Asymmetric Counteranion-Directed Catalysis (ACDC)

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Outlines

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   1.2 Representative Asymmetric Activation Modes
   1.3 The Progression of ACDC

2. Application
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   2.4 Chiral Anion Phase-Transfer Catalysis

3. Summary

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The progression of chiral anions from concepts to applications in asymmetric catalysis

Robert J. Phipps, Gregory L. Hamilton and F. Dean Toste*
Background

**Born** in 1971 in Tercelra, Azores, Portugal, but soon moved to Canada.

**Majored** in Chemistry and Biochemistry and went on to obtain a M.Sc. in Organic Chemistry While at the University of Toronto.

**Pursued** Ph.D. with Prof. Barry Trost at Stanford and a post-doctoral appointment with Prof. Robert Grubbs at Caltech.

**Currently** is the Chevron Professor of Chemistry at UC Berkeley.
Representative Asymmetric Activation Modes

a. Coordinative interaction
   'Lewis acid catalysis'

b. Double hydrogen-bonding interaction
   'Hydrogen-bonding catalysis'

c. Single hydrogen-bonding interaction
   'Brønsted acid catalysis'

d. Electrostatic interaction only
   'Chiral anion catalysis'
The Progression of ACDC: Early Use of Chiral Anion

Resolve basic compound

Determine the enantioenrichment

Chiral anion catalysis mode

1. Copper(I)-catalysed aziridination

\[
\text{Ph} = \begin{array}{c}
\text{Ph} \\
10
\end{array} + \text{PhINTs} \xrightarrow{3 \text{ mol\% } [\text{Cu(NCMe}_4{\text{)}][5]}} \text{Benzene, 0 °C}
\]

\[
\text{T}_{\text{s}} \quad \text{Ph}
\]

86% yield, 7% e.e.

2. Ring-opening of meso-aziridinium ions

\[
\text{Ph} \quad \text{Cl} \quad \text{N} \quad \text{Ph} \\
13 \xrightarrow{\text{BnNH}_2} 50 \text{ mol\% } [\text{X}][5] \quad \text{Ph} \quad \text{NHBn} \\
\]

\[
\text{X} = \text{Et}_{2}\text{NH}_2, \text{Et}_3\text{NH}, \text{Na}^+, \text{Ag}^+
\]

e.e. < 15%

Points: chiral anions can be used for asymmetric catalysis reaction. New asymmetric counteranion is need.

The Progression of ACDC: Chiral Phosphate Anion

1. Combination of metal and phosphoric acid catalyst

Inanaga, J. et al., Synlett. 1997. 1, 79
The Progression of ACDC: Chiral Phosphate Anion

2. Defined as Brønsted Acid Catalysts

\[
\text{HO-Ph} + \text{Me-OEt} \xrightarrow{10 \text{ mol\% (R)-19-H}} \text{HO-Ph} \quad \text{PhCH}_3, -78^\circ \text{C}
\]

87:13 syn/anti 100% yield, 96% e.e.

\[
\text{HN-Ph} + \text{20} \xrightarrow{2 \text{ mol\% (R)-23-H}} \text{HN-Ph} \quad \text{CH}_2\text{Cl}_2, \text{r.t.}
\]

99% yield, 95% e.e.

The Progression of ACDC: Chiral Phosphate Anion

3. Work as counteranion, give birth to ACDC

![Chemical Reaction Diagram]

List, B. et al., Angew. Chem. Int. Ed. 2006. 45, 4193
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Application: Derived from Brønsted Acid Catalysts

**Goal:** Using substrates in which hydrogen bonding with the catalyst would be mechanistically improbable.

1. Conversion of β-chloro tertiary amine

Application: Derived from Brønsted Acid Catalysts

2. Mukaiyama aldol reaction

Application: Metal Catalysis with Chiral Counteranion

**Goal:** Inducing asymmetry by using chiral ions that interact with a metal only through electrostatic interactions, rather than using chiral ligands that coordinate tightly to the metal.

*Comparison* between chiral ligand and chiral counteranion!

*Comparison* between chiral phosphine and chiral phosphate!
1. Intramolecular hydroalkoxylation of allenes

Toste, F. D. et al., Science 2007. 317, 496

Benzene for the highest enantioselectivities
2. Tsuji–Trost reaction

List, B. et al., J. Am. Chem. Soc. 2007. 129, 11336
Application: Metal Catalysis with Chiral Counterions

3. Jacobsen–Katsuki epoxidation

Application: Metal Catalysis with Chiral Counterions

4. Other breakthroughs

**Overman rearrangement**

```
Ph
\[\text{Ph} \quad \text{CHCl}_3, 35 \degree C, 40 \text{ h} \]
\[\begin{align*}
1 \text{ mol}\% \text{ palladacycle} \\
2 \text{ mol}\% \text{ (S)-27-Ag}
\end{align*}\]
```

Palladacycle = (S)-65
Palladacycle = 66
93% yield, 98% e.e.
94% yield, 94% e.e.

**Semi-Pinacol rearrangement**

```
\[\begin{align*}
\text{PhCF}_3, 55 \degree C, 48 \text{ h} \\
\text{10 mol}\% \text{ Pd(OAc)}_2 \\
\text{20 mol}\% \text{ (S)-TRIP} \\
\text{2 eq. benzoquinone}
\end{align*}\]
```

59% yield, 8:1 d.r., 97% e.e.

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Application: Hydrogen-Bonding Catalysts

1. Asymmetric Pictet–Spengler

Application: Hydrogen-Bonding Catalysts

2. Other breakthroughs

Application: Phase-Transfer Catalysis

1. Fluorocyclization of enol ether

2. Fluorination of cyclic enamide

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Acknowledgment

- Prof. Huang
- All members here
Thanks for your attention!