Non-Directed Oxidation of Unactivated C(sp\(^3\))-H Bonds

LSPN GROUP SEMINAR BY BALÁZS BUDAI
28.02.2019
Non-Directed C(sp³)-H oxidation

Focus on:
• Non-directed C(sp³)-H oxidation
• Non-activated C(sp³)-H bonds

Challenges
C(sp³)-H bond properties:
1. BDE ~96-101 kcal/mol
2. Lack of high energy n orbital
3. Lack of low energy π* orbital
4. Very high pKa

Overoxidation
1. Product is often more reactive than SM
2. FG tolerance

Regioselectivity – strategies:
1. Tune redox potential of reagent
2. Play with steric elements
3. Directing group
4. Intramolecular reaction

Briefly or Not Discussed:
• Activated C(sp³)-H bonds
• Methods with low synthetic utility
• Supramolecular systems
• Enzymatic oxidations
• Heterogeneous methods
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"C(sp3)-H oxidation" in the literature

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- Activated C(sp³)-H bonds
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- Heterogeneous methods

Note that the numbers are still very small!

Is it the beginning of something bigger?
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- Heterogeneous methods

“C(sp³)-H oxidation” in the literature

Sum of Times Cited by Year

Booming literature – concept change

Before 2007
Directing group / molecular recognition is necessary to distinguish between C-H bonds

Following 2007
Electronic, steric and stereoelectronic effects together can control selectivity between C-H bonds

Is it the beginning of something bigger?

Note that the numbers are still very small!
Historical overview

Henry J.H. Fenton
\[ \text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^+ \]
\[ \text{Fe}^{3+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{2+} + \text{HOO}^- + \text{H}^+ \]
- HO-H bond BDE = 119 kcal/mol
  (2\textsuperscript{nd} strongest after H-F BDE 136 kcal/mol)
- Oxidizes everything
- Wastewater treatment

1894

Shilov
stoichiometric in Pt
overoxidation

Periana
catalytic in Pt
no overoxidation
high yield (70% in one pass)

1969
Shilov system
CH\(_4\) + PtCl\(_6^{2-}\) + H\(_2\)O \(120\^\circ\)C \(\rightarrow\) CH\(_3\)OH + PtCl\(_6^{2-}\) + 2 HCl

1982
Bergman
C(sp\(^3\))-H oxidative addition

1998
Shilov-Periana process

TFDO / Curci JOC 1988 3890
DMDO / Murray, JOC 1985 2847
Oxaziridine / DesMarteau JOC 1993 4754
Periana Science 1998 560

Oxaziridine
Stable at r.t.
selective for 3° C-H bonds
easy to prepare

“Gif systems are geographically based:
G for Gif-sur-Yvette, O for Orléans, A for Aggie, Texas A&M, and Ch is for Chemogolovka, Russia.” - Barton, D. H. R.

Fenton, JChemSocTrans 1894 899-910
Shilov Zhurnal Fizicheskoi Khimii 1969 2174-2175
Bergman JACS 1982 352

Gif reaction (1983)
Barton

DMDO (1985)

Periana
Science 1998 560

Oxaziridine
DesMarteau
JOC 1993 4754

TFDO
Curci
JOC 1988 3890

DMDO
Murray,
JOC 1985 2847

Oxaziridine
Gif
AcOH / H\(_2\)O
Fe(III), Na\(_2\)S, O\(_2\)
Pyr
Gif
Oxidation reaction

Stereoretentive C(sp\(^3\))-H ox.
Historical overview

Henry J.H. Fenton
\[ \text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{H}^+ \]
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Gif reaction and its varieties by Barton

Heme and non-heme Fe/Mn cat.:
- Bernard Meunier
- John T. Groves
- Lawrence Que
- Miquel Costas
- David Goldberg

C-H oxidative addition (via preexisting function)

Fenton, JChemSocTrans 1894 899-910
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Bergman JACS 1982 352
Ligands developed for C(sp3)-H oxidation (before 2007)

Scheme 5.12 Iron catalysts with tridentate N-based ligands. OTf stands for CF$_3$SO$_3$ anion.

Scheme 5.14 Schematic representation of relevant tetradentate ligands used to prepare mononuclear iron(II) complexes to perform alkane oxidations.
White – the first preparatively useful method

Reaction development

\[
\text{PivO}^\text{t} \xrightarrow{\text{cat. (5 mol\%)} \ \text{AcOH} \ \text{H}_2\text{O}_2 \ (1.2 \text{ equiv})} \xrightarrow{\text{MeCN, r.t.}} \text{PivO}^\text{t} \quad \text{d.r. >99:1}
\]

\[
\begin{align*}
\text{Fe}^{2+} & \quad \text{Fe}^{2+} \\
\text{Fe}^{2+}(S,S\text{-PDP}) & \quad \text{(BbFe)}_2
\end{align*}
\]

\[
\text{[Fe}^{2+}(S,S\text{-bpbp})(\text{MeCN})_2]^{2+}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>AcOH(equiv.)</th>
<th>Yield (%)</th>
<th>Conv. (%)²</th>
<th>Select (%)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Fe&quot;(mep)(CH}_3\text{CN})_2]^{2+}</td>
<td>0</td>
<td>7</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>[Fe&quot;(S,S-bpbp)(CH}_3\text{CN})_2]^{2+}</td>
<td>0</td>
<td>14</td>
<td>15</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>[Fe&quot;(mep)(CH}_3\text{CN})_2]^{2+}</td>
<td>0.5</td>
<td>26</td>
<td>41</td>
<td>62</td>
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<td>4</td>
<td>[Fe&quot;(S,S-bpbp)(CH}_3\text{CN})_2]^{2+}</td>
<td>0.5</td>
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<td>42</td>
<td>90</td>
</tr>
<tr>
<td>5°</td>
<td>[Fe&quot;(S,S-bpbp)(CH}_3\text{CN})_2]^{2+}</td>
<td>0.5</td>
<td>51</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

² Based on yield.
White – the first preparatively useful method

Reaction development

\[
\text{cat (5 mol\%), AcOH, } \text{H}_2\text{O}_2 (1.2 \text{ equiv}) \rightarrow \text{MeCN, r.t.}
\]

\[
\text{d.r. >99:1}
\]

**“e) iterative addition protocol”** = added 3x(cat+reagent+additive)

Real equivalents are: **cat (15 mol%), AcOH (1.5 equiv.), H_2O_2 (3.6 equiv)**

| Entry | Catalyst | AcOH(equiv.) | Yield (%) | Conv.(|%) | Select (%) |
|-------|----------|--------------|-----------|-----------|-----------|
| 1     | [Fe^{II}(mep)(CH_3CN)]_2^{2+} | 0 | 7 | 12 | 56 |
| 2     | [Fe^{III}(S,S-bpbp)(CH_3CN)]_2^{2+} | 0 | 14 | 15 | 92 |
| 3     | [Fe^{III}(mep)(CH_3CN)]_2^{2+} | 0.5 | 26 | 41 | 62 |
| 4     | [Fe^{III}(S,S-bpbp)(CH_3CN)]_2^{2+} | 0.5 | 38 | 42 | 90 |
| 5’    | [Fe^{III}(S,S-bpbp)(CH_3CN)]_2^{2+} | 0.5 | 51 | – | – |
White – the first preparatively useful method

Reaction development

```
cat (5 mol%)  
AcOH  
H₂O₂ (1.2 equiv)  
MeCN, r.t.  

OH  

PivO⁻  

H  

Me  

PivO⁺  

Me  
```

\[
\text{d.r. >99:1}
\]

Real equivalents are:
- cat (15 mol%), AcOH (1.5 equiv.), H₂O₂ (3.6 equiv)

---

**Scope and observations**

```

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"e) iterative addition protocol" = added 3x(cat+reagent+additive)

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**Reaction development Scope and observations**

---
**White – the first preparatively useful method**

Reaction development

\[
\text{cat (5 mol\%)} \quad \text{AcOH} \quad \text{H}_2\text{O}_2 (1.2 \text{ equiv}) \quad \text{MeCN, r.t.} \quad \text{d.r. >99:1}
\]

\[
\begin{align*}
\text{PiV}^\bullet & \quad \rightarrow \quad \text{PiV}^\bullet \\
\text{OH} & \quad \rightarrow \quad \text{NCMe} \\
\text{Fe(S,S-PDP)} & \quad \rightarrow \quad (\text{BdFe})^2+
\end{align*}
\]

Real equivalents are:
- **cat** (15 mol%), **AcOH** (1.5 equiv.), **H\textsubscript{2}O\textsubscript{2}** (3.6 equiv)

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<td>21</td>
<td>52</td>
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\(\text{rsm} = \%\text{ recovered oxidized starting material} \quad \text{starting material was recycled five times} \quad \text{GC yield}\)

"\textit{e) iterative addition protocol" = added 3x(cat+reagent+additive)}

Mechanism – electrophilic oxygen C-H insertion?

- No proposed mechanism
- Competitors (Que, Costas) has already investigated and proposed mechanism - they are barely mentioned among the references
- Reaction is not exactly stereospecific.
Accepted Mechanism

Hammett plot and BDE-correlation experiment
Accepted Mechanism

Hammett plot and BDE-correlation experiment

- $\rho = 1.0$

1. $e$- demanding TS
2. $H$-abs. by O-rad. $-(p) = 0.4-0.6$
3. $H$-abs. by TM $-(p) = 1.1-2.0$

Linear correlation with BDE $\rightarrow$ common mechanism
Accepted Mechanism

Hammett plot and BDE-correlation experiment

\[
\log \left( \frac{k_1}{k_0} \right) = 1.0 - 1.005x - 0.020 \\
R^2 = 0.999
\]

\( y = -1.005x - 0.020 \)

- (Hammett \( \rho \)) = 1.0

1. e- demanding TS
2. H-abs. by O-rad. - (p) = 0.4-0.6
3. H-abs. by TM - (p) = 1.1-2.0

C-H bond cleavage is rate determining step

KIE – characteristic values

Linear correlation with BDE \( \rightarrow \) common mechanism

Mechanistic studies summary

\begin{tabular}{|c|c|c|c|c|c|}
\hline
Complex & \( k_{ir}/k_0 \) & \( RC(\%) \) cis-1,2-DMCH & \( ^{18}O(\%) \) from \( H_2^{18}O \) & \hline
\hline
\( C_4H_4(C_4D_4) \) & 0 °C & 20 °C & 30 °C & cis-1,2-DMCH & adamantan \\
\hline
1 & 3.5 & 4.1 & > 99 & > 99 & > 99 & – & – \\
4 & 3.8 & 4.7 & > 99 & 98.6 & 98.6 & 18 (2.3) & 27 (9.1) \\
5 & 3.9 & 3.8 & > 99 & 97.1 & 94.3 & 7 (1.5) & 18 (2.1) \\
\hline
\end{tabular}

KIE

1-2

\( \approx 4 \)

H-abs. by high-valent oxometal specie

Slope = -0.32

Abstracting agent

OH rad.

\( tBuO \) rad.

OBt rad.

Fe

Mn

Ru

11-27

3.2-4.3

2.2-4.3

4.2-6.5
Accepted Mechanism

Hammett plot and BDE-correlation experiment

- - (Hammett $\rho$) = 1.0
1. e-demanding TS
2. H-abs. by O-rad. -(p) = 0.4-0.6
3. H-abs. by TM -(p) = 1.1-2.0

C-H bond cleavage is rate determining step

Mechanistic studies summary

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<tr>
<th>Complex</th>
<th>$k_u/k_0^*$</th>
<th>$RC$ (%) cis-1,2-DMCH</th>
<th>$^{18}O$ (%) from $H_2^{18}O$</th>
<th>0°C</th>
<th>20°C</th>
<th>30°C</th>
<th>cis-1,2-DMCH adamantane</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-CH$_2$-</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erosion of stereochemistry

"cis-1,2-DMCH"
**Accepted Mechanism**

**Hammett plot and BDE-correlation experiment**

- (Hammett $\rho$) = 1.0

$\log (k_{\text{OH}}/k_{\text{Me}}) = -1.095x - 0.020$

$R^2 = 0.999$

![Graph showing Hammett plot and BDE correlation.]

C-H bond cleavage is rate determining step

**Mechanistic studies summary**

<table>
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<tr>
<th>Complex</th>
<th>$k_d/k_o$</th>
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<tbody>
<tr>
<td>$\text{C}<em>4\text{H}</em>{10}/\text{C}<em>4\text{D}</em>{10}$</td>
<td>0 °C</td>
<td>20 °C</td>
<td>30 °C</td>
</tr>
<tr>
<td>1</td>
<td>3.5</td>
<td>4.1</td>
<td>&gt; 99</td>
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**KIE – characteristic values**

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<tr>
<th>Abstracting agent</th>
<th>OH rad.</th>
<th>tBuO rad.</th>
<th>tBtO rad.</th>
<th>Fe</th>
<th>Mn</th>
<th>Ru</th>
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<tr>
<td>KIE</td>
<td>1-2</td>
<td>11-27</td>
<td>$3.2-4.3$</td>
<td>$2.2-4.3$</td>
<td>$4.2-6.5$</td>
<td></td>
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**Erosion of stereochemistry**

"cis-1,2-DMCH"
Accepted Mechanism

Proposed mechanism

\[
\begin{align*}
M^{II} & \rightarrow M^{III}=O \rightarrow \frac{M^{V}=O}{H_{2}^{18}O \text{ was added}} \rightarrow H-C_r_1 \rightarrow M^{IV}=O \rightarrow H^{radical} \rightarrow H-C_r_1 \\
\text{(short lived radical lifetime < } 10^{-10} \text{ s)} & \quad (radical clock exp.)
\end{align*}
\]

Acetic acid mediated Fe(V) generation

\[
[(L)M^{III}X_2] \text{ or } M^{II} \rightarrow O-H \rightarrow O-H \\
\]

Water mediated Fe(V) generation

\[
[(L)M^{III}X_2] \text{ or } M^{II} \rightarrow O-H \rightarrow M^{V}=O
\]

Mechanistic studies:


and many more references therein...

$^{18}$O incorporation suggest M=O intermediate
White – further contributions

New catalyst with complimentary reactivity

(S,S)-Fe(POP) 2007

(S,S)-Fe(CF₃-POPOP) 2013
White – further contributions

New catalyst with complimentary reactivity

- CF₃ → resistance to oxidation
- Restricted approach trajectory
- EWG → more electrophilic oxidant (methylene BDE – 98 kcal/mol)
New catalyst with complimentary reactivity

- **CF₃** → resistance to oxidation
- **EWG** → more electrophilic oxidant (methylene BDE – 98 kcal/mol)

### Table

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<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Oxidation Products</th>
<th>Site Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(+)-3</td>
<td>(+)-4</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>(+)-5</td>
<td>(+)-6</td>
<td>2:3</td>
</tr>
<tr>
<td>3</td>
<td>(+)-7</td>
<td>(+)-8</td>
<td>2:3</td>
</tr>
<tr>
<td>4</td>
<td>(+)-9</td>
<td>(+)-10</td>
<td>3:2</td>
</tr>
<tr>
<td>5</td>
<td>(+)-11</td>
<td>(+)-12</td>
<td>3:2</td>
</tr>
<tr>
<td>6</td>
<td>(+)-13</td>
<td>(+)-14</td>
<td>2:3</td>
</tr>
<tr>
<td>7</td>
<td>(+)-15</td>
<td>(+)-16</td>
<td>2:3</td>
</tr>
<tr>
<td>8</td>
<td>(+)-17</td>
<td>(+)-18</td>
<td>2:3</td>
</tr>
</tbody>
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---

White – further contributions
White – further contributions

New catalyst with complimentary reactivity

1. (S,S)-Fe(PDP) 2007

2. (S,S)-Fe(CF₂-PDP) 2013

- CF₃ \rightarrow resistance to oxidation
- Restricted approach trajectory

EWG \rightarrow more electrophilic oxidant (methylene BDE – 98 kcal/mol)

More complex examples

- 22% yield
- 57% yield
- 53% yield
- (+)-artemisinin

Entry | Starting material | Oxidation products | Site-selectivity
--- | --- | --- | ---
1 | 7 | 41 | 1:1
2 | 7 | 51 | 1:1
3 | 7 | 26 | 2:1
4 | 7 | 7 | 10:1
5 | 11 | 16 | 1.2
6 | 11 | 56 | 1.2
7 | (+)-13 | 28 | 1.2
8 | (+)-13 | 56 | 4:1
9 | (+)-16 | 32 | 1.1
10 | (+)-16 | 6 | 9:1
Diversification of peptides and amino acids

Diversification of peptides and amino acids

White – further contributions

Diversification of peptides and amino acids

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The Nitrogen Problem

White - overcoming amide and amine incompatibility

The Nitrogen Problem

White - overcoming amide and amine incompatibility

Costas – importance of α–substituents

The Nitrogen Problem

White - overcoming amide and amine incompatibility

Costas – importance of α–substituents

Important observation

α-position remains intact!

By far the best yields in the scope

The Nitrogen Problem

White - overcoming amide and amine incompatibility

Costas – importance of α-substituents

Important observation

Rationalization

Does the amide function "activates and deactivates" at the same time?


Costas – First enantioselective example

Important factors

\[
\begin{align*}
\text{R} = \text{alkyl, } O-\text{alkyl, } CF_3 \\
\text{cat. (2 mol\%)} \\
\text{H}_2\text{O}_2 \text{ (3.5 eq.)} \\
\text{CO}_2\text{H} \text{ (17 equiv)} \\
\text{MeCN, } -40^\circ\text{C, 30 min} \\
50-85\%, 65-96\% \text{ ee}
\end{align*}
\]
Important factors

Significant improvement in conversion and yield (Carbamate and acetyl groups are also OK)

- Oxidatively robust acid additive
- Propionic acid gave similar results
- Note catalyst loading

Ecp-type ligands were not successful with iron catalysis, whereas the ligands are very often “interchangeable”
Important factors

- Significant improvement in conversion and yield (Carbamate and acetyl groups are also OK)
- Oxidatively robust acid additive
- Propionic acid gave similar results
- Note catalyst loading

Scope – substituents on the cyclohexyl ring

- (5,5)-Mn<sup>II</sup>(N<sup>3</sup>ecp)

ecp-type ligands were not successful with iron catalysis, whereas the ligands are very often “interchangeable”
Important factors

Significant improvement in conversion and yield (Carbamate and acetyl groups are also OK)

**Enantiodetermining step**

A) Enantioselection at the OH transfer step

B) Enantioselection at the HAT transfer step

• Oxidatively robust acid additive
• Propionic acid gave similar results
• Note catalyst loading

**Scope – substituents on the cyclohexyl ring**

- Compare with Fu, Jacobsen, Lee&Tan

ecp-type ligands were not successful with iron catalysis, whereas the ligands are very often “interchangeable”
Baran

2-step / 1-pot protocol – only tertiary or activated C(sp3)-H bond ox.

Unactivated C(sp3)-H bond ox.

 Proposed mechanism

A. Current mechanistic hypothesis

{CuBr₂, F-TEDA⁺}
{CuBr₂-TEDA⁺} + HF

{Cu⁺}

[Cu⁺] [Cu⁺] n = 1 or 2

MeCN

Me

NHAc

yield is based on oxidant

19 - 91% yield

15
2-step / 1-pot protocol – only tertiary or activated C(sp3)-H bond ox.

Unactivated C(sp3)-H bond ox.

Proposed mechanism

A. Current mechanistic hypothesis

Substrate Product Yield\(^{a}\)  Yield\(^{b}\)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield(^{a})</th>
<th>Yield(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>NHAc</td>
<td>90(^{c})</td>
<td>88(^{c})</td>
</tr>
<tr>
<td>20</td>
<td>NHAc</td>
<td>39</td>
<td>63</td>
</tr>
<tr>
<td>21</td>
<td>NHAc</td>
<td>51</td>
<td>72</td>
</tr>
<tr>
<td>22</td>
<td>NHAc</td>
<td>62</td>
<td>90</td>
</tr>
<tr>
<td>23</td>
<td>NHAc</td>
<td>62</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>NHAc</td>
<td>25(^{d})</td>
<td>28(^{e})</td>
</tr>
<tr>
<td>25</td>
<td>NHAc</td>
<td>36(^{f})</td>
<td>55(^{f})</td>
</tr>
<tr>
<td>26</td>
<td>NHAc</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>27</td>
<td>NHAc</td>
<td>10(^{g})</td>
<td>31(^{h})</td>
</tr>
</tbody>
</table>
Baran

Optimization and important factors

**Key:** choice of redox mediator

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from above</th>
<th>Yield %</th>
<th>C2/C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B as the mediator</td>
<td>39</td>
<td>2.1/1</td>
</tr>
<tr>
<td>2</td>
<td>C as the mediator</td>
<td>9</td>
<td>2.0/1</td>
</tr>
<tr>
<td>3</td>
<td>D as the mediator</td>
<td>19</td>
<td>1.1/1</td>
</tr>
<tr>
<td>4</td>
<td>E, F, G, or H as the mediator</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>0.4 equiv. of A</td>
<td>30</td>
<td>5.4/1</td>
</tr>
<tr>
<td>6</td>
<td>added A portionwise (0.5 equiv. x 2)</td>
<td>42</td>
<td>4.9/1</td>
</tr>
<tr>
<td>7</td>
<td>LiClO4 instead of Me3NBF4</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>Et4NO2 instead of Me3NBF4</td>
<td>57</td>
<td>4.2/1</td>
</tr>
<tr>
<td>9</td>
<td>no HFIP</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>10</td>
<td>TFA (1.0 equiv.) instead of HFIP</td>
<td>&lt;5</td>
<td>n.d.</td>
</tr>
<tr>
<td>11</td>
<td>AcOH (2.0 equiv.) instead of HFIP</td>
<td>15</td>
<td>3.9/1</td>
</tr>
<tr>
<td>12</td>
<td>under Ar</td>
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<td>n.d.</td>
</tr>
<tr>
<td>13</td>
<td>stainless steel cathode</td>
<td>49</td>
<td>2.8/1</td>
</tr>
<tr>
<td>14</td>
<td>Cu cathode</td>
<td>45</td>
<td>6/1</td>
</tr>
<tr>
<td>15</td>
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<td>36</td>
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</tr>
<tr>
<td>16</td>
<td>10 mA, 6 h</td>
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<td>4.9/1</td>
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<table>
<thead>
<tr>
<th>Mediators</th>
<th>Quinuclidine (A)</th>
<th>Aceclidine (B)</th>
<th>DABCO (C)</th>
<th>NMO (D)</th>
<th>X = H, NHPI (E)</th>
<th>X = Cl, TCHNHP (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactions</td>
<td>conducted on 0.2 mmol scale.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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**Electrochemical oxidation of sclareolide**

Quinuclidine (green) and Aceclidine (yellow) has the highest thermodynamic potential (E$_{1/2}$) → they are the best performing mediators.

HFIP was also essential.

**Cyclic voltammograms of selected mediators.**

Current (μA) vs. Voltage (V)
Optimization and important factors

**Electrochemical oxidation of scolareide**

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**HFIP was also essential**

Quinuclidine (green) and Aceclidine (yellow) has the highest thermodynamic potential (E_{1/2}) → they are the best performing mediators.

**Scope of the reaction**

- Quinuclidine radical cation formation
- Homolytic C-H abstraction
- Allyl radical formation
- Aerobic oxidation

**Proposed mechanism**

[Diagram of the mechanism]

How safe it is to run the cell filled with MeCN and air?

**Secondary C-H**

- Ar = 4-CIC6H4
  - 3.72% (β = 3.1)
  - 80% (β = 7.1)
  - 60% (β = 1.9)

- Ar = 4-CIC6H4
  - 50% (β = 3.2)

- Ar = 4-CIC6H4
  - 50% (β = 1.8)

- X-ray from isosteviol ethyl ester

**Activated secondary C-H**

- Ar = 4-CIC6H4
  - 45%

- Ph
  - 65%

- AcO
  - 55%

- Tertiary C-H

- Ar = 4-CIC6H4
  - 56% (d.r. = 1.4:1)

- Ar = 4-CIC6H4
  - 62%

- Ar = 4-CIC6H4
  - 56%
Hartwig – C-N bond formation

**Method**

![Chemical reaction diagram]

**Mechanism**

![Mechanism diagram]

Conclusions from preliminary studies

1. Tertiary alkyl radical is generated (lifetime <10⁻⁹ sec)
2. C-H bond cleavage is turnover limiting step (KIE = 5)
3. Iron is involved in C-N bond formation (Fe-N₃ intermediate)
4. In MeCN, C-H lysis is faster, radical rebound is slower
5. In EtOAc, C-H lysis is slower, radical rebound is faster
Hartwig – C-N bond formation

Method

\[
\text{Hartwig, J. F.} \quad \text{ACS Cent. Sci.} \quad 2016, \quad 2(10), \quad 715–724.
\]

\[
\text{Hartwig, J. F.} \quad \text{Nature} \quad 2015, \quad 517(7536), \quad 600–604.
\]

Mechanism

Conclusions from preliminary studies

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5. In EtOAc, C-H lysis is slower, radical rebound is faster
**C-H chlorination and bromination**

\[
\text{C3 : C2 : C1} \quad 76\% : 19\% : 5\%
\]

\[
\text{Cl}^+ \quad 3\% \quad 38-74\%
\]

\[
\text{Br}^- \quad 42\% \quad \text{BDE} = 100 \text{ kcal/mol}
\]

**C-H fluorination**

\[
\text{cat. (6-8 mol\%)} \quad \text{PhIO (6 equiv)} \quad \text{AgF (3 equiv)} \quad \text{TBAF-3H}_2\text{O (0.3 equiv)} \quad \text{MeCN-DCM 3:1, 50\^\circ\text{C, 6-8 hours}}
\]
Groves – C-H halogenation

C-H chlorination and bromination

\[
\text{H} + \text{NaOCl or NaOBr (aq, sol.)} \rightarrow \text{Cl}_n \text{H} \quad n = 0-3 \quad 38-74\%
\]

Cl : C2 : C1 76%:19%-5%

\[
\text{H} + \text{H} \rightarrow \text{Br}_n \text{H} \quad n = 0-3 \quad 42\%
\]

C-H fluorination

\[
\text{H}_2 \text{H} + \text{AgF} \rightarrow \text{F}_n \text{H} \quad n = 0-3 \quad 31% \quad \text{BDE} = 100 \text{ kcal/mol}
\]


Mechanism – “heteroatom rebound catalysis”

C-H chlorination / bromination

C-H fluorination

Effect of apical – trans ligands

Alexanian, Vanderwal – HLF-type halogenation

C-H bromination

H\_ + \text{F\_3C-} - \text{C} = \text{O} - \text{NMe}_2 - \text{NMe}_2 - \text{Br} \rightarrow \text{Br}

visible light, benzene, r.t.

HLF reaction needs strong acidic media (H\_2SO\_4)

**C-H bromination**

HLF reaction needs strong acidic media ($H_2SO_4$)

---


Alexanian, Vanderwal – HLF-type halogenation

C-H bromination

\[
\text{H} + \text{F}_3\text{C}-\text{NO}-\text{Me} + \text{Br} \rightarrow \text{Br}
\]

visible light, benzene, r.t.

HLF reaction needs strong acidic media (H$_2$SO$_4$)

C-H chlorination

\[
\text{H} + \text{F}_3\text{C}-\text{NO}-\text{Me} + \text{Cl} \rightarrow \text{Cl}
\]

visible light, Cs$_2$CO$_3$ (1 equiv)

benzene, 55°C

Trace acid could promote Cl$_2$ generation \(\rightarrow\) polychlorinated product

Alexianan, Vanderwal – HLF-type halogenation

C-H bromination

Visible light, benzene, r.t.

C-H chlorination

Visible light, Cs$_2$CO$_3$ (1 equiv) benzene, 55°C

HLF reaction needs strong acidic media ($\text{H}_2\text{SO}_4$)

High selectivity to methylene C–H bonds

Trace acid could promote Cl$_2$ generation $\rightarrow$ polychlorinated product

Lectka – photocatalyzed C-H fluorination

Conditions

\[
\begin{aligned}
&\text{H} & & \text{F} \\
\to & \text{NC} & & \text{CN} \\
& & & (0.1 \text{ equiv}) \\
& & & \text{Selectfluor} (2.2 \text{ equiv}) \\
& & & \text{UV light, MeCN}
\end{aligned}
\]

Working hypothesis for mechanism

Lectka – photocatalyzed C-H fluorination

Conditions

$$\text{H} \quad \text{CN} \quad \text{CN} \quad \text{CN} \quad \text{CN}$$

(0.1 equiv)

Selectfluor (2.2 equiv)

UV light, MeCN

$$\text{F}$$

Scope of transformation

Working hypothesis for mechanism

Overview

Major branches of C(sp3)-H oxidation chemistry

1. **C-O bond formation**
   1. Heme or Non-heme Fe / Mn catalytic systems (White, Groves, Costas)
   2. Electrochemical methods (Baran)
   3. Hypervalent iodine based systems (Maruoka – not presented)

2. **C-N bond formation**
   1. Iron / Hypervalent iodine system (Hartwig)
   2. Metal-nitrenoid chemistry (Du Bois – not presented)

1. **C-X bond formation**
   1. Heme or Non-heme Fe / Mn catalytic systems (Groves)
   2. Intermolecular HLF reaction based halogenation (Alexanian)
   3. Photocatalyzed halogenation (Lectka and others)

Take home message

1. *Subtle electronic, steric and stereoelectronic factors determine the reaction outcome*
2. *Fe / Mn – based systems dominate the field*
3. *Short-lived radicals allow asymmetric C-H functionalization*
Questions

Where will the oxidation take place?

Explain the selectivity!
Important reviews/perspectives:


Fe / Mn

4. doi:10.1021/ja048528h

C-N and C-X bond

Thank you for your attention!