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FULL PAPER

Continuous Flow Homolytic Aromatic Substitution with Electrophilic Radicals – A Fast and Scalable Protocol for Trifluoromethylation

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Abstract: Herein, we report an operationally simple and rapid continuous flow radical C─C bond formation under Minisci-type reaction conditions. The transformations are performed at or below room temperature employing hydrogen peroxide (H_2O_2) and dimethylsulfoxide (DMSO) as reagents in the presence of an Fe(II) catalyst. For electron rich aromatic and heteroaromatic substrates C─C bond formation proceeds satisfactorily with electrophilic radicals including $\cdot CF_3$, $\cdot C_4F_9$, $\cdot CH_2CN$ and $\cdot CH_2CO_2Et$. In contrast, electron poor substrates exhibit minimal reactivity. Importantly, trifluoromethylations and nonafluororobutylations using CF_3I and C_4F_9I as reagents proceed exceedingly fast with high conversion for selected substrates in residence times of a few seconds. The attractive features of the present process are the low cost of the reagents and the extraordinary high reaction rates. The direct application of the protocol to dihydroergotamine, a complex ergot alkaloid, yielded the corresponding trifluoromethyl ergoline derivative within a reaction time of 12 seconds in a continuous flow microreactor on a 0.6 kg scale. The trifluoromethyl derivative of dihydroergotamine is a promising therapeutic agent for the treatment of migraine.

Introduction

An increasing number of new drugs and drug candidates as well as a number of agrochemicals contain a trifluoromethyl moiety.[1] Indeed, fluorinated and trifluoromethylated compounds are routinely evaluated in drug-discovery and drug-development programs. The incorporation of fluorine into a pharmaceutical ingredient frequently increases metabolic stability and improves lipophilicity, membrane permeability and bioavailability.[1] Considerable efforts have been devoted towards the development of new methods for the selective introduction of the CF_3-moiety into organic molecules. Traditional techniques for the generation of aryl-CF_3 compounds have been limited to deoxofluorination of carboxylic acids and to perchlorination of aromatic methyl groups with subsequent exchange of chloride by fluoride.[2] In the last decades, however, a range of reagents and protocols for the direct introduction of the CF_3 group into aromatic and heteroaromatic compounds have been developed.[2] Typically, the introduction of the CF_3 moiety is accomplished by transition-metal-mediated cross-coupling of suitably functionalized aromatic compounds with either nucleophilic or electrophilic CF_3-sources.[3] Furthermore, methods for the direct CH-trifluoromethylation of unactivated aromatic and heteroaromatic precursors by

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homolytic aromatic substitution have become available.[4] The generation of perfluoroheptyl radicals by thermal homolysis of the C-I bond of perfluoroheptyliodide in an autoclave at 250 °C was reported by Tiers in 1960.[5] The thermally generated radical could be utilized to convert simple aromatic substrates, such as benzene, toluene, naphthalene and halobenzenes, to the perfluoroalkyled products.[5] More recently, reagents including $Na_2S_2O_4$,[6] Et_3B/O_2,[7] and Me_3Al,[8] have been used to initiate radical trifluoromethylation under mild reaction conditions. Baran and co-workers introduced an effective protocol using CF_3SO_2Na (Langlois reagent) and *t*BuOOH as a source for the trifluoromethyl radical in biphasic solutions.[9] The method allowed the trifluoromethylation of a variety of electron-deficient and electron-rich heteroaromatic systems after reaction times of 3 to 24 h at room temperature.[9] Moreover, various researchers have demonstrated that photoredox catalysis allows the efficient generation of the CF_3 radical from various CF_3-sources under reaction conditions compatible with a wide range of functional groups.[10,11]

The generation of alkyl radicals from alkyl iodides, hydrogen peroxide, DMSO and Fe(II) as catalyst was described by Minisci and co-workers in 1988 (Scheme 1).[12,13] Simple alkyl iodides form nucleophilic radicals which add to electron-poor olefins and heteroaromatic bases with good regio- and chemo-selectivity.[13] On the other hand, electrophilic radicals generated from halides with electron-withdrawing groups in the α-position, such as ICH_2CO_2R, ICH_2CN, or $ICH(CO_2R)_2$, show the potential to add to electron-rich aromatic compounds and olefins.[14] Importantly, Baciocchi and Muraglia demonstrated the applicability of Minisci-type reaction conditions for the perfluoroalkylation of pyrroles starting from perfluoroalkyl iodides.[15] The reaction was further explored by Minisci,[16] and Yamakawa.[17] Moreover, Yamakawa and coworkers demonstrated that these conditions are suitable for the production of 5-trifluoromethyluracil from uracil and CF_3I on a 50 kg scale in a 600 L stirred tank reactor.[18]

Due to the extreme reaction speed and exothermicity of Minisci-type alkylation reactions, hydrogen peroxide typically has to be dosed dropwise over a period of hours to a cooled, well-stirred reaction mixture to keep the reaction under control.[12-18] Microreactors provide significantly improved control over reaction conditions, and reactions often can be performed under conditions which would be infeasible or impossible to use in batch reactors.[19] Fast mixing can be achieved in microfluidic devices with dedicated mixing structures, and the high surface-to-volume ratio allows rapid dissipation of excess heat.[19] Thus, mass and energy transport

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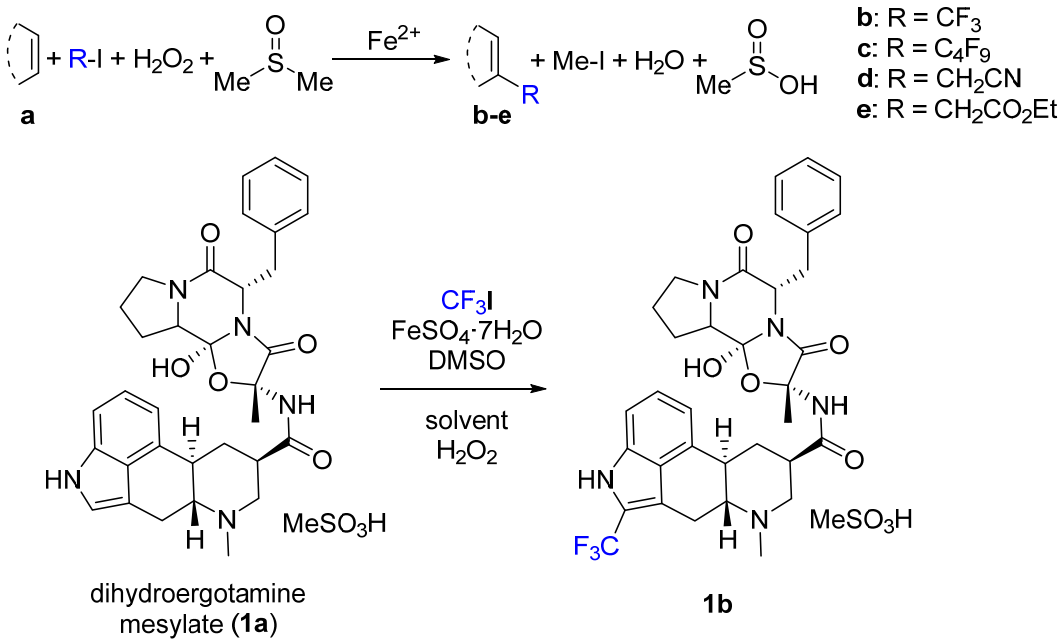
limitations can be eliminated even for fast and highly exothermic reactions and the intrinsic reaction kinetics can be fully exploited.[20]

Herein we disclose a continuous flow protocol for the radical CH-trifluoromethylation of unactivated aromatic compounds using hydrogen peroxide/DMSO/iron as the radical source.[12,13] Importantly, this protocol allows the direct transformation of unprotected dihydroergotamine mesylate **1a** to the corresponding trifluoromethyl derivative **1b** within residence times of only seconds in a continuous flow microreactor (Scheme 1). Dihydroergotamine, a semi-synthetic form of ergotamine, is a well-established pharmaceutical product, with over 70 years of use in the treatment of migraine.[21] However, since dihydroergotamine causes several negative side effects, such as nausea, its use has recently declined and it has become increasingly replaced by more selective (and generally significantly more expensive) 5-HT agonists (*e.g.* sumatriptan).[21] Newer receptor activity studies have suggested that the fluoro derivatives of ergotamines are promising therapeutic agents for the treatment of migraine. In particular, the trifluoromethyl derivative of dihydroergotamine (**1b**) is active against receptors responsible for antimigraine effects while exhibiting reduced activity against receptors responsible for side-effects.[22] An economic and selective strategy for the late-stage trifluoromethylation of dihydroergotamine **1b** is thus of significant interest.



Scheme 1. Perfluoroalkylations under Minisci-type conditions.

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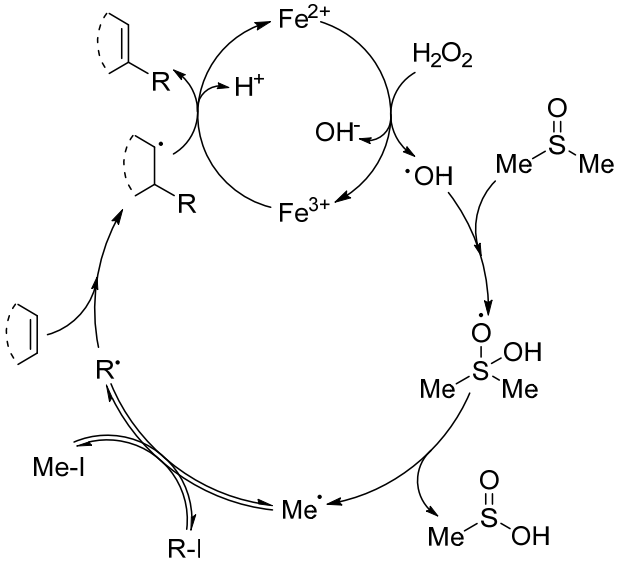
Results and Discussion

The addition of H_2O_2 to a solution of substrate, perfuoroalkyl iodide and Fe(II) in DMSO as solvent starts a complex, but fairly selective and well-understood series of redox reactions (Scheme 1).[13] The intermediate reactions are very fast and exothermic, with some reaction rates close to the diffusion-controlled limit. The sequence starts with the fast reduction of H_2O_2 by Fe(II) to a hydroxyl radical and a hydroxide ion (Fenton reaction). The extreme reactivity of the hydroxyl radical is controlled by the use of DMSO as the solvent. The hydroxyl radical quickly adds to DMSO to form a $(CH_3)_2SO_2H\cdot$ radical, and unselective reactions of the hydroxyl radical with other reagents, substrate or product are thus prevented.[13] The radical adduct of the OH radical with DMSO subsequently decomposes to methylsulfinic acid and a methyl radical. The highly reactive methyl radical further reacts with the alkyl iodide in an equilibrium reaction. This reaction is very fast as well, and successfully competes with other potential side-reactions, such as addition of the methyl radical to the substrate.[13] The alkyl radical finally adds to the double bond of the substrate, the intermediate radical is oxidized by Fe(III), and the catalytic cycle in Fe is thus closed (Scheme 2).[13]



Scheme 2. Mechanism for Minisci-type C─C bond formation.[12,13]

A crude kinetic model using the mechanism shown in Scheme 2 and rate constants derived from those reported in the literature, revealed that the whole reaction sequence ought to proceed to conversions >90% in a fraction of a second (see Figure S3 in the Supporting Information). As

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mentioned above, this reactivity cannot be harnessed in traditional stirred tank reactors due to limited mass and heat transfer, and slow addition of the H_2O_2 to the reaction mixture is necessary to avoid severe concentration gradients and to control reaction temperature.[12-18] Thus a continuous flow microreactor setup was assembled. The flow setup for the first experiments consisted of a continuous syringe pump to introduce a solution containing substrate, reagents and catalyst (feed A; *cf*. Table 1), and a second syringe pump to introduce the hydrogen peroxide (feed B). The two feed solutions were mixed in a standard Y-connector (thru hole: 0.5 mm; 1.7 µL), at 0 °C, and the combined mixture went through a short residence tubing at 0 °C (perfluoroalkoxy alkanes (PFA), 0.8 mm i.d., 500 µL internal volume). Initial experiments were performed with 3-methylindole **2a** as a model substrate and CF_3I as reagent with stoichiometries close to those reported by Yamakawa and co-workers.[17] Trifluoroiodomethane is a comparatively cheap, non-toxic, gaseous CF_3 source (b.p. -23 °C),[23] and has been previously used in continuous flow processes.[11c-e] For the flow reactions, the desired amount of CF_3I was condensed into a vessel cooled to ~ -60 °C, and the remaining reagents dissolved in DMSO/MeCN 2:1 as solvent were added (feed A). This solution was loaded into the sample loop of a 6-port injection valve. When the reaction was started, the injection valve was switched to connect the sample loop in line with the carrier stream (DMSO/MeCN). The feed solution A was carried into the mixer with a flow rate of 4.7 mL/min, where it was combined with the 30% aqueous hydrogen peroxide feed pumped with a flow rate of 0.3 mL/min (feed B).[19e] The yellowish feed solution immediately turned deep-red upon contact with the hydrogen peroxide. The mixture went through the residence tubing at 0 °C and was collected into a quench solution of aqueous sodium bicarbonate and ethyl acetate (6 s nominal residence time). The best conversion and selectivity was obtained with 0.4 equiv of $FeSO_4 \cdot 7H_2O$, 0.8 equiv of H_2SO_4, 1.2 to 1.6 equiv of CF_3I and 1.6 equiv of H_2O_2 (see Table S1 to S3 in the Supporting Information). A conversion of 92% and a selectivity of 84% for the 2-trifluoromethylated product were attained according to HPLC-UV/Vis peak area integration at 215 nm. The main side-product was a bis-trifluoromethylated 3-methylindole (~7%). The position of the trifluoromethyl groups could not be unequivocally established. Additionally, further mono- and bis-trifluoromethylated isomers could be detected in the crude reaction mixture in small quantities by GC-MS analysis (see Figure S4 in the Supporting Information). Minisci-type reactions are usually performed with an H_2O_2 amount larger than stoichiometric, since it is consumed in various, poorly understood, side reactions.[12,13] Also the iron is consumed by side reactions, and the use of close-to-stoichiometric

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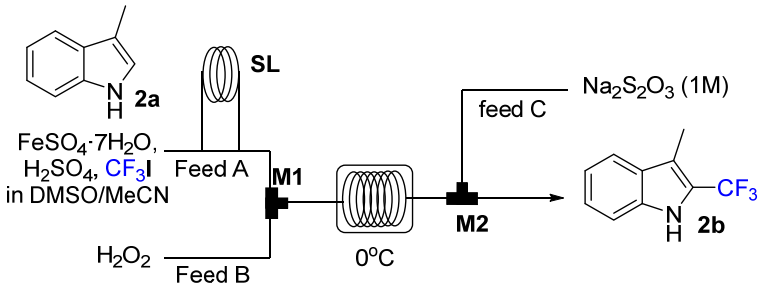
amounts is common.[13] An increase of the amount of $FeSO_4 \cdot 7H_2O$ above ~0.4 equiv or a larger excess of H_2O_2 did not increase the conversion further (see Table S1 and S3 in the Supporting Information). Sulfuric acid increased the solubility of the iron sulfate and prevented quick oxidation of Fe(II) to Fe(III) in the feed solution by atmospheric oxygen. However, the concentration of sulfuric acid had little effect on the trifluoromethylation reaction (Table S2 in the Supporting Information). Furthermore, longer reaction times or heating did not drive the reaction to completion. It has been frequently observed that Minisci-type reactions proceed only to a certain point and then stop.[12] Often this is indeed the main limitation of Minisci reactions.

To further explore the effect of reaction time, residence tubes of various residence volumes were connected to the Y-mixer, and a quench solution of $Na_2S_2O_3$ was mixed into the reaction mixture after the residence tube using a second Y-shaped mixer (Table 1).[24] With a total flow rate of 5 mL/min and a PFA residence tube with a length of 6.4 cm (0.4 i.d., internal volume of 8 µL), the nominal residence time was reduced to 100 ms. Even with this short residence time, no appreciable decrease in conversion was observed (Table 1).

Table 1. Continuous flow trifluoromethylation under Minisci-type conditions.[a]



Entry	CF_3I [equiv]	reactor [µL]	flow rate A/B [mL/min]	rt [s]	conv. [%][b]	sel. [%][b]
1	1.2	125	4.75/0.25	1.5	89	85
2	1.2	41	4.75/0.25	0.5	90	83
3	1.2	41	9.5/0.5	0.25	79	88
4	1.2	17	4.75/0.25	0.2	93	87
6	1.6	170	4.75/0.25	2.0	95	81
7	1.6	87	4.75/0.25	1.0	88	80
8	1.6	41	4.75/0.25	0.5	70	87
9	1.6	8	4.75/0.25	0.1	91	77

[a] Conditions: Feed A: 3.2 mL of 0.32 M solution of 2-methylindole **2a**, CF_3I, $FeSO_4 \cdot 7H_2O$ (0.4 equiv) and H_2SO_4 (0.8 equiv) in DMSO/MeCN 2:1 as solvent; Feed B: 30% aqueous H_2O_2 (1.6 equiv). [b] Conversion and selectivity was determined by HPLC peak area integration at 215 nm. rt = nominal residence time; SL = sample loop; M1, M2 = Y connectors.

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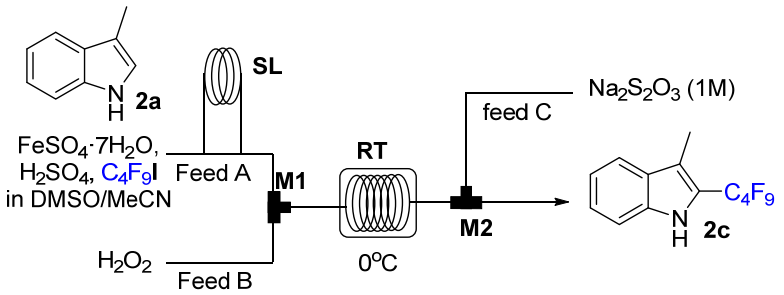
Slightly higher selectivities but similar conversions were obtained for reactions using nonafluororoiodobutane as reagent (Table 2). The reaction proceeded to conversions of around 90% after residence times of 1 s. Lower reaction times resulted in reduced conversions (entries 2 and 3 in Table 2). Further experiments were performed with microreactors of various designs. Microreactors typically incorporate channels with active mixing geometries to ensure efficient turbulent mixing of reaction streams, and they show superior performance when the diffusional mixing provided by simple Y connectors is too slow. However, the results obtained in the tested microreactors were similar to those obtained with a combination of Y connectors and tube reactors. For instance, the employed Chemtrix microreactor had 3 reagent inputs and a total volume of 19 µL.[25] The feed solutions A and B (H_2O_2) were pumped into the microreactor by two syringe pumps. The feed solutions were pre-cooled in the channels of the microreactor before they were mixed in the SOR-mixing zone (staggered oriented ridge).[25]

Table 2. Continuous flow nonafluoromethylation under Minisci-type conditions.[a]



Entry	C_4F_9I [equiv]	reactor (vol [µL])	Flow Rates A/B [mL/min]	rt [s]	conv. [%][b]	sel. [%][b]
1	1.2	tubing (87)	4.75/0.25	1.0	93	94
2	1.2	tubing (8)	4.75/0.25	0.1	61	96
3	1.2	tubing (4)	4.75/0.25	0.045	51	96
4	1.6	tubing (330)	4.75/0.25	4.0	84	93
5	1.6	chip (1800)[c]	4.75/0.25	22	95	92
6	1.6	chip (1800)[c]	9.5/0.5	11	94	94
7	1.6	chip (19)[d]	0.95/0.05	2.7	93	95
8	1.6	chip (19)[d]	1.9/0.1	0.6	92	94
9	1.6	chip (19)[d]	3.8/0.2	0.3	95	93

[a] Conditions: Feed A: 3.2 mL of 0.31 M solution of 2-methylindole **2a**, C_4F_9I, $FeSO_4·7H_2O$ (0.4 equiv) and H_2SO_4 (0.8 equiv) in DMSO/MeCN 2:1 as solvent; Feed B: 30% aqueous H_2O_2 (1.6 equiv). [b] Conversion and selectivity was determined by HPLC peak area integration at 215nm. [c] Uniqsis glass static mixer [ref. 26]. [d] Chemtrix glass static mixer [ref. 25]. rt = nominal residence time; SL = sample loop; M1, M2 = Y connectors.

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After mixing, the combined stream passed through the residence time channel. The processed mixture was then combined with the quench solution of $Na_2S_2O_3$ in the second SOR-mixing zone and left the reactor through the outlet. A conversion of 95% after a nominal residence time of 0.3 s was obtained for this reaction (entry 9 in Table 2).

Under the optimized conditions, we examined the trifluoromethylation and nonafluorobutylation of various aromatic and heteroaromatic compounds. The reactions shown in Figure 1 were performed in a glass static mixer with 1.8 mL mixing volume (Uniqsis).[26] With flow rates of 4.75 and 0.25 mL/min for feed A and feed B, respectively, a residence time of 22 s was obtained. The CF_3 radical is a highly reactive, electrophilic radical with a low-lying SOMO.[4] Accordingly, reactions with electron-rich heteroaromatics such as pyrroles and indoles progressed to high conversions. As expected, the reaction with indole **3a** formed a mixture of trifluoromethylated products. In contrast, pyrrole **4a** was alkylated at the 2-postion with high selectivity and the products **4b** and **4c** were isolated in good to excellent yields after column chromatography. Furthermore, reactions with strongly electron-rich aromatic compounds proceeded satisfactorily. However, due to the extraordinary reactivity of the CF_3 radical, no or only modest regioselectivity was observed for substrates with two or more positions of similar reactivity. The CH-trifuoromethylation of dihydroxybenzene **6a** yielded a mixture of mono- and bis-substituted products. Reducing the reaction time had almost no effect on the selectivity. Similarly, trifluoromethylation of the particularly electron-rich aniline **7a** furnished a roughly 1:1 mixture of mono- and bis-substituted products, regardless of the chosen reaction time. Importantly, reactions with 2,6-dichloroaniline (**8a**) proceeded to acceptable conversions (~60%) and afforded the *p*-CF_3 derivative with a selectivity of ~80% (see Table S4 in the Supporting Information for further details). The product **8b** is the key-structure in various widely used pesticides of the phenylpyrazole family, including the insecticide fipronil and its derivatives acetoprole and ethiprole (Figure 1). Reactions with substrates without a strongly activating substituent generally stopped before acceptable conversions were obtained, while electron-poor substrates did not give any reaction (see Table S5 in the Supporting Information for further details). Attempts to further optimize the reaction were mostly fruitless. Nevertheless, the obtained yields compare well with those reported in the literature for related batch radical reactions.[17] Reactions with nonafluororobutyliodide (C_4F_9I) under the standard reaction conditions usually proceeded to higher conversions and yielded the products with better selectivities compared to reactions with CF_3I (Figure 1).

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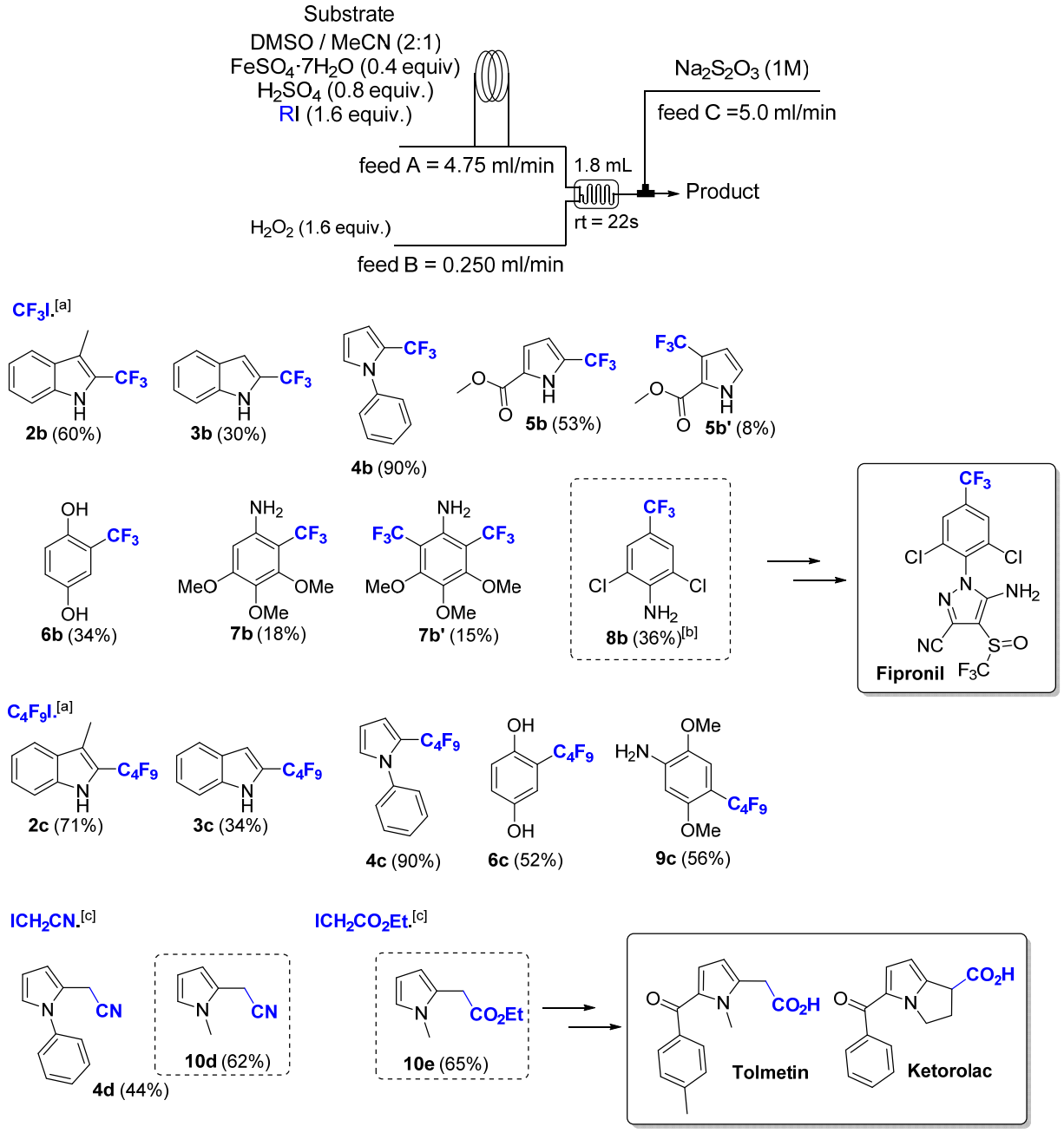

Figure 1. Continuous flow C-C bond formation with electrophilic radicals. Yields correspond to isolated and fully characterized products. [a] Conditions: Feed A: substrate, CF_3I of C_4F_9I (1.6 equiv), $FeSO_4{\cdot}7H_2O$ (0.4 equiv) and H_2SO_4 (0.8 equiv) in DMSO/MeCN 2:1 as solvent; Feed B: 30% aqueous H_2O_2 (1.6 equiv); residence time: 22 s. [b] See Experimental Section and Table S4 in the Supporting Information for details. [c] Conditions: Feed A: substrate (10.0 equiv), ICH_2CN or ICH_2CO_2Et, $FeSO_4{\cdot}7H_2O$ (0.4 equiv) in DMSO as solvent; Feed B: 30% aqueous H_2O_2 (12.0 equiv); residence time 12 min.

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In contrast, CH-functionalization with iodoacetonitrile was significantly slower than reactions with perfluoroalkyl iodides. The reaction of pyrroles with iodoacetontirile required 12 equiv of H_2O_2 and a reaction time of 12 min to attain conversions of ~90%. To get sufficient residence time, a 10 mL PFA tube reactor was connected to the outlet of the glass static mixer. The best results were obtained in DMSO as solvent without the addition of sulfuric acid. No in-line quench was performed for these reactions and the product was directly collected into a solution of H_2O/Et_2O. With 1-phenylpyrrole as the substrate, the 2-substituted product **4d** was formed with a selectivity of 50% with 1.6 equiv of iodoacetontirile. The main side product was the bis-substituted compound. In contrast, a high selectivity was obtained with phenylpyrrole in excess (10 equiv), and the product was isolated in 44% yield after column chromatography (yield with respect to iodoacetonitrile). Similarly, reactions with 1-methylpyrrole (10 equiv) afforded 1-methyl-2-pyrroleacetonitrile **10d** with a selectivity > 90%. However, the low boiling point of the product caused significant losses during isolation. CH-Functionalization of 1-methyl-pyrrole with ethyl iodoacetate afforded the corresponding pyrrole-2-acetate **10e** in 65% yield. The pyrrole-2-acetic acid structure is contained in a wide variety of molecules of pharmaceutical interest, most notably non-steroidal anti-inflammatory drugs including tolmetin and ketorolac (Figure 1). Traditional methods for the generation of this important structural motif involve Friedel–Crafts acylation of pyrrole with ethyl oxalyl chloride and subsequent reduction of the glyoxalate ester,[27] or alternatively reaction of pyrrole with explosive ethyl diazoacetate in the presence of Cu catalysts.[28] The generation of pyrrol-2-acetic acids by a radical mediated CH-functionalization under Minisci-type conditions was first reported by Baciocchi and coworkers in 1992,[14] and the value of this transformation for the generation of natural products and pharmaceuticals has been demonstrated.[29] For the original batch procedure, hydrogen peroxide was slowly dropped to the reaction mixture containing 15 to 75 equiv of substrate, and the pyrrole acetates were isolated in yields comparable to those reported herein for the continuous flow reactions.[14]

The extraordinary high reaction rate of the radical CH-perfuoroalkylation allows the generation of large amounts of material in a microreactor of small volume. To demonstrate the scalability of the reaction, the injection loop was removed and the feed A solution was directly introduced into the glass microreactor by two continuous syringe pumps at a combined flow rate of 19 mL/min. In the microreactor the solution was mixed with H_2O_2 at a flow rate of 1 mL/min. After the residence unit the mixture was again quenched with aqueous $Na_2S_2O_3$. With a

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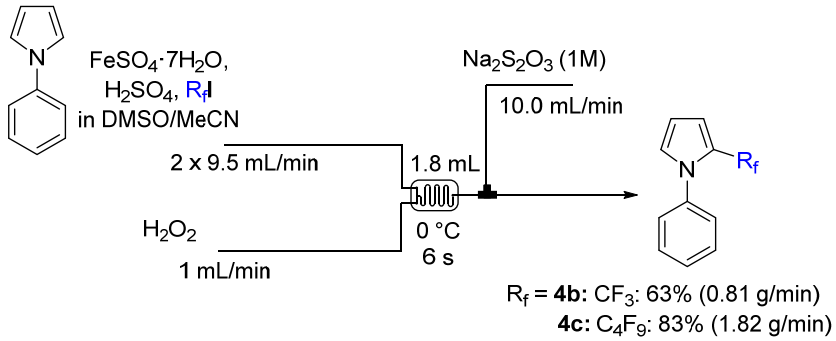
microreactor of 1.8 mL residence volume a residence time of ~ 6 s was obtained. With this setup 10 mmol of a 0.32 M solution of 1-phenylpyrrole were processed within only 1.6 min (Scheme 3). Both the reaction with CF_3I and with C_4F_9I proceeded with extraordinary selectivity (92% and 99%; see Figure S5 in the Supporting Information). The trifluoromethylated and nonafluorobutylated pyrroles were isolated in yields of respectively 63% (0.81 g/min) and 83% (1.82 g/min) after column chromatography (Scheme 3).



Scheme 3. Continuous flow C─H perfluoroalkylation (see Experimental Section for details).

Finally the reaction conditions were used to convert dihydroergotamine mesylate **1a** to the corresponding trifluoromethyl derivative (Scheme 4). This and related fluoroergoline analogs are explored as less toxic ergoline derivatives to treat and/or prevent primary headache disorders such as migraine.[22] Preliminary batch experiments revealed Minisci-type trifluoromethylation as a promising strategy for the selective late-stage functionalization for this complex alkaloid. However, the yield for the batch experiments was unsatisfactory and the reaction poorly reproducible. For the continuous flow reactions, dihydroergotamine mesylate (**1a**), $FeSO_4·7H_2O$ and H_2SO_4 in DMSO/MeCN 2:1 as solvent were charged into a jacketed three-neck flask equipped with a mechanical stirrer (see Figure S6 in the Supporting Information). The mixture was cooled to -10 °C and the respective amounts of CF_3I were introduced into the flask under stirring through an immersion tube. The continuous flow reactions were performed using the Modular MicroReaction System from Ehrfeld Mikrotechnik BTS (MMRS).[30] MMRS is a modular, continuous flow platform which allows multiple unit operation elements, including mixers, residence time modules, heat exchangers and back-pressure regulators, to be mounted on a common base plate.[30] The reaction mixture was directly pumped from the flask into the flow system by a syringe pump. Hydrogen peroxide was delivered by a second syringe pump. Both feed solutions were pre-cooled in a heat-exchanger (1.2 mL internal volume) before they were

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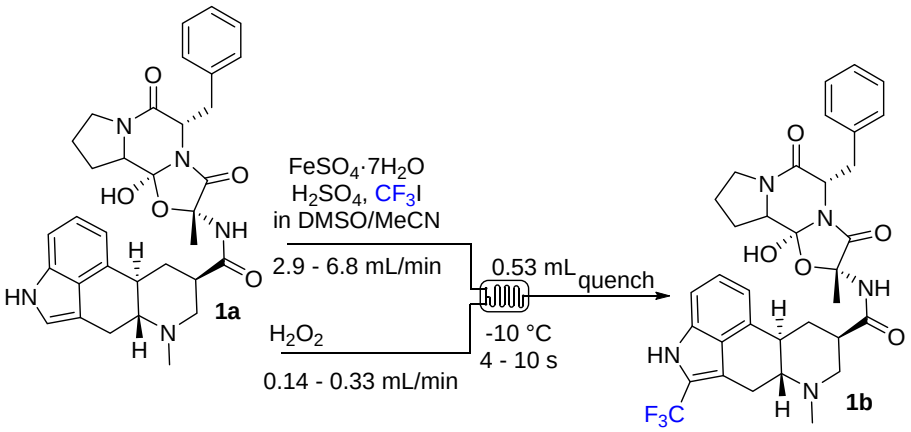
combined in the mixer. As reactor for the initial optimization reactions we explored the Lonza FlowPlate® Lab with a curvature-based mixing geometry and 0.4 mL internal volume (Lonza FlowPlate® SZ or TG).[31] With 2 equiv of CF_3I and 0.2 equiv of $FeSO_4 \cdot 7H_2O$, conversions of 98% and selectivities up to 85% were obtained at a reaction temperature of -10 °C (HPLC-UV/Vis analysis at 270 nm). Again, increasing the residence time did not further improve the conversion and virtually identical results were obtained with residence times ranging from 10 s to 4 s (Figure 2).



Scheme 4. Trifluoromethylation of dihydroergotamine mesylate **1a** under Minisci conditions.

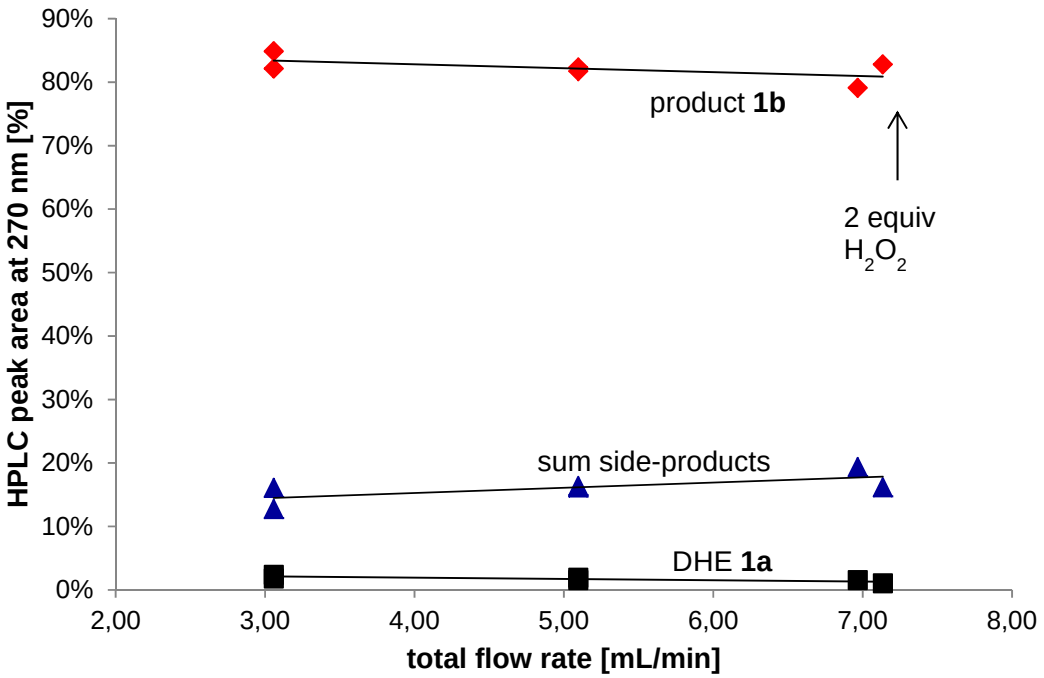


Figure 2. Trifluoromethylation of dihydroergotamine mesylate (DHE, **1a**) at various flow rates (residence time of 10 to 4 s). Conditions: Feed A: substrate **1a**, CF_3I (2 equiv), $FeSO_4 \cdot 7H_2O$ (0.2 equiv) and H_2SO_4 (0.75 equiv) in DMSO/MeCN 2:1 as solvent; Feed B: 33% aqueous H_2O_2 (4.0 equiv); see Experimental Section for reaction details.

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The main side-product of this reaction was a bis-trifluoromethylated derivative of not yet fully elucidated structure. Apart from this, the trifluoromethylation under Minisci conditions exhibited remarkable functional group tolerance and no protection of OH or NH groups was required. Increasing the stoichiometry of CF_3I above 2 equiv pushed the reaction to conversions beyond 98% at the cost of reaction selectivity, due to the formation of bis-trifluoromethylated side-products. Indeed, the best selectivity for the desired product was obtained with 1.5 equiv of CF_3I and 2 equiv of H_2O_2 (Figure S7 in the Supporting Information). A slightly reduced selectivity was obtained at 0 °C instead of -10 °C.

For the generation of larger amounts of material, a reactor consisting of 4 plates of A6 format was installed (FlowPlate® A6; total volume: 16.5 mL; see Figure 3). Neat CF_3I was pumped into the reactor as a separate feed from a cooled pump reservoir at a flow rate of 284 µL/min (1.5 equiv). The solution of dihydroergotamine mesylate (**1a**), $FeSO_4 \cdot 7H_2O$ (0.25 equiv) and H_2SO_4 (0.7 equiv) in DMSO/MeCN, and H_2O_2 (34.5%; 2 equiv) were pumped at flow rates of 15.1 mL/min and 439 µL/min, respectively. Both the substrate feed and the H_2O_2 feed were pre-cooled to -10 °C in a heat-exchanger (Figure 3). The substrate feed was first combined with CF_3I in a SZ-mixer of 2.05 mL internal volume, before the resulting mixture was merged with H_2O_2 in a second mixer (3.08 mL internal volume; Figure 3), resulting in an overall residence time of 12 s. The processed mixture was finally quenched with aqueous Na_2SO_3 in a continuous stirred tank reactor. In total, the reactor was operated continuously for 5 h. A sample of 600 g of dihydroergotamine mesylate (**1a**) was processed during this time. The product was formed with a stable conversion of 98% and a product selectivity of 85 to 86% (HPLC peak area integration at 270 nm). 10.5 kg of the effluent biphasic product mixture were collected for work-up. Extraction with ethyl acetate and evaporation of the solvent provided the crude product as the sulfate salt in 87% yield, according to ^{19}F-NMR with trifluorobenzene as internal standard (see Experimental Section for details).

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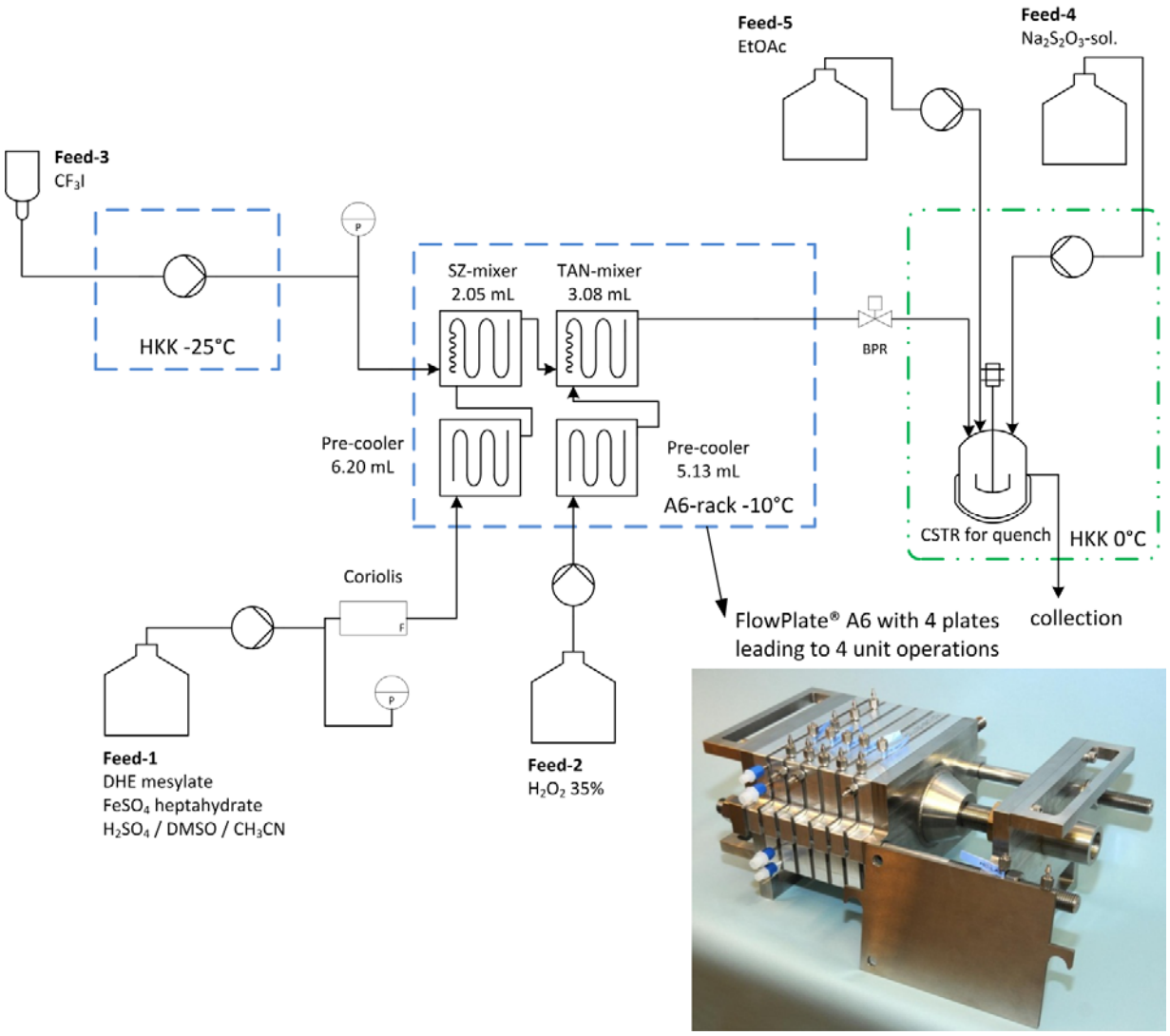

Figure 3. Reaction in a Lonza FlowPlate® A6 rack on a 0.6 kg scale. CF_3I and the substrate feed were combined in a mixer at -10 °C before the mixture was merged with H_2O_2 in a second mixer. The combined stream then went through a residence module at -10 °C. HKK = heating/cooling circuit.

Conclusion

In conclusion we have demonstrated a scalable continuous flow protocol for the CH-functionalization of various aromatic and heteroaromatic compounds with CF_3I, C_4F_9I, ICH_2CN and ICH_2CO_2Et under Minisci-type reaction conditions. Though rarely used, radical reactions with alkyl iodides and H_2O_2/DMSO/Fe(II) constitute a broadly applicable and valuable method to generate carbon–carbon bonds. The distinguishing feature of this reaction is its experimental

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simplicity, the mild reaction conditions, the availability of a large number of inexpensive radical precursors that can be successfully applied, and the particularly low price of H_2O_2 and Fe(II) salts. No prefunctionalization of the substrate is needed. The main limitation arises from the possibility of generating undesired isomers if more than one position is amenable to substitution. Furthermore, the reaction frequently does not proceed to completion and isolated yields are often modest. However, even with these genuine limitations, Minisci reactions are extremely useful. The continuous flow process reported herein allows this reaction to be performed with extraordinary efficiency. Due to the exceptional heat and mass transfer capacity of microreactors, the reaction could be performed within reaction times of a few seconds or less. The short reaction time, in turn, allows the production of large amounts of material in reactors of small volume. Thus, the process reported herein appears to be especially appealing for industrial applications where reaction time and reactor cost are important economic factors. Importantly, the reaction exhibits remarkable functional group tolerance. Dihydroergotamine mesylate, a complex semisynthetic ergot alkaloid, could be directly converted under mild conditions to the corresponding trifluoromethyl derivative without the need of protection groups. High conversions and good selectivities were obtained within reaction times of only 12 seconds on a 0.6 kg scale.

Experimental Section

General Remarks. All compounds and solvents were obtained from standard commercial vendors and used without further purification. ^{1}H-NMR and ^{13}C spectra were recorded on a 300 or 400 MHz instrument using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, qt and m are used to indicate a singlet, doublet, triplet, quadruplet, quintuplet and multiplet, respectively. Melting points were determined on a standard melting point apparatus. Analytical HPLC analysis was carried out on a C-18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1 % TFA) and B (MeCN + 0.1 % TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 8 min, hold at 100% solution B for 2 min. For new compounds, HRMS experiments were performed on a TOF LC/MS instrument equipped with an APCI ion source (positive ionization mode).

General Experimental Procedure for the Continuous Flow Trifluoromethylation of 1a (kg Scale) . For a Scheme of the flow setup see Figure 3. The reactor consisted of Lonza FlowPlates®

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of A6 format (total volume: 16.5 mL). Neat CF_3I was pumped into the reactor from a cooled pump reservoir at a flow rate of 284 µL/min (1.5 equiv; Teledyne Isco syringe pump). Neat CF_3I was pumped into the reactor from a cooled pump reservoir at a flow rate of 284 µL/min (1.5 equiv; Teledyne Isco syringe pump). For these experiments, the CF_3I was condensed into the pre-cooled cylinder of the Isco pump (-25 °C). The liquefied CF_3I was then pushed by the plunger of the Isco pump into the continuous flow reactor. The solution of dihydroergotamine mesylate **1a** (10.5 wt%), $FeSO_4 \cdot 7H_2O$ (0.25 equiv) and H_2SO_4 (0.7 equiv) in DMSO/MeCN 2:1 was pumped via a gear pump controlled by a Coriolis mass flow meter at a flow rate of 15.1 mL/min. Hydrogen peroxide (34.5%, 2 equiv) was delivered at a flow rate of 439 µL/min by a syringe pump (SyrDos). The substrate feed and the H_2O_2 feed were pre-cooled in a heat-exchanger to -10 °C (6.2 mL and 5.13 mL, respectively). CF_3I and the substrate feed were combined in a SZ-mixer (2.05 mL) before the mixture was merged with H_2O_2 in a second mixer (TAN-mixer; 3.08 mL). The mixture was finally quenched with aqueous $Na_2S_2O_3$ in a continuous stirred tank reactor (10% aqueous $Na_2S_2O_3$ at 12.5 g/min and ethyl acetate at 12.5 g/min). In total, the reactor was operated continuously for 5 h. A sample of 600 g of dihydroergotamine mesylate was processed during this time. 10.5 kg of the effluent biphasic product mixture were collected for work-up. Extraction with ethyl acetate and evaporation of the solvent provided the crude product as the sulfate salt in 87% yield according to ^{19}F-NMR with trifluorobenzene as internal standard. Redissolution of the organic residue in ethyl acetate and extraction with aqueous Na_2CO_3 yielded the crude free base as an oil after concentration. The free base was precipitated from acetonitrile/water mixtures. The crude solid was redissolved in ethanol (50 °C) and the product was precipitated by the addition of ethanolic HCl (1.25 M). Recrystallization of the precipitate from ethanol yielded the product as the hydrochloride salt in 97% purity (HPLC at 270 nm). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (s, 1H), 11.54 (s, 1H), 9.75 (s, 1H), 7.38 – 7.33 (m, 2H), 7.31 – 7.29 (m, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.3 Hz, 1H), 7.05 – 7.02 (m, 1H), 6.51 (d, J = 1.6 Hz, 1H), 4.54 – 4.50 (m, 1H), 3.79 – 3.53 (m, 5H), 3.44 – 3.15 (m, 5H), 3.09 – 2.91 (m, 5H), 2.01-1.97 (m, 3H), 1.77-1.60 (m, 2H), 1.53 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6, carbons lost in the background noise) δ 173.76, 166.16, 164.80, 139.15, 134.13, 130.20, 128.26, 126.44, 124.40, 122.44 (q, $J_{C\text{-}F}$ = 268.0 Hz), 118.74 (q, $J_{C\text{-}C\text{-}F}$ = 38.2 Hz), 114.71, 110.97, 103.30, 86.41, 64.27, 60.23, 56.66, 46.25, 38.99, 30.19, 26.36, 24.26, 22.20, 14.56. ^{19}F NMR (376 MHz, DMSO) δ -56.89.

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General Experimental Procedure for Continuous Flow Trifluoromethylation (2b-7b', Lab Scale). For a detailed description of the flow setup see Figure S1 in the Supporting Information. Feed A: Trifluoroiodomethane (1.6 equiv) was condensed into a vessel cooled in a 2-proponal/liquid N_2 bath. Substrate (2.0 mmol, 0.32 M), $FeSO_4 \cdot 7H_2O$ (0.4 equiv. 0.222g), and H_2SO_4 (0.8 equiv, 43.0 µL) dissolved in DMSO/MeCN (5.4 mL, 2:1) were added. The solution was introduced into the injection loop. H_2O_2 (30%, 1.6 equiv) was pumped into the Uniqsis microchip (1.8 mL internal volume) at a flow rate of 0.25 mL/min (feed B). DMSO/MeCN was pumped into the reactor via pump A at a flow rate of 4.75 mL min^{-1}. When the flow system was stable, the reaction mixture was carried from the injection loop into the reactor. The mixture leaving the microchip was quenched into a solution of $Na_2S_2O_3$ (1 M) at flow rate of 5.00 mL min^{-1}. The products were collected in an open flask and the residue was purified by flash chromatography to afford the desired compounds in analytical purity.

3-Methyl-2-(trifluoromethyl)-1H-indole **(Figure 1, 2b).** Substrate: 3-methlyindole. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 4%) afforded the title compound in 60 % yield (237 mg, 1.19 mmol) as a colorless solid. Mp: 65.9-68.7°C (lit.[32] 73.0-74.0 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.35 (ddd, J = 11.3, 8.9, 4.5 Hz, 2H), 7.20 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 2.45 (q, J = 1.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2, 128.1, 124.8, 121.5 (q, $J_{C\text{-}C\text{-}F}$ = 37.1 Hz), δ 122.12 (q, $J_{C\text{-}F}$ = 268.4 Hz), 120.4, 120.1, 114.2 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.0 Hz), 111.6, 8.3. ^{19}F NMR (282 MHz, $CDCl_3$) δ -58.63 (s, 3F).

2-(Trifluoromethyl)-1H-indole **(Figure 1, 3b).** Substrate: indole. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 10%) afforded the title compound in 30 % yield (111 mg, 0.60 mmol) as a colorless solid. Mp: 94.2-95.8 °C (lit.[32] 107.0-108.0 °C). ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.25 (s, 1H), 7.67 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.01 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, CF_3-carbon lost in the background noise) δ 136.7, 125.9, 124.8 (q, $J_{C\text{-}C\text{-}F}$ = 38.3 Hz), 124.2, 121.7, 120.4, 112.3, 103.1 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.4 Hz). ^{19}F NMR (282 MHz, DMSO-d_6) δ -58.82 (s, 3F).

1-Phenyl-2-(trifluoromethyl)-1H-pyrrole **(Figure 1, 4b).** Substrate: 1-phenylpyrrole. Isolation by flash chromatography with petroleum ether afforded the title compound in 66 % yield (278 mg, 1.31 mmol) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 3H), 7.41 – 7.36 (m, 2H), 6.89 (dd, J = 2.5, 2.1 Hz, 1H), 6.74 (ddd, J = 3.7, 1.7, 0.8 Hz, 1H), 6.30 – 6.25 (m, 1H). ^{13}C

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NMR (75 MHz, $CDCl_3$, *C*-CF_3carbon lost in the background noise) δ 139.2, 129.1, 128.6, 127.4, 126.7, 121.3 (q, J_{C-F} = 266.9 Hz), 112.9 (q, $J_{C-C-C-F}$ = 3.4 Hz), 108.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -55.94 (s, 3F).

Methyl 5-(trifluoromethyl)-1H-pyrrole-2-carboxylate **(Figure 1, 5b).** Substrate: methyl 2-pyrrolecarboxylate. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 10%) afforded the title compound in 53 % yield (207 mg, 1.07 mmol) as a white solid. Mp: 95.2-96.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.23 (s, 1H), 6.88 – 6.80 (m, 1H), 6.68 (ddd, *J* = 3.7, 2.5, 0.9 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 125.7, 123.8 (q, J_{C-C-F} = 39.4 Hz), 120.6 (q, J_{C-F} = 267.3 Hz), 114.6, 110.7 (q, $J_{C-C-C-F}$ = 3.0 Hz), 51.7. ^{19}F NMR (282 MHz, DMSO-d_6) δ -58.44 (s, 3F).

Methyl 3-(trifluoromethyl)-1H-pyrrole-2-carboxylate **(Figure 1, 5b').** Side product of the preparation of methyl 5-(trifluoromethyl)-1H-pyrrole-2-carboxylate. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 10%) afforded the title compound in 7.5 % yield (28.9 mg, 0.15 mmol) as a white solid. Mp: 89.6-91.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.69 (s, 1H), 7.10 (t, *J* = 2.8 Hz, 1H), 6.53 (t, *J* = 2.5 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.0, 123.1 (q, J_{C-F} = 266.8 Hz), 122.8, 119.6 (q, $J_{C-C-C-F}$ = 3.1 Hz), 117.4 (q, J_{C-C-F} = 37.0 Hz), 109.6 (q, $J_{C-C-C-F}$ = 4.0 Hz), 51.8. ^{19}F NMR (282 MHz, DMSO-d_6) δ -55.51 (s, 3F).

2-(Trifluoromethyl)benzene-1,4-diol **(Figure 1, 6b).** Substrate: hydroquinone. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 40%) afforded the title compound in 34 % yield (121 mg, 0.68 mmol) as a brown solid. Mp: 96.0-97.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.69 (s, 1H), 9.20 (s, 1H), 6.92 – 6.76 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.3, 148.0 (q, *J* = 1.9 Hz), 123.9 (q, J_{C-F} = 272.0 Hz), 120.4, 118.0, 115.41 (q, J_{C-C-F}= 29.8 Hz), 112.16 (q, $J_{C-C-C-F}$ = 5.1 Hz). ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.91 (s, 3F).

3,4,5-Trimethoxy-2-(trifluoromethyl)aniline **(Figure 1, 7b).** Substrate: 3,4,5-trimethoxyaniline. Isolation by flash chromatography with petroleum ether/diethyl ether (0 to 10%) afforded the title compound in 18.0 % yield (90.4 mg, 0.36 mmol) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.23 (s, 1H), 5.36 (s, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.62 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.4, 152.67 (q, *J* = 1.8 Hz), 143.8, 132.7, 125.6 (q, J_{C-F} = 272.2 Hz), 97.10 (q, J_{C-C-F} = 28.1 Hz), 95.9, 61.2, 60.5, 55.4. ^{19}F NMR (282 MHz, DMSO-d_6) δ -52.19 (s, 3F). HRMS (APCI): *m*/*z*: calcd for $C_{10}H_{12}F_3NO_3$ $[(M+H)]^+$: 252.084204, found: 252.083851.

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3,4,5-Trimethoxy-2,6-bis(trifluoromethyl)aniline **(Figure 1, 7b').** Side product of the preparation of 3,4,5-trimethoxy-2-(trifluoromethyl)aniline. Isolation by flash chromatography with petroleum ether/diethyl ether (0 to 10%) afforded the title compound in 15 % yield (28.9 mg, 0.15 mmol) as a yellow oil.^{1}H NMR (300 MHz, DMSO-d_6) δ 5.51 (s, 2H), 3.88 (s, 6H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 141.9, 136.7, 124.6 (q, J_{C-F} = 274.0 Hz), 102.6 (q, J_{C-C-F} = 27.7 Hz), 61.6, 60.8.^{19}F NMR (282 MHz, DMSO-d_6) δ -53.34 (s, 3F). HRMS (APCI): *m*/*z*: calcd for $C_{11}H_{11}F_6NO_3$ $[(M+H)]^+$: 318.057036, found: 318.057609.

3-Methyl-2-(perfluorobutyl)-1H-indole **(Figure 1, 2c).** Substrate: 3-methlyindole. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 4%) afforded the title compound in 71 % yield (494 mg, 1.41 mmol) as a yellow solid. Mp: 70.0-71.1°C (lit.[33] 67.1-68.8 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.44 – 7.30 (m, 2H), 7.21 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 2.45 (t, *J* = 2.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, C_4F_9-carbons lost in the background noise) δ 136.1, 128.5, 125.1, 120.5, 120.2, 119.6 (t, J_{C-C-F} = 28.4 Hz), 116.9 (t, $J_{C-C-C-F}$ = 3.4 Hz), 111.7, 8.7 (d, *J* = 1.4 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -80.99 (tt, *J* = 9.7, 2.6 Hz, 3F), -108.76 – -108.93 (m, 2F), -122.93 – -123.18 (m, 2F), -125.85 – -126.11 (m, 2F).

2-(Perfluorobutyl)-1H-indole **(Figure 1, 3c).** Substrate: indole. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 10%) afforded the title compound in 34 % yield (230 mg, 0.69 mmol) as a yellow solid. Mp: 43.2-44.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.20 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 7.04 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, C_4F_9-carbons lost in the background noise) δ 137.3, 126.3, 124.3, 122.9 (t, J_{C-C-F} = 29.7 Hz), 121.7, 120.5, 112.4, 105.3 (t, $J_{C-C-C-F}$ = 4.7 Hz). ^{19}F NMR (282 MHz, DMSO-d_6) δ -80.53 (ddd, *J* = 12.4, 6.2, 3.0 Hz, 3F), -107.12 (t, *J* = 12.1 Hz, 2F), -122.02 – -123.17 (m, 2F), -124.99 – -125.99 (m, 2F).

2-(Perfluorobutyl)-1-phenyl-1H-pyrrole **(Figure 1, 4c).** Substrate: 1-phenylpyrrole. Isolation by flash chromatography with petroleum ether afforded the title compound in 90 % yield (645 mg, 1.78 mmol) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 3H), 7.38 – 7.31 (m, 2H), 6.91 – 6.86 (m, 1H), 6.77 – 6.71 (m, 1H), 6.33 (dd, *J* = 3.7, 2.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, C_4F_9-carbons lost in the background noise) δ 139.8, 129.2 (m), 128.8, 127.5, 121.3, 120.2 (t, J_{C-C-F} = 29.7 Hz), 115.2 (t, $J_{C-C-C-F}$ = 5.4 Hz), 108.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ -

81.09 (tt, *J* = 9.8, 2.9 Hz, 3F), -101.15 (t, *J* = 13.3 Hz, 2F), -121.30 – -121.59 (m, 2F), -125.79 – -125.98 (m, 2F).

2-(Perfluorobutyl)benzene-1,4-diol **(Figure 1, 6c).** Substrate: hydroquinone. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 40%) afforded the title compound in 52 % yield (342 mg, 1.04 mmol) as a yellow solid. Mp: 84.4-86.1 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 9.22 (s, 1H), 6.89 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 2.7 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, C_4F_9-carbons lost in the background noise) δ 149.6, 149.3 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.1 Hz), 121.1, 118.5, 113.7 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ = 8.8 Hz), 113.0 (t, $J_{C\text{-}C\text{-}F}$ = 22.4 Hz). ^{19}F NMR (282 MHz, DMSO-d_6) δ -80.48 (tt, *J* = 9.7, 2.7 Hz, 3F), -107.41 (td, *J* = 13.3, 2.5 Hz, 2F), -121.76 (h, *J* = 9.6 Hz, 2F), -125.70 (dq, *J* = 19.9, 9.9 Hz, 2F). HRMS (APCI): *m*/*z*: calcd for $C_{10}H_5F_9O_2$ $[(M+H)]^+$: 327.007307, found: 327.007136.

2,5-Dimethoxy-4-(perfluorobutyl)aniline **(Figure 1, 9c).** Substrate: 2,5-dimethoxyaniline. Isolation by flash chromatography with petroleum ether/dichloromethane as eluent (0 to 50%) afforded the title compound in 56 % yield (417 mg, 1.12 mmol) as a brown solid. Mp: 53.9-55.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.73 (s, 1H), 6.46 (s, 1H), 5.58 (s, 2H), 3.72 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, C_4F_9-carbons lost in the background noise) δ 153.8 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.0 Hz), 143.6, 139.5, 110.2 (t, $J_{C\text{-}C\text{-}C\text{-}F}$ = 9.0 Hz), 99.5 (t, $J_{C\text{-}C\text{-}F}$ = 23.7 Hz), 98.1, 56.0, 55.9. ^{19}F NMR (282 MHz, DMSO-d_6) δ -80.51 (t, *J* = 9.7 Hz, 3F), -104.35 (td, *J* = 12.9, 1.6 Hz, 2F), -121.72 (h, *J* = 9.0 Hz, 2F), -125.57 – -125.90 (m, 2F). HRMS (APCI): *m*/*z*: calcd for $C_{12}H_{10}F_9NO_2$ $[(M+H)]^+$: 372.064059, found: 372.064469.

General Experimental Procedure for the Continuous Flow Synthesis of *2,6-Dichloro-4-(trifluoromethyl)aniline* **(Figure 1, 8b).** Feed A consisting of a mixture of 2,6-dichloroaniline (2.0 mmol, 0.28 M), $FeSO_4.7H_2O$ (1.6 equiv, 0.888 g), H_2SO_4 (3.2 equiv, 342 µL), and trifluoroiodomethane (1.6 equiv, 251.0 µL) dissolved in a 5% solution of DMSO in H_2O (5.4 mL), and feed B containing H_2O_2 (30%, 4.0 equiv) were pumped, at room temperature, into a Uniqsis microchip (1.8 mL internal volume) by two syringe pumps (Asia Syrris) at flow rates of 4.150 mL min^{-1} and 0.850 mL/min, respectively. The mixture leaving the microchip was quenched into a solution of diethyl ether/ H_2O *out line*. The product was collected in an open flask and the residue was purified by flash chromatography to afford the desired compound in analytical purity. Substrate: 3,4,5-Trimetoxyaniline. Isolation by flash chromatography with petroleum ether/diethyl ether (0 to 5%) afforded the title compound in 32 % yield (166 mg, 0.72 mmol) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.59 (m, 2H), 6.21 (s, 2H). ^{13}C NMR

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(75 MHz, DMSO-d_6) δ 145.2, 125.5 (q, $J_{C\text{-}C\text{-}C\text{-}F}$ = 3.7 Hz), 124.0 (q, $J_{C\text{-}F}$ = 270.8 Hz), 118.0, 116.8 (q, $J_{C\text{-}C\text{-}F}$ = 33.7 Hz). ^{19}F NMR (282 MHz, DMSO-d_6) δ -59.56.

General Experimental Procedure for the Continuous Flow Synthesis of Acylpyrroles (Figure 1, 4d, 10d and 10e). Feed A consisting of a mixture of the substrate (10.0 equiv), $FeSO_4.7H_2O$ (0.4 equiv, 0.222g) and iodoacetonitrile or ethyl iodoacetate (2.0 mmol, 0.26M, 1.0 equiv) dissolved in DMSO (5.4 mL), and feed B containing H_2O_2 (30%, 12.0 equiv) were pumped, at room temperature, into a Uniqsis microchip (1.8 mL internal volume) connected by a T mixer to a coil (10 mL internal volume) by two syringe pumps (Asia Syrris) at flow rates of 0.700 mL min^{-1} and 0.300 mL/min, respectively. After 12 min of residence time, the mixture leaving the coil was quenched into a solution of diethyl ether/ H_2O *out line*. The product was collected in an open flask and the residue was purified by flash chromatography to afford the desired compounds in analytical purity.

2-(1-Phenyl-1H-pyrrol-2-yl)acetonitrile **(Figure 1, 4d).** Substrate: 1-phenylpyrrole. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 10%) afforded the title compound in 44 % yield (160 mg, 0.88 mmol) as a yellow solid. Mp: 48.7-49.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 – 7.83 (m, 2H), 7.81 – 7.72 (m, 3H), 7.33 (dd, *J* = 2.7, 2.0 Hz, 1H), 6.60 (dd, *J* = 2.9, 2.1 Hz, 1H), 6.54 (t, *J* = 3.2 Hz, 1H), 4.34 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.2, 130.1, 128.1, 125.8, 124.0, 121.8, 118.4, 110.4, 109.0, 16.2.

2-(1-Methyl-1H-pyrrol-2-yl)acetonitrile **(Figure 1, 10d).** Substrate: *N*-methylpyrrole. Isolation by flash chromatography with petroleum ether/diethyl ether as eluent (0 to 40%) afforded the title compound in 62 % yield (151 mg, 1.25 mmol) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.75 – 6.70 (m, 1H), 6.03 – 5.95 (m, 1H), 5.96 – 5.89 (m, 1H), 4.02 (s, 2H), 3.56 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 123.2, 121.1, 118.1, 107.8, 106.6, 33.3, 14.8.

Ethyl 2-(1-Methyl-1H-pyrrol-2-yl)acetate **(Figure 1, 10e).** Substrate: *N*-methylpyrrole. Isolation by flash chromatography with petroleum ether/ethyl acetate as eluent (0 to 10%) afforded the title compound in 70 % yield (234 mg, 1.40 mmol) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, *J* = 1.9 Hz, 1H), 6.10 – 6.07 (m, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 2H), 3.59 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 125.0, 122.5, 108.7, 107.0, 61.0, 33.9, 32.7, 14.2.

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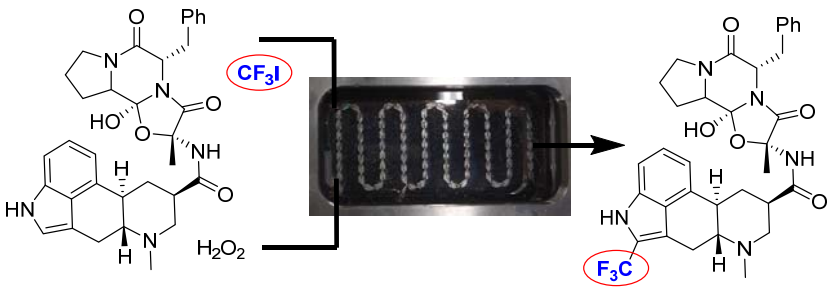
TOC Graphic



Trifluoromethylation in seconds: Radical C─C bond formation with CF_3I, H_2O_2, dimethylsulfoxide and Fe(II) as catalyst yields trifluoromethylated products within reaction times of seconds in a continuous flow microreactor. The reaction proceeds satisfactory with selected electrophilic radicals, including $\cdot C_4F_9$, $\cdot CH_2CN$ and $\cdot CH_2CO_2Et$. The protocol allowed the trifluoromethylation of dihydroergotamine on a 0.6 kg scale.

Keywords: Trifluoromethylation • Fenton reagent • Minisci reaction • Radical reactions • Flow chemistry