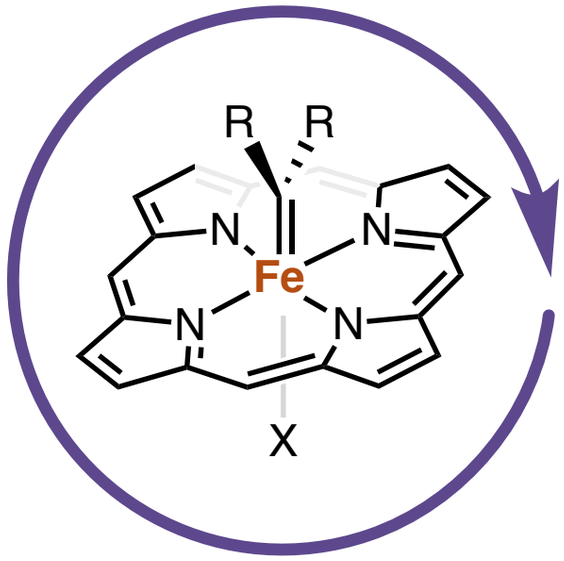
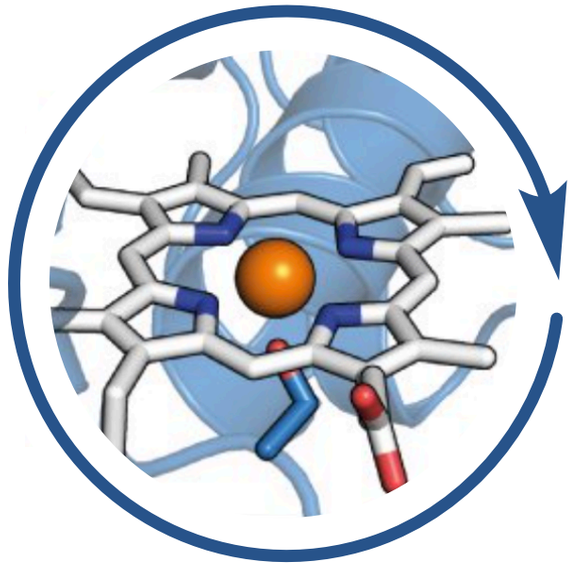
Iron Porphyrins as Catalysts for Carbene-Based Synthetic Transformations





Nathan Dow

MacMillan Group

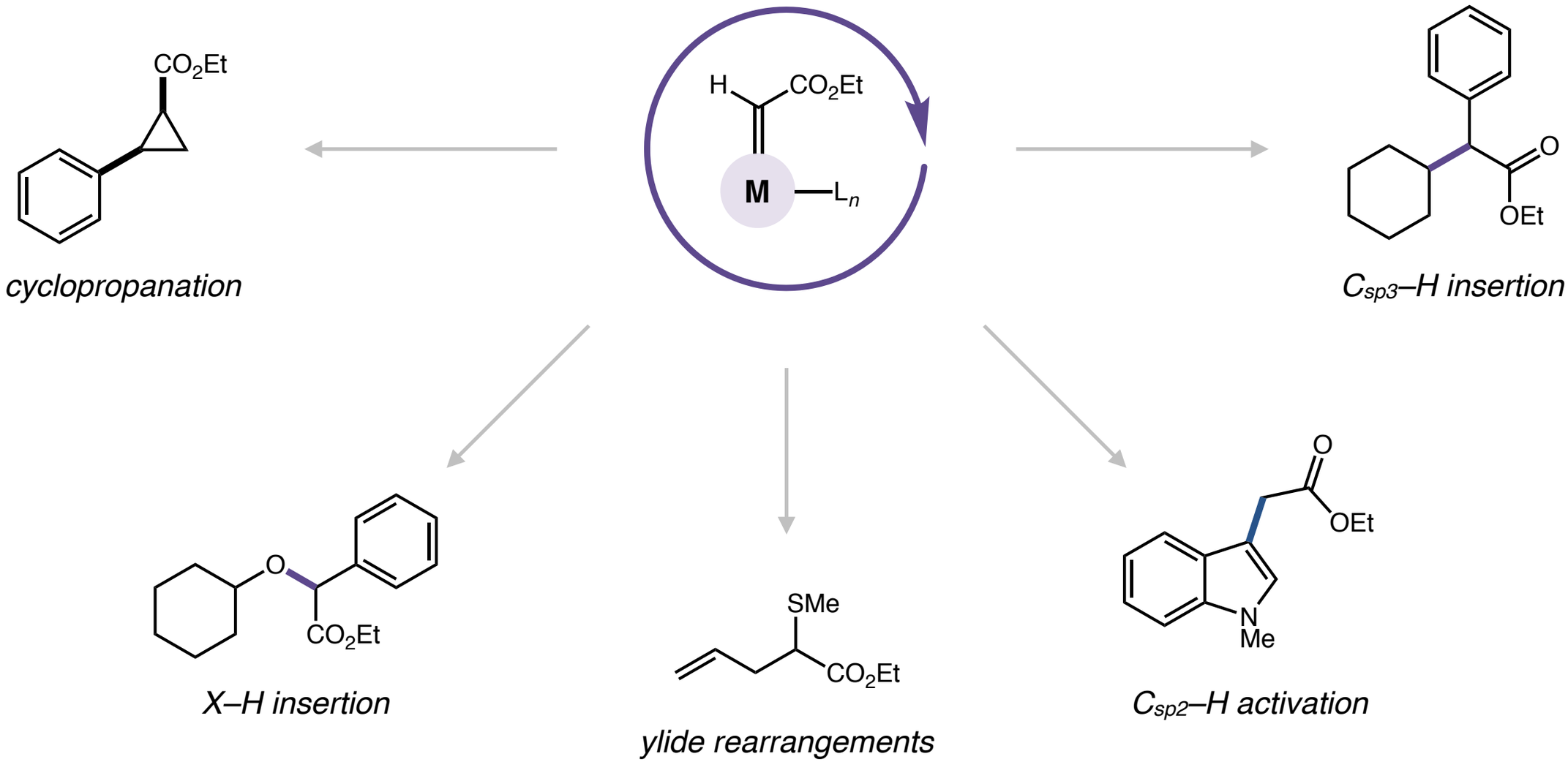
Literature Presentation

June 14th, 2022

Metal carbenes are essential intermediates in synthetic chemistry

free carbenes – highly reactive, often difficult to control for selective, efficient transformations

metal carbenes enable a wide variety of valuable, complexity-building reactions



cyclopropanation

C_{sp3}–H insertion

X–H insertion

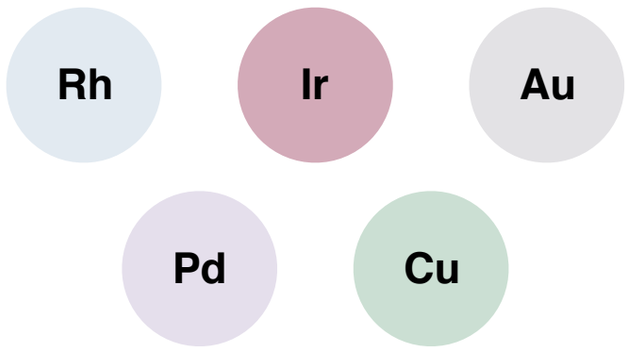
ylide rearrangements

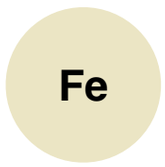
C_{sp2}–H activation

Frémont, P. d.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862.

Making the transition away from classic metal carbenes

typical metals for carbene reactions

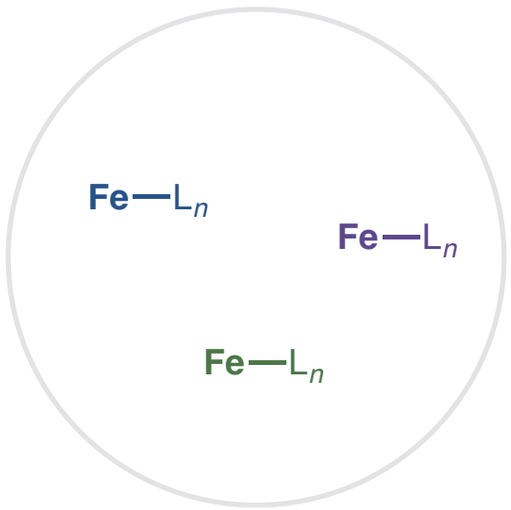


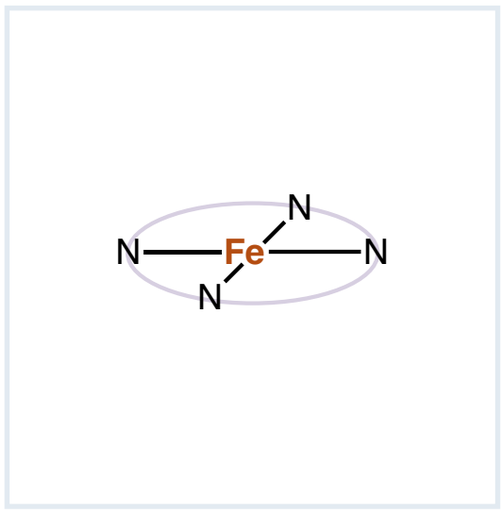


can we use alternative base metals for important carbene reactions?

#1 – abundance and cost of reagents may lead to new reactivity

many combinations of available precatalysts, ligands to rapidly evaluate



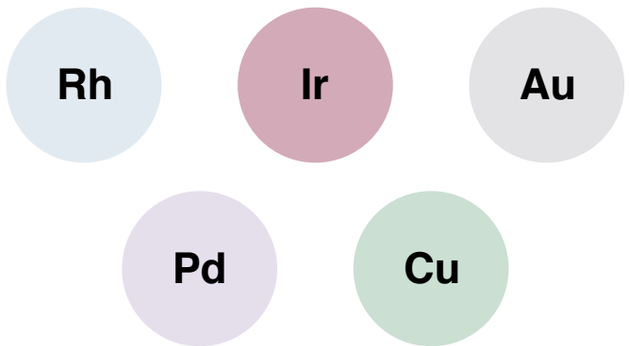


discovery of new catalysts for selective, efficient carbene reactions

Weissenborn, M. J.; Koenigs, R. M. *ChemCatChem* **2020**, *12*, 2171.

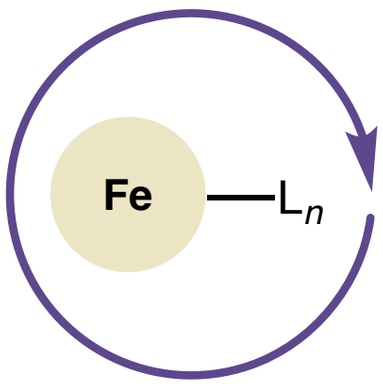
Making the transition away from classic metal carbenes

typical metals for carbene reactions



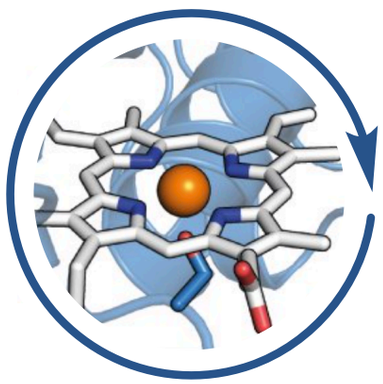
can we use alternative base metals for important carbene reactions?

#2 – previous knowledge from chemical and biochemical contexts can be harnessed

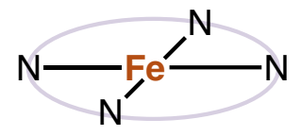


Homogenous Fe coordination complexes well-understood

+



Fe cofactors well-studied as biological catalysts



established principles aiding the discovery of new catalysts

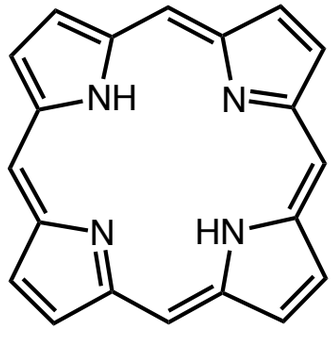
Weissenborn, M. J.; Koenigs, R. M. *ChemCatChem* **2020**, *12*, 2171.

Designing the right iron catalyst for carbene chemistry

Fe

ideal, low-cost metal

+



porphyrins and hemes

Why have porphyrin ligands emerged as privileged scaffolds for Fe carbene chemistry?

What have we learned about the reactivity and selectivity of these Fe porphyrin catalysts?

What kinds of transformations do these systems enable (and in what contexts can they take place)?

Weissenborn, M. J.; Koenigs, R. M. *ChemCatChem* **2020**, *12*, 2171.

Outline

- ***Development of small molecules iron porphyrin catalysts for carbene reactions***

- *Development of hemoprotein catalysts for biocatalytic carbene reactions*

- *Summarizing the carbene-based transformations enabled by iron porphyrins*

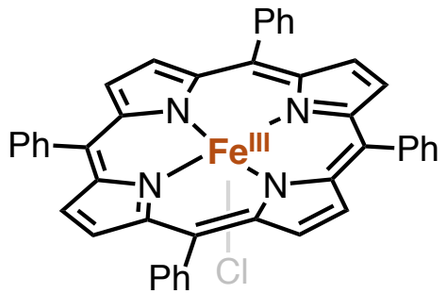
- *Future directions in iron porphyrin-catalyzed carbene chemistry*

The first isolable iron porphyrin (halo)carbenes

Fe-carbene complexes featuring common ligand scaffolds were characterized as early as 1970's

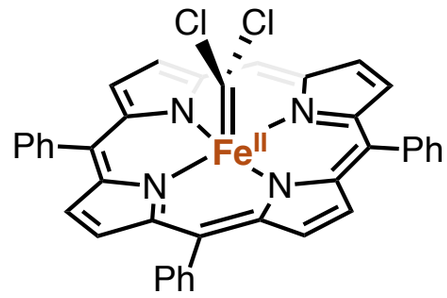
Mansuy, D.; Lange, M.; Chottard, J. C.; Guerin, P.; Morliere, P.; Brault, D.; Rougee, M. *J. Chem. Soc., Chem. Commun.* **1977**, *1*, 648.
Ziegler, C. J.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5306.

The first isolable iron porphyrin (halo)carbenes



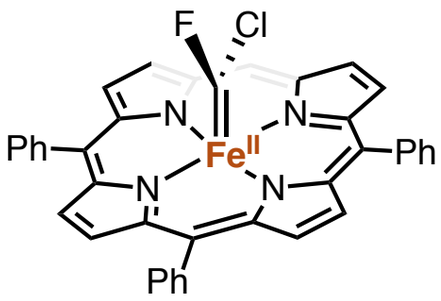
reductant ($Na_2S_2O_4$ or Fe^0)

CCl_4 (*anaerobic conds.*)



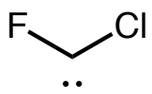
purified by recrystallization

stable halocarbene complexes – stoichiometric reactivity only induced by photolysis

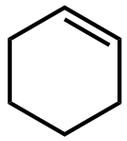


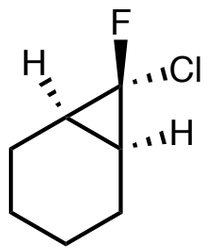
hv (λ > 360 nm)

– Fe(TPP)



free dihalocarbene





90% yield

ratio of 0.55 for "syn-F" to "syn-Cl"

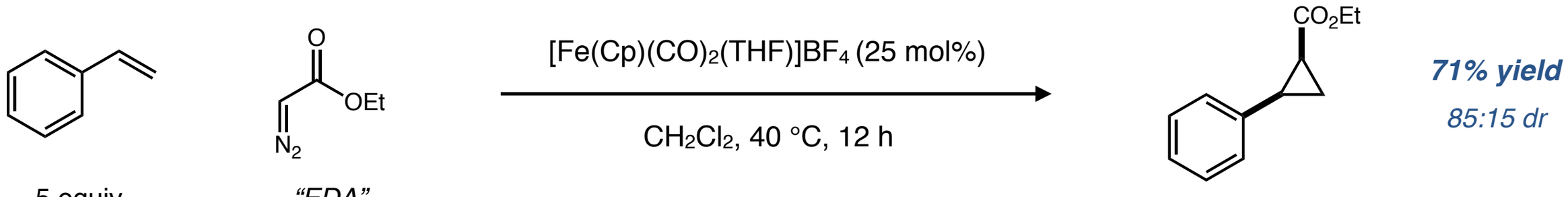
same product distribution using $HCFCl_2$ and base – evidence of free, dissociated carbene intermediate

Mansuy, D.; Lange, M.; Chottard, J. C.; Guerin, P.; Morliere, P.; Brault, D.; Rougee, M. *J. Chem. Soc., Chem. Commun.* **1977**, *1*, 648.

Ziegler, C. J.; Suslick, K. S. *J. Am. Chem. Soc.* **1996**, *118*, 5306.

The first catalytic reaction involving iron-carbene intermediates

Almost twenty years passes until first catalytic reactions involving Fe porphyrin-bound carbenes



5 equiv.

"EDA"

71% yield

85:15 dr

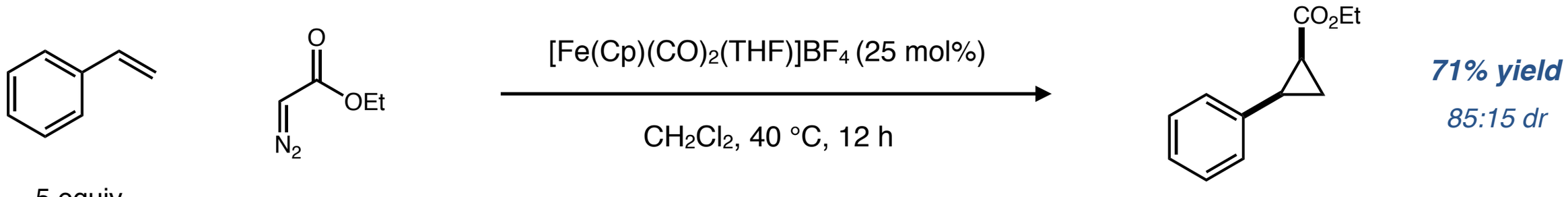
unexpected result *– first cis-selective cyclopropanation reaction involving these two partners*

unusual outcome inspires greater efforts in Fe-catalyzed carbene reactions

Seitz, W. J.; Saha, A. K.; Casper, D.; Hossain, M. M. *Tetrahedron Lett.* **1992**, *33*, 7755.

The first catalytic reaction involving iron-carbene intermediates

Almost twenty years passes until first catalytic reactions involving Fe porphyrin-bound carbenes



5 equiv.

71% yield

85:13 dr

Many new questions for Fe carbene catalysis begin to emerge, including:

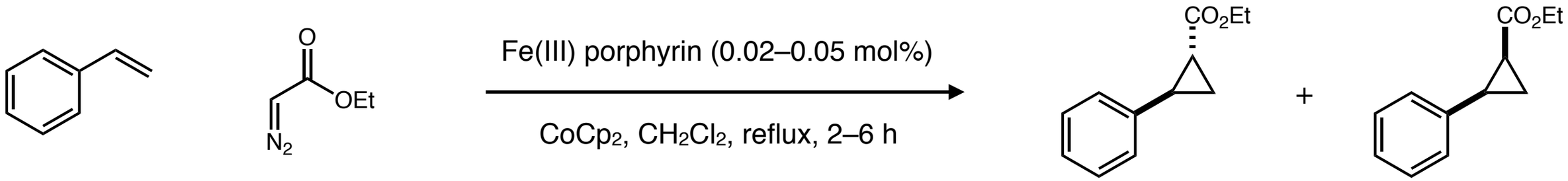
Will other Lewis acidic Fe complexes catalyze these reactions?

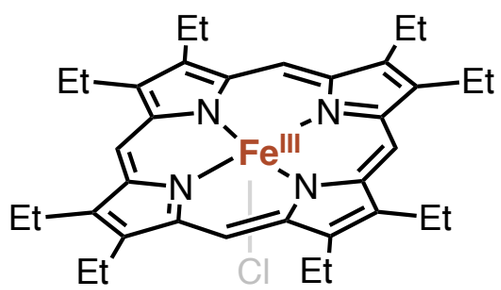
What will substrate scopes and reactivity patterns look like for other ligands?

Will the selectivities be the same using other ligands?

Seitz, W. J.; Saha, A. K.; Casper, D.; Hossain, M. M. *Tetrahedron Lett.* **1992**, *33*, 7755.

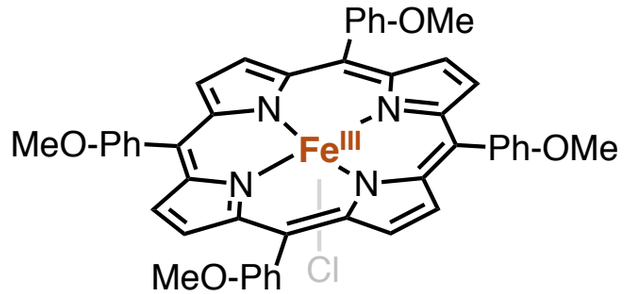
Porphyrin effects on reactivity and selectivity





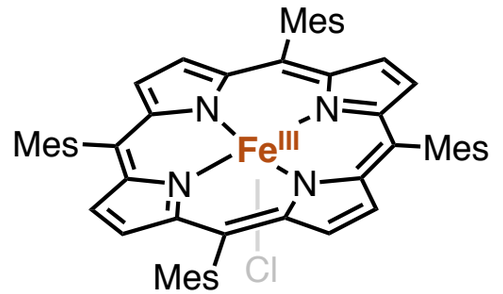
TON: 300

trans/cis: 10:1



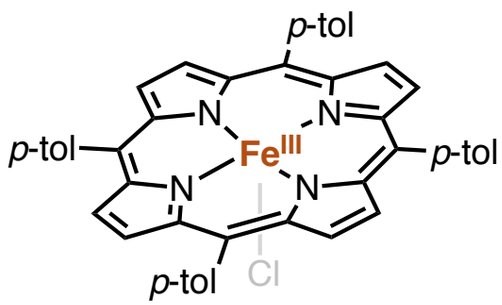
TON: 730

trans/cis: 9:1



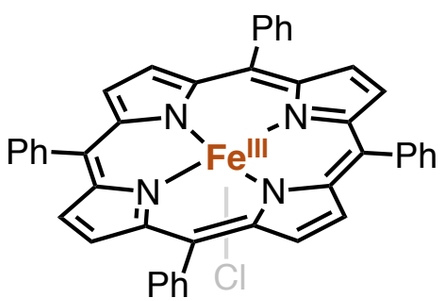
TON: 900

trans/cis: 13:1



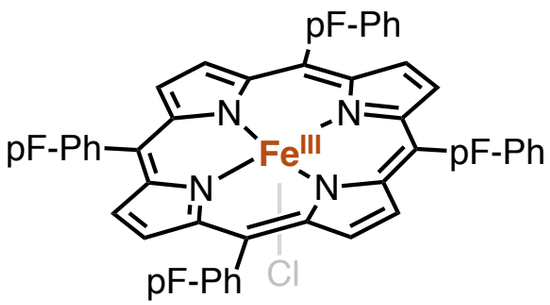
TON: 1300

trans/cis: 8.8:1



TON: 910

trans/cis: 8.7:1

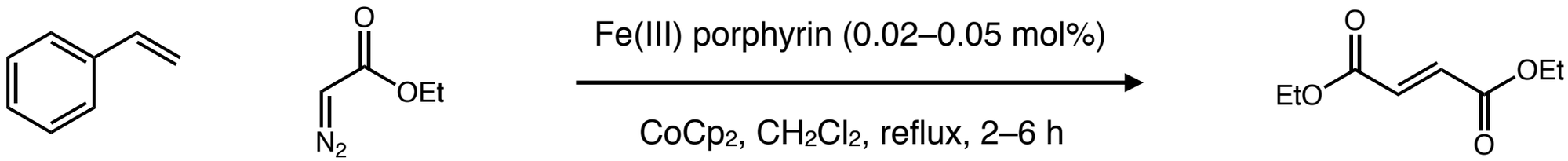


TON: 4200

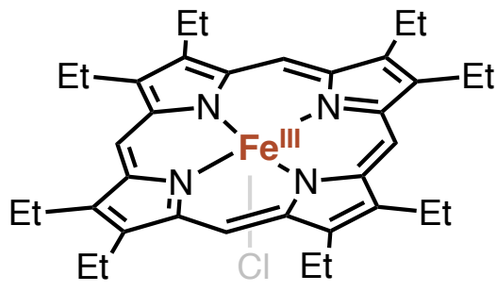
trans/cis: 6:1

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

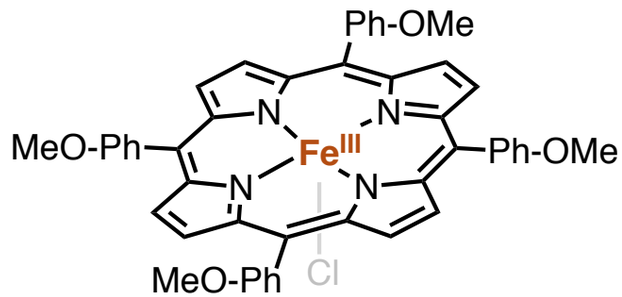
Porphyrin effects on reactivity and selectivity



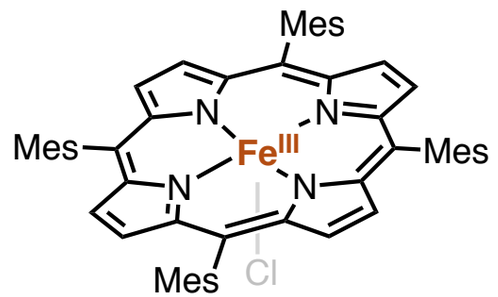
diethyl maleate byproduct



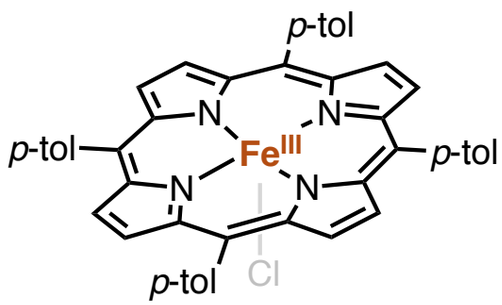
cyclopropane/maleate:
>95:5



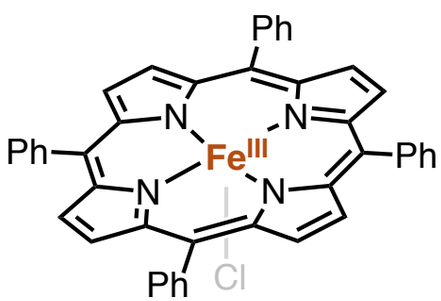
cyclopropane/maleate:
>95:5



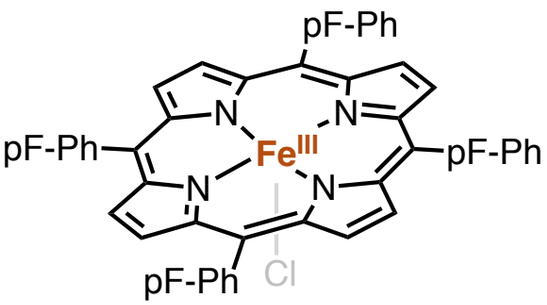
cyclopropane/maleate:
>95:5



cyclopropane/maleate:
>95:5



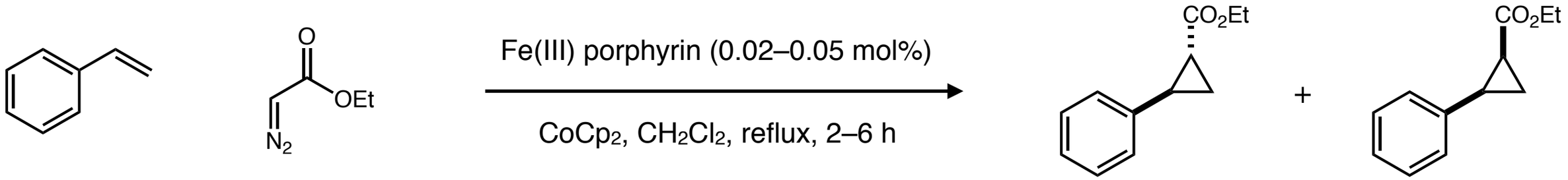
cyclopropane/maleate:
80:20

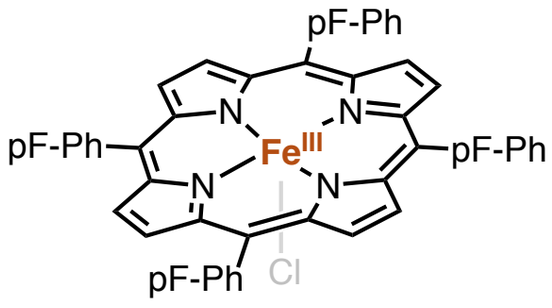


cyclopropane/maleate:
75:25

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Porphyrin effects on reactivity and selectivity





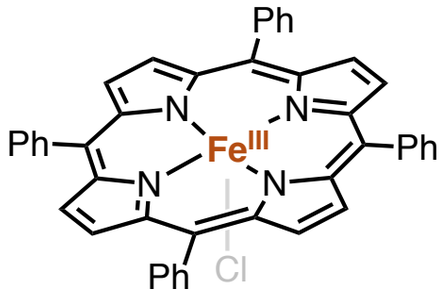
extremely reactive for carbene transfer, which leads to:

- *lower selectivity between trans- and cis-cyclopropane isomers*
- *larger amounts of carbene dimerization/decomposition byproducts*

What makes this electron-deficient porphyrin system so effective for cyclopropanation?

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Rationales for enhanced reactivity of electron-deficient porphyrins

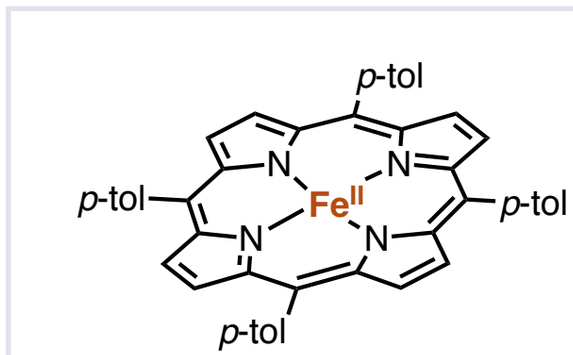


turnover numbers for styrene cyclopropanation under Ar

Δ (40 °C)	$CoCp_2$ (reductant)	$CoCp_2$, under air
400 (over 10 h)	**910** (over 2 h)	**no quantifiable reactivity**

implication – active catalyst for metal carbene generation is air-sensitive Fe(II) complex

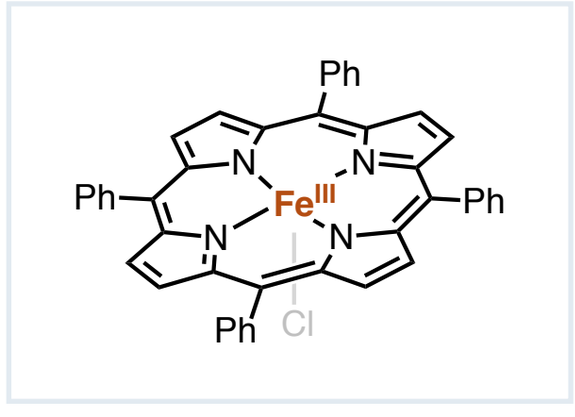
Fe(TPP)
independently prepared in reduced state

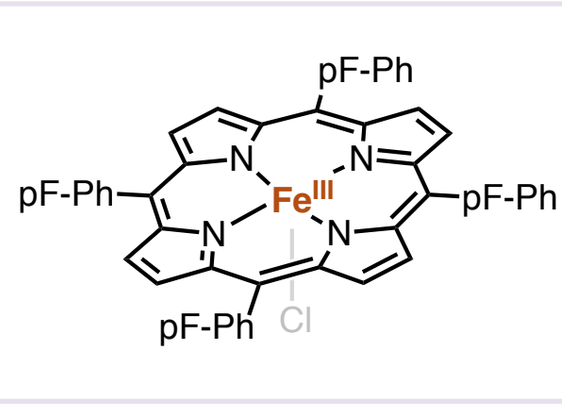


TON for cyclopropanation:
>1000

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

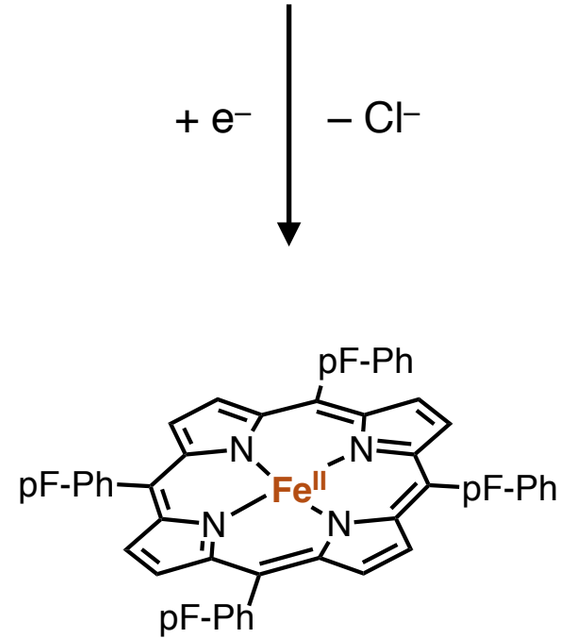
Rationales for enhanced reactivity of electron-deficient porphyrins





Rationale #1:

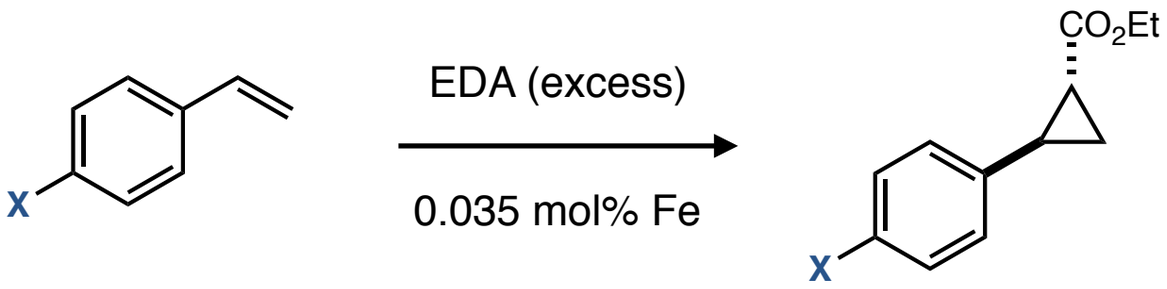
easier reduction of precatalyst to catalytically-relevant Fe(II) state



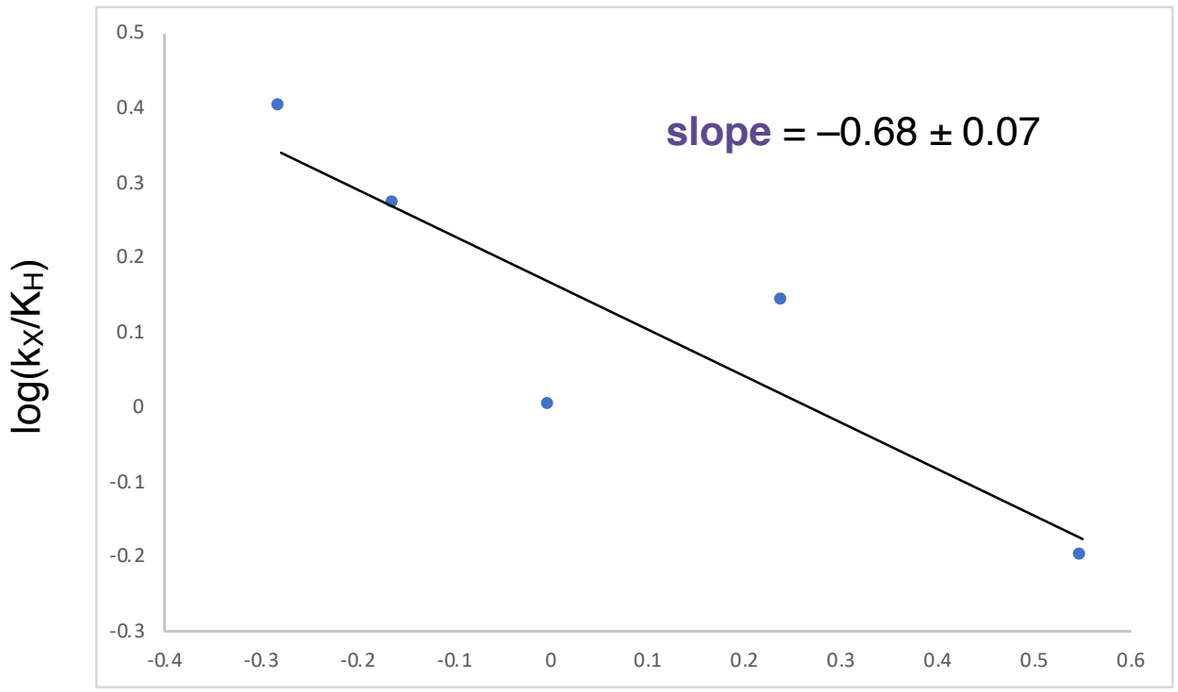
Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Rationales for enhanced reactivity of electron-deficient porphyrins

Hammett studies for styrene cyclopropanation using Fe(TTP) as Fe(II) catalyst



X *= OMe, Me, H, Cl, CF_3*

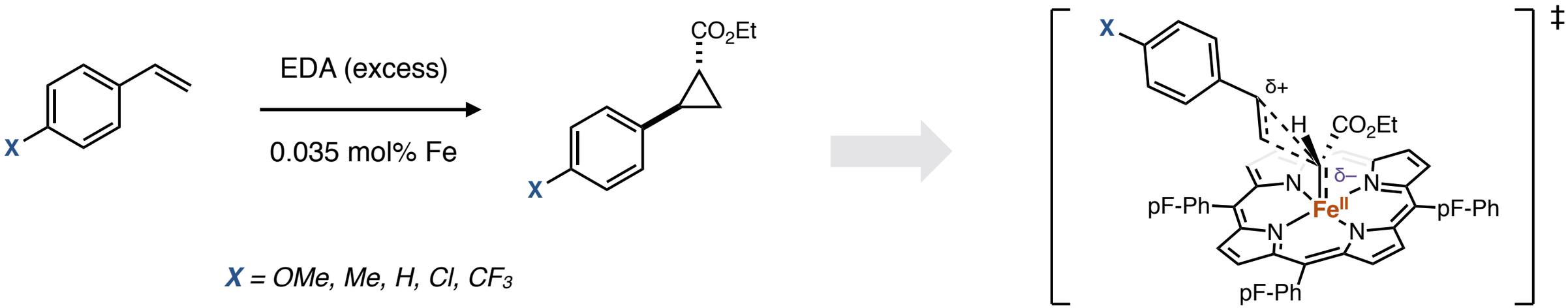


Buildup of δ+ character on styrene in cyclopropanation TS – behaves as electrophilic Fischer carbene

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Rationales for enhanced reactivity of electron-deficient porphyrins

Result consistent with polarity-driven, step-wise mechanism for cyclopropanation



***X** = OMe, Me, H, Cl, CF_3*

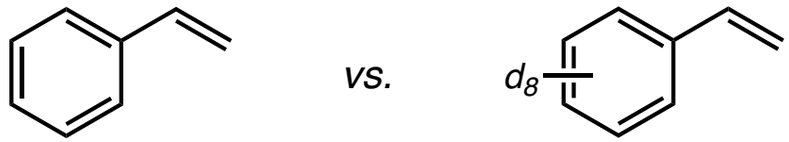
Rationale #2:

electron-deficient ligands render carbene more electrophilic, lower barrier to π-nucleophile addition

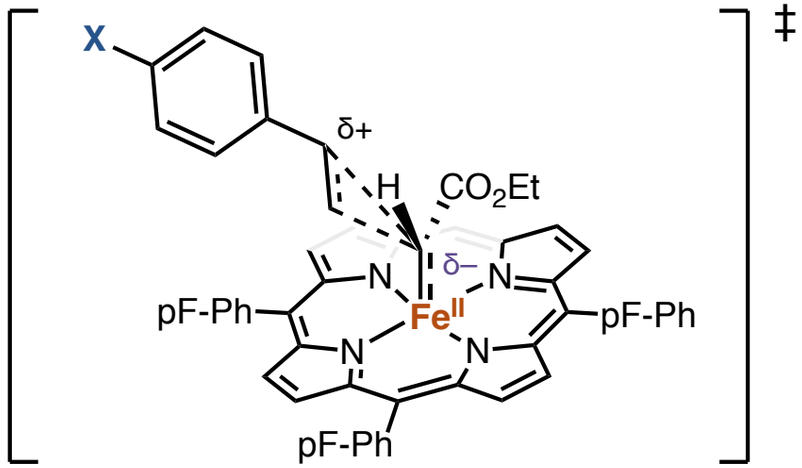
Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Rationales for enhanced reactivity of electron-deficient porphyrins

Competition experiments



inverse 2° KIE of 0.87 ± 0.07 observed

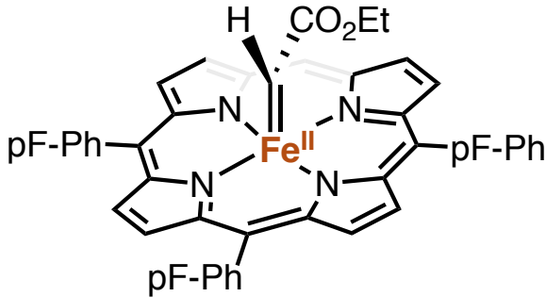


Rehybridization confirms step-wise cyclopropanation with substantial bond-forming character in TS

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

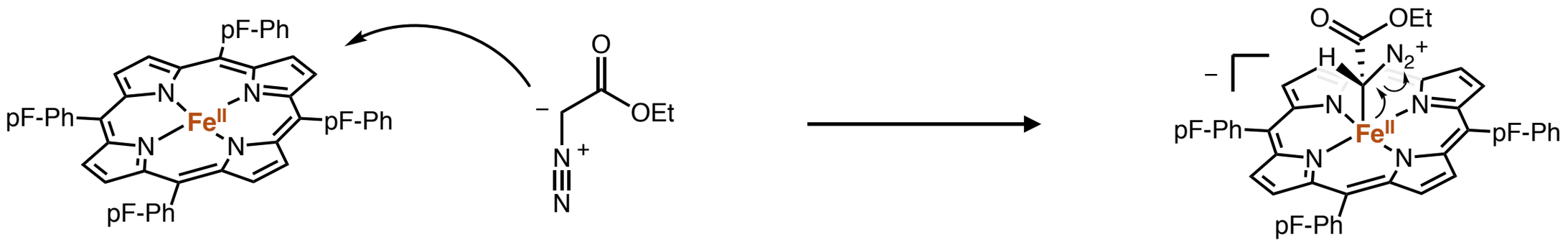
Rationales for enhanced reactivity of electron-deficient porphyrins

Electronic impact on Fe center also consistent with polar, step-wise mechanism for diazo transfer to metal catalysts



a more electrophilic Fe(II) complex

a zwitterionic nucleophile

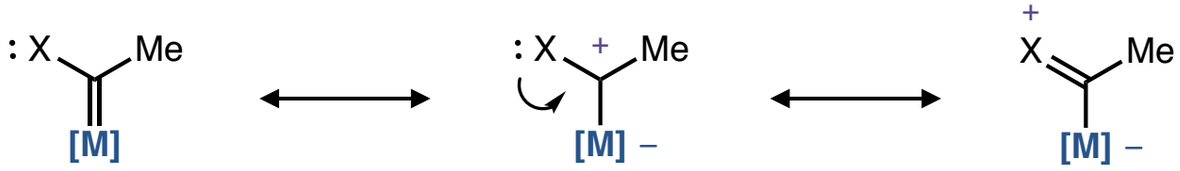


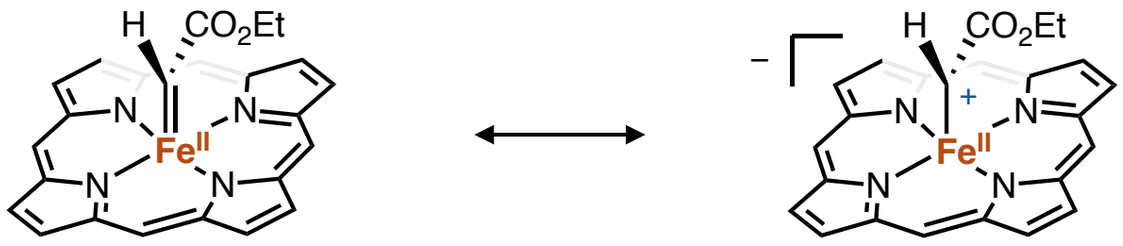
Kaur, P.; Tyagi, V. *Adv. Synth. Catal.* **2021**, *363*, 877.

Properties of electrophilic carbenes

How do Fe porphyrin carbenes compare to "traditional" Fischer intermediates?

- *low oxidation state metal (π-backbonding)*
- *π-acceptor ligands to stabilize metal*
- *π-donor substituents on carbene*





carbene vs. carbenoid: anionic character

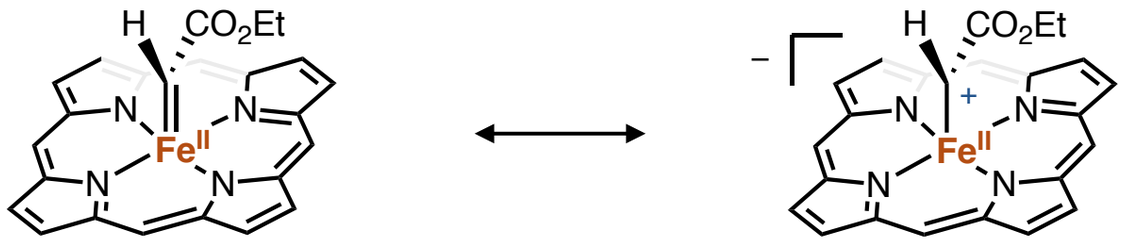
stabilized in LUMO by porphyrin π-acceptor

- ***higher oxidation state Fe***
- ***destabilizing EWG***
- ***lack of π-donor substitutents***

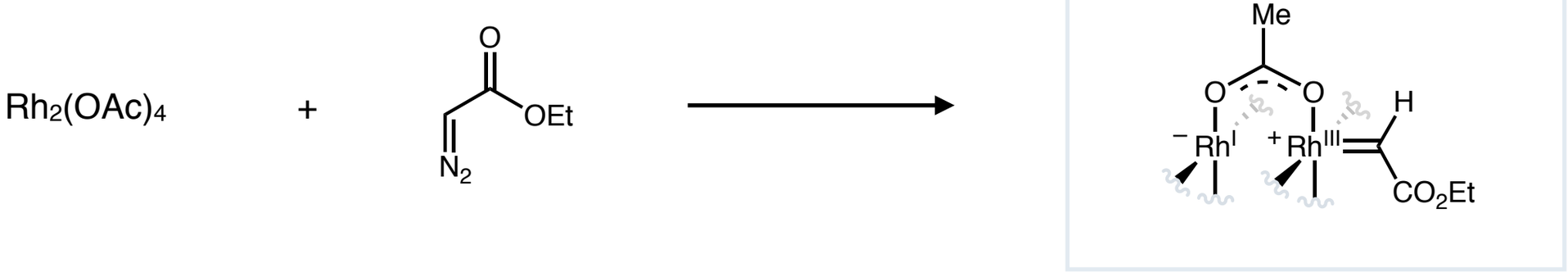
Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227.

Properties of electrophilic carbenes

Fe porphyrin carbenes can still render acceptor-substituted carbenes (i.e. most common diazos) electrophilic



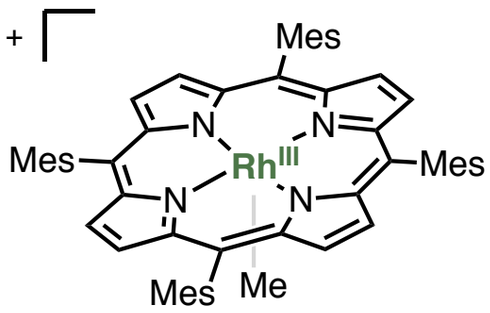
Despite being mononuclear, comparable to electrophilic dirhodium carbene complexes:



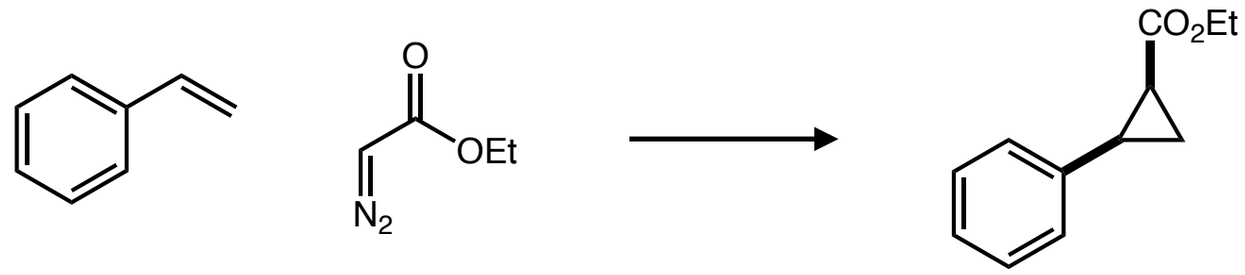
Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227.

Comparison of iron vs. late metals in porphyrin-stabilized carbene complexes

Do Fe porphyrin complexes exhibit the same carbene transfer reactivity as late metal porphyrins?



isoelectronic with Fe(II), but more thoroughly studied (since 1980)



modest stereochemical preference for cis diastereomer

Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

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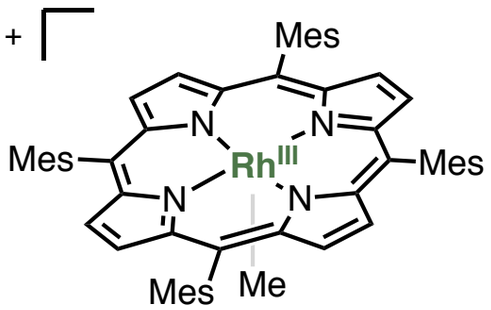

isoelectronic with Fe(II), but more thoroughly studied (since 1980)

X *= OMe, Me, H, Cl, CF_3*

no significant electronic effects on cyclopropanation rates

(generally high across many substrates)

Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

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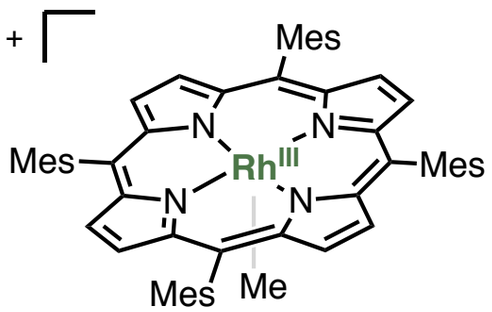


isoelectronic with Fe(II), but more thoroughly studied (since 1980)

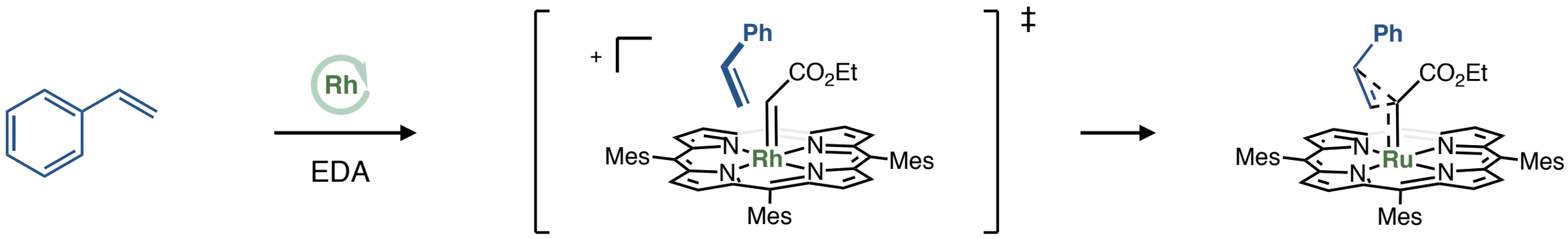
negligible 2° KIE in competition experiments

Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.

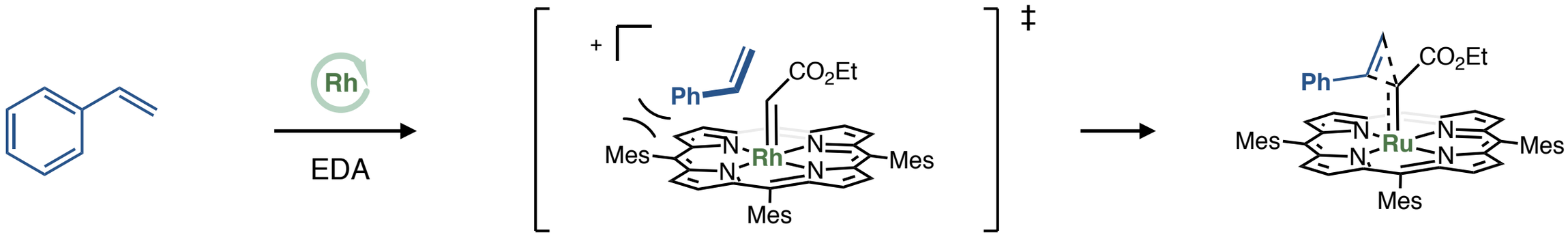
Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Modeling the transition states that explain divergent reactivity and selectivity

Cationic Rh porphyrins display earlier TS with minimal bond-forming character



minimized interaction between olefin and bulky porphyrin substituents ***– favored*** ✓



ligand-substrate steric repulsion ***– disfavored*** ***X***

Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

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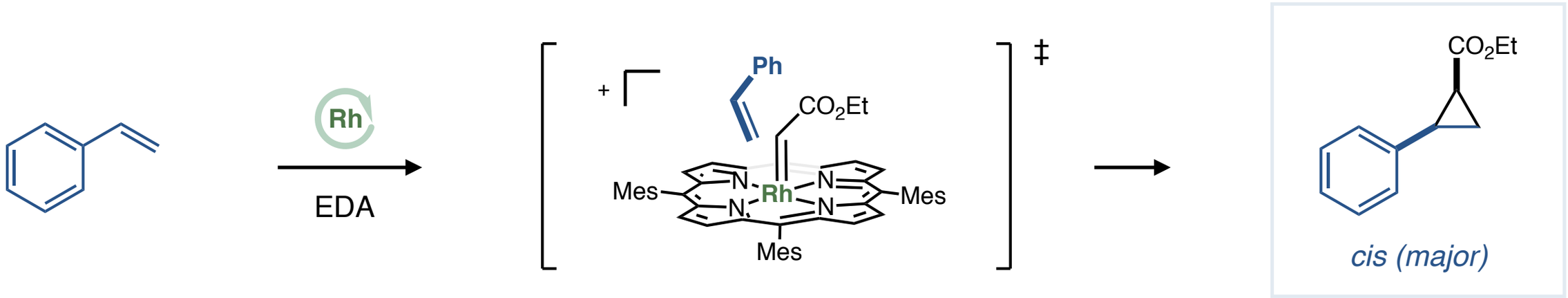
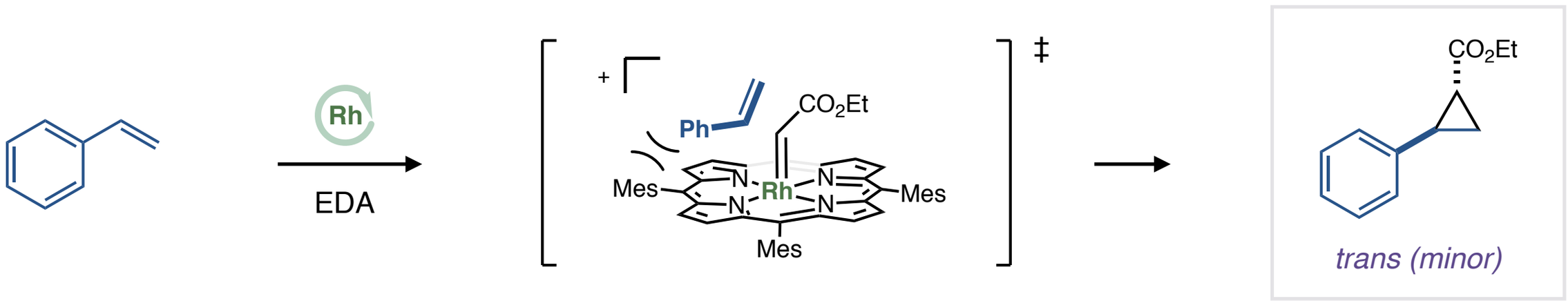


minimized interaction between olefin and bulky porphyrin substituents ***– favored*** ✓



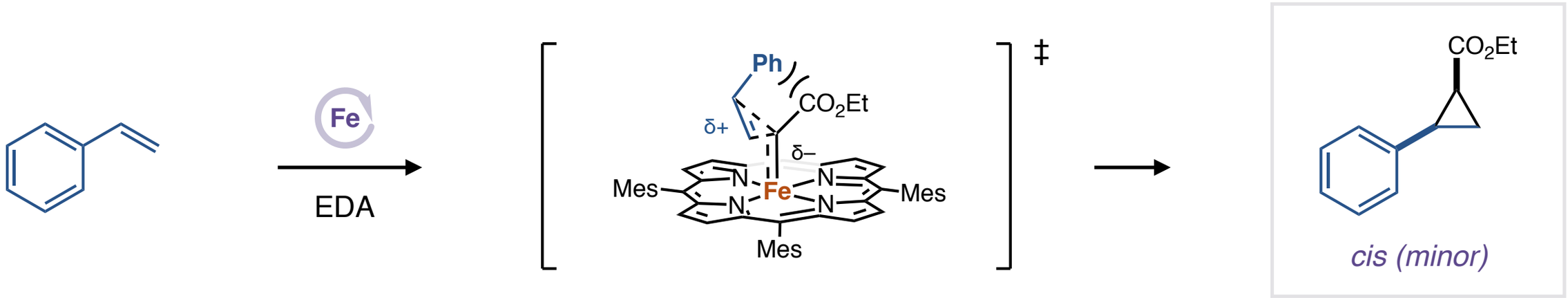
ligand-substrate steric repulsion ***– disfavored*** ***X***

Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.

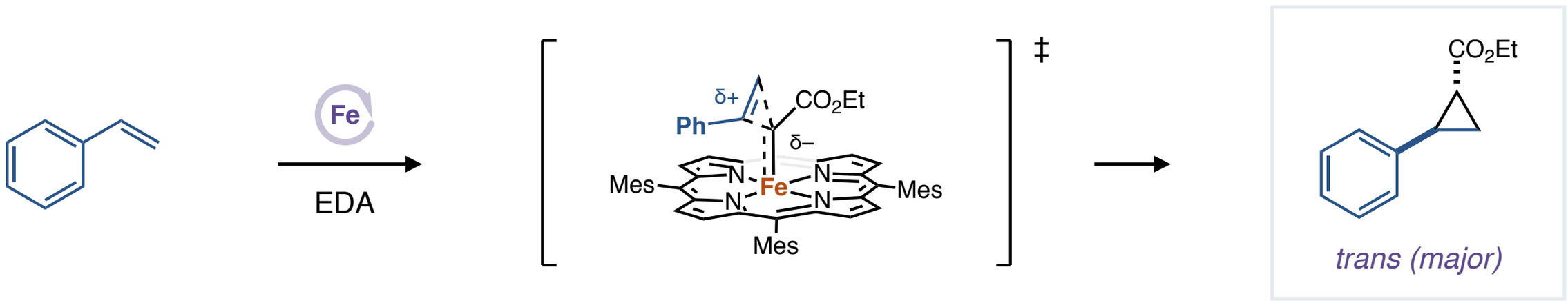
Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Modeling the transition states that explain divergent reactivity and selectivity

In contrast, Fe porphyrins have later TS with significant bond reorganization and charged character



steric repulsion between developing cyclopropane substituents ***– disfavored*** ***X***

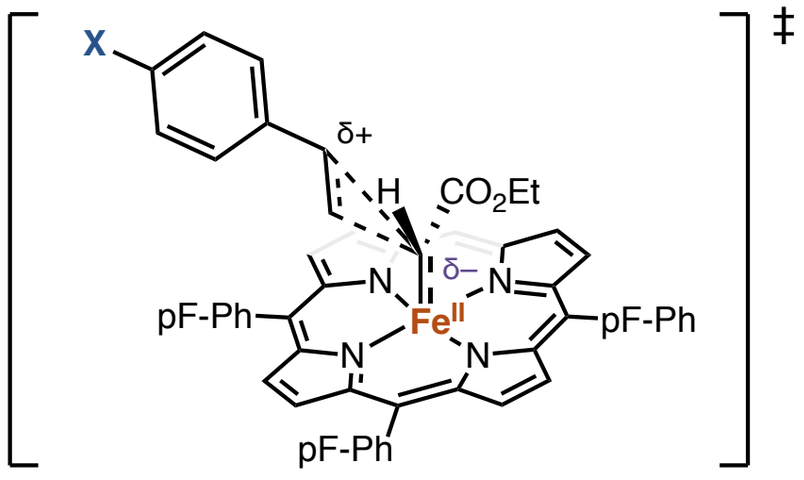


minimal interaction of Ph and ester substituents ***– favored*** ✓

Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336.

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Late transition states dictate conventional reactivity of iron porphyrin carbenes



Late TS translates to reactivity patterns in cyclopropanations and other reactions, including:

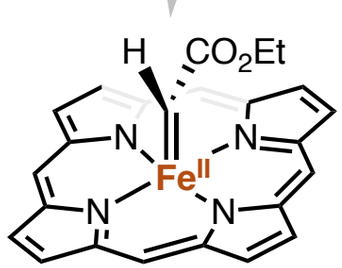
- *exclusive use of bound carbene as “electrophilic” partner*
- *highly specific reactivity with nucleophiles that best stabilize δ+ buildup in TS*
- *consistently high preference for trans diastereoselectivity*

Batista, V. F.; Pinto, D. C. G. A.; Silva, A. M. S. *ACS Catal.* **2020**, *10*, 10096.

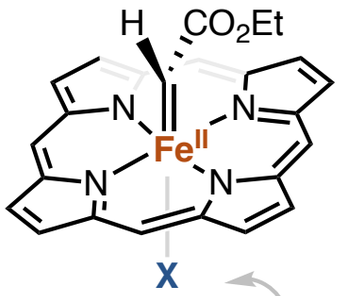
The role of axial ligands

For metal porphyrin complexes, the sixth coordination site must also be considered

predictable carbene electronics



well-described porphyrin effects



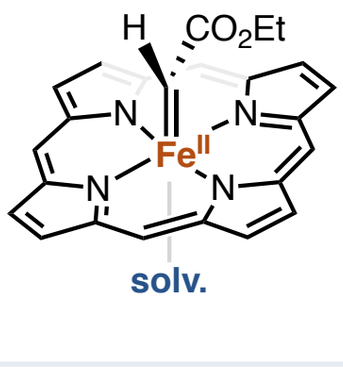
does this axial ligand play an important role?

Lai, T.S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *1*, 4845.

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

The role of axial ligands

Generally assumed that solvent occupies axial binding site of catalytically-relevant Fe(II) porphyrin



treated as incidental consideration of specific reaction conditions

with less relevance to reactivity than porphyrin structure

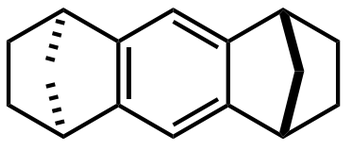
impact of solvent on styrene cyclopropanation with EDA using Fe(TTP) catalyst

	toluene	CH_2Cl_2	ether	acetonitrile	THF
trans/cis ratio	**8:1**	**8.8:1**	**9.3:1**	**12:1**	**13:1**

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

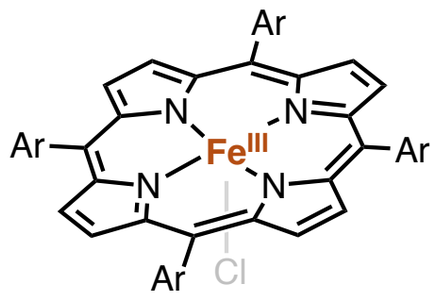
The role of axial ligands

Can general additives be used to influence reactions more dramatically than solvent?



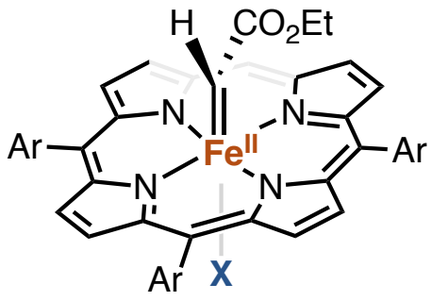
"Ar"

"Halterman" Fe porphyrin



EDA (>100 eq.)

Lewis base (20 eq.)



pyridine and N-methylimidazole adducts observed by ESI-MS

indicates stable, catalytically-relevant axial complexes can be formed in-situ

Lai, T.S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *1*, 4845.

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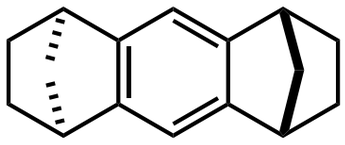
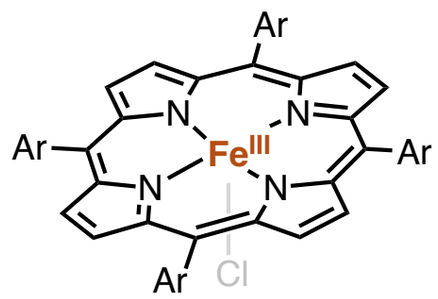
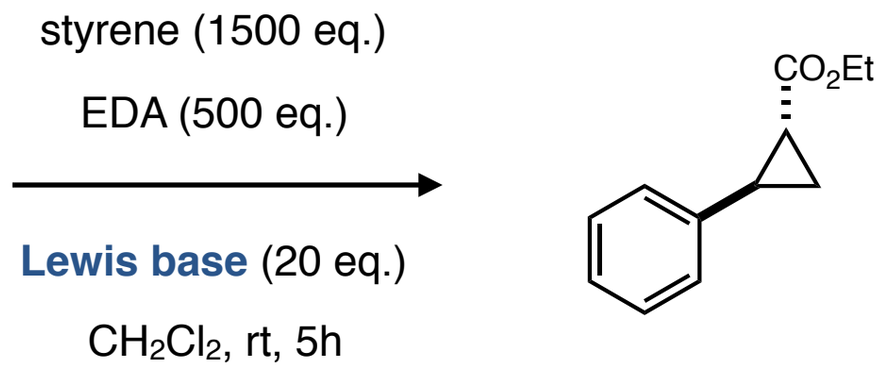


"Ar"

"Halterman" Fe porphyrin





	none	pyridine	DMAP	N-Me imid.	N-Me pyrrolidine	DMSO
trans/cis ratio	**12:1**	**33:1**	**24:1**	**26:1**	**27:1**	**17:1**
TON	**368**	**307**	**321**	**275**	**293**	**385**

Lai, T.S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *1*, 4845.

The role of axial ligands

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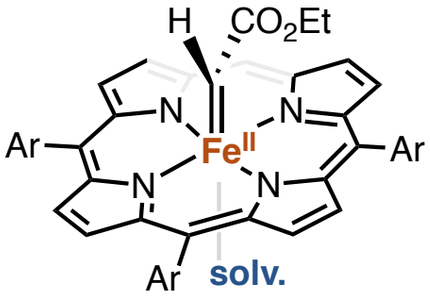
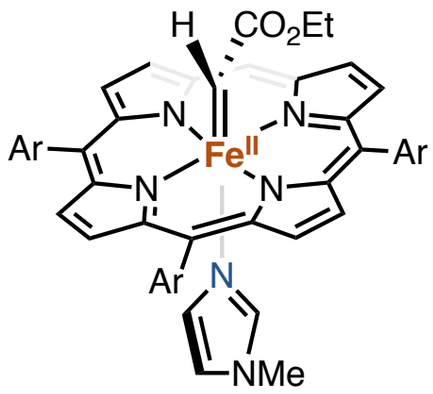
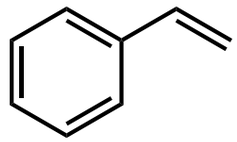


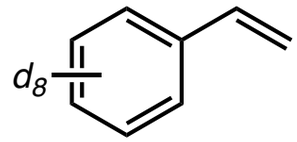
vs.



Competition experiments



vs.



no additive: inverse 2° KIE of 0.87 ± 0.01

with imidazole: inverse 2° KIE of 0.81 ± 0.01

more inverse KIE indicates more styrene sp^3-character, resulting in even later TS with imidazole axial ligand

Lai, T.S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *1*, 4845.

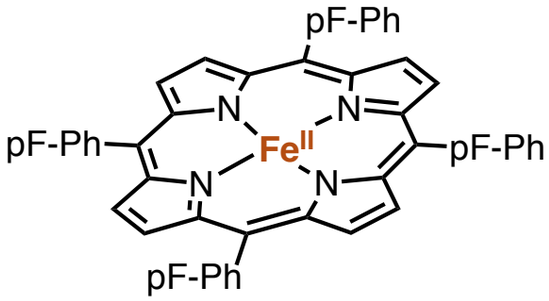
The role of axial ligands

recall – later TS more susceptible to diastereocontrol based on cyclopropane substituent interactions

axial electron-donor ligand should increase trans-selectivity, consistent with observations

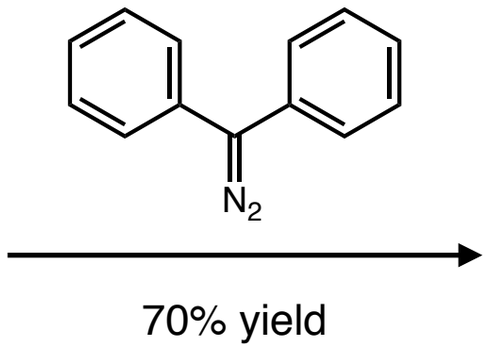
Lai, T.S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *1*, 4845.

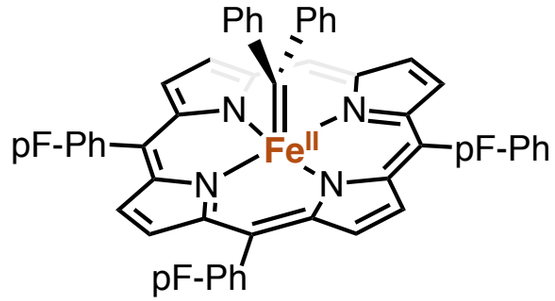
Evaluating an alternative iron carbene via X-ray crystallography



prepared via reduction of Fe(III)Cl complex

(air-sensitive)



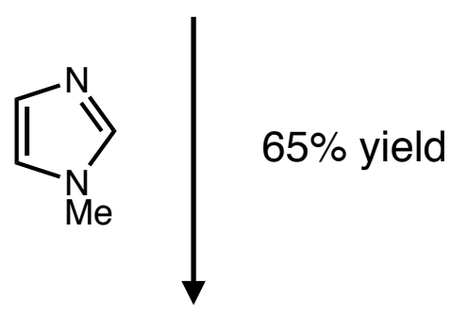


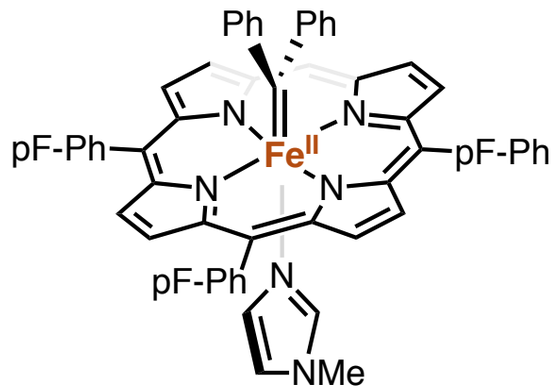
isolable via column

chromatography

New possibilities for characterizing diazo carbene transfer

intermediates via anaerobic crystallography





carbene destabilized relative

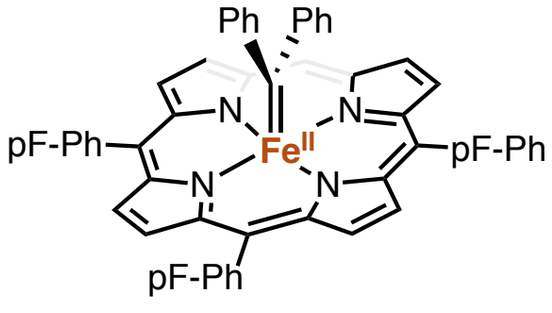
to non-ligated precursor?

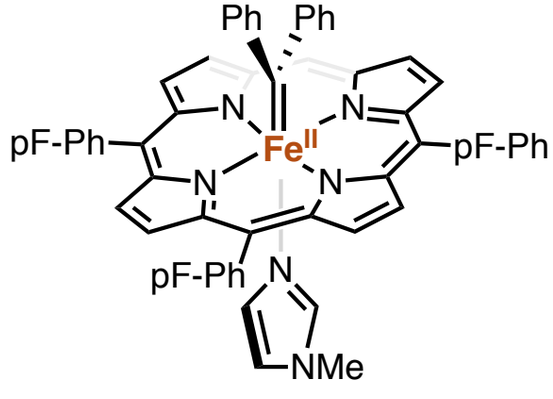
decomposed when exposed

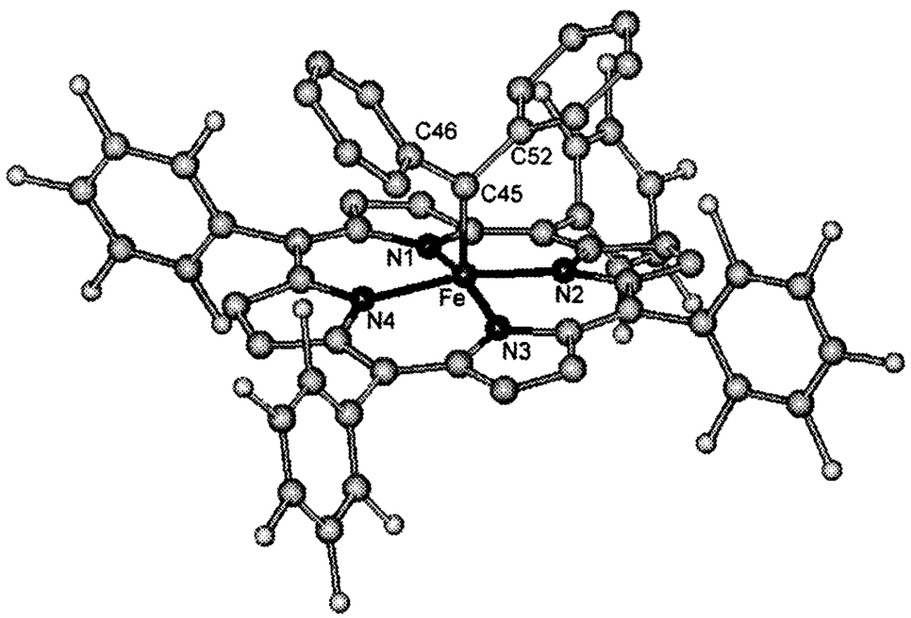
to air or moisture

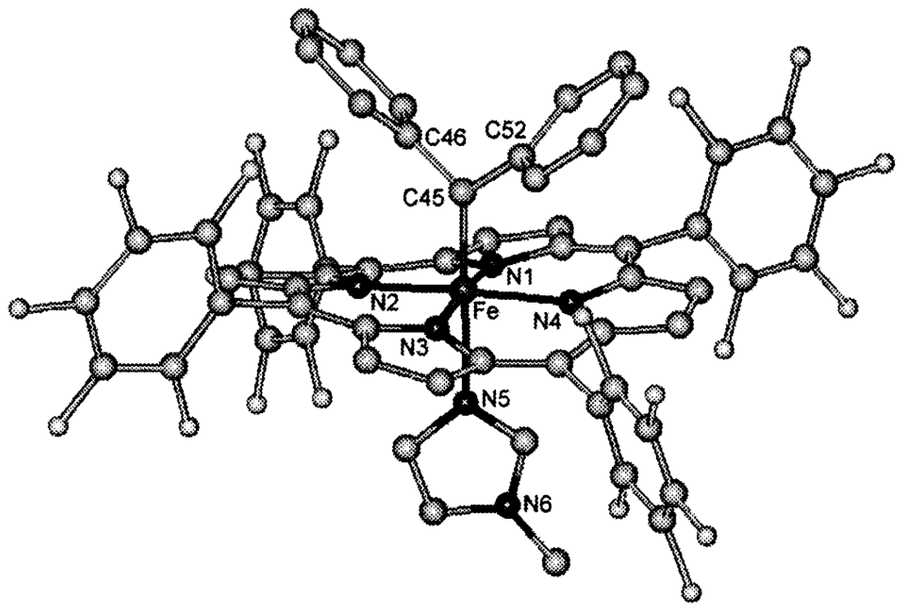
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Evaluating an alternative iron carbene via X-ray crystallography





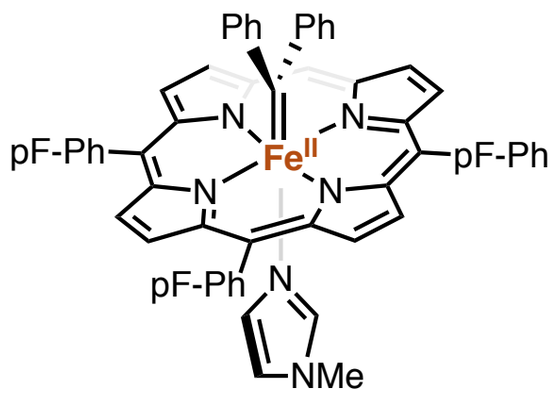




Several key structural features of iron porphyrin carbenes evident

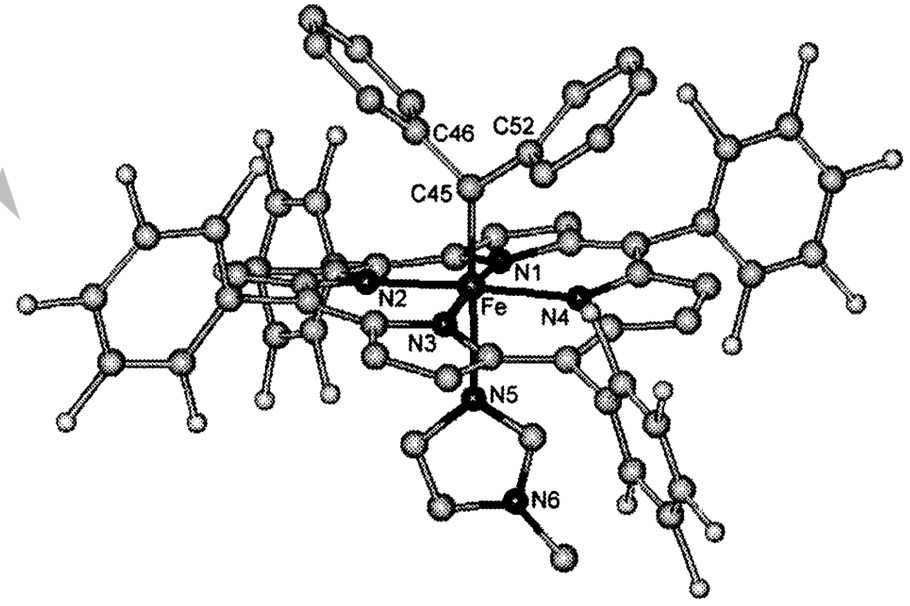
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Evaluating an alternative iron carbene via X-ray crystallography



1. out-of-plane rotation of aromatic substituents

while planarity would increase conjugation, sterics interactions minimized at dihedral angles nearing 90°



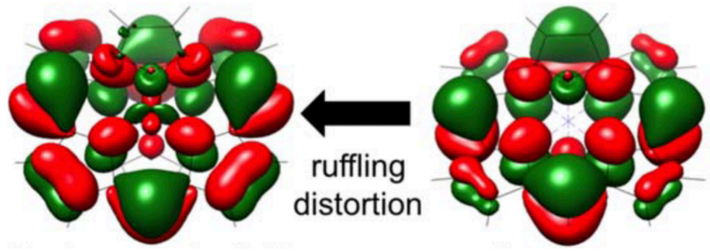
rotation explains why arene electronics have modest (not dramatic) effect on carbene reactivity

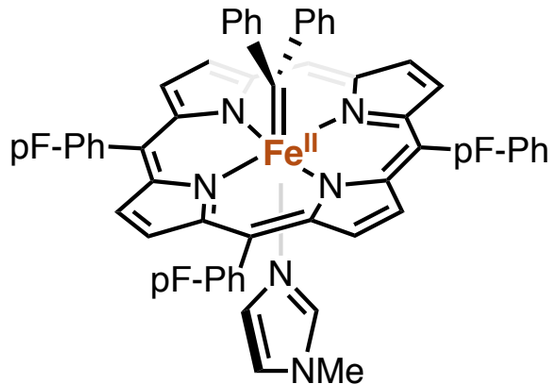
Eaton, S. S.; Eaton, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 3660.

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Evaluating an alternative iron carbene via X-ray crystallography

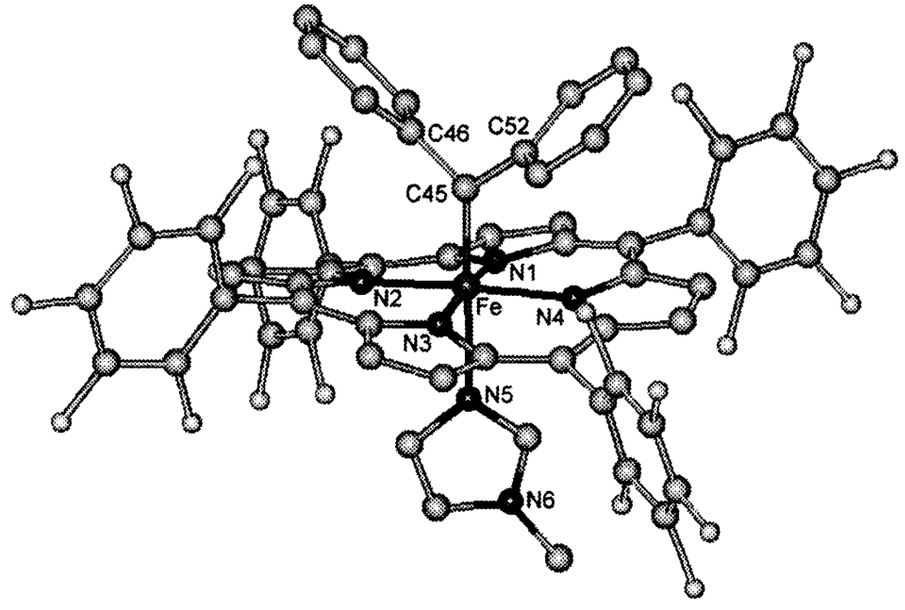
2. "ruffling" distortion away from planarity





Fe(II) center destabilized, d_{xy} raised due to increased antibonding interactions with porphyrin

increased electronic donation from Fe to carbene?

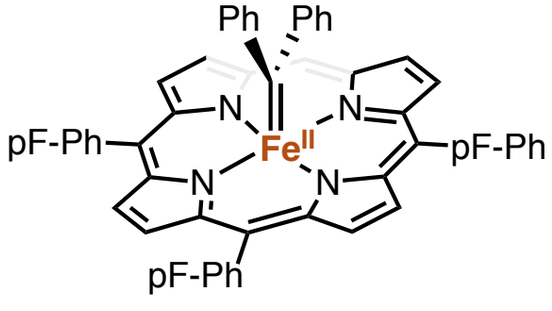


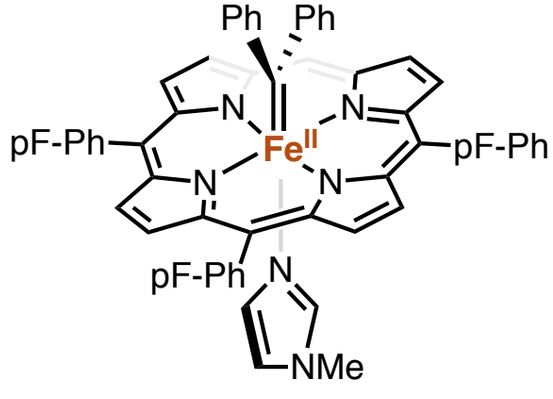
for porphyrin atoms – mean deviation from planarity = 0.198 Å

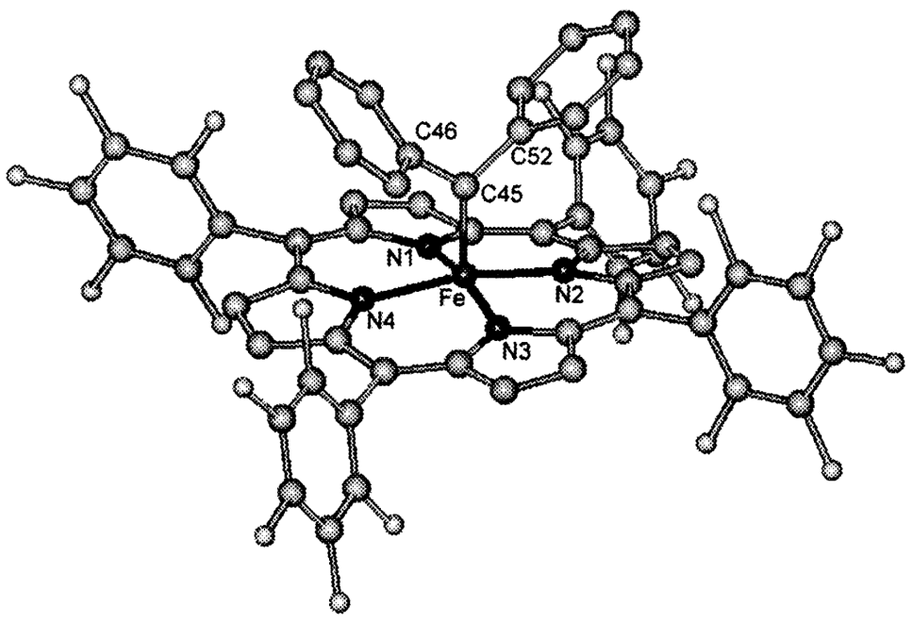
Imada, Y.; Nakamura, H.; Takano, Y. *J. Comp. Chem.* **2018**, *39*, 143.

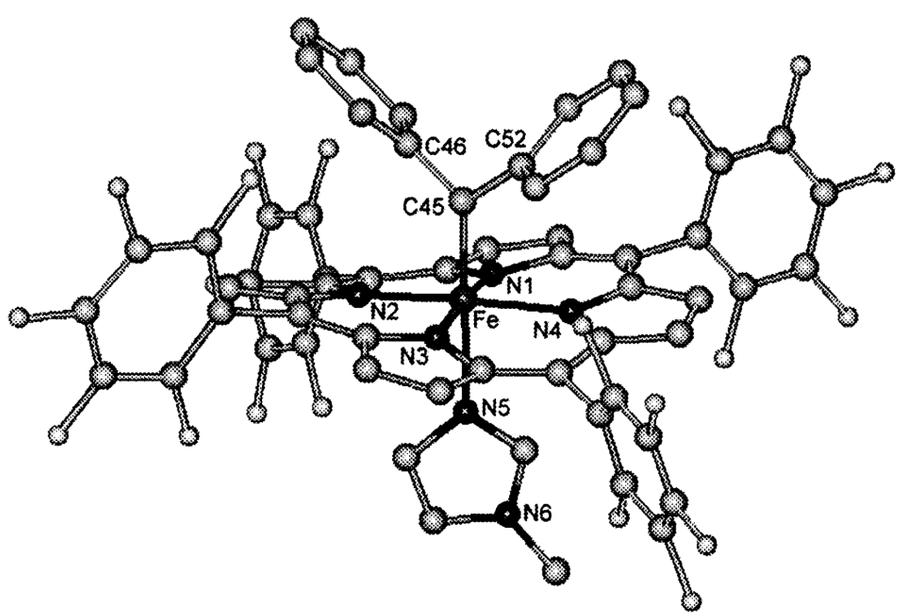
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Evaluating an alternative iron carbene via X-ray crystallography









Fe–C_{45}: 1.767 Å

Fe–C_{45}: 1.827 Å

3. Axial ligands exhibit pronounced trans influence on carbene ligands

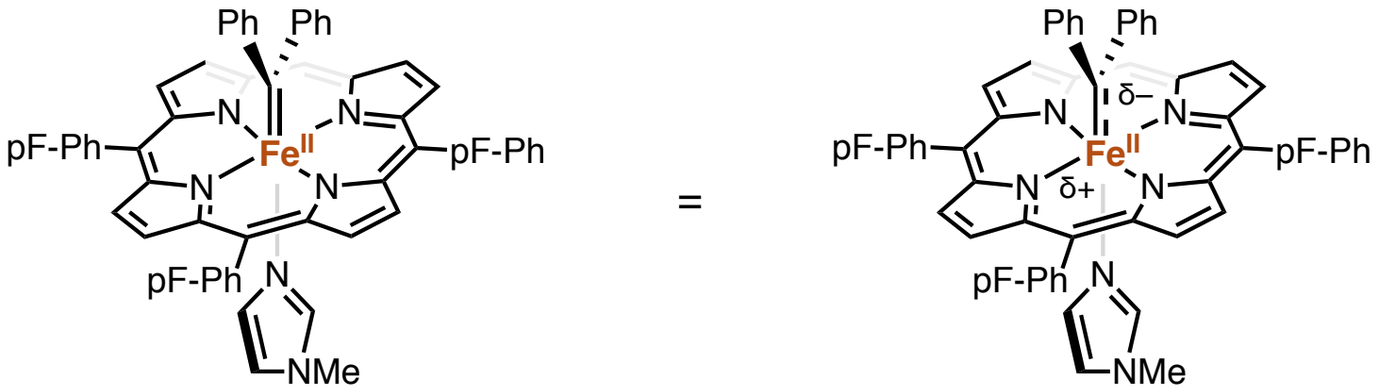
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Evaluating an alternative iron carbene via X-ray crystallography

Trans effect – kinetic impact on ligand lability

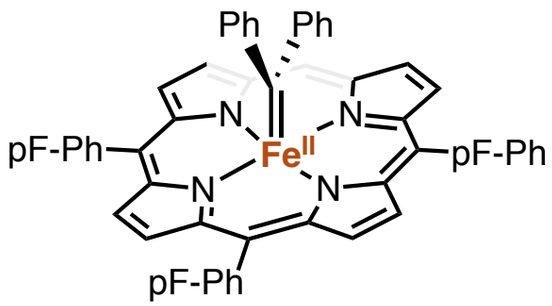
vs.

Trans influence – ground state destabilization (thermodynamic)



decreased Fe–C bond order,

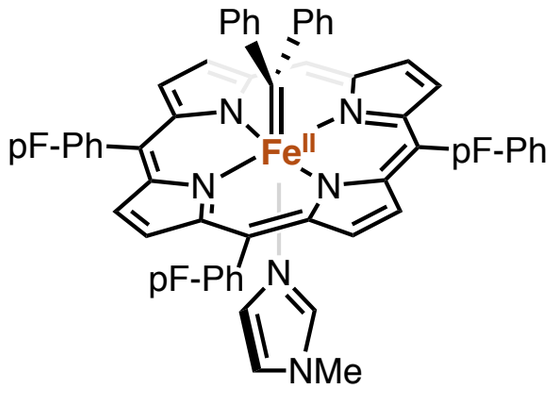
less stabilized, ***more reactive***



styrene

Δ

no reaction



styrene

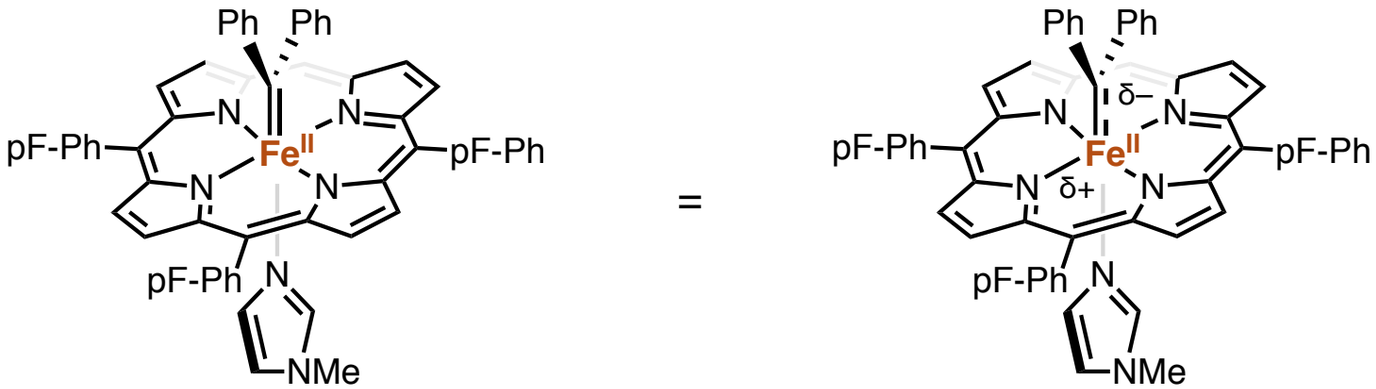
Δ

53% yield of Cp pdt

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

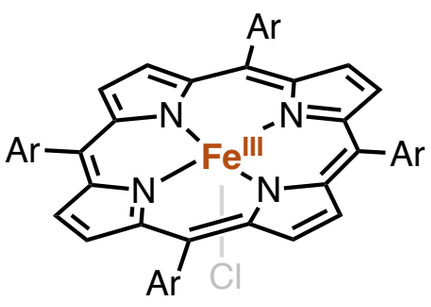
Evaluating an alternative iron carbene via X-ray crystallography

Do these stoichiometric findings have any relevance to highly trans-selective catalytic reactions?



decreased Fe–C bond order, less stabilized, ***more reactive***

vs.

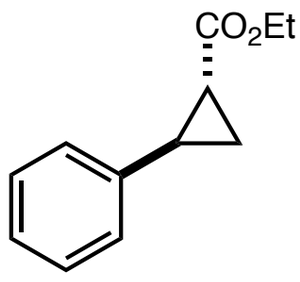


styrene (1500 eq.)

EDA (500 eq.)

Lewis base (20 eq.)

CH_2Cl_2, rt, 5h

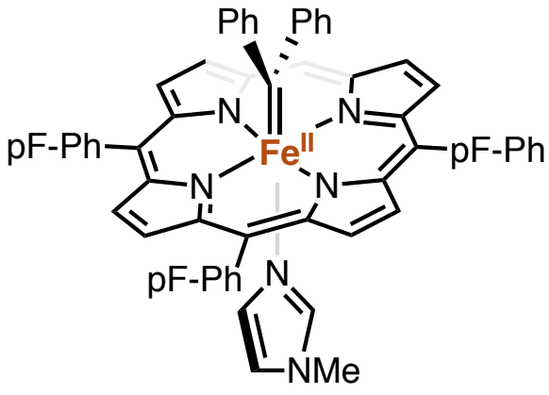


	none	pyridine
trans/cis ratio	**12:1**	**33:1**
TON	**368**	**307**

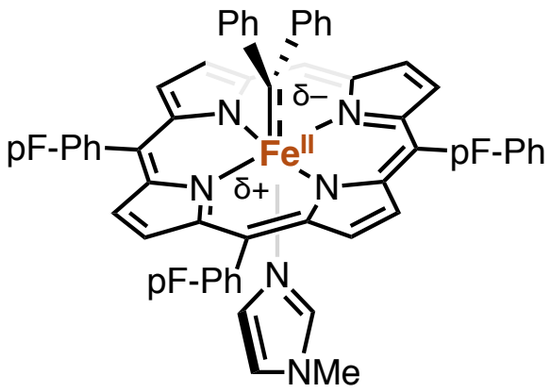
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Explaining the high trans-selectivity imparted by axial ligands

Must consider the impact of axial binding on thermodynamics and kinetics of carbene transfer



decreased Fe–C bond order, ***thermodynamically more reactive*** *due to ground state destabilization*



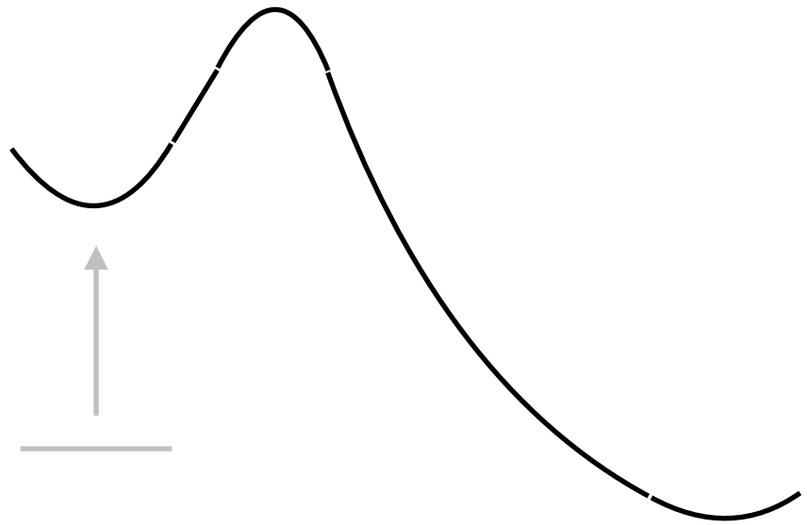
trans influence decreases electrophilicity of iron carbene,

kinetically less reactive *for cyclopropanation*

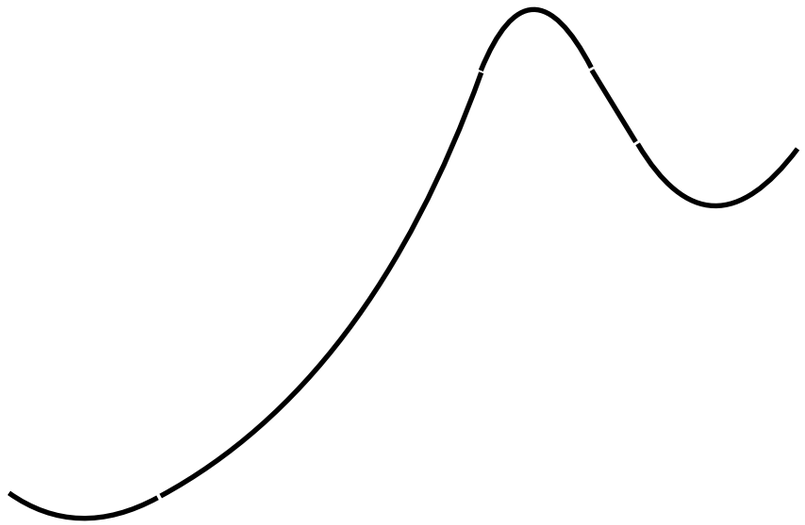
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Hammond's postulate narrows down the possibilities

early (SM-like) TS – favored for more exothermic processes



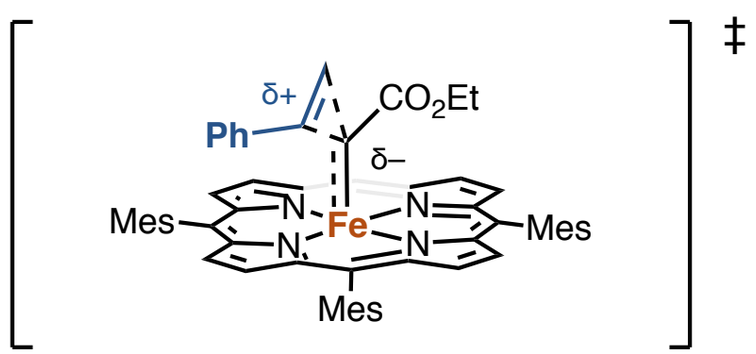
late (pdt-like) TS – favored for more endothermic processes



thermodynamic trans influence (ground-state destabilization) could lead to earlier TS

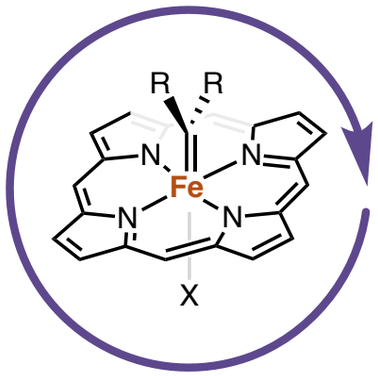
***BUT** in this case, we know that late, product-like TS results in high trans-selectivity*

kinetics – axial ligand imparts high selectivity by reducing electrophilicity of carbene, slowing reaction rate



Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

So why use iron porphrins as catalysts for carbene transfer?



synthetic framework with easily accessible derivatives, furnishes stable complexes (SAR)

modulates Fe(III)–Fe(II) $E°_{red}$, electrophilicity of carbene to enhance catalytic performance

predictable trans influence effects to further destabilize carbene, or to tune electrophilicity

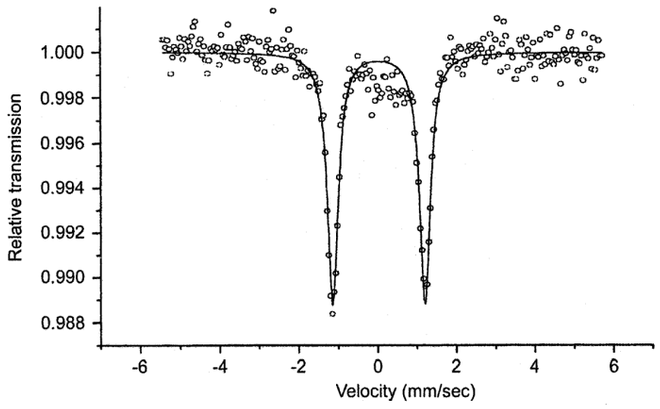
Weissenborn, M. J.; Koenigs, R. M. *ChemCatChem* **2020**, *12*, 2171.

A brief discussion on the oxidation state of iron

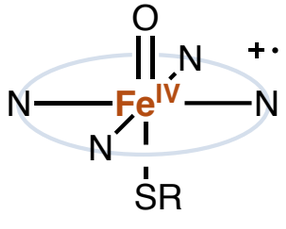
rationale for Fe(IV)

Mössbauer consistent with Fe(IV)

(isomer shift, quadrupole splitting)



Viewed as congener of well-characterized Compound I in CYP oxidation (little other evidence)

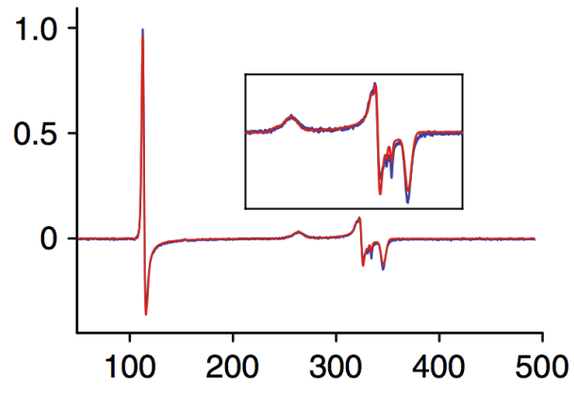


rationale for Fe(III)

Would formally exist as Fe(III) and carbene radical anion

↓

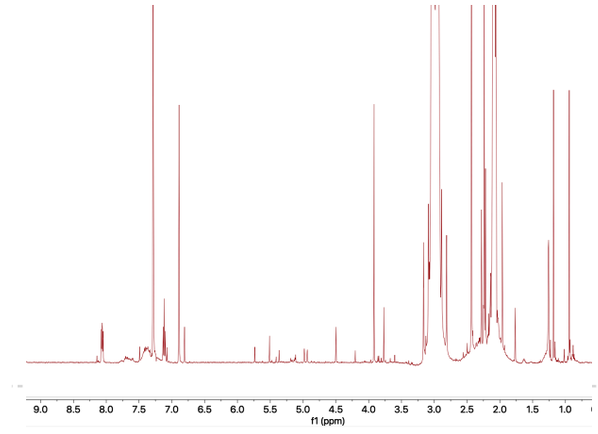
Mössbauer or EPR detection



While known for other ligands, uncommon to observe radical mechanisms in these reactions

rationale for Fe(II)

NMR data generally diamagnetic for model complexes



indicates low-spin, d^6 Fe(II)

First principles: carbene neutral $2e^-$ donor for Fischer complexes

↓

Most commonly accepted formalism

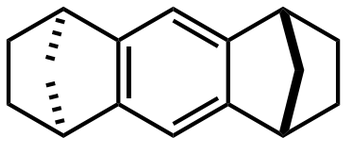
Hayashi, T.; Tinzl, M.; Mori, T.; Krengel, U.; Proppe, J.; Soetbeer, J.; Klose, D.; Jeschke, G.; Reiher, M.; Hilvert, D. *Nat. Catal.* **2018**, *1*, 578.

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Limitations of iron porphyrins – stereoselectivity

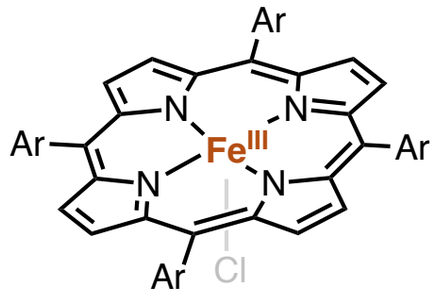
Beyond challenges in cis-diastereoselectivity, porphyrins struggle to in delivering high enantiopurity

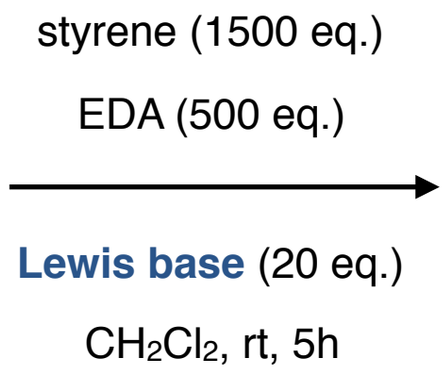
*chiral meso-substitution must be large to influence TS… **but** prevents substrate access, decreases reactivity*

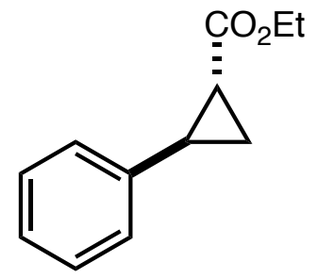


"Ar"

best non-biocat. ee to date



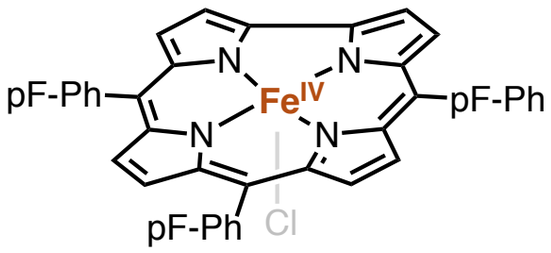




	none	pyridine	DMAP	N-Me imid.	N-Me pyrrolidine	DMSO
trans/cis ratio	**12:1**	**33:1**	**24:1**	**26:1**	**27:1**	**17:1**
TON	**368**	**307**	**321**	**275**	**293**	**385**
ee	**80%**	**82%**	**81%**	**83%**	**86%**	**82%**

Lai, T.S.; Chan, F.-Y.; So, P.-K.; Ma, D.-L.; Wong, K.-Y.; Che, C.-M. *Dalton Trans.* **2006**, *1*, 4845.

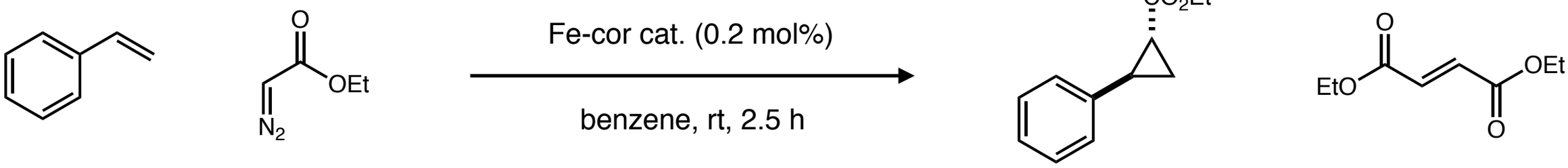
Other macrocyclic ligands – iron corrole complexes



Fe-cor

can stabilize Fe(III) or Fe(IV) oxidation states in precatalyst

Fe(III) state is active catalyst



10 eq.

63% yield

1.5:1 dr

30% yield

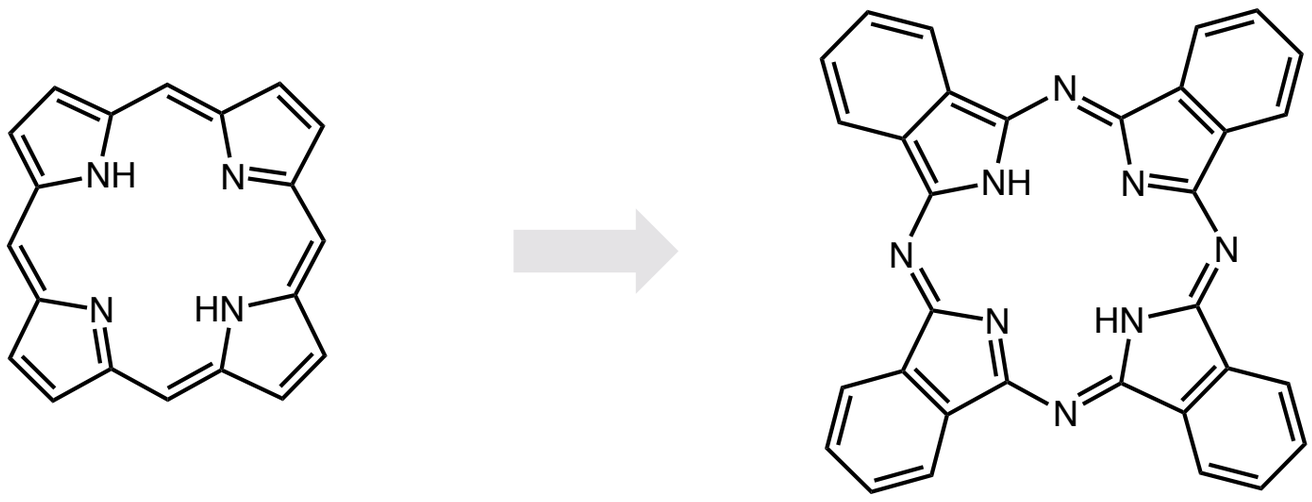
capable system, but higher oxidation state renders catalyst too reactive

decomposition to bypdts

consistently low dr

Simkhovich, L.; Mahammed, A.; Goldberg, I.; Gross, Z. *Chem. Eur. J.* **2001**, *7*, 1041.

Other macrocyclic ligands – iron phthalocyanine complexes



high degrees of structural similarity

Is this a feasible alternative ligand?

select cases reported *(up to 5:1 dr favoring trans, with inferior performance to porphyrins),* ***but…***

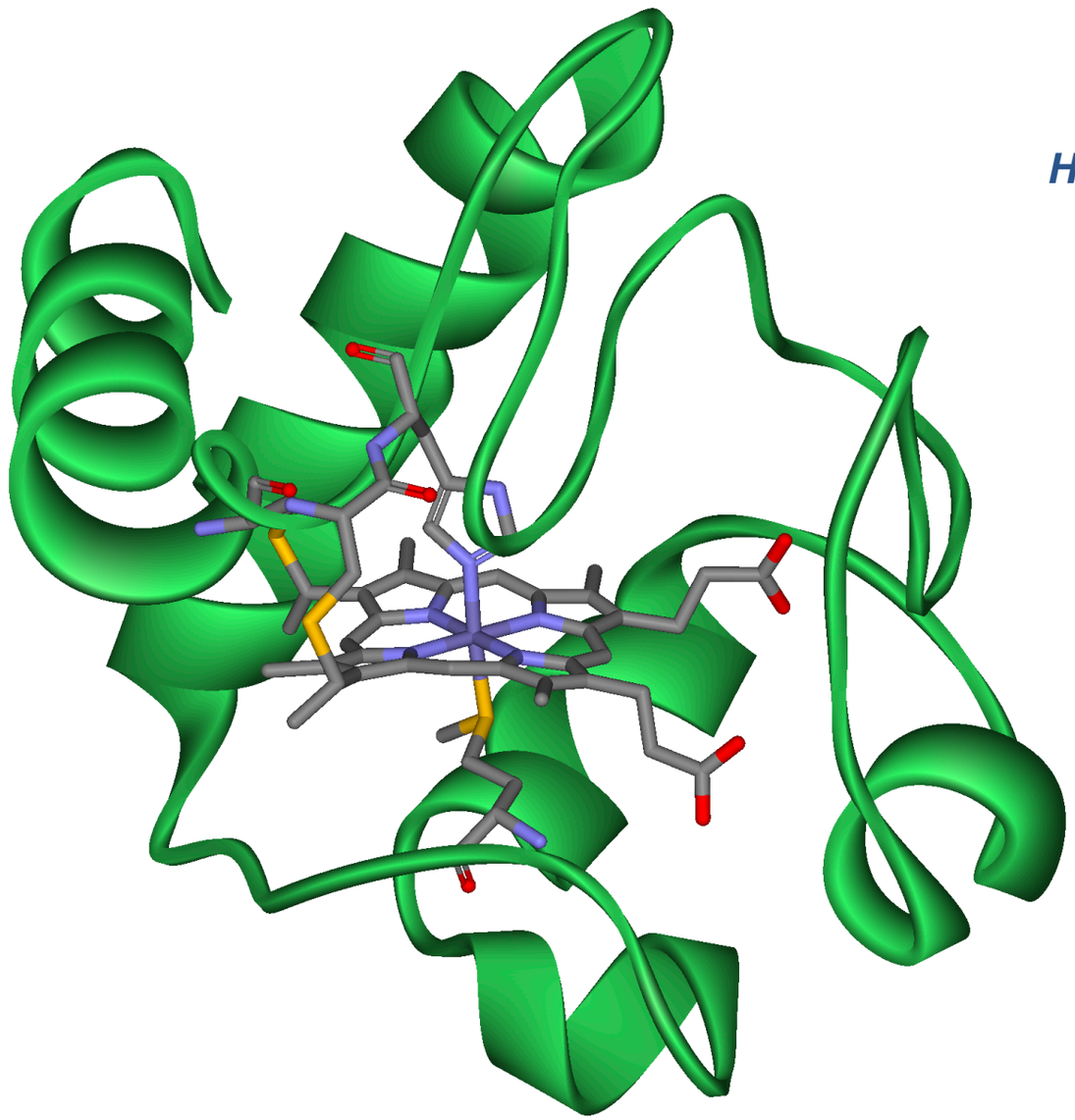
Most Fe phthalocyanines poorly soluble in solvents for diazo reactions, no systematic studies on SAR for phthalocyanine ligand framework

Liu, H.-H.; Wang, Y.; Shu, Y.-J.; Zhou, X.-G.; Wu, J.; Yan, S.-Y. *J. Mol. Catal. A: Chem.* **2006**, *246*, 49.

Outline

- *Development of small molecules iron porphyrin catalysts for carbene reactions*
- ***Development of hemoprotein catalysts for biocatalytic carbene reactions***
- *Summarizing the carbene-based transformations enabled by iron porphyrins*
- *Future directions in iron porphyrin-catalyzed carbene chemistry*

The translation of carbene reactivity to biocatalytic systems



Heme prosthetic groups are commonly found in biology, exploited for gas/electron transport and catalysis

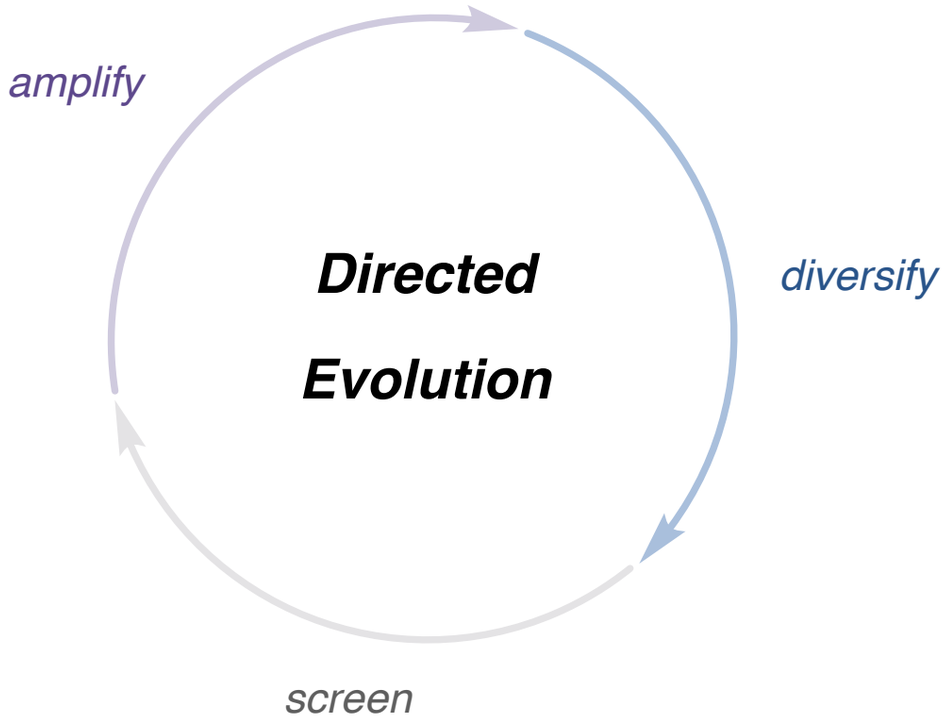
examples include:

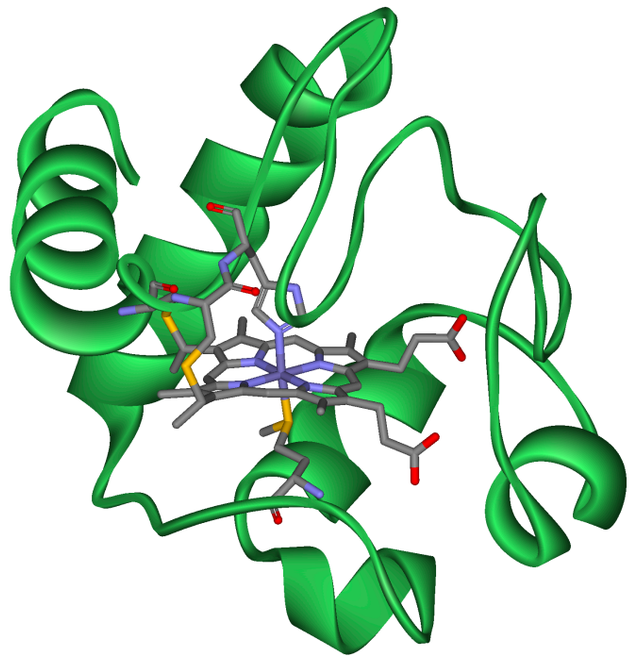
- *hemoglobin*
- *myoglobin*
- *cyctochromes*
- *peroxidases*
- *catalases*

Can we redirect nature's hemoproteins to perform abiological Fe porphyrin reactions?

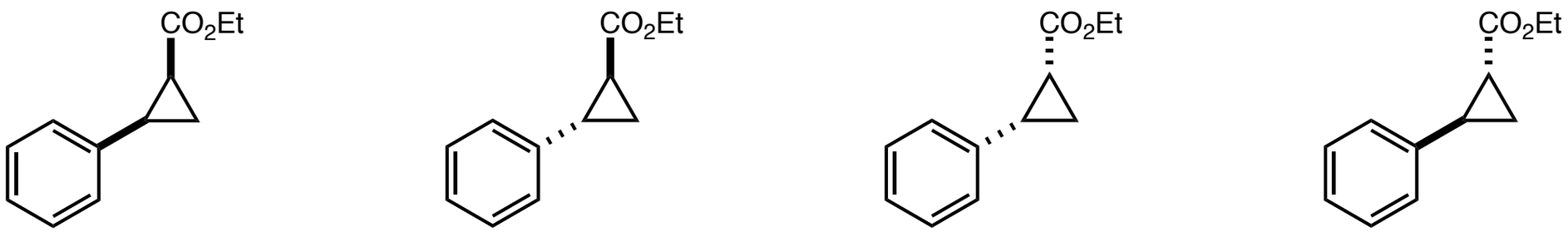
Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Advantages of employing hemoproteins for carbene transfer





evolutionary pressure can optimize reactivity – no need for "rational design" (non-natural cofactors, residues, etc.)

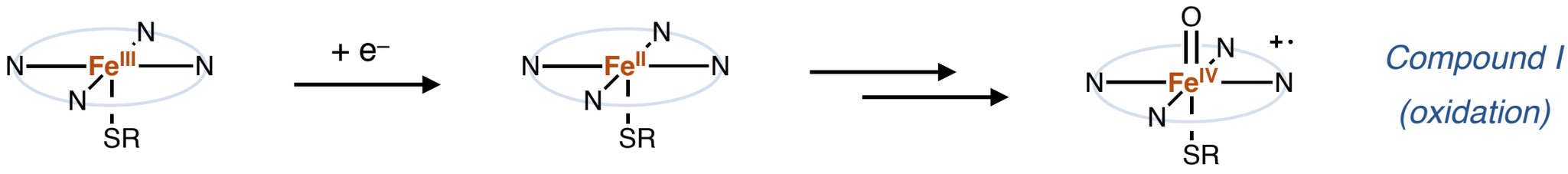


most feasible way to access to all possible stereoisomers

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

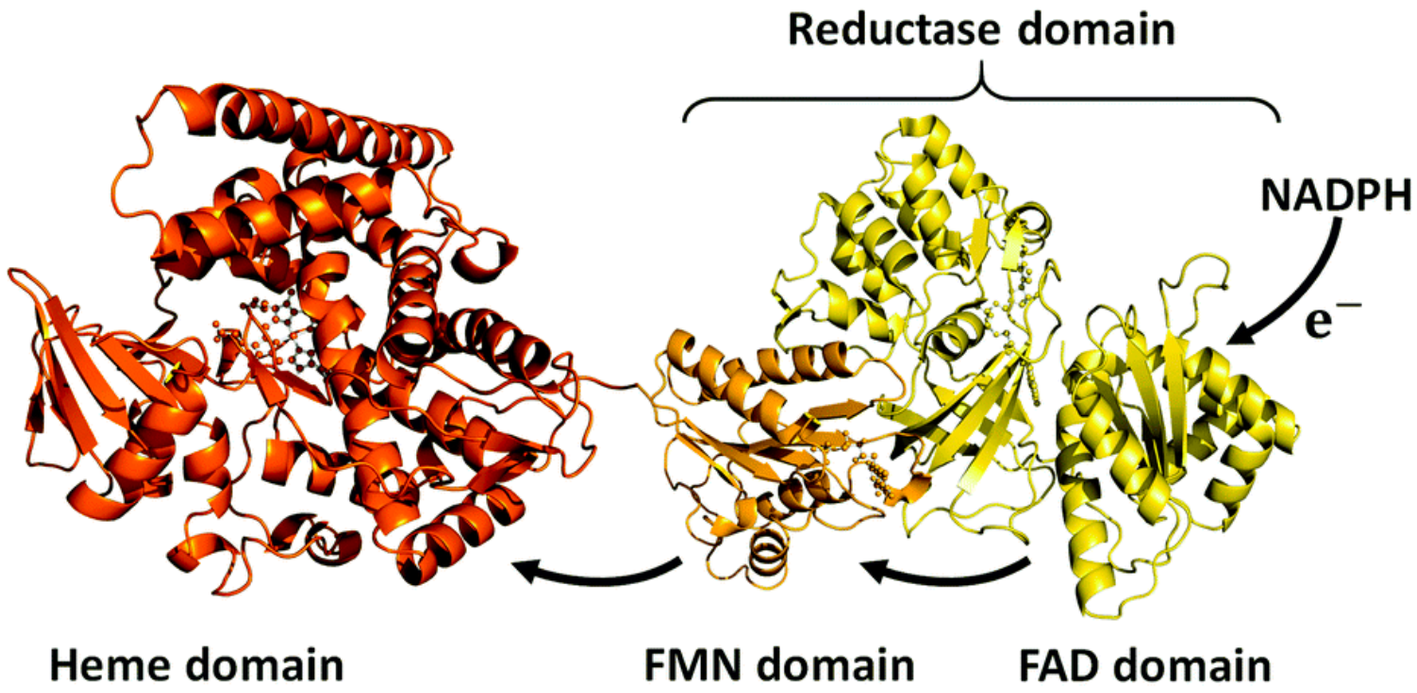
Accessing the key reduced state for biocatalysis

CYP enzymes undergo Fe(III) reduction, much like carbene transfer catalysts:



Compound I

(oxidation)

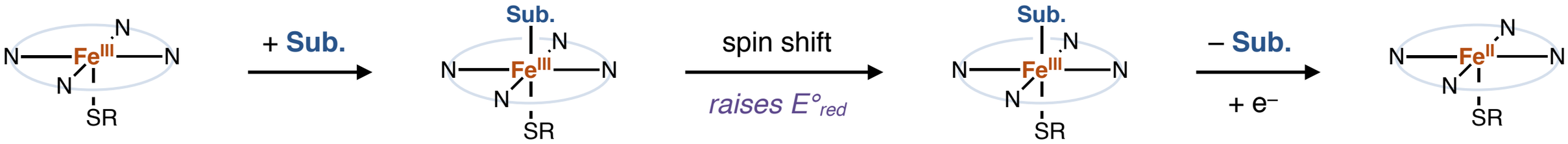


Omura, K.; Aiba, Y.; Onoda, H.; Stanfield, J. K.; Ariyasu, S.; Sugimoto, H.; Shiro, Y.; Shoji, O.; Watanabe, Y. *Chem. Commun.* **2018**, *54*, 7892.

Coelho, P. S.; Wang, Z. J.; Ener, M. E.; Baril, S. A.; Kannan, A.; Arnold, F. H.; Brustad, E. M. *Nat. Chem. Biol.* **2013**, *9*, 485.

Accessing the key reduced state for biocatalysis

Substrate binding – triggering the key reduction step



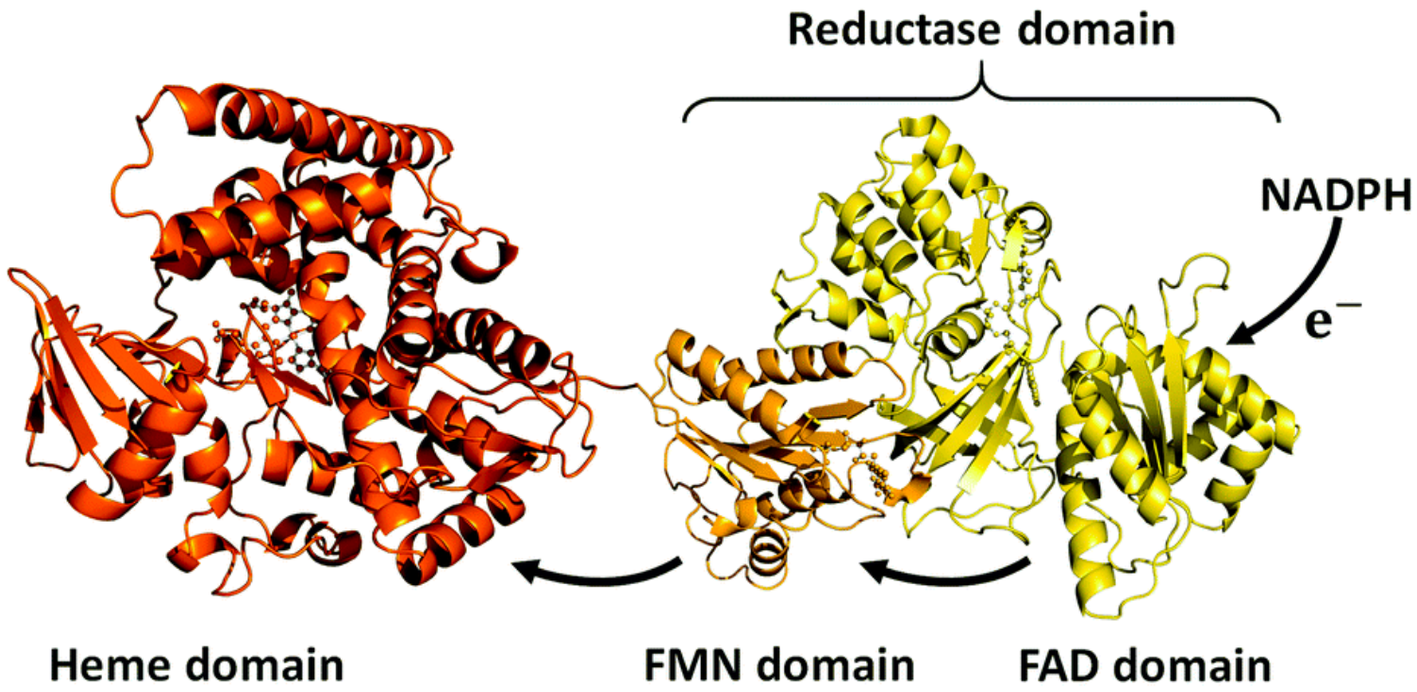
diazo compounds: weaker binding than natural substrates, cannot induce reductase e⁻ transfer

Solution #1:

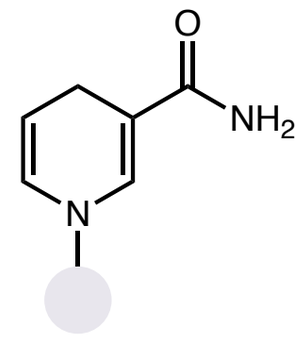
stronger reductant

$Na_2S_2O_4$

$E°_{red} = -660$ *mV*



NADPH



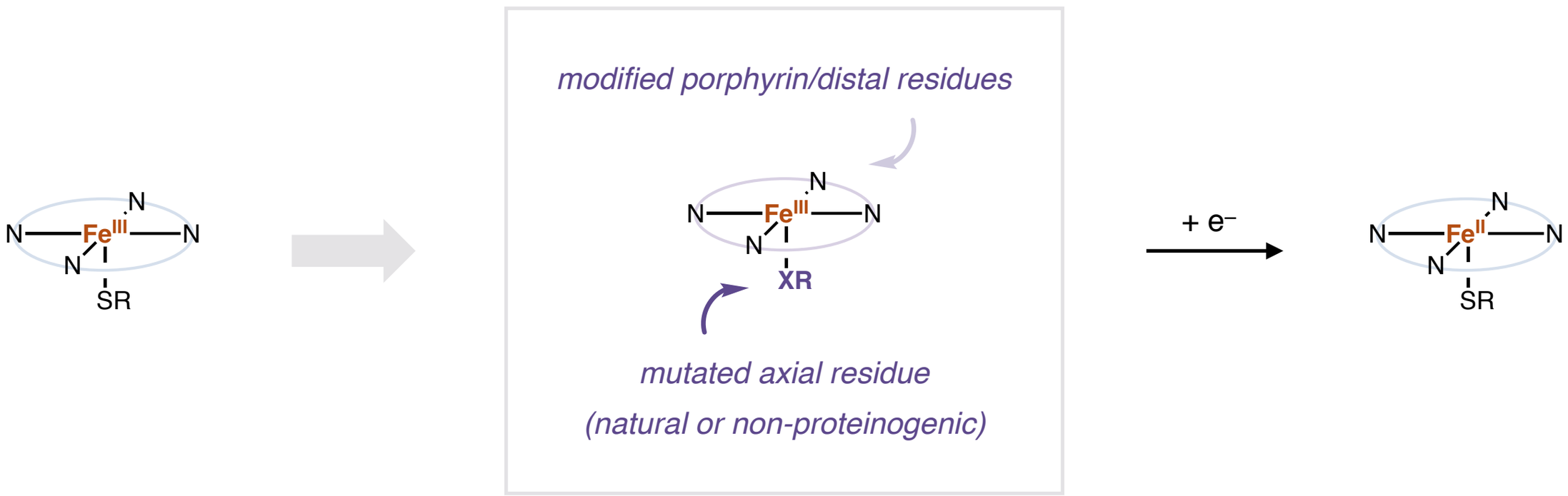
$E°_{red} = -320$ *mV*

Omura, K.; Aiba, Y.; Onoda, H.; Stanfield, J. K.; Ariyasu, S.; Sugimoto, H.; Shiro, Y.; Shoji, O.; Watanabe, Y. *Chem. Commun.* **2018**, *54*, 7892.

Coelho, P. S.; Wang, Z. J.; Ener, M. E.; Baril, S. A.; Kannan, A.; Arnold, F. H.; Brustad, E. M. *Nat. Chem. Biol.* **2013**, *9*, 485.

Accessing the key reduced state for biocatalysis

Solution #2: keep NAD(P)H as reductant, but modify heme to raise unbound $E°_{red}$

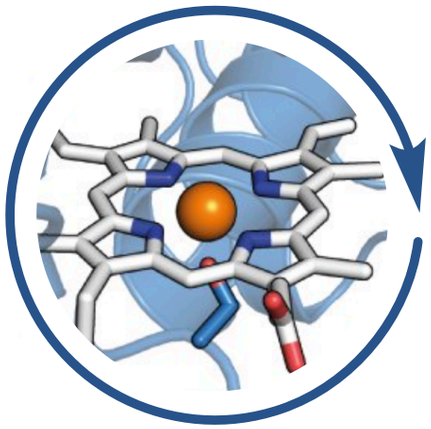


As seen before, modifications that raise $E°_{red}$ also likely to furnish more electrophilic carbene

Omura, K.; Aiba, Y.; Onoda, H.; Stanfield, J. K.; Ariyasu, S.; Sugimoto, H.; Shiro, Y.; Shoji, O.; Watanabe, Y. *Chem. Commun.* **2018**, *54*, 7892.

Coelho, P. S.; Wang, Z. J.; Ener, M. E.; Baril, S. A.; Kannan, A.; Arnold, F. H.; Brustad, E. M. *Nat. Chem. Biol.* **2013**, *9*, 485.

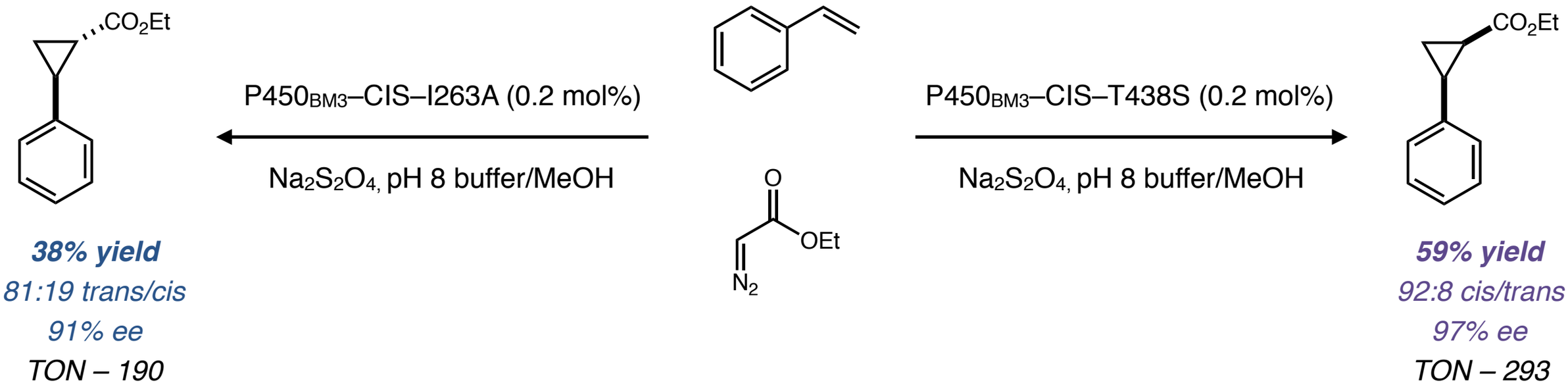
First demonstration of in vitro carbene reactions catalyzed by hemoproteins



While HRP, Cyt C and Mb provided activity,

P450 was most readily optimized for divergent selectivity

single mutations (often introduction of alanine in active site) could have a dramatic impact:

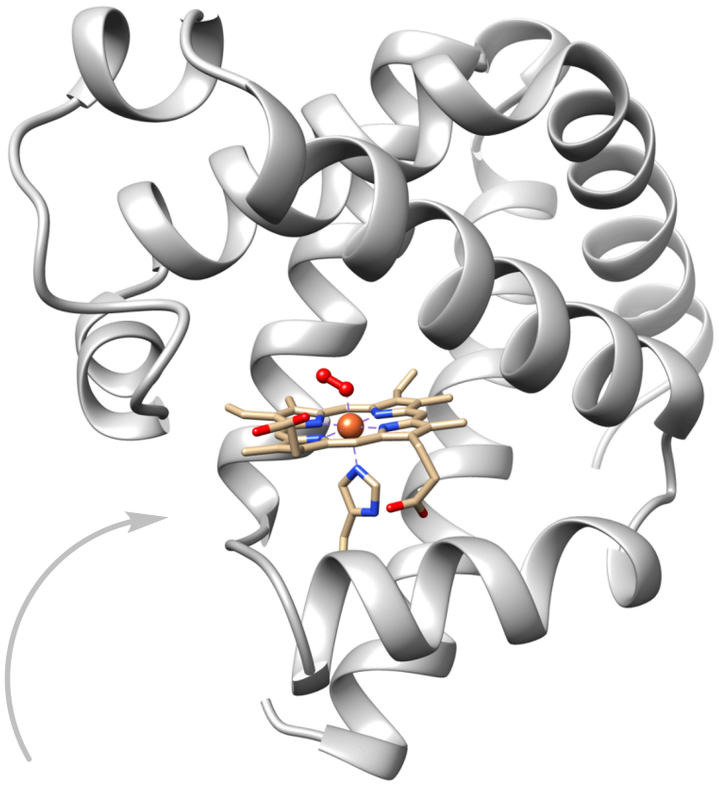


38% yield
81:19 trans/cis
91% ee
TON – 190

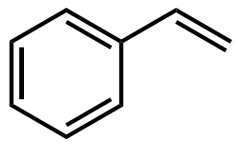
59% yield
92:8 cis/trans
97% ee
TON – 293

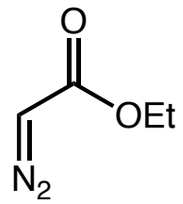
Coelho, P. S.; Brustad, E. M.; Kannan, A.; Arnold, F. H. *Science* **2012**, *339*, 307.

Distal modifications to enhance reactivity of His-stabilized Myoglobin



proximal His
stabilizing heme

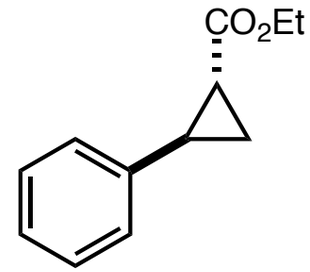




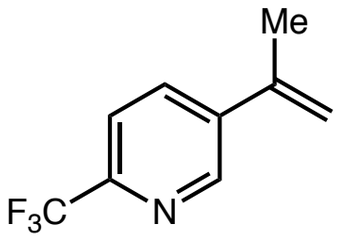
2 eq.

Mb variant (0.2 mol%)

$Na_2S_2O_4$ (1 eq.), KPi (pH = 7)

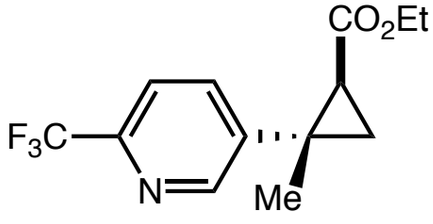


	conversion	TON	de_{trans}	ee_{trans}
Mb (wild-type protein)	**36%**	**180**	**86%**	**6%**
Mb (L29T, H64V, V68L)	**58%**	**305**	**>99.9%**	**92%**



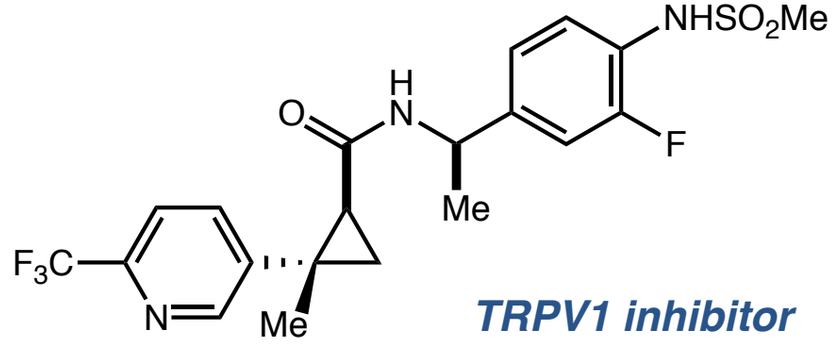
Mb variant, EDA

$Na_2S_2O_4$, KPi (pH = 7)



75% yield (0.83 g)

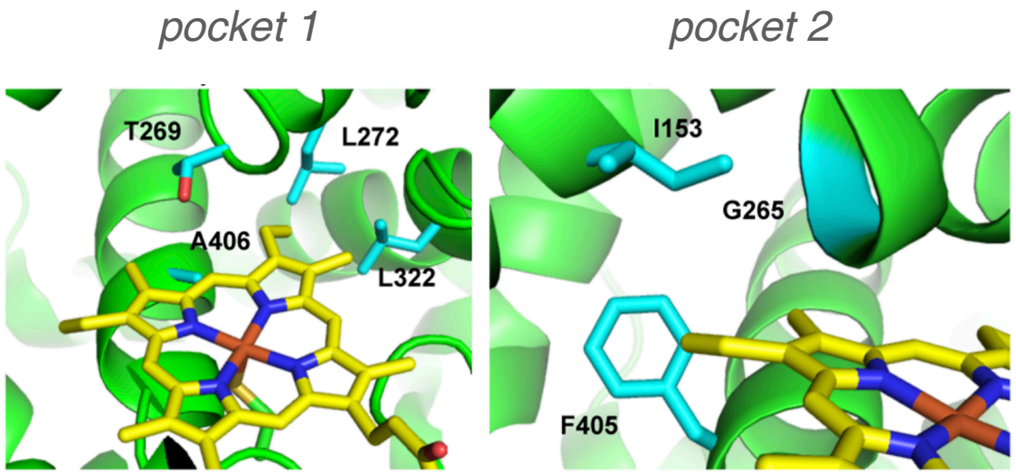
99.9% de, 99.9% ee



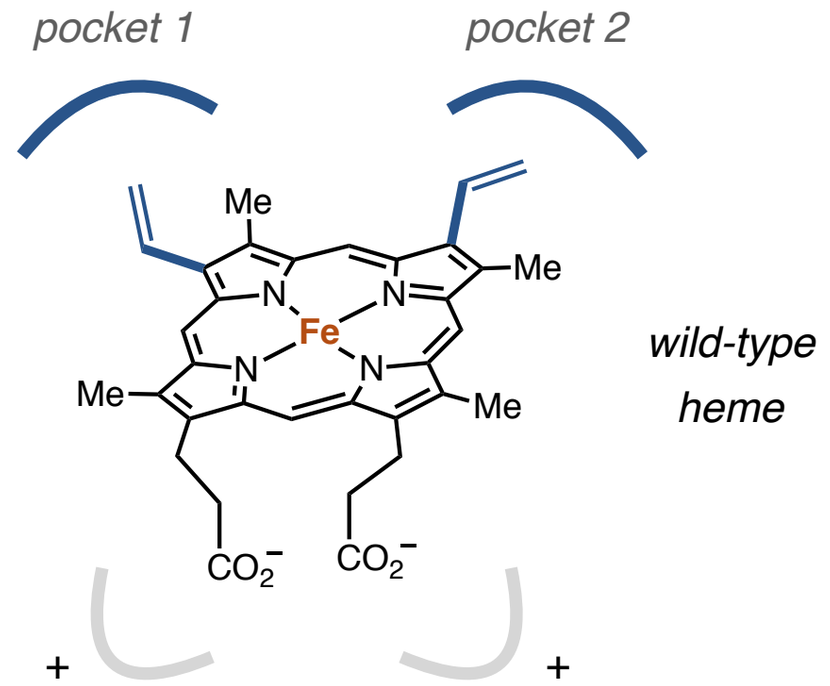
TRPV1 inhibitor

Bajaj, P.; Sreenilayam, G.; Tyagi, V.; Fasan, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 16110.

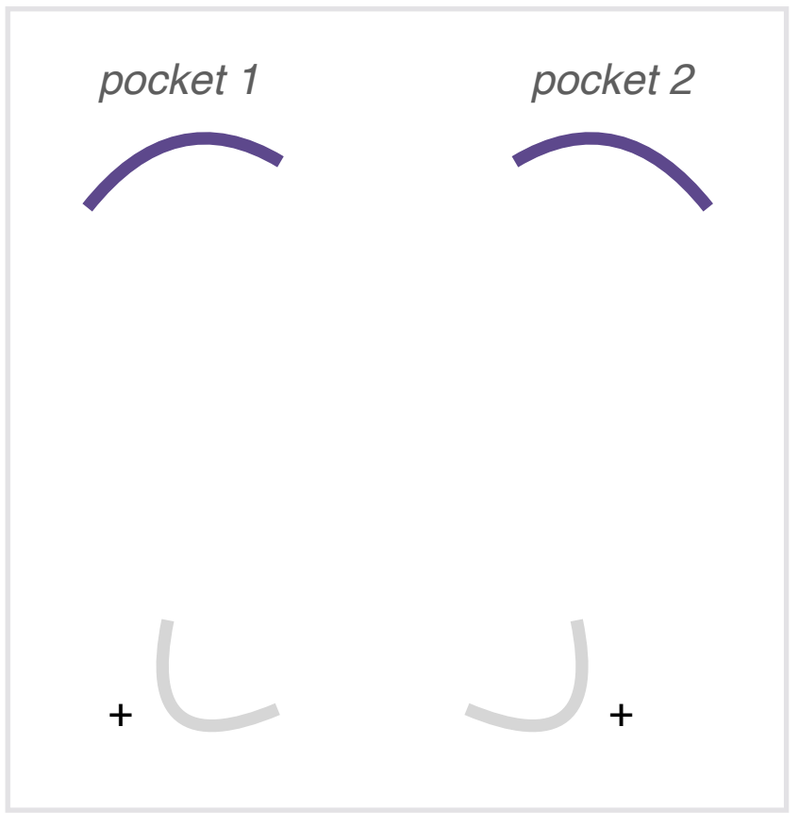
Incorporation of non-proteinogenic prosthetic groups in P450s

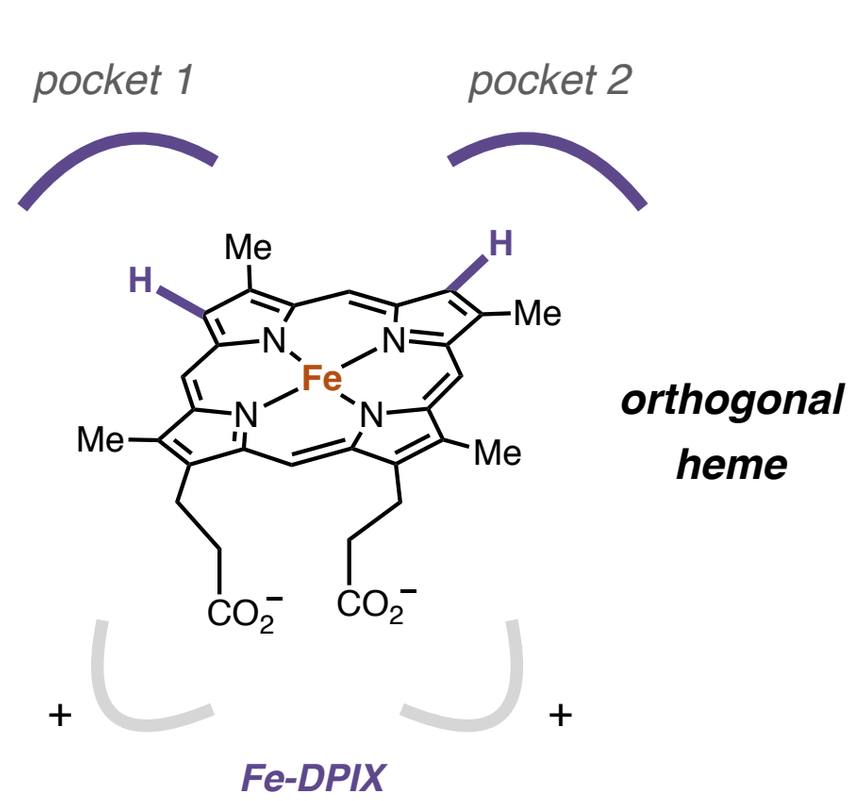


targeted mutations



orthogonal enzyme





orthogonal heme

Reynolds, E. W.; McHenry, M. W.; Cannac, F.; Gober, J. G.; Snow, C. D.; Brustad, E. M. *J. Am. Chem. Soc.* **2016**, *138*, 12451.

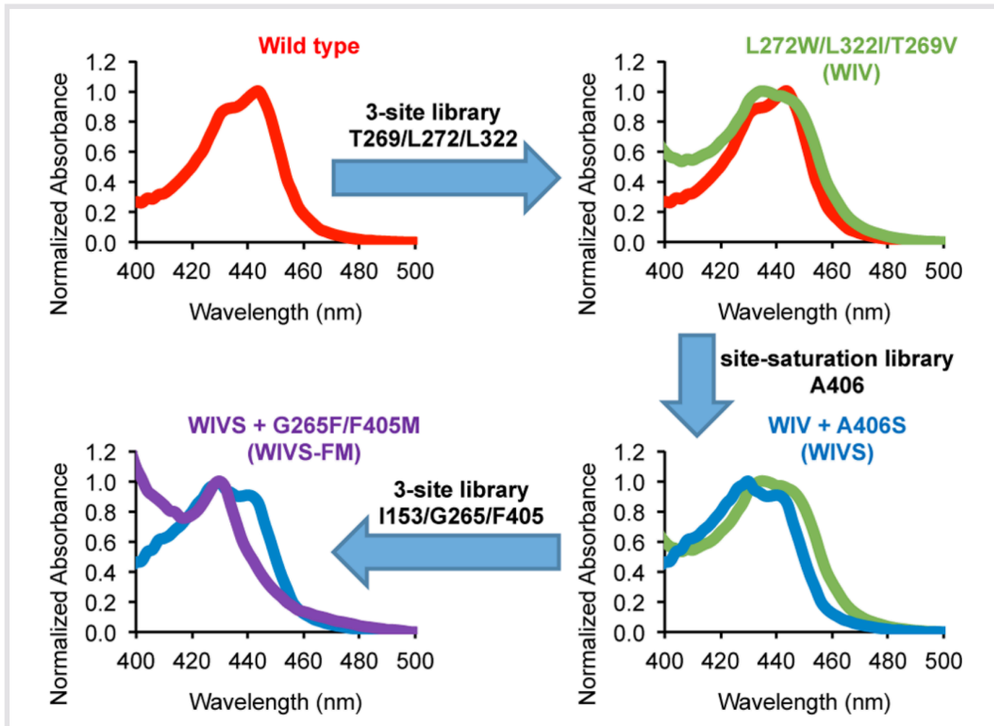
Incorporation of non-proteinogenic prosthetic groups in P450s

3 libraries, 6 total mutations

(4 in pocket 1, 2 in pocket 2)

selective incorporation of Fe-DPIX over native P450$_{BM3}$ heme

(via UV-Vis of ferrous–CO Soret shift)



TON trends with that of free cofactor

new reactivity opportunities via evolved enzyme/cofactor pairs

	yield	TON	dr$_{trans/cis}$	ee$_{trans}$
heme	**7%**	**35**	**84:16**	**11%**
Fe-DPIX	**5%**	**23**	**87:13**	**11%**
P450$_{BM3}$ T268A/heme	**57%**	**284**	**99:1**	**92%**
WIVS-FM T268A/Fe-DPIX	**44%**	**221**	**88:12**	**46%**

Reynolds, E. W.; McHenry, M. W.; Cannac, F.; Gober, J. G.; Snow, C. D.; Brustad, E. M. *J. Am. Chem. Soc.* **2016**, *138*, 12451.

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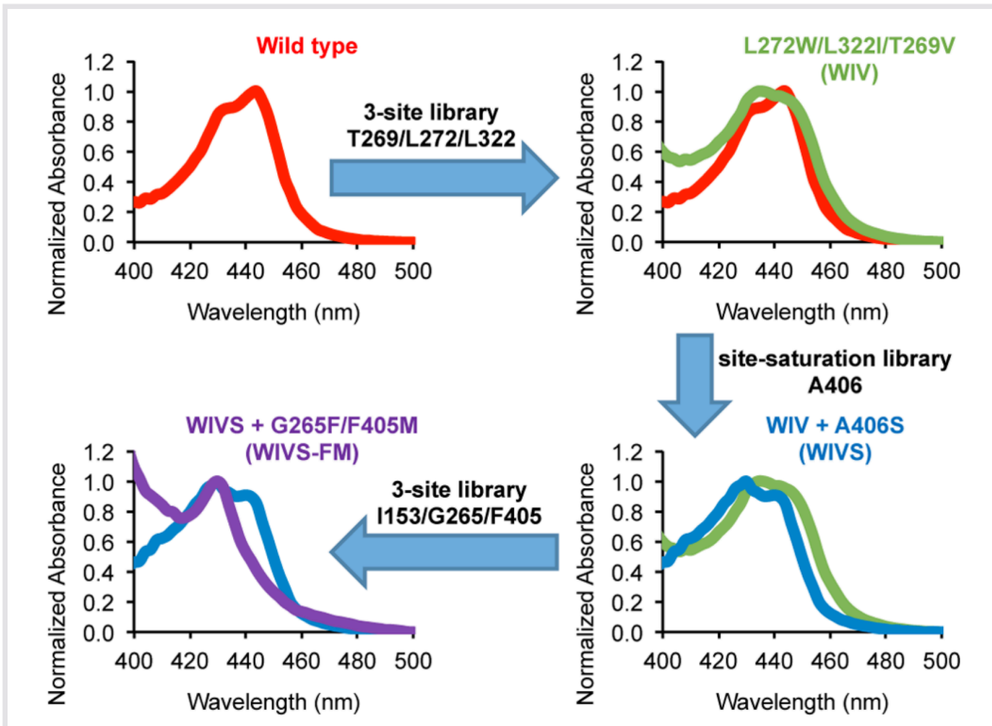


new opportunities for chemoselectivity by eliminating side reactions of native enzyme/heme

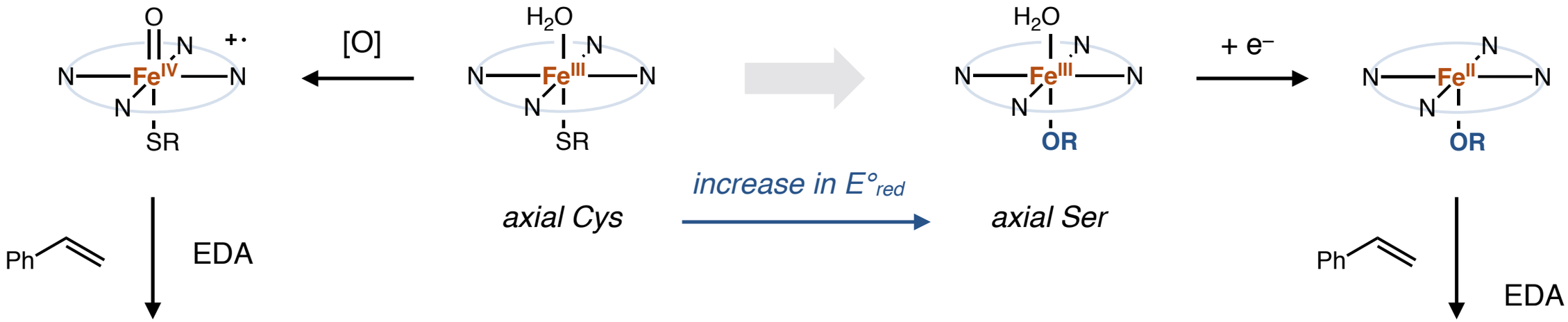
		yield	TON	dr$_{trans/cis}$	ee$_{trans}$
competent for monooxygenation →	*P450$_{BM3}$ T268A/heme*	**57%**	**284**	**99:1**	**92%**
not capable of monooxygenation →	*WIVS-FM T268A/Fe-DPIX*	**44%**	**221**	**88:12**	**46%**

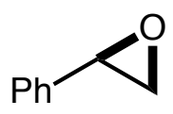
Reynolds, E. W.; McHenry, M. W.; Cannac, F.; Gober, J. G.; Snow, C. D.; Brustad, E. M. *J. Am. Chem. Soc.* **2016**, *138*, 12451.

Design of a fully proteinogenic, catalytically-active cytochrome "P411"

conventional pathway (no NADPH reduction)

axial mutant pathway (NADPH reduction)

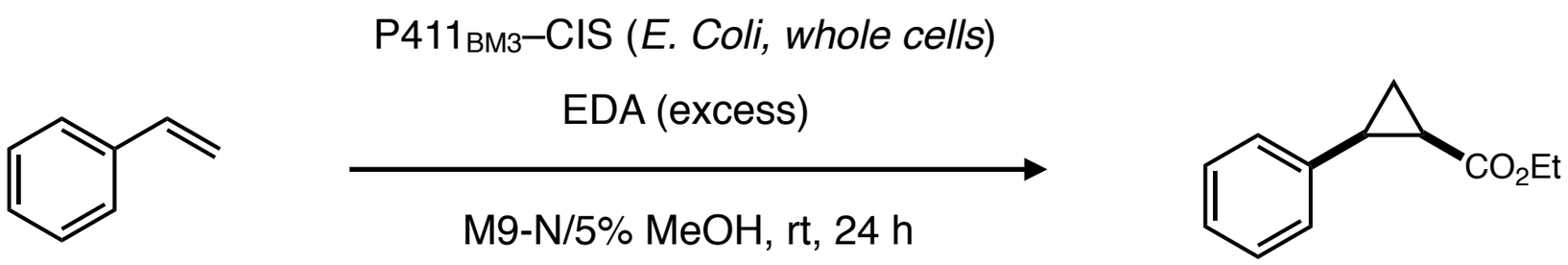




epoxide products

cyclopropane products

C400S mutation produces shift in Fe–CO Soret band (411 nm), ***enables NAD(P)H-driven catalysis using E. coli expression***



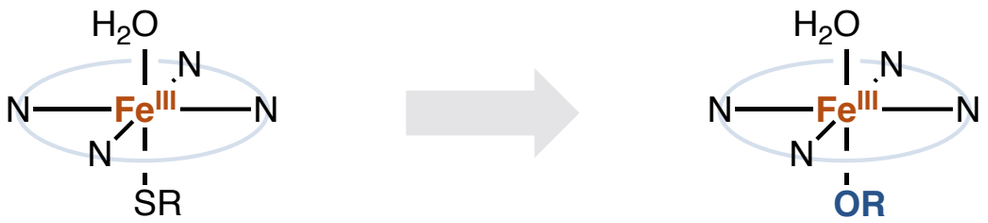
72% yield, 67800 TTN

9:1 dr, 99% ee

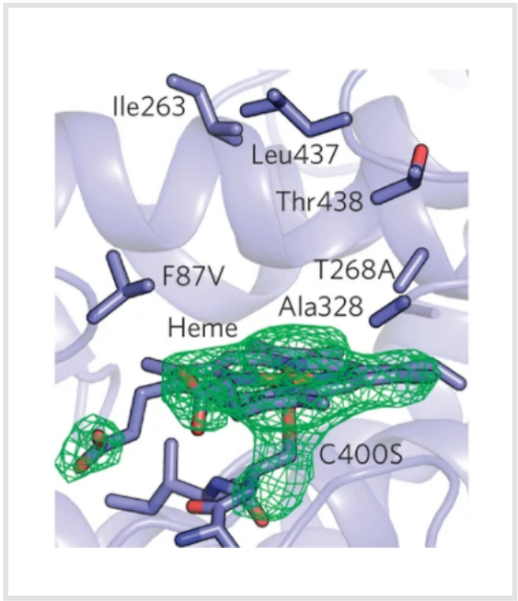
Coelho, P. S.; Wang, Z. J.; Ener, M. E.; Baril, S. A.; Kannan, A.; Arnold, F. H.; Brustad, E. M. *Nat. Chem. Biol.* **2013**, *9*, 485.

Design of a fully proteinogenic, catalytically-active cytochrome “P411”

Beyond cyclopropanation activity, C400S mutation produces variety of unique properties for P411

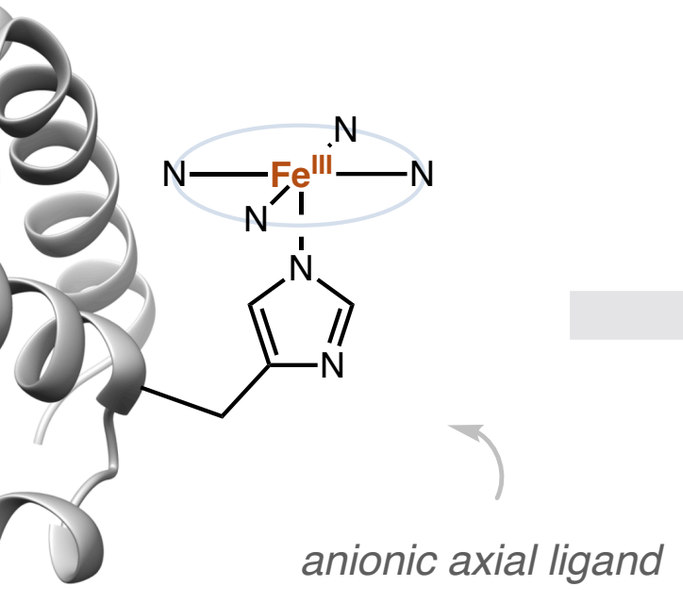


- *increase in thermostability (of purified heme domain)*
- *decrease in protein expression (3-fold lower than P450)*
- *ability to be reduced by either reductase domain or NAD(P)H itself*



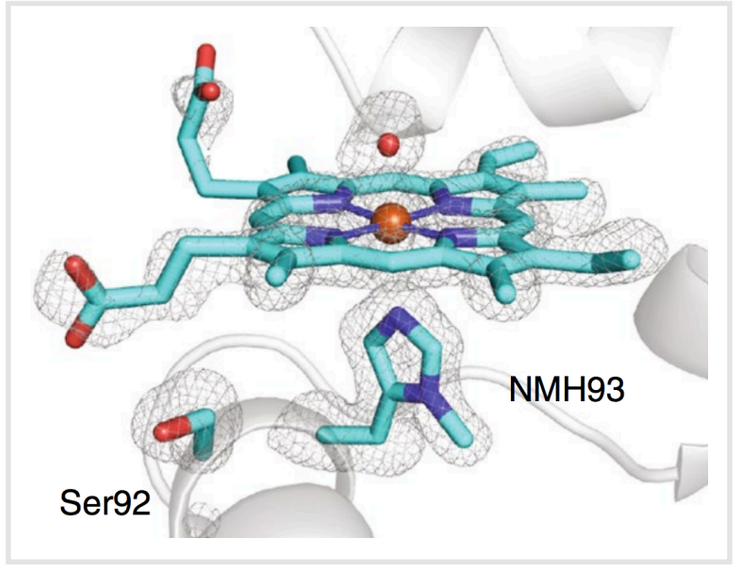
Coelho, P. S.; Wang, Z. J.; Ener, M. E.; Baril, S. A.; Kannan, A.; Arnold, F. H.; Brustad, E. M. *Nat. Chem. Biol.* **2013**, *9*, 485.

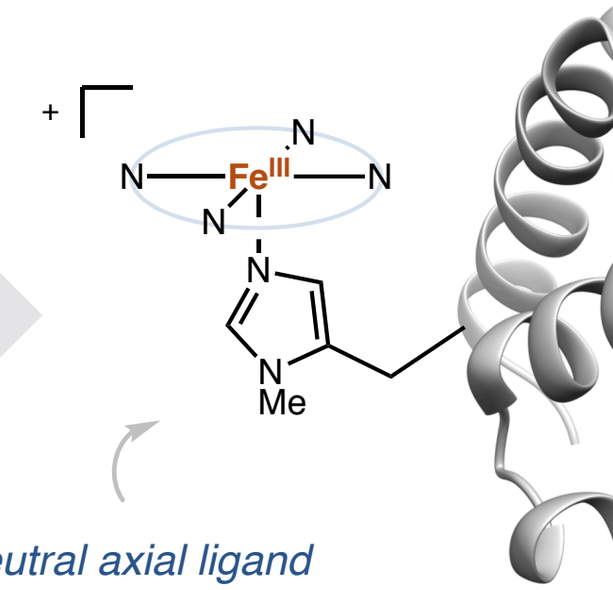
Proximal modifications to enhance reactivity of Myoglobin



anionic axial ligand

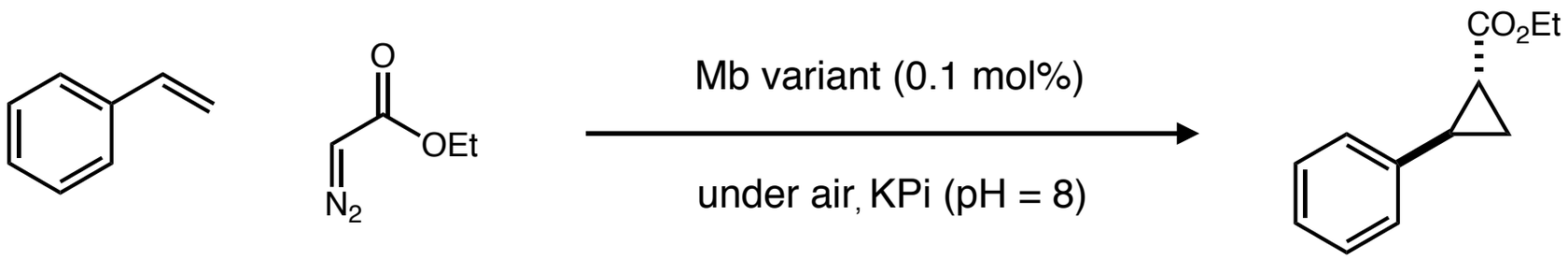
low E°$_{red}$, poor electrophilicity





neutral axial ligand

higher E°$_{red}$, more electrophilic

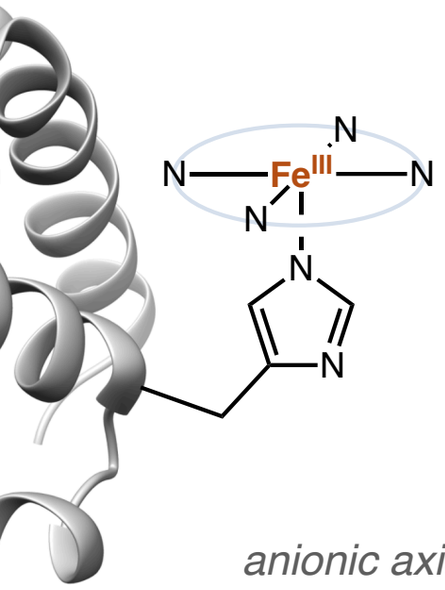


quantitative yield over 20 h, under aerobic and reductant-free conditions

>99% de, >99% ee

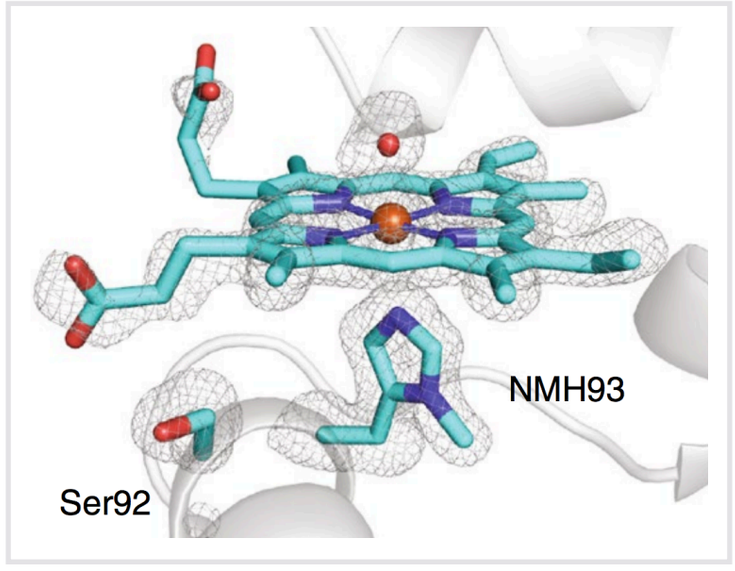
Hayashi, T.; Tinzl, M.; Mori, T.; Krengel, U.; Proppe, J.; Soetbeer, J.; Klose, D.; Jeschke, G.; Reiher, M.; Hilvert, D. *Nat. Catal.* **2018**, *1*, 578.

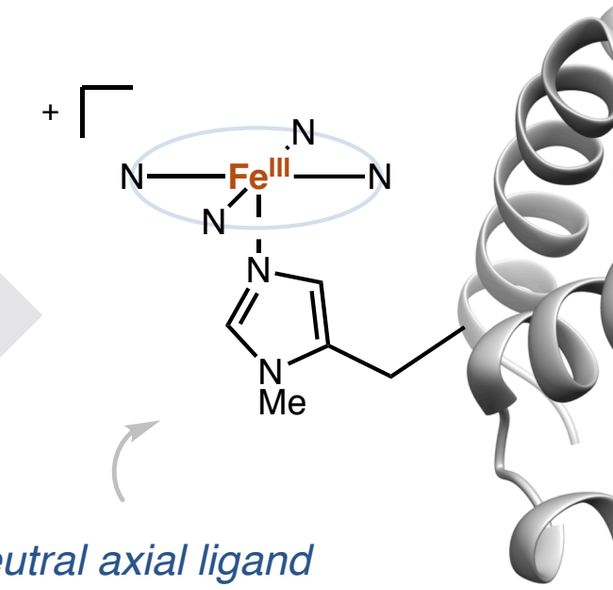
Proximal modifications to enhance reactivity of Myoglobin



anionic axial ligand (H93)

low E°$_{red}$, poor electrophilicity

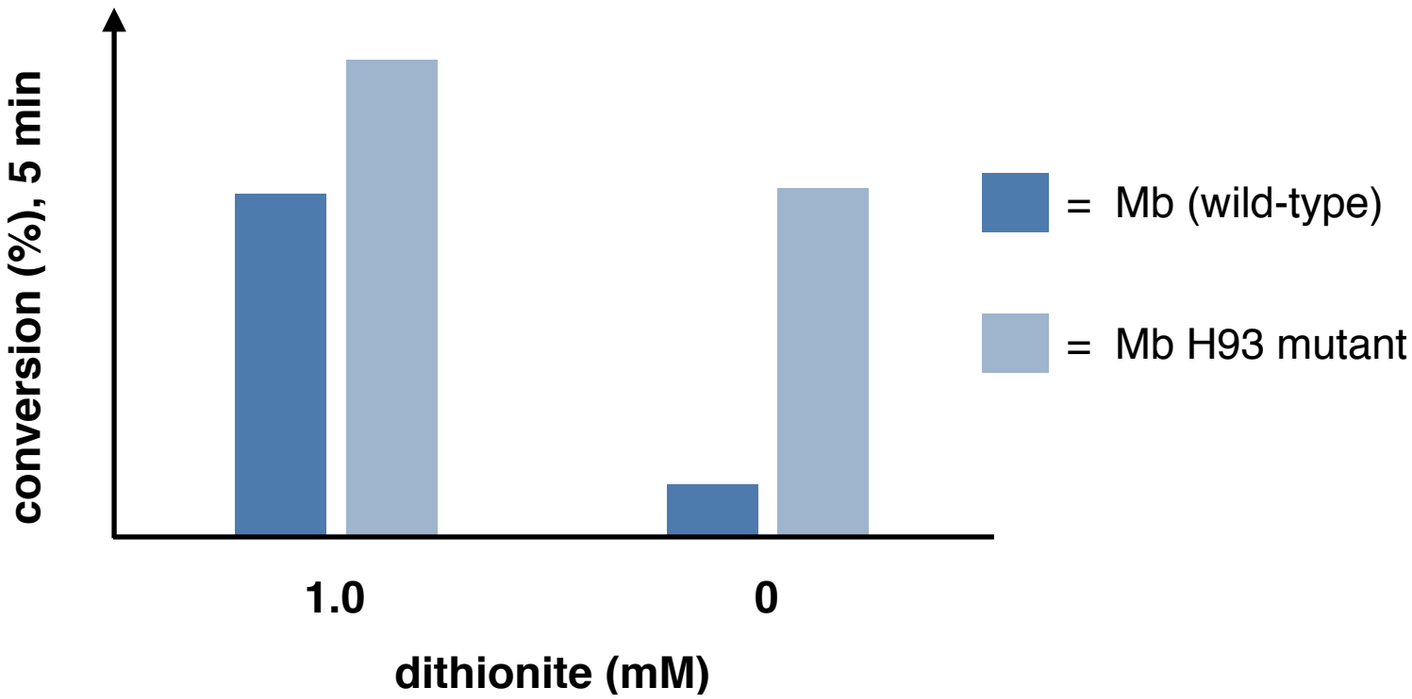




neutral axial ligand

higher E°$_{red}$, more electrophilic

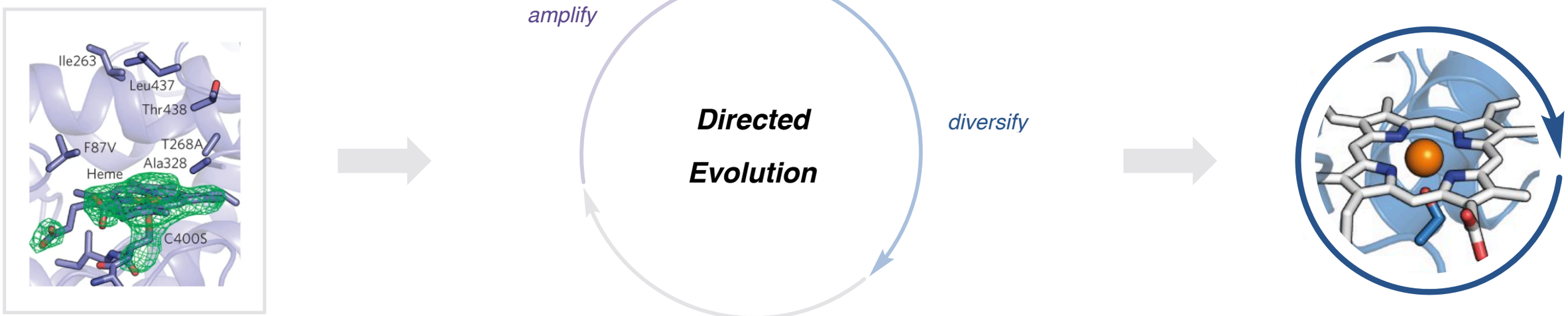
although this method requires non-proteinogenic amino acid, only a single (predictable) mutation required

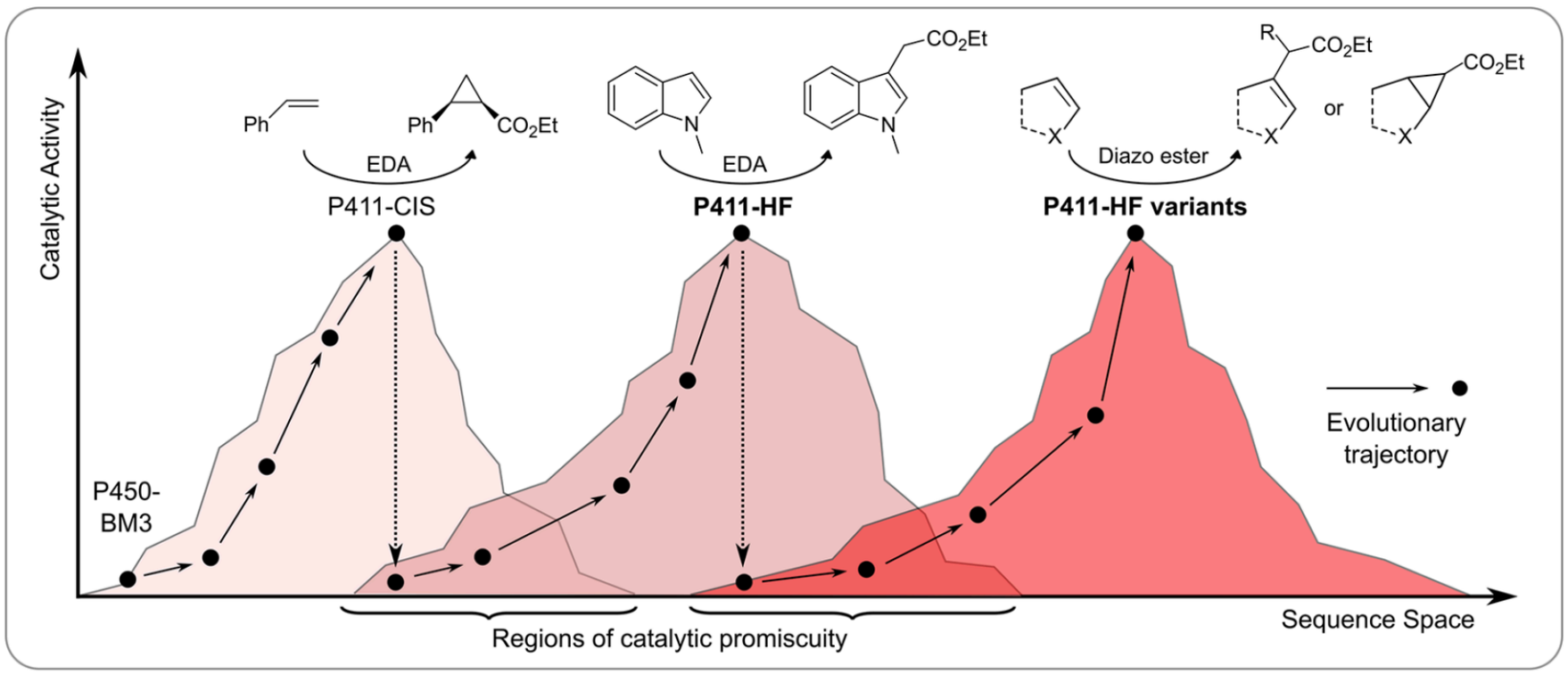


Hayashi, T.; Tinzl, M.; Mori, T.; Krengel, U.; Proppe, J.; Soetbeer, J.; Klose, D.; Jeschke, G.; Reiher, M.; Hilvert, D. *Nat. Catal.* **2018**, *1*, 578.

Directed evolution in the discovery of new P411s for indole alkylation

six rounds, 12 mutations through site-selective and random mutagenesis





Brandenberg, O. F.; Chen, K.; Arnold, F. H. *J. Am. Chem. Soc.* **2019**, *141*, 8989.

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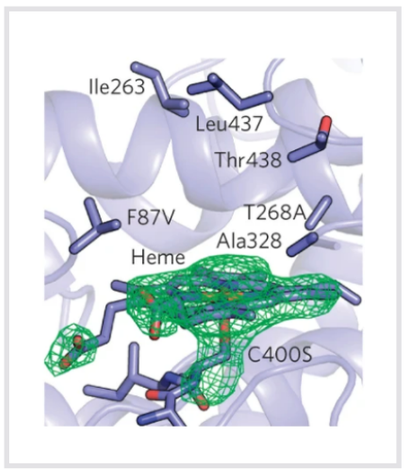
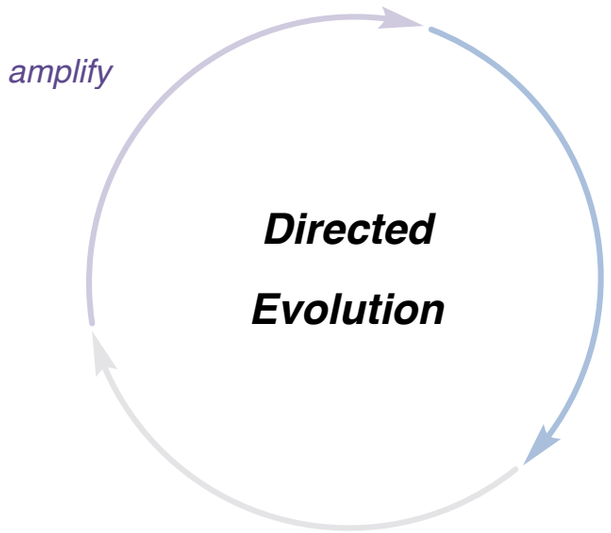
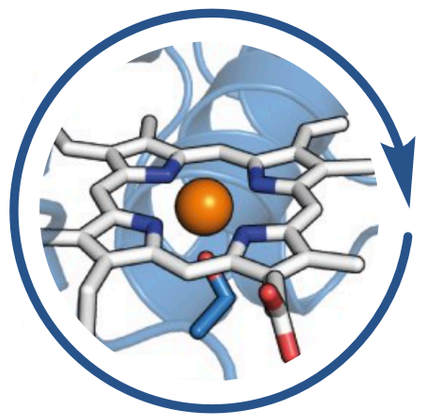
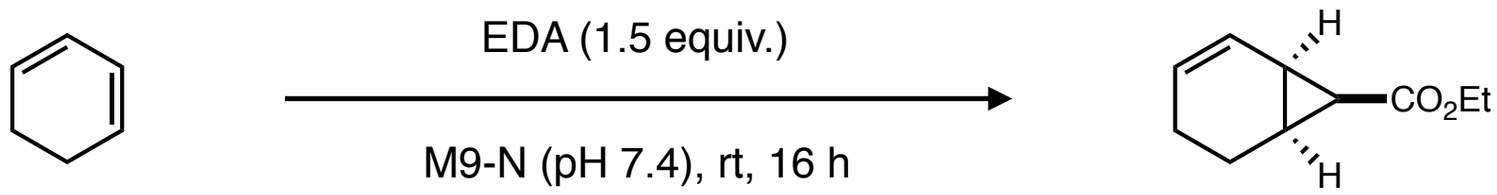






highly active hemoprotein catalyst under aerobic, NAD(P)H-free conditions that is entirely genetically encoded



100 TTN

91:9 dr, 73% ee

additional evolution campaigns can alter C_2/C_3 regioselectivity, enable new reactions with non-styrene olefins, etc.

Brandenberg, O. F.; Chen, K.; Arnold, F. H. *J. Am. Chem. Soc.* **2019**, *141*, 8989.

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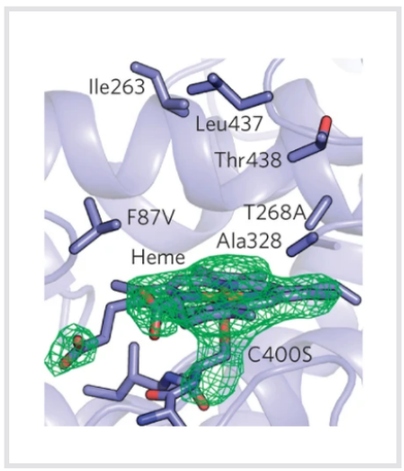
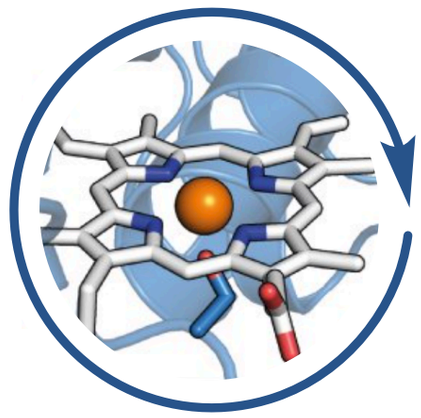


amplify

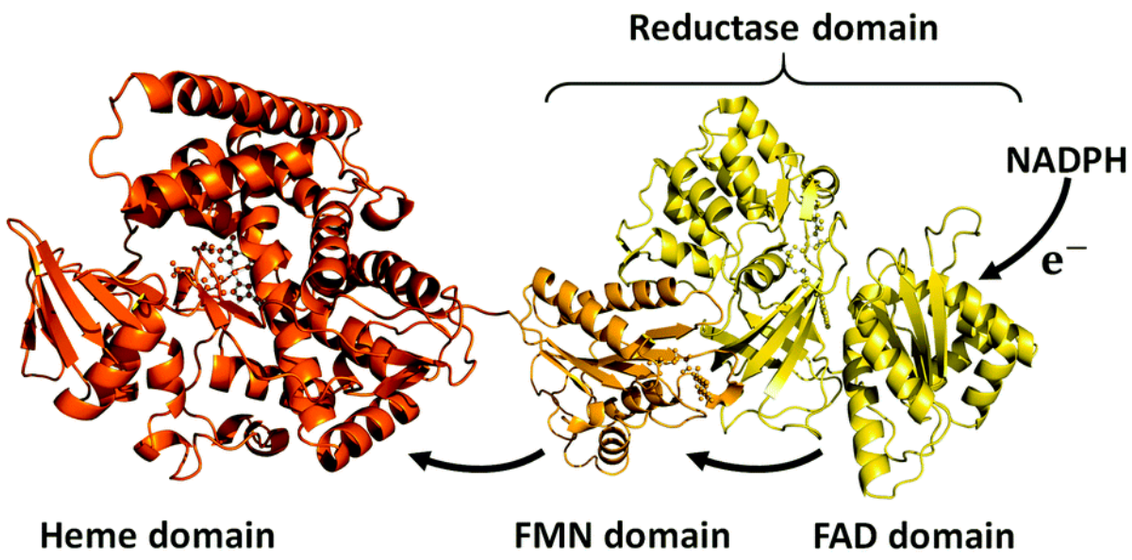
Directed Evolution

diversify



screen

highly active hemoprotein catalyst under aerobic, NAD(P)H-free conditions that is entirely genetically encoded



high expression, but highly truncated FAD domain (reductase not active)

P450: dimer through FAD domain – oxidation

P411: ferrous monomer – carbene transfer?

Brandenberg, O. F.; Chen, K.; Arnold, F. H. *J. Am. Chem. Soc.* **2019**, *141*, 8989.

Accessing all stereoisomers for a given carbene reaction using hemoproteins

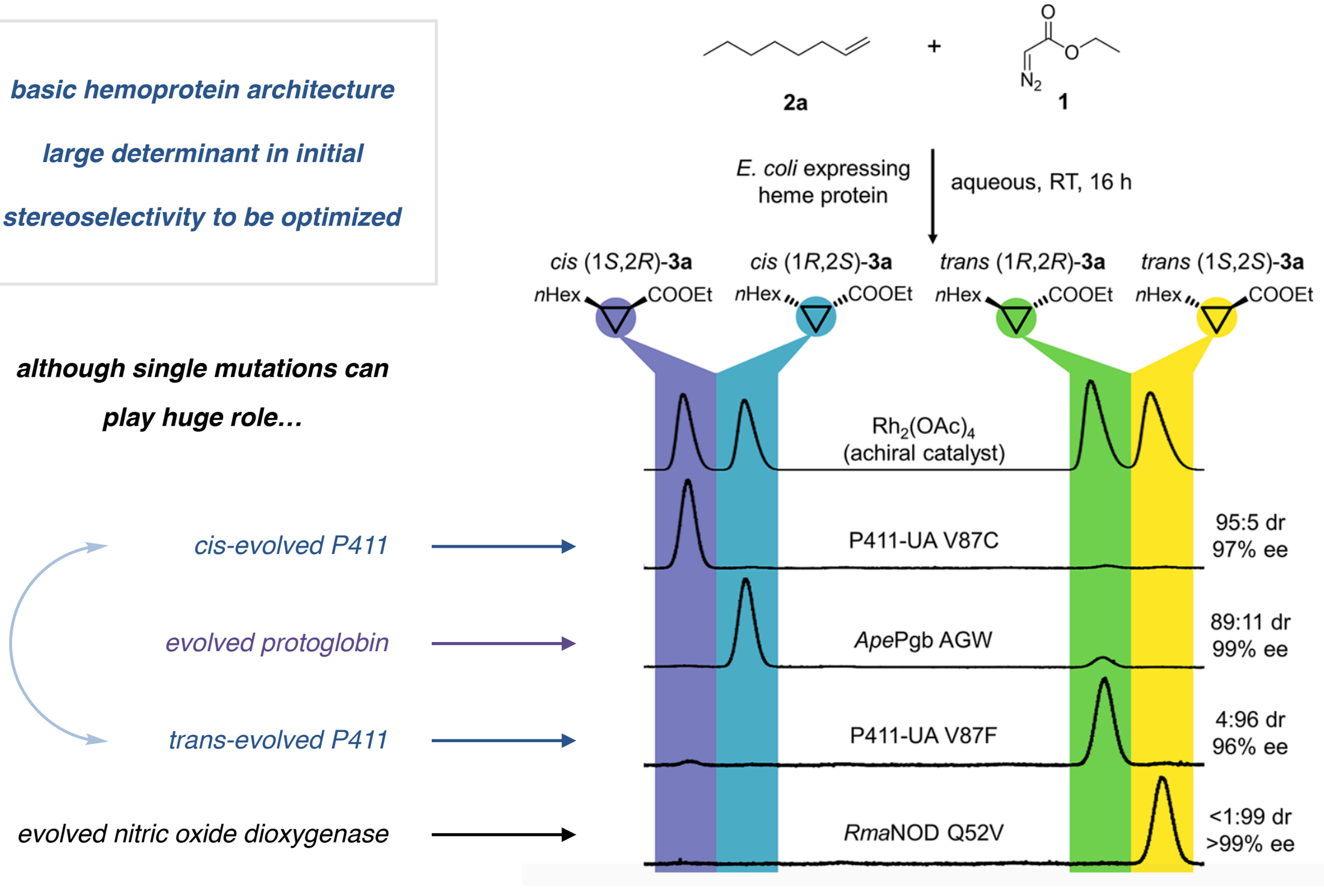
basic hemoprotein architecture

large determinant in initial

stereoselectivity to be optimized

although single mutations can

play huge role…

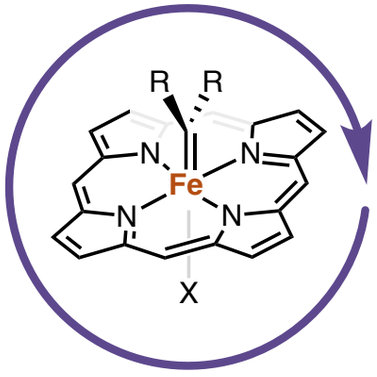


Knight, A. M.; Kan, S. B. J.; Lewis, R. D.; Brandenberg, O. F.; Chen, K.; Arnold, F. H. *ACS Cent. Sci.* **2018**, *4*, 372.

Outline

- *Development of small molecules iron porphyrin catalysts for carbene reactions*
- *Development of hemoprotein catalysts for biocatalytic carbene reactions*
- ***Summarizing the carbene-based transformations enabled by iron porphyrins***
- *Future directions in iron porphyrin-catalyzed carbene chemistry*

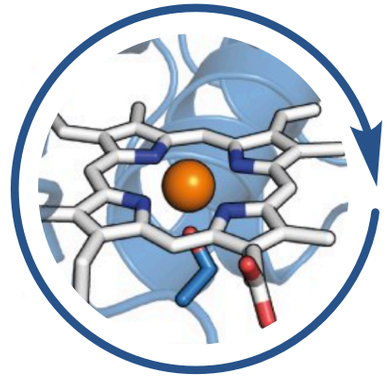
Transformations – cyclopropanation



extremely well-studied in small molecule and enzymatic catalytic contexts

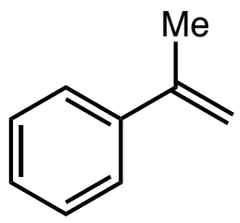
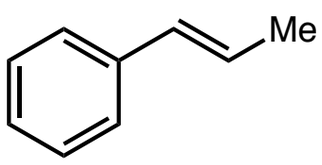
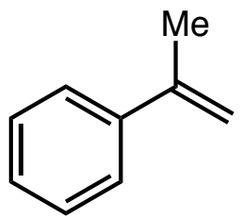
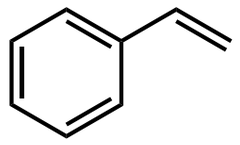
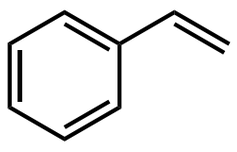
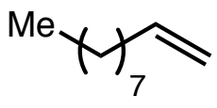
(quintessential model reaction)

only reaction with access to all possible stereoisomers (biocatalysis)



competition studies

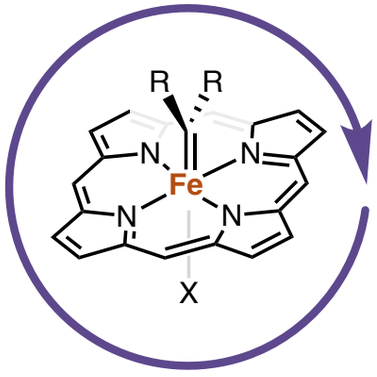
cyclopropanation of equimolar amounts of two alkenes using EDA, Fe(TPP) cat.

substrate **1**	substrate **2**	ratio of products derived from **1**/**2**
		**>99:1**
		**3:1**
		**74:1**

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

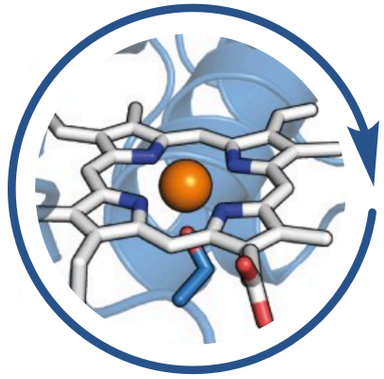
Transformations – cyclopropanation



extremely well-studied in small molecule and enzymatic catalytic contexts

(quintessential model reaction)

only reaction with access to all possible stereoisomers (biocatalysis)



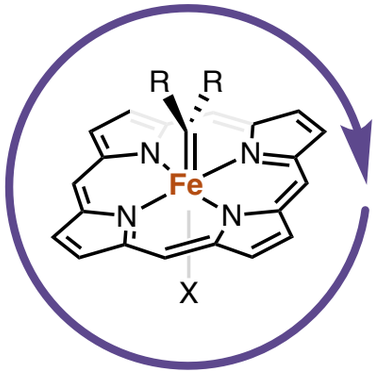
while diazo can be highly varied, δ+ stabilization, sterics play role in determining olefin partners

Most useful for terminal/1,1-disubstituted styrenes, dienes and heteroatom-bound alkenes (alkyl vinyl ethers)

Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

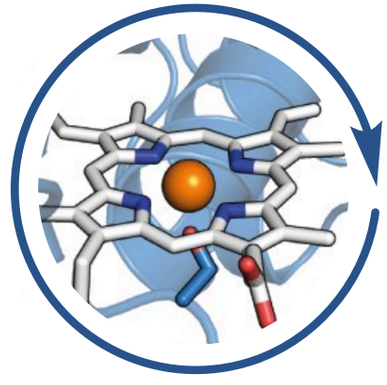
Transformations – cyclopropanation



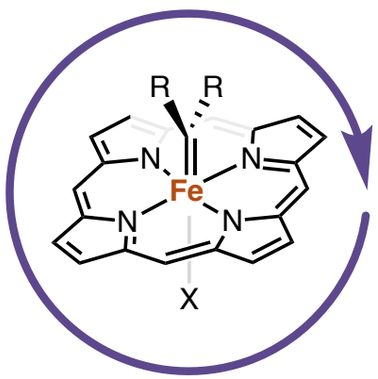
extremely well-studied in small molecule and enzymatic catalytic contexts

(quintessential model reaction)

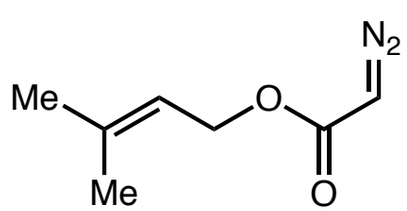
only reaction with access to all possible stereoisomers (biocatalysis)



While polarity effects in TS greatly favor styrenes over unactivated alkenes, some examples exist



intramolecular, using pyridine activator:

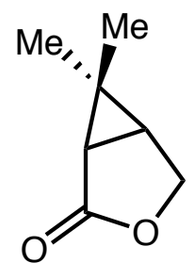


$Fe(TpF\text{-}PP)(CPh_2)$ (0.5 mol%)

2,6-dichloropyridine (0.5 mol%)

CH_2Cl_2, 40 °C, 13 h

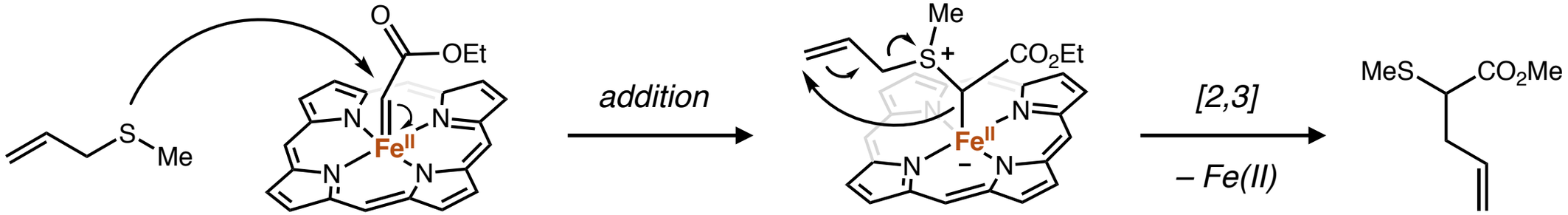
92% yield



Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M.; You, X.-Z. *J. Am. Chem. Soc.* **2002**, *124*, 13185.

Transformations – Doyle-Kirmse rearrangements

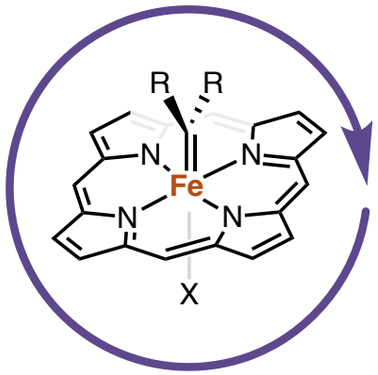
classic Doyle-Kirmse mechanism – a [2,3]-sigmatropic rearrangement using diazo electrophiles

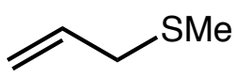


many nucleophiles (sulfides, pyridines, amines, phosphines, etc.) can be used for ylide generation

Transformations – Doyle-Kirmse rearrangements

robust small molecule reaction – intermolecular, variety of allyl sulfide substructures



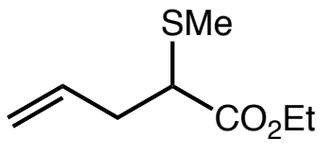


Fe(TpF-PP)Cl (0.2 mol%)

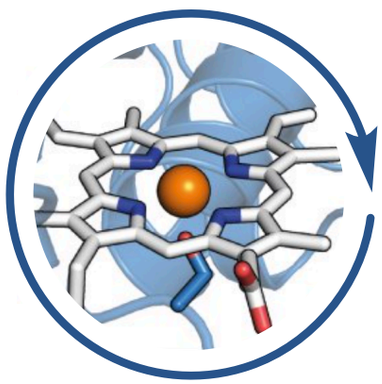
EDA (1 equiv.)

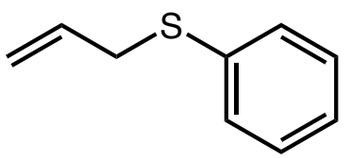
CH_2Cl_2, rt, 1 min.

95% yield



sigmatropic rearrangements are generally rare biocatalytic reactions, but they can happen:



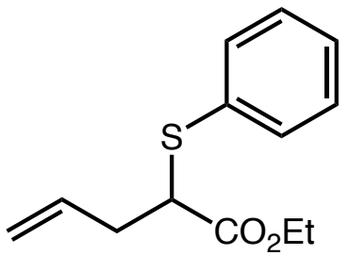


Mb(L29A, H64V) (0.2 mol%)

EDA (1 equiv.), $Na_2S_2O_4$

KPi (pH 7), 4 °C, 12 h

390 TTN, *unknown ee*



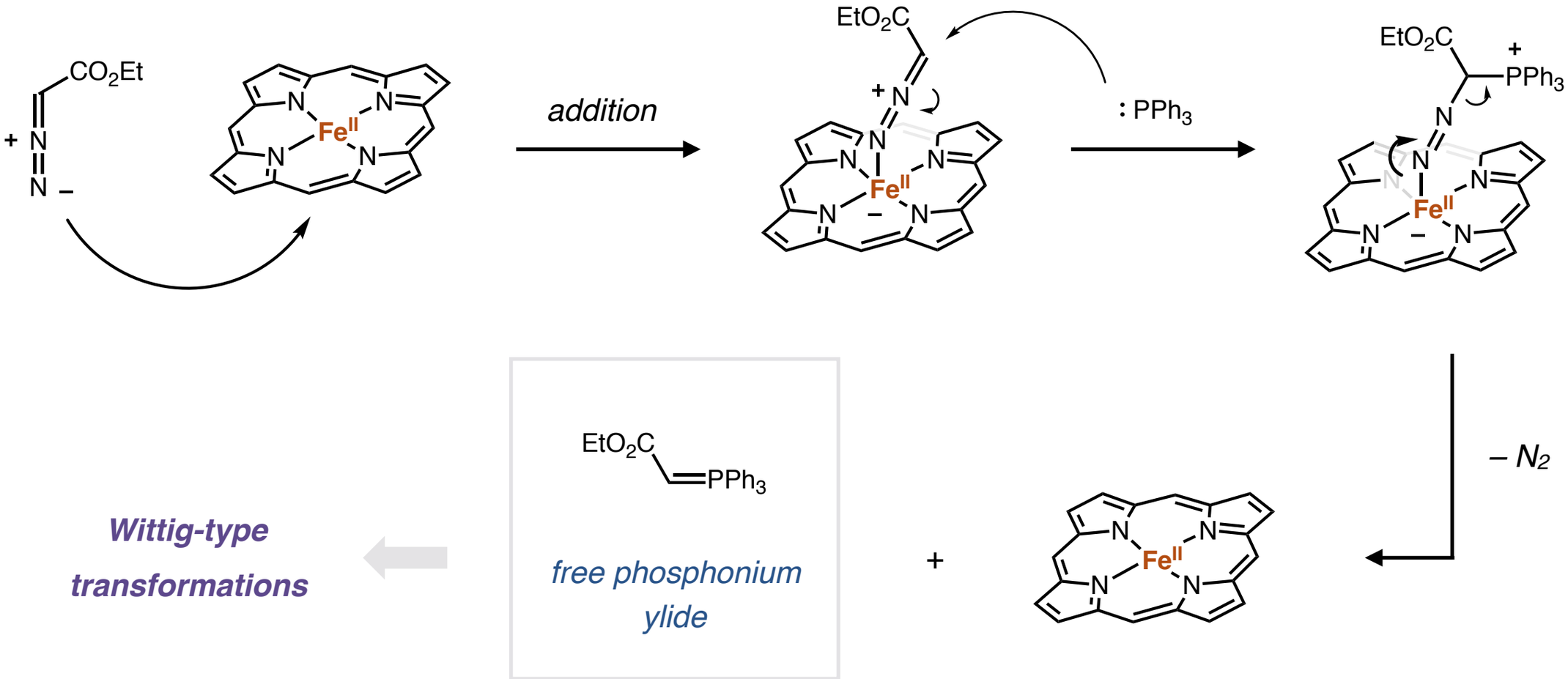
(later expanded as synthetic method via protein engineering, up to >99% yield, 71% ee)

Aviv, I.; Gross, Z. *Chem. Eur. J.* **2008**, *14*, 3995.

Tyagi, V.; Bonn, R. B.; Fasan, R. *Chem. Sci.* **2010**, *14*, 284.

Transformations – carbonyl olefination

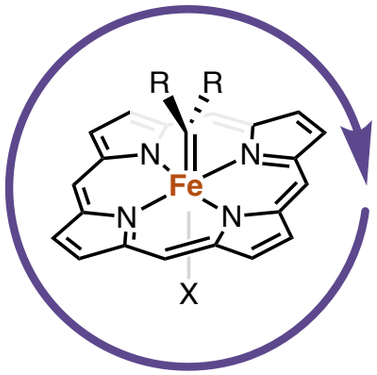
Lewis acidic generation of phosphonium ylides – an alternative Fe-catalyzed diazo activation



Tyagi, V.; Fasan, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 2512.

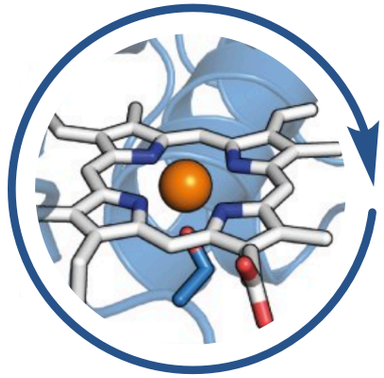
Weissenborn, M. J.; Löw, S. A.; Borlinghaus, N.; Kuhn, M.; Kummer, S.; Rami, F.; Plietker, B.; Hauer, B. *ChemCatChem* **2016**, *8*, 1636.

Transformations – carbonyl olefination



known in both small molecule and enzymatic catalytic contexts

recent developments primarily in biocatalytic systems

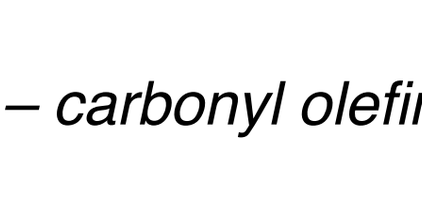


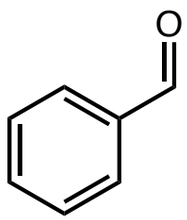
Mb(F43V, V68F) (*E. coli*)

EDA (1 eq.), $Na_2S_2O_4$

$AsPh_3$, KPi (pH 8), rt, 12 h

>99% conv., *1170 TTN, >99:1 E/Z*





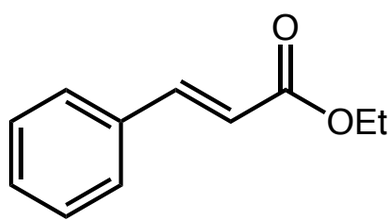
2 eq.

YfeX(S234A) (*E. coli*)

EDA (1 eq.), $Na_2S_2O_4$

$AsPh_3$, KPi (pH 7.5), rt, 1 h

17.3 TTN, 96:4 E/Z



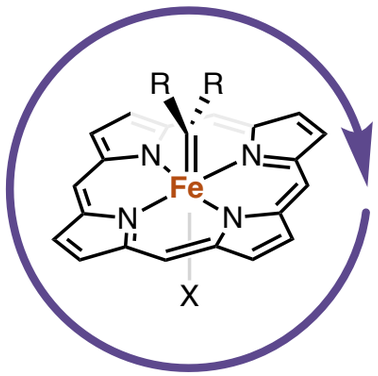
control studies using pre-formed ylide in place of diazo give identical E/Z selectivity

product likely formed outside of active site

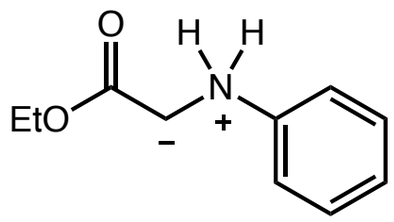
Tyagi, V.; Fasan, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 2512.

Weissenborn, M. J.; Löw, S. A.; Borlinghaus, N.; Kuhn, M.; Kummer, S.; Rami, F.; Plietker, B.; Hauer, B. *ChemCatChem* **2016**, *8*, 1636.

Transformations – other "free ylide" rearrangements

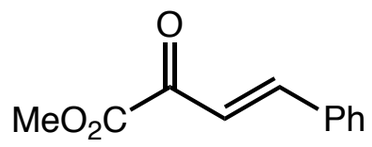


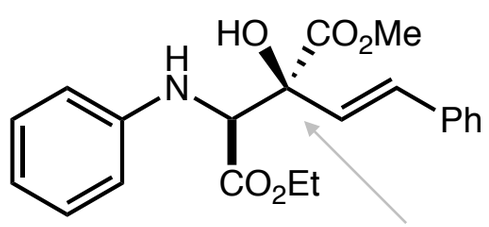
several other types of ylides can be generated from EDA, under small molecule catalyst conditions



ammonium ylide

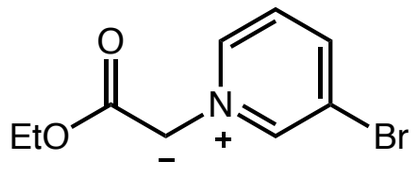
direct addition





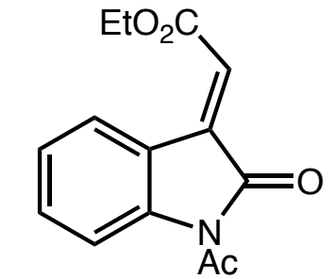
4:1 syn/anti

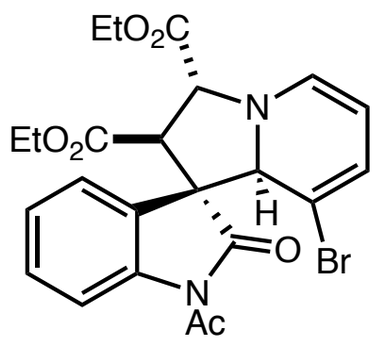
82% yield



pyridinium ylide

dearomatizing [3+2] cycloaddition





89% yield

single diastereomer

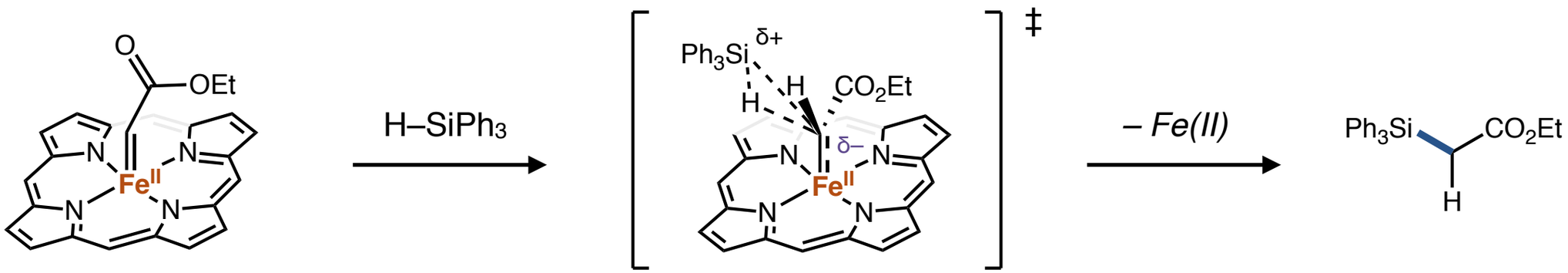
Ma, C.; Xing, D.; Zhai, C.; Che, J.; Liu, S.; Wang, J.; Hu, W. *Org. Lett.* **2013**, *15*, 6140.

Day, J.; McKeever-Abbas, B.; Dowden, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 5809.

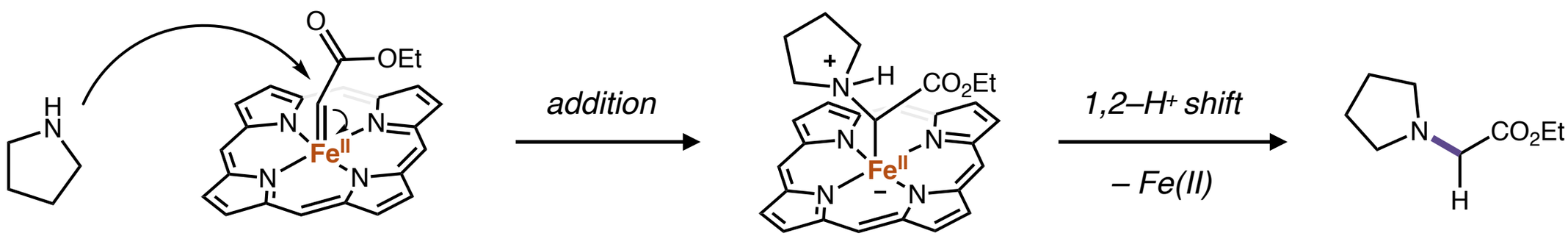
Transformations – X–H bond insertions

Two basic mechanisms of Fe porphyrin-catalyzed X–H insertion

#1 – concerted (for non-polarized or hydridic X–H bonds: C, B, Si, Sn, P, etc.)



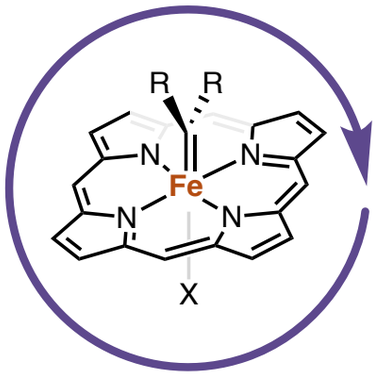
#2 – stepwise via nucleophilic addition (for acidic X–H bonds on nucleophilic heteroatoms: S, N, O, etc.)



Aviv, I.; Gross, Z. *Chem. Eur. J.* **2008**, *14*, 3995.

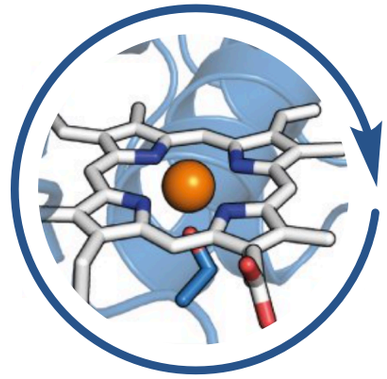
Wang, E.-H.; Ping, Y.-J.; Li, Z.-R.; Qin, H.; Xu, Z.-J.; Che, C.-M. *Org. Lett.* **2018**, *20*, 4641.

Transformations – X–H bond insertions

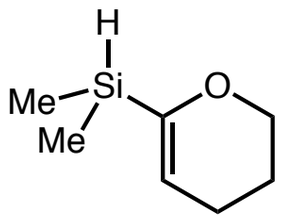


Beyond O–H, widely developed in small molecule and enzymatic catalysis

Again, useful enantioselectivity only in biocatalytic systems



very hydridic, large variety of tolerated silane substituents

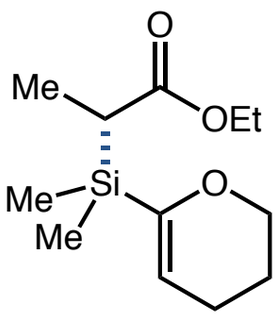


(2 equiv.)

Rma cyt c (V75T, M100D, M103E) (*E. coli*)

Me–EDA (1 eq.), $Na_2S_2O_4$

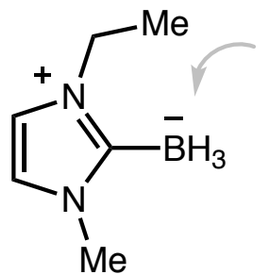
M9-N (pH 7.4), rt, 4 h



930 TTN

>99% ee

to be sufficiently hydridic, anionic boronate often required

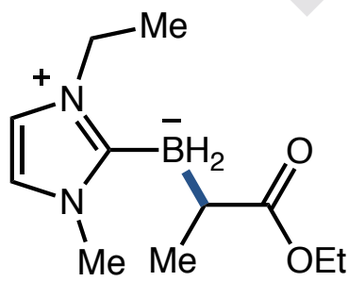


(1 equiv.)

Rma cyt c (“BOR^{R1}”) (*E. coli*)

Me–EDA (1 eq.)

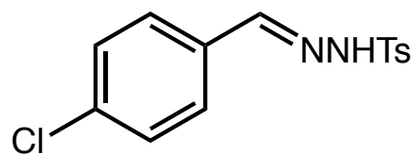
M9-N (pH 7.4), rt, 6 h



2020 TTN

98% ee

in-situ diazo precursor (following deprotonation)



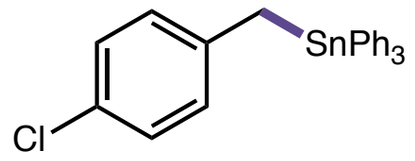
H—$SnPh_3$

(2 equiv.)

Fe(TPP)Cl (2 mol%)

NaH (1.2 eq.)

toluene, 80 °C, 14 h



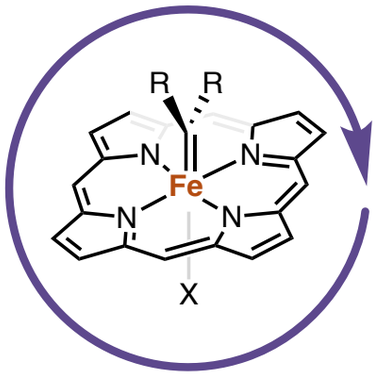
72% yield

Kan, S. B. J.; Lewis, R. D.; Chen, K.; Arnold, F. H. *Science* **2016**, *354*, 1048.

Kan, S. B. J.; Huang, X.; Gumulya, Y.; Chen, K.; Arnold, F. H. *Nature* **2017**, *552*, 132.

Wang, E.-H.; Ping, Y.-J.; Li, Z.-R.; Qin, H.; Xu, Z.-J.; Che, C.-M. *Org. Lett.* **2018**, *20*, 4641.

Transformations – X–H bond insertions



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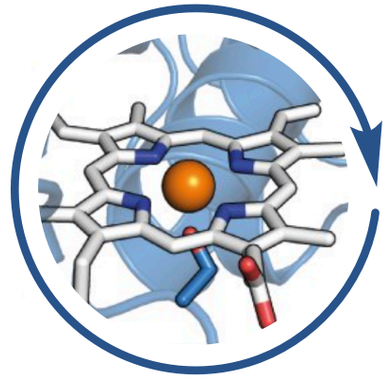
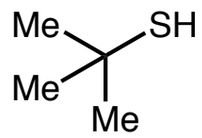
Again, useful enantioselectivity only in biocatalytic systems



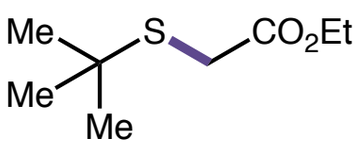
alkylthiols and thiophenols, but must be protic (avoid ylide chemistry)



Fe(TpF-PP)Cl (0.1 mol%)

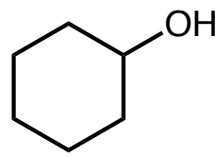
EDA (1 equiv.)

CH_2Cl_2, rt, <1 min

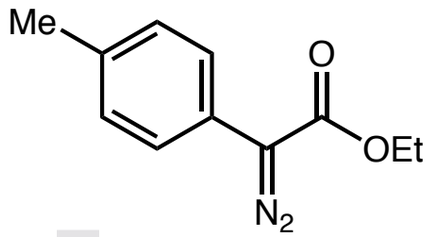


92% yield

alcohols or phenols, but requires highly activated diazo due to decreased nucleophilicity

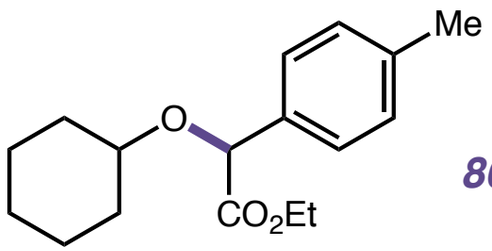


(2 equiv.)



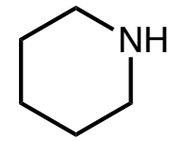
Fe(TPP)Cl (1 mol%)

CH_2Cl_2, 40 °C, 8 h



86% yield

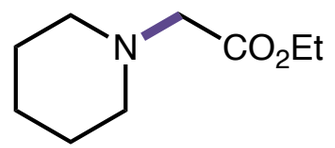
various amines, anilines and ammonia, but must be protic (avoid ylide chemistry)



Fe(TpF-PP)Cl (0.1 mol%)

EDA (1 equiv.)

Et_2O, rt, 7 min



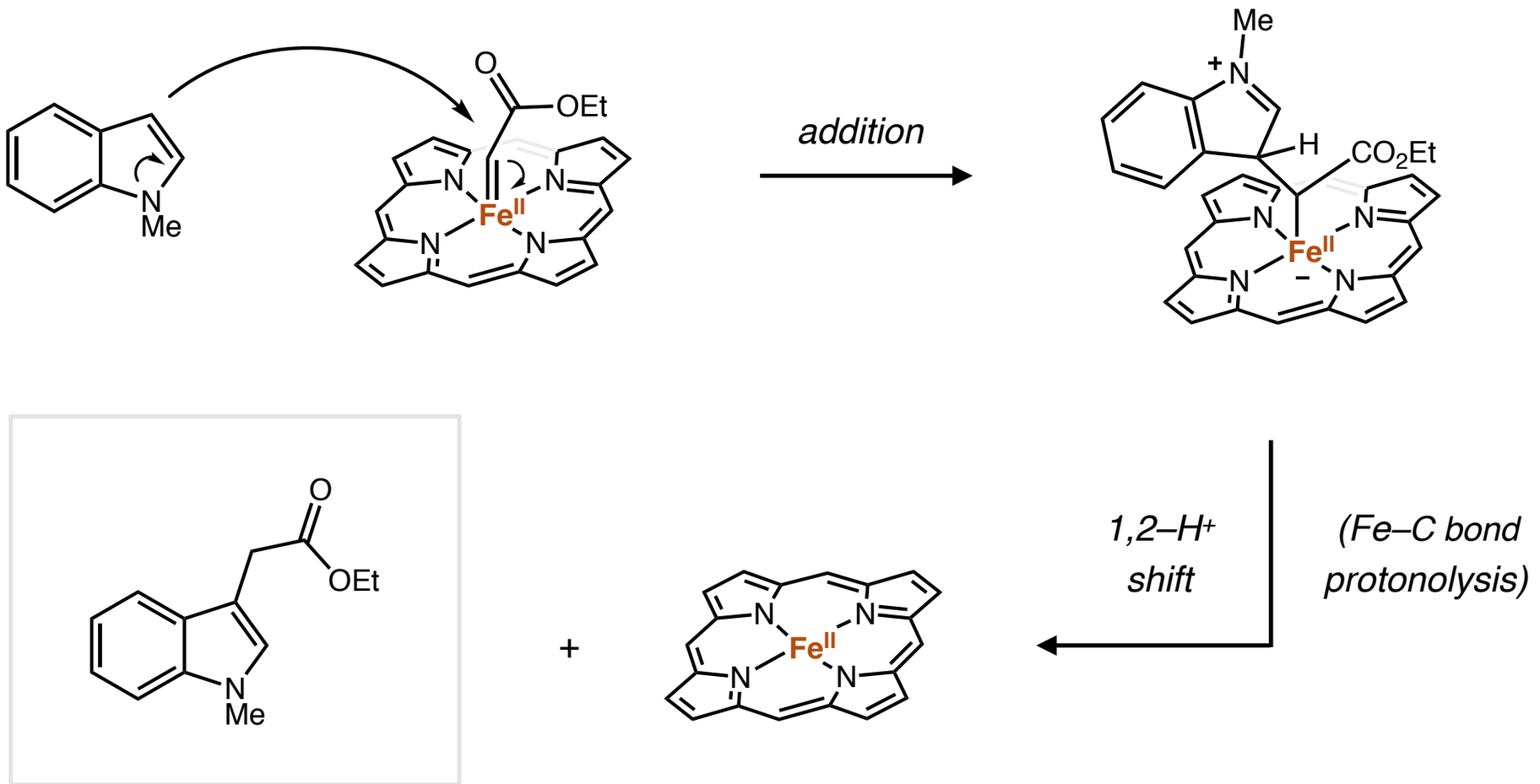
97% yield

Aviv, I.; Gross, Z. *Chem. Eur. J.* **2008**, *14*, 3995.

Mbuvi, H. M.; Klobukowski, E. R.; Roberts, G. M.; Woo, L. K. *J. Porphyr. Phthalocyanines.* **2010**, *14*, 284.

Transformations – aromatic C–H "insertion"

Friedel-Crafts-type C–H activation – proceeds via step-wise mechanism

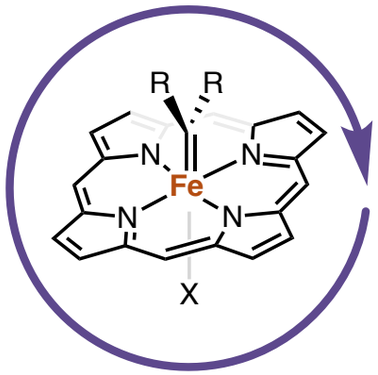


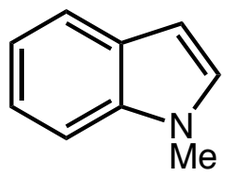
Hock, K. J.; Knorrscheidt, A.; Hommelsheim, R.; Ho, J.; Weissenborn, M. J.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2019**, *58*, 3630.

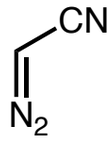
Vargas, D. A.; Tinoco, A.; Tyagi, V.; Fasan, R. *Angew. Chem., Int. Ed.* **2018**, *57*, 9911.

Transformations – aromatic C–H "insertion"

several small molecule examples – intermolecular, electron-rich heteroarenes (primarily indoles, but also e⁻-rich benzenes)





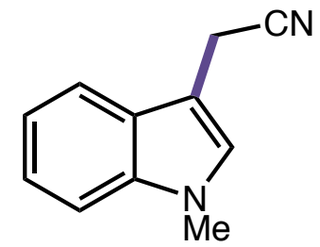


(excess)

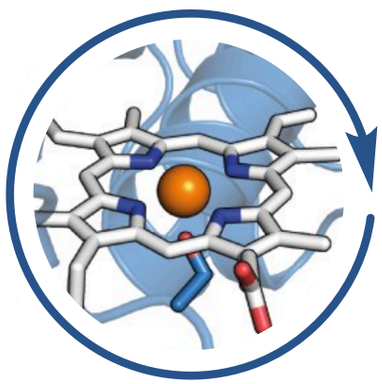
Fe(TPP)Cl (1 mol%)

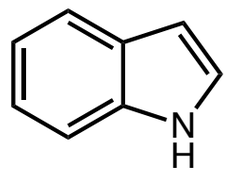
CH_2Cl_2/H_2O, 55 °C, 2 h

92% yield



several intermolecular biocatalytic examples: Fasan (Mb), Arnold (P411), etc. – indoles + pyrroles, limited to C_2 or C_3



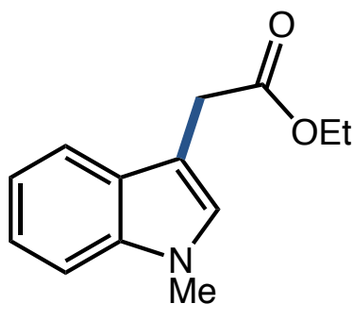


Mb(H64V, V68A) (*E. coli*)

EDA (2 eq.), $Na_2S_2O_4$

KPi (pH 7), rt, 16 h

>99% conv., *82 TTN*



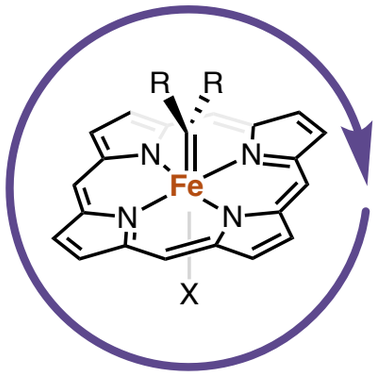
Hock, K. J.; Knorrscheidt, A.; Hommelsheim, R.; Ho, J.; Weissenborn, M. J.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2019**, *58*, 3630.

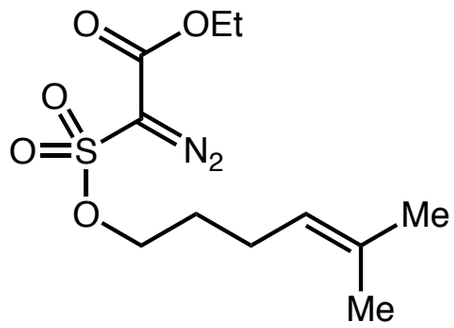
Vargas, D. A.; Tinoco, A.; Tyagi, V.; Fasan, R. *Angew. Chem., Int. Ed.* **2018**, *57*, 9911.

Transformations – aliphatic C–H insertion

few transformations using small molecule catalysts – intramolecular, allylic/benzylic (activated)

(intermolecular benzylic – competes with arene Friedel-Crafts activation… allylic – competes with cyclopropanation)



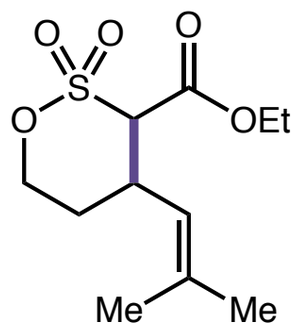


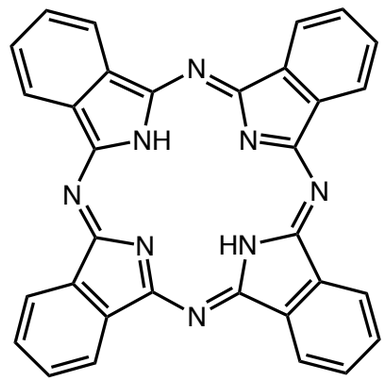
Fe(**PC**)Cl (10 mol%)

$NaBAr^{F}_4$ (10 mol%)

CH_2Cl_2, 45 °C, 2–12 h

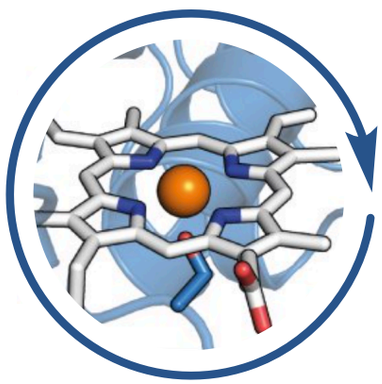
53% yield

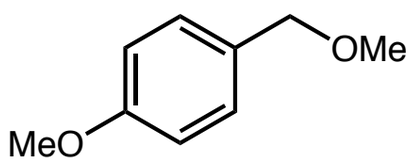




PC

several biocatalytic examples – intermolecular, allylic/benzylic/propargylic and α–oxy (electron-rich)



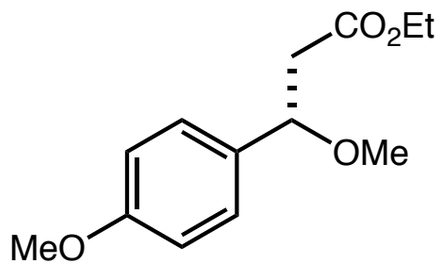


P411–CHF (*E. coli*)

EDA (1 eq.)

M9-N/EtOH, 4 °C, 18 h

82% yield, *96% ee, 1060 TTN*



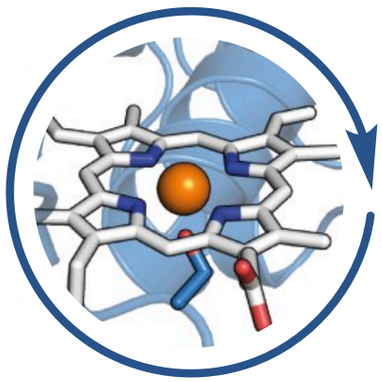
perfect chemoselectivity after evolution: no cyclopropanation of allylic/propargylic substrates

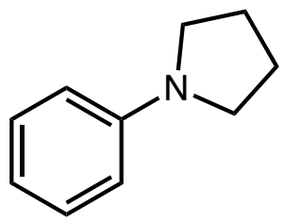
Griffin, J. R.; Wendell, C. I.; Garwin, J. A.; White, M. C. *J. Am. Chem. Soc.* **2017**, *139*, 13624.

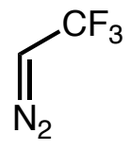
Zhang, R. K.; Chen, K.; Huang, X.; Wohlschlager, L.; Renata, H.; Arnold, F. H. *Nature* **2019**, *565*, 67.

Transformations – aliphatic C–H insertion

biocatalytic – intermolecular, α–amino







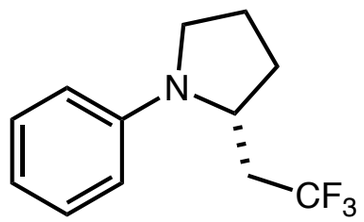
(excess)

P411–PFA cat.

$Na_2S_2O_4$, glucose, GOx

M9-N/EtOH, rt, 12 h

64% yield, *98% ee, 4070 TTN*



for different evolved P411, "standard" acceptor diazos can be used

8 mutations (<2% sequence difference) leads to other enantiomer in greater >90% ee

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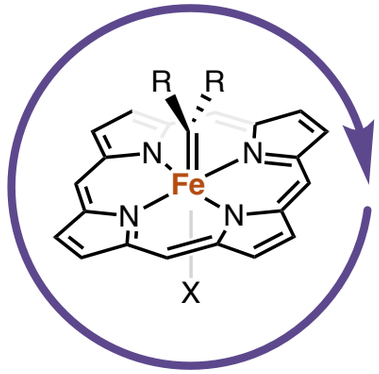
Unlike Rh carbenes, no general method exists for unactivated C–H insertion for Fe (porphyrin) carbenes

Zhang, J.; Huang, X.; Zhang, R. K.; Arnold, F. H. *J. Am. Chem. Soc.* **2019**, *141*, 9798.

Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008**, *27*, 637.

Transformations – aliphatic C–H insertion



…but promising signs for eventual use in catalytic insertion of unactivated C_{sp3}–H bonds

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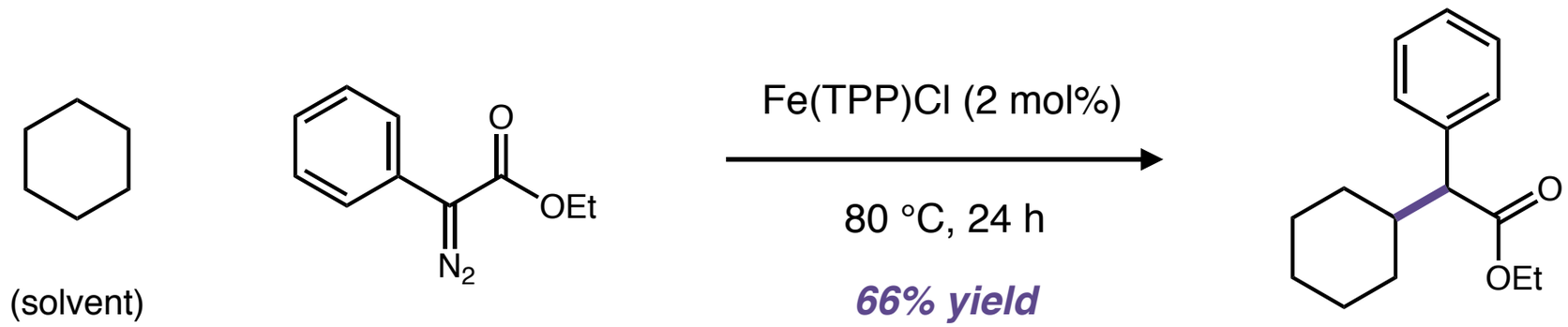


Hammett studies show $\rho = -1.11 \pm 0.05$

beyond solvent quantity of C–H partner, still limited to specific carbenes of extreme electrophilicity

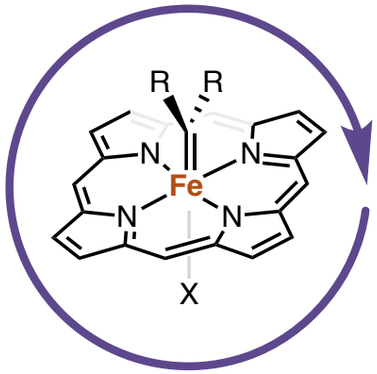
Zhang, J.; Huang, X.; Zhang, R. K.; Arnold, F. H. *J. Am. Chem. Soc.* **2019**, *141*, 9798.

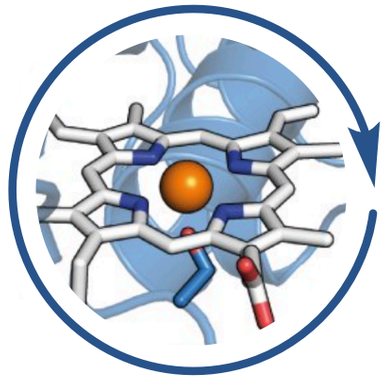
Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008**, *27*, 637.

Outline

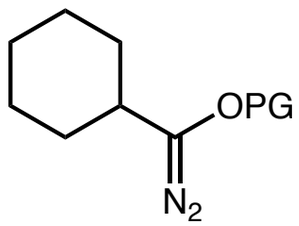
- *Development of small molecules iron porphyrin catalysts for carbene reactions*
- *Development of hemoprotein catalysts for biocatalytic carbene reactions*
- *Summarizing the carbene-based transformations enabled by iron porphyrins*
- ***Future directions in iron porphyrin-catalyzed carbene chemistry***

Future directions for iron porphyrin carbene catalysis



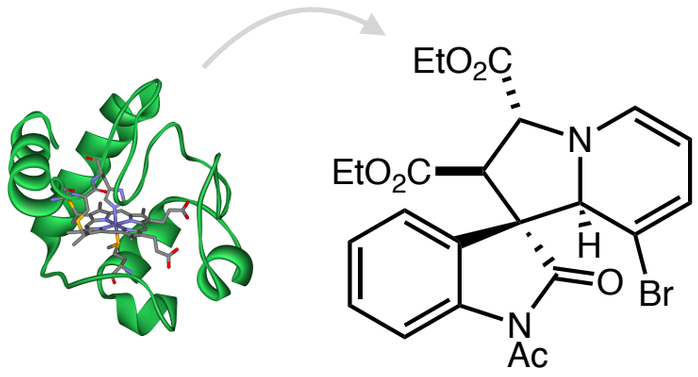


use of more nucleophilic (donor-substituted) carbenes



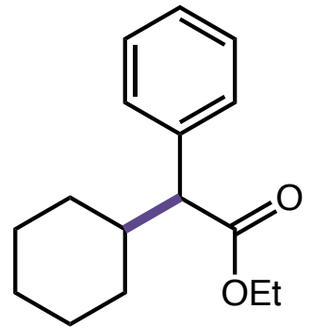
limitation of synthetic access to diazo compouds

use of hemoprotein catalysts for enantioselective, complexity-building rearrangements/cascades



no Fe small molecule equivalent to achieve high ee

further investigation into unactivated C–H bond insertion



potentially valuable application, particularly in biocatalysis