Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reactions
Previous enatioselective Pictet-Spengler Reactions

2. Substrate-controlled Pictet-Spengler cyclization.
3. Compound 3 (89:11, major isomer in 57 % yield).
4. 79 % yield, 92 %ee from 3 to 6.
5. Chiral auxiliary was recovered in 92 % yield.
Catalytic approach

2. Cyclic imines accessed by Bischler-Napieralski reaction.
3. Asymmetric hydrogenation of cyclic imines.
4. 77~97 %ee in 72~99 % yield.
5. 0.4 mol% loading of Ru catalyst.
Chiral Lewis acid-mediated enatioselective Pictet-Spengler reactions of N\textsubscript{\beta}-Hydroxytryptamin with aldehydes

2. The use of superstoichiometric quantaties of boron reagents.
3. Restricted to N\textsubscript{\beta}-hydroxytryptamine-derived nitrones.
4. Up to 90 \%ee

<table>
<thead>
<tr>
<th>Table 2. Pictet–Spengler Reaction of Nitrones Catalyzed by (+)-Ipc\textsubscript{2}BCl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>entry</td>
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<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>9: R = OH</td>
</tr>
</tbody>
</table>

Gil Ma @ Wipf Group 4 9/12/2004
1. The challenge of an asymmetric catalytic Pictet-Spengler reaction; the low reactivity of the imine substrates
2. Strong Bronsted acids; racemic pathway. Lewis acid catalysis; highly reactive reagents, high temperature often.
3. A screen of potential chiral catalysts didn’t afford any useful leads.

↓

More reactive intermediates; under relatively mild conditions
1. How to enhance the reactivity of imine or iminium intermediates; N-acyliminium intermediates; highly active electrophiles.
2. by a relatively mild Lewis or Bronsted acid catalyst.
3. Chiral thiourea catalyst; activate a weakly Lewis basic N-acyliminium ion using a chiral hydrogen bond donor.
Thiourea catalyst

2. Reversible formation of an imine-catalyst complex, presumably through a hydrogen bond between the imine nitrogen and an acidic proton of the catalyst.
3. Only the two urea hydrogens of the catalyst is essential for catalyst activity.
4. Increasing the steric bulk of the amino acid side chain had a beneficial effect.
5. A thiourea group improve enantioselectivity.
6. Wider range of substrate in Strecker reaction.
Scheme 1. Asymmetric Strecker Reaction Catalyzed by 1

\[
\text{Scheme 1. Asymmetric Strecker Reaction Catalyzed by 1}
\]

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

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

\[
\text{R}^1 = \text{aryl or alkyl, } \text{R}^2 = \text{H or Me} \\
\text{R}^3 = \text{aryl, alkyl, heteroatom} \\
\]

> 50 examples

85-99% yield
70-99% ee

\[
\text{Table 2. Mannich Reactions Catalyzed by 1c}
\]

\[
\begin{align*}
\text{Boc} & \quad \text{NH} & \quad \text{R} \\
\text{3a-n} & \quad \text{OTBS} & \quad \text{4c}
\end{align*}
\]

1. 1c (5 mol%) toluene, 48 h
2. TFA, 2 min

-40°C, 48 h
R = aryl, >90% yield, >90% ee

\[
\text{JACS, 2002, 12964}
\]
**Table 1.** Optimization of Catalyst Structure

![Chemical Structures](image)

- **1a**: R = CH₃, R = R'' = CH₃
- **1b**: R₁ = CH₃, R' = R'' = Ph
- **1c**: R = CH₃, R = R'' = CH₃
- **1d**: R = CH₃, R' = R'' = Ph
- **1e**: R = CH₃, R' = CH₃, R'' = Ph
- **1f**: R = i-Bu, R' = CH₃, R'' = Ph

Chemical reaction:

\[
\text{2} \xrightarrow{\text{AcCl (1.0 equiv.)}} \xrightarrow{\text{2,6-lutidine (1.0 equiv.)}} \xrightarrow{\text{catalyst (10 mol%)}} \xrightarrow{\text{Et₂O, -78°C → -30°C}} \text{3a}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield (%)&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>1a</td>
<td>65</td>
<td>59</td>
</tr>
<tr>
<td>1b</td>
<td>45</td>
<td>61</td>
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<tr>
<td>1c</td>
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<td>93</td>
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<tr>
<td>1f</td>
<td>70</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield determined by NMR.

<sup>b</sup> Enantiomeric excess measured by chiral HPLC.
**Table 2.** Asymmetric Acyl-Pictet–Spengler Reactions Catalyzed by 1f

![Chemical structure]

1) R'CHO (1.05 equiv.)
2) AcCl (1.0 equiv.)
3) 2,6-lutidine (1.0 equiv.)
4) 1f (5-10 mol%)
5) Et₂O, -78°C → T°C

<table>
<thead>
<tr>
<th>product</th>
<th>R</th>
<th>R'</th>
<th>T (°C)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>CH(CH₂CH₃)₂</td>
<td>-30</td>
<td>65c</td>
<td>93</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>CH(CH₃)₂</td>
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<tr>
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<td>H</td>
<td>n-C₅H₁₁</td>
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<td>95</td>
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<tr>
<td>3d</td>
<td>H</td>
<td>CH₂CH(CH₃)₂</td>
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<tr>
<td>3e</td>
<td>H</td>
<td>CH₂CH₂OTBDPS</td>
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<td>77d</td>
<td>90</td>
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<tr>
<td>3f</td>
<td>5-MeO</td>
<td>CH(CH₂CH₃)₂</td>
<td>-40</td>
<td>81c</td>
<td>93</td>
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<tr>
<td>3g</td>
<td>6-MeO</td>
<td>CH(CH₂CH₃)₂</td>
<td>-50</td>
<td>76d</td>
<td>86</td>
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</table>

Limitation; The substrates derived from aromatic aldehydes or trimethylacetaldehyde display low activity.
1. Access to a range of substituted tetrahydro-\(\beta\)-carboline in high ee.
2. Enantioselective transformation using a chiral H-bond donor.

3. Examination of the mechanism of this transformation.
4. Application in alkaloid synthesis.