Towards Ideal Asymmetric Synthesis: Dual Activation with Bifunctional Organocatalysts

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Enzymatic asymmetric synthesis

- Nature is highly proficient in assembling complex molecules with complete stereoselectivity and outstanding efficiency

- Enzymes bind reactants (and also high energy transition states) via covalent and non-covalent interactions in catalytic reactions

Aldolases and C–C bond forming reactions

- Aldol reactions can occur via enamine pathways (class II)

\[
\begin{align*}
\text{C} + \text{C} \rightarrow \text{C} - \text{C} \\
\text{C} + \text{C} \rightarrow \text{C} - \text{C}
\end{align*}
\]

(A. Heine et al., Science, 2001, 294, 369)
Bifunctional catalysis: dual activation

- Nature’s way of catalysis: activation of two (or more) components

Traditional catalysis
- Single active site
- Activation of one species

Bifunctional catalysis
- Two (or more) active sites
- Simultaneous activation of two species
- Lower entropic cost
- Synergistic catalysis

(M. Shibasaki et al., Chem. Rev. 2002, 102, 2187)
From natural to designer catalysts
Proline: Nature’s “simplest enzyme”

- Bifunctional enamine chemistry is dominated by catalysis by proline and its derivatives

- One of 20 naturally occurring amino acids

- Known to perform biologically relevant enamine-related transformations (e.g. aldol reactions)

- First amine-catalyzed asymmetric direct intermolecular aldol reaction reported in 2000 by List and co-workers

(S. Mukherjee et al., Chem. Rev. 2007, 107, 5471; M. Movassaghi et al., Science 2002, 298, 1904)
Proline-catalyzed aldol reactions

- Elucidation of the mechanism began with catalyst modification

\[
\text{excess} \quad \text{cat. (30 mol%)} \quad \text{DMSO}
\]

\[
\text{R} = p-\text{NO}_2\text{C}_6\text{H}_4
\]

(S. Mukherjee et al., Chem. Rev. 2007, 107, 5471)
Reaction mechanism for proline catalysis

Proposed mechanism:

- Hydrolysis
- Iminium formation
- Addition
- Tautomerization

(S. Mukherjee et al., Chem. Rev. 2007, 107, 5471)
Selectivity models

- Bifunctional character critical to enantiodetermining transition state

Computational studies and modeling

- Can predict the proper sense of stereochemistry and approximate ee by simple transition state analog calculations (molecular mechanics)

\[ \text{Favored} \quad \text{Disfavored} \]

(Some H’s omitted for clarity) (Experimental ee’s in parentheses)

(C. Allemann et al., Acc. Chem. Res. 2004, 37, 558)
Other enamine-catalyzed reactions

- Reactions with a) imines, b) diazo compounds, c) nitroso compounds, and d) nitroalkenes:

  a) [Diagram]
  b) [Diagram]
  c) [Diagram]
  d) [Diagram]

- Others include α-ketoacids, singlet O₂, electrophilic halogens, etc.

Hydroxyamination of aldehydes

- Maruoka recently reported an enantioselective hydroxyamination of aldehydes with nitroso compounds (regioselectively distinct from proline-catalyzed aminohydroxylation)

Regioselective addition to nitrosobenzenes

- Catalyst design around binaphthyl framework allows for selective binding of the O instead of the N

\[ \text{aminohydroxylation} \]

\[ \text{hydroxyamination} \]

Nucleophilic catalysis with *Cinchona* alkaloids

- Natural or modified *Cinchona* alkaloids constitute a majority of bifunctional nucleophilic catalysts

- Alkaloids exist as pseudoenantiomeric pairs

- Catalysis dates back to 1912 with the hydrocyanation of aldehydes

The Morita-Baylis-Hillman reaction

- Involves combination of Michael acceptors and aldehydes/ketones

\[
\text{EWG} + \text{R}^\bullet \text{O} + \text{R}^\bullet \text{CHO} \rightarrow \text{EWG} \quad \text{EWG = COOR', CONR'2}
\]

Proposed mechanism:

- Nature of proton transfer and regeneration of the catalyst depends on solvent
- Can be extended to an aza-variant

Cinchona alkaloid catalysis

- Selectivity and generality remains a challenge, but the general concept has proved successful.

(T. Marcelli et al., Angew. Chem. Int. Ed. 2006, 45, 7496)
Asymmetric Diels-Alder reaction of 2-pyrones

- Deng reported the use of bifunctional organocatalysis in the exo-selective [4+2] cycloaddition of 2-pyrones

\[
\text{Product} \quad \text{up to 100%}
\]

\[
\text{up to 97:3 exo}
\]

\[
\text{up to 98% ee}
\]

\(\text{cat.} \quad \text{EtOAc}\)

(Y. Wang et al., J. Am. Chem. Soc. 2007, 129, 6364)
A bifunctional approach to [4+2] cycloadditions

- Presence of α-OH group on pyrone critical to selectivity—suggests it is important for catalyst binding

- Simple catalyst alterations can lead to all diastereo- and enantioenriched products desired

(Y. Wang et al., J. Am. Chem. Soc. 2007, 129, 6364)
Lewis acid/Lewis base catalysis

- Combination of Lewis acids and Lewis bases is an efficient mode of bifunctional organocatalysis

- Typical motifs include thioureas, alcohols, and carboxylic acids with $N$-oxides, amines, and phosphine oxides

- Catalysis varies from Michael, aldol, and Henry reactions to dynamic kinetic resolutions (acylations) and even Diels-Alder chemistry

Ketone cyanosilylation by dual activation

- Earlier last year, Jacobsen and co-workers reported a full study on asymmetric ketone cyanosilylation catalyzed by thiourea complexes.

\[
\text{R} \quad \overset{\text{cat. (5 mol\%)} }{\xrightarrow{\text{TMSCN, CF}_3\text{CH}_2\text{OH}}} \quad \text{R} \quad \overset{\text{TMS-O-CN}}{\xrightarrow{-78^\circ C}}
\]

up to 98%
up to 98% ee

\[
\text{cat.} = \text{MeHN} \quad \overset{\text{MeHN}_\text{Pr}_2}{\xrightarrow{\text{N}^\text{Pr}_2}}
\]

Preliminary support

Simplified mechanism:

Suggests rate-limiting addition of HCN, followed by silylation

Role of the Lewis acidic thiourea

- Addition of substituted pyridines inhibits reaction but not the ee

Role of the Lewis acidic thiourea: binding

- Addition of CH$_3$CN shows a similar trend to that of added pyridines
- By analogy, pyridines, CH$_3$CN, and HCN must bind to the thiourea protons via the N lone pair

Role of the Lewis basic amine

- Addition of trialkylamines interestingly gives the same inhibition trend but reduces the ee—external amines catalyze a racemic pathway

Deuterium labeling experiments

Replacing HCN with DCN gives higher rates at low concentrations and lower rates at high concentrations.

The intrinsic isotope effect (low [HCN]) is approximately $k_H/k_D \sim 0.64$

Full mechanism on ketone cyanosilylation

Proposed mechanism:

An oxy-Michael reaction

- A formal oxy-Michael reaction was reported this year

- Addresses the problem of reversibility and poor nucleophilicity of alcohols and water by masking O as a boronic acid

(D.R. Li et al., J. Am. Chem. Soc. 2008, 130, 46)
Conjugate addition with boronic acids

- Combination of thiourea and amine serves the desired purpose

(D.R. Li et al., J. Am. Chem. Soc. 2008, 130, 46)
Summary and outlook

- Simultaneous binding of multiple components
- Dual activation of the nucleophile and electrophile provides enhanced reactivity
- Favorable positioning of reacting species often increases selectivity
- Understanding the mechanism allows us to design even more efficient catalysts
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