CF$_3$-substituted carbocations: underexploited intermediates with great potential in modern synthetic chemistry

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Abstract

“The extraordinary instability of such an “ion” accounts for many of the peculiarities of organic reactions” – Franck C. Whitmore (1932). This statement from Whitmore came in a period where carbocations began to be considered as intermediates in reactions. Ninety years later, pointing at the strong knowledge acquired from the contributions of famous organic chemists, carbocations are very well known reaction intermediates. Among them, destabilized carbocations – carbocations substituted with electron-withdrawing groups – are, however, still predestined to be transient species and sometimes considered as exotic ones. Among them, the CF$_3$-substituted carbocations, frequently suggested to be involved in synthetic transformations but rarely considered as affordable intermediates for synthetic purposes, have long been investigated. This review highlights recent and past reports focusing on their study and potential in modern synthetic transformations.

Introduction

Carbocations are pivotal intermediates in organic chemistry, and carbocation-based synthetic chemistry continues to be a vital part of industrial and academic chemistry [1]. A countless number of carbocations have been generated and studied [2,3], and many famous organic chemists strongly participated in their development. Carbocations that are especially intriguing are the destabilized ones that have been elegantly reviewed over the past years by Gassman, Tidwell, and Creary [4-6]. The so-called electron-deficient carbocations, i.e., carbocations substituted with electron-withdrawing groups, drive original reactions, and the most important one among these cations is probably the α-(trifluoromethyl) carbocation. Many efforts are currently devoted to develop methods allowing the efficient insertion of fluorine atoms or fluorinated groups into organic
molecules [7-12]. The increasing demand for fluorinated scaffolds, due to the striking beneficial effects generally resulting from the introduction of these fluorinated motifs [13], also participated in this development. These fluorine effects are nowadays remarkably established in many domains, including medicinal, organic, and organometallic chemistry, catalysis, chemical biology, and material sciences [14-17]. In this context, deciphering the impact that can be exerted by the trifluoromethyl group on a cation and the associated consequences when facing the challenge of developing innovative synthetic methods are the subjects of this review.

Review
Quantitative parameters accounting for the electron-donating or -withdrawing ability of substituents are of major importance in synthetic organic chemistry. The Hammett constant $\sigma$ for a variety of substituents [18,19] and improved values, known as $\sigma^*$, furnished by Brown et al. [20,21] – some of which are listed in Table 1 for selected substituents – were developed towards this aim. Following this classification, the CF$_3$ group is amongst the most electron-withdrawing substituents, with a $\sigma^*$ value of +0.612 for the para-position.

Table 1: Selection of Hammett constant $\sigma^*$ values for selected functional groups X, extracted from References [20,21].

| X     | $\sigma^*$ | meta | para |
|-------|------------|------|------|
| NMe$_2$ | n.d.      | -1.7 |      |
| NH$_2$   | -0.16      | -1.3 |      |
| OH       | +0.12$^a$  | -0.92|      |
| OMe      | +0.047     | -0.778|     |
| CH$_3$   | -0.066     | -0.311|     |
| SiMe$_3$ | +0.011     | +0.021|     |
| Ph       | +0.109     | -0.179|     |
| H        | 0          | 0    |      |
| SMe      | +0.158     | -0.604|     |
| F        | +0.352     | -0.073|     |
| Cl       | +0.399     | +0.114|     |
| Br       | +0.405     | +0.150|     |
| I        | +0.359     | +0.135|     |
| NMe$_3^+$ | +0.359     | +0.408|     |
| CO$_2$Et  | +0.366     | +0.482|     |
| C(O)Me   | +0.38$^a$  | +0.50$^a$| |
| CF$_3$   | +0.52      | +0.612|     |
| CN       | +0.562     | +0.659|     |
| NO$_2$   | +0.674     | +0.790|     |

However, as noted by Reynolds et al. [22,23], “the electronic effect of a substituent depends to a certain extent upon the electron demand in the system to which it is attached”. Thus, despite the strong intrinsic electron-withdrawing character, the trifluoromethyl group was shown to modestly act as a $\pi$-electron donor when substituting a carbenium ion. Ab initio calculations were performed to account for the $\pi$-electron-donating ability of several substituents conjugated with carbocations (Table 2). It is noteworthy that amongst the several substituents studied, the CF$_3$ group exhibits the lowest $\pi$-electron-donation ability in each investigated carbenium series, reflecting, as one could expect, the very poor stabilizing power by $\pi$-electron donation. A trend exists in the magnitude of the parameter according to the nature of the carbenium ions, which is in line with the carbenium ion stability (alkyl < allylic < benzylic).

Thus, an increased $\pi$-electron transfer is present in the least-stabilized alkylcarbenium ions, in which a higher electronic contribution from neighboring substituents is required.

Table 2: $\pi$-Electron-transfer parameters from STO-3G calculations with optimized C-X bond length (established as $q_{C\equiv X}$, without unit) for substituents X in alkyl, allylic, and benzylic carbenium ions. Parameters for neutral phenyl derivatives are given for comparison. Negative values indicate $\pi$-electron donation by the substituent [22,23].

| X     | $q_{C\equiv X}$ |
|-------|-----------------|
| NH$_2$ | -566            |
| OH    | -486            |
| CH=CH$_2$ | -427        |
| F     | -353            |
| CN    | -262            |
| CHO   | -155            |
| CH$_3$| -113            |
| NO$_2$| -76             |
| CF$_3$| -29             |
| H     | 0               |

Detailed ab initio studies have been focused on the stability of the CF$_3$CH$_2^+$ cation and provide pieces of thoughts on the origins of the stabilizing interactions in $\alpha$-(trifluoromethyl)carbenium ions. The optimization of the geometry for CF$_3$CH$_2^+$ at the STO-3G level led to an energy minimum, in which one of the fluorine atoms is significantly closer to the positive carbon center (Figure 1, top, $\theta = 101^\circ$) [24]. However, exactly the same structural distortion was calculated for the ethyl cation. Furthermore, the very small $\pi$-electron density calculated in the 2p$_C$ orbital of CF$_3$CH$_2^+$ (0.04 electrons) led the authors to conclude that “there is no hyperconjugative stabilization by the CF$_3$ group”. The presence of this attractive interaction should, how-
ever, not be discarded. Indeed, the quantitative PMO analysis at the 6-31G* level allowed, by calculating fragment orbitals (FO), the identification of the nature of this attractive interaction [25]. The latter arose from a homoconjugation interaction (−5.3 kcal⋅mol−1) of one fluorine lone pair (nF FO) with the empty 2pC orbital of the cationic carbon center (Figure 1, top). A second stabilizing interaction was also found and came from hyperconjugation of the CF3 substituent, involving interactions between the empty 2pC orbital with the πCF3 FO (−5.2 kcal⋅mol−1). In 2018, spectroscopic evidence for the generation of the first observable fluoronium ion 1 by Letcka et al., which can be seen as a strong nF→2pC interaction (Wiberg bond order of 0.53 for each C–F bond), gave additional credit to these calculations (Figure 1, bottom) [26-28].

The thermochemical data can also provide information on the effect of the CF3 group on the stability of the carbenium ions. Calculations of the isodesmic reactions (1), (2), and (3) demonstrate the overall destabilizing effect of CF3 compared to H or CH3 when directly attached to a carbenium ion (i.e., α position, Scheme 1) [5,29]. Even an oxonium ion appears to be significantly destabilized by the presence of the CF3 group. These data globally suggest, as one could expect, an electronic destabilizing effect of the CF3 group when attached closely to a carbenium ion. However, any strong nF→2pC interaction might also influence the overall stability of any system.

Any perspectives toward CF3-containing carbocation-based synthesis must take this trend into account, especially studies on the specific α-(trifluoromethyl)carbenium ions. This review aims to systematically relate the reported work in this field. For each part, a focus on a series of α-(trifluoromethyl)carbenium ions differing in its chemical environment will be scrutinized. The chapter will summarize kinetic studies and concomitant theoretical investigations on the cations formation and stability data as well as synthetic perspectives offered by the studied carbenium ions. Any discussion of the results coming from the ionization of perfluorinated substrates will not be addressed in this review [30-33].

### Aryl-substituted trifluoromethylated carbenium ions

#### α-(Trifluoromethyl)-substituted carbenium ions:
At the dawn of their outstanding studies on carbocation chemistry, Olah et al. empirically demonstrated that despite exhibiting the highest Pauling electronegativity, the fluorine atoms, when directly linked to a carbenium ion, can be engaged in significant resonance electron donation (Scheme 2) [34]. While stabilizing the positively charged carbon center via lone pair conjugation, the electron density at the fluorine atom decreases, and this phenomenon is shown by a large downfield shift in the 19F NMR spectrum of 8 compared to the neutral precursor 7.

Following these studies on the evaluation of fluorine atom(s) substitution on cation behavior, Olah et al. then investigated the expected destabilizing effect resulting from the presence of fluorine atoms close to a carbenium ion [35]. Thus, Olah et al. envisioned the possibility to generate α-(trifluoromethyl)carbenium ions, and this achievement led to the first direct observation of these species using low-temperature NMR experiments in situ [35]. In this study, the authors furnished spectroscopic evidence for the complete ionization of several α-(trifluoromethyl) alcohol precursors 9a-c in a superacidic FSO3H–SbF5–SO2 medium. They also brought experimental
$^{19}$F NMR variation values up to $\Delta \delta = +24.8$ ppm (Scheme 3). This suggests a partial stabilization of the cationic center by hyperconjugation and/or fluorine lone pair interaction, resulting in a certain degree of a positive charge of one fluorine atom. Interestingly, at least one phenyl substituent was required to allow the ionization of the starting alcohols into the corresponding carbenium ions. When the aromatic substituent was absent or upon installation of an additional CF$_3$ group, only the corresponding protonated alcohols 10d–g were observed.

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Olah et al. also reported the $^{13}$C NMR chemical shifts for carbenium ion 10c upon ionization of the alcohol precursor 9c in a superacid (Scheme 4) [36]. A large downfield shift was observed predominantly at the benzyl position ($\Delta \delta^{13C} = 110.1$ ppm), with minor impacts at the ortho- and para-positions ($\Delta \delta^{13C} \approx 20$ ppm) relative to the starting alcohol 9c [37]. These variations are fully consistent with the presence of a positive charge located at the benzyl position, with only partial stabilization of the cationic center by the phenyl groups.

Similarly, Laali et al. observed significant $^{19}$F NMR downfield chemical shifts upon the formation of $\alpha$-(trifluoromethyl)pyrenylcarbenium- and $\alpha$-(trifluoromethyl)anthracenyl-

carbenium ions 12a–d from the corresponding carbinols 11a–d (Scheme 5) [38].

Tidwell et al. explored the influence of a CF$_3$ group on the solvolysis reaction of various benzylic sulfonate derivatives [39,40]. They found a linear free-energy relationship between the solvolysis rate of sulfonate 13f in different solvents compared to the one of 2-adamantyl tosylate, the latter being known to undergo solvolysis via the formation of a carbenium ion. Hence, the formation of a highly destabilized $\alpha$-(trifluoromethyl)carbenium ion 14f$_{\text{OTs}}$ was established as the rate-limiting step in the solvolysis reactions of 13f (Scheme 6). Furthermore, the authors determined a $k_{\text{CH}_3}/k_{\text{CD}_3}$ ratio of 1.54, highlighting an isotopic effect consistent with a solvolysis
mechanism involving a carbenium ion \((k_{\text{CH}_3}/k_{\text{CD}_3} = 1.48\) for 2-methyl-2-adamantyl tosylate). Also, \(k_{\text{H}}/k_{\text{CF}_3} = 2.10^5\) was established, illustrating the retarding \(\alpha\)-CF\(_3\) effect in the production of a carbenium ion [41]. In the solvolysis reaction of 13f, a mixture of the major product 15f, resulting from solvent substitution, and the minor elimination product 16f was observed. Further, \(^{14}\text{C}\) labeling experiments on 13f confirmed that the formation of the ion pair 14f\(_{\text{OTs}}\) was a reversible process [42].

Later, Liu et al. explored the solvolysis of aryl derivatives 13a–i to highlight the importance of the nature of the aromatic substituent on the solvolysis rate (Figure 2) [43]. As anticipated, a faster rate was observed for electron-donating groups, while electron-withdrawing groups slowed the process down. Plotting the Hammett–Brown correlation, established as log\((k) = f(\sigma^+))\, gave a linear dependence of the rate with the \(\sigma^+\) parameters of the aryl substituents, with a behavior in agreement with the transient formation of a carbenium ion. The slope of the straight line, \(\rho^+ = -7.46\), reflects the very high electron demand induced by the CF\(_3\) group. Remarkably, they found that CF\(_3\) deactivates to such an extent that benzylic tosylate 13f was approximately 10 times less reactive than benzylic tosylate 17 (Figure 2, top). Similarly to the previous study, the Grunwald–Winstein plot [44] gave a linear free-energy relationship between the solvolysis rate for derivatives 13f or 13g and the solvent polarity parameter \(Y_{\text{OTs}}\) [45]. The solvent participation in the solvolysis of these tertiary benzylic tosylates was thus defined as “unimportant” by the authors.

Gassman and Harrington successfully measured the solvolysis kinetics of CF\(_3\)-substituted allylic triflates 18 and 19, showing a significant solvolysis retardation with CF\(_3\)-substituted substrates (Figure 3) [46]. These results are in accordance with an earlier study that revealed that 20 was unreactive in acetone/H\(_2\)O 70:30, even over a period of 35 days at 50 °C [47].

Encouraged by these preliminary results, Tidwell et al. envisioned the possibility to study the solvolysis reaction of secondary benzylic sulfonates [48]. In tertiary benzylic sulfonates [39,43], a linear free-energy relationship between the solvolysis rate for the secondary benzylic tosylates 21 (Figure 4) and \(Y_{\text{OTs}}\) was obtained. Similarly, the nature of the aromatic substituent influenced the solvolysis rate, with an observed acceleration for substrates adorned with electron donor substituents and a deceleration for those carrying electron-withdrawing substituents. The Hammett–Brown correlation gave a straight line, with \(\rho^+ = -10.1\) (80% EtOH, 25 °C), a significantly greater magnitude than for the tertiary derivatives (−7.46), in agreement with the transient formation of a more destabilized carbenium ion (i.e., a secondary carbenium ion). They also noticed that the greatest magnitude of \(\rho^+\) was obtained in the most nucleophilic and less ionizing solvents, in agreement with an increased electron demand on the aromatic substituent in a poorly ionizing solvent. This also suggests that the positive charge is delocalized to a higher extent on the aromatic substituent for the secondary tosylates than for the tertiary ones. These data support the hypothesis that the transient formation of a carbenium ion is the rate-limiting step and the absence of significant solvent par-

**Scheme 6**: Illustration of the ion pair solvolysis mechanism for sulfonate 13f. YOH = solvent.
A different behavior emerged from triflate derivatives 22 (Figure 5a). In addition to their enhanced reactivity ($k_{Tf}/k_{Ts} = 2 \times 10^4$), a nonlinear free-energy relationship between the solvolysis rate and $Y_{OTs}$ was obtained, suggesting an important solvent participation in these cases. Further investigations on 22f showed deuterium isotope effects in agreement with the transient formation of a carbenium ion. A solvent dependence of the $k_H/k_D$ ratio was also noticed, with the higher ratios being obtained in the most ionizing and less nucleophilic solvents (i.e., $1.34 \pm 0.07$ in HFIP vs $1.21 \pm 0.01$ in 80% EtOH). The subsequent solvolysis of enantioenriched triflate ($R$)-(−)22f evidenced that in a poorly ionizing solvent, such as AcOH, solvolysis occurred with 41% inversion (and 59% racemization, i.e., product 23f was obtained with an enantiomeric ratio of ca. 70:30 in favor of the (S)-enantiomer), while complete racemization was observed in more ionizing TFA or HFIP as the solvent (Figure 5b) [48]. These observations are in agreement with a process generating a carbenium ion in highly ionizing solvents (TFA, HFIP, etc.) for the tosylates derivatives, and with the concomitant formation of a contact ion pair $25f_{OTf}$ favoring the $S_N2$ process in less ionizing solvents (Figure 5c).

Recent studies conducted by Moran et al. support the ionization via a $S_N1$ process for trifluoromethylcarbinol derivatives related to 22 under TiOH–HFIP activation [51].

Tidwell et al. investigated CF$_3$-containing naphthyl- and anthracenylsulfonate derivatives 26 and 29 [52]. They reported that while the solvolysis of 26 afforded the expected compounds 27 and 28, that of 29 exclusively gave the ring-substituted products 30–32 (Scheme 7). A Grunwald–Winstein plot gave linear dependences of the solvolysis rate against $Y_{OTs}$ in both cases, suggesting that the formation of the carbenium ions was the rate-limiting step. Thus, the formation of products 30–32 is best explained by a complete charge delocalization from an α-(trifluoromethyl)carbenium ion to anthracenylcarbenium ion 33, with subsequent trapping of 33 by the solvent.

The solvolysis of the bisarylated α-CF$_3$-substituted tosylates bearing electron-withdrawing substituents was investigated by Liu and Kuo [53]. The Hammett–Brown correlation considering derivatives 34 (Figure 6) gave a linear free-energy correlation with $\rho^\equiv = -3.98$, which is approximately half the value of those previously reported for the benzylic α-CF$_3$-substituted tosylate derivatives 13 substituted by a methyl group (Figure 2).
The presence of the additional phenyl group, in addition to the CF$_3$ group, was suggested to induce a lower $\rho^+$ value. This could be explained in terms of a twisted electron-poor aryl ring, which was not in the plane of the carbenium ion for stereoelectronic reasons. The cation is thus stabilized by the additional phenyl ring in 35 (Figure 6).

As an extension of the previous study, Liu et al. explored the solvolysis of tertiary, highly congested benzylic $\alpha$-CF$_3$-substituted halides 36 (Figure 7) [54]. Similar to their previous results, they obtained straight lines upon plotting the Hammett–Brown or Yukawa–Tsuno correlations, with $\rho^+$ values from −5.9 to −7.4, depending on the solvent and on the chosen treatment. These values are close to those obtained from previous studies, suggesting a significant stabilization of the transient carbenium ion by the ring.

Exploiting this impact of the trifluoromethyl substituent in the cationic Nazarov electrocyclization, the synthesis of CF$_3$-substituted indenes 39a–c from the $\alpha$-(trifluoromethyl)allyl-substituted benzyl alcohols 38a–c in strong acids has been reported (Scheme 9) [59]. The significant rate retardation observed upon the addition of further CF$_3$ groups, illustrated by the need for harsh reaction conditions, strongly supports the formation of delocalized $\alpha$-(trifluoromethyl)carbenium ions 40a–c.
Vasilyev et al. also investigated this Nazarov electrocyclization for the synthesis of indene derivatives. Thus, a variety of indenes 42 could be readily obtained from α-(trifluoromethyl)allyl-substituted benzyl alcohols 41a or the corresponding silyl ethers 41b upon the reaction in a dichloromethane solution of sulfuric acid or triflic acid [60,61]. The authors also reported that indenes 42 could undergo a subsequent Friedel–Crafts alkylation when 41b was reacted in the presence of an external aromatic partner Ar′H in pure triflic acid. Thus, a variety of α-(trifluoromethyl) silyl ethers 41b was converted into the corresponding indanes 43 in low to high yields [62]. The trans-isomers were generally obtained as the major product (Scheme 10).

**Scheme 10:** Brønsted acid-catalyzed synthesis of indenes 42 and indanes 43.

Bis[α-(trifluoromethyl)]-substituted carbenium ions: More destabilized bis(trifluoromethyl)-substituted carbenium ions have also been suggested to exist as reaction intermediates. During their investigations on the reactivity of sulfuranes under acidic conditions, Martin et al. reported that sulfurane 44 reacts with triflic acid to provide alcohol 9g and sultine 46, according to 1H and 19F NMR assignments, and triflate 45f, which was isolated after basic workup of the reaction (59% yield) [63]. Hence, protonation of 44 led to dialkoxy sulphonium triflate 47 along with the release of alcohol 9g. The subsequent formation of the excellent sultine leaving group 46 (assumed to be as good of a leaving group as N2) [63] is the driving force for the decomposition of 47, generating collaterally bis(trifluoromethyl)-substituted carbenium ion intermediate 48fOTf. Finally, triflate 45f is formed after ion pair recombination (Scheme 11). Similar experiments conducted with 18O-labeled 44 confirmed the proposed mechanism, including the transient formation of 48fOTf.

The solvolysis of triflate 45f was explored next [63]. Heating 45f in water or methanol resulted in the expected solvolyzed products 9g or 49 and the concomitant formation of 50a or 50b (Scheme 12a). A S_N1 mechanism was thus suggested, with formation of the benzylic cation intermediate 48f ↔ 48f', stabilized by the phenyl group (Scheme 12b).

**Scheme 11:** Reactivity of sulfurane 44 in triflic acid.

**Scheme 12:** Solvolysis of triflate 45f in alcoholic solvents.

Substrate 51, bearing a tert-butyl group in the para-position, was also submitted to solvolysis in labeled H_218O, generating the labeled benzylic alcohol 18O-52 (Scheme 13). The solvolyzed products were confirmed by NMR spectroscopy.
ysis of 51 was found to be much faster than that of 45f by at least a factor of 10, encouraging the authors to suggest “a transition state resembling 48f in the rate-limiting step”.

Sulfurane 53, bearing OC(CF₃)₃ groups, was also treated with triflic acid, affording dialkylsulfonium species 54 in 91% yield along with perfluoro-tert-butyl alcohol (Scheme 14) [63]. No further decomposition was observed in this case, suggesting that the especially challenging perfluoro-tert-butylcarbenium ion 55 cannot be generated.

Highly deactivated bis(trifluoromethyl)-substituted carbenium ions and their precursors were also explored in detail by Tidwell et al. [64-66] and Richard et al. [67] in solvolysis studies of di(trifluoromethyl)-substituted tosylates 56 in comparison to the monosubstituted analogue 21f (Figure 8). A linear free-energy relationship was found upon plotting the solvolysis rate against $Y_{\text{OTs}}$ and $\rho^+ = -10.7$ (TFA) for the Hammett–Brown correlation. The linear dependence of the rate on the solvent ionizing power, in addition to the strong effect of the substituents on the reactivity, are in agreement with the conclusions of Martin et al. [63] as they strongly support the formation of a bis(trifluoromethyl)-substituted carbenium ion 48.

Surprisingly, a relatively low kinetic effect ($k_H/k_{\text{CF3}} = 2.5$ (HFIP) was obtained. These ratios are very small compared to typical $k_H/k_{\text{CF3}}$ ratios in the $10^{-4}$-$10^{-7}$ range [39-41,43,48,68]. Thus, while introducing one CF₃ group dramatically alters the reactivity, an additional CF₃ group does not seem to significantly impact the reactivity any further. The hypothesis of a ground-state strain release to explain this behavior was discarded as an analysis of the structures of 56f, 13f, and 21f by X-ray diffraction crystallography revealed similar bond angle distortions [64,65]. A considerable delocalization of the positive charge in the aryl ring was therefore suggested (Scheme 15): in the dominant resonance form 25f', 48f', or 14f', the α-substituent (i.e., H, CH₃, or CF₃) would have a poor impact. Gas phase calculations by Tsuno et al. provided evidence for the significantly increased resonance stabilization contribution in 14f ↔ 14f' ($r = 1.4$) relative to the t-cumyl cation 57 ($r = 1.0$) [69].

α-(Trifluoromethyl)heteroarylcarbenium ions

The presence of a strong electron-donating substituent could compensate the extreme deactivating power of the CF₃ group, favoring a further exploitation for synthetic purposes. In this context, Tidwell and Kwong-Chip compared the solvolysis of N-methylpyrrole 58 to 59 (Figure 9) [70].

A very similar rate was determined for 58 and 59, with $k_{\text{CF3}} = 4.40 \times 10^{-4}$ s⁻¹ and $k_H = 1.84 \times 10^{-2}$ s⁻¹, respectively, providing a rate ratio of $k_H/k_{\text{CF3}} = 41.8$. Plotting the solvolysis rate of 58 against $Y_{\text{OTs}}$ led to a linear free-energy relationship supporting the rate-limiting formation of a carbenium ion 60. The small $k_H/k_{\text{CF3}}$ ratio suggests here that the positive charge is highly delocalized in the pyrrole ring and should be regarded as a pyrrolium ion 60' rather than an α-(trifluoromethyl)carbenium ion 60 (Scheme 16).
Similarly, trifluoromethyl-substituted indolium ions were invoked as intermediates in the recently reported gallium-catalyzed synthesis of unsymmetrical CF$_3$-substituted 3,3’- and 3,6’-bis(indolyl)methanes from trifluoromethylated 3-indolylmethanols [71]. Alcohol 61 reacts with indole 62 to provide a product 63 or 64, depending on the temperature (Scheme 17).

Chen et al. reported the synthesis of C2-phosphorylated indoles via 1,2-phosphorylation of 3-indolylmethanols with H-phosphine oxides or H-phosphonates under Brønsted acid activation [72]. The scope of the reaction includes one example of a CF$_3$-substituted 3-indolylmethanol, 68, which is efficiently phosphorylated by 69 in the presence of a catalytic amount of camphor sulfonic acid (CSA) at 60 °C, affording 70. The authors suggested the transient formation of an analogous indolium ion 71 (Scheme 19).
exhibiting a thiophene core [73]. At 0 °C, thiophenes 72-Cl and 72-Br undergo electrophilic dimerization, affording a mixture of 73-Cl and 73-Br (Scheme 20). When the reaction was cooled to −60 °C < T < −40 °C in the presence of aromatic nucleophiles, thiophenes 72-Cl and 72-Br could be converted into 74-Cl and 74-Br derivatives via a side-chain arylation reaction. When the reaction was conducted at −40 °C, the reactivity was shown to be governed by the nature of the halogen atom. For the brominated derivatives 72-Br, the corresponding side-chain arylation reaction occurred at −60 °C, but a further hydrodehalogenation led to the bromine-free derivatives 75. For the chlorinated derivatives 72-Cl, a similar side-chain arylation–hydrodehalogenation sequence occurred, but an additional Friedel–Crafts arylation at the C4-position led to derivatives 76. In this latter case, a two-step one-pot process was developed in order to access derivatives bearing two different aromatic rings.

Mechanistic investigations were then undertaken by in situ low-temperature NMR experiments, allowing the observation of thiophenium ions 77Me-Cl and 77Me-Br (Scheme 21). 19F NMR analysis showed significant downfield shifts for the signal of the CF₃ group compared to the neutral precursors, characteristic of α-(trifluoromethyl)carbenium ions. However, and as expected, the 13C NMR spectra showed considerable downfield shifts for the carbon atoms C2 and C6, suggesting a highly delocalized positive charge in the heteroaromatic ring as depicted below.

α-(Trifluoromethyl)allylcarbenium ions

In 1976, Poulter et al. exploited the powerful electron-withdrawing effect of the CF₃ group to elucidate the prenyltransferase-catalyzed condensation mechanism [74,75]. The authors envisioned that substituting a methyl group in isopentenyl pyrophosphate (IPP) by a CF₃ group (Scheme 22, 79 → 78) should greatly reduce the reaction rate in the case of an ionization–condensation–elimination mechanism, while a small acceleration should be observed in the case of a displacement–elimination mechanism.

Promising results were first obtained during investigations conducted on CF₃-substituted derivatives in SN₁- and SN₂-mechanism-based reactions (Scheme 23). A profound retardation effect for the solvolysis of 81 in acetone–H₂O (SN₁) with kCH₃/kCF₃ = 5.4 × 10⁵ was observed, while 85 promoted the Finkelstein reaction (SN₂) about 11 times faster than 84 (kCH₃/kCF₃ = 8.9 × 10⁻², Scheme 23). This is the result of a destabilized cationic intermediate in the first case and a stabilized negatively charged transition state in the second.

When 78 was incubated in the presence of IPP and the enzyme prenyltransferase, a rate of 5.1 × 10⁻⁴ nmol·min⁻¹·mg⁻¹ was measured for the condensation reaction (Scheme 24), which is to be compared to a value of 7.4 × 10² nmol·min⁻¹·mg⁻¹ observed for the condensation involving IPP and geranyl pyrophosphate (GPP). 78 was 1.5 × 10⁶ times less reactive than geranyl pyrophosphate, allowing to conclude that the condensation mechanism involving prenyltransferase as a catalyst occurs via an ionization–condensation–elimination sequence.

As suggested by the aforementioned studies, α-(trifluoromethyl)-substituted allylic carbenium ions could exist in solution. The solvolysis of CF₃-substituted allyl sulfonates was thus
thoroughly examined by Gassmann and Harrington [76]. The solvolysis of doubly CF₃-deactivated 90 in trifluoroethanol (TFE) required the presence of 2,6-lutidine, leading to ketone 91 and triflate 92. This observation suggests that lutidine allows the isomerization of 90 into 93, followed by a nucleophilic attack of the solvent at the sulfur atom (Scheme 25).

The reactivity of analogous monotrifluoromethyl-substituted allyl derivatives 94, bearing an aryl group in the vinylic position was also explored (Scheme 26). Trifluoroethanolysis of secondary triflate 94 gave a mixture of (Z)-95 and (E)-95 in a combined 70% yield, with an E/Z ratio of 17:83–8:92, depending on the nature of the aryl substituent (p-OMe or p-Cl, respectively). It is worth noting that the formation of SN₂ product 96 was not observed. Similar observations have been reported by Langlois et al. [77]. In order to get some insights into the mechanism, derivative 96 was synthesized and subjected to solvolysis. However, this compound was found to be stable under the reaction conditions [52]. When primary triflate 97 was subjected to solvolysis, the expected product (Z)-95 was obtained, and the rate was 50–100 times faster than when starting from 94. The Hammett–Brown correlation gave a poor dependence of the rate on the nature of the aryl substituent, and thus suggesting that the aryl group does not participate in the positive-charge stabilization. Finally, the Grunwald–Winstein plot gave a linear free-energy relationship between the rate and YOTs, supporting the formation of a carbenium ion.
From these observations, the authors concluded that 94 dissociates into an ion pair 98 in the rate-limiting step, in which the delocalized positive charge is highly concentrated in the γ-CF₃ position (see 98*), which is the electronically and sterically privileged position for the solvent approach, to subsequently give 95 (Scheme 27).

More recently, Vasilyev et al. reported that Lewis acid activation of α-(trifluoromethyl)allyl alcohol 101 allowed the transient formation of the corresponding α-(trifluoromethyl)allylcarbenium ion 103 ↔ 103', the resonance form 103 of which could be trapped with arenes to afford (trifluoromethyl)vinyl-substituted derivatives 102 (Scheme 29) [79,80]. It was also suggested that the resonance form 103' has a nonnegligible contribution as this α-(trifluoromethyl)allylcarbenium ion could be trapped by some electron rich arenes (i.e., xylene, cumene, etc.). The products 104 further react to afford indanes 105 after hydroarylation. A closely related study on dibrominated allylic α-(trifluoromethyl) alcohols also invoked the transient formation of allylic carbenium ions, such as 103 [81].

α-(Trifluoromethyl)alkynylcarbenium ions

It has been reported that the complex of Co₂(CO)₆ and propargyl alcohols allows the facile generation of the corresponding propargylium ions (Nicholas reaction) in a relatively strong acidic medium (i.e., TFA, BF₃⋅Et₂O, etc.). These cobalt-cluster-stabilized propargylium ions exhibit a surprisingly high thermodynamic stability, comparable to that of triarylmethylcarbenium ions and are readily observable by NMR spectroscopy or isolable as salts with relatively weakly coordinating anions (BF₄⁻, PF₆⁻, etc.) [82]. In this context, Gruselle et al. exploited the strong stabilization provided by Co–Co and Co–Mo bimetallic clusters to generate α-(trifluoromethyl)propargylium ions (Scheme 30). While the tertiary carbenium ion 108 was isolable as a solid [83,84], the tertiary carbenium ion 109 and the secondary derivatives 112a–c and 113a,b afforded oils. The secondary derivatives were much more sensitive in spite of the use of electron-rich Co–Mo clusters and could only be characterized by NMR and IR spectroscopy [85]. Upon ionization, the change in the electronic density is directly reflected by the downfield shift of the ¹⁹F NMR chemical shift of the CF₃ group but also by a CO shift to a higher frequency. As a
Scheme 29: Lewis acid activation of CF₃-substituted allylic alcohols.

In general, 111a (δ₁⁹F = −75.9 ppm; νCO = 2051, 2001, 1984, and 1942 cm⁻¹) affords 113a (δ₁⁹F = −59.2 ppm; νCO = 2104, 2065, 2055, 2006, and 1989 cm⁻¹), which exhibits the previously mentioned features, with Δδ₁⁹F = +16.7 ppm and ΔνCO ≈ +50 cm⁻¹.

Beyond the synthetic challenges associated with the generation of such species, the authors explored their use in organic synthesis. These metal-stabilized α-(trifluoromethyl)propargylium ions 114 could be engaged in useful transformations, such as reductions, eliminations, as well as C–O, C–N, or C–C bond formations (Scheme 31).

α-(Trifluoromethyl)propargylium has also been suggested as an intermediate in superacid-mediated Friedel–Crafts reactions [86]. When [α-(trifluoromethyl)propargyl]allyl silyl ether 120 was added to a dichloromethane solution of triflic acid in the presence of benzene, the original [3.2.2]-bridged CF₃-substituted product 121 was obtained. The authors proposed an elimination of TMSOH to generate the propargyl-substituted α-(trifluoromethyl)allylcarbenium ion 122 at first, which is a resonance form of the benzylic carbenium ion 122'. Subsequently, 122' reacts in a Friedel–Crafts reaction with benzene to generate 123. After two successive hydroarylation reactions, the final product 121 is produced via the formation of vinylic and benzylic carbenium ions 124 and 125, respectively (Scheme 32).
Moran et al. also investigated the reactivity of a variety of CF$_3$-substituted propargyl alcohols (Scheme 33) [87]. The reactivity of the benzylic (trifluoromethyl)propargyl alcohol 126 strongly depends on the reaction conditions, as allenes 127 or indenes 128 were both obtained under FeCl$_3$ activation. Indeed, with a longer reaction time, allenes 127 undergo a subsequent intramolecular hydroarylation reaction leading to indenes 128. The authors suggested the formation of FeCl$_3$–HFIP complexes being involved in a Lewis acid-assisted Brønsted acid catalysis. The CF$_3$-substituted propargyl alcohol 129 was found to undergo tandem Friedel–Crafts hydroxylation reactions to give derivatives 130 under TIOH activation at 50 °C. Finally, CF$_3$-substituted chromene derivatives 132 were obtained under the same reaction conditions from ortho-hydroxy or ortho-silyloxy derivatives 131a and 131b, respectively. The common intermediate in these reactions is supposed to be α-(trifluoromethyl)propargylium ion 133↔133'.

**Heteroatom-substituted α-(trifluoromethyl)carbenium ions**

The stabilization of carbenium ions through oxygen lone pair back-donation [35] is a common feature in organic synthesis [88-90]. In this context, Olah, Pittman, et al. investigated the protonation of a variety of trifluoromethyl ketones in a superacid [35,91]. Trifluoromethyl ketone protonation was observed by NMR spectroscopy at −60 °C in a superacidic FSO$_3$H–SbF$_5$–SO$_2$ solution (Scheme 34).

The $^{19}$F chemical shift variation for the generated oxygen-substituted trifluoromethylated carbaium ions ranged from +7.6 to +1.4 ppm, significantly lower than for carbon-substituted α-(trifluoromethyl)carbenium ions (e.g., the carbenium ion 10a, $\Delta \delta = +24.8$ ppm), confirming the considerable contribution of the oxygen lone pair to the stabilization of the cation 142↔142' (Scheme 35).

Oxygen-stabilized α-(trifluoromethyl)carbenium ions (oxyccarbenium ions) have been exploited for chemical synthesis [92-94]. Ketone 143a and ketoxime 143b undergo Friedel–Crafts
Scheme 34: Direct NMR observation of the protonation of some trifluoromethyl ketones in situ and the corresponding $^{19}$F NMR chemical shifts. $\Delta \delta = \delta_{19F, \text{product}} - \delta_{19F, \text{precursor}}$ ($\delta$ in ppm).

Scheme 35: Selected resonance forms in protonated fluoroketone derivatives.

Scheme 36: Acid-catalyzed Friedel–Crafts reactions of trifluoromethyl ketones 143a,b and 147a–c.

Ma et al. managed the enantioselective arylation of aromatic trifluoromethyl ketones 150 with (S)-TRIP (Scheme 37) [96]. A variety of CF$_3$-substituted enantioenriched benzylic alcohols 61 were thus synthesized after the trapping of protonated CF$_3$-substituted ketones 134 (Scheme 37). Interestingly, these benzylic alcohols 61 did not undergo further arylation and were stable under the reaction conditions. In agreement with computational studies [97], this behavior was assigned to the presence of the CF$_3$ group, which induces a shortening of the C–O bond ($d_{C-O} = 1.438 \, \text{Å}$) and strongly inhibits the formation of the $\alpha$-(trifluoromethyl)bisarylcarbenium ion, as illustrated by the higher activation energy needed for the dehydration ($\Delta E_{\text{CF3}} = 21.0 \, \text{kcal mol}^{-1}$ vs $\Delta E_{\text{CH3}} = 14.8 \, \text{kcal mol}^{-1}$ at the B3LYP/6-31+G(d,p) level). On the other hand, the first arylation reaction seems to be facilitated by the CF$_3$ group ($\Delta E_{\text{CF3}} = 16.9 \, \text{kcal mol}^{-1}$ vs $\Delta E_{\text{CH3}} = 21.2 \, \text{kcal mol}^{-1}$ at the B3LYP/6-31+G(d,p) level). Raising the temperature finally favors the dehydration and the second Friedel–Crafts reaction to afford bisarylated products 151.

In complementary studies, Sasaki et al. reported the acid-catalyzed mono- and diarylation of CF$_3$-substituted $\alpha,\beta$-ynones 152a [98], Wu et al. reported the one-pot two-step acid-catalyzed diarylation of trifluoroacetyl coumarins 152b [99], and Yuan et al. reported the acid-catalyzed diarylation of CF$_3$-substituted cyclopropyl ketone 152c [100] (Scheme 38). In these reactions, oxygen-stabilized $\alpha$-(trifluoromethyl)carbenium ions 142 are supposed to be generated by protonation or Lewis acid activation of the starting ketones.
Klumpp et al. explored the reactivity of CF₃-substituted super-electrophiles (defined as multiply charged cationic electrophiles [101]) generated in superacid media [102]. Hence, when trifluoroacetyl pyridine 156 was treated with benzene in triflic acid, alcohol derivative 157 was obtained. In a superacid, 156 generates a dication 158 in which the electrophilicity is enhanced through a strong charge repulsion (Scheme 39). This dication reacts with benzene to provide pyridinium–oxonium dication 159 in solution. Further arylation does not occur spontaneously, which was evident because alcohol 157 was isolated at the end of the reaction. Upon heating at 60 °C, the second arylation takes place, presumably via the formation of dicationic superelectrophile 160. Again, due to charge repulsions as well as due to the strong electron-withdrawing effect of the CF₃ group, the positive charge adjacent to the CF₃ group is highly delocalized within the phenyl ring, and arylation occurs regioselectively at the para-position, affording biaryl species 161.

Using this strategy, several trifluoromethyl ketones 162 and alcohols 163 bearing heteroaryl substituents (i.e., benzothiazole, quinoline, isoquinoline, benzimidazole, or imidazole) prone to be protonated were elegantly converted into the corresponding alcohols 163 and biphenyl compounds 161 in high yield (Scheme 40, top). The reaction of CF₃-substituted 1,3-diketones 165a–d in TfOH was also deeply investigated by Klumpp et al. [101]. The syn-indanes 166a–d could cleanly be generated after successive well-defined arylation reactions via 167 (Scheme 40, bottom). Moreover, the CF₃ group was found to be essential in this reaction as 2,4-pentanedione did not react with benzene under similar conditions.

The use of acetal derivatives in place of ketones as precursors of oxygen-stabilized α-(trifluoromethyl)carbenium ions was also investigated. For instance, the readily available hemiacetal 168 was shown to react with benzene in the presence of a Lewis acid or H₂SO₄ to form compounds 169–172 in various amounts, depending on the acid used (Scheme 41) [103]. It is assumed...
that an oxygen-stabilized α-(trifluoromethyl)carbenium ion is involved. It was shown that 168 could also react with (hetero)arenes [104,105] and alkenes [106] under Lewis acid activation but also with electron-rich arenes under thermal activation [107-109].

Nitrogen-stabilized α-(trifluoromethyl)carbenium ions have also been extensively investigated. Under electrochemical conditions, trifluoromethylated iminium ions 182 were successfully generated by Fuchigami et al. [115]. Starting from tertiary amines 178a–c, the corresponding hemiaminal ethers 179a–c were obtained (Scheme 43). The reaction is highly regioselective as no methoxylation of 178a and 178b was observed on the nontrifluoromethylated alkyl substituent (Me or Et). Hence, although amines 178a–c are more difficult to oxidize than their nonfluorinated analogues (E_{ox}(PhNMMe_2) = +0.71 V (SCE)), the radical cation 180 is formed under the reaction conditions, and deprotonation at the methylene unit near the CF_3 group is highly favored because of the higher acidity, accounting for the observed high regioselectivity. In addition, the transient stabi-
lization of radical 181 by the captodative effect could also favor the general process.

Lewis acid activation of trifluoromethylated hemiaminal ethers has also been studied by Fuchigami et al. [115,116]. For instance, when 179b is treated with a slight excess of TiCl4 in dichloromethane, iminium ion 182b can be trapped by TMSCN to furnish α-(trifluoromethyl)-α-aminonitrile 183 in 40% yield. The iminium was also successfully trapped by a silyl enol ether, affording a mixture of ketone 184 and heterocycle 185 (Scheme 44).

The trifluoromethyl-substituted derivatives 186a–c have then been exploited as a convenient source of trifluoromethylated iminium ions 187 (Scheme 45) [117-119].

Langlois, Billard, and Blond reported on the Mannich-type reaction between silylated trifluoromethylated hemiaminal derivatives 189 [120] and enolizable ketones 188 [121]. The intermediate formation of trifluoromethylated iminium ion 192 by Lewis acid activation was suggested by the authors (Scheme 46). The resulting CF3-substituted β-amino ketones 190 could then be efficiently transformed in a one-pot procedure into the corresponding CF3-substituted enones 191 upon Brønsted acid treatment.

Langlois and Billard then exploited the reactivity of the trifluoromethylated iminium ion 192 and extended the scope of the reaction to a larger panel of nucleophiles, including alcohols, amines, aromatic and vinyl derivatives, as well as silylated nucleophiles (Scheme 47) [122].

Brigaud and Huguenot also suggested the formation of a trifluoromethylated iminium ion 187 during the course of their studies on a Strecker-type reaction [123]. Starting from trifluromethylated imines 193 or oxazolidines 194 and 195 bearing enantiopure chiral auxiliaries, the authors accessed the corresponding cyano derivatives 196–198 with different levels of diastereoselectivity (Scheme 48). Further development by Brigaud et al. allowed the synthesis of CF3-substituted pseudoprolines structurally related to oxazolidines 194 and 195 [124].
Viehe et al. also contributed by developing the chloroalkylamino reagent 199, bearing a geminal CF$_3$ group, which proved to be a valuable synthon for the introduction of the CF$_3$ group into molecules [125]. Thus, 199 exhibits a high reactivity towards many functionalities, as depicted below (Scheme 49). Interestingly, 200 and 201 are sufficiently stable to be synthesized, presumably due to electron delocalization (guanidinium ions).

Following these seminal contributions, the chemistry of CF$_3$-substituted iminium ions 187 was extensively exploited for synthetic purposes [126-138].

The related thiaoacetals 204a was also studied and reacts with benzene upon treatment with strong Lewis acids (best with AlCl$_3$) [139]. In this case, the only product formed in the course of the reaction was 205, isolated in 83% yield (Scheme 50). The proposed cationic intermediate in this reaction is a sulfur-stabilized $\alpha$-(trifluoromethyl)carbenium ion 206 (an $\alpha$-(trifluoromethyl)-substituted sulfonium cation).

Analogous to thiaoacetals 204a, chloroalkylthio derivatives 207a–c, bearing an adjacent CF$_3$ group, were also investigated [140]. It appeared that a sulfur-stabilized $\alpha$-(trifluoromethyl)carbenium ion 208 can be generated from 207a by chloride abstraction following Lewis acid activation (e.g., SnCl$_4$ or ZnCl$_2$), opening an avenue for this cation to react with various nucleophiles (Scheme 51). Such a cation can also be trapped intramolecularly by a phenyl moiety; however, the length of the appended alkyl chain appeared to be of the utmost importance in this transformation.

Analogous to their work on the nitrogen counterparts (vide supra), Fuchigami et al. were successful in the electrochemical production of sulfur-stabilized $\alpha$-(trifluoromethyl)carbenium
Thereby, they converted sulfides 213a–h into thioacetals 204a–h (Scheme 52). It is worth to note that the presence of an aromatic substituent on the sulfur atom is essential for the sulfides to react. Also, lengthening the perfluoroalkyl chain from CF$_3$ to C$_2$F$_5$ or C$_3$F$_7$ resulted in a significant drop in the yield. Interestingly, while the electrochemical acetoxylation of 213a furnished 204a in an excellent yield of 93%, the Pummerer rearrangement of sulfoxide 214 under harsh conditions turned out to be less efficient, affording 204f in only 42% yield.

This reaction is thought to proceed stepwise via a first oxidative electron transfer, followed by deprotonation, a second oxidative electron transfer, and methoxylation or acetoxylation, respectively (Scheme 53). The driving force in this reaction is assumed to be the deprotonation of radical cation 215, a highly destabilized species due to the presence of the strongly electron-withdrawing CF$_3$ substituent, which leads to radical 216, synergistically stabilized by the electron-withdrawing CF$_3$ group and the electron donor sulfur atom through a captodative effect. Further oxidative electron transfer produces α-(trifluoromethyl)-substituted sulfonium ion 206, leading to 204a,f after reacting with the solvent.
α-(Trifluoromethyl)alkylcarbenium ions

Hypothetical formation of CF₃-containing alkylcarbenium ions from diazonium salts: In 1967, Mohrig et al. successfully observed the first aliphatic diazonium ion 218a by protonation of the corresponding diazo precursor [142] 217a in a superacid by in situ NMR spectroscopy (Scheme 54) [143]. The remarkable characteristic of this strategy was the installation of a CF₃ group in the α-position of the N₂ moiety. This strategy relies on the high electron-withdrawing effect of the CF₃ group, which greatly destabilizes nearby positive charges. As a result, the dissociation rate for the generation of molecular nitrogen was considerably reduced, allowing the observation of the diazonium ion at a low temperature. However, warming the diazonium solution up to −20 °C resulted in a vigorous evolution of N₂ gas along with the clean formation of the resulting fluorosulfonate 219, with no direct observation of the α-(trifluoromethyl)carbenium ion.

Further studies were conducted by Lenoir and Dahn to shed light on the mechanism of the solvolysis of CF₃-substituted diazoalkane derivatives (Figure 10a) [144]. They measured an inverse kinetic isotope effect of k_H/k_D = 0.25 for the solvolysis of 217a in dioxane/H₂O 60:40 in the presence of HClO₄ (3 ≤ pH ≤ 4) and mentioned that this low value is “typical of a preequilibrium protonation reaction” and the rate-limiting solvolysis of diazonium ion 218a (Figure 10b, in blue). Furthermore, the addition of a strong nucleophile dramatically increased the rate. The authors thus concluded that these observations are pieces of evidence for an A2 bimolecular process, which is also in agreement with the preferred decomposition pathway of other deactivated diazoalkanes (i.e., diazoacetate, k_H/k_D = 0.34) [145,146]. Extending the investigations to diazo compound 217b led to a different conclusion as a “normal” isotope effect of k_H/k_D = 1.67 was obtained in this case. Diderich found a comparable ratio of k_H/k_D = 2.13 for diazo compound 217c [147]. In these latter cases, the solvolysis of diazoalkanes 217b and 217c is supported by an A-Sₑ₂ mechanism including a rate-limiting proton transfer (Figure 10b, in green) as the solvolysis rate approximately corresponds to the transfer rate of a proton (or deuteron). The difference in the reactivity between 217a and 217b,c would thus be due to the easier protonation of 217b,c compared to 217a, in a similar way as how one can expect secondary carbanions to be more basic than primaries.

Studies on CF₃-substituted diazonium ions were next conducted by Kirmse and Gassen to determine the solvolysis mechanism [148]. They found that upon deamination of 221 using a solution of sodium nitrite in aqueous perchloric acid at pH 3.5, a 60:40 mixture of the elimination product 224 and alcohols 222 and 223 was obtained in a 95% overall yield. These alcohols result from either solvolysis (223, 40.3%) or rearrangement (222, 59.7%, reaction (1) in Scheme 55). Further investigations on the stereochemical aspects leading to product 223 showed that when enantioenriched amine (S)-221 (94% ee) was subjected to deamination, product (R)-223 was obtained, with an inverted configuration and an eroded enantiomeric purity of...
65% ee (reaction (2) in Scheme 55). The authors thus concluded that the formation of \((R)-223\) from (S)-221 occurred by a nucleophilic substitution mechanism, with 70% inversion. Since the racemization via diazo ↔ diazonium equilibrium was excluded due to negligible \(^2\)D incorporation (i.e., <1%) when \(D_2O\) was used, the 30% racemization noted in the process would account for the transient formation of a trifluoromethyl-substituted carbenium ion.

Attempts to elucidate the mechanism for the formation of 222 revealed that deuterium-labeled 221-d\(_2\) furnished products 223-d\(_2\) and 222-d\(_2\) upon deamination in a similar ratio and yield (Scheme 56, 41.2:58.8, 32%) as for the unlabeled 221 (Scheme 55, 40.3:59.7, 38%). This is a strong evidence for the transient formation of a carbenium ion as the isotope effect for the 1,2-H-shift is known to be very small in carbenium ions. It has been indeed previously demonstrated that a 1,2-H-shift isotope effect of \(k_H/k_D = 1.2–1.3\) was obtained starting from 2-butyldiazonium ion \(225\), which is known to decay via a carbenium ion [149,150].

In the absence of the CF\(_3\) group, 225-d\(_2\) decays in a mixture of alkenes and alcohols. By taking only the alcohol mixture into account, alcohol 227-d\(_2\) was considered to have been obtained via a nucleophilic substitution mechanism (88%) with 25% inversion and 226-d\(_2\) via rearrangement (12%, Scheme 57).

This would be consistent with a less labile C–N bond in 218d and the formation of the extremely reactive \(\alpha\)-(trifluoromethyl)carbenium ion 228 that is therefore more prone to undergo rearrangements to generate the more stabilized \(\beta\)-(trifluoromethyl)carbenium ion 229 (Scheme 58).
Further rearrangements were confirmed by the authors when alcohol 233, resulting from a twofold 1,2-H-shift, was generated from diazonium salt 230 (Scheme 59).

The β- and γ-CF₃ effects on the carbenium ions were also investigated by the same authors by systematically comparing the reactivity of a selected series of CF₃-containing and analogous nonfluorinated diazonium ions toward solvolysis. The diazonium ion 234 led exclusively to alcohol 222, with the absence of any detectable rearranged products, while the CF₃-free analogous species 225 underwent 12% rearrangement (reaction (1) in Scheme 60). The diazonium ion 235 furnished alcohols 232 and 233 in a 71:29 ratio, without the detectable formation of α-(trifluoromethyl) alcohol 231, while the analogous compound 236 provided 237 and 238 in a 84:16 ratio (reaction (2) in Scheme 60). Similarly, the terminal diazonium ion 239 decayed to produce a 97.5:2.5 ratio of alcohols 222 and 226 in a 71:29 ratio (reaction (3) in Scheme 60).

Even though the direct observation of α-(trifluoromethyl)carbenium ions was not the purpose of this study, it successfully brought a better understanding on the effect of a CF₃ group close to a positive charge.

**Hypothetical formation of CF₃-containing alkyldiazenonium ions by activation of alcohol derivatives:** The solvolysis reaction of alkyl tosylates has attracted the attention of many chemists, and successive studies revealed that hydrogen or methyl shifts were effective and most prominent in strongly acidic solvents, such as HSO₃F, with H₀ = −15.1 [151] (Scheme 61) [152-154]. This is the result of the lack of solvation of intermediate carbenium ion 245 in strong acids due to the high ionizing power and low nucleophilicity, favoring the stabilization by hyperconjugation, followed by 1,2-H-shift [155].

In this context, Myhre and Andrews explored the reaction of α- and β-(trifluoromethyl) tosylates 248 and 249 in strongly acidic solvents (Scheme 62) [156]. Contrary to what could have been expected, no rearranged products were formed in either case, even in magic acid, HSO₃F–SbF₅ (H₀ = −23 [151]).

The solvolysis study on aliphatic trifluoromethyl tosylate derivatives in strong acids was conducted following theoretical studies [156,157]. While 248 and 252 showed a solvolysis rate...
comparable to that of 253 in 85–100% H$_2$SO$_4$, derivative 249 underwent solvolysis at a significantly slower rate (Figure 11). This counterintuitive behavior was not considered to be in line with the intermediary formation of a carbenium ion, as β-(tri-fluoromethyl)carbenium ion 254 generated from 249 is expected to be more stable than α-(trifluoromethyl)carbenium ion 2 generated from 252.

To rationalize this trend under these reaction conditions, the authors submitted the enantioenriched alcohol (+)-255 ([α]$_{365}$ +2.682, the absolute configuration was not mentioned) to two distinct reaction pathways (Scheme 63). No erosion of the specific rotation, neither through path ABDE ([α]$_{365}$ +2.692), nor CDE ([α]$_{365}$ +2.679) was observed, suggesting that an α-(trifluoromethyl)carbenium ion cannot be considered as a reactive intermediate.

Further labeling experiments revealed that the $^{18}$O percentage in $^{18}$O-255 (24.6% ± 0.3%) remained unchanged before and after being subjected to the path A–B–D–E (24.4% ± 0.3%) or C–D–E (24.3% ± 0.3%). Hence, no C–O bond cleavage happens in any of these steps. The authors rationalized the experimental observations by invoking a dissociation mechanism involving the cleavage of the weak O–S bond, as depicted in Scheme 64. These experimental results strongly oppose those collected by Tidwell and Koshy [39] on benzylic α-(trifluoromethyl)-substituted tosylate derivatives (see section on α-(trifluoromethyl)-substituted carbenium ions), presumably due to the presence of a stabilizing phenyl moiety in the latter case.

Analogous investigations on triflate derivatives were realized by Tidwell et al. [41]. Triflates are more reactive than tosylates – as illustrated by $k_{Tf}/k_{Ts}$ = 7 × 10$^4$ for the elimination reactions of 259 and 260 – and were thus of interest in the context of solvolysis studies. The solvolysis of 260 in various solvents led to the sole formation of the elimination product, and no nucleophilic substitution of the triflate by the solvent was observed. Similar results were also reported previously by the authors for 259 (Scheme 65) [39]. Interestingly, no dependence of the elimination rate on the ionizing power of the solvents was
observed, suggesting that the formation of an ion pair (either intimate or solvent-separated) was not the limiting step. However, the faster rate obtained in the most nucleophilic solvents implies that the solvent is involved in the rate-limiting step.

Kinetic isotope effects in the elimination reactions of 260, 260-\(d_3\), and 260-\(d_6\) were found to be \(k_{260}/k_{260-d_3} = 1.78\) and \(k_{260}/k_{260-d_6} = 3.80\). The effect of the solvents and added salts on the rate proved that the medium (solvent and salt) is involved in the rate-limiting step. Furthermore, the values obtained for the secondary isotope effect agreed with the elimination as the rate-limiting step and strongly support the hypothesis that the latter occurred from an intimate ion pair.

Starting from 261, no elimination product could be formed during the solvolysis reaction, and a 1,2-methyl shift occurred to generate 262 after solvent trapping, as reported by Roberts and Hall (Scheme 66) [158]. Kinetic studies revealed a linear free-energy relationship between the rate of the solvolysis against the \(Y_{OTf}\) values. The isolated product 262 as well as the kinetic data strongly support the formation of the \(\beta\)-(trifluoromethyl)carbenium ion 263 in the rate-limiting step with considerable neighboring group participation, characteristic of a \(k_\Delta\) pathway.

Bonnet-Delpon et al. successfully took advantage of the intramolecular stabilization of a cation induced by the presence of a CF₃ group to develop a method to access 1-(trifluoromethyl)tetralins [159]. For instance, upon the solvolysis of systems such as 264 in TFA/TFAA, the cyclized products 265 were obtained. Furthermore, it is known that the nontrifluoromethylated tosylate analogue undergoes the same cyclization via a \(k_\Delta\) process rather than a \(k_c\) process [160]. The authors thus proposed that the aryl ring stabilizes the cation concomitantly after the elimination of the triflate anion to form the transition state 266 in the solvolysis reaction of derivatives 264. The same cyclization reaction occurred when derivatives such as 267 were solvolyzed in TFA/H₂SO₄, affording 268 (Scheme 67). However, while the nature of the aryl substituent \(R^1\) had a negligible effect on the rate, the latter had a convincing dependence on the nature of the substituent \(R^2\). For benzylc systems 267, the authors proposed a \(k_c\) pathway involving the formation of the more stable benzyl \(\alpha\)-(trifluoromethyl)carbenium ion 269, with a subsequent cyclization reaction.

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Gassman and Doherty suggested that the introduction of a strongly electron-withdrawing group in the \(\alpha\)-position of a positively charged carbon center could magnify the neighboring group participation so as to compensate for the increased electron deficiency at the incipient cationic center [4,161]. Using this strategy, Tilley et al. reported the first synthesis of strained CF₃-substituted bicyclo[1.1.0]butane 271a via \(\gamma\)-silyl elimination of \(\alpha\)-(trifluoromethyl)cyclobutyl tosylate 270a (Scheme 68) [162]. The reaction was proposed to occur via neighboring-group participation of the silicon-based group, through homoconjugative stabilization of the pC orbital of the incipient \(\alpha\)-R₃-substituted carbenium ion by a percaudal (back lobe) par-
ticipation of the \(\sigma_{C-Si}\) orbital (272, Scheme 68). Importantly, the initial W-conformation in the starting material 270a,b was mandatory to allow a sufficient orbital overlap as the U-conformation (endo-sickle-like isomer) failed to react within the reaction time (\(\approx 12\) h). In 272, the positive charge is thus significantly delocalized at the silicon center, allowing a facile nucleophilic displacement at the silicon atom by a solvent molecule to afford 271a,b. The CF\(_3\) moiety strongly affects the stability in 271a, which was found to be stable “indefinitely” when stored under an inert atmosphere at a low temperature and did not suffer from polymerization.

Further investigations by Tilley et al. were conducted in order to enlarge the scope of the above-mentioned 1,3-silyl elimination of \(\alpha\)-(trifluoromethyl) tosylate, which was restricted so far to cyclobutyl derivatives, and a variety of linear or cyclic \(\alpha\)-(trifluoromethyl)-\(\gamma\)-silyl sulfonates was targeted (Scheme 69) [163,164]. While the solvolysis was readily performed with tosylate-like leaving groups in the case of aromatic substituents being present, as in 273a–h, or in the cyclic systems 274a,b, a better leaving group, such as triflate, was generally required for alkyl derivatives 275a–d.

Interestingly, CF\(_3\)-substituted cyclopropanes 281 could be obtained from linear derivative 280 but also from cyclic 279 (cis-279 or trans-279) via an alternative mechanism. The proposed mechanism for the conversion of 279 into 281 invokes an alkyl shift, leading to the generation of a carbenium ion 283, stabilized by the \(\beta\)-effect of silicon (via the transition state 282), and further \(\beta\)-silyl elimination affords product 281 (Scheme 70). In addition, trans-279 reacted approximately 12 times faster than cis-279, and thus suggesting a neighboring-group participation via the \(\sigma_{C-Si}\) orbital in the proposed transition state 282.

Very recently, Creary reported a study on the generation of CF\(_3\)-substituted \(\gamma\)-silylcarbenium ions via a cyclopropylcarbinyl rearrangement [164]. When cyclopropylcarbinylcarbenium ion
284 is generated, this species is in an equilibrium with the homoallylcarbenium and cyclobutylcarbenium ions 285 and 286 (Scheme 71) [164].

Scheme 71: The cyclopropyl-substituted homoallylcyclobutylcarbenium ion manifold.

Creary investigated the solvolysis of CF₃-substituted cyclopropylcarbinyl triflate 287a and obtained a mixture of bicyclobutane 271a and unarranged solvent-substitution product 289a in 71% and 29% yield, respectively (Scheme 72) [164]. This result was in stark contrast with those obtained with Ph- and H-substituted analogues 287b and 287c because the main products of the reactions in the latter cases were bicyclobutanes 290b and 290c. As mentioned previously, this is the result of an enhanced neighboring-group participation induced by the presence of the CF₃ group in 287a. A stronger percaudal stabilization is thus present in carbenium intermediate 272a, which leads mainly to 271a by solvent-assisted γ-silyl elimination.

Scheme 72: Reactivity of CF₃-substituted cyclopropylcarbinyl derivatives 287a–c. LG = leaving group.

Hypothetical formation of CF₃-containing alkylcarbenium ions by alkene activation: Because 1,1,1-trifluoropropene (TFP) undergoes an anti-Markovnikov addition in the presence of hydrogen halide, Myhre and Andrews anticipated that a similar regioselectivity may occur with HSO₃F [156]. Submitting the fluorinated olefin to HSO₃F unexpectedly led to a dimerization of TFP. The provided mechanistic explanation involves a C–F activation by the HSO₃F Brønsted superacid to generate difluorinated allylcarbenium ion 295. It must then react with another molecule of TFP to give 296 (Scheme 74). A subsequent 1,3-hydrogen shift, driven by the formation of an allylic carbenium ion 297 from a primary carbenium ion 296, furnished the isolated product 298 after fluorine abstraction from the anion.

Scheme 73: Reactivity of CF₃-substituted cyclopropylcarbinyl derivatives 291a–c.

Hypothetical formation of CF₃-containing alkylcarbenium ions by alkene activation: Because 1,1,1-trifluoropropene (TFP) undergoes an anti-Markovnikov addition in the presence of hydrogen halide, Myhre and Andrews anticipated that a similar regioselectivity may occur with HSO₃F [156]. Submitting the fluorinated olefin to HSO₃F unexpectedly led to a dimerization of TFP. The provided mechanistic explanation involves a C–F activation by the HSO₃F Brønsted superacid to generate difluorinated allylcarbenium ion 295. It must then react with another molecule of TFP to give 296 (Scheme 74). A subsequent 1,3-hydrogen shift, driven by the formation of an allylic carbenium ion 297 from a primary carbenium ion 296, furnished the isolated product 298 after fluorine abstraction from the anion.
Further evidence for the formation of the putative difluorinated allylcarbenium ion 295 was obtained by dissolving TFP in less acidic HSO$_3$Cl ($H_0 = -13.8$ [151]). In this superacidic medium, difluoroallyl sulfonate 299, resulting from the direct trapping of 295 by the more coordinating SO$_3$Cl$^-$ anion (compared to SO$_3$F$^-$), was smoothly formed (Scheme 75) [165]. Hence, this demonstrated that the C–F activation of the CF$_3$ moiety to generate a difluoroallylcarbenium ion 295 was favored over the formation of a secondary $\alpha$-CF$_3$-substituted species or a primary aliphatic $\beta$-(trifluoromethyl)carbenium ion 254. Indeed, no evidence for the protonation of TFP was obtained, highlighting once more the extraordinary electron-withdrawing and deactivating potential of the CF$_3$ group [68].

Jacobsen et al. elegantly exploited the stabilizing effect of an aromatic ring through skeletal rearrangement via a phenonium ion intermediate [166]. Recently, Gilmour et al. synthesized highly fluorinated scaffolds using this strategy (Scheme 76) [167]. The widely accepted mechanism for this transformation involves a first fluoroiodination of an olefin 301a–c to give 303a–c, followed by an anachronistically assisted iodonium elimination to generate the phenonium ions 304a–c and a subsequent regioselective fluoride addition to furnish compounds 305a–c (Scheme 76) [168]. In this example, the phenonium species 304a–c can be regarded as a “hidden” $\alpha$-(trifluoromethyl)carbenium ion 306a–c, in which the fluorine atom in the $\alpha$ position stabilizes the cation by lone pair back-donation (see 306’a–c), favoring the whole process.

To overcome the difficulty to generate trifluoromethyl-substituted allylcarbenium ions after the activation of trifluoromethyl-substituted alkenes, the stabilization by a neighboring group could be envisaged. In the enantioselective gem-difluorination of styrenes catalyzed by hypervalent iodoarene species, Jacobsen et al. elegantly exploited the stabilizing effect of an aromatic ring through skeletal rearrangement via a phenonium ion intermediate [166]. Recently, Gilmour et al. synthesized highly fluorinated scaffolds using this strategy (Scheme 76) [167]. The widely accepted mechanism for this transformation involves a first fluoroiodination of an olefin 301a–c to give 303a–c, followed by an anachronistically assisted iodonium elimination to generate the phenonium ions 304a–c and a subsequent regioselective fluoride addition to furnish compounds 305a–c (Scheme 76) [168]. In this example, the phenonium species 304a–c can be regarded as a “hidden” $\alpha$-(trifluoromethyl)carbenium ion 306a–c, in which the fluorine atom in the $\alpha$ position stabilizes the cation by lone pair back-donation (see 306’a–c), favoring the whole process.
investigated the reactivity of \( \text{CF}_3 \)-substituted pentyne 307. The solvolysis of 307 in TFA and \( \text{CF}_3\text{CO}_2\text{Na} \) led to cyclobutanone 308 and alcohol 309. The isolation of 308 suggests the transient formation of \( \beta \)-(trifluoromethyl)vinyl cation 310. However, no trace of a cyclopropyl ketone 311 was observed, indicating that this route is prohibited as it requires the generation of a more destabilized \( \alpha \)-(trifluoromethyl)vinyl cation 312 of higher energy (Scheme 77).

The photochemical formation of \( \alpha \)-(trifluoromethyl)vinylcarbenium ions has also been suggested by Lodder et al. (Scheme 78) [170]. UV irradiation of vinyl compound 313 led to the formation of acetylene product 315, which is suggested to be formed via \( \beta \)-H-elimination from an open \( \alpha \)-(trifluoromethyl)vinylcarbenium ion 314. A kinetic isotope effect study gave a \( k_H/k_D = 1.22 \) ratio, which is in perfect agreement with \( \beta \)-secondary isotope effect values for reactions proceeding through a carbenium ion. The observation of product 317 strongly supports this cationic mechanism, as it is not unlikely that carbenium ion 314 undergoes a 1,2-fluorine shift (although such a rearrangement has not been experimentally demonstrated so far) to generate the more stable difluorinated allyl cation 316, which leads to 317 after internal return. Noteworthy, it has been calculated that such a vinyl cation 314 is 42.1 kcal-mol\(^{-1}\) higher in energy than the corresponding \( \text{CH}_3 \)-substituted analogues.

Nonclassical \( \alpha \)-(trifluoromethyl)carbenium ions

The very existence of nonclassical carbocations (3 centers, \( 2\pi \)-electrons) has been the subject of debate for decades. The 2-norbornyl cation became the most emblematic example, and its structure has been proposed either as two carbenium ions, 318a and 318b, in a rapid equilibrium or as a symmetrical cation 318c, displaying a nonclassical pentacoordinated carbon atom (Figure 12) [171-173]. Krossing et al. eventually put an end to this debate by achieving the crystal growth and crystal structure determination of the 2-norbornyl cation, the structure of which was unequivocally assigned as 318c [174].

In 1984, as part of their investigations on carbocation stabilization by neighboring group participation, Gassman and Hall brought evidence for the nonclassical model using a strategy involving a progressive destabilization of the resulting cation by the introduction of \( \text{CF}_3 \) groups in the norbornene derivatives 319–321 (Figure 13) [175]. They found a cumulative effect of the \( \text{CF}_3 \) groups on the solvolysis rate, with a \( 10^6 \)-fold decelerating effect upon the introduction of each \( \text{CF}_3 \) unit. The authors concluded that “the fact that each \( \text{CF}_3 \) group decreases the rate of ionization by \( 10^6 \) provides overwhelming evidence that the interactions of the double bond […] with the incipient carbocation involve symmetrical (nonclassical) transition states 322, rather than pairs of rapidly equilibrating (classical) cations”.

2-Adamantyl tosylate is one of the main references to describe the \( \text{S}_\text{N}1 \) mechanism in which the carbenium character is maxi-
The solvolysis of cyclopropyl-substituted α-(trifluoromethyl) tosylate 328 was investigated by Meyer and Hanack, who reported a high tendency of 328 for rearrangements [177]. Hence, the hydrolysis of 328 led to 329 and to a mixture of the rearranged products 330–332 (Scheme 80).

Suspecting that 330 and 331 were obtained from the solvent trapping of the rearranged carbenium ions 336 and 337, respectively (Scheme 81), the cyclobutyl tosylate 333 and the cyclopropyl tosylate 334 were also solvolyzed (Table 3). Interestingly, while 328 yielded 3.5% of the direct solvent-substituted product 329, 333, and 334 yielded 25% of 330 and 92% of 331, respectively, as a result of the lower tendency to rearrange, due to the higher ion stability.

This suggests that 329 generates a highly reactive α-(trifluoromethyl)carbenium ion 335 upon solvolysis, which rapidly either rearranges via an alkyl shift to the β-(trifluoromethyl)carbenium ion 336 to give 330, or to the γ-(trifluoromethyl)car-
benium ion 338 via αC–C bond donation (i.e., a homoaromatic species), which is trapped at the primary carbon atom, similar as in norbornyl derivatives, to give 332. Also, 336 can further rearrange by alkyl shift to give the γ-(trifluoromethyl)carbenium ion 337, which leads to 331. What is striking from these observations is the effect of the CF$_3$ group on the stability and electronic features that reduce their lifetimes. CF$_3$-substituted carbenium ions have thus pro-

Conclusion
Destabilized carbenium ions exhibit structural and electronic features that reduce their lifetimes. CF$_3$-substituted carbenonium ions are probably the cations that have long been regarded as the worst possible intermediates to be generated in an organic transformation, and therefore were deeply studied as exotic species. The study of CF$_3$-substituted carbenonium ions has therefore produced valuable contributions to understand their implications in synthetic transformations. Through these efforts, which are the subjects of this review, great perspectives in modern synthetic chemistry are expected as a result of the exploitation of these underestimated cationic intermediates.

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Table 3: Solvolysis products of compounds 328, 333, and 334.

| Product | 329 | 330 | 331 | 332 |
|---------|-----|-----|-----|-----|
| OTs     | 3.5%| 28% | 32% | 34% |
| CF$_3$H |     |     |     |     |
| F$_3$C  |     |     |     |     |
| OTs     |     |     |     |     |
| F$_3$C  |     |     |     |     |

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