Activation by One Electron Oxidation

B4 Kimihiro Miyauchi
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Introduction

Examples of one electron oxidation

• Initiating cycloaddition

\[
\text{MeO} \quad \text{R}^1 \quad \text{R}^2 \\
/ \quad / \\
\text{R}^2 \quad \text{R}^1 \quad \text{MeO} \\
\]

\[
\text{FeCl}_3 \quad \text{(cat)} \\
\text{MeCN} \\
\]

\[
\text{MeO} \quad \text{R}^1 \quad \text{R}^2 \\
/ \quad / \\
\text{R}^2 \quad \text{R}^1 \quad \text{MeO} \\
\]

\[
\text{R}^2 = \text{EDG, EWG} \\
\]


• Bioconjugation

\[
\text{tyrosine residues} \\
/ \\
\text{major product} \\
/ \\
\text{minor product} \\
\]

\[
\text{R} = \text{-CH}_3, \text{PEG, peptide} \\
\]

Contents

- Mesolytic Cleavage of Radical Cation
- Oxidative $S_N$Ar Pathway
- Application to Biomolecular
- Summary
Contents

■ Mesolytic Cleavage of Radical Cation

■ Oxidative $S_{N\text{Ar}}$ Pathway

■ Application to Biomolecular

■ Summary
Mesolytic Cleavage of Radical Cation

• Conventional Alkylation Strategies
  ➢ Strong acids or Lewis acids required for generating carbocation.

\[
\begin{align*}
R^3R^2R^1X & \xrightarrow{\text{Lewis Acid / Strong Acid}} R^2^+R^1\ R^3 \\
\end{align*}
\]

➢ Alkylation reagents are very reactive.

- MeI
- H₂CₙN⁺N⁻
- Me⁺₂Me⁻BF₄⁻
Mesolytic Cleavage of Radical Cation

- Previous works


- Generating carbocation by mesolytic cleavage of radical cation
- Under mild conditions without Lewis/strong acid
Electrochemically activated methylation

- Stable and unreactive in neutral form without electrochemical stimuli.

Optimization

Table 2. Electrochemical Methylation of Benzoic Acid Using TEMPO–Me: Influence of Reaction Parameters

<table>
<thead>
<tr>
<th>entry</th>
<th>electrolyte</th>
<th>solvent</th>
<th>base (eq.)</th>
<th>electrolytic conditions (mA)</th>
<th>E-mol⁻¹</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu₄NBF₄</td>
<td>MeCN</td>
<td>Cs₂CO₃</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>2</td>
<td>Bu₄NBF₄</td>
<td>MeCN</td>
<td>K₂CO₃</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>3</td>
<td>Bu₄NBF₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>4</td>
<td>Bu₄NBF₄</td>
<td>CH₂Cl₂</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>5</td>
<td>Bu₄NBF₄</td>
<td>THF</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>6</td>
<td>Bu₄NBF₄</td>
<td>DMSO</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>7</td>
<td>Bu₄NPF₆</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>8</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(1.1)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>9</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(0.25)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>10</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(0.10)</td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>11</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>none</td>
<td></td>
<td>10</td>
<td>12.2</td>
</tr>
<tr>
<td>12</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(0.10)</td>
<td>5</td>
<td>6.1</td>
</tr>
<tr>
<td>13</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(0.10)</td>
<td>15</td>
<td>18.3</td>
</tr>
<tr>
<td>14</td>
<td>Bu₄NCIO₄</td>
<td>MeCN</td>
<td>2,6-(t-Bu)₂C₆H₄N</td>
<td>(0.10)</td>
<td>10</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Reactions consisted of 2a (0.5 mmol), 1 (0.55 mmol, 1.1 equiv), and base (stated equivalents) in an electrolyte solution (10 mL; 0.1 M) electrolyzed in a 10 mL undivided cell at room temperature open to air for 18 h using an IKA Electrasyn 2.0 and two graphite electrodes, unless otherwise specified. Yield with respect to 2a. Yield obtained when the cell polarity was reversed every 10 min. 2.0 equiv of 1.
Optimization

Chemical Oxidants

(c) $2a + 1$

\[
\begin{align*}
\text{O} & \quad \text{N} - \text{O} \text{Me} \\
\text{OH} & \quad \text{N} - \text{O} \text{Me}
\end{align*}
\]

Photoredox Catalysis

(d) $2a + 1$

\[
\begin{align*}
\text{O} & \quad \text{N} - \text{O} \text{Me} \\
\text{OH} & \quad \text{N} - \text{O} \text{Me}
\end{align*}
\]

- Neither stoichiometric oxidants nor PC facilitated methylation

➢ Electrochemistry is crucial for this reaction

Substrate scope

Methylation achieved in moderate to high yield

Bearing functional groups susceptible to reduction → divided cells

Mechanism

(a) TEMPO–Me (1)

(b) TEMPO–Me (1) + py

(c) \( \text{pyMe}^+ / \text{pyMe}^- \)

(d) \( \text{TEMPO}^+ / \text{TEMPO}^- \)

Solid line: Scan 1
Dotted line: Scan 2

Potential (V) vs Ag/AgCl

(e) \( \text{NOMe} \) → \( \text{NOMe}^+ / \text{NOMe}^- \) → pyridine

Electrochemically activated methylation under mild condition.

TEMPO-Me is stable in neutral form.

There is still some room for improvement of the substrate scope and the reactivity of the donor.

Contents

- Mesolytic Cleavage of Radical Cation
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- Summary
Oxidative $S_{N}Ar$ Pathway

- Common $S_{N}Ar$ pathway

\[
\begin{array}{c}
\text{EWG} \\
\text{X} = \text{F, Cl}
\end{array} \xrightarrow{\text{Nu}} \begin{array}{c}
\text{EWG} \\
\text{Nu}
\end{array} \xrightarrow{\text{Meisenheimer complex}} \begin{array}{c}
\text{EWG} \\
\text{Nu}
\end{array}
\]

Cannot be applied to electron-rich arenes

- Attempts to facilitate $S_{N}Ar$ with electron neutral/rich arenes

\[
\text{Meisenheimer complex}
\]

\[
\begin{array}{c}
\text{Me} \quad \text{F} \\
\text{HN} \quad \text{N}
\end{array} \xrightarrow{210 \degree C, \text{K}_3\text{PO}_4} \begin{array}{c}
\text{Me} \\
\text{N}
\end{array}
\]

High temperature is needed

Oxidative $S_{\text{NAr}}$ Pathway

- Previous reports
  - Substitution at C–OMe

  ![Chemical Reaction](image)


  - Defluorinative substitution

  ![Chemical Reaction](image)

  Required excess amount of fluoroarene

S_NAr reaction with electron rich or neutral arene under mild condition

- Amine or carboxylic acid can be used as nucleophile

Table 1. Catalyst Development for Fluorotoluene S$_{\text{NAr}}$

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>$R^1$</th>
<th>X</th>
<th>$E_{1/2}^{\text{red}}$ (V)$^a$</th>
<th>yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>NPh</td>
<td>+2.10</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>H</td>
<td>NPh</td>
<td>+2.21</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>O</td>
<td>+2.51</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>H</td>
<td>O</td>
<td>+2.66</td>
<td>35%</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>F</td>
<td>O</td>
<td>+2.57</td>
<td>55%</td>
</tr>
</tbody>
</table>

$^a$Saturated calomel electrode (SCE) as reference. $^b$Yield determined by $^1$H NMR using HMDSO as an internal standard.
Optimization (Heteroarene)

Table 2. Optimization of Fluorotoluene $S_N$Ar using Pyrazole

<table>
<thead>
<tr>
<th>entry</th>
<th>deviations from the above conditions</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>4%</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>HFIP as solvent</td>
<td>72%</td>
</tr>
<tr>
<td>5</td>
<td>3 equiv of pyrazole</td>
<td>68%</td>
</tr>
<tr>
<td>6</td>
<td>2 equiv of pyrazole</td>
<td>51%</td>
</tr>
<tr>
<td>7</td>
<td>1 equiv of pyrazole</td>
<td>45%</td>
</tr>
<tr>
<td>8</td>
<td>0.01 equiv of catalyst</td>
<td>48%</td>
</tr>
<tr>
<td>9</td>
<td>0.075 equiv of catalyst; HFIP</td>
<td>72%</td>
</tr>
<tr>
<td>10</td>
<td>456 nm Kessils</td>
<td>63%</td>
</tr>
<tr>
<td>11</td>
<td>427 nm Kessils</td>
<td>62%</td>
</tr>
<tr>
<td>12</td>
<td>427 nm Kessils with foil barrier</td>
<td>82%</td>
</tr>
</tbody>
</table>

$^a$Yield determined by $^1$H NMR using HMDSO as an internal standard


Using HFIP as solvent gave higher yield.
Substrate Scope (Heteroarene)

<table>
<thead>
<tr>
<th>Arene Scope</th>
<th>Azole Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="1" alt="Chemical Structures" /> 67%</td>
<td><img src="3" alt="Chemical Structures" /> 23%</td>
</tr>
<tr>
<td><img src="2" alt="Chemical Structures" /> 69%</td>
<td><img src="4" alt="Chemical Structures" /> 65%</td>
</tr>
<tr>
<td><img src="5" alt="Chemical Structures" /> 60%</td>
<td><img src="6" alt="Chemical Structures" /> 43%</td>
</tr>
<tr>
<td><img src="7" alt="Chemical Structures" /> 44%</td>
<td><img src="8" alt="Chemical Structures" /> 29%</td>
</tr>
<tr>
<td><img src="9" alt="Chemical Structures" /> 63%</td>
<td><img src="10" alt="Chemical Structures" /> 50%</td>
</tr>
<tr>
<td><img src="11" alt="Chemical Structures" /> 56%</td>
<td><img src="12" alt="Chemical Structures" /> 36%</td>
</tr>
<tr>
<td><img src="13" alt="Chemical Structures" /> 82%</td>
<td><img src="14" alt="Chemical Structures" /> 84%</td>
</tr>
</tbody>
</table>

Optimization (Amine, Carboxylic acid)

- Xanthylum salt catalyst is not compatible with amine as nucleophile

\[
\begin{array}{c}
\text{R} \\
\text{Ar} \\
\text{O} \\
\text{R}
\end{array}
\quad \xrightarrow{\text{H}_2\text{N-R}^1} \quad
\begin{array}{c}
\text{R} \\
\text{Ar} \\
\text{N} \\
\text{R}^1 \\
\text{R}
\end{array}
\]


- Using acridinium salt catalyst (Catalyst B) instead

![Catalyst B](image_url)
## Optimization (Amine, Carboxylic acid)

Catalyst G (0.05 equiv.)
Ammonium Carbamate (4 equiv.)

TFE (0.1 M)
bLEDs, 18 h

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviations from above conditions</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>TFE:DCE (2:1)</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>TFE:DCE (1:1)</td>
<td>48%</td>
</tr>
<tr>
<td>4</td>
<td>TFE:DCE (1:2)</td>
<td>64%</td>
</tr>
<tr>
<td>5</td>
<td>TFE:DCE (1:3)</td>
<td>74%</td>
</tr>
<tr>
<td>6</td>
<td>1 equiv. ammonium carbamate; TFE:DCE (1:3)</td>
<td>18%</td>
</tr>
<tr>
<td>7</td>
<td>2 equiv. ammonium carbamate; TFE:DCE (1:3)</td>
<td>50%</td>
</tr>
<tr>
<td>8</td>
<td>3 equiv. ammonium carbamate; TFE:DCE (1:3)</td>
<td>54%</td>
</tr>
<tr>
<td>9</td>
<td>5 equiv. ammonium carbamate; TFE:DCE (1:3)</td>
<td>72%</td>
</tr>
<tr>
<td>10</td>
<td>0.03 equiv Catalyst G; TFE:DCE (1:3)</td>
<td>57%</td>
</tr>
<tr>
<td>11</td>
<td>0.05 equiv Catalyst B; TFE:DCE (1:3)</td>
<td>72%</td>
</tr>
<tr>
<td>12</td>
<td>0.05 equiv Catalyst H; TFE:DCE (1:3)</td>
<td>48%</td>
</tr>
<tr>
<td>13</td>
<td>0.05 equiv Catalyst I; TFE:DCE (1:3)</td>
<td>55%</td>
</tr>
<tr>
<td>14</td>
<td>0.05 equiv Catalyst J; TFE:DCE (1:3)</td>
<td>43%</td>
</tr>
</tbody>
</table>

*aYield determined by $^1$H NMR using HMDSO as an internal standard*
Substrate Scope (Amine, Carboxylic acid)

<table>
<thead>
<tr>
<th>Condition A</th>
<th>Condition B</th>
<th>Condition C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catalyst B (0.05 equiv) Ammonium Carbamate (4 equiv) 3:1 DCE:TFE (0.1 M) 427 nm Kessils, 18 h 45-50 °C</td>
<td>Catalyst B (0.05 equiv) 2-(aminomethyl)pyridine (3 equiv) TFE (0.1 M), 427 nm Kessils 18 h, 45-50 °C</td>
<td>Catalyst B (0.05 equiv) Benzoic Acid (4 equiv) NaHCO₃ (2 equiv) TFE (0.1 M), 456 nm Kessils 18 h, 45-50 °C</td>
</tr>
</tbody>
</table>

Arenes Scope

17
A-78%
B-69%
C-43%
18
A-54%
B-70%
C-46%
19
A-57%
B-52%
C-65%
20
A-50%
B-52%
C-65%
21
A-55%
B-83%
C-90%
22
A-52%
B-55%
C-28%
23
A-46%
B-41%
C-28%
24
A-52%
B-37%
C-27%
25
A-40%
B-82%
C-32%
26
A-59%
B-76%
C-28%
27
A-37%
B-61%
C-N.R.
28
A-26%
B-17%
C-35%

“Average isolated yields are reported (0.3–0.5 mmol, n = 2); 45–50 °C represents the ambient temperature of the light setup using external fan cooling.”

“Eleven percent C–O substitution product.”

“0.10 equiv of Catalyst B used.”

“Ratio determined by ¹H NMR.”

“Nine percent dissubstitution observed.”

“3 equiv of benzyl amine as nucleophile.”

“Isolated yield (0.150 mmol, n = 1).”

“Yield determined by ¹H NMR using HMDSO as an internal standard.”

“Isolated yield (0.050 mmol, n = 1).”

“0.075 equiv of Catalyst B used.”

“DCE used as in place of TFE.”

“4 equiv of carboxylic acid and 2 equiv of NaHCO₃ employed.”

Substrate Scope (Amine, Carboxylic acid)

Condition A

Catalyst B (0.05 equiv)  
Ammonium Carbamate (4 equiv)  
3:1 DCE:TFE (0.1 M)  
427 nm Kessils, 18 h  
45-50 °C

Condition B

Catalyst B (0.05 equiv)  
2-(aminomethyl)pyridine (3 equiv)  
TFE (0.1 M), 427 nm Kessils  
18 h, 45-50 °C

Condition C

Catalyst B (0.05 equiv)  
Benzoic Acid (4 equiv)  
NaHCO₃ (2 equiv)  
TFE (0.1 M), 456 nm Kessils  
18 h, 45-50 °C

29  
A-65%, 1:2:1 (C1:C3)  
B-65%, 1:1:9 (C1:C3)  
C-41%, 1:5:1 (C1:C3)

30  
A-62%  
B-75%  
C-25%

31  
A-66%  
B-61%  
C-31%

32  
A-48%  
B-58%  
C-28%

33  
A-N.R.  
B-24%  
C-44%

34  
A-48%  
B-24%  
C-44%

35  
A-N.R.  
B-N.R.  
C-24%

36  
A-14%  
B-18%  
C-N.R.

37  
A-32%  
B-N.R.  
C-53%

38  
A-N.R.  
B-N.R.  
C-25%

39  
A-N.R.  
B-N.R.  
C-18%

40  
A-N.R.  
B-16%  
C-22:1 (C1:C3)

Note:  

A-N.R. indicates no reaction observed.  
B-N.R. indicates the compound was not reactive under the given conditions.

Average isolated yields are reported (0.3–0.5 mmol, n = 2); 45–50 °C represents the ambient temperature of the light setup using external fan cooling.  

Eleven percent C–O substitution product.  

0.10 equiv of Catalyst B used.  

Ratio determined by ¹H NMR.  

Nine percent disubstitution observed.  

1.3 equiv of benzyl amine as nucleophile.  

Isolated yield (0.150 mmol, n = 1).  

Yield determined by ¹H NMR using HMDSO as an internal standard.  

Isolated yield (0.050 mmol, n = 1).  

0.075 equiv of Catalyst B used.  

DCE used as in place of TFE.  

4 equiv of carboxylic acid and 2 equiv of NaHCO₃ employed.
Substrate Scope (Amine, Carboxylic acid)

Modification without racemizing → 46~48

Applicable to drug compound, but resulted in low to moderate yield.

Proposed Mechanism

\[\text{Mes-Acr}^+ \xrightarrow{\text{hv}} \text{Mes-Acr}^* \xrightarrow{+e^-} \text{Mes-Acr} \xrightarrow{-e^-} \text{Mes-Acr}^+ \xrightarrow{-\text{MeOH}} 13\]

J. Am. Chem. Soc. 2017, 139, 16100–16104
Rational for regioselectivity

A. Computed Electron Density of 4-fluoroanisole (ground state and cation radical)

Positive charge resides on C-F

Short Summary

Electron neutral ~ rich arene

Reverse the reactivity of electron-rich arene with single-electron oxidation.

Late-stage functionalization of pharmaceutical compounds

Contents

- Mesolytic Cleavage of Radical Cation
- Oxidative $S_N$Ar Pathway
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Application to Biomolecular

- Previous reports

  - Decarboxylative C term modification

  - Ligand directed Tyr modification


Site-selective Tyr Modification

- Tyrosine selective modification
- Further functionalization with versatile handle

II. Reaction optimization with bivalirudin (3)

<table>
<thead>
<tr>
<th>entry</th>
<th>phenoxyazine (equiv.)</th>
<th>lumiflavin</th>
<th>reaction time</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenoxazine monoamide S1 (10 equiv.)</td>
<td>1 equiv.</td>
<td>3 hours</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>phenoxazine dialdehyde 1 (10 equiv.)</td>
<td>3 equiv.</td>
<td>3 hours</td>
<td>46%</td>
</tr>
<tr>
<td>3</td>
<td>phenoxazine dialdehyde 1 (10 equiv.)</td>
<td>3 equiv.</td>
<td>5 hours</td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td>phenoxazine dialdehyde 1 (100 equiv.)</td>
<td>3 equiv.</td>
<td>5 hours</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>phenoxazine dialdehyde 1 (100 equiv.)</td>
<td>0 equiv.</td>
<td>5 hours</td>
<td>0% (am recovered)</td>
</tr>
<tr>
<td>6</td>
<td>phenoxazine dialdehyde 1 (100 equiv.)</td>
<td>3 equiv.</td>
<td>5 hours (dark)</td>
<td>0% (am recovered)</td>
</tr>
</tbody>
</table>

Substrate Scope of Peptide or Protein

- Site-selective Tyr modification was achieved

Rational for Site-selectivity

Fig. 2 | Tyrosine microenvironments. Representative tyrosines from human lysozyme (6) in their respective microenvironments. Y20 and Y54 are not reactive due to steric constraints or deactivating cation–π interactions, whereas Y45 is labelled with high efficiency because it is surface-exposed and hydrogen-bond-donating to surrounding aqueous media.

- A residue surface-exposed and activated is modified.
- Sterically hindered or deactivated Tyr did not react.
- Cation-π interaction reduces π electron density.

Proposed Mechanism

From excited state absorption, flavin oxidates phenoxazine not Tyr.

Further Functionalization

- Aldehyde selective and one-pot transformation

78% of the native activity was retained.
Influence on Protein Structure

- CD spectra of native and modified protein

  \[ \text{\(\alpha\)-Lactalbumin (9)} \]

  \[ \text{Chymotrypsinogen A (11)} \]

- Secondary structures were generally retained

Short Summary

- Reactive Tyr residue is functionalized selectively.
- Further functionalization with various biorthogonal moieties
- Retaining 3D structure or enzymatic activities
Summary

• Reaction proceeds generally under mild condition

• Reversing reactivity of the substrates unreactive in conventional pathways

• Applicable to biomolecular modification