Real-time spectroscopic analysis enabling quantitative and safe consumption of fluoroform during nucleophilic trifluoromethylation in flow.

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ABSTRACT: The productive use of toxic waste materials derived from industrial processes is one of the main goals of modern chemical research to increase sustainability of the large scale production. Here we devise a simple and robust strategy for the utilization of trifluoromethane, obtained in large quantities from polytetrafluoroethylene (PTFE) manufacture, and the conversion of this greenhouse gas into valuable fluorinated compounds. The generation of the trifluoromethyl carbanion and its direct and complete consumption through trapping with a number of electrophiles were achieved by a fully contained flow reactor setup. The adoption of modern in-line analytical tools, such as portable FT-IR and NMR devices, allowed the accurate reagent dosing with considerable benefits in terms of controlling the environmental impact during this continuous process. The advantages of the method, with respect to the batch procedure, will be discussed and demonstrated experimentally.

KEYWORDS: trifluoromethylation, continuous process, in-line analysis, bench-top NMR, fluoroform.

INTRODUCTION

There is a clear need to develop modern synthetic strategies which employ renewable starting materials. Furthermore, there is also a need to convert waste materials derived from certain industrial processes into valuable synthetic compounds improving the sustainability of large scale production.[1-3] A case in point is the industrial manufacture of PTFE which generates very large amounts of trifluoromethane (CF_3H) as a by-product.[4] CF_3H is listed as a potent greenhouse gas, with a lifetime of 270 years, which is the approximate amount of time it would take for CF_3H concentration to return to its natural level.[5] Its disposal requires expensive procedures, such as high temperature incineration. Consequently there is interest in the development of affordable transformations which utilize CF_3H for the direct generation of useful functional fluorinated compounds,[6-12] which are endowed with improved medicinal or physical chemical properties.[13-15] In particular, significant advances have been achieved during the last decade in the development of new reagents and general approaches for trifluoromethylation, including electrophilic, radical and nucleophilic reactions.[16-24] Among these methods, the use of CF_3H for installing directly the trifluoromethyl moiety into an organic compound remains an appealing approach, in terms of raw material availability and atom-economy. Nevertheless, as a greenhouse gas, CF_3H must not be dispersed into the atmosphere. Thus, an accurate determination of CF_3H is vital during the usage of this reagent to make it eco-sustainable and chemically efficient. The recent introduction of flow technologies into modern laboratory practice has enabled the improved performance of gas-liquid reactions by expediting the mass

transfer between the two phases.[25-32] In particular, membrane-based reactors have been successfully applied to enable the gas-liquid contact, avoiding the occurrence of biphasic flow regime, which may lead to less efficient and controllable dosing of the gas.[33] Few years ago we contributed to the development of a tube-in-tube reactor for gas–liquid reactions, consisting of a pair of concentric capillaries in which the central capillary functions as a gas-permeable membrane (Teflon AF-2400).[34,35] This system has been applied to several synthetic programs, exploiting the permeability of Teflon AF-2400 to a range of gases (carbon monoxide, hydrogen, ozone, carbon dioxide, oxygen, ammonia, ethylene and diazomethane).[36-42] More importantly, the advent of a number of innovative in-line analytical tools has greatly advanced reaction monitoring and subsequent adjustment of reaction conditions.[43-46] In this context, an increasing number of new applications have been reported on the use of portable flow IR devices[47-50] and bench-top low field NMR equipment,[51-56] which greatly enabled real-time monitoring of continuous flow chemistry.

The generation of the carbanion from trifluoromethane by deprotonation has been extensively investigated and numerous reports on the lifetime of this intermediate suggest that it is prone to rapid fluoride atom loss and conversion into the extremely reactive difluorocarbene intermediate.[57-62] Despite the increasing interest in the cost-efficient and sustainable use of CF_3H as trifluoromethylating reagent, there are still concerns relating to its clean applications and interception in organic synthesis programs.

Here we describe a continuous chemical approach for the use of CF_3H as a source of trifluoromethanide anion, and its direct use as a nucleophile to react with a range of carbonyl compounds and chlorosilanes. We demonstrate the practical benefits derived from the introduction of the Infrared (FT-IR) and the Nuclear Magnetic Resonance (NMR) in-line analytic

tools for the accurate dosing of CF_3H gas and the quantitative trapping of the highly reactive and unstable trifluoromethanide anion intermediate.

RESULTS AND DISCUSSION

A first screening of conditions highlighted that the temperature, residence time, pressure and mixing were all crucial reaction parameters. The process setup resulted particularly pivotal in order to reach the optimum reagent stoichiometry and avoid collateral reactions due to the decomposition of the trifluoromethanide anion (Figure 1a). A 4-way cross connection valve for high pressure was installed to allow efficient mixing of the three reaction streams (flow rate 0.2 ml/min each) containing respectively the base, the electrophile and the CF_3H solution. The resulting mixture was then passed through a PTFE coil reactor (14 ml). Both the mixing zone and the reaction zone were maintained at a controlled temperature (-20 °C) by using a cooling device (Polar Bear Plus from Cambridge Reactor Design). The gas was introduced into the system using the tube-in-tube reactor, which is reported as a simple and efficient method to afford homogeneous solutions of reactive gases in flow (Figure 1b).

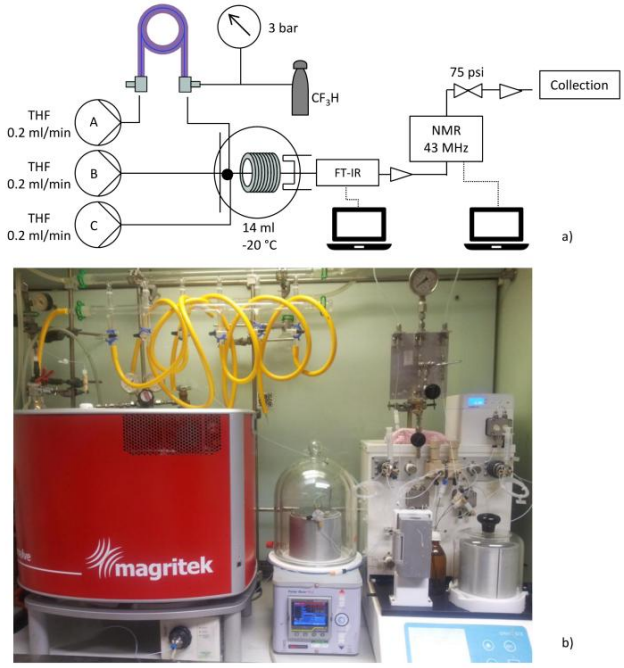


Figure 1. a) Schematic of the flow reactor setup using three pumps (FR_A=FR_B=FR_C= 0.2 ml/min), a tube-in-tube reactor (1.0 m of AF-2400 tubing), a PTFE coil reactor (14 ml), a cooling device (-20 °C), a FT-IR instrument and a bench-top NMR machine (43 MHz). b) Picture of the apparatus.

First, it was verified that the Teflon AF-2400 membrane of the inner tube, containing THF, was permeable to CF_3H. For this purpose, an in-line FT-IR instrument (FlowIR™ from Mettler Toledo) was used and the signal at 1129 cm^{-1} was monitored (Figure 2a) until the steady state was reached (Figure 2b).

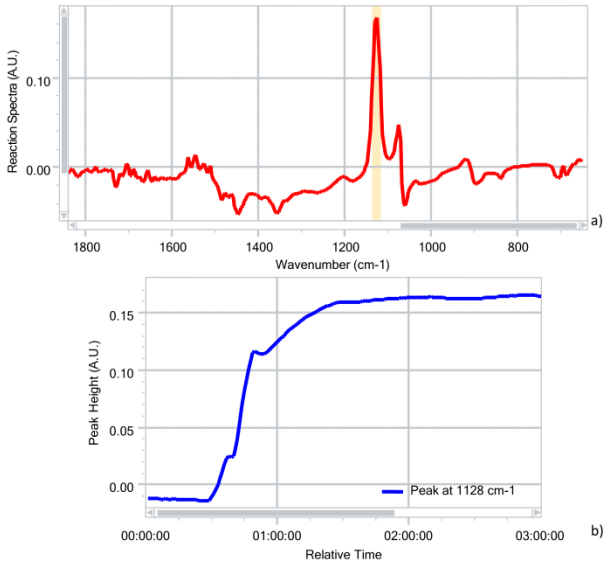


Figure 2. a) In-line FT-IR monitoring. b) Trend of the signal at 1128 cm^{-1} assigned to CF_3H.

Aiming to quantify the concentration of CF_3H in the efflux stream from the coil reactor (-20 °C), a solution of $PhCF_3$ in THF (0.3 M) was used as internal standard, and, thus, pumped through the stream C (flow rate 0.2 ml/min). The signal at 1328 cm^{-1} in the corresponding FT-IR spectrum was monitored until the steady state was reached (Figure 3a). At this point a ^{19}F NMR spectrum was recorded (Figure 3b), using the in-line bench-top NMR machine (43 MHz, Spinsolve from Magritek) installed soon after the in-line FT-IR device. Comparing the integral values of the signals assigned respectively to $PhCF_3$ (singlet at -63.46 ppm) and to CF_3H (doublet at -79.49 ppm), it was determined the concentration of the gas dissolved in the solution under these conditions, equated to 0.738 M.

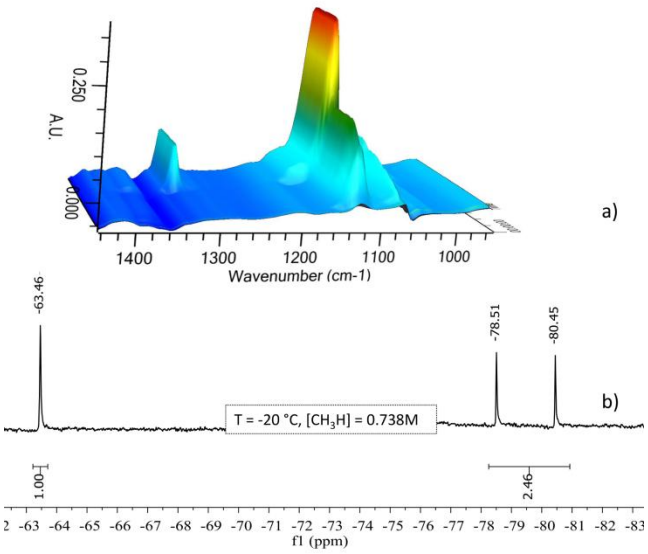
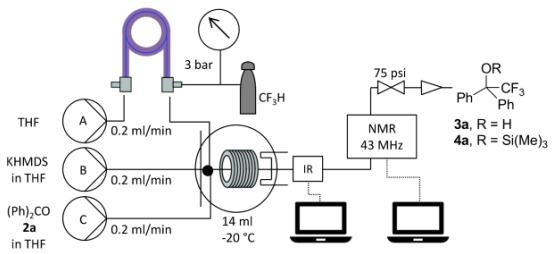


Figure 3. a) In-line FT-IR monitoring the signals respectively at 1129 cm^{-1} (CF_3H) and at 1328 cm^{-1} ($PhCF_3$). b) In-line ^{19}F NMR spectrum of the solution containing $PhCF_3$ as internal standard (-63.46 ppm) and CF_3H (-79.49 ppm).

Once the exact amount of CF_3H in the reaction mixture was known, we could then optimize the concentrations of the other reagents involved in the CF_3H deprotonation / electrophile trapping sequence. The activation of fluoroform with KHMDS and addition of the formed trifluoromethanide anion to carbonyl compounds in batch mode was described by Prakash et al. The resulting fluorinated products were obtained with modest to good yields (10 – 81% yields), depending on the substrates.[60] The addition of CF_3H was realized by bubbling the gas into the reaction mixture over different time and with different flow rates. The amount of the total gas was calculated according to the difference in the weight of the gas cylinder before and after the addition. Aiming to demonstrate the importance of the accurate dosing of CF_3H on the productivity of the reaction, a screening of the optimum reagent concentrations was conducted, using potassium bis(trimethylsilyl)amide (KHMDS) as a base with benzophenone **2a** as an electrophile (Table 1). When an excess of CF_3H (2.46 equiv) was reacted with benzophenone

(1.0 equiv) and KHMDS (1.16 equiv) the alcohol **3a** was obtained smoothly (93% conversion) in 30 minutes (Table 1, entry 1). When the concentration of the electrophile and the base were both increased (1.0 M), keeping constant the concentration of CF_3H (0.738 M), full conversion to the alcohol **3a** was observed (Table 1, entry 2; conversion 99%). Interestingly, the formation of *O*-protected alcohol **4a** was detected when an excess of base was used with respect to benzophenone and CF_3H. Increasing the concentration of KHMDS led to increased formation of **4a** (Table 1, entries 3-4). Bis(trimethylsilyl)amine (HMDS), which is formed during the deprotonation step of CF_3H by KHMDS, is reported to be a weak trimethylsilyl donor. In an effort to study its role in the formation of the trimethylsilyl ether **4a**, HMDS (0.8 M) was added to the reaction mixture. In this case a selective formation of **3a** was observed, together with only traces (0.1%) of **4a** (Table 1, entry 5). By contrast, the trimethylsilyl ether **4a** was formed exclusively when a strong trimethylsilyl donor, such as chlorotrimethylsilane (TMSCl), was used as additive (Table 1, entry 6). Literature data from magnetic resonance experiments of KHMDS suggest it exists in THF solution as a polymeric THF-solvate $[(KHMDS)_2(THF)_2]_\infty$ where molecules of solvent can be displaced by Lewis donors, causing the monomerization of the complex.[63] It is likely that when an excess of KHMDS is present in the reaction mixture a polymeric THF-solvate $[(KHMDS)_2(THF)_2]_\infty$ exists and, spontaneously, leads to the transfer of the trimethylsilyl moiety to oxygen, due to a proximity effect. The presence of HMDS could then cause the decomplexation of the polymeric THF-solvate.

Table 1. Screening of the optimum reagent concentrations during the trifluoromethyl carbanion generation and *in situ* trapping with benzophenone **2a**. Conversions were determined by NMR, using $PhCF_3$ as internal standard.



Entry	[**2a**], M	[KHMDS], M	[CF_3H], M	[Additive], M	Ratio **3a**:**4a**	Conversion, %
1	0.3	0.35	0.738	None	100:0	93
2	1.0	1.0	0.738	None	100:0	99
3	0.3	1.0	0.738	None	58:42	99
4	0.15	1.0	0.738	None	29:71	99
5	0.3	1.0	0.738	HMDS, 0.8	99.9:0.1	71
6	0.3	1.0	0.738	TMSCl, 0.3	0:100	37

The real-time ^{19}F NMR monitoring provided important information concerning the reaction progress under the conditions described in Table 1 - entry 3, where a mix of **3a** and **4a** (ratio 58:42) was observed in the crude reaction mixture. According to the NMR spectra recorded in-line, compound **4a** should be generated first (Figure 4b). The formation of the alcohol **3a** is delayed respect to **4a** and could be ascribed to the progressive decomplexation of the polymeric THF-solvate $[(KHMDS)_2(THF)_2]_\infty$ induced by the formation of HMDS during the CF_3H deprotonation. This would give rise to the gradual formation of **3a** (see Table 1, entry 5). Also the hypothesis of a progressive cleavage of the trimethylsilyl group from **4a** was taken into account, whereby the fluoride anion, derived hypothetically from the decomposition of the trifluoromethanide anion, would be responsible. According to this explanation, fluorotrimethylsilane (TMSF) would be formed simultaneously (Figure 4a). However, no signal in the ^{19}F NMR spectra could be assigned to this compound (Figure 4b).

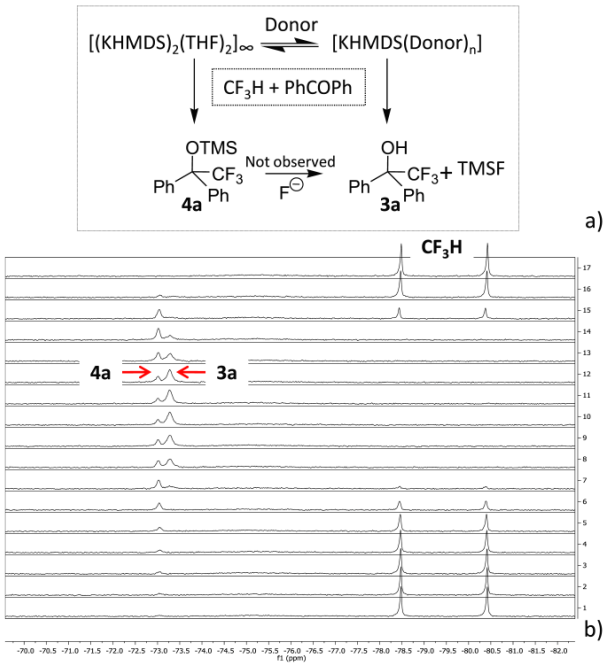


Figure 4. a) Possible reaction pathways of trifluoromethane (CF_3H) with benzophenone (PhCOPh) in presence of KHMDS. b) In-line ^{19}F NMR monitoring of the reaction mixture over the time containing **4a** (at -73.06 ppm), **3a** (-73.30 ppm) and CF_3H (-79.49 ppm).

The protocol which has been developed for the generation of trifluoromethyl carbanion and its *in situ* trapping with benzophenone (Table 1, entry 2) resulted beneficial with respect to the corresponding batch method,[60] in terms of reaction time (23 minutes *vs* 12 hours), accurate control of CF_3H dosing, productivity (4.6 mmol/h *vs* 0.225 mmol/h), and, more importantly, complete consumption of the CF_3H used in the process.

The insertion of a fourth stream containing a solution of TMSCl in THF (0.3 M; pump D: flow rate 0.6 ml/min; Chart 1) and the introduction of a further PTFE coil reactor (16 ml) permitted the in-line derivatization of the alcohols **3**, and therefore gave access to a number of substituted trimethylsilyl ethers **4a-4f** with excellent yields (isolated yields after chromatographic purification 71 – 95%) and in a relative short time (1.15 h).

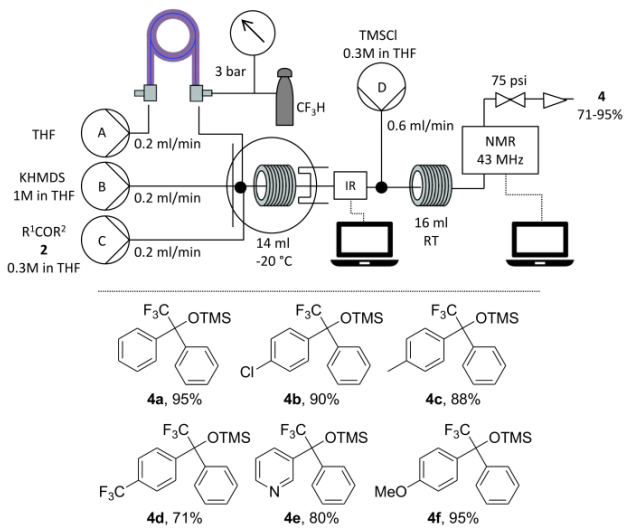


Chart 1. Synthesis of *O*-trimethylsilyl fluorinated ethers **4a-4f** by an intensified process (trifluoromethyanide carbanion – nucleophilic addition to ketones **2a-2f** – product derivatization) with in-line FT-IR and NMR monitoring.

Next, the preparation of trifluoromethyl carbinols **6a-6g** starting from a number of aldehydes was explored. Shibata et al. reported on the use of sterically hindered organo-superbases to stabilize the naked trifluoromethanide carbanion and enable the trapping with aldehydes.[59] Aiming to develop a more sustainable process for large scale production, we investigated the use of a less expensive non-nucleophilic strong base (weaker than amide bases), such as potassium *tert*-butoxide (*t*-BuOK). While this reaction is reported to perform well in dimethylformamide (DMF), which acts as trifluoromethylanion reservoir,[64] the conversion to the corresponding fluorinated products occurs in modest yields when the same reaction is performed in pure THF.[60]

Similar moderate results were obtained when a mixture of CF_3H, *t*-BuOK and benzaldehyde **5a** was reacted in flow, using the same flow setup developed for the nucleophilic trifluoromethylation of the ketones **2**. A screening of the reaction conditions and the process design, demonstrated that a noticeably improved result could be obtained when a solution of

aldehyde **5** in DMF (0.3 M) was mixed at -20 °C with two streams containing respectively CF_3H (0.738 M in THF) and *t*-BuOK (1.0 M in THF). The resulting mixture, reacting at -20 °C within a PTFE reactor coil (16 ml, residence time 27 minutes), gave the corresponding fluorinated carbinols **6a-6g** with excellent results (Chart 2; yields after chromatographic purification 75 – 97%). Importantly, the real-time ^{19}F NMR monitoring confirmed that no fluorinated by-product was formed under these reaction conditions and that complete consumption of CF_3H was achieved.

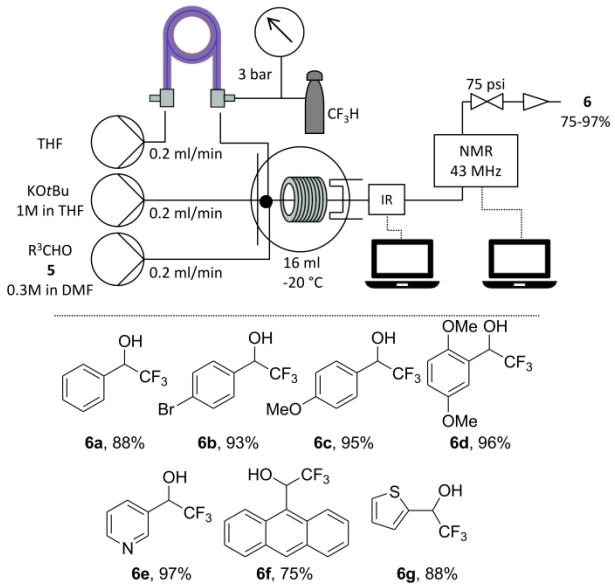


Chart 2. Synthesis of fluorinated carbinols **6a-6g** *via* generation of trifluoromethanide carbanion and *in situ* trapping with aldehydes **5a-5g** with in-line FT-IR and NMR monitoring.

Finally, we extended our study to the development of a continuous scalable production of fluorinated organosilicon compounds, which are extensively applied in organic synthesis as fluoroalkylation reagents.[65] There is a growing interest in developing more environmentally benign methods for their large scale production, which would circumvent the use of the ozone-depleting bromotrifluoromethane (CF_3Br) as starting material.[66] In particular, we turned our

efforts to the preparation of trifluoromethyltriethylsilane **8**, which is widely used as a trifluoromethyl precursor.[67,68] The reaction conditions were accurately investigated, taking advantage of the real-time monitoring of the reaction mixture. It was found that a lower temperature (-40 °C) and longer residence time (57 minutes) were crucial parameters to succeed in the formation of **8**. The concentration of CF_3H in the solution under the new flow setup (Figure 5a; T = -40 °C; $FR_A = FR_B = FR_C$ = 0.1 ml/min) was measured by using the in-line ^{19}F NMR analysis (figure 5b; α, α, α-trifluorotoluene as internal standard, 0.3 M; $[CF_3H]$ = 0.732).

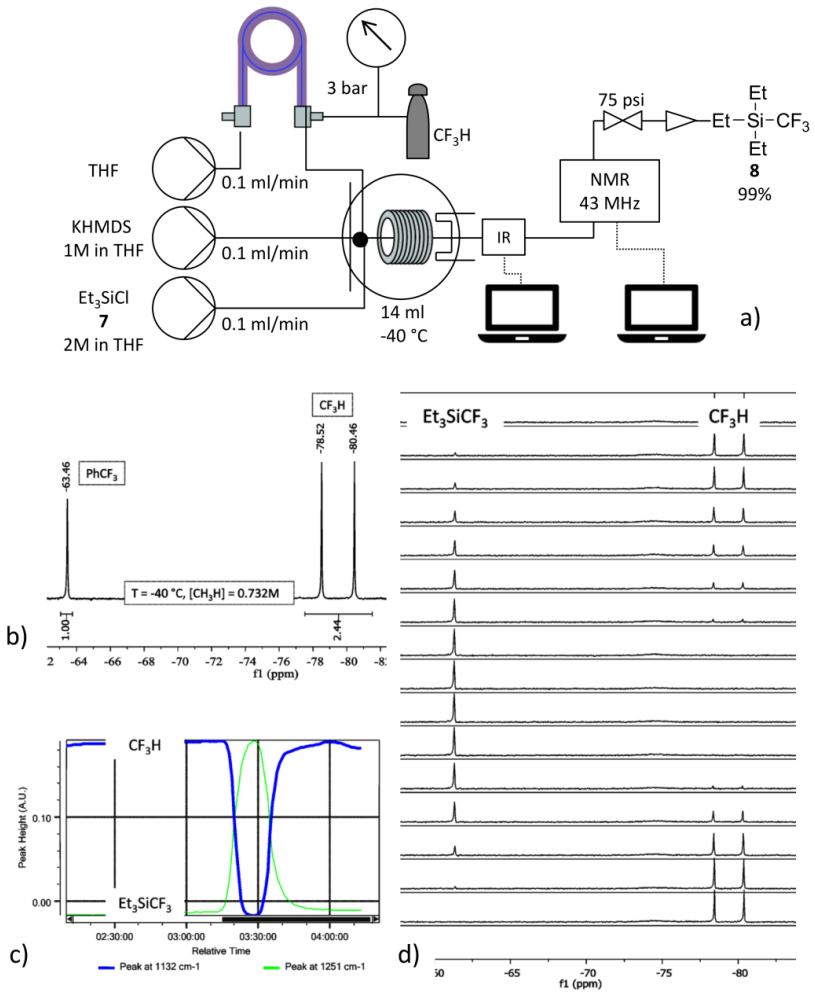


Figure 5. a) Schematic of the flow reactor setup for the synthesis of trifluoromethyltriethylsilane **8** using three pumps (FR_A=FR_B=FR_C= 0.1 ml/min), a tube-in-tube reactor (1.0 m of AF-2400

tubing), a PTFE coil reactor (14 ml), a cooling device (-40 °C), a FT-IR instrument and a bench-top NMR machine (43 MHz). b) In-line ^{19}F NMR spectrum of the solution containing $PhCF_3$ as internal standard (-63.46 ppm) and CF_3H (-79.49 ppm) at -40 °C. c) In-line FT-IR analysis by monitoring the trend of CF_3H and Et_3Si CF_3. c) In-line ^{19}F NMR analysis by monitoring the trends of CF_3H and Et_3Si CF_3.

The reaction was continuously monitored by FT-IR (Figure 5c) and by ^{19}F NMR (Figure 5d), discovering that an excess of chlorotriethylsilane (Et_3SiCl, 2M), used as electrophile, was crucial to suppress the formation of triethylsilyl fluoride (Et_3SiF; signal at -151.02 ppm in the ^{19}F NMR spectrum) as by-product. Under these reaction conditions, full consumption of CF_3H was observed (Figure 5c, blue line, trend of the peak at 1132 cm^{-1}; Figure 5d, disappearance of the doublet at -79.49 ppm) and clean formation of compound **8** was detected (Figure 5d, green line, trend of the peak at 1251 cm^{-1}; Figure 5d, appearance of the singlet at -61.44 ppm).

CONCLUSION

In conclusion a synthetic approach which allows the safe utilization of a potent greenhouse gas, such as trifluoromethane, has been developed. Exploiting the discovered permeability of the Teflon AF-2400 membrane to CF_3H, a controlled introduction of this gas into the reaction mixture was achieved. The real-time spectroscopic analysis (FT-IR and NMR) enhanced the precise measurement of CF_3H in the solution, with clear benefits on the selectivity in the products formation. The process described was fully contained and any possible dispersion of fluoroform into the atmosphere was accurately controlled and minimized. The fast and complete interception of the trifluoromethyl carbanion intermediate by ketones, aldehydes and chlorosilanes gave access to functional fluorinated products with high yields. The spontaneous decomposition of the trifluoromethyl carbanion intermediate to difluorocarbene was completely

suppressed, resulting in simpler downstream processing. The successful production of trifluoromethyltriethylsilane, as trifluoromethylation reagent, also could extend applications of the flow reactor setup to the trifluoromethylation of enolizable carbonyl compounds, which were not suitable substrates in this work. The reactor design and the real-time analytical tools adopted in this work could find application in other similar synthesis programs.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures and characterization of compounds (PDF).

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Author Contributions.

The paper was written through contributions of all authors. All authors have given approval to the final version of the paper.

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Notes

The authors declare no competing commercial interests.

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ABBREVIATIONS

CF_3H, trifluoromethane; NMR, nuclear magnetic resonance; FT-IR, Fourier-transform infrared spectroscopy; PTFE, polytetrafluoroethylene; THF, tetrahydrofuran; KHMDS, potassium bis(trimethylsilyl)amide; HMDS, bis(trimethylsilyl)amine; *t*-BuOK, *tert*-butoxide; DMF, dimethylformamide; $PhCF_3$, α, α, α, trifluorotoluene; FR, flow rate.

SYNOPSIS: Safe handling and accurate measurement of fluoroform towards a clean and efficient production of fluorinated compounds in flow.

REFERENCES

(1) Llevot, A.; Meier, M. A. R. Renewability – a principle of utmost importance! *Green Chem.* **2016**, *18* (18), 4800–4803. DOI 10.1039/C6GC90087A.

(2) Sheldon, R. A. The E factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* **2017**, *19* (1), 18–43. DOI 10.1039/C6GC02157C.

(3) Clark, J. H. From waste to wealth using green chemistry: The way to long term stability. *Curr. Opin. Green Sustain. Chem.* **2017**, *8*, 10–13. DOI 10.1016/j.cogsc.2017.07.008.

(4) Carlson, D. P.; Schmiegel, W. **2000**. Fluoropolymers, Organic. *Ullmann's Encyclopedia of Industrial Chemistry*.

(5) Lowe, D. C.; Zealand, N. *Changes in Atmospheric Constituents and in Radiative Forcing* **2007**, *30* (22), 129–234.

(6) Okusu, S.; Tokunaga, E.; Shibata, N. Difluoromethylation of Terminal Alkynes by Fluoroform. *Org. Lett.* **2015**, *17* (15), 3802–3805. DOI 10.1021/acs.orglett.5b01778.

(7) Iida, T.; Hashimoto, R.; Aikawa, K.; Ito, S.; Mikami, K. Umpolung of fluoroform by C-F bond activation: Direct difluoromethylation of lithium enolates. *Angew. Chemie - Int. Ed.* **2012**, *51* (38), 9535–9538. DOI 10.1002/anie.201203588.

(8) Yang, X.; He, L.; Tsui, G. C. Hydroxytrifluoromethylation of Alkenes Using Fluoroform-Derived $CuCF_3$. *Org. Lett.* **2017**, *19* (9), 2446–2449. DOI 10.1021/acs.orglett.7b01085.

(9) He, L.; Yang, X.; Tsui, G. C. Domino Hydroboration/Trifluoromethylation of Alkynes Using Fluoroform-Derived [CuCF3]. *J. Org. Chem.* **2017**, *82* (12), 6192–6201. DOI 10.1021/acs.joc.7b00755.

(10) Geri, J. B.; Szymczak, N. K. Recyclable Trifluoromethylation Reagents from Fluoroform. *J. Am. Chem. Soc.* **2017**, *139* (29), 9811–9814. DOI 10.1021/jacs.7b05408.

(11) He, L.; Tsui, G. C. Fluoroform-Derived CuCF3 for Trifluoromethylation of Terminal and TMS-Protected Alkynes. *Org. Lett.* **2016**, *18* (12), 2800–2803. DOI 10.1021/acs.orglett.6b00999.

(12) Thomoson, C. S.; Wang, L.; Dolbier, W. R. Use of fluoroform as a source of difluorocarbene in the synthesis of N-CF_2H heterocycles and difluoromethoxypyridines. *J. Fluor. Chem.* **2014**, *168*, 34–39. DOI 10.1016/j.jfluchem.2014.08.015.

(13) Lewandowski, G.; Meissner, E.; Milchert, E. Special applications of fluorinated organic compounds. *J. Hazard. Mater.* **2006**, *136* (3), 385–391. DOI 10.1016/j.jhazmat.2006.04.017.

(14) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58* (21), 8315–8359. DOI 10.1021/acs.jmedchem.5b00258.

(15) Ni, C.; Hu, J. The unique fluorine effects in organic reactions: recent facts and insights into fluoroalkylations. *Chem. Soc. Rev.* **2016**, *45* (20), 5441–5454. DOI 10.1039/C6CS00351F.

(16) Ma, J. A.; Cahard, D. Strategies for nucleophilic, electrophilic, and radical trifluoromethylations. *J. Fluor. Chem.* **2007**, *128* (9), 975–996. DOI 10.1016/j.jfluchem.2007.04.026.

(17) Alonso, C.; Martínez De Marigorta, E.; Rubiales, G.; Palacios, F. Carbon trifluoromethylation reactions of hydrocarbon derivatives and heteroarenes. *Chem. Rev.* **2015**, *115* (4), 1847–1935. DOI 10.1021/cr500368h.

(18) Baumann, M.; Baxendale, I. R.; Martin, L. J.; Ley, S. V. Development of fluorination methods using continuous-flow microreactors. *Tetrahedron* **2009**, *65* (33), 6611–6625. DOI 10.1016/j.tet.2009.05.083.

(19) Okusu, S.; Hirano, K.; Yasuda, Y.; Tokunaga, E.; Shibata, N. Flow trifluoromethylation of carbonyl compounds by Ruppert–Prakash reagent and its application for pharmaceuticals, efavirenz and HSD-016. *RSC Adv.* **2016**, *6* (86), 82716–82720. DOI 10.1039/C6RA19790F.

(20) Morstein, J.; Hou, H.; Cheng, C.; Hartwig, J. F. Trifluoromethylation of Arylsilanes with [(phen)CuCF$_3$]. *Angew. Chemie - Int. Ed.* **2016**, *55* (28), 8054–8057. DOI 10.1002/anie.201601163.

(21) Merino, E.; Nevado, C. Addition of CF_3 across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.* **2014**, *43* (18), 6598–6608. DOI 10.1039/C4CS00025K.

(22) Geri, J. B.; Szymczak, N. K. Recyclable Trifluoromethylation Reagents from Fluoroform. *J. Am. Chem. Soc.* **2017**, *139* (29), 9811–9814. DOI 10.1021/jacs.7b05408.

(23) Mormino, M. G.; Fier, P. S.; Hartwig, J. F. Copper-mediated perfluoroalkylation of heteroaryl bromides with (phen)CuRF. *Org. Lett.* **2014**, *16* (6), 1744–1747. DOI 10.1021/ol500422t.

(24) Bos, M.; Poisson, T.; Pannecoucke, X.; Charette, A. B.; Jubault, P. Recent Progress Toward the Synthesis of Trifluoromethyl- and Difluoromethyl-Substituted Cyclopropanes. *Chem. - A Eur. J.* **2017**, *23* (21), 4950–4961. DOI 10.1002/chem.201604564.

(25) Mallia, C. J.; Baxendale, I. R. The Use of Gases in Flow Synthesis. *Org. Process Res. Dev.* **2016**, *20* (2), 327–360. DOI 10.1021/acs.oprd.5b00222.

(26) Cossar, P. J.; Hizartzidis, L.; Simone, M. I.; McCluskey, A.; Gordon, C. P. The expanding utility of continuous flow hydrogenation. *Org. Biomol. Chem.* **2015**, *13* (26), 7119–7130. DOI 10.1039/C5OB01067E.

(27) Ouchi, T.; Battilocchio, C.; Hawkins, J. M.; Ley, S. V. Process intensification for the continuous flow hydrogenation of ethyl nicotinate. *Org. Process Res. Dev.* **2014**, *18* (11), 1560–1566. DOI 10.1021/op500208j.

(28) Straathof, N. J. W.; Su, Y.; Hessel, V.; Noël, T. Accelerated gas-liquid visible light photoredox catalysis with continuous-flow photochemical microreactors. *Nat. Protoc.* **2015**, *11* (1), 10–21. DOI 10.1038/nprot.2015.113.

(29) Kurt, S. K.; Warnebold, F.; Nigam, K. D. P.; Kockmann, N. Gas-liquid reaction and mass transfer in microstructured coiled flow inverter. *Chem. Eng. Sci.* **2017**, *169*, 164–178. DOI 10.1016/j.ces.2017.01.017.

(30) Su, Y.; Kuijpers, K.; Hessel, V.; Noël, T. A convenient numbering-up strategy for the scale-up of gas–liquid photoredox catalysis in flow. *React. Chem. Eng.* **2016**, *1* (1), 73–81. DOI 10.1039/C5RE00021A.

(31) Pieber, B.; Glasnov, T.; Kappe, C. O. Flash carboxylation: fast lithiation–carboxylation sequence at room temperature in continuous flow. *RSC Adv.* **2014**, *4* (26), 13430–13433. DOI 10.1039/c4ra01442a.

(32) Chapman, M. R.; Kwan, M. H. T.; King, G.; Jolley, K. E.; Hussain, M.; Hussain, S.; Salama, I. E.; González Niño, C.; Thompson, L. A.; Bayana, M. E.; et al. Simple and Versatile Laboratory Scale CSTR for Multiphasic Continuous-Flow Chemistry and Long Residence Times. *Org. Process Res. Dev.* **2017**, *21* (9), 1294–1301. DOI 10.1021/acs.oprd.7b00173.

(33) Noël, T.; Hessel, V. Membrane microreactors: Gas-liquid reactions made easy. *ChemSusChem* **2013**, *6* (3), 405–407. DOI 10.1002/cssc.201200913.

(34) O'Brien, M.; Baxendale, I. R.; Ley, S. V. Flow ozonolysis using a semipermeable Teflon AF-2400 membrane to effect gas - Liquid contact. *Org. Lett.* **2010**, *12* (7), 1596–1598. DOI 10.1021/ol100322t.

(35) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. Hydrogenation in flow: Homogeneous and heterogeneous catalysis using Teflon AF-2400 to effect gas–liquid contact at elevated pressure. *Chem. Sci.* **2011**, *2* (7), 1250-1257. DOI 10.1039/c1sc00055a.

(36) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. Flow chemistry: Intelligent processing of gas-liquid transformations using a tube-in-tube reactor. *Acc. Chem. Res.* **2015**, *48* (2), 349–362. DOI 10.1021/ar500359m.

(37) Yang, L.; Jensen, K. F. Mass transport and reactions in the tube-in-tube reactor. *Org. Process Res. Dev.* **2013**, *17* (6), 927–933. DOI 10.1021/op400085a.

(38) Kouridaki, A.; Huvaere, K. Singlet oxygen oxidations in homogeneous continuous flow using a gas–liquid membrane reactor. *React. Chem. Eng.* **2017**, *2* (4), 590–597. DOI 10.1039/C7RE00053G.

(39) Mallia, C. J.; Burton, P. M.; Smith, A. M. R.; Walter, G. C.; Baxendale, I. R. Catalytic Chan-Lam coupling using a "tube-in-tube" reactor to deliver molecular oxygen as an oxidant. *Beilstein J. Org. Chem.* **2016**, *12*, 1598–1607. DOI 10.3762/bjoc.12.156.

(40) Koolman, H. F.; Kantor, S.; Bogdan, A. R.; Wang, Y.; Pan, J. Y.; Djuric, S. W. Automated library synthesis of cyclopropyl boronic esters employing diazomethane in a tube-in-tube flow reactor. *Org. Biomol. Chem.* **2016**, *14* (27), 6591–6595. DOI 10.1039/C6OB00715E.

(41) Dallinger, D.; Kappe, C. O. Lab-scale production of anhydrous diazomethane using membrane separation technology. *Nat. Protoc.* **2017**, *12* (10), 2138–2147. DOI 10.1038/nprot.2017.046.

(42) O'Brien, M. An automated colorimetric inline titration of CO_2 concentrations in solvent flow streams using a Teflon AF-2400 tube-in-tube device. *J. CO_2 Util.* **2017**, *21*, 580–588. DOI 10.1016/j.jcou.2017.08.020.

(43) Reizman, B. J.; Jensen, K. F. Feedback in Flow for Accelerated Reaction Development. *Acc. Chem. Res.* **2016**, *49* (9), 1786–1796. DOI 10.1021/acs.accounts.6b00261.

(44) Fabry, D. C.; Sugiono, E.; Rueping, M. Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems. *React. Chem. Eng.* **2016**, *1* (2), 129–133. DOI 10.1039/C5RE00038F.

(45) Sans, V.; Cronin, L. Towards dial-a-molecule by integrating continuous flow, analytics and self-optimisation. *Chem. Soc. Rev.* **2016**, *45* (8), 2032–2043. DOI 10.1039/C5CS00793C.

(46) Jensen, K. F. Flow chemistry—microreaction technology comes of age. *AIChE Journal* **2017**, *63* (3), 858–869. DOI 10.1002/aic.15642.

(47) Carter, C. F.; Baxendale, I. R.; O'Brien, M.; Pavey, J. B. J.; Ley, S. V. Synthesis of acetal protected building blocks using flow chemistry with flow I.R. analysis: preparation of butane-2,3-diacetal tartrates. *Org. Biomol. Chem.* **2009**, *7* (22), 4594–4597. DOI 10.1039/b917289k.

(48) Carter, C. F.; Lange, H.; Ley, S. V; Baxendale, I. R.; Wittkamp, B.; Goode, J. G.; Gaunt, N. L. ReactIR Flow Cell: A New Analytical Tool for Continuous Flow Chemical Processing. *Org. Process Res. Dev.* **2010**, *14* (2), 393–404. DOI 10.1021/op900305v.

(49) Fabry, D. C.; Sugiono, E.; Rueping, M. Online monitoring and analysis for autonomous continuous flow self-optimizing reactor systems. *React. Chem. Eng.* **2016**, *1* (2), 129–133. DOI 10.1039/C5RE00038F.

(50) Chung, R.; Hein, J. E. The More, The Better: Simultaneous In Situ Reaction Monitoring Provides Rapid Mechanistic and Kinetic Insight. *Top. Catal.* **2017**, *60* (8), 594–608. DOI 10.1007/s11244-017-0737-9.

(51) Picard, B.; Gouilleux, B.; Lebleu, T.; Maddaluno, J.; Chataigner, I.; Penhoat, M.; Felpin, F. X.; Giraudeau, P.; Legros, J. Oxidative Neutralization of Mustard-Gas Simulants in an On-Board Flow Device with In-Line NMR Monitoring. *Angew. Chemie - Int. Ed.* **2017**, *56* (26), 7568–7572. DOI 10.1002/anie.201702744.

(52) Ahmed-Omer, B.; Sliwinski, E.; Cerroti, J. P.; Ley, S. V. Continuous Processing and Efficient in Situ Reaction Monitoring of a Hypervalent Iodine(III) Mediated Cyclopropanation Using Benchtop NMR Spectroscopy. *Org. Process Res. Dev.* **2016**, *20* (9), 1603–1614. DOI 10.1021/acs.oprd.6b00177.

(53) Blümich, B. Introduction to compact NMR: A review of methods. *TrAC - Trends Anal. Chem.* **2016**, *83*, 2–11. DOI 10.1016/j.trac.2015.12.012.

(54) Sans, V.; Porwol, L.; Dragone, V.; Cronin, L. A self optimizing synthetic organic reactor system using real-time in-line NMR spectroscopy. *Chem. Sci.* **2015**, *6* (2), 1258–1264. DOI 10.1039/C4SC03075C.

(55) Foley, D. A.; Dunn, A. L.; Zell, M. T. Reaction monitoring using online vs tube NMR spectroscopy: Seriously different results. *Magn. Reson. Chem.* **2016**, *54* (6), 451–456. DOI 10.1002/mrc.4259.

(56) Edwards, J. C.; Giammatteo, P. J. Process NMR Spectroscopy: Technology and On-line Applications. In *Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries*; Bakeev, K. Ed.; Blackwell-Wiley 2010.

(57) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K. O.; Mathew, T.; Olah, G. A. Long-Lived Trifluoromethanide Anion: A Key Intermediate in Nucleophilic Trifluoromethylations. *Angew. Chemie - Int. Ed.* **2014**, *53* (43), 11575–11578. DOI 10.1002/anie.201406505.

(58) Burton, D. J.; Hahnfeld, J. L. The Preparation and Reactions of Fluoromethylenes. In *Chemistry Reviews*, Vol. 8; Tarrant, P., Ed.; Marcel Dekker Inc.: New York, 1977.

(59) Kawai, H.; Yuan, Z.; Tokunaga, E.; Shibata, N. A sterically demanding organo-superbase avoids decomposition of a naked trifluoromethyl carbanion directly generated from fluoroform. *Org. Biomol. Chem.* **2013**, *11* (9), 1446–1450. DOI 10.1039/c3ob27368g.

(60) Prakash, G. K. S.; Jog, P. V; Batamack, P. T. D.; Olah, G. A. Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers. *Science* **2012**, *338*, 1324–1327. DOI 10.1126/science.1227859.

(61) Langlois, B. R.; Billard, T. Some Recent Results in Nucleophilic Trifluoromethylation and Introduction of Fluorinated Moieties. *Synthesis* **2003**, *2*, 185–194. DOI 10.1055/s-2003-36812.

(62) Billard, T.; Bruns, S.; Langlois, B. R. New Stable Reagents for the Trifluoromethylation of Carbonyl Compounds with N -Formylmorpholine Derivatives. *Org. Lett.* **2000**, *2*, 2101–2103. DOI 10.1021/ol005987o.

(63) Ojeda-Amador, A. I.; Martínez-Martínez, A. J.; Robertson, G. M.; Robertson, S. D.; Kennedy, A. R.; O'Hara, C. T. Exploring the solid state and solution structural chemistry of the utility amide potassium hexamethyldisilazide (KHMDS). *Dalt. Trans.* **2017**, *46* (19), 6392–6403. DOI 10.1039/c7dt01118k.

(64) Large, S.; Roques, N.; Langlois, B. R. Nucleophilic trifluoromethylation of carbonyl compounds and disulfides with trifluoromethane and silicon-containing bases. *J. Org. Chem.* **2000**, *65* (26), 8848–8856. DOI 10.1039/c7dt01118k.

(65) Prakash, G. K. S.; Yudin, A. K. Perfluoroalkylation with Organosilicon Reagents. *Chem. Rev.* **1997**, *97* (3), 757–786. DOI 10.1021/cr9408991.

(66) Ramaiah, P.; Krishnamurti, R.; Prakash, G. K. S. 1-Trifluoromethyl-1-cycloexanol. *Org. Synth.* **1995**, *72*, 232. DOI 10.15227/orgsyn.072.0232.

(67) Prakash, G. K. S.; Wang, F. **2010**. Trifluoromethyltriethylsilane. *e-EROS Encyclopedia of Reagents for Organic Synthesis.* DOI: 10.1002/047084289X.rn01198.

(68) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. The Palladium-Catalyzed Trifluoromethylation of Aryl Chlorides. *Science* **2010**, *328* (5986), 1679–1681. DOI 10.1126/science.1190524.

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