Radical Carbofluorination of Unactivated Alkenes with Fluoride Ions

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Wipf Group Current Literature
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Why fluorine?

- About 1/3 of drugs approved by the FDA contain fluorine
- Reduce basicity of nearby functional groups
- Increase stability and slow down hydrolytic metabolism
- Introducing fluorine on aliphatics remains a problem

Some current methods

- Nucleophilic fluorination (HF/pyridine, TBAF)
  - Dual reactivity: base and nucleophile
  - Deoxyfluorination (DAST, Deoxofluor)
    - Requires an alcohol
- Hypervalent halogen-based fluorination (IPy₂BF₄, p-Tol-IF₂)
- Electrophilic fluorination (“F⁺”)
  - N-F, O-F, Xe-F, F-F bonds
    - Low selectivity, difficult preparation, high toxicity

- Catalytic methods improve selectivity and yields, but usually still implement these reagents

Chem. Soc. Rev., 2016, 45, 6270-6288
Carbofluorination

- **R1**
- **R2**

\[ \text{SelectFluor, AgNO}_3 (0.2 \text{ eq}) \]
\[ \text{H}_2\text{O/CH}_2\text{Cl}_2/\text{AcOH/H}_3\text{PO}_4 \]
\[ 50 \, ^\circ\text{C}, 24 \text{ h} \]
\[ 44-92\% \]

- **I**
- **X**

\[ \text{Pd}_2(\text{dba})_3 (5 \text{ mol\%}) \]
\[ \text{Ligand (20-30 mol\%)} \]
\[ \text{AgF (1.5 eq)} \]

\[ \text{BF}_3\text{OEt}_2 (2.0 \text{ eq}) \]
\[ \text{CH}_2\text{Cl}_2 (2.5 \text{ mM}) \]
\[ \text{rt, 10 min} \]
\[ 40-83\% \]

- **NTs**

- **OAc**

\[ \text{SelectFluor} \]
\[ \text{MeCN/H}_2\text{O} \]
\[ \text{rt, 3 h} \]
\[ 25-57\% \]

*Chem. Sci.*, 2013, 4, 1216–1220
Title Paper

• Fluorotrichloromethylation

• Carbofluorination with alkyl chlorides
  • Inter/intramolecular

• Fluorotrifluoromethylation

• Mechanistic studies
Chlorine vs. Fluorine Atom Transfer

- CAT is a faster process than FAT
Fluorotrichloromethylation Optimization

\[
\begin{align*}
\text{entry} & \quad \text{reagents (equiv)} & \quad \text{yield (\%)} \\
1 & \quad \text{Cu(OTf)}_2 (0.3), \ L1 (0.3), \text{CsF (2.0)} & \quad <5 \quad 0 \\
2 & \quad \text{CuF}_2 (0.7), \ L1 (0.7) & \quad 5 \quad 0 \\
3 & \quad \text{Cu(OTf)}_2 (0.7), \ L1 (0.7), \text{AgF (2.0)} & \quad 7 \quad 1 \\
4 & \quad \text{Cu(OTf)}_2 (0.7), \ L1 (2.7), \text{AgF (2.0)} & \quad 4 \quad 20 \\
5 & \quad \text{Cu(OTf)}_2 (0.7), \ L1 (0.7), \text{CsF (2.0), [Ag]} & \quad 27 \quad 52 \\
6 & \quad \text{Cu(OTf)}_2 (0.7), \ L2 (0.7), \text{CsF (2.0), [Ag]} & \quad 15 \quad 8 \\
7 & \quad \text{Cu(OTf)}_2 (0.7), \ L3 (0.7), \text{CsF (2.0), [Ag]} & \quad 24 \quad 63 \\
8 & \quad \text{Cu(OTf)}_2 (1.0), \ L3 (1.0), \text{CsF (2.0), [Ag]} & \quad 30 \quad 57 \\
9 & \quad [\text{Cu(L3)}_3]\_\text{F}_2\_\text{H}_2\text{O (1.0), [Ag]} (2.0) & \quad 10 \quad 71 \\
10 & \quad [\text{Cu(L3)}_3]\_\text{F}_2\_\text{H}_2\text{O (1.2), [Ag]} (2.0) & \quad <5 \quad 77 \\
11 & \quad [\text{Cu(L3)}_3]\_\text{F}_2\_\text{H}_2\text{O (1.0)} & \quad 55 \quad 0 \\
12 & \quad [\text{Cu(L3)}_3]\_\text{F}_2\_\text{H}_2\text{O (1.2), AgBF}_4 (2.0) & \quad 7 \quad 14 \\
13 & \quad [\text{Ag}] (2.0) & \quad 0 \quad 0
\end{align*}
\]
Fluorotrichloromethylation Scope

Negligible CAT for 1,1'-disubstituted alkenes

CAT predominated for monosubstituted alkenes

- R = p-CN-C6H4, 77%
- R = o-CO2Me-C6H4, 80%
- R = furan-2-yl, 71%

73%, dr 95:5
Carbofluorination with Alkyl Chlorides

These substrates are inaccessible by other carbofluorination methods.
Intramolecular Carbofluorination

\[ \text{[Cu(L3)F}_2\text{]}\text{H}_2\text{O (1.2 eq)} \]
\[ \text{[Ag] (2.0 eq)} \]

MeCN, N\(_2\), 80 °C, 12 h

\[ \text{73% 5-exo} \]
\[ \text{75% 6-exo} \]
\[ \text{24% 7-endo} \]
Why fluorotrichloromethylation?

• Although the authors mention no specific reason…

• Some natural products contain trichloromethyl groups

• Pharmaceuticals (uncommon)

• Proof of concept

• Show it can work for alkyl chlorides (which is more useful)

*Chem. Asian J.*, 2011, 6, 2260 – 2263
Improvements?

- Stoichiometric copper
- Tri/dichloro substituents are uncommon
  - CF₃ groups are more common
- Pursued fluorotrifluoromethylation

Fluorotrifluoromethylation

\[
\text{CsF (2.0 eq), } [\text{CF}_3] (1.7 \text{ eq}) \quad \text{Cu(OTf)}_2 (30 \text{ mol } \%), \text{ BC (20 mol } \%) \quad \text{L3 (40 mol } \%) \quad \text{hv (11 W)}
\]

MeCN, 80 °C, 6 h

<table>
<thead>
<tr>
<th>entry</th>
<th>variation</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>dark (no hv)</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>L3 in place of BC</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>BC in place of L3</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>without BC</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>without L3</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>without visible light and BC</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>without visible light and L3</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>without Cu(OTf)_2</td>
<td>0</td>
</tr>
</tbody>
</table>

[CF_3]

Umemoto’s reagent

5/26/18

Nikhil Tasker @ Wipf Group
Fluorotrifluoromethylation Scope

CsF, [CF$_3$]Cu(OTf)$_2$, L3/BC
MeCN, 80 ºC, 6 h visible light

84%

82%

76%

60% cis/trans 50:50

73%

18%
Proposed Mechanism

\[ \text{Proposed Mechanism} \]

\[ \text{MeCN, 80 °C, 10 h, visible light} \]

\[ \text{CsF, [CF}_{3}]_{2}, \text{Cu(OTf)}_{2}, \text{L3/BC} \]

\[ \text{Ts} \rightarrow \text{F} \]

\[ \text{F} \]

\[ \text{Ts} \]

\[ \text{F} \]

\[ \text{MeCN, 80 °C, 10 h, visible light} \]

\[ \text{CsF, [CF}_{3}]_{2}, \text{Cu(OTf)}_{2}, \text{L3/BC} \]

\[ \text{Ts} \rightarrow \text{F} \]

\[ \text{F} \]

\[ \text{Ts} \]

\[ \text{F} \]

\[ \text{MeCN, 80 °C, 10 h, visible light} \]

\[ \text{CsF, [CF}_{3}]_{2}, \text{Cu(OTf)}_{2}, \text{L3/BC} \]

\[ \text{Ts} \rightarrow \text{F} \]

\[ \text{F} \]

\[ \text{Ts} \]

\[ \text{F} \]

\[ \text{MeCN, 80 °C, 10 h, visible light} \]

\[ \text{CsF, [CF}_{3}]_{2}, \text{Cu(OTf)}_{2}, \text{L3/BC} \]

\[ \text{Ts} \rightarrow \text{F} \]

\[ \text{F} \]

\[ \text{Ts} \]

\[ \text{F} \]
Isolated Catalyst

- Computational studies suggest perpendicular approach to plane of dimer results in insensitivity to steric factors
UV/Vis Studies

- G – Cu(OTf)₂, CsF
- C – Cu(OTf)₂, CsF, L₃, BC
- F – Cu(OTf)₂, CsF, BC
- H – [Cu(L₃)F₂·H₂O
- J – BC

Conclusion: BC helps to excite electron to initiate reaction. L₃ increases rate of FAT.
Summary

- Mild and practical
- Broad scope and functional group tolerant
- Moderate to good yields

- **L3, [Ag]**, Umemoto’s reagent = $$$
- Not stereoselective – substrate control
- Racemic mixtures (mostly) and best suited for achiral substrates/products
- Tri-substituted alkenes?