Enantioselective Organo-Cascade Catalysis
JACS, 2005, ASAP

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Current Literature
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Why are these articles significant?

- Use chiral amines as enantioselective catalysts (iminium and enamine intermediates) to rapidly assemble complex structures

- MacMillan and co-workers use amine catalysts to mimic an enzymatic ‘cascade catalysis’ that controls product stereochemistry via intermolecular reactions

- List and co-workers use a single amine catalyst to generate complexity via an intramolecular tandem sequence

- Both achieve products with high yields and selectivities (diastereo- and enantioselectivity) under user-friendly conditions with safe and simple starting materials
Asymmetric Aminocatalysis

- Amines can activate carbonyl groups (i.e., acetone) as do Lewis or Brønsted acids
  - Iminium ion enhances both electrophilicity and α-C-H-acidity

- Two aminocatalytic pathways:
  1. Iminium catalysis - Knoevenagel-type condensations, cyclo- and nucleophilic additions
  2. Enamine catalysis - Electrophilic addition and pericyclic reactions

- Aminocatalysis is a biomimetic strategy used by important enzymes such as class I aldolases (enamine catalysis) and ketoacid decarboxylases (iminium catalysis)

Direct Catalytic Asymmetric Three-Component Mannich Reaction (List and co-workers)

\[
\begin{align*}
\text{O} & \quad \text{CHO} \quad \text{NH}_2 \\
20 \text{ mol}\% & \quad \text{NO}_2 \quad \text{OMe} \\
\end{align*}
\]

\[
\xrightarrow{\text{L-Proline (35 mol\%)} \quad \text{DMSO 50\%}}
\]

\[
\text{HN} \quad \text{O}_2 \quad \text{Me} \\
94\% \text{ ee}
\]


Direct Catalytic Asymmetric \(\alpha\)-Amination of Aldehydes (List and co-workers)

\[
\begin{align*}
\text{H} & \quad \text{CHO} \quad \text{N} \quad \text{N} \quad \text{CO}_2\text{Bn} \\
\text{i-Pr} & \quad \text{BnO}_2\text{C} \quad \text{Cbz} \quad \text{Cbz} \quad \text{HO} \\
\end{align*}
\]

\[
\xrightarrow{(\text{S})\text{-Proline (10 mol\%)} \quad \text{CH}_3\text{CN, 0 }^\circ\text{C} \quad \text{then NaBH}_4, \text{EtOH 95\%}}
\]

\[
\xrightarrow{>95\% \text{ ee}}
\]

New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction (MacMillan and co-workers)

Enantioselective Organo-Cascade Catalysis
(ASAP Article, MacMillan and co-workers)

- Use amine catalysts to perform a ‘cascade catalysis’ of discrete events that mimic a biocatalytic assembly line, as opposed to the traditional ‘stop and go’ sequences

  - Specifically, polyketide natural products (i.e., erythromycin and actinomycyes) are assembled by polyketide synthases, which perform a successive decarboxylative condensations of simple precursors


- Imidazolidinone-based catalytic cycles are used to generate complex structures without catalyst-catalyst interactions

Cascade Catalysis: Merging Iminium (Im) and Enamine (En) Activation

Organo-Cascade Catalysis: Effect of Catalyst and Solvent

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>% conversion</th>
<th>dr (syn:anti)</th>
<th>% ee</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>EtOAc</td>
<td>3</td>
<td>1:1</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>EtOAc</td>
<td>10</td>
<td>5:1</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>EtOAc</td>
<td>79</td>
<td>9:1</td>
<td>97</td>
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<tr>
<td>4</td>
<td>12</td>
<td>EtOAc</td>
<td>78</td>
<td>8:1</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>EtOAc</td>
<td>78</td>
<td>11:1</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>CHCl₃</td>
<td>54</td>
<td>8:1</td>
<td>94</td>
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</tbody>
</table>

*Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether).*  
*Absolute and relative configuration assigned by chemical correlation.*  
*Enantiomeric excess determined by chiral GLC analysis (Bodman β-DM).*
Organo-Cascade Catalysis: Scope of Enal Component and Representative Nucleophiles

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>temp (°C)</th>
<th>% yield</th>
<th>dr&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% ee&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>Me</td>
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<td>86</td>
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</tr>
<tr>
<td>2</td>
<td>Pr</td>
<td></td>
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<td>74</td>
<td>13:1</td>
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<tr>
<td>3</td>
<td>CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td></td>
<td>-60</td>
<td>80</td>
<td>22:1</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td></td>
<td>-40</td>
<td>82</td>
<td>11:1</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td></td>
<td>-40</td>
<td>83</td>
<td>9:1</td>
<td>99</td>
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<tr>
<td>6</td>
<td>i-Pr</td>
<td></td>
<td>-40</td>
<td>67</td>
<td>12:1</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Absolute and relative configuration assigned by chemical correlation.

<sup>b</sup> Enantiomeric excess determined by chiral GLC analysis.
Organo-Cascade Catalysis: Employment of Discrete Amine Catalysts to Enforce Cycle-Specific Selectivities

Summary

MacMillan and co-workers:

- Developed a new strategy for organo-catalysis based on the biochemical blueprints of cascade catalysis
- Rapid access to structural complexity while achieving exquisite levels of enantiocontrol (combining catalytic cycles leads to enantioenrichment)
- Studies in the area of triple cascade catalysis are underway