Strategies in Biomimetic Catalysis

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MacMillan Lab Group Meeting
November 29th 2016
Enzymes as an inspiration for reaction development

Biochemical reactions are catalysed by enzymes with a high degree of precision, under mild conditions.

Regioselective hydroxylation in cholesterol biosynthesis

Asymmetric transamination in amino acid biosynthesis

There has been significant interest in mimicking the effect of enzymes in synthetic processes.
**Biocatalysis and Biomimetic catalysis**

Biocatalysis:
The use of enzymes or whole cells as catalysts for synthetic chemistry

Biomimetic catalysis:
Chemical catalysis that mimics key features of enzymatic systems

**Strategies in Biomimetic Catalysis**

- Enzyme structure consists of an active site surrounded by a protein superstructure

**Binding site - Binds and orients substrate**
- Provides control for selectivity of reaction
- Usually specific to a particular substrate

**Catalytic site - Groups which catalyze reaction**
- For example groups of amino acid residues
- Or metal cofactors bound by protein structure

**Attempts made to mimic the effects of both sites**
Strategies in Biomimetic Catalysis

Metalloporphyrins - Development of new reactivity from an enzyme cofactor

Artificial enzymes - Use of supramolecular structures to mimic substrate binding
Strategies in Biomimetic Catalysis

**Metalloporphyrins - Development of new reactivity from an enzyme cofactor**

- **Metalloporphyrin**: Fe
- **Cofactor** with Cys, S, N, O, Me, CO₂H

**Artificial enzymes - Use of supramolecular structures to mimic substrate binding**

- **Artificial enzyme** structure with supramolecular binding motifs
C–H functionalization inspired by oxidase enzymes

- Oxidase enzymes are integral in the biosynthesis of many natural products and metabolic processes

\[ \text{Taxadiene oxidation in the biosynthesis of taxol} \]

- A number of oxidase enzymes have been utilized in industrial scale processes

\[ \text{Selective enzyme mediated oxygenation in the fermentation of artemisinic acid} \]


C–H functionalization inspired by oxidase enzymes

heme based catalysts

Cytochrome P450

peroxoflavin catalysts

Monoamine Oxidases

non-heme metal based catalysts

Oxyhemocyanin

Reactive oxygenation agents at the active sites of some common oxidase enzymes

C–H functionalization inspired by oxidase enzymes

Heme based catalysts: Cytochrome P450

Peroxoflavin catalysts: Monoamine Oxidases

Non-heme metal based catalysts: Oxyhemocyanin

Reactive oxygenation agents at the active sites of some common oxidase enzymes

Cytochrome P450 class of enzymes

Class of enzymes containing an iron heme cofactor, responsible for biological C–H oxidations

Mechanism proceeds through dioxygen activation and atom transfer via a high valent Fe^{IV} intermediate

Structure has inspired the development of a number of catalytic strategies based on high valent metals
Cytochrome P450 - Mechanism of action

1. $e^-$
2. $H^+$

Nam, W. Acc. Chem. Res. 2007, 40, 522
First synthetic reactions by Fe porphyrin complexes

Iodosyl benzene used to generate active iron-oxo catalyst

<table>
<thead>
<tr>
<th>Substrate</th>
<th>products</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[O]</td>
<td>Epoxide: 55%</td>
</tr>
<tr>
<td></td>
<td>[O][OH]</td>
<td>Alcohol: 15%</td>
</tr>
<tr>
<td></td>
<td>[O][OH]</td>
<td>Cyclohexanol: 8%</td>
</tr>
<tr>
<td></td>
<td>[O]</td>
<td>Cyclohexanone: 0%</td>
</tr>
<tr>
<td></td>
<td>[O][OH]</td>
<td>Cis isomer: 82%</td>
</tr>
<tr>
<td></td>
<td>[O][OH]</td>
<td>Trans isomer: trace</td>
</tr>
</tbody>
</table>

Oxidation reactions utilizing metalloporphyrin catalysts

<table>
<thead>
<tr>
<th>Metals</th>
<th>Axial ligands</th>
<th>Terminal oxidants</th>
</tr>
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<tbody>
<tr>
<td>Mn</td>
<td>Cl⁻</td>
<td>O₂/air</td>
</tr>
<tr>
<td>Fe</td>
<td>OH⁻</td>
<td>H₂O₂</td>
</tr>
<tr>
<td>Co</td>
<td>AcO⁻</td>
<td>PhIO</td>
</tr>
<tr>
<td>Ru</td>
<td>CF₃SO₃⁻</td>
<td>NaClO</td>
</tr>
<tr>
<td>Os</td>
<td>MeOH</td>
<td>KHSO₅</td>
</tr>
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Catalyst design by variation of porphyrin substituents, metal and axial ligand

- In general more electron deficient porphyrin ligands lead to a more oxidising catalyst
- Effects of axial ligand arise from trans effect - more electron donating ligand weakens M=O bond
- Reaction mechanism has been adapted for unnatural reactions such as amination
Effect of axial donation on the energies of the frontier orbitals of iron oxo complexes

Oxidation reactions utilizing metalloporphyrin catalysts

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<td>O&lt;sub&gt;2&lt;/sub&gt;/air</td>
</tr>
<tr>
<td>Fe</td>
<td>OH&lt;sup&gt;-&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Co</td>
<td>AcO&lt;sup&gt;-&lt;/sup&gt;</td>
<td>PhIO</td>
</tr>
<tr>
<td>Ru</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;SO&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;-&lt;/sup&gt;</td>
<td>NaClO</td>
</tr>
<tr>
<td>Os</td>
<td>MeOH</td>
<td>KHSO&lt;sub&gt;5&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

C-H hydrocarbon oxidation has been a major focus of metalloporphyrin chemistry

**Oxidation reactions utilizing metalloporphyrin catalysts**

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**Oxidation of other functionalities such as arenes and olefins has also been explored**

Hydroxylation of unactivated C–H bonds by Fe porphyrins

Catalyst (0.5 mol%) PhI(OAc)₂

Oxidation of other functionalities such as arenes and olefins has also been explored

Fluorinated aromatic on porphyrin core protects against oxidative degradation

**Hydroxylation of unactivated C–H bonds by Fe porphyrins**

Substrate | products | yield |
--- | --- | --- |
Cyclohexane | Cyclohexanol (37%) |  |
 | Cyclohexanone (6%) |  |
Cyclooctane | Cyclooctanol (47%) |  |
 | Cyclooctanone (7%) |  |
1-Methylcyclohexane |  | Both products (17%) |
1,2-dimethylcyclohexane | | 1,2 dMe (10%) |
 | | 2,3 and 3,4 dMe (17%) |

Metalloporphyrin catalyzed C–H amination

First example of C-H amination on aromatic steroid substrate

47% yield
approx 40 turnovers

Unlike corresponding oxidation process, no side reaction on aromatic ring

Yang, J.; Weinberg, R.; Breslow, R. Chem. Commun. 2000, 531
Metalloporphyrin catalyzed C–H amination

- Conditions expanded to allow for the use of amines as aminating agent

![Conditions expanded to allow for the use of amines as aminating agent](image)

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<tr>
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<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td>81%</td>
</tr>
<tr>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td>90%</td>
</tr>
<tr>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td>83%</td>
</tr>
<tr>
<td><img src="image" alt="Substrate" /></td>
<td><img src="image" alt="Product" /></td>
<td>85%</td>
</tr>
</tbody>
</table>
Amination of unactivated C–H bonds

Metal nitrene catalysts cannot functionalize unactivated hydrocarbons as readily as their oxo analogues.

Use of an axial NHC ligand increases the reactivity of the Ru nitrene and carbene intermediates.
### Metalloporphyrin catalyzed C–H amination

**Amination using aryl azides as nitrogen source**

![Diagram](https://example.com/diagram.png)

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<tr>
<th>Substrate</th>
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<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://example.com/cyclohexane.png" alt="Cyclohexane" /></td>
<td><img src="https://example.com/cyclohexylamine.png" alt="Cyclohexyl amine" /></td>
<td>90%</td>
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<tr>
<td><img src="https://example.com/4-methylbenzene.png" alt="4-Methylbenzene" /></td>
<td><img src="https://example.com/4-methylbenzylamine.png" alt="4-Methylbenzyl amine" /></td>
<td>92%</td>
</tr>
<tr>
<td><img src="https://example.com/naphthalene.png" alt="Naphthalene" /></td>
<td><img src="https://example.com/naphthylamine.png" alt="Naphthyl amine" /></td>
<td>96%</td>
</tr>
<tr>
<td><img src="https://example.com/anthracene.png" alt="Anthracene" /></td>
<td><img src="https://example.com/anthrylamine.png" alt="Anthryl amine" /></td>
<td>96%</td>
</tr>
</tbody>
</table>

Metalloporphyrin catalyzed C–H amination

Intramolecular C–H amination with arylsulfonyl azide

Ruppel, J. V.; Kamble, R. M.; Zhang, X. P. Org. Lett. 2007, 9, 4889
**C–H amination using an engineered P450**

Intramolecular C–H amination with arylsulfonyl azide via "chemomimetic" enzyme modification

\[
\begin{align*}
\text{Free Enzyme (0.1 mol\%)} & & \text{Turnovers} & & \%\text{ee} \\
\text{Wild type P450} & & 2.1 & & \text{nd} \\
\text{Modified P450} & & 383 & & 73
\end{align*}
\]

\[
\begin{align*}
\text{Enzyme (E. Coli)} & & \%\text{Yield} & & \text{Turnovers} & & \%\text{ee} \\
\text{Wild type P450} & & 0.5 & & 5.1 & & \text{nd} \\
\text{Modified P450} & & 58 & & 430 & & 87
\end{align*}
\]

*First example of a highly active enzyme catalyst for C–H amination*

Use of strongly donating axial ligands stabilizes M-OH species, and slows down radical recombination

Allows for substitution of fluoride onto metal center

**C–H halogenation via metalloporphyrin catalysis**

\[
\begin{array}{ccc}
\text{Substrate} & \text{Product} & \text{Yield} \\
\hline
\text{Cyclohexane} & \text{Cyclohexane-F} & 49\% \\
\text{Cyclohexanol} & \text{Cyclohexanol-F} & 44\% \\
\text{Cyclohexanecarboxylic acid} & \text{Cyclohexanecarboxylic acid-F} & 51\% \\
\end{array}
\]

C–H halogenation via metalloporphyrin catalysis

Catalyst (6-8 mol%) PhIO, AgF, TBAF

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<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>42% α:β = 3.1</td>
</tr>
<tr>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>42% α:β = 4.5</td>
</tr>
</tbody>
</table>

C–H halogenation via metalloporphyrin catalysis

\[
\text{Catalyst (6-8 mol\%)} \quad \text{PhIO, AgF, TBAF}
\]

<table>
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<tr>
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<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>16%</td>
</tr>
<tr>
<td><img src="image3.png" alt="Substrate 2" /></td>
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<td>(\alpha:\beta = 7.8)</td>
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<tr>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>23%</td>
</tr>
<tr>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>(\alpha:\beta = 6.2)</td>
</tr>
</tbody>
</table>
Strategies in Biomimetic Catalysis

Metalloporphyrins - Development of new reactivity from an enzyme cofactor

Artificial enzymes - Use of supramolecular structures to mimic substrate binding
**Supramolecular complexes as enzyme mimics**

- "Artificial Enzymes" designed around an active site linked to a supramolecular scaffold

- Structures contain well defined binding pockets capable of stabilizing reactive intermediates

- Artificial enzymes display a range of binding modes, including H bonding, π–π Interactions, etc

- Reactions isolated from the surrounding environment, allowing for enzyme-like selectivity


Marchetti, L.; Levine, M. *ACS Catal.* 2011, 1, 1090
Supramolecular complexes as enzyme mimics

A range of scaffolds have been utilized as host structures for supramolecular enzyme models.
Cyclodextrins as a scaffold for substrate binding

- Cyclodextrin family of compounds consists of a range of cyclic oligosaccarides

\[ \beta\text{-Cyclodextrin} \]

Conical structure

- Hydrophobic cavity can accommodate a number of hydrophobic guest molecules
- A number of isomers readily available, subject of many early reports on artificial enzymes

Catalytic systems using the cyclodextrin moiety

Initial report of an enzyme mimic

First description of an "artificial enzyme" for the hydrolysis of p-nitrophenyl acetate

Catalyst consists of metal complex covalently linked to β-cyclodextrin scaffold

Hydrolysis shows a 4x rate enhancement compared to the free metal complex alone

Rate acceleration attributed to substrate binding within hydrophobic cyclodextrin pocket

Artificial P450 enzyme for Stereoid Hydroxylation

Artificial Cytochrome P450 enzyme to mimic selectivity seen in steroid biosynthesis

Catalyst system based on metalloporphyrin core with appended cyclodextrin rings

- Ester side chains required to facilitate binding to cyclodextrin groups on catalyst and control regioselectivity
- Selective oxidation observed at C-6 position, without overoxidation to ketone

Artificial P450 enzyme for Steroid Hydroxylation

- Artificial Cytochrome P450 enzyme to mimic selectivity seen in steroid biosynthesis

Second generation catalyst contains fluorinated aromatic to prevent oxidative degradation

- Selective oxidation observed with increased efficiency at C-6 position, without overoxidation to ketone
- Substrates without both ester side chains give a mix of products

Artificial P450 enzyme for Steroid Hydroxylation

- Artificial Cytochrome P450 enzyme to mimic selectivity seen in steroid biosynthesis

Second generation catalyst contains fluorinated aromatic to prevent oxidative degradation

Supramolecular enzyme mimic as an artificial peptidase

Peptide bond cleavage is a major biological process, catalyzed by a number of enzymes.

Internal X-Pro residues are difficult to cleave, with few enzymes that are able to do so.

Stable Internal X-Pro linkages often used to protect proteins against degradation.

Few enzyme class and synthetic methods known to cleave them specifically.

Supramolecular enzyme mimic as an artificial peptidase

- Pd aqua complexes found to selectively cleave all X-Pro linkages

\[
\text{Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg} \xrightarrow{[\text{Pd(H}_2\text{O)}_4]^{2+}} \text{Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg}
\]

- As Pro residues do not deprotonate, do not form metal amidate complex that suppresses hydrolysis
- However, sequence specific peptideavage often required for biochemical applications

\[\text{Cyclodextrin moiety intended to bind aromatic side chains}
\]

Thus specific to X-Pro-Ar sequences (Phe, Tyr and Trp)
Supramolecular enzyme mimic as an artificial peptidase

- Pd aqua complexes found to selectively cleave all X-Pro linkages

- With modified catalyst structure, selective peptide cleavage observed adjacent to Phe residue

- Selectivity attributed to binding of aromatic ring inside cyclodextrin hydrophobic cavity

Non-covalent self assembled molecules have been used as "enzyme mimics" to encapsulate reactions.

Container molecules made up of non-covalent linkages, eg. H-bonding, metal coordination, etc.

Well defined binding pocket, but present some flexibility when incorporating guest complexes.

 Easily prepared by combining components which assemble through complementary interactions.
Self-assembled "Container" molecules

- Directing regioselectivity of Diels-Alder reaction by M₆L₄ molecular cage

Diels-Alder of anthracene and phthalimide proceeds to yield adduct bridging at the center ring

Proposed to use host complexes to override the selectivity of uncatalyzed D-A reaction

Self-assembled "Container" molecules

Directing regioselectivity of Diels-Alder reaction in molecular hosts

Use of supramolecular catalyst found to override selectivity in favor of terminal D-A adduct

Substrates without bulky group on phthalamide found to give bridging product
Self-assembled "Container" molecules

- Directing regioselectivity of Diels-Alder reaction in molecular hosts

\[
\text{OH} \quad \text{N-Cy} \quad \text{Catalyst (10 mol%)} \quad \text{HO}
\]

Regioselectivity explained via fixed orientation of guest molecules prior to reaction

Bent structure of product leads to a lower affinity for host than substrates, allowing catalytic turnover

Supramolecular hosts for transition metal catalysis

- $M_4L_6$ have a smaller aperture and an interior more segregated from bulk solution than $M_6L_4$.

- Encapsulation occurs with entropically favorable liberation of solvent molecules.

- Anionic host framework has a stabilizing effect on cationic guests and intermediates.


Supramolecular hosts for transition metal catalysis

Control of the rate of a step of a catalytic cycle via encapsulation rather than via ligand

Merger of biomimetic environment control with unnatural mode of reactivity

Supramolecular hosts for transition metal catalysis

Stoichiometric reductive elimination from dimethyl Au complex

4000-fold rate acceleration seen with catalyst (20 weeks to 53 min)

Background reactivity measured using strongly binding Et₄P⁺ to clock binding pocket

Proposed mechanism based on pre-equilibrium between neutral and cationic substrates:

Kinetic investigation indicates enzyme like mechanism following Michaelis-Menten like kinetics
**Supramolecular hosts for transition metal catalysis**

- Applied to stoichiometric sp\(^3\)-sp\(^3\) coupling using a Pt catalyst

```
Me—I
Me₃Sn—Me
KF
```

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mol% Pt</td>
<td>Me—Me</td>
</tr>
<tr>
<td>10 mol% Pt</td>
<td>Me₃Sn—F</td>
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- Efficient coupling observed only with both catalysts, deuteration indicates both starting materials incorporated

**Modified catalyst allows for Better incorporation of MeI into host complex**


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