Visible-light-induced Trifluoromethylation of highly functionalized arenes and heteroarenes in continuous flow

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Visible light induced trifluoromethylation of highly functionalized arenes and heteroarenes in continuous flow

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Abstract: We report a continuous-flow protocol for the trifluoromethylation of arenes, heteroarenes and benzofused heterocycles. This photoredox methodology relies on the use of solid $\text{CF}_3\text{SO}_2\text{Na}$ as trifluoromethylating agent and $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2](\text{dtbpy})\text{PF}_6$ as photoredox catalyst. A diverse set of highly functionalized heterocycles proved compatible with the methodology, and moderate to good yields were obtained within 30 minutes residence time.

Key words Trifluoromethylation; Photoredox catalysis; Continuous flow; Langlois reagent; Visible light

Novel methodologies for the trifluoromethylation of arenes and heteroarenes are highly demanded in the chemical and pharmaceutical industry.¹ In structure-activity relationship (SAR) studies, the introduction of fluorine atoms can greatly impact the electronic properties, acidity and lipophilicity of drug candidates.² These effects are due to the high electronegativity of the fluorine atom, to its relatively small radius and to the less polarizable nature of C–F bonds compared to C–H bonds.^{1b} The replacement of methyl groups with their trifluoromethyl counterparts represents a conservative substitution in terms of steric hindrance, while constituting a valuable strategy to block potential metabolically labile sites in drug candidates, prolonging their half-life and metabolic stability.^{1a}

The initially reported trifluoromethylation protocols relied on transition-metal catalyzed cross-coupling methods, but suffered from the need for prefunctionalized substrates and for stoichiometric amounts of metal salts.³ More recently, several strategies reported in the literature demonstrated the utility of photocatalytic protocols for the trifluoromethylation of alkenes, thiols, heterocycles and arenes.⁴ The most commonly used trifluoromethyl sources include expensive Togni and Umemoto's reagents, unstable triflyl chloride ($\text{CF}_3\text{SO}_2\text{Cl}$), gaseous CF_3I and

readily available trifluoroacetic anhydride.^{4e, 5} In addition, Langlois' reagent ($\text{CF}_3\text{SO}_2\text{Na}$) can be regarded as an easy-to-handle, inexpensive and solid trifluoromethylating agent, capable of generating CF_3 radicals in the presence of a strong oxidant (e.g. $t\text{BuOOH}$).^{6, 7}

As part of our interest to develop efficient continuous-flow protocols as enabling tools for drug discovery, we envisioned a photocatalytic strategy for the trifluoromethylation of a variety of highly functionalized heteroarenes, which are of interest in medicinal chemistry.^{4a, 4b, 8} Such substrates are often ignored in many reports since these compounds are known to be highly challenging and thus low yielding. In order to develop a practical and widely applicable methodology, we opted to use the stable, inexpensive and solid Langlois reagent ($\text{CF}_3\text{SO}_2\text{Na}$) as trifluoromethyl source.

We commenced our investigations by performing luminescence quenching studies, which allowed us to rapidly select the optimal photocatalyst for our transformation (see Supporting Information).⁹ Among the photocatalysts tested, the luminescence of both *fac*- $\text{Ir}(\text{ppy})_3$ and $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2](\text{dtbpy})\text{PF}_6$ was significantly quenched by increasing equivalents of $\text{CF}_3\text{SO}_2\text{Na}$, as depicted in **Figure 1**. This suggests that the excited state of both photocatalysts can be oxidatively quenched by the Langlois reagent thus generating a CF_3 radical. In particular, a high luminescence quenching percentage of 58% was obtained for $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2](\text{dtbpy})\text{PF}_6$ in the presence of 300 equivalents of Langlois' reagent, while 2500 equivalents of $\text{CF}_3\text{SO}_2\text{Na}$ were needed to obtain a quenching percentage of only 44% in the case of *fac*- $\text{Ir}(\text{ppy})_3$ (**Figure 1**). The higher quenching efficiency observed with $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2](\text{dtbpy})\text{PF}_6$ is consistent with the higher excited state reduction potential reported for this catalyst compared to *fac*- $\text{Ir}(\text{ppy})_3$ (1.21 V vs 0.31 V respectively,

both values are reported versus the saturated calomel electrode (SCE)).¹⁰ As reported by Glorius and co-workers, a quenching percentage higher than 25% should be considered as significant and relevant for photocatalytic reaction purposes.^{9b} Therefore, we selected $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$ as the photocatalyst for our further investigations.

Figure 1 Luminescence quenching percentage of $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (squares) and $\text{fac-Ir}(\text{ppy})_3$ (dots) in presence of increasing amounts of Langlois reagent. Experimental conditions: the solutions of both photocatalysts were prepared in degassed acetonitrile with a $10\mu\text{M}$ concentration. Solutions with increasing concentrations of quencher ($\text{CF}_3\text{SO}_2\text{Na}$) were prepared in degassed acetonitrile and tested. Compared to the amount of catalyst present, the concentrations and number of equivalents of $\text{CF}_3\text{SO}_2\text{Na}$ employed were the following: 25 mM , (≈ 2500 equivalents), 50 mM , (≈ 5000 equivalents); 100 mM , (≈ 10000 equivalents), 300 mM (≈ 30000 equivalents). For $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ a concentration of 0.3 mM (≈ 300 equivalents and corresponding to reaction conditions) was also tested. For more details on the procedure followed and for the calculation of the quenching percentages see ESI.

The trifluoromethylation of caffeine was selected as the benchmark reaction for our optimization studies in flow (Table 1). The photoflow reactor consists of a Vapourtec UV-150 photoreactor equipped with a 10 mL capillary reactor (I.D. 1.3 mm), which was subjected to 450 nm irradiation (54 blue LEDs; 24 W). DMSO was chosen as a suitable solvent, which ensured high solubility of the densely functionalized substrates and thus avoided the occurrence of microreactor clogging. At 40°C , unsatisfactory yields were observed in flow for the trifluoromethylated caffeine (Table 1, Entries 1 and 2). We rationalized that the addition of an oxidant might assist the re-aromatization of the radical intermediate to the final product. Indeed, in the presence of 1 equivalent of $(\text{NH}_4)_2\text{S}_2\text{O}_8$ as an oxidant, an improved LC-MS yield of 48% was obtained (Table 1, Entry 3). Next, diacetoxyiodobenzene was tested as the oxidant, however, this resulted in a lower 32% isolated yield (Table 1, Entry 4). Increasing the amount of Langlois reagent to 3 equivalents further boosted the LC-MS yield to 54% (Table 1, Entry 5) (45% isolated yield). Notably, in the same reaction conditions the reaction with $\text{fac-Ir}(\text{ppy})_3$ gave 38% yield (Table 1, Entry 6), thus confirming the choice of photocatalyst based on the luminescence quenching studies. Increasing the reaction temperature to 60°C did not lead to a further improvement of the reaction yield (Table 1, Entry 7). Control experiments revealed the photocatalytic nature of our protocol as little to no product

was observed in the absence of either light or photocatalyst (Table 1, Entries 8 and 9). Finally, irradiation of the reaction mixture with a 365 nm UV lamp resulted in 46% of the target compound, which can be attributed to the UV-tailing absorption of the iridium photocatalyst (Table 1, Entry 10). Nevertheless, it should be noted that, especially for the synthesis of densely functionalized drug candidates, irradiation with low-energy blue light is preferred over higher-energy ultraviolet in order to minimize the occurrence of side reactions and compound degradation.¹¹

Table 1: Optimization of reaction conditions for the trifluoromethylation of caffeine in continuous flow^a

Entry	Changes from optimized conditions ^a	LC-MS Yield (%)
1	20 min residence time, no oxidant	5
2	No oxidant, 1.5 eq $\text{CF}_3\text{SO}_2\text{Na}$	12
3	1 eq $(\text{NH}_4)_2\text{S}_2\text{O}_8$, 1.5 eq $\text{CF}_3\text{SO}_2\text{Na}$	48
4	1 eq Diacetoxyiodobenzene, 1.5 eq $\text{CF}_3\text{SO}_2\text{Na}$	32 ^b
5	none	54 (45 ^b)
6	$\text{fac-Ir}(\text{ppy})_3$ as photocatalyst	38
7	60°C	50
8	No light	6
9	Light, no $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$	-
10	365 nm LEDs	46

^aReaction conditions: 0.2 mmol of caffeine, $1\text{ mol}\%$ $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbpy})]\text{PF}_6$, 3 equivalents $\text{CF}_3\text{SO}_2\text{Na}$, 1 equivalent $(\text{NH}_4)_2\text{S}_2\text{O}_8$ in 2 mL DMSO (0.1 M). Reactions performed in a commercially available Vapourtec UV-150 photoreactor, irradiation with 450 nm blue LEDs and 30 min residence time. ^bIsolated yield.

With the optimized reaction conditions in hand, our photocatalytic trifluoromethylation strategy was evaluated on a wide range of heteroarenes and arenes as well as benzofused heterocycles (Scheme 1). We focused our attention specifically to halogen-bearing substrates, which are of high value for drug discovery programs. In these programs, such functionalized substrates are key building blocks for the very popular cross-coupling methods which allow to construct carbon-carbon or carbon-heteroatom bonds.¹²

Scheme 1: Scope of the trifluoromethylation of heteroarenes, benzofused heterocycles and arenes. Reaction conditions: 0.5 mmol of substrate, 1 mol% $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2](\text{dtbpy})\text{PF}_6$, 3 equivalents $\text{CF}_3\text{SO}_2\text{Na}$, 1 equivalent $(\text{NH}_4)_2\text{S}_2\text{O}_8$ in 2 ml DMSO (0.1M). Reactions performed in a vapourtec UV-150 photoreactor, irradiation with 450 nm blue LEDs and 30 min residence time, isolated yields. ^bLC-MS yields ^cRegioselectivity was determined by ¹H NMR analysis of the crude reaction mixture.

3-methyl and 2-methylindole derivatives **2b** and **2c** were obtained in satisfactory yields (62% and 69% respectively). Notably, the presence of an iodo substituent on the indole was well tolerated (**2d**; 50% isolated yield; C2:C3, 1:1). We then explored our transformation on a series of benzimidazole derivatives. Unlike indoles, benzimidazoles showed higher reactivity for the C4 and C6 position on the aromatic ring.¹³ For example, trifluoromethyl benzimidazole **2e** was obtained in 50%

yield as a separable mixture of C4:C6 (3:2) isomers as well as the 2-Br trifluoromethyl derivative **2f** (52% yield; C4:C6, 3:2, separable mixture). Interestingly, 5-Cl benzimidazole showed a different selectivity, and was trifluoromethylated at positions C4 and C7 (**2g**, 45%; C4:C7 2:1) probably due to the electronic and steric effect of the chlorine atom. Notably, the possibility to easily separate the regioisomers obtained in compounds **2d** to **2g** renders our strategy advantageous for the simultaneous synthesis of fluorinated analogues relevant for medicinal chemistry SAR studies. Next, we tested pyridone and pyrimidone, which are frequently used scaffolds in the synthesis of novel active pharmaceutical ingredients (APIs).¹⁴ Trifluoromethylated pyrimidone **3a** and Br-pyridone **3b** were obtained in good to excellent yields (80% and 60% respectively). We further investigated the reactivity of pyridine, obtaining trifluoromethylated pyridine derivatives **3d**, **3e** and **3f** in modest yields (40%, 35% and 53%). Furthermore, 4-Ph pyrazole could be trifluoromethylated on the phenyl substituent and isolated in 28% yield (**3g**). Conversely, the tetrahydropyran-substituted 4-amino pyrazole derivative **3h** was trifluoromethylated at position C5 on the pyrazole ring and isolated in a reasonable 45% yield. Br-dimethyl pyridine **3i** was successfully trifluoromethylated in 38% yield. Finally, we explored the scope of our methodology with regard to unactivated arene substrates. Trifluoromethylated mesitylene and iodo mesitylene **3j** and **3k** were obtained in good to excellent yields, 53% and 80% respectively. Trifluoromethylation of unactivated arenes is a particularly challenging transformation, often requiring long reaction times (18-24 hours), and so far rarely reported in photoredox-based protocols.^{4h, 15} Therefore, we were pleased to observe significant product formation in our system within only 30 minutes reaction time. The main reason for the remarkable acceleration of the reaction rate observed in our protocol lies in the improved irradiation of the reaction mixture obtained in the microflow reactor.^{11, 16} Moreover, to showcase the potential of microreactors in terms of productivity, we performed a scale-up experiment on Br-pyridone.^{16c, 17} The vapourtec UV-150 photoreactor was continuously run for 3.5 hours without any intervention, affording 545 mg of trifluoromethylated derivative **3b** (56%).

In conclusion, we developed a continuous-flow trifluoromethylation strategy for arenes, heteroarenes and benzofused heterocycles. Luminescence quenching studies were employed to accelerate initial protocol optimization and to select the best photocatalyst for the transformation. Easy to handle $\text{CF}_3\text{SO}_2\text{Na}$ (Langlois' reagent) was successfully used as trifluoromethylating agent. A variety of substrates of high interest in drug discovery programs were trifluoromethylated in good to excellent yields. Moreover, bromo, chloro and iodo containing substrates were well tolerated, thus demonstrating the compatibility of our methodology with cross-coupling methods. Process intensification in a microflow reactor afforded reduced reaction times (30 minutes residence time) and a high productivity. Therefore, we anticipate that our methodology will find application in the late stage functionalization of pharmaceutical ingredients as well as in the preparation of key intermediates in drug discovery programs.

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The UPLC (Ultra Performance Liquid Chromatography) measurement was performed using an Acquity® IClass UPLC® (Waters) system comprising a

sampler organizer, a binary pump with degasser, a column oven, a diode-array detector (DAD) and a column as specified below. The MS detector (Waters, SQD or QTOF) was configured with an ESI dual ionization source (electrospray combined with atmospheric pressure chemical ionization). Nitrogen was used as the nebulizer gas. The source temperature was maintained at 140 °C. Data acquisition was performed with MassLynx-Openlynx software.

For IClass-SQD: Reversed phase UPLC was carried out on a RRHD Eclipse Plus-C18 (1.8 µm, 2.1 x 50 mm) from Agilent, with a flow rate of 1.0 ml/min, at 50°C. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40 % A, 60 % B in 1.2 minutes, to 5% A, 95% B in 0.6 minutes, held for 0.2 minutes. Injection volume 1.0 µl. Low-resolution ESI mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 seconds using an inter-channel delay of 0.08 second. The capillary needle voltage was 3 kV. The cone voltage was 25 V for positive ionization mode and 30 V for negative ionization mode.

For IClass-QTOF: Reversed phase UPLC was carried out on a BEH-C18 (1.7 µm, 2.1 x 50 mm) from Waters, with a flow rate of 1.0 ml/min, at 50°C. The gradient conditions used are: 95 % A (0.5 g/l ammonium acetate solution + 5 % acetonitrile), 5 % B (acetonitrile), to 40 % A, 60 % B in 1.2 minutes, to 5% A, 95% B in 0.6 minutes, held for 0.2 minutes. Injection volume 1.0 µl. High resolution ESI mass spectra were recorded on a Xevo G2-S QTOF mass spectrometer (Waters) configured with an electrospray ionization source, maintained at 140 °C, using nitrogen as the nebulizer gas, argon as collision gas and Lockmass device for mass calibration using Leucine-Enkephalin as standard substance. Spectra were acquired either in positive or in negative ionization mode, by scanning from 50 to 1200 Da in 0.1 s. In positive mode the capillary needle voltage was 0.25 kV and the cone voltage was 25 V. In negative mode the capillary needle voltage was 2.0 kV and the cone voltage was 25 V.

GCMS: GC measurements were performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and auto sampler, J&W HP-5MS column (20 m x 0.18 mm, 0.18 µm) from Agilent Technologies coupled to a 5973N MSD Mass Selective Detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source/chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 5.51 scan/s. The source temperature was maintained at 230 °C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software.

Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. The reactions were carried out in a Vapourtec photoreactor UV-150 fixed on an E-series Vapourtec equipment. ¹H NMR spectra were recorded on Bruker DPX-400 or Bruker AV-500 spectrometers with standard pulse sequences, operating at 400MHz and 500MHz respectively. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. All microfluidic fittings were purchased from IDEX Health and Science. The syringes were connected to the capillary using ¼-28 flat-bottom flangeless fittings. A syringe pump (Fusion 200 Classic) equipped with 5 or 10 mL syringes was used to feed liquid reagents through a high purity perfluoroalkoxyalkane (PFA) capillary tubing (ID = 1.3 mm) to a Tefzel® tee mixer (ID = 1.25 mm).

Procedures

General procedure: In an oven-dried vial equipped with a magnetic stirrer and a PTFE septum, 5.6 mg (1 mol %) of [Ir(dF(CF₃)ppy)₂](dtbpy)]PF₆ was added to a mixture of the hetero-arene substrate (0.5 mmol, 1 equiv.), NaSO₂CF₃ (1.5 mmol, 3 equiv.) and (NH₄)₂S₂O₈ (0.5 mmol, 1 equiv.) in 5 ml of DMSO. The solution was pumped into the Vapourtec Photoreactor (fluoropolymer tube, 1.3 mm ID, 10 mL) and the liquid flowrate was set at 0.33 mL/min (30 minutes residence time). The reactor was irradiated with 54 blue LEDs (450 nm, total power 24W). The reaction mixture collected from the outlet was diluted with H₂O and extracted with Et₂O (3x). The combined organic

layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude was then pre-adsorbed onto silica, dried in vacuo and purified by flash chromatography to yield the trifluoromethylated product.

1H-Purine-2,6-dione,3,9-dihydro-1,3-dimethyl-8-(trifluoromethyl)(2a)^{6a}: Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethyl acetate 75/25 afforded the desired product as a **white solid** (59 mg, 45%. M.p. = 130.85 °C).

¹H NMR (500MHz, CDCl₃): δ = 4.14-4.19 (m, 3H), 3.60 (s, 3H), 3.42 ppm (s, 3H).

¹³C NMR (101MHz, CDCl₃): δ = 155.5, 151.3, 146.5, 138.9, 119.5, 109.6, 33.2, 29.9, 28.2 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -62.37 ppm (s).

HRMS (ESI) m/z calcd for C₉H₉F₃N₄O₂ + [M+H]⁺ 263.0749, found 263.0742.

3-methyl-2-(trifluoromethyl)-1H-indole (2b)¹⁸: Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethyl acetate 80/20 afforded the desired product as a **white solid** (61.8 mg, 62%. M.p. = amorphous solid).

¹H NMR (400MHz, CDCl₃): δ = 8.18 (br s, 1H), 7.64 (d, J=8.1 Hz, 1H), 7.37-7.41 (m, 1H), 7.29-7.35 (m, 1H), 7.15-7.23 (m, 1H), 2.45 ppm (q, J=1.8 Hz, 3H).

¹³C NMR (101MHz, CDCl₃): δ = 135.2, 128.1, 124.8, 124.6, 121.6, 122.2, 120.1, 114.1, 8.4 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -58.65 ppm(s).

HRMS (ESI) m/z calcd for C₁₀H₈F₃N + [M+H]⁺ 200.0680, found 200.0683.

2-methyl-3-(trifluoromethyl)-1H-indole (2c)^{4f}: Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethyl acetate 80/20 afforded the desired product as a **white solid** (68.7 mg, 69%. M.p. = 147.45 °C).

¹H NMR (500MHz, CDCl₃): δ = 8.18 (br s, 1H), 7.67 (br d, J=7.5 Hz, 1H), 7.24-7.32 (m, 1H), 7.09-7.22 (m, 2H), 2.49 ppm (s, 3H).

¹³C NMR (101MHz, CDCl₃): δ = 133.9, 121.8, 121.3, 120.2, 119.1, 117.3, 113.7, 110.7, 99.3, 12.4 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -54.63 ppm; (s).

HRMS (ESI) m/z calcd for C₁₀H₈F₃N + [M+H]⁺ 200.0680, found 200.0686.

5-iodo-3-(trifluoromethyl)-1H-indole (2d): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethyl acetate 90/10 afforded the desired product as a transparent oil (**39 mg**, 25%).

¹H NMR (400MHz, CDCl₃): δ = 8.47 (br s, 1H), 8.10 (s, 1H), 7.56 (dd, J=8.6, 1.6 Hz, 1H), 7.51 (dd, J=2.7, 1.3 Hz, 1H), 7.23 ppm (s, 1H).

¹³C NMR (101MHz, CDCl₃): δ = 138.0, 134.9, 132.2, 128.4, 125.1, 125.0, 124.2, 113.5, 85.2 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -57.37 ppm(s).

HRMS (ESI) m/z calcd for C₉H₅F₃IN [M]⁺ 309.9345, found 309.9368.

5-iodo-2-(trifluoromethyl)-1H-indole (2d): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 80/20 afforded the desired product as a transparent oil (**39 mg**, 25%).

¹H NMR (500MHz, CDCl₃): δ = 8.52 (br s, 1H), 8.03 (s, 1H), 7.58 (d, J=10.4 Hz, 1H), 7.22 (d, J=8.4 Hz, 1H), 6.85 ppm (s, 1H).

¹³C NMR (101MHz, CDCl₃): δ = 135.2, 133.2, 130.9, 129.1, 126.7, 126.4, 121.9, 113.7, 103.4, 84.5 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -60.73 ppm(s).

HRMS (ESI) m/z calcd for C₉H₅F₃IN [M]⁺ 309.9345, found 309.9368.

4-(trifluoromethyl)benzimidazole (2e, C4:C6 3:2)¹³: Product prepared according to the general procedure, purification in flash chromatography

on silica gel using as eluent heptane/ethylacetate 80/20 afforded the desired product as **a white solid (27 mg, 29% M.p. = amorphous solid).**

¹H NMR (500MHz, CD₃OD): δ = 8.20 (s, 1H), 7.63-7.88 (br s, 1H), 7.48 (br d, *J*=7.2 Hz, 1H), 7.31 ppm (t, *J*=7.8 Hz, 1H).

¹³C NMR (126MHz, CD₃OD): δ = 164.1, 143.0, 133.2, 125.2, 123.1, 100.0, 99.8 ppm.

¹⁹F NMR (471MHz, CD₃OD): δ = -64.21 ppm(s).

HRMS (ESI) *m/z* calcd for C₈H₅F₃N₂ [M]⁺ 185.0331, found 185.0337.

6-(trifluoromethyl)benzimidazole (2e C4:C6 3:2): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 80/20 afforded the desired product as a yellow oil (**19 mg, 20%**).

¹H NMR (400MHz, CDCl₃): δ = 8.25 (s, 1H), 7.99 (s, 1H), 7.74 (d, *J*=8.6 Hz, 1H), 7.57 ppm (d, *J*=8.6 Hz, 1H).

¹³C NMR (101MHz, CDCl₃): δ = 142.6, 128.7, 126.0, 125.7, 125.4, 123.3, 120.1 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -62.20 ppm(s).

HRMS (ESI) *m/z* calcd for C₈H₅F₃N₂ [M]⁺ 185.0331, found 185.0337.

2-bromo-4-(trifluoromethyl)benzimidazole (2f C4:C6 3:2): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate in gradient from 100/0 to 50/50 afforded the desired product as **a white solid (40.2 mg, 30%. M.p. = 214.7 °C).**

¹H NMR (400MHz, CD₃OD): δ = 7.85 (s, 1H), 7.68 (d, *J*=8.6 Hz, 1H), 7.55 ppm (d, *J*=8.6 Hz, 1H).

¹³C NMR (101MHz, CD₃OD): δ = 140.8, 131.2, 130.1, 126.2, 122.2, 120.8, 115.7, 113.7 ppm.

¹⁹F NMR (471MHz, CD₃OD): δ = -62.40 ppm (s).

HRMS (ESI) *m/z* calcd for C₈H₄BrF₃N₂ [M]⁺ 262.9436, found 262.9434.

2-bromo-6-(trifluoromethyl)benzimidazole (2f C4:C6 3:2): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate in gradient from 100/0 to 50/50 afforded the desired product as **a white solid (26.7 mg, 20%. M.p. = 214.7 °C).**

¹H NMR (400MHz, CDCl₃): δ = 8.25 (s, 1H), 7.99 (s, 1H), 7.74 (d, *J*=8.6 Hz, 1H), 7.57 ppm (d, *J*=8.6 Hz, 1H).

¹³C NMR (101MHz, CDCl₃): δ = 142.6, 128.7, 126.0, 125.7, 125.4, 123.3, 120.1 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -62.20 ppm(s).

HRMS (ESI) *m/z* calcd for C₈H₄BrF₃N₂ [M]⁺ 262.9436, found 262.9434.

5-chloro-2-methyl-7-(trifluoromethyl)-1H-benzimidazol (2g C4:C7 2:1): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 80/20 afforded the desired product as a **white solid (23.8 mg, 20%. M.p. = amorphous solid).**

¹H NMR (400MHz, CDCl₃): δ = 9.48 (br s, 1H), 7.82 (br s, 1H), 7.47 (s, 1H), 2.68 ppm (s, 3H).

¹³C NMR (101MHz, CD₃OD): δ = 157.3, 128.1, 126.1, 123.4, 120.7, 105.2, 14.3 ppm.

¹⁹F NMR (471MHz, CD₃OD): δ = -62.87 ppm(s).

HRMS (ESI) *m/z* calcd for C₉H₆ClF₃N₂ [M]⁺ 233.0098, found 233.0108.

5-chloro-2-methyl-4-(trifluoromethyl)-1H-benzimidazol (2g C4:C7 2:1): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 80/20 afforded the desired product as a **white solid (35.2 mg, 30%. M.p. = amorphous solid).**

¹H NMR (500MHz, CDCl₃): δ = 9.50 (br s, 1H), 7.74 (d, *J*=8.4 Hz, 1H), 7.34 (d, *J*=8.4 Hz, 1H), 2.66 ppm (s, 3H).

¹³C NMR (126MHz, CDCl₃): δ = 153.3, 143.5, 131.9, 127.0, 125.1, 122.9, 15.3 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -57.09 ppm(s).

HRMS (ESI) *m/z* calcd for C₉H₆ClF₃N₂ [M]⁺ 233.0098, found 233.0108.

5-(trifluoromethyl)pyrimidin-4(3H)-on (3a): Product prepared according to the general procedure, the solvent was evaporated in Genevac turboevaporator in overnight, the rests of the reaction mixture were washed with dichloromethane and the solvent was evaporated, purification in flash chromatography on silica gel MeOH/NH₄OH(9:1)/Dichloromethane 0-10% the desired product as a yellow oil (**65.9 mg, 80%**).

¹H NMR (400MHz, DMSO-*d*₆): δ = 8.44 (s, 1H), 8.40 ppm (s, 1H)

¹³C NMR (126MHz, CDCl₃): δ = 154.7, 152.1, 129.7, 121.9 ppm

¹⁹F NMR (471MHz, CDCl₃): δ = -65.35 ppm(s).

HRMS (ESI) *m/z* calcd for C₅H₃F₃N₂O [M]⁺ 163.0124, found 163.0129.

5-bromo-3-(trifluoromethyl)-1H-pyridin-2-one (3b)¹⁹: Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 50/50 afforded the desired product as a **yellow solid (72.6 mg 60%. M.p. = 213.39°C).**

¹H NMR (500MHz, CDCl₃): δ = 12.52-14.24 (m, 1H), 7.92 (d, *J*=2.0 Hz, 1H), 7.76 ppm (d, *J*=2.3 Hz, 1H).

¹³C NMR (126MHz, CDCl₃): δ = 160.0, 143.8, 139.4, 121.5, 121.9, 97.7 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -65.98 ppm.

HRMS (ESI) *m/z* calcd for C₆H₃BrF₃N₂O [M]⁺ 239.9277, found 239.9272.

2,4,6-trimethoxy-5-(trifluoromethyl)pyrimidine (3c): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 80/20 afforded the desired product as a **pink solid (71.4 mg, 60%. M.p. = 123.6°C).**

¹H NMR (500MHz, CDCl₃): δ = 4.03 (s, 6H), 4.01 ppm (s, 3H).

¹³C NMR (101MHz, CDCl₃): δ = 169.8, 165.0, 123.5, 89.3, 55.1, 55.0 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -55.97 ppm(s).

4-methoxy-3-(trifluoromethyl)pyridin-2-amine (3d): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 40/60 afforded the desired product as a **yellow solid (38.5 mg, 40%. M.p. = 213.4°C).**

¹H NMR (400MHz, CDCl₃): δ = 8.07 (d, *J*=5.8 Hz, 1H), 6.31 (dd, *J*=5.9, 0.8 Hz, 1H), 5.00-5.20 (m, 2H), 3.88 ppm (s, 3H).

¹³C NMR (101MHz, CDCl₃): δ = 166.3, 156.6, 152.8, 124.9, 98.3, 56.1 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -55.42 ppm(s).

HRMS (ESI) *m/z* calcd for C₇H₇F₃N₂O [M]⁺ 191.0437, found 191.0423.

2-iodo-3-methoxy-5-(trifluoromethyl)pyridine (3e): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent pentane/diethyl ether 90/10 afforded the desired product as a transparent oil (**52.9 mg, 35%**).

¹H NMR (400MHz, CDCl₃): δ = 7.59 (d, *J*=8.6 Hz, 1H), 7.05 (d, *J*=8.6 Hz, 1H), 3.98 ppm (s, 3H).

¹³C NMR (101MHz, CDCl₃): δ = 157.4, 140.4, 134.2, 121.0, 116.1, 111.7, 56.7 ppm.

¹⁹F NMR (471MHz, CDCl₃): δ = -66.70 ppm.

HRMS (ESI) *m/z* calcd for C₇H₅F₃INO [M+H]⁺ 303.9488, found 303.9492.

3-[4-(trifluoromethyl)phenyl]-1H-pyrazole (3g): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 40/60 afforded the desired product as transparent oil (**29.7 mg, 28%**).

¹H NMR (400MHz, CDCl₃): δ = 7.90 (d, *J*=8.1 Hz, 2H), 7.65-7.70 (m, 1H), 7.62-7.74 (m, 2H), 6.70 ppm (d, *J*=2.3 Hz, 1H).

¹³C NMR (101MHz, CDCl₃): δ = 136.0, 131.8, 129.5, 129.0, 128.8, 126.0, 125.7, 124.6, 122.6, 103.3 ppm.

^{19}F NMR (471MHz, CDCl_3): δ = -62.58 ppm(s).

HRMS (ESI) m/z calcd for $\text{C}_{10}\text{H}_7\text{F}_3\text{N}_2$ [M] $^+$ 211.0488, found 211.0486.

1-tetrahydropyran-4-yl-5-(trifluoromethyl)pyrazol-4-amine (3h): Product prepared according to the general procedure, purification in flash chromatography on silica gel using as eluent heptane/ethylacetate 50/50 afforded the desired product as a dark yellow oil (52.9 mg, 45%).

^1H NMR (400MHz, CDCl_3): δ = 7.16 (s, 1H), 4.24 (tt, J =11.5, 4.0 Hz, 1H), 4.10 (dd, J =11.8, 4.6 Hz, 2H), 3.50 (td, J =12.2, 2.0 Hz, 2H), 3.28-3.42 (m, 2H), 2.26 (qd, J =12.4, 4.6 Hz, 2H), 1.78-1.92 ppm (m, 2H).

^{13}C NMR (101MHz, CDCl_3): δ = 130.8, 130.0, 121.8, 114.9, 67.1, 57.0, 32.9 ppm.

^{19}F NMR (471MHz, CDCl_3): δ = -56.70 ppm(s).

HRMS (ESI) m/z calcd for $\text{C}_9\text{H}_{12}\text{F}_3\text{N}_3\text{O}$ [M] $^+$ 234.2859, found 234.2855.

3-bromo-2,6-dimethyl-5-(trifluoromethyl)pyridine (3i): Product prepared according the general procedure. The organic layer was evaporated and the crude was analysed by LC-MS (38%).

^1H NMR (400MHz, CDCl_3): δ = 7.97 (s, 1H), 2.68 (s, 3H), 2.62-2.64 ppm (m, 3H).

^{19}F NMR (471MHz, CDCl_3): δ = -62.23 ppm.

1,3,5-trimethyl-2-(trifluoromethyl)benzene (3j): Product prepared according the general procedure. The organic layer was evaporated and the crude was analysed by LC-MS (53%).

2-iodo-1,3,5-trimethyl-4-(trifluoromethyl)benzene (3k): Product prepared according the general procedure. The organic layer was evaporated and the crude was analysed by LC-MS (80%).

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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