SuFEx-Enabled, Chemoselective Synthesis of Triflates, Triflamides and Triflimidates

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2. General Information

$^1$H NMR spectra
$^1$H NMR spectra were recorded on a Bruker Avance III HD 400 (at 400 MHz) spectrometer. Samples were dissolved in CDCl$_3$ (residual solvent peak at 7.26 ppm, singlet) or DMSO-$d_6$ (2.50 ppm, quintet) or methanol-$d_4$ (3.35 ppm, quintet; 4.78 ppm, singlet). The spectra were measured at room temperature and calibrated using tetramethylsilane as an internal standard in CDCl$_3$ and DMSO-$d_6$. The $\delta$-values are expressed in ppm. Small amounts of solvent traces (H$_2$O, EtOAc or Heptane) might be visible in some of the reported spectra. In the case of the presence of more significant amounts of solvent (indicated at the respective spectra), this was considered in the reported isolated yields. For those compounds, further purification was not performed due to volatile properties.

$^{13}$C NMR spectra
$^{13}$C NMR spectra were recorded on Bruker Avance III HD 400 (working at 101 MHz) spectrometer. The spectra were measured at room temperature and calibrated using the deuterated solvents as internal standard (for CDCl$_3$ a triplet at 77.00 ppm and for DMSO-$d_6$ a quintet at 39.52 ppm methanol-$d_4$). The $\delta$-values are expressed in ppm.

$^{19}$F NMR spectra
$^{19}$F NMR spectra were recorded on Bruker Avance III HD 400 (working at 377 MHz) spectrometer or Bruker Avance III HD 500 (working at 471 MHz) spectrometer. Samples were dissolved in CDCl$_3$ or DMSO-$d_6$ or methanol-$d_4$. The spectra were measured at room temperature and calibrated with trichlorofluoromethane as an internal standard. The $\delta$-values are expressed in ppm.

IR spectra
FT-IR spectra of unreported products were measured on a Bruker Alpha-T FT-IR spectrometer with universal sampling module. Data were acquired using Bruker OPUS 7.5 and analyzed using ACD/Spectrus Processor 2016.1.1 software. The band frequencies are given to the nearest 1 cm$^{-1}$ and their intensity is provided (very strong (vs), strong (s), medium (m), weak (w), broad (br)).

Melting points
Melting points of unreported products were measured on an Electrothermal IA 9300 melting point apparatus (serial no. R209000150) at a heating rate of 5.0 °C/min at the first time and 0.5°C/min at the second time.

CHN analysis
CHN (carbon, hydrogen, nitrogen) elemental analyses of unreported products were obtained with the aid of a Thermo Scientific Interscience Flash 2000 Elemental analyser.

HRMS analysis
Spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3μL/min and spectra were obtained in positive (or: negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

APCI spectra were obtained by infusion on a quadrupole/time-of-flight mass spectrometer (Synapt G2, Waters, Milford, MA).

HPLC analysis
The enantiomeric excess of the product was determined by chiral HPLC using an LC instrument on Chiralpak AD-3 column.

Chromatography
TLC analysis was performed using Sigma-Aldrich 20 x 20 cm precoated glass TLC plates with fluorescent indicator at 254 nm (article number 99571: layer thickness 250 μm, particle size 8.0-12.0 μm, average pore diameter 60 Å). Visualization of the products and their fluorescence features were achieved by UV-radiation at 254 nm.

Manual column chromatography was performed by using MP silica 40-60 micrometer (average pore diameter 60 Å).

Flash column chromatography (MPLC) was performed using a Büchi Sepacore® flash system, consisting of a Büchi C-660 Fraction Collector, a Büchi C-615 Pump Manager, a Knauer WellChrom K-2501 spectrophotometer (working at 254 nm), two Büchi C-605 Pump Modules and a Linseis D120S plotter. Büchi PP cartridges (12/150 mm) were filled with 8 g of Acros ultra-pure silica gel for column chromatography (article number 360050300: particle size 40-60 μm, average pore diameter 60 Å) using a Büchi C-670 Cartridger.

Materials
All chemicals were obtained from commercially available sources and were used without any further purification. Reactions were magnetically stirred. Solvents were evaporated with a rotary evaporator at a temperature of 50 °C.
3. Optimization study

3.1 N-Phenyl-bis(trifluoromethanesulfonimide) as Precursor

A. First Solvent Screen in Chamber A

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium fluoride (KF, 99 wt%, 197.2 mg, 2.5 mmol, 2.5 eq.). Next, chamber B was charged with 192.0 mg of 4-fluoro-4’-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). After putting the reactor in a cold water bath, acetonitrile (MeCN, 4.0 mL, 0.25 M), N,N-diisopropylethylamine (DIPEA, 0.52 mL, 3.0 mmol, 3.0 eq.) and trifluorotoluene (99 wt%, 124 μL, 1.0 mmol) as an internal standard were added to chamber B. Then, dimethylformamide (DMF, 1.75 mL, 0.86 M) was added to chamber A. Finally, the vessel was closed, and the appropriate solvent was added by injection through the septum in chamber A. The reaction was stirred for 18 hours at room temperature. The reaction mixture was analyzed by 19F NMR. (Table S1. H⁺ Source screen in chamber A for the fluorosulfation of 4-fluoro-4’-hydroxybiphenyl with trifluoromethanesulfonyl fluoride gas from PhNTf₂.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>H⁺ source</th>
<th>Volume of H⁺ Source (mL)</th>
<th>Conversion (%)</th>
<th>Yield (§) (%)</th>
<th>Final Ratio 1a:2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^a]</td>
<td>TFA</td>
<td>1 mL</td>
<td>49</td>
<td>1.5</td>
<td>97:3</td>
</tr>
<tr>
<td>2[^b][^c]</td>
<td>TFA</td>
<td>1 mL</td>
<td>11</td>
<td>trace</td>
<td>99.9:0.1</td>
</tr>
<tr>
<td>3</td>
<td>0.1 M H₂SO₄</td>
<td>0.75 mL</td>
<td>92</td>
<td>85</td>
<td>8:92</td>
</tr>
<tr>
<td>4</td>
<td>0.1 M K₂SO₄</td>
<td>0.75 mL</td>
<td>82</td>
<td>29</td>
<td>38:62</td>
</tr>
<tr>
<td>5</td>
<td>0.3 M K₂SO₄</td>
<td>0.75 mL</td>
<td>100</td>
<td>47</td>
<td>0:100</td>
</tr>
<tr>
<td>6</td>
<td>0.5 M K₂SO₄</td>
<td>0.75 mL</td>
<td>99</td>
<td>45</td>
<td>3:97</td>
</tr>
<tr>
<td>7</td>
<td>H₂O</td>
<td>0.75 mL</td>
<td>75</td>
<td>68</td>
<td>27:73</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>95</td>
<td>89</td>
<td>6:94</td>
</tr>
</tbody>
</table>

[^a] Determined by 19F NMR using trifluorotoluene as an internal standard. PhNTf₂ = N-phenyltrifluoromethanesulfonimide, KF = potassium fluoride, DMF = dimethylformamide, MeCN = acetonitrile. DIPEA = N,N-diisopropylethylamine, TFA = trifluoroacetic acid. [^b] Chamber A without DMF as solvent. [^c] 6.0 eq. KF.

B. F⁻ Source and Solvent Screen in Chamber A
Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluormethanesulphonimide (PhNTf₂, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and appropriate F⁻ source. Next, chamber B was charged with 192.0 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). After putting the reactor in a cold water bath, acetonitrile (MeCN, 0.25 M, 4.0 mL), N,N-diisopropylethylamine (DIPEA, 0.52 mL, 3.0 mmol, 3.0 eq.) and trifluorotoluene (99 wt%, 124 μL, 1.0 mmol) as an internal standard were added to chamber B. Finally, the vessel was closed and 1.75 mL solvent was added by injection through the septum in chamber A. The reaction was stirred for 18 hours at room temperature. The reaction mixture was analyzed through ¹⁹F NMR. (Table S2)

Table S2. F⁻ Source and solvent screen in chamber A for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with trifluromethanesulfonyl fluoride gas from PhNTf₂.

<table>
<thead>
<tr>
<th>Entry</th>
<th>F⁻ Source</th>
<th>Amount of F⁻ Source</th>
<th>Solvent in Chamber A</th>
<th>Conversion (%)</th>
<th>Yield[a] (%)</th>
<th>Final Ratio 1a:2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table S1 Entry 8</td>
<td>KF</td>
<td>2.5 eq.</td>
<td>DMF</td>
<td>95</td>
<td>89</td>
<td>6:94</td>
</tr>
<tr>
<td>1</td>
<td>KF</td>
<td>2.5 eq.</td>
<td>Anhydrous DMF</td>
<td>100</td>
<td>91</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>KF</td>
<td>2.5 eq.</td>
<td>Anhydrous MeCN</td>
<td>99</td>
<td>99</td>
<td>1:99</td>
</tr>
<tr>
<td>3</td>
<td>KF (sat.)</td>
<td>0.75 mL</td>
<td>DMF</td>
<td>32</td>
<td>27</td>
<td>72:28</td>
</tr>
<tr>
<td>4</td>
<td>KHF₂ (sat.)</td>
<td>0.75 mL</td>
<td>DMF</td>
<td>92</td>
<td>83</td>
<td>8:92</td>
</tr>
<tr>
<td>5</td>
<td>KHF₂ (sat.)</td>
<td>1.5 mL</td>
<td>None</td>
<td>89</td>
<td>75</td>
<td>12:88</td>
</tr>
<tr>
<td>6</td>
<td>KHF₂</td>
<td>2.5 eq.</td>
<td>MeCN</td>
<td>100</td>
<td>99</td>
<td>0:100</td>
</tr>
<tr>
<td>7</td>
<td>KHF₂</td>
<td>2.5 eq.</td>
<td>MeCN</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
</tbody>
</table>

[a] Determined by ¹⁹F NMR using trifluorotoluene as an internal standard. PhNTf₂ = N-phenyltrifluormethanesulphonimide, KF = potassium fluoride, KHF₂ = potassium bifluoride, DMF = dimethylformamide, MeCN = acetonitrile. DIPEA = N,N-diisopropylethylamine.

C. Amount of PhNTf₂ and KF-HF Optimization in chamber A and Solvent Screen in Chamber B

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with the appropriate amount of N-phenyltrifluormethanesulphonimide (PhNTf₂, 98 wt%) and potassium bifluoride (KHF₂, 99+ wt%). Next, chamber B was charged with 192.0 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). After putting the reactor in a cold water bath, the appropriate solvent, N,N-diisopropylethylamine (DIPEA, 0.52 mL, 3.0 mmol, 3.0 eq.) and trifluorotoluene (99 wt%, 124 μL, 1.0 mmol) as an internal standard were added to chamber B. Finally, the vessel was closed, and acetonitrile (MeCN, 1.75 mL) was added by injection through the septum in chamber A. The reaction was stirred for 18 hours at room temperature. The reaction mixture was analyzed by ¹⁹F NMR. (Table S3)

Table S3. Amount of PhNTf₂ and KF-HF optimization in chamber A and solvent screen in chamber B.
Determined by $^{19}$F NMR using trifluorotoluene as an internal standard. PhNTf$_2$ = N-phenyltrifluoromethanesulfonimide, KHF$_2$ = potassium bifluoride, MeCN = acetonitrile. DIPEA = N,N-diisopropylethylamine.

D. Optimization of the Amount of DIPEA in chamber B and Screening of the Reaction Time

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium bifluoride (KHF$_2$, 99+ wt%, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was charged with 192.0 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). After putting the reactor in a cold water bath, the acetonitrile (MeCN) (3.0 mL), H$_2$O (1.0 mL), appropriate amount of N,N-diisopropylethylamine (DIPEA) and trifluorotoluene (99 wt%, 124 $\mu$L, 1.0 mmol) as an internal standard were added to chamber B. Finally, the vessel was closed, and the acetonitrile (MeCN, 1.75 mL) was added by injection through the septum in chamber A. The reaction was stirred for the appropriate amount of time at room temperature. The reaction mixture was analyzed by $^{19}$F NMR (Table S4).

![Diagram of the reaction process]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of PhNTf$_2$ (Eq.)</th>
<th>Amount of KHF$_2$ (Eq.)</th>
<th>Solvent in Chamber B (mL)</th>
<th>Conversion Rates (%)</th>
<th>Yield$^{[a]}$ (%)</th>
<th>Final Ratio 1a:2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table S2 Entry 7</td>
<td>1.5</td>
<td>2.5</td>
<td>MeCN (4)</td>
<td>100</td>
<td>99</td>
<td>0:100</td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
<td>2.5</td>
<td>MeCN:H$_2$O = 3:1</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>1.3</td>
<td>2.5</td>
<td>MeCN:H$_2$O = 3:1</td>
<td>99</td>
<td>89</td>
<td>1:99</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>2.0</td>
<td>MeCN:H$_2$O = 3:1</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>1.5</td>
<td>MeCN:H$_2$O = 3:1</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>1.0</td>
<td>MeCN:H$_2$O = 3:1</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>0.5</td>
<td>MeCN:H$_2$O = 3:1</td>
<td>85</td>
<td>85</td>
<td>15:85</td>
</tr>
</tbody>
</table>

[a] Determined by $^{19}$F NMR using trifluorotoluene as an internal standard. PhNTf$_2$ = N-phenyltrifluoromethanesulfonimide, KHF$_2$ = potassium bifluoride, MeCN = acetonitrile. DIPEA = N,N-diisopropylethylamine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amount of DIPEA (Eq.)</th>
<th>Reaction Time (h)</th>
<th>Conversion (%)</th>
<th>Yield$^{[a]}$ (%)</th>
<th>Final Ratio 1a:2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table S3 Entry 5</td>
<td>3.0</td>
<td>18</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>18</td>
<td>100</td>
<td>99</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>18</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>18</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>18</td>
<td>87</td>
<td>84</td>
<td>17:83</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>1</td>
<td>29</td>
<td>13</td>
<td>84:16</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>2</td>
<td>91</td>
<td>72</td>
<td>11:89</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>3</td>
<td>100</td>
<td>91</td>
<td>0.5:99.5</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>4</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>5</td>
<td>100</td>
<td>&gt;99</td>
<td>0:100</td>
</tr>
</tbody>
</table>

[a] Determined by $^{19}$F NMR using trifluorotoluene as an internal standard. PhNTf$_2$ = N-phenyltrifluoromethanesulfonimide, KHF$_2$ = potassium bifluoride, MeCN = acetonitrile. DIPEA = N,N-diisopropylethylamine. [b] The reactor was not put in a cold water bath, but was directly exposed in the room temperature at the beginning.
3.2. Triflic Anhydride as Precursor

Small optimization of F Source and Solvent Screen in Chamber A

Chamber A of a flame-dried small two-chamber reactor (Figure S1) was filled with the appropriate F source. Next, chamber B was charged with 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.192 g, 1.0 mmol, 1.0 eq.). After closing the reactor firmly, it was purged with N2 and put in a cold-water bath. Subsequently, acetonitrile (MeCN, 0.25 M, 4.0 mL) and N,N-diisopropylethylamine (DIPEA, 0.26 mL, 1.5 mmol, 1.5 eq.) were added to chamber B. Finally, chamber A was charged with trifluoromethanesulfonic anhydride (Tf2O, 0.25 mL, 1.5 mmol, 1.5 eq.) and the appropriate anhydrous solvent in this particular order by injection through the septum. The reaction was stirred for 16 hours at room temperature. The reaction mixture was analyzed by 19F NMR (Table S5).

Table S5. F Source and solvent screen in chamber A for the triflylation of 4-fluoro-4'-hydroxybiphenyl with trifluoromethanesulfonyl fluoride gas from Tf2O.

<table>
<thead>
<tr>
<th>Entry</th>
<th>F source</th>
<th>Amount of F Source (mmol)</th>
<th>Solvent in chamber A</th>
<th>Amount of solvent in chamber A (mL)</th>
<th>Conversion (%)</th>
<th>Yield [%]</th>
<th>Final Ratio of 1a:2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KF</td>
<td>2.5</td>
<td>TFA</td>
<td>1.0</td>
<td>100</td>
<td>70</td>
<td>0:100</td>
</tr>
<tr>
<td>2</td>
<td>KF</td>
<td>4.0</td>
<td>TFA</td>
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<td>98</td>
<td>1:99</td>
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<tr>
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<td>KHF2</td>
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<td>Anhydrous MeCN</td>
<td>1.75</td>
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[a] Determined by 19F NMR using trifluorotoluene as an internal standard. Tf2O = triflic anhydride, KF = potassium fluoride, KHF2 = potassium bifluoride, MeCN = acetonitrile, DIPEA = N,N-diisopropylethylamine. [b] The solvent in chamber B is altered to a biphasic solvent mixture of MeCN: H2O (3.0 mL: 1.0 mL).

3.3 Optimization study of peptide triflation

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonylimide (PhNTf2, 98 wt%) and potassium bifluoride (KHF2, 99+ wt%) to generate the FSO2CF3 gas. Next, chamber B was charged with L-tyrosine (4 µmol, 1.0 eq). Then the appropriate buffer was added to chamber B. Finally, the vessel was closed and acetonitrile (MeCN, 1.0 mL) was added by injection through the septum in chamber A. The reaction was stirred for several hours at the appropriate temperature. The cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another 5 minutes to ensure that all trifluoromethanesulfonyl fluoride gas was extracted out of the fume hood. (Table S5).

After checking 12 experiments to optimize the conditions, we found that under pH = 9.0, the triflation of L-tyrosine could go up to 93.4 %AUC in the room temperature (table S6, entry 7 & 8). Besides, the improvement of the gas amount to 50 eq. (table S6, entry 11 & 12), the concentration of starting material in Chamber B (table S6, entry 10 &12), temperature to 37 °C (table S6, entry 4, 5 & 6) and longer the reaction time to 24 h, or even to 72 h (table S6, entry 1–6 & 9) cannot make the assay yield improve obviously. Also, changing the pH value to 8.0 and 10.0 could reduce the assay yield (table S6, entry 1, 2 & 3).
Table S6. Optimization study of peptide triflation using L-tyrosine as starting material

<table>
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<tr>
<th>Entry</th>
<th>Gas equivalent in Chamber A (eq.)</th>
<th>pH</th>
<th>Solvent volume in chamber B (mL)</th>
<th>Temperature (℃)</th>
<th>Reaction time (h)</th>
<th>Assay Yield ( %AUC )</th>
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<td>2 (a)</td>
<td>25</td>
<td>4</td>
<td>94.9</td>
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</tbody>
</table>

[a] How to add 4 μmol L-tyrosine in Chamber B: weighed 3.7 mg L-Tyrosine (98 wt%, 20 μmol), and then dissolved in 10 mL MeCN; after sonication, added into chamber B according to the needed of optimization reaction. [b] The equivalent of gas depends on the amount of PhNTf₂, and the ratio of PhNTf₂ and KHF₂ always equals to 1.5:1.0. [c] pH 8.0 → 100 mL 0.025 M Na₂B₄O₇·10H₂O (borax) + 41.0 mL of 0.1 M HCl; pH 9.0 → 100 mL 0.025 M Na₂B₄O₇·10H₂O (borax) + 9.2 mL of 0.1 M HCl; pH 10.0 → 100 mL 0.05 M Na₂B₄O₇·10H₂O (borax) + 41.0 mL of 0.1 M NaOH. [d] The number means the volume of buffer : the volume of MeCN in which the L-Tyrosine was dissolved. [e] Determined by LC-MS, "%AUC" = area under curve. KHF₂ = potassium bifluoride, MeCN = acetonitrile. [f] The duplicated reaction of entry 7. [g] weighed 3.7 mg L-Tyrosine (98 wt%, 20 μmol), and then dissolved in 5 mL MeCN and 5 mL 9.0 pH buffer; after sonication, added into chamber B the mixture 2 mL in total.
4. General Procedure

4.1. General Procedures of Synthesize the Triflates

4.1.1. General procedure A (Synthesis aryl triflates from N-phenyltrifluoromethanesulfonimide)

Chamber A - Gas generation
PhNTf₂ (1.5 eq.)
KHF₂ (1.0 eq.)
MeCN (1.75 mL)

Chamber B - Transformation
DIPEA (1.5 eq.)
MeCN:H₂O (3:1)

(1.0 mmol)  R

Scheme S1. Synthesis of aryl trifluoromethanesulfonates via ex situ generated trifluoromethanesulfonyl fluoride gas in a two-chamber reactor.

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium bifluoride (KHF₂, 99+ wt%, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was charged with phenol (1.0 mmol, 1.0 eq.). Then the acetonitrile (MeCN, 3.0 mL), H₂O (1.0 mL), trifluorotoluene (99 wt%, 0.25 mL, 1.0 mmol) as an internal standard and N,N-diisopropylethylamine (DIPEA, 0.26 mL, 1.5 mmol, 1.5 eq.) were added to chamber B. Finally, the vessel was closed and acetonitrile (MeCN, 1.75 mL) was added by injection through the septum in chamber A (Scheme S1). The reaction was monitored by ¹⁹F NMR. The cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another 5 minutes to ensure that all trifluoromethanesulfonyl fluoride gas was extracted out of the fume hood. The content of chamber B was transferred to a 100 mL separatory funnel. Chamber B was rinsed five times with 5 mL of ethyl acetate (EtOAc); the fractions were collected in the same funnel. The mixture was washed with saturated NH₄Cl (3 x 50 mL). Then the water phase was re-extracted by EtOAc (2 x 10 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na₂SO₄ and then concentrated in vacuo to give the crude product. Further purification is reported in the respective experimental data.

Caution!

1) After reaction, chamber A was quenched with NaOH (1M) to neutralize trifluoroacetic acid and the in situ formed HF. The alkaline solution was discarded in basic waste. Etching of the glassware of Chamber A was seen after multiple experiments.

2) The maximally allowed pressure in the two-chamber vessel is 5 bar. In order not to exceed this pressure in the small 20-mL two-chamber vessel, the amount of generated gas should be calculated based on the rest inner volume of reactor (20 mL total minus the volume of solvent) at room temperature before setting up the experiment.

4.1.2. General procedure B (Synthesis aryl triflates from trifluoromethanesulfonic anhydride)

Chamber A of a small flame-dried two-chamber reactor (Figure S1) was charged with potassium bifluoride (KHF₂, 99+ wt%, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was filled with phenol (1.0 mmol, 1.0 eq.). The two-chamber reactor was closed and was purged 3x with Argon. Disopropylethylamine (DIPEA, 0.26 mL, 1.5 mmol, 1.5 eq.), acetonitrile (CH₃CN, 3.0 mL) and water (H₂O, 1.0 mL) were added to chamber B. Trifluoromethanesulfonic anhydride (Tf₂O, 0.25 mL, 1.5 mmol, 1.5 eq.) was added to chamber A. The reaction was stirred, for 5 min in a cold- water bath and subsequent at room temperature for about 18 hours (Scheme S1). The reaction was monitored with TLC and ¹⁹F NMR. After completion, the cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another 10 minutes to ensure that all trifluoromethanesulfonyl fluoride gas is extracted out of the fume hood. The content of chamber B was transferred to a 250 mL separatory funnel. Chamber B was rinsed five times with 3 mL of ethyl acetate (EtOAc); the fractions were collected in the same funnel. The mixture was washed with saturated NH₄Cl (3 x 50 mL). Then the water phase was re-extracted by EtOAc (2 x 10 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the crude product. Further purification is reported in the respective experimental data.

4.1.3. General procedures C, D and E of Benchmark methods (Parallel Experiments Between Published Methods)
**General procedure C: Aryl triflates were prepared using the triflic anhydride**

Under argon, phenol (1.0 mmol, 1.0 eq.), anhydrous dichloromethane (2.0 mL) and analytical grade triethylamine (99 wt%, 0.28 mL, 2.0 mmol, 2.0 eq.) were added successively into a 25-mL Schlenk flask containing a magnetic stirring bar. After the solution was chilled to 0 °C in an ice/water bath, triflic anhydride (99 wt%, 0.2 mL, 1.2 mmol, 1.2 eq.) was added dropwise over 2 minutes. The resulting mixture was slowly warmed up to room temperature and kept stirring for 18 hours. At the end of the reaction (monitored by $^{19}$F NMR), the mixture was concentrated on a rotary evaporator under reduced pressure and the residue was directly subjected to flash chromatography to afford the desired aryl triflates. This procedure is set up on the reference[3].

**General procedure D: Aryl triflates were prepared using the triflic anhydride under aqueous conditions**

Reactions conducted at 0 °C with slow addition of Tf$_2$O (99 wt%, 0.2 mL, 1.2 mmol, 1.2 eq.) to a toluene (2.1 mL)/30% (w/v) aqueous K$_3$PO$_4$ (2.1 mL, 3.0 mmol, 3.0 eq.) biphasic mixture of phenol (1.0 mmol, 1.0 eq.) followed by warming to room temperature for 30 min. At the end of the reaction (monitored by $^{19}$F NMR), the content of 25-mL round bottle was transferred to a 100 mL separatory funnel and the bottle was rinsed five times with 5 mL of methyl tert-butyl ether (MTBE); the fractions were collected in the same funnel. The mixture was washed with saturated NH$_4$Cl (1 x 20 mL). Then the water phase was re-extracted by MTBE (2 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over anhydrous Na$_2$SO$_4$ and then concentrated in vacuo to give the crude product. Further purification is reported in the respective experimental data. This procedure is according to the reference[4].

**General procedure E: Aryl triflates could be synthesized adding the N-phenyltrifluoromethanesulfonimide (PhNTf$_2$) directly**

Phenol (1 mmol, 1.0 eq.), N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.), DMAP (99 wt%, 12.3 mg, 0.1 mmol, 0.1 eq.) were added to a flame-dried round bottomed flask. The flask was purged with nitrogen. DCM (2 mL, 0.5 M) and Et$_3$N (99 wt%, 0.28 mL, 2.0 mmol, 2.0 eq.) were added successively into a 25-mL Schlenk flask containing a magnetic stirring bar. After the solution was chilled to 0 °C in an ice/water bath, triflic anhydride (99 wt%, 0.2 mL, 1.2 mmol, 1.2 eq.) was added dropwise over 2 minutes. The resulting mixture was stirred at room temperature for 3 h. At the end of the reaction (monitored by $^{19}$F NMR), volatiles were removed under reduced pressure and concentrated in vacuo to afford the crude material, which was purified by flash chromatography to afford the desired aryl triflate. This procedure is based on the reference[5].

### 4.1.4. General Procedure F of Peptide Substrates Triflates Synthesis

![Scheme S3. Synthesis of Peptide Substrates Triflates via optimized conditions](image)

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with 36.5 mg N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 100 μmol, 25.0 eq.) and 5.3 mg potassium bifluoride (KHF$_2$, 99+ wt%, 66.7 μmol, 16.7 eq.) to generate the FSO$_2$CF$_3$ gas. Next, chamber B was charged with the solution of L-lysine or peptide (4 μmol, 1.0 eq) dissolved in MeCN: pH 9.0 borax buffer (2 mL:2 mL). Finally, the vessel was closed and acetonitrile (MeCN, 1.0 mL) was added by injection through the septum in chamber A. The reaction was stirred for 4 hours at the room temperature. The cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another 5 minutes to ensure that all trifluoromethanesulfonyl fluoride gas was extracted out of the fume hood. Then the solvent in Chamber B was taken to be checked the assay yield via LC-MS (Scheme S3).

### 4.2. General Procedure G of Analysis of Allowed Solvent-Base Combinations

- **Stock solutions:** in 40 mL of solvent, 2-bromophenol (1.730 g, 10 mmol, 0.25 M) and dibenzyl ether as the internal standard (2.203 g, 10 mmol, 0.25 M) were dissolved.
- **Solvents selected (6 total):** MeCN, DMF, DMSO, toluene, THF, 1,4-dioxane
- **Bases selected (7 total):** DIPEA, TMG, DBU, K$_2$CO$_3$, KHCO$_3$, K$_3$PO$_4$, NaO$t$Bu
- **Experiment:** 4 mL of stock solution, along with 1.5 mmol of the designated base, was brought in the chamber B of a 20 mL two-chamber reactor, Chamber A was charged with PhNTf$_2$ (547 mg, 1.5 mmol) and KFHF (79 mg, 1.0 mmol). Lastly, MeCN (1.75 mL) was added to chamber A and the vessel was quickly closed while stirring at room temperature.
- **Sampling:** After 4 h and 22 h, an aliquot of ±100 μL was taken from chamber B with a needle (without opening the vessel). This was partitioned between 200 μL of water and 1.5 mL of MTBE in a 2 mL sample vial, which was submitted for GC-MS measurement.
- **Calibration:** The starting material (2-bromophenol), the product (2-bromophenyl triflate) and the internal standard (dibenzyl ether) were dissolved in MTBE in a 1:1:1 molar ratio, and a sample of this solution was submitted to GC-MS. The calibration was carried out in...
duplicate, and integration of the AUC gave a response factor (RF) of 0.452 of SM relative to IS, and 0.888 of P relative to IS. These corrections were further used for quantification of remaining starting material (RSM) and product yield. (Table S7)

\[
RSM = \frac{AUC_{SM}}{AUC_{IS} \times RF_{SM}} \quad \text{yield}_P = \frac{AUC_P}{AUC_{IS} \times RF_P}
\]

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(n.d. = not determined)

4.3. General Procedure H of ‘One Pot Two Steps’ Suzuki Cross Coupling via Aryl Trifluoromethanesulfonate

Scheme S4. General procedures of ‘one pot two steps’ Suzuki cross coupling via aryl trifluoromethanesulfonate.

Step 1:
Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf2, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium bifluoride (KF, 99+ wt%, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was charged with phenol (1.0 mmol, 1.0 eq.). Then 207.4 mg potassium carbonate (K2CO3, 99.9 wt%, 1.5 mmol, 1.5 eq.) and anhydrous tetrahydrofuran (THF, 3.0 mL, 0.33 M) were added into chamber B. Finally, the vessel was closed and anhydrous dimethylformamide (DMF, 1.75 mL, 0.86 M) was added by injection through the septum in chamber A and instant gas formation was observed. The reaction was monitored by TLC. The cap on chamber B, which kept closed until the step 2 finished, was carefully removed to release the residual pressure. The reaction was stirred for another 5 minutes to ensure that all trifluoromethanesulfonyl fluoride gas was extracted out of the fume hood.

Step 2:
According to the literature\[5\], step 2 was followed. A 10 mL single chamber tube C (Error! Reference source not found.) was charged with boronic acid 3 (1.1 mmol, 1.1 eq.), palladium(II) acetate (Pd(OAc)\(_2\), 98+ wt%, 2.3 mg, 0.01 mmol, 0.01 eq.), tricyclohexylphosphine (PCy\(_3\), 97 wt%, 3.5 mg, 0.012 mmol, 0.012 eq.) and potassium fluoride (KF, 99.9 wt%, 203.5 mg, 3.5 mmol, 3.5 eq.). Then the vessel was closed. After changing the air in tube C into nitrogen using Schlenk system three times, the content of chamber B was transferred to a 100 mL separatory funnel. Tube C was rinsed five times with 5 mL of methyl tert-butyl ether (MTBE); the fractions were collected in the same funnel. The mixture was washed with 1M HCl (20 mL). Then the combined water phase was re-extracted by MTBE (2 x 10 mL). The combined organic layers were washed with brine (1 x 20 mL), dried over anhydrous Na\(_2\)SO\(_4\) and then concentrated in vacuo to give the crude product. Further purification and the amount of some reagents mentioned above is reported in the respective experimental data.

Caution!

1) Choose 0.90 x 70 mm BL/LB needle to transfer the mixture from Chamber B into tube C; otherwise, the base has chance to block the needle.

2) When the mixture in Chamber B was suck out using the injector, keep stirring the magneton in case the base in Chamber B would sink in the bottom, which would cause the transfer procedure hardly.

4.4. General Procedure I of ’One Pot One Step’ Amide Synthesis via Acyl Fluoride Intermediate

Chamber A of a 20 mL oven-dried two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf\(_2\), 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium bifluoride (KHF\(_2\), 99+ wt%, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was charged with carboxylic acid 5 (1.0 mmol, 1.0 eq.) and amine 6 (2.0 mmol, 2.0 eq.). Then the anhydrous acetonitrile (anhydrous MeCN, 3.0 mL) and N,N-diisopropylethylamine (DIPEA, 0.52 mL, 3.0 mmol, 3.0 eq.) were added to chamber B. Finally, the vessel was closed and anhydrous acetonitrile (anhydrous MeCN, 1.75 mL, 0.86 M) was added by injection through the septum in chamber A (Scheme S5). The reaction was monitored by TLC. The cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another 5 minutes to ensure that all trifluoromethanesulfonyl fluoride gas was extracted out of the fume hood. The content of chamber B was transferred to a 100 mL separatory funnel. Chamber B was rinsed five times with 5 mL of ethyl acetate (EtOAc); the fractions were collected in the same funnel. The mixture was washed sequentially with NaHCO\(_3\) (sat.) (1 x 20 mL), 1.0 M HCl (1 x 20 mL) and brine (1 x 20 mL). The organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and then concentrated in vacuo to give the crude product. Further purification is reported in the respective experimental data.

This procedure is modified from the reference\[6\].

4.5. General Procedure J of Triflimidates Synthesis

4.5.1. General Procedure J1 of the Trifluoromethanesulfinamides Synthesis (First Step of Synthesize the Triflimidates)

All of the trifluoromethanesulfinamides have been prepared by the following procedure. To a solution of 1.971 g (12 mmol) of sodium trifluoromethanesulfinate (95 wt%, 1.971 g, 12 mmol, 2.0 eq.) in 12 mL of ethyl acetate was added at room temperature 0.555 mL of phosphoryl chloride (99 wt%, 6.0 mmol, 1.0 eq.) and 6 mmol of amine (1.0 eq.) was added dropwise and the reaction mixture was stirred for an additional 30 mins at room temperature. The reaction mixture was then washed with brine (20 mL) and extracted with ethyl acetate (20 mL). The combined ethyl acetate fractions were dried over Na\(_2\)SO\(_4\) and...
concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the desired product (Scheme S6).

This procedure is modified from the reference\cite{7}.

**Caution!** The trifluoromethanesulfinamides are not stable under Air. Need to seal trifluoromethanesulfinamides under N\textsubscript{2} flush and then put it in the fridge (\(< 4\, ^\circ \text{C}\)) for longer storage.

### 4.5.2. General Procedure J2 of the Sulfonimidoyl Fluoride Synthesis (Second Step of Synthesize the Triflimidates)

![Scheme S7](image)

To a stirred solution of sulfinamide (3.0 mmol) and NCS (98 wt\%, 450 mg, 3.3 mmol, 1.1 eq.) in MeCN (15 mL) was added TBAF (1 M in THF, 3.3 mL, 3.3 mmol, 1.1 eq.) in a round-bottomed flask at 0 °C. The reaction mixture was allowed to be warmed to room temperature over 30 mins. Then the reaction mixture was concentrated to dryness in vacuo. Further purification is reported in the respective experimental data (Scheme S7).

This procedure is modified from the reference\cite{8}.

**Caution!** The Sulfonimidoyl Fluoride are not stable under room temperature. Need to put it in the fridge (\(<4\, ^\circ \text{C}\)) for longer storage.

### 4.5.3. General Procedure J3 of the Triflimidates Synthesis

![Scheme S8](image)

A 10 mL small glass tube was filled with sulfonimidoyl fluoride (0.2 mmol, 1.0 eq.) and phenol (0.3 mmol, 1.5 eq.). Then the acetonitrile (MeCN, 0.6 mL), H\textsubscript{2}O (0.2 mL), trifluorotoluene (99 wt\%, 25 \(\mu\text{L}, 1.0\) mmol) as an internal standard and \(N,N\)-diisopropylethylamine (DIPEA, 99 wt\%, 53 \(\mu\text{L}, 0.3\) mmol, 1.5 eq.) as base were followed. Finally, the vessel was closed, and the reaction was monitored by \(^{19}\text{F}\) NMR. The content of glass tube was transferred to a baker with anhydrous Na\textsubscript{2}SO\textsubscript{4} to dried over directly without extraction to give the crude product. Further purification is reported in the respective experimental data (Scheme S8).

### 4.6. General Procedure K of Triflamides Synthesis

![Scheme S9](image)

Chamber A of a small two-chamber reactor (Figure S1) was charged with \(N\)-phenyltrifluoromethanesulfonimide (PhNTf\textsubscript{2}, 98 wt\%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium bifluoride (KHF\textsubscript{2}, 99+% wt, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was filled with amine derivative (1.0 mmol, 1.0 eq.) and 4-dimethylaminopyridine (DMAP, 99+% wt, 53 \(\mu\text{L}, 0.3\) mmol, 1.5 eq.) as base were followed. The two-chamber reactor was closed, and the reaction was monitored by \(^{19}\text{F}\) NMR. After completion, the cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another
10 minutes to ensure that all trifluoromethanesulfonyl fluoride gas is extracted out of the fume hood. The content of chamber B was transferred to a 250 mL separatory funnel. Chamber B was rinsed five times with 3 mL of ethyl acetate (EtOAc); the fractions were collected in the same funnel. The mixture was extracted with HCl 1M (3 x 25 mL). The combined organic fractions were washed with brine (2 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to give the crude product. Further purification is reported in the respective experimental data.

4.7. Procedure L of Triflate (4-Bromophenyl Trifluoromethanesulfonate) Gram-scale Synthesis

Scheme S10. Gram-scale synthesis of aryl trifluoromethanesulfonates via ex situ generated trifluoromethanesulfonyl fluoride gas in a large two chamber reactor.

**Figure S2.** a) Large two-chamber reactor. (Inner volume = 400 mL. Invented by the Skrydstrup group.); b) gram-scale reaction photo; c) the crude product after extraction.

Chamber A (left chamber) of a 400 mL large two-chamber reactor (Figure S1 S2, a) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 3.129 g, 8.583 mmol, 1.5 eq.) and potassium bifluoride (KHF$_2$, 99+ wt%, 0.451 g, 5.722 mmol, 1.0 eq.). Next, chamber B was charged with 1.0 g 4-bromophenol (5.722 mmol, 1.0 eq.). Then the acetonitrile (MeCN, 17.0 mL), H$_2$O (5.7 mL), trifluorotoluene (99 wt%, 0.071 mL, 0.1 mmol) as an internal standard and N,N-diisopropylethylamine (DIPEA, 1.5 mL, 8.583 mmol, 1.5 eq.) were added to chamber B. Finally, the vessel was closed, and acetonitrile (MeCN, 10.0 mL) was added by injection through the septum in chamber A (Scheme S10). The reaction was monitored by $^{19}$F NMR. The cap on chamber B was carefully removed to release the residual pressure. The reaction was stirred for another 10 minutes to ensure that all trifluoromethanesulfonyl fluoride gas was extracted out of the fume hood. The content of chamber B was transferred to a 250 mL separatory funnel. Chamber B was rinsed five times with 30 mL of ethyl acetate (EtOAc); the fractions were collected in the same funnel. The mixture was washed with saturated NH$_4$Cl (1 x 50 mL), water (1 x 50 mL) and then brine (1 x 50 mL), dried over anhydrous Na$_2$SO$_4$ and then concentrated in vacuo to give the crude product. Caution!

For the large two-chamber vessel, the amount of generated gas was limited to 50 mmol at room temperature. This was calculated based on an inner volume of 300 mL (400 mL total minus 100 mL solvent). Pressure measurements revealed that the internal pressure never exceeded 2.8 bar when the general procedure was followed (vide infra).

4.8. Procedure M of Triflimidate (Phenyl Trifluoro-N-(4-nitrophenyl)methanesulfonimide) Large-scale Synthesis
Scheme S11. Procedure M of the Triflimidates (Phenyl Trifluoro-N-(4-nitrophenyl)methanesulfonimidate) Large-scale Synthesis

A 25 mL round-bottom flask was filled with 544.9 mg sulfonimidoyl fluoride S5 (2.0 mmol, 1.0 eq.) and phenol (99.0 wt%, 285.2 mg, 3.0 mmol, 1.5 eq.). Then the acetonitrile (MeCN, 6.0 mL), H₂O (2.0 mL), trifluorotoluene (99 wt%, 248 μL, 1.0 mmol) as an internal standard and N,N-diisopropylethylamine (DIPEA, 99 wt%, 0.53 mL, 3.0 mmol, 1.5 eq.) as base were followed. Finally, the flask was closed, and the reaction was monitored by ¹⁹F NMR. After 1h, the flask was rinsed three times with 20 mL of dichloromethane (DCM); the fractions were collected in the same funnel. The mixture was washed with water (1 x 20 mL) and brine (1 x 20 mL), dried over anhydrous Na₂SO₄ and then concentrated in vacuo to give the crude product.
5. Additional experiments with bis-nucleophilies

5.1. Stability test of catechol ditriflate (compound 15, cas number: 17763-91-6)

Knowing the $^19F$ NMR chemical shift of catechol ditriflate 15 is -73.6269 ppm; after long time (3 months) storage under N$_2$ atmosphere and room temperature, the 15 was still pure and the $^19F$ NMR showed the peak was -73.6229 ppm.

**Conclusion:** the catechol ditriflate could be stable in the N$_2$ atmosphere and room temperature for a long time; but is capable of transferring the [SO$_2$CF$_3$] group to other nucleophiles such as water or other phenols.

5.2. Stoichiometry test of 1-(4-hydroxyphenyl)-piperazine triflation

5.2.1. 2.5 Equivalent of CF$_3$SO$_2$F Gas Condition to Confirm about the Chemoselectivity:

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 911.3 mg, 2.5 mmol, 2.5 eq.) and potassium bifluoride (KHF$_2$, 99+ wt%, 131.7 mg, 1.67 mmol, 1.67 eq.). Next, chamber B was charged with 221.3 mg of 1-(4-hydroxyphenyl)-piperazine (97 wt%, 1.0 mmol, 1.0 eq.) . Then the acetonitrile (MeCN, 3.0 mL), H$_2$O (1.0 mL), trifluorotoluene (99 wt%, 124 μL, 1.0 mmol) as an internal standard and triethylamine (TEA, 0.35 mL, 2.5 mmol, 2.5 eq.) were added to chamber B. Finally, the vessel was closed and acetonitrile (MeCN, 1.75 mL) was added by injection through the septum in chamber A (Scheme S1). The reaction was monitored by $^19F$ NMR.

After 48 hours, the $^19F$ NMR showed the yield of monotriflation product was >99%. Most importantly, there was no N-nucleophile would undergo triflation.

**Conclusion:** when there was water in the system, even we used higher amount of CF$_3$SO$_2$F gas (2.5 eq.), the N-nucleophile would not undergo triflation.

5.2.2. 1.0 Equivalent of CF$_3$SO$_2$F Gas condition to test the reactivity difference of phenols and amine groups:
Conclusion: Comparing the reactivity difference of phenols and amine groups, the results showed whatever the base we used, under only 1.0 equivalent of FSOF3CF3 and anhydrous conditions, the phenols always behaved more reactively than the amine groups after 30 hours.

5.3. Hydrolytic stability test of 1-(4-hydroxyphenyl)-piperazine ditriflate (compound 60)

\[ \text{DIPEA (2.5 eq)} \rightarrow \text{in MeOD} \quad ^{19}\text{F NMR:} \\
\text{dry MeCN (0.5 mL)} \\
\text{H2O (0.15 mL)} \\
\text{PhCF3 (0.1 mmol)} \\
\text{48 h} \\
\]

-73.1783, -75.5426 ppm (MeOD, ^{19}\text{F NMR})

Conclusion: after 48h, the 1-(4-hydroxyphenyl)-piperazine ditriflate was still not hydrolyzed under the same condition of synthesizing 1-(4-hydroxyphenyl)-piperazine monotriflate; which means, there was no possibility that we got ditriflate first and then in situ it was hydrolyzed to monotriflate.

5.4. Hydrolytic stability test of indole ditriflate (compound 70)

\[ \text{DIPEA (2.5 eq)} \rightarrow -72.9847(1.13), -75.5051(1.15) \\
\text{dry MeCN (0.5 mL)} \\
\text{H2O (0.15 mL)} \\
\text{PhCF3 (0.1 mmol)} \\
\text{48 h} \\
\]

-73.0219, -75.5304 ppm (MeOD, ^{19}\text{F NMR})

Conclusion: Seems around 9% indole ditriflate hydrolyzed into monotriflate after 48 h. which means, when we synthesized the monotriflate, it is unlikely that synthesizing the ditriflate first and then in situ totally hydrolyzed into monotriflate in 18 h.
6. Experimental studies of Piperidine to complement the in silico findings

Paper Figure 1B, Entry 1

\[ \text{HN} \quad \text{1.5 eq. gas} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-62.84 (-75.74) (1.0; PhCF)_3 (0.57; product)

Paper figure 1B, Entry 2 (Blank control experiment)

\[ \text{HN} \quad \text{1.0 eq.} \quad \text{1.5 eq.} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-61.85 (-75.70) (1.0; PhCF)_3 (1.07; product)

Paper Figure 1B, Entry 3

\[ \text{HN} \quad \text{1.0 eq.} \quad \text{1.5 eq.} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-62.95 (-75.97) (1.0; PhCF)_3 (1.07; product)

Paper Figure 1B, Entry 4

\[ \text{HN} \quad \text{1.0 eq. gas} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-62.82 (-75.72) (1.0; PhCF)_3 (0.82; product)

Paper Figure 1B, Entry 5

\[ \text{HN} \quad \text{1.0 eq.} \quad \text{1.5 eq.} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-63.17 (1.0) -75.76 (1.01)

Paper Figure 1B, Entry 6

\[ \text{HN} \quad \text{1.0 eq. gas} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-63.16 (1.0) -75.76 (0.46)

Paper Figure 1B, Entry 7

\[ \text{HN} \quad \text{1.0 eq.} \quad \text{1.5 eq.} \quad \text{O} \quad \text{N} \quad \text{PhCF}_3 \quad \text{18 h} \]

-63.17 (1.0) -75.76 (0.02)
7. Experimental Data

7.1. Experimental Data of Synthesized Aryl Triflates (precursor PhNTf₂)

4'-fluoro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (compound 1, cas number: 2377919-62-3)

General procedure A was followed using 192.0 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 4 hours (>99% yield determined by ¹⁹F NMR). The extraction yield is 97%. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.40, n-heptane/ethyl acetate = 200/1). The title compound was obtained as colorless oil (272.2 mg, 85%).

¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, J = 8.4 Hz, 2H), 7.48–7.44 (m, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.10 (t, J = 8.3 Hz, 2H) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 162.89 (d, ¹JCF = 248.7 Hz), 148.93, 140.64, 135.38, 128.77 (d, ³JCF = 8.2 Hz) 128.66, 121.65, 118.84 (q, ⁵JCF = 322.0 Hz), 115.86 (d, ⁷JCF = 21.7 Hz) ppm.

¹⁹F NMR (377 MHz, CDCl₃): δ -73.30 (d, ¹²JFF = 2.1 Hz, 3F), -114.81 (s, F) ppm. These data are in agreement with literature data [9].

4-bromophenyl trifluoromethanesulfonate (compound 2, cas number: 66107-30-0)

Chemical Formula: C₇H₄BrF₃O₃S

Exact Mass: 303.9017

General procedure A was followed using 192.0 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 4 hours (>99% yield determined by ¹⁹F NMR). The title compound was obtained after extraction as yellowish oil (292.9 mg, 96%).

¹H NMR (400 MHz, CDCl₃): δ 7.56 (dt, J = 9.8, 2.8 Hz, 2H), 7.15 (dt, J = 9.7, 2.7 Hz, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 148.45, 133.34, 123.00, 118.67 (q, ¹JCF = 321.9 Hz) ppm. ¹⁹F NMR (377 MHz, CDCl₃): δ -73.30 (d, ¹JFF = 2.1 Hz, 3F) ppm. Spectral data are consistent with those previously reported [10].

Gram-scale reaction: procedure L was followed using 1.0 g of 4-bromophenol (99 wt%, 5.722 mmol, 1.0 eq.). The reaction was stirred at room temperature for 4 hours (97% yield determined by ¹⁹F NMR). The title compound was obtained after extraction as yellowish oil (1.2998 g, 75%).

4-methoxyphenyl trifluoromethanesulfonate (compound 3, cas number: 66107-29-7)

Chemical Formula: C₈H₇F₃O₃S

Exact Mass: 256.0017

General procedure A was followed using 125.4 mg of 4-methoxyphenol (99 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by ¹⁹F NMR). The extraction yield is 84%. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.35, n-heptane/ethyl acetate = 19/1). The title compound was obtained as yellowish oil (192.3 mg, 75%).

¹H NMR (400 MHz, CDCl₃): δ 7.18 (dt, J = 10.3, 3.1 Hz, 2H), 6.90 (dt, J = 10.3, 3.1 Hz, 2H), 3.78 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 159.13, 143.02, 122.26, 118.78 (q, ¹JCF = 322.0 Hz), 114.97, 55.50 ppm. ¹⁹F NMR (377 MHz, CDCl₃): δ -73.28 (s, 3F) ppm. These data are in agreement with literature data [11].

4-(3-oxobutyl)phenyl trifluoromethanesulfonate (compound 4, cas number: 261157-51-1)
General procedure A was followed using 165.9 mg of 4-(4-hydroxyphenyl)-2-butanone (raspberry ketone, 99+ wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The extraction yield is 98%. The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.4$, DCM). The title compound was obtained as yellowish oil (229.9 mg, 78%).

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.29–7.25 (m, 2H), 7.17 (dt, $J = 8.9, 2.4$ Hz, 2H), 2.92 (t, $J = 7.4$ Hz, 2H), 2.14 (s, 3H) ppm.

**$^{13}$C NMR** (101 MHz, CDCl$_3$): $\delta$ 206.95, 147.82, 141.69, 130.04, 121.12, 118.63 (q, $^1J_{CF} = 322.0$ Hz), 44.45, 29.82, 28.70 ppm.

**$^{19}$F NMR** (377 MHz, CDCl$_3$): $\delta$ -73.40 (s, 3F) ppm. These data are in agreement with literature data[12].

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate (compound 5, cas number: 1027059-48-8)

General procedure A in which changing the solvent in two chambers into anhydrous MeCN was followed using 144.3 mg of 4-hydroxyphenylboronic acid (97 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). The reaction was stirred at room temperature for 12 hours (86% yield determined by $^{19}$F NMR). The crude reaction mixture was evaporated directly and then was transferred into a 25 mL round bottle and reacted with 143.23 mg of pinacol (99 wt%, 1.2 mmol, 1.2 eq.) in 10 mL DCM for 12 hours. The crude reaction mixture purified by short column chromatography on silica gel ($R_f = 0.50$, n-heptane/ethyl acetate = 9/1). The title compound was obtained as white crystal (271.1 mg, 77%). Melting point = 88.0–89.5 °C. **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.90 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 1.34 (s, 12H) ppm. **$^{13}$C NMR** (101 MHz, CDCl$_3$): $\delta$ 151.80, 136.87, 123.52, 120.53, 118.74 (q, $^1J_{CF} = 321.8$ Hz), 84.29, 24.78 ppm. **$^{19}$F NMR** (377 MHz, CDCl$_3$): $\delta$ -63.40 (s, 3F, CF$_3$), -73.19 (s, 3F, OTf) ppm. These data are in agreement with literature data[13].

3-(trifluoromethyl)phenyl trifluoromethanesulfonate (compound 6, cas number: 199188-30-2)

General procedure A was followed using 165.4 mg of 3-(trifluoromethyl)phenol (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 1.5 hours (>99% yield determined by $^{19}$F NMR). The title compound was obtained after extraction and low pressure vacuuming as yellowish oil (261.8 mg, 89%).

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.67 (d, $J = 7.8$ Hz, 1H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.55 (s, 1H), 7.50–7.48 (m, 1H) ppm. **$^{13}$C NMR** (101 MHz, CDCl$_3$): $\delta$ 149.47, 133.11 (q, $^3J_{CF} = 34.0$ Hz), 131.12, 125.34 (q, $^1J_{CF} = 3.7$ Hz), 124.96, 122.95 (q, $^3J_{CF} = 273.6$ Hz), 118.82 (q, $^3J_{CF} = 3.9$ Hz), 118.80 (q, $^1J_{CF} = 321.7$ Hz) ppm. **$^{19}$F NMR** (377 MHz, CDCl$_3$): $\delta$ -63.40 (s, 3F, CF$_3$), -73.19 (s, 3F, OTF) ppm. These data are in agreement with literature data[13].

3-(((trifluoromethyl)sulfonyl)oxy)benzoic acid (compound 7, cas number: 32578-33-9)

General procedure A was followed using 138.1 mg of 3-Hydroxybenzoic Acid (99 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (99+% yield determined by $^{19}$F NMR). The title compound was obtained after extraction and vacuuming.
as white solid (257.3 mg, 95%). Melting point = 92.5–93.5 °C. 1H NMR (400 MHz, DMSO-d6): δ 13.59 (br s, 1H), 8.08 (dt, J = 7.6, 1.3 Hz, 1H), 7.93–7.92 (m, 1H), 7.82–7.79 (m, 1H), 7.74 (t, J = 8.0, 1H) ppm. 13C NMR (101 MHz, DMSO-d6): δ 165.61, 149.11, 133.54, 131.34 129.69, 125.89, 121.79, 118.25 (q, J = 321.2 Hz) ppm. 19F NMR (377 MHz, DMSO-d6): δ -72.29 (s, 3H) ppm. IR (neat) v = 2954, 1686, 1414, 1214 cm⁻¹. HRMS (ESI): Calcd for C₈H₄F₃O₅S [M-H]-: 268.9737, found: 268.9827.

2-bromophenyl trifluoromethanesulfonate (compound 8, cas number: 129112-25-0)

General procedure A was followed using 176.5 mg of 2-bromophenol (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 4 hours (>99% yield determined by 19F NMR). The title compound was obtained after extraction as yellowish oil (280.7 mg, 92%).

4-formyl-2-methoxyphenyl trifluoromethanesulfonate ((Vanillin Triflate, compound 9, cas number: 194018-68-3)

General procedure A was followed using 153.7 mg of vanillin (99 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 12 hours (>99% yield determined by 19F NMR). The extraction yield is 98%. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.40, n-heptane/ethyl acetate = 6/1). The title compound was obtained as colorless oil (222.2 mg, 78%). 1H NMR (400 MHz, CDCl3): δ 9.99 (s, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.52 (dd, J = 8.2, 1.8 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 4.00 (s, 3H) ppm. 13C NMR (101 MHz, CDCl3): δ 190.29, 152.17, 142.65, 136.76, 123.98, 123.14, 118.63 ppm. 19F NMR (377 MHz, CDCl3): δ -73.87 (s, 3F) ppm. These data are in agreement with literature data.

4-allyl-2-methoxyphenyl trifluoromethanesulfonate (compound 10, cas number: 1073426-46-6)

General procedure A was followed using 167.6 mg of eugenol (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 22 hours (93% yield determined by 19F NMR). The extraction yield is 88%. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.40, n-heptane/ethyl acetate = 15/1). The title compound was obtained as yellowish oil (211.2 mg, 72%). 1H NMR (400 MHz, CDCl3): δ 7.12 (d, J = 8.2 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.79 (dd, J = 8.3, 1.9 Hz, 1H), 5.30–5.89 (m, 1H), 5.14 (t, J = 1.3 Hz, 1H), 5.11–5.09 (m, 1H), 3.89 (s, 3H), 3.40 (s, 1H), 3.38 (s, 1H) ppm. 13C NMR (101 MHz, CDCl3): δ 151.16, 141.78, 137.09, 136.25, 122.12, 120.77, 118.74 ppm. 19F NMR (377 MHz, CDCl3): δ -74.42 (s, 3F) ppm. These data are in agreement with literature data.

3,5-dimethylphenyl trifluoromethanesulfonate (compound 11, cas number: 219667-41-1)
General procedure A was followed using 123.4 mg of 3,5-dimethylphenol (99+ wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The extraction yield is 87%. The crude reaction mixture was purified by column chromatography on silica gel ($R_{f} = 0.5$, n-heptane/ethyl acetate = 25/1). The title compound was obtained as yellowish oil (203.1 mg, 80%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.98 (s, 1H), 6.87 (s, 2H), 2.32 (s, 6H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 149.54, 140.41, 129.95, 118.78 ($q$, $J_{CF} = 321.7$ Hz), 118.67, 21.00 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.57 (s, 3F) ppm. These data are in agreement with literature data.[16]

2,6-dimethylphenyl trifluoromethanesulfonate (compound 12, cas number: 86364-02-5)

General procedure A was followed using 123.4 mg of 2,6-dimethylphenol (99 wt%, 1.0 mmol, 1.0 eq.) and 3 mL MeCN in chamber B rather than MeCN: H$_2$O. The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The mixture in chamber B was concentrated in vacuo to give the crude product directly. The crude reaction mixture was purified by column chromatography on silica gel ($R_{f} = 0.3$, n-heptane/ethyl acetate = 100/1). The title compound was obtained as colorless oil (203.4 mg, 80%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.15–7.09 (m, 3H), 2.37 (s, 6H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 146.90, 131.47, 129.86, 127.95, 118.64 ($q$, $J_{CF} = 320.8$ Hz), 17.08 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -74.08 (s, 3F) ppm. These data are in agreement with literature data.[14]

naphthalen-2-yl trifluoromethanesulfonate (compound 13, cas number: 3857-83-8)

General procedure A was followed using 145.6 mg of 2-naphthol (99+ wt%, 1.0 mmol, 1.0 eq.) and 3 mL MeCN in chamber B rather than MeCN: H$_2$O. The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The title compound was obtained as yellow oil (270.7 mg, 98%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.76–7.69 (m, 3H), 7.65 (d, $J = 2.4$ Hz, 1H), 7.46–7.42 (m, 2H), 7.27 (dd, $J = 9.0$, 2.5 Hz, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 147.02, 133.23, 132.26, 130.50, 127.85, 127.77, 127.42, 127.06, 119.34, 119.10, 118.88 ($q$, $J_{CF} = 321.9$ Hz) ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.30 (s, 3F) ppm. These data are in agreement with literature data.[11]

2-hydroxyphenyl trifluoromethanesulfonate (compound 14, cas number: 133617-36-4)

General procedure A was followed using 111.2 mg of catechol (99 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). In chamber A, using N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 911.3 mg, 2.5 mmol, 2.5 eq.) and potassium bifluoride (KHF$_2$, 99+ wt%, 131.7 mg, 1.67 mmol, 1.67 eq.) to generate 2.5 eq. trifluoromethanesulfonyl fluoride gas. The reaction was stirred at room temperature for 4 days (>99% yield determined by $^{19}$F NMR). The extraction yield is 95%. The crude reaction mixture was purified by
short column chromatography on silica gel ($R_f = 0.3$, n-heptane/ethyl acetate = 4/1). The title compound was obtained as yellow oil (207.0 mg, 86%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.23–7.18 (m, 2H), 7.00–6.97 (m, 1H), 6.96–6.92 (m, 1H), 5.48 (s, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 147.43, 137.51, 129.40, 122.33, 121.50, 118.64 (q, $^1$J$_{CF} = 312.6$ Hz), 118.17 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.95 (s, 3F) ppm. IR (neat) ν = 3530 (m, O-H stretching, free), 3307 (br, O–H stretching, intermolecular bonded), 2992 (w, O-H stretching, intermolecular bonded), 1702 (s, aromatic C=C stretching), 1463 (s, aromatic C=C stretching), 1418 (s, S=O stretching), 1203 (vs, C–F stretching), 1036 (m, S=O stretching) cm$^{-1}$.

1,2-phenylene bis(trifluoromethanesulfonate) (compound 15, cas number: 17763-91-6)

Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 911.3 mg, 2.5 mmol, 2.5 eq.) and potassium bifluoride (KHF$_2$, 99+ wt%, 131.7 mg, 1.67 mmol, 1.67 eq.). The vessel was closed and air switching to Argon atmosphere was required. Next, chamber B was charged with 111.2 mg of catechol (99 wt%, 1.0 mmol, 1.0 eq.). Then the anhydrous acetonitrile (MeCN, 3.0 mL), trifluorotoluene (99 wt%, 124 μL, 1.0 mmol) as an internal standard and N,N-diisopropylethylamine (DIPEA, 99 wt%, 0.44 mL, 2.5 mmol, 2.5 eq.) were added to chamber B. Finally, anhydrous acetonitrile (MeCN, 1.75 mL) was added by injection through the septum in chamber A and instant gas formation was observed (Scheme S1). The reaction was stirred at room temperature for 6 hours (85% yield determined by $^{19}$F NMR). The mixture in chamber B was concentrated in vacuo to give the crude product directly. The crude reaction mixture was purified by a very short column chromatography on silica gel ($R_f = 0.5$, n-heptane/ethyl acetate = 9/1). The title compound was obtained as yellowish oil (207 mg, 55%, storage under N$_2$ atmosphere).

$^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.63 (s, 3F) ppm. These data are in agreement with literature data [17].

3-(trifluoromethylsulfonyl)naphth-2-ol (compound 16, cas number: 342890-35-1)

General procedure A was followed using 108.3 mg of 2,3-naphthalenediol (98 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). In chamber A, using N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 911.3 mg, 2.5 mmol, 2.5 eq.) and potassium bifluoride (KHF$_2$, 99+ wt%, 131.7 mg, 1.67 mmol, 1.67 eq.) to generate 2.5 eq. trifluoromethanesulfonyl fluoride gas. The reaction was stirred at room temperature for 48 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.25$, n-heptane/ethyl acetate = 6/1). The title compound was obtained as a white solid (272.0 mg, 92%). Melting point = 68.0–69.0 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.70 (d, J = 8.1 Hz, 1H), 7.70 (s, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.36 (t, J = 7.4 Hz, 1H), 7.26 (s, 1H), 5.97 (br s, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 145.25, 138.09, 133.24, 128.06, 127.73, 127.56, 126.26, 125.13, 120.68, 118.72 (s, J$_{CF} = 321.8$ Hz), 113.01 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.82 (s, 3F) ppm. These data are in agreement with literature data [17].

naphthalene-2,3-diyl Bis(trifluoromethanesulfonate) (compound 17, cas number: 125261-31-6)

Chemical Formula: C$_{12}$H$_6$F$_6$O$_6$S$_2$

Exact Mass: 423.9510

S24
General procedure A was followed using 108.3 mg of 2,3-naphthalenediol (98 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). In camber A, using N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 911.3 mg, 2.5 mmol, 2.5 eq.) and potassium bifluoride (KHF₂, 99+ wt%, 131.7 mg, 1.67 mmol, 1.67 eq.) to generate 2.5 eq. trifluoromethanesulfonyl fluoride gas. The reaction was stirred at room temperature for 1.5 hours (70% yield determined by \(^{19}\)F NMR). The extraction yield is 61%. The crude reaction mixture was purified by column chromatography on silica gel (RF = 0.3, n-heptane/ethyl acetate = 8/1). The title compound was obtained as white solid (221.0 mg, 52%).

**8-quinolinyl trifluoromethanesulfonate (compound 18, cas number: 108530-08-1)**

[Chemical Structure Image]

**Chemical Formula:** C₁₅H₁₂F₃NO₃S

**Exact Mass:** 277.0020

8-quinolinyl trifluoromethanesulfonate (compound 18, cas number: 108530-08-1)

General procedure A was followed using 146.6 mg of 8-hydroxyquinoline (99+ wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (99% yield determined by \(^{19}\)F NMR). The title compound was obtained after extraction as white crystal (252.3 mg, 91%).

**Melting point** = 57.5 – 65.2 °C.

\(^1\)H NMR (400 MHz, CDCl₃): δ 9.00 (dd, J = 4.2, 1.6 Hz, 1H), 8.16 (dd, J = 8.4, 1.6 Hz, 1H), 7.81 (dd, J = 8.2, 1.1 Hz, 1H), 7.60 (dd, J = 7.6, 0.9 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.47 (q, J = 4.19 Hz, 1H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl₃): δ 151.52, 145.90, 140.84, 135.72, 129.65, 128.22, 125.81, 122.54, 120.85, 118.86 (q, JCF = 321.5 Hz) ppm.

\(^{19}\)F NMR (377 MHz, CDCl₃): δ -74.51 (s, 3F) ppm. These data are in agreement with literature data [1].

**1H-indol-5-yl trifluoromethanesulfonate (compound 19, cas number: 128373-13-7)**

[Chemical Structure Image]

**Chemical Formula:** C₉H₆F₃NO₃S

**Exact Mass:** 265.0020

General procedure A was followed using 146.6 mg of 8-hydroxyquinoline (99+ wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (99% yield determined by \(^{19}\)F NMR). The title compound was obtained after extraction as white crystal (252.3 mg, 91%).

**Melting point** = 57.5 – 65.2 °C.

\(^1\)H NMR (400 MHz, CDCl₃): δ 9.00 (dd, J = 4.2, 1.6 Hz, 1H), 8.16 (dd, J = 8.4, 1.6 Hz, 1H), 7.81 (dd, J = 8.2, 1.1 Hz, 1H), 7.60 (dd, J = 7.6, 0.9 Hz, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.47 (q, J = 4.19 Hz, 1H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl₃): δ 151.52, 145.90, 140.84, 135.72, 129.65, 128.22, 125.81, 122.54, 120.85, 118.86 (q, JCF = 321.5 Hz) ppm.

\(^{19}\)F NMR (377 MHz, CDCl₃): δ -74.51 (s, 3F) ppm. These data are in agreement with literature data [1].

**benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate (compound 20, cas number: 109586-40-5)**

[Chemical Structure Image]

**Chemical Formula:** C₈H₆F₃O₃S

**Exact Mass:** 269.9810

General procedure A was followed using 137.3 mg of 5-hydroxyindole (97 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). In camber A, using N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 911.3 mg, 2.5 mmol, 2.5 eq.) and potassium bifluoride (KHF₂, 99+ wt%, 131.7 mg, 1.67 mmol, 1.67 eq.) to generate 2.5 eq. trifluoromethanesulfonimide fluoride gas. The reaction was stirred at room temperature for 18 hours (>99% yield determined by \(^{19}\)F NMR). The extraction yield is 80%. The crude reaction mixture was purified by column chromatography on silica gel (RF = 0.3, n-heptane/ethyl acetate = 8/1). The title compound was obtained as yellowish oil (295.6 mg, 84%).

**Melting point** = 48.5 – 49.0 °C.

\(^1\)H NMR (400 MHz, CDCl₃): δ 6.79 (d, J = 8.4 Hz, 1H), 6.73 (td, J = 7.4, 2.4 Hz, 1H), 7.00 (dd, J = 8.9, 2.4 Hz, 1H), 6.50–6.49 (m, 1H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl₃): δ 143.56, 134.54, 127.99, 126.85, 118.85 (q, JCF = 322.0 Hz), 114.82, 112.80, 112.02, 103.10 ppm.

\(^{19}\)F NMR (377 MHz, CDCl₃): δ -73.30 (s, 3F) ppm. These data are in agreement with literature data [1].

**methyl 3-(((trifluoromethyl)sulfonyl)oxy)thiophene-2-carboxylate (compound 21, cas number: 313697-13-1)**

[Chemical Structure Image]

**Chemical Formula:** C₈H₅F₃O₂S

**Exact Mass:** 269.9810
General procedure A was followed using 163.1 mg of methyl 3-hydroxythiophene-2-carboxylate (97 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The extraction yield is 82%. The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.3$, n-heptane/ethyl acetate = 9/1). The title compound was obtained as yellow oil (208.3 mg, 72%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.57 (d, $J = 5.5$ Hz, 1H), 7.02 (d, $J = 5.5$ Hz, 1H), 3.93 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 159.94, 145.39, 130.47, 122.39, 122.04, 118.63 (q, $^1J_{CF} = 322.0$ Hz), 52.42 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -73.99 (s, 3F) ppm. These data are in agreement with literature data.

5-chloropyridin-2-yl trifluoromethanesulfonate (compound 22, cas number: 87412-10-0)

General procedure A was followed using 133.6 mg of 5-chloro-2-hydroxypyridine (97 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 6 hours (>99% yield determined by $^{19}$F NMR). The mixture was washed with saturated NaHCO$_3$ (3 x 20 mL) and the extraction yield is 80%. The title compound was obtained as colorless oil (198.8 mg, 76%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.37 – 8.35 (m, 1H), 7.88 (dt, $J = 8.6$, 2.9 Hz, 1H), 7.18 (dd, $J = 8.6$, 2.0 Hz, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 153.86, 147.30, 140.61, 132.41, 118.54 (q, $^1J_{CF} = 321.7$ Hz), 116.24 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -73.43 (s, 3F) ppm. These data are in agreement with literature data.

3-(methoxycarbonyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-1-ium chloride (compound 23)

General procedure A was followed using 156.3 mg of methyl 5-hydroxynicotinate (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 6 hours (>99% yield determined by $^{19}$F NMR). The mixture was washed with saturated NaHCO$_3$ (3 x 20 mL) and the extraction yield is 99%. The title compound was obtained as white solid after salt formation with 2N HCl solution in diethyl ether (315.2 mg, 98%). Melting point = 48.8 – 49.8 °C.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.25 (d, $J = 1.5$ Hz, 1H), 8.77 (d, $J = 2.7$ Hz, 1H), 7.18 (dd, $J = 2.7$, 1.7 Hz, 1H), 4.01 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 163.83, 150.27, 146.43, 146.38, 129.80, 127.66, 118.67 (q, $^1J_{CF} = 322.1$ Hz), 52.97 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): $\delta$ -72.94 (s, 3F) ppm.

CHN: calculated for C$_8$H$_7$ClF$_3$NO$_5$S: C 29.87%, H 2.19%, N 4.35%; found: C 28.05%, H 2.28%, N 1.67% (average number based on three run rounds). IR (neat) ν = 2922 (br, amine salt N–H stretching), 1722 (s, ester C=O stretching), 1385 (s, S=O stretching), 1207 (vs, C–F stretching), 1066 (m, S=O stretching) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_8$H$_7$F$_3$NO$_5$S [M+H]$^+$: 285.9992, found: 285.9982.

(S)-1-methoxy-1-oxo-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propan-2-aminium chloride (compound 24, cas number: 2253981-98-3)
General procedure A was followed using 236.4 mg of L-tyrosine methyl ester hydrochloride (98 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). The reaction was stirred at room temperature for 6 hours (>99% yield determined by $^{19}$F NMR). The mixture was washed with saturated NaHCO$_3$ (3 x 20 mL) and the extraction yield is 98%. The title compound was obtained as white solid after salt formation with 2N HCl solution in diethyl ether (331.0 mg, 91%). Melting point = 162.5–164.0°C.

$^1$H NMR (400 MHz, Methanol-d$_4$): δ 7.37 (dt, $J$ = 9.2, 2.3 Hz, 2H), 7.28 (dt, $J$ = 9.3, 2.3 Hz, 2H), 4.76 (br s, 3 H), 4.29 (t, $J$ = 6.9 Hz, 1H), 3.70 (s, 3 H), 3.26–3.14 (m, 2H) ppm.

$^{13}$C NMR (101 MHz, Methanol-d$_4$): δ 170.17, 150.60, 136.62,132.76,123.07,120.15 (q, $J_{CF} = 320.3$ Hz), 54.90, 53.66, 36.57 ppm.

$^{19}$F NMR (377 MHz, Methanol-d$_4$): δ -73.24 (s, 3F) ppm.

CHN: calculated for C$_{11}$H$_{13}$ClF$_3$NO$_5$S: C 36.32%, H 3.60%, N 3.85%; found: C 36.36%, H 3.63%, N 1.79% (average number based on three run rounds).

IR (neat) $\nu$ = 2800 (br, amine salt N–H stretching), 1743 (s, ester C=O stretching), 1382 (s, S=O stretching), 1204 (vs, C–F stretching), 1052 (m, S=O stretching) cm$^{-1}$.

HRMS (ESI) m/z: Calcd for C$_{11}$H$_{13}$ClF$_3$NO$_5$S [M+H]$^+$: 328.0461, found: 328.0463.

(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propanoic acid (compound 25, cas number: 2093022-49-0)

General procedure A was followed using 287.0 mg of Boc-Tyr-OH (98 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The title compound was obtained as yellowish oil after the extraction (379.8 mg, 92%).

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 12.54 (br s, 1H), 7.45–7.39 (m, 4H), 7.16 (d, $J$ = 8.6 Hz, 1H, NH), 4.18–4.03 (m, 1H), 3.10 (dd, $J$ = 13.8, 4.4 Hz, 1H), 2.86 (dd, $J$ = 13.7, 10.9 Hz, 1H), 1.33–1.25 (m, 9H) ppm.

$^{13}$C NMR (101 MHz, DMSO-d$_6$): δ 173.28, 172.02, 155.40, 147.87, 139.26, 131.36, 120.99, 118.26 (q, $J_{CF} = 322.1$ Hz), 78.09, 54.90, 54.67, 35.77, 28.07 ppm.

$^{19}$F NMR (377 MHz, DMSO-d$_6$): δ -73.40 (s, 3F) ppm.

HPLC enantiomeric ratio 99.5:0.5 (details, see Section 10). IR (neat) $\nu$ = 3420 (w, N–H stretching), 2982 (br, carboxylic acid O–H stretching), 1713 (s, carboxylic acid C=O stretching), 1419 (s, S=O stretching), 1209 (vs, C–F stretching), 1054 (m, S=O stretching) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_{15}$H$_{18}$F$_3$NNaO$_7$S [M+Na]$^+$: 436.0648, found: 436.0643.

(R)-2,5,7,8-tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl trifluoromethanesulfonate (compound 26, cas number: 261929-85-5)

General procedure A was followed using 287.0 mg of Boc-Tyr-OH (98 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The title compound was obtained as yellowish oil after the extraction (379.8 mg, 92%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 2.58 (t, $J$ = 6.5 Hz, 2H), 2.21 (s, 3H), 2.18 (s, 3H), 2.10 (s, 3H), 1.81–1.74 (m, 2H), 1.58–1.48 (m, 3H), 1.46–1.03 (m, 21H), 0.88–0.84 (m, 12H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 150.92, 139.66, 128.06, 126.67, 124.34, 118.74 (q, $J_{CF} = 321.0$ Hz), 170.40, 75.58, 39.95, 39.42, 37.49, 37.42, 37.33, 32.82, 32.67, 30.87, 27.99, 24.85, 24.47, 23.73, 22.66, 22.73, 20.97, 20.67, 19.69, 19.59, 13.89, 13.07, 11.88 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): δ -74.11 (s, 3F) ppm. These data are in agreement with literature data.

(8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (compound 27, cas number: 167845-80-9)
General procedure A was followed using 280.8 mg of beta-estradiol (97 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 48 hours (>99% yield determined by $^{19}$F NMR). The extraction yield is 95%. The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.3, n-heptane/ethyl acetate = 7/3). The title compound was obtained as yellowish oil (303.3 mg, 75%).

$^1H$ NMR (400 MHz, CDCl$_3$): $\delta$ 7.33 (d, $J$ = 8.6 Hz, 1H), 7.01 (dd, $J$ = 8.6, 2.6 Hz, 1H), 6.96 (d, $J$ = 2.6 Hz, 1H), 3.73 (t, $J$ = 8.5 Hz, 1H), 2.89–2.86 (m, 2H), 2.34–2.28 (m, 1H), 2.25–2.18 (m, 1H), 2.16–2.05 (m, 1H), 1.99–1.88 (m, 3H), 1.75–1.67 (m, 1H), 1.57–1.25 (m, 6H), 1.23–1.15 (m, 1H), 0.78 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 147.36, 140.81, 139.43, 127.05, 121.00, 118.65 (q, $^1J_{CF}$ = 322.0 Hz), 117.97, 81.55, 49.92, 43.97, 43.04, 38.11, 36.48, 30.33, 29.38, 26.66, 25.97, 22.98, 10.92 ppm.

$^{19}$F NMR (377 MHz, Methanol-d$_4$): $\delta$ -73.32 (s, 3F) ppm. These data are in agreement with literature data$^{[21]}$.

4-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)piperazin-1-ium chloride (compound 28)

General procedure A was followed using 221.3 mg of 1-(4-hydroxyphenyl)-piperazine (97 wt%, 1.0 mmol, 1.0 eq.) and 0.44 mL DIPEA (2.5 mmol, 2.5 eq.). The reaction was stirred at room temperature for 4 hours (>99% yield determined by $^{19}$F NMR). The mixture was washed with saturated NaHCO$_3$ (3 x 20 mL) and the extraction yield is 95%. The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.40, n-heptane/ethyl acetate = 100/1, 251.1 mg, 81%). The title compound was obtained as yellowish solid after salt formation with 2N HCl solution in diethyl ether (221.9 mg, 64%).

Melting point = 158.7–159.5 °C.

$^1H$ NMR (400 MHz, Methanol-d$_4$): $\delta$ 7.16 (dt, $J$ = 10.2, 3.0 Hz, 2H), 7.02 (dt, $J$ = 10.2, 3.0 Hz, 2H), 3.36–3.34 (m, 4H), 3.25–3.20 (m, 4H) ppm.

$^{13}$C NMR (101 MHz, Methanol-d$_4$): $\delta$ 151.69, 144.48, 123.18, 120.18 (q, $^1J_{CF}$ = 321.1 Hz), 118.70, 47.64, 44.75 ppm.

$^{19}$F NMR (377 MHz, Methanol-d$_4$): $\delta$ -73.17 (s, 3F) ppm.

CHN: calculated for C$_{11}$H$_{14}$ClF$_3$N$_2$O$_3$: C 38.10%, H 4.07%, N 8.08%; found: C 34.03%, H 4.01%, N 4.86% (average number based on three run rounds). IR (neat) $\tilde{\nu}$ = 3080 (br, amine salt N–H stretching), 1433 (s, C=O stretching), 1345 (m, aromatic amine C–N stretching), 1251 (m, C–N stretching), 1206 (vs, C–F stretching), 1050 (m, S=O stretching) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_{11}$H$_{14}$ClF$_3$N$_2$O$_3$: [M+H]$^+$: 311.0672, found: 311.0669.

4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenyl trifluoromethanesulfonate (compound 29)

General procedure A was followed using 474.3 mg of amodiaquin dihydrochloride dihydrate (98 wt%, 1.0 mmol, 1.0 eq.) and 0.49 mL N,N-Diethylethanamine (TEA, 3.5 mmol, 3.5 equiv.) and DMSO (0.25 M, 4.0 mL). The reaction was stirred at room temperature for 18 h (>99% yield determined by $^{19}$F NMR). The mixture was washed with saturated NaHCO$_3$ (3 x 20 mL) and the extraction yield is 95%. The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.3, n-heptane/ethyl acetate = 1/1). The title compound was obtained as white solid (401.6 mg, 82%).

Melting point = 187.3–187.7 °C. $^1H$ NMR (400 MHz, CDCl$_3$): $\delta$ 8.57 (d, $J$ = 5.3 Hz, 1H), 8.00 (d, $J$ = 2.1 Hz, 1H), 7.95 (d, $J$ = 9.0 Hz, 1H), 7.60 (d, $J$ = 2.4 Hz, 1H), 7.40 (dd, $J$ = 9.0, 2.2 Hz, 1H), 7.34 (br s, 1H), 7.27–7.20 (m, 2H), 7.02 (d, $J$
= 5.3 Hz, 1H), 3.64 (s, 2H), 2.54 (q, \(J = 7.1\) Hz, 4H), 1.01 (t, \(J = 7.1\) Hz, 6H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 151.72, 149.62, 147.16, 134.91, 135.65, 135.52, 128.70, 126.30, 124.01, 122.36, 121.64, 121.13, 118.57 (q, \(J_{CF} = 321.5\) Hz), 188.42, 103.10, 51.56, 46.97, 11.59 ppm. \(^{19}\)F NMR (377 MHz, CDCl\(_3\)): \(\delta\) -74.20 (s, 3F) ppm. IR (neat) \(\nu\) = 3049 (br, N–H stretching), 1372 (s, S=O stretching), 1265 (s, aromatic amine C–N stretching), 1203 (vs, C–F stretching), 1141 (s, S=O stretching), 1080 (w, C–N stretching), 870 (s, C–Cl stretching) cm\(^{-1}\). HRMS (ESI) \(m/z\): Calcd for C\(_{21}\)H\(_{22}\)ClF\(_3\)N\(_3\)O\(_3\)S \([\text{M}+\text{H}]^+\): 488.1017, found: 488.1010.

7.2. Experimental Data of Synthesized Aryl Triflates (precursor Tf\(_2\)O)

4'-fluoro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (compound 1(B))

General procedure B was followed using 192.0 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 16 hours (>99% yield determined by \(^{19}\)F NMR). The title compound was obtained as yellow oil (286 mg, 89%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65–7.60 (m, 2H), 7.57–7.51 (m, 2H), 7.39–7.34 (m, 2H), 7.21–7.14 (m, 2H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.9 (d, \(J_{CF} = 247.3\) Hz), 148.9, 140.7, 135.4 (d, \(J_{CF} = 3.2\) Hz, 2C), 128.9, 128.8, 128.8 (d, \(J_{CF} = 0.8\) Hz), 121.7 (2C), 118.8 (q, \(J_{CF} = 320.5\) Hz), 115.9 (d, \(J_{CF} = 21.6\) Hz, 2C) ppm. \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta\) -72.8 (s, 3F), -114.3 (s, 1F) ppm. These data are in agreement with literature data.\(^{[9]}\)

4-methoxyphenyl trifluoromethanesulfonate (compound 3(B))

General procedure B was followed using 127 mg of 4-methoxyphenol (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by \(^{19}\)F NMR). The crude reaction mixture was purified by column chromatography on silica gel (\(R_f = 0.35\), n-heptane/ethyl acetate (95/5)). The title compound was obtained as colorless oil (58 mg, 23%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.24–7.19 (m, 2H), 6.97–6.92(m, 2H), 3.84 (s, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.1, 143.1, 122.3, 118.8 (q, \(J_{CF} = 321\) Hz), 115.1, 55.7 ppm. \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta\) -72.8 (s, 3F), -114.3 (s, 1F) ppm. These data are in agreement with literature data.\(^{[11]}\)

2-bromophenyl trifluoromethanesulfonate (compound 8(B))

General procedure B was followed using 177 mg of 2-bromophenol (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (97% yield determined by \(^{19}\)F NMR). The crude reaction mixture was purified by column chromatography on silica gel (\(R_f = 0.22\), n-heptane (100%)). The title compound was obtained as colorless oil (102 mg, 34%). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 7.92 (app ddd, \(J = 7.9, 1.3, 0.4\) Hz, 1H), 7.64–7.57 (m, 2H), 7.50–7.43 (m, 1H) ppm. \(^{13}\)C NMR (101 MHz, DMSO-d\(_6\)) \(\delta\) 146.4, 134.6, 130.7, 130.2, 123.3, 118.1 (q, \(J_{CF} = 321.4\) Hz), 115.2 ppm. \(^{19}\)F NMR (377 MHz, DMSO-d\(_6\)) \(\delta\) -73.25 (s, 3F) ppm. These data are in agreement with literature data.\(^{[10]}\)

4-formyl-2-methoxyphenyl trifluoromethanesulfonate ((Vanillin Triflate, compound 9(B)))

General procedure B was followed using 177 mg of 2-bromophenol (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (97% yield determined by \(^{19}\)F NMR). The crude reaction mixture was purified by column chromatography on silica gel (\(R_f = 0.22\), n-heptane (100%)). The title compound was obtained as colorless oil (102 mg, 34%). \(^1\)H NMR (400 MHz, DMSO-d\(_6\)): \(\delta\) 7.92 (app ddd, \(J = 7.9, 1.3, 0.4\) Hz, 1H), 7.64–7.57 (m, 2H), 7.50–7.43 (m, 1H) ppm. \(^{13}\)C NMR (101 MHz, DMSO-d\(_6\)) \(\delta\) 146.4, 134.6, 130.7, 130.2, 123.3, 118.1 (q, \(J_{CF} = 321.4\) Hz), 115.2 ppm. \(^{19}\)F NMR (377 MHz, DMSO-d\(_6\)) \(\delta\) -73.25 (s, 3F) ppm. These data are in agreement with literature data.\(^{[10]}\)
General procedure B was followed using 155 mg of vanillin (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.26$, n-heptane/ethyl acetate (85/15)). The title compound was obtained as off-white crystalline solid (143 mg, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.01 (s, 1H), 7.60 (app d, $J$ = 1.8 Hz, 1H), 7.54 (app dd, $J$ = 8.2, 1.8 Hz, 1H), 7.44 (app d, $J$ = 8.1 Hz, 1H), 4.03 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 190.3, 152.3, 142.8, 136.8, 124.1, 123.2, 118.7 (q, $^1$J$_{CF}$ = 320.1 Hz), 111.8, 56.5 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -73.68 (s, 3F) ppm. These data are in agreement with literature data.$^{[14]}$

8-Quinolinyl trifluoromethanesulfonate (compound 18(B))

![8-Quinolinyl trifluoromethanesulfonate](image)

General procedure B was followed using 148 mg of 8-hydroxyquinoline (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 48 hours (82% yield determined by $^{19}$F NMR). The title compound was obtained after preparative TLC ($R_f$: 0.25, n-heptane/ethyl acetate/Et$_3$N (85/15/0.1)) as yellow oil (107 mg, 39%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.09 (app dd, $J$ = 4.2, 1.6 Hz, 1H), 8.26 (app ddd, $J$ = 8.3, 1.7, 0.3 Hz, 1H), 7.89 (app dd, $J$ = 8.0, 1.5 Hz, 1H), 7.67–7.64 (m, 1H), 7.61–7.55 (m, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 151.7, 146.1, 141.1, 135.8, 129.8, 128.3, 126.0, 122.7, 121.0, 118.9 (q, $^1$J$_{CF}$ = 320.53 Hz) ppm. $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -73.76 (s, 3F) ppm. These data are in agreement with literature data.$^{[2]}$

7.3. Experimental Data of Synthesized Peptides Substrate Scope

(S)-2-amino-3-((trifluoromethyl)sulfonyl)oxy)phenylpropanoic acid (compound 30)

![Chemical Structure](image)

Chemical Formula: C$_{14}$H$_{12}$F$_3$N$_8$O$_5$S
Exact Mass: 313.02318

General procedure F was followed using 4 mL in-advance prepared solution of 1 mM L-Tyrosine in MeCN:pH 9.0 borax buffer = 1:1 (4 $\mu$mol L-Tyrosine in total, 1.0 eq.). The reaction was stirred at room temperature for 4 hours. The assay yield is 93.4% (average over two runs, standard deviation = 0.032), defined by dividing the [M+132] peak area by the total AUC of the HPLC-MS TIC chromatogram (Method: DA-40-40-70-100_20-40-2MIN_+.M; D = MeOH; A = H$_2$O + 0.1% HCOOH).

((S)-2-amino-3-((trifluoromethyl)sulfonyl)oxy)phenyl)glycylglycyl-L-phenylalanyl-L-leucine (compound 31)

![Chemical Structure](image)

Chemical Formula: C$_{29}$H$_{38}$F$_3$N$_7$O$_9$S
Exact Mass: 687.2186

General procedure F was followed using 2.3 mg Leucine Enkephalin acetate salt hydrate (95 wt%, 4 $\mu$mol, 1.0 eq.) in MeCN:pH 9.0 borax buffer = 2 mL:2 mL. The reaction was stirred at room temperature for 4 hours. The assay yield is 71.3% (average over two runs, standard deviation = 0.862), defined by dividing the [M+132] peak area by the total AUC of the HPLC-MS TIC chromatogram (Method: DA-40-40-70-100_20-40-2MIN_+.M; D = MeOH; A = H$_2$O + 0.1% HCOOH).

4-((S)-2-amino-3-((S)-2-(((S)-1-amino-1-oxo-3-phenylpropan-2-yl)amino)-3-(1H-indol-3-yl)-1-oxopropan-2-yl)carbamoyl)[pyrrolidin-1-yl]oxopropyl)phenyl trifluoromethanesulfonate (compound 32)
General procedure F was followed using 2.6 mg Endomorphin-1 (95 wt%, 4 μmol, 1.0 eq.) in MeCN:pH 9.0 borax buffer = 2 mL:2mL. The reaction was stirred at room temperature for 4 hours. The assay yield is 85.4% (average over two runs, standard deviation = 0.103), defined by dividing the [M+132] peak area by the total AUC of the HPLC-MS TIC chromatogram (Method: DA-20-60-100_20-10-5MIN_+.M; D = MeOH; A = H2O + 0.1% HCOOH).

7.4. Experimental Data of Synthesized Suzuki Cross-Coupling compounds via Aryl Trifluoromethanesulfonate

4-fluoro-1,1':4',1''-terphenyl (compound 33, cas number: 3799-84-6)

General procedure H was followed using 192.0 mg of 4-Fluoro-4-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 eq.) in Chamber B. Reaction of step 1 was stirred at room temperature for 4 hours. Then step 2 was following 136.9 mg phenylboronic acid (98+ wt%, 1.1 mmol, 1.1 eq.) and then stirred at room temperature for 18 hours. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.3, n-heptane). The title compound was obtained as white solid (216.0 mg, 87%).

\[ \text{Melting point} = 208.0 \text{–} 214.5 ^\circ \text{C}. \]

\[ \text{1H NMR (400 MHz, CDCl}_3) \delta 7.68–7.64 (m, 3H), 7.63–7.56 (m, 5H), 7.48–7.44 (m, 2H), 7.38–7.34 (m, 1H), 7.17–7.11 (m, 2H) \text{ppm.} \]

\[ \text{13C NMR (101 MHz, CDCl}_3) \delta 162.51 (d, J_{CF} = 247.4 \text{ Hz}), 140.58, 140.13, 139.13, 136.81 (d, J_{CF} = 3.3 \text{ Hz}), 128.82, 128.56 (d, J_{CF} = 8.1 \text{ Hz}), 127.54, 127.48, 127.39, 127.34, 127.02, 115.67 (d, J_{CF} = 21.5 \text{ Hz}) \text{ppm.} \]

\[ \text{19F NMR (377 MHz, CDCl}_3) \delta -116.16 (s, F) \text{ppm.} \]

These data are in agreement with literature data [22].

2-phenylnaphthalene (compound 34, cas number: 612-94-2)

General procedure H was followed using 145.6 mg of 2-naphthol (99+ wt%, 1.0 mmol, 1.0 eq.) in Chamber B. Reaction of step 1 was stirred at room temperature for 6 hours. Then step 2 was following 136.9 mg phenylboronic acid (98+ wt%, 1.1 mmol, 1.1 eq.) and then stirred at room temperature for 18 hours. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.3, n-heptane:ethyl acetate = 100:1). The title compound was obtained as white solid (186.5 mg, 91%).

\[ \text{Melting point} = 101.5 \text{–} 102.0 ^\circ \text{C}. \]

\[ \text{1H NMR (400 MHz, CDCl}_3) \delta 8.02 (s, 1H), 7.89–7.83 (m, 3H), 7.73–7.69 (m, 3H), 7.47–7.44 (m, 4H), 7.37–7.34 (m, 1H) \text{ppm.} \]

\[ \text{13C NMR (101 MHz, CDCl}_3) \delta 141.09, 138.52, 133.66, 132.59, 128.82, 128.38, 128.17, 127.61, 127.40, 127.31, 126.25, 125.89, 125.77, 125.56 \text{ppm.} \]

These data are in agreement with literature data [23].

5-chloro-2-fluoro-2,3-bipyridine (compound 35, cas number: 942206-10-2)
Chamber A of a 20 mL small two-chamber reactor (Figure S1) was filled with N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 546.8 mg, 1.5 mmol, 1.5 eq.) and potassium bisulfide (KHF₂, 99+ wt%, 78.9 mg, 1.0 mmol, 1.0 eq.). Next, chamber B was charged with 133.6 mg of 5-chloro-2-hydroxypyridine (97 wt%, 1.0 mmol, 1.0 eq.) and potassium bifluoride (KHF₂, 99.9 wt%, 0.024 mmol, 0.024 eq.) and then stirred at room temperature for 3 days. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.25, n-heptane/ethyl acetate = 7/1). The title compound was obtained as yellowish oil (149.6 mg, 80%). This product was recrystallized from pentane/ethyl acetate and dried in vacuo to give the crude product.

The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.2, n-heptane/ethyl acetate = 12/1). The title compound was obtained as beige solid (131.5 mg, 63%). Melting point 99.0 – 100.0 °C. 1H NMR (400 MHz, CDCl₃) δ 8.68 (dd, J = 2.4, 0.6 Hz, 1H), 8.54 (ddd, J = 9.8, 7.7, 2.1 Hz, 1H), 8.27 (ddd, J = 4.8, 1.9, 1.4 Hz, 1H), 7.88 (ddd, J = 8.5, 1.7, 0.7 Hz, 1H), 7.35 (ddd, J = 7.5, 4.8, 2.0 Hz, 1H) ppm. 13C NMR (101 MHz, CDCl₃) δ 163.04 (d, J_CF = 241.5 Hz), 149.27 (d, J_CF = 7.1 Hz), 148.81, 147.88 (d, J_CF = 15.2 Hz), 141.26 (d, J_CF = 3.5 Hz), 136.41, 131.64, 124.66 (d, J_CF = 11.5 Hz), 122.07 (d, J_CF = 4.4 Hz), 121.10 (d, J_CF = 26.5 Hz) ppm. 19F NMR (377 MHz, CDCl₃) δ -69.48 (s, F) ppm. These data are in agreement with literature data[24].

5-(2-fluorophenyl)-3-methylpyridine (compound 36, cas number: 713143-67-0)

General procedure H was followed using 110.2 mg of 6-methyl-3-pyridinol (99 wt%, 1.0 mmol, 1.0 eq.) in Chamber B. Reaction of step 1 was stirred at room temperature for 24 hours. Then step 2 was following 158.7 mg 3-fluorophenylboronic acid (97 wt%, 1.1 mmol, 1.1 eq.), 4.5 mg palladium(II) acetate (Pd(OAc)₂, 98+ wt%, 0.02 mmol, 0.02 eq.), 6.9 mg tricyclohexylphosphine (PCy₃, 97 wt%, 0.024 mmol, 0.024 eq.) and then stirred at room temperature for 3 days. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.25, n-heptane/ethyl acetate = 7/1). The title compound was obtained as yellowish oil (149.6 mg, 80%). 1H NMR (400 MHz, CDCl₃) δ 8.68 (dd, J = 2.1, 1 Hz, 1H), 7.38 (td, J = 7.9, 5.9 Hz, 1H), 7.30 (dt, J = 7.7, 2.6 Hz, 1H), 7.22 (dt, J = 10.0, 2.1 Hz, 1H), 7.18 (dd, J = 8.0 Hz, 1H), 7.06–7.00 (m, 1H), 2.58 (s, 3H) ppm. 13C NMR (101 MHz, CDCl₃) δ 163.04 (d, J_CF = 247.2 Hz), 157.68, 147.18, 139.96 (d, J_CF = 7.8 Hz), 134.36, 132.26 (d, J_CF = 2.2 Hz), 130.32 (d, J_CF = 8.3 Hz), 122.96, 122.33 (d, J_CF = 2.9 Hz), 114.36 (d, J_CF = 21.3 Hz), 113.59 (d, J_CF = 22.2 Hz), 23.86 ppm. 19F NMR (377 MHz, CDCl₃) δ -112.79 (s, 1F) ppm. These data are in agreement with literature data[29].

5-(3-fluorophenyl)-2-methylpyridine (compound 36, cas number: 713143-67-0)

5-(2-fluorophenyl)-3-methylpyridine (compound 37, cas number: 740804-24-4)
General procedure H was followed using 140.9 mg of sesamol (98 wt%, 1.0 mmol, 1.0 eq.) in Chamber B. Reaction of step 1 was stirred at room temperature for 4 hours. Then step 2 was following 145.1 mg 3-thienylboronic acid (97 wt%, 1.1 mmol, 1.1 eq.), 4.5 mg palladium(II) acetate (Pd(OAc)$_2$), 98+ wt%, 0.02 mmol, 0.02 eq.), 6.4 mg tricyclohexylphosphine (PCy$_3$, 97 wt%, 0.022 mmol, 0.022 eq.) and then stirred at room temperature for 3 hours. The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.35, n-heptane/ethyl acetate = 20/1). The title compound was obtained as yellowish solid (202.2 mg, 99%).

**Melting point** = 69.5–70.5 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34–7.32 (m, 1H), 7.30–7.27 (m, 2H), 7.06–7.04 (m, 2H), 6.83–6.80 (m, 1H), 5.95 (s, 2H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.00, 146.74, 141.99, 130.24, 126.25, 126.06, 119.86, 119.31, 108.50, 107.02, 101.03 ppm. These data are in agreement with literature data[26].

**7.5. Experimental Data of Synthesized Amides via Acyl Fluoride Intermediate**

**N-phenylbenzamide (compound 38, cas number: 93-98-1)**

![Chemical Structure](image)

Chemical Formula: C$_{13}$H$_{11}$NO

Exact Mass: 197.0841

General procedure I was followed using 122.7 mg of benzoic acid (99.5+ wt%, 1.0 mmol, 1.0 eq.) and 0.18 mL aniline (99.8 wt%, 186 mg, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 5 hours. The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.25, DCM/TEA = 100/1). The title compound was obtained as white solid (180.0 mg, 91%). **Melting point** = 162.5–163.5 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.23 (s, 1H), 7.97 (d, $J$ = 7.2 Hz, 2H), 7.80 (d, $J$ = 7.7 Hz, 2H), 7.59 (t, $J$ = 7.2 Hz, 1H), 7.53 (t, $J$ = 7.3 Hz, 2H), 7.36 (t, $J$ = 7.8 Hz, 2H), 7.11 (t, $J$ = 7.3 Hz, 1H) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$) $\delta$ 165.51, 139.14, 134.97, 131.44, 128.52, 128.29, 127.58, 123.58 ppm. These data are in agreement with literature data[27].

**2-chloro-N-(4'-chloro-[1,1'-biphenyl]-2-yl)nicotinamide (compound 39, cas number: 188425-85-6)**

![Chemical Structure](image)

Chemical Formula: C$_{16}$H$_{12}$Cl$_2$N$_2$O

Exact Mass: 342.0327

General procedure I was followed using 159.1 mg of 2-chloronicotinic acid (99 wt%, 1.0 mmol, 1.0 eq.) and 428.8 mg 2-amino-4'-chlorobiphenyl (95 wt%, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 18 hours. Without extraction, the crude reaction mixture was purified by column chromatography on silica gel directly ($R_f$ = 0.20, n-heptane/ethyl acetate = 2/1). The title compound was obtained as yellowish solid (238.6 mg, 70%). **Melting point** = 143.0–143.6 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.35 (dd, $J$ = 4.7, 1.9 Hz, 1H), 8.31 (dd, $J$ = 8.2 Hz, 1H), 8.22 (s, 1H), 8.03 (dd, $J$ = 7.6, 1.3 Hz, 1H), 7.44–7.38 (m, 3H), 7.33–7.24 (m, 5H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 162.50, 151.00, 146.58, 139.70, 136.25, 134.19, 134.15, 132.46, 131.05, 130.65, 130.11, 129.07, 128.69, 125.33, 122.67, 122.38 ppm. These data are in agreement with literature data[27].

**(3,4-dihydroisoquinolin-2(1H)-yl)(thiophen-2-yl)methanone (compound 40, cas number: 349097-64-9)**

![Chemical Structure](image)

Chemical Formula: C$_{21}$H$_{29}$O$_4$
General procedure I was followed using 129.4 mg of 2-thiophenecarboxylic acid (99 wt%, 1.0 mmol, 1.0 eq.) and 280.4 mg 1,2,3,4-tetrahydroisoquinoline (95 wt%, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 5 hours. During extraction procedure, the mixture was washed sequentially with NH₄Cl (sat.) (1 x 20 mL) and brine (1 x 20 mL). The crude reaction mixture was purified by column chromatography on silica gel directly (Rf = 0.35, n-heptane/ethyl acetate = 2/1). The title compound was obtained as yellowish oil (183.8 mg, 76%).

1H NMR (400 MHz, CDCl₃) δ 7.44 – 7.42 (m, 1H), 7.37 – 7.36 (m, 1H), 7.19 – 7.13 (m, 3H), 7.09 (br s, 1H), 7.07 – 7.04 (m, 1H), 4.85 (s, 2H), 3.93 – 3.89 (m, 2H), 2.93 (t, J = 5.9 Hz, 2H) ppm.

13C NMR (101 MHz, CDCl₃) δ 163.65, 137.40, 134.27, 132.80, 128.71, 128.66, 128.49, 126.62, 126.36, 126.21, 47.33 (br s), 43.76 (br s), 28.97 ppm. These data are in agreement with literature data[28].

2,2-diphenyl-1-(1H-1,2,4-triazol-1-yl)ethan-1-one (compound 41, cas number: 80928-24-1)

General procedure I was followed using 216.6 mg of diphenylacetic acid (98+ wt%, 1.0 mmol, 1.0 eq.) and 138.8 mg 1,2,4-triazole (99.5 wt%, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 5 hours. During extraction procedure, the mixture was washed sequentially with NH₄Cl (sat.) (1 x 20 mL) and brine (1 x 20 mL). The crude reaction mixture was purified by column chromatography on silica gel directly (Rf = 0.35, n-heptane/ethyl acetate = 2/1). Then the product was extracted with NaHCO₃ (sat.) (1 x 20 mL) and ethyl acetate (1 x 20 mL). The title compound was obtained as white solid (217.3 mg, 83%). Melting point = 75.0 – 78.0 °C.

1H NMR (400 MHz, CDCl₃) δ 8.91 (s, 1H), 7.96 (s, 1H), 7.39 – 7.37 (m, 4H), 7.33 – 7.29 (m, 4H), 7.27 – 7.23 (m, 2H), 6.36 (s, 1H) ppm.

13C NMR (101 MHz, CDCl₃) δ 169.53, 152.90, 143.99, 136.80, 128.76, 128.74, 128.61, 128.42 127.69, 127.05, 54.93 ppm. These data are in agreement with literature data[6].

N-(2-methylbut-3-yn-2-yl)-2-(p-tolyl)acetamide (compound 42, cas number: 1488858-94-1)

General procedure I was followed using 151.7 mg of p-tolylacetic acid (99 wt%, 1.0 mmol, 1.0 eq.) and 0.22 mL 2-methyl-3-butyln-2-amine (95 wt%, 175.0 mg, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 18 hours. During extraction procedure, the mixture was washed sequentially with 1 M HCl (1 x 20 mL), NaHCO₃ (sat.) (1 x 20 mL) and brine (1 x 20 mL). The crude reaction mixture was purified by column chromatography on silica gel directly (Rf = 0.15, n-heptane/ethyl acetate = 2/1). The title compound was obtained as white solid (217.3 mg, 83%). Melting point = 115.0 – 123.5 °C.

1H NMR (400 MHz, CDCl₃) δ 7.16 – 7.11 (m, 4H), 5.59 (br s, 1H), 3.49 (s, 2H), 2.34 (s, 3H), 2.30 (s, 1 H), 1.56 (s, 6 H) ppm. 13C NMR (101 MHz, CDCl₃) δ 170.21, 152.90, 143.99, 136.80, 128.76, 128.74, 128.61, 128.42 127.69, 127.05, 54.93 ppm. These data are in agreement with literature data[6].

(3r,5r,7r)-N-phenyladamantane-1-carboxamide (compound 43, cas number: 3796-79-0)

General procedure I was followed using 180.3 mg of 1-adamantanecarboxylic acid (99 wt%, 1.0 mmol, 1.0 eq.) and 0.18 mL aniline (99 wt%, 186.6 mg, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 5 hours. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.30, n-heptane/ethyl acetate = 10/1). The title compound was obtained as white solid (235 mg, 92%). Melting point = 183.0 – 186.0 °C. 1H NMR (400 MHz, CDCl₃) δ 7.54 – 7.51 (m, 2H), 7.34 (br s, 1H), 7.32 – 7.29 (m, 2H), 2.33 (s, 3H), 7.30 (s, 1H) ppm. 13C NMR (101 MHz, CDCl₃) δ 170.21, 136.81, 131.72, 129.58, 129.36, 129.25, 129.12, 86.97, 69.02, 47.46, 43.87, 28.75, 21.00 ppm. These data are in agreement with literature data[6].
7.27 (m, 2H), 7.10–7.05 (m, 1H), 2.09 (s, 3H), 1.96 (d, J = 2.7 Hz, 6H), 1.79–1.71 (m, 6H) ppm. \( ^{13} \text{C} \) NMR (101 MHz, CDCl\(_3\)) δ 175.98, 138.05, 128.83, 124.00, 119.95, 41.43, 39.22, 36.39, 28.11 ppm. These data are in agreement with literature data\(^{[27]}\).

tert-butyl (S)-(1-oxo-3-phenyl-1-((2,4,4-trimethylpentan-2-yl)amino)propan-2-yl)carbamate (compound 44, new compound)

Chemical Formula: C\(_{22}\)H\(_{36}\)N\(_2\)O\(_3\)

Exact Mass: 376.2726

General procedure I was followed using 268.0 mg of Boc-Ph-OH (99 wt%, 1.0 mmol, 1.0 eq.) and 0.32 mL tert-octylamine (99 wt%, 261.1 mg, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 18 hours. Without extraction, the crude reaction mixture was purified by column chromatography on silica gel directly (\(R_f = 0.30\), \(n\)-heptane/ethyl acetate = 5/1). The title compound was obtained as white solid (316.3 mg, 84%). Melting point = 128.0–129.0 °C.

\( ^{1} \text{H} \) NMR (400 MHz, CDCl\(_3\)) δ 7.30–7.20 (m, 5H), 5.63 (br s, 1H), 5.22 (t, J = 8.2 Hz, 1H), 4.18 (q, J = 7.0 Hz, 1H), 3.05–2.97 (m, 2H), 1.67 (d, J = 14.8 Hz, 1H), 1.47 (s, 1H), 1.41 (s, 9H), 1.31 (s, 3H), 1.26 (s, 3H), 0.90 (s, 9H) ppm.

\( ^{13} \text{C} \) NMR (101 MHz, CDCl\(_3\)) δ 169.66, 155.27, 137.10, 129.35, 128.47, 126.68, 79.77, 55.51, 52.22, 47.88, 47.72, 38.62, 38.29, 28.09, 17.95, 17.83 ppm.

IR (neat) \( \nu = 3305 \text{ (m, N–H stretching)}, 2974 \text{ (m, N–H stretching)}, 1687 \text{ (s, C=O stretching)}, 1655 \text{ (s, C=O stretching)} \text{ cm}^{-1} \).

HRMS (ESI) m/z: Calcd for C\(_{22}\)H\(_{37}\)N\(_2\)O\(_3\) \([\text{M}+\text{H}]^{+}\): 377.2799, found: 377.2804.

Chiral-HPLC (Daicel Chiralpak AD-3 \( n\)-hexane/iPrOH = 95:5, flow rate 1.0 mL/min, detection at 250 nm and 273 nm): \( t_R = 13.0 \text{ min, } t_R = 26.3 \text{ min; } 40\% \text{ ee was detected.} \)

methyl (tert-butoxycarbonyl)-L-phenylalanyl-D-alaninate (compound 45, cas number: 15136-30-8)

Chemical Formula: C\(_{18}\)H\(_{26}\)N\(_2\)O\(_5\)

Exact Mass: 350.1842

General procedure I was followed using 268 mg of Boc-L-phenylalanine (99.0 wt%, 1.0 mmol, 1.0 eq.) and 285 mg D-Alanine methyl ester hydrochloride (98 wt%, 2.0 mmol, 2.0 eq.) in Chamber B. Reaction was stirred at room temperature for 24 hours. The crude reaction mixture was purified by column chromatography on silica gel (\(R_f = 0.25\), \(n\)-heptane/ethyl acetate = 3/1). The title compound was obtained as white solid (345 mg, 98%). Melting point = 88.5–89.0 °C.

\( ^{1} \text{H} \) NMR (400 MHz, CDCl\(_3\)) δ 7.29–7.20 (m, 5H), 6.81 (br s, 0.0682 H, NH), 6.63 (br s, 0.8950 H, NH) (according to the ratio of integration area, the dr. value would be 92:8), 5.35 (d, J = 8.1 Hz, 1H), 4.55–4.47 (m, 1H), 4.44 (s, 1H), 3.69 (s, 3H), 3.06 (d, J = 5.5 Hz, 2H), 1.39 (d, J = 1.6 Hz, 9H), 1.34 (d, J = 7.1 Hz, 0.2888 H), 1.24 (d, J = 6.6 Hz, 2.9733 H) ppm.

\( ^{13} \text{C} \) NMR (101 MHz, CDCl\(_3\)) δ 172.90, 170.71, 155.26, 126.63, 129.25, 129.20, 128.39, 128.47, 79.82, 55.51, 52.22, 47.88, 47.72, 38.62, 38.29, 38.09, 17.95, 17.83 ppm. These data are in agreement with literature data\(^{[29]}\).

7.6. Experimental Data of Synthesized Trifluoromethanesulfonamides, Sulfonimidoyl Fluoride and Triflimidates

N-(4-bromophenyl)-1,1,1-trifluoromethanesulfinamide (compound S1) (cas number: 868395-08-8)

Chemical Formula: C\(_{17}\)H\(_{17}\)BrF\(_3\)S

Exact Mass: 286.9227

General procedure J1 was followed using 1.053 g of 4-bromoaniline (98 wt%, 6.0 mmol, 1.0 eq.). Reaction was stirred at room temperature for 1 h. The crude reaction mixture was purified by column chromatography on silica gel (\(R_f = 0.30\), n-heptane/ethyl acetate = 7/1). The title compound was obtained as yellowish solid (987.7 mg, 57%). Melting point = 95.8–96.6 °C. \( ^{1} \text{H} \) NMR (400 MHz, CDCl\(_3\)) δ 7.49 (d, J = 11.8 Hz, 2H), 7.01 (d, J = 11.7 Hz, 2H), 6.32 (br s, 1H, amine) ppm. \( ^{13} \text{C} \) NMR (101 MHz, CDCl\(_3\)) δ 173.90, 170.71, 155.26, 126.63, 129.25, 129.20, 128.39, 128.47, 79.82, 55.51, 52.22, 47.88, 47.72, 38.62, 38.29, 38.09, 17.95, 17.83 ppm. These data are in agreement with literature data\(^{[29]}\).

1,1,1-trifluoro-N-(4-nitrophenyl)methanesulfonamide (compound S2) (new compound)
Chemical Formula: C<sub>7</sub>H<sub>6</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S

Exact Mass: 253.9973

General procedure J1 was followed using 0.846 g of 4-nitroaniline (98 wt%, 6.0 mmol, 1.0 eq.). Reaction was stirred at room temperature for 30 min. The crude reaction mixture was purified by column chromatography on silica gel (R<sub>f</sub> = 0.30, n-heptane/ethyl acetate = 3/1). The title compound was obtained as yellow solid (1.220 g, 80%). Melting point = 105.0–106.5 °C. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 11.01 (s, 1H), 8.24 (dt, J = 10.2, 2.7 Hz, 2H), 7.39 (dt, J = 10.2, 2.7 Hz, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-d<sub>6</sub>) δ 146.34, 142.57, 125.70, 123.92 (q, J<sup>CF</sup>= 338.4 Hz), 117.52 ppm. <sup>19</sup>F NMR (377 MHz, DMSO-d<sub>6</sub>) δ -75.81 (s, 3F) ppm. IR (neat) ν = 3407 (br, N–H stretching), 1148 (vs, C–F stretching), 1035 (vs, S=O stretching) cm<sup>-1</sup>. HRMS (APCI) m/z: Calcd for C<sub>7</sub>H<sub>6</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S·[M+Na]<sup>+</sup>: 252.9900, found: 252.9911.

1,1,1-trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfinamide (compound S3) (new compound)

Chemical Formula: C<sub>9</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S

Exact Mass: 259.0490

General procedure A was followed using 0.877 g of 2-[2-(2-propyn-1-yloxy)ethoxy]ethylamine (6.0 mmol, 1.0 equiv.). Reaction was stirred for 1 h at room temperature. The crude reaction mixture was purified by column chromatography on silica gel (n-heptane/ethyl acetate = 1/1). The title compound was obtained as yellow oil (0.683 g, 44%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.30 (s, 1H, NH), 4.21 (d, J = 2.4 Hz, 2H, CH<sub>2</sub>), 3.72–3.59 (m, 6H, CH<sub>3</sub>), 3.55–3.34 (m, 1H), 3.37–3.30 (m, 1H), 2.48 (t, J = 4.4 Hz, 1H, CH<sub>2</sub>) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 123.63 (q, J<sup>CN</sup>= 336.30 Hz, CF<sub>3</sub>), 79.24, 74.73, 70.27, 70.06, 68.87, 58.23, 41.47 ppm. <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>) δ -77.55 (s, 3F) ppm. IR (neat) ν = 3253 (br, N–H stretching), 2117 (w, C=C stretching), 1172 (vs, C–F stretching), 1154 (s, alicyclic ether C–O stretching), 1136 (s, alicyclic ether C–O stretching), 1072 (s, S=O stretching) cm<sup>-1</sup>. HRMS (ESI) m/z: Calcd for C<sub>9</sub>H<sub>12</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub>S·[M+Na]<sup>+</sup>: 282.0382, found: 282.0381.

N-(4-bromophenyl)-1,1,1-trifluoromethanesulfinimidoyl fluoride (compound S4) (cas number: 2273795-55-2)

Chemical Formula: C<sub>7</sub>H<sub>4</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S

Exact Mass: 304.9133

General procedure J2 was followed using 0.9154 g of N-(4-bromophenyl)-triflimide (>99 wt%, 3.2 mmol, 1.0 eq.). 0.467 g N-chlorosuccinimide (NCS, 98 wt%, 3.5 mmol, 1.1 eq.) and 3.50 mL tetra-n-butylammonium fluoride (TBAF, 1 M in THF, 3.5 mmol, 1.1 eq.) was added. Reaction was stirred at room temperature for 30 min. The crude reaction mixture was purified by column chromatography on silica gel (R<sub>f</sub> = 0.30, n-heptane/ethyl acetate = 20/1). The title compound was obtained as orange oil (0.743 g, 76%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.46 (d, J = 11.3 Hz, 2H, ArH), 7.02 (d, J = 11.0 Hz, 2H, ArH) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 134.87 (d, J<sup>CF</sup>= 8.9 Hz), 132.69 (d, J<sup>CF</sup>= 1.2 Hz), 125.35 (d, J<sup>CF</sup>= 6.7 Hz), 119.21 (d, J<sup>CF</sup>= 2.6 Hz), 118.00 (qd, J = 372.3, 76.6 Hz, CF<sub>3</sub>) ppm. <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>) δ 60.04 (q, J = 16.2 Hz, 1F), -72.91 (d, J = 16.2 Hz, 3F) ppm. IR (neat) ν = 1217 (vs, C–F stretching), 1067 (S=O stretching), 643 (s, C–Br stretching) cm<sup>-1</sup>. HRMS (APCI) m/z: Calcd for C<sub>7</sub>H<sub>4</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>3</sub>S·[M+Na]<sup>+</sup>: 305.9206 found 306.1361.

1,1,1-trifluoro-N-(4-nitrophenyl)methanesulfinimidoyl fluoride (compound S5) (new compound)

Chemical Formula: C<sub>7</sub>H<sub>4</sub>F<sub>4</sub>N<sub>2</sub>O<sub>3</sub>S

Exact Mass: 271.9879

General procedure J2 was followed using 1.220 g of N-(4-nitrophenyl)-triflimide (>99 wt%, 4.8 mmol, 1.0 eq.). 0.719 g N-chlorosuccinimide (NCS, 98 wt%, 5.28 mmol, 1.1 eq.) and 5.28 mL tetra-n-butylammonium fluoride (TBAF, 1 M in THF, 5.28 mmol, 1.1 eq.) was added. Reaction was stirred at room temperature for 15 min. The crude reaction mixture was purified by column chromatography on silica gel (R<sub>f</sub> = 0.30, n-heptane/ethyl acetate = 20/1). The title compound was obtained as orange oil (0.682 g, 52%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.26–8.22 (m, 2H, ArH), 7.32–7.28 (m, 2H, ArH) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 145.38, 141.82 (d, J<sup>CF</sup>= 6.3 Hz), 125.31 (d, J<sup>CF</sup>= 1.1 Hz), 124.37 (d, J<sup>CF</sup>= 4.9 Hz), 118.00 (qd, J<sup>CF</sup>= 319.11, 61.45 Hz, CF<sub>3</sub>) ppm. <sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>) δ 58.98 (q, J
1,1,1-trifluoro-N-2-(2-(prop-2-yn-1-yl oxy)ethyl) methanesulfonimidoyl fluoride (compound 56, new compound)

\[ \text{CF}_3 \text{S} = \text{O} \]

Chemical Formula: C\(_{13}\)H\(_{9}\)BrF\(_3\)NO\(_2\)S

Exact Mass: 378.9489

General procedure J3 was followed using 63 mg of N-(4-bromophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 29 mg phenol (99 wt%, 0.3 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h. The crude reaction mixture was purified by column chromatography on silica gel (R\(_f\) = 0.35, n-heptane:MTBE = 50:1). The title compound was obtained as yellowish oil (0.682 g, 52%). HRMS (ESI) m/z: Calcd for C\(_{11}\)H\(_{11}\)F\(_3\)N\(_2\)O\(_3\)S [M+Na\(^+\)]: 300.0288, found: 300.0284.

**Phenyl N-(4-bromophenyl)trifluoromethanesulfonimidate (compound 46, new compound)**

\[ \text{CF}_3 \text{S} = \text{O} \]

Chemical Formula: C\(_{13}\)H\(_{9}\)BrF\(_3\)NO\(_2\)S

Exact Mass: 378.9489

General procedure J3 was followed using 63 mg of N-(4-bromophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 29 mg phenol (99 wt%, 0.3 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h. The crude reaction mixture was purified by column chromatography on silica gel (R\(_f\) = 0.35, n-heptane:MTBE = 50:1). The title compound was obtained as yellowish oil (0.682 g, 52%). HRMS (ESI) m/z: Calcd for C\(_{11}\)H\(_{11}\)F\(_3\)N\(_2\)O\(_3\)S [M+Na\(^+\)]: 300.0288, found: 300.0284.

**4-formyl-2-methoxyphenyl N-(4-bromophenyl)trifluoromethanesulfonimidate (compound 47, new compound)**

\[ \text{CF}_3 \text{S} = \text{O} \]

Chemical Formula: C\(_{13}\)H\(_{9}\)BrF\(_3\)NO\(_2\)S

Exact Mass: 436.9544

General procedure J3 was followed using 68.5 mg of N-(4-bromophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.22 mmol, 1.0 eq.) and 36.5 mg vanillin (99 wt%, 0.24 mmol, 1.1 eq.). Reaction was stirred at room temperature for 1 h. The crude reaction mixture was purified by column chromatography on silica gel (R\(_f\) = 0.28, iso-hexane:ethyl acetate = 4:1). The title compound was obtained as brown oil (64.3 mg, 67%). HRMS (APCI) m/z: Calcd for C\(_{10}\)H\(_{12}\)BrF\(_3\)N\(_2\)O\(_4\)S [M+2Na-H\(^+\)]: 423.9202, found 424.4567.

**Note:** solvent are present in the IR spectra, this is taken into account when determining the reported isolated yield and is left as such as the compound is rather small scale and unstable.

**methyl 3-(N-(4-bromophenyl)-S-(trifluoromethyl)sulfonimidoyl)oxy)thiophene-2-carboxylate (compound 48, new compound)**

S37
General procedure J3 was followed using 61 mg of N-(4-bromophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 38 mg phenol (99 wt%, 0.24 mmol, 1.2 eq.). Reaction was stirred at room temperature for 3 h (60% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.23, iso-hexane/ethyl acetate = 10/1). The title compound was obtained as brown oil (44.5 mg, 50%).

**1H NMR** (400 MHz, CDCl$_3$) δ 7.52 (d, $J$ = 5.5 Hz, 1H, aromatic), 7.39–7.35 (m, 2H, aromatic), 7.00 (d, $J$ = 5.5 Hz, 1H, aromatic), 6.92–6.89 (m, 2H, aromatic), 3.66 (s, 3H, CH$_3$) ppm.

**13C NMR** (101 MHz, CDCl$_3$) δ 171.16 (C=O), 160.30, 146.73, 137.27, 132.22, 130.22, 125.46, 123.06, 122.52, 119.18, 117.82, 119.08 (q, $^1J_{CF}$ = 323.2 Hz, CF$_3$), 52.25 (methyl) ppm.

**19F NMR** (377 MHz, CDCl$_3$) δ -74.23 (s, 3F) ppm.

**IR** (neat) $\tilde{\nu}$ =  1714 (s, ester C=O stretching), 1210 (vs, C–F stretching), 1158 (s, ester C–O stretching), 1064 (s, S=O stretching), 652 (s, C–Br stretching) cm$^{-1}$.

**HRMS** (APCI) m/z: Calcd for C$_{13}$H$_9$BrF$_3$NNaO$_4$S$_2$ [M+Na]$^+$: 465.9001, found: 466.1741.

**phenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 49, new compound)**

General procedure J3 was followed using 54.5 mg of N-(4-nitrophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 28.5 mg phenol (99 wt%, 0.3 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h (96% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.30, n-heptane/ethyl acetate = 20/1). The title compound was obtained as yellow oil (65.1 mg, 94%).

**1H NMR** (400 MHz, CDCl$_3$) δ 8.14–8.12 (m, 2H), 7.46–7.42 (m, 2H), 7.40–7.36 (m, 1H), 7.28–7.25 (m, 2H), 7.12 (dt, $J$ = 9.6, 2.6 Hz, 2H) ppm.

**13C NMR** (101 MHz, CDCl$_3$) δ 148.78, 145.28, 144.23, 130.25, 128.32, 125.04, 123.90, 122.03, 119.20 (q, $^1J_{CF}$ = 329.8 Hz) ppm.

**19F NMR** (377 MHz, CDCl$_3$) δ -74.08 (s, 3F) ppm.

**IR** (neat) $\tilde{\nu}$ =  1516 (s, nitro compound N–O stretching), 1202 (vs, C–F stretching), 1067 (m, S=O stretching) cm$^{-1}$.

**HRMS** (APCI) m/z: Calcd for C$_{13}$H$_{10}$F$_3$N$_2$O$_4$ [M+H]$^+$: 347.0308, found: 347.0311.

Large-scale reaction: procedure M was followed using 573.0 mg of N-(4-nitrophenyl)-triflimidoyl fluoride (99.9 wt%, 2.0 mmol, 1.0 eq.) and 285.2 mg phenol (99 wt%, 3.0 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h (96% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.30, n-heptane/ethyl acetate = 20/1). The title compound was obtained as yellow oil (564.8 mg, 82%).

**4-allyl-2-methoxyphenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 50, new compound)**

General procedure J3 was followed using 54.5 mg of N-(4-nitrophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 49.8 mg eugenol (99 wt%, 0.3 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h (80% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.15, n-heptane/ethyl acetate = 30/1). The title compound was obtained as brown oil (59.9 mg, 72%).

**1H NMR** (400 MHz, CDCl$_3$) δ 8.14 (dt, $J$ = 9.7, 2.6 Hz, 2H), 7.17 (dt, J = 9.7, 2.6 Hz, 2H), 7.12 (d, J = 8.2 Hz, 1H), 6.80 (dd, J = 8.2, 1.9 Hz, 1H), 6.74 (d, J = 1.8 Hz, 1H), 5.96–5.88 (m, 1H), 5.14–5.07 (m, 2H), 3.61 (s, 3H), 3.38 (d, J = 6.7 Hz, 2H) ppm.

**13C NMR** (101 MHz, CDCl$_3$) δ 151.24, 145.73, 143.98, 141.57, 137.07, 136.27, 124.73, 124.32, 125.04, 123.90, 122.03, 119.20 (q, $^1J_{CF}$ = 322.5 Hz), 116.72, 112.90, 55.61, 39.95 ppm.

**19F NMR** (377 MHz, CDCl$_3$) δ -74.96 (s, 3F) ppm. **IR** (neat) $\tilde{\nu}$ = 1516 (s, nitrile compound N–O stretching), 1210 (vs, C–F stretching), 1067 (m, S=O stretching) cm$^{-1}$. **HRMS** (APCI) m/z: Calcd for C$_{13}$H$_{15}$F$_3$N$_2$O$_4$S [M+H]$^+$: 437.0308, found: 437.0311.

Chemical Formula: C$_{13}$H$_{15}$F$_3$N$_2$O$_4$S

Exact Mass: 416.0654

General procedure J3 was followed using 54.5 mg of N-(4-nitrophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 49.8 mg eugenol (99 wt%, 0.3 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h (80% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.15, n-heptane/ethyl acetate = 30/1). The title compound was obtained as brown oil (59.9 mg, 72%).
1602 (m, C=C stretching), 1515 (s, nitro compound N–O stretching), 1203 (vs, C–F stretching), 1177 (s, C–O stretching), 1067 (m, S=O stretching) cm⁻¹. HRMS (ESI) m/z: Calcd for C_{17}H_{16}F_{3}N_{2}O_{5}S [M+H]⁺: 417.0727, found: 417.0733.

2-bromophenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 51, new compound)

General procedure J3 was followed using 54.5 mg of N-(4-nitrophenyl)-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 53.0 mg 2-bromophenol (98 wt%, 0.3 mmol, 1.5 eq.). Reaction was stirred at room temperature for 1 h (>99% yield determined by ¹⁹F NMR). The crude reaction mixture was purified by column chromatography on silica gel (R_f = 0.2, n-heptane/ethyl acetate = 50/1). The title compound was obtained as yellow oil (68.4 mg, 80%).

1H NMR (400 MHz, CDCl₃) δ 8.12 (d, J = 8.6 Hz, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.42–7.36 (m, 2H), 7.27–7.22 (m, 1H), 7.13 (dt, J = 9.6, 2.4 Hz, 2H) ppm.

13C NMR (101 MHz, CDCl₃) δ 146.73, 144.81, 144.39, 134.34, 129.33, 129.07, 124.93, 124.16, 123.60, 119.04 (q, ¹JCF = 323.7 Hz), 116.69 ppm.

19F NMR (377 MHz, CDCl₃) δ -74.29 (s, 3F) ppm.

IR (neat) ʋ = 1516 (s, nitro compound N–O stretching), 1204 (vs, C–F stretching), 1069 (m, S=O stretching), 698 (s, C–Br stretching) cm⁻¹. HRMS (ESI) m/z: Calcd for C_{13}H_{9}BrF_{3}N_{2}O_{4}S [M+H]⁺: 424.9413, found: 424.9460.

phenyl trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfonimidate (compound 52, new compound)

A 10 mL small glass tube was filled with 55.4 mg 2-[2-(2-propyn-1-yloxy)ethoxy]ethyl-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 28.5 mg phenol (0.3 mmol, 1.5 eq.). Then the acetonitrile (MeCN, 0.6 mL), H₂O (0.2 mL), trifluorotoluene (99 wt%, 25 μL, 1.0 mmol) as an internal standard and 46.4 mg 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 98 wt%, 0.3 mmol, 1.5 eq.) as base were followed. Finally, the vessel was closed and was stirred at 50 °C for 1 h (96% yield determined by ¹⁹F NMR). The content was transferred to a 25 mL separatory funnel. The glass tube was rinsed five times with 5 mL of EtOAc; the fractions were collected in the same funnel. The mixture was extracted with H₂O (1 x 5 mL) and EtOAc (3 x 5 mL). The combined organic layers were washed with brine (1 x 5 mL), dried over anhydrous Na₂SO₄ and then concentrated in vacuo to give the crude product. The crude reaction mixture was purified by column chromatography on silica gel (R_f = 0.15, n-heptane/ethyl acetate = 20/1). The title compound was obtained as yellowish oil (52.1 mg, 74%).

1H NMR (400 MHz, CDCl₃) δ 7.43–7.39 (m, 2H), 7.33–7.30 (m, 1H), 7.28–7.26 (m, 2H), 4.18 (d, J = 2.4 Hz, 2H), 3.67–3.59 (m, 4H), 3.56–3.47 (m, 4H), 2.42 (t, J = 2.4 Hz, 1H) ppm.

13C NMR (101 MHz, CDCl₃) δ 149.13, 129.80, 129.51, 122.23, 119.24 (q, ¹JCF = 324.5 Hz), 79.55, 74.46, 71.12, 70.15, 58.34, 44.25 ppm.

19F NMR (377 MHz, CDCl₃) δ -74.75 (s, 3F) ppm.

IR (neat) ʋ = 2118 (w, CΞC stretching), 1194 (vs, C–F stretching), 1137(s, aliphatic ether C–O stretching), 1102 (s, aliphatic ether C–O stretching), 1025 (m, S=O stretching) cm⁻¹. HRMS (APCI) m/z: Calcd for C_{14}H_{17}F_{3}NO_{4}S [M+H]^+: 352.0825, found: 352.0817.

methyl (2S)-2-amino-3-((4-((N-(2-(2-(prop-2-yloxy)ethoxy)ethyl)-S-(trifluoromethyl)sulfonimidoyl)oxy)phenyl)propanoate (compound 53, new compound)

A 10 mL small glass tube was filled with 55.4 mg 2-[2-(2-propyn-1-yloxy)ethoxy]ethyl-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 59.7 mg L-tyrosine methyl ester (0.3 mmol, 1.5 eq.). Then the acetonitrile (MeCN, 0.6 mL), H₂O (0.2 mL), trifluorotoluene (99 wt%, 25 μL, 1.0 mmol) as an internal standard and 46.4 mg 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 98 wt%, 0.3 mmol, 1.5 eq.) as base were followed.
were followed. Finally, the vessel was closed and was stirred at 50 °C for 1 h (81% yield determined by 19F NMR). The content of glass tube was transferred to a baker with anhydrous Na2SO4 to dried over directly without extraction to give the crude product. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.25, ethyl acetate). The title compound was obtained as yellow oil (57.2 mg, 61%).

1H NMR (400 MHz, CDCl3) δ 7.28–7.17 (m, 4H), 4.18 (d, J = 2.4 Hz, 2H), 3.74–3.71 (m, 4H), 3.68–3.60 (m, 4H), 3.55–3.48 (m, 4H), 3.08 (dd, J = 13.6, 5.3 Hz, 1H), 2.89 (dd, J = 13.7, 7.8 Hz, 1H), 2.44 (t, J = 2.3 Hz, 1H), 1.75 (br s, 2H) ppm.

13C NMR (101 MHz, CDCl3) δ 175.10, 148.03, 148.02, 136.75, 130.60, 122.24, 119.22 (q, 1JCF = 324.6 Hz), 115.54, 79.55, 74.50, 71.09, 70.14, 58.33, 55.59, 51.99, 44.24, 40.28 ppm.

19F NMR (377 MHz, CDCl3) δ -74.6402 (s, 3F, one of enantiomers), -74.6451 (s, 3F, one of enantiomers) ppm.

IR (neat) ν = 3293 (br, N–H stretching), 2110 (w, CΞC stretching), 1736 (s, ester C=O stretching), 1193 (vs, C–F stretching), 1138 (s, aliphatic ether C–O stretching), 1101 (s, aliphatic ether C–O stretching), 1030 (m, S=O stretching) cm⁻¹.


4-(3-oxobutyl)phenyl trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfonimidate (compound 54, new compound)

A 10 mL small glass tube was filled with 55.4 mg 2-[2-(2-propyn-1-yloxy)ethoxy]ethyl-triflimidoyl fluoride (>99.5 wt%, 0.2 mmol, 1.0 eq.) and 50.3 mg 4-(4-hydroxyphenyl)-2-butanone (0.3 mmol, 1.5 eq.). Then the acetonitrile (MeCN, 0.6 mL), H2O (0.2 mL), trifluorotoluene (99 wt%, 25 μL, 1.0 mmol) as an internal standard and 46.4 mg 1,8-Diazabicyclo[5,4,0]undec-7-ene (DBU, 98 wt%, 0.3 mmol, 1.5 eq.) as base were followed. Finally, the vessel was closed and was stirred at 50 °C for 1 h (89% yield determined by 19F NMR). The content of glass tube was transferred to a baker with anhydrous Na2SO4 to dried over directly without extraction to give the crude product. The crude reaction mixture was purified by column chromatography on silica gel (Rf = 0.2, n-heptane/ethyl acetate = 2/1). The title compound was obtained as yellow oil (68.7 mg, 81%).

1H NMR (400 MHz, CDCl3) δ 7.23–7.16 (m, 4H), 4.18 (d, J = 2.4 Hz, 2H), 3.68–3.60 (m, 4H), 3.55–3.47 (m, 4H), 2.90 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.43 (t, J = 2.4 Hz, 1H), 2.15 (s, 3H) ppm.

13C NMR (101 MHz, CDCl3) δ 207.32, 147.41, 140.45, 129.66, 129.31, 122.18, 119.25 (q, 1JCF = 324.6 Hz), 115.29, 79.56, 74.50, 71.14, 70.17, 69.02, 58.36, 44.78, 44.24, 30.03, 28.88 ppm.

HRMS (ESI) m/z: Calcd for C18H23F3NO5S [M+H]+: 422.1243, found: 422.1250.

Unsuccessful substrates:

Unsuccessful targeted products:

Figure S3. Unsuccessful targeted products

7.7. Experimental Data of Synthesized Triflamides

1-phenyl-4-((trifluoromethyl)sulfonyl)piperazine (compound 55, new compound)
General procedure K was followed using 166 mg of 1-phenylpiperazine (97 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was concentrated in vacuo over a longer period of ±5h. The title compound was obtained as taupe solid (234 mg, 80%).

Melting point: 85.0 – 87.0 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.36 – 7.30 (m, 2H), 7.01 – 6.94 (m, 2H), 3.77 – 3.60 (m, 4H), 3.37 – 3.21 (m, 4H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 150.5, 129.4, 121.5, 120.1 (q, $^1$J$_{CF}$ = 323.6 Hz), 117.3, 49.9, 46.5 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): δ -75.21 (s, 3F) ppm.

IR (neat) $\tilde{\nu}$ = 1599 (m, aromatic), 1580 (w, aromatic), 1495 (m, aromatic), 1447 (w, aromatic) cm$^{-1}$.

HRMS (ESI) m/z calcld for C$_{11}$H$_{14}$F$_3$N$_2$O$_2$S [M+H]$^+$: 295.0723, found 295.0718.

4-phenyl-1-((trifluoromethyl)sulfonyl)piperidine (compound 56, new compound)

General procedure K was followed using 165 mg of 1-phenylpiperidine (97 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 72 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.37, n-heptane/ethyl acetate (87/13)). The title compound was obtained as white solid (191 mg, 65%).

Melting point: 40 – 44 °C.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.40 – 7.34 (m, 2H), 7.31 – 7.21 (m, 3H), 4.12 (dqui, J = 13.2, 2.28 Hz, 2H), 3.19 (t, $^1$J = 12.58 Hz, 2H), 2.74 (tt, $^1$J = 12.22, 3.63 Hz, 1H), 2.05 – 1.97 (m, 2H), 1.91-1.78 (m, 2H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 144.2, 128.8, 126.9, 126.6, 120.2 (q, $^1$J$_{CF}$ = 324.9 Hz), 47.4, 41.7, 33.0 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): δ -75.35 (brs, 3F) ppm.

IR (neat) $\tilde{\nu}$ = 1601 (m, aromatic), 1494 (m, aromatic), 1466 (m, aromatic), 1452 (m, aromatic), 1380 (s, S=O stretching), 1224 (vs, C–F stretching), 1176 (S=O stretching) cm$^{-1}$.

HRMS (APCI) m/z calcld for C$_{12}$H$_{13}$F$_3$KNO$_2$S [M+2K-H]$^+$: 369.9888, found 370.0765 ; MS (ASAP$^+$) m/z calcld for C$_{12}$H$_{15}$F$_3$NO$_2$S [M+H]$^+$: 294.08, found 294.0.

4-((trifluoromethyl)sulfonyl)morpholine (compound 57)

General procedure K was followed using 89 mg of morpholine (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 72 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel ($R_f$ = 0.37, n-heptane/ethyl acetate (87/13)). The title compound was obtained as yellow oil (194 mg, 89%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.8 (t, $^1$J = 4.7 Hz, 4H), 3.56 – 3.48 (m, 4H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 120.1 (q, $^1$J$_{CF}$ = 323.5 Hz), 66.4, 46.5 ppm.

$^{19}$F NMR (377 MHz, CDCl$_3$): δ -75.13 (s, 3F) ppm. These data are in agreement with literature data.

4-((trifluoromethyl)sulfonyl)thiomorpholine 1,1-dioxide (compound 58)

General procedure K was followed using 0.175 mg of thiomorpholine 1,1-dioxide HCl (98 wt%, 1.0 mmol, 3.0 eq.) and 367 mg DMAP (99wt%, 3.0 mmol, 3.0 eq.). The reaction was stirred at room temperature for 48 hours (98% yield determined by $^{19}$F NMR). After extraction of the crude mixture, the organic phase was concentrated under vacuo for a longer period of time (± 4h) to remove all traces of solvent. The title compound was obtained as white powder (164 mg, 61%).

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 3.93 (m, 4H), 3.39 (m, 4H), 3.56 – 3.48 (m, 4H) ppm.

$^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 120.1 (q, $^1$J$_{CF}$ = 323.5 Hz), 66.4, 46.5 ppm.

4-((trifluoromethyl)sulfonyl)thiomorpholine 1,1-dioxide (compound 58)

General procedure K was followed using 0.175 mg of thiomorpholine 1,1-dioxide HCl (98 wt%, 1.0 mmol, 3.0 eq.) and 367 mg DMAP (99wt%, 3.0 mmol, 3.0 eq.). The reaction was stirred at room temperature for 48 hours (98% yield determined by $^{19}$F NMR). After extraction of the crude mixture, the organic phase was concentrated under vacuo for a longer period of time (± 4h) to remove all traces of solvent. The title compound was obtained as white powder (164 mg, 61%).

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 3.93 (m, 4H), 3.39 (m,
2-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline (compound 59)

General procedure K was followed using 0.13 mL of 1,2,3,4-tetrahydroisoquinoline (98 wt%, 136 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 48 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.41$, n-heptane/ethyl acetate (95/5)). The title compound was obtained as colourless oil (152 mg, 54%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.28–7.24 (m, 2H), 7.23–7.18 (m, 1H), 7.14–7.09 (m, 1H), 4.69 (brs, 2H), 3.8 (brs, 2H), 3.02 (t, $J$ = 5.8 Hz, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 132.6, 130.7, 129.2, 127.4, 126.9, 126.0, 120.1 (q, $J_{CF} = 322.9$ Hz), 47.55, 44.4, 28.9 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -75.51 (s, 3F) ppm. These data are in agreement with literature data.

4-(4-((trifluoromethyl)sulfonyl)piperazin-1-yl)phenyl trifluoromethanesulfonate (compound 60, new compound)

General procedure K was followed using 221.3 mg of 1-(4-hydroxyphenyl)-piperazine (97 wt%, 1.0 mmol, 1.0 eq.) and 431.9 mg DMAP (99wt%, 3.5 mmol, 3.5 eq.) in chamber B and 911.3 mg of N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 2.5 mmol, 2.5 eq.) and 131.7 mg of potassium bifluoride (KHF$_2$, 99+ wt%, 1.67 mmol, 1.67 eq.) in chamber A to generate 2.5 eq. trifluoromethanesulfonyl fluoride gas. The reaction was stirred at room temperature for 30 hours (>99% yield determined by $^{19}$F NMR). After extraction the crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.5$, n-heptane/ethyl acetate = 8:2). The title compound was obtained as white solid (357.1 mg, 85%). Melting point = 82.0–82.5 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.19 (dt, $J$ = 10.2, 3.0 Hz, 2H), 6.93 (dt, J = 10.2, 3.0 Hz, 2H), 3.65 (s, 4H), 3.28 (s, 4H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 150.20, 143.25, 122.22, 120.04 (q, $J_{CF} = 324.4$ Hz), 118.76 (q, $J_{CF} = 322.1$ Hz), 117.93, 49.43, 46.29 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.34 (s, 3F), -75.82 (s, 3F) ppm. IR (neat) $\tilde{\nu}$ = 1384 (s, S=O stretching), 1201 (vs, C–F stretching), 1181 (vs, C–F stretching), 1065 (s, S=O stretching) cm$^{-1}$. HRMS (ESI) $m/z$: Calcd for C$_{12}$H$_{13}$F$_6$N$_2$O$_5$S$_2$: [M+H]$^+$: 443.0164, found: 433.0160.
General procedure K was followed using 353 mg of fluoxetine HCl (98 wt%, 1.0 mmol, 1.0 eq.) and 368 mg of DMAP (99 wt%, 3.0 mmol, 3.0 eq.). The reaction was stirred at room temperature for 18 hours (92% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel (RI = 0.35, n-heptane/ethyl acetate (85/15)). The title compound was obtained as colourless oil (267 mg, 94%*). $^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.49–7.44 (m, 2H), 7.42–7.30 (m, 5H), 6.93–6.89 (m, 2H), 5.26 (dd, J = 9.0 Hz, 3.7 Hz, 1H), 3.80–3.44 (m, 2H), 3.08 (app q, $^3$J$_{CF3}$ = 32.9 Hz; M3), 120.2 (q, $^1$J$_{C=CF3}$ = 312.9 Hz; M5), 123.3 (q, $^2$J$_{C=CF3}$ = 32.9 Hz; M3), 115.8, 77.21, 48.0, 37.2, 35.7 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -96.6 (s, 3F), -74.86 (s, 3F) ppm. IR (neat) $\nu$ = 2954–2898 (alkyl), 1614 (m, aromatic), 1591 (w, aromatic), 1517 (m, aromatic), 1495 (w, aromatic), 1455 (w, methyl), 1387 (s, S=O stretching), 1325 (vs, phenyl-CF$_3$), 1247 (vs, C–F stretching), 1225 (vs, alkyl-aryl ether), 1178 (s, phenyl-CF$_3$), 1158 (s, S=O stretching), 1108 (s, phenyl-CF$_3$), 1009 (m, ether) cm$^{-1}$. HRMS (ESI and APCI) no conclusion; *note: part of the quartet lies underneath other Carbon signals.

$^{+}$H$_2$N-[(1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]methyl]-1,1,1-trifluoromethanesulfonamide (compound 63, new compound)

![Chemical Structure](image1)

Chemical Formula: C$_{11}$H$_{18}$F$_3$NO$_2$S

Exact Mass: 285,10103

General procedure K was followed using 156 mg of (-)-cis-myrtanylamine (98 wt%, 1.0 mmol, 1.0 eq.) and 368 mg of DMAP (99 wt%, 3.0 eq.) in chamber B and 714 mg of N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 2.0 mmol, 2.0 eq.) and 105 mg of potassium bifluoride (KHF$_2$, 99 wt%, 1.34 mmol, 1.34 eq.) in chamber A to generate 2.0 eq. trifluoromethanesulfon fluoride gas. The reaction was stirred at room temperature for 48 hours (96% yield determined by $^{19}$F NMR). The crude reaction mixture was washed with isohexane to precipitate the remaining starting material. The isohexane solution was transferred to another flask and was concentrated under vacuo. The title compound was obtained as orange/brown oil (267 mg, 94%*). $^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 4.84 (bs, 1H), 3.39–3.24 (m, 2H), 2.50–2.35 (m, 1H), 2.34–2.19 (m, 1H), 2.06–1.88 (m, 5H), 1.57–1.42 (m, 1H), 1.24 (s, 3H), 1.02 (s, 3H), 0.97–0.93 (m, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 119.7 (q, $^1$J$_{CF}$ = 321.9 Hz), 49.7, 43.0, 41.7, 42.1, 38.6, 33.0, 27.8, 25.7, 23.1, 19.3 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -77.20 (s, 3F) ppm. IR (neat) $\nu$ = 3316–3291 (br, NH stretching), 2911–2871 (alkyl), 1366 (s, S=O stretching), 1229 (vs, C–F stretching), 1143 (s, S=O stretching) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_{11}$H$_{18}$F$_3$NO$_2$S [M-3H$^-$]: 284.0937, found 284.0937.

*Note: solvent traces are present in the $^{1}H$ NMR spectra, this is taken into account when determining the reported isolated yield and is left as such as the compound is rather volatile.

$^{+}$N-(3-chlorophenyl)-1,1,1-trifluoromethanesulfonamide (compound 64)

![Chemical Structure](image2)

Chemical Formula: C$_{15}$H$_{13}$F$_3$NO$_2$S

Exact Mass: 284.0937

General procedure K was followed using 0.11 mL of 3-chloroaniline (95 wt%, 128 mg, 1.0 mmol, 1.0 eq.), 368 mg of DMAP (99 wt%, 3.0 mmol, 3.0 eq.) in chamber B and 714 mg of N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 2.0 mmol, 2.0 eq.) and 105 mg of potassium bifluoride (KHF$_2$, 99 wt%, 1.34 mmol, 1.34 eq.) in chamber A to generate 2.0 eq. trifluoromethanesulfon fluoride gas. The reaction was stirred at 50 °C for 18 hours (>99% yield determined by $^{19}$F NMR). The title compound was obtained as brown/orange crystalline solid (228 mg, 88%). $^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.39–7.30 (m, 3H), 7.22–7.18 (m, 1H), 6.94 (bs, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 135.4, 134.8, 130.7, 127.8, 123.4, 121.3, 119.6 (q, $^1$J$_{CF}$ = 322.6 Hz) ppm. $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ -75.30 (s, 3F) ppm. These data are in agreement with literature data.[33]

$^{1,1,1}$-trifluoro-$^{+}$N-(3-methylisoxazol-5-yl)methanesulfonamide (compound 65, new compound)
General procedure K was followed using 3-amo-5-methylisoxazole (97 wt%, 101 mg, 1.0 mmol, 1.0 eq.) 368 mg of DMAP (99wt%, 3.0 mmol, 3.0 eq.) in chamber B and 714 mg of N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 2.0 mmol,2.0 eq.) and 105 mg of potassium bifluoride (KHF₂, 99% wt, 1.34 mmol, 1.34 eq.) in chamber A to generate 2.0 eq. trifluoromethanesulfonyl fluoride gas. The reaction was stirred at 50 °C for 48 hours (>99% yield determined by HRMS). The title compound was obtained as white crystalline solid (195 mg, 71%).

Melting point: 140.4–142.7 °C. 1H NMR (400 MHz, CDCl₃) δ 8.13 (app d, J = 3.0 Hz, 1H), 7.96–7.90 (m, 2H), 7.53–7.46 (m, 3H), 6.89 (app d, J = 3.0 Hz, 1H) ppm. 13C NMR (101 MHz, CDCl₃) δ 159.7, 153.0, 130.3, 129.0 (2C), 126.8 (2C), 119.1 (q, JCF = 32.3 Hz), 109.5 ppm. 19F NMR (377 MHz, CDCl₃) δ -74.24 (s, 3F) ppm. IR (neat) ν = 3180 (br, N–H stretching), 3087 (w, 5-membered heterocycle), 3012 (w, 5-membered heterocycle), 1605.23 (w, aromatic), 1545.36 (m, aromatic), 1507 (w, aromatic), 1455 (m, aromatic), 1385 (s, S=O stretching), 1229 (vs, C–F stretching), 1168 (S=O stretchings, ) cm⁻¹. HRMS (APCI) m/z: Calcd for C₁₀H₁₁F₂N₂O₃S [M+H]+: 277.0253, found 277.0257.

3-iodo-1-((trifluoromethyl)sulfonyl)-1H-pyrazole (compound 67, new compound)

Chemical Formula: C₉H₇F₃I₂N₂O₃S
Exact Mass: 377,9017

General procedure K was followed using 258 mg of 3-iodo-1H-pyrazolo-[3,4-b]pyridine (95 wt%, 1.0 mmol, 1.0 eq.) and anhydrous potassium carbonate (anh. K₂CO₃, 99% wt, 209 mg, 1.5 mmol, 1.5 eq.) rather than DMAP as base in chamber B and 714 mg of N-phenyltrifluoromethanesulfonimide (PhNTf₂, 98 wt%, 2.0 mmol, 2.0 eq.) and 105 mg of potassium bifluoride (KHF₂, 99% wt, 1.34 mmol, 1.34 eq.) in chamber A to generate 2.0 eq. trifluoromethanesulfon fluoride gas. The reaction was stirred at room temperature for 72 hours (>99% yield determined by 19F NMR). After extraction of the crude reaction mixture the organic fraction is partly crystallized. The crystals (pure product) are separated from the liquid phase (impure product mixture). The liquid fraction was purified by column chromatography on silica gel (Rf = 0.31, n-heptane/ethyl acetate/triethylamine (9/1/0.05)). The title compound was obtained as off-white solid (95 mg, 25%).

Melting point: 126.3–127.6 °C. 1H NMR (400 MHz, CDCl₃) δ 8.85 (app dd, J = 4.7, 1.6 Hz, 1H), 7.99 (app. dd, J = 8.1 Hz, 1.6 Hz, 1H). 7.56 (dd, J = 8.1 Hz, 4.7 Hz, 1H) ppm. 13C NMR (101 MHz, CDCl₃) δ 152.7, 152.3, 132.3, 123.2, 122.0, 119.2 (q, JCF = 324.0 Hz), 105.3 ppm. 19F NMR (377 MHz, CDCl₃) δ -73.99 (s, 3F) ppm. IR (neat) ν = 3156.16 (w, 5 membered heterocycle), 3178 (w, 5-membered heterocycle), 3078 (w, 5-membered heterocycle), 1606.23 (w, aromatic), 1545.36 (m, aromatic), 1507 (w, aromatic), 1455 (m, aromatic), 1385 (s, S=O stretching), 1229 (vs, C–F stretching), 1168 (S=O stretchings, ) cm⁻¹. HRMS (ESI) m/z: Calcd for C₁₀H₁₂F₃I₂N₂O₃S [M+H]^+: 228.9900, found 228.9892.

3-phenyl-1-((trifluoromethyl)sulfonyl)-1H-pyrazole (compound 66, new compound)

Chemical Formula: C₁₀H₁₁F₂N₂O₃S
Exact Mass: 276,01803

Melting point: 91.7–92.7 °C. 1H NMR (400 MHz, CDCl₃) δ 8.13 (app d, J = 3.0 Hz, 1H), 7.96–7.90 (m, 2H), 7.53–7.46 (m, 3H), 6.89 (app d, J = 3.0 Hz, 1H) ppm. 13C NMR (101 MHz, CDCl₃) δ 159.7, 153.0, 130.3, 129.0 (2C), 126.8 (2C), 119.1 (q, JCF = 32.3 Hz), 109.5 ppm. 19F NMR (377 MHz, CDCl₃) δ -74.24 (s, 3F) ppm. IR (neat) ν = 3180 (br, N–H stretching), 3087 (w, 5-membered heterocycle), 3012 (w, 5-membered heterocycle), 1605.23 (w, aromatic), 1545.36 (m, aromatic), 1507 (w, aromatic), 1455 (m, aromatic), 1385 (s, S=O stretching), 1229 (vs, C–F stretching), 1168 (S=O stretchings, ) cm⁻¹. HRMS (ESI) m/z: Calcd for C₁₀H₁₁F₂N₂O₃S [M+H]^+: 228.9900, found 228.9892.
2-phenyl-1-((trifluoromethyl)sulfonyl)-4,5-dihydro-1H-imidazole (compound 68, new compound)

Chemical Formula: C_{10}H_{10}F_{3}N_{2}O_{2}S
Exact Mass: 278.03368

General procedure K was followed using 149 mg of 2-phenyl-2-imidazoline (98 wt%, 1.0 mmol, 1.0 eq.). The reaction was stirred at room temperature for 18 hours (>99% yield determined by $^{19}$F NMR). The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.2$, isohexane/ethyl acetate/triethylamine (85/15/1)) The title compound was obtained as white crystalline solid (149 mg, 54%). Melting point: 91–92.2 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.69-7.63 (m, 2H), 7.56-7.50 (m, 1H), 7.47–7.41 (m, 2H), 4.27–4.20 (m, 2H), 4.17–4.10 (m, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.5, 131.4, 129.2, 128.8, 128.7, 128.0, 127.0, 119.8 (q, $^1J_{CF} = 324.3$ Hz), 54.4, 50.6 (q, $^4J_{CF} = 0.9$ Hz) ppm. $^{19}$F NMR (377 MHz, CDCl$_3$) δ -74.73 (s, 3F) ppm. IR (neat) $\tilde{\nu} = 3065-2920$ (br, 5-membered heterocycle), 1651 (m, aromatic), 1599 (w, aromatic), 1494 (w, aromatic), 1401 (s, S=O Stretching), 1195 (vs, C–F stretching) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_{10}$H$_{10}$F$_3$N$_2$O$_2$S [M+H]$^+$: 279.0410, found 279.0413.

2-phenyl-1-((trifluoromethyl)sulfonyl)-4,5-dihydro-1H-imidazole (compound 69, new compound)

Chemical Formula: C$_8$H$_8$F$_3$N$_2$O$_2$S$_2$
Exact Mass: 295,99010

General procedure K was followed using 168 mg of 2-(methylmercapto)benzimidazole (98 wt%, 1.0 mmol, 1.0 eq.) and anhydrous potassium carbonate (anh. K$_2$CO$_3$, 99% wt, 209 mg, 1.5 mmol, 1.5 eq.) rather than DMAP as base in Chamber B. The reaction was stirred at room temperature for 36 hours (>99% yield determined by $^{19}$F NMR). The title compound was obtained as off-white crystalline solid (251 mg, 85%). Melting point: 101.5–102.8 °C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.78–7.75 (m, 1H), 7.75–7.72 (m, 1H), 7.52–7.42 (m, 2H), 2.78 (s, 3H) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$) δ 155.1, 142.8, 133.6, 127.1, 125.8, 119.8, 119.6 (q, $^1J_{CF} = 325.2$ Hz), 113.1, 15.8 ppm. $^{19}$F NMR (377 MHz, DMSO-$d_6$) δ -74.12 (s, 3F) ppm. IR (neat) $\tilde{\nu} = 3067$ (w, 5-membered heterocycle), 3025 (w, 5-membered heterocycle), 2929 (w, 5-membered heterocycle), 2852 (w, 5-membered heterocycle), 1416 (s, S=O Stretching), 1195 (vs, C–F stretching) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_9$H$_8$F$_3$N$_2$O$_2$S$_2$ [M+H]$^+$: 296.9974, found 296.9940.

1-((trifluoromethyl)sulfonyl)-1H-indol-5-yl trifluoromethanesulfonate (compound 70, new compound)

Chemical Formula: C$_{10}$H$_6$F$_6$NO$_5$S$_2$
Exact Mass: 396,95133

General procedure K was followed using 137.3 mg of 5-hydroxyindole (97 wt%, 1.0 mmol, 1.0 eq.) and 308.5 mg DMAP (99 wt%, 2.5 mmol, 2.5 eq.) in chamber B and using 911.3 mg N-phenyltrifluoromethanesulfonimide (PhNTf$_2$, 98 wt%, 2.5 mmol, 2.5 eq.) and 131.7 mg potassium bifluoride (KHF$_2$, 99 wt%, 1.67 mmol, 1.67 eq.) in chamber A to generate 2.5 eq. trifluoromethanesulfonyl fluoride gas. The reaction was stirred at room temperature for 4 hours (95% yield determined by $^{19}$F NMR). The mixture in chamber B was concentrated in vacuo to give the crude product directly. The crude reaction mixture was purified by column chromatography on silica gel ($R_f = 0.5$, n-heptane/ethyl acetate = 5/1). The title compound was obtained as yellow oil (295.6 mg, 74%). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.01 (app d, $^1J = 9.2$ Hz, 1H), 7.63–7.60 (m, 1H), 7.53 (app d, $J = 3.8$ Hz, 1H), 7.35 (dd, $J = 9.12, 2.22$ Hz, 1H), 6.88 (d, $J = 3.8$ Hz, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 146.67, 134.21, 131.87, 128.65, 119.46 (q, $^1J_{CF} = 324.5$ Hz), 118.94, 118.81 (q, $^1J_{CF} = 321.8$ Hz), 115.17, 114.73, 111.25 ppm. $^{19}$F NMR (377 MHz, CDCl$_3$): δ -73.16 (s, 3F), -75.81 (s, 3F) ppm. IR (neat) $\tilde{\nu} = 1454$ (s, S=O stretching), 1417 (s, S=O stretching), 1197 (vs, C–F stretching), 1138 (s, S=O stretching), 745 (s, C=C bending) cm$^{-1}$. HRMS (ESI) m/z: Calcd for C$_{10}$H$_6$F$_6$NO$_5$S$_2$ [M+H]$^+$: 397.9586, found 397.9566.
Unsuccessful substrates:

**amines:**

- ![Structure](image1)
  - no product observed
- ![Structure](image2)
  - >99% NMR yield, purification difficulties
- ![Structure](image3)
  - no product observed
- ![Structure](image4)
  - imine formed as major product
- ![Structure](image5)
  - no product observed

**azoles:**

- ![Structure](image6)
  - no conversion
- ![Structure](image7)
  - no conversion
- ![Structure](image8)
  - no conversion
- ![Structure](image9)
  - no conversion
- ![Structure](image10)
  - <30% conversion

(bases tried: DMAP, KF, K₂CO₃, Cs₂CO₃
solvents: MeCN, DMF, NMP, DMSO)

Figure S4. Unsuccessful Substrates of Amines and Azoles
7.8. Experimental Data of other common nucleophiles

Chamber A (1.5 eq. gas)

H₂C=N=N=N + KF+HF + N≡ +

H₂C=CHOH + KF + HF + N≡ +

1-Decanol (1.0 mmol, 1.0 eq.)

DPEA (1.5 eq.)

MeCN (3 mL)

Internal standard (1.0 eq)

n. 18 h
dry

13FnNMR showed no expected F peaks;
on TLC, with KIO₃ stain, did not show new spots.

Chamber B

4-Fluorobenzyl alcohol (1.0 mmol, 1.0 eq.)

DPEA (1.5 eq.)

MeCN (3 mL)

Internal standard (1.0 eq)

n. 6 h
dry

13FnNMR showed lots of F peaks and almost full conversion.
on TLC, lots of spots showed SM seemed to be decomposed.

Chamber A (1.5 eq. gas)

Thiophen (1.0 mmol, 1.0 eq.)

DPEA (1.5 eq.)

MeCN (3 mL)

Internal standard (1.0 eq)

n. 18 h
dry

70% isolated yield (no expected triflated thiophenol product formed)

Chamber B

Dibutyl malonate (1.0 mmol, 1.0 eq.)

DPEA (1.5 eq.)

MeCN (3 mL)

Internal standard (1.0 eq)

n. 18 h
dry

13FnNMR showed no expected F peaks;
on TLC, with KIO₃ stain, showed two new spots and SM no full conversion;
checked GC-MS, no expected peaks showed.

Chamber A (1.5 eq. gas)

Dimethyl malonate (1.0 mmol, 1.0 eq.)

DPEA (1.5 eq.)

MeCN (3 mL)

Internal standard (1.0 eq)

n. 18 h
dry

13FnNMR showed no expected F peaks;
on TLC, with KIO₃ stain, showed one light new spot and SM still left a lot;
checked GC-MS, no expected peaks showed.

Chamber B

Phenylnmagnesium bromide (1.0 mmol, 1.0 eq, 3.0 M in diethyl ether)

THF (3 mL)

Internal standard (1.0 eq)

n. 6 h
dry

13FnNMR showed no expected F peaks;
on TLC, showed lots of new spots and SM was gone;
checked GC-MS, no expected peaks showed; seemed SM decomposed.
8. Computational details

8.1. Metadynamics simulations

Input preparation

Simulating chemical reactions using ab-initio molecular dynamics (A IMD) is usually an insurmountable task due to the limited timescale (order of picoseconds) that is currently available to these computationally demanding simulations. With metadynamics, the sampling efficiency is enhanced by placing a number of artificial Gaussian potentials along a predetermined set of collective variables (CVs) that describe the reaction coordinate.[34] Doing so, effectively flattens the potential energy surface which enables the ab-initio dynamic simulation of a chemical reaction. In this work, all ab-initio simulations were performed using the open-source CP2K code (Version 6.1) with the Quickstep implementation.[35] Forces driving the simulations were calculated on the fly at the DFT level using the PBE GGA functional[36] including Grimme’s D3 long-range dispersion corrections[37] and the DZVP-MOLOPT-GTH plane wave basis set[38] with the grid level cut-off set at 350 Ry and the relative cut-off set at 50 Ry.

The choice of functional was based on its accuracy in describing the interactions between an amine and triflylfluoride, which were the key reactants in this study. To benchmark the performance of different DFT methods, a DMAP-triflylfluoride complex was constructed. The functional was based on its accuracy in describing the interactions between an amine and triflylfluoride, which were the key reactants in this study. To benchmark the performance of different DFT methods, a DMAP-triflylfluoride complex was constructed. To ensure the complex corresponded to an actual minima on the potential energy surface, a vibrational analysis was performed. Next, using the same method, a relaxed scan starting from the optimized complex was initiated where the |N distance was varied from 1.75 Å to 3.75 Å in steps of 0.25 Å resulting in 9 additional structures. The optimization and frequency calculations were performed using the Gaussian software (Revision 16.A).[39] Next, for these 10 structures, single point energy calculations were performed at the cc-pVTZ/DLPNO-CCSD(T) level of theory at the normal accuracy level (normal PNO cut-off scheme: T [CUPANO] = 10^-4, T [CUPNO] = 3.33 x 10^-7, T [CUMN] = 10^-3).[40] Latter calculations were performed using the open-source Orca package (version 4.1) and the energy values served as benchmarking reference.[41] Using the exact same geometries of the 10 structures, single point energy calculations were performed using the DZVP-MOLOPT-GTH plane wave basis set and a set of DFT functionals available in the CP2K code and computationally tractable to perform the simulations. The functionals considered in our benchmark were: LDA[42], PBE-D3[43], revPBE-D3[44] and BLYP-D3[50]. From the results of the benchmark study, it becomes clear that the PBE-D3 functional describes the energetics associated to the amine-triflylfluoride interactions most accurately, based on the root-mean-square deviations (RMSDs) with respect to the relative energies computed at the cc-pVTZ/DLPNO-CCSD(T) level of theory. Besides the lowest RMSD, PBE-D3 and cc-pVTZ/DLPNO-CCSD(T) methods provide similar variation of the energy as a function of the |N distance, i.e. the energy minimum corresponds to the same structure. (Table S8 and Figure S5).

Table S8. Benchmark study using relative energies of different triflyl fluoride-DMAP complexes computed at different levels of theories. cc-pVTZ/DLPNO-CCSD(T) relative energies served as benchmarking reference. All DFT computations were performed with the DZVP-MOLOPT-GTH plane wave basis set and the functional mentioned.

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<th>[N_{DMAP-S_{ trifly}}] distance (Å)</th>
<th>cc-pVTZ/DLPNO-CCSD(T) (kcal mol⁻¹)</th>
<th>LDA (kcal mol⁻¹)</th>
<th>BLYP-D3 (kcal mol⁻¹)</th>
<th>PBE-D3 (kcal mol⁻¹)</th>
<th>revPBE-D3 (kcal mol⁻¹)</th>
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</table>

[40] [N_{DMAP-S_{ trifly}}] distance for optimized complex at the 6-31+G(d)/B3LYP-D3 level of theory including acetonitrile as a solvent implicitly using the SMD solvent model.
Figure S5. Left: evolution of the relative energies as a function of the |N_{DMAP}-S triflyl| distance at different levels of theory. Right: mean absolute deviation (MAD) and root-mean-square deviation (RMSD) of the relative energies obtained with different DFT functionals, computed with respect to the relative energies obtained with the cc-pVTZ/DLPNO-CCSD(T) method.

All simulations were performed in an NVT ensemble with the temperature controlled by the CSVR thermostat using a time constant of 1 fs. For all simulations, the temperature was set at 298 K to match the experimental ambient conditions. Moreover, each system underwent an equilibration phase by performing non-biased AIMD simulations for 5 ps, with a timestep of 1 fs. After this equilibration, Gaussian potentials were added every 25 steps along 2 CVs with a hill height of 2.0 kJ mol\(^{-1}\) and a width scale of 0.02. CVs were defined as coordination numbers (CN) describing the bonding between two atoms in the molecular system using the following mathematical expression.

\[
CN = \sum_{i,j} \left( \frac{r_{ij}}{r_0} \right)^6 \frac{1}{1 - \left( \frac{r_{ij}}{r_0} \right)^{12}}
\]

Here \(r_{ij}\) represents the distance between atom \(i\) and \(j\), while \(r_0\) is a preset reference distance. Details concerning the choice of CN and reference distance for each system are listed in Table S9 to S12.

Reactants together with the solvent (acetonitrile) were randomly placed in a cubic, periodic simulation box using the packmol software. Additionally, the mass of all hydrogens was set to the mass of tritium to dampen excessive proton fluctuations at the 1 fs timestep, which would cause the simulation to be unstable. For each reactive system, simulations were ran in triplicate to ensure statistical relevance of the results. Below the details are presented for each system concerning the simulation box settings, coordination number choice, as well as an example input file.

Entry I

\[
\text{Entry I}
\]

**Table S9.** Details simulation box settings and collective variables for reactive system 1.

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<th>Species</th>
<th>Box edge (Å)</th>
<th>CV1 (CN1) (/ r_0^1) (Å)</th>
<th>CV2 (CN2) (/ r_0^2) (Å)</th>
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\[1^{[4]}\] A half harmonic bias potential was added to CN1 at a value of 0.015 and force constant \(K = 300.0\) a.u. to reduce the sampling region to a relevant chemical space.
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  F  7.187 10.659 -2.129
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PERIODIC XYZ

**&END CELL**

**&N-S**

**&COORDINATION**

ATOMS FROM 9
ATOMS TO 1
R0 [Å] 2.1
**&END COORDINATION**

**&END COLVAR**

**&S-F**

**&COORDINATION**

ATOMS FROM 1
ATOMS TO 4
R0 [Å] 1.8
**&END COORDINATION**

**&END COLVAR**

**&TOPOLOGY**

**&END TOPOLOGY**

**&KIND C**

BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q4

**&END KIND**

**&KIND H**

MASS 3
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q1

**&END KIND**

**&KIND O**

BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q6

**&END KIND**

**&KIND F**

BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q7

**&END KIND**
&END KIND
&KIND N
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q5
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&KIND S
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q5
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&END SUBSYS
&END FORCE_EVAL
&GLOBAL
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RUN_TYPE MD
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&MOTION
&PRINT
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&END RESTART_HISTORY
&TRAJECTORY
&EACH
MD 2
&END EACH
FORMAT DCD
&END TRAJEKTORY
&END PRINT
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ENSEMBLE NVT
STEPS 20000
TIMESTEP 1.0
TEMPERATURE 298
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TYPE CSVR
&CSVR
TIMECON 1
&END CSVR
&END THERMOSTAT
&END MD
&FREE_ENERGY
&METADYN
DO_HILLS TRUE
NT_HILLS 25
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SCALE 0.02
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POSITION 0.015
&DIRECTION WALL_MINUS
K 300.0
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&END WALL
&METAVAR
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SCALE 0.02
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&COLVAR
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&EACH
MD 1
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&END FREE_ENERGY
&END MOTION

Entry II
Table S10. Details simulation box settings and collective variables for reactive system 2.

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<th>Species</th>
<th>Box edge (Å)</th>
<th>CV1 (CN1) / $r_0^1$ (Å)</th>
<th>CV2 (CN2) / $r_0^2$ (Å)</th>
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<td>N_DMAP</td>
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<td>1 x piperidine</td>
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<td>1 x DMAP</td>
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<tr>
<td>17 x acetonitrile</td>
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</tbody>
</table>

[a] A half harmonic bias potential was added to CN1 and CN2 at a value of 0.015 and force constant $K = 300.0$ a.u. to reduce the sampling region to a relevant chemical space.

Input file
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&FORCE_EVAL
  METHOD QS
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      POISSON_SOLVER_PERIODIC
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    POTENTIAL_FILE_NAME GTH_POTENTIALS
    CHARGE 0
    &END QS
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    &XC_FUNCTIONAL PBE
    &END XC_FUNCTIONAL
  &VDW_POTENTIAL
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    PARAMETER_FILE_NAME dftd3.dat
    REFERENCE_FUNCTIONAL PBE
    &END PAIR_POTENTIAL
    &END VDW_POTENTIAL
  &END XC
  &SCF
    EPS_SCF 1.0E-5
    SCF_GUESS RESTART
    &OT
      MINIMIZER DIIS
      PRECONDITIONER FULL_SINGLE_INVERSE
    &END OT
    &END SCF
  &MGRID
    CUTOFF 350
    REL_CUTOFF 50
    COMMENSURATE TRUE
    &END MGRID
  &END DFT
  &SUBSYS
    &COORD
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    C        12.195132        1.210060       -0.705855
    H        10.795523       -0.414862       -2.263381
    H        10.374228       -1.541542       -0.854710
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    H        11.314672        3.259106        0.546817
    H        9.050218        2.068413       -1.726472
    H        10.016247        2.002396       -1.935239
    H        9.172700        0.107528        0.351058
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    H        12.391943        1.412841       -1.753707
    H        11.383755        0.350736       -0.932779
    H        10.692221       -0.337600       -0.547332
    S        1.000000        8.861081        9.568364
    O        1.390398        7.834695       10.446245
    O        1.338001        9.651419        8.567272
    F        3.205155        8.139004        8.816501
    C        3.046763        10.192810       10.314124
    F        2.331180        10.829572       11.134615
    F        3.464410        11.104465        9.443508
    F        4.096400        9.581917       10.967257
    C        13.681665        9.261227        2.559884
    C        12.459516        9.843574        2.419559
    C        13.440365        11.898839        2.707037
    C        14.736830        11.425356        2.604047
    C        14.881499        10.517447        2.385670
    H        16.83101         8.145345        2.104231
    H        15.534626        9.238781        2.395698
    H        13.217563        12.963487        2.752371
    H        15.610242        12.138192        2.738192
    H        13.337773        11.183090        2.893676
    N        16.150461        9.484607        2.363791
    C        16.388392        8.097188        1.993608
    H        17.447168        7.941194        1.839216
    H        16.008841        7.403233        2.764925
    H        15.905294        7.787711        1.056590
    C        17.240175        10.374504        2.675204
    H        16.576757        10.932070        3.605139
    H        18.168495        9.840111        2.856237
    H        17.313763        11.122994        1.866223
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PERIODIC XYZ
&END CELL

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ATOMS_TO 18
R0 [Å] 2.1
&END COORDINATION
&END COLVAR

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ATOMS_FROM 17
ATOMS_TO 35
R0 [Å] 1.2
&END COORDINATION
&END COLVAR

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MASS 3
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RUN_TYPE MD
&END GLOBAL

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TEMPERATURE 298
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TYPE CSVR
CSVR
TIMECON 1
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&END MD
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NT_HILLS 25
WW [kJ/mol] 2.0
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POSITION 0.015
&QUADRATIC
DIRECTION WALL_MINUS
K 300.0
&END QUADRATIC
&END WALL
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&METAVAR 2
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**Entry III**

Table S11. Details simulation box settings and collective variables for reactive system 3.

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<th>Box edge (Å)</th>
<th>CV1 (CN1) / ( r_1 ) (Å)</th>
<th>CV2 (CN2) / ( r_2 ) (Å)</th>
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<tr>
<td>17 x acetonitrile</td>
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\(^[a]A\) half harmonic bias potential was added to CN1 and CN2 at a value of 0.015 and force constant 300.0 a.u. to reduce the sampling region to a relevant chemical space.

**Input file**

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  POTENTIAL_FILE_NAME GTH_POTENTIALS
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  &KO
  &END KO
  &XC
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  &END XC_FUNCTIONAL
  &VDW_POTENTIAL
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  PARAMETER_FILE_NAME dftd3.dat
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  &END VDW_POTENTIAL
  &END XC
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  SCF_GUESS RESTART
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  PRECONDITIONER FULL_SINGULAR_INVERSE
  &END OT
  &END SCF
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Entry III
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<td>6.039110</td>
<td>13.363333</td>
</tr>
<tr>
<td>C</td>
<td>8.406658</td>
<td>6.943331</td>
<td>15.847677</td>
</tr>
<tr>
<td>H</td>
<td>8.913926</td>
<td>7.543956</td>
<td>15.916323</td>
</tr>
<tr>
<td>H</td>
<td>7.334269</td>
<td>6.558093</td>
<td>16.150288</td>
</tr>
<tr>
<td>H</td>
<td>8.934890</td>
<td>5.925872</td>
<td>16.566988</td>
</tr>
</tbody>
</table>

END COORD

&CELL

ABC 12.07 12.07 12.07
PERIODIC XYZ

&END CELL

&COLVAR

&COORDINATION
ATOMS_FROM 16
ATOMS_TO 18
R0 [angstrom] 2.1
&END COORDINATION

&END COLVAR

&N-H

&COLVAR

&COORDINATION
ATOMS_FROM 17
ATOMS_TO 26
R0 [angstrom] 1.2
&END COORDINATION

&END COLVAR

&TOPOLOGY

&KIND C
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q4
&END KIND

&KIND H
MASS 3
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q1
&END KIND

&KIND O
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q8
&END KIND

&KIND F
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q7
&END KIND

&KIND N
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q5
&END KIND

&KIND S
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q9
&END KIND

&END SUBSYS

&FORCE_EVAL

&GLOBAL
PRINT_LEVEL LOW
PROJECT md
RUN_TYPE MD
&END GLOBAL

&AMOTION
Entry IV

Table S12. Details simulation box settings and collective variables for entry IV.

<table>
<thead>
<tr>
<th>Species</th>
<th>Box edge (Å)</th>
<th>CV1 (CN1) / ( r_1^0 ) (Å)</th>
<th>CV2 (CN2) / ( r_2^0 ) (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x triflyfluoride</td>
<td>11.92</td>
<td>( N_{\text{pip1}}S_{\text{ trif}}/)</td>
<td>( N_{\text{pip1}}H_{\text{ trif}}/)</td>
</tr>
<tr>
<td>2 x piperidine</td>
<td>2.1 Å</td>
<td>2.1 Å</td>
<td>1.2 Å</td>
</tr>
<tr>
<td>17 x acetonitrile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[4] A half harmonic bias potential was added to CN1 and CN2 at a value of 0.015 and force constant \( K = 300.0 \) a.u. to reduce the sampling region to a relevant chemical space.
METHOD QS
&DFT
&POISSON
PERIODIC XYZ
POISSON_SOLVER PERIODIC
&END POISSON
BASIS_SET_FILE_NAME BASIS_MOLOPT
POSSON_SOLVER PERIODIC
&POTENTIAL_FILE_NAME GTH_POTENTIALS
CHARGE 0
&AQS
&END QS
&XC
XC_FUNCTIONAL PBE
&END XC_FUNCTIONAL
&DV_POTENTIAL
&PAIR_POTENTIAL
TYPE DFTD3
PARAMETER_FILE_NAME dftd3.dat
REFERENCE_FUNCTIONAL PBE
&END PAIR_POTENTIAL
&END DV_POTENTIAL
&END XC
&SCF
EPS_SCF 1.0E-5
SCF_GUESS RESTART
&OT
MINIMIZER DIIS
PRECONDITIONER FULL_SINGLE_INVERSE
&END OT
&END SCF
&MGRID
CUTOFF 350
REL_CUTOFF 50
COMMENSURATE TRUE
&END MGRID
&END DFT
&SUBSYS
&COORD
S          7.540390       8.390260       10.096187
O          8.191679       7.159264       10.099788
O          8.166865       9.673798       10.008153
F          6.548922       8.590472       11.331284
C          6.046457       8.228096        9.073243
F          5.132298       9.033597        9.356463
F          5.531978       7.067039        9.525965
F          6.279486       8.022781        7.761414
C          6.586982       -0.138470        0.662556
C          6.218902       -1.187535        2.850682
C          4.700763       -0.867766        2.824259
C          4.495899       -0.309322        1.853455
C          5.090513        0.19467         0.49389
H          6.466365       -2.091618        3.386500
H          7.048902       -0.802222        1.085692
H          7.059616       -0.334789       -0.313888
H          4.202647       -1.764126        2.441844
H          4.241692       -0.711426        3.808471
H          3.426686        0.611722        1.61067
H          5.009948       1.208330        2.302755
H          4.632260       -0.800340        0.111001
H          4.876017        0.965421       -0.189822
H          6.646406       -0.312622        3.459641
N          6.777609       -1.321488        1.533256
H          7.671328       -1.778804        1.488628
C          10.391541       8.208779        0.920854
C          9.058601       7.151638        2.732269
C          10.336389       6.581574        3.347152
C          11.457056       6.428100        2.311685
C          11.734497       7.722281        1.498276
H          8.345546       7.429922        3.484396
H          10.062733       7.555581        0.106188
H          10.560269       9.168246        0.401089
H          10.733927       7.240418        4.167088
H          10.135394       5.610842        3.766040
H          12.363366       6.249510        2.942364
H          11.363294       5.566490        1.806454
H          12.151472       8.414145        2.159422
H          12.372813       7.621624        0.620025
H          8.514150       6.389505        2.162866
H          9.308379       8.289852        1.870132
H          9.534121       9.131644        2.460093
N          3.221008       3.305517       -0.528522
C          2.436827       2.303240        0.034956
C          4.097334       4.273277        1.145805
H          5.133189       4.074227        0.876262
H          3.994548       4.274651        2.243380
H          3.845158       5.275171       -0.72688
C          3.095991       7.847837       -0.203699
C          3.345692       8.098968        0.937055
N          2.642314       7.555455       -1.583055
C          3.454283       7.025494       -2.578160
C          2.748271       6.931592       -1.663638
H          2.418651       6.840892       -2.156268
C          1.345018       2.014583        6.271512
N          2.774375       1.850026        6.116698
C         -0.050274       2.242745        6.570036
H         -0.267111       2.950872        5.895515
H          0.125857       2.641811        7.590314
H          0.294730       1.272883        6.580947
C          8.926208       3.303108       10.818781
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<th>Y</th>
<th>Z</th>
</tr>
</thead>
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<td>2.550010</td>
<td>10.414146</td>
</tr>
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<td>C</td>
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<td>4.058154</td>
<td>11.34792</td>
</tr>
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<td>H</td>
<td>7.309894</td>
<td>4.963933</td>
<td>2.906791</td>
</tr>
<tr>
<td>C</td>
<td>10.414146</td>
<td>2.550010</td>
<td>10.414146</td>
</tr>
<tr>
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<td>9.554122</td>
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<td>2.617801</td>
</tr>
<tr>
<td>C</td>
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<td>0.806791</td>
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<td>2.989424</td>
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<tr>
<td>C</td>
<td>12.317181</td>
<td>2.728423</td>
<td>1.518700</td>
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<tr>
<td>H</td>
<td>11.469820</td>
<td>2.032551</td>
<td>0.028766</td>
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<tr>
<td>C</td>
<td>12.317181</td>
<td>2.728423</td>
<td>1.518700</td>
</tr>
<tr>
<td>H</td>
<td>12.317181</td>
<td>2.728423</td>
<td>1.518700</td>
</tr>
</tbody>
</table>

**&END COORD**

**&CELL**

**ABC** 11.92 11.92 11.92

**PERIODIC XYZ**

**&END CELL**

**#N-S1**

**&COLVAR**

**&COORDINATION**

**ATOMS_FROM 24**

**ATOMS_TO 1**

**R0 [angstrom] 2.1**

**&END COORDINATION**

**&END COLVAR**

**#N-H**

**&COLVAR**

**&COORDINATION**

**ATOMS_FROM 41**

---

S61
ATOMS TO 25
R0 [angstrom] 1.2
&END COORDINATION
&END COLVAR
&TOPOLOGY
&END TOPOLOGY
&KIND C
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q4
&END KIND
&KIND H
MASS 3
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q1
&END KIND
&KIND O
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q6
&END KIND
&KIND F
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q7
&END KIND
&KIND N
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q5
&END KIND
&KIND S
BASIS_SET DZVP-MOLOPT-GTH
POTENTIAL GTH-PBE-q6
&END KIND
&END SUBSYS
&END FORCE_EVAL
&GLOBAL
# PREFERRED FFT_LIBRARY FFTSG
PRINT_LEVEL LOW
PROJECT md
RUN_TYPE MD
&END GLOBAL
&MOTION
&DEND_CONSTRAINT
&DPRINT
&RESTART_HISTORY
&EACH
MD 2000
&DEND EACH
&END RESTART_HISTORY
&TRAJECTORY
&EACH
MD 2
&DEND EACH
FORMAT DCD
&DEND TRAJECTORY
&DEND PRINT
&MD
ENSEMBLE NVT
STEPS 10000
TIMESTEP 1.0
TEMPERATURE 298
&THERMOSTAT
TYPE CSVR
&CSVR
TIMECON 1
&DEND CSVR
&DEND THERMOSTAT
&DEND MD
&DFREE_ENERGY
&METADYN
DO_HILLS TRUE
NT_HILLS 25
WW [kjmol] 2.0
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COLVAR 1
SCALE 0.02
&WALL
TYPE QUADRATIC
POSITION 0.015
&DIRECTION WALL_MINUS
K 300.0
&DEND QUADRATIC
&DEND WALL
&DEND METAVAR
&METAVAR 2
COLVAR 2
SCALE 0.02
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TYPE QUADRATIC
POSITION 0.015
&DIRECTION WALL_MINUS
K 300.0
&DEND QUADRATIC
&DEND WALL
&DEND METAVAR
&DPRINT
&COLVAR
COMMON_ITERATION_LEVELS 2
&EACH
MD 1
Analysis

From the trajectories obtained, bond length analyses were performed to gain insight into the reaction pathway for each system. The plots shown in Figure S6, indicate that all reactions occur through a concerted mechanism, as the S-N bond formation and the S-F bond breaking occurs simultaneously. Furthermore, from this analysis a time-interval of the simulation where the transition state occurs can be defined. Accurate determination of the transition state was established by taking a snapshot at the moment when the system reaches its maximum potential energy. At this point, the partial derivatives of the potential energy with respect to the collective variables is equal to zero, indicating a stationary point in the potential energy surface defined in collective variable space. Having localized the transition state in the simulation, the Helmoltz free energy of activation ($\Delta F^\ddagger$) is calculated by equation (2), where $k_B$ denotes the Boltzmann constant, $T$ the temperature, $P_{TS}$ the population at the transition state and $P_{sum}$ the sum of all calculated populations.

Activation energies for each simulation is provided in Table S13.

\[
\Delta F^\ddagger = -k_B T \ln \frac{P_{TS}}{P_{sum}}
\]

Table S13. Helmoltz free energy of activation ($\Delta F^\ddagger$) for each metadynamics simulation performed in this work.

<table>
<thead>
<tr>
<th>entry</th>
<th>run</th>
<th>$\Delta F^\ddagger$ (in kcal mol$^{-1}$)</th>
</tr>
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<tr>
<td>1</td>
<td>A</td>
<td>25.288</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>27.746</td>
</tr>
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<td></td>
<td>C</td>
<td>32.903</td>
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<td>Average</td>
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<td>29 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>12.951</td>
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<tr>
<td></td>
<td>B</td>
<td>12.129</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>14.278</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>13 ± 1</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>21.591</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>22.264</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>22.481</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>22.1 ± 0.5</td>
</tr>
</tbody>
</table>
To elucidate the differences between the DMAP-mediated and the Et₃N-mediated triflylation of piperidine, a Non-Covalent Interaction (NCI) analysis was performed on the transition states of both reactions. Established in 2010, NCI is a method which allows to visualize and quantify both inter- and intramolecular noncovalent interactions in a molecular system or solids based on the relationship between the product of the electron density and the sign of the second eigenvalue of the electron density Hessian matrix ($\rho \text{sign}(\lambda_2)$) and the reduced density gradient ($s$). The reduced density gradient is defined by equation 3, with $\rho$ being the electron density and $\nabla \rho$ its gradient. In this work, the electron density of systems 2 and 3 at the transition states was obtained by performing a single point energy calculation at the 6-31+G(d)/PBE level of theory using the coordinates from the transition state obtained from the metadynamics simulation. Previous studies have shown the robustness of the NCI approach towards the choice of exchange-correlation functional and basis set. As our focus was to single out the interactions between the reactants, we removed the coordinates related to the solvent in this case. Coordinates of the respective transition states in absence of solvent molecules can be found below. The NCIPLOT program version 4.0 was used to run the calculations, while visualization of the isosurfaces in 3D was accomplished by the VMD software version 1.9.3.

$$s = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla \rho|}{\rho^{4/3}}$$
9. Copies of the NMR Spectra

$^1$HNMR spectrum of 1

$^{13}$C NMR spectrum of 1
$^{13}$CNMR spectrum of 2

$^{19}$FNMR spectrum of 2
$^1$HNMR spectrum of 3

$^{13}$CNMR spectrum of 3
$^{19}$FNMR spectrum of 3

![Chemical structure of 3](image)

$^1$HNMR spectrum of 4

![Chemical structure of 4](image)
$^{13}$CNMR spectrum of 4

$^{19}$FNMR spectrum of 4
$^1$HNMR spectrum of 5

\[ \text{NMR spectrum image} \]

$^{13}$CNMR spectrum of 5

\[ \text{NMR spectrum image} \]
$^{13}$CNMR spectrum of 6

$^{19}$FNMR spectrum of 6
$^1$HNMR spectrum of 7 (DMSO-d6)

$^{13}$CNMR spectrum of 7 (DMSO-d6)
$^{19}$F NMR spectrum of 7 (DMSO-d$_6$)

$^1$HNMR spectrum of 8
$^{13}$CNMR spectrum of 8

$^{19}$FNMR spectrum of 8
$^1$HNMR spectrum of 9

$^{13}$CNMR spectrum of 9
$^{19}$FNMR spectrum of 9

$^1$HNMR spectrum of 10
$^{13}$CNMR spectrum of 10

10

$^{19}$FNMR spectrum of 10

10
$^1$HNMR spectrum of 11

$^{13}$CNMR spectrum of 11
$^{19}$F NMR spectrum of 11

1H NMR spectrum of 12
$^{19}$CNMR spectrum of 12

$^{19}$FNMR spectrum of 12
$^1$HNMR spectrum of 13

$^{13}$CNMR spectrum of 13
$^{19}$F-NMR spectrum of 13

$^1$H-NMR spectrum of 14
$^1$HNMR spectrum of 15

$^{13}$CNMR spectrum of 15
$^{19}$F NMR spectrum of 15

1H NMR spectrum of 16
$^{13}$CNMR spectrum of 16

$^{19}$FNMR spectrum of 16
$^1$H NMR spectrum of 17

$^{13}$C NMR spectrum of 17
$^{19}$FNMR spectrum of 17

$^1$HNMR spectrum of 18
$^{13}$CNMR spectrum of 18

![CNMR spectrum of 18](image)

$^{19}$FNMR spectrum of 18

![FNMR spectrum of 18](image)
$^1$HNMR spectrum of 19

$^{13}$CNMR spectrum of 19
$^{19}$FNMR spectrum of 19

$^1$HNMR spectrum of 20
$^{13}$CNMR spectrum of 20

$^{19}$FNMR spectrum of 20
$^1$HNMR spectrum of 21

$^{13}$CNMR spectrum of 21
$^{19}$F NMR spectrum of 21

1H NMR spectrum of 22

21

22
$^{13}$CNMR spectrum of 22

![CNMR spectrum of 22](image)

$^{19}$FNMR spectrum of 22

![FNMR spectrum of 22](image)
$^1$HNMR spectrum of 23

$^{13}$CNMR spectrum of 23
\( ^{19}\text{FNMR} \text{ spectrum of 23} \)

\( ^{1}\text{HNMR} \text{ spectrum of 24 (Methanol-}d_4) \)
$^{13}$CNMR spectrum of 24 (Methanol-$d_4$)

$^{19}$FNMR spectrum of 24 (Methanol-$d_4$)
$^1$HNMR spectrum of 25 (in DMSO-$d_6$)

$^{13}$CNMR spectrum of 25 (in DMSO-$d_6$)
$^{19}$FNMR spectrum of 25 (in DMSO-$d_6$)

$^1$HNMR spectrum of 26
$^{13}$CNMR spectrum of 26

$^{19}$FNMR spectrum of 26
$^1$HNMR spectrum of 27

$^{13}$CNMR spectrum of 27
$^{19}$FNMR spectrum of 27 (Methanol-$d_4$)

$^1$HNMR spectrum of 28 (Methanol-$d_4$)
$^{13}$CNMR spectrum of 28 (Methanol-d$_4$)

$^{19}$FNMR spectrum of 28 (Methanol-d$_4$)
$^1$H NMR spectrum of 29

$^{13}$C NMR spectrum of 29
$^{19}$FNMR spectrum of 29

$^1$HNMR spectrum of 33
$^{19}$CNMR spectrum of 33

$^{19}$FNMR spectrum of 33
$^{1}$HNMR spectrum of 34

$^{13}$CNMR spectrum of 34
$^1$HNMR spectrum of 35

$^{13}$CNMR spectrum of 35
$^{19}$FNMR spectrum of 35

$^1$HNMR spectrum of 36
$^{19}$F NMR spectrum of 36

$^{13}$C NMR spectrum of 36

36
$^1$HNMR spectrum of 37

$^{13}$CNMR spectrum of 37

37
$^1$HNMR spectrum of 38 (DMSO-$d_6$)

$^{13}$C NMR spectrum of 38 (DMSO-$d_6$)
$^1$HNMR spectrum of 39

39

$^{13}$C NMR spectrum of 39

39
$^1$HNMR spectrum of 40

$^{13}$C NMR spectrum of 40
$^1$H NMR spectrum of 42

$^{13}$C NMR spectrum of 42
$^1$HNMR spectrum of 43

$^{13}$CNMR spectrum of 43
$^1$HNMR spectrum of 44

$^{13}$CNMR spectrum of 44
$^{1}$HNMR spectrum of 45

$^{13}$CNMR spectrum of 45
$^1$HNMR spectrum of S1

$^{13}$CNMR spectrum of S1
$^{19}$FNMR spectrum of S1

![FNMR spectrum of S1](image)

$^1$HNMR spectrum of S2 (DMSO-d6)

![HNMR spectrum of S2](image)
$^{13}$C NMR spectrum of S2 (DMSO-$d_6$)

$^{19}$F NMR spectrum of S2 (DMSO-$d_6$)
$^1$HNMR spectrum of S3

$^{13}$CNMR spectrum of S3
$^{19}$F NMR spectrum of S3

$^1$H NMR spectrum of S4
$^{13}$CNMR spectrum of S4

$^{19}$FNMR spectrum of S4
$^1$HNMR spectrum of S5

$^{13}$C NMR spectrum of S5
$^{19}$F NMR spectrum of S5

$^1$H NMR spectrum of S6

S4

S5
$^{13}$CNMR spectrum of S6

$^{19}$FNMR spectrum of S6
$^1$HNMR spectrum of 46

$^{13}$CNMR spectrum of 46
$^{13}$CNMR spectrum of 47

$^{19}$FNMR spectrum of 47
$^1$HNMR spectrum of 48

$^{13}$CNMR spectrum of 48
$^{19}$F NMR spectrum of 48

$^1$H NMR spectrum of 49
$^{13}$CNMR spectrum of 49

![CNMR spectrum of 49](image)

$^{19}$FNMR spectrum of 49

![FNMR spectrum of 49](image)
$^1$HNMR spectrum of 50

$^{13}$CNMR spectrum of 50
$^{19}$F NMR spectrum of 50

$^1$H NMR spectrum of 51
$^{13}$CNMR spectrum of 51

$^{19}$FNMR spectrum of 51
$^1$HNMR spectrum of 52

$^{13}$CNMR spectrum of 52
$^{19}$FNMR spectrum of 52

$^1$HNMR spectrum of 53
$^{13}$CNMR spectrum of 53

$^{19}$FNMR spectrum of 53
$^1$HNMR spectrum of 54

$^{13}$CNMR spectrum of 54
$^{19}$FNMR spectrum of 54

$^1$HNMR spectrum of 55
$^{13}$CNMR spectrum of 55

$^{19}$FNMR spectrum of 55
$^1$HNMR spectrum of 56

$^{13}$CNMR spectrum of 56
$^{19}$F NMR spectrum of 56

$^1$H NMR spectrum of 57
$^{13}$CNMR spectrum of 57

$^{19}$FNMR spectrum of 57
$^1$HNMR spectrum of 58 (CDCl$_3$ and DMSO-$d_6$)

$^{13}$CNMR spectrum of 58 (DMSO-$d_6$)
$^{19}$FNMR spectrum of 58 (DMSO-d6)

$^1$HNMR spectrum of 59
$^{13}$CNMR spectrum of 59

$^{19}$FNMR spectrum of 59
$^1$HNMR spectrum of 60

$^{13}$CNMR spectrum of 60
$^{19}$F NMR spectrum of 60

$^1$H NMR spectrum of 61
$^{13}$CNMR spectrum of 61

$^{19}$FNMR spectrum of 61
$^1$HNMR spectrum of 62

$^{13}$CNMR spectrum of 62
$^{19}$F NMR spectrum of 62

$^1$H NMR spectrum of 63
$^{13}$CNMR spectrum of 63

$^{19}$FNMR spectrum of 63
$^1$HNMR spectrum of 64

$^{13}$CNMR spectrum of 64
$^{19}$F NMR spectrum of 64

$^1$H NMR spectrum of 65
$^{13}$CNMR spectrum of 65

$^{19}$FNMR spectrum of 65
$^1$HNMR spectrum of 66

\[ \text{HNMR spectrum of 66} \]

$^{13}$CNMR spectrum of 66

\[ \text{CNMR spectrum of 66} \]
$^{13}$F NMR spectrum of 66

$^1$H NMR spectrum of 67
$^{13}$CNMR spectrum of 67

$^{19}$FNMR spectrum of 67
$^{19}$FNMR spectrum of 68

\[
\text{Chemical structure of 68}
\]

$^1$HNMR spectrum of 69 (DMSO-$d_6$)

\[
\text{Chemical structure of 69}
\]
$^{13}$CNMR spectrum of 69 (DMSO-d$_6$)

$^{19}$FNMR spectrum of 69 (DMSO-d$_6$)
$^{1}\text{HNMR}$ spectrum of 70

$^{13}\text{CNMR}$ spectrum of 70
$^{19}$FNMR spectrum of 70
10. Copies of the HPLC Spectra

To verify whether racemization had taken place under the triflation conditions of method A (scheme 2 in the paper), tyrosine derivative 25 was subjected to chiral HPLC analysis for the separation of enantiomers. Because the carboxylic acid group of 25 was incompatible with the column, the compound was methylated to give the N,O-bisprotected derivative Boc-L-Tyr(OTf)-OMe as shown below. Separation conditions: CHIRALPAK® AD-H heptane/iPrOH 70:30 0.6 mL/min, (R) and (S)-enantiomers at 8.7 min and 12.4 min, respectively.
Chemical Formula: C_{22}H_{38}N_{2}O_{3}
Exact Mass: 376.2726
Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=250,4 Ref=off

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<tr>
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<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>[min]</td>
<td>[min]</td>
<td>[mAU*s]</td>
<td>[mAU]</td>
<td>[mAU]</td>
<td>[mAU]</td>
</tr>
<tr>
<td>1</td>
<td>6.121B</td>
<td>0.2383</td>
<td>1350.74524</td>
<td>81.09950</td>
<td>49.4625</td>
</tr>
<tr>
<td>2</td>
<td>10.543B</td>
<td>0.3601</td>
<td>1380.10413</td>
<td>53.12610</td>
<td>50.5375</td>
</tr>
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</table>

Totals : 2730.84937 134.22561

Signal 2: DAD1 G, Sig=273,4 Ref=off

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>[min]</td>
<td>[min]</td>
<td>[mAU*s]</td>
<td>[mAU]</td>
<td>[mAU]</td>
<td>[mAU]</td>
</tr>
<tr>
<td>1</td>
<td>6.122B</td>
<td>0.2237</td>
<td>187.00113</td>
<td>11.56481</td>
<td>48.6384</td>
</tr>
<tr>
<td>2</td>
<td>10.536B</td>
<td>0.3155</td>
<td>197.47086</td>
<td>7.64063</td>
<td>51.3616</td>
</tr>
</tbody>
</table>

Totals : 384.47198 19.20464

*** End of Report ***

Chemical Formula: C_{22}H_{36}N_{2}O_{3}
Exact Mass: 376.2726
Data File E:\Chem32\1\Data\all\def_LC_Purge 2021-12-13 11-22-10\OnlineEdited0.D
Sample Name: ly-71-c-6

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Do not use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=250,4 Ref=off

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[min]</td>
<td>[mAU*s]</td>
<td>[mAU]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6.112</td>
<td>0.2408</td>
<td>764.91138</td>
<td>45.35095</td>
<td>30.3219</td>
</tr>
<tr>
<td>2</td>
<td>10.500</td>
<td>0.3578</td>
<td>1757.72583</td>
<td>66.62794</td>
<td>69.6781</td>
</tr>
</tbody>
</table>

Totals : 
2522.63721 111.97889

Signal 2: DAD1 G, Sig=273,4 Ref=off

<table>
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<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td># [min]</td>
<td>[min]</td>
<td>[mAU*s]</td>
<td>[mAU]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6.112</td>
<td>0.2131</td>
<td>105.79185</td>
<td>6.45851</td>
<td>30.1656</td>
</tr>
<tr>
<td>2</td>
<td>10.494</td>
<td>0.3157</td>
<td>244.91148</td>
<td>9.37764</td>
<td>69.8344</td>
</tr>
</tbody>
</table>

Totals : 
350.70334 15.83614

*** End of Report ***
11. Copies of the LC-MS Spectra

LC-MS spectra of L-Tyrosine (starting material of 30)

<table>
<thead>
<tr>
<th>Retention Time (min)</th>
<th>MS Area</th>
<th>Mol. Weight</th>
<th>Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.719</td>
<td>4633693</td>
<td>226.20 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>204.20 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>183.15 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>182.20 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>181.55 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>165.20 I</td>
<td></td>
</tr>
</tbody>
</table>
LC-MS spectra of L-Tyrosine triflate (30) _first test

| Acq. Operator | ：Seq. Line : 28 |
| Acq. Instrument | ：Instrument 1 Location : Vial 39 |
| Injection Date | ：13/04/2021 3:03:02 Inj : 1 |
| Acq. Method | ：D:\DATA\2021\STD_SEQ 2021-04-12 12-12-50\DA_40-40-70-100_20- |
| Last changed | ：5/03/2010 15:30:00 by bds |
| Analysis Method | ：D:\METHODS\KOLOM 2\PREVAIL3U\BA_0-100-100_40-10MIN+_M |
| Last changed | ：13/04/2021 12:41:00 |
| Additional Info | ：Peak(s) manually integrated |

Signal 1: DAD1 A, Sig=215.4 Ref=360,100

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.795</td>
<td>BV</td>
<td>1.5395</td>
<td>2757.19385</td>
<td>21.00307</td>
<td>5.1293</td>
</tr>
<tr>
<td>2</td>
<td>4.654</td>
<td>MM</td>
<td>0.7729</td>
<td>8066.42334</td>
<td>173.95300</td>
<td>15.0062</td>
</tr>
<tr>
<td>3</td>
<td>10.455</td>
<td>MM</td>
<td>1.0579</td>
<td>4.29304e4</td>
<td>676.34216</td>
<td>79.8645</td>
</tr>
</tbody>
</table>
MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

<table>
<thead>
<tr>
<th>Retention Time (MS)</th>
<th>MS Area</th>
<th>Mol. Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.095</td>
<td>1903775</td>
<td>366.95 I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>227.10 I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>195.05 I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>182.20 I</td>
</tr>
<tr>
<td>10.905</td>
<td>27338038</td>
<td>315.10 I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>314.15 I</td>
</tr>
<tr>
<td>43.186</td>
<td>19683</td>
<td>1330.80 I</td>
</tr>
</tbody>
</table>

---

Peak RetTime Type Width Area Height Area %
1 5.095 MM 1.2092 1.00378e6 2.62392e4 6.5061
2 10.905 MM 1.4598 2.73388e7 3.12131e5 53.4267
3 43.186 MM 0.0491 1.96833e4 6675.27344 0.0673

Totals: 2.92615e7 3.45045e5

---

*MSD1 SPC, time=4.397.5.746 of D:\DATA\2021\STD_SEQ 2021-04-12 12-12-5031U2438.D ES-API, Pos, Scan, Frag: 70
Max: 4395
LC-MS spectra of L-Tyrosine triflate (30) _second test

Acq. Operator:  Seq. Line:  28
Acq. Instrument: Instrument 1  Location: Vial 32
Injection Date: 21/04/2021 1:11:12  Inj: 1
                Inj Volume: 10.0 μl
Acq. Method: D:\DATA\2021\STD_SEQ 2021-04-20 11-30-45\DA_40-40-70-100_20-
Last changed: 5/03/2010 15:30:00 by bds
Analysis Method: D:\METHODS\ROLOM 2\PREVAIL30\DA_0-60_20MIN+.M
Last changed: 21/04/2021 15:33:41
(modified after loading)
Additional Info: Peak(s) manually integrated
Signal 1: DADl A, Sig=215.4 Ref=380,100

Peak RetTime Type Width Area Height Area %
---|-------|-------|-------|-------|
1 4.674 MM 0.6636 5767.93066 144.85756 10.5749
2 9.832 MM 1.0359 4.87759e4 784.72253 89.4251

Totals : 5.45437e4 929.58009

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention Time (MS) MS Area Mol. Weight
5.113 1781098 227.05 I
195.00 I
10.240 25129796 315.10 I
314.10 I

Peak RetTime Type Width Area Height Area %
---|-------|-------|-------|-------|
1 5.113 MM 1.2359 1.78110e6 2.40197e4 6.6185
2 10.240 MM 1.2469 2.51298e7 3.35903e5 93.3815

Totals : 2.69109e7 3.59923e5
LC-MS spectra of Leu-enkephalin (starting material of 31)

S184

Acq. Operator : 
Seq. Line : 3
Acq. Instrument : Instrument 1 
Location : Vial 35
Injection Date : 12/04/2021 12:59:04
Inj : 1
Inj Volume : 10.0 μl
Acq. Method : D:\DATA\2021\STD_SEQ 2021-04-12 12-12-50\DA_40-40-70-100_20-
Last changed : 9/03/2020 12:30:00 by 1ds
Analysis Method : D:\DATA\2021\STD_SEQ 2021-05-07 10-41-44\BA_STAB0_20MIN+t_SELAM.M
Last changed : 7/05/2021 15:53:20
(modified after loading)
Additional Info : Peak(s) manually integrated

Signal 1: DAD1 A, Sig=215,4 Ref=360,100 (2021STD_SEQ 2021-04-12 12-12-5031U2432.D)

Peak RetTime Type Width Area Height Area
# | [min] | [min] | [nAU*sec] | [nAU] | %
--- | ------ | ------ | ----------- | ------ | ----
1 | 4.608 MM | 0.5553 | 7359.66553 | 220.89052 | 17.1594
2 | 5.894 MM | 0.7283 | 3.55304e4 | 813.12646 | 82.8406

Totals : 4.26900e4 1034.01690

MSD1 TIC, MS File (D:\DATA\2021\STD_SEQ 2021-04-12 12-12-5031U2432.D) ES-API, Pos, Scan, Frag:70

Peak RetTime Type Width Area Height Area
# | [min] | [min] | [nAU*sec] | [nAU] | %
--- | ------ | ------ | ----------- | ------ | ----
1 | 5.058 MF | 0.8761 | 1.51273e6 | 2.8778e4 | 10.4412
2 | 6.353 FM | 0.9465 | 1.29755e7 | 2.28488e5 | 85.3588

Totals : 1.44883e7 2.57266e8

S184
Peak #1 at 5.058 min (4.124 to 5.567 min)

Peak #2 at 6.353 min (5.567 to 9.606 min)

*** End of Report ***
LC-MS spectra of Leu-enkephalin triflate (31) _first test

Signal 1: DAD1 A, Sig=215.4 Ref=360,100

Peak RetTime Type Width Area Height Area %
---|-----|----|----------|-----|-------|-------|
1 4.364 BV 0.4607 4020.65308 123.21447 6.3293 6.3293
2 5.737 VV 0.4657 2902.80347 90.61417 4.5696 4.5696
3 6.658 VB 0.7006 1.47658e4 290.70630 23.2441 23.2441
5 23.336 BB 2.6250 3.61303e4 165.31367 56.8759 56.8759
6 55.282 BB 0.7918 576.43280 8.58016 0.9074 0.9074
7 58.873 BV 1.1495 1459.36593 14.99378 2.2973 2.2973
8 63.905 BBA 0.6972 1093.51245 18.83832 1.7214 1.7214

Totals : 6.35247e4 728.83930

---

S186
MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

<table>
<thead>
<tr>
<th>Retention (min)</th>
<th>MS Area</th>
<th>Mol. Weight</th>
<th>Mole or Ion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.013</td>
<td>4331612</td>
<td>195.10 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>154.20 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>153.30 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>152.65 I</td>
<td></td>
</tr>
<tr>
<td>7.147</td>
<td>2850464</td>
<td>578.30 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>557.40 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>556.40 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>159.30 I</td>
<td></td>
</tr>
<tr>
<td>12.019</td>
<td>105652</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.960</td>
<td>18464312</td>
<td>690.30 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>689.30 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>680.30 I</td>
<td></td>
</tr>
<tr>
<td>64.260</td>
<td>449081</td>
<td>692.30 I</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>670.25 I</td>
<td></td>
</tr>
</tbody>
</table>

[Graph of MSD1 TIC, MS File, showing retention times and peak areas]

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [min]</th>
<th>Height [e6]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MF</td>
<td>1.3466</td>
<td>4.33161e6</td>
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</tr>
<tr>
<td>2</td>
<td>FM</td>
<td>0.8829</td>
<td>2.85046e6</td>
<td>5.38094e4</td>
<td>10.8792</td>
</tr>
<tr>
<td>3</td>
<td>MM</td>
<td>0.7941</td>
<td>1.05652e5</td>
<td>2217.47437</td>
<td>0.4032</td>
</tr>
<tr>
<td>4</td>
<td>MM</td>
<td>4.1050</td>
<td>1.86643e7</td>
<td>7.49671e4</td>
<td>70.4715</td>
</tr>
<tr>
<td>5</td>
<td>MM</td>
<td>0.8371</td>
<td>4.49081e5</td>
<td>8941.00879</td>
<td>1.7140</td>
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</table>

Totals: 2.62011e7 1.93546e5
# LC-MS spectra of Leu-enkephalin triflate (31) second test

Acq. Operator : 13
Acq. Instrument : Instrument 1
Injection Date : 14/06/2021 20:35:16
Inj Volume : 10.0 μl
Acq. Method : D:\DATA\2021\STD_SEQ 2021-06-14 12-57-09\DA_40-40-70-100_20-
Last changed : 5/03/2010 15:30:00 by bds
Analysis Method : D:\METHODS\KOLMO 1\ZORBAX\FLUSH.M
Last changed : 15/06/2021 15:04:00
(modified after loading)
Additional Info : Peak(s) manually integrated

![DAD1 A, Sig=215,4 Ref=360,100 (2021)STD_SEQ 2021-06-14 12-57-0931U2579.D]  

<table>
<thead>
<tr>
<th>Signal: DAD1 A, Sig=215,4 Ref=360,100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak RetTime</td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td>1 2.294 MM</td>
</tr>
<tr>
<td>2 4.327 MM</td>
</tr>
<tr>
<td>3 5.779 MM</td>
</tr>
<tr>
<td>4 8.659 MM</td>
</tr>
<tr>
<td>5 13.568 MM</td>
</tr>
<tr>
<td>6 61.828 D5A</td>
</tr>
</tbody>
</table>

Totals : 1.0252805 1136.88791

================================================================================================
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

<table>
<thead>
<tr>
<th>Retention Time (min)</th>
<th>MS Area</th>
<th>Mol. Weight or Ion</th>
</tr>
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<tbody>
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<td>5.027</td>
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<td></td>
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<td>195.00 I</td>
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<td></td>
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<td>159.00 I</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
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<td>557.30 I</td>
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<tr>
<td>9.068</td>
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<tr>
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<tr>
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<tr>
<td>1</td>
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<tr>
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<td>57.282</td>
<td>MF</td>
</tr>
<tr>
<td>7</td>
<td>62.578</td>
<td>FM</td>
</tr>
</tbody>
</table>

Totals: 7.66255e7 5.52934e5
LC-MS spectra of Endomorphin-1 (starting material of 32)

Acq. Instrument : Instrument 1  Location : Vial 33
Injection Date : 5/05/2021 17:43:34   Inj : 1
Inj volume : 10.0 µl
Acq. Method :   D:\DATA\2021\STD_SEQ 2021-05-05 12-36-16\DA_20-60-60-100_20-
Last changed :   17/03/2010 10:30:31 by bds
Analysis Method :   D:\DATA\2021\STD_SEQ 2021-05-07 10-41-44\BA_STAB0_20MIN_+_SSLAM.M
Last changed :   7/05/2021 15:39:50
(modified after loading)
Additional Info :  Peak(s) manually integrated

Signal 1: DAD1 A, Sig=215.4 Ref=360,100 (2021\STD_SEQ 2021-05-05 12-36-16\3U2513.D)

Peak RetTime Type Width Area Height Area %
---|-----|-----|----------|-----|-----|-----|-------|-------|
1  3.239 BV  0.5558  2667.64575  57.23273  1.9456
2  4.317 VV  0.4821  8770.92676  244.71590  6.4101
3  4.683 VV  0.2412  3746.41431  236.03462  2.7380
4  6.149 VV  0.7031  4747.68604  91.54134  3.4698
5  25.960 MF  1.0135  1.12588e5  1849.42041  82.1958
6  27.826 FM  0.5554  4428.57910  133.36994  3.2366

Totals :  1.36829e5  2612.31393

MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

Retention  Mol. Weight
Time (MS)   MS Area  or Ion
4.718   865182  227.05 I
26.384   13462094  612.40 r
                        611.40 I
28.356   1176929  613.35 I
                        612.40 I
                        611.40 I
29.710   183188

S196
**LC-MS spectra of Endomorphin-1 triflate (32)_first test**

---

| Acq. Operator | : | Seq. Line : | 30 |
| Acq. Instrument | : | Location : | Vial 34 |
| Injection Date | : | Inj : | 1 |
| | | Inj Volume : | 10.0 µl |
| Acq. Method | : | Last changed : | 17/03/2010 10:30:31 by bds |
| Analysis Method | : | Last changed : | 7/05/2011 15:39:50 |
| | | (modified after loading) |
| Additional Info | : | Peak(s) manually integrated |

**Signal 1: DAD1 A, Sig=215.4 Ref=360.100**

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<td>7</td>
<td>32.319</td>
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<td>1.08917e5</td>
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**Totals :**

1.37707e5 2630.25995

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MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

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<td>5.325</td>
<td>293116</td>
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<td>10.454</td>
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<td>654.20 I</td>
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<td>22.544</td>
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<td>26.992</td>
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<td></td>
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<td>32.632</td>
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<td>744.30 I</td>
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<td>743.35 I</td>
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[Graph of MSD1 TIC, MS File (D:\DATA\2021\STD_SEQ 2021-05-06 12-36-16\31U2515.D) ES-API, Pos, Scan, Frag: 70]

Peak RetTime Type Width Area Weight Area %
# | [min] | [min] | | | | | |
1 | 4.682 | MF | 0.7133 | 6.85758e5 | 1.60224e4 | 3.0401 |
2 | 5.325 | RH | 0.4173 | 2.93116e5 | 1.17082e4 | 1.2994 |
3 | 10.454 | MM | 0.0460 | 3.59877e4 | 1.27772e4 | 0.1595 |
4 | 22.544 | MM | 0.7298 | 2.32916e5 | 5315.23682 | 1.0326 |
5 | 26.992 | MF | 0.7744 | 2.21156e6 | 4.75985e4 | 9.8042 |
6 | 29.332 | RH | 0.0549 | 1.93559e5 | 5515.57471 | 0.8581 |
7 | 29.460 | RH | 0.4380 | 6.40077e4 | 2435.51343 | 0.2838 |
8 | 32.632 | MF | 1.2913 | 1.77542e7 | 2.29155e5 | 78.7075 |
9 | 34.318 | RH | 0.5019 | 1.08608e6 | 3.60683e4 | 4.8148 |
Totals: | 2.25572e7 | 3.66600e8 |

S200
LC-MS spectra of Endomorphin-1 triflate (32)_second test

---

Acq. Operator : Seq. Line : 19
Acq. Instrument : Instrument 1 Location : Vial 33
Injection Date : 8/05/2021 4:52:57 Inj : 1
Inj Volume : 10.0 µl
Acq. Method : D:\DATA\2021\STD_SEQ 2021-05-07 16-26-30\DA_20-60-60-100_20-
Last changed : 17/03/2010 10:30:31 by bds
Analysis Method : D:\DATA\2021\STD_SEQ 2021-05-07 10-41-44\BA_STAB0_20MIN+_SELAM.M
Last changed : 10/05/2021 20:05:31
(modified after loading)
Additional Info : Peak(s) manually integrated

---

Signal 1: DAD1 A, Sig=215,4 Ref=360,100

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Totals : 1.38047e5  2580.38558

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S204
MS Signal: MSD1 TIC, MS File, ES-API, Pos, Scan, Frag: 70
Spectra averaged over upper half of peaks.
Noise Cutoff: 1000 counts.
Reportable Ion Abundance: > 10%.

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Totals: 2.15729e7 3.36098e5

================================================================================================
12. Copies of the IR Spectra

3-(((trifluoromethyl)sulfonyl)oxy)benzoic acid (compound 7, cas number: 32578-33-9)

Chemical Formula: C₈H₅F₃O₅S
Exact Mass: 269.9810
2-hydroxyphenyl trifluoromethanesulfonate (compound 14, cas number: 133617-36-4)
1,2-phenylene bis(trifluoromethanesulfonate) (compound 15, cas number: 17763-91-6)
3-(methoxycarbonyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-1-ium chloride (compound 23)
(S)-1-methoxy-1-oxo-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propan-2-aminium chloride
(compound 24, cas number: 225381-98-3)
(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propanoic acid
(compound 25, cas number: 2093022-49-0)
4-((4-(((trifluoromethyl)sulfonyl)oxy)phenyl)piperazin-1-ium chloride (compound 28)
4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenyl trifluoromethanesulfonate (compound 29)
tert-butyl (S)-(1-oxo-3-phenyl-1-((2,4,4-trimethylpentan-2-yl)amino)propan-2-yl)carbamate
(compound 44, new compound)

Chemical Formula: C_{22}H_{36}N_{2}O_{3}
Exact Mass: 376.2726
1,1,1-trifluoro-N-(4-nitrophenyl)methanesulfonamide (compound S2) (new compound)
1,1,1-trifluoro-N-(2-(2-prop-2-yn-1-yl)oxy)ethyl)methanesulfinamide (compound S3) (new compound)
N-(4-bromophenyl)-1,1,1-trifluoromethanesulfonimidoyl fluoride (compound S4) (cas number: 2273795-55-2)
1,1,1-trifluoro-N-(4-nitrophenyl)methanesulfonimidoyl fluoride (compound S5) (new compound)
1,1,1-trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulphonimidoyl fluoride (compound S6) (new compound)
phenyl \(N\)-(4-bromophenyl)trifluoromethanesulfonimidate (compound 46)

Chemical Formula: \(C_{13}H_9BrF_3NO_2S\)
Exact Mass: 378.9489
4-formyl-2-methoxyphenyl N-(4-bromophenyl)trifluoromethanesulfonimidate (compound 47)

Chemical Formula: C_{16}H_{11}BrF_3NO_5S
Exact Mass: 436.9544
methyl 3-((N-(4-bromophenyl)-S-(trifluoromethyl)sulfonimidoyl)oxy)thiophene-2-carboxylate (compound 48)

Chemical Formula: $\text{C}_{13}\text{H}_9\text{BrF}_3\text{NO}_4\text{S}_2$

Exact Mass: 442.9108
phenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 49, new compound)

Chemical Formula: C_{13}H_9F_3N_2O_4S
Exact Mass: 346.0235
4-allyl-2-methoxyphenyl trifluoro-N-(4-nitrophenyl)methanesulfonimide (compound 50, new compound)
2-bromophenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 51, new compound)
phenyl trifluoro-N-(2-(2-[(prop-2-yn-1-1-ol)oxy]ethyl)methanesulfonimidate (compound 52, new compound)

Chemical Formula: C_{14}H_{16}F_{3}NO_{4}S
Exact Mass: 351.0752
methyl (2S)-2-amino-3-(4-((N-(2-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)S-(trifluoromethyl)sulfonimidoyl)oxy)phenyl)propanoate (compound 53, new compound)
4-(3-oxobutyl)phenyl trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulphonimide (compound 54, new compound)
1-phenyl-4-((trifluoromethyl)sulfonyl)piperazine (compound 55)

Chemical Formula: $\text{C}_{11}\text{H}_{13}\text{F}_3\text{N}_3\text{O}_2\text{S}$

Exact Mass: 294.06
4-phenyl-1-((trifluoromethyl)sulfonyl)piperidine (compound 56)
4-(4-((trifluoromethyl)sulfonyl)piperazin-1-yl)phenyl trifluoromethanesulfonate (compound 60)
N-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-1,1,1-trifluoromethanesulfonamide (compound 62)
N-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-1,1,1-trifluoromethanesulfonamide (compound 63)
1,1,1-trifluoro-N-(3-methylisoxazol-5-yl)methanesulfonamide (compound 65)
3-phenyl-1-((trifluoromethyl)sulfonyl)-1H-pyrazole (compound 66)
3-iodo-1-((trifluoromethyl)sulfonyl)-1H-pyrazolo[3,4-b]pyridine (compound 67)
2-phenyl-1-((trifluoromethyl)sulfonyl)-4,5-dihydro-1H-imidazole (compound 68)
2-phenyl-1-((trifluoromethyl)sulfonyl)-4,5-dihydro-1H-imidazole (compound 69)
1-((trifluoromethyl)sulfonyl)-1H-indol-5-yl trifluoromethanesulfonate (compound 70, new compound)
13. Copies of the HRMS Spectra

3-(((trifluoromethyl)sulfonyl)oxy)benzoic acid (compound 7, cas number: 32578-33-9)

Chemical Formula: C₉H₆F₃O₅S
Exact Mass: 269.9810

3-(methoxycarbonyl)-5-(((trifluoromethyl)sulfonyl)oxy)pyridin-1-ium chloride (compound 23)

Chemical Formula: C₈H₇ClF₃NO₅S
Exact Mass: 320.9686
(S)-1-methoxy-1-oxo-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propan-2-aminium chloride (compound 24, cas number:2253981-98-3)

(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)propanoic acid (compound 25, cas number:2093022-49-0)
4-((trifluoromethyl)sulfonyloxy)phenyl)piperazin-1-ium chloride (compound 28)

Chemical Formula: C₁₁H₁₄ClF₃N₂O₃S
Exact Mass: 346.03658

Chemical Formula: C₂₁H₂₁ClF₃N₃O₃S
Exact Mass: 487.0944
4-((7-chloroquinolin-4-yl)amino)-2-((diethylamino)methyl)phenyl trifluoromethanesulfonate (compound 29)

Chemical Formula: C_{22}H_{36}N_{2}O_{3}
Exact Mass: 376.2726

 tert-butyl (S)-(1-oxo-3-phenyl-1-((2,4,4-trimethylpentan-2-yl)amino)propan-2-yl)carbamate (compound 44, new compound)

Chemical Formula: C_{7}H_{10}F_{3}N_{2}O_{3}S
Exact Mass: 253.9973
1,1,1-trifluoro-N-(4-nitrophenyl)methanesulfinamide (compound S2) (new compound)

Chemical Formula: C₉H₁₂F₃NO₃S
Exact Mass: 259.0490

1,1,1-trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfinamide (compound S3) (new compound)

Chemical Formula: C₇H₇BrF₄NOS
Exact Mass: 304.9133
N-(4-bromophenyl)-1,1,1-trifluoromethanesulfonimidoyl fluoride (compound S4) (cas number: 2273795-55-2)

1,1,1-trifluoro-N-(4-nitrophenyl)methanesulfonimidoyl fluoride (compound S5) (new compound)

1,1,1-trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfonimidoyl fluoride (compound S6, new compound)
phenyl N-(4-bromophenyl)trifluoromethanesulfonimidate (compound 46, new compound)

4-formyl-2-methoxyphenyl N-(4-bromophenyl)trifluoromethanesulfonimidate (compound 47, new compound)
methyl 3-((N-(4-bromophenyl)-S-(trifluoromethyl)sulfonimidoyl)oxy)thiophene-2-carboxylate (compound 48, new compound)
phenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 49, new compound)

4-allyl-2-methoxyphenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 50, new compound)
2-bromophenyl trifluoro-N-(4-nitrophenyl)methanesulfonimidate (compound 51, new compound)

phenyl trifluoro-N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfonimidate (compound 52, new compound)
methyl (2S)-2-amino-3-(4-((N-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethyl)-S-(trifluoromethyl)sulfonimidoyl)oxy)phenyl)propanoate (compound 53, new compound)

4-(3-oxobuty)phenyl trifluoro-N-(2-((prop-2-yn-1-yloxy)ethoxy)ethyl)methanesulfonimide (compound 54, new compound)
1-phenyl-4-((trifluoromethyl)sulfonyl)piperazine (compound 55)
4-phenyl-1-((trifluoromethyl)sulfonyl)piperidine (compound 56)
4-(4-((trifluoromethyl)sulfonyl)piperazin-1-yl)phenyl trifluoromethanesulfonate (compound 60)

Chemical Formula: C_{12}H_{13}F_{3}N_{2}O_{3}S_{2}

Exact Mass: 442.0092

No mass corresponding (HRMS, APCI, Water radian)

N-((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-1,1,1-trifluoromethanesulfonamide (compound 62)
N-(((1S,2R,5S)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl)-1,1,1-trifluoromethanesulfonamide (compound 63)
1.1.1-trifluoro-N-(3-methylisoxazol-5-yl)methanesulfonamide (compound 65)

Chemical Formula: 
C_{3}H_{5}F_{3}N_{2}O_{2}S 
Exact Mass: 276.02 

3-phenyl-1-((trifluoromethyl)sulfonyl)-1H-pyrazole (compound 66)
3-iodo-1-((trifluoromethyl)sulfonyl)-1H-pyrazolo[3,4-b]pyridine (compound 67)

2-phenyl-1-((trifluoromethyl)sulfonyl)-4,5-dihydro-1H-imidazole (compound 68)
2-phenyl-1-((trifluoromethyl)sulfonyl)-4,5-dihydro-1H-imidazole (compound \textit{69})

1-((trifluoromethyl)sulfonyl)-1H-indol-5-yl trifluoromethanesulfonate (compound \textit{70}, new compound)
14. References


15. Additional literature

- Selected references where the OTf leaving group outperforms the halide series, due to difference of the chemical environment or absence of side reactions:

$$\text{X} = \text{OTf} > \text{I} > \text{Br} > \text{Cl}$$


- References that have investigated the role of solvent, metal and ligand on (pseudo)halide selectivity:

$$X > \text{OTf} \quad \text{Ni or Pd}^0 \quad \text{apolar} \quad \text{OTf} \quad \text{vs.} \quad \text{OTf} \quad \text{Pd}^{II} \quad \text{polar} \quad \text{OTf} > X$$


- References that discuss chemodivergence in halophenyl triflates:


- Iterative cross-coupling of OTf-containing halobenzenes:


- References that report selective cross-electrophile coupling involving aryl triflates:


- References that discuss cationic metal complexes involving non-coordinating OTf ligands: