Anion Phase-Transfer Catalysis Applied to the Direct Enantioselective Fluorinative Dearomatization of Phenols

Reporter: Zhang-Pei Chen
Checker: Ran-Ning Guo
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Toste, F. D. et al.
Representative Asymmetric Activation Modes

Coordinative interaction
Lewis acid catalysis

Double hydrogen-bonding interaction
Hydrogen-bonding catalysis

Single hydrogen-bonding interaction
Brønsted acid catalysis

Electrostatic interaction only
Chiral anion catalysis

Anion Phase-Transfer Catalysis

**Chiral Phosphoric Acid Catalysis**

- H-Bond
- Electrophile latent until protonated
- Limited to reactive nucleophiles

**Chiral Anion Phase Transfer Catalysis**

- Ion Pair
- Electrophile latent until solubilized
- Nucleophile scope expanded?

Interaction of non-symmetrical phenol with catalyst may allow face-selective fluorinative dearomatization
### Initial Findings – *para*-Fluorination

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Ratio 2a:2b:2c:2d</th>
<th>Net *para:*ortho</th>
<th>Yield 2a (% conv.)</th>
<th>ee 2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-C&lt;sub&gt;8&lt;/sub&gt;TRIP</td>
<td>1: 0.28: 0.51: 0.15</td>
<td>1.1:1</td>
<td>41% (&gt;95)</td>
<td>27</td>
</tr>
<tr>
<td>(S)-TCYP</td>
<td>1: 0.19: 0.51: 0.32</td>
<td>1.0:1</td>
<td>41% (&gt;95)</td>
<td>63</td>
</tr>
<tr>
<td>none</td>
<td>1: 0.11: 0.23: 0.00</td>
<td>2.9:1</td>
<td>17% (23)</td>
<td>--</td>
</tr>
</tbody>
</table>
**ortho-Fluorination**

2,3-Disubstituted phenol

\[
\text{1b} \quad \xrightarrow{5 \text{ mol\% (S)-TCYP, Selectfluor, } \text{Na}_2\text{CO}_3, \text{Toluene}} \quad \text{3b}
\]

96% ee, 75% yield

Absence of substitution at the 3-position

\[
\text{1b} \quad \xrightarrow{[\text{3b}]} \quad \text{4}
\]
Scope of Fluorinative Phenols Dearomatization

\[
\begin{align*}
\text{OH} & \quad \text{Cl} \\
R^1 & \quad R^2 \\
R^3 & \quad \text{F} \\
\text{N} & \quad \text{Boc}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{F} \\
\text{O} & \quad \text{F} \\
\text{O} & \quad \text{F} \\
\text{O} & \quad \text{F}
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{R}^1 \\
\text{F} & \quad \text{R}^2 \\
\text{F} & \quad \text{R}^3
\end{align*}
\]

5 mol% (S)-TCYP, Na\textsubscript{2}CO\textsubscript{3}, Toluene

<table>
<thead>
<tr>
<th>Product</th>
<th>ee %</th>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>96</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>87</td>
<td>54</td>
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<tr>
<td>3</td>
<td>96</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>90</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>91</td>
<td>70</td>
</tr>
</tbody>
</table>
Dimerization of Phenols Lacking 3-Substitution

\[
\text{R}_1 \text{O} \quad \text{R}_2 \quad \text{Cl} \quad \text{N} \quad \text{R}_3 \quad \text{2BF}_4^\text{−}
\]

\[
\text{R}_1 \text{O} \quad \text{F} \quad \text{R}_2 \quad \text{R}_3
\]

\[
5 \text{ mol}\% \ (S)$-\text{TCYP} \quad \text{Na}_2\text{CO}_3, \text{Toluene}
\]

\[
\frac{\text{[4+2]}}{\text{O}}
\]

97% ee, 81% yield

91% ee, 77% yield

90% ee, 65% yield

92% ee, 51% yield

87% ee, 71% yield

91% ee, 96% yield

79% ee, 75% yield

90% ee, 67% yield
Further Application

Retro-[4+2]/[4+2] derivatization of products

Asymmetric synthesis of Grandifloracin analogue 7
Fluorinative Dearomatization of Phenols

Catalytic dearomatization strategy

Fluorinative Dearomatization of Indole

A: Selectfluor (1.2 equiv) 
(DHQ)$_2$PHAL (1.2 equiv) 
NaHCO$_3$ (1.2 equiv), -78 °C

B: NFSI (1.2 equiv) 
(DHQ)$_2$PHAL (0.2 equiv) 
K$_2$CO$_3$ (6 equiv), -78 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cond.</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>XH</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>H</td>
<td>Me</td>
<td>OH</td>
<td>56</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>OMe</td>
<td>Me</td>
<td>OH</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>OBn</td>
<td>Me</td>
<td>OH</td>
<td>69</td>
<td>84</td>
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<tr>
<td>5</td>
<td>A</td>
<td>H</td>
<td>Me</td>
<td>NHTs</td>
<td>54</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>H</td>
<td>Me</td>
<td>NHTs</td>
<td>59</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>OMe</td>
<td>Me</td>
<td>NHTs</td>
<td>55</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>Mes</td>
<td>Me</td>
<td>NHCOMe</td>
<td>65</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>H</td>
<td>Me</td>
<td>NHCO$_2$Bn</td>
<td>40</td>
<td>78</td>
</tr>
<tr>
<td>10</td>
<td>A</td>
<td>H</td>
<td>Me</td>
<td>NHBoc</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>B</td>
<td>H</td>
<td>Me</td>
<td>NHBoc</td>
<td>70</td>
<td>78</td>
</tr>
</tbody>
</table>
Fluorinative Dearomatization of Indole

A: Selectfluor (1.2 equiv)
(DHQ)$_2$PHAL (1.2 equiv)
NaHCO$_3$ (1.2 equiv), rt

B: NFSI (1.2 equiv)
(DHQ)$_2$PHAL (0.2 equiv)
K$_2$CO$_3$ (6 equiv), rt

50% yield
68% ee
50% yield
60% ee

Crystal structure of 4
Fluorinative Dearomatization of Indole

Fluorinative Dearomatization of Indole

![Chemical reaction and product structures](image)

The reaction is carried out with Selectfluor (2.0 equiv) and NaHCO₃ (1.0 equiv) in MeCN, followed by 4Å MS at 0 °C. Yields of the products are indicated as follows:

- 81% for the first product
- 76% for the second product
- 66% for the third product
- 54% for the fourth product
- 62% for the fifth product
Fluorinative Dearomatization of Indole

\[
\begin{align*}
1a & \quad \xrightarrow{\text{Selectfluor/NaHCO}_3/\text{H}_2\text{O}} \quad \text{acetone, 0 }^\circ\text{C} \quad 15 \text{ min} \\
& \quad 34\% \text{ recovered}
\end{align*}
\]

\[
\begin{align*}
5a & \quad 45\%
\end{align*}
\]

\[
\begin{align*}
2a & \quad 21\%
\end{align*}
\]

\[
\begin{align*}
5a & \quad \xrightarrow{\text{Selectfluor/NaHCO}_3/\text{H}_2\text{O}} \quad \text{MeCN, 0 }^\circ\text{C} \quad 30 \text{ min}
\end{align*}
\]

\[
\begin{align*}
2a & \quad 80\%
\end{align*}
\]
Fluorinative Dearomatization of Indole

\[ \text{Selectfluor} \]

1. \[ R^1 = H \]
2. \[ R^1 = H \]
3. \[ R^1 = H \]
4. \[ R^1 = H \]
5. \[ R^1 = H \]
Fluorinative Dearomatization of Pyrazol Derivatives


\[ \text{R}_1^1 \text{N} - \text{N} - \text{R}_2^2 + \text{R} - \text{NO}_2 \rightarrow \text{N} - \text{N} - \text{R}_1^1 \text{O} - \text{R}_2^2 \text{R} - \text{NO}_2 \]

Cat., PhCO\(_2\)H, Toluene

\( \text{NFSI, rt, 24 h} \)

21 examples, ee 87% to 98%, dr 9:1 to 99:1
Fluorinative Dearomatization of Pyrazol Derivatives

(Determined by $^1$H and $^{13}$C NMR)
Fluorinative Dearomatization of Pyrazol Derivatives
Fluorinative Dearomatization of Isoxazol derivatives

Summary

1. Scope of aromatic compounds:

   Phenol; Indole; Pyrazol; Isoxazol

2. Catalysts:

   ![Catalysts diagram]

3. Fluorination reagents:

   ![Fluorination reagents diagram]
The rapid and controlled generation of complex, readily functionalizable three-dimensional structures from simple planar starting materials is a highly attractive goal, as it allows fast access to diverse molecular architectures. Dearomatization of arenes is a powerful approach that has been proposed as a key component in putative biosynthetic pathways for a range of bioactive natural products, inspiring a range of elegant syntheses. A highly desirable factor in such constructions is the induction of asymmetry into the product, which has generally been achieved by three distinct chemical approaches: diastereoselective dearomatization of a substrate bearing an existing stereocenter; dearomatization followed by enantioselective desymmetrization of the prochiral intermediate; and finally, direct asymmetric dearomatization, which requires discrimination between the enantiotopic faces of the arene during the dearomatizing event. The last category represents a significant challenge, and to date, several elegant albeit noncatalytic metal- and hypervalent iodine-mediated approaches have been reported. To the best of our knowledge, only a handful of direct catalytic asymmetric arene dearomatization protocols exist (all but one being intramolecular), although the benefits are evident. Herein we report an intermolecular dearomatization that incorporates a quaternary fluorine stereocenter into the product, which is desirable because of the current interest in the effect of fluorine incorporation into pharmaceuticals but has been restricted by the limited number of general approaches to the asymmetric construction of such stereocenters.
In summary, we have demonstrated the broad generality of our chiral anion phase-transfer catalysis strategy by applying it to the asymmetric fluorinative dearomatization of phenols. Notably, it represents a rare application of chiral phosphoric acid catalysts to simple phenol nucleophiles by virtue of our chiral-anion PTC approach to activation of Selectfluor. The small but densely functionalized products incorporating an enantioenriched quaternary F-containing stereocenter represent valuable building blocks of potential interest in synthetic and medicinal chemistry. Their close relationship to well-studied o-quinols provides numerous avenues for elaboration as well as exciting opportunities for bioisosteric replacement of −OH with −F in the numerous natural products thought to be derived from o-quinols.