Asymmetric Nucleophilic Catalysis

Vedejs, E.; Daugulis, O. J. Am. Chem. Soc. 2003, 125, 4166-4173
Shaw, S. A.; Aleman, P.; Vedejs, E. J. Am. Chem. Soc. 2003, 125, 13368-13369
Nucleophilic Catalysis: The Basics
Reactions Catalyzed by Nucleophiles

Addition of alcohols to ketenes:

\[
\text{Ph-}OH + \text{O=C-} + \text{C} \xrightarrow{\text{Catalyst}} \text{Ph-}O\text{-}C\text{-}Me
\]

Acylation of alcohols to anhydrides:

\[
\text{Ph-Me-}OH + \text{Me-}O\text{C-}O\text{-}Me \xrightarrow{\text{Catalyst}} \text{Me-}O\text{C-}Me
\]

Rearrangement of O-acylated enolates:

\[
\text{Me-}O\text{C-}O + \text{Me} \xrightarrow{\text{Catalyst}} \text{Me-}O\text{C-}O\text{-}Me
\]
Nucleophilic Catalysis: The Basics
Acylation of Alcohols

Nucleophilic Catalysis: The Basics
Steglich Rearrangement

This can also be done with pyridine as the catalyst, but it takes 24 hrs at 100 °C versus a few minutes at room temp.

**Kinetic Resolutions: Theory**

Kinetic resolutions are the best way for getting extremely enantioenriched compounds, usually utilizing an enzyme to preferentially react away one enantiomer of the substrate, leaving behind the other enantiomer of the substrate.

\[
s = \frac{\ln[(1-c)(1-\text{ee})]}{\ln[(1-c)(1+\text{ee})]} = \frac{k_{\text{fast-reacting enantiomer}}}{k_{\text{slow-reacting enantiomer}}}
\]

- \(s\) = selectivity
- \(c\) = conversion

\[
c = 1 - \frac{A + B}{A_0 + B_0}
\]

\(\text{ee} = \%\text{ee of recovered substrate}\)

\(A_0 = \text{initial amt. of fast-reacting enantiomer}\)

\(B_0 = \text{initial amt. of slow-reacting enantiomer}\)

\(A = \text{amt. of fast-reacting enantiomer @ time } T\)

\(B = \text{amt. of slow-reacting enantiomer @ time } T\)

---


Equation was numerically solved by Clark, C. T. using a TI-85 graphing calculator
**Kinetic Resolutions: Theory Pt. 2**

What about the other half of what you have? What is the %ee of the product at a given percent conversion with a known value of $s$?

$$s = \frac{\ln(1-c^*(1+ee))}{\ln(1-c^*(1-ee))} = \frac{k_{\text{fast-reacting enantiomer}}}{k_{\text{slow-reacting enantiomer}}}$$

$s = \text{selectivity}$  
$c = \text{conversion}$  
$c = 1 - \frac{A + B}{A_0 + B_0}$

$ee = \%ee$ of product

$A_0 = \text{initial amt. of fast-reacting enantiomer}$  
$B_0 = \text{intial amt. of slow-reacting enantiomer}$

$A = \text{amt. of fast-reacting enantiomer @ time T}$  
$B = \text{amt. of slow-reacting enantiomer @ time T}$


Equation was numerically solved by Clark, C. T. using a TI-85 graphing calculator
Enantioselective Acylations with Chiral Phosphines: Early Work with Non-Enzymes

\[
\text{RL}_1 + \text{R}_2\text{C} = \text{O} + \text{CH}_2\text{Cl}_2 \xrightarrow{5-10 \text{ mol}\% \text{catalyst}} \text{RL}_1\text{R}_2\text{C} = \text{O} + \text{RL}_1\text{R}_2\text{OH}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>anhydride</th>
<th>%ee 5 (conv.)</th>
<th>selectivity (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>3</td>
<td>Ac$_2$O</td>
<td>9 (40)</td>
<td>1.2</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>4</td>
<td>Ac$_2$O</td>
<td>11 (60)</td>
<td>1.3</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>6a</td>
<td>Ac$_2$O</td>
<td>65 (66)</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>6b</td>
<td>Ac$_2$O</td>
<td>42 (80)</td>
<td>2.6</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>6a</td>
<td>Ac$_2$O</td>
<td>52 (10)</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>3</td>
<td>Ac$_2$O</td>
<td>50 (40)</td>
<td>2.9</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>6a</td>
<td>Ac$_2$O</td>
<td>27 (22)</td>
<td>1.2</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>4</td>
<td>Bz$_2$O</td>
<td>22 (31)</td>
<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>6a</td>
<td>Bz$_2$O</td>
<td>68 (84)</td>
<td>5.5</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>6b</td>
<td>Bz$_2$O</td>
<td>58 (70)</td>
<td>4.7</td>
</tr>
<tr>
<td>11</td>
<td>PhCH(OH)Ph</td>
<td>6a</td>
<td>3-ClBz$_2$O</td>
<td>81 (25)</td>
<td>12-15</td>
</tr>
</tbody>
</table>

meso substrates

perdeuterated Ac$_2$O give monoacetate without loss of deuterium: no ketene mechanism operative

This was the largest s value for a non-enzyme at the time

chiral phosphines:

3

6a, R = Me
6b, R = Et

**Enantioselective Acylations with Chiral Phosphines: An Improved Catalyst**

A selectivity of 12 – 15 is good, but can it be improved? Yes!

New catalysts:

![Catalysts 1, 2, and 3](image)

Retrosyntheses of catalysts:

![Retrosyntheses](image)

**Enolate Alkylations Using Lactate Triflates**

![Chemical Reaction Diagram]

How do you access the minor diastereomer? Use a cryptand-like ester

![Chemical Reaction Diagram]
Continued Synthesis of Phosphine Catalysts

\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]
\[
\text{OH} \quad \text{OH}
\]

\[
\text{SOCl}_2 \quad \text{CCl}_4 \quad \text{reflux}
\]
\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]
\[
\text{O} \quad \text{O}
\]

\[
\text{RuCl}_3 \cdot 3\text{H}_2\text{O}
\]
\[
\text{NaIO}_4
\]
\[
\text{H}_2\text{O}, 60\%
\]
\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]
\[
\text{O} \quad \text{O}
\]

\[
\text{PhPHLi} \quad \text{THF}
\]
\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]
\[
\text{O} \quad \text{O} \quad \text{Li}_2\text{SO}_3
\]

\[
\text{BuLi}
\]
\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]
\[
\text{O} \quad \text{O} \quad \text{Li}_2\text{SO}_3
\]

\[
\text{BH}_3 \cdot \text{THF} \quad 85\%
\]
\[
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me}
\]
\[
\text{BH}_3
\]
\[
\text{P}
\]

36:1 d.r.
### Acylation of Alcohols Using Phenyl Catalyst

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Anhydride R</th>
<th>R1</th>
<th>R2</th>
<th>Relative rate</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>t-Bu</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>t-Bu</td>
<td>0.1(−40°)</td>
<td>67</td>
</tr>
<tr>
<td>1-naphthyl</td>
<td>Ph</td>
<td>t-Bu</td>
<td>0.02</td>
<td>25</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>t-Bu</td>
<td>0.6</td>
<td>16</td>
</tr>
<tr>
<td>i-Pr</td>
<td>Ph</td>
<td>i-Pr</td>
<td>0.1</td>
<td>13</td>
</tr>
<tr>
<td>Ph</td>
<td>2-naphthyl</td>
<td>Me</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>i-Pr</td>
<td>c-C₃H₅</td>
<td>Me</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>i-Pr</td>
<td>i-Pr</td>
<td>Me</td>
<td>0.1</td>
<td>1</td>
</tr>
</tbody>
</table>
Syntheses of Other Phosphine Catalysts

\[ \text{Me}_3\text{SiSO}_2 \overset{\text{ArPHLi}}{\xrightarrow{\text{THF}}} \text{Me}_3\text{SiSO}_3\text{Li} \overset{\text{BuLi}}{\rightarrow} \]

2 \( \text{Ar}=3,5\text{-Me}_2\text{C}_6\text{H}_3 \)
3 \( \text{Ar}=3,5\text{-t-Bu}_2\text{C}_6\text{H}_3 \)

\[ \overset{\text{BH}_3\text{-THF}}{\xrightarrow{85\%}} \]

2 = 43:1
3 = 91:1
### Evaluation of Me₂Ph-PBO

<table>
<thead>
<tr>
<th>Anhydride R</th>
<th>R1</th>
<th>R2</th>
<th>Solvent</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>t-Bu</td>
<td>Toluene</td>
<td>8.1</td>
</tr>
<tr>
<td>i-Bu</td>
<td>2-naphthyl</td>
<td>Me</td>
<td>Toluene</td>
<td>14</td>
</tr>
<tr>
<td>i-Bu</td>
<td>Ph</td>
<td>i-Pr</td>
<td>Heptane</td>
<td>14</td>
</tr>
<tr>
<td>i-Bu</td>
<td>Ph</td>
<td>i-Bu</td>
<td>Heptane</td>
<td>12</td>
</tr>
</tbody>
</table>
### Evaluation of \( t\text{-Bu}_2\text{Ph-PBO} \)

![Chemical structure of \( t\text{-Bu}_2\text{Ph-PBO} \)]

<table>
<thead>
<tr>
<th>Anhydride R</th>
<th>R1</th>
<th>R2</th>
<th>Solvent/Temp</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>( t\text{-Bu} )</td>
<td>tol/RT</td>
<td>10</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>Ph</td>
<td>( i\text{-Pr} )</td>
<td>hept/RT</td>
<td>20</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>Ph</td>
<td>( i\text{-Pr} )</td>
<td>hept/(-40 , ^\circ \text{C} )</td>
<td>99 (117)</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>2-naphthyl</td>
<td>Me</td>
<td>tol/RT</td>
<td>17</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>Ph</td>
<td>( n\text{-Bu} )</td>
<td>hept/RT</td>
<td>18</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>Ph</td>
<td>( n\text{-Bu} )</td>
<td>hept/(-40 , ^\circ \text{C} )</td>
<td>55 (60)</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>( 2,4,6\text{-Me}_3\text{C}_6\text{H}_2 )</td>
<td>Me</td>
<td>tol/RT</td>
<td>15</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>( 2,4,6\text{-Me}_3\text{C}_6\text{H}_2 )</td>
<td>Me</td>
<td>tol/(-40 , ^\circ \text{C} )</td>
<td>220 (328)</td>
</tr>
<tr>
<td>( i\text{-Pr} )</td>
<td>( 2,4,6\text{-Me}_3\text{C}_6\text{H}_2 )</td>
<td>Me</td>
<td>tol/(-40 , ^\circ \text{C} )</td>
<td>390</td>
</tr>
</tbody>
</table>
Summary of Acylations Using PBO Catalysts

- Phosphabicyclooctane catalysts can be effectively used for a number of kinetic resolutions of benzylic alcohols.
- Separation of enantiomers of these catalysts is not exceptionally difficult, done through use of lactate esters and recrystallizations.
- Enantioselectivities are exceptional, with values of $s = 380$.
- Selectivities high enough to warrant correction for %ee of catalyst.
- Synthesis is quite air-sensitive at parts, yields of the alkylations are low, and the catalyst must be stored as the borane complex, due to interconversion of diastereomers at phosphorus.
- The full paper only covered the use of a few catalysts.
- Will this replace using enzymes for kinetic resolutions? Not yet, I think.
Chiral Nucleophilic Pyridine Catalysts: Background

- DMAP: Two mirror planes
- Substitution with a chiral group will also make a chiral DMAP
  - Greg Fu was the first person to use these types of catalysts for catalytic enantioselective work

Vedejs' Catalyst

Fu's Catalysts:
Acylations Catalyzed by Planar-Chiral DMAP Analogs

\[
\begin{align*}
\text{Ph-} & \text{Me} + \text{MeO} \quad \text{2 mol\% cat} \\
\text{solvent, rt} & \quad \text{Ph-} \quad \text{Me} \\
\text{2 mol\% cat} & \quad \text{Ph-} \quad \text{Me} + \text{Ph-} \quad \text{Me}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>% conv. after 1 h</th>
<th>selectivity</th>
<th>entry</th>
<th>solvent</th>
<th>% conv. after 1 h</th>
<th>selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>6</td>
<td>3.4</td>
<td>6</td>
<td>EtOAc</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$CN</td>
<td>10</td>
<td>3.6</td>
<td>7</td>
<td>toluene</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>14</td>
<td>7.0</td>
<td>8</td>
<td>Et$_2$O</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>acetone</td>
<td>8</td>
<td>8.7</td>
<td>9</td>
<td>t-amyl alcohol</td>
<td>38</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>4</td>
<td>9.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Desymmetrizations:

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

\[
\begin{align*}
\text{1\% cat, Ac$_2$O} & \quad \text{1\% cat, Ac$_2$O} \\
\text{NEt$_3$, 0 °C} & \quad \text{NEt$_3$, 0 °C} \\
\text{t-amyl alcohol} & \quad \text{t-amyl alcohol} \\
\end{align*}
\]

Synthesis of a New Chiral Nucleophilic Catalyst

\[
\text{Ph}_3\text{CCOOH} \xrightarrow{\text{LAH}} \text{Ph}_3\text{CCH}_2\text{OH} \xrightarrow{\text{TPAP, NMO, 63\%}} \text{Ph}_3\text{CCHO}
\]

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Bu} & \quad \text{Li} \\
\text{Ac} & \quad \text{Ph}_3
\end{align*}
\]

Ab initio geometry of acyl pyridinium

**Comparison of Pyridine Catalyst and t-Bu$_2$Ph-PBO Catalyst**

![Chemical structures](image)

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>Catalyst</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>DMAP</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>Me</td>
<td>Bn</td>
<td>PBO</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Bn</td>
<td>Ph</td>
<td>DMAP</td>
<td>99</td>
<td>95</td>
</tr>
<tr>
<td>Bn</td>
<td>Bn</td>
<td>PBO</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>allyl</td>
<td>Ph</td>
<td>DMAP</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>allyl</td>
<td>Bn</td>
<td>PBO</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>℧Bu</td>
<td>Ph</td>
<td>DMAP</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>℧Bu</td>
<td>Bn</td>
<td>PBO</td>
<td>87</td>
<td>92</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>DMAP</td>
<td>95</td>
<td>58</td>
</tr>
<tr>
<td>Ph</td>
<td>Bn</td>
<td>PBO</td>
<td>96</td>
<td>20</td>
</tr>
</tbody>
</table>
Substrate Scope for the Chiral Nucleophilic Pyridine Catalyzed Steglich Rearrangement

![Chemical structures and reactions involving chiral catalysts and substrates with yield and enantiomeric excess (ee) data.]
Summary of Vedejs’ Nucleophilic Asymmetric Catalysts

- Four new asymmetric nucleophilic catalysts have been synthesized and evaluated by the Vedejs group
- Catalysts are straightforward to make in moderate yields
- \(t\text{-Bu}_2\text{Ph-PBO}\) and the chiral pyridine catalyst both show high enantioselectivities when catalyzing a Steglich rearrangement
- PBO catalysts have exceptional \(s\) values for kinetic resolutions of benzylic alcohols, and, based on Fu’s research, Vedejs’ chiral pyridine catalyst could also work well in this reaction