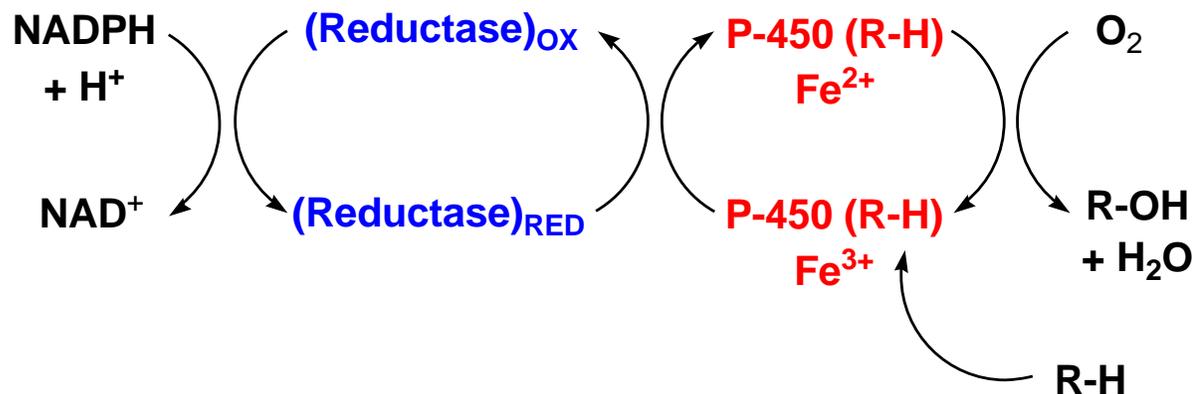
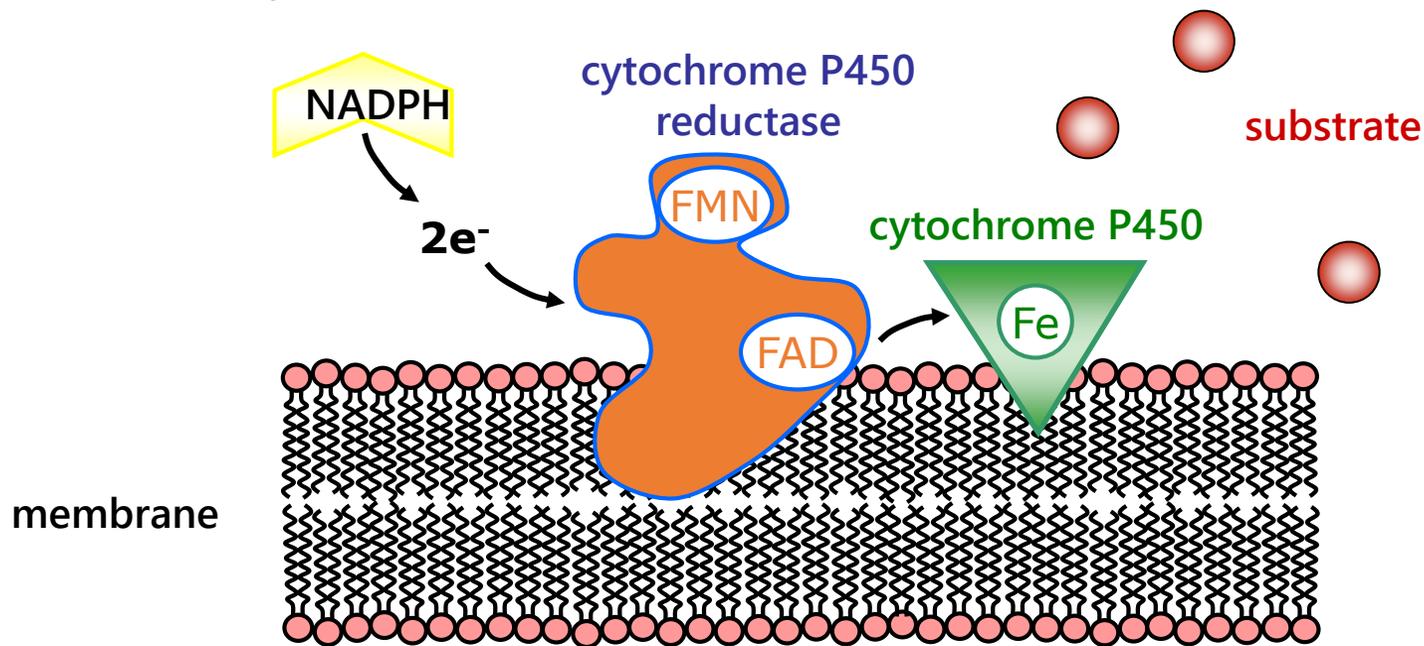


Cytochrome P450

- Membrane-bound enzyme that detoxifies compounds in the liver
- Oxidizes steroids, fatty acids, xenobiotics



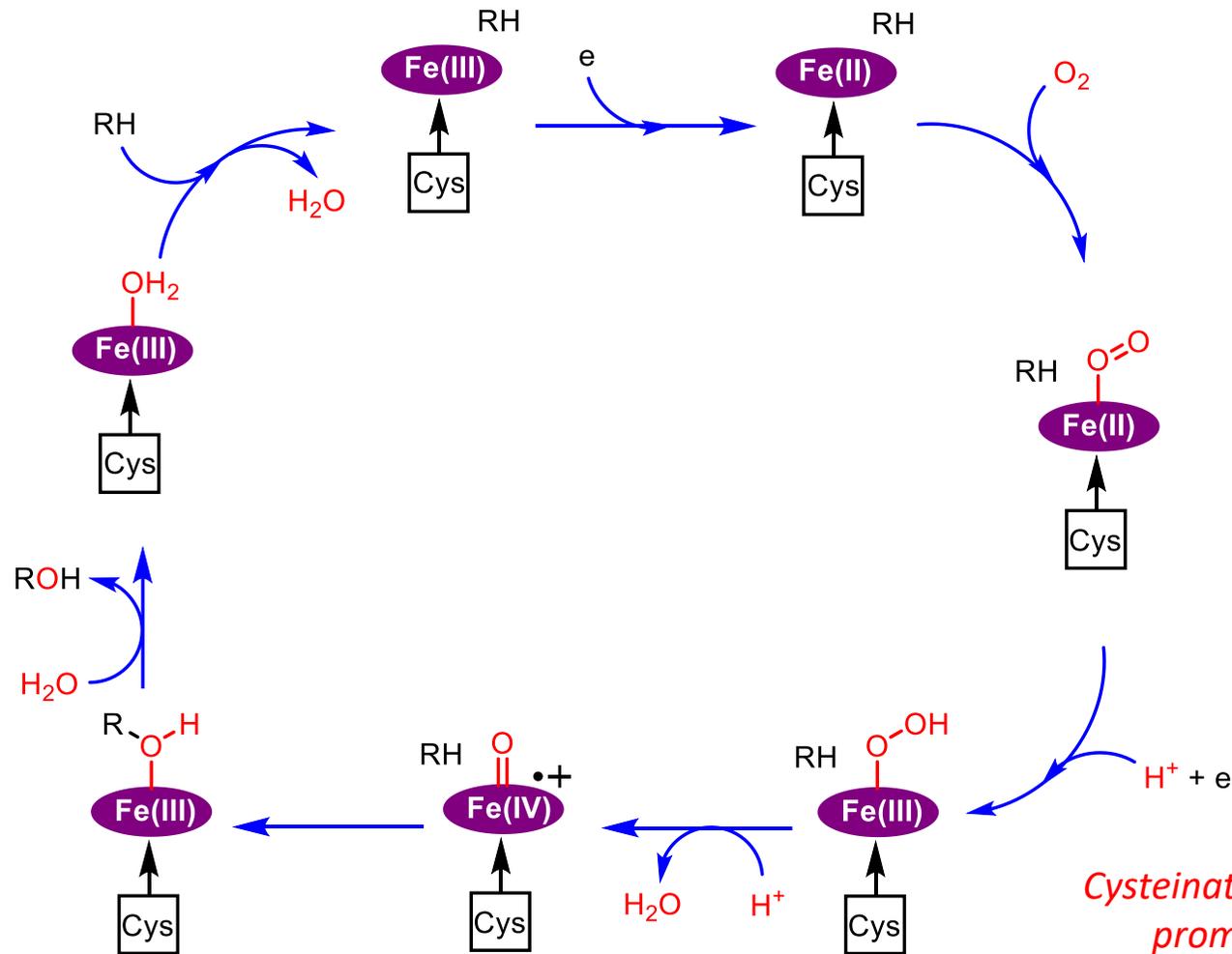
*(NADPH: nicotinamide adenine dinucleotide phosphate;
FAD: flavine adenine nucleotide;
FMN: flavine mononucleotide)*

Cytochrome P450

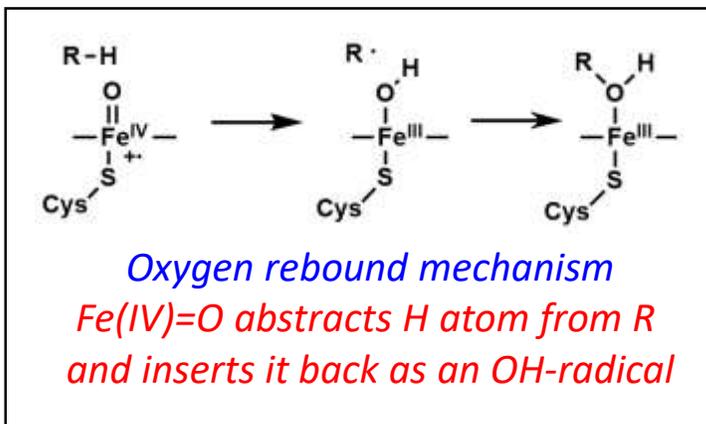
*expulsion of H₂O → Fe from low spin to high spin
and increase in reduction potential*

only Fe(II) porphyrin binds O₂

Catalytic cycle



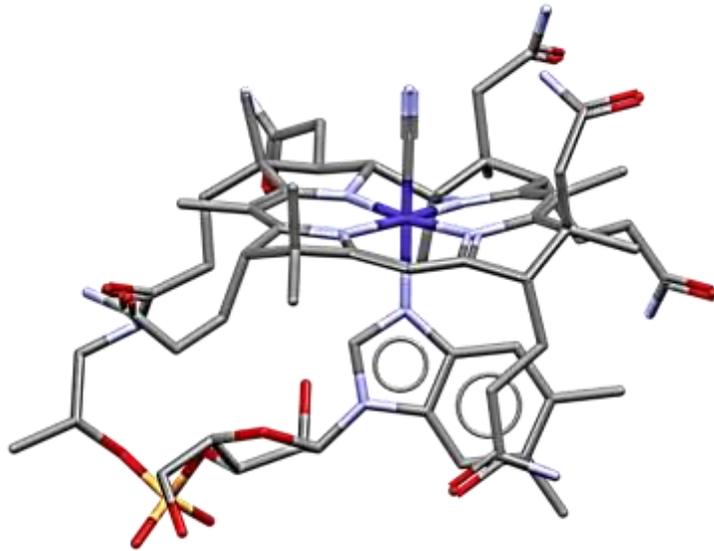
*Cysteinate axial ligand
promotes O-O
dissociation and increases
electron density on metal*



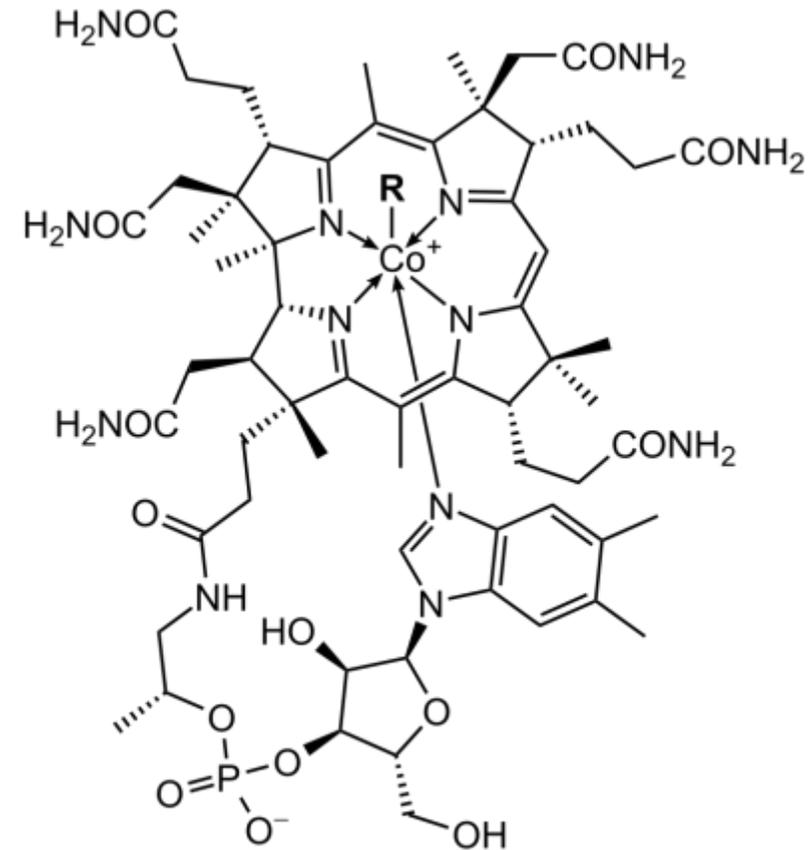
Vitamin B12

Cofactor for biological methyl transfer and radical-based rearrangements

- ✓ Co center coordinated inside a **corrin** ring
- ✓ One X-type and one L-type axial ligand



X-ray structure **cyanocobalamin** (R = CN)

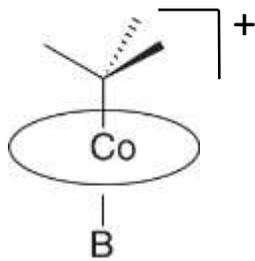


R = 5'-deoxyadenosyl, CH₃, OH, CN

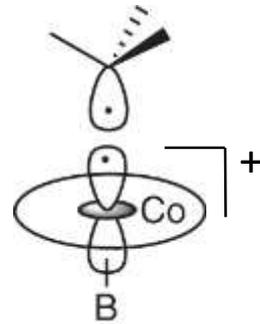
Vitamin B12

Coenzyme B12: **corrin** with **benzimidazole** and **5'-deoxyadenosyl** as axial ligands for Co

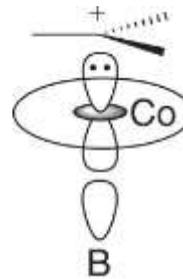
At pH 7: three possible Co oxidation states, all low spin configurations



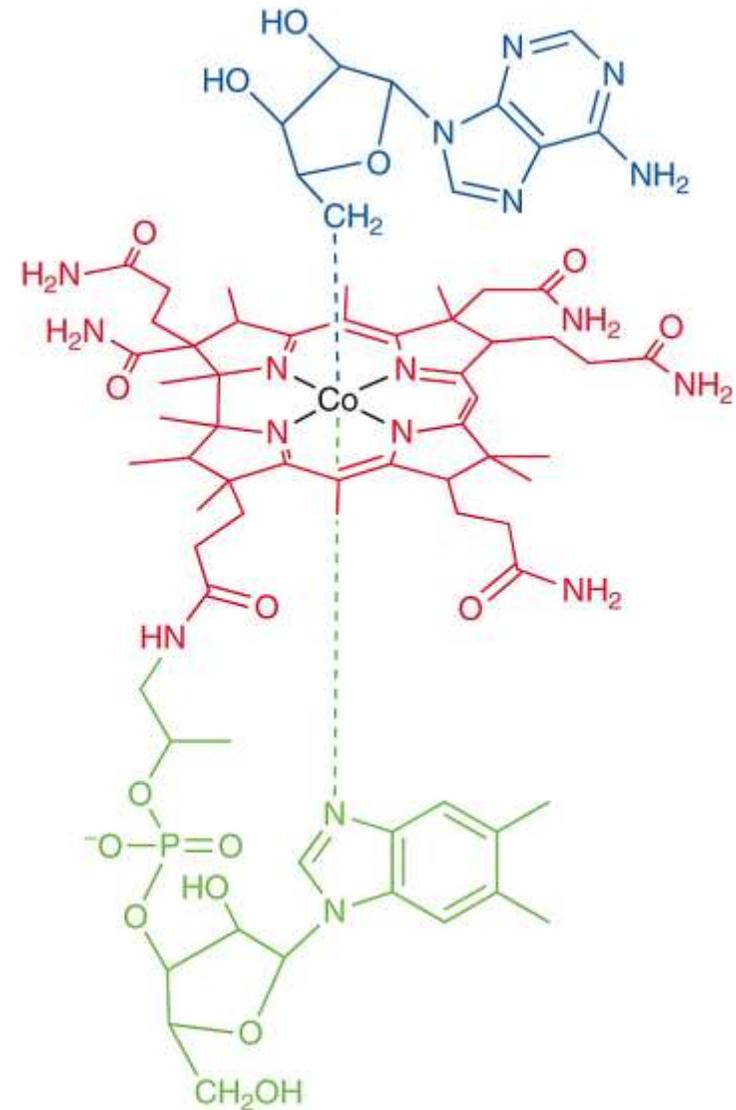
Co(III)
 d^6 , 18e
6-coordinate
octahedral
'base-on'



Co(II)
 d^7 , 17e
5-coordinate
square-pyramidal
'base-on'
Unpaired electron
in d_{z^2}

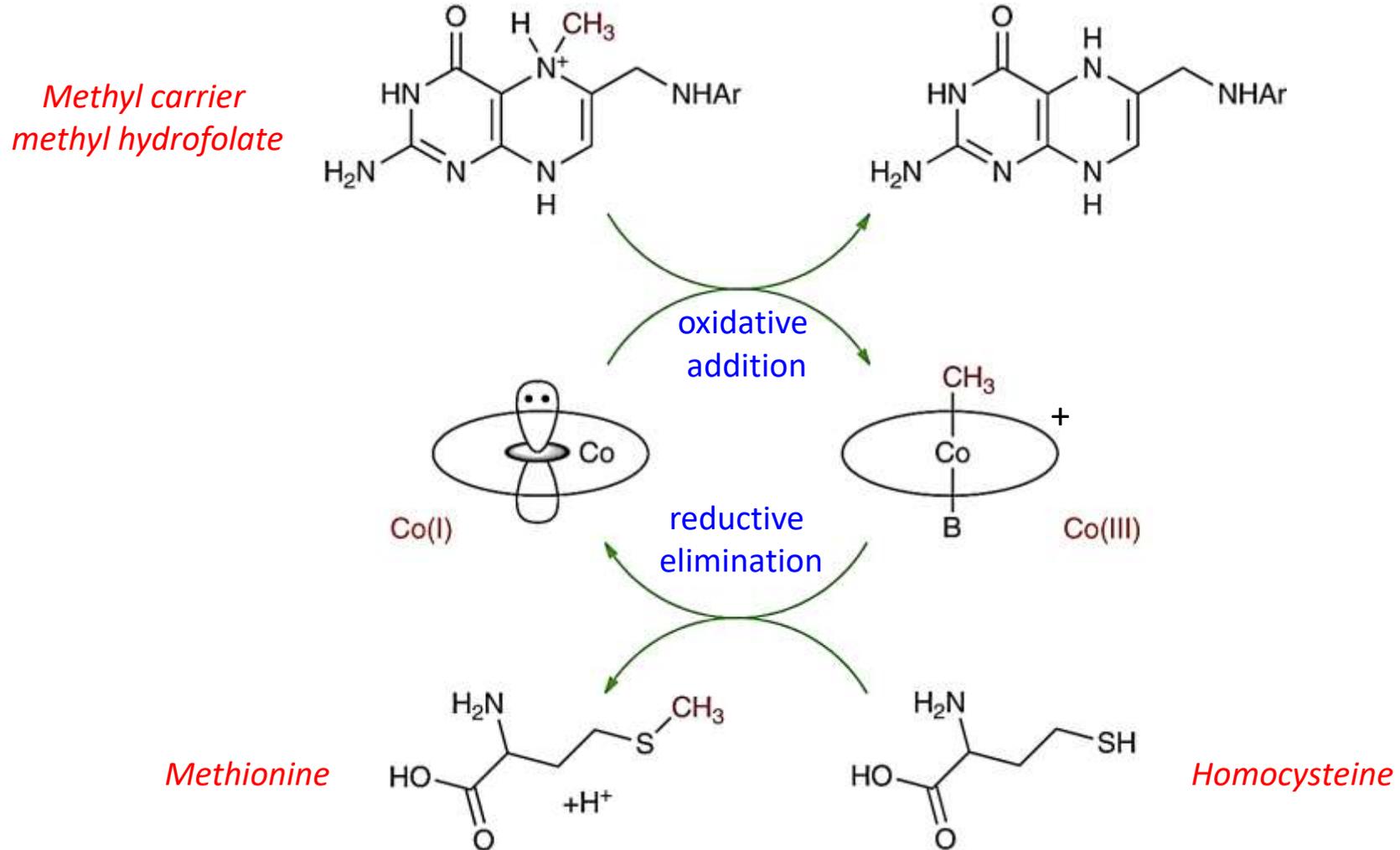


Co(I)
 d^8 , 16e
4-coordinate
square planar
'base-off'



Vitamin B12

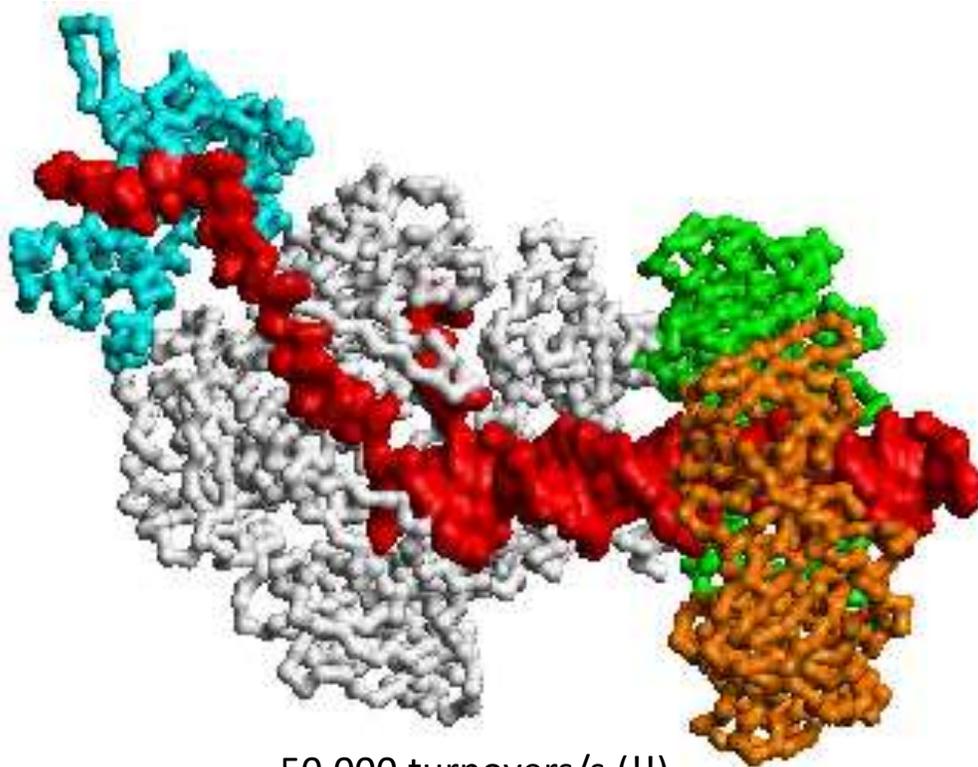
Mechanism of biosynthesis of methionine by **methionine synthase**



Processive enzymes

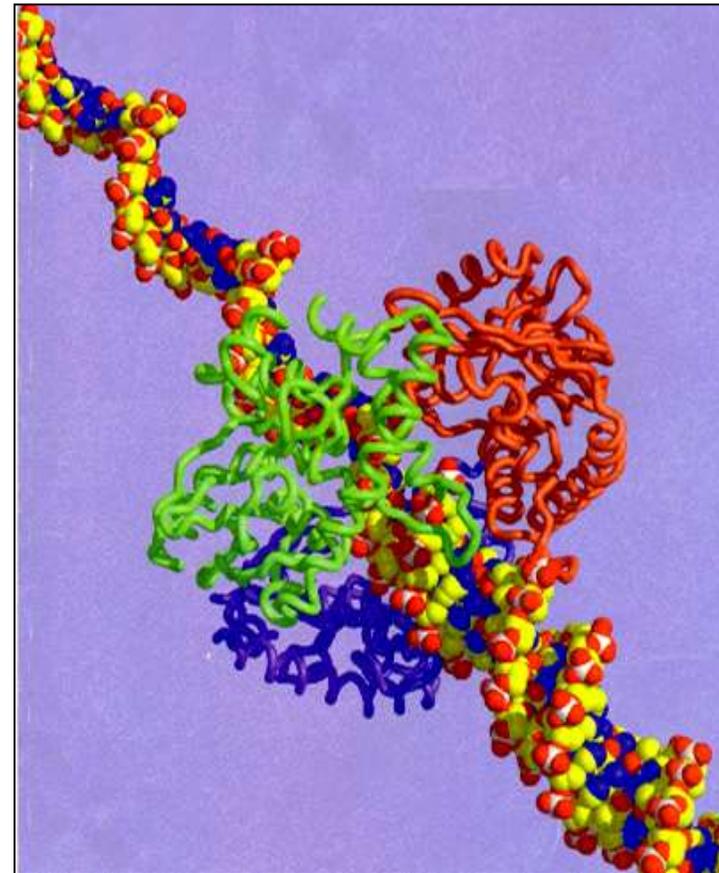
Processive catalysis: catalyst stays connected to a (polymeric) substrate and does multiple rounds of catalysis before it dissociates

DNA Polymerase III

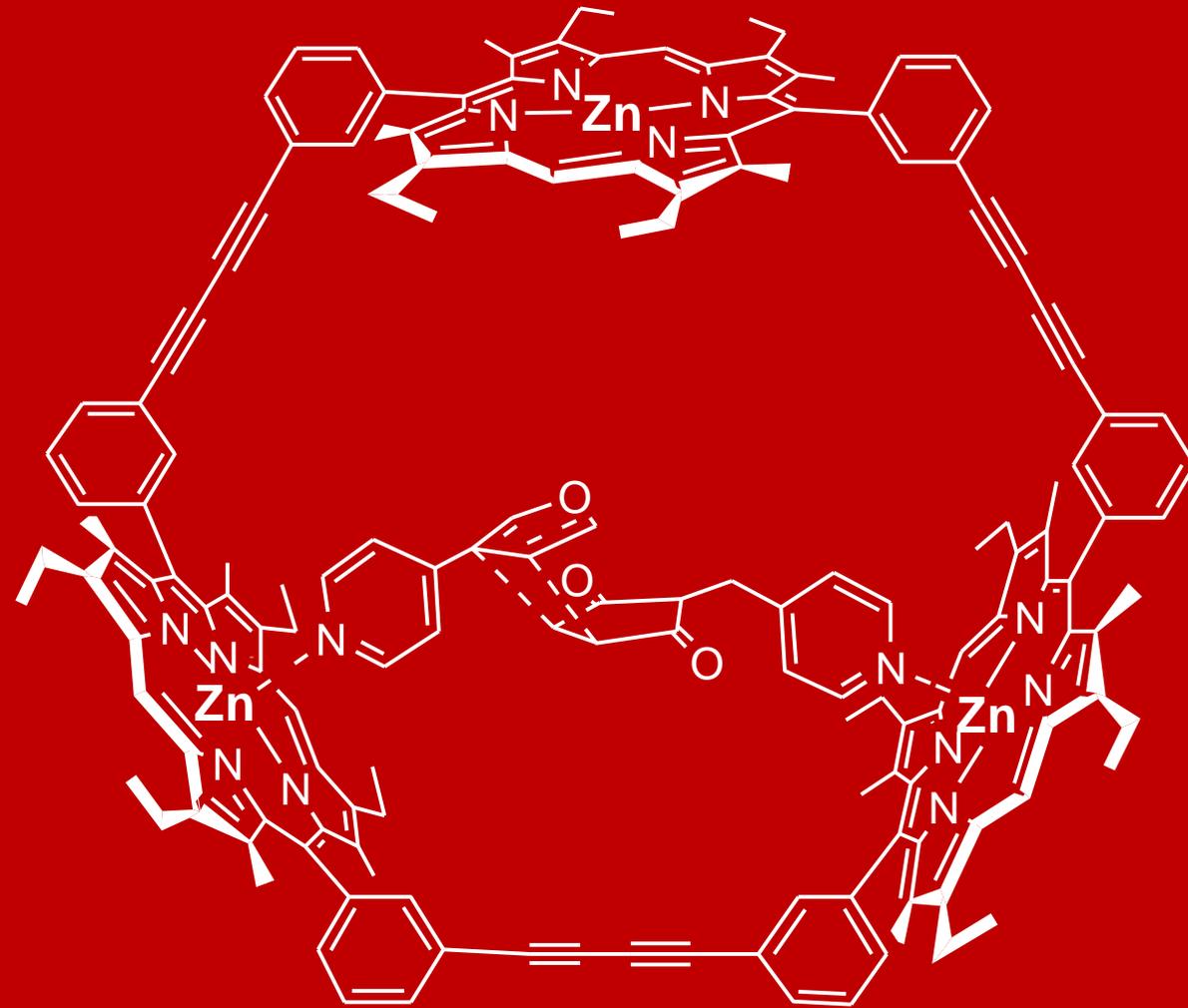


50.000 turnovers/s (!!)

λ -Exonuclease



Biomimetic catalysis



Biomimetic chemistry

Synthetic simplified model systems that mimic the behaviour of systems in nature

Synthetic enzyme model systems: “synzymes”

Why would we want them?

Need for catalysts with equal efficiency and selectivity as natural enzymes

Why synthetic?

Natural enzymes are:

- often only available in small quantities
- not always straightforward to extract
- often unstable outside an organism
- restricted in their use to aqueous environments
- restricted to a limited number of chemical reactions

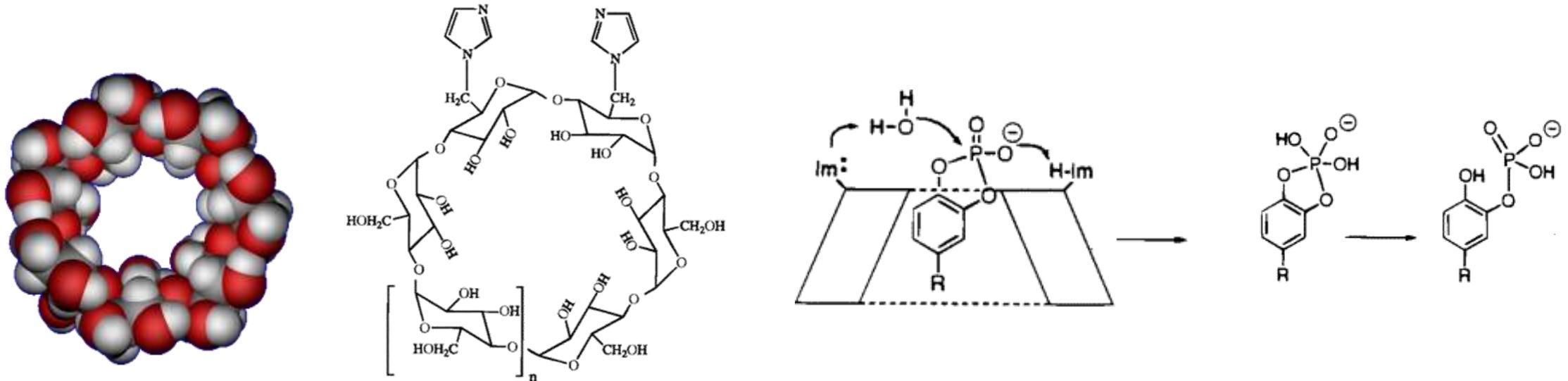
General approach

Combine a synthetic cavity-containing molecule with a catalytically active site

Ribonuclease A mimic

Ribonuclease A: enzyme that cleaves phosphates in single stranded RNA, using two histidines for general acid-base catalysis

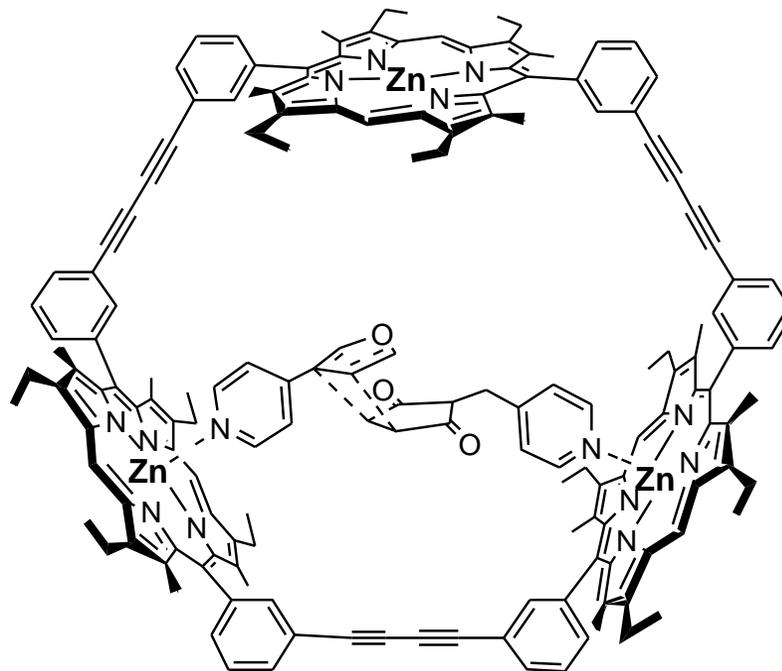
Enzyme mimic by attaching two imidazoles to a **cyclodextrin** cavity



- Apolar part of substrate bound in cavity via **hydrophobic effect**
- 100-fold rate acceleration, 99+% selectivity for one of the hydrolysis products

Preorganization of substrates

Acceleration of a Diels-Alder reaction

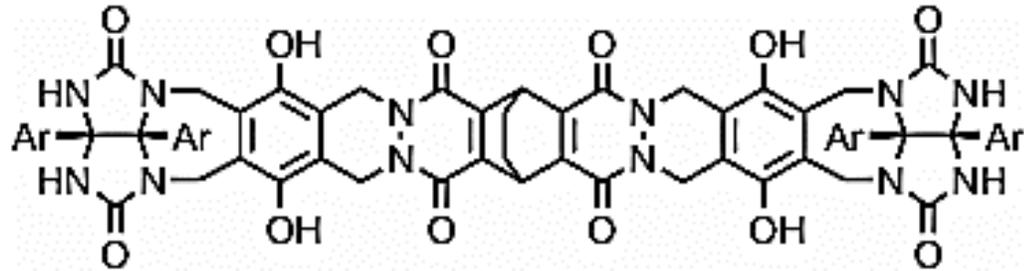


- Reactants are **preorganized** in geometry that resembles the **transition** state
- 200-fold rate acceleration, only the **exo-product** is formed
- Complete **inhibition** of the reaction when cavity is blocked by competitive guest

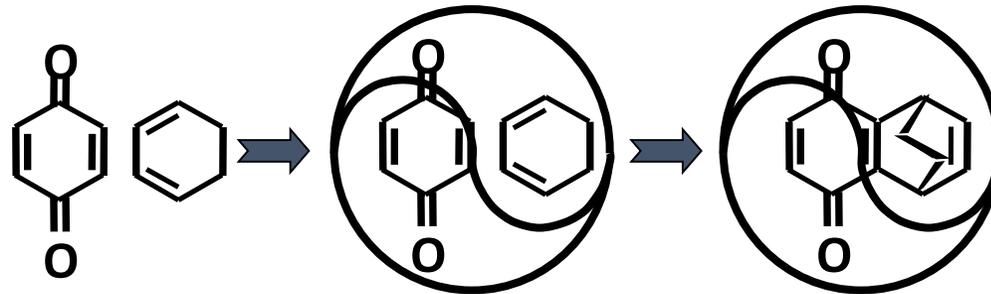
Complication: product also blocks the cavity so turnover = 1 (product inhibition)

Self-assembled nanoreactor

Acceleration of a Diels-Alder reaction in a self-assembled "Molecular Softball"



16 hydrogen bonds

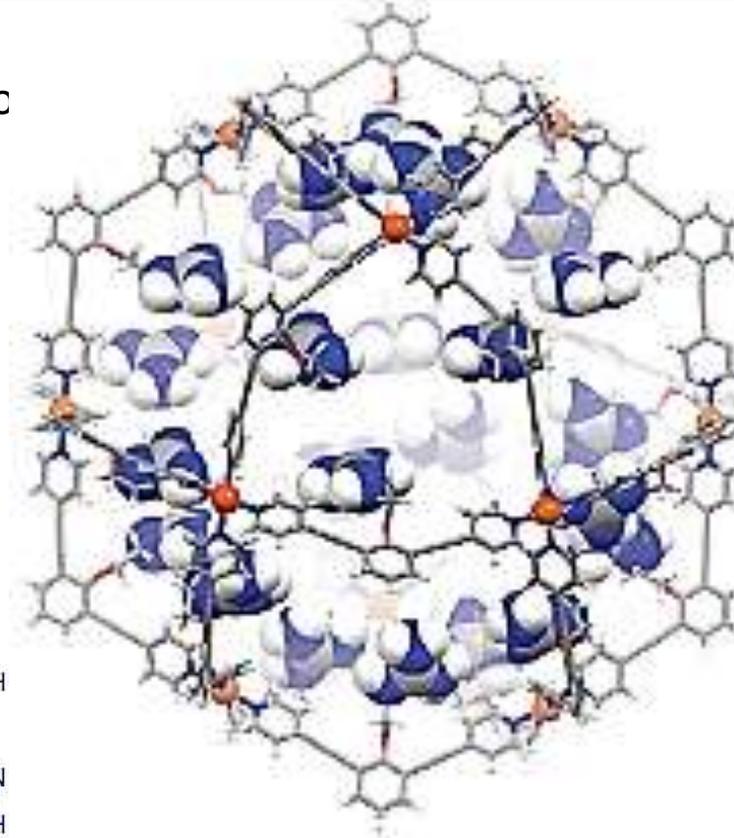
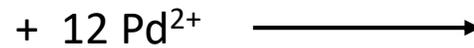
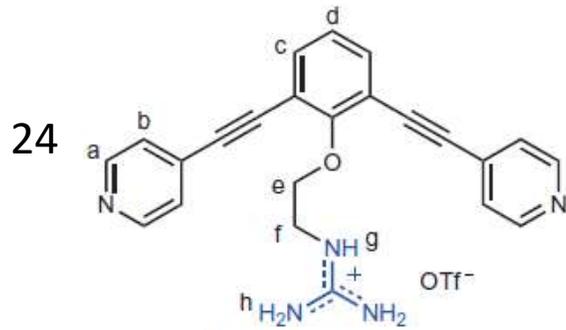


- Reactants are **preorganized** in close proximity in a favorable geometry
- In absence softball: reaction complete after a year. In presence softball: 1 minute

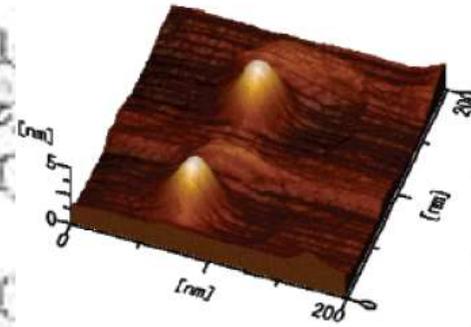
Complication (again): product blocks the cavity so turnover = 1 (product inhibition)

Self-assembled nanoreactor

Quantitative formation of a 36 component 'hollow' capsule c
5 nm size (**preorganization** & **self-repair**)

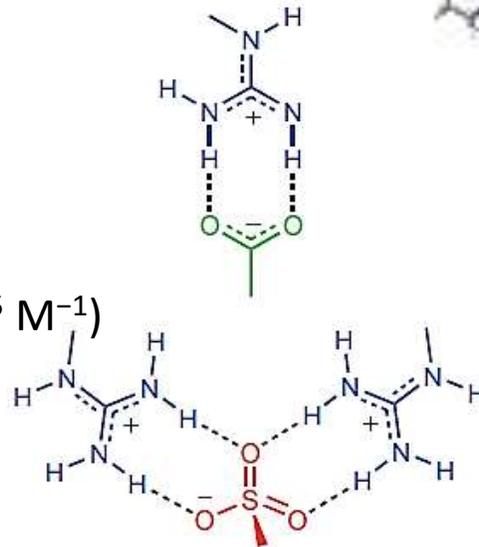


AFM image

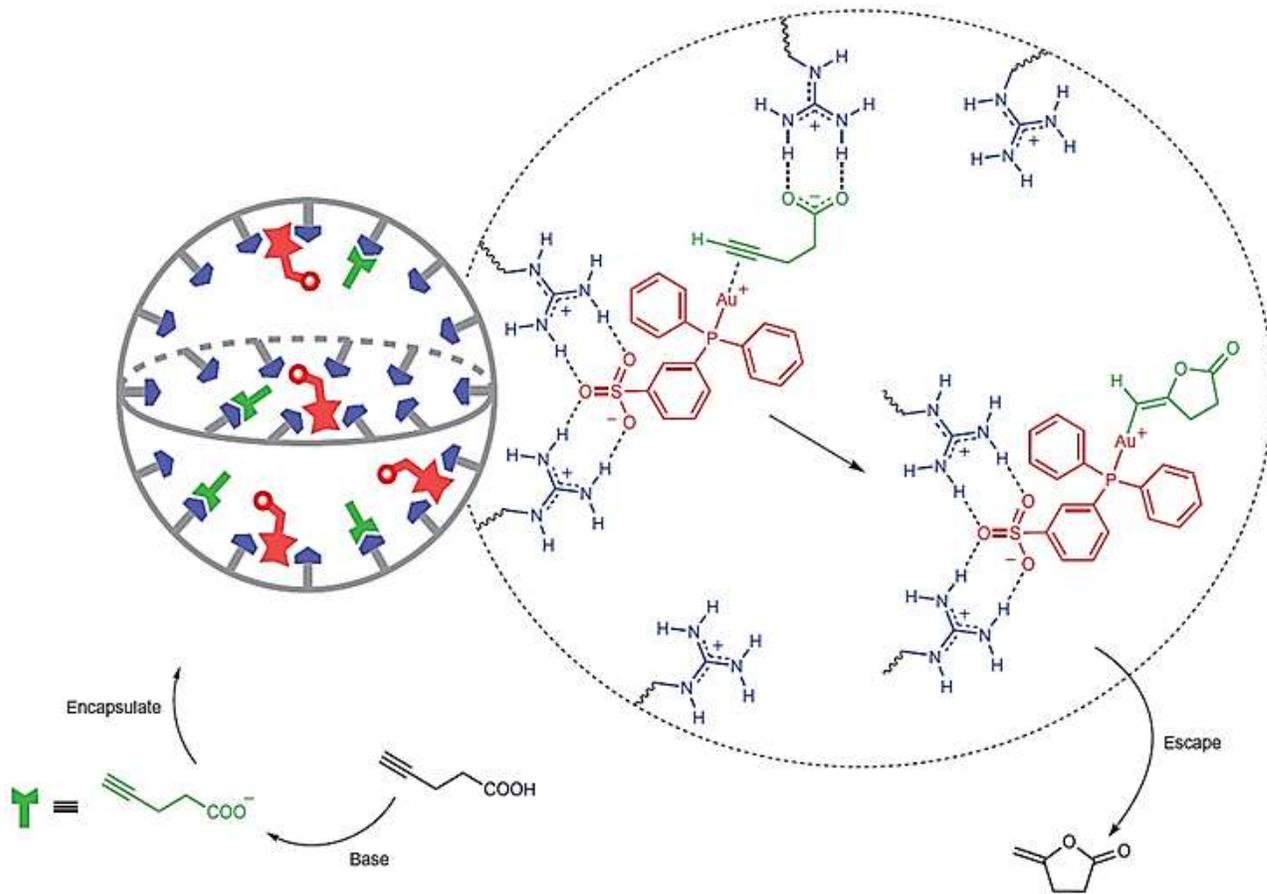
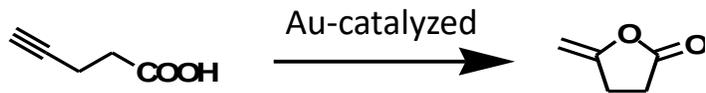


Relatively weak binding of carboxylates

Much stronger binding of sulfonates ($K_a = 10^5 \text{ M}^{-1}$)
via **cooperative interactions**



Self-assembled nanoreactor

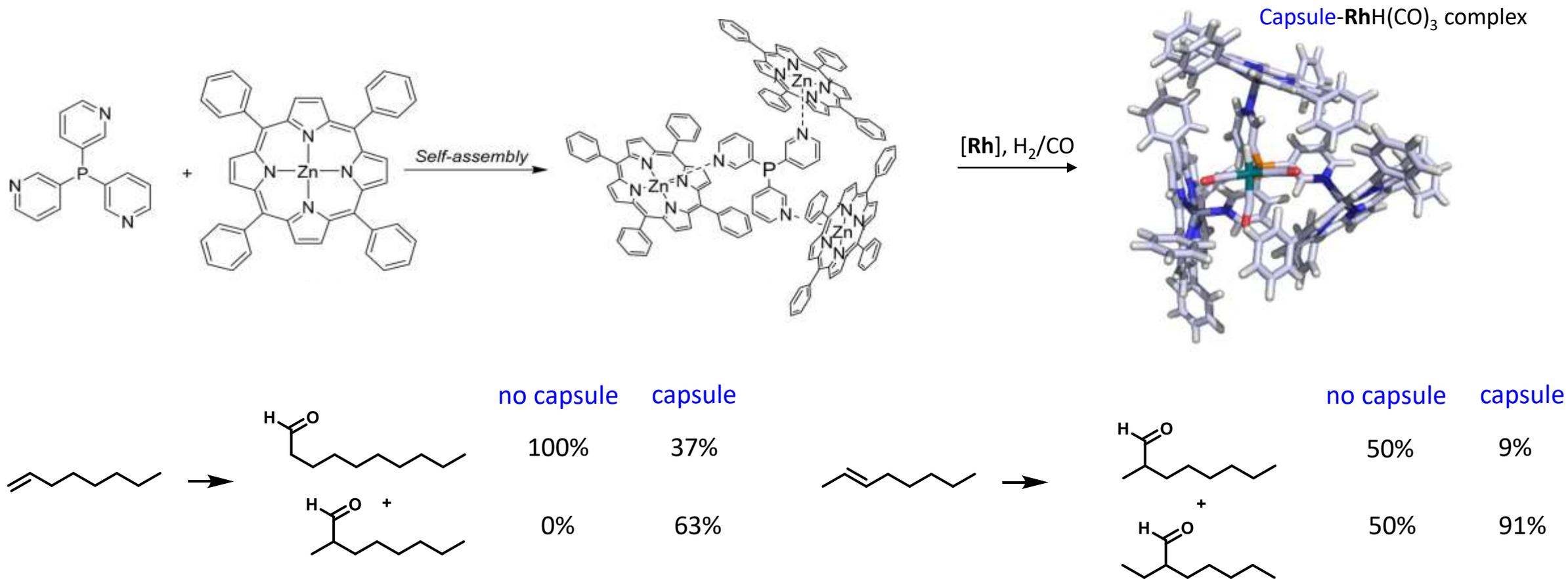


Conditions	Conversion*	TOF _{ini} (h ⁻¹) [†]
TPPMSAu ⁺	44%	0.45
TPPMSAu ⁺ + sphere	17%	0.14
TPPMSAu ⁺ + sphere + NEt ₃	>95%	5.75
TPPMSAu ⁺ + NEt ₃	19%	0.19
Sphere	-	-

- Preorganization of catalysts and substrates (proximity effects)
- Turnover by generation of neutral, non-binding product
- Inhibition by addition of p-toluenesulfonate

Second coordination sphere catalysis

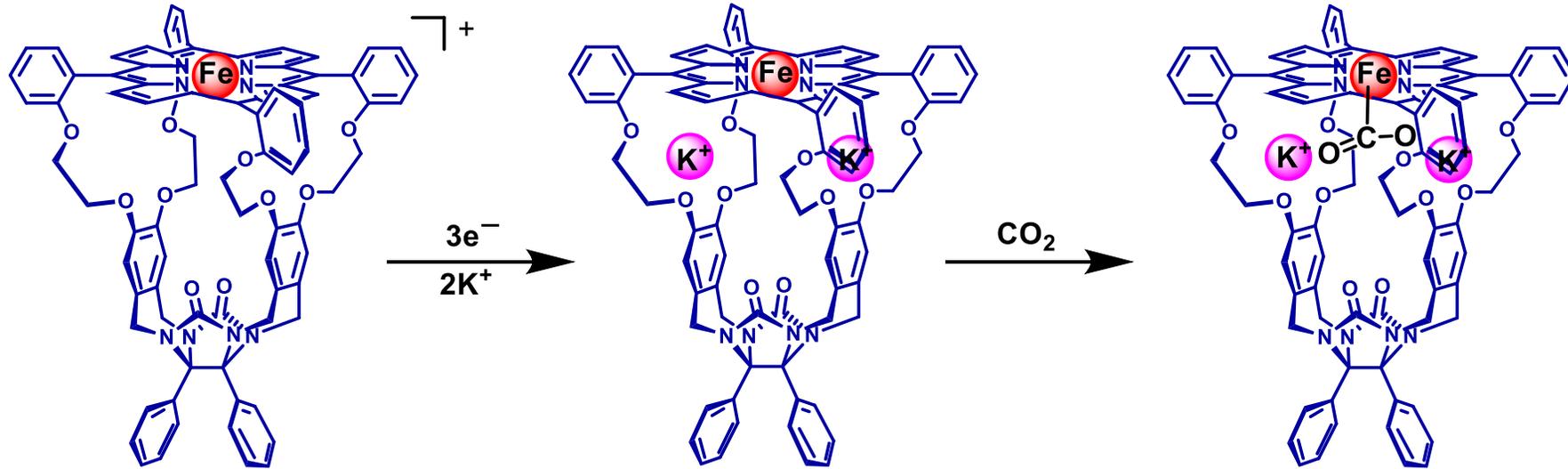
Example: encapsulated hydroformylation catalyst



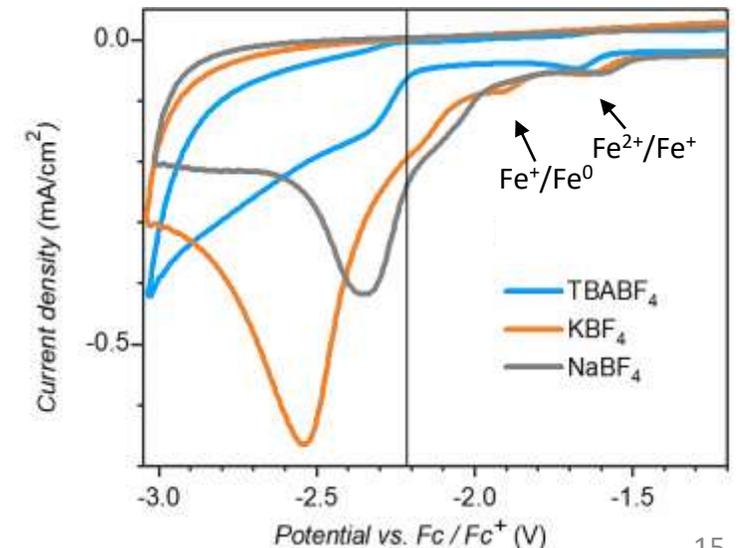
Confined space in **capsule** influences product selectivity

Second coordination sphere catalysis

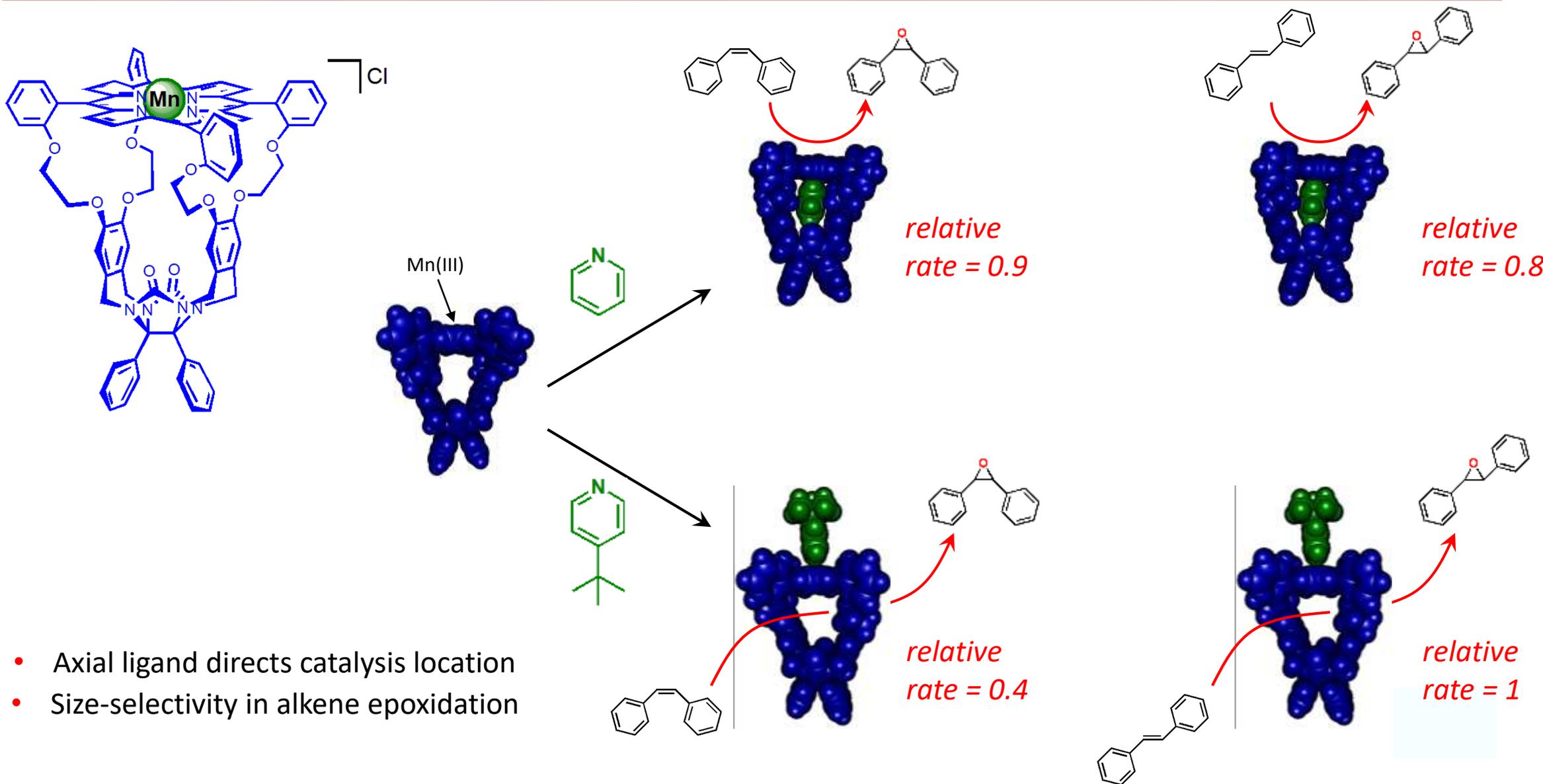
Example: electrocatalyzed CO₂ reduction



- Electrochemical reduction Fe^{III} to Fe⁰ in K⁺ electrolyte
- K⁺ binds in spacers of cage and assists binding of CO₂ inside cage
- K⁺ activates CO₂ for reduction to CO
- Compared to Fe tetraphenyl porphyrin:
 - Overpotential 0.2 V lower
 - High selectivity for CO formation (>90%)
 - Yield CO > 1.5 times higher

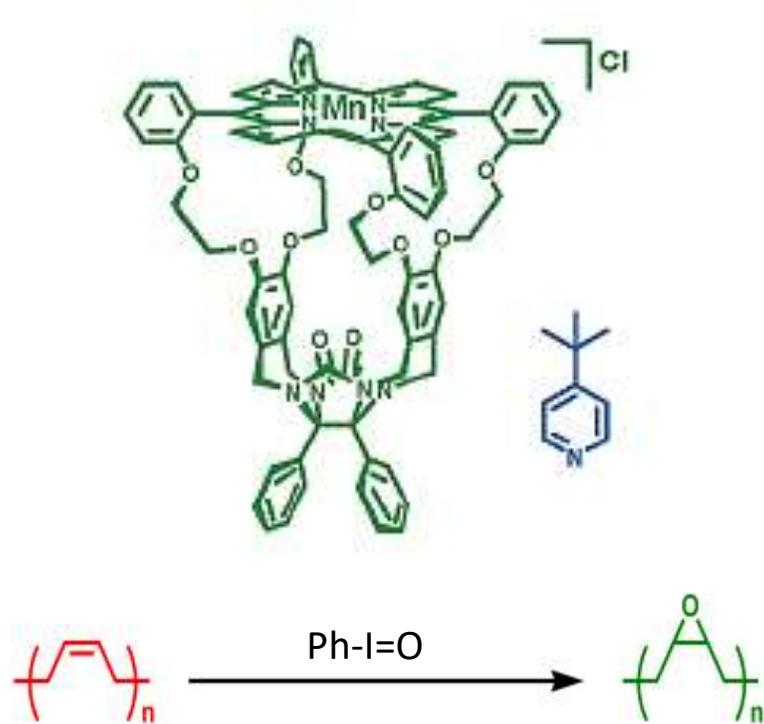


Porphyrin cage as a cytochrome P450 mimic

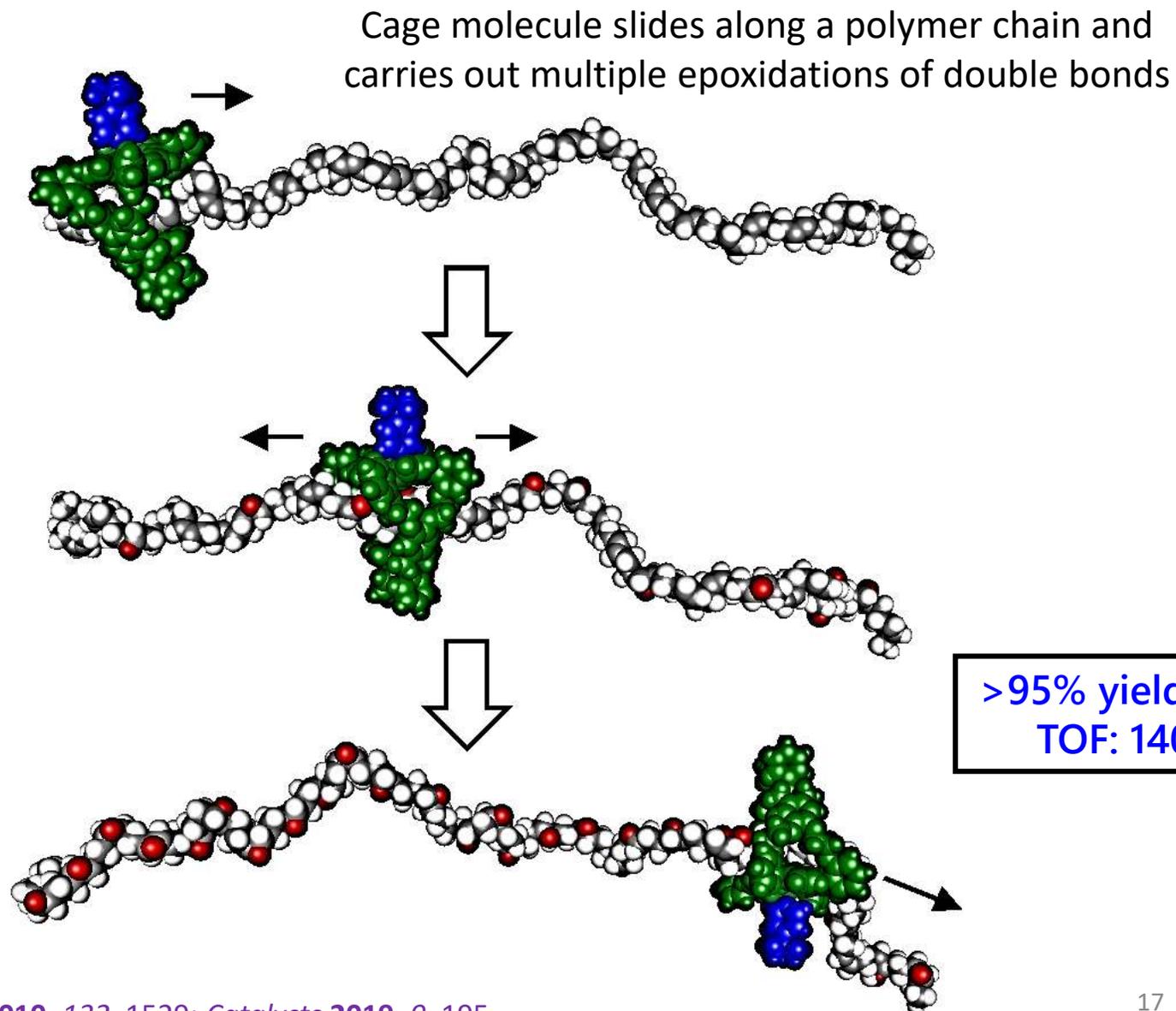


- Axial ligand directs catalysis location
- Size-selectivity in alkene epoxidation

Porphyrin cage as a processive catalyst

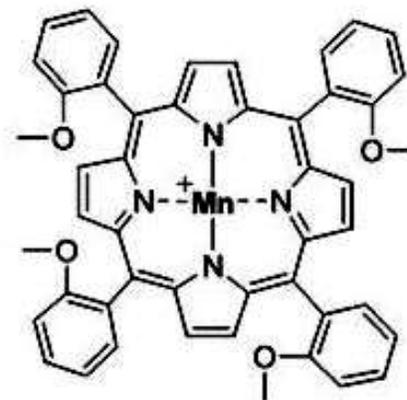
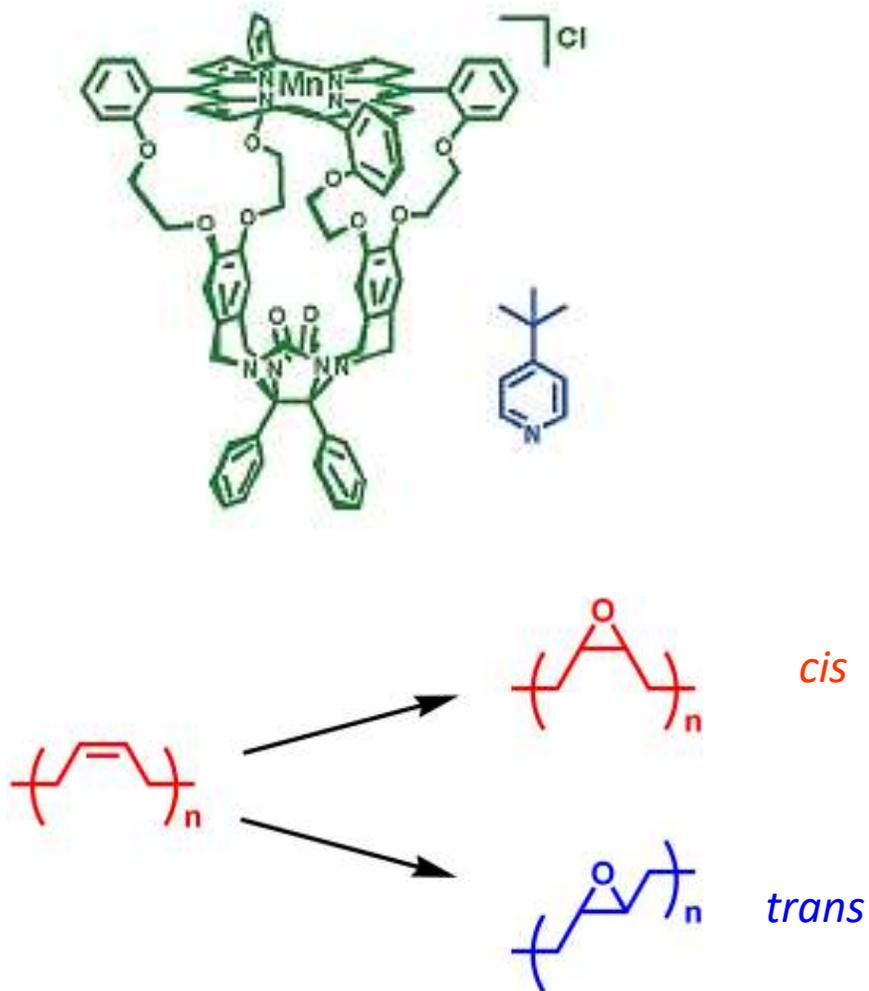


Polybutadiene M_w 300,000;
98% *cis*; [C=C] = 250 mM; [cat] = 1 mM

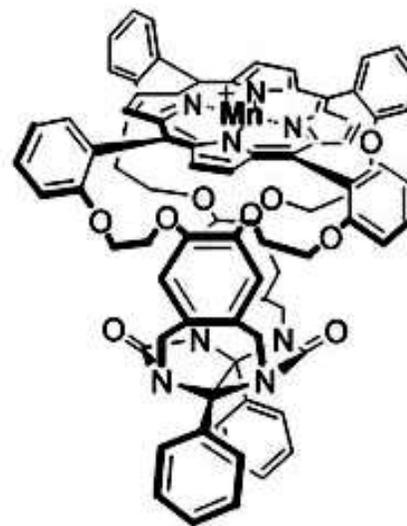


Porphyrin cage as a processive catalyst

Stereoselectivity



78% *cis* 22% *trans*
 $\text{trans/cis} = 0.28$



20% *cis* 80% *trans*
 $\text{trans/cis} = 4.0$

Trans-epoxide fits better in the cavity of the cage

Study material

Learning goals

- You understand the working mechanisms of natural enzymes
- You understand the role of the hydrophobic effect in enzyme catalysis
- You know the mechanisms by which natural enzymes stabilize transition states of a catalytic reaction
- You know the goals, approaches, and limitations of biomimetic catalysis

Study material

- These lecture slides
- Catalysis: An Integrated Textbook for Students (U. Hanefeld & L. Lefferts, Eds): Sections: 4.1, 4.2, 4.3.1.3, 4.3.1.4