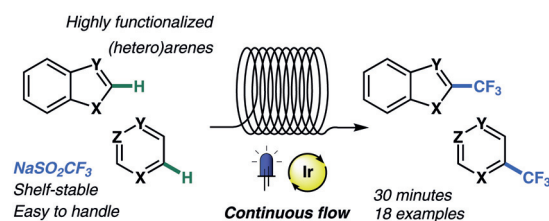


# Visible-Light-Induced Trifluoromethylation of Highly Functionalized Arenes and Heteroarenes in Continuous Flow

Irini Abdiaj<sup>a</sup>  
 Cecilia Bottecchia<sup>b</sup>  
 Jesus Alcazar<sup>\*a</sup>  
 Timothy Noël<sup>\*b</sup>

<sup>a</sup> Janssen Research & Development, Jarama 75A, 45007 Toledo, Spain  
 jalcazar@its.jnj.com

<sup>b</sup> Department of Chemical Engineering and Chemistry, Micro Flow  
 Chemistry & Process Technology, Eindhoven University of Technology,  
 Den Dolech 2, 5612 AZ Eindhoven, The Netherlands  
 t.noel@tue.nl



Received: 07.06.2017

Accepted after revision: 07.07.2017

Published online: 09.08.2017

DOI: 10.1055/s-0036-1588527; Art ID: ss-2017-e0382-op

**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 sodium trifluoromethanesulfinate ( $\text{CF}_3\text{SO}_2\text{Na}$ ) as the trifluoromethylating agent and the iridium complex  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbpy})]\text{PF}_6$  as the photoredox catalyst. A diverse set of highly functionalized heterocycles proved compatible with the methodology, and moderate to good yields were obtained within 30 minutes of residence time.

**Key words** trifluoromethylation, photoredox catalysis, continuous flow, Langlois reagent, visible light

Novel methodologies for the trifluoromethylation of arenes and heteroarenes are in high demand in the chemical and pharmaceutical industry.<sup>1</sup> In structure–activity relationship (SAR) studies, the introduction of fluorine atoms can greatly impact the electronic properties, acidity, and lipophilicity of drug candidates.<sup>2</sup> 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.<sup>1b</sup> 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.<sup>1a</sup>

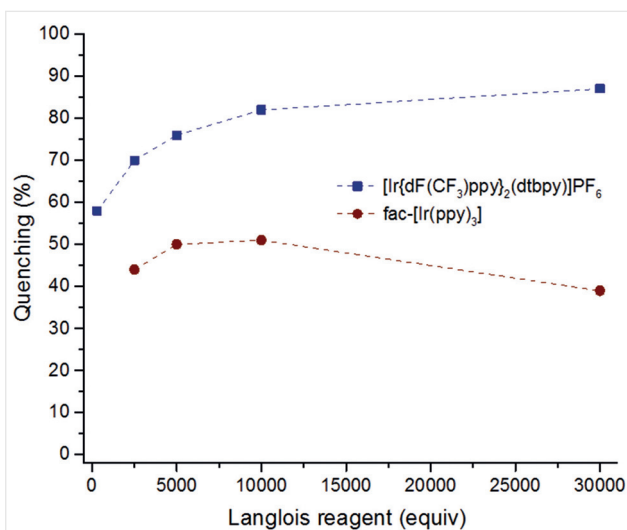
The initially reported trifluoromethylation protocols relied on transition-metal-catalyzed cross-coupling methods, but suffered from the need for prefunctionalized substrates and stoichiometric amounts of metal salts.<sup>3</sup> More recently, several strategies reported in the literature demonstrated the utility of photocatalytic protocols for the trifluoromethylation of alkenes, thiols, heterocycles, and arenes.<sup>4</sup> The most commonly used trifluoromethyl sources include ex-

pensive Togni and Umemoto's reagents, unstable triflyl chloride ( $\text{CF}_3\text{SO}_2\text{Cl}$ ), gaseous  $\text{CF}_3\text{I}$ , and readily available trifluoroacetic anhydride.<sup>4e,5</sup> In addition, the 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  $\text{CF}_3$  radicals in the presence of a strong oxidant (e.g., *t*-BuOOH).<sup>6,7</sup>

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.<sup>4a,b,8</sup> 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).<sup>9</sup> 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 reductively quenched by the Langlois reagent, thus generating a  $\text{CF}_3$  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 the 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, re-

spectively; both values reported versus the saturated calomel electrode (SCE)].<sup>10</sup> As reported by Glorius and co-workers, a quenching percentage higher than 25% should be considered as significant and relevant for photocatalytic reaction purposes.<sup>9b</sup> 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  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbpy})]\text{PF}_6$  (squares) and  $\text{fac-Ir}(\text{ppy})_3$  (dots) in the 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 equiv), 50 mM (5000 equiv), 100 mM (10000 equiv), 300 mM (30000 equiv). For  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbpy})]\text{PF}_6$ , a concentration of 0.3 mM (300 equiv and corresponding to reaction conditions) was also tested. For more details on the procedure followed and for the calculation of the quenching percentages, see the Supporting Information.

The trifluoromethylation of caffeine was selected as the benchmark reaction for our optimization studies in flow (Table 1). The photoflow reactor consisted 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, ensuring high solubility of the densely functionalized substrates and thus avoiding 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  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (1 equiv) as an oxidant, an improved LC-MS yield of 48% was obtained (entry 3). Next, diacetoxyiodobenzene was tested as the oxidant, but this resulted in a

lower 32% isolated yield (entry 4). Increasing the amount of Langlois reagent to three equivalents further boosted the LC-MS yield to 54% (entry 5) (45% isolated yield). Notably, under the same reaction conditions, the reaction with  $\text{fac-Ir}(\text{ppy})_3$  gave 38% yield (entry 6), thus confirming the choice of the 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 (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 (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 (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, to minimize the occurrence of side reactions and compound degradation.<sup>11</sup>

**Table 1** Optimization of Reaction Conditions for the Trifluoromethylation of Caffeine in Continuous Flow<sup>a</sup>

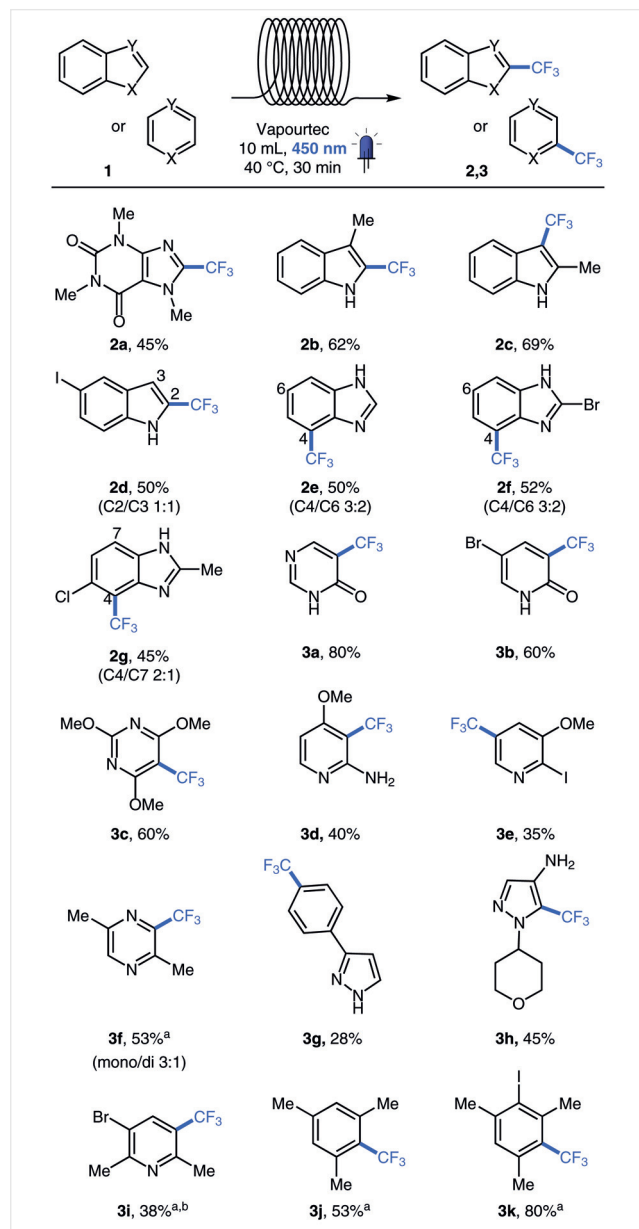
Entry	Changes from optimized conditions <sup>a</sup>	Yield by LC-MS (%)
1	20 min residence time, no oxidant	5
2	no oxidant, $\text{CF}_3\text{SO}_2\text{Na}$ (1.5 equiv)	12
3	$(\text{NH}_4)_2\text{S}_2\text{O}_8$ (1 equiv), $\text{CF}_3\text{SO}_2\text{Na}$ (1.5 equiv)	48
4	diacetoxyiodobenzene (1 equiv), $\text{CF}_3\text{SO}_2\text{Na}$ (1.5 equiv)	32 <sup>b</sup>
5	none	54 (45 <sup>b</sup> )
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

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

<sup>b</sup> Isolated 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 on 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 the construction of carbon–carbon or carbon–heteroatom bonds.<sup>12</sup>



3-Methyl and 2-methylindole derivatives **2b** and **2c** were obtained in satisfactory yields (62% and 69%, respectively; Scheme 1). 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 positions on the aromatic ring.<sup>13</sup> For example, (trifluoromethyl)benzimidazole **2e** was obtained in 50% yield as a separable mixture of C4/C6 (3:2) isomers; the 2-bromo trifluoromethyl derivative **2f** was obtained in 52% yield (C4/C6, 3:2, separable mixture). Interestingly, 5-chlorobenzimidazole showed 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 for 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).<sup>14</sup> Trifluoromethylated pyrimidone **3a** and bromopyridone **3b** were obtained in good to excellent yields (80% and 60%, respectively; Scheme 1). We further investigated the reactivity of pyridine, obtaining trifluoromethylated pyridine derivatives **3d**, **3e**, and **3f** in modest yields (40%, 35%, and 53%, respectively). Furthermore, phenylpyrazole could be trifluoromethylated on the phenyl substituent and isolated in 28% yield (**3g**). Conversely, the tetrahydropyran-substituted 4-aminopyrazole derivative **3h** was trifluoromethylated at position C5 on the pyrazole ring and isolated in a reasonable 45% yield. 3-Bromo-2,5-dimethylpyridine was successfully trifluoromethylated, giving **3i** in 38% yield.

Finally, we explored the scope of our methodology with regard to unactivated arene substrates (Scheme 1). Trifluoromethylated mesitylene and iodomesitylene **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 h), and has so far rarely been reported in photoredox-based protocols.<sup>4h,15</sup> Therefore, we were pleased to observe significant product formation in our system within only 30 minutes of 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.<sup>11,16</sup> Moreover, to showcase the potential of microreactors in terms of productivity, we performed a scale-up experiment on bromopyridone.<sup>16c,17</sup> 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 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.

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 an RRHD Eclipse Plus-C18 (1.8  $\mu\text{m}$ , 2.1  $\times$  50 mm) from Agilent, with a flow rate of 1.0 mL/min, at 50 °C. The gradient conditions used were: 95% A (0.5 g/L ammonium acetate solution + 5% acetonitrile), 5% B (acetonitrile), to 40% A, 60% B in 1.2 min, to 5% A, 95% B in 0.6 min, held for 0.2 min. Injection volume 1.0  $\mu\text{L}$ . Low-resolution ESI mass spectra (single quadrupole, SQD detector) were acquired by scanning from 100 to 1000 in 0.1 s using an interchannel delay of 0.08 s. 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  $\mu\text{m}$ , 2.1  $\times$  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 min, to 5% A, 95% B in 0.6 min, held for 0.2 min. Injection volume 1.0  $\mu\text{L}$ . 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.

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  $\times$  0.18 mm, 0.18  $\mu\text{m}$ ) 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 scans per second. The source temperature was maintained at 230 °C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software. TLC was carried out on silica gel 60 F254 plates (Merck), using reagent grade solvents. Unless otherwise speci-

fied, 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.  $^1\text{H}$  NMR spectra were recorded on Bruker DPX-400 or Bruker AV-500 spectrometers with standard pulse sequences, operating at 400 MHz and 500 MHz, respectively. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard.  $^{13}\text{C}$  NMR spectra were recorded on the same spectrometers operating at 101 MHz and 126 MHz, respectively.  $^{19}\text{F}$  NMR spectra were recorded on the Bruker AV-500 spectrometer operating at 471 MHz. 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 (i.d. 1.3 mm) to a Tefzel® tee mixer (i.d. 1.25 mm). The melting points were measured on DSC equipment (Mettler 823 Toledo; method: 30–300 °C, 10 °C/min).

#### Trifluoromethylation; General Procedure:

In an oven-dried vial equipped with a magnetic stirrer and a PTFE septum,  $[\text{Ir}\{\text{dF}(\text{CF}_3)\text{ppy}\}_2(\text{dtbpy})]\text{PF}_6$  (5.6 mg, 1 mol%) was added to a mixture of the substrate (0.5 mmol, 1 equiv),  $\text{CF}_3\text{SO}_2\text{Na}$  (1.5 mmol, 3 equiv), and  $(\text{NH}_4)_2\text{S}_2\text{O}_8$  (0.5 mmol, 1 equiv) in DMSO (5 mL). The solution was pumped into the Vapourtec photoreactor (fluoropolymer tube, 1.3 mm i.d., 10 mL) and the liquid flowrate was set at 0.33 mL/min (30 min residence time). The reactor was irradiated with 54 blue LEDs (450 nm, total power 24 W). The reaction mixture collected from the outlet was diluted with  $\text{H}_2\text{O}$  and extracted with  $\text{Et}_2\text{O}$  (3 $\times$ ). The combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , 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.

#### 1,3,7-Trimethyl-8-(trifluoromethyl)-7H-purine-2,6-dione (2a)<sup>6a</sup>

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 75:25); this afforded the desired product as a white solid.

Yield: 59 mg (45%); mp 130.9 °C.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 4.14–4.19 (m, 3 H), 3.60 (s, 3 H), 3.42 (s, 3 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 155.5, 151.3, 146.5, 138.9, 119.5, 109.6, 33.2, 29.9, 28.2.

$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –62.37 (s).

HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_9\text{H}_9\text{F}_3\text{N}_4\text{O}_2$ : 263.0749; found: 263.0742.

#### 3-Methyl-2-(trifluoromethyl)-1H-indole (2b)<sup>18</sup>

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a white amorphous solid.

Yield: 61.8 mg (62%).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 8.18 (br s, 1 H), 7.64 (d,  $J$  = 8.1 Hz, 1 H), 7.37–7.41 (m, 1 H), 7.29–7.35 (m, 1 H), 7.15–7.23 (m, 1 H), 2.45 (q,  $J$  = 1.8 Hz, 3 H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 135.2, 128.1, 124.8, 124.6, 121.6, 122.2, 120.1, 114.1, 8.4.

$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ):  $\delta$  = –58.65 (s).

HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{10}H_8F_3N$ : 200.0680; found: 200.0683.

#### 2-Methyl-3-(trifluoromethyl)-1H-indole (2c)<sup>df</sup>

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a white solid.

Yield: 68.7 mg (69%); mp 147.5 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.18 (br s, 1 H), 7.67 (br d,  $J$  = 7.5 Hz, 1 H), 7.24–7.32 (m, 1 H), 7.09–7.22 (m, 2 H), 2.49 (s, 3 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 133.9, 121.8, 121.3, 120.2, 119.1, 117.3, 113.7, 110.7, 99.3, 12.4.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>):  $\delta$  = –54.63 (s).

HRMS (ESI):  $m/z$   $[M + H]^+$  calcd for  $C_{10}H_8F_3N$ : 200.0680; found: 200.0686.

#### 5-Iodo-3-(trifluoromethyl)-1H-indole (2d-C3 isomer)

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 90:10); this afforded the desired product as a transparent oil.

Yield: 39 mg (25%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.47 (br s, 1 H), 8.10 (s, 1 H), 7.56 (dd,  $J$  = 8.6, 1.6 Hz, 1 H), 7.51 (dd,  $J$  = 2.7, 1.3 Hz, 1 H), 7.23 (s, 1 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 138.0, 134.9, 132.2, 128.4, 125.1, 125.0, 124.2, 113.5, 85.2.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>):  $\delta$  = –57.37 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_9H_5F_3IN$ : 309.9345; found: 309.9368.

#### 5-Iodo-2-(trifluoromethyl)-1H-indole (2d-C2 isomer)

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a transparent oil.

Yield: 39 mg (25%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.52 (br s, 1 H), 8.03 (s, 1 H), 7.58 (d,  $J$  = 10.4 Hz, 1 H), 7.22 (d,  $J$  = 8.4 Hz, 1 H), 6.85 (s, 1 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 135.2, 133.2, 130.9, 129.1, 126.7, 126.4, 121.9, 113.7, 103.4, 84.5.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>):  $\delta$  = –60.73 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_9H_5F_3IN$ : 309.9345; found: 309.9368.

#### 4-(Trifluoromethyl)benzimidazole (2e-C4 isomer)<sup>13</sup>

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a white amorphous solid.

Yield: 27 mg (29%).

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  = 8.20 (s, 1 H), 7.63–7.88 (br s, 1 H), 7.48 (br d,  $J$  = 7.2 Hz, 1 H), 7.31 (t,  $J$  = 7.8 Hz, 1 H).

<sup>13</sup>C NMR (126 MHz, CD<sub>3</sub>OD):  $\delta$  = 164.1, 143.0, 133.2, 125.2, 123.1, 100.0, 99.8.

<sup>19</sup>F NMR (471 MHz, CD<sub>3</sub>OD):  $\delta$  = –64.21 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_8H_5F_3N_2$ : 185.0331; found: 185.0337.

#### 6-(Trifluoromethyl)benzimidazole (2e-C6 isomer)

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a yellow oil.

Yield: 19 mg (20%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.25 (s, 1 H), 7.99 (s, 1 H), 7.74 (d,  $J$  = 8.6 Hz, 1 H), 7.57 (d,  $J$  = 8.6 Hz, 1 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.6, 128.7, 126.0, 125.7, 125.4, 123.3, 120.1.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>):  $\delta$  = –62.20 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_8H_5F_3N_2$ : 185.0331; found: 185.0337.

#### 2-Bromo-4-(trifluoromethyl)benzimidazole (2f-C4 isomer)

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, in gradient from 100:0 to 50:50); this afforded the desired product as a white solid.

Yield: 40.2 mg (30%); mp 214.7 °C.

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD):  $\delta$  = 7.85 (s, 1 H), 7.68 (d,  $J$  = 8.6 Hz, 1 H), 7.55 (d,  $J$  = 8.6 Hz, 1 H).

<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD):  $\delta$  = 140.8, 131.2, 130.1, 126.2, 122.2, 120.8, 115.7, 113.7.

<sup>19</sup>F NMR (471 MHz, CD<sub>3</sub>OD):  $\delta$  = –62.40 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_8H_4BrF_3N_2$ : 262.9436; found: 262.9434.

#### 2-Bromo-6-(trifluoromethyl)-1H-benzimidazole (2f-C6 isomer)

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, gradient 100:0 to 50:50); this afforded the desired product as a white solid.

Yield: 26.7 mg (20%); mp 214.7 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.25 (s, 1 H), 7.99 (s, 1 H), 7.74 (d,  $J$  = 8.6 Hz, 1 H), 7.57 (d,  $J$  = 8.6 Hz, 1 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 142.6, 128.7, 126.0, 125.7, 125.4, 123.3, 120.1.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>):  $\delta$  = –62.20 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_8H_4BrF_3N_2$ : 262.9436; found: 262.9434.

#### 5-Chloro-2-methyl-7-(trifluoromethyl)-1H-benzimidazole (2g-C7 isomer)

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a white amorphous solid.

Yield: 23.8 mg (20%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 9.48 (br s, 1 H), 7.82 (br s, 1 H), 7.47 (s, 1 H), 2.68 (s, 3 H).

<sup>13</sup>C NMR (101 MHz, CD<sub>3</sub>OD):  $\delta$  = 157.3, 128.1, 126.1, 123.4, 120.7, 105.2, 14.3.

<sup>19</sup>F NMR (471 MHz, CD<sub>3</sub>OD):  $\delta$  = –62.87 (s).

HRMS (ESI):  $m/z$   $[M - H]^-$  calcd for  $C_9H_6ClF_3N_2$ : 233.0098; found: 233.0108.

**5-Chloro-2-methyl-4-(trifluoromethyl)-1H-benzimidazole (2g-C4 isomer)**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a white amorphous solid. Yield: 35.2 mg (30%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 9.50 (br s, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 2.66 (s, 3 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 153.3, 143.5, 131.9, 127.0, 125.1, 122.9, 15.3.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –57.09 (s).

HRMS (ESI): *m/z* [M – H]<sup>–</sup> calcd for C<sub>9</sub>H<sub>6</sub>ClF<sub>3</sub>N<sub>2</sub>: 233.0098; found: 233.0108.

**5-(Trifluoromethyl)pyrimidin-4(3H)-one (3a)**

The product was prepared according to the general procedure, after which the solvent was evaporated in a Genevac turboevaporator overnight. The rests of the reaction mixture were washed with CH<sub>2</sub>Cl<sub>2</sub> and the solvent was evaporated; the product was purified by flash chromatography (silica gel, MeOH–NH<sub>4</sub>OH, 9:1/CH<sub>2</sub>Cl<sub>2</sub>, 0–10%); this afforded the desired product as a yellow oil.

Yield: 65.9 mg (80%).

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 8.44 (s, 1 H), 8.40 (s, 1 H)

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 154.7, 152.1, 129.7, 121.9

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –65.35 (s).

HRMS (ESI): *m/z* [M – H]<sup>–</sup> calcd for C<sub>5</sub>H<sub>3</sub>F<sub>3</sub>N<sub>2</sub>O: 163.0124; found: 163.0129.

**5-Bromo-3-(trifluoromethyl)-1H-pyridin-2-one (3b)<sup>19</sup>**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 50:50); this afforded the desired product as a yellow solid.

Yield: 72.6 mg (60%); mp 213.3 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 12.52–14.24 (m, 1 H), 7.92 (d, *J* = 2.0 Hz, 1 H), 7.76 (d, *J* = 2.3 Hz, 1 H).

<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ = 160.0, 143.8, 139.4, 121.5, 121.9, 97.7.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –65.98.

HRMS (ESI): *m/z* [M – H]<sup>–</sup> calcd for C<sub>6</sub>H<sub>3</sub>BrF<sub>3</sub>NO: 239.9277; found: 239.9272.

**2,4,6-Trimethoxy-5-(trifluoromethyl)pyrimidine (3c)**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 80:20); this afforded the desired product as a pink solid.

Yield: 71.4 mg (60%); mp 123.6 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 4.03 (s, 6 H), 4.01 (s, 3 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 169.8, 165.0, 123.5, 89.3, 55.1, 55.0.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –55.97 (s).

**4-Methoxy-3-(trifluoromethyl)pyridin-2-amine (3d)**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 40:60); this afforded the desired product as a yellow solid.

Yield: 38.5 mg (40%); mp 213.4 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 8.07 (d, *J* = 5.8 Hz, 1 H), 6.31 (dd, *J* = 5.9, 0.8 Hz, 1 H), 5.00–5.20 (m, 2 H), 3.88 (s, 3 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 166.3, 156.6, 152.8, 124.9, 98.3, 56.1.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –55.42 (s).

HRMS (ESI): *m/z* [M – H]<sup>–</sup> calcd for C<sub>7</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O: 191.0437; found: 191.0423.

**2-Iodo-3-methoxy-5-(trifluoromethyl)pyridine (3e)**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, pentane–Et<sub>2</sub>O, 90:10); this afforded the desired product as a transparent oil.

Yield: 52.9 mg (35%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.59 (d, *J* = 8.6 Hz, 1 H), 7.05 (d, *J* = 8.6 Hz, 1 H), 3.98 (s, 3 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 157.4, 140.4, 134.2, 121.0, 116.1, 111.7, 56.7.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –66.70.

HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>7</sub>H<sub>5</sub>F<sub>3</sub>INO: 303.9488; found: 303.9492.

**2,5-Dimethyl-3-(trifluoromethyl)pyrazine (3f)**

The product was prepared according to the general procedure. The organic layer was evaporated and the crude was analyzed by LC-MS and GC-MS; yield: 53%.

**3-[4-(Trifluoromethyl)phenyl]-1H-pyrazole (3g)**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 40:60); this afforded the desired product as a transparent oil.

Yield: 29.7 mg (28%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.90 (d, *J* = 8.1 Hz, 2 H), 7.65–7.70 (m, 1 H), 7.62–7.74 (m, 2 H), 6.70 (d, *J* = 2.3 Hz, 1 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 136.0, 131.8, 129.5, 129.0, 128.8, 126.0, 125.7, 124.6, 122.6, 103.3.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –62.58 (s).

HRMS (ESI): *m/z* [M – H]<sup>–</sup> calcd for C<sub>10</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>: 211.0488; found: 211.0486.

**1-Tetrahydropyran-4-yl-5-(trifluoromethyl)pyrazol-4-amine (3h)**

The product was prepared according to the general procedure and was purified by flash chromatography (silica gel, heptane–EtOAc, 50:50); this afforded the desired product as a dark yellow oil.

Yield: 52.9 mg (45%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.16 (s, 1 H), 4.24 (tt, *J* = 11.5, 4.0 Hz, 1 H), 4.10 (dd, *J* = 11.8, 4.6 Hz, 2 H), 3.50 (td, *J* = 12.2, 2.0 Hz, 2 H), 3.28–3.42 (m, 2 H), 2.26 (qd, *J* = 12.4, 4.6 Hz, 2 H), 1.78–1.92 (m, 2 H).

<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ = 130.8, 130.0, 121.8, 114.9, 67.1, 57.0, 32.9.

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –56.70 (s).

HRMS (ESI): *m/z* [M – H]<sup>–</sup> calcd for C<sub>9</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>O: 234.2859; found: 234.2855.

**3-Bromo-2,6-dimethyl-5-(trifluoromethyl)pyridine (3i)**

The product was prepared according to the general procedure. The organic layer was evaporated and the crude was analyzed by LC-MS; yield: 38%.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.97 (s, 1 H), 2.68 (s, 3 H), 2.62–2.64 (m, 3 H).

<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>): δ = –62.23.

**1,3,5-Trimethyl-2-(trifluoromethyl)benzene (3j)**

The product was prepared according to the general procedure. The organic layer was evaporated and the crude was analyzed by LC-MS; yield: 53%.

**2-Iodo-1,3,5-trimethyl-4-(trifluoromethyl)benzene (3k)**

The product was prepared according to the general procedure. The organic layer was evaporated and the crude was analyzed by LC-MS; yield: 80%.

**Funding Information**

The authors acknowledge the European Union for a Marie Curie ITN Grant (Photo4Future, Grant No. 641861). Further financial support for this work was provided by a VIDJ grant (T.N., SensPhotoFlow, No. 14150).

**Acknowledgment**

The authors would like to thank Dr. José Manuel Alonso for the support with NMR analysis.

**Supporting Information**

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1588527>.

**References**

- (1) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
- (2) (a) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832. (b) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041.
- (3) (a) Barata-Vallejo, S.; Postigo, A. *Coord. Chem. Rev.* **2013**, *257*, 3051. (b) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (c) Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013**, *5*, 941.
- (4) (a) Straathof, N. J. W.; Cramer, S. E.; Hessel, V.; Noël, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 15549. (b) Bottecchia, C.; Wei, X. J.; Kuijpers, K. P.; Hessel, V.; Noel, T. *J. Org. Chem.* **2016**, *81*, 7301. (c) Lefebvre, Q.; Hoffmann, N.; Rueping, M. *Chem. Commun.* **2016**, *52*, 2493. (d) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. *Acc. Chem. Res.* **2016**, *49*, 2284. (e) Beatty, J. W.; Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *Nat. Commun.* **2015**, *6*. (f) Straathof, N. J. W.; Gemoets, H. P. L.; Wang, X.; Schouten, J. C.; Hessel, V.; Noël, T. *ChemSusChem* **2014**, *7*, 1612. (g) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (h) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (i) Iqbal, N.; Choi, S.; Kim, E.; Cho, E. J. *J. Org. Chem.* **2012**, *77*, 11383. (j) Cui, L.; Matusaki, Y.; Tada, N.; Miura, T.; Uno, B.; Itoh, A. *Adv. Synth. Catal.* **2013**, *355*, 2203.
- (5) (a) Pan, X.; Xia, H.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 1163. (b) Barata-Vallejo, S.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, *20*, 16806.
- (6) (a) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411. (b) Wang, D.; Deng, G.-J.; Chen, S.; Gong, H. *Green Chem.* **2016**, *18*, 5967. (c) Langlois, B. R.; Billard, T.; Mulatier, J.-C.; Yezeguelian, C. *J. Fluorine Chem.* **2007**, *128*, 851. (d) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525. (e) Tordeux, M.; Langlois, B.; Wakselman, C. *J. Org. Chem.* **1989**, *54*, 2452.
- (7) (a) Lefebvre, Q. *Synlett* **2016**, *28*, 19. (b) Zhang, C. *Adv. Synth. Catal.* **2014**, *356*, 2895.
- (8) (a) Huck, L.; Berton, M.; de la Hoz, A.; Diaz-Ortiz, A.; Alcazar, J. *Green Chem.* **2017**, *19*, 1420. (b) Wirth, T. *ChemSusChem* **2012**, *5*, 215. (c) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 1.
- (9) (a) Teders, M.; Gómez-Suárez, A.; Pitzer, L.; Hopkinson, M. N.; Glorius, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 902. (b) Hopkinson, M. N.; Gómez-Suárez, A.; Teders, M.; Sahoo, B.; Glorius, F. *Angew. Chem. Int. Ed.* **2016**, *55*, 4361. (c) Demissie, T. B.; Hansen, J. H. *Dalton Trans.* **2016**, *45*, 10878.
- (10) Teegardin, K.; Day, J. I.; Chan, J.; Weaver, J. *Org. Process Res. Dev.* **2016**, *20*, 1156.
- (11) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276.
- (12) (a) Brown, D. G.; Boström, J. *J. Med. Chem.* **2016**, *59*, 4443. (b) Alonso, N.; Miller, L. Z.; de M. Muñoz, J.; Alcázar, J.; McQuade, D. T. *Adv. Synth. Catal.* **2014**, *356*, 3737. (c) Egle, B.; Muñoz, J.; Alonso, N.; De Borggraeve, W.; de la Hoz, A.; Díaz-Ortiz, A.; Alcázar, J. *J. Flow Chem.* **2014**, *4*, 22. (d) de M. Muñoz, J.; Alcázar, J.; de la Hoz, A.; Díaz-Ortiz, A. *Adv. Synth. Catal.* **2012**, *354*, 3456. (e) Noël, T.; Musacchio, A. J. *Org. Lett.* **2011**, *13*, 5180. (f) Cooper, T. W. J.; Campbell, I. B.; Macdonald, S. J. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 8082.
- (13) Gao, G.-L.; Yang, C.; Xia, W. *Chem. Commun.* **2017**, *53*, 1041.
- (14) (a) Linghu, X.; Wong, N.; Iding, H.; Jost, V.; Zhang, H.; Koenig, S. G.; Sowell, C. G.; Gosselin, F. *Org. Process Res. Dev.* **2017**, *21*, 387. (b) Peng, A.; Jiang, J.; Hu, P.; Luo, Y. *J. Chromatogr., B* **2010**, *878*, 2442.
- (15) (a) Chang, B.; Shao, H.; Yan, P.; Qiu, W.; Weng, Z.; Yuan, R. *ACS Sustainable Chem. Eng.* **2017**, *5*, 334. (b) Li, L.; Mu, X.; Liu, W.; Wang, Y.; Mi, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2016**, *138*, 5809.
- (16) (a) Noël, T. *Photochemical Processes in Continuous-Flow Reactors*; World Scientific: New Jersey, **2017**. (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2012**, *51*, 4144. (c) Elliott, L. D.; Knowles, J. P.; Koovits, P. J.; Maskill, K. G.; Ralph, M. J.; Lejeune, G.; Edwards, L. J.; Robinson, R. I.; Clemens, I. R.; Cox, B.; Pascoe, D. D.; Koch, G.; Eberle, M.; Berry, M. B.; Booker-Milburn, K. I. *Chem. Eur. J.* **2014**, *20*, 15226. (d) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025.

- (17) (a) Elliott, L. D.; Berry, M.; Harji, B.; Klauber, D.; Leonard, J.; Booker-Milburn, K. I. *Org. Process Res. Dev.* **2016**, *20*, 1806.  
(b) Abdiaj, I.; Alcázar, J. *Bioorg. Med. Chem.* **2016**, in press; DOI: 10.1016/j.bmc.2016.12.041. (c) Su, Y.; Kuijpers, K.; Hessel, V.; Noël, T. *React. Chem. Eng.* **2016**, *1*, 73.
- (18) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *ACS Catal.* **2014**, *4*, 2530.
- (19) Gleave, R. J.; Beswick, P. J.; Brown, A. J.; Giblin, G. M. P.; Haslam, C. P.; Livermore, D.; Moses, A.; Nicholson, N. H.; Page, L. W.; Slingsby, B.; Swarbrick, M. E. *Bioorg. Med. Chem.* **2009**, *19*, 6578.