Organocatalytic α-trifluoromethylthiolation of silylenol ethers: batch vs continuous flow reactions

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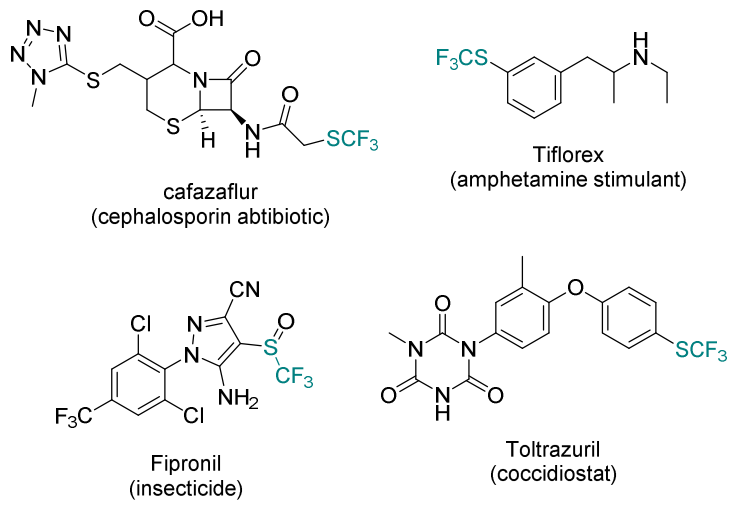
ABSTRACT

This work describes the organocatalytic α–trifluoromethylthiolation of silylenol ethers using *N*-(trifluoromethylthio)saccharin as trifluoromethylthiolating reagent that is activated by the presence of catalytic amounts of a Lewis base. Tetrahydrothiophene was identified as the best organocatalyst and it was successfully employed to promote the synthesis of different α–trifluoromethylketones; the reaction has been performed under a traditional batch methodology and under continuous flow conditions. In general, yields obtained using the traditional batch process were higher than those observed when the reaction was performed under flow conditions. However, short reaction times, higher productivity and higher space time yields were observed when a flow system process was employed. Preliminary DFT calculations were also performed in order to elucidate the mechanism of the reaction.

KEYWORDS: organocatalysis, trifluoromethylthiolation, flow chemistry, silylenol ether, Lewis bases.

1. INTRODUCTION

The incorporation of a SCF_3 group into organic molecules is a topic of great interest, especially for the pharmaceutical and agrochemical industries.[1] Due to its high lipophilicity and high electron-withdrawing character (Hansch lipophilicity parameter π_R= 1.44 vs π_R= 0.88 for CF_3),[2] the SCF_3 moiety represent a powerful opportunity to influence the pharmacokinetics properties of a drug molecule increasing the transmembrane permeation. [3, 4] A few examples of molecular targets with a SCF_3 group possessing biological activities are reported in Scheme 1.



Scheme 1: Agrochemicals and active pharmaceutical ingredients containing a SCF_3 group.

In the last few decades, numerous methods for the introduction of a trifluoromethylthio group into organic compounds have been reported;[5, 6] however, the development of efficient methods to introduce catalytically and directly the SCF_3 to the *alpha*- position of a carbonyl function is still a challenge. The first example of a metal-free, but non catalytic, SCF_3 electrophilic substitution on a carbonyl compound was reported by Haas in 1980, where diethyl malonate reacts with highly toxic electrophilic gas $ClSCF_3$ to form mono- and di- substituted products.[7] Few years later also the trifluoromethylthiolation of ketones,[8] cyclic β-diketones,[9] β-keto acids,[10] α,β-unsaturated cyclic ketones[11] trimethylsilyl enol ethers[12] and enamines[12, 13] performed with $ClSCF_3$ were reported in good yields. In the last few years, with the aim to employ less dangerous compounds as SCF_3 sources, the trifluoromethylthiolation of amino-indoles and α-bromo ketones promoted by octadecyl-*S*-trifluorothiol carbonate were investigated.[14] Other non- catalytic metodologies involving the generation of different "$^{+}SCF_3$" sources for the synthesis of trifluoromethylthiolated aldehydes[15-17] ketones,[15, 18] β-ketoesters[16, 17] indoles and oxindoles[19] were developed.

On the other hand, to date, only a very few organocatalytic α-trifluoromethylthiolation reactions of carbonyl compounds have been described in literature. Starting from 2013, Shen and Rueping, independently, reported the stereoselective cinchona catalyzed trifluoromethylthiolation of indanone-derived β-ketoesters[20, 21] and of oxindoles[22, 23] using respectively α-trifluoromethylthiolated hypervalent iodine reagent and trifluoromethylthiophthalimide as an electrophilic SCF_3 source. Cinchona alkaloids derivatives were also employed as organocatalysts in the α-trifluoromethylthiolation of 3-thiooxindoles.[24] In 2014, Liu and Tan reported another version of enantioselective trifluoromethylthiolation of oxindoles performed with an *in situ* generation of an electrophilic trifluoromethylthio reagent involving as precursors trichloroisocyanuric acid and $AgSCF_3$.[25]

However, it must be noted that all these catalytic methodologies, cannot be applied to simple ketones or aldehydes and work exclusively with activated carbonyl compounds such as keto esters and β-

diketones. On the best of our knowledge, the first catalytic methodology involving the use of not-activated carbonyl compounds was reported by Billard in 2014.[26] In this approach catalytic amounts of Me_3SiCl activated the trifluoromethanesulfenamide and promote the transfer of SCF_3. More recently, Wu and Sun published another example of α-trifluoromethylthiolation of simple aldehydes by enamine catalysis using the Hayashi-Jørgensen catalyst.[27]

Therefore, despite considerable efforts, at the moment, only two examples of catalytic α-trifluoromethylthiolation of un-activated carbonyl compounds exist. As a part of our continuing development of Lewis base activation of Lewis acids, and on the basis of the experience of some of us in α-thiofunctionalization reactions,[28] we report herein the catalytic α-trifluoromethylhthiolation of ketone-derived enoxysilanes promoted by Lewis basis.

2. EXPERIMENTAL

2.1. Experimental instrument and materials

^{1}H-NMR, ^{13}C-NMR and ^{19}F-NMR spectra were recorded with instruments at 300 MHz (Bruker F300). Proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). ^{13}C NMR spectra were recorded operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{19}F NMR spectra were recorded operating at 282 MHz. Fluorine chemical shifts are reported in ppm (δ) relative to CF_3Cl. All the solvents were used are commercially available (≥99%, chromatographic grade, purchased from Sigma Aldrich) and stored under nitrogen over molecular sieves (bottles with crown cap). Reactions were monitored by analytical thin-layer chromatography (TLC) using Aluminium oxide or silica gel 60 F_{254} pre-coated glass plates and visualized using UV light. Chromatographic purification where performed on Aluminium oxide, neutral, Brockmann I 50-200 μm 60A previously deactivated with 3% of H_2O.

2.2. Experimental procedure

2.2.1 Synthesis of $AgSCF_3$

AgF (1 eq, 47.4 mmol, 6 g), CS_2 (2.1 eq, 99.3 mmol, 6 mL) in CH_3CN (12 mL) were placed in a dark flask under N_2 atmosfere and heated to reflux for 18h. After this time, the mixture was cooled to RT and all the volatile parts were removed under reduced pressure. The remaining black residue was then dissolved in AcOEt, all the insoluble parts were removed by filtration and the liquid phase was concentrated with the aid of a rotary evaporator. The resulting pale yellow solid was then dissolved in a small amount of CH_3CN and 40 mL of Et_2O were carefully layered on top of this solution. The mixture was then placed at -15 °C for 24h to produce a needle-shaped white solid that was recovered by filtration and washed with cooled Et_2O. The solid was stored at 5 °C with the exclusion of light. Yield: 0.62 g, 76%. ^{19}F-NMR (CD_3CN) : δ -22.51 (s) ppm

2.2.2 Synthesis of *N*-chlorophthalimide

$AlCl_3$ (1 eq, 10 mmol, 1.36g) was added to a solution of $Pb(OAc)_4$ (1 eq, 10 mmol, 4.52g) in dry CH_3CN (100 mL). The mixture was stirred at RT for 5 min, then phthalimide (1 eq, 10 mmol, 1.5 g) was added. The resulting mixture was gently refluxed until nitrogen for 20h, then cooled to RT. The solvent was removed by rotary evaporation, and the crude was purified by chromatographic purification with pure DCM as eluent. Yield: 1.32 g, 71%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.82-7.79 (m, 2H) ppm.

2.2.3 Synthesis of *N*-chlorosaccharin

$AlCl_3$ (1 eq, 10 mmol, 1.36g) was added to a solution of $Pb(OAc)_4$ (1 eq, 10 mmol, 4.52g) in dry CH_3CN (100 mL). The mixture was stirred at RT for 5 min, then phthalimide (1 eq, 10 mmol, 1.5 g) was added. The resulting mixture was gently refluxed until nitrogen for 20h, then cooled to RT. The solvent was removed by rotary evaporation, and the crude was purified by chromatographic purification with pure DCM as eluent. Yield: 1.32 g, 71%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.94-7.91 (m, 2H), 7.82-7.79 (m, 2H) ppm.

2.2.4 Synthesis of *N*-(trifluoromethylthio)phthalimide (**2a**)

$AgSCF_3$ (1.3 eq, 2.4 mmol, 500 mg) was added to a solution of *N*-chlorophthalimide (1 eq, 1.8 mmol, 330 mg) in CH_3CN (8 mL) under N_2 atmosphere. The mixture was stirred for 3h at RT, then the solvent was removed by rotary evaporation. The crude obtained was dissolved in DCM, filtered through a celite pad and the solvent was removed by rotary evaporation to give a white solid. Yield: 0.40 g, 89%.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, 2H, J = 6Hz, J = 3Hz), 7.88 (dd, 2H, J = 6Hz, J = 3Hz) ppm. ^{19}F-NMR ($CDCl_3$): δ -49.32 (s, 3F) ppm. ^{13}C-NMR ($CDCl_3$): δ 165.7, 135.4, 131.4, 127.9 (q, J = 322.5 Hz), 124.7 ppm.

2.2.5 Synthesis of *N*-(trifluoromethylthio)saccharin (**2b**)

N-chlorosaccharin (1 eq, 1.15 mmol, 250 mg) and $AgSCF_3$ (1.2 eq, 1.38 mmol, 288 mg) were dissolved in CH_3CN (4 mL) under N_2 atmosphere. The mixture was stirred vigorously at room temperature for 10 min. The CH_3CN was then drained under reduced pressure. And the residue was extracted
with CH_2Cl_2 (3mL x 3). The solution was combined and the solvent was evaporated under vacuum. The residue was further dried under high vacuum to give compound **2b** as a white solid. Yield 251 mg, 77%. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.20 (d, 1H J = 7.5 Hz), 8.08-7.99 (m, 2H), 7.98-7.91 (m, 1H).

^{19}F-NMR ($CDCl_3$): δ -47.73 (s, 3F) ppm. ^{13}C-NMR ($CDCl_3$): 158.4, 137.9, 136.4, 135.0, 127.8 (q, J = 315 Hz), 126.5, 126.1, 122.0 ppm

2.3. General procedure for trifluoromethylthiolation of silylenol ethers (batch conditions)

A solution of desired silylenol ether **1a-d** (1 eq, 0.14 mmol) in 900 uL of solvent was charged in a two necks 10 ml round bottom flask (provided with a condenser when necessary) containing compound **2a** or **2b** (1 eq, 0.14 mmol). A solution of desired silylenol ether **1a-d** (1 eq, 0.14 mmol) in 900 uL of solvent was then added (final concentration: 0.1 M). The reaction mixture was stirred at the desired temperature for the desired time, then a quench with 1 mL of $NaHCO_3$ saturated solution was performed. The mixture was further diluted with 2 mL of AcOEt, then two layers were separated and the organic phase was recovered, dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude was then purified by chromatographic purification on Aluminium oxide, with a mixture of Hexane:DCM 9:1.

2.4. General procedure for α–trifluoromethylthiolation of silylenol ethers performed using Chemtrix Labtrix® Start Standard platform (flow conditions)

A Labtrix® Start Standard system, with a 10 µl glass microreactor was used. In a typical experiment, syringe A was filled with a mixture obtained dissolving 0.2 mmol of desired silylenol ether **1a-d**, 0.02 mmol of biphenyl as internal standard, and 0.02 mmol of THT in 1000 µL of dry CH_3CN in order to have 0.2 M concentration of silylenol ether**.** Syringe B was filled with a solution obtained dissolving 0.2 mmol of trifluoromethylthiolating agent in 1000 µL of dry CH_3CN in order to have 0.2 M concentration of "$^{+}SCF_3$" source (the concentrations of all reagents in the syringe were doubled with respect to the batch conditions, to achieve the same concentration after mixing). Mixtures A and B were pumped into the microreactor with the desired flow rate for the desired residence time. Three reactor volumes were discarded before starting sample collection in order to reach steady-state conditions. Then the mixture was collected in a 400 µL of 1:1 AcOEt:$NaHCO_{3(SS)}$ solution and the organic phase was directly analyzed by GC. Conversions were reported in tables.

2.5. Product analysis

*2.5.1. 1-phenyl-2-((trifluoromethyl)thio)propan-1-one (**3a**)*

The title compound was prepared according to typical experimental procedure. Yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.00 (d, 2H, J = 9.1 Hz), 7.6 (t, 1H, J = 7.4 Hz), 7.54 (m, 2H), 4.99 (q, 1H, J = 7.1 Hz), 1.74 (d, 3H, J = 7.1 Hz). ^{19}F-NMR ($CDCl_3$): δ -39.80 (s, 3F) ppm; ^{13}C-NMR ($CDCl_3$): 196.3, 134.0, 130.7 (q, J = 305.2 Hz), 129.0, 128.7, 44.5, 19.8 ppm.

2.5.2 1-(4-methylphenyl)-2-((trifluoromethyl)thio)propan-1-one (**3b**)

The title compound was prepared according to typical experimental procedure. Isolated as yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.98 (d, 2H, J = 7.5 Hz), 7.00 (d, 2H, J = 7.5 Hz), 4.97 (q, 1H, J = 7.1 Hz), 3.92 (s, 3H), 1.74 (d, 3H, J = 7.0 Hz) ppm. ^{19}F-NMR ($CDCl_3$): δ -39.85 (s, 3F) ppm; ^{13}C-NMR ($CDCl_3$): 194.7, 164.3, 132.9, 132.0 (q, J = 305.25 Hz), 114.2, 55.6, 44.3, 20.0 ppm.

2.5.3 1-((trifluoromethyl)thio)-2-cyclohexanone (**3c**)

The title compound was prepared according to typical experimental procedure. Isolated as yellow oil using pentane:DCM 9:1 mixture. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.65 (t, 1H, J = 6.2 Hz), 2.40 (t, 2H, J = 6.5 Hz), 2.07 (m, 2H), 1.70-1.55 (m,4H). ^{19}F-NMR ($CDCl_3$): δ -39.23 (s, 3F).

2.5.4. 2-((trifluoromethyl)thio)-3,4-dihydronaphthalen-1(2H)-one (**3d**)

The title compound was prepared according to typical experimental procedure. Isolated as yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.07 (dd, 1H, J = 7.9, 1.4 Hz), 7.55 (td, 1H, J = 7.5, 1.4 Hz), 7.37 (t, 1H, J = 7.6 Hz), 7.29 (d, 1H, J = 6.6 Hz), 4.38 (dd, 1H, J = 10.7, 4.4 Hz), 3.21-3.09 (m, J = 7.3, 4.9 Hz, 2H), 2.77-2.67 (m 1H), 2.48-2.36 (m, 1H). ^{19}F-NMR ($CDCl_3$): δ -38.74 (s, 3F) ppm; ^{13}C-NMR ($CDCl_3$): 192.1, 142.9, 135.1, 131.5 (q, J = 305.2 Hz), 131.1, 128.7, 128.1, 126.4, 51.7, 31.2, 28.2 ppm.

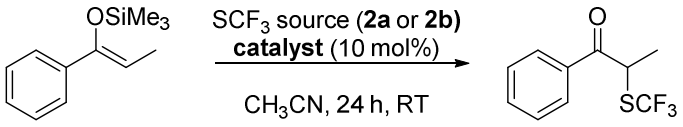
3. RESULTS AND DISCUSSION

For preliminary studies, we selected as model substrate the (Z)-(1-phenylpropenyloxy)silane **1,** prepared from acetophenone by treatment with LDA followed by the addition of trimethylsilyl chloride in THF at low temperature. The E:Z selectivity will be dictated by the reaction conditions, as described by Ireland[29]and in our case E:Z ratio was major than 1:99. The second step was to determine a suitable sulfur(II) reagent ("$^{+}SCF_3$" donor). In this sense, the quantitative scale for the trifluoromethylthio cation-donating ability of electrophilic trifluoromethylthiolating reagents reported by Xue and Cheng[30] was taken into account. According to this scale, a new parameter called trifluoromethylthiocation donating ability ($Tt^{+}DA$), was introduced as a quantitative descriptor for the propensity of electrophilic trifluoromethylthiolating reagents to transfer a SCF_3 moiety to organic compounds. Based on that, *N*-(trifluoromethylthio)phthalimide (**2a**) developed by Munavalli[31] present a $Tt^{+}DA$ = 33 Kcal/mol and it is known to be able to transfer the SCF_3 group to enamines at room temperature without the presence of a catalyst. For this reason, this trifluoromethylthiolating reagent represents a good choice for preliminary investigation. In addition, the more reactive *N*-(trifluoromethylthio)saccharin **2b** ($Tt^{+}DA$ = 17.9 Kcal/mol), developed by Shen[16] was also considered as a valid alternative.

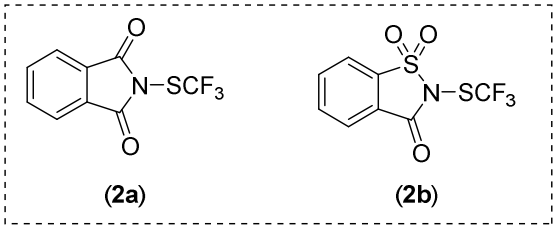
3.1 Studies performed under batch conditions

As initial conditions, 1 eq of pure (Z)-(1-phenylpropenyloxy)silane **1a** was reacted under traditional batch conditions with 1 eq of triffluoromethylthiolating reagent **2a-b** in CH_3CN as solvent (0.1 M) for 24 h at room temperature. Results of this initial screening are reported in Table 1.

Table 1: Survey of bases for the α-trifluoromethylthiolation of (Z)-**1**.



(**1a**) (**3a**)

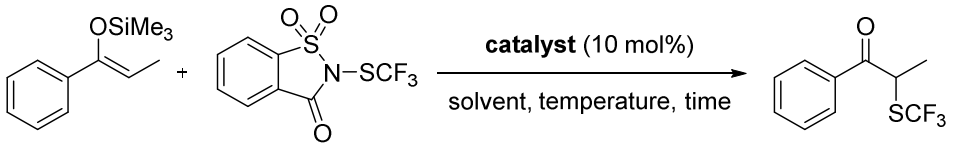


(**2a**) (**2b**)

Entry	Reagent	Catalyst	^{1}H-NMR conv (%)	yield (%)
1	2a	-	-	-
2	2a	TEA	-	-
3	2a	THT	< 5%	Not isolated
4	2b	-	-	-
5	2b	TEA	60	55
6	2b	DABCO	22	20
7	2b	DBU	19	15
8	2b	THT	55	50
9	2b	HMPA	30	27
10	2b	Ph_2Se	28	25

As showed, no reaction occurred when either **2a** or **2b** were used in the absence of catalyst and no product was formed when *N*-(trifluoromethylthio)phthalimide was employed in combination with catalytic amount of triethylamine (TEA) or tetrahydrothiophene (THT). However, *N*-(trifluoromethylthio)saccharin gave product **3a** in 55% yield in the presence of triethylamine (10 mol%), demonstrating that the reaction could be performed under catalytic conditions. Different tertiary amines where then tested, such as DABCO and DBU, but lower yields were observed (entries 6 and 7). The use of HMPA and diphenylselenide were also investigated and, in this case, product **3a** was isolated in 27 and 25% yield (entries 9-10). Nevertheless, the reaction performed using tetrahydrothiophene as organocatalys gave a product with 50% yield. On the basis of these data, triethylamine and tetrahydrothiophene were selected for further optimization studies. Few selected results are reported in table 2.

Table 2: Screening of reaction conditions under batch conditions.



(**1a**) (**2b**) (**3a**)

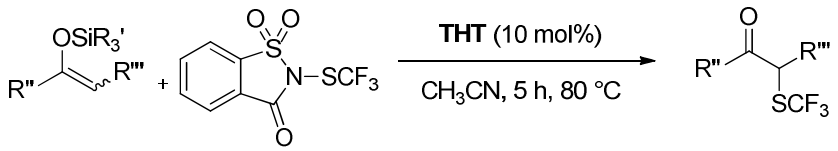
Entry	Catalyst (loading)	Solvent	Temperature (°C)	Time (h)	^{1}H-NMR conv (%)	Yield (%)
1	TEA (10 mol%)	DCM	25	20	27	25
2	TEA (10 mol%)	THF	60	20	-	-
3	TEA (10 mol%)	Toluene	80	20	-	-
4	TEA (10 mol%)	CH_3CN	80	20	74	66
6	TEA (5 mol%)	CH_3CN	80	5	38	32
7	TEA (1 mol%)	CH_3CN	80	5	24	13
8	THT (10 mol%)	CH_3CN	80	5	74	66
9	THT (5 mol%)	CH_3CN	80	5	56	51
10	THT (1 mol%)	CH_3CN	80	5	38	30
11[a]	THT (10 mol%)	CH_3CN	80	5	100	97

[a]2 equivalents of **2b** were used.

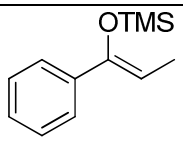
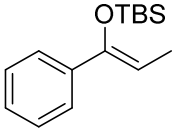
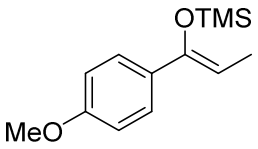
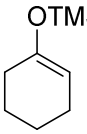
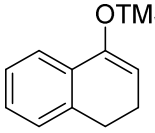
From a careful screening of solvent, temperature and reaction time, acetonitrile was selected as the preferred reaction medium; performing the reaction at 80 °C for 20 hour using 10 mol% TEA as catalyst, the product **3a** was obtained in 66% yield (entry 4).

The same chemical efficiency was also obtained using 10 mol% THT, but in only 5 hours (entry 9), demonstrating that the latter catalyst present a better chemical efficiency than triethylamine. Under the best experimental conditions, it was attempted to lower the catalyst loading: by decreasing the amount of TEA to 5 mol% and to 1 mol%, **3a** was formed in 38% yield and 24% respectively (entries 9 and 10); instead, 5 mol% of THT gave the desired product in 56% yield (entry 10). When 2 equivalents of trifluoromethylthiolated saccharin **2b** were employed (entry 12), a quantitative yield was observed; however, since **2a** is the most expensive reagent in this type of transformation, we decided to use a 1:1 ratio of substrates with 10 mol% of THT in acetonitrile at 80 °C for 5h as best reaction conditions. We next extended the scope of the reaction to differently substituted silyl enol ethers to verify the general applicability of this methodology.

Table 3: trifluoromethylthiolation of various silyl enol ethers.



(**1a-e**) (**2b**) (**3a-d**)

Entry	Substrate		Product	^{1}H-NMR conv (%)	yield (%)
1[a]		**1a**	**3a**	74	66
2[a]		**1b**	**3a**	52	42
3[a]		**1c**	**3b**	48	40
4		**1d**	**3c**	75	70
5		**1e**	**3d**	44	32

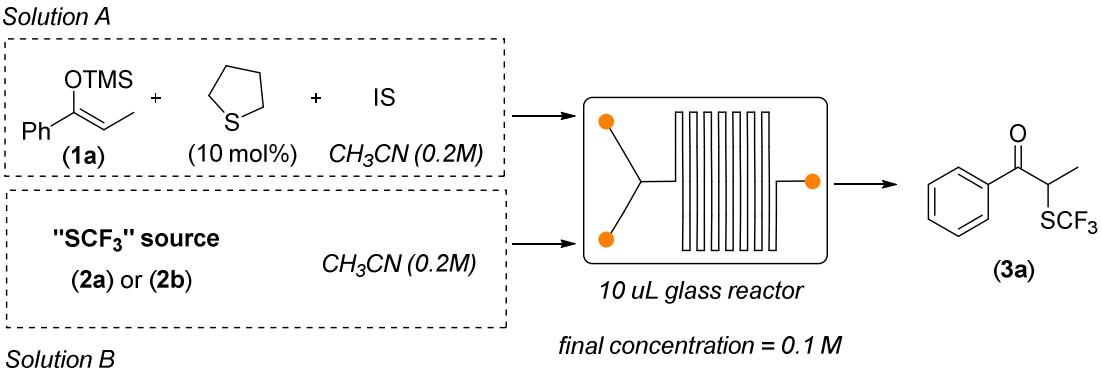
[a]Z:E ratio was > 99:1

The presence of a bulky protecting group such as tertbutyldimethylsilyl (TBS) seem to slightly interfere in the formation of product **3a**, that was obtained in 42% yield when substrate **1b** was used (table 3, entry 2). Furthermore, the presence of electron donating substituents seems to cause a yield decrement, as product **3b** was isolated in 40% yield. Interesting, good results were obtained using cyclic compounds: (*E*)-silylenol ether **1d** was converted in product **3c** in 75% yield (entry 4) but more rigid compound **1e** gave α-trifluoromethylthiolated compound **3d** with 32% yield only.

3.2 Studies performed under flow conditions

In order to improve the efficiency of the organocatalytic α-trifluoromethylthiolation of silylenol ethers, we then investigated the new reaction under continuous flow conditions.[32] For the screening of reaction conditions and for synthesis of compounds, we used a commercially available Chemtrix Labtrix® Start Standard platform equipped with two syringe pumps (Chemix Fusion 100) to deliver the reagents through

two Hamilton gastight 500 µL syringes into a glass microreactor (Chemtrix SOR 3223; 10 µL volume, channel width 300 µm and channel depth 120 µm). Conversions were determined by GC using biphenyl as internal standard (IS). Scheme **2** reports a simplified picture of the microreactor in which a 0.2 M solution of silylenol ether (**1**), containing 10 mol% of tetrahydrothiophene and byphenyl (as internal standard) in acetonitrile (Solution A) and a 0.2 M solution of trifluoromethylthiolating reagent (solution B) were fed into the microreactor. Preliminary results are reported in table 4.



Scheme 2: Organocatalytic α-trifluoromethylthiolation of silylenol ethers under flow conditions.

Table 4: Screening of reaction conditions under flow conditions using **2b** as trifluoromethylthio source.

Entry	Temp (°C)	Flow rate[a] (µL/min)	Residence time (min)	Conv[b] (%)
1[c]	60	2	5	-
2	RT	2	2.5	15
3	RT	1	5	19
4	RT	0.5	10	37
5	40	2	2.5	24
6	40	1	5	28
7	40	0.5	10	35
8	60	2	2.5	22
9	60	1	5	33
10	**60**	**0.5**	**10**	**52**
11	60	0.33	15	41
12	70	0.5	10	36
13[d]	80	2	2.5	19
14[d]	80	1	5	22
15[d]	100	2	2.5	18
16[d]	100	1	5	19

17 [d]	120	2	2.5	16
18 [d]	150	2	2.5	12

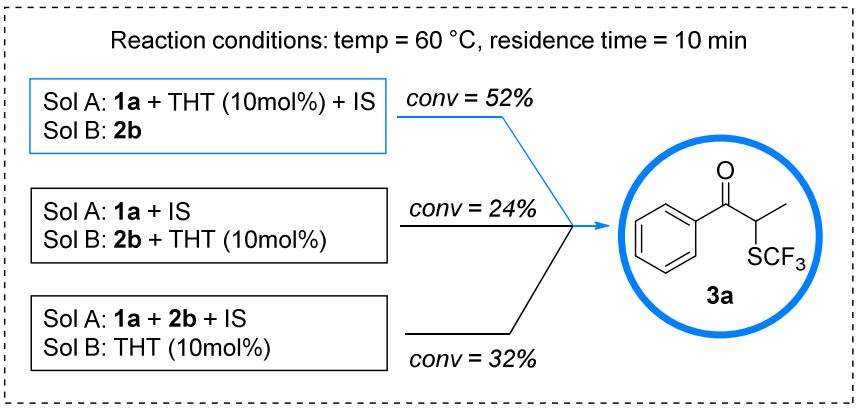
[a]The total flow rate is given by the sum of the flow rate of the two syringe pumps that feed reagents with the same rate. [b]Monitored by GC using biphenyl as internal standard. [C]Reaction performed using 0.2 M solution of **2a**. [d]A 100 psi back pressure regulator was mounted at the end of the microreactor.

As in the case of batch conditions, product formation was not observed when a 0.2 M solution of *N*-(trifluoromethylthio)phthalimide (**2a**) was employed (table 4, entry 1). However, we were glad to find that product **3a** could be detected with 19% yield at RT after 5 min residence time using a 0.2 M solution of **2b** (entry 3). Increasing the residence time to 10 min gave the desired product in 37% yield. The same level of chemical efficiency was observed when the temperature was increased to 40°C (entries 4 vs 7).

On the basis of these data, a screening of different temperature as well as flow conditions was performed, and best results were obtained when operating at 60 °C, with 10 minutes of residence time; in this case the formation of the desired product occurred in 52% yield (entry 10). It must be noted that comparable yield was obtained using 10 mol% of THT at RT after 24 h (table 1, entry 8) proving that, in this reaction, the flow approach is more efficient than the traditional one.

Operating at temperature higher than 60°C, in the presence of a back pressure regulator valve at the end of the microreactor (in order to avoid the evaporation of the solvent), a strong degradation of the starting silylenol ether was observed, with concomitant decrement of product yields. (entries 13-16).

In order to understand whether different initial catalyst-substrate pre-coordination phenomena may play a role in the α-trifluoromethylthiolation of silylenol ethers, various combinations of feeding mixtures were studied, showing that also the feeding system can influence the chemical efficiency of the process (scheme 3).

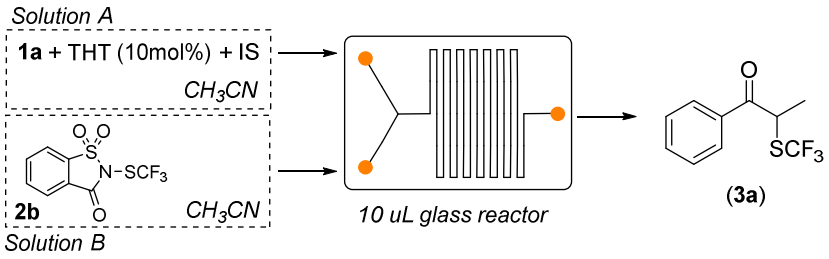


Scheme 3

Generally, during all experiments, no clogging problems were encountered; however, the attempt to perform the reaction using more concentrated solution failed, due to a solubility problems of *N*-(trifluoromethylthio)saccharin. On the other hands, when more diluted solutions were used, poor results

were obtained. (Table 5, entry 1). When 0.2 M solution of *N*-(trifluoromethylthio)saccharin **2b** was fed into the microreactor with a 0.1 M solution of silylenol ether (2:1 ratio), product **3a** was formed with lower yields (entries 2-7). Since it was not possible to increase the concentration of **2b** more than 0.2 M (syringe B), we next changed the stoichiometric ratio of the reaction simply by varying the flow rate of the two solutions. In this case, best results were obtained operating at 60 °C, where compound **3a** was obtained in 34% yield after 10 minutes.

Table 5: Screening of reaction conditions with different concentrations and molar ratio.



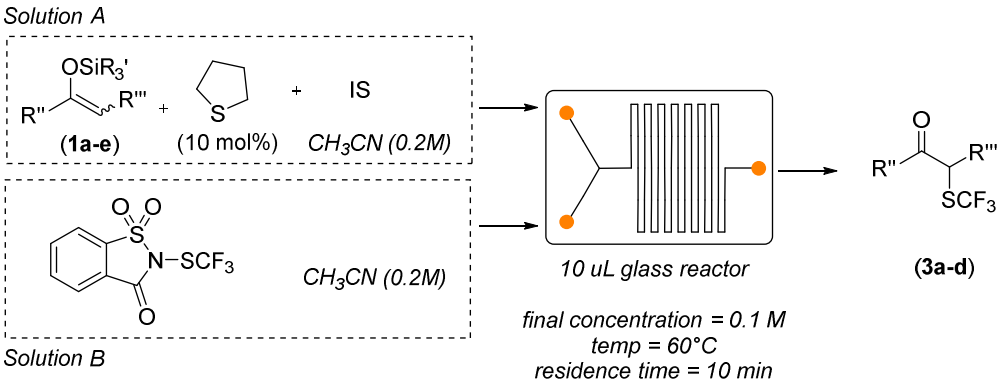
Entry	Temp (°C)	**1a** eq [M]	**2b** eq [M]	Flow rate Syringe A (µL/min)	Flow rate Syringe B (µL/min)	Total flow rate (µL/min)	Residence time (min)	Conv[a] (%)
1	60	1 (0.1)	1 (0.1)	0.5	0.5	1	10	10
2	RT	1 (0.1)	2 (0.2)	1	1	2	5	11
3	RT	1 (0.1)	2 (0.2)	0.5	0.5	1	10	12
4	40	1 (0.1)	2 (0.2)	1	1	2	5	11
5	40	1 (0.1)	2 (0.2)	0.5	0.5	1	10	13
6	60	1 (0.1)	2 (0.2)	1	1	2	5	10
7	60	1 (0.1)	2 (0.2)	0.5	0.5	1	10	14
8	RT	1 (0.2)	2 (0.2)	1.33	2.67	4	2.5	9
9	RT	1 (0.2)	2 (0.2)	0.66	1.27	2	5	20
10	RT	1 (0.2)	2 (0.2)	0.33	0.67	1	10	26
11	40	1 (0.2)	2 (0.2)	1.33	2.67	4	2.5	18
12	40	1 (0.2)	2 (0.2)	0.66	1.27	2	5	25
13	40	1 (0.2)	2 (0.2)	0.33	0.67	1	10	33
14	60	1 (0.2)	2 (0.2)	0.33	0.67	1	10	34

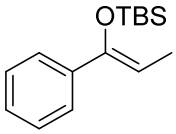
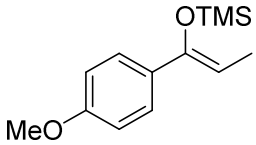
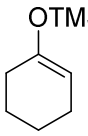
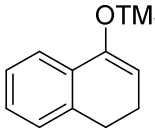
[a] Monitored by GC using biphenyl as internal standard.

After having established the best reaction conditions for the α-trifluoromethylthiolation of silylenol ether **1a** in flow, the reaction was extended to the synthesis of compounds **3a-d** under continuous flow

conditions, in the same, identified optimized experimental conditions: 1:1 molar ratio, 0.2 M concentration at 60 °C with 10 min as residence time (table 4, entry 10). The results are reported in table 6.

Table 6: Trifluoromethylthiolation of various silyl enol ethers performed under flow conditions.



Entry	Substrate		Product	Conv (%)
1[a]		**1b**	**3a**	25[b]
2[a]		**1c**	**3b**	32[c]
3		**1d**	**3c**	11[c]
4		**1e**	**3d**	19[c]

[a] Z:E ratio > 99:1. [b] Monitored by GC using biphenyl as internal standard and confirmed by ^{1}H-NMR. [c]Determined by ^{19}F-NMR.

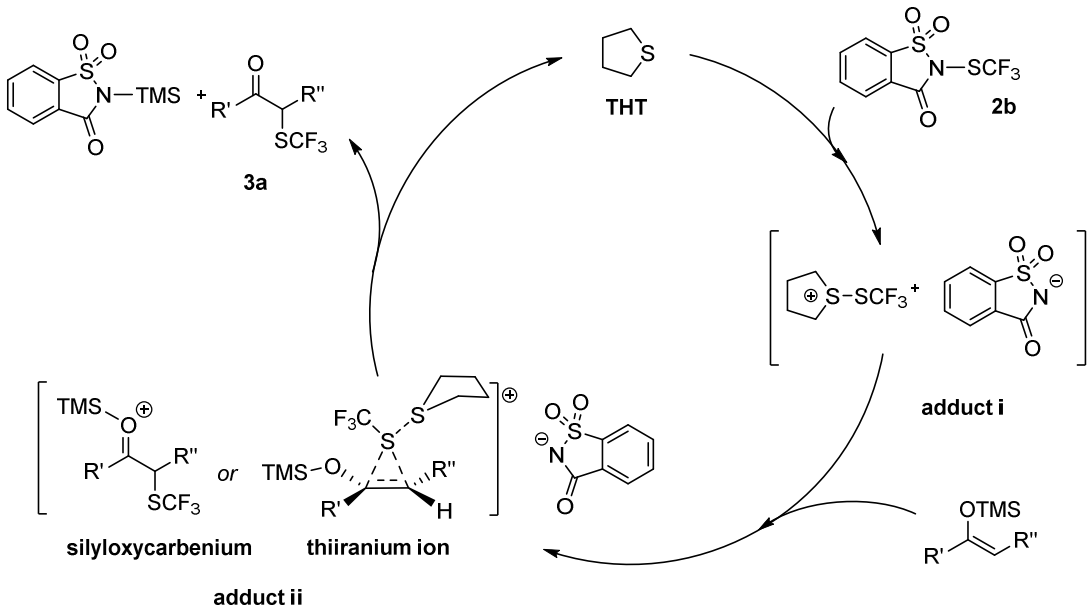
As for the in batch reactions, the tertbutyldimethylsilyl (TBS) enol ether gave lower yields than the TMS derivative, as well the p-methoxy derivative **1c** reacted to give the product in modest yields. Unexpectedly, also the cyclic silylenol ether **1d** gave the product in very low yields, showing that for the process in continuo further studies are necessary to find the optimized reaction conditions for each substrate.

However, it is interesting to make a comparison between the two approaches, taking in account the productivity and the space-time concepts.[33] The calculated productivity for the traditional flask synthesis of α-trifluoromethylthiolated ketone **3a** (80 °C, 5 h, 74% yield) is 1480 h^{-1}, while the productivity obtained for

the flow process is 1.5 time higher (2228 h^{-1}; calculated for 60 °C, 10 min, 52% yield). Moreover, also the space-time yield for the flow process ($2x10^{-1}$, measured as [mass (product) / (vol(reactor) x reaction time) expressed as $Kg/m^3\ s^{-1}$ is about 200 times higher than the traditional one, showing that in this case, the flow approach offer clear advantages than the traditional batch process.

4. MECHANISM STUDY

A proposed mechanism for the α-trifluoromethylthiolation is depicted in scheme 4. In analogy with ketone-derived enoxysilanes sulfenylation,[28] the first step involves the interaction of the Lewis base with *N*-(trifluoromethylthio)saccharin for the generation of adduct ***i*.** This active trifluoromethylthiosulfenylating agent then reacts with the silylenol ether to produce thiiranium ion or a silyloxycarbenium (adduct ***ii***) that after nucleophilic removal of the silyl-protecting group by the saccharin anion affords the desired product with the concomitant release of the catalyst.



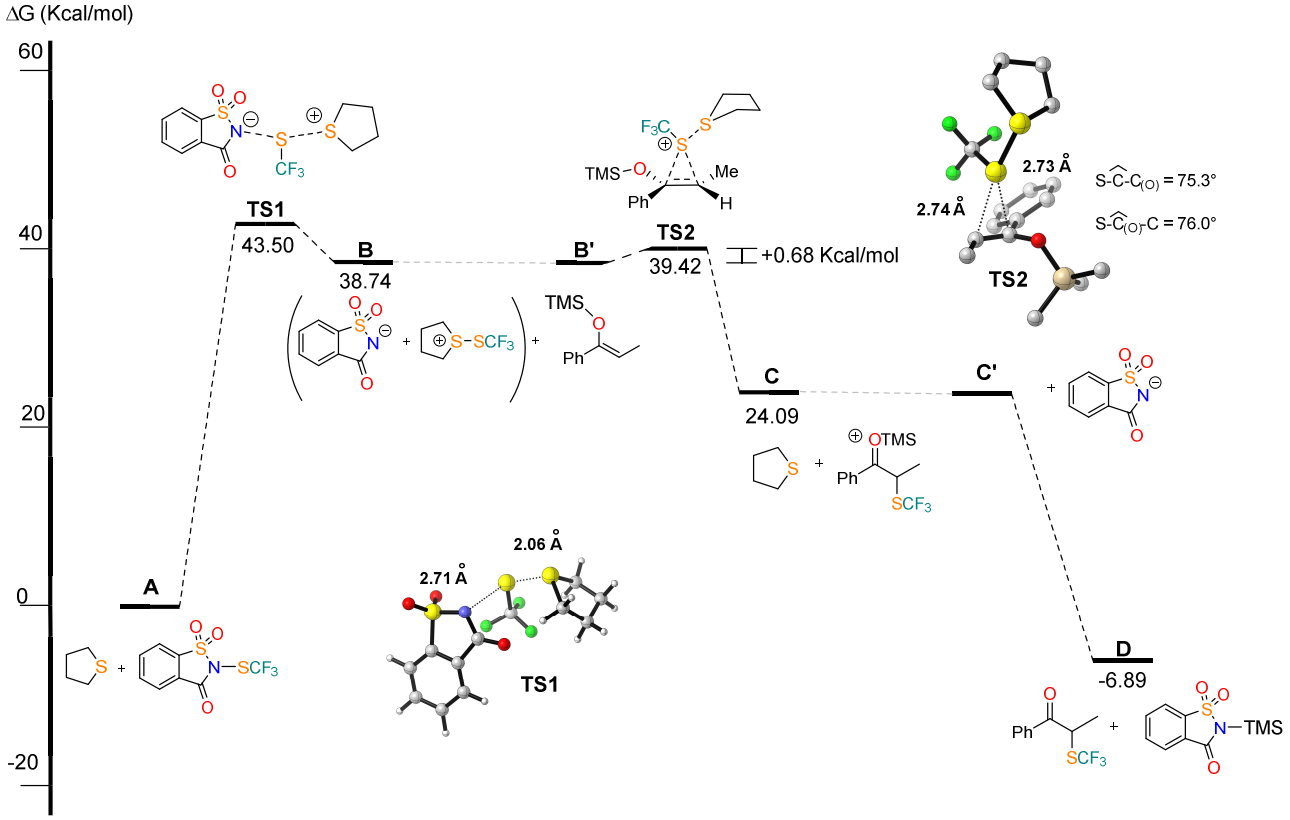
Scheme 5: Proposed catalytic cycle

Since this transformation requires high temperatures to take place (in opposite to the α-sulfenylation reaction), we started to perform some DFT calculation (M062X / 6-31G(2d,2p) level of theory) in order to provide more detailes on the mechanism. At the beginning, a conformational analysis with Monte Carlo techniques using OPLS_2005 force field[34] on a simple model of all the structures was performed; then refined structures were generated by DFT calculations. All the calculations were performed in vacuum by using Gaussian G09 rev D package. [35]

The first calculations focused on the interaction of the Lewis base with *N*-(trifluoromethylthio)saccharin, by determining the energy barrier required for the activation of the "SCF_3" group. The calculated energy

profiles for this activation is shown in scheme 6, while the coordinates of all the optimized structures are described in the Supporting information.

Interestingly, it was found that the transfer of the SCF_3 group from *N*-(trifluoromethylthio)saccharin to tetrahydrothiophene is an high-energy demanding step, with a barrier estimated in 43.5 kcal/mol. This is in accordance with the fact that, experimentally, high temperatures are required in order to observe product formation. After this activation, the distance between nitrogen atom and the SCF_3 group in *N*-(trifluoromethylthio)saccharin increase from 1.69 Å to 3.2 Å, with consequent formation of THT-SCF_3 adduct in a *s*-cis conformation geometry.



Scheme 6: Calculated reaction profile for the α-trifluoromethylthiolation of silylenol ether by DFT calculations at M062X / 6-31G(2d,2p) level of theory.

At this point, the new formed THT-SCF_3 adduct interacts with the silylenol ether and according to literature, the formation of the thiiranium ion could be hypothesized.[36] The formation of thiiranium ion **TS2** was effectively located as transition state and it was found that this structure is very close in energy compared to activated intermediates (only +0.68 Kcal/mol); however it is very far away from the starting materials (+39.42 kcal/mol). The silyloxycarbenium ion **C'** was instead located as a stable entity. Since the activation of the *N*-(trifluoromethylthio)saccharin is more energetic demanding respect to the formation of the thiiranium ion, it could be considered as the rate determining step. It must be noted that the thiiranium ion is quite symmetrical since there are no significantly differences in terms of distances and angles between

the sulfur atom and the two carbons of the enol ether ($d_{S\text{-}C}$ = 2.7 Å, $S\hat{C}C_{(O)} \cong S\widehat{C_{(O)}C}$ = 76°). As final step, the nucleophilic attach of the saccharin anion to the silyloxycarbenium **C'** occurs, releasing the final product with an additional increase of the energy gain for the process.

CONCLUSIONS

We have developed a novel approach for the α-trifluoromethylthiolation of unactivated ketones, starting from the corresponding silylenol ethers, in the presence of catalytic amounts of tetrahydrothiophene and *N*-(trifluoromethylthio)saccharin. This transformation was performed both under traditional batch conditions and, for the first time, under continuous flow conditions. Generally speaking, higher yields were observed using THT catalysts in a traditional batch process, but flow processes afforded the products with higher productivity and 200 times higher space-time yields. Preliminary DFT investigations on the activation mechanism of the trifluoromethylthiolating reagent were also performed, showing that relatively high temperatures are required in order to observe product formation.

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APPENDIX A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at XXXXXXXXX

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