CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201100551

The Role of the Counterion and of Silicon Chelation in the Selective Mono(trifluoromethylation) of Tartaric Acid Derived 1,4-Diketones

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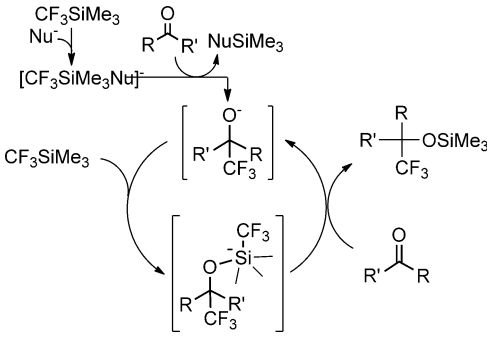
Abstract: The addition of trifluoromethyl(trimethyl)silane (TFMTMS) to tartaric acid derived aromatic 1,4-diketones was reported to be highly stereoselective but also chemoselective towards a monoaddition product. This chemoselectivity remained unexplained. Complementary experiments and monitoring of the reaction by electrospray ionization mass spectrometry (ESI-MS) show that: i) the countercation (tetrabutylammonium (TBA^+) or Cs^+) associated to the initiator and the charged intermediates in the chain reaction plays a crucial role and ii) in the case of a tetrabutylammonium salt initiator, the second addition on the preformed monoadduct does occur but the resulting bis(trifluoromethyl)carbinolate is unable to evolve through the chain-transfer process and it exhibits an intramolecular Si–O interaction.

Keywords: ketones · mass spectrometry · reaction mechanisms · silicon · trifluoromethylation

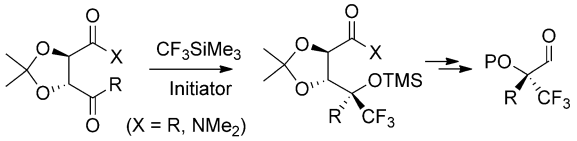
Introduction

The nucleophilic trifluoromethylation of carbonyl compounds by using trifluoromethyl(trimethyl)silane (TFMTMS; Ruppert–Prakash reagent)[1,2] is a widely applied methodology to have access to trifluoromethyl (TFM) derivatives,[3] an important class of organic chemicals. This reaction proceeds through a chain mechanism: the initiation is induced by nucleophilic activation of TFMTMS and the chain transfer proceeds by reaction of the intermediate TFM-carbinolate with TFMTMS (Scheme 1). The key advantage of this methodology and of this reagent lies in the stabilization of the TFM anion within a silicate species, which prevents its decomposition into difluorocarbene.[4] The need for only a catalytic amount of the nucleophilic activator is in accordance with this chain mechanism.



Scheme 1. Chain mechanism of trifluoromethylation with CF_3SiMe_3.

We recently reported the preparation of enantiopure α-alkoxy-α-TFM aldehydes from L-tartaric acid derived diketones[5] or ketoamides.[6] The first step was the fluoride-induced[5,6] or carbonate-induced[6] diastereoselective and chemoselective addition of TFMTMS (Scheme 2). If the selective monotrifluoromethylation of ketoamides was rather expected, we found the highly selective monoaddition on the diketone intriguing. Indeed, the bisphenone derivative **1** was converted, under tetrabutylammonium fluoride trihydrate (TBAF) or tetrabutylammonium difluorotriphenylsilicate (DFTPSi; DeShong reagent[7]) initiation,[8] into the corresponding ketocarbinol silyl ether **2**, even with an excess of TFMTMS (Scheme 3, Table 1). In contrast, the bisadduct **3** was obtained by using CsF as the initiator, in accordance with previous results for simple diketones.[9,10] We were keen on investigating this reaction more deeply to understand the reasons for such selectivity. Electrospray ionization mass spectrometry (ESI-MS) is a powerful tool for reactivity studies.[11,12] We made use of this analytical technology, in addi-



Scheme 2. Monotrifluoromethylation of tartaric acid derived diketones or ketoamides. TMS: trimethylsilyl.

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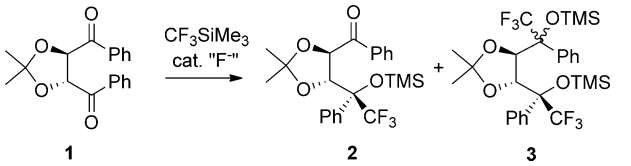
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201100551.



Scheme 3. The selectivity of the trifluoromethylation of tartaric acid derived diketone **1** varied according to the fluoride salt initiator.

Table 1. Selectivity of trifluoromethylation of tartaric acid derived diketone **1** versus fluoride salt initiator.[a]

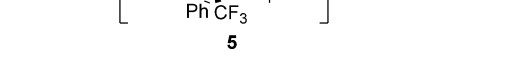
Equivalents of CF_3SiMe_3	Initiator	Reaction conditions[b]	Yield of **2** [%] (*de* [%])	Yield of **3** [%]
1–3	TBAF·3 H_2O	THF, 0 °C or RT, 0.33 h	90 (96)	0
1–3	$TBA^+Ph_3SiF_2^-$	CH_2Cl_2, 0 °C, 0.5–2 h	99 (92–96)	0
1	CsF	DME, −40 °C, 3 h	90 (40)	0
3	CsF	DME, RT, 12 h	9 (0)	54[c]

[a] Taken from reference [5]. [b] THF: tetrahydrofuran; RT: room temperature; DME: 1,2-diemthoxyethane. [c] Ratio of diastereoisomers: C2 symmetrical product/C2 symmetrical product/C1 symmetrical product 16/84/0, as determined by ^1H NMR spectroscopy.

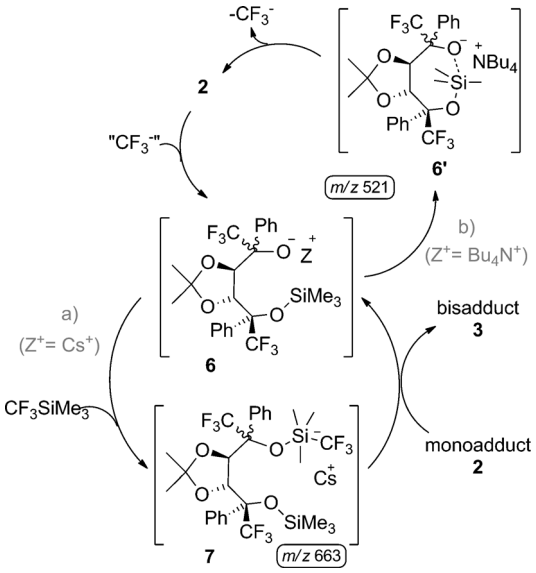
tion to complementary chemical experiments, to revisit our reaction. We report herein this study, which highlights the role of the cation and of the silyl moiety.

Results and Discussion

Before detailing the study on bisphenylketone **1**, we have to disclose some side results observed during the preparative aspect of this study. When the monoTFM adduct derived from the corresponding bis(ethylketone) was treated with TFMTMS under TBAF activation, the second addition took place, even if its diastereoselectivity was lower.[13] In contrast, adduct **2** was recovered after a new treatment under the same conditions. Thus, the conjugated character and/or the steric environment of the remaining carbonyl group affects its reactivity. The reaction giving monoadduct **2** does not deserve particular comment with regard to the chain mechanism, which is depicted in Scheme 4, including intermediates **4** and **5** and the corresponding *m*/*z* figures (for the anion species). As regards a possible subsequent reaction of **2** with TFMTMS, the situation seems not so clear. With CsF as the initiator, we can assume that a similar chain reaction occurs (Scheme 5, path a). With TBAF or DFTPSi, both



Scheme 4. First addition of CF_3SiMe_3 onto diketone **1**.

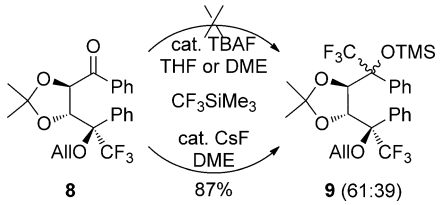


Scheme 5. Reaction of monoadduct **2** with CF_3SiMe_3.

bringing a tetrabutylammonium counterion, the pathway is obviously different. Our basic hypothesis took into account the fact that intermediate **6**, resulting from the trifluoromethylation of **2** would bear both a silyl ether moiety and an alkoxide moiety (Scheme 5). Owing to the high oxophilicity of silicon, a strong intramolecular interaction, not to say a bond, could induce a particular behavior of this intermediate, which also depends on the countercation. Thus, an Si-chelated species would be favored under TBAF or DFTPSi initiation, which would prevent the chain-addition process from continuing (Scheme 5, path b). We have attempted to assess such an hypothesis by two approaches: complementary chemical experiments and monitoring of reactions by ESI-MS under various conditions.

Chemical experiments: Bis(trifluoro)methylation occurred under CsF initiation and the reaction with CsF needed DME as a solvent, so we first checked that using this solvent with TBAF did not modify the chemoselectivity for monoaddition on **1**.

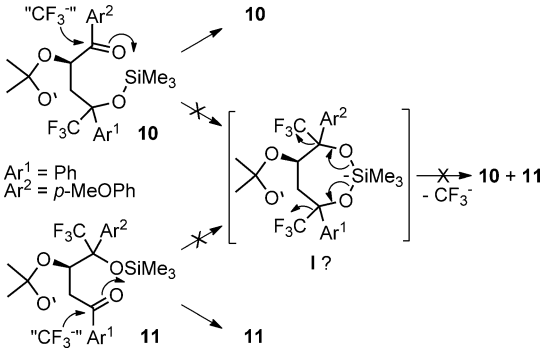
To gain insights into the possible role of the TMS group in stopping the reaction at the monoadduct stage, the *O*-allyl ketoether analogue **8** was prepared from the corresponding amido ether[6] and treated with TFMTMS under similar conditions (TBAF, THF). We were unable to isolate the bisTFM derivative **9**, even after adding an excess of reagents (Scheme 6).[14] This observation means that chelation of silicon, if there is any, is not the only parameter responsi-



Scheme 6. Tentative reaction of CF_3SiMe_3 with a ketoether.

ble for the chemoselectivity of the monoaddition. Given that the nature of the fluoride salt is important to control the chemoselectivity of the addition on the O-silylated monoadduct **2**, the reaction of the *O*-allyl analogue **8** was performed under CsF initiation in DME and, indeed, the second addition took place to give the bisTFM derivative **9** in 87% yield after isolation (two diastereomers in a ratio of 31:69). Once again, a control experiment with TBAF in DME enabled us to exclude any role of the solvent. These experiments led us to conclude that the nature of the counterion is a decisive factor in stopping the reaction after monoaddition (TBA^+) or allowing the second addition to take place (Cs^+), whatever the substituent on the oxygen atom. The influence of the size of the cation associated to the fluoride ion has already been observed in the case of TFMTMS addition on sulfinimides,[15] in which case tetramethylammonium fluoride proved to be more effective than TBAF. In a reaction of similar type, fluoride-induced (phenylsulfonyl)difluoromethylation of carbonyl compounds from the parent TMS reagent was effective by using DFTPSi as an initiator for aldehydes, but CsF was needed for ketones.[16] The countercation is the only difference in the first example,[15] which seems indicative of the influence of its size, even if the hydrated nature of TBAF may also be of importance with the strong Lewis base character of sulfinimides. In the second example,[16] both the cation (TBA^+ or Cs^+) and the nature of the fluoride species (fluoride ion or the bulky DFTPSi) are different and their relative influence is not so clear. Let us remember that DFTPSi and TBAF gave the same results and selectivity in our case, which indicates that the chemoselectivity is closely linked to the TBA^+ countercation. Nevertheless, we cannot rule out silicon chelation in the case of further reaction on compound **2**.

In order to assess the degree of possible Si chelation in the intermediate, we reasoned that covalent bonding between the oxygen and silicon atoms should give a pseudosymmetrical intermediate **I** and release the trifluoromethide anion from one or the other TFM carbinolate moiety (Scheme 7). Either of the keto silyl ethers **10** and **11** should give a mixture of both of them. Compounds **10** and **11** were prepared[17] and treated under similar conditions with the TFMTMS/TBAF system. In each case, only the starting material was recovered, which rules out the occurrence of the covalently chelated intermediate **I**. Similar results were obtained with analogues in which the methoxyphenyl group was replaced by an ethyl group.



Scheme 7. Does a pseudosymmetrical intermediate exist during the second addition step? Conditions: CF_3SiMe_3 (1.1 equiv), TBAF (0.05 equiv), THF, −20 °C.

We thus propose that, if any chelation takes place, then intermediate **6** (resulting from trifluoromethylation of the monoadduct **2**) evolves, under TBAF or DFTPSi initiation, via a chelated form of type **6′**, with an Si–O intramolecular interaction that is weaker than a covalent bond (Scheme 5). The possible occurrence of such an intermediate cannot be confirmed by chemical means, which justifies the following ESI-MS study.

ESI-MS study: The chemical approach afforded some insight into the mechanism of these transformations based on reaction products. We have undertaken an ESI-MS study in order to have access to the postulated intermediates. Samples of crude reaction medium were directly introduced into the mass spectrometer ion source, with the instrument operating in the negative ESI^- ion mode (all of the trifluoromethylated intermediate species are negatively charged). The key parameters for this study are the reaction time, initial stoichiometry of TFMTMS, and nature of the fluoride salt initiator.

The difluorosilicate (DFTPSi) salt was chosen as representative of the tetraalkylammonium-type initiators allowing a selective monoaddition and was compared to caesium fluoride. Selected experiments were presented in Figure 1–4. Diketone **1** was first treated with a substoichiometric amount of TFMTMS to approach the intermediates involved in the very first addition process depicted in Scheme 4. As exhibited in Figure 1, the ESI-MS spectra contain a peak corresponding to the nonsilylated intermediate **4** (*m*/*z* 379),[18] but no trace of the silylated compound **5** (*m*/*z* 521) was detected (Scheme 4). This means that the chain-transfer step is very fast and that the reaction kinetics are controlled by the step from **4** to **5**. On the other hand, the absence of a signal at *m*/*z* 521 is of importance to make easier further interpretation and discrimination between **5** and the isomeric species **6**/**6′**.

We next examined the behavior of the monoadduct **2** with TFMTMS under DFTPSi initiation, reaction conditions under which no apparent reaction occurred (Scheme 5, path b). Small peaks at *m*/*z* 379 (Figure 2) correspond to de-

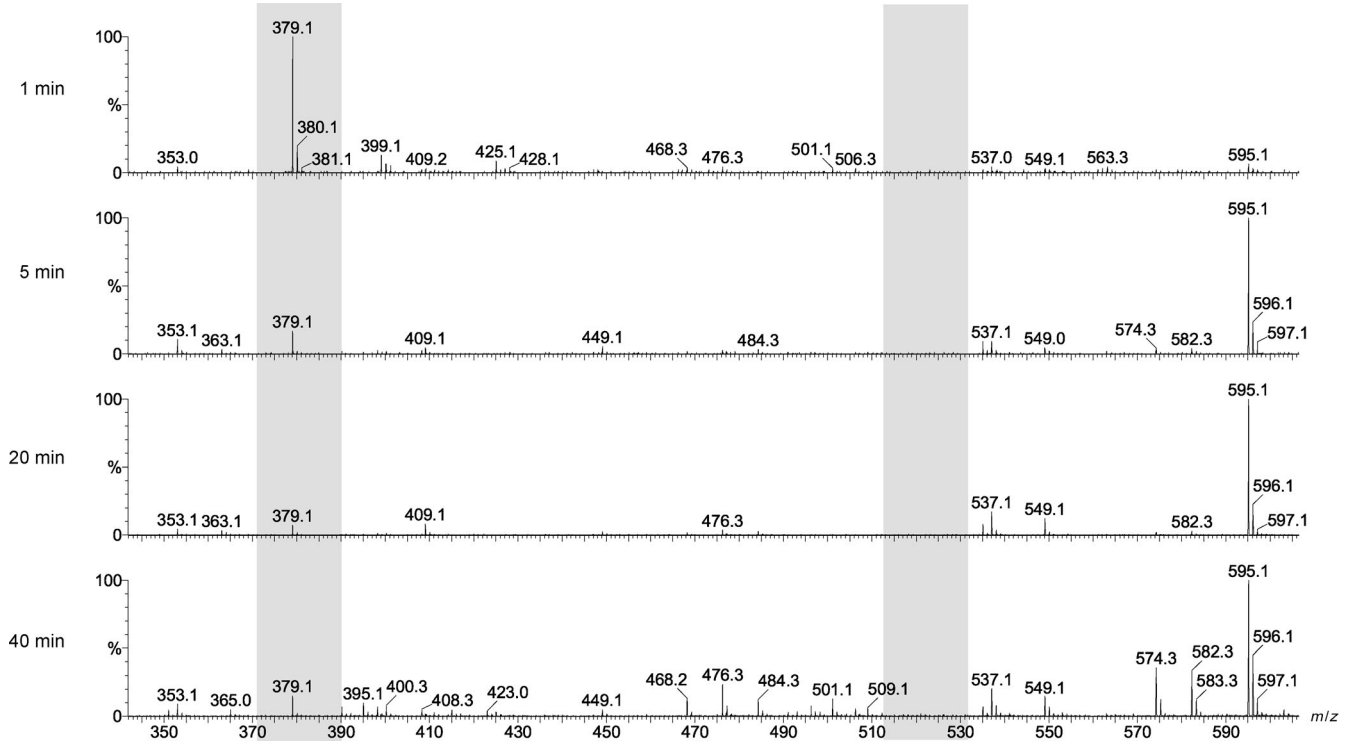


Figure 1. ESI-MS spectra for diketone **1** and CF_3SiMe_3 (0.8 equiv) with initiation by $TBA^+Ph_3SiF_2^-$.

silylation of starting material, which is not surprising owing to the possibility of TMS transfer to fluoride or alkoxide species. A peak appears at *m*/*z* 521[18] and disappears after 25 min. This is in accordance with an addition occurring to give an intermediate adduct that, instead of initiating a chain process, decomposes by releasing CF_3^- (see below)

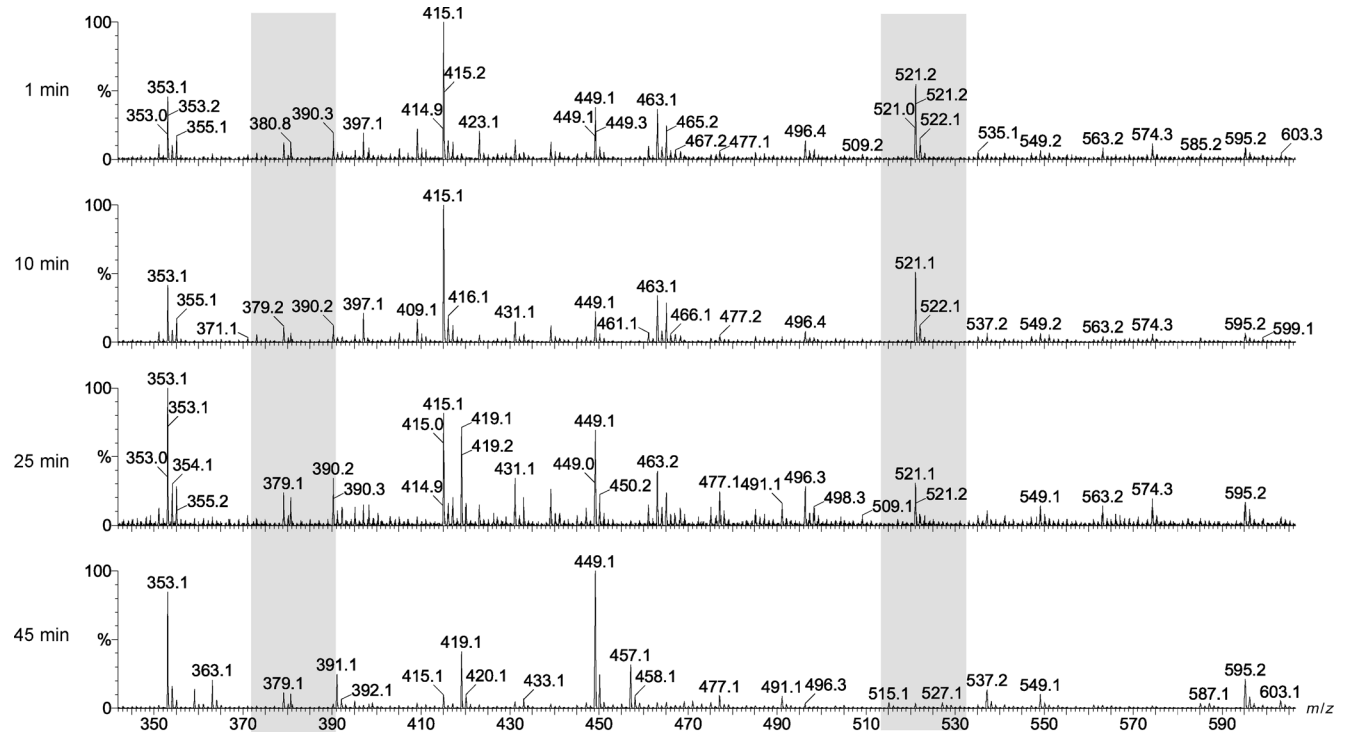


Figure 2. ESI-MS spectra for monoadduct **2** and CF_3SiMe_3 (1.6 equiv) with initiation by $TBA^+Ph_3SiF_2^-$.

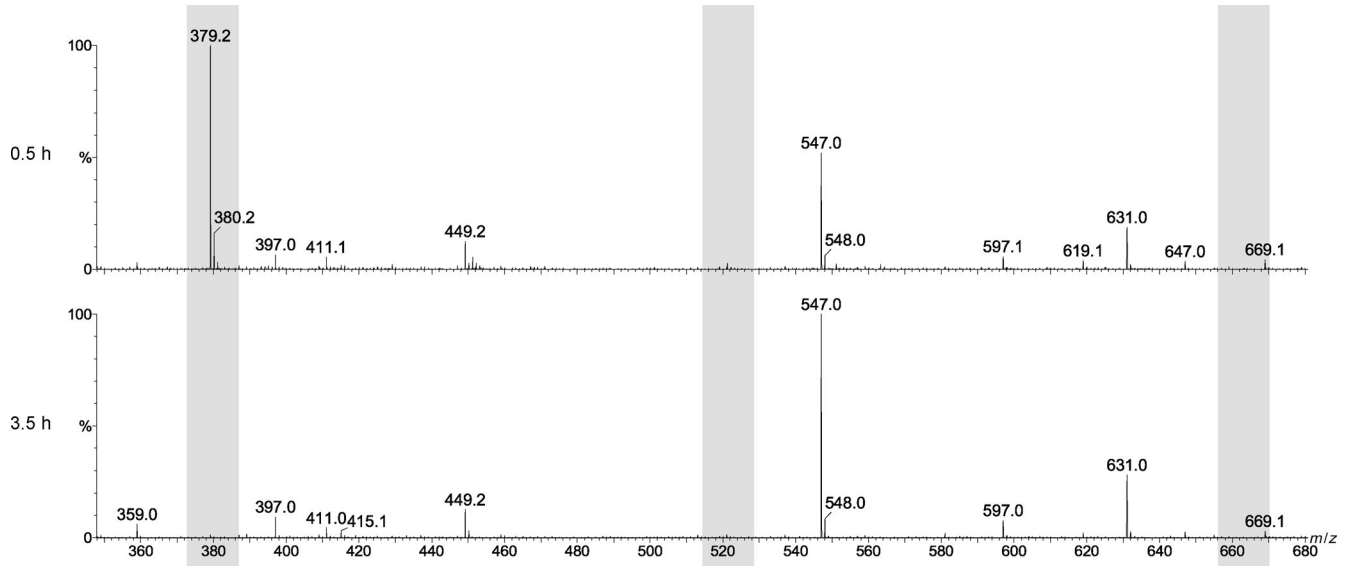


Figure 3. ESI-MS spectra for diketone **1** and CF_3SiMe_3 (3 equiv) with initiation by CsF.

and the starting compound **2**, until total consumption of the TFMTMS.

At this stage, it is still difficult to comment more accurately on the nature of this intermediate. The next experiment is more enlightening on that point. The spectra for the monitoring of the reaction of diketone **1** with an excess of TFMTMS initiated with CsF are shown in Figure 3. Intermediate **5** was undetected during the first addition, and intermediate **7** (*m*/*z* 663), its counterpart in the second addition process, was also undetected (Scheme 4 and Scheme 5, path a). More interestingly, the lack of a signal at *m*/*z* 521 under these conditions in which bisadduct **3** was formed via intermediate **6** means that such a signal under DFTPSi initiation could correspond to the chelated intermediate **6′** (Scheme 5, path b).

We have attempted in a last experiment to corroborate the previous observations by monitoring the reaction of diketone **1** with an excess of TFMTMS under DFTPSi initiation (Figure 4). The peak at *m*/*z* 379 is present at the very beginning of the reaction and the peak at *m*/*z* 521 was detected from the sample taken at 30 min. At such a concentration of TFMTMS, the first addition takes place rapidly and, as expected, the degenerated chain process through intermediate **6′** was observed after completion of the first addition.

Complementary observations: Remarkably, in most of the ESI-MS experiments, a mass peak at *m*/*z* 69 corresponding to the TFM anion[18] was observed.[19] Moreover, a concomitance between the appearance of this peak and the disappearance of the peak at *m*/*z* 521 in the tentative second addition on the monoadduct seems to corroborate the hypothesis of the release of CF_3^- from the intermediate **6**/**6′**. Even if this observation is worthy of note considering the very low stability of the TFM anion, we have not taken into account this observation as a decisive argument, owing to the qualitative character of this study and the very low relative intensity of the peak at *m*/*z* 69.

Concluding remarks

The chemical investigation disclosed that the counterion associated firstly to the initiator and then to the intermediates is of crucial importance to direct the selectivity towards the monoTFM product **2** (with TBA^+) or the bisTFM product **3** (with Cs^+). The ESI-MS study informed us of an intramolecular Si–O association in the intermediate, which results from a second addition in the case of a TBA^+ counterion, with subsequent collapse of this intermediate towards the monoadduct **2**. The failure of the reaction of TFMTMS with ketoether **8** under TBA salt initiation, in contrast to its achievement under CsF activation, indicated that the chelation of silicon is not the cause but a consequence of the difficulty of the TBA intermediate **6** to undergo the chain-transfer step. These experiments confirm the sensitivity of the second addition to steric hindrance, as already mentioned at the beginning of this discussion. The much higher ionic volume of TBA^+ (0.2951 nm^3)[20] compared to that of Cs^+ (0.0206 nm^3)[20,21] and its weaker solvation could explain both the lower chain reactivity of intermediate **6**/**6′** and the effective releasing of steric pressure to give back compound **2**.

Experimental Section

Procedures for chemical experiments and structural data of compounds **8**–**11** are given in the Supporting Information.

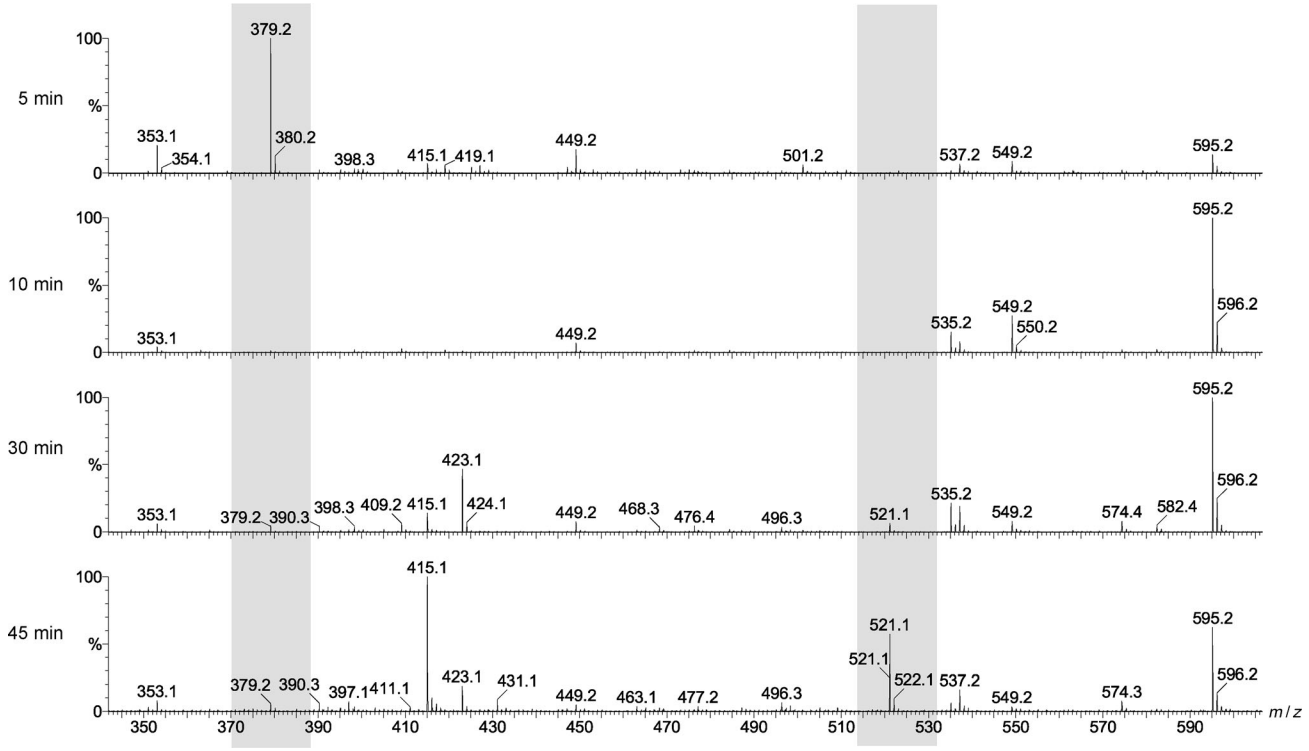


Figure 4. ESI-MS spectra for diketone **1** and CF_3SiMe_3 (3 equiv) with initiation by $TBA^+Ph_3SiF_2^-$.

All electrospray ionization mass spectrometry experiments (MS and HRMS) were carried out by using a hybrid tandem quadrupole/time-of-flight (Q-TOF) instrument, equipped with a pneumatically assisted electrospray (Z-spray) ion source (Micromass, Manchester, UK) operated in negative mode (ESI^-). Nitrogen was used as the nebulizer gas, and the samples were introduced into the ESI source through a needle at a flow rate of 5 $\mu L\,min^{-1}$. The main conditions were: capillary voltage 3000 V, cone voltage 40 V, source temperature 80 °C, and desolvation temperature 110 °C. The relative peak intensities observed in the spectra are in arbitrary units, with 100% assigned to the highest peak in the mass domain considered.

ESI-HRMS of intermediates observed: intermediate **4**: *m/z* calcd for $C_{20}H_{18}F_3O_4^-$: 379.1157 [M^-]; found: 379.1150; intermediate **6′**: *m/z* calcd for $C_{24}H_{27}F_6O_4Si^-$: 521.1583 [M^-]; found: 521.1580; trifluoromethyl anion: *m/z* calcd for CF_3^-: 68.9952 [M^-]; found: 68.9958.

Acknowledgements

This work has been supported by CNRS, Région Champagne–Ardenne and Ville de Reims.

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[13] The isolated monoadduct, treated with TFMTMS (1.1 equiv) and TBAF (0.05 equiv) in THF at −40 °C, was converted after 4 h into the bisaddition product in 75% yield (75:25 d.r.). In contrast, the direct formation of the bisadduct by treating the diethyl ketone with an excess of TFMTMS failed.
[14] The reaction was performed by using initially 1.05 equivalents of TFMTMS and 0.2 equivalent of TBAF in THF at 0 °C, followed by the addition of the same amounts of TFMTMS and initiator 8 h later.

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[17] Diketones **10** and **11** were prepared by aryl magnesium condensation with the corresponding *N*-methoxy-*N*-methyl- or *N*,*N*-dimethylamidoketone (see the Supporting Information).
[18] The structures of all intermediates considered in this ESI-MS study were confirmed by ESI-HRMS.
[19] To the best of our knowledge, the trifluoromethyl anion has never been observed in condensed medium by mass spectrometry.
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Received: February 18, 2011
Revised: May 23, 2011
Published online: August 11, 2011

