Chiral Anions in Asymmetric Catalysis

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Burke Group Literature Seminar
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**Key Activation Modes for Asymmetric Catalysis**

*Coordination interaction*

*‘Lewis acid catalysis’*

Lewis acidic metal (M) and Lewis basic ligand (L) form chiral net Lewis acidic species

*Double hydrogen-bonding interaction*

*‘Hydrogen bonding catalysis’*

Directional H-bonds provide electrophilic activation and stereodefined environment

*Single hydrogen-bonding interaction*

*‘Bronsted acid catalysis’*

High acidity of chiral phosphoric acid and Bronsted basicity of phosphoryl O activate electrophile and nucleophile

*Electrostatic interaction only*

*‘Chiral anion catalysis’*

Ion pairing between fully protonated substrate and phosphate counterion

**Chiral Anion Catalysis**

- Combination of *achiral* but catalytically active species (transition metal complex, Lewis base, Lewis acid) with *chiral* counterion

- In nonpolar media, species will exist as tight ion pair and *influence of counterion* can be *stereochemically significant*

- *Generalizable strategy* as many reactions are known to proceed through cationic intermediates

- Most examples here: *achiral cationic metal complex with chiral counterion*
**Metal Catalysis with Chiral Counterions**

**Generalized Strategy**

- *Chiral ions* interact with metal only through *electrostatic* interactions
  - Traditionally *chiral ligands* which directly *coordinate* to metal center are used

- Phosphoric acid ligands regarded as *highly dissociated* compared to conventional ligands (eg phosphines)

Gold (I)-Catalyzed Enantioselective Allene Hydroamination

Original Methodology NOT a Chiral Anion Strategy

Dinuclear Gold(I)-Phosphine Complexes

Silver activates gold complexes through formation of cationic gold species via halide extraction.

\[
\begin{align*}
&\text{P–Au–X} \\
&\text{P–Au–Y} \\
&\text{A} \\
&\text{catalytically inactive}
\end{align*}
\]

\[
\begin{align*}
&\text{P–Au–X} + Y^- \\
&\text{P–Au} \\
&\text{B} \\
&\text{catalytically active}
\end{align*}
\]

\[
\begin{align*}
&\text{P–Au}^2+ \text{X}^- \text{Y}^- \\
&\text{C}
\end{align*}
\]

- Phosphinegold(I) complexes known to be chemoselective for activation of C-C multiple bonds
  - Useful for additions to allenes, alkenes, alkynes
- Few enantioselective Au(I) reactions known at the time
- Silver activates gold by forming cationic Au(I) via halide extraction

Gold (I)-Catalyzed Enantioselective Allene Hydroamination

Original Methodology NOT a Chiral Anion Strategy

- Increase in enantioselectivity with assumed monocationic species indicated that remaining coordinated counterion (Cl⁻) was critical for stereoinduction

- Hypothesized that replacing chloride with larger coordinating counterion may further enhance enantioselectivity

Gold (I)-Catalyzed Enantioselective Allene Hydroamination

Original Methodology NOT a Chiral Anion Strategy

Electronic and steric tuning of coordinated counterion possible with benzoates
- Must still be able to form active cationic catalyst

Results indicate that anionic counterion likely involved in discriminating between diastereomeric transition states

Asymmetric catalysis with gold(I) complexes is notoriously difficult. Chiral counterion rather than chiral ligand strategy may lead to higher stereoselectivity.
Gold(I)-Catalyzed Enantioselective Allene Hydroalkoxylation

Chiral Ligand Strategy Leads to Low Enantioselectivity

Chiral phosphine ligand and achiral silver anion complex

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{CHR} = \text{CHR} & \quad \text{CHR} = \text{CHR}
\end{align*}
\]

\[3 \text{ mol\%} \quad \text{P} - \text{Au} - \text{Cl}\]

\[
\begin{align*}
\text{AgBF}_4 & \quad 68\%, \ 0\% \ \text{ee} \\
\text{AgOPNB} & \quad 89\%, \ 8\% \ \text{ee}
\end{align*}
\]

OPNB = \(p\)-nitrobenzoate

Chiral gold complex

\[
\begin{align*}
\text{PAR}_2 \text{AuCl} & \quad \text{PAR}_2 \text{AuCl}
\end{align*}
\]

\(\text{Ar} = m\text{-xylene}\)

Achiral phosphine ligand and chiral silver anion complex

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{CHR} = \text{CHR} & \quad \text{CHR} = \text{CHR}
\end{align*}
\]

\[2.5 \text{ mol\%} \quad \text{Ph}_2\text{P} - \text{Au} - \text{Cl}\]

\[5 \text{ mol\%} \quad (R)-\text{AgTRIP}\]

Solvent effect

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_3\text{NO}_2)</td>
<td>60%</td>
<td>18% ee</td>
</tr>
<tr>
<td>acetone</td>
<td>72%</td>
<td>37% ee</td>
</tr>
<tr>
<td>THF</td>
<td>83%</td>
<td>76% ee</td>
</tr>
<tr>
<td>benzene</td>
<td>90%</td>
<td>97% ee</td>
</tr>
</tbody>
</table>

- At time of publication, only gold(I) complexes had successfully promoted asymmetric allene hydroalkoxylation, but with limited scope

**Gold (I)-Catalyzed Enantioselective Allene Hydroalkoxylation**

*Use of Chiral Ligand and Chiral Counterion is Productive Strategy*

![Reaction Scheme]

- **2.5 mol%** \( \text{L(AuCl)}_2 \)
- **5 mol%** \((R)\) or \((S)\)-AgTRIP

In benzene, the reaction produces an allene hydroalkoxylation.

**Table: Results**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield (%)</th>
<th>Enantiomeric Excess (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{dppm(AuCl)}_2, (R))-AgTRIP</td>
<td>96%</td>
<td>80% ee</td>
</tr>
<tr>
<td><strong>Achiral gold ligand with chiral silver counteranion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( [(S,S)\text{-DIPAMP(AuCl)}_2, (S))-AgTRIP</td>
<td>96%</td>
<td>92% ee</td>
</tr>
<tr>
<td><strong>Chiral gold ligand AND chiral silver counteranion</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Chiral Anion Strategy for Asymmetric Tsuji-Trost Allylation

Achiral Cationic π-Allyl Pd(II) Complex Ion Paris with Chiral Phosphoric Acid

Mechanistic hypothesis

Chiral Anion Strategy for Asymmetric Tsuji-Trost Allylation

Catalytic Asymmetric Allylation of α-Branched Aldehydes

\[ \text{R}^1 \text{CHO} + \text{R}^2 \text{CHO} \rightarrow \text{R}^3 \text{CHO} \]

1.5 mol% (R)-TRIP
3 mol% Pd(PPh\(_3\))\(_4\)
5 Å MS, MTBE, 40 °C
then 2N HCl, Et\(_2\)O

85%
98.5:1.5 er

85%
98:2 er

45%
95:5 er

65%
85:15 er

reaction run at 110 °C

40%
96:4 er

reaction run at 60 °C

(R)-TRIP counterion

Chiral Anion Phase Transfer Catalysis
Inversion of Traditional PTC Uses Chiral Anionic Transfer Catalyst

Halocyclization

Traditional PTC

Organic phase

Reagent

Lipophilic chiral cation salt (mediates reactivity)

Activated anionic substrate

Inverted PTC

Organic phase

Substrate

Lipophilic chiral anion salt (mediates reactivity)

Activated cationic reagent

Chiral Anion Phase Transfer Catalysis

Chiral Anionic Phase Transfer Catalyst Solubilizes Electrophilic Fluorine Source

Chiral Anion Phase Transfer Catalysis

Chiral Anionic Phase Transfer Catalyst Solubilizes Electrophilic Fluorine Source

Dihydropyran substrates

\[
\text{O} \quad \text{N} \quad \text{H} \quad \text{R}
\]

5 mol% catalyst
1.25 equiv Selectfluor
1.1 equiv Proton Sponge
\[\text{C}_6\text{H}_5\text{F}, -20 \, ^\circ\text{C}\]

<table>
<thead>
<tr>
<th>Product</th>
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<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>[\text{O} \quad \text{F} \quad \text{N} \quad \text{R}]</td>
<td>84%</td>
<td>95% ee</td>
</tr>
<tr>
<td>[\text{O} \quad \text{F} \quad \text{N} \quad \text{Br}]</td>
<td>95%</td>
<td>95% ee</td>
</tr>
<tr>
<td>[\text{O} \quad \text{F} \quad \text{N} \quad \text{t-Bu}]</td>
<td>73%</td>
<td>9:1 dr</td>
</tr>
</tbody>
</table>

Dihydronaphthalene and chromene substrates

\[
\text{O} \quad \text{NH} \quad \text{O} \quad \text{R}
\]

10 mol% catalyst
1.5 equiv Selectfluor
1.25 equiv \(\text{Na}_2\text{CO}_3\)
1:1 \(\text{C}_6\text{H}_5\text{F}/\text{hexanes}, 23 \, ^\circ\text{C}\)

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<th>Yield</th>
<th>ee</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>[\text{O} \quad \text{F} \quad \text{I} \quad \text{R}]</td>
<td>71%</td>
<td>93% ee</td>
<td>70%</td>
</tr>
<tr>
<td>[\text{O} \quad \text{F} \quad \text{R}]</td>
<td>70%</td>
<td>92% ee</td>
<td></td>
</tr>
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(R)-TRIP derived catalyst