Green Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Open Access Article. Published on 30 ottobre 2017. Downloaded on 19/10/2025 16:00:43.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Check for updates

Cite this: *Green Chem.*, 2018, **20**, 108

Received 26th September 2017,
Accepted 30th October 2017

DOI: 10.1039/c7gc02913f

rsc.li/greenchem

Utilization of fluoroform for difluoromethylation in continuous flow: a concise synthesis of α-difluoromethyl-amino acids†

Manuel Köckinger,[a] Tanja Ciaglia,[a] Michael Bersier,[b] Paul Hanselmann,[b] Bernhard Gutmann *[a,c] and C. Oliver Kappe *[a,c]

Fluoroform (CHF_3) can be considered as an ideal reagent for difluoromethylation reactions. However, due to the low reactivity of fluoroform, only very few applications have been reported so far. Herein we report a continuous flow difluoromethylation protocol on sp^3 carbons employing fluoroform as a reagent. The protocol is applicable for the direct C^{α}-difluoromethylation of protected α-amino acids, and enables a highly atom efficient synthesis of the active pharmaceutical ingredient eflornithine.

The difluoromethyl group is found in an increasing array of pharmaceutical and agrochemical products.[1] Not surprisingly, therefore, significant efforts have been devoted towards the development of novel protocols for the introduction of the CHF_2-moiety into organic molecules.[2] In addition to well-established methods based on the deoxyfluorination of aldehydes, various methods for direct difluoromethylation have recently become available.[2] Among the cheapest and most versatile reagents for direct CHF_2-transfer is chlorodifluoromethane (CHF_2Cl, Freon 22). Chlorodifluoromethane is produced on a massive scale, particularly for the production of fluoropolymers, and it is available at a relatively low cost (Fig. 1). With sufficiently strong bases, CHF_2Cl can be deprotonated. The so-formed carbanion, chlorodifluoromethanide (CF_2Cl^-), immediately loses chloride to generate an electrophilic singlet difluorocarbene ($CF_2Cl^- \rightarrow CF_2 + Cl^-$). The short-lived difluorocarbene can then be trapped with a suitably reactive nucleophilic species to produce the difluoromethylated product (Fig. 1).[2] This reaction has been shown to proceed successfully with a range of NH-, OH- and CH-acidic compounds.[2] However, CHF_2Cl is a strong ozone depleting gas and it is controlled under the Montreal Protocol. As a consequence, its production and usage has become increasingly limited and expensive. A plethora of alternative difluoromethane sources have been developed in recent years, including $TMSCF_2Br$, $(EtO)_2POCF_2Br$, $PhCOCF_2Cl$ and CHF_2OTf.[2] Although these reagents cover the needs of chemists for difluoromethylation on a laboratory scale, their high cost, low atom economy and limited commercial availability prohibit their usage in an industrial setting.

The most attractive CF_3- and CHF_2-source is fluoroform (CHF_3, Freon 23). Fluoroform is generated as a large-volume waste-product during the synthesis of chlorodifluoromethane (Fig. 1). It is a nontoxic and ozone-friendly gas with a boiling point of −82 °C. Since fluoroform has an extraordinary global warming potential (14 800 times higher than carbon dioxide over a 100-year period),[3] its discharge into the environment is restricted by the Kyoto Protocol. As a consequence, fluoroform needs to be destroyed or, alternatively, captured and used as a feedstock for manufacturing. The latter option, though vastly preferable, is difficult to realize due to the extraordinarily low reactivity of fluoroform. Only very recently have the first synthetically relevant transformations involving fluoroform started to emerge.[4] Most relevant for the present work is a series of seminal publications from the laboratories of Mikami.[5–7] Mikami and co-workers have shown that fluoro-

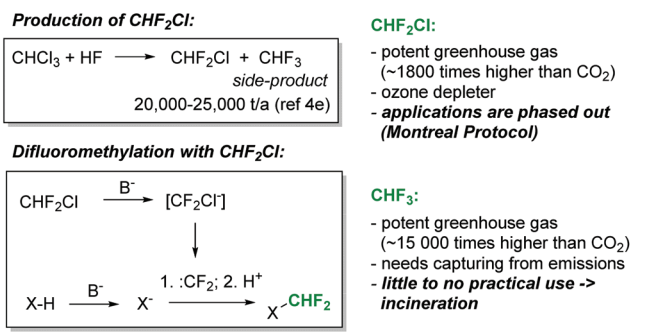


Fig. 1 CHF_3 is a large-volume by-product in the synthesis of CHF_2Cl.

[a]*Institute of Chemistry, University of Graz, NAWI Graz, Heinrichstrasse 28, 8010 Graz, Austria. E-mail: bernhard.gutmann@uni-graz.at, oliver.kappe@uni-graz.at*
[b]*Microreactor Technology, Lonza AG, CH-3930 Visp, Switzerland*
[c]*Research Center Pharmaceutical Engineering GmbH (RCPE), Inffeldgasse 13, 8010 Graz, Austria*

†Electronic supplementary information (ESI) available: Experimental procedures, further optimization data and characterization of all compounds. See DOI: 10.1039/c7gc02913f

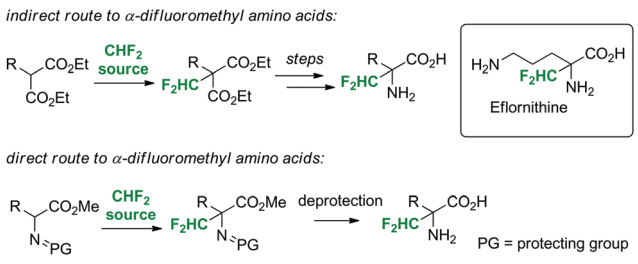
This journal is © The Royal Society of Chemistry 2018

Open Access Article. Published on 30 ottobre 2017. Downloaded on 19/10/2025 16:00:43.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

form can be utilized for the direct difluoromethylation of a variety of substrates utilizing strong lithium bases (lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LiHMDS)).[5–7] In addition to Mikami's work, the difluoromethylation reactions of alkynes with CHF_3 and *t*BuOK,[8] as well as the difluoromethylation of phenols and malonates with aqueous KOH,[9] have been described by Shibata and Dolbier, respectively. The mechanism of the difluoromethylation reaction is believed to resemble that of the corresponding reaction with CHF_2Cl.[8–10] An electrophilic singlet difluorocarbene is formed by the deprotonation of CHF_3 and the subsequent rapid α-elimination of fluoride. Difluorocarbene then reacts with the anion of the substrate (Fig. 1).

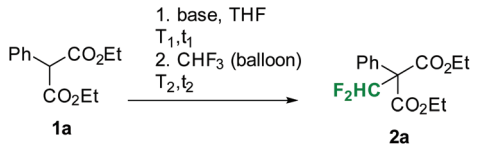
The main objective of the present work was to establish a scalable, continuous flow synthesis route to C^{α}-difluoromethyl amino acids using fluoroform as the reagent (Scheme 1). C^{α}-Difluoromethyl amino acids are potent and selective irreversible inhibitors of their respective α-amino acid decarboxylases.[11] Representatives of this class of compounds exhibit a broad spectrum of biological activities, such as antibacterial, antihypertensive, cancerostatic, and cytotoxic activities.[11] Currently, only D,L-α-difluoromethylornithine (eflornithine), an inhibitor of ornithine decarboxylase, is in medical use (Scheme 1). Eflornithine has been explored as an anticancer agent, and it is in clinical use for the treatment of African sleeping sickness as well as of *Pneumocystis carinii pneumonia*, the most frequent opportunistic infection associated with acquired immunodeficiency syndrome (AIDS).[11] It is on the World Health Organization's Model List of Essential Medicines. Two different strategies can be employed for the generation of C^{α}-difluoromethyl amino acids: (i) construction of the amino acids from fluorine-containing building blocks (*e.g.* α-difluoromethyl malonates),[12,13] or (ii) direct substitution of the α-hydrogen of amino acids with a CHF_2 moiety (Scheme 1).[14] The direct C^{α}-difluoromethylation of Schiff base-protected α-amino acid methyl esters with CHF_2Cl as the reagent has been demonstrated by Bey and others.[14] The α-difluoromethylation of protected amino acids with CHF_3 is currently not reported. Indeed, the protocol described herein is, to the best of our knowledge, the first example where fluoroform is utilized for the preparation of a pharmaceutical end-product.

First preliminary batch experiments were performed with diethyl phenylmalonate (**1a**) as a model substrate (Table 1).



Scheme 1 Synthesis of D,L-C^{α}-difluoromethyl amino acids.

Table 1 Difluoromethylation of diethyl phenylmalonate **1a** with CHF_3[a]



	Base (equiv.)	t_1 (min)	T_1 (°C)	t_2 (min)	T_2 (°C)	Conv[b] (%)	Sel[b] (%)
1	*t*BuOK (3)	5	25	60	25	28	0
2	*t*BuOLi (3)	5	25	60	25	4	0
3	LDA (2)	5	25	5	25	0	0
4	*n*BuLi (2)	5	25	5	25	0	0
5	*n*BuLi (2)	5	−80	5	−80	0	0
6	LiHMDS (2)	5	25	60	25	2	100
7[c]	KOH (15)	30	25	120	25	32[d]	0

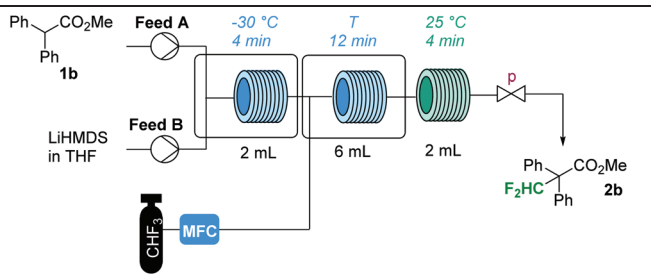
[a] Reaction conditions: 0.5 mmol diethyl phenylmalonate **1a** in 0.5 mL THF, base and CHF_3 (balloon). [b] Analyzed by HPLC-UV/VIS at 215 nm. [c] Method B in ref. 9*a*. [d] 20% ethyl phenylacetate (by hydrolysis and decarboxylation).

For these reactions, malonate was dissolved in the desired solvent and a base was added. After stirring the mixture for a few minutes at the indicated temperatures (t_1, T_1 in Table 1), fluoroform was slowly passed through the reaction mixture under vigorous stirring (t_2, T_2 in Table 1). Using phenylmalonate **1a** as a substrate, no product was formed with *n*BuLi, LDA or *t*BuOK as a base (entries 1 to 5 in Table 1). Furthermore, attempts to reproduce the results reported by Dolbier and co-workers failed in our hands.[9] According to Dolbier's procedure, the phenylmalonate **1a** is stirred in aqueous KOH for 30 min at room temperature. MeCN or dioxane is then added and fluoroform is bubbled through the solution.[9] Our experiments under these reaction conditions did not yield any difluoromethylated product (entry 7 in Table 1). Small amounts of the desired product were formed using LiHMDS as a base (entry 6 in Table 1). Mikami and co-workers have already shown that fluoroform in combination with LiHMDS can be utilized for the direct difluoromethylation of cyclic amides, cyclic and open esters, and certain simple malonates.[5] According to the authors, the reaction proceeds best with 2 equiv. of base and 5 equiv. of CHF_3. Reaction times of 6 to 48 h at reaction temperatures of 0 to 25 °C were needed to provide the desired products in good yields.[5]

Encouraged by this result, we were keen to develop a continuous flow protocol for this reaction. Continuous processing techniques have had a significant impact on the development of more sustainable manufacturing routes for several pharmaceuticals.[15–18] For gas–liquid reactions, several specific advantages exist: high pressure operation and fast gas–liquid mass transfer enhance the availability of the gaseous reagent in the liquid phase.[16,17] In addition, the gaseous reagent can be dosed into the liquid phase with precise stoichiometry using mass flow controllers.[16,17] Our initial flow setup consisted of two continuous syringe pumps to introduce (i) a 0.5 M solution of substrate in THF (Feed A, Table 2), and (ii) a

Open Access Article. Published on 30 ottobre 2017. Downloaded on 19/10/2025 16:00:43.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Table 2 Difluoromethylation of methyl diphenylacetate **1b** under flow conditions[a]



	T (°C)	p (bar)	Conv[b] (%)	Sel[b] (%)
1	40	5	63	81
2	25	5	65	80
3	−10	5	82	88
4	−15	10	86	91
5	−15	12	92	91

[a] Reaction conditions: Feed A: 0.5 M diethyl phenylmalonate **1b** in THF; Feed B: 1 M LiHMDS in THF; with flow rates for Feed A/Feed B/CHF_3 = 0.30 : 0.20 : 8.3 mL min^{-1}, respectively, the following conditions were obtained: LiHMDS (1.33 equiv.); CHF_3 (2.5 equiv.). [b] Analyzed by GC-FID. For a detailed description of the experiments, see the ESI.

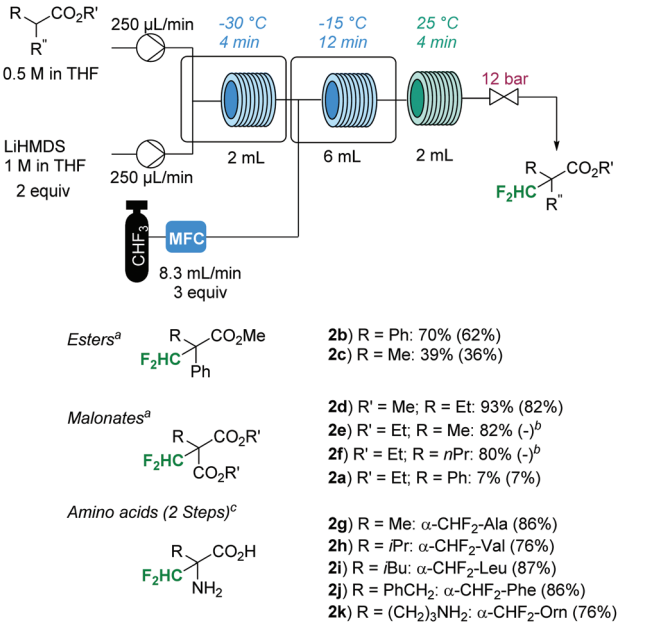


Fig. 2 Continuous flow C^{α}-difluoromethylation with fluoroform. [a] ^{19}F-NMR yields (trifluorotoluene as an internal standard); isolated yields (TLC) in parentheses. [b] Isolation was not attempted. [c] Isolated yields after 2 steps (C^{α}-difluoromethylation and hydrolysis of the *N*-benzylidene- and the *O*-methyl-protecting groups). For experimental details, see the ESI.†

commercial solution of LiHMDS (Feed B, Table 2). The two feeds were mixed in a Y-shaped connector in a cooling bath. The substrate is deprotonated in a 2 mL residence loop (reactor 1), before the mixture is combined with fluoroform in a second Y-shaped connector in a second cooling bath. The flow rate of the fluoroform stream was controlled using a calibrated mass flow controller (MFC). The combined mixture then went through a second cooled residence loop (reactor 2) and left the flow system through a third residence loop at room temperature (reactor 3) and an adjustable back pressure regulator. With pressures of ~5 bar and temperatures below ~25 °C for reactor 2, fluoroform dissolved completely in the liquid feed. At higher temperatures at this pressure, distinct gas–liquid segments were formed. The processed reaction mixture was finally collected in a quench solution of aqueous HCl/Et_2O and the organic phase was analyzed by GC-FID and ^{19}F-NMR spectroscopy. Methyl diphenylacetate **1b** was used as the model substrate for the initial optimization. With flow rates of 300 µL min^{-1} for Feed A, 200 µL min^{-1} for Feed B and 8.3 mL min^{-1} for fluoroform, a stoichiometry of 1 : 1.3 : 2.5 for substrate/LiHMDS/CHF_3 and a total residence time of ~20 min was obtained. The flow reactions clearly revealed that the conversion increased with a decrease in temperature and an increase in pressure (Table 2). Also the selectivity increased slightly with decreasing temperatures (Table 2). As already observed by Mikami and co-workers, the best results are obtained with 2 equiv. of base (see Table S1 in the ESI†). Also, for fluoroform, 2 to 3 equiv. were identified as the ideal amount.

The general reaction conditions were suitable for a variety of substrates (Fig. 2). Malonates with sterically benign alkyl groups in the α-position performed particularly well (**1d** to **1f** in Fig. 2), while the phenyl derivative **1a** resulted in low conversion. The reaction was remarkably clean, with the unreacted substrate and tris(trimethylsilyl)amine being the only contaminants in the crude mixture after washing with water. The analytically pure compounds were isolated by preparative thin-layer chromatography (TLC). The yield of diethyl methylmalonate **2e** was the same as that previously reported for the batch protocol, even though the reaction time for the present procedure was significantly shorter (20 min *vs.* 20 h for the batch procedure).[5] The yield of product **2c** was lower than that reported for the batch procedure (39% *vs.* 78% according to ^{19}F-NMR spectroscopy).[5] The other difluoromethylated compounds prepared in this work have not been previously reported.

As mentioned in the introduction, the synthesized α-difluoromethyl malonates can be converted to the respective α-difluoromethyl amino acids in a multi-step transformation (Scheme 1).[12,13] However, since a direct difluoromethylation of natural α-amino acids has clear advantages, reactions with Schiff base-protected α-amino acid methyl esters were investigated.[14] The *N*-benzylidene-protected α-amino acid methyl esters were readily available from the parent amino esters using literature procedures (for experimental details, see the ESI†).[14] Gratifyingly, subjecting the *N*-benzylidene-protected α-amino acid methyl esters **1g** to **1k** to the general reaction conditions resulted in >95% conversion to the desired product. Indeed, the reaction was remarkably clean with only one CHF_2-moiety (two doublets of doublets) detectable in

 This journal is © The Royal Society of Chemistry 2018

Open Access Article. Published on 30 ottobre 2017. Downloaded on 19/10/2025 16:00:43.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

the ^{19}F-NMR spectra of the crude reaction mixtures. Difluoromethylation on the imine carbon, a side reaction typically encountered in reactions with CHF_2Cl as a reagent, was not observed.[14b] Due to the instability of the Schiff base to hydrolysis, isolation of the intermediate products was not attempted. Instead, the *N*-benzylidene- and the *O*-methyl-protecting groups were directly removed by heating the crude product in 6 N HCl in a microwave batch autoclave (150 °C for 45 min). The released benzaldehyde was removed by extracting with ether and the aqueous phase was concentrated. After recrystallization from MeOH/EtOH, the C^{α}-difluoromethyl amino acids were obtained as their monohydrochloride salts (dihydrochloride salt for product **2k**). As expected, $[\alpha]_D^{20}$ measurements of product **2h** revealed that the chirality of the substrate was lost. The yields were above 70% for all tested amino acids over the two reaction steps, *i.e.* difluoromethylation and deprotection (Fig. 2). Importantly, eflornithine (**2g**) was isolated in 76% yield after the two reaction steps. The yield of eflornithine for the present chromatography-free method is significantly higher than that previously reported for the less desirable process based on chlorodifluoromethane (37% to 40%).[14d,e]

It should be noted that the process described herein consumes only two of the three introduced equivalents of fluoroform. For large scale applications, the separation of fluoroform from the processed solution and recycling needs to be considered.[19] Further optimization of the difluoromethylation process, in particular with regard to stoichiometry and reaction time, is ongoing in our laboratories and will be reported in due course.

Conclusions

A gas–liquid continuous flow difluoromethylation protocol employing fluoroform as a reagent was reported. Fluoroform, a by-product of Teflon manufacture with little current synthetic value, is the most attractive reagent for difluoromethylation reactions. The continuous flow process allows this reaction to be performed within reaction times of 20 min with 2 equiv. of base and 3 equiv. of fluoroform. Importantly, the protocol allows the direct C^{α}-difluoromethylation of protected α-amino acids. These compounds are highly selective and potent inhibitors of pyridoxal phosphate-dependent decarboxylases. The starting materials are conveniently derived from the commercially available α-amino acid methyl esters, and the final products are obtained in excellent purities and yields after simple hydrolysis and precipitation. The developed process appears to be especially appealing for industrial applications, where atom economy, sustainability, reagent cost and reagent availability are important factors.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) *Fluorine-containing Amino Acids, Synthesis and Properties*, ed. V. P. Kukhar and V. A. Soloshonok, Wiley & Sons, Chichester, 1995; (*b*) *Organofluorine Compounds in Medicinal Chemistry & Biomedical Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elsevier, Amsterdam, 1993.
2 For recent reviews, see: (*a*) C. Ni and J. Hu, *Synthesis*, 2014, 842–863; (*b*) D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem. – Eur. J.*, 2017, **23**, 14676–14701.
3 P. Forster, V. Ramaswamy, P. Artaxo, T. Berntsen, R. Betts, D. W. Fahey, J. Haywood, J. Lean, D. C. Lowe, G. Myhre, J. Nganga, R. Prinn, G. Raga, M. Schulz and R. Van Dorland, in *Changes in atmospheric constituents and in radiative forcing. In Climate change 2007: The Physical Science Base, Fourth Assessment Report of the Intergovernmental Panel on Climate Change*, ed. S. Soloman, D. Qin, M. Manning, Z. Chen, M. Marquis, K. B. Averyt, M. Tignor and H. L. Miller, Cambridge University Press, Cambridge, 2007.
4 For selected publications, see: (*a*) T. Shono, M. Ishifune, T. Okada and S. Kashimura, *J. Org. Chem.*, 1991, **56**, 2–4; (*b*) B. Folléas, I. Marek, J.-F. Normant and L. Saint-Jalmes, *Tetrahedron*, 2000, **56**, 275–283; (*c*) J. Russell and N. Roques, *Tetrahedron*, 1998, **54**, 13771–13782; (*d*) A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz and V. V. Grushin, *J. Am. Chem. Soc.*, 2011, **133**, 20901–20913; (*e*) P. Novák, A. Lishchynskyi and V. V. Grushin, *J. Am. Chem. Soc.*, 2012, **134**, 16167–16170; (*f*) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack and G. A. Olah, *Science*, 2012, **338**, 1324–1327.
5 T. Iida, R. Hashimoto, K. Aikawa, S. Ito and K. Mikami, *Angew. Chem., Int. Ed.*, 2012, **51**, 9535–9538.
6 K. Aikawa, K. Maruyama, K. Honda and K. Mikami, *Org. Lett.*, 2015, **17**, 4882–4885.
7 K. Aikawa, K. Maruyama, J. Nitta, R. Hashimoto and K. Mikami, *Org. Lett.*, 2016, **18**, 3354–3357.
8 S. Okusu, E. Tokunaga and N. Shibata, *Org. Lett.*, 2015, **17**, 3802–3805.
9 (*a*) C. S. Thomoson and W. R. Dolbier, *J. Org. Chem.*, 2013, **78**, 8904–8908; (*b*) C. S. Thomoson, L. Wang and W. R. Dolbier, *J. Fluorine Chem.*, 2014, **168**, 34–39.
10 For an alternative mechanistic hypothesis suggested by Mikami and co-workers, see ref. 5.
11 For a review on the synthesis of C^{α}-difluoromethyl amino acids, see: (*a*) X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711–6745; (*b*) R. Smits, C. D. Cadicamo, K. Burger and B. Koksch, *Chem. Soc. Rev.*, 2008, **37**, 1727–1739.
12 B. Gutmann, P. Hanselmann, M. Bersier, D. Roberge and C. O. Kappe, *J. Flow Chem.*, 2017, **7**, 46–51.
13 (*a*) P. Bey, F. Gerhart, V. V. Dorsselaer and C. Danzin, *J. Med. Chem.*, 1983, **26**, 1551–1556; (*b*) T. Tsushima, K. Kawada, S. Iahihara, N. Uchida, O. Shiratori, J. Higaki and M. Hirata, *Tetrahedron*, 1988, **44**, 5375–5387;

Open Access Article. Published on 30 ottobre 2017. Downloaded on 19/10/2025 16:00:43.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

(*c*) D. Schirlin, F. Gerhart, J. M. Hornsperger, M. Hamon, J. Wagner and M. J. Jungs, *J. Med. Chem.*, 1988, **31**, 30–36; (*d*) S. N. Osipov, A. S. Golubev, N. Sewald and K. Burger, *Tetrahedron Lett.*, 1979, **38**, 5965–5966; (*e*) T. Tsushima and K. Kawada, *Tetrahedron Lett.*, 1985, **26**, 2445–2448; (*f*) P. Bey and D. Schirlin, *Tetrahedron Lett.*, 1978, **52**, 5225–5228; (*g*) S. N. Osipov, A. S. Golubev, N. Sewald, T. Michel, A. F. Kolomiets, A. V. Fokin and K. Burger, *J. Org. Chem.*, 1996, **61**, 7521–7528; (*h*) I. I. Gerus, A. A. Kolomeitsev, M. I. Kolycheva and V. P. Kukhar, *J. Fluorine Chem.*, 2000, **105**, 31–33.

14 (*a*) P. Bey and J. P. Vevert, *Tetrahedron Lett.*, 1978, **14**, 1215–1218; (*b*) P. Bey, J. B. Ducep and D. Schirlin, *Tetrahedron Lett.*, 1984, **25**, 5657–5660; (*c*) P. Bey, J.-P. Vevert, V. V. Dorsselaer and M. Kolb, *J. Org. Chem.*, 1979, **44**, 2732–2742; (*d*) M. Seki, M. Suzuki and K. Matsumoto, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 1024–1025; (*e*) P. Bey and M. Jung (Merrell Toraude et Compagnie), Method of treating benign prostatic hypertrophy, *US* 4330559, 1982; (*f*) P. Bey and M. Jung (Merrell Toraude et Compagnie), 2-(Difluoromethyl)-2,5-diaminopentanoic acid, *US* 4413141, 1983.

15 D. Dallinger and C. O. Kappe, *Curr. Opin. Green Sust. Chem.*, 2017, **7**, 6–12 and references cited therein.

16 (*a*) B. Gutmann, D. Cantillo and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2015, **54**, 6688–6728; (*b*) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley and C. V. Stevens, *Chem. Soc. Rev.*, 2016, **45**, 4892–4928; (*c*) M. B. Plutschack, B. Pieber, K. Gilmore and P. H. Seeberger, *Chem. Rev.*, 2017, **117**, 11796–11893.

17 (*a*) H. P. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque and T. Noël, *Chem. Soc. Rev.*, 2016, **45**, 83–117; (*b*) C. J. Mallia and I. R. Baxendale, *Org. Process Res. Dev.*, 2016, **20**, 327–360.

18 For a recent protocol for introducing CF_2 using photochemistry in a continuous flow, see: X.-J. Wei, W. Boon, V. Hessel and T. Noël, *ACS Catal.*, 2017, **7**, 7136–7140.

19 Methods for continuous flow gas–liquid separation are well developed. For previous reports on continuous *inline* gas removal, see: (*a*) P. Koos, U. Gross, A. Polyzos, M. O'Brien, I. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2011, **9**, 6903–6908; (*b*) M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale and S. V. Ley, *Chem. Sci.*, 2011, **2**, 1250–1257; (*c*) K. Skowerski, S. J. Czarnocki and P. Knapkiewicz, *ChemSusChem*, 2014, **7**, 536–542; (*d*) M. J. Fink, M. Schön, F. Rudroff, M. Schnurch and M. D. Mihovilovic, *ChemCatChem*, 2013, **5**, 724–727; (*e*) D. Cantillo, B. Wolf, R. Goetz and C. O. Kappe, *Org. Process Res. Dev.*, 2017, **21**, 125–132.

 This journal is © The Royal Society of Chemistry 2018