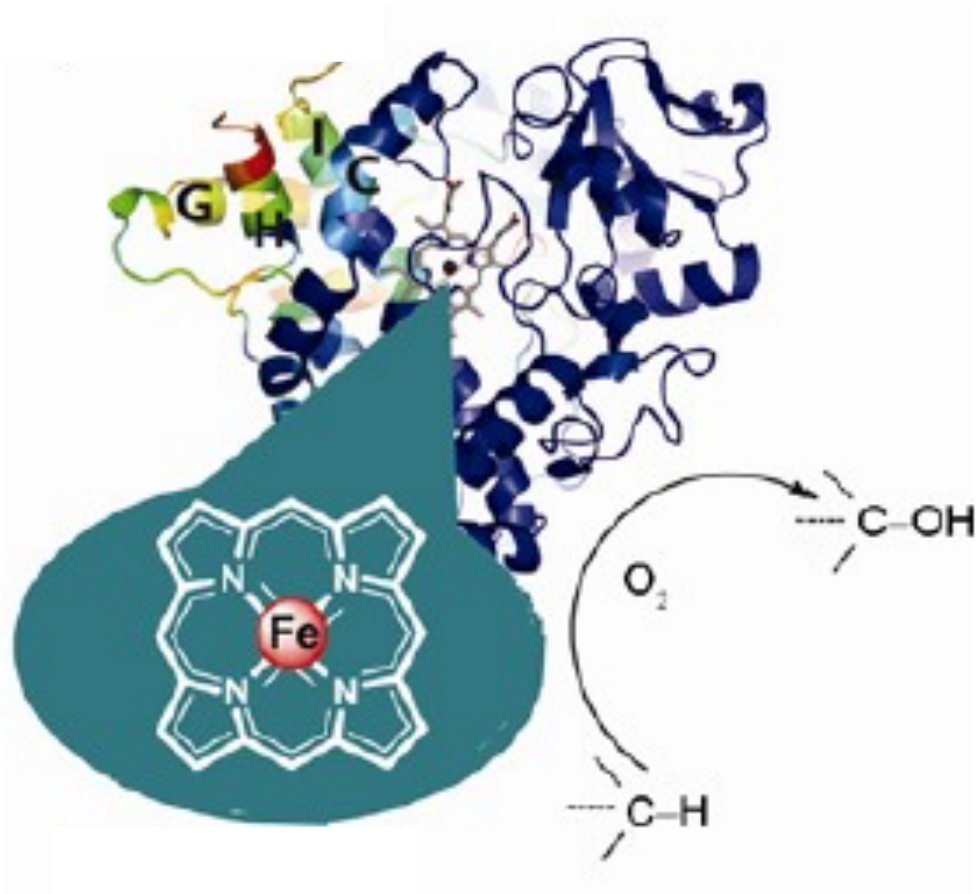
Strategies in Biomimetic Catalysis



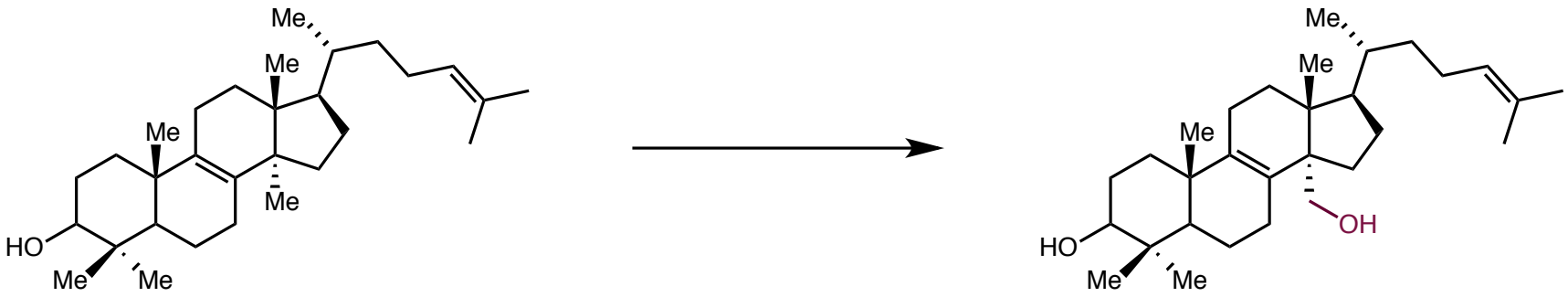
Tomer. M. Faraggi

MacMillan Lab Group Meeting

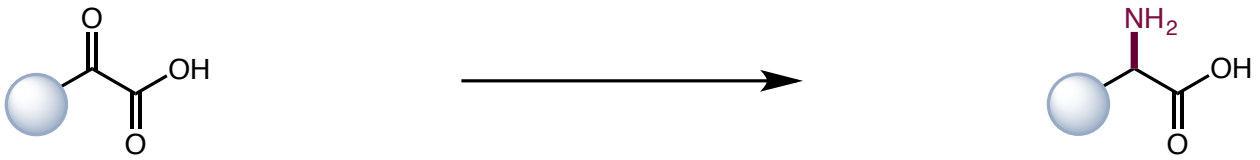
November 29th 2016

Enzymes as an inspiration for reaction development

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



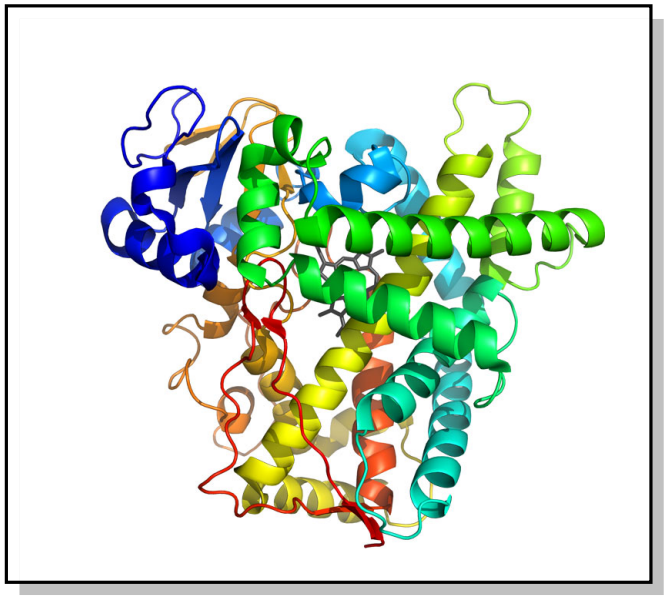
Regioselective hydroxylation in cholesterol biosynthesis

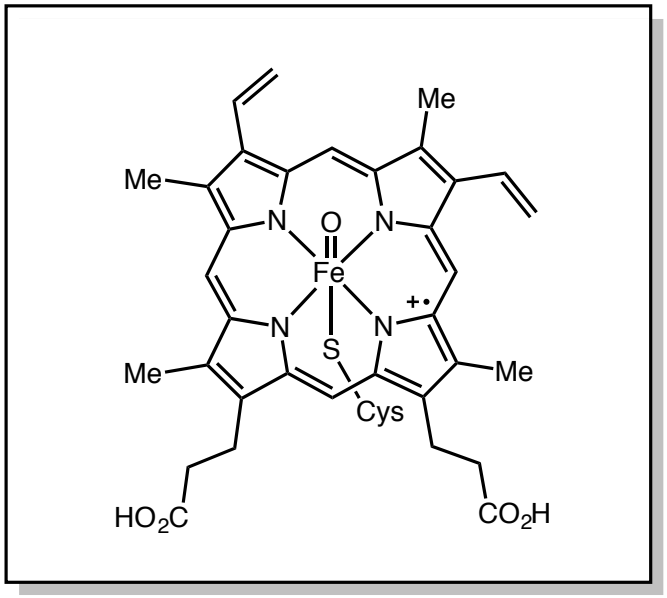


Asymmetric transamination in amino acid biosynthesis

- 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

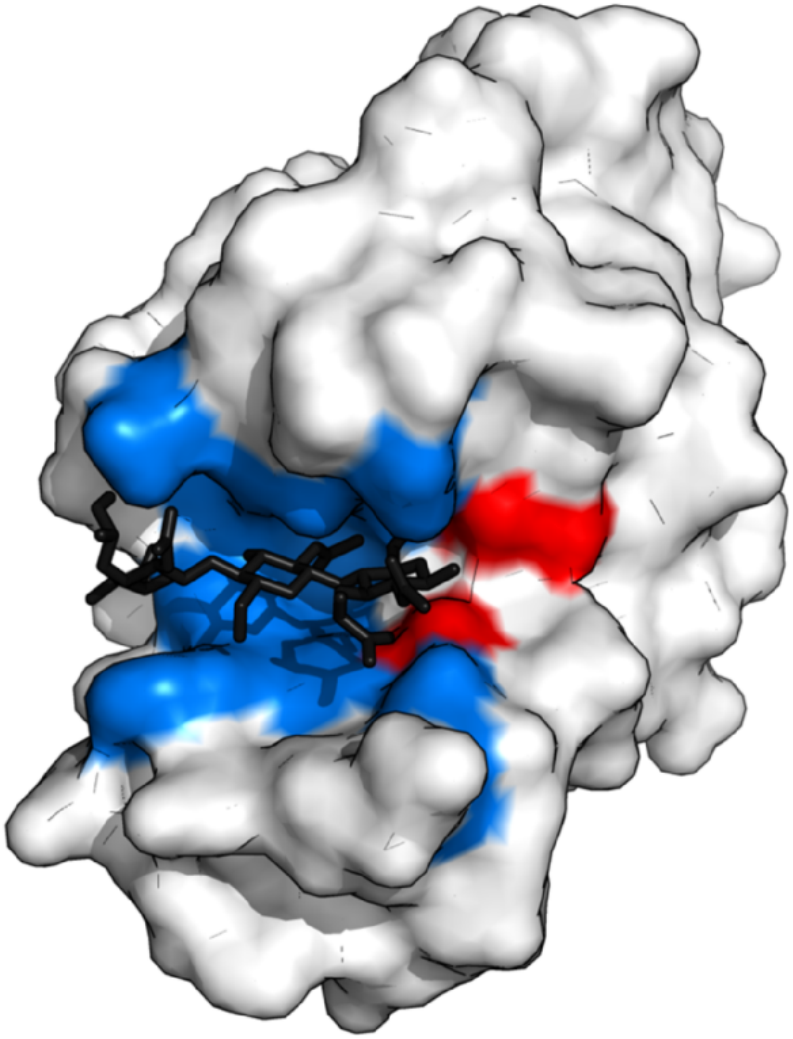
Biomimetic catalysis:

Chemical catalysis that mimics key features of enzymatic systems

Marchetti, L.; Levine, M. *ACS Catal.* **2011,** *1*, 1090.

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

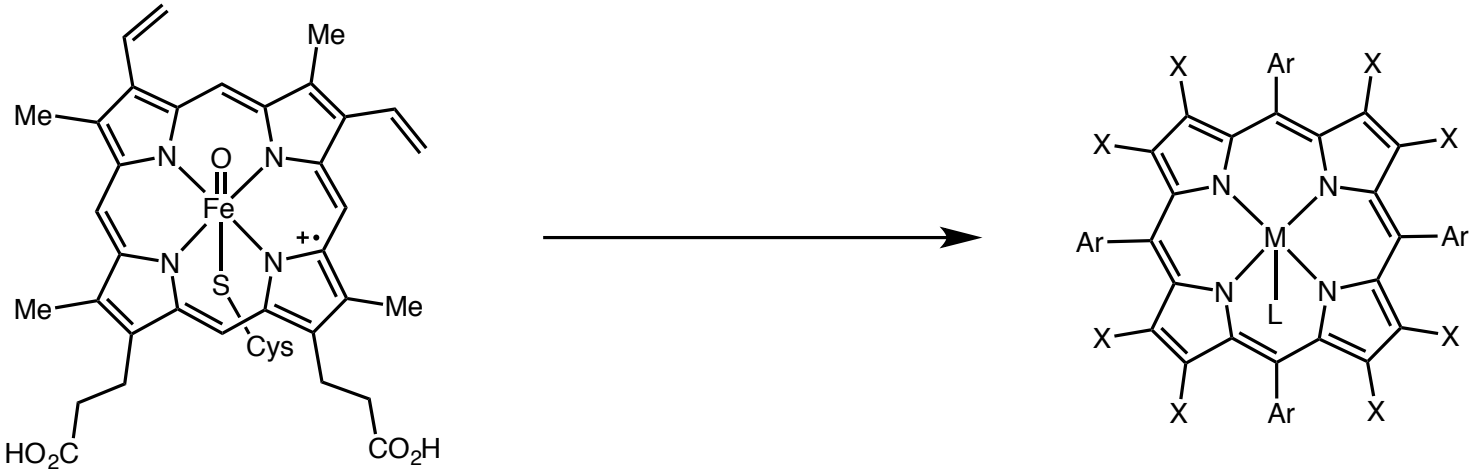
For example groups of amino acid residues

Or metal cofactors bound by protein structure

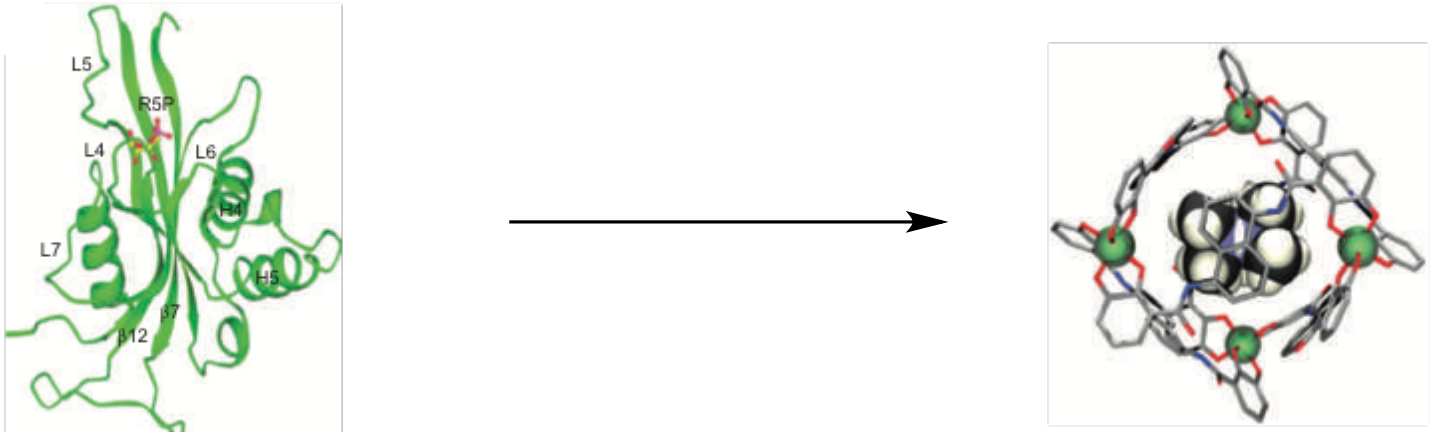
Attempts made to mimic the effects of both sites

Strategies in Biomimetic Catalysis

Metalloporphyrins - Development of new reactivity from an enzyme cofactor

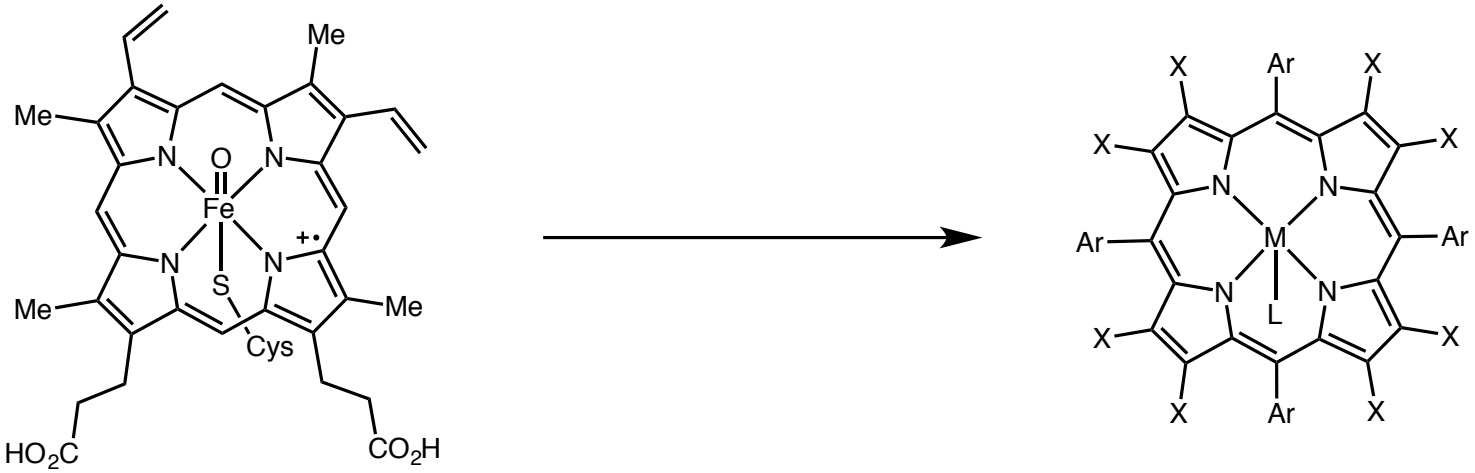


Artificial enzymes - Use of supramolecular structures to mimic substrate binding



Strategies in Biomimetic Catalysis

Metalloporphyrins - Development of new reactivity from an enzyme cofactor



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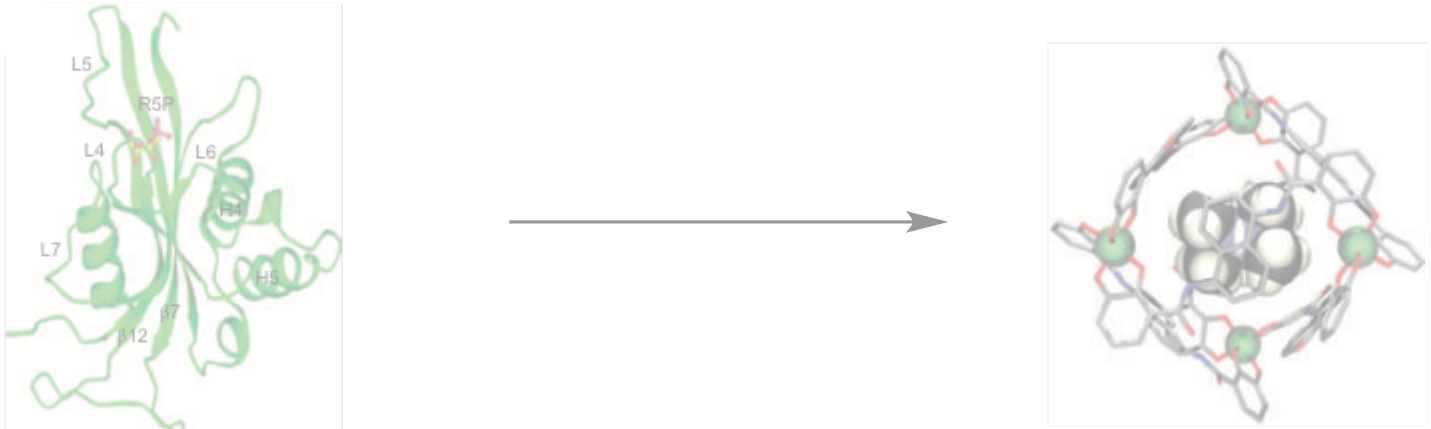
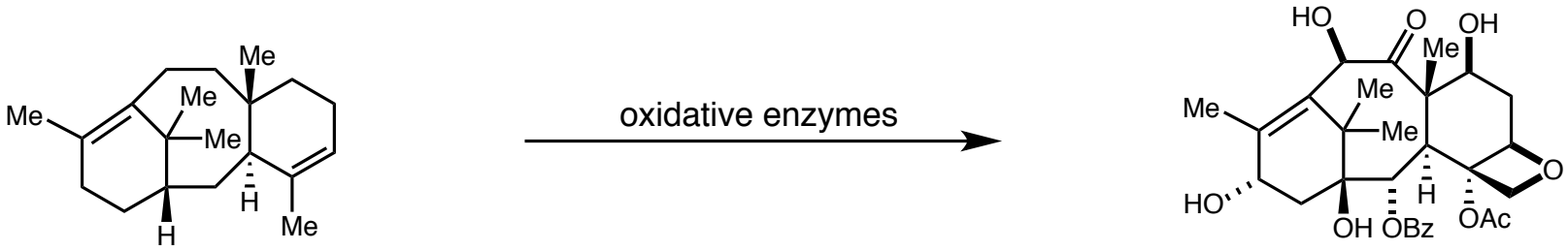


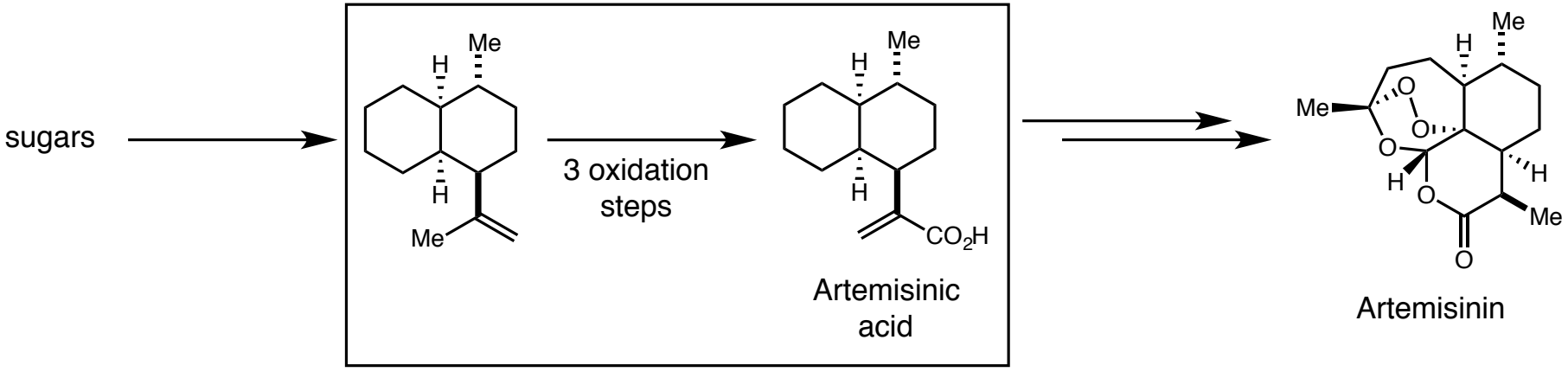
C–H functionalization inspired by oxidase enzymes

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



Taxadiene oxidation in the biosynthesis of taxol

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

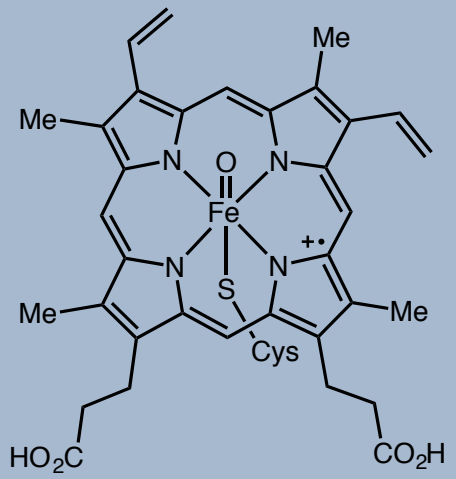


Selective enzyme mediated oxygenation in the fermentation of artemisinic acid

Li, X-W.; Nay, B. *Nat. Prod. Rep.* **2014,** *31*, 533

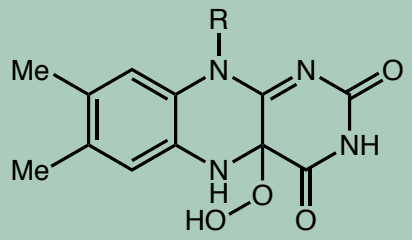
Holtmann, D.; Fraajie, M. W.; Arends, I. W. C. E.; Opperman, D. J.; Hollmann, F. *Chem. Commun.* **2014,** *50*, 13180

C–H functionalization inspired by oxidase enzymes



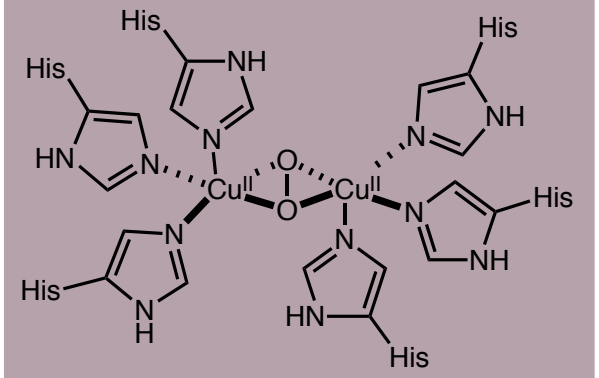
heme based catalysts

Cytochrome P450



peroxoflavin catalysts

Monoamine Oxidases



non-heme metal based catalysts

Oxyhemocyanin

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

Gamez, P.; Aubel, P. G.; Driessen, W. L.; Reedijik, J. *Chem. Soc. Rev.* **2001,** *30*, 376

Holtmann, D.; Fraajie, M. W.; Arends, I. W. C. E.; Opperman, D. J.; Hollmann, F. *Chem. Commun.* **2014,** *50*, 13180

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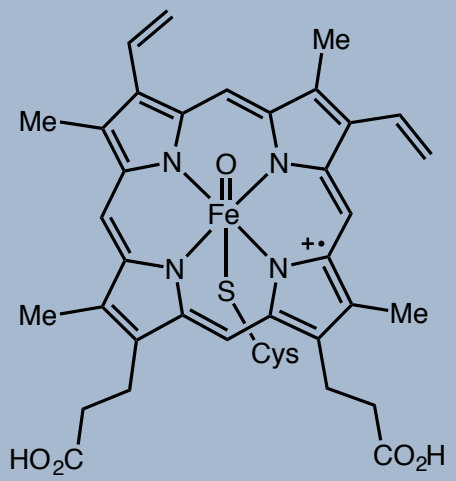
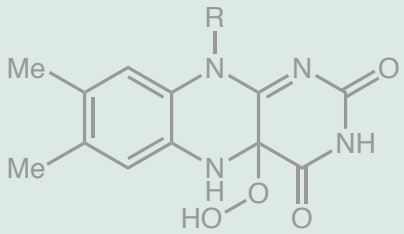


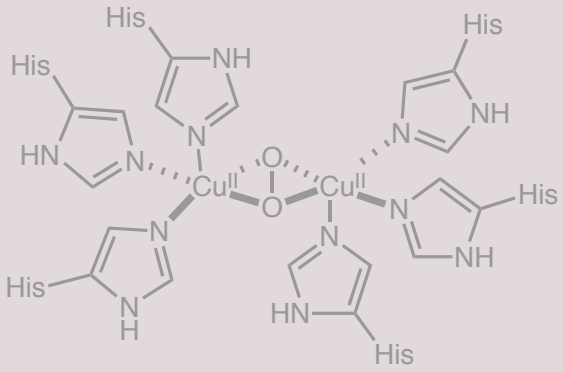
heme based catalysts

Cytochrome P450



peroxoflavin catalysts

Monoamine Oxidases



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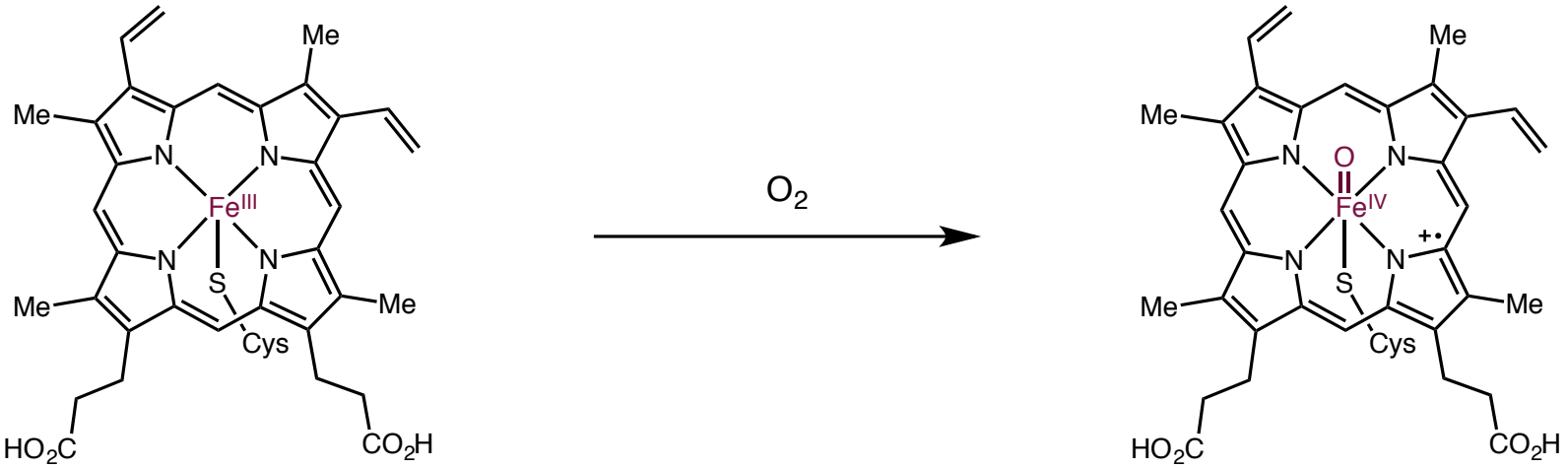
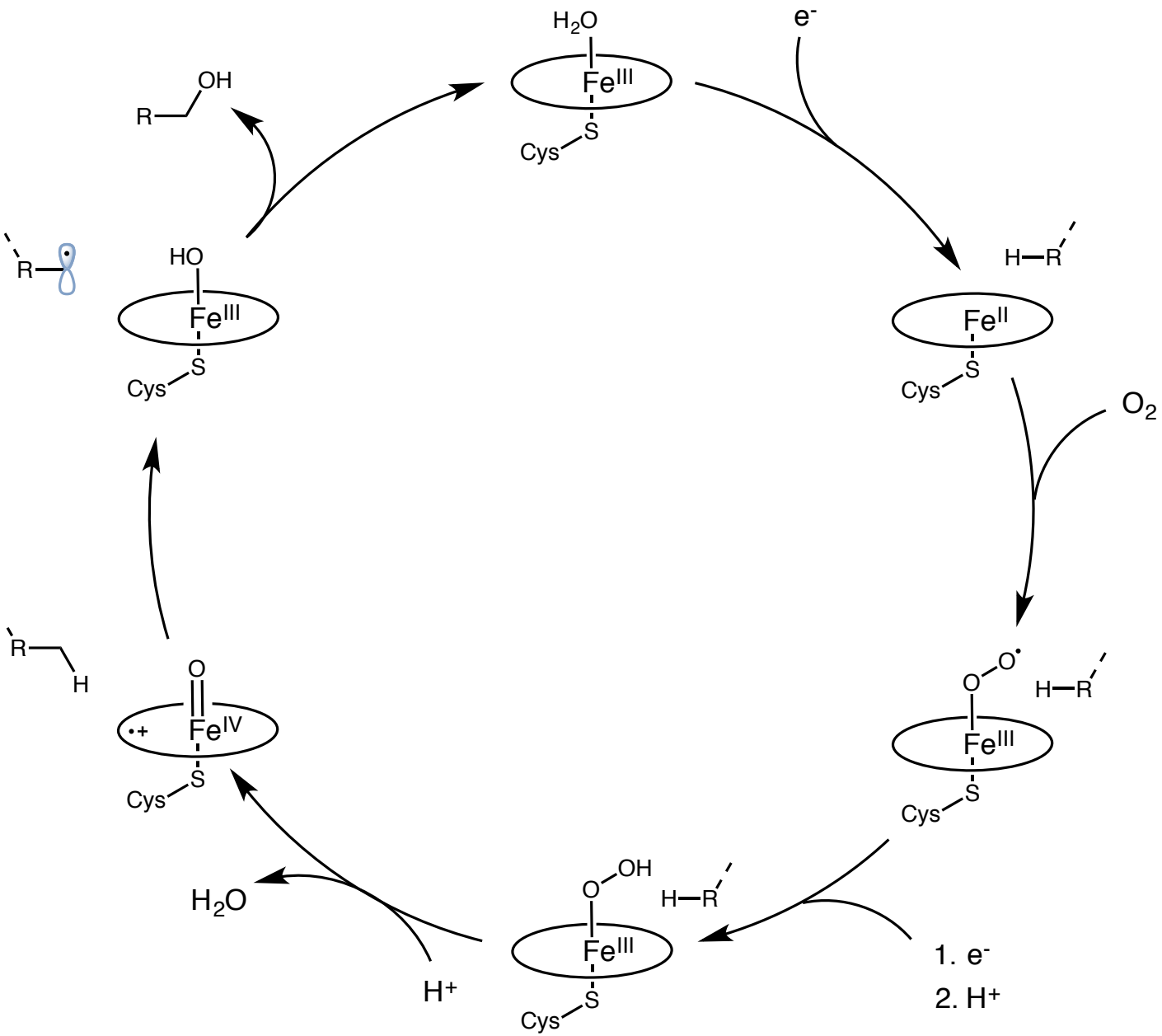
Cytochrome P450 class of enzymes



- 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

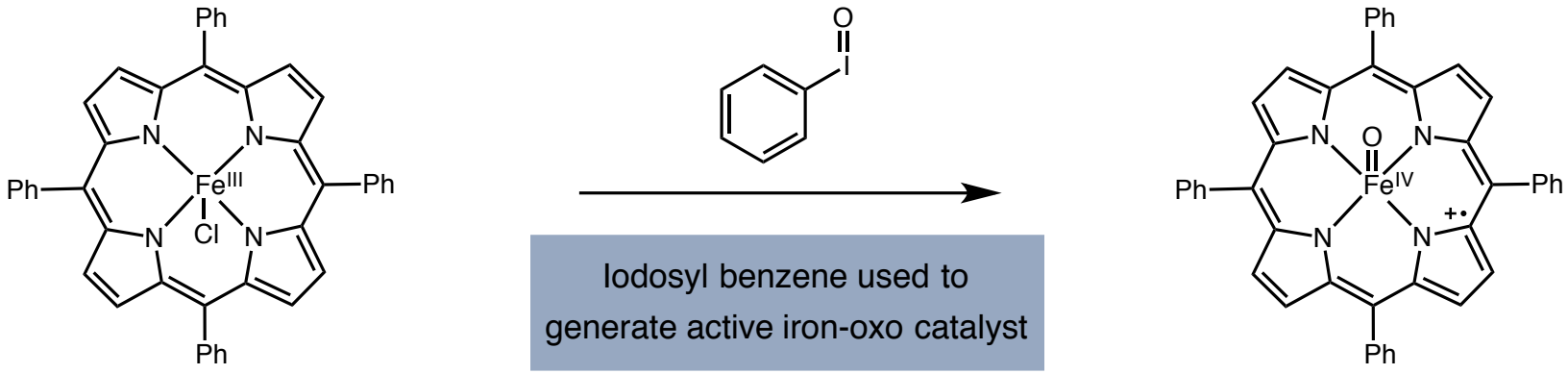
Nam, W. *Acc. Chem. Res.* **2007,** *40*, 522

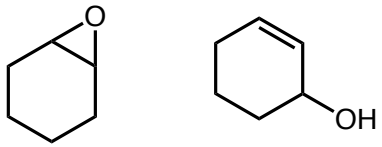
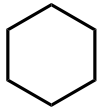
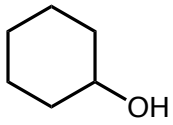
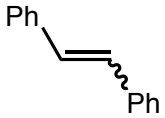
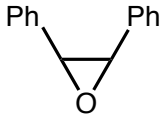
Cytochrome P450 - Mechanism of action



Nam, W. *Acc. Chem. Res.* **2007,** *40*, 522

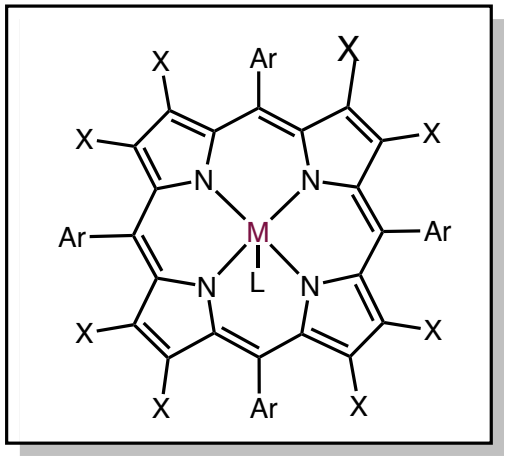
First synthetic reactions by Fe porphyrin complexes



Substrate	products	yield
		Epoxide: 55% Alcohol: 15%
		Cyclohexanol: 8% Cyclohexanone: 0%
		Cis isomer: 82% Trans isomer: trace

Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979,** *101*, 1032

Oxidation reactions utilizing metalloporphyrin catalysts



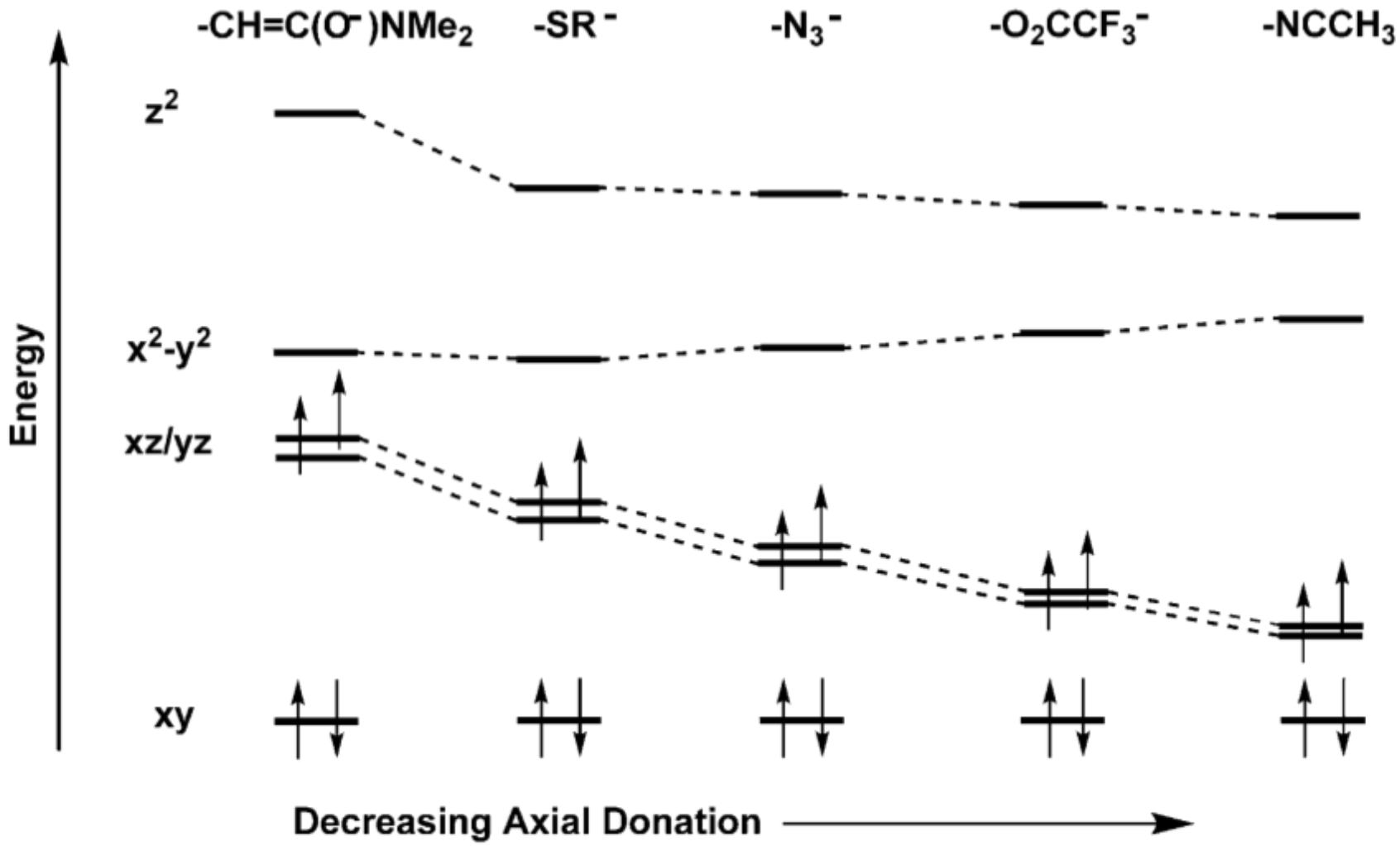
Metals	Axial ligands	Terminal oxidants
Mn	Cl^-	O_2/air
Fe	OH^-	H_2O_2
Co	AcO^-	PhIO
Ru	$CF_3SO_3^-$	NaClO
Os	MeOH	$KHSO_5$

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

Che, C-M.; Lo, V.; Zhou, C-Y.; Huang, J-S. *Chem. Soc. Rev.* **2011,** *40*, 1950

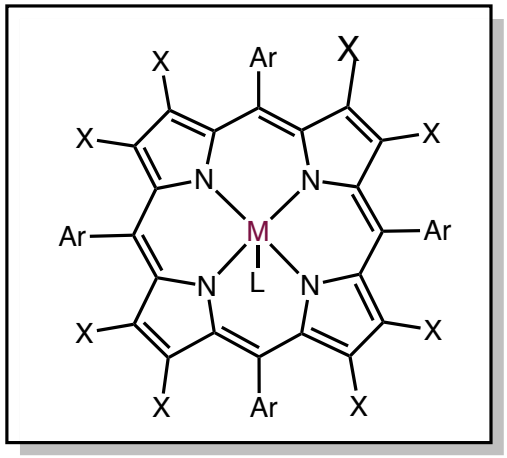
Oxidation reactions utilizing metalloporphyrin catalysts



Effect of axial donation on the energies of the frontier orbitals of iron oxo complexes

Engelmann, X.; Monte-Pérez, I.; Ray, K. *Angew. Chem. Int. Ed.* **2016,** *55*, 7632

Oxidation reactions utilizing metalloporphyrin catalysts



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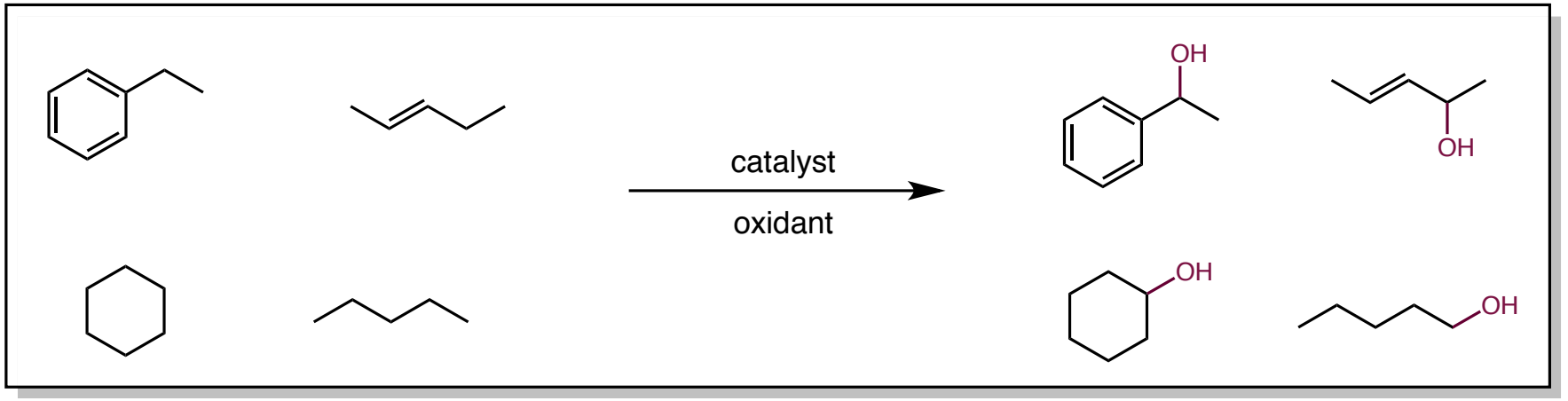
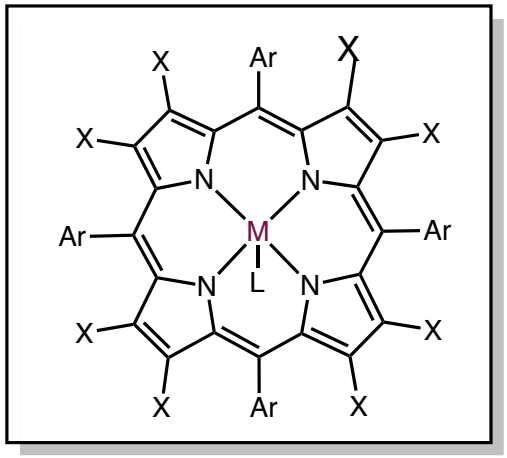


C-H hydrocarbon oxidation has been a major focus of metalloporphyrin chemistry

Che, C-M.; Lo, V.; Zhou, C-Y.; Huang, J-S. *Chem. Soc. Rev.* **2011**, *40*, 1950

Oxidation reactions utilizing metalloporphyrin catalysts



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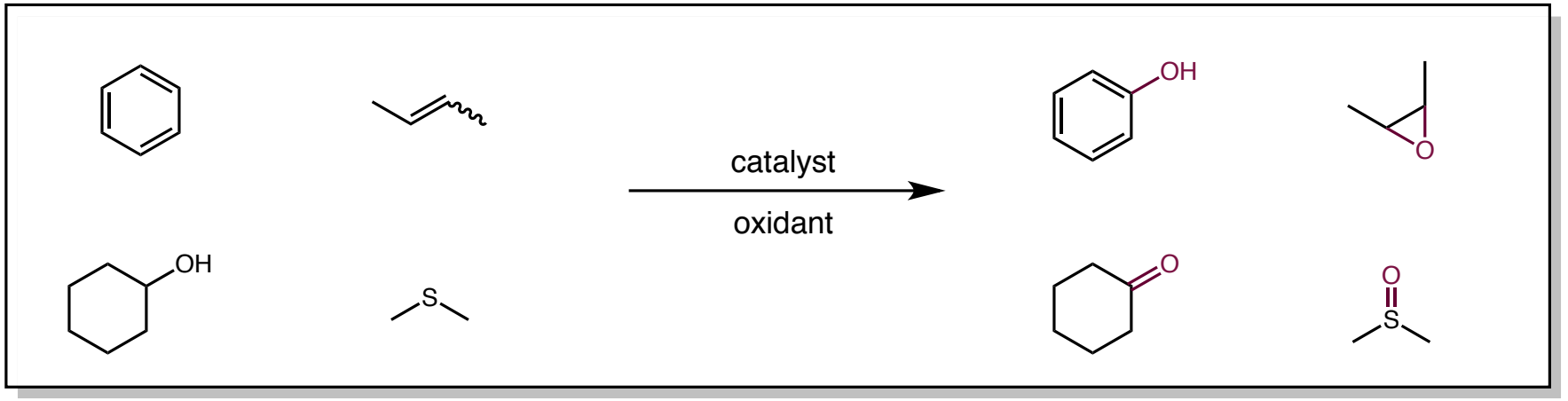
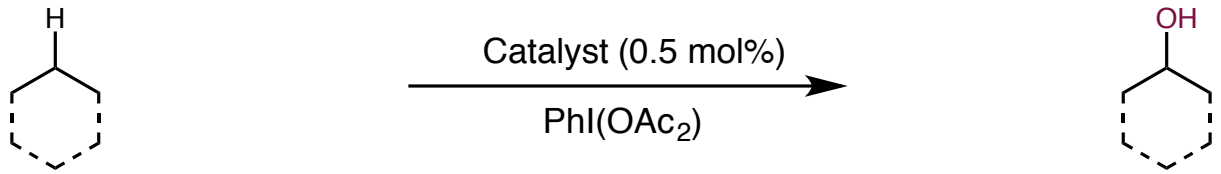


Oxidation of other functionalities such as arenes and olefins has also been explored

Che, C-M.; Huang, J-S. *Chem. Commun.* **2009**, 3996

Hydroxylation of unactivated C–H bonds by Fe porphyrins



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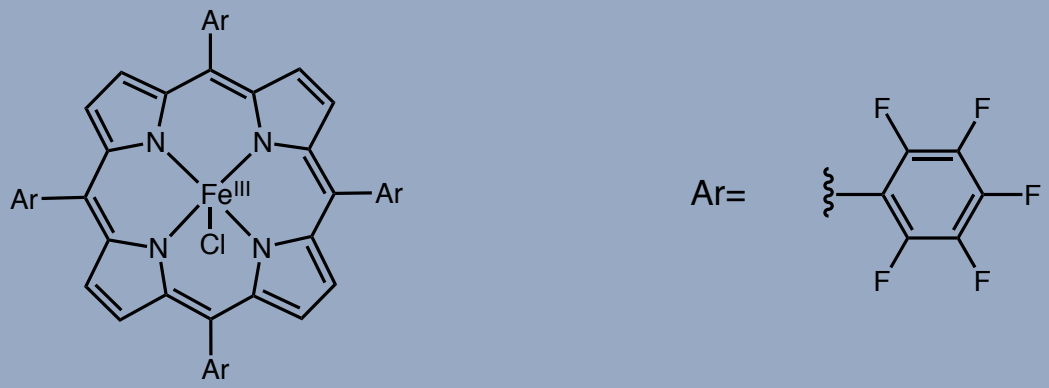
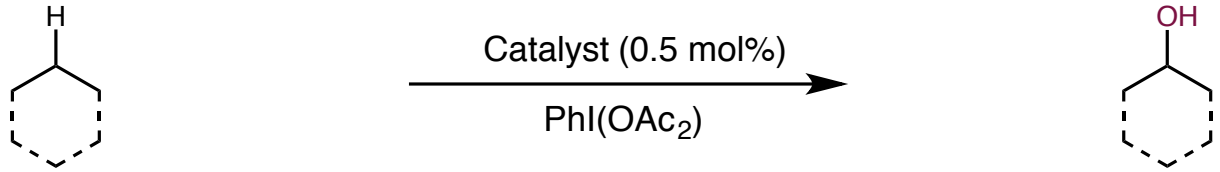
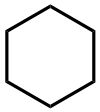
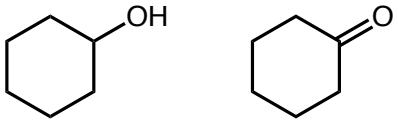
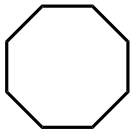
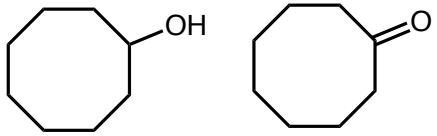
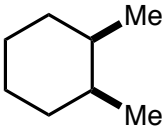
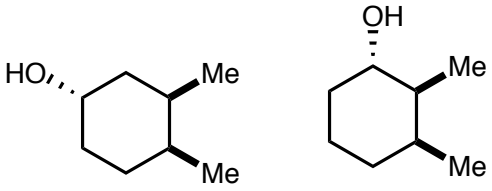
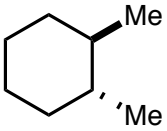
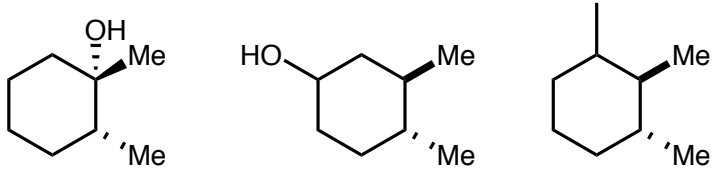


Fluorinated aromatic on porphyrin core protects against oxidative degradation

In, J-H.; Park, S-E.; Song, R.; Nam, W. *Inorg. Chimica. Acta* **2003,** *343*, 373

Hydroxylation of unactivated C–H bonds by Fe porphyrins

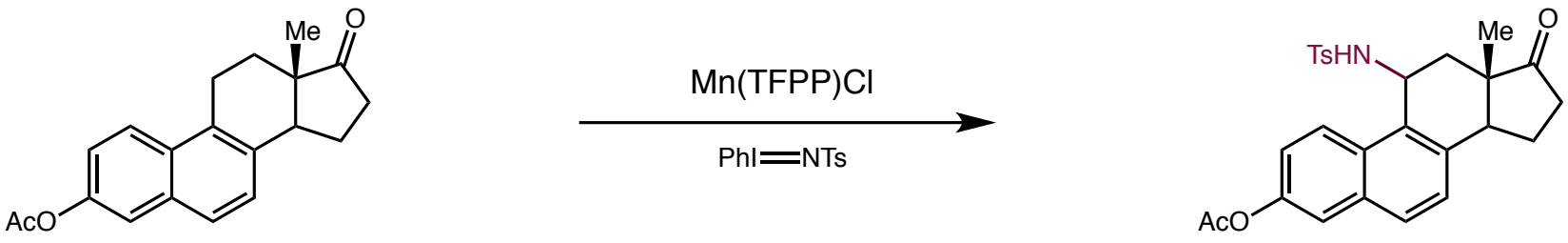


Substrate	products	yield
		cyclohexanol: 37% cyclohexanone: 6%
		cyclooctanol: 47% cyclooctanone: 7%
		Both products: 17%
		1,2 dMe: 10% 2,3 and 3,4 dMe: 17%

In, J-H.; Park, S-E.; Song, R.; Nam, W. *Inorg. Chimica. Acta* **2003,** *343*, 373

Metalloporphyrin catalyzed C–H amination

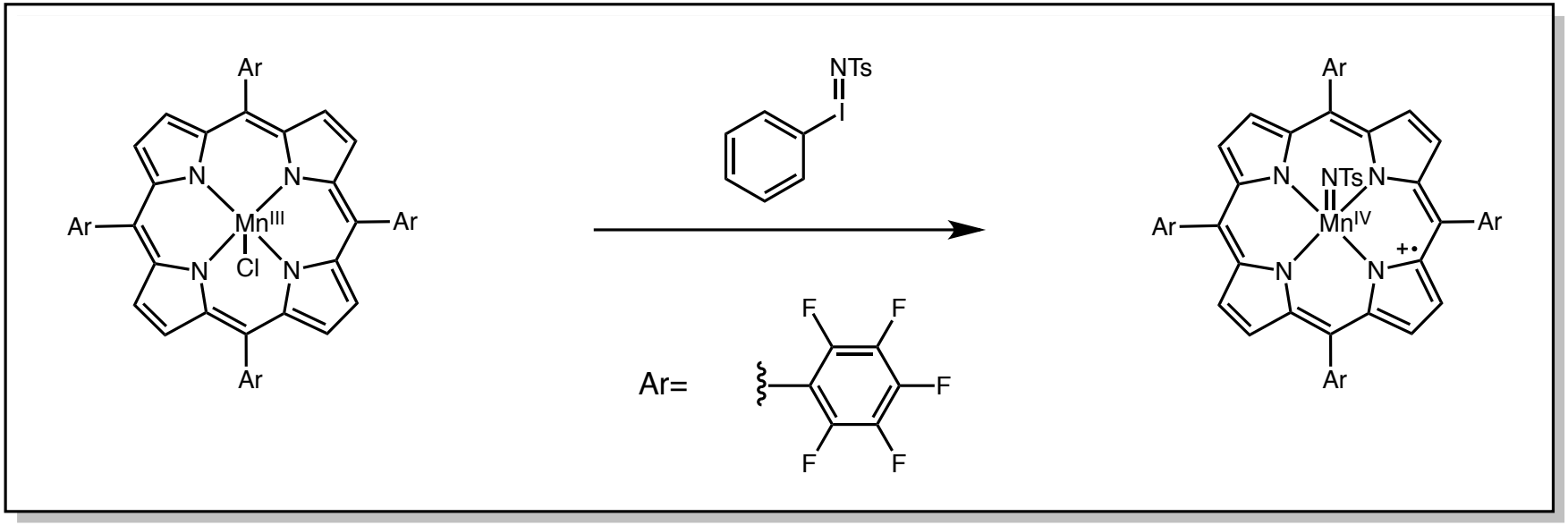
- First example of C-H amination on aromatic stereoid sybstrate



47% yield

approx 40 turnovers

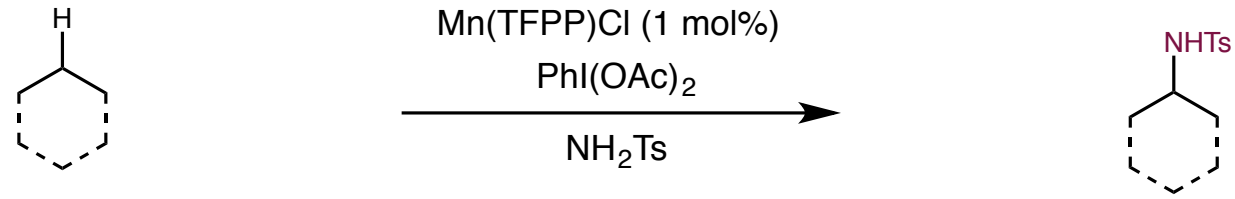
Unlike corresponding oxidation process, no side reaction on aromatic ring

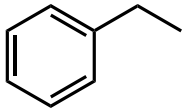
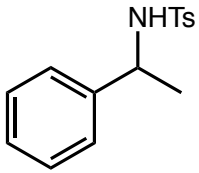
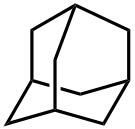
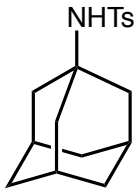
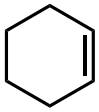
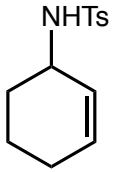
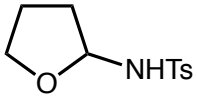


Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531

Metalloporphyrin catalyzed C–H amination

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

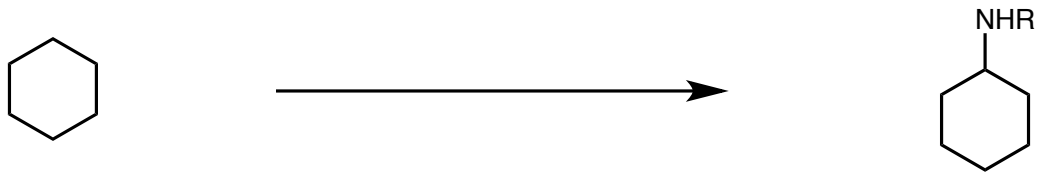


Substrate	product	yield
		81%
		90%
		83%
		85%

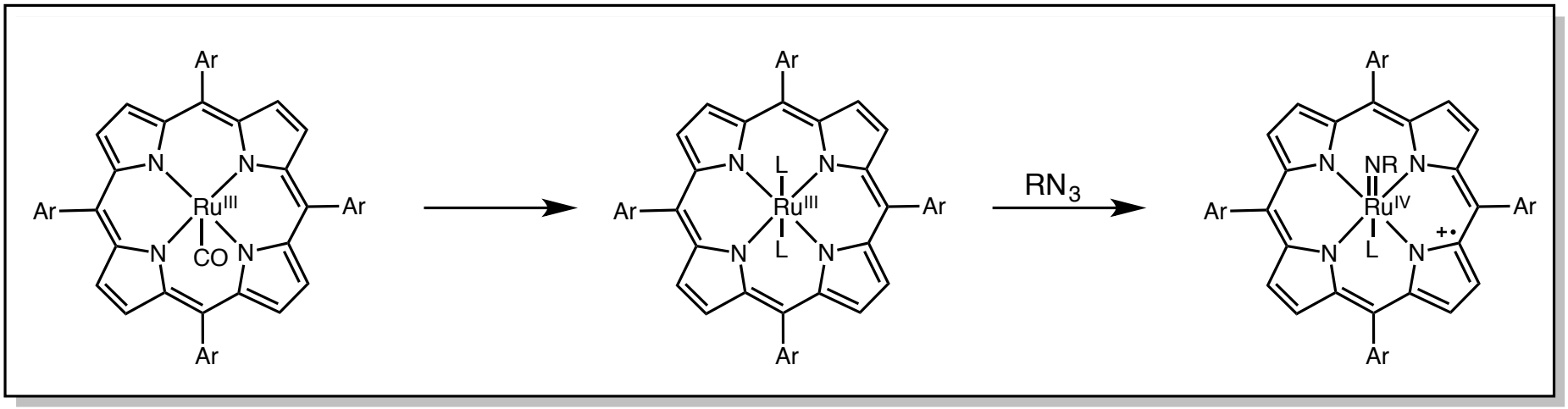
Yu, X-Q.; Huang, J-E.; Zhou, X-G.; Che, C-M. *Org. Lett.* **2000**, 2, 2233

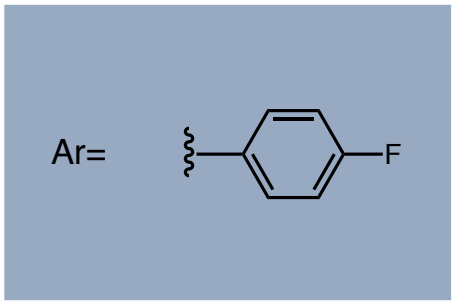
Amination of unactivated C–H bonds

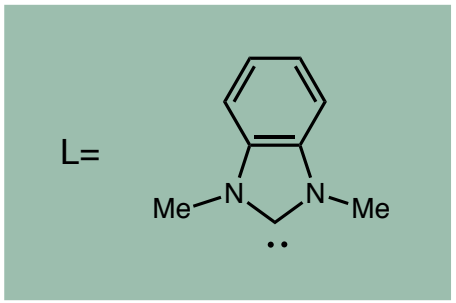
- Metal nitrene catalysts cannot functionalize unactivated hydrocarbons as readily as their oxo analogues



- Use of an axial NHC ligand increases the reactivity of the Ru nitrene and carbene intermediates



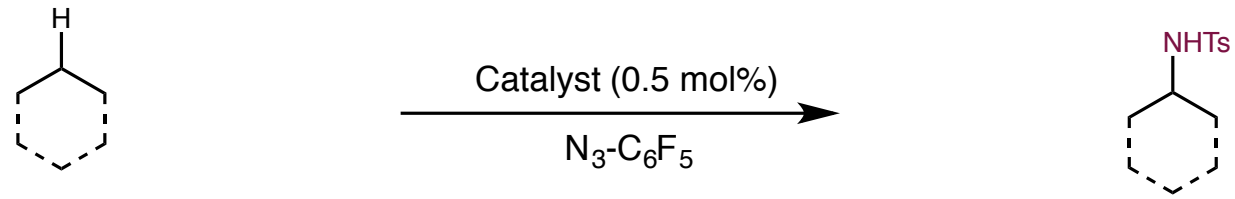


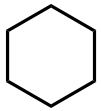
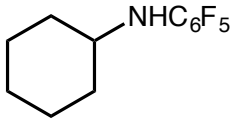
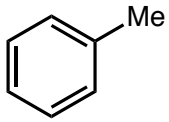
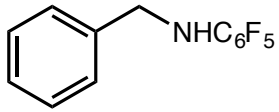
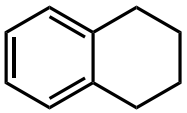
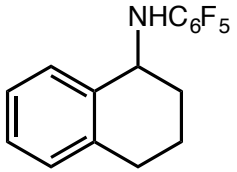
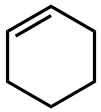
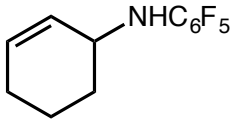


Chan, K-H.; Guan, X.; Lo, V. K-Y.; Che, C-M. *Angew. Chem. Int. Ed.* **2014**, 53, 2982

Metalloporphyrin catalyzed C–H amination

- Amination using aryl azides as nitrogen source

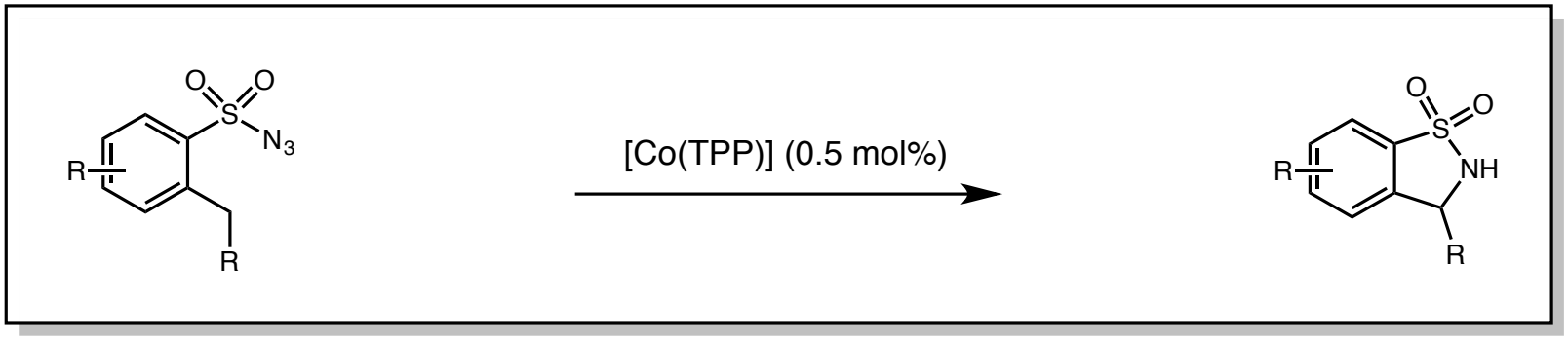


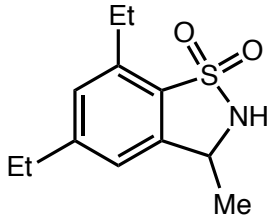
Substrate	product	yield
		90%
		92%
		96%
		96%

Chan, K-H.; Guan, X.; Lo, V. K-Y.; Che, C-M. *Angew. Chem. Int. Ed.* **2014**, 53, 2982

Metalloporphyrin catalyzed C–H amination

- Intramolecular C–H amination with arylsulfonyl azide





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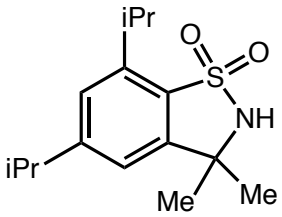

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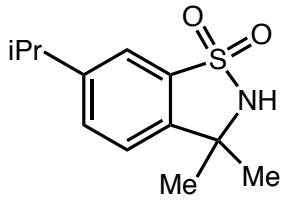

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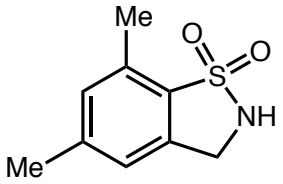

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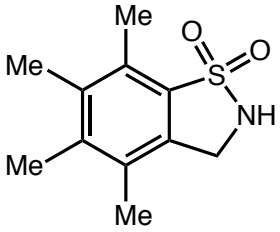

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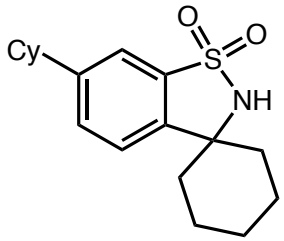

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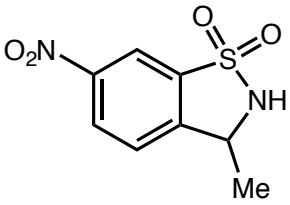

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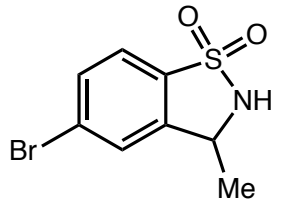
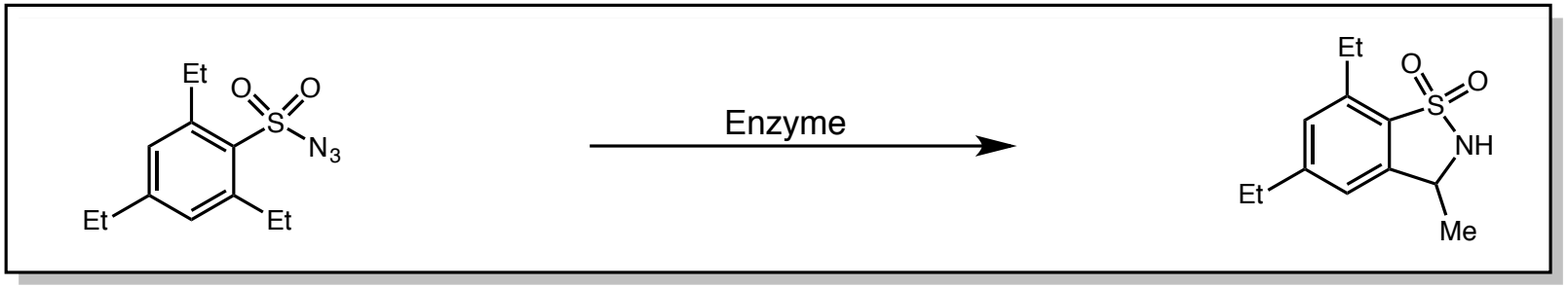


93%

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



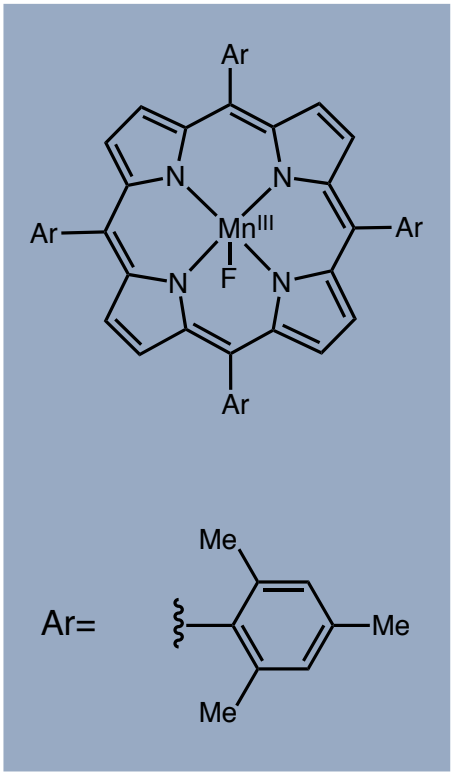
Free Enzyme (0.1 mol%)	Turnovers	%ee
Wild type P450	2.1	nd
Modified P450	383	73

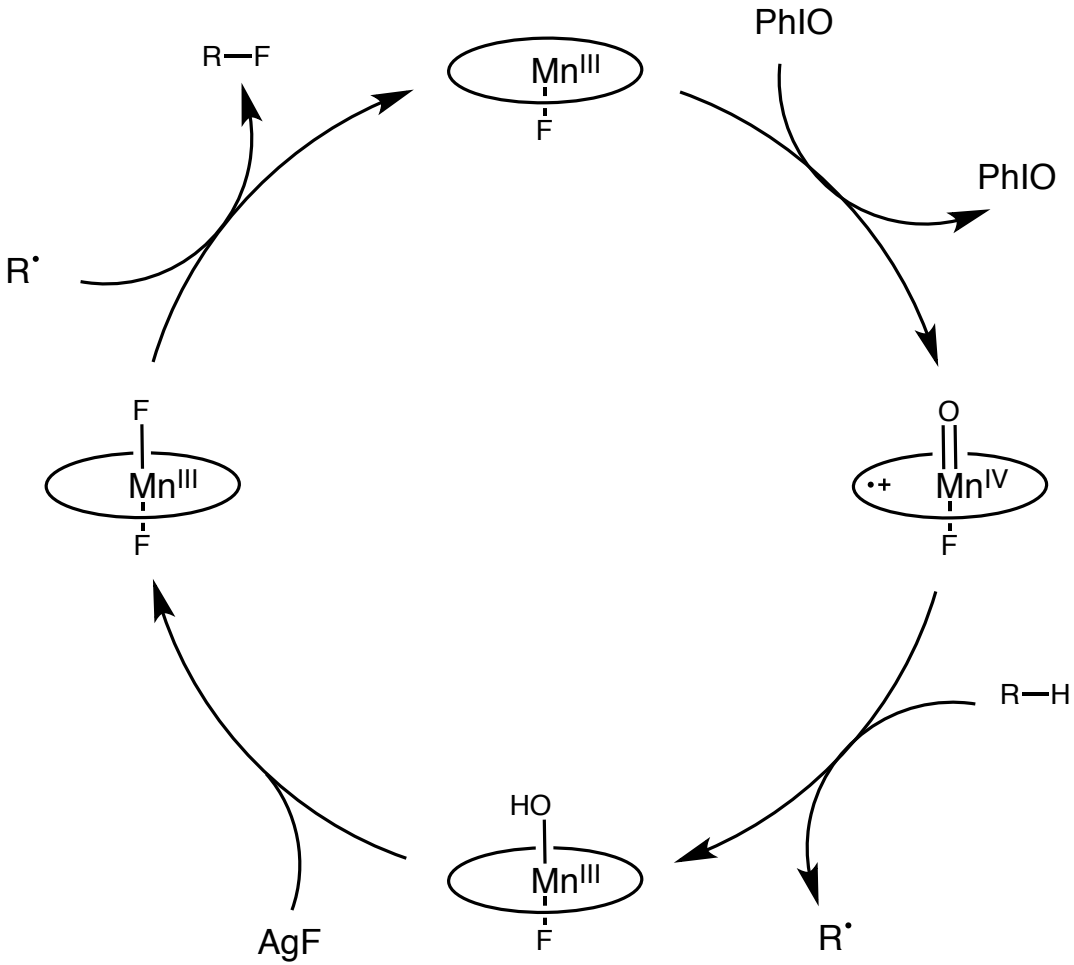
Enzyme (*E. Coli*)	% Yield	Turnovers	%ee
Wild type P450	0.5	5.1	nd
Modified P450	58	430	87

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

McIntosh, J. A.; Coelho, P. S.; Farwell, C. C.; Wang, Z. J.; Lewis, J. C.; Brown, T. R.; Arnold, F. H. *Angew. Chem. Int. Ed.* **2013**, *53*, 9309

C–H halogenation via metalloporphyrin catalysis

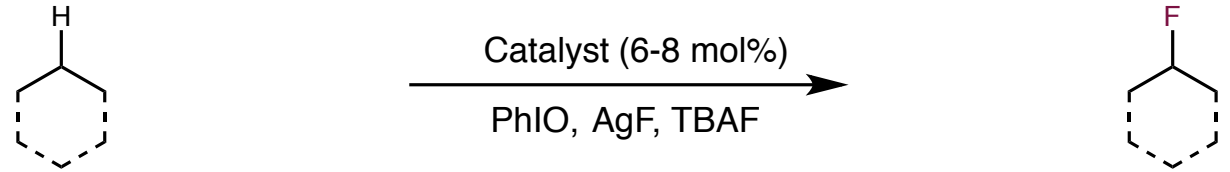


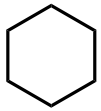
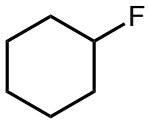
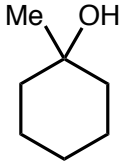
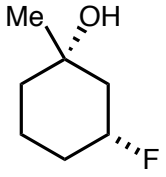
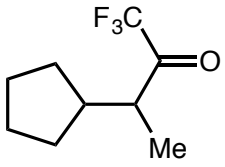
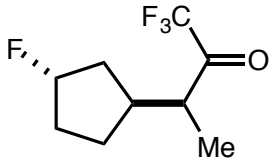


- Use of strongly donating axial ligands stabilizes M-OH species, and slows down radical recombination
- Allows for substitution of fluoride onto metal center

Liu, W.; Huang, X. Y.; Cheng, M. J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, 337, 1322

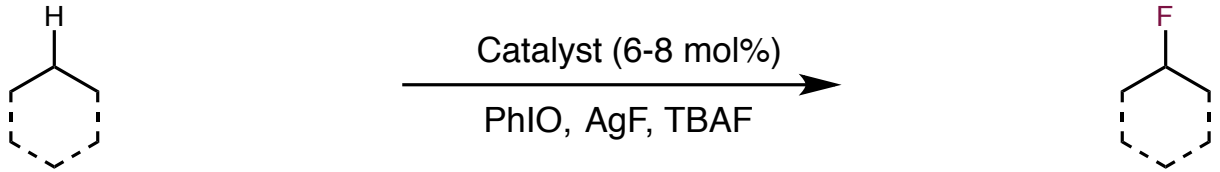
C–H halogenation via metalloporphyrin catalysis

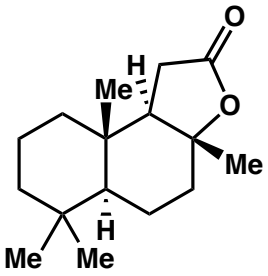
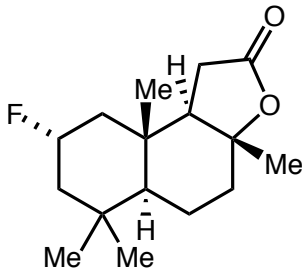
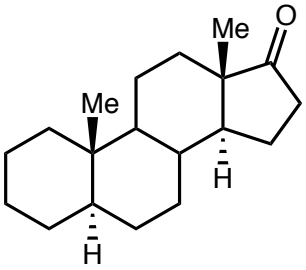
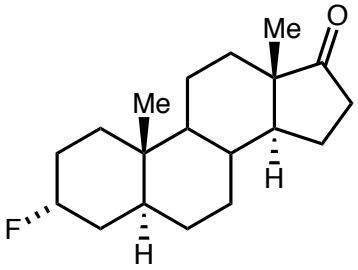


Substrate	Product	Yield
		49%
		44% dr= 8:1
		51% dr=1.5:1

Liu, W.; Huang, X. Y.; Cheng, M. J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, 337, 1322

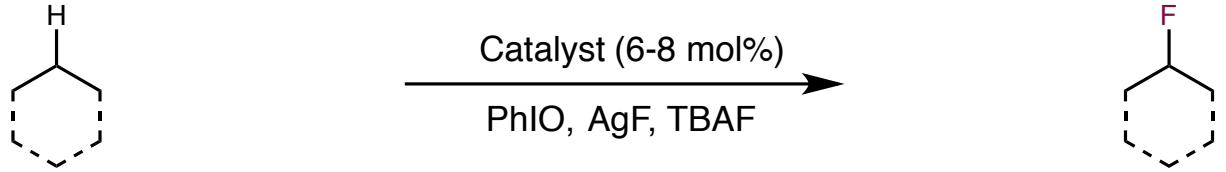
C–H halogenation via metalloporphyrin catalysis

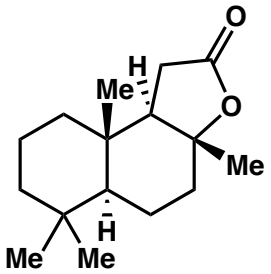
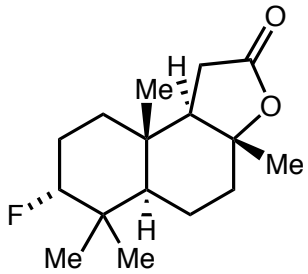
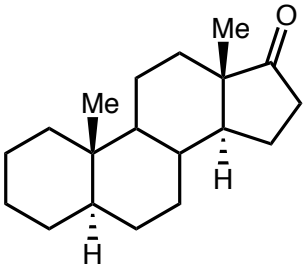
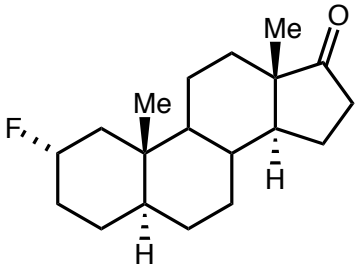


Substrate	Product	Yield
		42% α:β= 3.1
		42% α:β= 4.5

Liu, W.; Huang, X. Y.; Cheng, M. J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, 337, 1322

C–H halogenation via metalloporphyrin catalysis

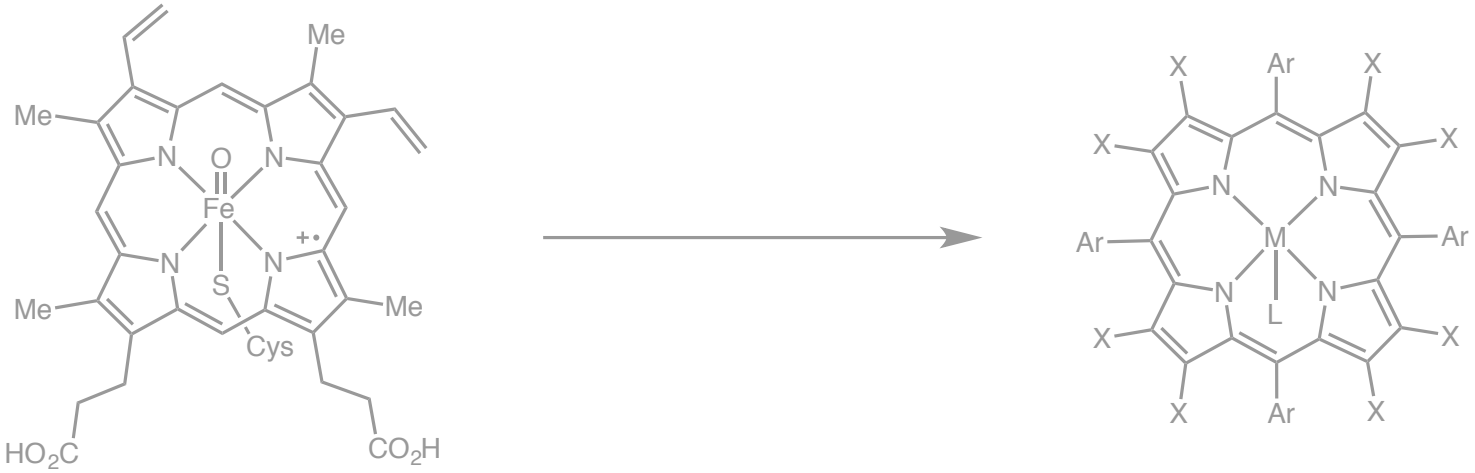


Substrate	Product	Yield
		16% α:β= 7.8
		23% α:β= 6.2

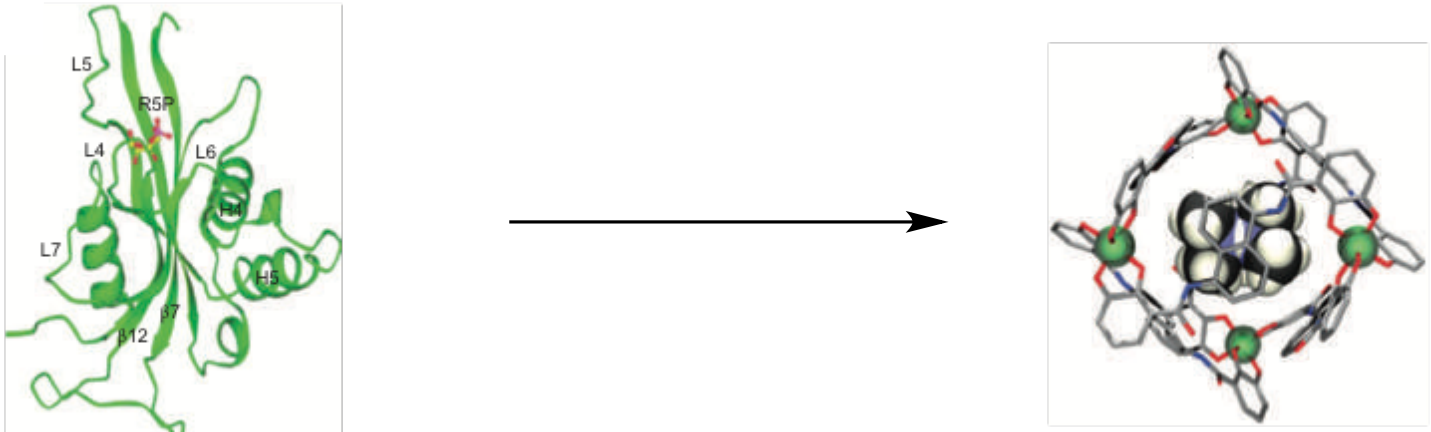
Liu, W.; Huang, X. Y.; Cheng, M. J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012**, 337, 1322

Strategies in Biomimetic Catalysis

Metalloporphyrins - Development of new reactivity from an enzyme cofactor

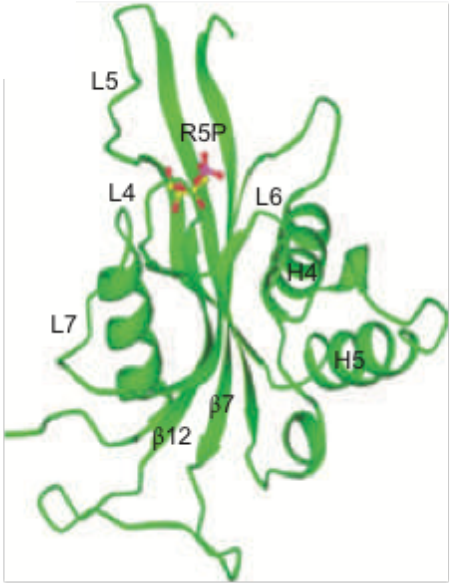


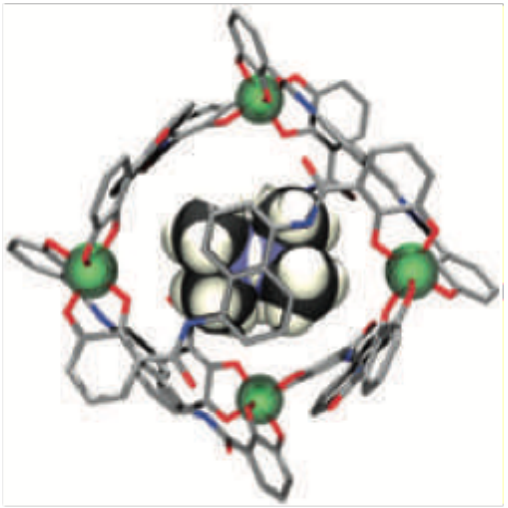
Artificial enzymes - Use of supramolecular structures to mimic substrate binding



Supramolecular complexes as enzyme mimics

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





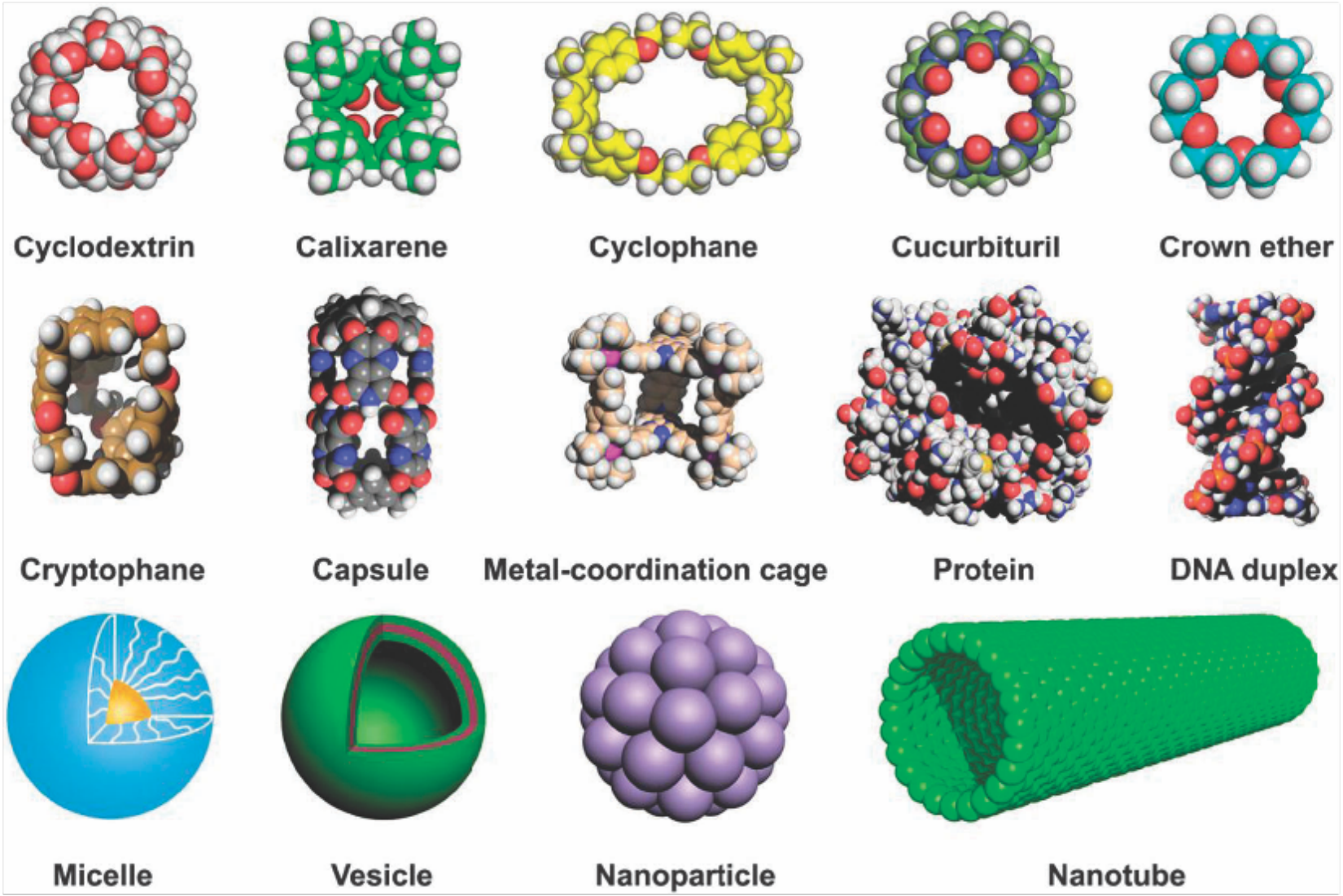
- Structures contain well defined binding pockets capable of stabilizing reactive intermediates
- Artificial enzymes display a range of binding modes, including H bonding, π–π Interactions, etc
- Reactions isolated from the surrounding environment, allowing for enzyme-like selectivity

Raynal, M.; Ballester, P. Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014,** *43*, 1734

Marchetti, L.; Levine, M. *ACS Catal.* **2011,** *1*, 1090

Supramolecular complexes as enzyme mimics

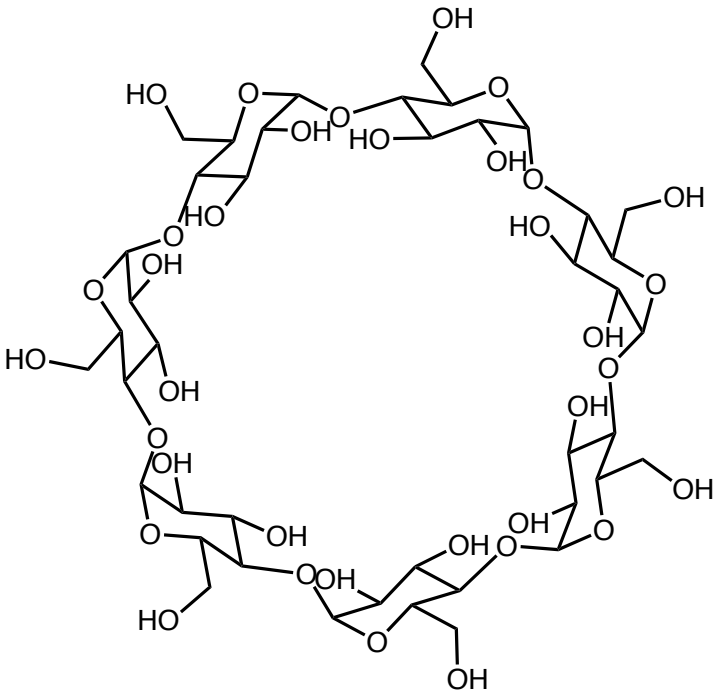
- A range of scaffolds have been utilized as host structures for supramolecular enzyme models



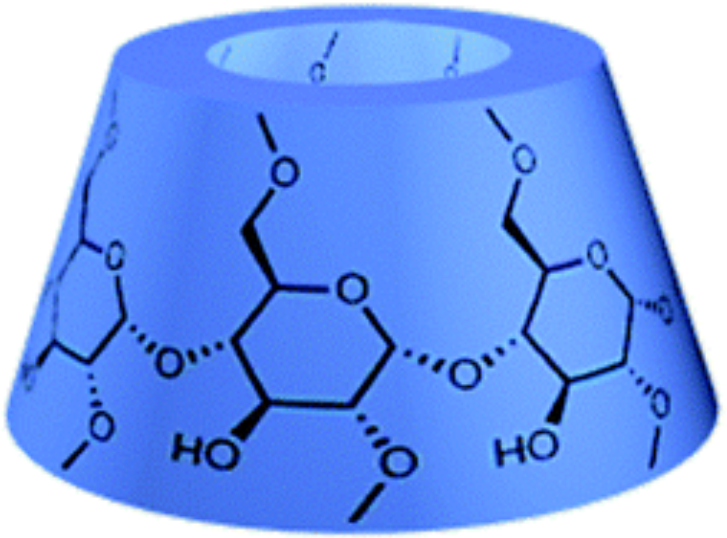
Dong, Z.; Luo, Q.; Liu, J. *Chem. Soc. Rev.* **2012**, *41*, 7890

Cyclodextrins as a scaffold for substrate binding

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



β-Cyclodextrin

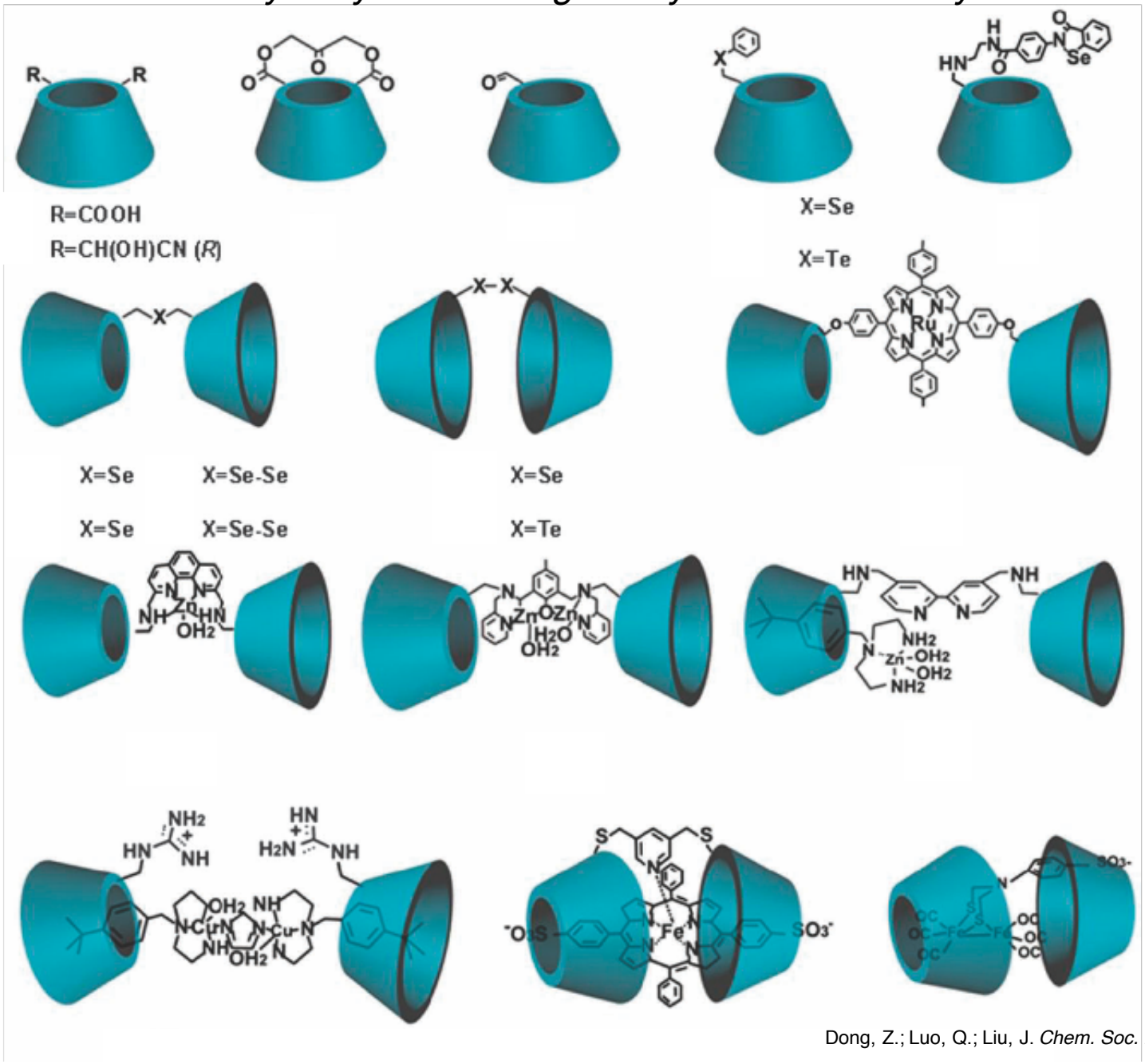


Conical structure

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

Dong, Z.; Luo, Q.; Liu, J. *Chem. Soc. Rev.* **2012**, *41*, 7890

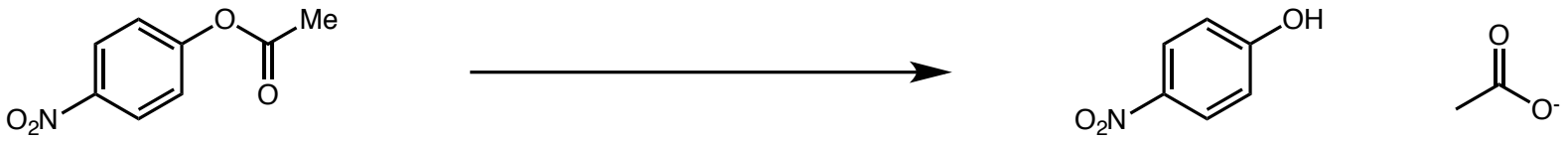
Catalytic systems using the cyclodextrin moiety

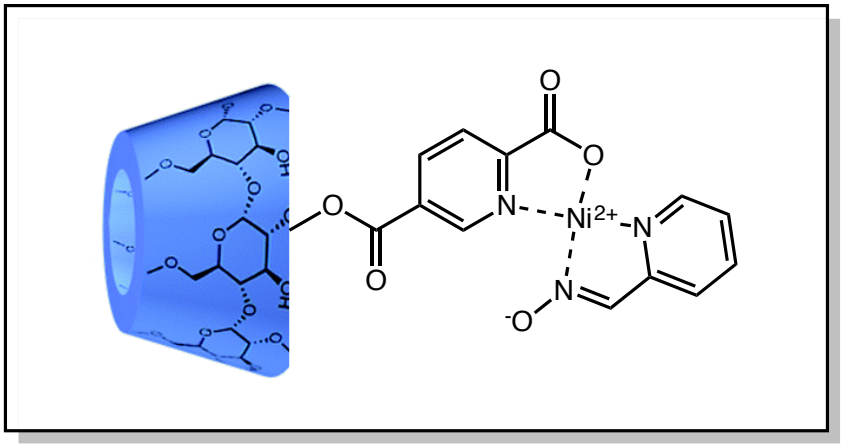


Dong, Z.; Luo, Q.; Liu, J. *Chem. Soc. Rev.* **2012**, *41*, 7890

Initial report of an enzyme mimic

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



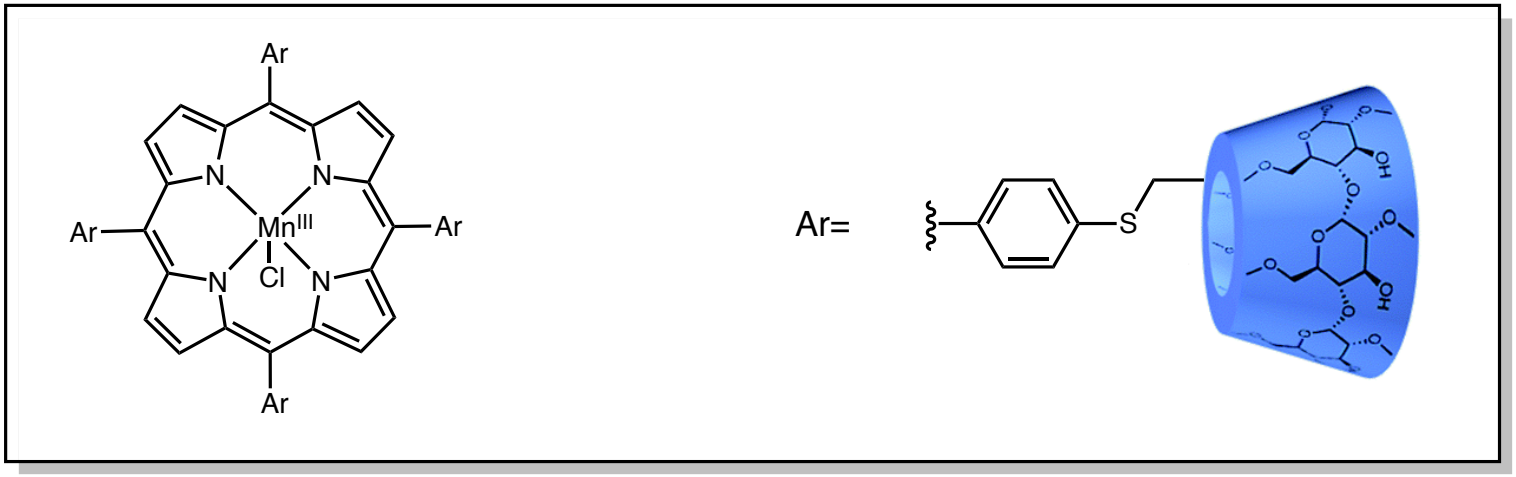


- Catalyst consists of metal complex covalently linked to β-cyclodextrin scaffold
- Hydrolysis shows a 4x rate enhancement compared to the free metal complex alone
- Rate acceleration attributed to substrate binding within hydrophobic cyclodextrin pocket

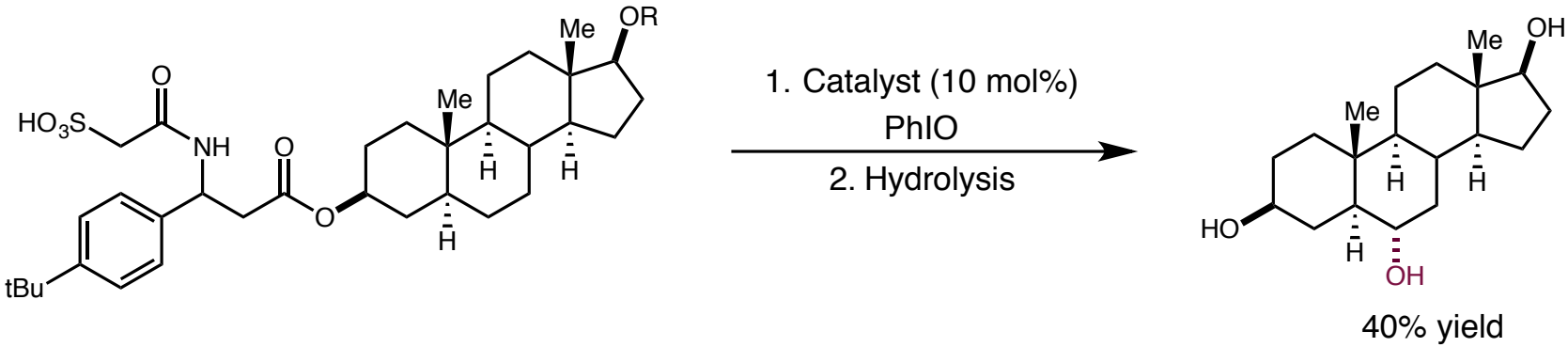
Breslow, R.; Overman, L. E. *J. Am. Chem. Soc.* **1970**, *92*, 1075

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



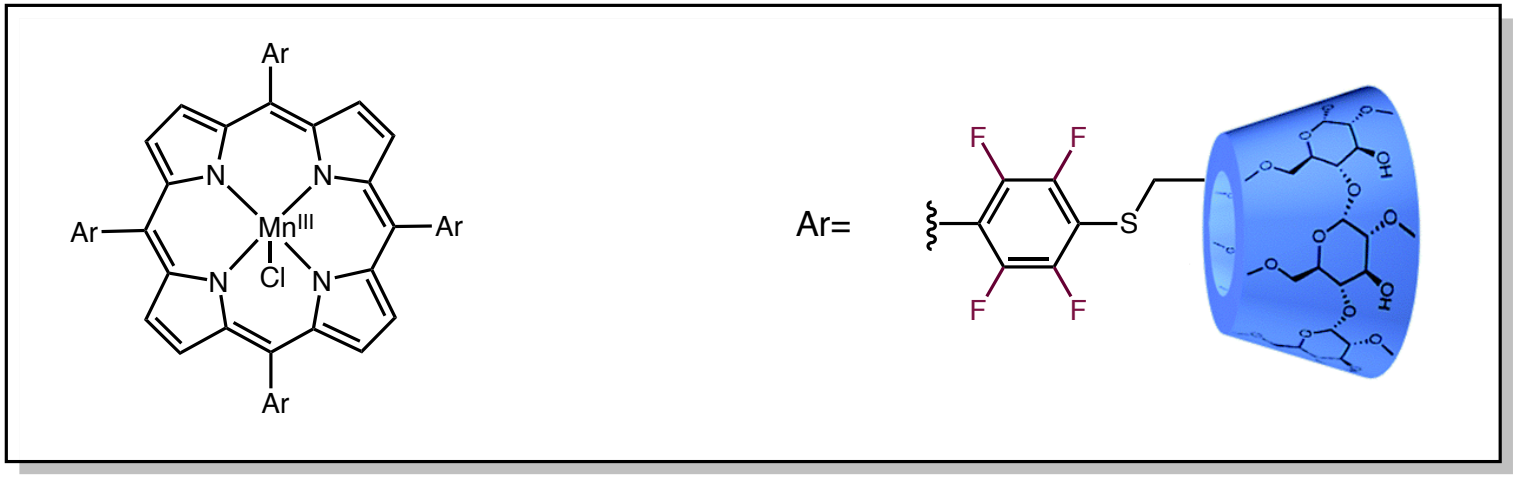
40% yield

- 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

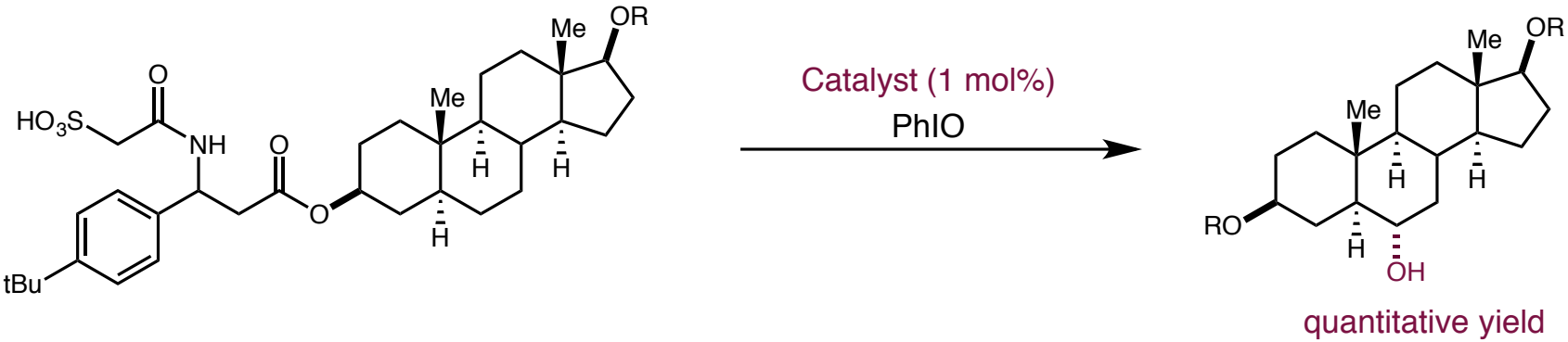
Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *92*, 1075

Artificial P450 enzyme for Stereoid Hydroxylation

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



Second generation catalyst contains fluorinated aromatic to prevent oxidative degradation



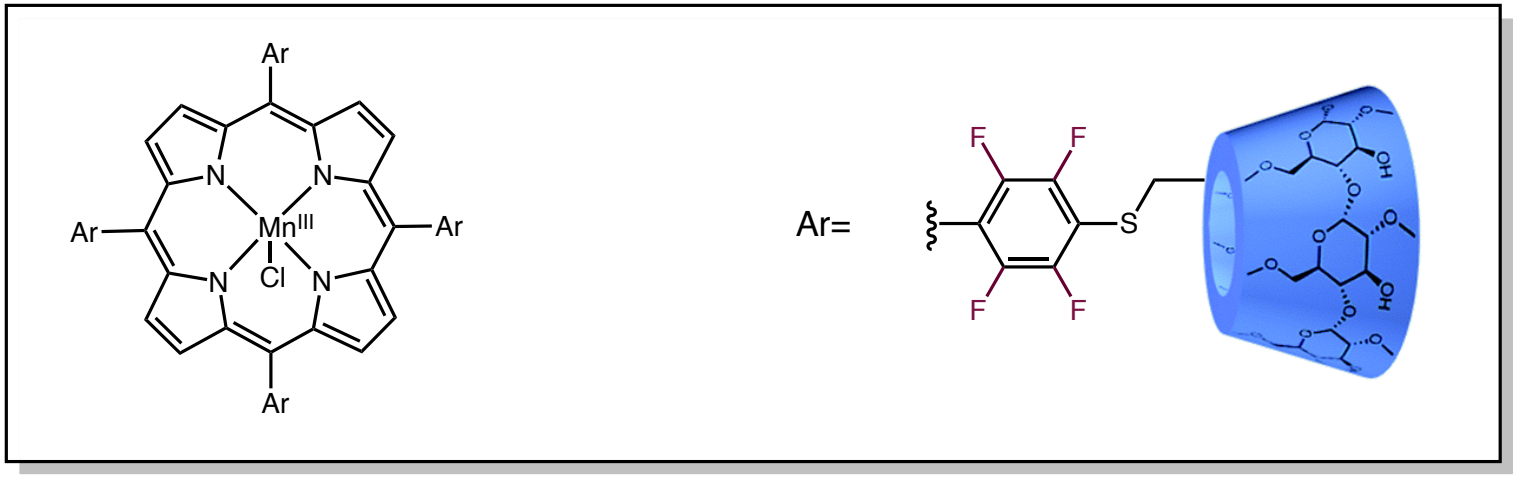
quantitative yield

- 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

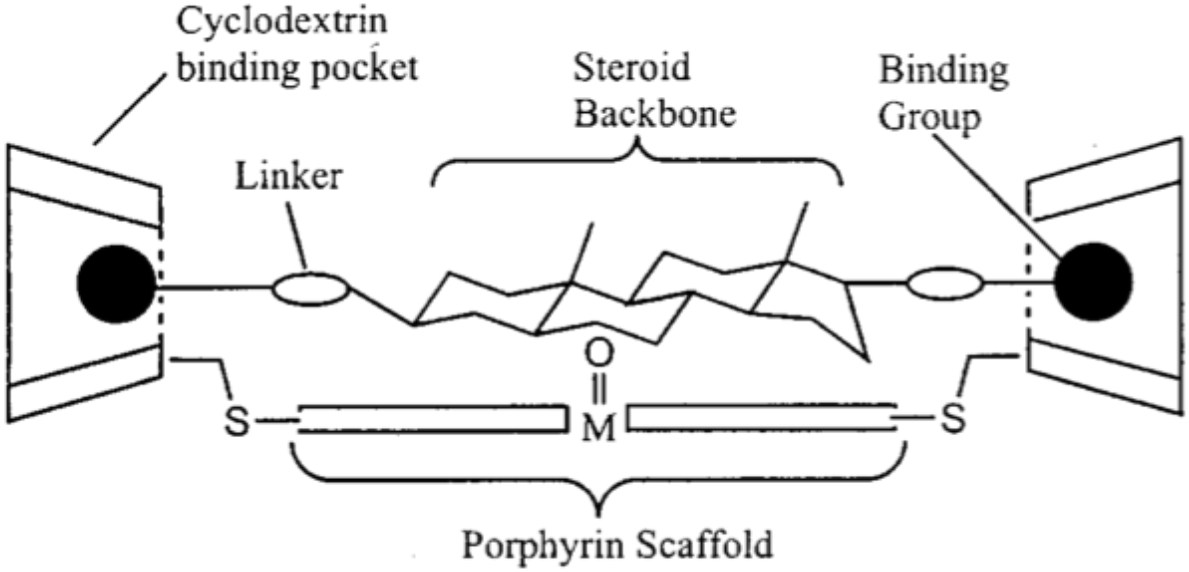
Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057

Artificial P450 enzyme for Stereoid Hydroxylation

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



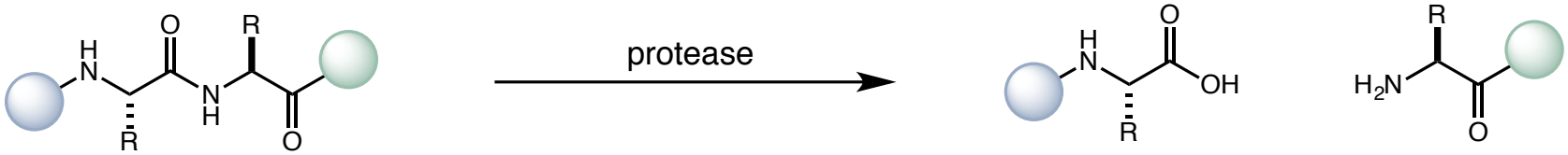
Second generation catalyst contains fluorinated aromatic to prevent oxidative degradation



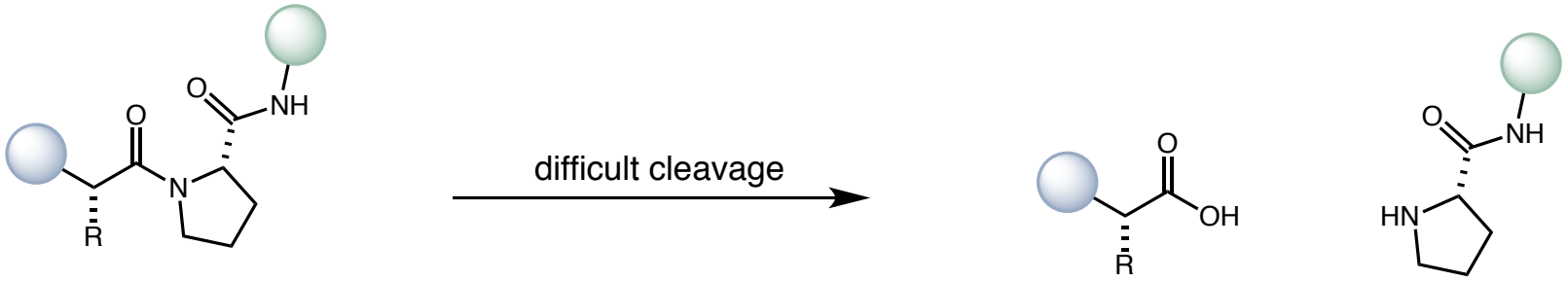
Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057

Supramolecular enzyme mimic as an artificial peptidase

- Peptide bond cleavage is a major biological process, vatalyzed by a number of enzymes



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

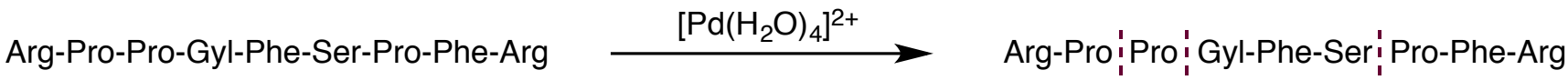


- Stable Internal X-Pro linkages often used to protect proteins against degradation
- Few enzyme class and synthetic methods known to cleave them specifically

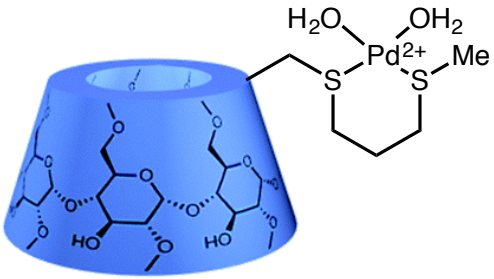
Milovic, N. M.; Badjic, J. D.; Kostic, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 696

Supramolecular enzyme mimic as an artificial peptidase

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



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



Cyclodextrin moiety intended to bind aromatic side chains

Thus specific to X-Pro-Ar sequences (Phe, Tyr and Trp)

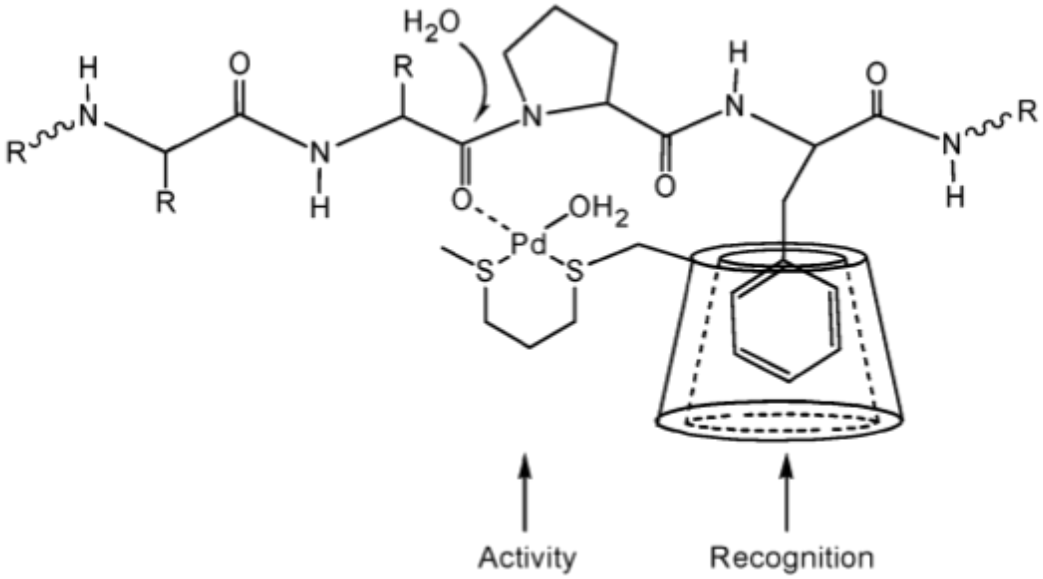
Milovic, N. M.; Badjic, J. D.; Kostic, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 696

Supramolecular enzyme mimic as an artificial peptidase

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

Arg-Pro-Pro-Gyl-Phe-Ser-Pro-Phe-Arg —(Pd catalyst)→ Arg-Pro-Pro-Gyl-Phe-Ser | Pro-Phe-Arg

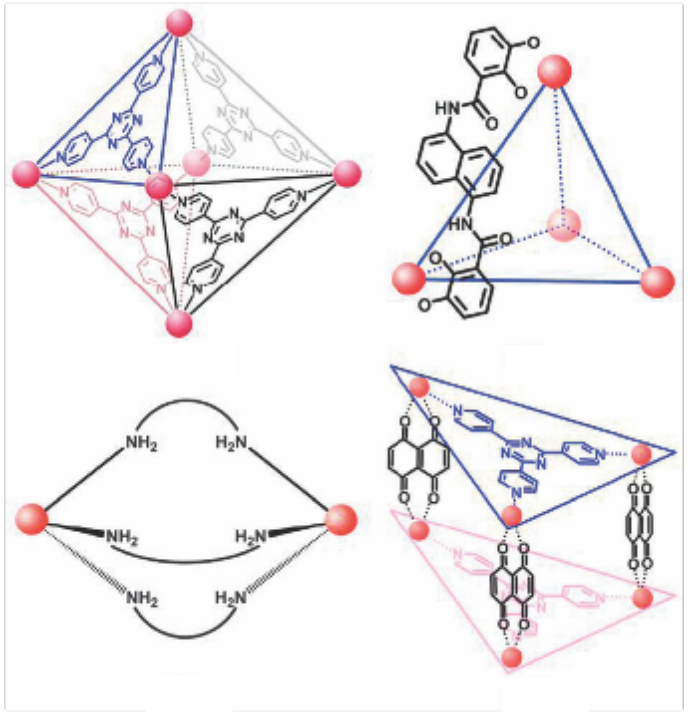
- With modified catalyst structure, selective peptide cleavage observed adjacent to Phe residue
- Selectivity attributed to binding of aromatic ring inside cyclodextrin hydrophobic cavity

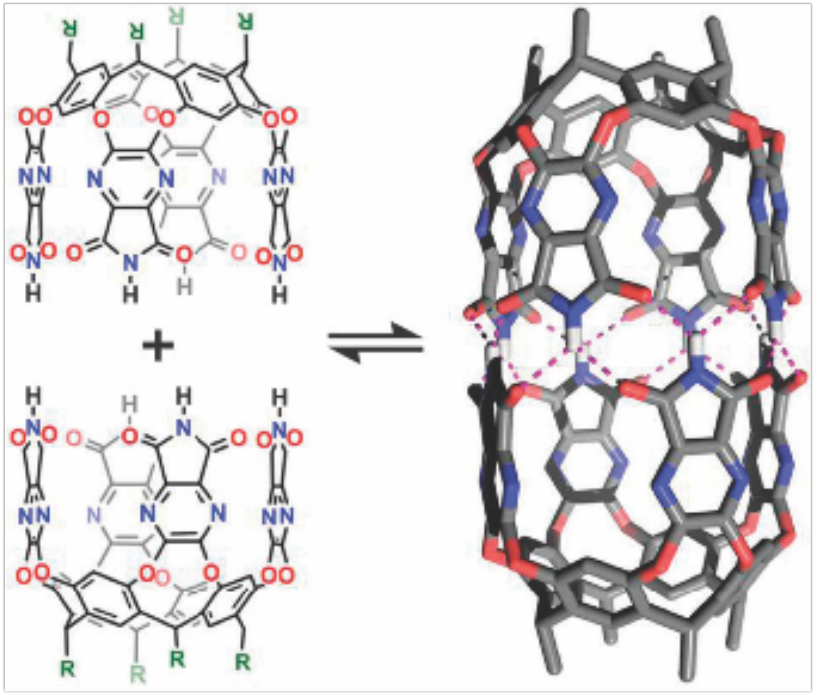


Milovic, N. M.; Badjic, J. D.; Kostic, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 696

Self-assembled "Container" molecules

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



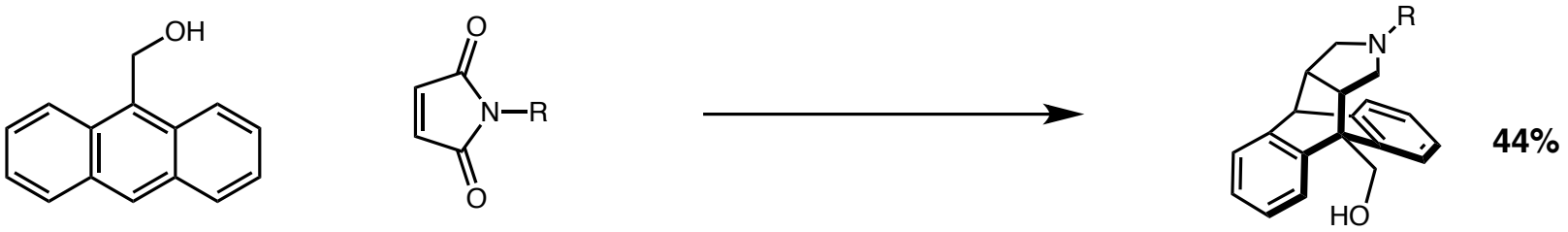


- Container molecules made up of non-covalent linkages, eg. H-bonding, metal coordination, etc.
- Well defined binding pocket, but present some flexibility when incorporating guest complexes
- Easily prepared by combining components which assemble through complementary interactions

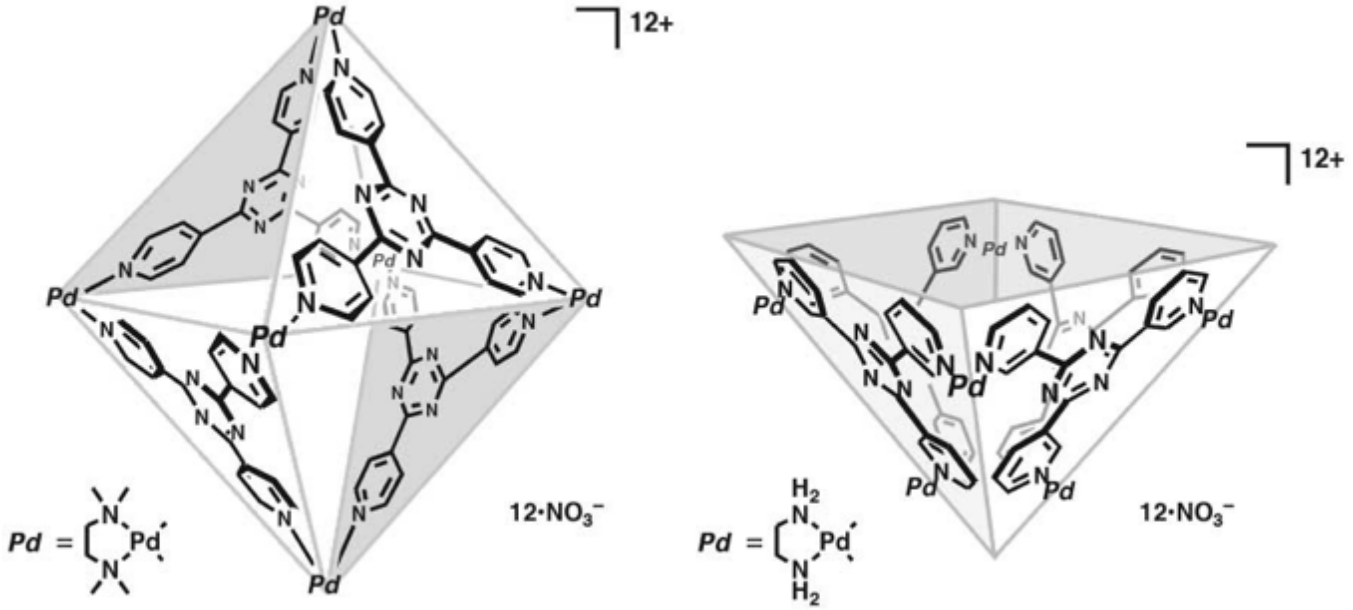
Dong, Z.; Luo, Q.; Liu, J. *Chem. Soc. Rev.* **2012**, *41*, 7890

Self-assembled "Container" molecules

- Directing regioselectivity of Diels-Alder reaction by M_6L_4 molecular cage



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

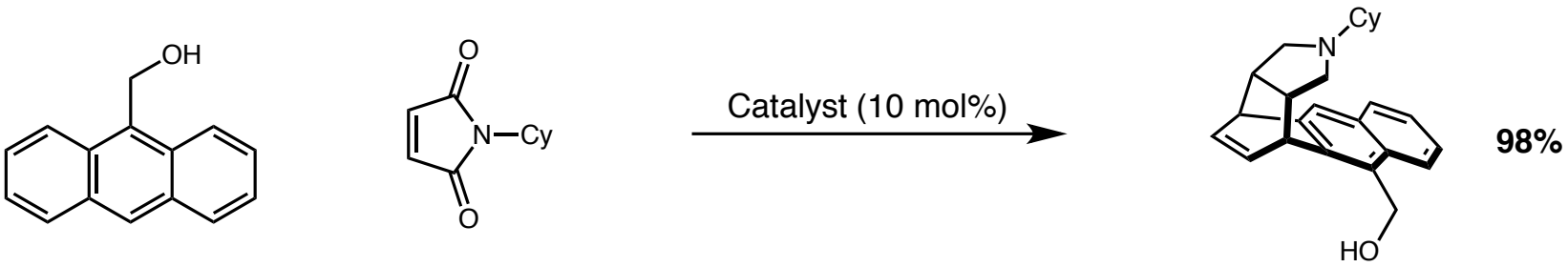


Proposed to use host complexes to override the selectivity of uncatalyzed D-A reaction

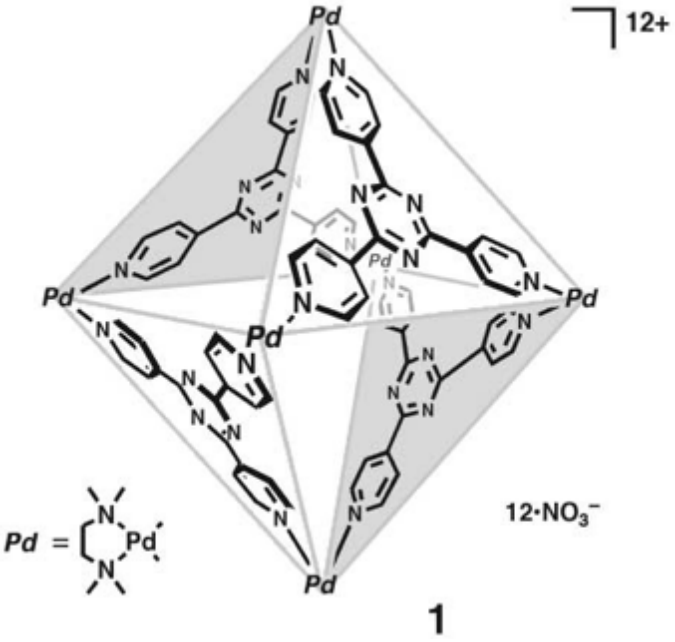
Yoshizawa, M.; Tamura, M.; Fujita, M. *Science,* **2006**, *312*, 251

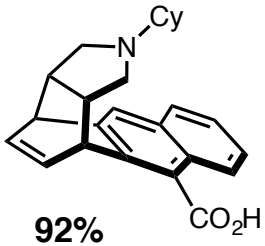
Self-assembled "Container" molecules

- Directing regioselectivity of Diels-Alder reaction in molecular hosts

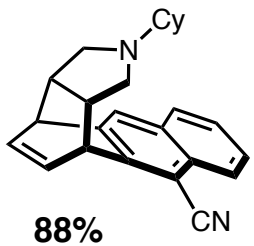


Use of supramolacular catalyst found to override selectivity in favor of terminal D-A adduct

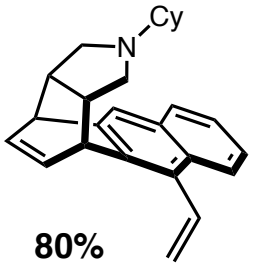




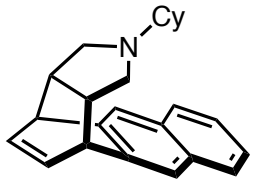
92%



88%



80%



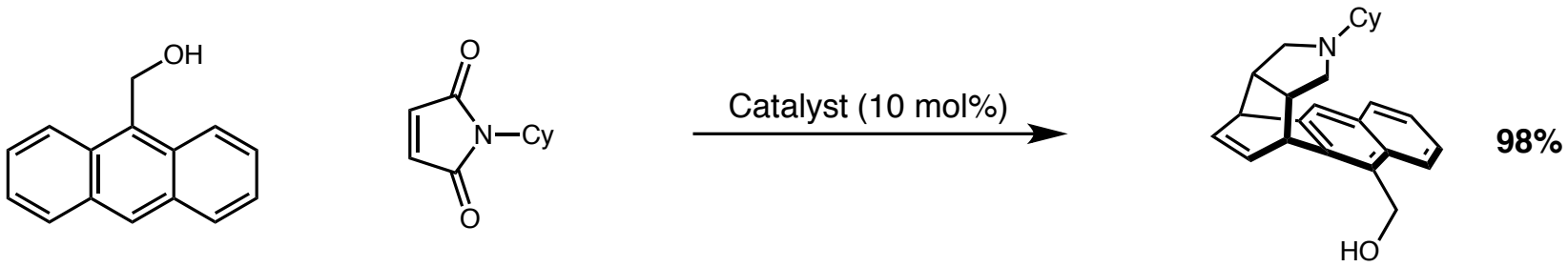
55%

Substrates without bulky group on phthalamide found to give bridging product

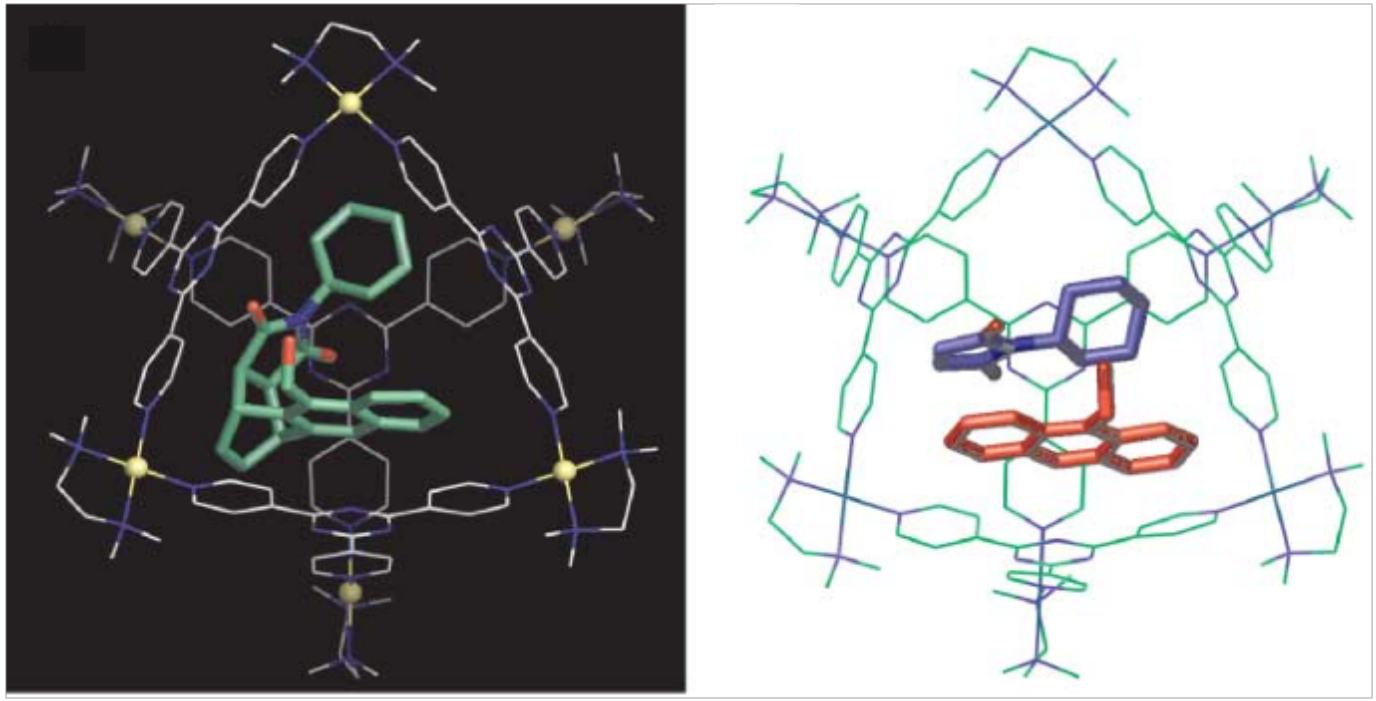
Yoshizawa, M.; Tamura, M.; Fujita, M. *Science,* **2006**, *312*, 251

Self-assembled "Container" molecules

- Directing regioselectivity of Diels-Alder reaction in molecular hosts



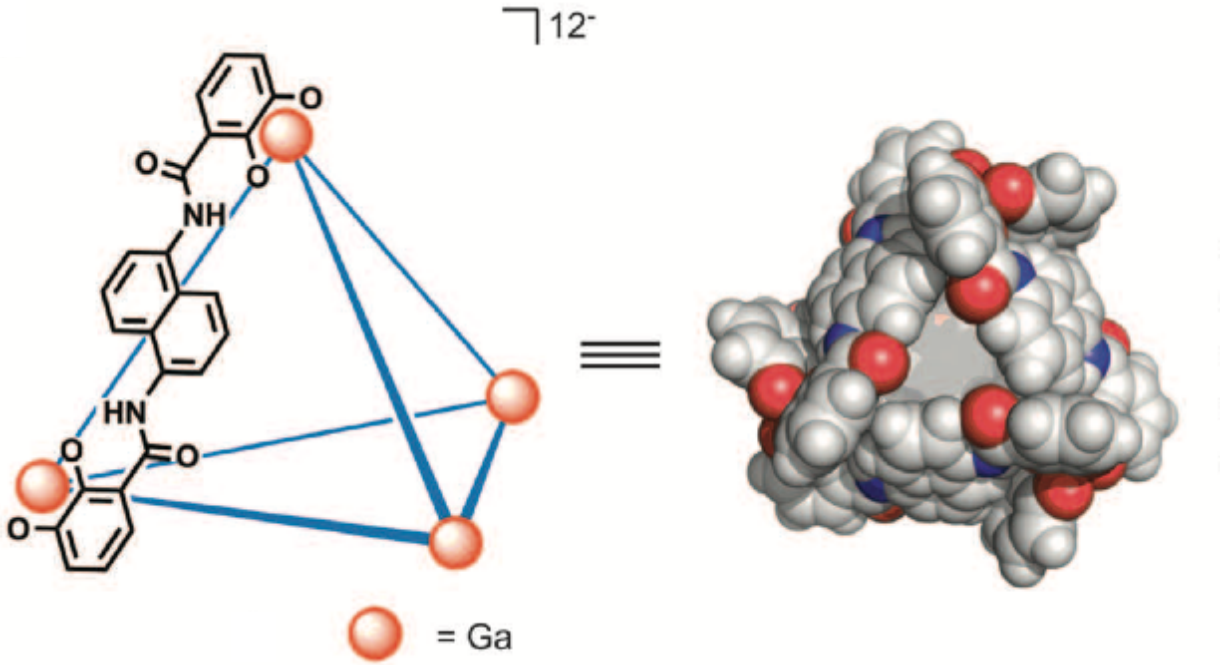
Regioselectivity explained via fixed orientation of guest molecules prior to reaction



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

Yoshizawa, M.; Tamura, M.; Fujita, M. *Science,* **2006**, *312*, 251

Supramolecular hosts for transition metal catalysis

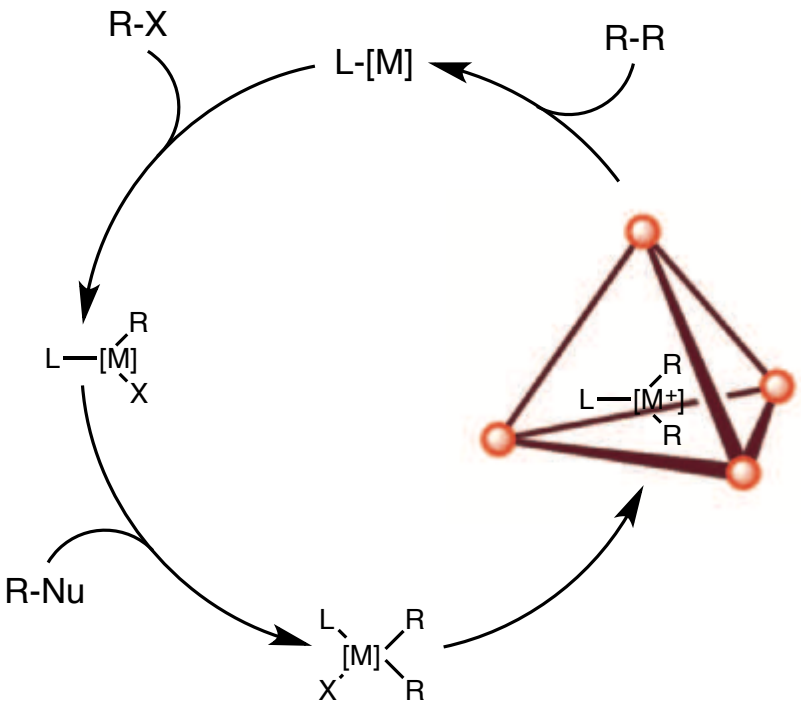


- M_4L_6 have a smaller aperture and an interior more segregated from bulk solution than M_6L_4
- Encapsulation occurs with entropically favorable liberation of solvent molecules
- Anionic host framework has a stabilizing effect on cationic guests and intermediates

Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. M. *Chem. Rev.* **2015**, *115*, 3012

Levin, M. D.; Kaphan, D. M.; Hong, C. M.; Bergman, R. G.; Raymond, K. M.; Toste, F. D. *J. Am. Chem. Soc.* **2016**, *138*, 9682

Supramolecular hosts for transition metal catalysis



One intermediate of a catalytic cycle
Selectively encapsulated by host complex

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

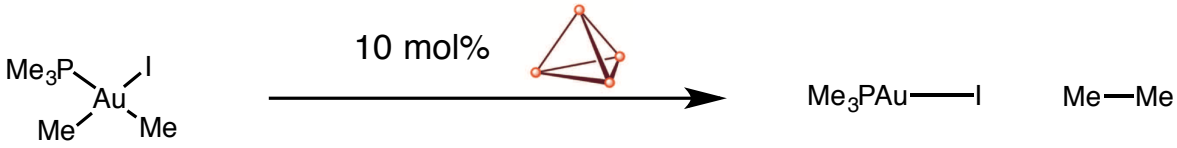
Merger of biomimetic envioronment control with unnatural mode of reactivity

Kaphan, D. M.; Levin, M. D.; Bergman, R. G.; Raymond, K. M. Toste, F. D. *Science* **2014**, *350*, 1235

Levin, M. D.; Kaphan, D. M.; Hong, C. M.; Bergman, R. G.; Raymond, K. M.; Toste, F. D. *J. Am. Chem. Soc.* **2016**, *138*, 9682

Supramolecular hosts for transition metal catalysis

- Stoichiometric reductive elimination from dimethyl Au complex

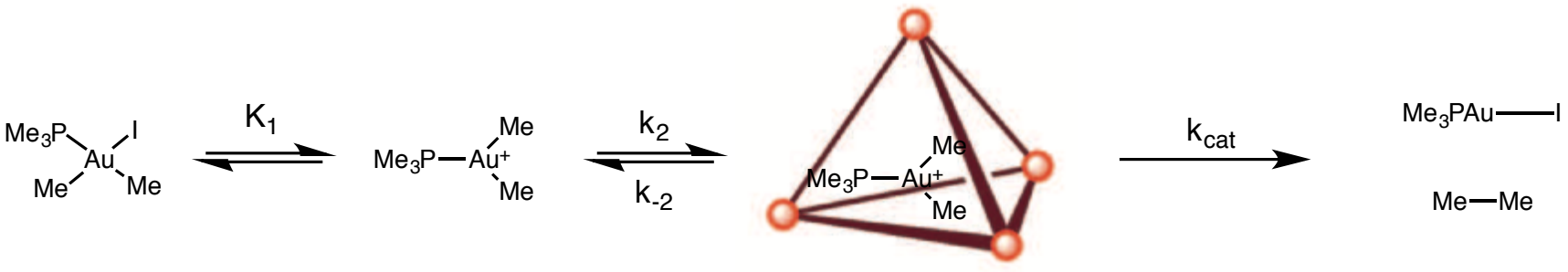


Halide	k_{rel}
I	1
Br	5.7
Cl	6.5

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

Background reactivity measured using strongly binding Et_4P^+ to clock binding pocket

Proposed mechanismbased on pre- equilibrium between neutral and cationic substrates:



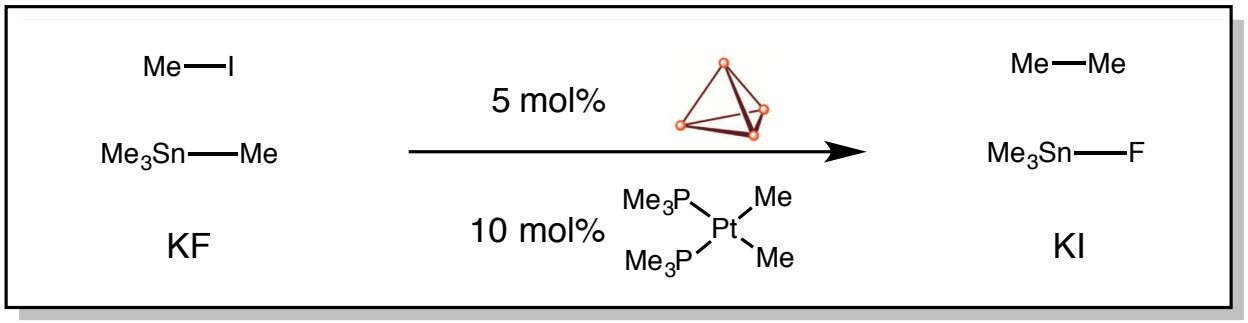
Kinetic invesigation indicates enzyme like mechanism following Michaelis-Menten like kinetics

Kaphan, D. M.; Levin, M. D.; Bergman, R. G.; Raymond, K. M. Toste, F. D. *Science* **2014**, *350*, 1235

Levin, M. D.; Kaphan, D. M.; Hong, C. M.; Bergman, R. G.; Raymond, K. M.; Toste, F. D. *J. Am. Chem. Soc.* **2016**, *138*, 9682

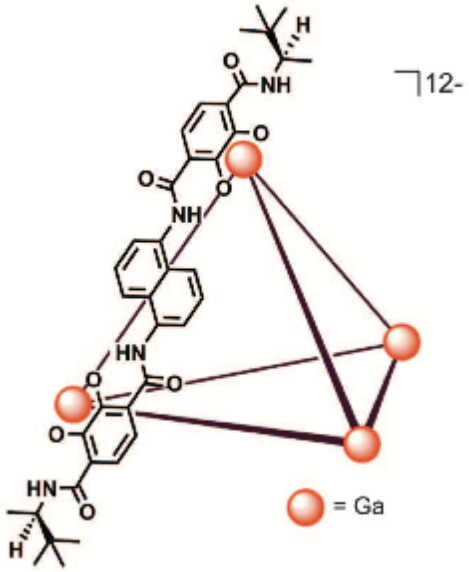
Supramolecular hosts for transition metal catalysis

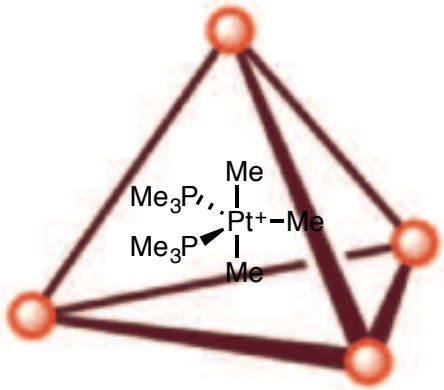
- Applied to stoichiometric sp^3-sp^3 coupling using a Pt catalyst



- Efficient coupling observed only with both catalysts, deuteration indicates both starting materials incorporated

Modified catalyst allows for
Better incorporation of
MeI into host complex



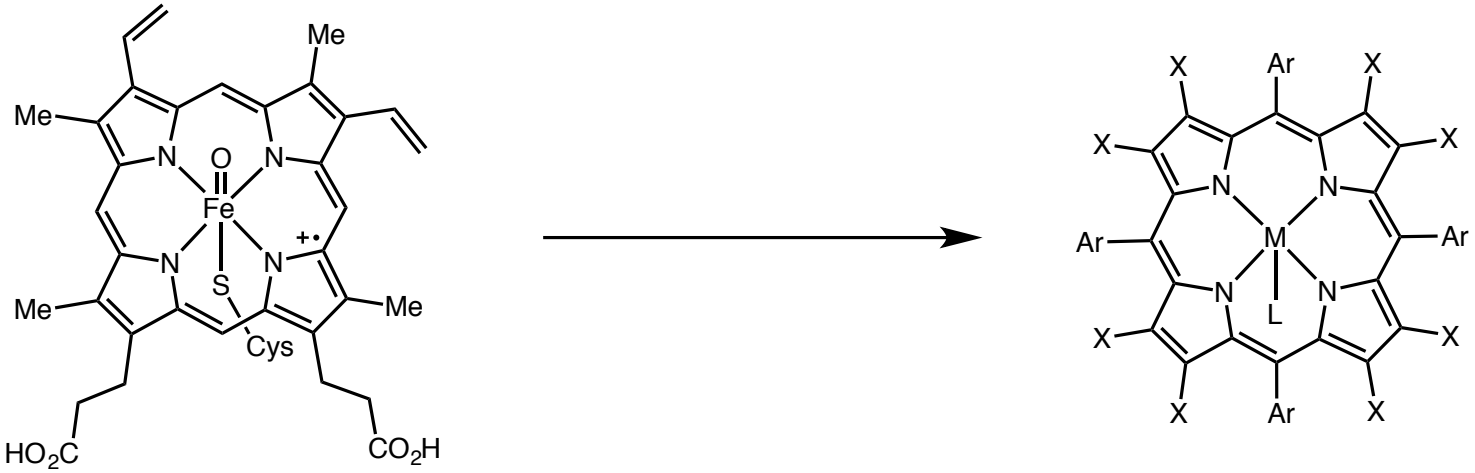


Kaphan, D. M.; Levin, M. D.; Bergman, R. G.; Raymond, K. M. Toste, F. D. *Science* **2014**, *350*, 1235

Levin, M. D.; Kaphan, D. M.; Hong, C. M.; Bergman, R. G.; Raymond, K. M.; Toste, F. D. *J. Am. Chem. Soc.* **2016**, *138*, 9682

Strategies in Biomimetic Catalysis

Metalloporphyrins - Development of new reactivity from an enzyme cofactor



Artificial enzymes - Use of supramolecular structures to mimic substrate binding