Catalysis by Small Peptides

Catalysis by small molecules

Enzyme catalysis

Catalysis by small peptides

2–20 amino acids
modular and facile synthesis
non-covalent interactions with substrates – high selectivity
nonnatural amino acids – diverse reactivity

design & understanding

diverse reactivity
tailor-made non-covalent interactions
exceptional selectivity

Catalysis by Small Peptides

**Catalysis by small molecules**

![Chemical structure]

- design & understanding
- enzyme-like selectivity

**Enzyme catalysis**

![Enzyme structure]

- directed evolution or merger with (photo-) catalysis
- nonnatural reactivity

**Catalysis by small peptides**

- 2–20 amino acids
- modular and facile synthesis
- non-covalent interactions with substrates – high selectivity
- nonnatural amino acids – diverse reactivity

Small Peptides as Organocatalysts

- Introduction
- Catalytically relevant properties of small peptides
- Small peptides as organocatalyst
- Small peptides in Lewis acid and transition metal catalysis
- Small peptides in photoredox catalysis
- Summary

This group meeting does not cover the available literature comprehensively. Instead, selected key studies are discussed in order to explain the underlying concepts.
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Structure of a Peptide Catalyst

Structure of a Peptide Catalyst

- backbone serves as a tailor-made spacer between the catalytically active moiety and the substrate binding moiety
- complex three-dimensional geometry determined by primary and secondary protein structure
- conformational flexibility due to high number of rotatable bonds
Design of the Secondary Structure

Natural secondary structure motifs

α-helix
Juliá-Collona epoxidation

β-turn
epoxidation catalyst (Miller)

Rigid unnatural amino acids

Reiser
Bur

Calmes, Amblard
Schreiner

Peptide design is often centered around such structures with reduced conformational flexibility.

Design of the Secondary Structure

NMR & calculations

highly regioselective in the epoxidation of farnesol

ensemble of closely related ground-state conformations

type II β-turn

epoxidation catalyst (Miller)

NMR & calculations

highly regio-and enantioselective in the epoxidation of farnesol

heterogeneous ensemble

epoxidation catalyst (Miller)

Even highly flexible, conformationally heterogeneous peptides may act as highly selective catalysts.

Highly regio- and enantioselective in the epoxidation of farnesol.
Facile synthesis of large peptide libraries by split and pool synthesis

- Exponential increase of complexity with the number of cycles
- Biased libraries by control the introduction of specific amino acids in each cycle
Strategies for Library Screening

Visualization of hits by co-immobilized fluorescent tags

library synthesis

100,000 peptides

combinatorial library

screening of ca. 1000 peptides

hit validation and sequencing

further optimization

Strategies for Library Screening

- Co-immobilization of substrates

Related work has been reported by Jacobsen, Bradley, Barbas, Davies, Berkessel, Snapper, Hoveyda, and others.

- Sorting of individual beads into individual vials

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Wennemers’ Tripeptide Catalyst

- **Hit identification by library screening**

- **Optimization in solution**

98%, 90% ee

**Wennemers’ Tripeptide Catalyst**

![Diagram of tripeptide catalyst]

**proline-catalyzed aldol reaction**

**lowest energy configuration of proline**

**lowest energy configuration of chiral peptide**

**proposed conjugate addition reaction**

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**Reversal of selectivity by switching the enantiomer of a single amino acid**

<table>
<thead>
<tr>
<th>Chiral Peptide</th>
<th>Conversion</th>
<th>Syn/Anti</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-Pro-Pro-Asp-NH₂</td>
<td>96%</td>
<td>10:1</td>
<td>-85%</td>
</tr>
<tr>
<td>H-D-Pro-Pro-Asp-NH₂</td>
<td>93%</td>
<td>25:1</td>
<td>95%</td>
</tr>
</tbody>
</table>
**Wennemers’ Tripeptide Catalyst**

**structure activity relationship**

- free carboxylic acid required
- D-Pro-Pro moiety is critical
- conformational flexibility in the backbone tolerated
- $K_{\text{trans/cis}}$ ratio influences selectivity

Rate-and enantioselectivity determining step

* cis lower dipole moment
* trans $n \rightarrow \pi^*$ interaction


Wennemers’ Tripeptide Catalyst

![Chemical structures](image)

10:1 trans/cis

46:1 trans/cis

71:1 trans/cis

1 mol% chiral peptide
1 mol% NMM, 20 °C, 2 h

major enantiomer [%] vs. trans conformer [%]

major diastereomer [%] vs. trans conformer [%]

- 9:1 CHCl₃/MeOH
- MeOH
- Dioxane
- THF
- MeCN
- DMF

Wennemers’ Tripeptide Catalyst

A higher proportion of the trans confromer leads to a higher enantio- and diastereoselectivity.

Wennemers’ Tripeptide Catalyst

10:1 trans/cis ▲
46:1 trans/cis ■
71:1 trans/cis ○

Lowest catalyst loading of a secondary amine organocatalyst reported to date.

Remote Desymmetrization by Chiral Peptides

Can this molecule be accessed by a desymmetrization?

Remote Desymmetrization by Chiral Peptides

Design of the initial library

active moiety
previously identified

model: hexapeptide

Case Study 2: Remote Desymmetrization by Chiral peptides

Optimization workflow

1st generation
42 peptides & reaction conditions
27%, 40% ee

2nd generation
24 peptides, i+2 & i+3 varied
25%, 49% ee

3rd generation
24 peptides, i+1 varied – deleterious
25%, 49% ee

4th generation
i+3–5 & lower temperature
72%, 79% ee

5th generation
i+4,5 varied – no influence
78%, 80% ee

truncation to tetrapeptide

variation of C-terminus

**Schreiner’s Lipophilic Oligopeptide Catalyst**


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**Mechanistic information**

- No secondary structure - central adamantyl group separates both ends.
- Adamantyl group holds the 3 stereocenters that determine stereochemistry in place.
- H-bonding to second hydroxyl group.
- Dispersion interaction between hydrophobic substituents and substrate.

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**Diagram**

- A diagram illustrates the structure of the Schreiner’s lipophilic oligopeptide catalyst, showing its flexibility and rigidity.
- The catalyst is immobilized in a rigid environment, with a chiral peptide substrate undergoing a reaction in toluene, leading to a 90% ee product.
Desymmetrization of cis-Diols

**Silyl protection**


Atroposelective Bromination

\[
\Delta G^\ddagger(rac) = 7 \text{ kcal}
\]

\[
\text{3 equiv. PhthNBr, 0.01 M in 97:3 CHCl}_3/\text{acetone, 25 °C, 18 h}
\]

\[
\Delta G^\ddagger(rac) = >30 \text{ kcal}
\]

10 examples, 70–94% ee

11 examples, up to 92% ee

14 examples, up to 98% ee

reoptimized peptide backbones used

Related projects


Atroposelective Bromination

3 different conformers observed by x-ray crystallography

35 distinct peptide – 53 crystal structures

wider $\tau$-angle $\rightarrow$ more flexible & more selective

Atroposelective Bromination

3 different conformers observed by x-ray crystallography

35 distinct peptide – crystal structures

Multiple conformers contribute to a transition state ensemble.

Atroposelective Bromination

Atroposelective Bromination

Substrate-association enforces a structural change of the peptide – induced fit.

Site-Selective Polyene Oxidation


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Pioneering Work on Peptides in Lewis Acid and Transition Metal Catalysis

Snapper & Hoveyda: cyanation, alkylation

Role of the peptide
creation of a chiral environment around the metal catalyst

Hoveyda: copper-catalyzed
conjugate additions

Hoveyda: copper-catalyzed
allylic alkylation

Helical Peptide-Ligated Rhodium-“Paddlewheel” Complexes

- Enantioselective insertion into Si–H bonds

\[
\begin{align*}
\text{R} & \quad \text{CO}_2\text{Me} \\
\text{PhSiMe}_2\text{SiH} & \quad \stackrel{\text{Rh}}{\rightarrow} \\
\text{R} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

7 examples with >90% ee

- Enantioselective cyclopropanation

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
\text{Rh} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

access to both enantiomers in >90% ee (7 examples)

Role of the peptide
creation of a chiral environment around the metal catalyst

Structure-Selective Protein Functionalization

Although tryptophan is most reactive, selective functionalization of E3-tyrosine or phenylalanines occurs even in presence of random tryptophane-containing peptides.

E3/K3 coiled coil assembly places side chain in close proximity of the rhodium carbenoid


Role of the peptide

substrate recognition by non-covalent interactions
Copper-Peptide-Mediated Cross-Coupling of Diarylmethanes

identification of the substrate–peptide interaction

A high $k_{rel}$ in the kinetic resolution of unsymmetrical substrates indicates a substrate–peptide interaction

$74\%, 84\%$ ee

A high $k_{\text{rel}}$ in the kinetic resolution of unsymmetrical substrates indicates a substrate–peptide interaction.

$\text{Cu} \quad \text{Cs}_2\text{CO}_3, \text{DMF/toluene}$

Identification of the substrate–peptide interaction

$74\%, \ 84\% \text{ ee}$

Copper-Peptide-Mediated Cross-Coupling of Diarylmethanes

identification of the substrate–peptide interaction

Proposed model

cation-π-interaction between substrate and ligated cesium

Role of the peptide

substrate recognition by non-covalent interaction

Copper-Peptide-Mediated Cross-Coupling of Diarylmethanes

- C–O coupling

- C–N coupling and catalyst-controlled cyclodehydration

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Enantioselective [2+2] Photocycloaddition

both diastereomers accessible in high yields, d.r., and ee values

Role of the peptide
creation of a chiral environment around the metal catalyst

Light-Driven Deracemization

- Photoredox strategy for an out-of-equilibrium deracemization

![Chemical structures and reactions](image)

- Racemic
- Enantioenriched

Role of the peptide
- Chiral hydrogen atom donor

Light-Driven Deracemization

electron transfer

enantioselective proton transfer
(R) is depleted

enantioselective hydrogen atom transfer
(S) is enriched

Ir$^{II}$
Ir$^{III+}$
Ir$^{III+}$

fast chiral phosphate

achiral

slow chiral phosphate

chiral peptide

(R)

(S)

(R)

(S)
Summary

- A diverse set of reactivity can be achieved using organocatalytic, organometallic, or merged activation modes.

- Peptides may control selectivity in catalytic transformations using non-covalent interactions.

- Control of the secondary structure is vital in order to place reactive groups in close proximity.

- A variety of screening technologies may assist in the discovery process.

Thank you for your attention.
Questions?