Bifunctional Asymmetric Catalysts: Design and Applications

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Enzyme Catalysis vs Small-Molecule Catalysis

- Activation of both substrates
- intramolecular reaction

- Activation of electrophile
- intermolecular reaction
Dual activation of reacting partners

2nd order kinetic dependence on catalyst
Proposed mechanism:

Dual activation by coordination of azide and epoxide to Cr catalyst

Bridging two reactive sites by covalent tethering

Intermolecular reaction
\[ k_{\text{obs}}/[\text{cat}] = 0.022 \text{ min}^{-1} \]
94% ee

Intramolecular reaction
\[ k_{\text{obs}}/[\text{cat}] = 0.97 \text{ min}^{-1} \]
93% ee

- Rate enhancement through covalent linkage without loss in enantioselectivity

Reaction types catalyzed by bifunctional catalysts

\[
\text{R}^1\text{H} + \text{TMSCN (1.2 equiv)} \rightarrow \text{R}^\prime\text{OH} \quad \text{R}^\prime\text{Me}
\]

\[
\text{R}^1\text{H} + \text{H-P-OMe} \rightarrow \text{R}^\prime\text{P-OMe} \quad \text{R}^\prime\text{P-OMe}
\]

\[
\text{R}^1\text{C} = \text{N}^\text{NO}_2 + \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \rightarrow \text{R}^\prime\text{C} = \text{N}^\text{NO}_2 \quad \text{MeO}_2\text{C} = \text{CO}_2\text{Me}
\]
Bifunctional catalysis

1. Lewis acid-Lewis base catalysts
2. Lewis acid-Bronsted base catalysts
3. Lewis acid-Lewis acid catalysts
4. Hydrogen-bonding catalysts
Al-BINOL-phosphine oxide: a Lewis acid-Lewis base catalyst

\[
\begin{align*}
&\text{R = alkyl} & \text{Bu}_3\text{P}=\text{O} & \text{Yields (\%)} & \text{ee} \\
&\text{R = alkenyl} & \text{Bu}_3\text{P}=\text{O} & \text{91-99} & \text{97-98} \\
&\text{R = aromatic} & \text{CH}_3\text{P(O)Ph}_2 & \text{86-98} & \text{90-96}
\end{align*}
\]

- phosphine oxide reduces Lewis acidity of catalyst
- Slow addition of TMSCN

Al-BINOL-phosphine oxide: cyanosilylation of aldehydes by bifunctional catalysis

Proposed mechanism:

- Lewis acid-activation of aldehyde
- Lewis base-activation of TMSCN

Al-BINOL-phosphine oxide: cyanosilylation of aldehydes by bifunctional catalysis

\[
\text{RCHO} + \text{TMSCN (1.2 equiv)} \rightarrow \text{RNCMe} \quad \text{catalyst =} \quad \begin{array}{c}
\text{Ph} \\
\text{Ph}
\end{array}
\]

1. catalyst (9 mol%) + additive (36 mol%) in \(\text{CH}_2\text{Cl}_2\), -40 °C
2. \(\text{H}^+\)

Catalysts:

Yield: 97%
ee: 97%

Yield: 56%
ee: 10%

Low yield – Internal quenching

Expanding Al-BINOL-phosphine oxide-catalyzed reactions: the Reissert-type reaction

Challenges in the asymmetric catalytic reaction:

Two limiting geometries → two different enantiomers
Al-BINOL-phosphine oxide-catalyzed Reissert-type reaction

First catalytic asymmetric Reissert-type reaction
83-96% ee, 72-99% yield for electron-rich quinolines

Cooperative Lewis base-Lewis acid catalysis for \( \beta \)-lactam synthesis

\[
\begin{align*}
| & \text{Product} & \text{In(OTf)}_3 & \text{Yield (\%)} & \text{ee} & \text{d.r.} \\
\hline
R = \text{Ph} & - & 65 & 99 & 99/1 \\
& 10 \text{ mol\%} & 95 & 98 & 60/1 \\
R = \text{OPh} & - & 45 & 99 & 99/1 \\
& 10 \text{ mol\%} & 93 & 97 & 22/1 \\
\end{align*}
\]

Without Lewis acid: yields: 45-65\%, dr 50/7 – 99/1, ee 95-99\%

With Lewis acid: yields: 92-98\%, dr 9/1 – 60/1, ee 96-99\%

Tandem activation of nucleophile and electrophile

A possible working model

Most stable conformation from molecular mechanics calculations

Bifunctional catalysis

1. Lewis acid-Lewis base catalysts

Combining well-studied modes of catalysis to generate new catalytic systems

2. Lewis acid-Bronsted base catalysts

3. Lewis acid-Lewis acid catalysts

4. Hydrogen-bonding catalysts
Lewis acid-Bronsted base catalysts from self-assembled metal complexes

“REMB catalyst”
RE = rare earth metals (Ln, Pr, Eu, Yb)
M = alkali metals (Li, Na, K)

Lewis acid-Bronsted base catalysts from self-assembled metal complexes

RE = rare earth metals (Ln, Pr, Eu, Yb)
M = alkali metals (Li, Na, K)

Simplified general mechanism:

E = electrophiles with Lewis basic site
H-Nu = aryl ketones, malonates, thiols, nitroalkanes

A Lewis acid-Bronsted base catalyst for different reactions

\[
\begin{align*}
\text{R}^1\text{CHO} + \text{R}^2\text{CO} &\xrightarrow{(S)\text{-LLB.KOH (8 mol\%)} \text{THF, -20 °C}} \text{R}_1\text{OH} + \text{R}_2\text{CO} \\
\text{ee} &= 30-93\%, \\
yields &= 50-91\%
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{CH} = \text{CH}_2 + \text{R}^2\text{C}(\text{S})\text{tBu} &\xrightarrow{(S)\text{-LnSB}} \text{R}^1\text{C} = \text{C}(\text{S})\text{tBu} + \text{R}^2\text{H} \\
\text{ee} &= 84-93\%, \\
yields &= 86-98\%
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{CHO} + \text{H}^\text{31P}-\text{OMe} &\xrightarrow{(R)\text{-LLB}} \text{R}^1\text{P} = \text{O}^\text{31P}-\text{OMe} \\
\text{ee} &= 36-95\%, \\
yields &= 63-93\%
\end{align*}
\]

Proposed working model for the aldol reaction

Expanding the reaction scope of REMB catalysts

Lewis acid-Bronsted base catalysis:

\[ \text{H-Nu} = \text{only nucleophiles with sufficiently low pK}_a \]

Lewis acid-Lewis acid catalysis?
REMB-catalyzed aza-Michael addition

![Chemical structures and reaction conditions]

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yields (%)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>aromatic</td>
<td>aromatic</td>
<td>80-97</td>
<td>81-96</td>
</tr>
</tbody>
</table>

A Lewis acid catalyst or a bifunctional catalyst?

- actual catalyst structure during catalysis?

- the role of the Ln center: structural element or Lewis acid?

The 7- and 8-coordinate LLB complex

- The metal can expand its coordination number beyond 6

Substrate binding at Ln center

- Cyclohexanone binds to both EuLB and EuLB-DMEDA adduct

Bifunctional catalysis

1. Lewis acid-Lewis base catalysts

2. Lewis acid-Bronsted base catalysts

3. Lewis acid-Lewis acid catalysts
   - A general class of catalysts with 2 possible modes of activation
   - Heterobimetallic catalysis and “two-center catalysis”
   - Mechanistic data that supports working model may be difficult to obtain

4. Hydrogen-bonding catalysts
Organocatalytic cyanosilylation of ketones

\[ \text{R}^1 \text{R}^2 \text{O} \quad \text{R}^1 \text{R}^2 \text{TMS} \quad \text{catalyst} \quad \text{TMSO} \quad \text{CN} \]

CF\textsubscript{3}CH\textsubscript{2}OH, CH\textsubscript{2}Cl\textsubscript{2}  
-78 °C

<table>
<thead>
<tr>
<th>( \text{R}^1 )</th>
<th>( \text{R}^2 )</th>
<th>Yields (%)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryl or vinyl</td>
<td>Me</td>
<td>81-98</td>
<td>89-98</td>
</tr>
<tr>
<td>Alkyl</td>
<td>Me</td>
<td>n.d.</td>
<td>8-79</td>
</tr>
</tbody>
</table>

Organocatalytic cyanosilylation of ketones: mechanistic studies

- Reaction rate shows first-order dependence of rate on [catalyst], [ketone] and [HCN]
- Pyridine is a potent inhibitor of the reaction
- Plot of rate against [pyridine]
- Plot of chemical shift against [pyridine]

Organocatalytic cyanosilylation of ketones: mechanistic studies

• Added trialkylamines decrease rate and enantioselectivity

• Plot of rate against [amine]

• Bronsted basicity of amine affects reaction

Organocatalytic cyanosilylation of ketones: 2 possible mechanisms
Organocatalytic cyanosilylation of ketones: DFT calculations

- co-planarity of C=O and C=C bonds preferred in transition state
Organocatalytic cyanosilylation of ketones: enantioselectivity explained
Bifunctional organocatalysts based on cinchona alkaloids

Bifunctional organocatalysts based on cinchona alkaloids

\[
\begin{align*}
\text{R} = & \text{NO}_2 \quad \text{MeO}_2\text{C} = \text{CO}_2\text{Me} \\
\text{catalyst} & \quad \text{MeO}_2\text{C} - \text{CO}_2\text{Me} \\
\text{R} & \quad \text{NO}_2
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Yields (%)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aryl</td>
<td>90-99</td>
<td>96-98</td>
</tr>
<tr>
<td>Alkyl</td>
<td>71-81</td>
<td>94</td>
</tr>
</tbody>
</table>

- Quinidine itself gives low selectivity
- Phenol does not catalyze reaction

Bifunctional organocatalysts based on cinchona alkaloids

Michael donors:

Yields = 73-94%, d.r. = 86:14 - >98:2, ee = 92 - >99%

- Various Michael donors and nitroalkenes are competent
- Implies that catalyst is tolerant of substitution pattern changes

Probing the active conformation of organocatalysts in Michael addition

Reaction was carried out with 2 catalysts:

Bifunctional catalysis

1. Lewis acid-Lewis base catalysts
2. Lewis acid-Bronsted base catalysts
3. Lewis acid-Lewis acid catalysts
4. Hydrogen-bonding catalysts

• One of the most well-characterized organocatalysts
• Hydrogen-bonding catalysis is a fundamentally new mode of catalysis
Concluding remarks

There are many types of catalysis:

- Lewis acid catalysis
- Lewis base catalysis
- Transition-metal catalysis
- Bronsted acid catalysis
- Bronsted base catalysis
- Iminium catalysis
- Enamine catalysis
- SOMO catalysis
- Hydrogen-bonding catalysis
- Counterion catalysis
- Phase-transfer catalysis

- Bifunctional catalysis is a combination of 2 or more of these types
Conclusions and outlook

• Combining known catalysts can lead to better reactivities and enantioselectivities

• Structural complexity of bifunctional catalysts can make mechanistic studies difficult

• “Mix-and-match” or combinatorial catalytic systems are likely to become more popular

• Merging transition-metal catalysis with other forms of catalysis may lead to discovery of new reactions
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