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Trifluoromethyl-substituted cyclopropanes

Oleksandr O. Grygorenko [a,b,*], Oleksiy S. Artamonov [a,b], Igor V. Komarov [a,b], Pavel K. Mykhailiuk [a,b,*]

[a] Enamine Ltd., Alexandra Matrosova Street 23, Kyiv 01103, Ukraine
[b] Kyiv National Taras Shevchenko University, Volodymyrska Street 64, Kyiv 01601, Ukraine

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1. Introduction

Incorporation of cyclopropane rings into organic molecules has been widely exploited to alter their chemical properties and/or to reduce conformational flexibilty.[1,2] Cyclopropane derivatives are widespread both among natural compounds and synthetic drugs;[3–8] this is partially due to the fact that a three-membered ring is the minimal structural motif providing conformational rigidity, which is believed to be an important feature characteristic of most biologically active compounds.[9–11] Introduction of a trifluoromethyl group into organic molecules represents another structural modification of importance to medicinal chemistry owing to the unique properties of fluorine.[12–14] As the steric requirements exhibited by the fluorine atom are close to that of hydrogen, trifluoromethyl-substituted compounds can be expected

* Corresponding authors. Tel.: +38 044 239 33 15; fax: +38 044 502 48 32; e-mail addresses: gregor@univ.kiev.ua (O.O. Grygorenko), pavel.mykhailiuk@gmail.com (P.K. Mykhailiuk).

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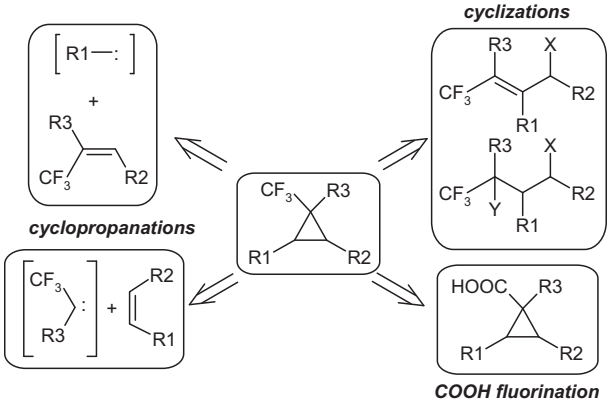
to follow interactions with potential biological targets similarly to the parent methyl analogues. At the same time, fluorinated analogues can often avoid undesired metabolic transformations observed for the parent compounds. On the other hand, due to the high electronegativity of the fluorine, the presence of a trifluoromethyl group in a molecule can diminish nucleophilicity or increase electrophilicity of the neighboring functional groups. In many cases, introducing trifluoromethyl groups results in enhanced lipophilicity.[12] Another important feature of fluorine-containing compounds is related to the intrinsic magnetic properties of the ^{19}F nucleus beneficial for NMR studies.[15,16]

Trifluoromethyl-substituted cyclopropanes, which constitute the subject of this review have attracted much attention of scientists in recent years. In medicinal chemistry, they were used as building blocks in the design of cannabinoid CB_1 receptor antagonists,[17] $hNa_v1.7$ channel blockers,[18] VLA-4 integrin antagonists,[19] HCV NS5B polymerase inhibitors,[20] agents for viral hepatitis,[21] non-opioid analgesics,[22] kinase modulators,[23] and potassium channel activators,[24] to name just a few applications. In this review, synthetic methods for trifluoromethyl-substituted cyclopropanes are surveyed, focusing mainly on the reports of the last two decades. To the best of our knowledge, this subject has been only partially covered by previous reviews;[25–30] in particular, a comprehensive survey on fluorinated carbenes, which refers to 1996 should be mentioned.[25] As far as possible, the literature data are categorized according to the synthetic approaches used for the construction of the title cores. In particular, cyclopropanations involving both trifluoromethyl-substituted alkenes and trifluoromethyl-substituted reagents, cyclizations of trifluoromethyl-substituted 1,3-bifunctional substrates and fluorinations of cyclopropanecarboxylic acids are discussed (Scheme 1). Specific transformations, which hardly can be considered as general synthetic methods for the preparation of a wide range of trifluoromethyl-substituted cyclopropanes (e.g., photochemical transformations of trifluoromethyl-substituted aromatic compounds[31–33]) are beyond the scope of this review. It should also be noted that transformations of organic compounds that already contain a trifluoromethyl-substituted cyclopropane ring are not surveyed comprehensively.



Scheme 1. Retrosynthetic transformations of trifluoromethyl-substituted cyclopropanes.

2. Cyclopropanation reactions

2.1. Cyclopropanation by trifluoromethyl-substituted carbene reagents

One of the most straightforward retrosynthetic disconnection of a trifluoromethyl-substituted cyclopropane ring leads to the corresponding alkene and trifluoromethyl-substituted carbene or carbene equivalent as the starting materials. Despite the first reports on [2+1] cycloadditions involving trifluoromethyl-substituted carbenes referring to 1960,[34] this approach became a valuable synthetic method only in the last decades when efficient synthetic procedures were elaborated.

A number of trifluoromethyl-substituted carbenes have been reported to date (Fig. 1).[25,35,36] They can be subdivided into three groups according to their structure and electronic properties:

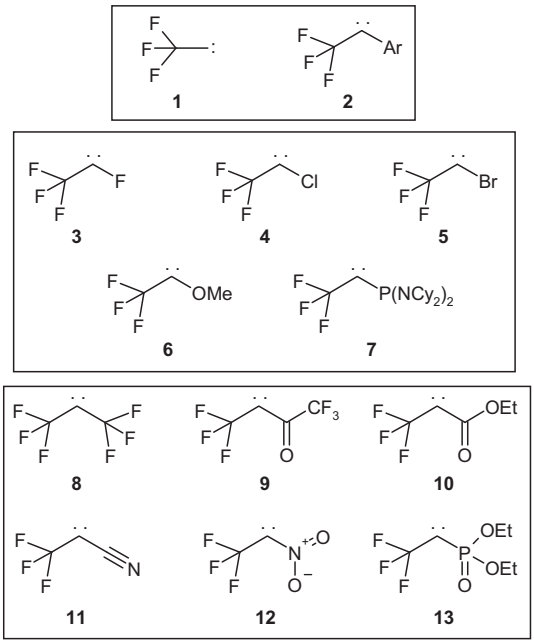


Fig. 1. Trifluoromethyl-substituted carbenes (Cy—cyclohexyl).

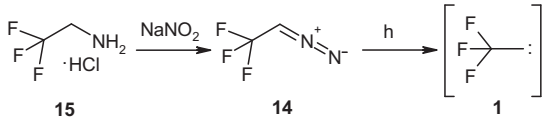
- (relatively) Unstabilized trifluoromethyl-substituted carbenes (**1** and **2**);
- Push–pull trifluoromethyl-substituted carbenes (**3**–**7**);
- Trifluoromethyl-substituted carbenes possessing an additional electron-withdrawing group (**8**–**13**).

The presence of the trifluoromethyl group adjacent to a carbene center in the molecules **1**–**13** increases their kinetic stability due to the strength and electron-deficient nature of the C–F bond, which prevents a fluorine 1,2-shift to form the corresponding alkene.[25] This stabilization is not strong enough, and hence the ground state of the carbenes **1** and **2** is a triplet. This is also the case when carbenes **8**–**13** are considered, although an additional electron-withdrawing group increases the reactivity of their molecules. Push–pull carbenes **3**–**7**, which have both a π-donating substituent and an electron-withdrawing trifluoromethyl group adjacent to a carbene center are stabilized thermodynamically by conjugation; their ground state is postulated to be a singlet.[25] This effect is particularly strong in the case of carbene **7**; it has been shown to be stable for weeks in solution at temperatures up to −30 °C.[35]

The increased stability imparted by the trifluoromethyl group has been exploited to investigate carbenes for which information on the hydrocarbon counterparts was difficult to obtain. The literature on the generation and chemical properties of trifluoromethyl-substituted carbenes has been surveyed thoroughly up to 1996.[25] Herein we will focus on some newer findings on their cycloaddition reactions with alkenes.

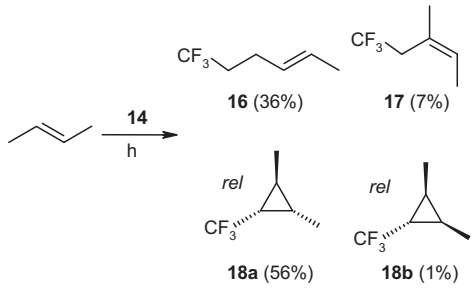
2.1.1. Unstabilized trifluoromethyl-substituted carbenes. The parent trifluoromethyl-substituted carbene **1** was reported first in 1960;[34] in the early preparations, it was generated by photolysis of

2,2,2-trifluoroethyldiazomethane **14**.[34,37–40] The latter is a relatively stable compound, which has been prepared by diazotisation of 2,2,2-trifluoroethylamine hydrochloride 15 (Scheme 2).[38] Photochemical generation of 1 in the presence of alkene (e.g., *E*-2-butene) resulted in both carbene CH-insertion and cyclopropanation giving the products **16**, **17**, and **18a**,**b**; nevertheless, the cyclopropane fraction of the products was shown to be mainly (98%) one compound (**18a**), which corresponded to the singlet state of the carbene **1** in the reaction (Scheme 3).[38] In the case of ethylene, trifluoromethylcyclopropane was obtained in 52% yield, whereas the reaction of propene gave an almost equimolar mixture of *cis*- and *trans*-1-methyl-2-trifluoromethylcyclopropanes in 68% total yield.[39]



15 **14** **1**

Scheme 2.

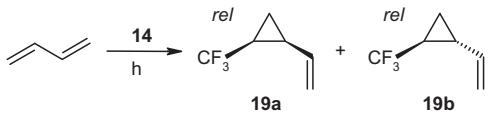


16 (36%) **17** (7%)

18a (56%) **18b** (1%)

Scheme 3.

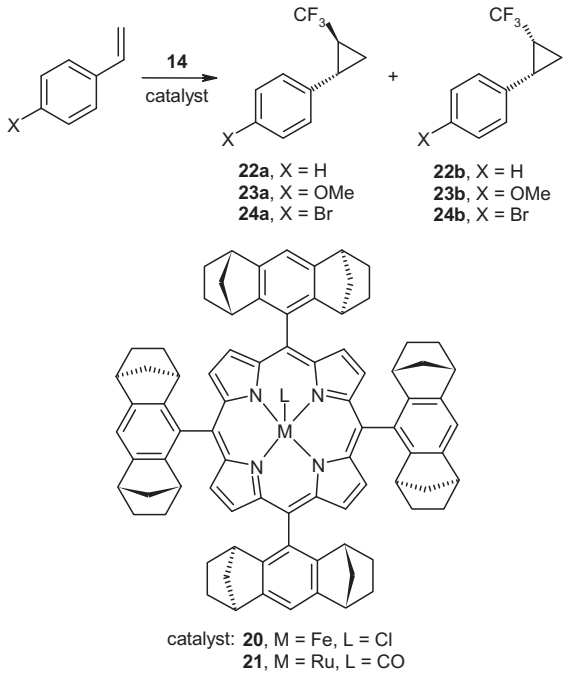
Until the end of the 20th century, the photochemical method remained the only one used for generating carbene **1**. In particular, a slightly modified procedure was applied for the preparation of 2-(trifluoromethyl)-1-vinylcyclopropane **19** by Dolbier and McClinton in 1995.[41] Compound **19** was obtained in 67% yield as a 1:1.2 mixture of *cis*- and *trans*-isomers **19a** and **19b**, which were separated by gas chromatography (Scheme 4).



19a **19b**

Scheme 4.

The first report on metal-catalyzed cyclopropanation of alkenes with **14** refers to 2006.[42] In this work, asymmetric addition of the carbene to styrene and its *p*-substituted derivatives was carried out using metalloporphyrin catalysts **20** and **21**, as well as their polymer-supported modifications (Scheme 5). The reaction was performed in dichloromethane at ambient temperature at a catalyst: 2,2,2-trifluoroethyldiazomethane:styrene ratio of 0.005:1:5. In the case of the homogeneous catalysts, the corresponding cyclopropanes **22**–**24** were obtained in 24–50% yields, the ruthenium porphyrin **21** giving a somewhat lower outcome of the product. An excellent diastereoselectivity was observed (de 96–98%), while the enantioselectivity was moderate (ee 30–79% for the trans-isomer), again lower values being obtained in the case of **21** as the catalyst. The use of polymer-supported modifications of **20** and **21** did not greatly affect the yields of the products **22**–**24** (31–52%); however, both the diastereoselectivity and enantioselectivity decreased (de 88–94%, ee 17–61%). The authors postulated metallocarbenes as the key intermediates in the cyclopropanation by 14 in the presence of the catalysts **20** and **21**.

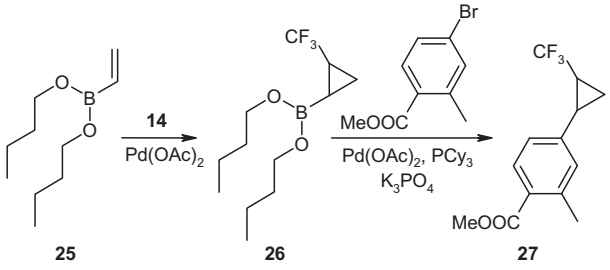


22a, X = H
23a, X = OMe
24a, X = Br

22b, X = H
23b, X = OMe
24b, X = Br

Scheme 5.

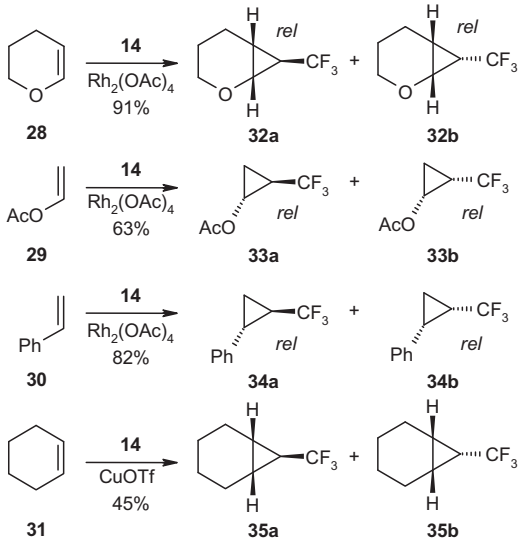
Cyclopropanation of vinylboronic acid dibutyl ester 25 with diazoalkane **14** was reported; in this case, palladium(II) acetate was used as a catalyst.[43,44] The reaction was performed in diethyl ether at ambient temperature; a 1.7 fold excess of **14** (solution in ether) and 3 mol %. of the catalyst were used. The corresponding product **26** was obtained as a 2:3 mixture of cis- and trans-isomers, which were used in the next step (Suzuki-type coupling giving **27**) without purification (Scheme 6).



25 **26** **27**

Scheme 6.

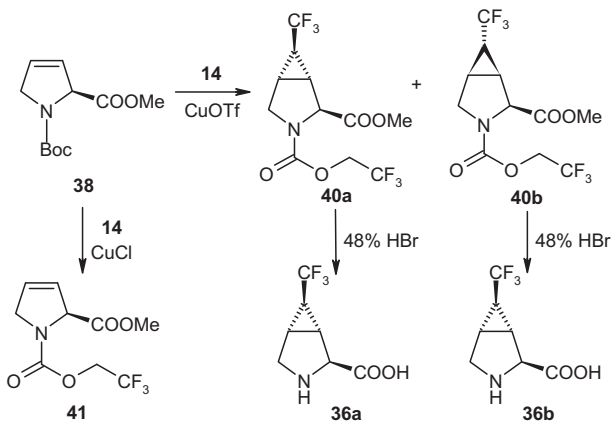
A study on the scope and limitations of metal-catalysed cyclopropanation with **14** was performed.[45] In particular, several alkenes **28**–**31** were chosen as standard substrates in this study (Scheme 7). In order to avoid isolation of 2,2,2-trifluoroethyldiazomethane **14**, which is potentially explosive and toxic, the modified procedure described previously for methylene generation[46] was used. Compound **14** obtained from concentrated aqueous solutions of 2,2,2-trifluoroethylamine hydrochloride **15** and sodium nitrite was gradually blown off the generator flask by an argon stream into a reaction vessel containing a neat alkene and a catalyst (10 mol %). This procedure allowed the maintaining of a constant concentration of **14** in the reaction mixture, thus avoiding the decomposition of **14** and preventing most of the undesired side reactions.



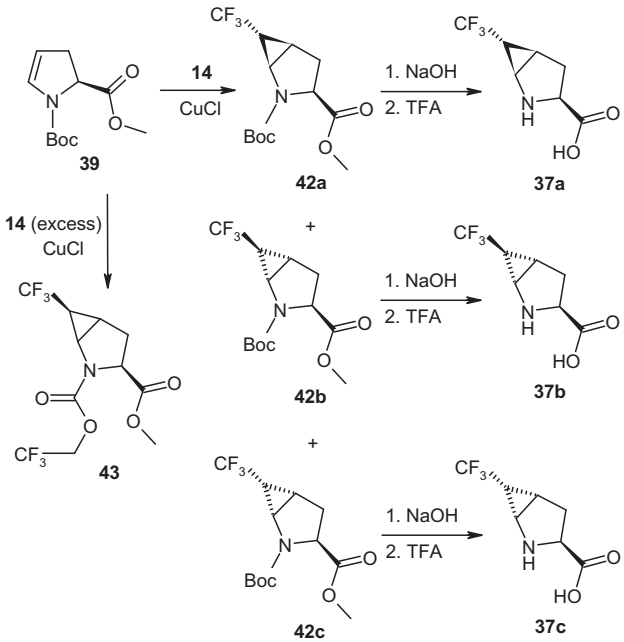
Scheme 7.

It has been found that the electron-rich olefins **28**–**30** smoothly underwent cyclopropanation under the conditions described above in the presence of dirhodium(II) tetraacetate as a catalyst. The corresponding cyclopropanes **32a**,**b**–**34a**,**b** were obtained in 63–91% yields. In the case of the less reactive cyclohexene **31**, the corresponding cyclopropanes **35a**,**b** were obtained only when copper(I) triflate was used to promote the reaction. It should be noted that moderate diastereoselectivity was observed in all the cases studied (*trans*:*cis*≈2:1).

The method described above was used in the synthesis of fluorinated amino acids. Namely, thifluoromethyl-substituted proline analogues **36a**,**b** and **37a**–**c** were obtained by cyclopropanation of the corresponding dehydroproline derivatives **38** and **39** (Schemes 8 and 9). It is appropriate to note that the regularities in the reactivity of diazoalkane **14** described above were reaffirmed in the case of compounds **38** and **39**. In particular, extensive experimentation was needed to find the optimal conditions for the cyclopropanation of **38**, because an electrophilic attack of the carbene at the carbamate moiety was the main transformation giving **41**. In fact, this reaction prevailed over the cyclopropanation if CuCl was used as a catalyst; a mixture of **40a** and **40b** was obtained in modest total yield (15%) if CuOTf was applied (Scheme 8).[47]



Scheme 8.

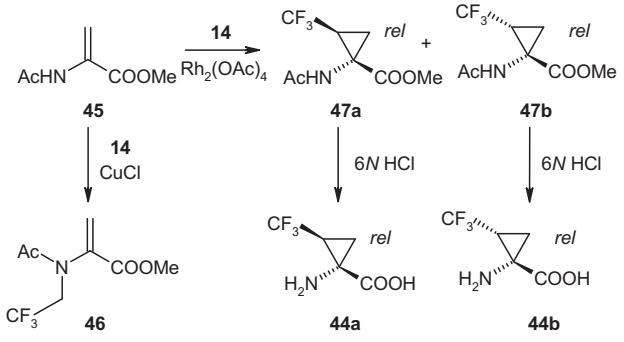


Scheme 9.

Cyclopropanation of **39** possessing a more electron-rich double bond turned out to be more fruitful. In this case, cyclopropanes **42a**–**c** were obtained in 66% overall yield (**42a**:**42b**:**42c**=1:0.9:0.7), even if CuCl was used as the catalyst. In contrast to the corresponding reaction of 38, formation of the side product **43** was observed only with prolonged reaction times (Scheme 9).

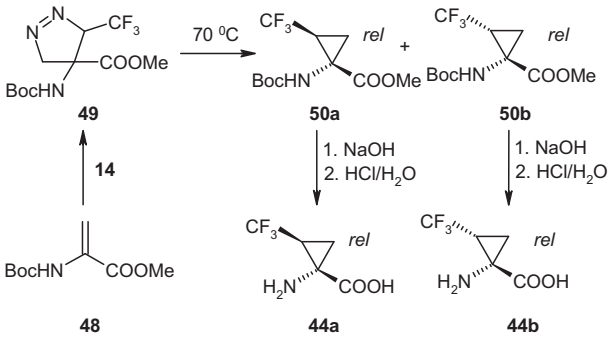
Amino acid **37a** was used as a fluorine label for studies of a proline-rich cell-penetrating peptide SAP (VRLPPPVRLPPPVRLPPP). Neither degradation/racemisation nor low reactivity of the corresponding *N*-Fmoc derivative was observed during the standard solid-phase synthesis of the SAP analogue containing a Pro–11/**37a** substitution. It was shown that this replacement resulted in stabilization of the PPII conformation of the peptide, which persisted even up to 50 °C.[47]

Another α-amino acid, trifluoronorcoronamic acid **44**, was prepared by cyclopropanation of the dehydroalanine derivative **45**.[45] Again, electrophilic attack at the amide moiety interfered with the cyclopropanation; the side product **46** was isolated in 15% yield when CuCl was used to promote the reaction. Nevertheless, cyclopropanes **47a** and **47b** were obtained (although in a modest total yield of 23%) when CuCl was replaced by $Rh_2(OAc)_4$. Hydrolysis of **47a** and **47b** afforded *trans*- and *cis*-trifluoronorcoronamic acid **44a** and **44b** quantitatively (Scheme 10).



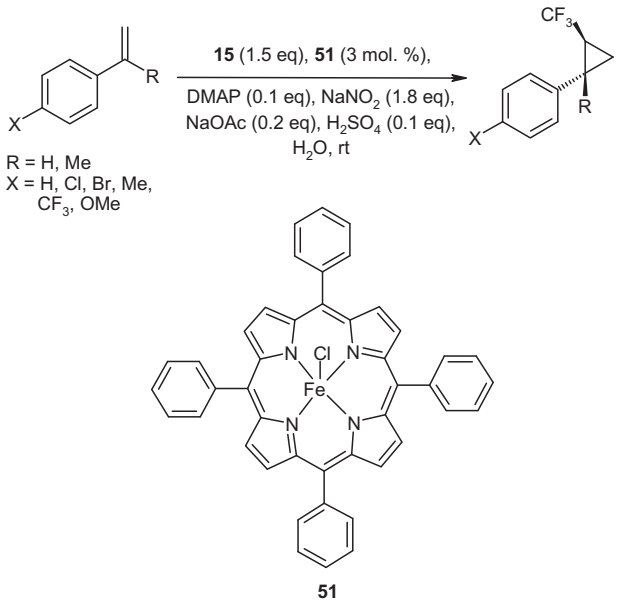
Scheme 10.

The approach to **44** described above suffered from low yield of the reaction sequence as well as from low effectiveness of the separation of diastereomers. Therefore, the procedure was modified to avoid these drawbacks, i.e., the Boc derivative **48** was used instead of acetamide **45**, and the cyclopropanation was carried out in two steps via pyrazoline **49** (Scheme 11).[48] Separation of diastereomers **50** was easily achieved by flash chromatography on a *ca.* 45-g scale due to a large difference in their retention factors. The reaction sequence used in this preparation of **44** (i.e., intermediate formation of pyrazolines followed by their thermal decomposition) can be a valuable method for the synthesis of trifluoromethyl-substituted cyclopropanes starting from other alkenes containing electron-withdrawing groups.



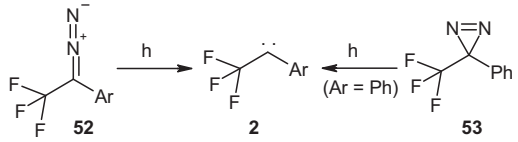
Scheme 11.

Recently, an interesting method for highly diastereoselective cyclopropanation of styrene derivatives was reported, which included direct iron(III)-catalyzed generation of carbenoid from **15**. The iron–porphyrin complex [Fe(TPP)Cl] **51** used as the catalyst is commercially available. Importantly, as little as 1.5 equiv of **15** was needed for full consumption of the olefin, which bodes well for the use of valuable substrates (Scheme 12). Some other iron-, ruthenium-, cobalt-, and copper-containing catalysts were also tested in this reaction; they appeared to be less effective, compared to **51**. Unfortunately, the method failed in the case of non-conjugated alkenes, such as 3-phenylpropene.[49]



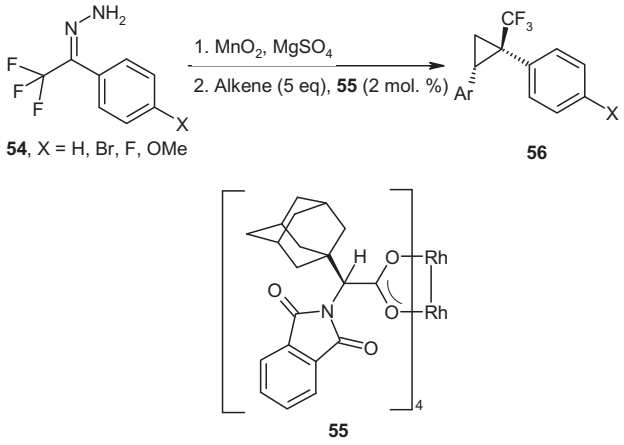
Scheme 12.

Introducing an aryl substituent adjacent to the carbene center significantly improved the stability of the carbenes **2**, although this stabilization is not strong enough to alter the ground state of **2** from triplet to singlet. Nevertheless, a few reports on cyclopropanation involving **2** can be found in the literature. In the early preparations, carbenes **2** were generated by photochemical decomposition of diazoalkanes **52** or diazirine **53** (Scheme 13).[25]



Scheme 13.

Rhodium-catalyzed enantioselective cyclopropanation of styrene derivatives by **52** was developed recently. In this approach, cyclopropanation was performed via a two-step procedure. Diazoalkanes **52** were generated first from the corresponding hydrazones **54** by MnO_2 oxidation. In the second step, cycloaddition of the corresponding carbenoid occurred; an excess (5 equiv) of the styrenes and 2 mol % of catalyst (Rh_2(*R*-PTAD)$_4$ **55**) were used. The overall reaction sequence resulted in good yields of the products **56** (61–80%), and high diastereoselectivities (de>94%) and enantioselectivities (ee 88–98%) (Scheme 14).[50]

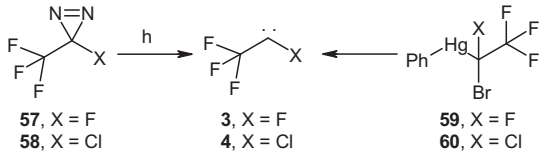


Scheme 14.

2.1.2. Push–pull trifluoromethyl-substituted carbenes. In the molecules of the carbenes **3**–**7**, both a π-donating substituent and the electron-withdrawing trifluoromethyl group are adjacent to the carbene center, and thus they can be named 'push–pull' carbenes. The major effect of the π-donating substituents is stabilization of the singlet state of carbenes by conjugation (Fig. 2). Despite the stabilization of push-pull carbenes being predicted by Pauling as early as in 1980,[51] only a limited number of papers reporting on the cycloaddition reactions of **3**–**7** with alkenes was published to date, few of them aiming at the development of practical synthetic methods.

Fig. 2. Stabilization of the push–pull trifluoromethyl-substituted carbenes.

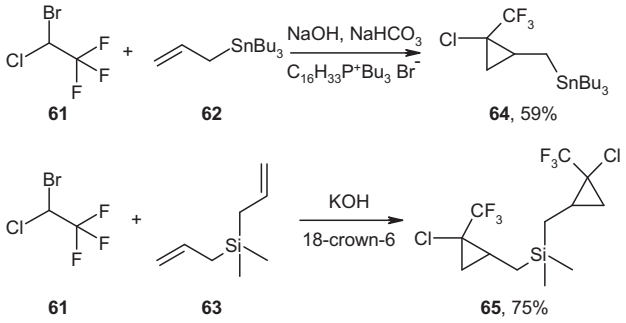
The early reports on the [2+1] cycloaddition of **3** and **4** with alkenes included generation of the carbene either by photochemical decomposition of diazirines **57**[52] and **58**[53] or thermolysis of organomercury derivatives **59**[54,55] and **60**[56,57] (Scheme 15). Despite



Scheme 15.

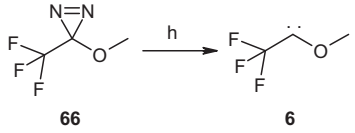
the rather drastic reaction conditions (i.e., 135–155 °C), the latter method resulted in good yields (70–98%) of the cyclopropanation in the case of **59** as the carbene source and simple alkenes, such as cyclooctene, cycloxehene, heptene and 3-(trimethylsilyl)propene, whereas in the case of (trimethylsilyl)ethylene, the outcome of the product was lower (16%). The reaction also showed moderate diastereoselectivity for the less hindered cyclopropane (1.8–5.8:1 ratio of isomers). Carbene **4** generated from **60** appeared to be less chemoselective; moreover, concurrent formation of **5** was also observed in this case.

Carbene **4** was also generated from 2-bromo-1,1,1-trifluoroethane **61** under phase-transfer reaction conditions. This approach was used for cyclopropanation of allyltin and allylsilicon compounds, in particular, alkenes **62** and **63** (Scheme 16). The reactions resulted in 50–75% yields of the corresponding tin- or silicon-containing cyclopropanes, e.g., **64** and **65**.[58,59]



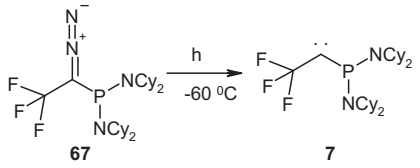
Scheme 16.

Cyclopropanation of alkenes with carbene **6** was studied. In this case, compound **6** was generated by photochemical decomposition of diazirine **66** (Scheme 17). It was shown that carbene **6** is highly unstable and unselective in the cyclopropanation of both electron-poor and -rich alkenes. Steric interactions were shown to be important in these transformations.[60]

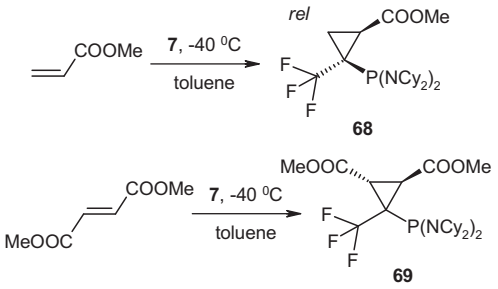


Scheme 17.

Carbenes **3**–**6** appeared to be not stable enough, which was attributed to the negative ('pull') inductive effect (−*I*) of the halogeno or methoxy substituent. The situation changed dramatically when these π-donating substituents were replaced by a phosphanyl group, which features both (+*M*) and (+*I*) electronic effects. Carbene **7**, obtained by photolysis of the corresponding diazoalkane **67** in ether, THF or toluene (Scheme 18), was stable in solution at −30 °C for weeks. Compound **7** did not react with electron-rich alkenes, but cleanly underwent cyclopropanation reactions with methyl acrylate and dimethyl fumarate at −40 °C, demonstrating its nucleophilic character. The reactions proceeded with high chemo- and stereoselectivity: the cyclopropanes **68** and **69** were obtained in 80 and 60% yields, respectively, as single diastereomers (Scheme 19).[35]

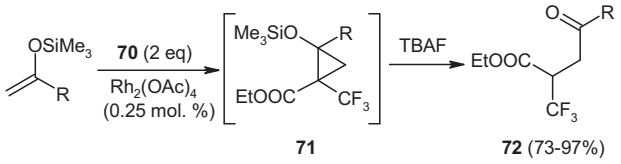


Scheme 18.

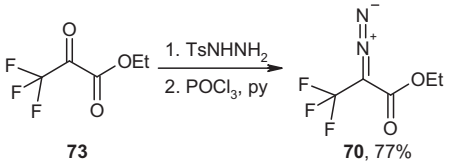


Scheme 19.

2.1.3. Trifluoromethyl-substituted carbenes possessing an additional electron-withdrawing group. Carbenes possessing at least one electron-withdrawing group (in particular, carbalkoxyl) historically have a central prominence among other carbenoids.[61] Therefore, it is not surprising that a number of transition metal-catalyzed cyclopropanations of alkenes involving carbene **10** or its carbenoid analogues has been described in the literature. To the best of our knowledge, the first report on reactions of this type refers to 1990. In this work, cyclopropanation of silyl enolates with the carbenoid generated from ethyl 3,3,3-trifluorodiazopropionate **70** was performed using $Rh_2(OAc)_4$ (0.25 mol %) as a catalyst. Cyclopropanes **71** were not isolated, but subjected to ring opening induced by TBAF, thus giving 2-(trifluoromethyl)-4-oxocarboxylates **72** in 73–97% yields (Scheme 20). Diazoester **70** used in the synthesis was prepared from the corresponding ketoester **73** (Scheme 21).[62]

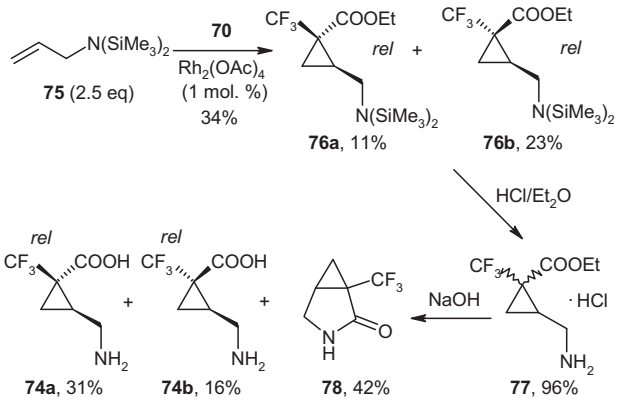


Scheme 20.



Scheme 21.

Cyclopropanation with **70** was used in the synthesis of a GABA analogue **74** starting from *N*-silylated allylamine **75**. Reaction of **70** and **75** in the presence of $Rh_2(OAc)_4$ (1 mol %) in refluxing ether afforded a mixture of diastereomers **76a** and **76b** (**76a**:**76b**=32:68) in 34% overall yield. Two-step hydrolysis of **76** (via **77**) led to the amino acid **74** as a mixture of diastereomers (47%, **74a**:**74b**=66:34) and bicyclic lactam **78** (42%) (Scheme 22).[63]



Scheme 22.

Some studies were performed to develop stereoselective methods for the cyclopropanation of unsaturated hydrocarbons with **70**. A set of catalysts of general formula Rh_2L_4 (see Fig. 3 for the structures of ligands L) was tested in these studies. Low enantioselectivities were observed in the case of 1,1-diphenylethylene and hex-1-yne as the substrates. The products **79** and **80** were obtained in 17–76% yields, and the highest ee values (40 and 24%, respectively) were observed when Rh_2[(*S*)-nttl]$_4$ was used as a catalyst (Scheme 23).[64]

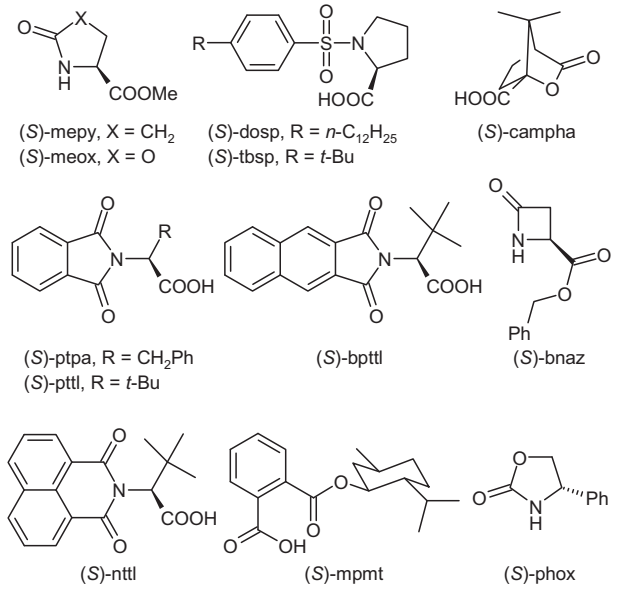
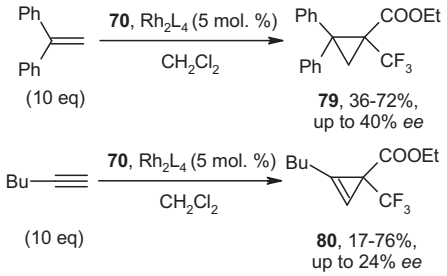
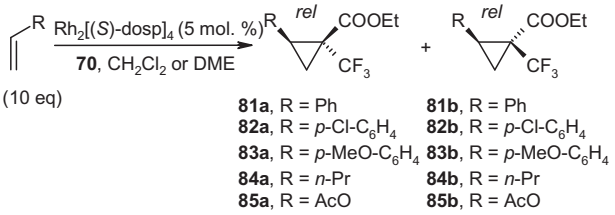


Fig. 3. Ligands for the rhodium-catalyzed enantioselective cyclopropanation.



Scheme 23.

A similar situation was observed when cyclopropanation of other olefins was studied. Carboxylate catalysts afforded generally higher yields, and the enantioselectivities of the products **81a**,**b**–**85a**,**b** were comparable to those provided by the carboxamidate complexes. In particular, Rh_2[(*S*)-dosp]$_4$ resulted in the highest ee values when styrenes were used as the substrates, the maximum ee value (75%) being achieved in the case of *p*-methoxystyrene. In addition, almost no diastereoselectivity was observed in the reactions (Scheme 24, Table 1). Finally, no cyclopropanation occurred with *trans*-oct-4-ene, *trans*-β-methylstyrene or *trans*-stilbene as the substrates.[64–66]



Scheme 24.

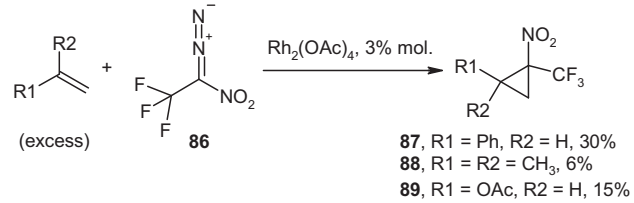
Table 1
Reaction of **70** with monosubstituted alkenes (Conditions: 70 (1 equiv), alkene (10 equiv), Rh_2[(*S*)-dosp]$_4$ (5 mol %), CH_2Cl_2, rt)

Product	Yield, %	**8*X*a**:**8*X*b**[a]	**8*X*a** ee, %	**8*X*b** ee, %
81	58	44:56	18	50
82	52	51:49	12	43
83	80	23:77	12	75
84	68	42:58	16	12
85	33	69:31	22	44

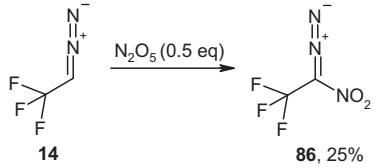
[a] **8*X*** refers to the compound number of the corresponding product (**81**–**85**).

The low stereoselectivity observed in the rhodium-catalyzed reactions of **70** with olefins (compared to other diazoesters) was ascribed to the strong electon-withdrawing effect of the trifluoromethyl group, which increased the electrophilicity of the carbene and hence enhanced its reactivity.[64]

Cyclopropanation of several electron-rich sterically undemanding alkenes (e.g., styrene, isobutene, and vinyl acetate) with 2,2,2-trifluoro-1-nitrodiazoethane **86** (as a source of carbenoid **12**) in the presence of $Rh_2(OAc)_4$ was reported. The reaction resulted in low yields of the products **87**–**89** and no diastereoselectivity (Scheme 25). Compound **86** used in these studies was obtained in 25% yield by the nitration of **14** with dinitrogen pentoxide (Scheme 26). Diazoalkane **86** appeared to be rather unstable (half life of about 2 h at rt).[67,68]

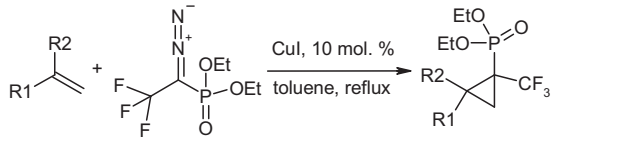


Scheme 25.



Scheme 26.

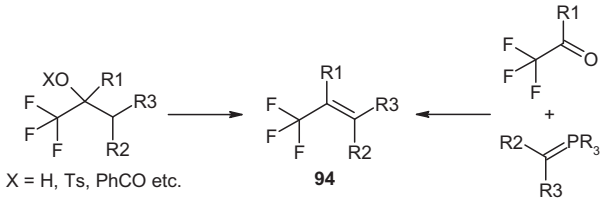
Recently, the cyclopropanation of alkenes with carbenoid **13** generated from diazophosphonate **90** has been reported. Screening of several rhodium and copper salts revealed that CuI (10 mol %) is as an optimal catalyst for these transformations. It was found that monosubstituted and 1,1-disubstituted alkenes (styrene, α-methylstyrene, and octene-1) are excellent substrates for the cyclopropanation with **90**; the corresponding cyclopropanes **91**–**93** were obtained in good-to-excellent yields (Scheme 27). In the case of cyclohexene (*cis*-1,2-disubstituted alkene), the yield of the cyclopropanation product diminished drastically (20%), whereas *trans*-1,2-disubstituted alkenes as well as electron-poor methyl acrylate did not react with **90**, even at elevated temperatures. Low diastereoselectivities were observed in all of the above reactions, the ratio of isomers varying from 1:1 to 1:2.[36] It could be concluded that carbenoid **13** is apparently more stable than its analogues **10** and **12**, probably due to lower electron-withdrawing properties of the phosphonate group.



Scheme 27.

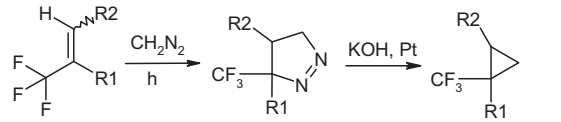
2.2. Cyclopropanation of trifluoromethyl-substituted alkenes

In the previous section, the methods for the construction of trifluoromethyl-substituted cyclopropanes starting from the corresponding alkenes and trifluoromethyl-substituted carbenes or carbene equivalents were discussed. An alternative retrosynthetic disconnection leads to trifluoromethyl-substituted alkenes and carbene equivalents as the starting materials (Scheme 1). In this part of the review, the synthetic methods that correspond to this retron are surveyed, including reactions with diazoalkanes or related carbene sources and ylides. In turn, the trifluoromethyl-substituted alkenes **94**, which act as the substrates in these transformations can be prepared by elimination reactions, Wittig-type olefinations or by other means (Scheme 28; see also below).

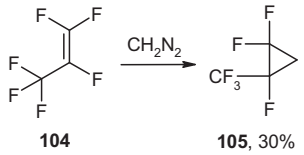


Scheme 28.

2.2.1. Reactions of trifluoromethyl-substituted alkenes with diazomethane. The first report on the cyclopropanation of trifluoromethyl-substituted alkenes refers to 1956, namely, photoinduced reactions of alkenes **95**–**97** and diazomethane were described resulting in the formation of pyrazolines **98**–**100**, which were subjected to pyrolysis (150–260 °C) to yield cyclopropanes **101**–**103** (Scheme 29).[69,70] In the case of perfluoropropene **104**, no promotion by UV light was required for the reaction; the cyclopropane **105** was isolated in 30% yield (Scheme 30).[69] It should be noted that, to the best of our knowledge, the transformations shown in Schemes 29 and 30 were the very first report on the synthesis of trifluoromethyl-substituted cyclopropanes.

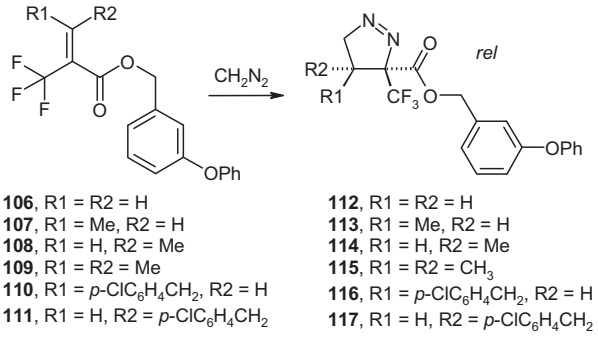


Scheme 29.

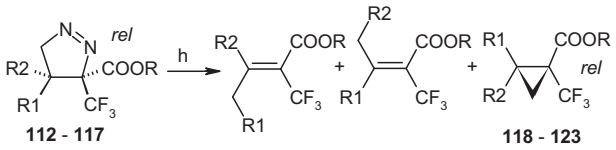


Scheme 30.

Reaction of 2-trifluoromethylacrylates **106**–**111** with diazomethane resulted in the quantitative formation of pyrazolines **112**–**117** (except **115**, which was isolated in 56% yield) (Scheme 31). Both thermal and photochemical decomposition of **112**–**117** were investigated; it was found that cyclopropane formation competed with methylene insertion, the latter being prevalent in the case of thermal conditions (toluene or xylene reflux). Thus, cyclopropanes **118**–**123** were obtained in 41–77% yields by irradiation of benzene solutions of pyrazolines **112**–**117** (Scheme 32).[71]

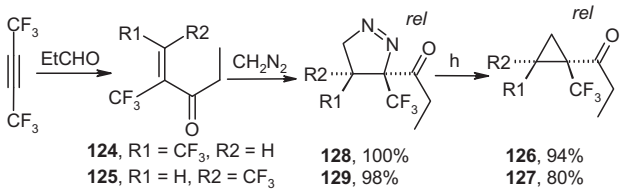


Scheme 31.



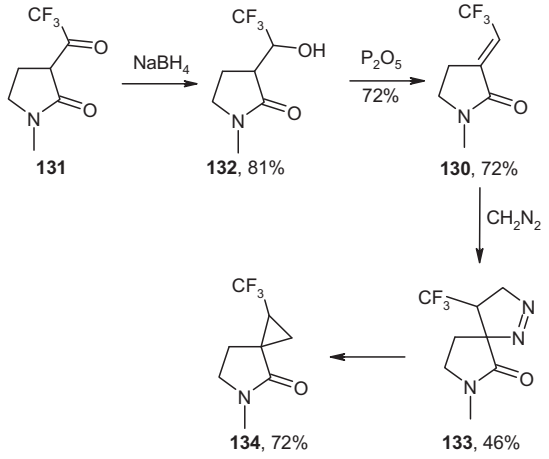
Scheme 32. (R=*m*-PhOC$_6$H$_4$CH$_2$, see Scheme 31 for R1 and R2).

An analogous transformation sequence was reported for (*Z*)- and (*E*)-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-ones **124** and **125**. Cyclopropanes **126** and **127** were obtained via pyrazolines **128** and **129** in good yields with high stereoselectivity; some minor products of side reactions were also isolated (Scheme 33).[72]



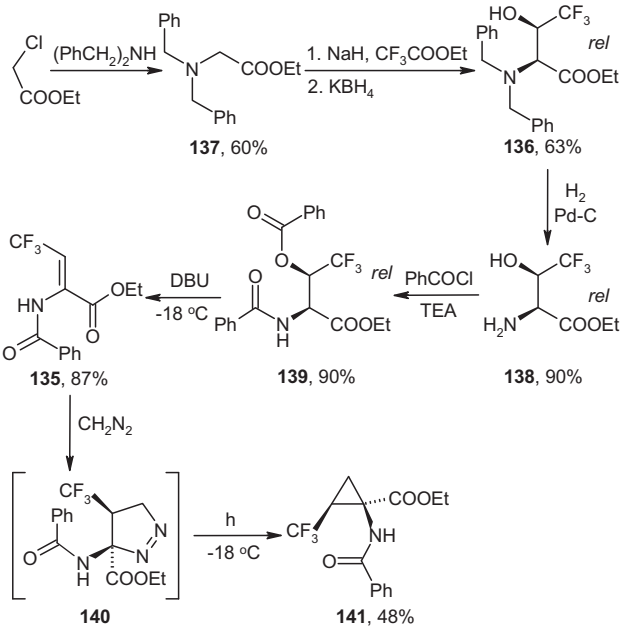
Scheme 33.

Cyclopropanation of 3-(2,2,2-trifluoroethylidene)lactam **130** has been documented in the literature. Compound **130** (90% de) was obtained in two steps from trifluoroacetyl-substituted lactam **131** via alcohol **132**. Treatment of **130** with 20-fold excess of diazomethane solution in ether afforded pyrazoline **133** in modest yield (46%; 65% conversion of **130**) as a single regio- and diastereomer. Heating of **133** under argon (160–170 °C) gave the spiro cyclopropane **134** in 72% yield (Scheme 34).[73]



Scheme 34.

The retrosynthetic approach to trifluoromethyl-substituted cyclopropanes discussed in this section was also used in the synthesis of trifluoronorcoronamic acid (**44**) derivatives. Synthesis of the corresponding α,β-dehydro amino ester **135** commenced from the trifluorothreonine derivative **136**, which was prepared in three steps from ethyl chloroacetate via the amino ester **137**. Compound **136** was debenzylated; the free amino ester **138** obtained was then benzoylated to give **139**. Treatment of **139** with DBU led to the formation of **135**. Reaction of **135** with diazomethane resulted in the formation of the rather unstable pyrazoline **140**, which was subjected to photochemical decomposition at −18 °C to yield the cyclopropane **141** (Scheme 35).[74]



Scheme 35.

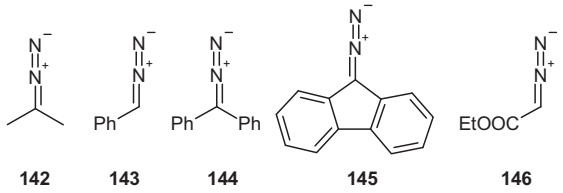
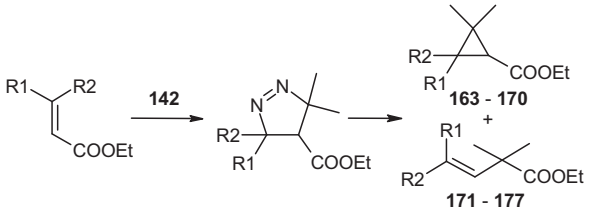


Fig. 4. Diazoalkanes used for the cyclopropanation of trifluoromethyl-substituted alkenes.

2.2.2. Reactions of trifluoromethyl-substituted alkenes with other carbene sources. A limited number of diazoalkanes other than diazomethane was used for the cyclopropanation of trifluoromethyl-substituted alkenes including compounds **142**–**146** (Fig. 4). Apart from this, reagents generating difluoro- and dichlorocarbenes were also used in [2+1] cycloaddition to trifluoromethyl-substituted olefins.

Reaction of fluorine-containing acrylates **147**–**154** (readily available as *E*/*Z* mixtures by the reaction of the appropriate ketones with ethoxycarbonylmethylenetriphenylphosphorane) with 2-diazopropane **142** proceeded smoothly to yield the pyrazolines **155**–**162** quantitatively, so that the reaction could be performed as a titration. Pyrolysis of **155**–**162** at 140 °C led to the cyclopropanes **163**–**170** as well as the rearrangement products **171**–**177**; the yield of the latter varied according to the total electronegativity of the groups at the C-3 position of the starting acrylates (Scheme 36). It was shown that the cyclopropanes **163**–**170** do not rearrange to **171**–**177** under pyrolysis conditions; hence, participation of an intermediate with ionic character in the transformation was suggested.[75]

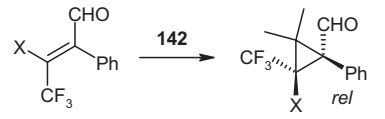


147, R1 = CF_3, R2 = Me
148, R1 = CF_3, R2 = Ph
149, R1 = R2 = CF_2H
150, R1 = CF_3, R2 = CF_2H
151, R1 = R2 = CF_3
152, R1 = CF_2Cl, R2 = CF_2H
153, R1 = R2 = CF_2Cl
154, R1 = CF_2Cl, R2 = CF_3

163 only
164 : **171** = 94 : 6
165 : **172** = 75 : 25
166 : **173** = 55 : 45
167 : **174** = 44 : 56
168 : **175** = 38 : 62
169 : **176** = 36 : 64
170 : **177** = 31 : 39

Scheme 36.

Cyclopropanation of trifluoromethyl-substituted acroleins **178**–**182** with **142** was described; cyclopropanes **183**–**187** were obtained in 70–85% yields with moderate-to-good stereoselectivity (Scheme 37) It is interesting to note that no pyrazoline intermediate resulting from the 1,3-dipolar cycloaddition has been detected.[76]

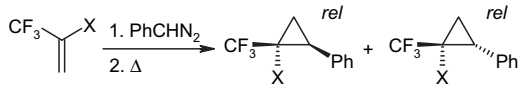


178, X = PhS
179, X = *n*-PrS
180, X = EtS
181, X = Cl
182, X = I

183, 80%, 40% *de*
184, 70%, 60% *de*
185, 78%, 36% *de*
186, 85%, 0% *de*
187, 85%, 60% *de*

Scheme 37.

Reaction of phenyldiazomethane **143** and 3,3,3-trifluoropropene derivatives **95**, **188**, and **189** afforded crude pyrazolines, which were not purified, but were subjected to pyrolysis directly in a VPC injection port (200 °C). The procedure allowed cyclopropanes **190a**,**b**–**192a**,**b** to be obtained as both pure cis- and trans-isomers (Scheme 38).[77]

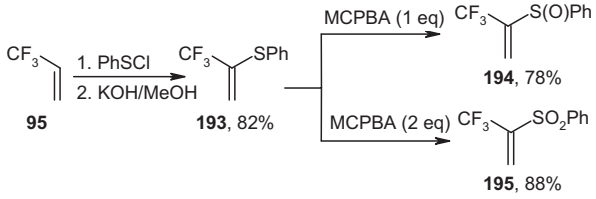


95, X = H
188, X = Br
189, X = CN

190a - 192a **190b - 192b**

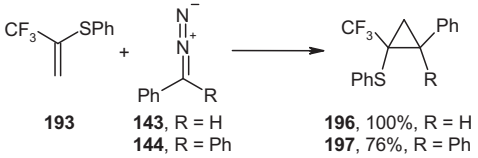
Scheme 38.

Cycloaddition of 2-phenylthio-3,3,3-trifluoropropene **193**, its sulfoxide **194** or sulfone **195** (Scheme 39) with various diazoalkanes (i.e., diazomethane, phenyldiazomethane **143**, diphenyldiazomethane **144**, and ethyl diazoacetate **146**) was explored. Upon reaction of diazoalkanes **143** and **144** with alkene 193, the cycloaddition occurred with nitrogen elimination, resulting in the formation of cyclopropanes **196** (100%, *Z*/*E*=56:44) and **197** (76%) (Scheme 40). Compound **198** (49%) and **199** (52%) were the major products in the reactions of **144** with **194** and **195**, although the process was complicated by the formation of side products **200** (24%) and **201** (26%), respectively (Scheme 41). In all other cases studied, analogous side reactions were dominating, rendering isolation of the expected cyclopropanes impossible.[78]



95 **193**, 82% **194**, 78% **195**, 88%

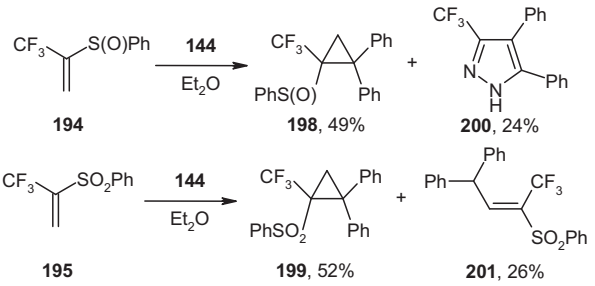
Scheme 39.



193 **143**, R = H **144**, R = Ph **196**, 100%, R = H **197**, 76%, R = Ph

Scheme 40.

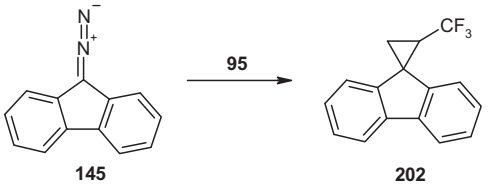
Reaction of 3,3,3-trifluoropropene 95 and diazofluorene **145** was mentioned in the literature. It resulted in the formation of a dibenzospiro[2.4]heptane derivative **202** (Scheme 42).[79]



194 **198**, 49% **200**, 24%

195 **199**, 52% **201**, 26%

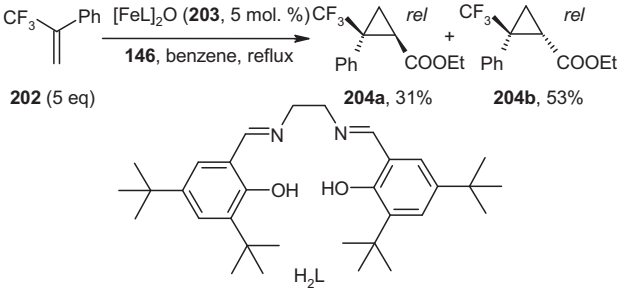
Scheme 41.



145 **202**

Scheme 42.

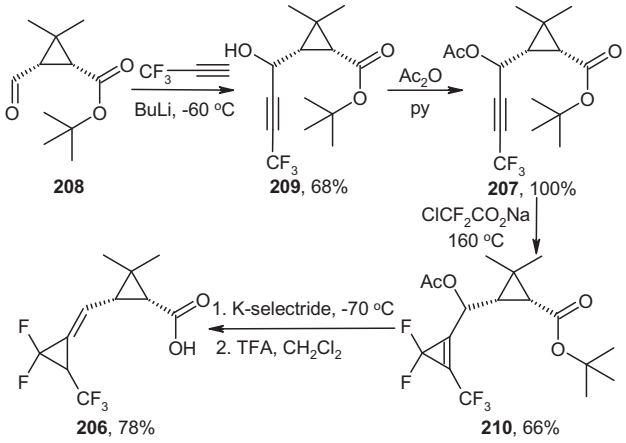
It is appropriate to note that most of the cyclopropanations discussed in this section have included intermediate pyrazoline formation, which were then decomposed either photochemically or by pyrolysis. As already mentioned, this reaction sequence is rather efficient for electron-poor alkenes. On the contrary, metal-catalyzed carbene transfer is an appropriate method in the case of electron-rich substrates; hence, this approach is hardly applicable to trifluoromethyl-substituted alkenes. Nevertheless, a successful example of a metal-catalyzed reaction between ethyl diazoacetate **146** and α-trifluoromethylstyrene **202** has been reported. The reaction was performed in refluxing benzene using a five-fold excess of **202**; an iron-containing complex [Fe(3,3′,5,5′-^{t}Bu$_4$Salen)]$_2$O (**203**, 5 mol %) was used as a catalyst. Cyclopropane **204** was obtained in 84% yield as a mixture of diastereomers **204a** and **204b** (**204a**:**204b**=1:1.7) (Scheme 43). The use of the catalyst significantly improved the outcome of the reaction, as, without **203**, compound **204** was obtained in only 28% yield with no diastereoselectivity.[80]



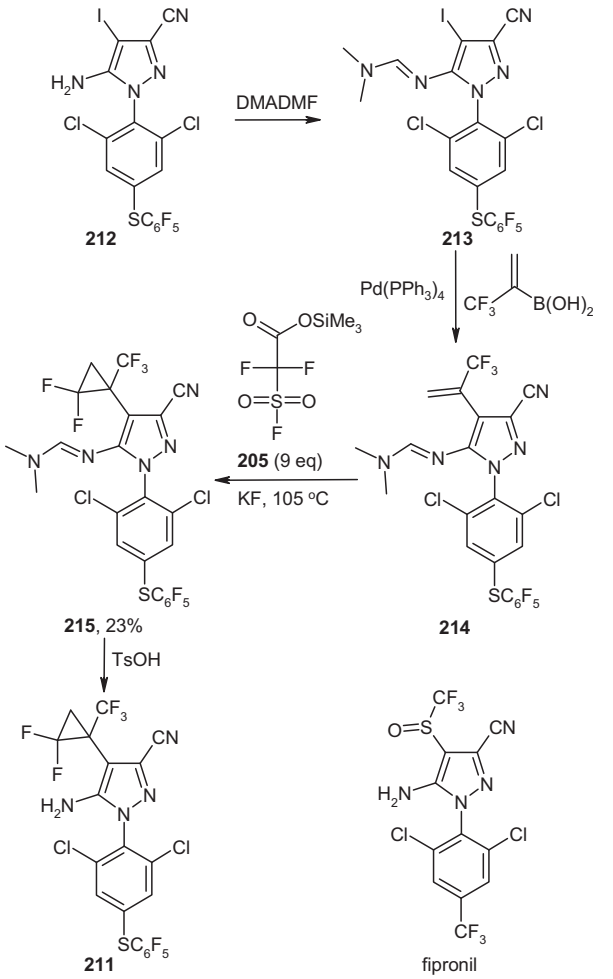
202 (5 eq) **204a**, 31% **204b**, 53%

Scheme 43.

Several sources of difluorocarbene were used for the cyclopropanation of trifluoromethyl-substituted olefins, including difluorotris(trifluoromethyl)phosphorane $(CF_3)_3PF_2$,[81] 2,2,3-trifluoro-3-(trifluoromethyl)oxirane (perfluoropropene oxide),[82] sodium difluorochloroacetate $CF_2ClCOONa$ and Dolbier's reagent (2-(fluorosulfonyl)-2,2-difluoroacetate; TFDA) **205** (see Scheme 45 for the structure of **205**). In particular, sodium difluorochloroacetate was used in the synthesis of a fluorinated pyrethroid **206**. As the key step of the synthetic scheme, alkyne **207** (obtained from aldehyde **208** via **209**) was heated with a 10-fold excess of $CF_2ClCOONa$ in diglyme at 160 °C to yield the cyclopropene derivative **210**, which was subjected to reductive allylic rearrangement followed by *tert*-butyl group removal to afford **206** (Scheme 44).[83]



Scheme 44.



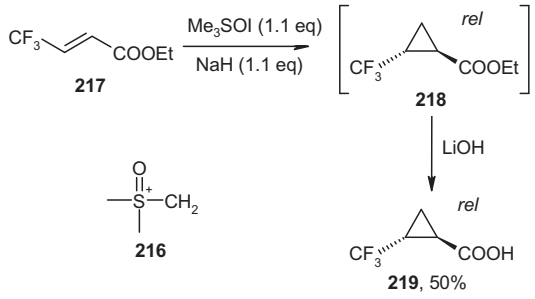
Scheme 45.

Cyclopropanation with the Dolbier reagent **205** was used in the synthesis of a parasiticidal agent **211**, which is an analogue of a broad-spectrum insecticide, fipronil. The synthetic scheme commenced from aminopyrazole **212**, which was subjected to protection of the amino group to afford compound **213**. Suzuki coupling of 213 and 1-(trifluoromethyl)vinylboronic acid led to the formation of trifluoromethyl-substituted alkene **214**. Reaction of **214** with a nine-fold excess of **205** in methyl benzoate in the presence of potassium fluoride (30 mol %) at 105 °C gave cyclopropane **215** in modest (23%) yield. Deprotection of the amino group in **215** allowed the final product **211** to be obtained (Scheme 45).[84]

Only a few reports on the cyclopropanation of trifluoromethyl-substituted alkenes with dichlorocarbene were found in the literature, all of them using trifluoro(trichloromethyl)silane CCl_3SiF_3 as the dichlorocarbene source. The reaction was carried out by heating CCl_3SiF_3 and an olefin (i.e., 3,3,3-trifluoropropene, 1,1,1,4,4,4-hexafluoro-2-butene and hexa-2-butyne) at 140–180 °C. The corresponding trifluoromethyl-substituted cyclopropanes were obtained in 40–85% yields.[81,85,86]

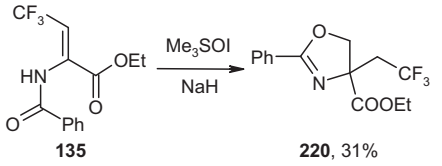
2.2.3. Reactions of trifluoromethyl-substituted alkenes with ylides. The major drawback of the diazoalkanes discussed previously as the most frequently used carbene sources is their potential explosive nature, which comprises a serious limitation to the scale up of the synthetic procedures. Ylides (in particular, sulfur ylides) represent another type of common reagent widely used for the cyclopropanation of electron-poor alkenes. In our opinion, cyclopropanation of trifluoromethyl-substituted alkenes possessing an additional electron-withdrawing group with sulfur ylides has great synthetic potential, which has been scarcely exploited to date.

The trimethylsulfoxonium iodide–sodium hydride system is a common reagent for generation of ylide **216**, which is widely used for the transfer of a methylene fragment to an alkene molecule. This reagent was used for the cyclopropanation of ethyl 4,4,4-trifluorocrotonate **217**. The crude ester **218** obtained was subjected to alkaline hydrolysis to give *trans*-2-trifluoro-1-carboxylic acid **219** (50% over two steps)—a promising low-molecular-weight building block for chemical synthesis and drug discovery (Scheme 46).[87]



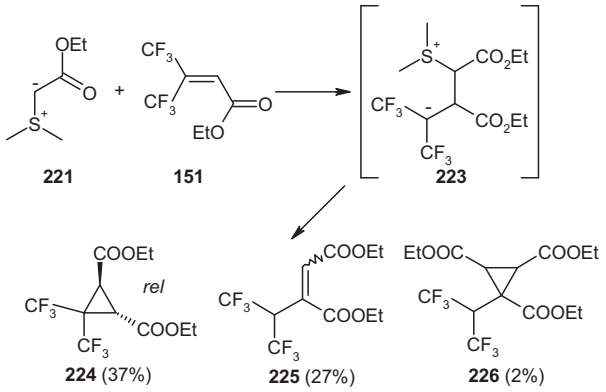
Scheme 46.

The method failed in the case of α,β-dehydro amino ester **135** due to interference from the amide function present in the starting molecule. Compound **135** was transformed into oxazoline derivative **220** in 31% yield upon treatment with trimethylsulfoxonium iodide–sodium hydride (Scheme 47).[74]



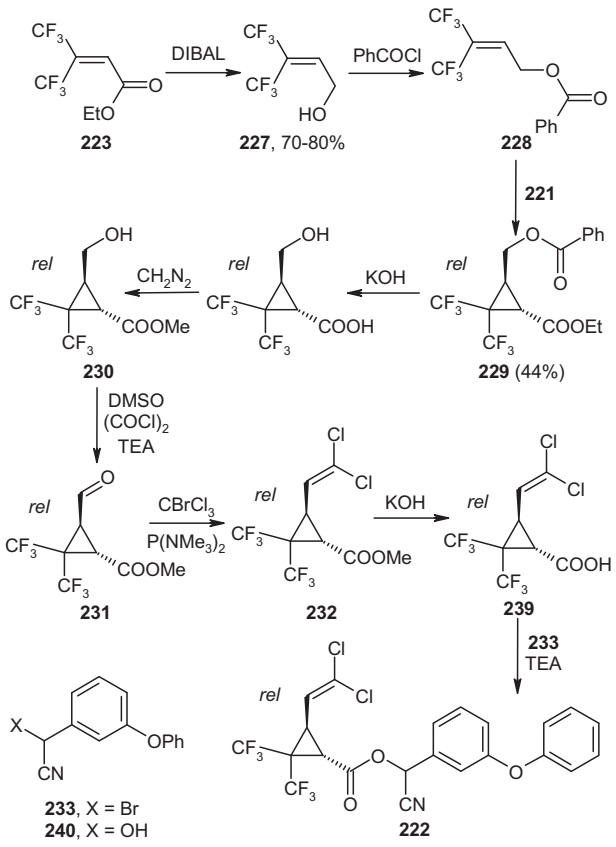
Scheme 47.

(Ethoxycarbonylmethylene)dimethylsulfurane **221** is another example of a sulfur ylide widely used for cyclopropanation of electron-poor alkenes. Compound **221** was involved in several preparations related to pyrethroid chemistry. In particular, hexafluorocypermethrin **222** was prepared in nine steps starting from ethyl hexafluorosenecioate **151**. It was found that reaction of **221** and **223** resulted in the formation of a mixture containing the targeted diester **224** (37%), alkene **225** (27%), and cyclopropropane **226** (2%) (Scheme 48). To avoid these side reactions, compound **223** was



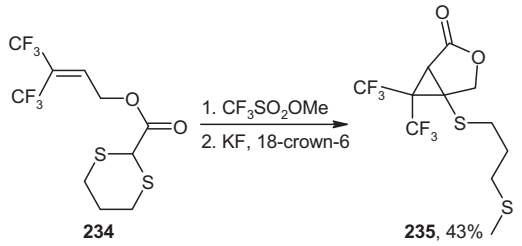
Scheme 48.

converted into alcohol **227**, which was benzoylated to give **228**. Cyclopropanation of alkene **228** resulted in the formation of *trans*-cyclopropane **229** in 44% yield as the only isolated product. Compound **229** was subjected to alkaline hydrolysis followed by esterification with diazomethane to yield hydroxy ester **230**. Swern oxidation of **230** led to the formation of aldehyde **231**, which was transformed into dichloride **232**. Hydrolysis followed by alkylation with **233** allowed hexafluorocypermethrin **222** to be obtained (Scheme 49).[88]



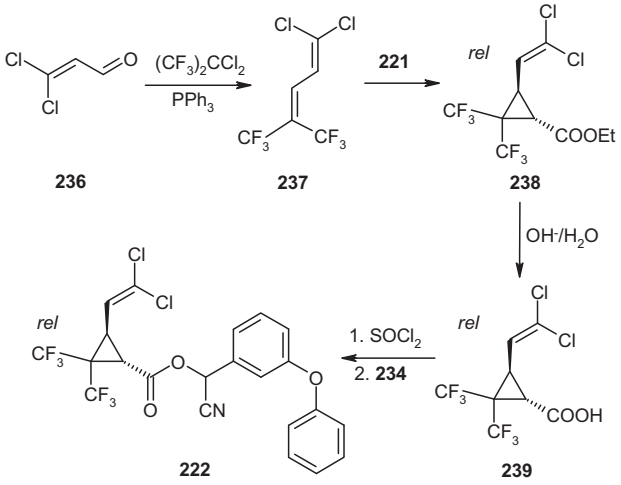
Scheme 49.

For the synthesis of the cis-isomer of **222**, several attempts were made to achieve intramolecular cyclopropanation leading to construction of the 3-oxabicyclo[3.1.0]hexane core. In particular, *S*-methylation of ester **234** with methyl triflate followed by cyclization (KF, 18-crown-6) resulted in dithiane ring opening leading to the formation of cyclopropane **235** in 43% yield (Scheme 50); however, further transformations of **235** into cis-substituted analogues of **222** appeared to be unfruitful.[88]



Scheme 50.

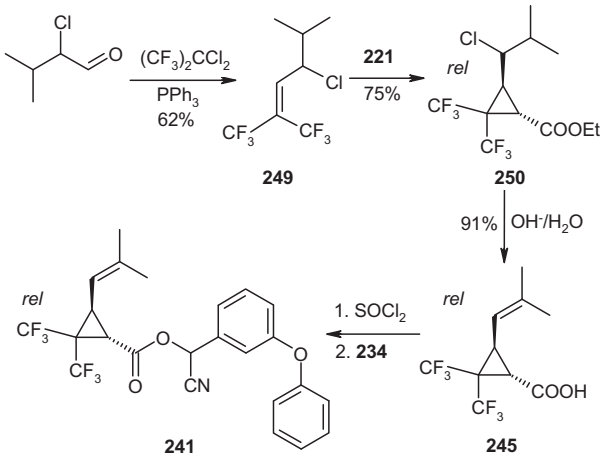
An alternative approach to the synthesis of **222** was reported. The synthesis commenced from 3,3-dichloroacrolein **236**, which was subjected to Wittig-type olefination to afford bis(trifluoromethyl)-substituted alkene **237**. It is appropriate to note that 3,3-dimethylacrolein failed to form the corresponding diene in the first step of these transformations. Reaction of **237** and ylide **221** afforded cyclopropane **238** with high diastereoselectivity. Pyrethroid **222** was obtained from **238** by a standard transformation sequence including hydrolysis giving carboxylic acid **239**, chloroanhydride formation and esterification using alcohol **240** (Scheme 51).[89,90]



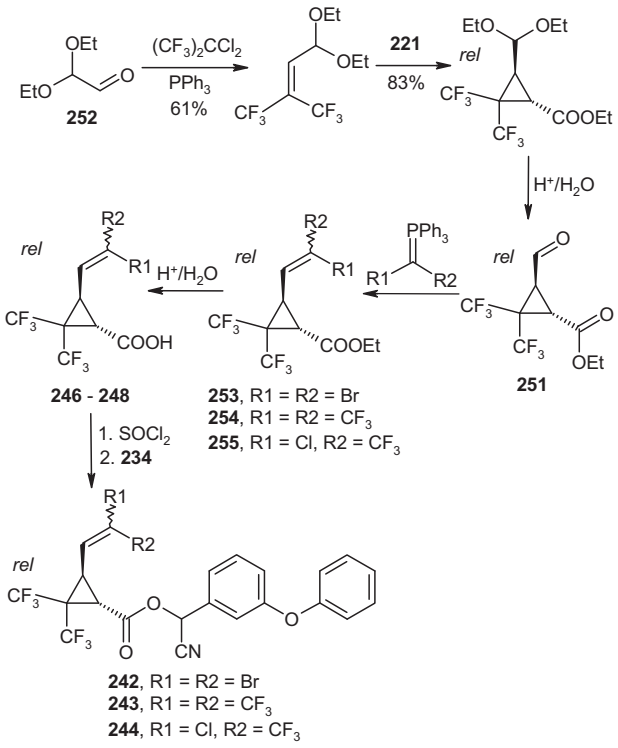
Scheme 51.

Analogously, pyrethroids **241**–**244** (including hexafluorodecamethrin **242**) were prepared by esterification of carboxylic acids **245**–**248**. Compound **245** was prepared starting from 2-chloroisovaleraldehyde, which was olefinated to give the alkene **249**. Cyclopropanation of **249** afforded cyclopropane derivative **250**. Alkaline hydrolysis of the ester moiety in the molecule of **250** was accompanied by elimination, resulting in the direct formation of **245** (Scheme 52). Carboxylic acids **246**–**248** were prepared via a common alhedyde intermediate **251**. Synthesis of **251** included olefination of 1,1-diethoxy **252** followed by cyclopropanation with **221** and subsequent carbonyl-group deprotection. Aldehyde **251** reacted with the corresponding phosphorus ylides to give the olefination products **253**–**255** (in 42–84% yields), which were converted into the carboxylic acids **246**–**248** upon acidic hydrolysis (Scheme 53).[89,90]

Synthesis of pyrethroid esters possessing a cis-configuration at the cyclopropane fragment has also been reported. The key intermediates in their preparations were lactones **256** and **257**. In the synthesis of **256**, aldehyde **258** was transformed into cyclopropane **259** in two steps by the method described above. After hydrolysis of the compound **259**, the corresponding ester **260** underwent epimerization followed by lactonization to yield **256**. Further transformations of **256** included lactone ring opening and elimination leading to the formation of ester **261** (Scheme 54).[90,91]



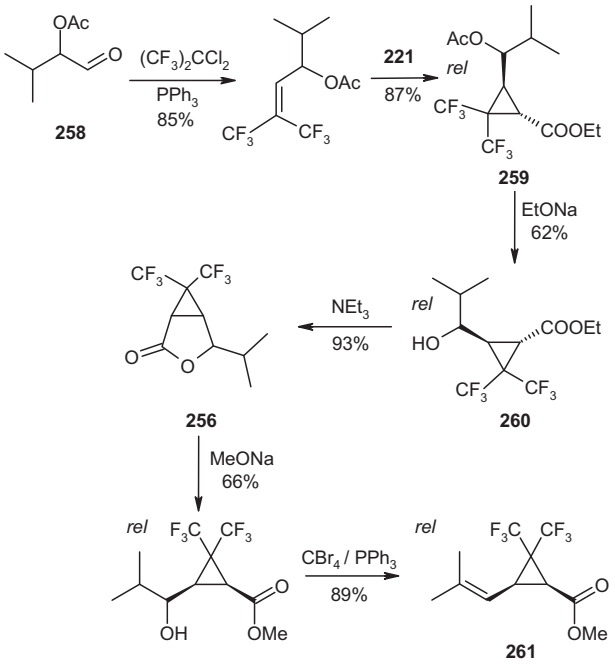
Scheme 52.



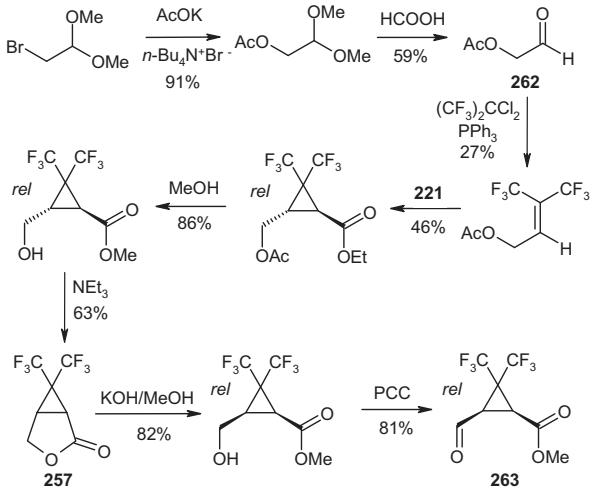
Scheme 53.

Lactone **257** was prepared starting from aldehyde **262** using an analogous scheme. Compound **257** was transformed into aldehyde **263** (Scheme 55), which was used as a convenient precursor to several pyrethroid esters possessing the cis-configuration.[91]

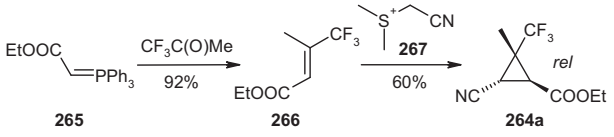
A related methodology was used for the preparation of monotrifluoromethyl-substituted pyrethroid precursors possessing both cis- and trans-configuration at the cyclopropane ring. For the synthesis of the trans-isomer **264a**, phosphorane **265** and 1,1,1-trifluroacetone reacted to give the alkene **266**, which was then cyclopropanated with **267** (Scheme 56). In the synthesis of cis-isomer **264b**, compounds **268** and **221** were used at the corresponding steps. Cyclopropanation of **269** was the key step in this case (Scheme 57). It should be noted that good stereoselectivities at the cyclopropanation steps were observed (88% and 75% of the major isomer for **264a** and **264b**, respectively). Compound **264b** was transformed into aldehyde **270**, which was applied to the synthesis of pyrethroids.[92]



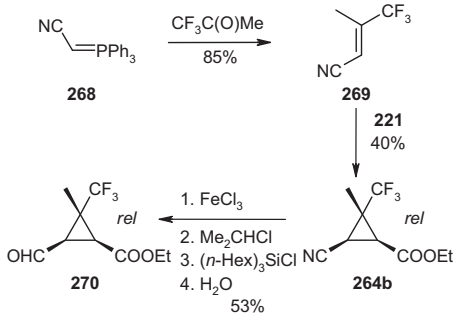
Scheme 54.



Scheme 55.

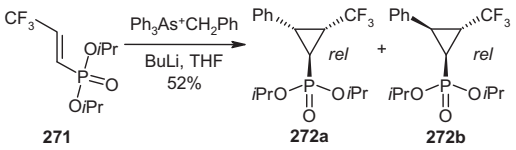


Scheme 56.



Scheme 57.

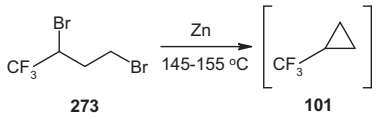
Cyclopropanation of trifluoromethyl-substituted alkenes using arsenic ylides has also been reported. In particular, reaction of phosphonate **271**, benzyltriphenylarsenium salt and *n*-butyllithium led to the formation of diastereomers **272a**,**b** (de 56%) in 52% total yield (Scheme 58).[93]



Scheme 58.

3. Intramolecular cyclizations

The idea of using the intramolecular cyclizations of appropriate 1,3-bifunctional substrates for the construction of trifluoromethyl-substituted cyclopropanes is rather old. One of the early reports described the attempted Freund reaction of dibromide **273** (Scheme 59). However, the product **101** was obtained in such a poor yield that purification was impossible.[69]

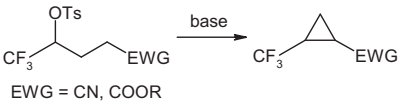


Scheme 59.

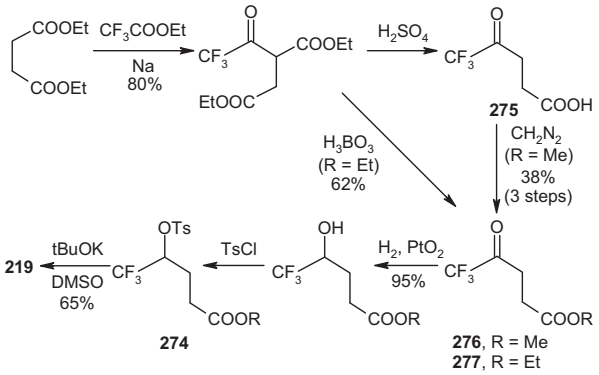
Nevertheless, nucleophilic intramolecular cyclizations appeared to be very efficient with stabilized γ-substituted carbon nucleophiles, such as enolates. These intermediates were generated either by deprotonation of the corresponding 1,3-bifunctional substrates or by Michael addition of the carbon nucleophiles to trifluoromethyl-substituted alkenes. Apart from these two types of nucleophilic cyclizations, other methods were also developed including intramolecular SET-induced reactions of non-activated olefins with CH-acids or addition of alkenes to tricarbonyl(vinylketene)iron(0) complexes. All of these transformations are discussed in the following sections. It should be noted that cyclopropanation of trifluoromethyl-substituted alkenes with ylides described in the previous section can also be considered as tandem Michael addition—nucleophilic cyclization.

3.1. Nucleophilic cyclizations of 1,3-bifunctional substrates

With few exceptions, all of the reactions discussed in this section can be represented as shown in Scheme 60, e.g., the first synthesis of 2-trifluoromethylcyclopropane-1-carboxylic acid **219** included base-induced cyclization of tosylate **274** (Scheme 61). The initial scheme for the synthesis of **274** included isolation of the free 5,5,5-trifluorolevulinic acid **275**, which was then subjected to esterification to give an ester **276** in 38% overall yield.[94] A modified procedure for the decarboxylation of the intermediate diester gave the monoester **277** in one step (62% yield).[95] Both esters were transformed to the corresponding tosylates **274**, which smoothly underwent cyclization into **219** upon treatment with potassium *tert*-butoxide in dimethylsulfoxide.

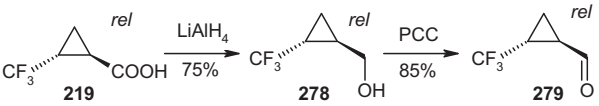


Scheme 60.



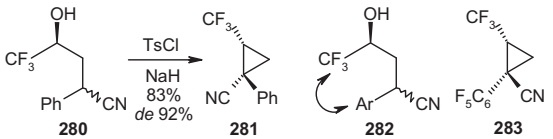
Scheme 61.

Compound **219** was the key intermediate in the synthesis of some other important trifluoromethyl-substituted building blocks of low-molecular-weight, e.g., alcohol **278**, aldehyde **279** and other compounds (Scheme 62).[94,95]



Scheme 62.

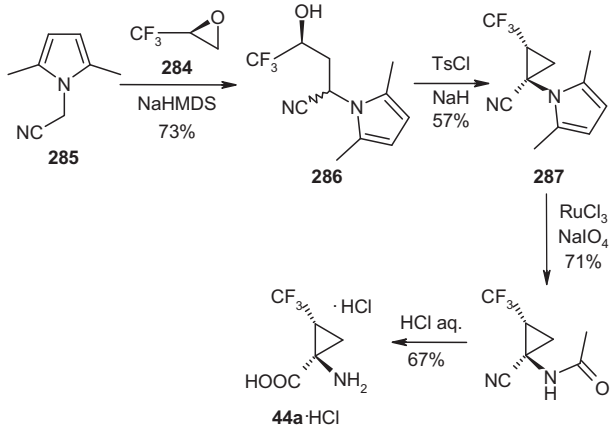
Cyclization of 4-cyano-4-phenyl-1,1,1-trifluoro-2-butanol **280** has been studied thoroughly. Under the optimized conditions (tosyl chloride (1.2 equiv), sodium hydride (4 equiv), THF, −20 °C), cyclopropane **281** was obtained in good yield (83%) and with excellent diastereoselectivity (de 92%). The method was efficient also for other alcohols of general formula **282**.[96] The corresponding cyclopropanes were obtained in good yields and with moderate-to-good diastereoselectivities. It was found that there was a linear correlation between the logarithms of the ratio of the two diastereomeric products and an estimated effective charge on the two *ortho* carbons of the aryl substituent. Therefore, the diastereoselectivity was controlled by intramolecular electrostatic repulsions between the local negative charge on the trifluoromethyl group and that on the aryl moiety. It is interesting to note that the opposite diastereoselectivity was observed when Ar=C_6F_5; cyclopropane **283** was found to be the major product in this case (Scheme 63).[97]



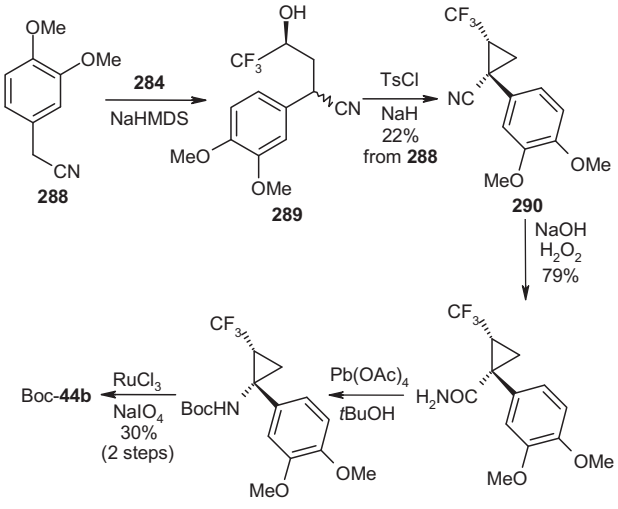
Scheme 63.

The utility of the method was demonstrated by elegant syntheses of optically pure *trans*- and *cis*-trifluoronorcoronamic acids **44a** and **44b**. Both compounds were obtained starting from the chiral epoxide **284** (75% ee). In the synthesis of **44a**, **284** reacted with nitrile **285** to give hydroxynitrile **286** with ca. 30% de, which was subjected to cyclization as described above to afford the cyclopropane **287** with 75% ee. After recrystallization, compound **287** was obtained in optically pure form (>99% de, >99% ee). Oxidation of the pyrrole ring in **287** followed by hydrolysis afforded the *trans*-isomer **44a** (Scheme 64). To obtain **44b**, **284** was

subjected to the reaction with nitrile **288**. Cyclization of the product **289** followed by recrystallization afforded the optically pure cyclopropane **290**. Further transformations of **290** included partial hydrolysis, modified Hoffmann rearrangement and oxidation of the aromatic ring (Scheme 65).[98]

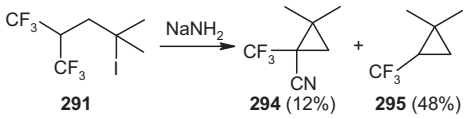


Scheme 64.

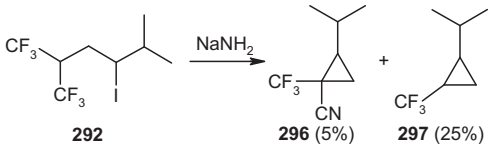


Scheme 65.

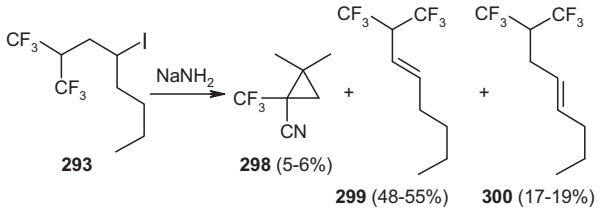
An unusual reaction resulting in the transformation of a trifluoromethyl group to nitrile occurred upon treatment of iodides **291**–**293** with sodium amide. In all three cases, no expected bis(trifluoromethyl)-substituted cyclopropanes were formed. Mixtures of cyclopropanes **294**/**295** and **296**/**297** were obtained from **291** to **292**, respectively (Schemes 66 and 67), whereas an analogous reaction of **293** afforded a mixture of cyclopropane **298** and alkenes **299** and **300** (Scheme 68). The mechanism proposed by the authors included intermediate formation of trifluoromethyl-substituted nitriles of general formula **301** (Scheme 69).[99]



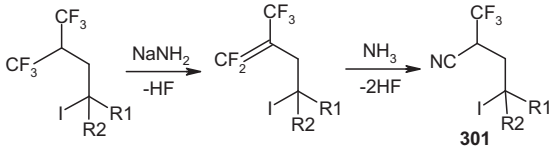
Scheme 66.



Scheme 67.



Scheme 68.

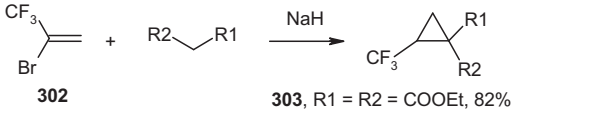


Scheme 69.

3.2. Tandem Michael additions—nucleophilic cyclizations

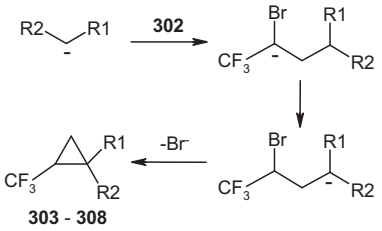
In the reactions discussed in the previous section, the stabilized carbanions nessessary for the formation of trifluoromethyl-substituted cyclopropanes were generated by deprotonation of appropriate 1,3-bifunctional substrates. Another common method for generation of carbanions includes Michael addition of carbon nucleophiles to electron-poor alkenes. Due to the electron-withdrawing properties of the trifluoromethyl group, trifluoromethyl-substituted alkenes are good Michael acceptors, especially if additional electron-withdrawing groups are present in their molecules. As mentioned above, cyclopropanation of trifluoromethyl-substituted alkenes with ylides described in the previous section represents an example of this transformation; some other tandem reactions of this type are now discussed.

In particular, the reaction of anions generated from methylene-active compounds with 2-bromo-3,3,3-trifluoropropene **302** resulted in the formation of cyclopropanes **303**–**308**. These products were obtained in good yields (80–90%); the reaction was somewhat sluggish only in the case of benzoylacetonitrile as the starting compound (Schemes 70 and 71). The method was used for the synthesis of (±)-*trans*-trifluoronorcoronamic acid **44a**. To achieve this, diester **303** was subjected to selective hydrolysis followed by Curtius rearrangement and deprotection (Scheme 72).[100]

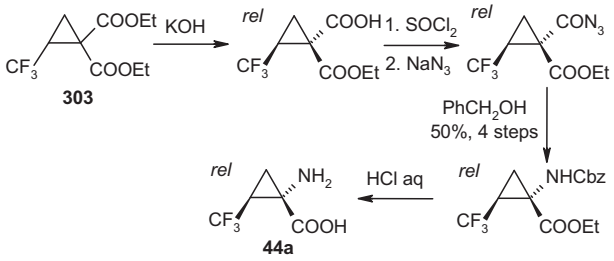


303, R1 = R2 = COOEt, 82%
304, R1 = R2 = CN, 83%
305, R1 = CN, R2 = COOEt, 80%
306, R1 = COOMe, R2 = SO_2Ph, 91%
307, R1 = CN, R2 = SO_2Ph, 90%
308, R1 = CN, R2 = COPh, 60%

Scheme 70.

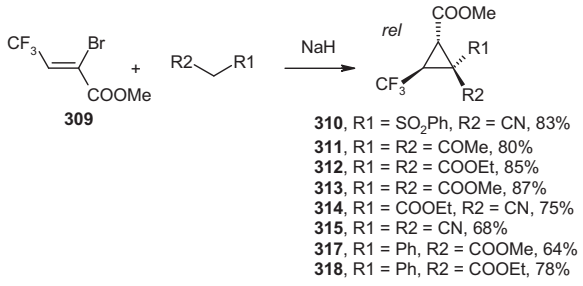


Scheme 71.

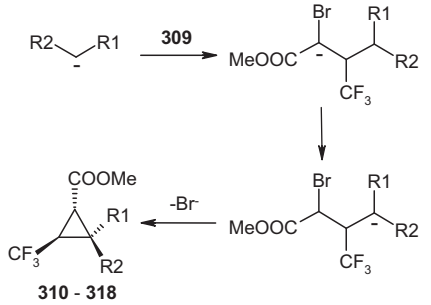


Scheme 72.

Analogously, the reaction of anions generated from methylene-active compounds with methyl (*Z*)-2-bromo-3,3,3-trifluoro-2-butenoate **309** afforded cyclopropanes. It is interesting to note that the generation of all stereocenters in the molecules of **310**–**318** proceeded in a stereospecific manner (Schemes 73 and 74).[101]

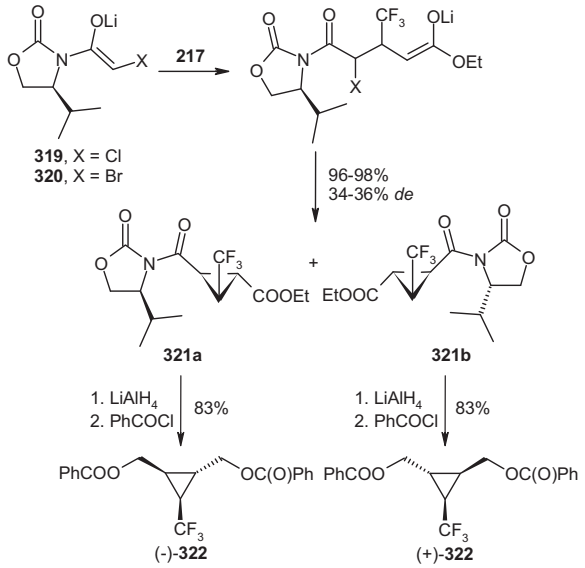


Scheme 73.



Scheme 74.

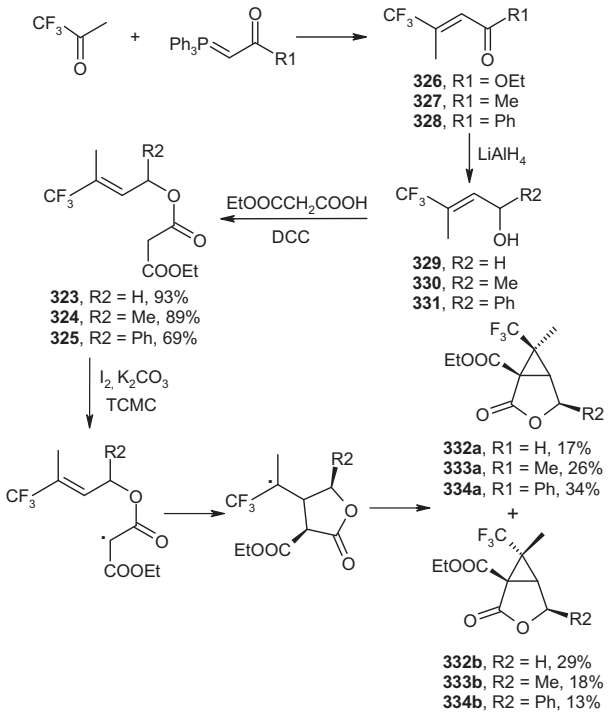
Reaction of ethyl 4,4,4-trifluorocrotonate **217** and oxazolidinones **319**–**320** resulted in the formation of a mixture of diastereomers **321a**,**b**. After separation and removal of the oxazolidinone moieties, the corresponding optically pure diols were isolated as the benzoyl derivatives, (+)- and (−)-**322** (Scheme 75). In this case, moderate asymmetric induction was observed at the cyclopropane formation step (de 34–36%); cyclopropanes **322** were obtained with high diastereo- but low enantioselectivity.[102]



Scheme 75.

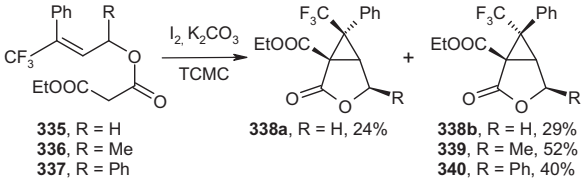
3.3. Electrophilic and SET-induced cyclizations

Electrophilic and radical cyclizations that lead to trifluoromethyl-substituted cyclopropanes are relatively rare. In particular, cyclization of malonic acid derivatives **323**–**325** upon treatment with iodine, potassium carbonate, and a phase-transfer catalyst is believed to be induced by single-electron transfer (SET). The reactions resulted in the formation of lactones **332a**,**b**–**334a**,**b** in 69–93% yields. The starting compounds **323**–**325** were obtained from 1,1,1-trifluoroacetone in three steps via the intermediates **326**–**328** and **329**–**331**, respectively. Moderate stereoselectivities were observed in the cyclization reactions (Scheme 76).[103]



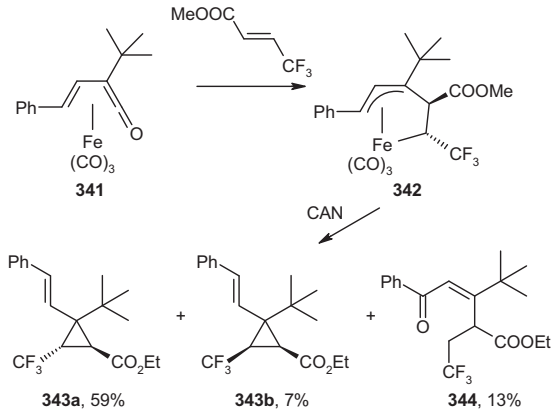
Scheme 76. (TCMC—tricaprylmethylammonium chloride).

Analogous reactions of the compounds **335**–**337** also resulted in the formation of the corresponding lactones **338**–**340**. Whereas compound **338** was obtained as an almost equimolar mixture of diastereomers, formation of **339** and **340** proceeded in a stereoselective manner (Scheme 77).[104,105] Steric factors were supposed to determine the stereochemistry of the reaction in the case of the compounds **332**–**334** and **338**–**340**.[103,104]



Scheme 77.

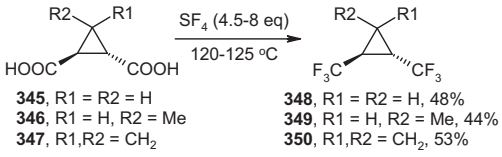
Reaction of a tricarbonyl(ketene)iron(0) complex **341** with ethyl 4,4,4-trifluorocrotonate yielded the air-stable adduct **342** in 57% yield. Oxidation of the complex **342** with an excess of cerium ammonium nitrate (CAN) resulted in the formation of a mixture of cyclopropanes **343a**,**b** and by-product **344** (Scheme 78).[106,107] The mechanism of the cyclopropane formation is unclear; either electrophilic or radical nature of the cyclization can be assumed.



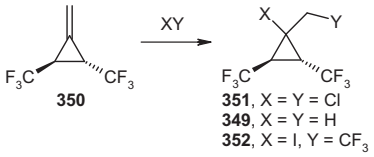
Scheme 78.

4. Fluorination of cyclopropanecarboxylic acids

All the methods for the synthesis of trifluoromethyl-substituted cyclopropanes described so far have relied on using starting compounds already containing a trifluoromethyl group. A completely different approach includes transformations of the functionalized compounds that already contain a cyclopropane ring in their molecules. The carboxylic group is a common equivalent of a trifluoromethyl moiety; trifluoromethylation of the carboxylic acids can be achieved by a number of reagents, sulfur tetrafluoride being one of the most often used.[108] Obviously, the reaction of cyclopropanecarboxylic acids with SF_4 would yield trifluoromethyl-substituted cyclopropanes. Nevertheless, the parent cyclopropanecarboxylic acid showed low reactivity in the reaction with SF_4; trifluoromethylcyclopropane **101** was obtained only in the presence of excess HF.[109] Trifluoromethylation with SF_4 was much more effective in the case of cyclopropanecarboxylic acids containing additional electron-withdrawing groups in their molecules. In particular, cyclopropanedicarboxylic acids **345**–**347** reacted with 4.5–8 equiv of sulfur tetrafluoride at 120–125 °C for 4.5–6 h to give the corresponding bis(trifluoromethyl)-substituted cyclopropanes **348**–**350** in 44–53% yield (Scheme 79). It is interesting to note that compound 350 reacted at the exocyclic double bond without opening the cyclopropane ring; in these transformations, bis(trifluoromethyl)-substituted cyclopropanes **349**, **351**, and **352** were obtained (Scheme 80).[110]

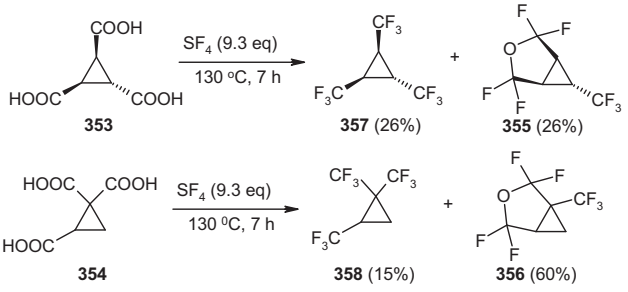


Scheme 79.



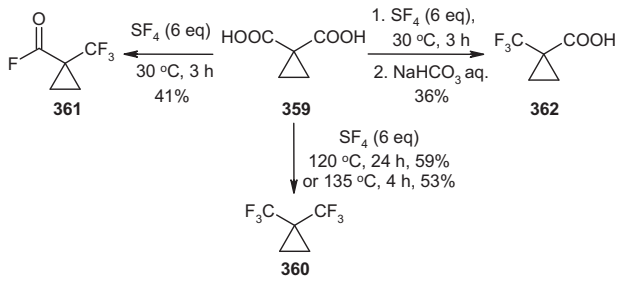
Scheme 80.

Analogous reactions of SF_4 with cyclopropanetricarboxylic acids **353** and **354** were complicated by the formation of the oxabicyclo[3.1.0]hexane derivarives **355** and **356**. The corresponding tris(trifluoromethyl)cyclopropanes **357** and **358** were obtained in low yields (26 and 15%, respectively, Scheme 81).[110]



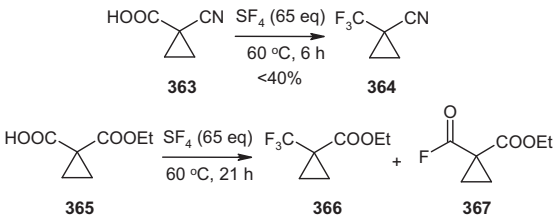
Scheme 81.

Under similar conditions (SF_4 (6 equiv), 120 °C, 24 h or 135 °C, 4 h), cyclopropane-1,1-dicarboxylic acid **359** was transformed into 1,1-bis(trifluoromethyl)cyclopropane **360** in 53–59% yield.[110,111] However, reaction of **359** and SF_4 (6 equiv) at 30 °C for 3 h led to the formation of the acyl fluoride **361**, which was isolated in 41% yield by distillation. If the crude reaction mixture obtained under these conditions was quenched with aqueous $NaHCO_3$ upon heating, 1-(trifluoromethyl)-1-cyclopropanecarboxylic acid **362** was obtained in 36% yield after the work-up (Scheme 82).[111]



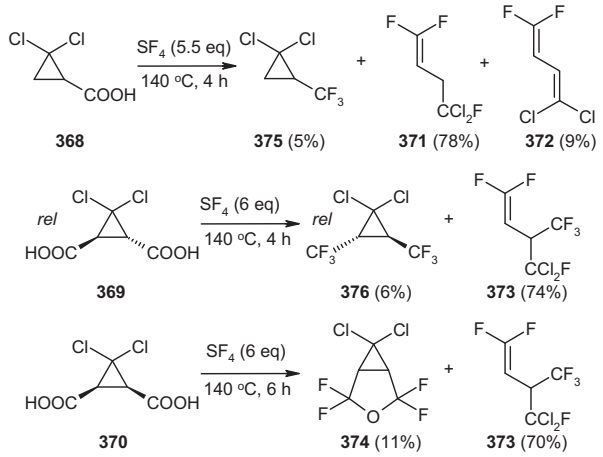
Scheme 82.

Fluorination of **363** (SF_4 (65 equiv), 60 °C, 4 h) allowed nitrile **364** to be obtained in less than 40% yield. Monoester **365** appeared to be less reactive: even after prolonged reaction time (21 h), a mixture of the targeted trifluoromethyl-substituted cyclopropane **366** and the intermediate acyl fluoride **367** was obtained (ca. 1.2:1 ratio) (Scheme 83).[112]



Scheme 83.

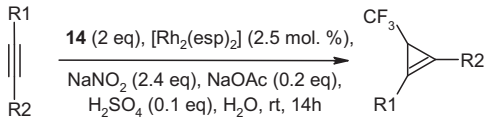
Trifluoromethylation of *gem*-dichloro-substituted cyclopropanecarboxylic acids **368**–**370** was found to be ineffective for the synthesis of trifluoromethyl-substituted cyclopropanes. The major products **371**–**374** of the reaction were formed by three-membered ring opening; the targeted cyclopropanes **375** and **376** were obtained from **368** to **369** only in 5–6% yields (Scheme 84).[113]



Scheme 84.

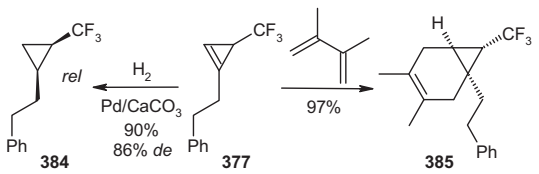
5. Conclusions and outlook

A number of methods are available for the synthesis of trifluoromethyl-substituted cyclopropanes. More classical approaches include the transformations of substrates that already contain a trifluoromethyl group (cyclopropanation of trifluoromethyl-substituted alkenes, intramolecular cyclizations); a limited availability of the starting materials can be considered to be a major drawback of these methods. Another methodology, which has gained momentum in the last two decades relies on using trifluoromethylating reagents, such as 2,2,2-trifluorodiazoethane or sulfur tetrafluoride. These methods (i.e., cyclopropanation with trifluoromethyl-substituted carbene reagents as well as fluorination of cyclopropanecarboxylic acids) can in principle be extended to a large range of the substrates. Some very recent publications can be considered as a proof of this. In particular, rhodium-catalyzed cyclopropenation of alkynes in aqueous media was reported, using a method analogous to that described for the cyclopropanation of alkenes (see Scheme 12). Trifluoromethyl-substituted cyclopropenes **377**–**383** (Scheme 85) obtained in these reactions are versatile intermediates, which can be transformed into various trifluoromethyl-substituted cyclopropanes. In particular, hydrogenation of **378** afforded *cis*-disubstituted cyclopropane **385** in 90% yield (86% de). Therefore, the alkyne cyclopropanation–hydrogenation sequence can be considered as complementary to the cyclopropanation of monosubstituted alkenes, which results in the formation of trans-isomers. Another interesting transformation of **378** is the Diels–Alder reaction with 2,3-dimethylbutadiene, which led to the formation of the bicyclic adduct **386** in 97% yield (Scheme 86).[114]



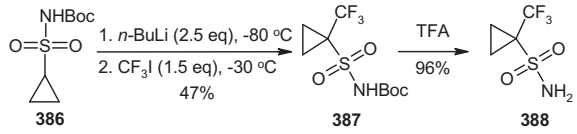
377, R1 = H, R2 = CH_2CH_2Ph, 78%
378, R1 = H, R2 = *n*-C_9H_{19}, 71%
379, R1 = H, R2 = $CH_2CH_2OCH_2Ph$, 71%
380, R1 = Me, R2 = CH_2CH_2Ph, 70%
381, R1 = Me, R2 = Ph, 67%
382, R1 = H, R2 = $CH_2CH(Me)OTBS$, 69%
383, R1 = H, R2 = CH2CH(*i*Pr)OTBS, 73%

Scheme 85. (esp—α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate).



Scheme 86.

In another recent publication, a method for the direct trifluoromethylation of functionalized cyclopropanes, which is completely different from the previous approach was disclosed. In this method, iodotrifluoromethane was used as a source of the trifluoromethyl group. Reaction of CF_3I with the dianion generated from compound **386** resulted in the formation of trifluoromethyl-substituted cyclopropane **387** in 47% yield; after deprotection, sulfamide **388** was obtained (Scheme 87).[115]



Scheme 87.

The variety of methods available for their synthesis resulted in the development of many low-molecular-weight trifluoromethyl-substituted cyclopropane building blocks. In conclusion of this review, we would like to outline some of these building blocks, which in our opinion, can be especially interesting for the needs of medicinal and agricultural chemistry. The following classes of building blocks are represented in Fig. 5: carboxylic acids (**219**,[87,94,95] **362**,[111] **389**,[116] and **390**[113]), alcohols (**278**[94,95] and **391**,[117] and **392**[116]), aldehydes (**279**[94,95]), amines (**393**[24,118] and **394**[118]), nitriles (**365**[112] and **395**[95]), boronates (**26**[43,44]), alkyl halogenides (**396**[94]), alkenes (**19a**,**b**[41]), and amino acids (**44a**,**b**[45,48,74,98,100] and **74a**,**b**[63]).

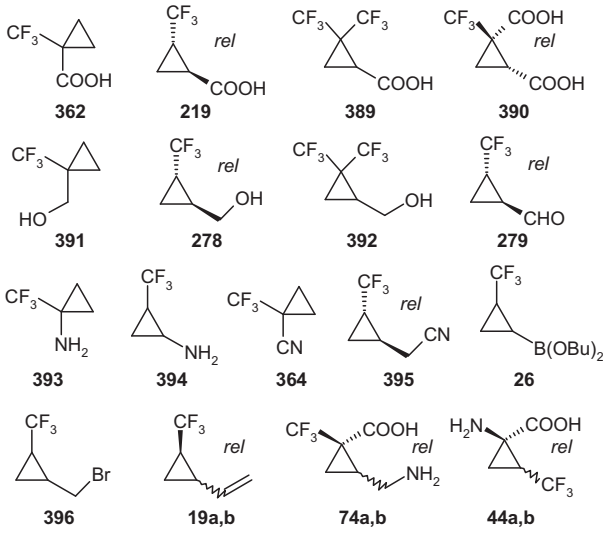


Fig. 5. Low-molecular-weight trifluoromethyl-substituted cyclopropane building blocks.

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Biographical sketch

Oleksandr Grygorenko was born in Brody, Lviv region, Ukraine in 1982. He received MS in chemistry (2004) and Ph.D. in organic chemistry (2007) from Kyiv National Taras Shevchenko University under supervision of Prof. Dr. Sci. Igov V. Komarov. A short post-doctoral fellowship at University of Zaragoza, Spain by Prof. Carlos Cativiela (INTAS YSF) followed in 2008. At present, Oleksandr divides his time between Kyiv National Taras Shevchenko University as an Assistant Professor, and Enamine Ltd. (Kyiv, Ukraine) as a Principal Scientist. His scientific interests include modern methods in organic synthesis, molecular rigidity concept, chemistry of amino acids, diamines, and related compounds, bioorganic and medicinal chemistry. He is a co-author of 16 papers.

Igor Komarov obtained his Ph.D. degree in 1991 in Organic Chemistry at Kyiv National Taras Shevchenko University under supervision of Prof. Mikhail Yu. Kornilov. Two post-doctoral fellowships followed: at the University Chemical Laboratory (Cambridge, UK) by Prof. Anthony J. Kirby FRS (NATO Post-doctoral Fellowship Award), and at the Institut für Organische Katalyseforschung (Rostock, Germany) by Prof. Armin Börner (Alexander von Humboldt Fellowship Award). He joined Organic Chemistry Department of Kyiv National Taras Shevchenko University in 1997 as an Assistant Professor and has been working there since then, holding presently positions of a Professor at the Organic Chemistry Department and Vice-Director of Institute of High Technologies. Igor Komarov received the Doctor of Science Degree in 2003 for the work on synthesis of model molecules to solve problems in stereochemistry, physical organic chemistry, and catalysis. The research work of Igor V. Komarov and his scientific group is directed to study molecular rigidity and its use in diverse areas of science—medicinal chemistry, bioorganic chemistry, stereochemistry, theoretical chemistry, and catalysis. Synthesis of model molecules, unusual amino acids, including fluorine-substituted and peptides from them, conformationally restricted diamines and other building blocks for drug design are within Igor Komarov's interests. Special effort is put in Igor's group to develop new synthetic approaches towards strained and polycyclic compounds.

Oleksiy Artamonov was born in Smila, Cherkasy region, Ukraine in 1986. He received BS (2007) and MS (2008) in chemistry from Kyiv National Taras Shevchenko University under supervision of Prof. Dr. Sci. Igov V. Komarov. At present, Oleksiy is a Synthetic Chemist at Enamine Ltd. (Kyiv, Ukraine). He also works towards his Ph.D. in organic chemistry on trifluoromethyl-substituted cyclopropanes at Kyiv National Taras Shevchenko University.

Pavel Mykhailiuk was born in Kerch, Ukraine in 1984. In 2005 he received his Ph.D. at the Technical University of Karlsruhe (Germany) after working with Prof. Anne Ulrich. Thereafter, he joined the Kyiv National Taras Shevchenko University (Ukraine), where he obtained his Ph.D. in Chemistry under the supervision of Prof. Igor Komarov. Currently, he is an Assistant Professor at this University. Since 2009 he is also the Head of Custom Synthesis Department at Enamine Ltd. (Kyiv, Ukraine). His current research activities include the synthesis of novel fluorine-containing compounds, conformationally restricted compounds, amino acids, and peptides. He is a co-author of 25 papers.