Gas/Liquid-Phase Micro-Flow Trifluoromethylation using Fluoroform: Trifluoromethylation of Aldehydes, Ketones, Chalcones, and *N*-Sulfinylimines

Kazuki Hirano,[a] Satoshi Gondo,[a] Nagender Punna,[a] Etsuko Tokunaga,[a] and Norio Shibata*[a, b]

A micro-flow nucleophilic trifluoromethylation of carbonyl compounds using gaseous fluoroform was developed. This method also allows the first micro-flow transformation of *N*-sulfinylimines into trifluoromethyl amines with excellent diastereoselectivity. To demonstrate the synthetic utility of this micro-flow synthesis, the formal micro-flow synthesis of Efavirenz is described.

Fluorine plays a unique role in pharmaceuticals and agrochemicals, as its introduction at key positions of biologically attractive organic molecules alters their original properties, sometimes enhancing their therapeutic efficacy.[1] Especially the trifluoromethyl (CF_3) group has garnered much attention due to its versatile biological activity (Figure 1).[2]
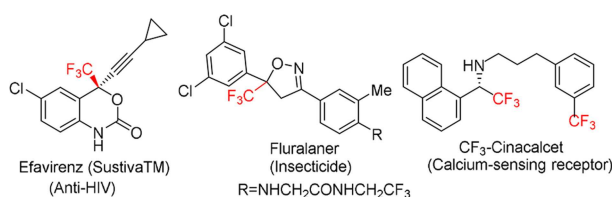

Figure 1. Representative biologically active molecules containing a trifluoromethyl group.

The preparation of CF_3-containing drugs usually requires expensive trifluoromethylation reagents regardless of the type of transformation (electrophilic, nucleophilic, or radical). Among these, the majority of nucleophilic trifluoromethylation reactions is performed using the Ruppert–Prakash reagent (CF_3SiMe_3), *i.e.*, a nucleophilic trifluoromethylation agent, which is not atom economical.[3] Towards more practical and industrially more efficient nucleophilic trifluoromethylation transformations, two improvements should be considered: i) novel practical methods and ii) atom-economical alternatives for the Ruppert–Prakash reagent that exhibit similar reactivity.

Although traditional organic synthesis is generally performed in round-bottomed flasks (batch system), new micro-flow technologies for the synthesis of organic compounds have recently emerged.[4] Flow synthesis based on special flow devices is considered more beneficial than batch reactions, as the former are faster and safer than the latter, reduce the energy consumption, and are easily scaled up (mg to kg).[5] However, performing batch reactions in micro-flow mode is not always easy and, depending on the reaction and substrates, many factors may have to be precisely optimized.[4,5,6] Given the rapid progress of a variety of flow reactions and flow reactors, the development of micro-flow trifluoromethylation processes has also attracted much attention. In 2016, our group demonstrated the first flow and micro-flow nucleophilic trifluoromethylation of carbonyl species using the Rupert–Prakash reagent.[7] While our (micro-)flow method efficiently produces trifluoromethylated carbinols, including the anti-HIV drug Efavirenz and the 11β-hydroxysteroid dehydrogenase type 1 inhibitor HSD016, in good to high yield, the fundamental green chemistry aspect of using trifluoromethylation reagents that are more atom-economical than the Ruppert–Prakash reagent remains unresolved.

Fluoroform (CF_3H) is a highly atom-economical gaseous source of CF_3 groups for the introduction in organic molecules that is readily available, given that fluoroform is a chemical waste product that accumulates during the manufacturing of Teflon®. Another critical aspect of fluoroform is the existing restrictions regarding its emission into the environment following the Kyoto protocol due to its very large global warming potential (GWP), which is 11,700-fold that of carbon dioxide, and an atmospheric lifetime of 264 years.[8] Thus, the development of efficient trifluoromethylation methods that use fluoroform instead of the Rupert–Prakash reagent would have a great impact both from a synthetic and environmental perspective.[9,10] Although the use of fluoroform for trifluoromethylations via the deprotonation with strong bases has been reported more than a quarter of a century ago by Shono and co-workers,[9a] taming fluoroform for trifluoromethylations has

[a] K. Hirano, S. Gondo, N. Punna, E. Tokunaga, Prof. Dr. N. Shibata
     Department of Life Science and Applied Chemistry, Department of Nano-pharmaceutical Sciences
     Nagoya Institute of Technology
     Gokiso, Showa-ku, Nagoya 466-8555, Japan
     E-mail: nozshiba@nitech.ac.jp
[b] Prof. Dr. N. Shibata
     Institute of Advanced Fluorine-Containing Materials
     Zhejiang Normal University
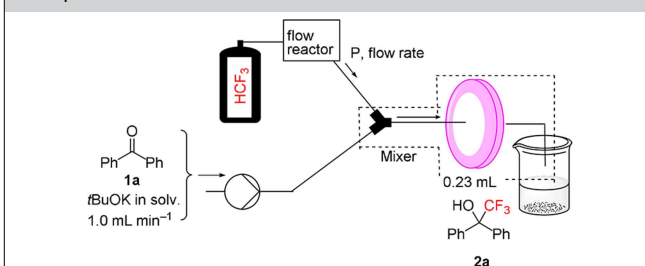   688 Yingbin Avenue, 321004 Jinhua, China

remained challenging. In 2011, Grushin and co-workers made a breakthrough on this matter by the direct cupration of fluoroform with a dialkoxycuprate, which was generated from CuCl and tBuOK, that afforded CuCF$_3$[10a] and thus significantly facilitated the use of fluoroform for a wide variety of trifluoromethylations.[10] In 2012, Prakash et al. reported nucleophilic trifluoromethylations with fluoroform via a deprotonation using potassium bases.[9e] Since then, numerous protocols have been reported that use fluoroform as a trifluoromethylation reagent.[9,10] Thus, we turned our attention on applying fluoroform as a trifluoromethylation reagent in a micro-flow system.[4e] Micro-flow methods should present several advantages in the gas/liquid phase due to the small volume of the micro reactors, which facilitates the mixing of the gaseous with the liquid phase.[11] In 2018, the groups of Kappe and Ley successfully used fluoroform in micro-flow systems for trifluoromethylation [11c] and difluoromethylation[11d] reactions; however, the substrate scope of these methods was severely limited. Herein, we disclose a micro-flow trifluoromethylation process using fluoroform that rapidly transforms a wide variety of carbonyl substrates, including diaryl ketones, aryl alkyl ketones, and aldehydes into the corresponding trifluoromethylated alcohols in good yield. Moreover, these micro-flow conditions also allow the regioselective 1,2-addition of chalcones. Furthermore, this method can be used for the highly stereoselective trifluoromethylation of non-racemic chiral N-sulfinylimines. The synthetic utility of this new method was demonstrated by the formal synthesis of the anti-HIV drug Efavirenz.

We started our experiments with benzophenone (1a) as the model substrate and tBuOK as the base in a mixture of DMF/THF at room temperature. Initially, 1a (1 equiv) and tBuOK (2 equiv) were dissolved in a DMF/THF, then the mixture was pumped through a mixer where it as mixed with the other stream. Via a different channel, fluoroform (8 equiv) was passed through the mixer (micro-flow rate: 25 mL min^{-1}; pressure: 0.2 MPa), which afforded the corresponding trifluoromethylated product (2a) in excellent yield (93%; Table 1, Entry 1). Reducing the pressure to 0.1 MPa did not affect the product yield (Table 1, Entry 2).

To evaluate the solvent effect, the same reaction was carried out in DMF, THF, and toluene. This screening revealed that DMF is superior to the other solvents, as it furnished the targeted product in quantitative yield. Subsequently, we increased the concentration of 1a up to 0.8 M (Table 1, Entries 6–8), and discovered that a concentration of 0.6 M affords the corresponding product in quantitative yield (99%, Table 1, Entry 7). We also performed the micro-flow reaction at a reduced micro-flow rate (15 mL min^{-1}), which furnished the desired product in moderate yield (Table 1, Entry 9). In all the cases, we detected the gas phase exists as large bubbles in the tube. Thus, the reaction would proceed as slug flow.

With the optimized reaction conditions in hand (Table 1, Entry 7), we screened the substrate scope for the trifluoromethylation of ketones using this micro-flow reaction system. Ketones 1a–l with different electronic properties were smoothly transformed into the desired trifluoromethylated products (2a–l) in good yield (Scheme 1). Substrates bearing an electron-

Table 1. Optimization of the micro-flow reaction using fluoroform and benzophenone

Entry	Conc. [M]	Solvent	Fluoroform			Yield[a] [%]
			Flow rate [mL min^{-1}]	Pressure [MPa]	X [equiv]	
1	0.14	DMF/THF	25	0.2	8.0	93
2	0.14	DMF/THF	25	0.1	8.0	94
3	0.14	DMF	25	0.1	8.0	99
4	0.14	THF	25	0.1	8.0	47
5	0.14	Toluene	25	0.1	8.0	15
6	0.3	DMF	25	0.1	3.6	99
7	0.6	DMF	25	0.1	1.7	99
8	0.8	DMF	25	0.1	1.5	82
9	0.6	DMF	15	0.1	1.1	68

[a] Yields were calculated based on the ^{19}F NMR spectra of the crude reaction mixture using PhCF$_3$ as the internal standard.
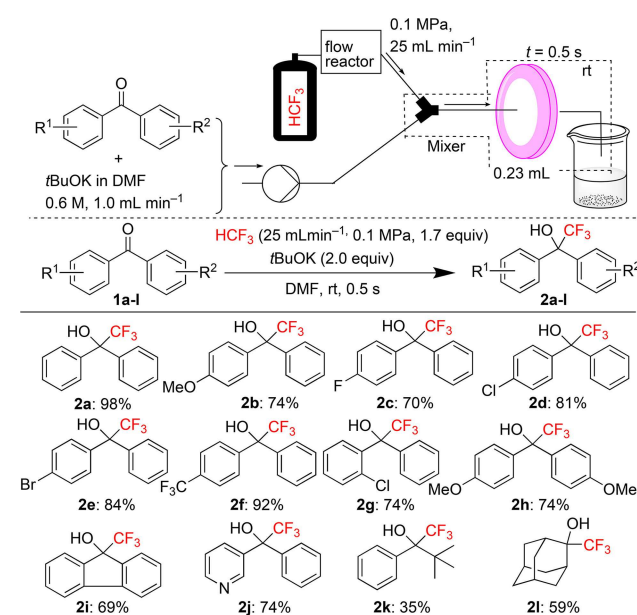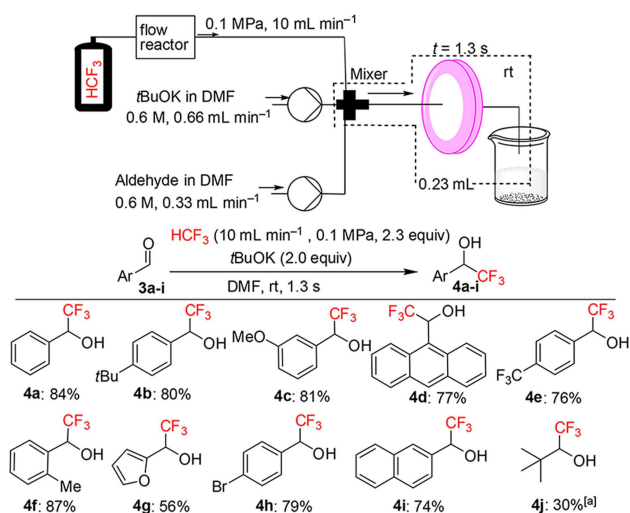

Scheme 1. Substrate scope with respect to ketones.

donating methoxy group were tolerated very well under the applied conditions, and the corresponding products were obtained in good yield (2b: 74%; 2h: 74%), whereas a substrate with an electron-withdrawing CF$_3$ group (1f) afforded the desired product in excellent yield (2f: 92%). Furthermore, halogen-substituted 1c (4-F), 1d (4-Cl), 1e (4-Br), and 1g (2-Cl) were also smoothly converted into the desired products in good to very good yield (2c: 70%; 2d: 81%; 2e: 84%; 2g: 74%). However, phenyl-tert-butyl-ketone 1k afforded the corre-

sponding product in low yield (**2k**: 35%), while adamantyl ketone **1l** furnished **2l** in moderate yield (59%).

Encouraged by these results, we turned our attention to the trifluoromethylation of aldehydes using the micro-flow reaction system. In this protocol, the base and substrate were separately deposited in the mixer in order to avoid the formation of the corresponding Cannizzaro product (for the details of the optimization, *cf.* Table S1). Substrates bearing electron-donating, electron-withdrawing, or halogen substituents on the phenyl ring underwent the micro-flow reaction smoothly to provide the corresponding trifluoromethylated carbinols in good yield of up to 87% (Scheme 2). Moreover, heterocyclic

Scheme 2. Substrate scope of with respect to aldehydes. [a] Yields were calculated based on the ^{19}F NMR spectra of the crude reaction mixture using PhCF$_3$ as the internal standard.

aldehyde furfural (**3g**) and extended π-conjugated aldehydes (naphthalene-**3i** and anthracene-**3d**) also tolerated the micro-flow reaction to afford the desired products in moderate to good yield (**4g**: 56%; **4d**: 77%; **4i**: 74%).

The regioselective 1,2-addition of fluoroform to chalcone **5a** also smoothly afforded the desired product (**6a**) in 61% yield under different optimized conditions using KHMDS in toluene (for the optimization details, *cf.* Table S2). Substrates bearing chloro (**5b**) and fluoro (**5c**) substituents afforded the corresponding products in moderate to good yield (**6b**: 67%; **6c**: 66%) (Scheme 3).

Subsequently, we turned our attention to the trifluoromethylation of *N*-sulfinylimines via this micro-flow reaction system. Based on our recent report,[9] we chose potassium bis(trimethylsilyl)amide (KHMDS) as the base and toluene as the solvent at room temperature; however, the reaction did not proceed. The reaction conditions were thus optimized by changing the temperature (−10 °C), substrate concentration (0.3 M), and base equivalents (3.3 equiv), which afforded the desired product in moderate yield (53%) and high diastereoselectivity (20:1) (for the optimization details, *cf.* Table S3). With the optimized reaction conditions in hand, we examined a
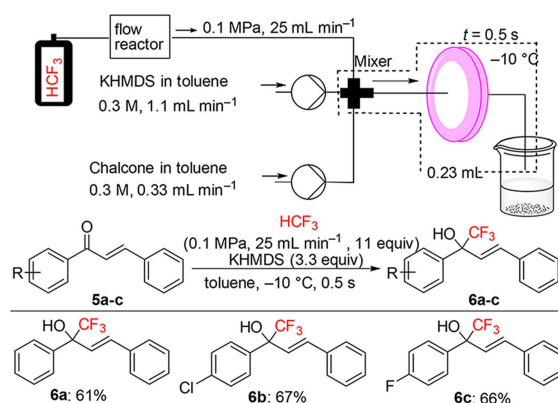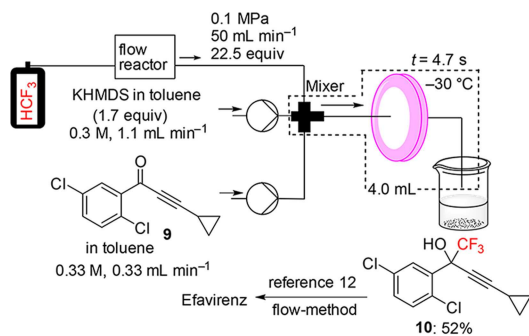
Scheme 3. Micro-flow trifluoromethylation of chalcones using fluoroform.

variety of *N*-sulfinylimines (**7a–k**), and all the substrates (with either electron-donating or -withdrawing substituents) underwent the reaction to afford the corresponding trifluoromethylated products in poor to moderate yield (up to 53%) with high diastereoselectivity (up to 35:1). *N*-sulfinylimines bearing chloro (**7b**) and bromo (**7c**) substituents furnished the products in fair yield (**8b**: 48%; **8c**: 43%) with good selectivity (**8b**: 21:1; **8c**: 16:1). The configuration of the desired products (*Ss,S*) was confirmed based on our previous report (Scheme 4).[9]
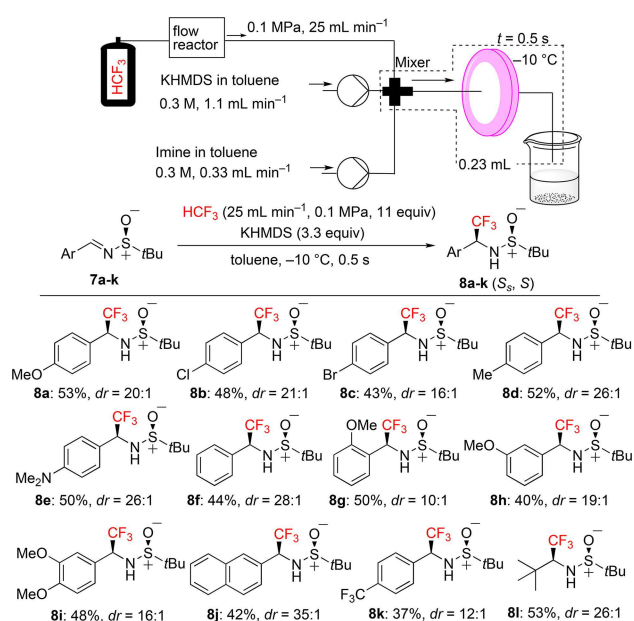
Scheme 4. Substrate scope with respect to imines. The *dr* values were calculated based on the crude ^{19}F NMR spectra.

Finally, we evaluated the potential application of this protocol for the micro-flow synthesis of Efavirenz. After a brief optimization of the reaction conditions including the base (1.7 equiv of KHMDS), solvent (toluene), micro-flow rate (50 mL min^{-1}), and temperature (−30 °C) (*cf.* Table S4), aryl alkenyl ketone **9** was rapidly converted into the corresponding trifluoromethylated carbinol **10** in moderate yield (52%). As **10**

Scheme 5. Trifluoromethylation of **9** to afford Efavirenz intermediate **10**.

has already been converted into Efavirenz via a micro-flow reaction by Seeberger et al.,[12] the transformation of **9** into **10** outlined here completes the formal micro-flow synthesis of Efavirenz (Scheme 5).

In summary, we have successfully developed a gas/liquid-phase micro-flow trifluoromethylation method for ketones, aldehydes, chalcones, and imines using the gaseous chemical waste fluoroform. We have also demonstrated the utility of this protocol for the formal total micro-flow synthesis of the anti-HIV drug Efavirenz. Further applications of this protocol in asymmetric micro-flow trifluoromethylation reactions are currently under investigation.

Experimental Section

General Procedure for the Trifluoromethylation to Ketones in Flow (Procedure A)

A solution of the ketone **1** (1.2 mmol) and tBuOK (2.4 mmol) in dry DMF (2.0 mL) was fed into two inlets mixer (SUS316, ID=0.5 mm, 60 μL internal volume, 1.0 mL min^{-1}) using syringe pump (YMC). Fluoroform was introduced into the two inlets mixer with 0.1 MPa, 25 mL min^{-1} controlled by mass flow controller (MFC) using Flow Factory (EYELA). The combined mixture went through a residence tubing (SUS316, ID=0.8 mm, residence volume V=0.23 mL) at rt. After gas flow rate was stabilized, we collected the product for 1 minute. The product stream was quenched with sat. NH$_4$Cl aq. The aqueous layer was extracted with Et$_2$O, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure, and purified by column chromatography on silica gel to give the products **2**. Residence time is 0.5 s (see Supporting Information (SI)).

General Procedure for the Trifluoromethylation to Aldehydes in Flow (Procedure B)

A solution of the aldehyde **3** (0.6 mmol) in dry DMF (1.0 mL) was fed into three inlets mixer (SUS316, ID=0.5 mm, 60 μL internal volume, 0.33 mL min^{-1}) using syringe pump (YMC), simultaneously tBuOK (1.2 mmol) in dry DMF (2.0 mL) was fed into the mixer (0.66 mL min^{-1}) using another syringe pump (YMC). Fluoroform was introduced into the mixer with 0.1 MPa, 10 mL min^{-1} controlled by mass flow controller (MFC) using Flow Factory (EYELA). The combined mixture went through a residence tubing (SUS316, ID=0.8 mm, residence volume, V=0.23 mL) at rt. After gas flow rate was stabilized, we collected the product for 1 minute. The product

stream was quenched with sat. NH$_4$Cl aq. The aqueous layer was extracted with Et$_2$O, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure, and purified by column chromatography on silica gel to give the products **4**. Residence time is 1.3 s (see SI).

General Procedure for the Trifluoromethylation to Chalcones in Flow (Procedure C)

A solution of the Chalcone **5** (0.6 mmol) in dry toluene (2.0 mL) was fed into three inlets mixer (SUS316, ID=0.5 mm, 60 μL internal volume, 0.33 mL min^{-1}) using syringe pump (YMC), simultaneously KHMDS (2.0 mmol) in dry toluene (6.6 mL) was fed into the mixer (1.1 mL min^{-1}) using another syringe pump (YMC). Fluoroform was introduced into the mixer with 0.1 MPa, 25 mL min^{-1} controlled by mass flow controller (MFC) using Flow Factory (EYELA). The combined mixture went through a residence tubing (SUS316, ID=0.8 mm, residence volume, V=0.23 mL) at −10°C. After gas flow rate was stabilized, we collected the product for 1 minute. The product stream was quenched with sat. NH$_4$Cl aq. The aqueous layer was extracted with Et$_2$O, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure, and purified by column chromatography on silica gel to give the products **6**. Residence time is 0.5 s (see SI).

General Procedure for the Trifluoromethylation to *N*-Sulfinylimines in Flow (Procedure D)

A solution of the *N*-sulfinylimine **7** (0.6 mmol) in dry toluene (2.0 mL) was fed into three inlets mixer (SUS316, ID=0.5 mm, 60 μL internal volume, 0.33 mL min^{-1}) using syringe pump (YMC), simultaneously KHMDS (2.0 mmol) in dry toluene (6.6 mL) was fed into the mixer (1.1 mL min^{-1}) using another syringe pump (YMC). Fluoroform was introduced into the mixer with 0.1 MPa, 25 mL min^{-1} controlled by mass flow controller (MFC) using Flow Factory (EYELA). The combined mixture went through a residence tubing (SUS316, ID=0.8 mm, residence volume, V=0.23 mL) at −10°C. After gas flow rate was stabilized, we collected the product for 1 minute. The product stream was quenched with sat. NH$_4$Cl aq. The aqueous layer was extracted with Et$_2$O, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure, and purified by column chromatography on silica gel to give the products **8**. Residence time is 0.5 s (see SI).

Procedure for the Trifluoromethylation to 1-(2,5-Dichlorophenyl)-3- cyclopropylprop-2-yn-1-one (9) (Procedure E)

A solution of the 1-(2,5-Dichlorophenyl)-3-cyclopropylprop-2-yn-1-one **9** (0.6 mmol) in dry toluene (2.0 mL) was fed into three inlets mixer (SUS316, ID=0.5 mm, 60 μL internal volume, 0.33 mL min^{-1}) using syringe pump (YMC), simultaneously KHMDS (1.0 mmol) in dry toluene (6.6 mL) was fed into the mixer (1.1 mL min^{-1}) using another syringe pump (YMC). Fluoroform was introduced into the mixer with 0.1 MPa, 50 mL min^{-1} controlled by mass flow controller (MFC) using Flow Factory (EYELA). The combined mixture went through a residence tubing (SUS316, ID=0.8 mm, residence volume, V=4.0 mL) at −30°C. After gas flow rate was stabilized, we collected the product for 4 minutes. The product stream was quenched with sat. NH$_4$Cl aq. The aqueous layer was extracted with Et$_2$O, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure, and purified by column chromatography on silica gel to give 2-(2,5-dichlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol **10**. Residence time is 4.7 s (see SI).

Conflict of Interest

The authors declare no conflict of interest.

[1] a) I. Ojima, In *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley-Blackwell, **2009**; b) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, *127*, 303–319; c) H. Kawai, N. Shibata, *Chem. Rec.* **2014**, *14*, 1024–1040; d) J. Wang, M. S. Rosello, J. L. Acena, C. d. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; e) X.-H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, *115*, 731–764.

[2] a) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455–529; b) S. M. E. Vrouenraets, F. W. N. M. Wit, J. V. Tongeren, J. M. A. Lange, *Expert Opin. Pharmacother.* **2007**, *8*, 851–871; c) S. Li, J.-A. Ma, *Chem. Soc. Rev.* **2015**, *44*, 7439–7448; d) M. Gassel, C. Wolf, S. Noack, H. Williams, T. Ilg, *Insect Biochem. Mol. Biol.* **2014**, *45*, 111; e) Y. Ozoe, *Adv. Insect Physiol.* **2013**, 44, 211–124.

[3] a) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683–730; b) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757–786.

[4] a) F. Darvas, V. Hessel, G. Dorman in *Flow Chemistry*, De Gruyter, **2014**; b) W. Reschetilowski in *Micro reactors in Preparative Chemistry*, Wiley-VCH: Weinheim, **2013**; c) J. Yoshida, Y. Takahashi, A. Nagaki, *Chem. Commun.* **2013**, *49*, 9896–9904; d) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38–54; e) H. Amii, A. Nagaki, J. Yoshida, *Beilstein J. Org. Chem.* **2013**, *9*, 2793–2802.

[5] a) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57; b) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583–4592; c) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389; d) V. Hessel, *Chem. Eng. Technol.* **2009**, *32*, 1655–1681; e) J. P. McMullen, K. F. Jensen, *Annu. Rev. Anal. Chem.* **2010**, *3*, 19–42; f) J. Hartwig, J. B. Metternich, N. Nikbin, A. Kirschning, S. V. Ley, *Org. Biomol. Chem.* **2014**, *12*, 3611–3615; g) T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274–1289; h) L. Malet-Sanz, F. Susanne, *J. Med. Chem.* **2012**, *55*, 4062–4098; i) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2–25.

[6] For selected recent articles, see: a) J. Lai, S. Sayalero, A. Ferrali, L. Osorio-Planes, F. Bravo, C. Rodríguez-Escrich, M. A. Pericàs, *Adv. Synth. Catal.* **2018**, *360*, 2914–2924; b) M. V. Enevoldsen, J. Overgaard, M. S. Pedersen,

A. T. Lindhardt, *Chem. Eur. J.* **2018**, *24*, 1204–1208; c) R. M. Neyyappa-dath, R. Chisholm, M. D. Greenhalgh, C. Rodríguez-Escrich, M. A. Pericàs, G. Hähner, A. D. Smith, *ACS Catal.* **2018**, *8*, 1067–1075.

[7] S. Okusu, K. Hirano, Y. Yasuda, E. Tokunaga, N. Shibata, *RSC Adv.* **2016**, *6*, 82716–82720.

[8] a) D. E. Oram, W. T. Sturges, S. A. Penkett, A. McCulloch, P. J. Fraser, *Geophys. Res. Lett.* **1998**, *25*, 35–38; b) A. McCulloch, A. A. Lindley, *Atmos. Environ.* **2007**, *41*, 1560–1566; c) W. Han, Y. Li, H. Tang, H. Liu, *J. Fluorine Chem.* **2012**, *140*, 7–16; d) V. V. Grushin, *Chim. Oggi* **2014**, *32*, 81–88.

[9] a) T. Shono, M. Ishifune, T. Okada, S. Kashimura, *J. Org. Chem.* **1991**, *56*, 2–4; b) R. Barhdadi, M. Troupel, J. Périchon, *Chem. Commun.* **1998**, 1251–1252; c) B. Folléas, I. Marek, J.-F. Normant, L. S. Jalmes, *Tetrahedron Lett.* **1988**, *39*, 2973–2976; d) J. Russell, N. Roques, *Tetrahedron* **1988**, *54*, 13771–13782; e) S. Large, N. Roques, B. R. Langlois, *J. Org. Chem.* **2000**, *65*, 8848–8856; f) G. K. S. Prakash, P. V. J. Patrice, T. D. Batamack, G. A. Olah, *Science* **2012**, *338*, 1324–1327; g) C. S. Thomoson, W. R. Dolbier, Jr., *J. Org. Chem.* **2013**, *78*, 8904–8908; h) H. Kawai, Z. Yuan, E. Tokunaga, N. Shibata, *Org. Biomol. Chem.* **2013**, *11*, 1446–1450; i) S. Potash, S. Rozen, *J. Org. Chem.* **2014**, *79*, 11205–11208; j) S. Okusu, E. Tokunaga, N. Shibata, *Org. Lett.* **2015**, *17*, 3802–3805; k) S. Okusu, K. Hirano, E. Tokunaga, N. Shibata, *ChemistryOpen* **2015**, *4*, 581–585; l) N. Punna, T. Saito, M. Kosobokov, E. Tokunaga, Y. Sumii, N. Shibata, *Chem. Commun.* **2018**, *54*, 4294–4297; m) T. Saito, J. Wang, E. Tokunaga, S. Tsuzuki, N. Shibata, *Sci. Rep.* **2018**, *8*, 11501–11508.

[10] a) A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz, V. V. Grushin, *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913; b) P. Novák, A. Lishchynskyi, V. V. Grushin, *Angew. Chem.* **2012**, *124*, 7887–7890; *Angew. Chem. Int. Ed.* **2012**, *51*, 7767–7772; c) P. Novák, A. Lishchynskyi, V. V. Grushin, *J. Am. Chem. Soc.* **2012**, *134*, 16167–16170; d) A. Lishchynskyi, M. A. Novikov, E. Martin, E. C. Escudero-Adán, P. Novák, V. V. Grushin, *J. Org. Chem.* **2013**, *78*, 11126–11146; e) A. Lishchynskyi, G. Berthon, V. V. Grushin, *Chem. Commun.* **2014**, *50*, 10237–10240; f) A. I. Konovalov, J. Benet-Buchholz, E. Martin, V. V. Grushin, *Angew. Chem.* **2013**, *125*, 11851–11855; *Angew. Chem. Int. Ed.* **2013**, *52*, 11637–11641; g) A. Lishchynskyi, M. F. Miloserdov, E. Martin, J. Benet-Buchholz, C. E. Escudero-Adán, I. A. Konovalov, V. V. Grushin, *Angew. Chem.* **2015**, *127*, 15504–15508; *Angew. Chem. Int. Ed.* **2015**, *54*, 15289–15293.

[11] a) S. C. K. D. Schepper, G. J. Heynderickx, G. B. Marin, *Chem. Eng. J.* **2008**, *138*, 349–357; b) M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res.* **2015**, *48*, 349–362; c) B. Musio, E. Gala, S. V. Ley, *ACS Sustainable Chem. Eng.* **2018**, *6*, 1489–1495; d) M. Köckinger, T. Ciaglia, M. Bersier, P. Hanselmann, B. Gutmann, C. O. Kappe, *Green Chem.* **2018**, *20*, 108–112; e) T. Fukuyama, T. Totoki, I. Ryu, *Org. Lett.* **2014**, *16*, 5632–5635; f) R. Breen, G. Sandford, D. S. Yufit, J. A. K. Howard, J. Fray, B. Patel, *Beilstein. J. Org. Chem.* **2011**, *7*, 1048–1054.

[12] a) C. A. Correia, D. T. McQuade, P. H. Seeberger, *Adv. Synth. Catal.* **2013**, *355*, 3517–3521; b) C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem.* **2015**, *127*, 5028–5032; *Angew. Chem. Int. Ed.* **2015**, *54*, 4945–4948.