (Scheme 1, reaction 3) [23,26-33]. Thus, methylcyclopropanes have been prepared by diastereoselective addition of Grignard reagents to cyclopropenylmethyl ethers, possessing a hydroxymethyl directing substituent at \( C3 \), in the absence or in the presence of a catalyst (copper or iron salt) [28-30]. Another representative transformation is the copper-catalyzed addition of Grignard reagents to secondary unprotected cyclopropenylcarbinols which proceeds with high levels of chirality transfer to afford alkylidene cyclopropanes possessing a quaternary stereocenter at \( C2 \) [31,33]. In this review, we shall exclusively focus on alternative strategies that rely either on a [2,3]-sigmatropic rearrangement (Scheme 1, reaction 4) or a [3,3]-sigmatropic rearrangement of cyclopropenylcarbinol derivatives (Scheme 1, reaction 5). These transformations have emerged as useful tools over the past few years to access hetero-substituted and/or functionalized alkylidene cyclopropanes.

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\begin{align*}
\text{A} & \xrightleftharpoons{\text{base}} \text{B} \\
\text{A}'(R = \text{Ph}, R^2 = R^3 = F) & \quad \text{B}'(R = \text{Ph}, R^2 = R^3 = F) \\
\text{A}''(R = \text{H}, R^2 = R^3 = F) & \quad \text{B}''(R = \text{H}, R^2 = R^3 = F) \\
\text{A}'''(R = \text{Ph}, R^2 = R^3 = F) & \quad \text{B}'''(R = \text{H}, R^2 = R^3 = F) \\
\text{C} & \quad \text{D} \\
\text{E} & \quad \text{M}^+ \\
\text{F} & \quad \text{E}^{-} \\
\text{R} & \quad \text{R}^2 \\
\text{R}^3 & \quad \text{R}^4 \\
\text{OR} & \quad \text{RO}^+ \\
\end{align*}
\]

**Scheme 1:** Representative strategies for the formation of alkylidene cyclopropanes from cyclopropenes and scope of the review.

**Review**

**[2,3]-Sigmatropic rearrangements involving cyclopropenylcarbinol derivatives**

Following their report on the synthesis of chiral alkylidene cyclopropanes by copper-catalyzed addition of Grignard reagents to enantioomerically enriched cyclopropenylcarbinols [31], Marek et al. investigated other classes of transformations involving those latter strained analogs of allylic alcohols as substrates. In 2007, the [2,3]-sigmatropic rearrangement of cyclopropenylcarbinyl phosphinates was reported as a route to chiral phosphines possessing an alkylidene cyclopropane backbone [34]. The starting cyclopropenylcarbinols were readily prepared by addition of the corresponding cyclopropenyl organolithium reagents, generated in situ by treatment of 1,1,2-tribromoalkane with n-butyllithium (2 equiv) [35], to various aldehydes and ketones. Marek et al. observed that the treatment
of cyclopropenylcarbinols 1a–h with chlorodiphenylphosphine in the presence of triethylamine (THF, rt) resulted in a very rapid formation of (alkylidenecyclopropyl)diphenylphosphine oxides 3a–h (85–94%), resulting from an efficient [2,3]-sigmatropic rearrangement of the in situ-generated phosphinites 2a–h. Primary or tertiary cyclopropenylcarbinols reacted equally well, as shown with the formation of phosphine oxides 3a (94%), 3b (93%) and 3c (87%). The [2,3]-sigmatropic rearrangement of phosphinites 2d–h derived from secondary cyclopropenylcarbinols led to the corresponding phosphine oxides 3d–h (85–93%) as a 80:20 mixture of E/Z geometric isomers, regardless of the substituent of the alcohol (at C4) and of the cyclopropene (at C2) [33,34].

The [2,3]-sigmatropic rearrangement of an optically enriched phosphinite 2f, prepared from the corresponding secondary cyclopropenylcarbinol (S)-1f (ee = 99%), which in turn is readily available by applying the Sharpless kinetic resolution procedure to (±)-1f [31], was also investigated. The resulting geometric isomers (Z)-3f and (E)-3f, which were separated by flash chromatography, were found to possess optical purities identical to that of the parent substrate (S)-1f (ee = 99%) thereby confirming that complete chirality transfer occurred (from C4 to C2) during the [2,3]-sigmatropic rearrangement [33,34]. It is also worth mentioning that the absolute configuration of (Z)-3f and (E)-3f, which is opposite at C2, was assigned by comparison of their computed and experimentally observed CD spectra [33,34]. To tentatively explain the observed stereochromatic outcome in the absence of additional knowledge on the transition state of the rearrangement [36], two reactive conformers G and G’ were considered which would lead to five-membered ring transition states in which the aryl group occupies a preferential pseudo-equatorial or a less favorable pseudo-axial orientation, respectively (Scheme 3) [33,34].

The authors also showed that phosphine oxide (E)-3f could be reduced to the corresponding phosphine 4 (94%) by treatment with trichlorosilane, without affecting the (arylmethylene)cyclopropane moiety (Scheme 4).

The great efficiency of the [2,3]-sigmatropic rearrangement of phosphinites 2a–h lacking substituents at C3 is in striking contrast with the reactivity of phosphinites possessing a geminal disubstitution at C3. In 2007, Rubin et al. reported their results on the [2,3]-sigmatropic rearrangement of cyclopropenylmethyl phosphinites derived from primary cyclopropenyl-
Selective reduction of phosphine oxide (E)-3f.

Carbinols [37]. As illustrated in the case of 5a, the substrates were prepared from the tert-butyldimethylsilyl (TBS) ether of propargyl alcohol by a rhodium-catalyzed cyclopropanation with an aryldiazooacetate followed by reduction of the ester moiety and protecting group manipulation. Phosphinite 6a, generated from alcohol 5a under standard conditions, did not undergo a [2,3]-sigmatropic rearrangement into the corresponding diastereomeric phosphine oxides 7a/7’a, even upon prolonged heating (toluene, 110 °C), and underwent slow decomposition instead (Scheme 5).

This observation was in agreement with DFT calculations which indicated that the rearrangement of cyclopropenylmethyl phosphinite I, although thermodynamically favored, displays a high activation barrier compared to that of the acyclic allyl analog H. An even higher activation barrier was calculated in the case of the 3-methyl and 3-phenyl-substituted cyclopropenes, I’ and I”’, respectively, which indicates that the concerted [2,3]-sigmatropic rearrangement would require high temperatures incompatible with such thermally labile strained substrates (Scheme 6) [37].

Interestingly, the authors detected traces of methylenecyclopropanes 7a/7’a when phosphorylation of alcohol 5a was conducted at room temperature for several hours which led them to consider that the amine could play a role in promoting the [2,3]-sigmatropic rearrangement. After a screening of different tertiary amines, Rubin et al. found that DBU could be used as a base in the phosphorylation reaction but also as an efficient catalyst for the subsequent [2,3]-sigmatropic rearrangement of phosphinite 6a which afforded a 73:27 mixture of the diastereomeric phosphine oxides 7a/7’a (86%). The major diastereomer 7a corresponds to a sigmatropic rearrangement occurring on the most hindered face (cis to the aromatic group) of the cyclopropene which was somewhat surprising. Substitution at the para-position of the aromatic group at C3 significantly affected the diasteomeric ratio with an increase observed with the mesomorphic donor methoxy group in favor of diastereomer 7b (7b/7’b = 78:22) compared to 7a/7’a, and a drop of diastereoselectivity when a fluorine atom (7d/7’d = 52:48) were present. An inversion of the face selectivity was detected in favor of diastereomer 7’e (7e/7’e = 43:57) arising from the rearrangement of phosphinite 6e possessing a p-trifluoromethylphenyl substituent. Replacement of the acetal protecting group of the hydroxymethyl substituent at C3 (R3 = CH2OMOM = CH2OCH2OMe) by an acetate (R3 = CH3OAc) did not affect the results, as illustrated in the case of 7f/7’f, but the presence of an ester moiety (R3 = CO2Me) led to the rearranged phosphine oxides 7g/7’g in rather low yield (47%) although the diastereomeric ratio remains
similar to that observed for 7a/7’a. Other substituents were tolerated on the phosphorus atom including an isopropyl or a cyclohexyl group and the corresponding phosphate oxides 7b/7’b and 7i/7’i were isolated in good yields. Increasing the steric hindrance around the phosphorus atom resulted in a higher diastereoselectivity. However, the sigmatropic rearrangement of the highly hindered di(tert-butyl)phosphinite 6j and tetra(isopropyl) phosphorodiamidite 6k did not occur (Scheme 7) [37].

The mechanism proposed by Rubin et al. involves a reversible addition of the Lewis base (DBU) on the cyclopropene double bond at C2 leading to zwitterionic intermediates 8 and 8’. This would result in an increase of conformational flexibility thereby facilitating the nucleophilic displacement of the ammonium by the phosphinite through transition states TS1 and TS2 (SN2-type process), respectively. Oxaphospholanium zwitterions 9 and 9’ would then be obtained and would eventually produce the diastereomeric phosphate oxides 7 and 7’. Computational studies indicated that the facial selectivity of the initial attack of the Lewis base (DBU) was not responsible for the observed diastereocontrol because of the low difference between the activation barriers of the reactions leading to 8 and 8’, regardless of the aromatic substituent. Since 8 and 8’ were in rapid equilibrium with phosphinite 6, the diastereoselectivity should depend on the relative stabilities of the transition states TS1 and TS’1. An electron-donating group at the para-position of the aromatic ring could contribute to the stabilization of TS1, in which the Ar–C3–C2–P dihedral angle is close to 0°, by considering the mesomeric form TS2. The observed dependence of the diastereoselectivity on the σ+Hammett constant of the para substituents further supported the proposed mechanism (Scheme 8) [37].

To date and to the best of our knowledge, reports on [2,3]-sigmatropic rearrangements of cyclopropenylcarbinol derivatives appear to be limited to the synthesis of alkylidenecyclopropanes incorporating a phosphorus atom. Cyclopropenylcarbinol derivatives can also lead to other heterosubstituted alkylidenecyclopropanes by using [3,3]-sigmatropic rearrangements.

[3,3]-Sigmatropic rearrangements involving cyclopropenylcarbinol derivatives

Access to heterosubstituted alkylidenecyclopropanes

The interest of secondary cyclopropenylcarbinol derivatives in [3,3]-sigmatropic rearrangements was first highlighted by Marek et al. who investigated the transposition of cyclopropenylcarbinyln esters [33,34]. The [3,3]-sigmatropic rearrangement of acetate 10a took place during filtration on silica gel and afforded alkylidene(acetoxycyclopropane) 11a in 90% yield. The ease with which the rearrangement of 10a occurred was attributed to the relief of ring strain but also to the favorable conjugation of the olefin with the two phenyl groups (R1 = R’1 = Ph). Alkylidenecyclopropane 11a could also be obtained in similar yields (92% or 87%, respectively) by heating acetate 10a in dichloromethane at reflux or by treatment with
Scheme 8: Proposed mechanism for the Lewis base-catalyzed rearrangement of phosphinites 6.

dry Amberlyst® (a sulfonic acid resin) [33,34]. The rearrangement of the tertiary acetates 10b (R1 = R1 = Me) and 10c (R1 = Ph, R1 = Me) could also be achieved by filtration through silica gel and led to 11b (91%) and 11c (83%). The latter non-symmetrical tetrasubstituted alkene 11c was obtained as a 67:33 mixture of geometric isomers (Scheme 9) [33,34].

The rearrangement of secondary cyclopropenylcarbinyl acetates 10d–g could be achieved in the presence of Amberlyst® 15 and led exclusively to the (E)-alkylidene(acyloxy)cyclopropanes 11d–g (E/Z > 99:1) in good yields (70–77%). The acetate could also be replaced by a benzoate as illustrated with the formation of alkylidene cyclopropane 11b (60%) from substrate 10h. The authors mentioned that the sigmatropic rearrangement did not proceed under such mild conditions for substrates possessing an alkyl group instead of an aryl group at C4 but no additional details were provided. The high diastereoselectivity was explained by considering a six-membered chair-like cyclic transition state model TS3 in which the substituent at the α position of the ester (C4) preferentially occupies a pseudo-equatorial position. Although a cationic mechanism could have also been envisioned under the acidic conditions used, the optically enriched acetates 10d and 10e (ee > 98%) led to the corresponding alkylidene cyclopropanes 11d and 11e with complete chirality transfer (ee > 98%) at C2, thereby probing the concerted suprafacial nature of the rearrangement (Scheme 10) [33,34]. The acidic promotor may be simply assisting the dissociation of the C4–O bond in the transition state TS3 whilst an aromatic group (R1 = Ar) would contribute to the stabilization of a developing positive charge at C4.

The [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl acetates provides a straightforward and stereoselective entry to alkylidene(acyloxy)cyclopropanes. Only a few compounds of this family had been previously generated by photochemical reactions (from 4-isopropylidene-3,3-dimethyl-1-thietan-2-thione [38] or from a 4-alkylidene-Δ1-pyrazoline [39]) or by pyrolysis of the sodium salt of 3-propionyloxytetramethylcyclobutanone tosyl hydrazone [40]. It is also worth mentioning that completely divergent reactivities have also been reported for cyclopropenylcarbinyl esters in the presence of transition metal catalysts [41,42].
[3,3]-Sigmatropic rearrangement of secondary cyclopropenylcarbinyl esters 10d–h.

Alkylidene(aminocyclopropane) derivatives constitute another interesting class of heterosubstituted alkylidenecyclopropanes which have been previously synthesized by a Curtius rearrangement of acyl azides derived from alkylidenecyclopropane carboxylic acids [43] or by elimination reactions applied to suitably substituted aminocyclopropane derivatives [44-46].

In 2014, Hyland et al. disclosed the Overman rearrangement [47] of cyclopropenylcarbinyl trichloroacetimidates [48]. The optimal conditions for the generation of imidates 12a–i involved treatment of secondary cyclopropenylcarbinols with trichloroacetonitrile in the presence of a catalytic amount of DBU (15 mol %) in CH$_2$Cl$_2$ (−78 °C to −10 °C, 2–3 h) [48,49]. The crude imidates 12a–i were then directly engaged in the [3,3]-sigmatropic rearrangement step which was triggered by heating in the presence of K$_2$CO$_3$ in CH$_2$Cl$_2$ (30 °C, 40 h).

These latter conditions, which were optimized for imidate 12a, enabled the formation of p-bromobenzylidene[(N-trichloroacet-ylamino)cyclopropane] 13a as a single (E)-isomer in 63% overall yield (two steps from the corresponding alcohol). Compound 13a was obtained in lower yield in the absence of a base (21%) or when DMF was used as the solvent (53%) though a considerable rate acceleration (22 h instead of 40 h) was observed compared to CH$_2$Cl$_2$. In the presence of PdCl$_2$(MeCN)$_2$ (5 mol %), only traces of 13a were detected and significant decomposition of 12a took place. As in the case of the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl acetates, the observed stereoselectivity was explained by invoking a chair-like transition state model TS4 in which the aryl group preferentially occupies a pseudo-equatorial orientation (Scheme 11) [48]. Although the presence of a halogen atom was tolerated, as illustrated with the formation of the benzyli-

[3,3]-Sigmatropic rearrangement of trichloroacetimidates 12a–i.

*enantioenriched substrates 10d and 10e (ee > 98%) were used.

*a-Imide 12j was not formed.

Scheme 10: [3,3]-Sigmatropic rearrangement of secondary cyclopropenylcarbinyl esters 10d–h.

Scheme 11: [3,3]-Sigmatropic rearrangement of trichloroacetimidates 12a–i.
denecyclopropanes $13\text{a}$ (63%) and $13\text{h}$ (48%), higher yields were obtained in the case of imidates $13\text{b}$–$d$, possessing an electro-neutral or an electron-rich aromatic group, which afforded compounds $13\text{b}$ (83%), $13\text{e}$ (98%) and $13\text{d}$ (77%), substituted by a phenyl, a $p$-tolyl or a $p$-anisyl group, respectively. The rearrangement of imidate $12\text{f}$ possessing a $m$-anisyl substituent afforded benzylidene cyclopropane $13\text{f}$ in a lower yield (47%) compared to $13\text{d}$ (77%). The rearrangement of imidate $12\text{i}$ possessing an electron-rich $N$-tosylypyrrol-2-yl heteroaromatic group, afforded alkylidenecyclopropane $13\text{i}$ in nearly quantitative yield. Conversely, no rearrangement took place in the case of imidates $12\text{e}$ and $12\text{g}$ in which the aromatic group was substituted by a strongly electron-withdrawing nitro group at the $p$-ara- or the $meta$-position, respectively. All these observations point toward the development of a positive charge at the C4 carbon atom (adjacent to the $R_1$ substituent) in the transition state $\text{TS}_4$, as was also suggested previously in the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl acetates. Alkylidenecyclopropane $13\text{j}$ could not be synthesized because trichloroacetimidate $12\text{j}$ was not obtained by treatment of the corresponding cyclopropenylcarbinol substituted by an $n$-undecyl group with trichloroacetonitrile, even under forcing conditions. The authors tentatively suggested this may be due to the sterically hindered $n$-undecyl chain although this issue was not fully investigated (Scheme 11) [48].

To access aminoicyclopropanes, the hydrogenation of (arylmethylenecyclopropane $13\text{f}$ was achieved in the presence of Pd/C as a catalyst. Concomitant hydrogenolysis of two carbon–chlorine bonds also took place under these conditions and a 71:29 diastereomeric mixture of the monochloracetamides $19\text{f}$/$19\text{f}'$ was obtained (41%). The rather small difference of steric hindrance between the methyl and the $N$-acylamino group explained the modest face selectivity of hydrogen addition which preferentially occurred on the face of the olefin opposite to the $N$-chloroacetylamino substituent (Scheme 13) [48].

3,3-Disubstituted cyclopropenylcarbinols could not be used as substrates in the Overman rearrangement. This limitation of the substrate scope is due to the instability of the corresponding trichloroacetimidates. Thus cyclopropenylcarbinols $20\text{a}$–$c$ possessing gem-dimethyl substitution at C3 were converted to imidates $21\text{a}$–$c$ but upon treatment with silica gel (CH$_2$Cl$_2$, $-10^\circ$C), those latter compounds were converted into $\alpha$-allenic tertiary alcohols $22\text{a}$–$c$ (30–61%). The formation of alcohols $22\text{a}$–$c$ was explained by a mechanism involving ionization of
the C4–O bond in imidates 21a–c, followed by ring opening of the alkylidencyclopropyl cationic intermediates 23a–c [52] and addition of water to the resulting α-allenic carbocations 24a–c (Scheme 14) [48].

As a complementary strategy, our group examined the [3,3]-sigmatropic rearrangement of cyanates derived from cyclopropenylcarbinols [53]. The allyl cyanate to isocyanate rearrangement displays many interesting features such as the possibility to generate the reactive species by dehydration of carbamates under mild conditions and the ultimate formation of isocyanates which can be derivatized in situ [54]. The conditions were optimized with alcohol 25 substituted by a 2-phenylethyl group at the oxygen-bearing carbon atom (C4) and possessing gem-disubstitution at C3 on the three-membered ring. Alcohol 25 was readily converted to carbamate 26 by reaction with trichloroacetyl isocyanate followed by cleavage of the trichloroacetyl group by alkaline hydrolysis. Dehydration of carbamate 26 was achieved by treatment with trifluoroacetic anhydride in the presence of triethylamine under mild conditions (CH2Cl2, −78 °C) [55] and the in situ-generated cyanate 27 underwent a sigmatropic rearrangement into the corresponding isocyanate 28. The formation of this reactive isocyanate intermediate was ascertained by the addition of morpholine which enabled the isolation of urea 29 in good yield (78%). It is worth noting that alkylidencyclopropane 29 was formed with high diastereoselectivity (E/Z ≥ 95:5) at low temperature (−78 °C) but a slight erosion of diastereoselectivity was observed (E/Z = 88:12) when the same sequence was performed at 0 °C. The stereochemical outcome was in agreement with a six-membered transition state model TS5 in which the three atoms of the cyanate (O=C=N) moiety would be arranged in an almost linear fashion (an angle of 173° was calculated in the allyl cyanate to isocyanate transition state) [56] and the substituent at C4 would preferentially occupy a pseudo-equatorial orientation. Additionally, the same sequence applied to the enantioenriched alcohol (R)-25 (ee = 88%) delivered urea (−)-29 with essentially the same optical purity (ee = 86%), thereby indicating that chirality transfer (from C4 to C2) occurred during the sigmatropic rearrangement of cyanate 27 into isocyanate 28 (Scheme 15) [53].
All attempts to isolate isocyanate 28 were unsuccessful but derivatization of this latter reactive intermediate could be achieved in situ by addition of a broad range of nucleophiles, which were either used as co-solvents or added in excess. Thus, reaction with pyrrolidine, imidazole, methanol, allyl alcohol, benzyl alcohol and 9-fluorenemethanol (FmOH) provided the corresponding urea 30, N-carbamoyl imidazole 31 and carbamates 32–35, respectively, in good yields (69–80%). The reaction of isocyanate 28 with tert-butanol was sluggish even by heating at 40 °C but could be accelerated by addition of Ti(OiPr)4 (10 mol %) to deliver the corresponding N-Boc-carbamate 36 (81%). The condensation of isocyanate 28 with N-Boc-glycine in the presence of DMAP (Goldschmidt–Wick coupling) [57] provided amide 37 in 70% yield (Scheme 16) [53].

The examination of the substrate scope indicated that a broad range of alkyl chains, possibly incorporating heteroatoms, were compatible with the dehydration-[3,3]-sigmatropic sequence, as illustrated with the isolation of compounds 38–40 (72–79%) after nucleophilic trapping of the generated isocyanate intermediates with allyl alcohol. Benzylidene cyclopropanes 41 was also obtained in good yield (70%) but the efficiency of the sigmatropic rearrangement dropped for carbamates in which the aromatic group at C4 is substituted by an electron-withdrawing group at the para-position. Indeed, N-Alloc (arylmethylene)-(aminocyclopropanes) 42 and 43, substituted by a p-fluorophenyl and a p-(trifluoromethyl)phenyl group, respectively, were isolated in moderate yield (53%). Moreover, (p-nitrophenylmethylene)cyclopropane 44 could not be obtained under these conditions [53]. These results indicate that the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl cyanates, as previously reported for their allylic counterparts [56], does not involve a synchronous process because dissociation of the C4–O bond is more advanced in the transition state TS5 than the formation of the C2–N bond (Scheme 15). The rearrangement of cyclopropenylcarbinyl cyanates accommodates various substituents at C3, as well as the presence of a substituent at C2 or even a fully substituted cyclopropane ring, as shown with the successful formation of alkylidene cyclopropanes 45–48 (58–86%, Scheme 17) [53].

Interestingly, alkylidene(isocyanatocyclopropanes) arising from the [3,3]-sigmatropic rearrangement of cyclopropenylcarbinyl cyanates could also be derivatized into trifluoroacetamides. This transformation was discovered fortuitously when carbamate 49 was treated with an excess of trifluoroacetic anhydride (2 equiv) in the presence of Et3N (3 equiv) to achieve the dehydration–sigmatropic rearrangement sequence. Trifluoroacetamide 50 (67%) was the product directly formed under these conditions and the Lewis basic character of the pyridine ring was suspected to be responsible for the observed reactivity (Scheme 18).

With the aim of achieving the same derivatization in the case of other substrates devoid of a pyridine ring, several 3,3-dimethyl-cyclopropenylcarbinyl carbamates were engaged in the dehydration–[3,3]-sigmatropic rearrangement sequence under the previously used conditions but trifluoroacetic anhydride (1.5 equiv) and pyridine (1.5 equiv) were then subsequently added to the reaction mixture. Under these conditions, the corresponding trifluoroacetamides 51–54 could be effectively isolated in good yields (73–85%). The addition of pyridine to the isocyanates J arising from the [3,3]-sigmatropic rearrangement would probably generate the zwitterionic intermediates K which would then react with trifluoroacetic anhydride to
produce N,O-bis(trifluoroacetyl)carbamates L. Trifluoroacetamides 51–54 would be generated from adducts L after hydrolysis of the reaction mixture (Scheme 19) [53].

To control the diastereoselectivity of the hydrogenation of alkylidene[(N-acylamino)cyclopropanes] possessing a single substituent at C2, it is possible to rely either on the steric hindrance or on the coordinating ability of the amide group. Thus, the hydrogenation of trifluoroacetamide 51 catalyzed by Pd/C afforded N-trifluoroacetylaminocyclopropane 55 as the major diastereomer (55/55' = 92:8) because of the preferential addition of hydrogen on the less hindered face of the trisubstituted alkene opposite to the trifluoroacetamide moiety. A reversal of face selectivity can be observed by performing a directed iridium(I)-catalyzed hydrogenation in the presence of Crabtree’s catalyst [58] which afforded aminocyclopropane 55' as the major diastereomer (55'/55 = 90:10, Scheme 20) [53].

The potential of [3,3]-sigmatropic rearrangements involving cyclopropenylcarbinol derivatives is not restricted to the synthesis of heterosubstituted alkylidenecyclopropanes and was also exploited to access functionalized alkylidenecyclopropanes, with creation of a new carbon–carbon bond on the three-membered ring with the control of two contiguous stereocenters.

Ireland–Claisen rearrangement of cyclopropenylcarbinyl esters

The Ireland–Claisen rearrangement of silyl ketene acetalts generated from allylic (or propargylic) esters is arguably one of the most useful variant of the Claisen rearrangement that has found countless applications in organic synthesis [59]. The feasibility of the Ireland–Claisen rearrangement of cyclopropenylocarbinyl esters was investigated in the case of glycolates 56a–l which were readily prepared by coupling of the corresponding cyclopropenylcarbinols with (4-methoxybenzyloxy)acetic acid. Enolization of glycolates 56a–l was carried out by treatment with Me3SiCl (4 equiv) followed by addition of KHMS (usually 4 equiv) in THF at −78 °C. The resulting silyl ketene acetalts of (Z)-configuration 57a–l, arising from O-silylation of the corresponding chelated potassium enolates [60], underwent an efficient [3,3]-sigmatropic rearrangement upon warming to room temperature. After an acidic work-up and treatment of the crude carboxylic acids with trimethylsilyldiazomethane, the resulting α-alkoxy methyl esters
Scheme 19: Formation of alkylidene((N-trifluoroacetylamino)cyclopropanes) 51–54.

Scheme 20: Diastereoselective hydrogenation of alkylidenecyclopropane 51.

58a–1, incorporating an alkylidenecyclopropane moiety, were obtained as single detectable diastereomers [61]. As in the previously discussed [3,3]-sigmatropic rearrangements, the observed stereochemical outcome was in agreement with a six-membered chair-like transition state model TS6 in which the substituent at the α-position of the oxygen atom (C4) preferentially occupies a pseudo-equatorial position. The scope of the reaction is rather broad as the substituent at C4 can be an alkyl chain, possibly incorporating a protected alcohol, as illustrated with the formation of alkylidenecyclopropanes 58a (86%), 58b (60%) and 58c (84%). It is worth mentioning that despite the use of a strong base (KHMDMS) and the acidity of the “vinyllic” protons of cyclopropenes which is comparable to that of a terminal alkyn [62], cyclopropenylcarbinyl glycolates devoid of substituents at C2 were viable substrates. The sequence allowed access to benzylidenecyclopropane 58d (93%) and to (arylmethylenecyclopropane 58e in excellent yield (90%), despite the presence of the electron-withdrawing trifluoromethyl substituent at the para-position of the aromatic ring. Some heteroaromatic groups were also tolerated at C4, as shown with the synthesis of (heteroarylmethylene) cyclopropanes 58f–h (60–72%). The gem-dimethyl substitution at C3 which was common to the previous cyclopropenylcarbinyl glycolates 56a–h, could be suppressed and the corresponding alkylidenecyclopropane 58i was produced in excellent yield (94%). More sterically hindered substituents were tolerated at C3, as illustrated with the isolation of the spirocyclic compounds 58j (60%) and 58k (77%), and alkylidenecyclopropane 58l possessing a fully substituted three-membered ring was also formed in excellent yield (96%). That the Ireland–Claisen rearrangement of cyclopropenylcarbinyl glycolates proceeded with chirality transfer was also verified in the case of alkylidenecyclopropanes 58a and 58i which were obtained with optical purities (ee = 87% and ee = 97%, respectively) identical to those of the corresponding enantioenriched precursors (R)-56a and (R)-56i (Scheme 21) [61].

The addition of a cyclopropenyllithium to an aldehyde is arguably the most widely used method to access cyclopropenylcarbinols but Gevorgyan et al. disclosed an interesting organocatalytic route to cyclopropenylcarbinols possessing gem-diester substitution at C3 [63]. As illustrated with the
preparation of alcohol 60, the strategy relies on a sila-Mori-
ta–Baylis–Hillman reaction between cyclopropenylsilane 59
and 3-phenylpropanal catalyzed by electron-rich tris(2,4,6-
trimethoxyphenyl)phosphine (TTMPP) [63]. After desilylation,
cyclopropenylcarbinol 60 was converted into glycolate 61 under
standard conditions and the latter ester was engaged in the
Ireland–Claisen rearrangement. Because the gem-diester substi-
tution at C3 increased the acidity of the proton at C2 in sub-
strate 61 [64], silylation of that position took place under the
reaction conditions prior to the Ireland–Claisen rearrangement
which eventually produced alkylidenecyclopropane 62 (56%)
with high diastereoselectivity. The trimethylsilyl substituent at
C2 could then be easily removed by treatment of 62 with teta-
butylammonium fluoride under buffered conditions (AcOH,
THF, 0 °C) to afford alkylidenecyclopropane 63 (92%, Scheme 22) [61].

The Ireland–Claisen rearrangement was then extended to a chal-
 lenging class of cyclopropylcarbinyl glycolates possessing gem-
difluoro substitution at C3 [65]. Gem-difluorocyclopropanes are
accessible by difluorocyclopropenation of alkynes with diflu-
orcarbene but these compounds display poor stability in most
cases and readily undergo hydrolysis into cyclopropenones
which possess an aromatic character [66,67]. Gem-difluorocy-
clopropenylcarbinyl glycolates 65a–n were prepared by slow
addition of an excess of trimethylsilyl fluorosulfonyldifluoro-
acetate (TFDA) [68] to a solution of propargyl glycolates 64a–n
containing NaF in diglyme at 120 °C. Difluorocyclopropene
65a could be purified by flash chromatography on silica gel and
was isolated in 86% yield but this compound rapidly underwent
decomposition upon storage. The instability of glycolates 65a–n
was a critical issue which was solved by carrying those interme-

tate compounds directly in the sigmatropic rearrangement. By-
products arising from the difluorocyclopropenation reaction
(CO$_2$, SO$_2$, and Me$_3$SiF) were simply removed by argon
sparging of the reaction mixture and the Ireland–Claisen rear-
rangment was then triggered by addition of Me$_3$SiCl (4 equiv)
and KHMS (4 equiv), (THF, −78 °C to rt). Subsequent hydro-
lysis and treatment with trimethylsilyldiazomethane afforded the
corresponding α-alkoxy methyl esters 66a–h, and 66k–n

Scheme 21: Ireland–Claisen rearrangement of cyclopropenylcarbinyl glycolates 56a–l.

*overall yield from the corresponding cyclopropenylcarbinol;
*enolization carried out with KHMS (2 equiv) and Me$_3$SiCl (2 equiv)
possessing a 3,3-difluoroalkylidene cyclopropane scaffold. This two-step difluorocyclopropenation–Ireland–Claisen rearrangement sequence was applied to propargyl glycolates 64a–e possessing a phenyl, a p-methoxophenyl, a p-bromophenyl, an o-chlorophenyl or a 1-naphthyl substituent at the acetylenic position, as illustrated with the formation of compounds 66a–e (63–76%, two steps from the corresponding propargyl glycolates). Not surprisingly, chirality transfer (from C4 to C2) also occurred in the Ireland–Claisen rearrangement, as demonstrated by the formation of (−)-66b (ee = 95%) from optically enriched (S)-64b (ee = 96%). Heteroaromatic groups (indol-3-yl and 3-thienyl) were tolerated at the acetylenic position and the corresponding glycolates 64f and 64g led to compounds 66f and 66g in 70% yield. A p-acytlenophenyl group was compatible as shown with the isolation of alkylidene cyclopropanes 66h (65%) but it should be noted that the electron-withdrawing methyl ketone was converted to a trimethylsilyl enol ether upon treatment with KHMSDEt3SiCl. By contrast, an electron-withdrawing p-nitrophenyl group was not tolerated because the intermediate cyclopropane 65i underwent decomposition under the reaction conditions of the Ireland–Claisen rearrangement, presumably because of competitive deprotonation at C4. A phenyl substituent was incompatible at C4 as the corresponding substrate 65j decomposed upon treatment with KHMSDEt3SiCl. This was explained by a competitive abstraction of the hydrogen at C4 by the base thereby resulting in side reactions. However, various alkyl substituents could be present at the propargyl position in glycolates 66k–n which afforded the corresponding rearranged compounds 66k–n in moderate yields (40–61%, Scheme 23) [65].

With the goal of accessing α-amino acid derivatives incorporating an alkylidene cyclopropane, the Ireland–Claisen rearrangement of N,N-diBoc glycinates 67a and 67b was explored. The reaction conditions were essentially the same as those described previously with glycolates 56a–l except that LiHMDS was used as the base in the enolization step [69]. The (Z)-silyl ketene acetals 68a and 68b were generated, in agreement with previous results disclosed by Carbery et al. with allylic N,N-diBoc glycinates [69], and underwent a Ireland–Claisen rearrangement to afford N,N-diBoc α-amino esters 69a (78%) and 69b (91%) in good yields and with high diastereoselectivity [61]. Although cleavage of the two Boc groups could not be achieved cleanly upon exposure of 69b to a large excess of trifluoroacetic acid, this operation could be accomplished in a sequential manner by addition of trifluoroacetic acid (2 equiv, CH2Cl2, 0 °C) and then by treatment of the resulting N-Boc carbamate 70 (97%) with trimethylsilyl triflate in the presence of 2,6-lutidine to generate α-amino ester 71 (99%, Scheme 24) [61].
of the PMB group and subsequent hydrogenation of the resulting α-hydroxy ester 75 (75%) in the presence of Crabtree's catalyst delivered the gem-difluorocyclopropane 76 (91%) as a single diastereomer. The reduction of ester 76 with LiAlH₄ and oxidative cleavage of the resulting 1,2-diol with NaIO₄ delivered the highly substituted gem-difluorocyclopropanecarboxaldehyde 77 (72%) possessing a quaternary stereocenter (Scheme 26) [65].
Other examples of post-functionalization involve iodolactonization reactions which were applied to 74 and 75 using N-iodosuccinimide (MeCN/H₂O, 50 °C) [70], or to the N-benzylamine generated from 66a (Scheme 27) [71]. These iodocyclizations led to the oxabicyclic compounds 78 (98%) and 79 (99%), and to the azabicyclic product 80 (45%), respectively, with high diastereoselectivities.

Conclusion
In recent years, [2,3]- and [3,3]-sigmatropic rearrangements of cyclopropenylcarbinol derivatives have emerged as useful tools for the stereoselective synthesis of a wide variety of alkylidene cyclopropanes, substituted by heteroatoms (P, O, N, F) and/or incorporating valuable functional groups (α-alkoxy or α-amino acid derivatives) which are potentially useful for further functionalization. The reactivity of heterosubstituted/functionalized alkylidene cyclopropanes arising from those sigmatropic rearrangements, which are not easily accessible by other strategies, has only been sparingly investigated to date but the results summarized in this short review, in conjunction with the very rich chemistry of alkylidene cyclopropanes, may stimulate further investigations in this particular area.

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See for the stereoselective [2,3]-sigmatropic rearrangement of acyclic allylic phosphinites.

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The reaction conditions are those indicated accurately in the experimental section.

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