Radical Rebound:
Nature’s Functionalization Toolbox

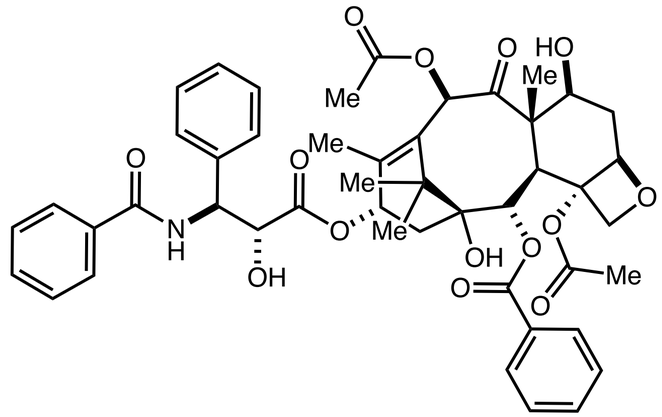
Johannes Grosskopf

Literature Talk

March 21, 2025

Pacific yew

Paclitaxel (Taxol)



Pacific yew

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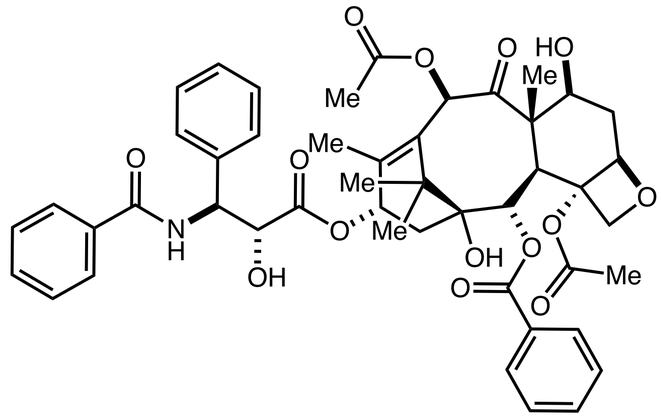
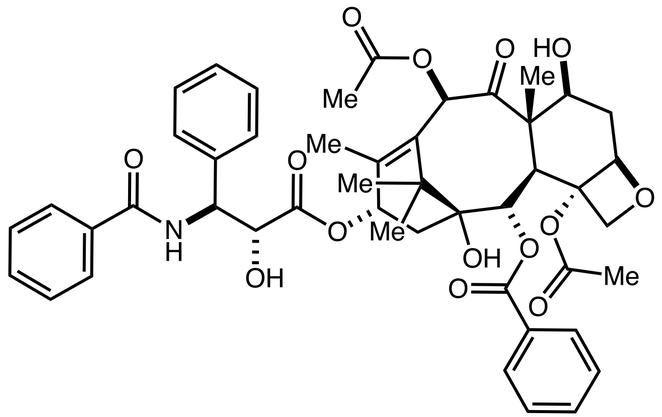


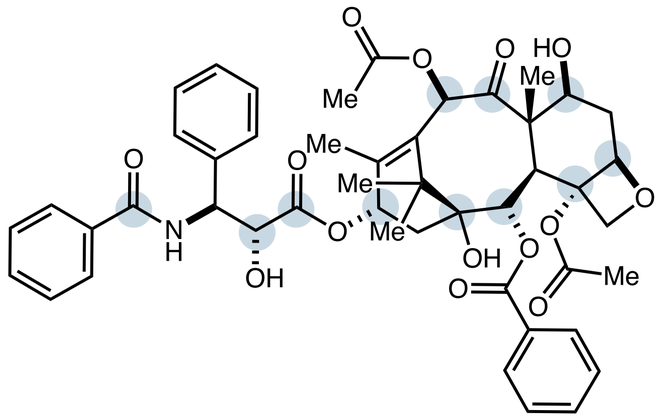
$1.2 B in annual sales (2023)

Prevalence of highly oxygenated natural products



Taxol

Prevalence of highly oxygenated natural products



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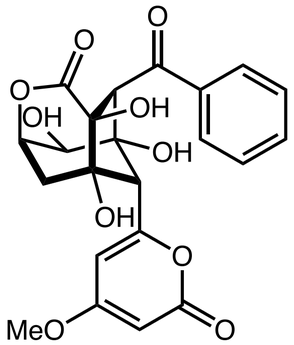
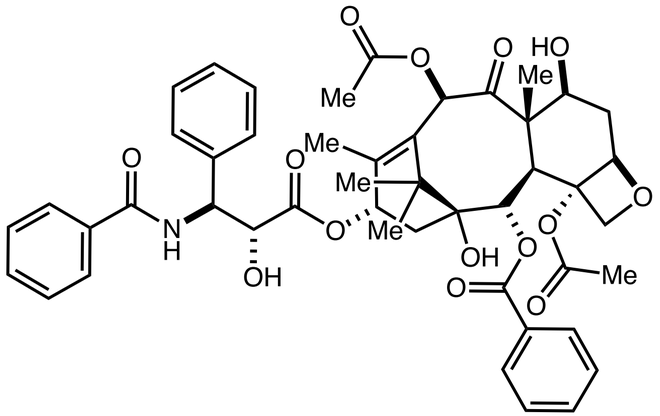


Enterocin



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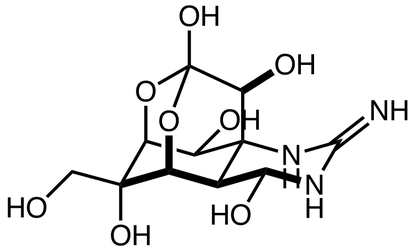
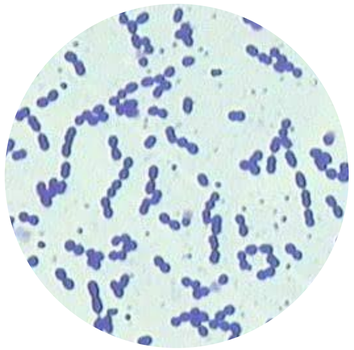


Tetrodotoxin

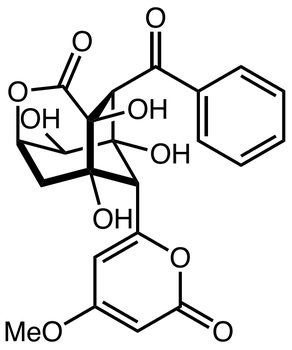
Prevalence of highly oxygenated natural products



enterococcus

pacific yew

puffer fish



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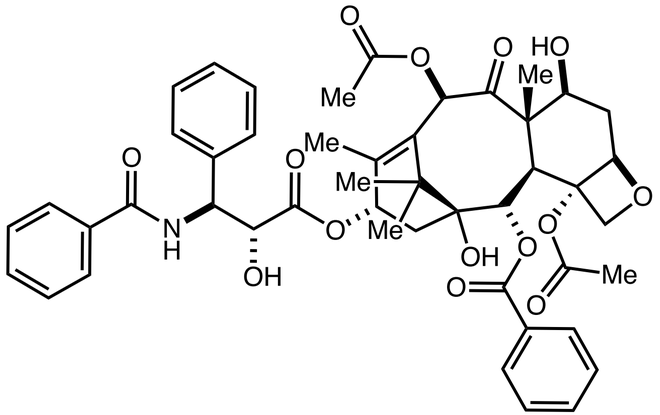
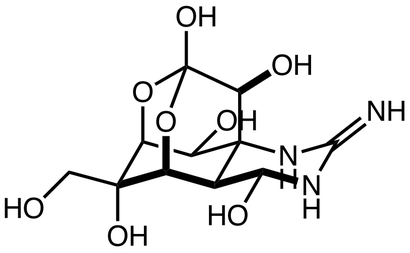


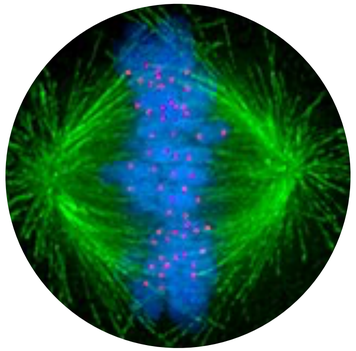
Taxol



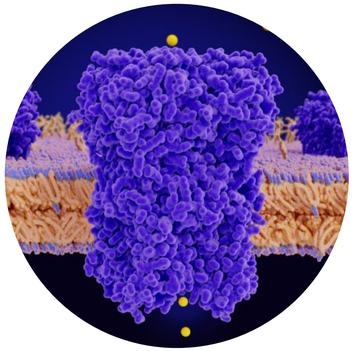
Tetrodotoxin

Prevalence of highly oxygenated natural products

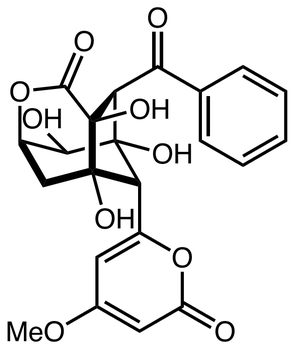
mitochondria



microtubules



ion channels



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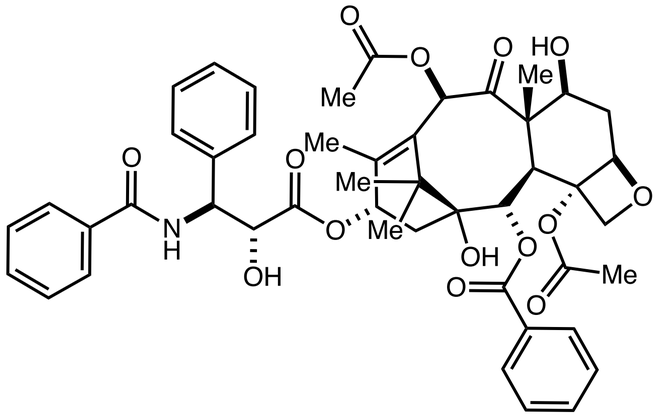

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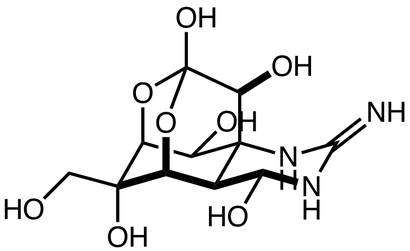

Tetrodotoxin

Prevalence of highly oxygenated natural products

Oxygenation as privileged motiv

increased bioavailability

possibility for multitude of (non-)covalent interaction

activity in electron transport

prevents self-toxicity by regulating bioactivity

Dibrell, S. E.; Tao, Y.; Reisman, S. E. *Acc. Chem. Res.* **2021**, *54*, 1360.

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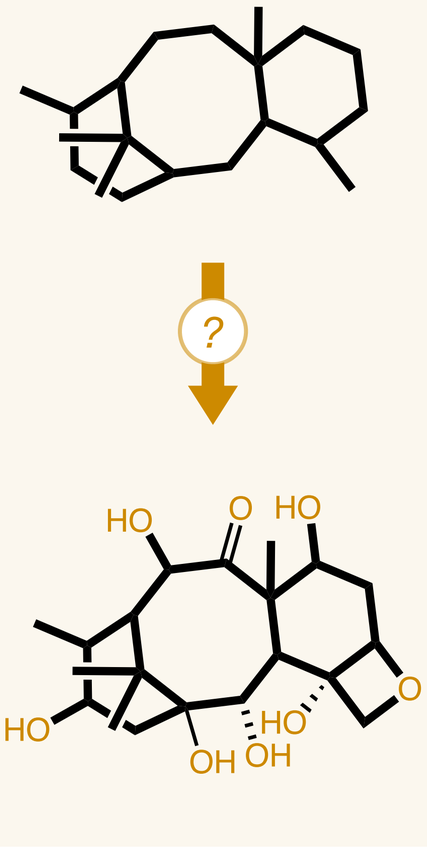

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Radical Rebound

Molecular oxygen as an oxidant

driving force for biological oxygenations

Huang, X.; Groves, J. T. *J. Biol. Inorg. Chem.* **2017**, *22*, 185.

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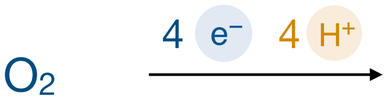

O_2 → $2\ H_2O$

ΔH = –80 kcal/mol

$E^{\circ}_{1/2}$ *= +1.229 V vs. SHE*

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Molecular oxygen as an oxidant

driving force for biological oxygenations

O_2 → $2\ H_2O$

ΔH = –80 kcal/mol

$E^{\circ}_{1/2}$ = +1.229 V vs. SHE

BUT:

triplet ground state kinetically slow oxidant

reduction of $^3O_2$ to $O2^{-\bullet}$ is endergonic (ΔH = +7.8 kcal/mol)

BDE of H–OO• only 47 kcal/mol

spin-flip barrier involving closed shell reaction partners

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Activation of O_2 by d-block metal cofactors

in multiple spin states and oxidation states

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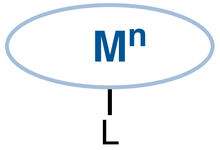

metal cofactor

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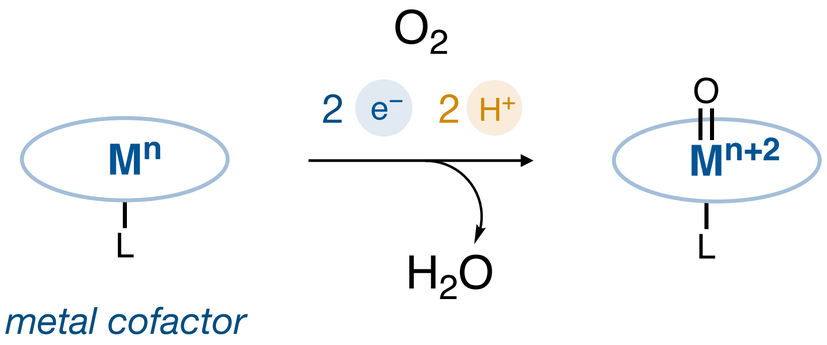

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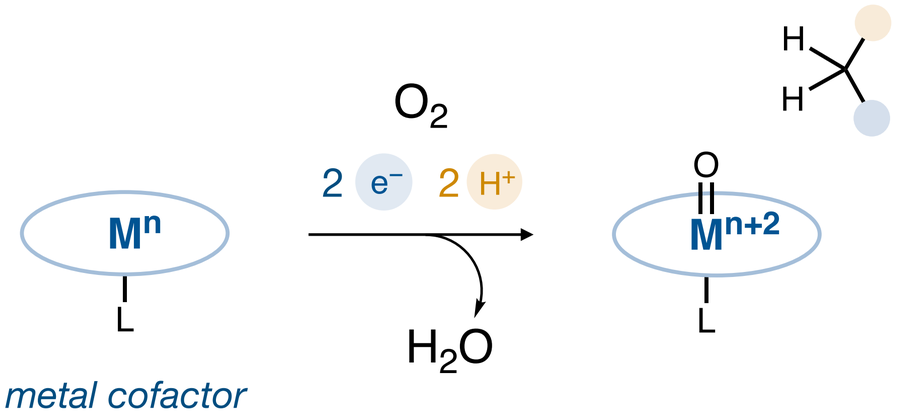

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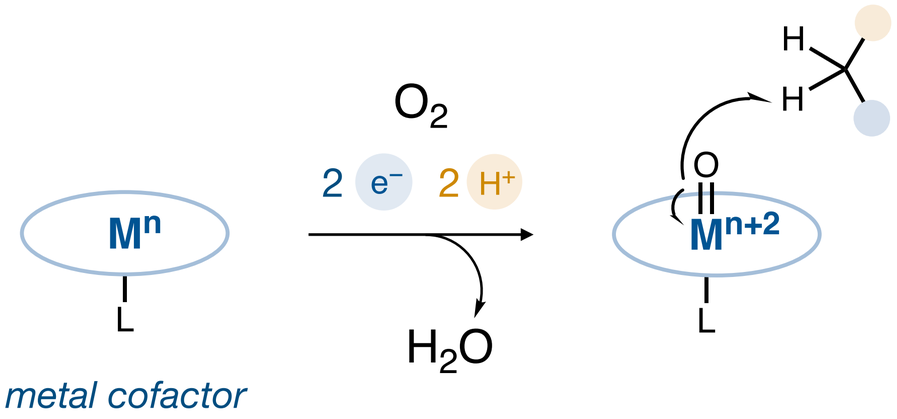

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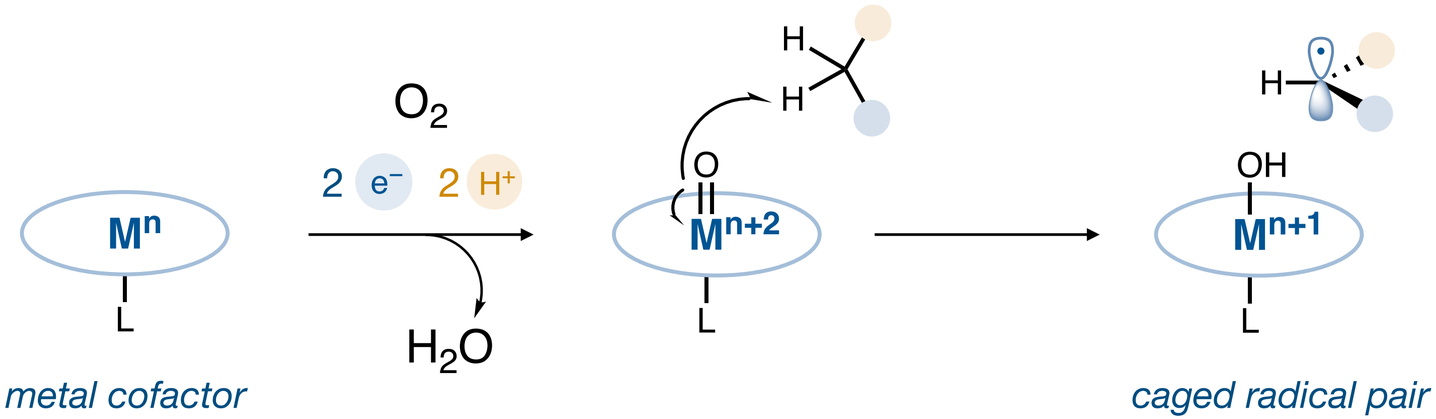

metal cofactor

caged radical pair

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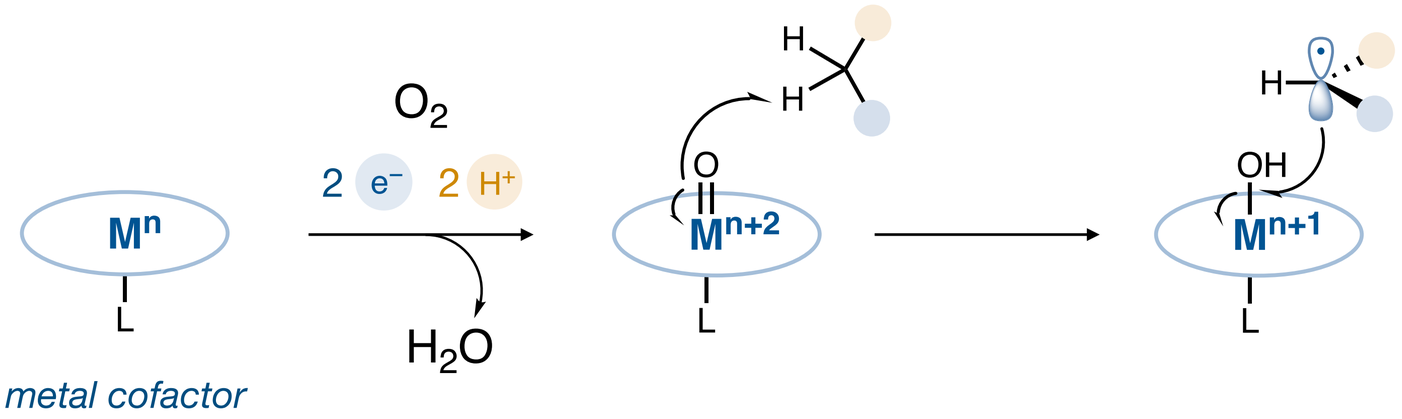

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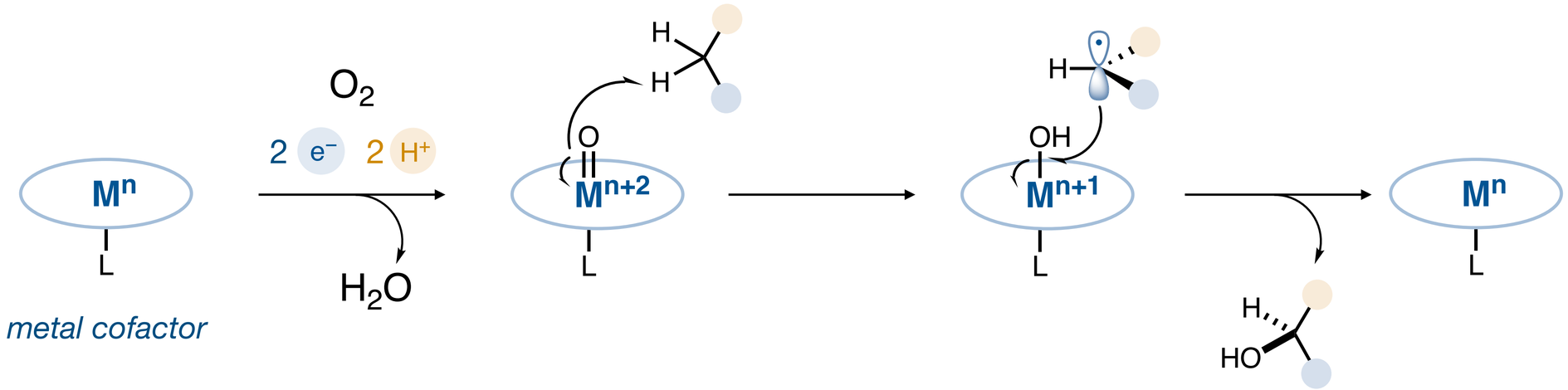

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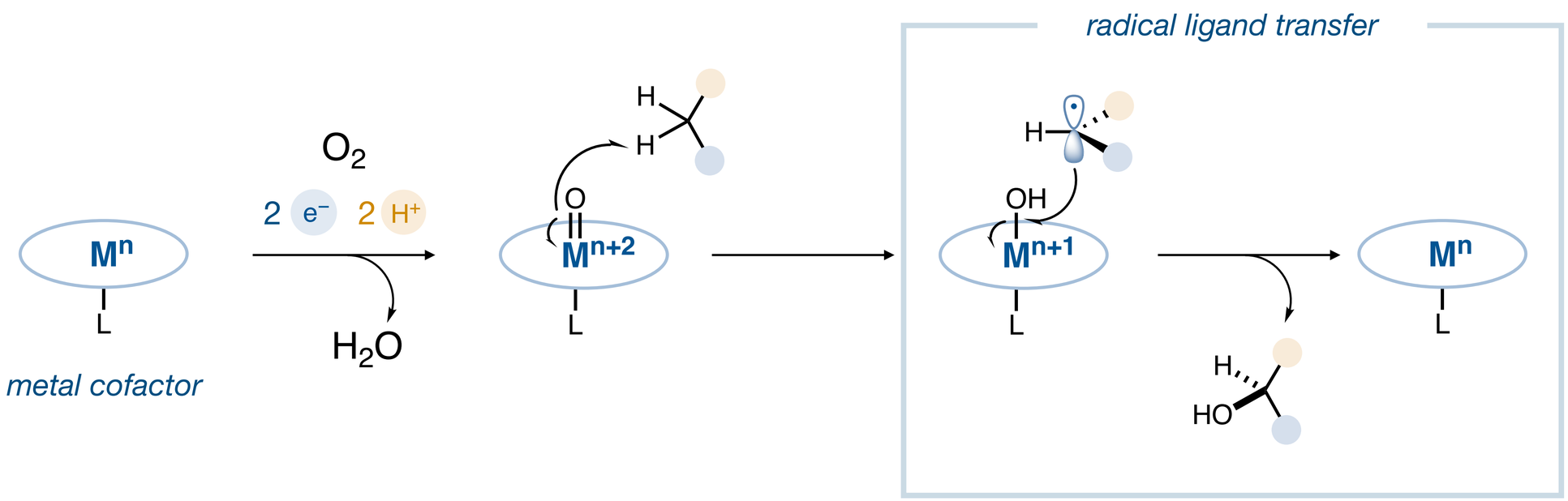

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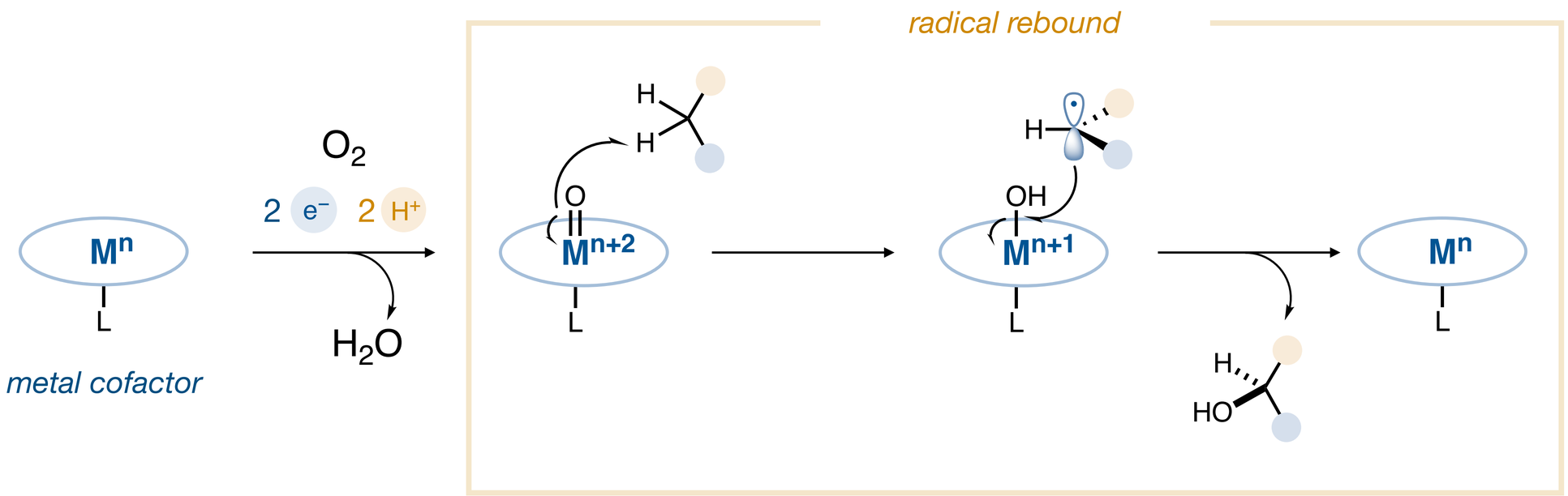

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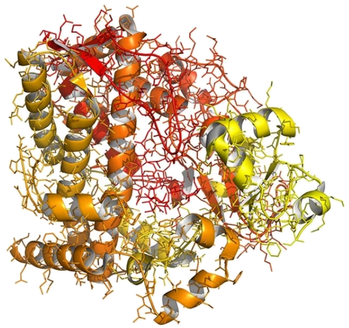
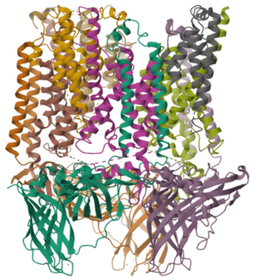
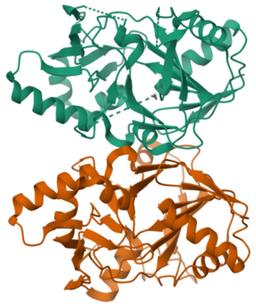
Radical rebound

enzymatic rebound







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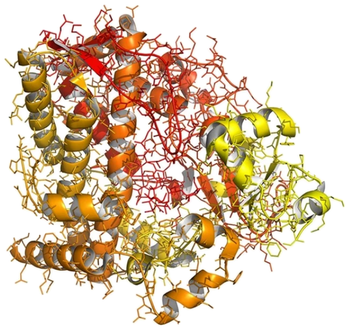
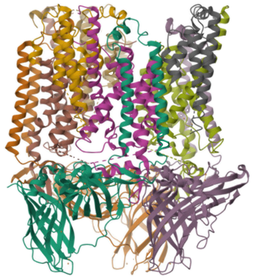
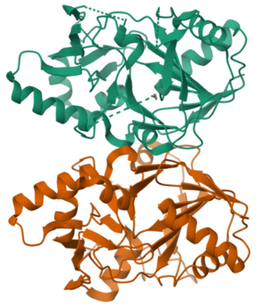
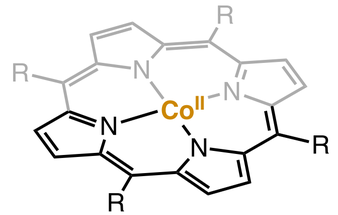
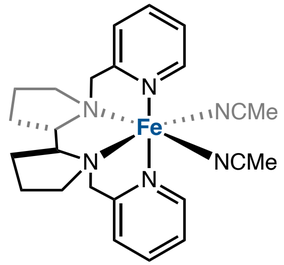


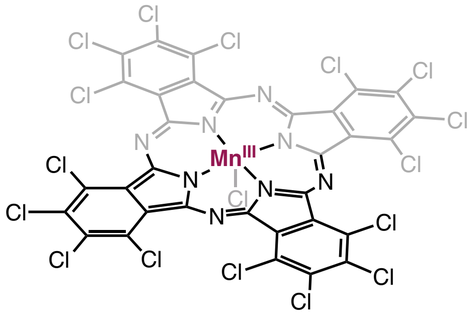




synthetic rebound







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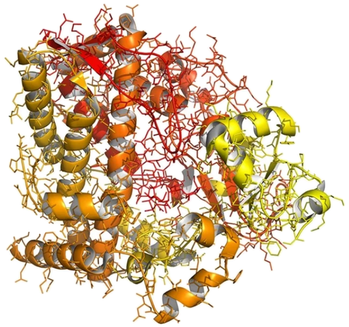

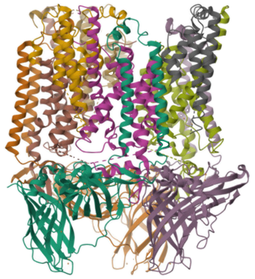

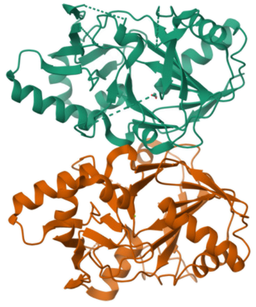

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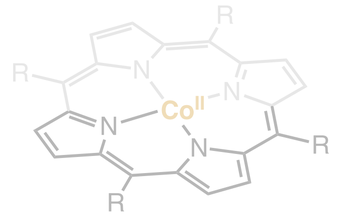
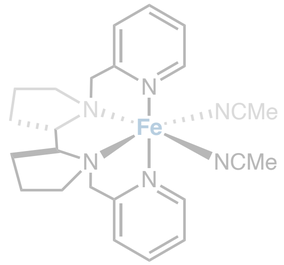
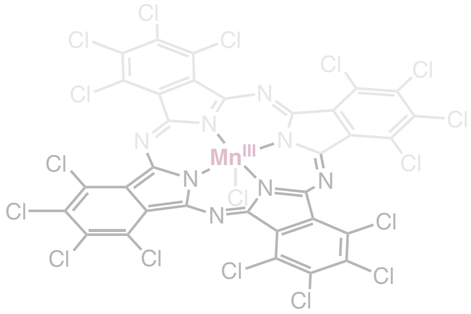
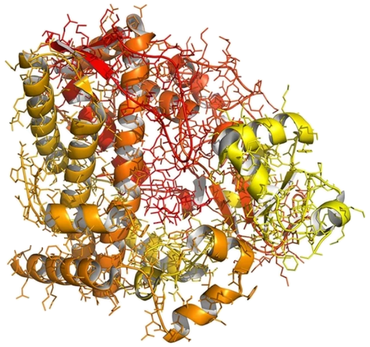


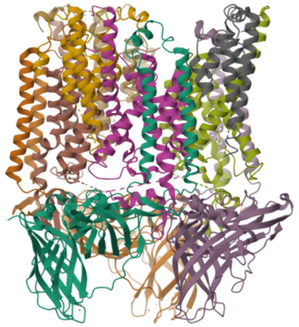




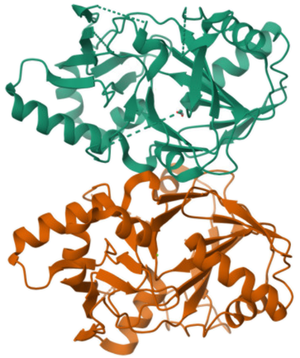
Radical rebound catalyzed by metallic cofactors



Cytochrome P450

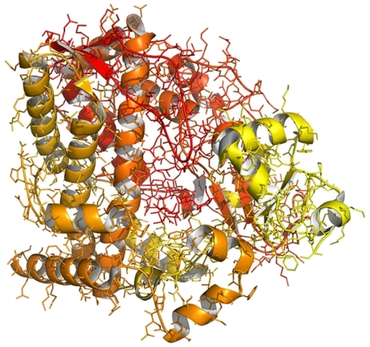


α-ketoglutarate-dependent hydroxylase



nonheme-diiron hydroxylase

Radical rebound catalyzed by metallic cofactors



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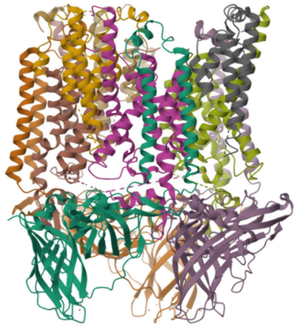

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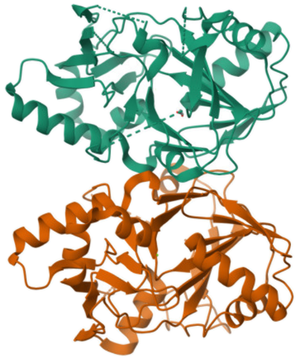
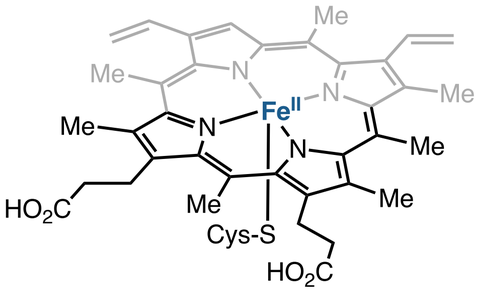
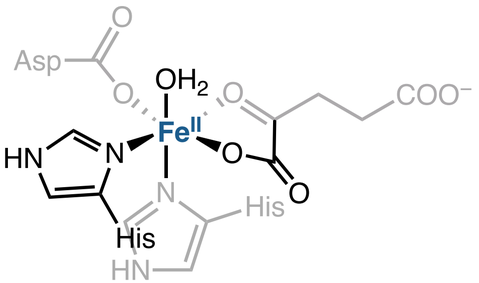
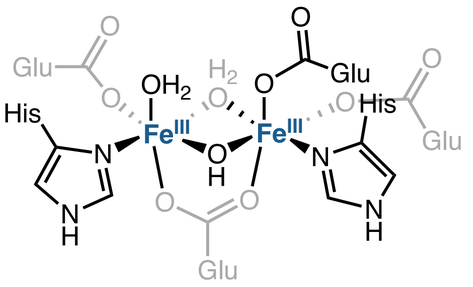


nonheme-diiron hydroxylase

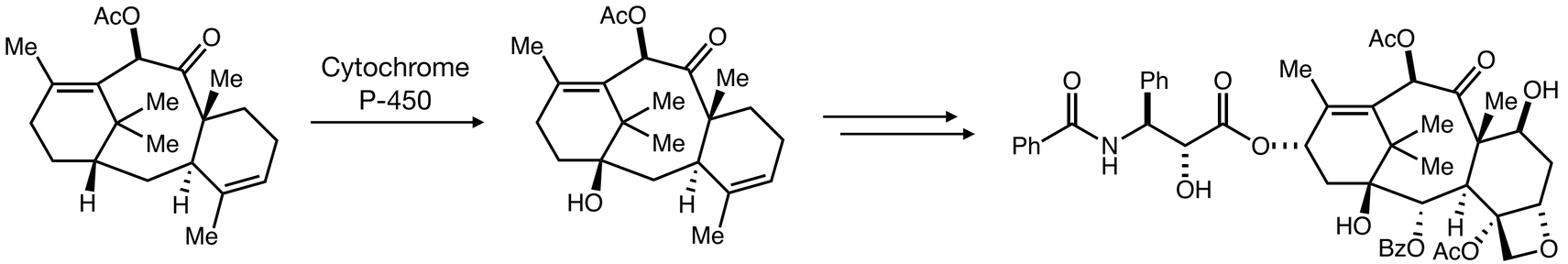






Cytochrome P450 Catalyzed Oxidations

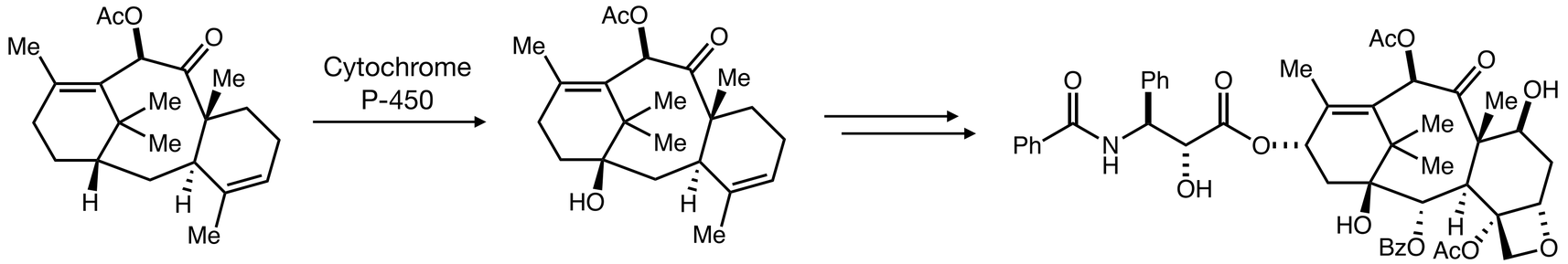
Biosynthesis of Taxol



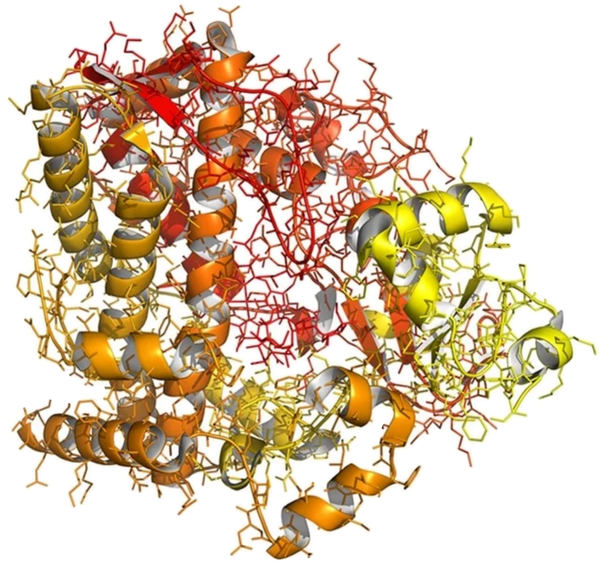
Taxol

Cytochrome P450 Catalyzed Oxidations

Biosynthesis of Taxol



Taxol



Cytochrome P450

Cytochrome P450 Catalyzed Oxidations

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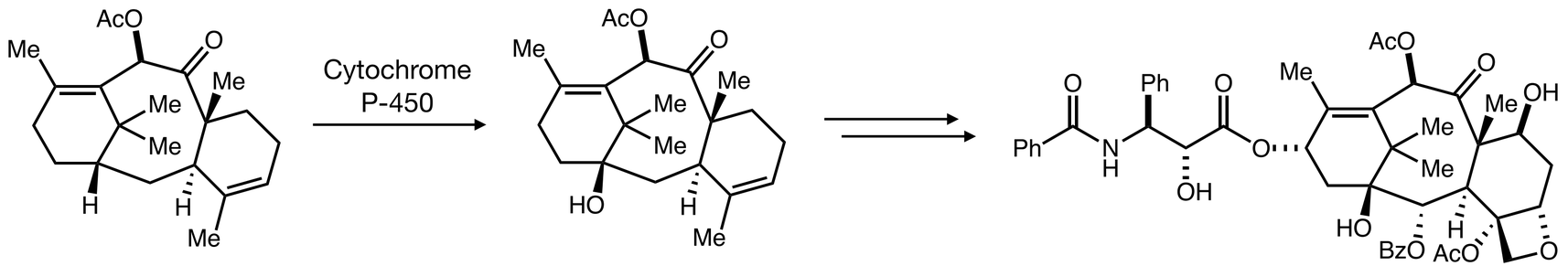
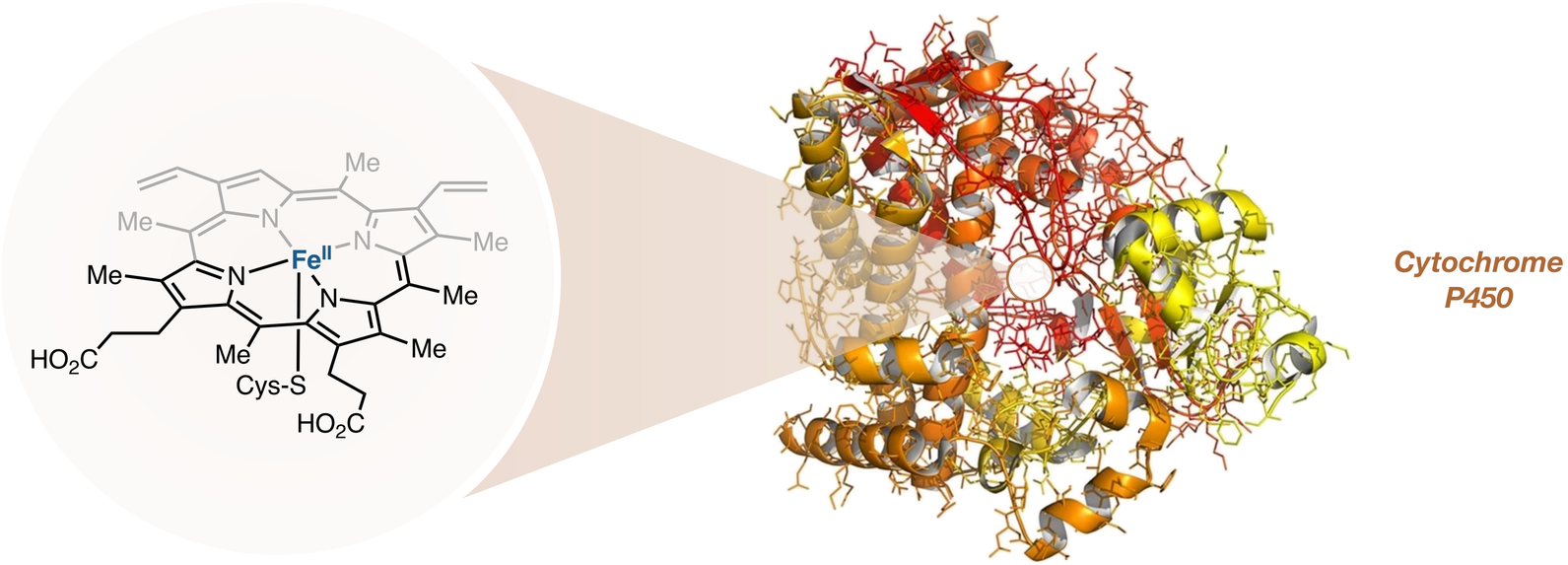
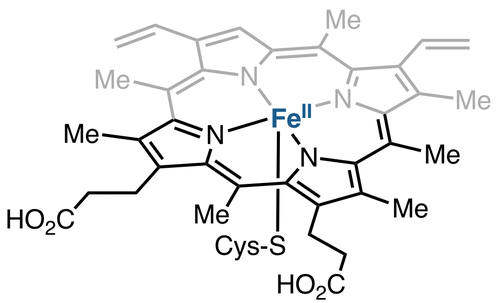


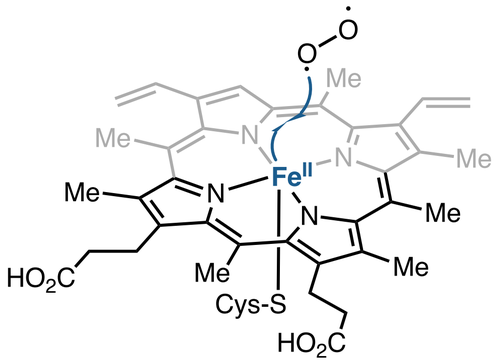


Cytochrome P450 catalyzed oxidations



Williams *J. Org. Chem* **2000,** *65*, 7865, Sligar *Science* **2000,** *287*, 1615.

Cytochrome P450 catalyzed oxidations



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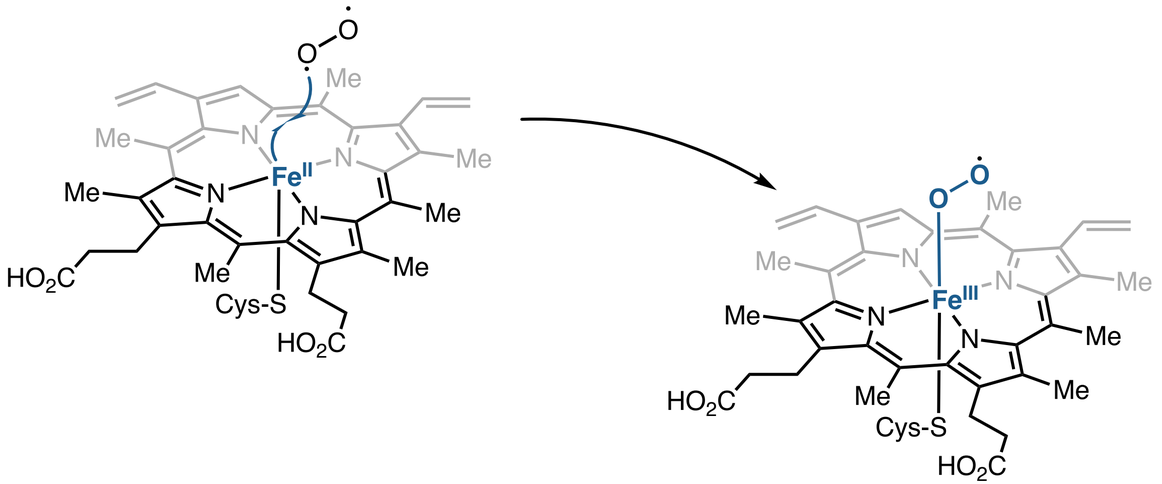

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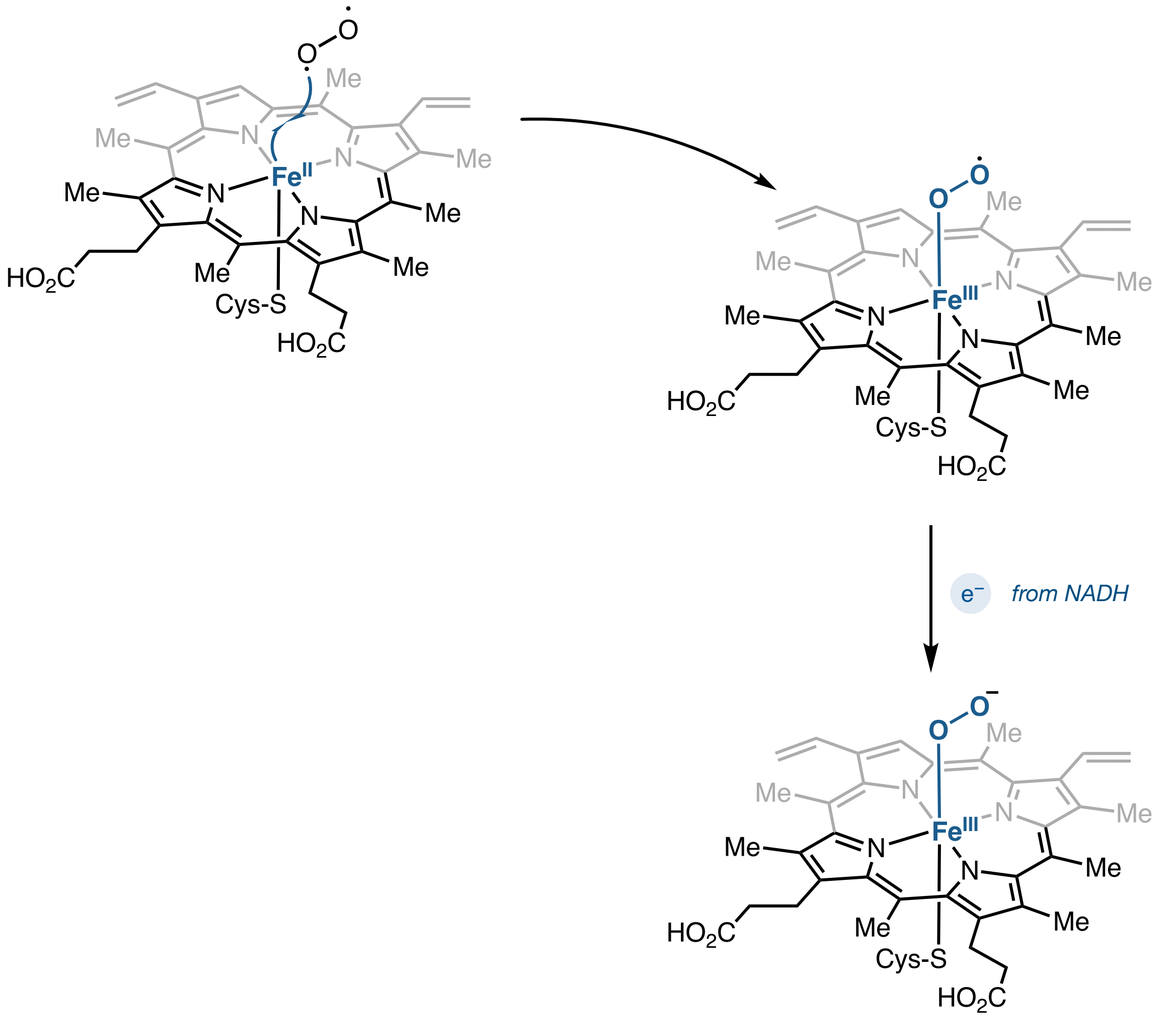

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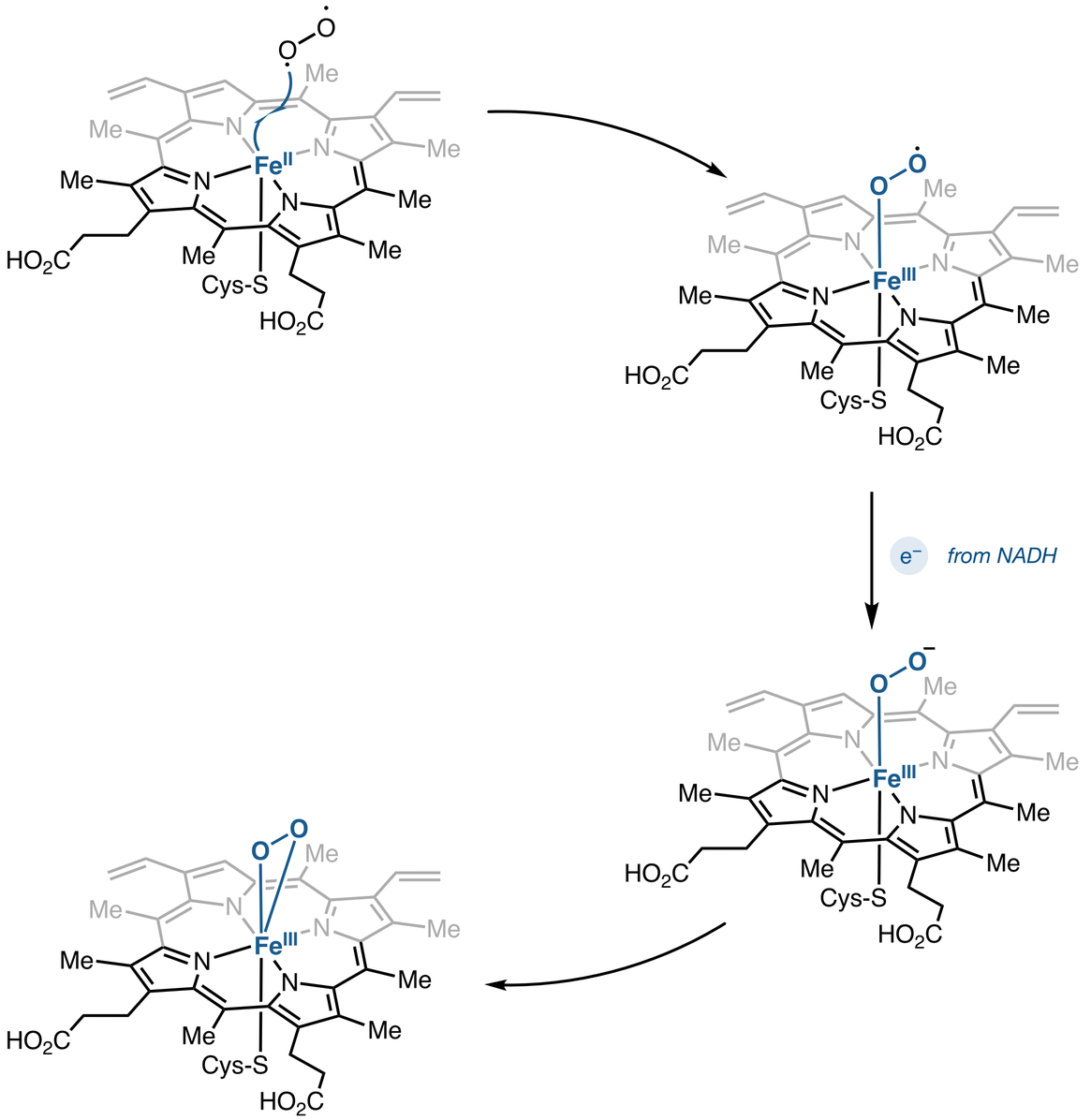

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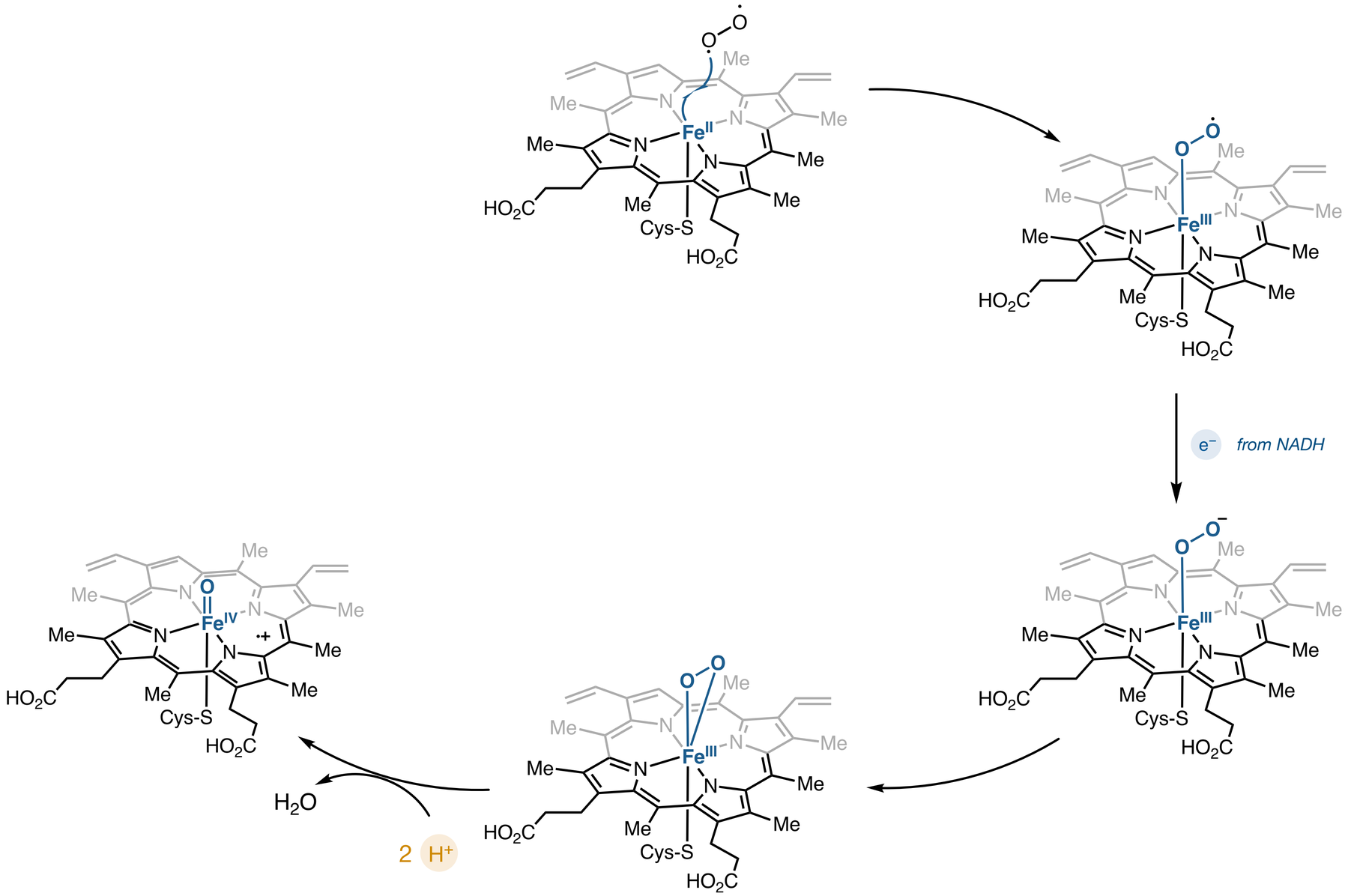

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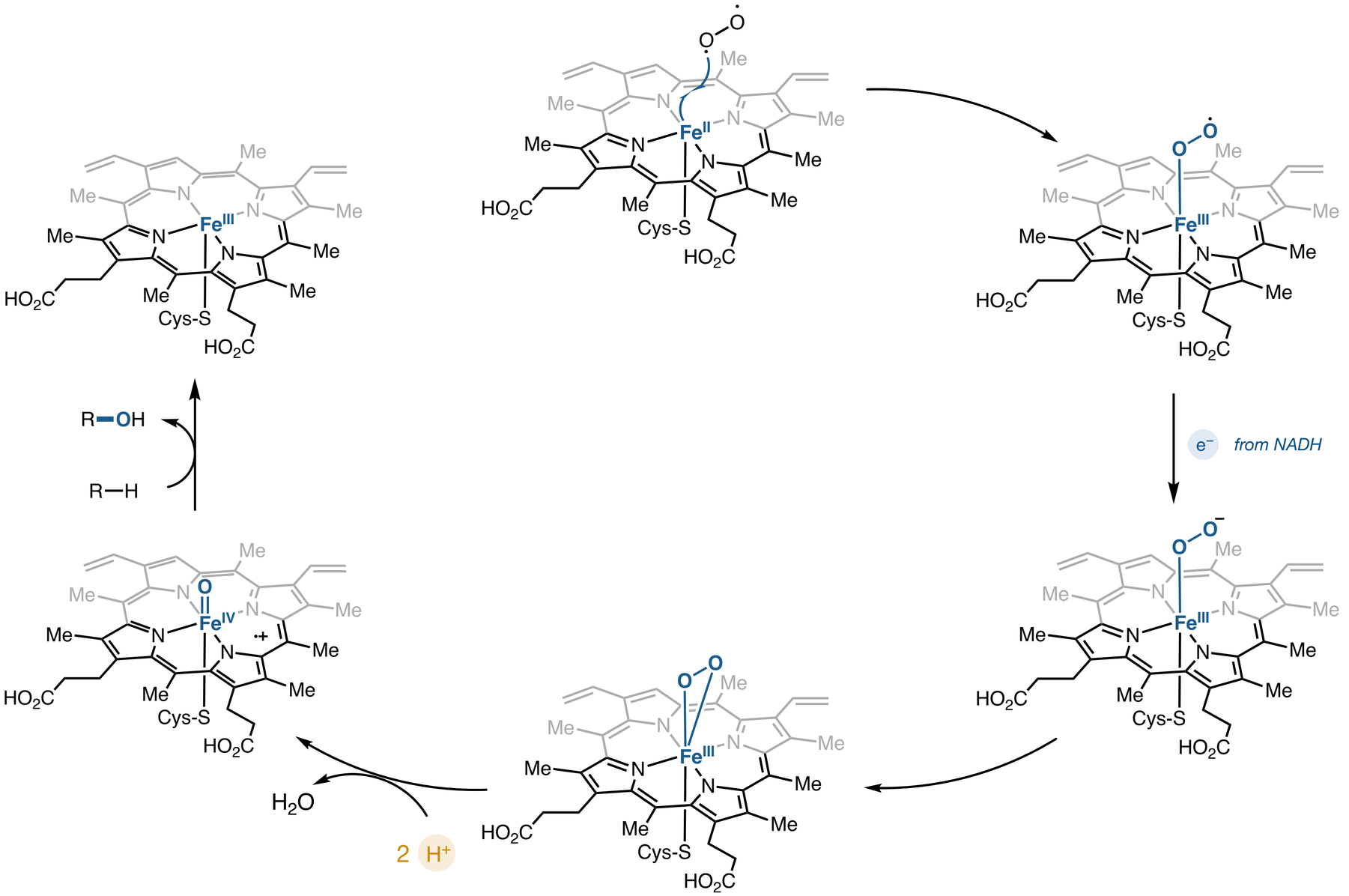

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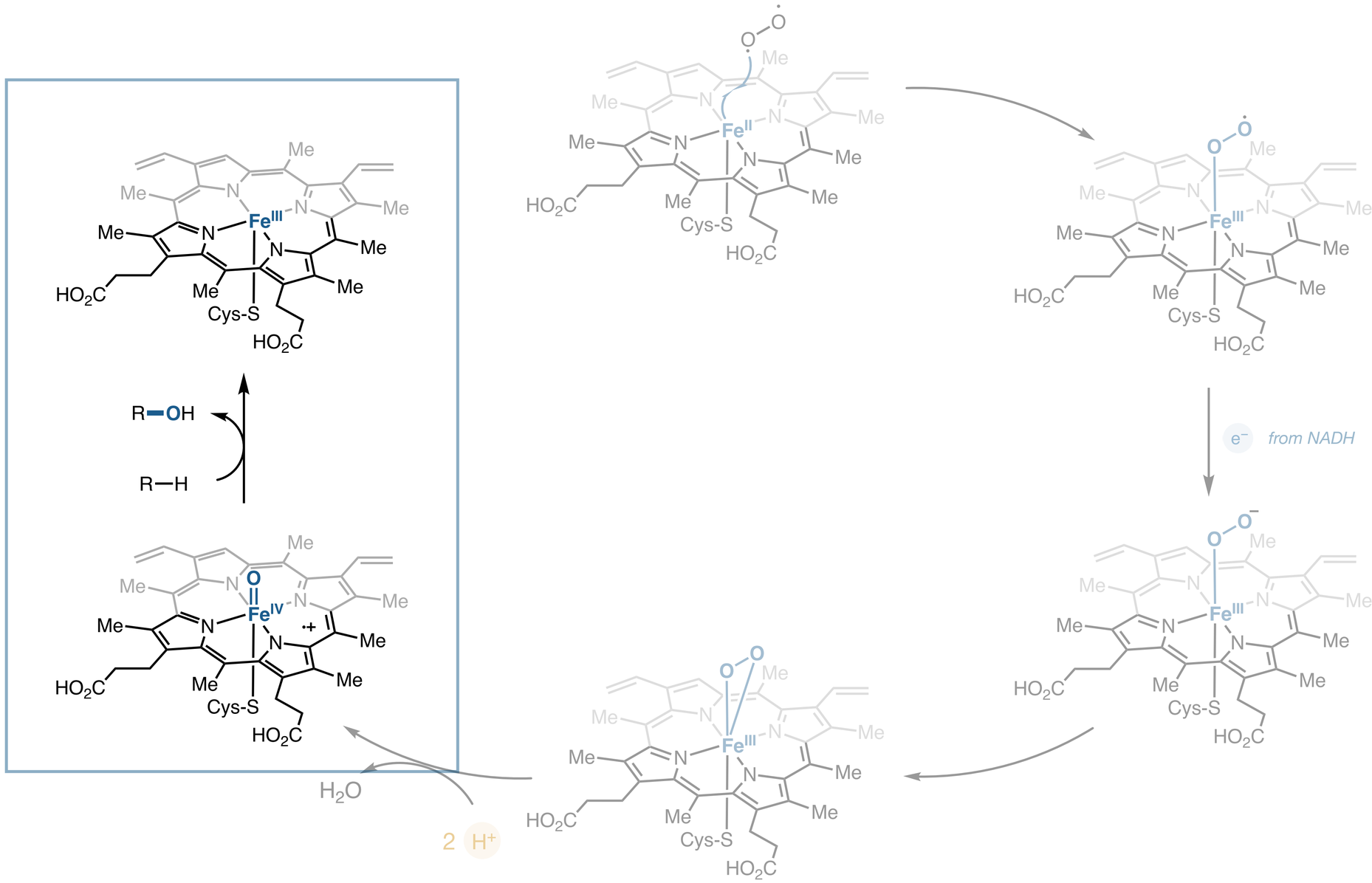

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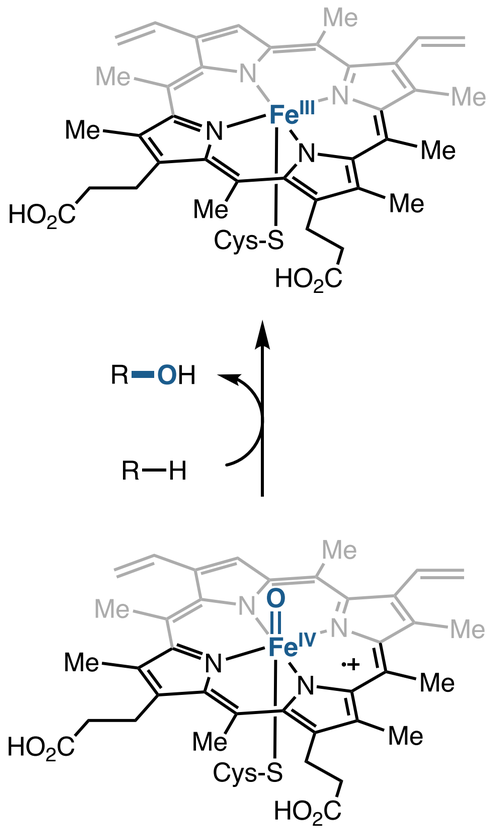

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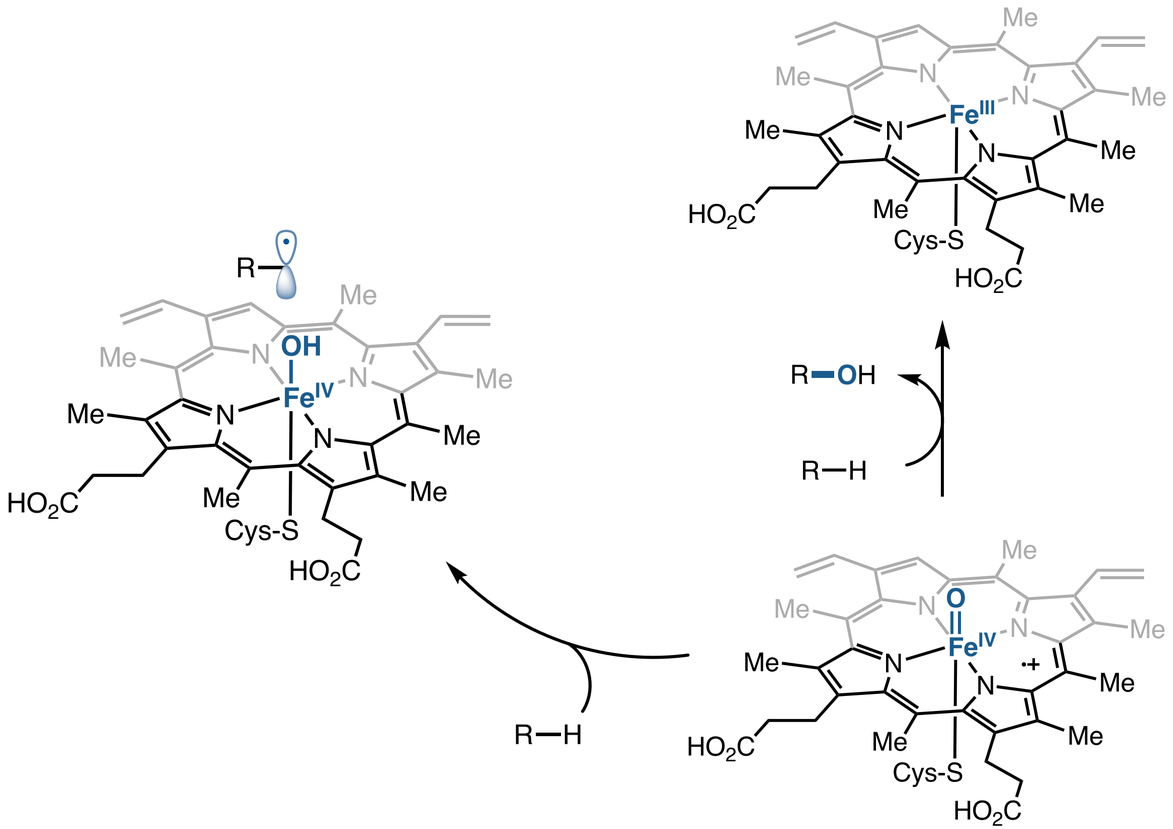

HAT selectivity similar to metal-oxo photocatalysts

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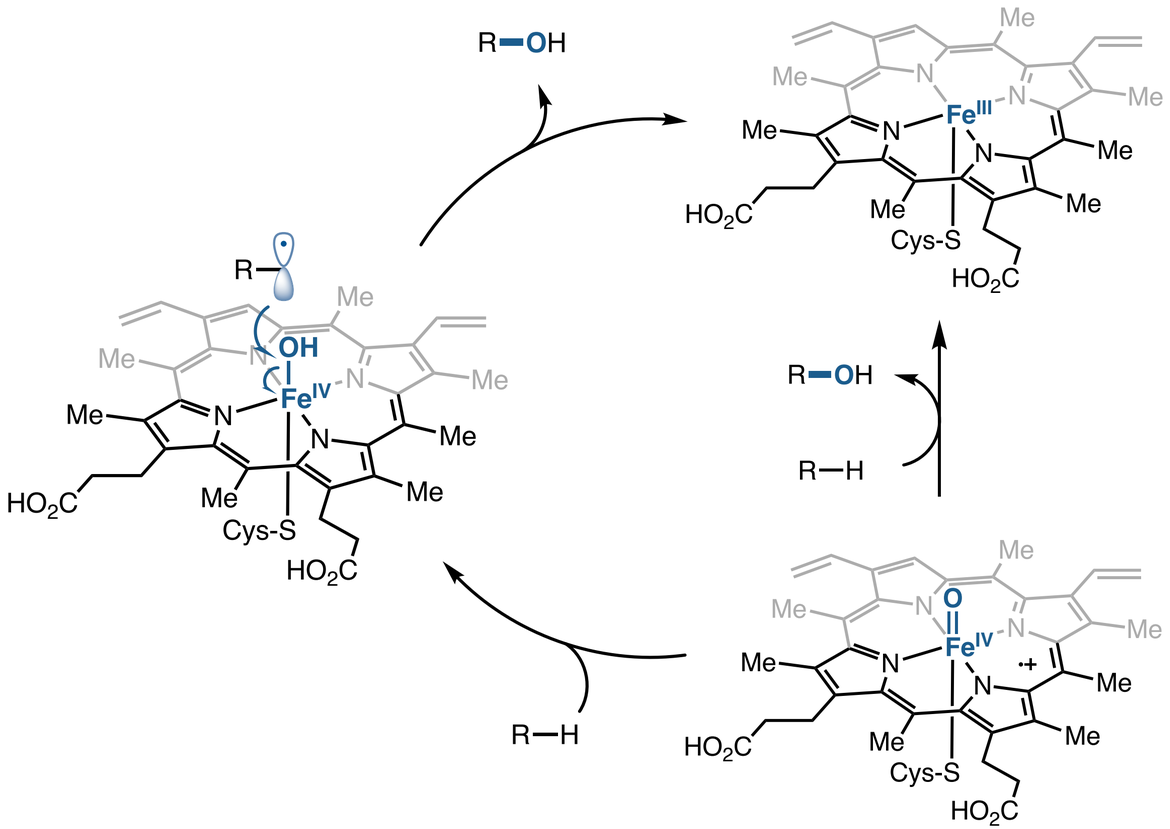
Cytochrome P450 catalyzed oxidations



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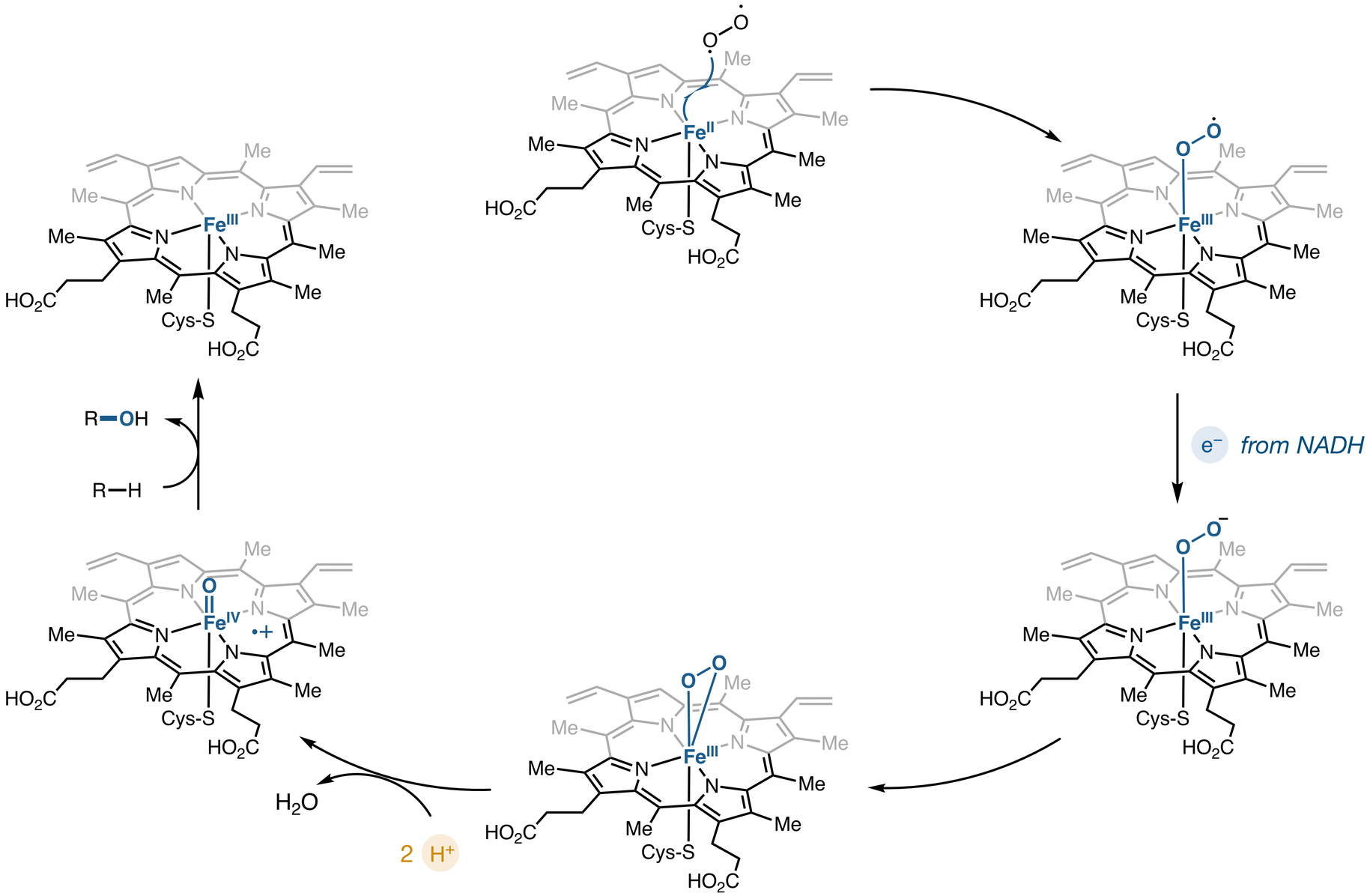

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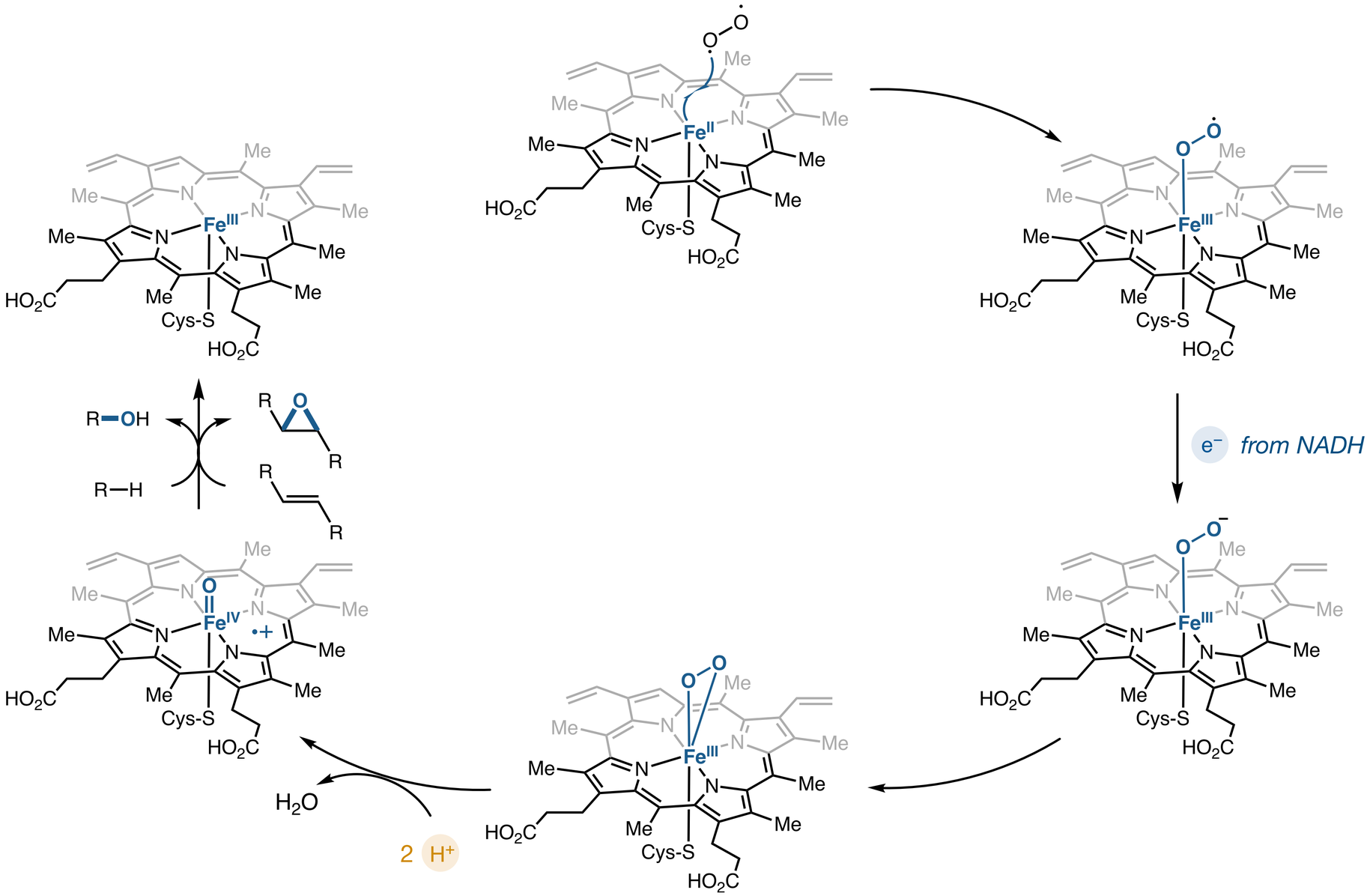

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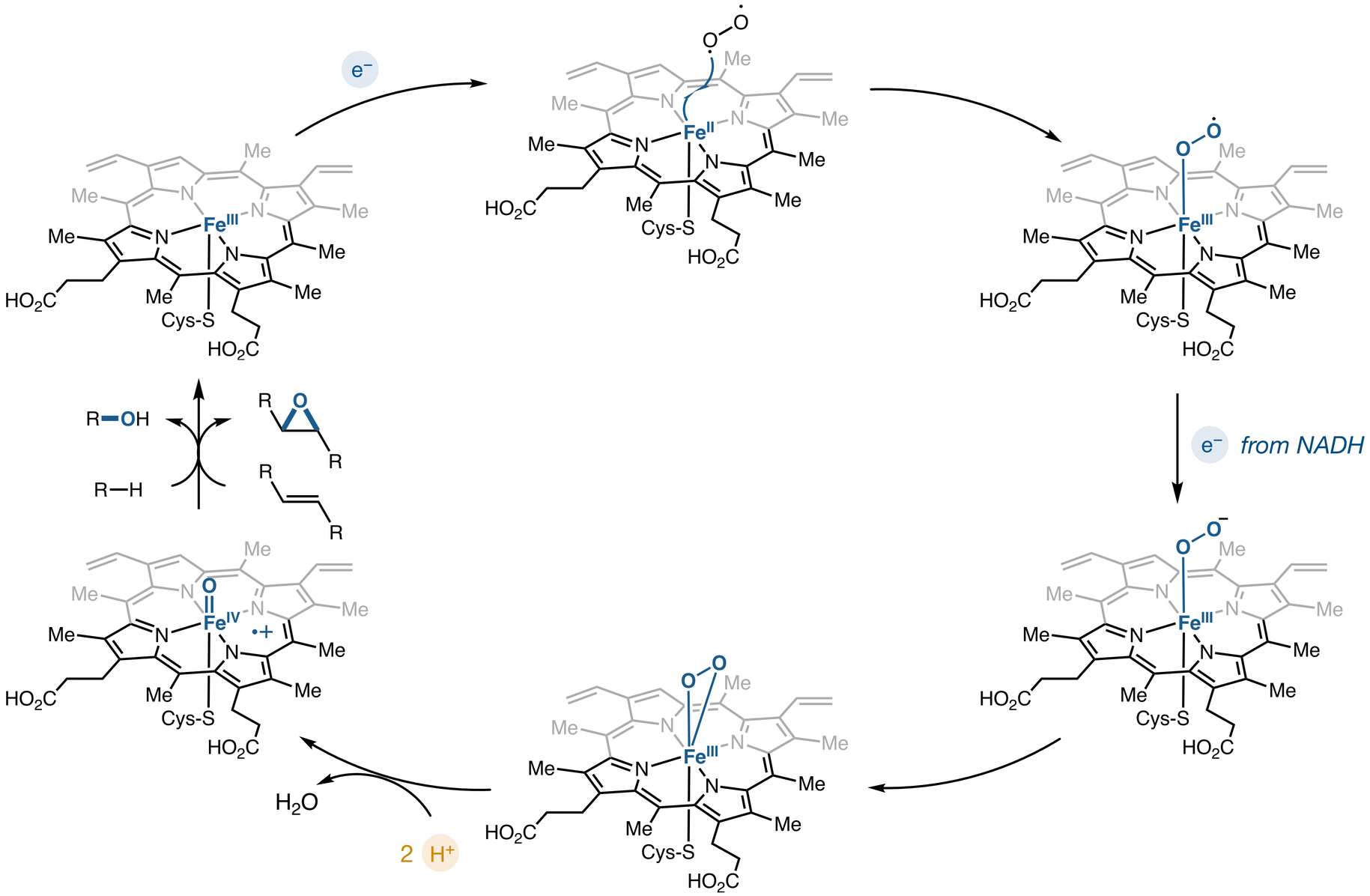

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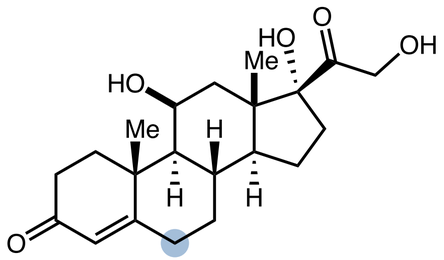
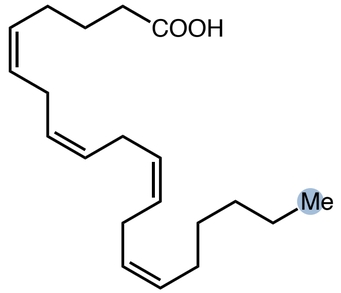
Substrate class of cytochrome P450 catalyzed oxidations

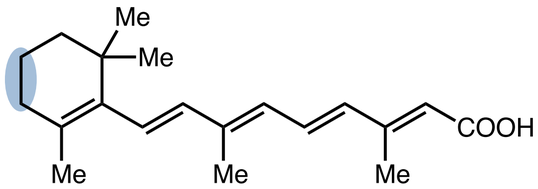
hormones



fatty acids



retinoic acid



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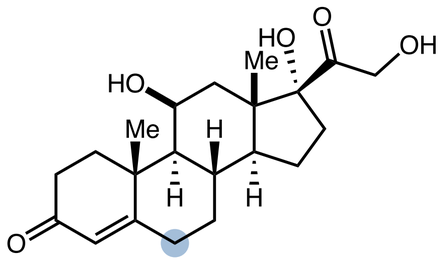
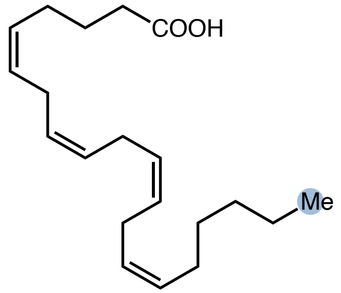


fatty acids



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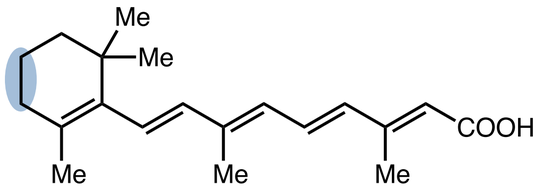
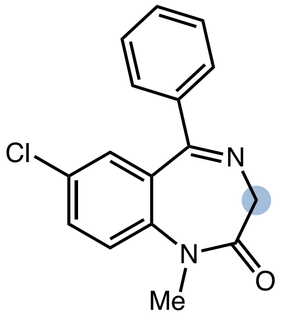
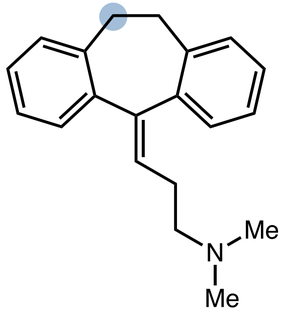
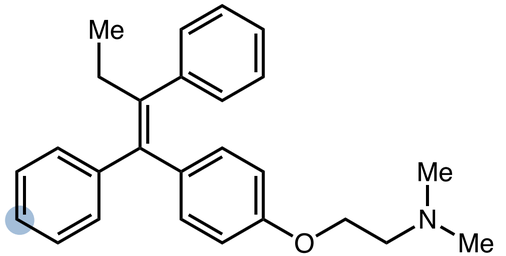


drugs





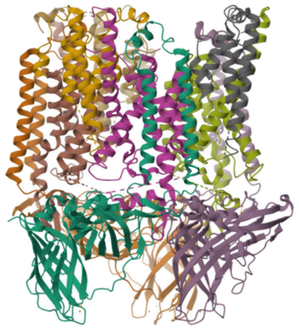
pro-drugs



Williams *J. Org. Chem* **2000,** *65*, 7865, Sligar *Science* **2000,** *287*, 1615.

α-ketoglutarate dependent non-heme enzymes

α-ketoglutarate-dependent hydroxylases



largest subfamily of non-heme iron enzymes

most diverse set of oxidative transformations (hydroxylations, desaturation, ring closure/expansion)

Hegg, E. L.; Que, L. *Eur. J. Biochem.* **2004,** 250, 625.

α-ketoglutarate dependent non-heme enzymes

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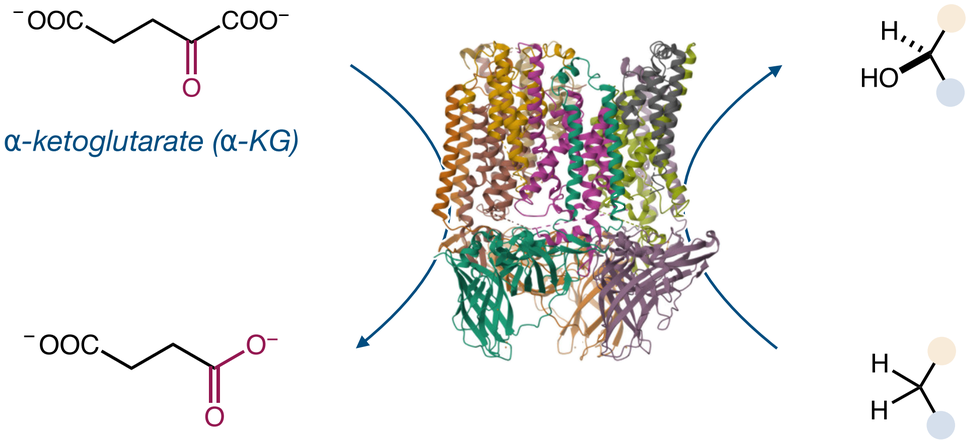

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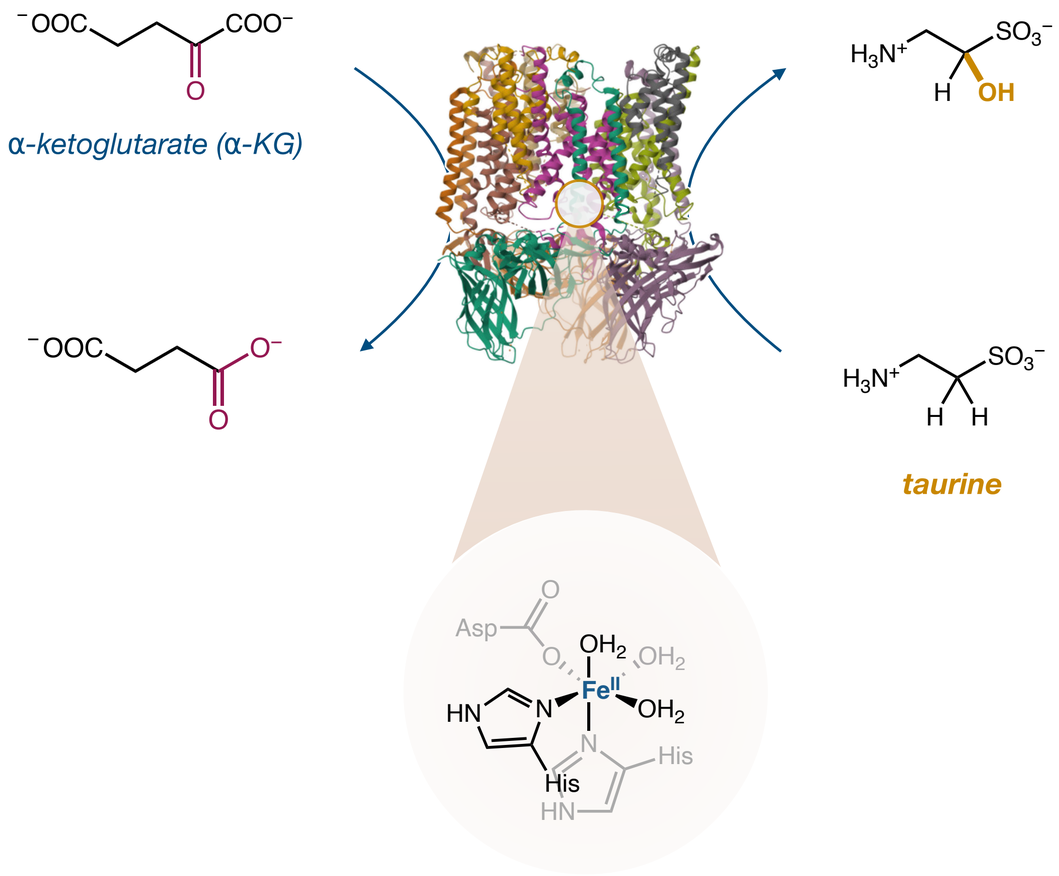
taurine dioxygenase



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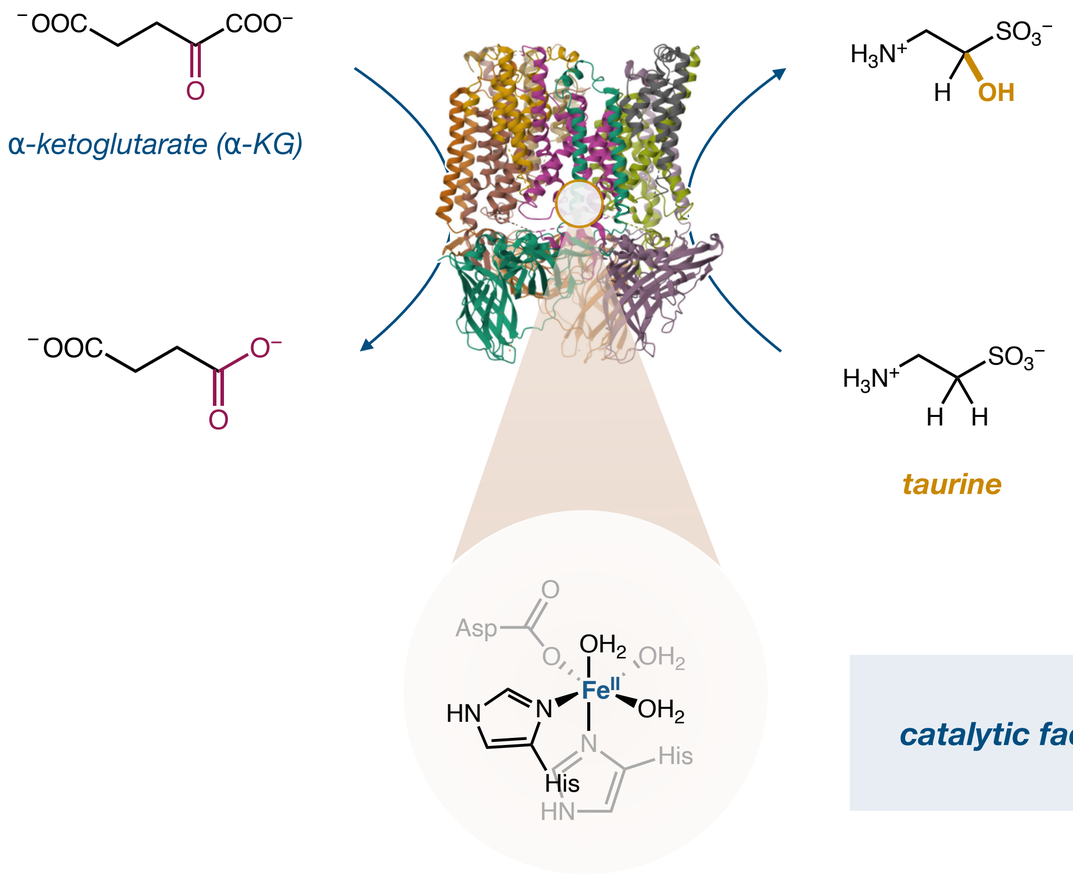
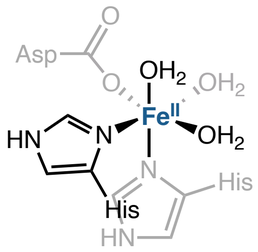
taurine dioxygenase



catalytic facial triad (His-His-Asp) crucial for activity

Hegg, E. L.; Que, L. *Eur. J. Biochem.* **2004,** 250, 625.

α-*ketoglutarate dependent non-heme enzymes*



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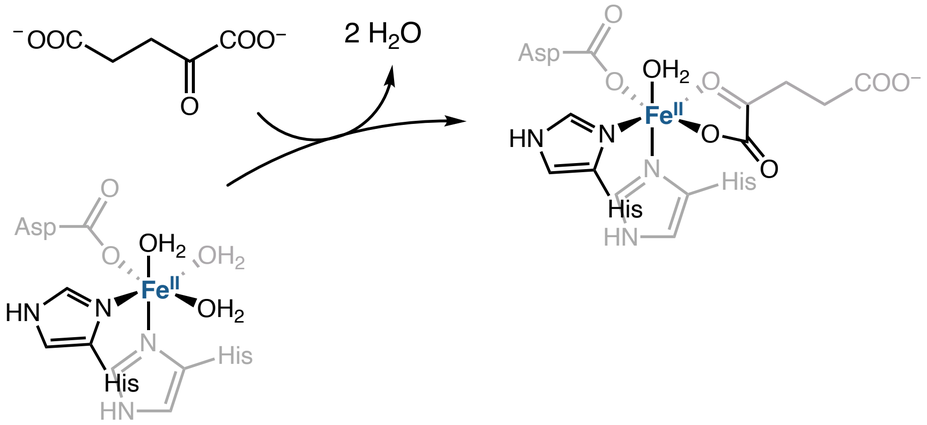

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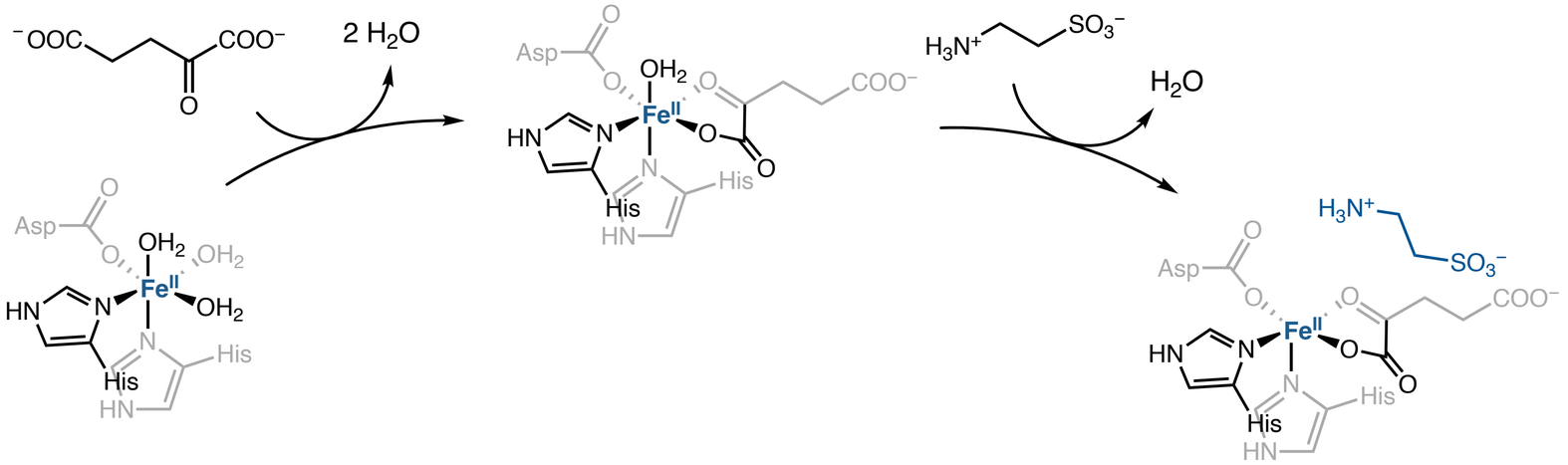

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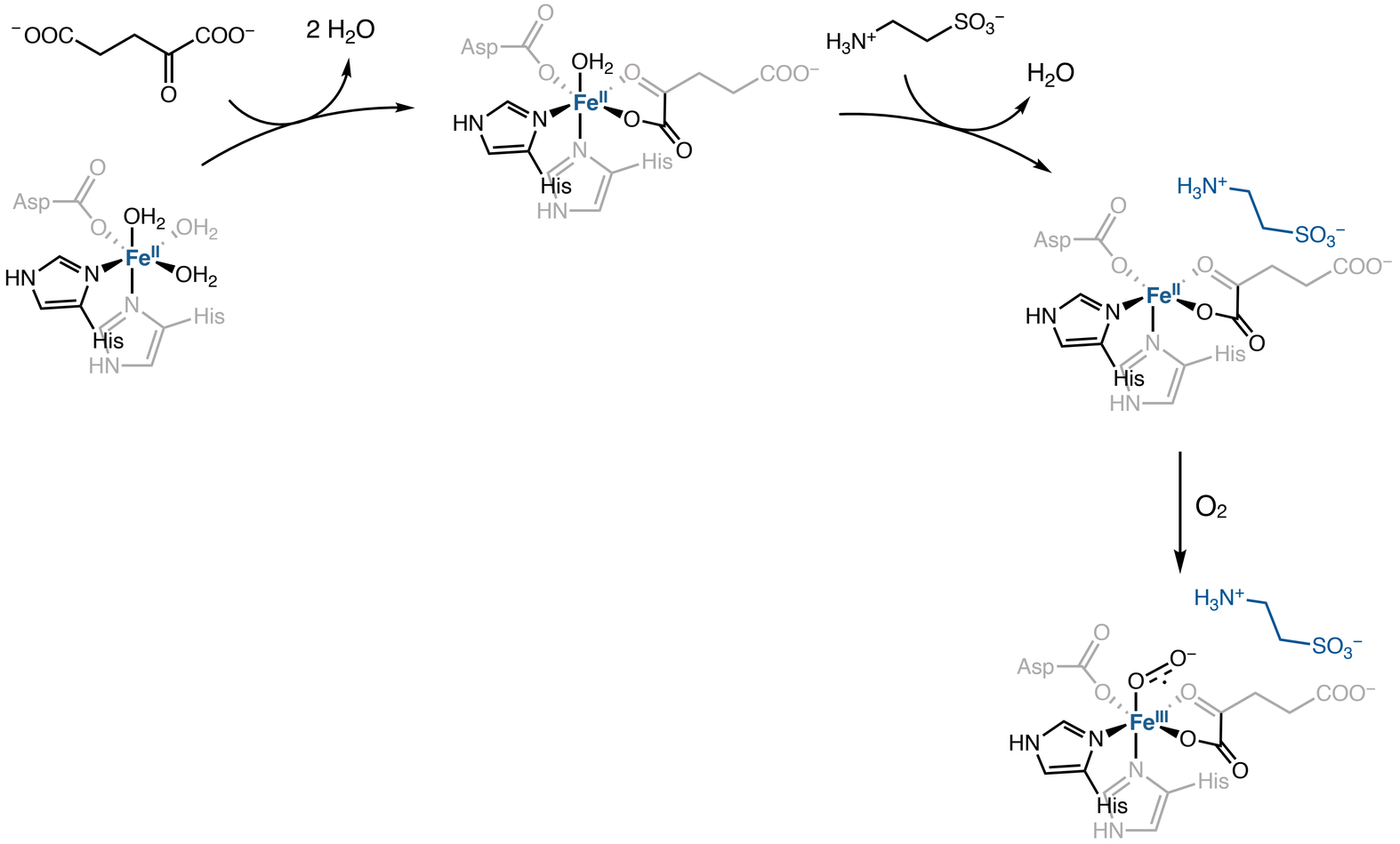

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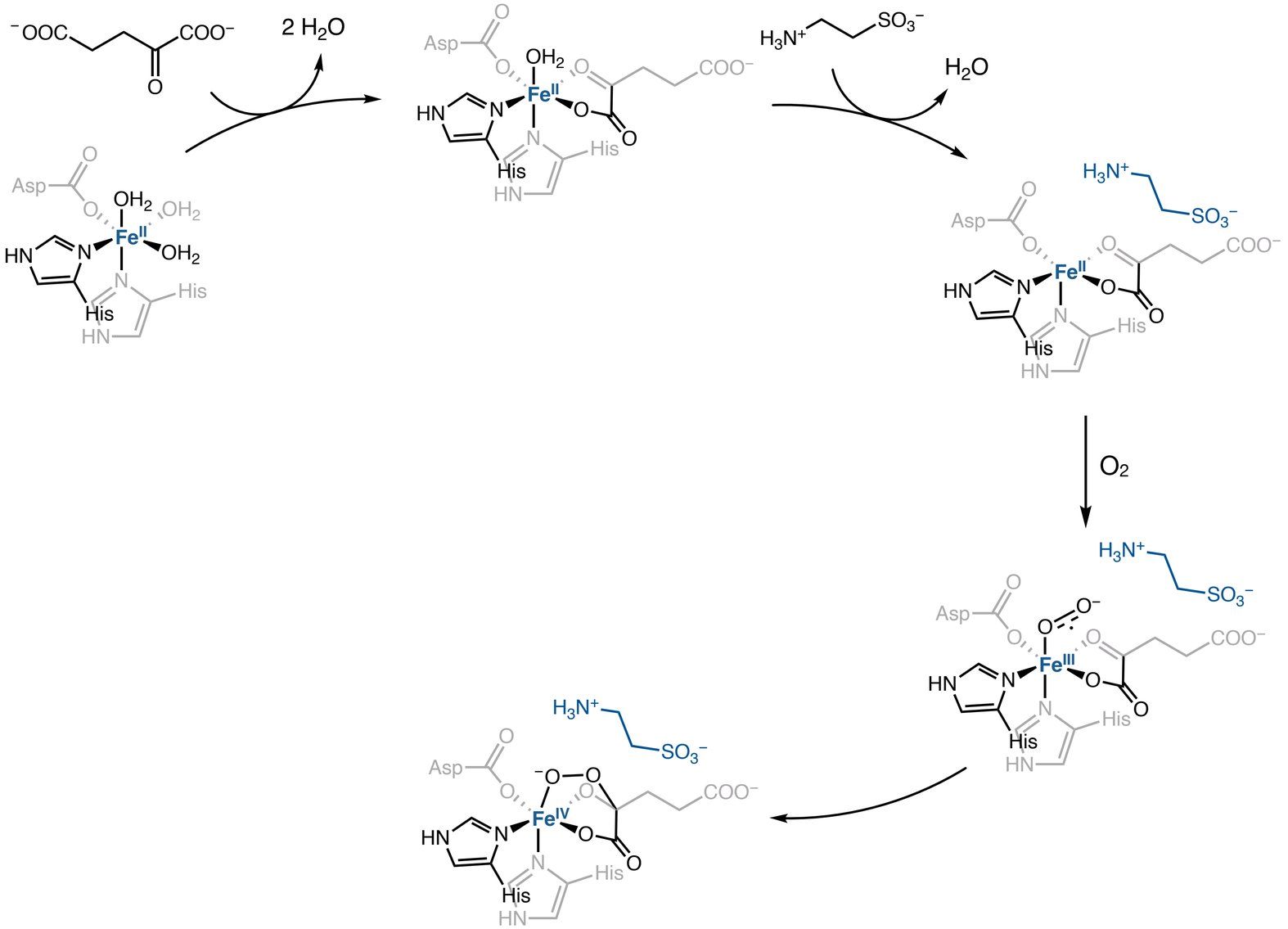

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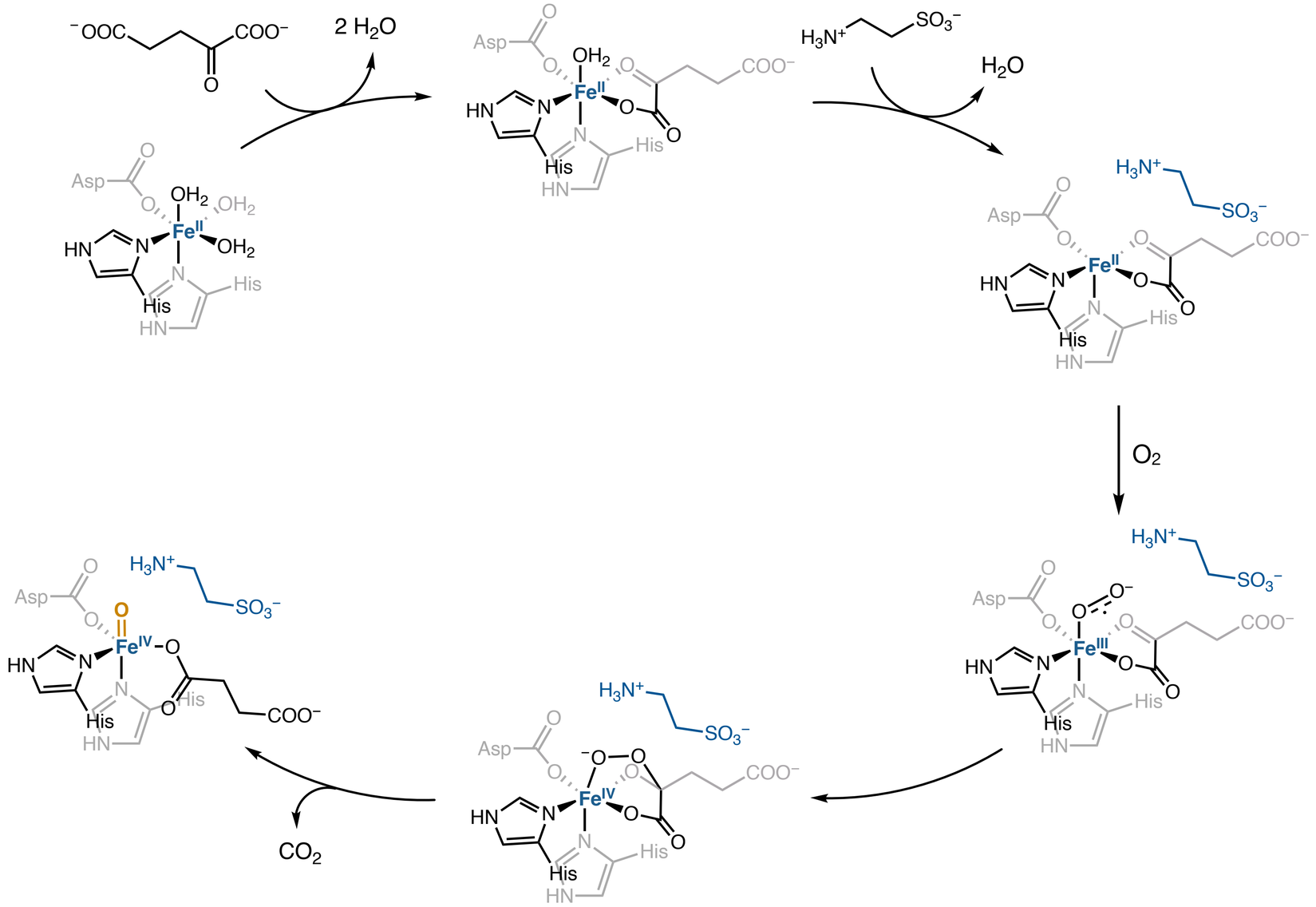

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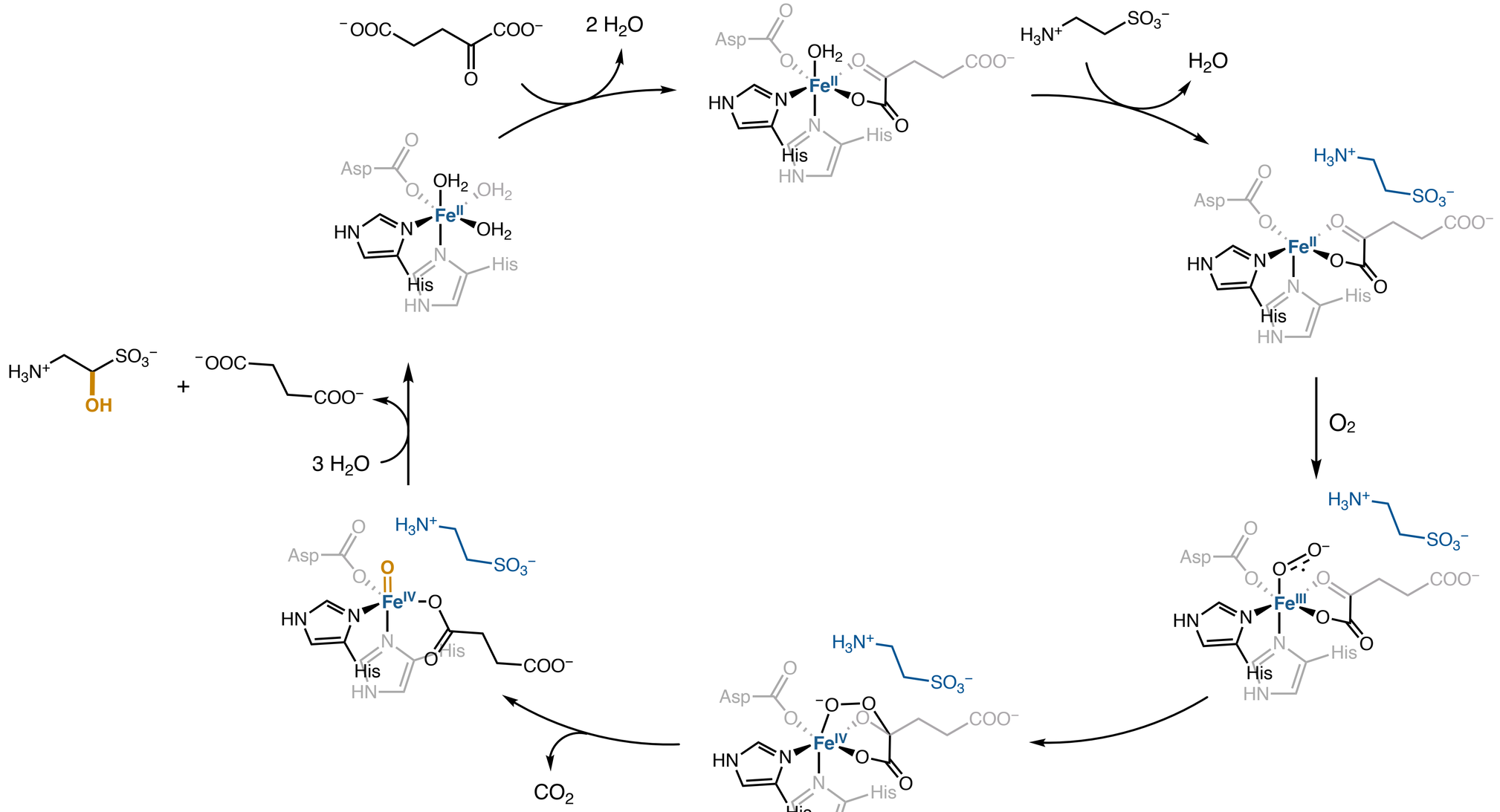

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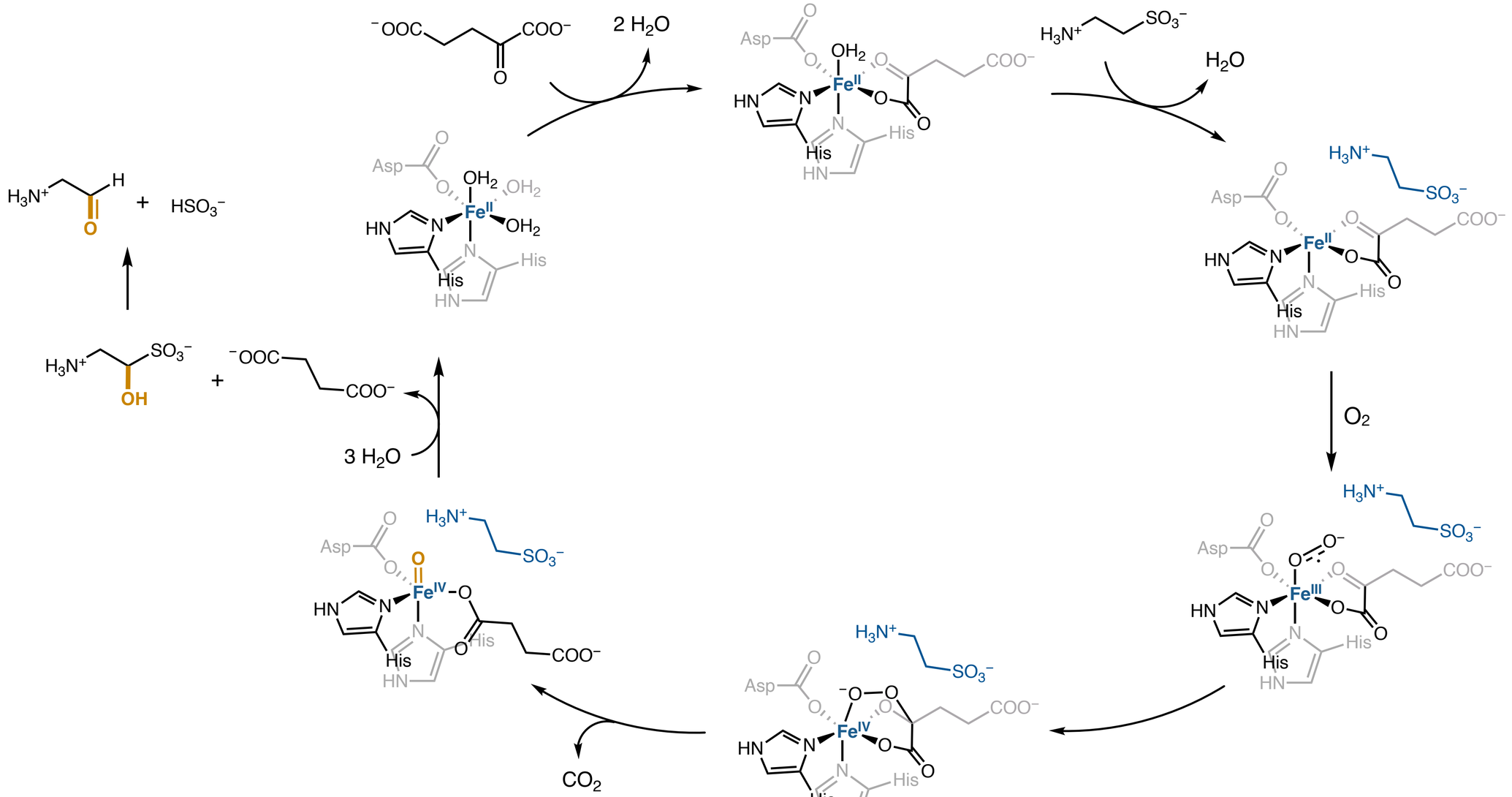

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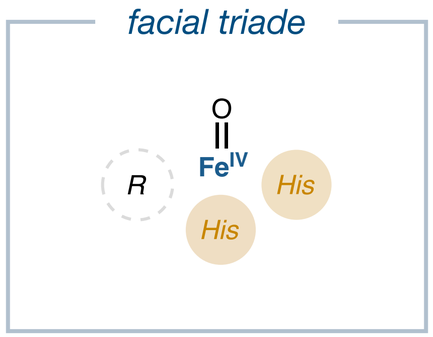
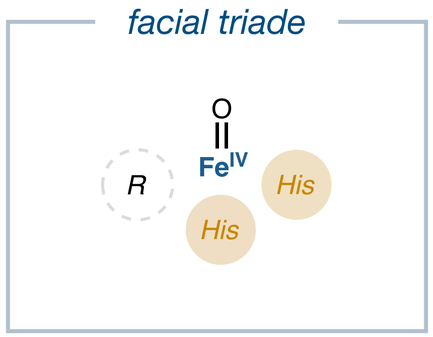
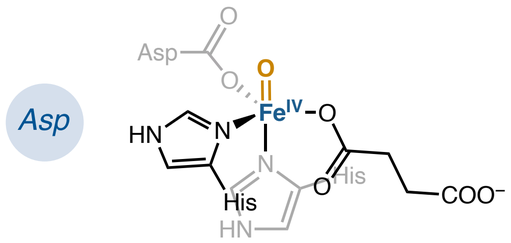
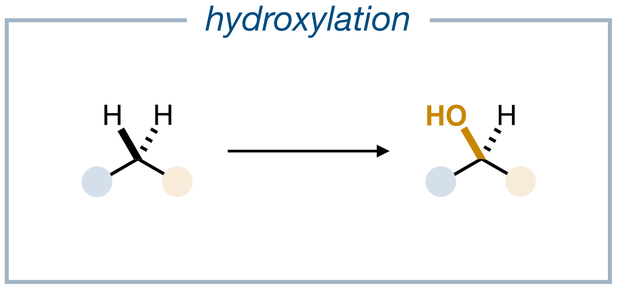


Vaillancourt, F. H.; Yin, J.; Walsh, C. T. *PNAS* **2005,** *102*, 10111; Borowski, T.; Noack, H.; Radoń, M.; Zych, K.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2010,** *132*, 12887.

α-ketoglutarate dependent non-heme enzymes







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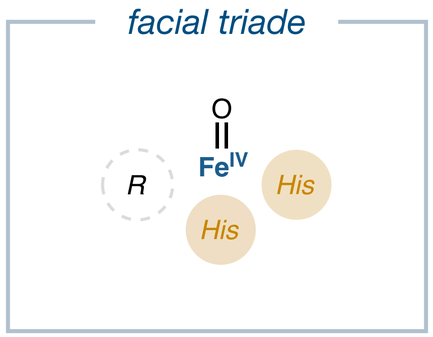
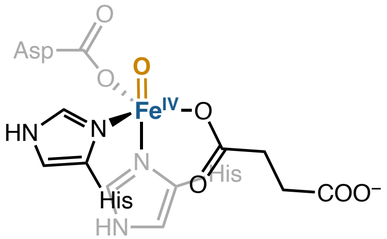
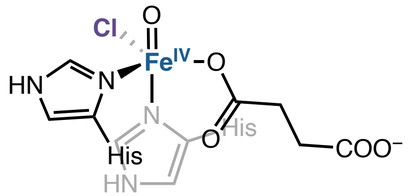
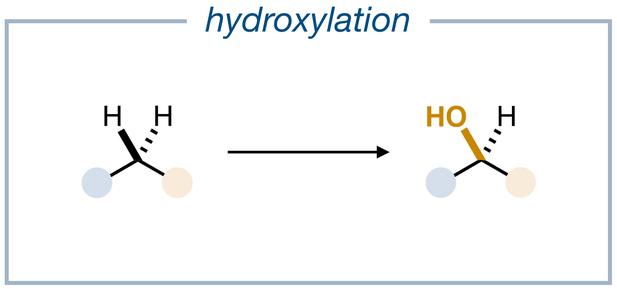


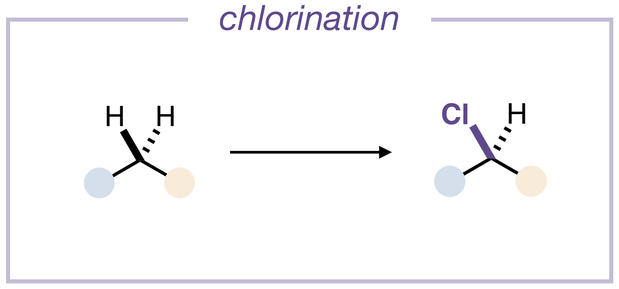
Asp



Cl

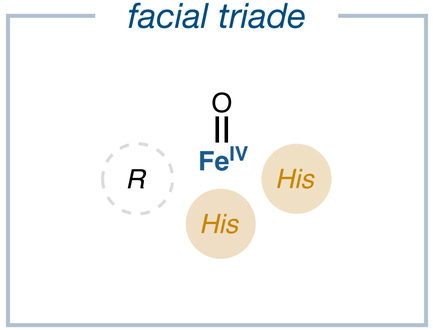






Vaillancourt, F. H.; Yin, J.; Walsh, C. T. *PNAS* **2005,** *102*, 10111; Borowski, T.; Noack, H.; Radoń, M.; Zych, K.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2010,** *132*, 12887.

α-ketoglutarate dependent non-heme enzymes



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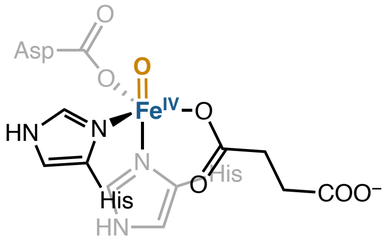

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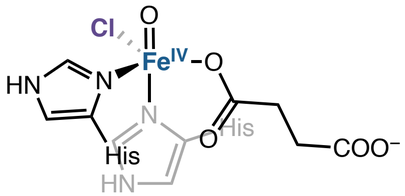
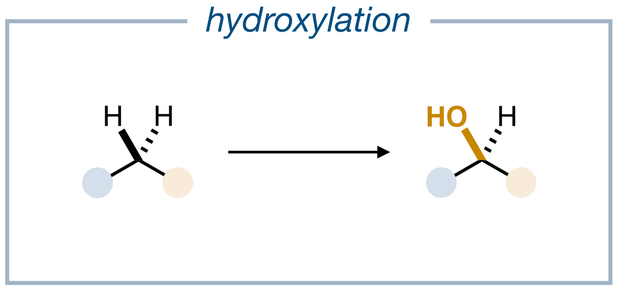
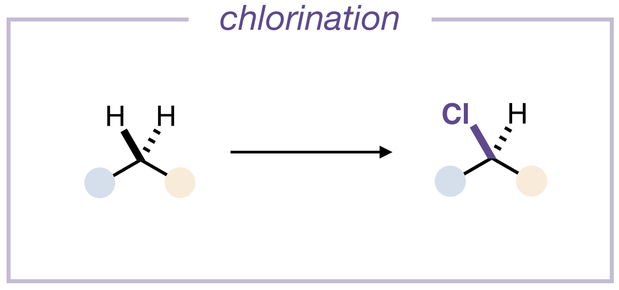


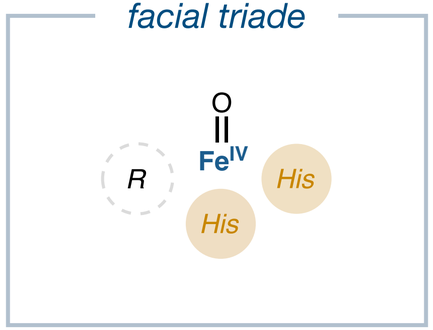
"chloride rebound" kinetically favored due to BDE (Fe-Cl) < BDE (Fe-OH)

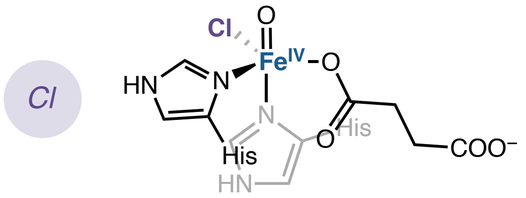


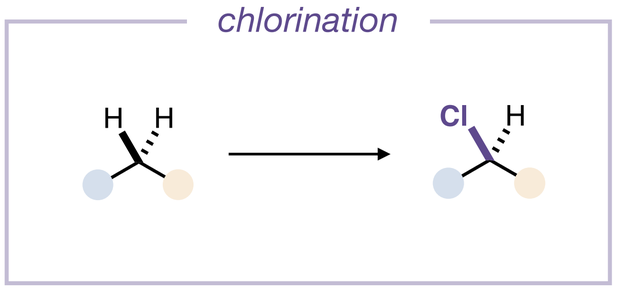


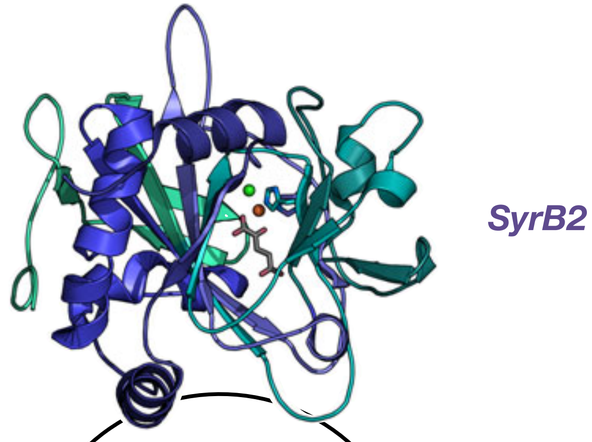
Vaillancourt, F. H.; Yin, J.; Walsh, C. T. *PNAS* **2005,** *102*, 10111; Borowski, T.; Noack, H.; Radoń, M.; Zych, K.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2010,** *132*, 12887.

α-ketoglutarate dependent non-heme enzymes







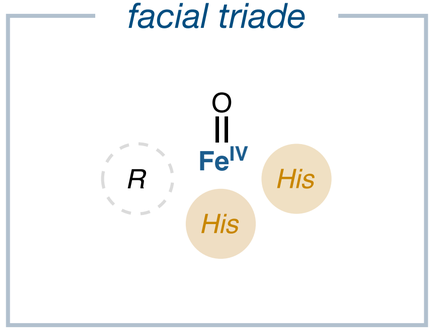


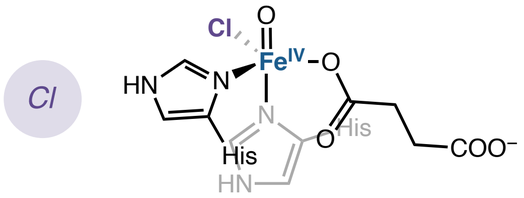
SyrB2

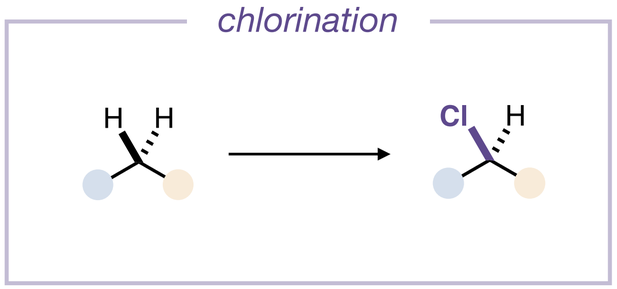
L-threonine
in combination with carrier protein

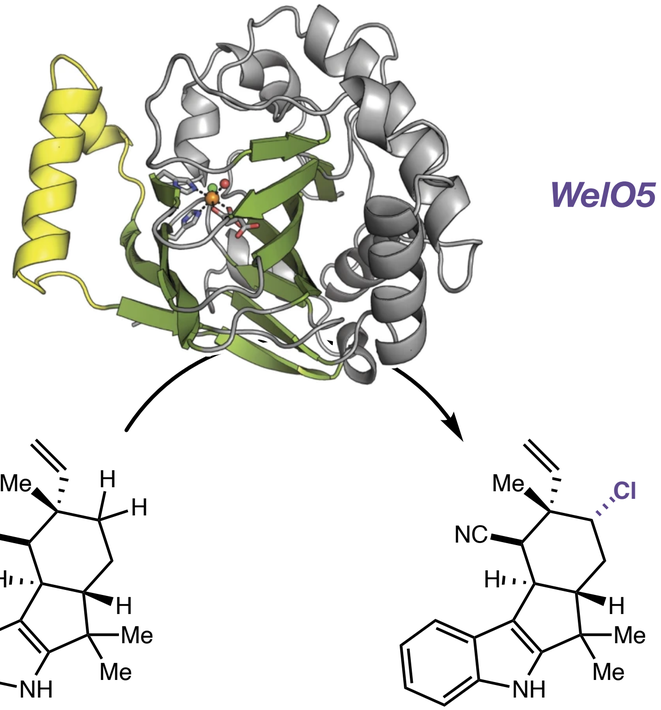
Vaillancourt, F. H.; Yin, J.; Walsh, C. T. *PNAS* **2005,** *102*, 10111; Borowski, T.; Noack, H.; Radoń, M.; Zych, K.; Siegbahn, P. E. M. *J. Am. Chem. Soc.* **2010,** *132*, 12887.

α-ketoglutarate dependent non-heme enzymes



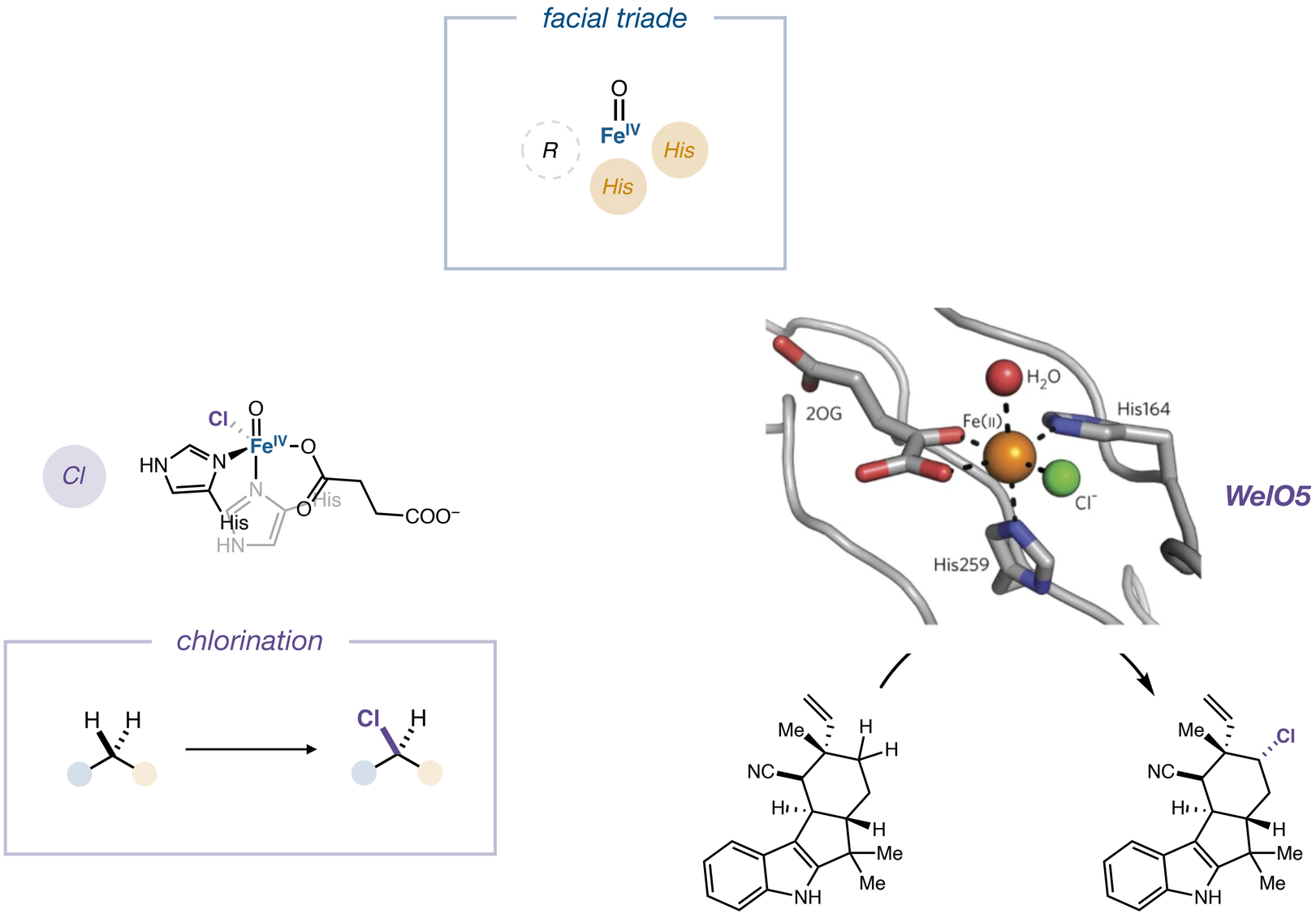






Boal *et. al. Nat. Chem. Bio.* **2016,** *12*, 636.

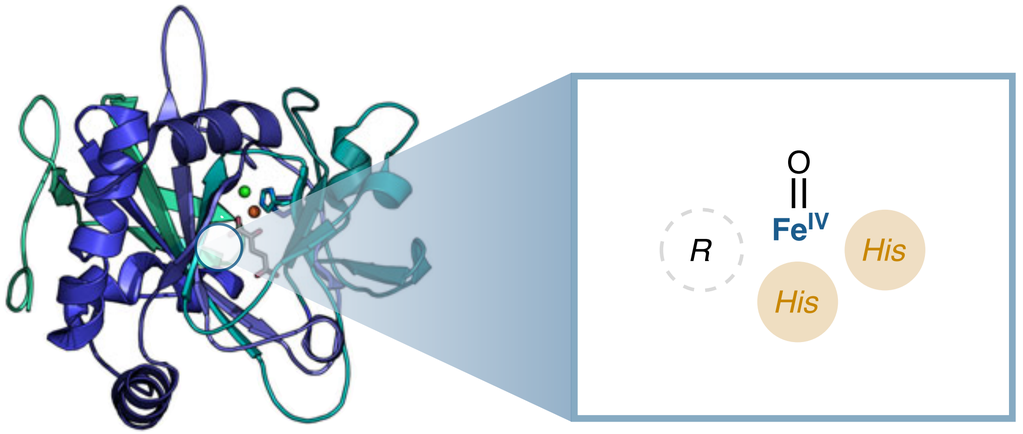
α-ketoglutarate dependent non-heme enzymes



Boal *et. al. Nat. Chem. Bio.* **2016,** *12*, 636.

Enzymatic engineering for unlocking new reactivities

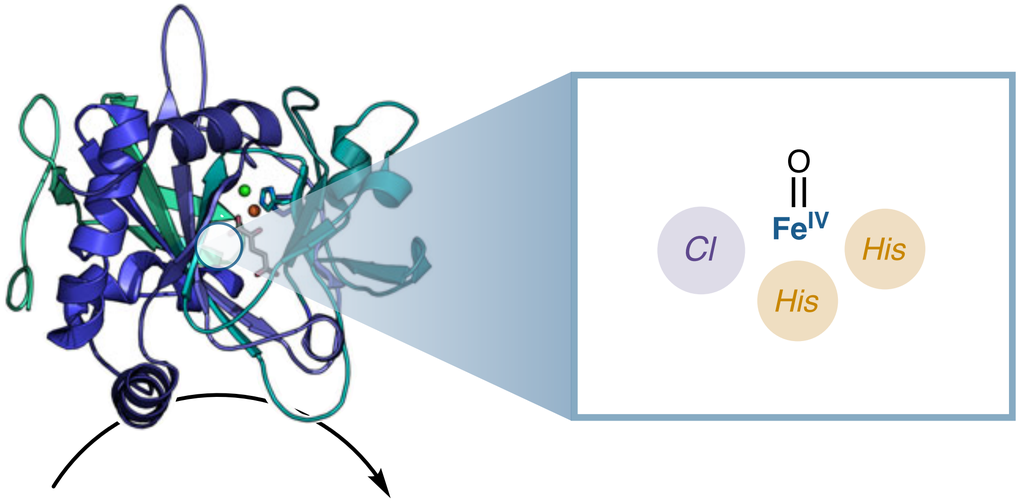
SyrB2 (wild type)



Bollinger *et. al. Nat. Chem. Bio.* **2014,** *10*, 209.

Enzymatic engineering for unlocking new reactivities

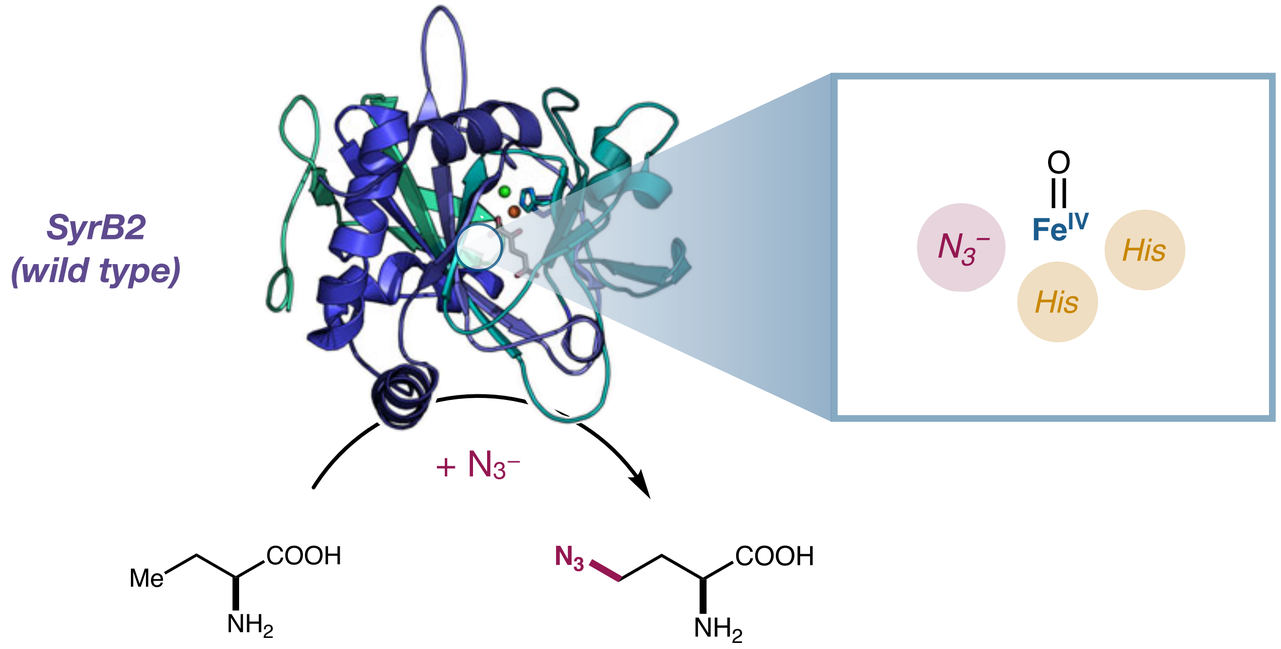
SyrB2 (wild type)



L-threonine
in combination with carrier protein

Bollinger *et. al. Nat. Chem. Bio.* **2014,** *10*, 209.

Enzymatic engineering for unlocking new reactivities



with carrier protein *4% yield*

preferential binding of spherical chloride anion over linear azide

Bollinger *et. al. Nat. Chem. Bio.* **2014,** *10*, 209.

Enzymatic engineering for unlocking new reactivities

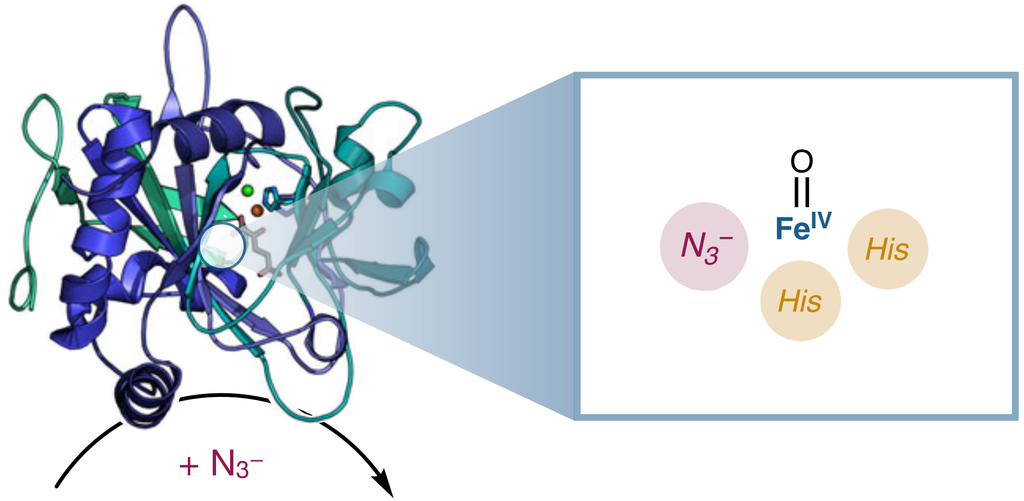
X^- pocket

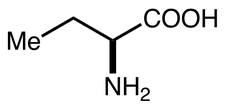
Me ➡ *H*

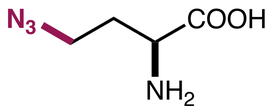
increased space in binding pocket

perturbing the relative triggering efficacies for O_2 binding

SyrB2 (engineered)







with carrier protein

52% yield

Suppression of chloride binding (1000-fold decrease) / azide binding unaffected

Bollinger *et. al. Nat. Chem. Bio.* **2014,** *10*, 209.

Enzymatic engineering for unlocking new reactivities

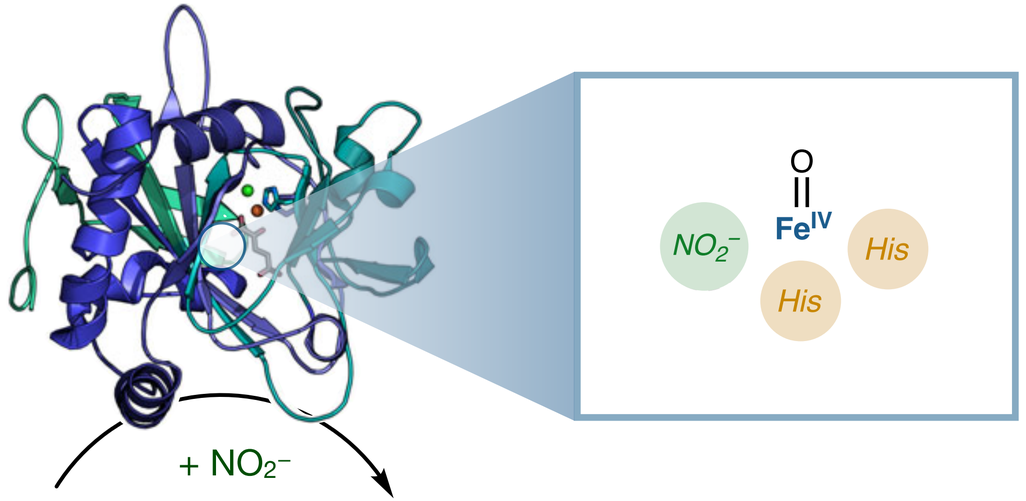
X⁻ pocket

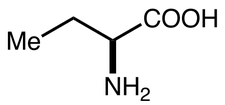
Me ➡ *H*

increased space in binding pocket

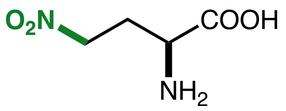
perturbing the relative triggering efficacies for O_2 binding

SyrB2 (engineered)





with carrier protein



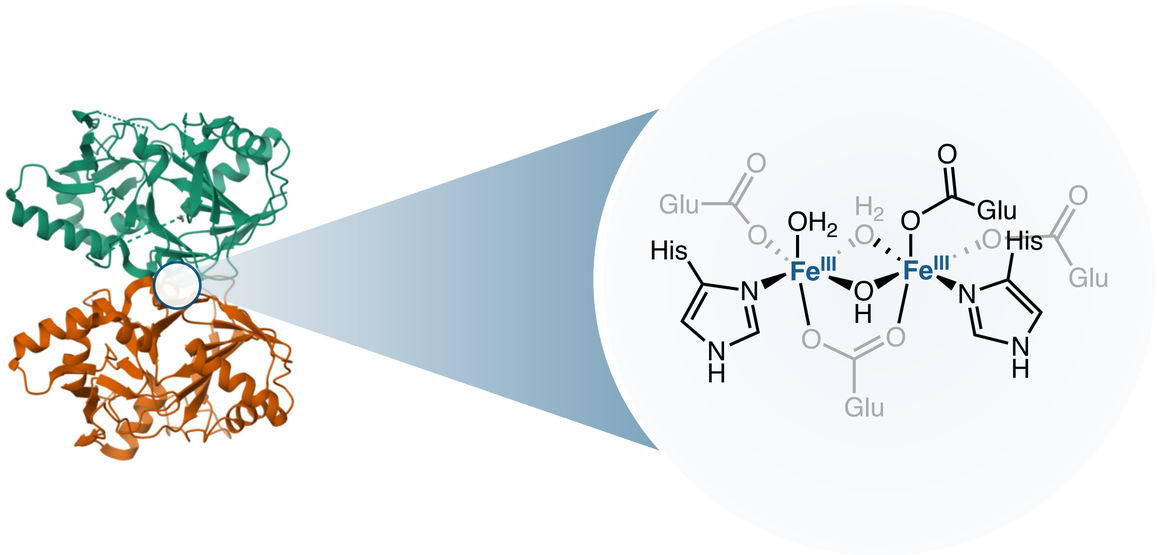
19% yield

Allows for effective nitration under native conditions

Bollinger *et. al. Nat. Chem. Bio.* **2014,** *10*, 209.

Nonheme-diiron hydroxylases

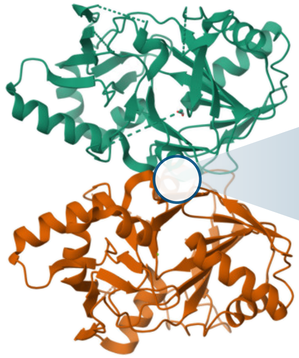
nonheme-diiron hydroxylase

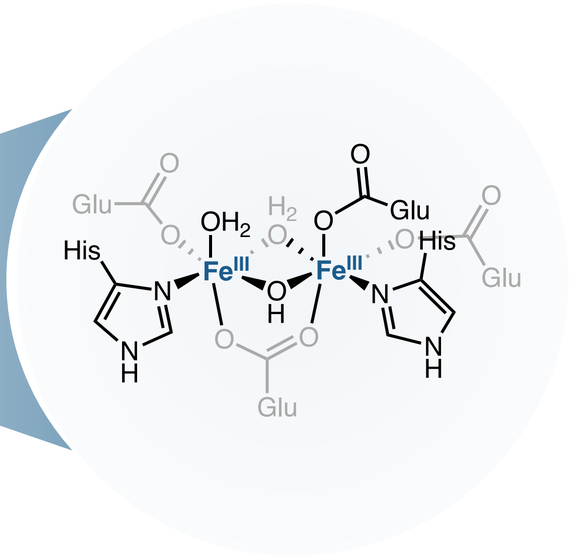


Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Nonheme-diiron hydroxylases

nonheme-diiron hydroxylase



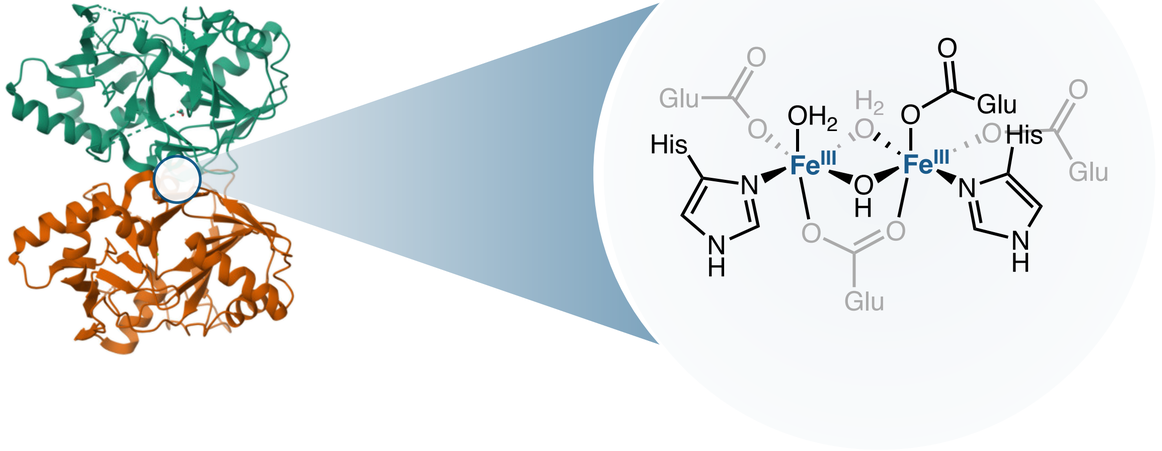


soluble methane monooxygenase (sMMO)

Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Nonheme-diiron hydroxylases

nonheme-diiron hydroxylase



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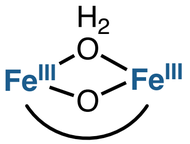
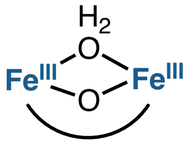


dinuclear Fe-Fe complex

soluble methane monooxygenase (sMMO)

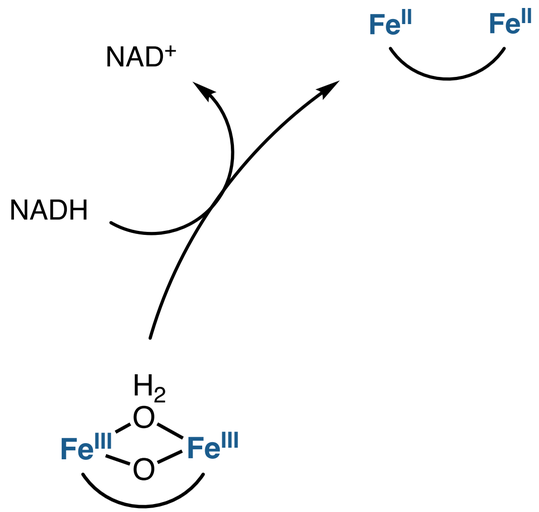
Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Nonheme-diiron hydroxylases



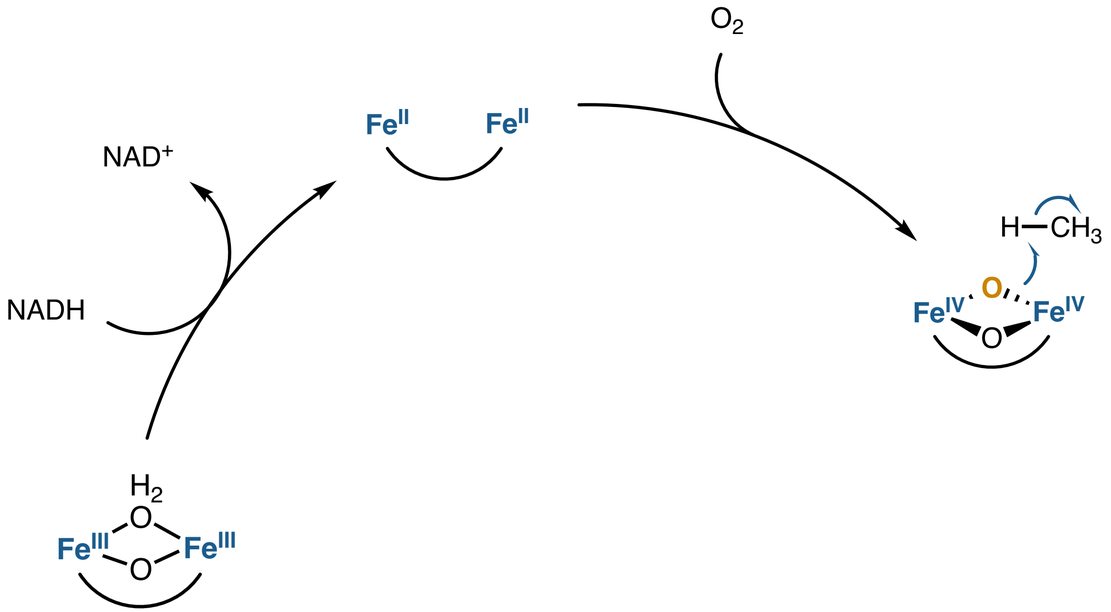
Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Nonheme-diiron hydroxylases



Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Nonheme-diiron hydroxylases



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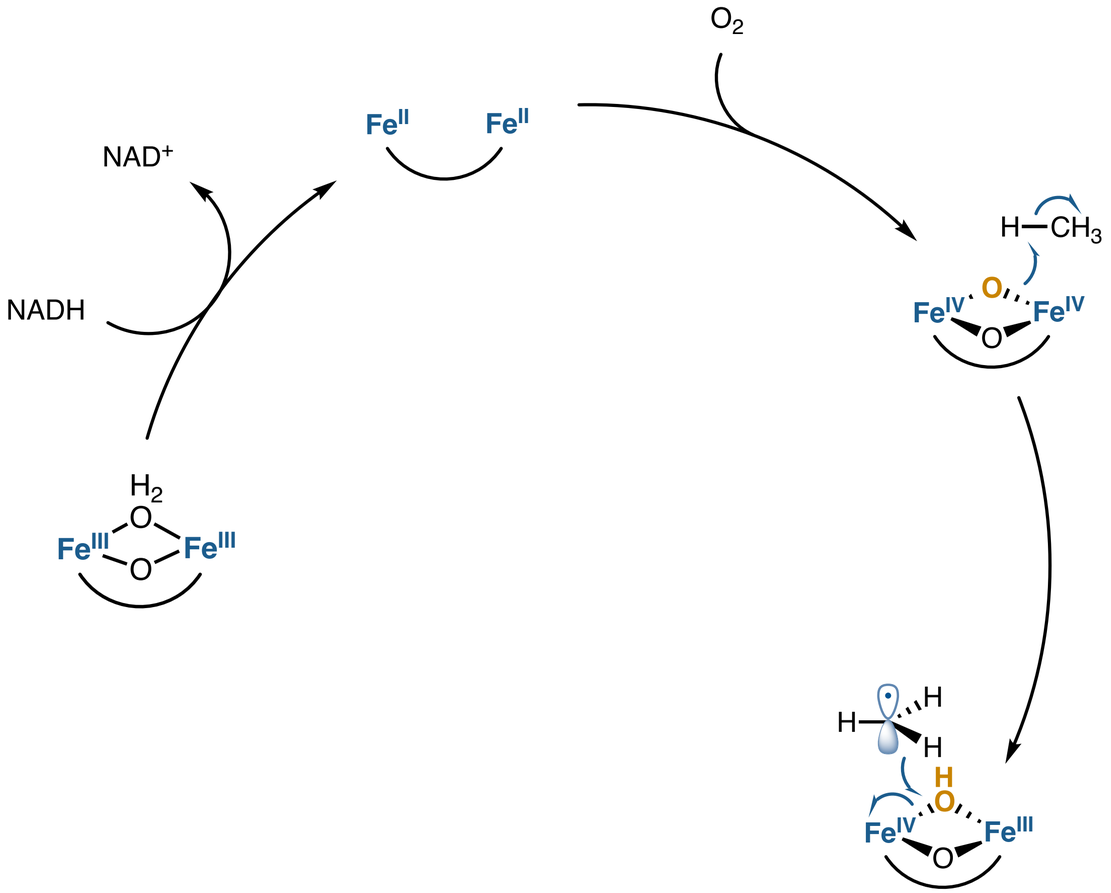
Nonheme-diiron hydroxylases



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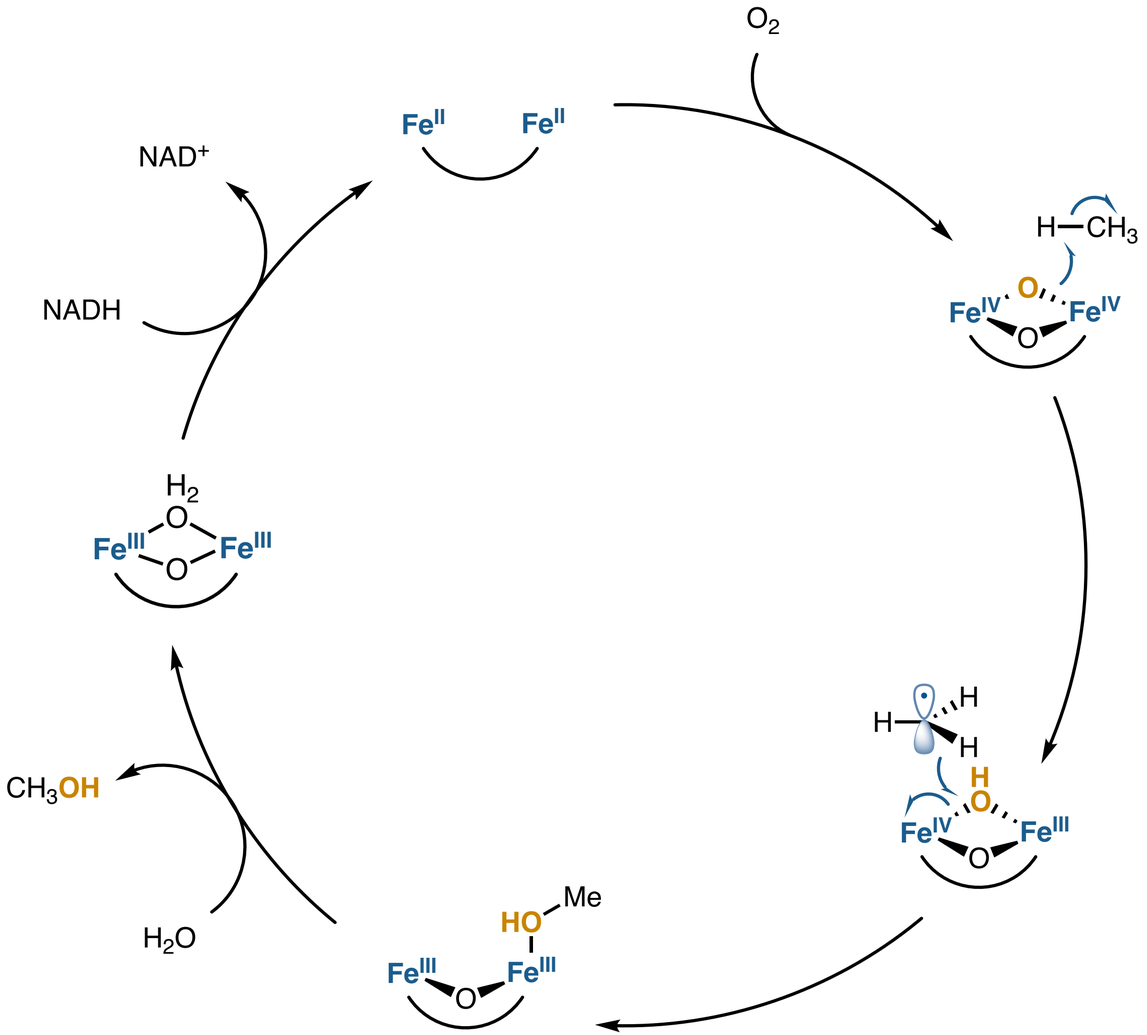
Nonheme-diiron hydroxylases



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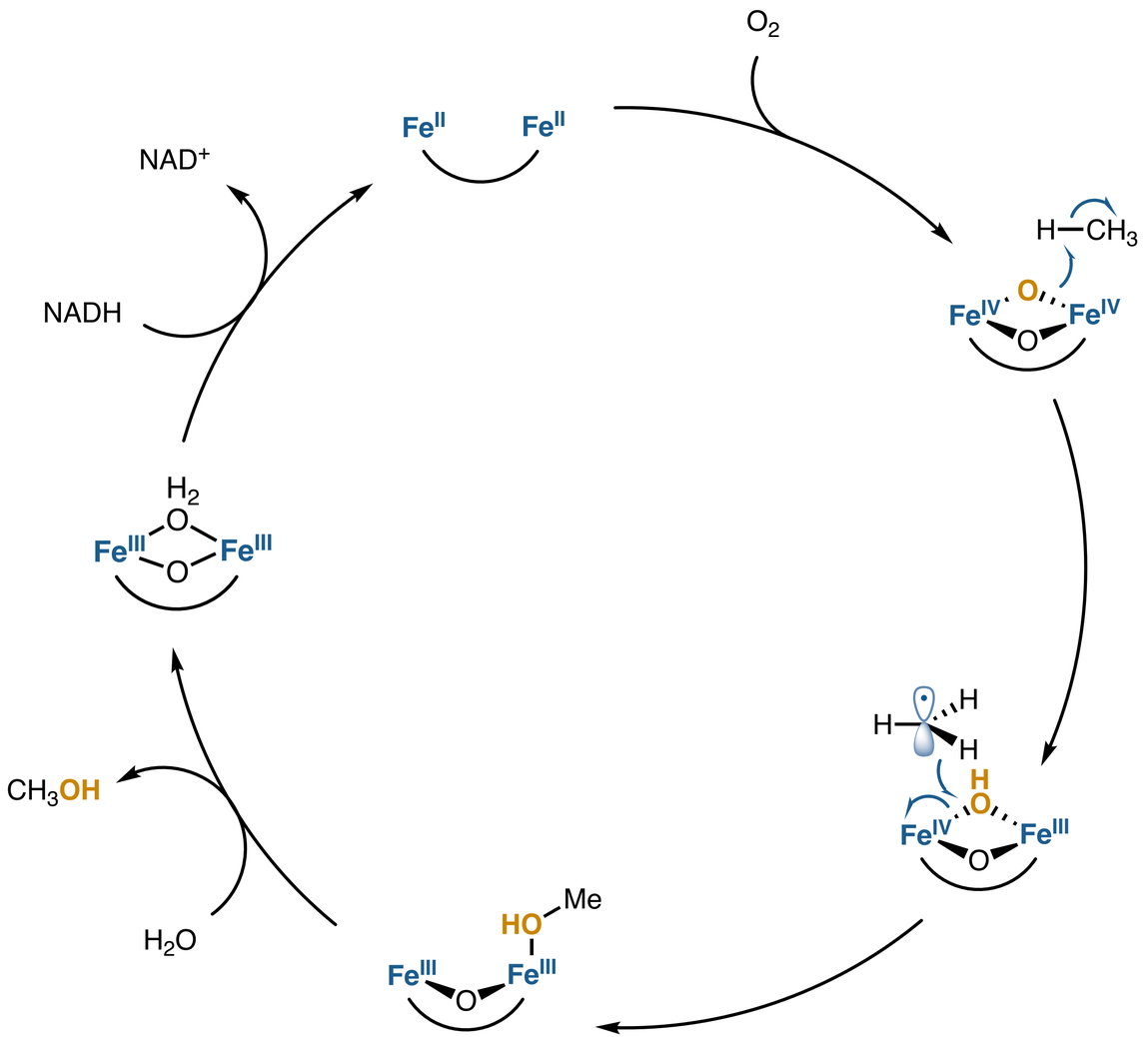
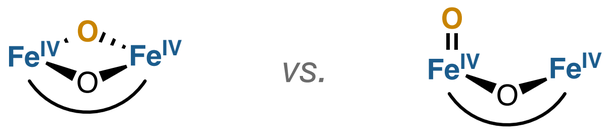
Nonheme-diiron hydroxylases

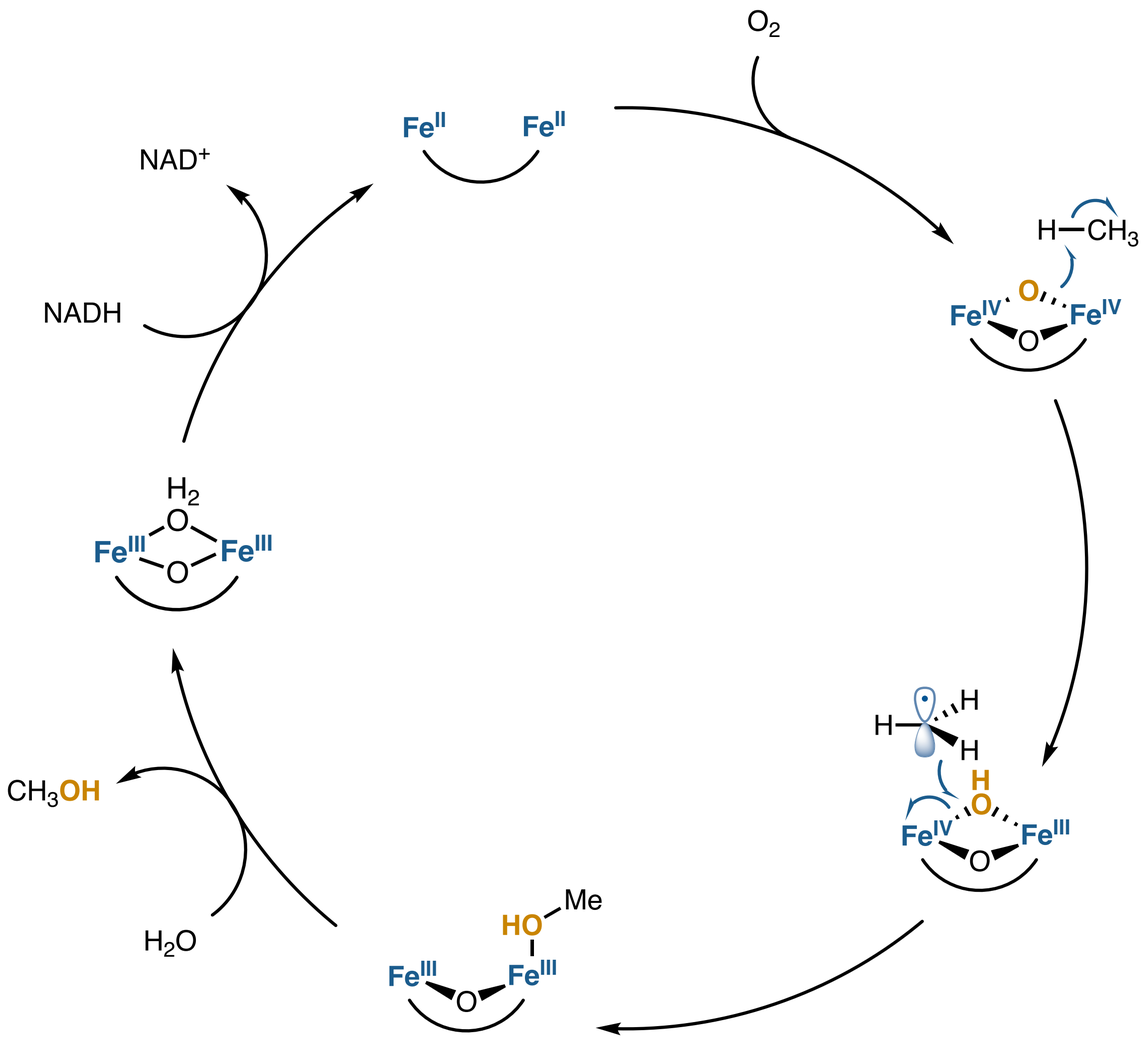


compound Q

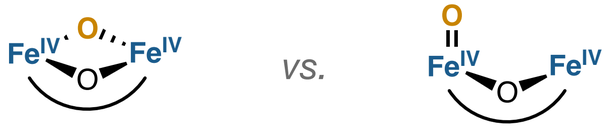


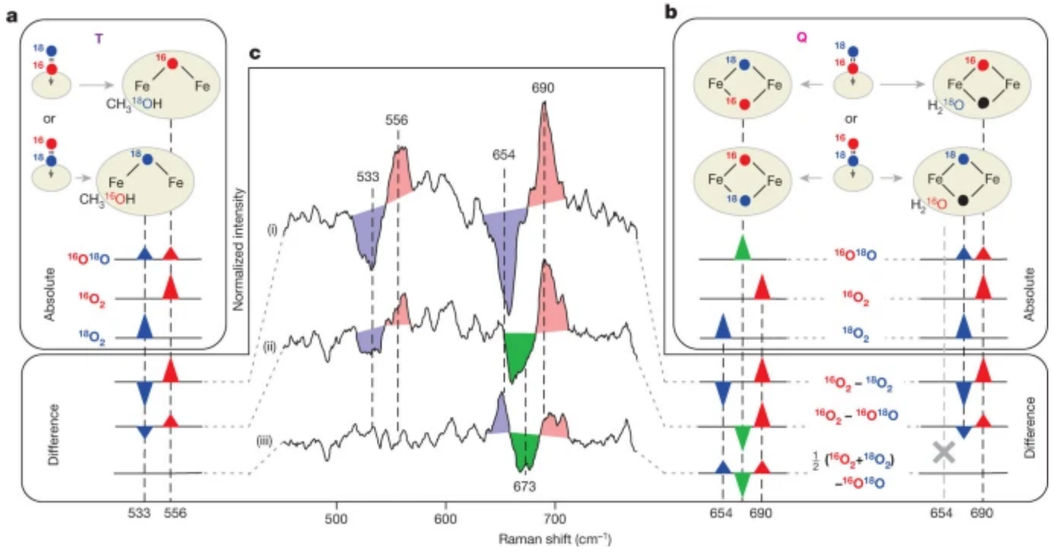
Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Nonheme-diiron hydroxylases



compound Q





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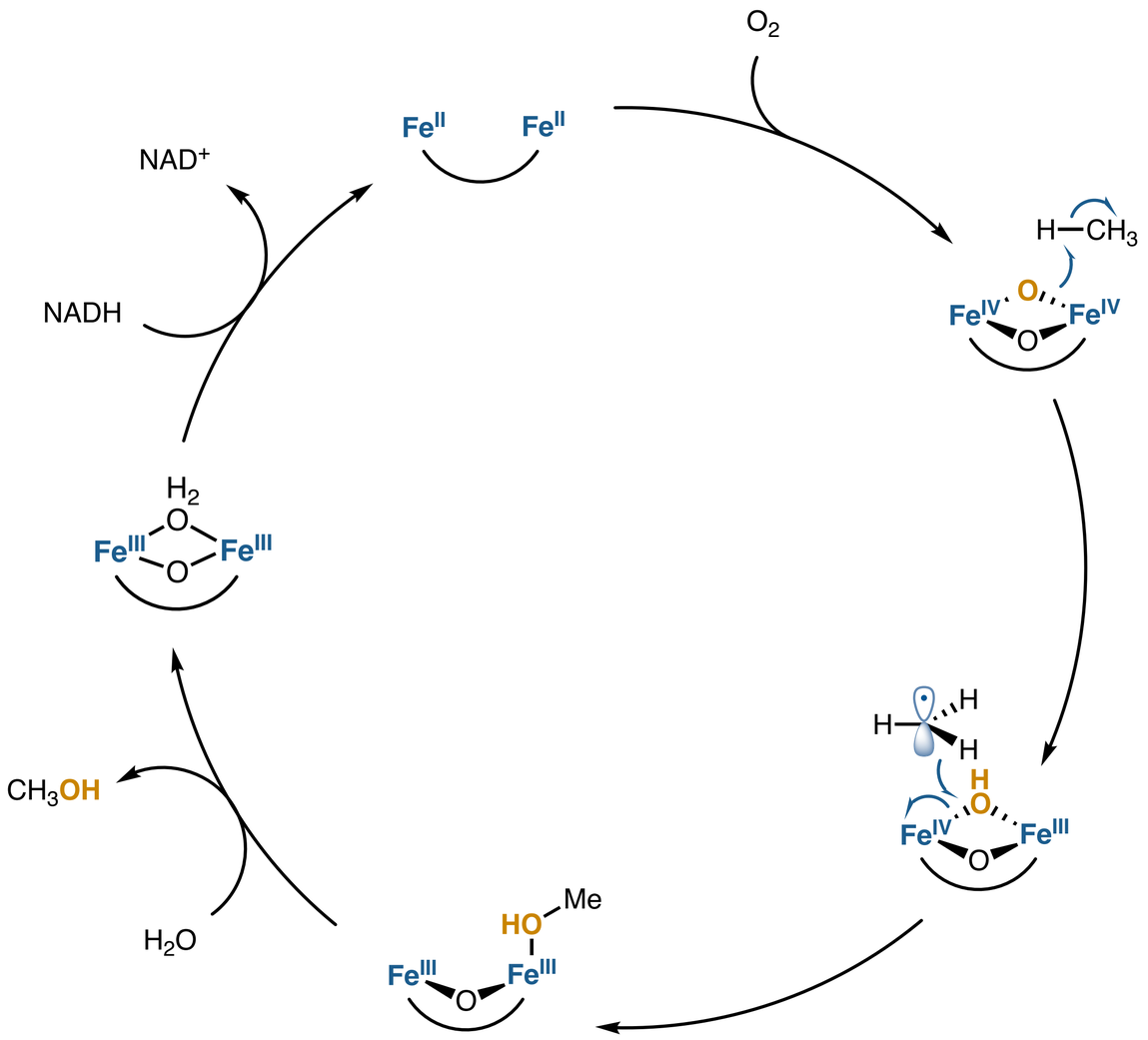
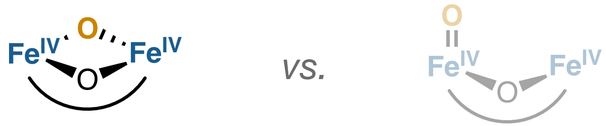
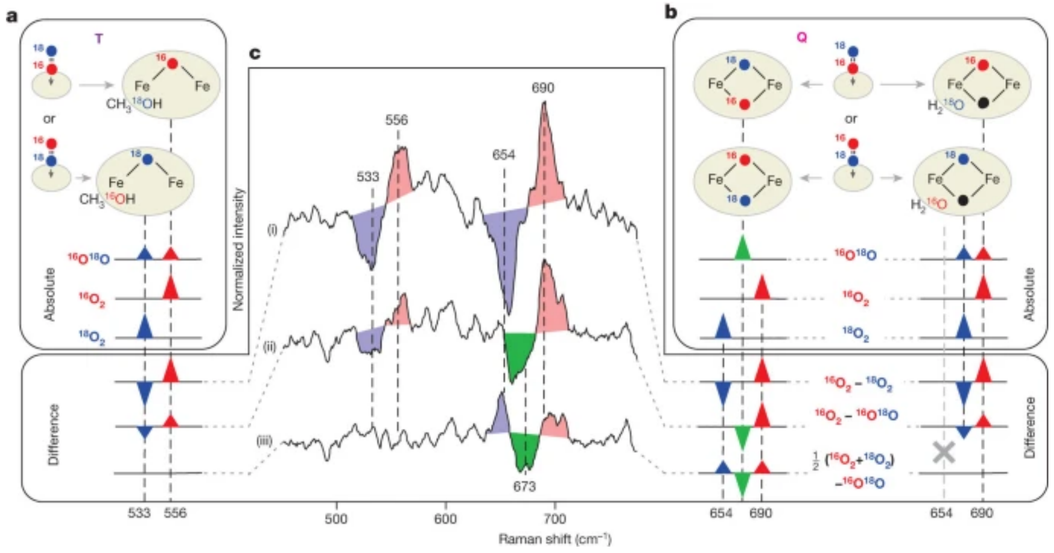
Nonheme-diiron hydroxylases



compound Q

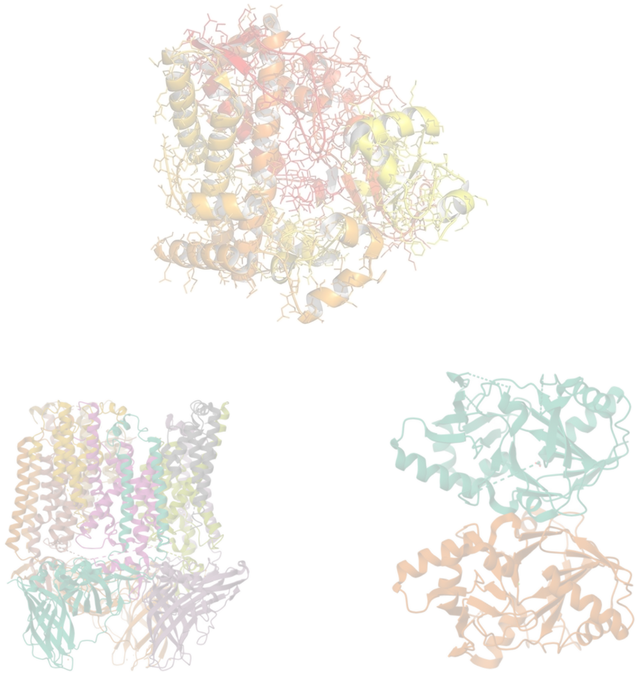




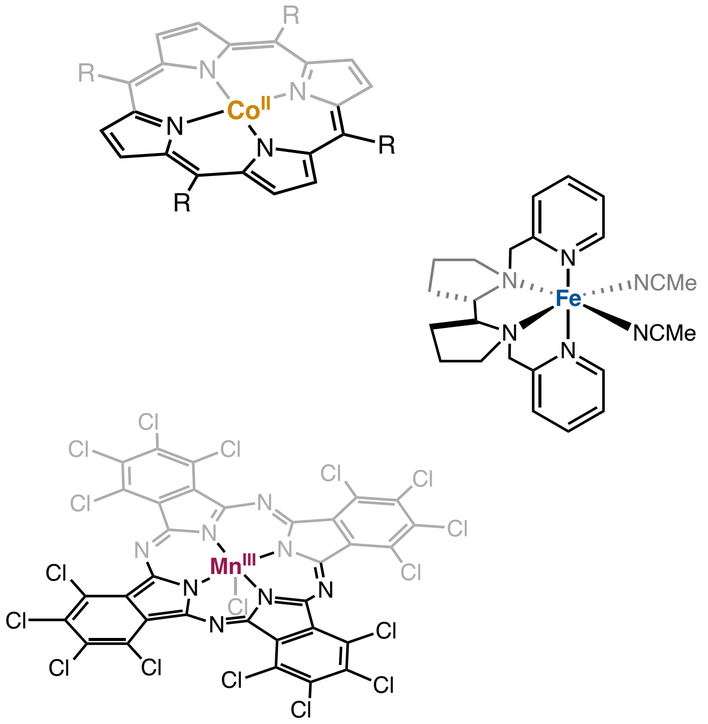
Banerjee, R.; Proshlyakov, Y.; Lipscomb, J. D.; Proschlyakov, D. A. *Nature* **2015,** *518*, 431.

Radical rebound

enzymatic rebound

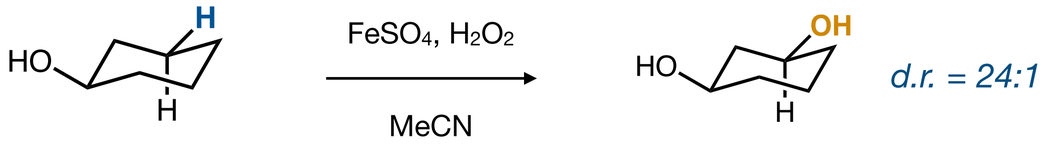


synthetic rebound



First steps in mimicking enzymatic rebound

Groves (1976)



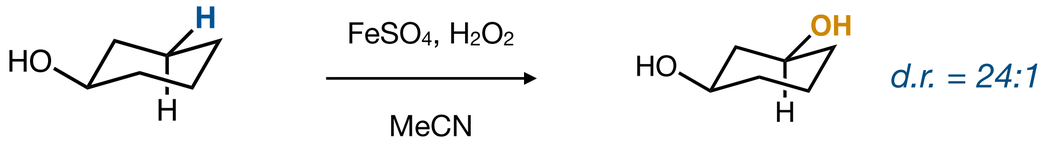
d.r. = 24:1

modification of Fenton's reaction

Groves *J. Am. Chem. Soc.* **1976**, *98*, 5290–5297; Groves *J. Am. Chem. Soc.* **1983**, *105*, 6243–6248; Mansuy *J. Chem. Soc., Chem. Commun.* **1986**, 341.

First steps in mimicking enzymatic rebound

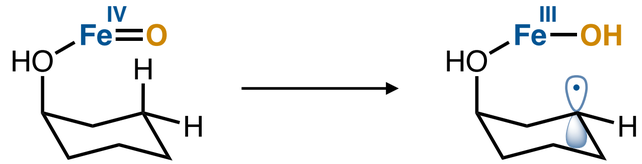
Groves (1976)



d.r. = 24:1

modification of Fenton's reaction

active Fe=O species



Groves *J. Am. Chem. Soc.* **1976**, *98*, 5290–5297; Groves *J. Am. Chem. Soc.* **1983**, *105*, 6243–6248; Mansuy *J. Chem. Soc., Chem. Commun.* **1986**, 341.

First steps in mimicking enzymatic rebound

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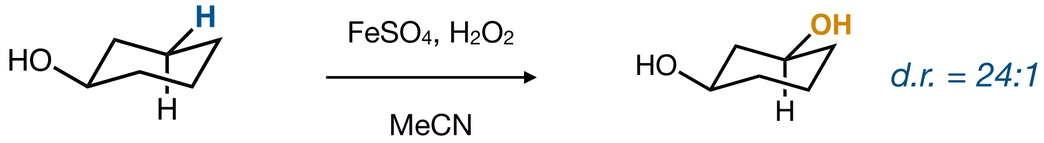

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modification of Fenton's reaction

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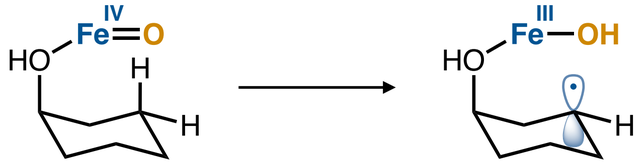
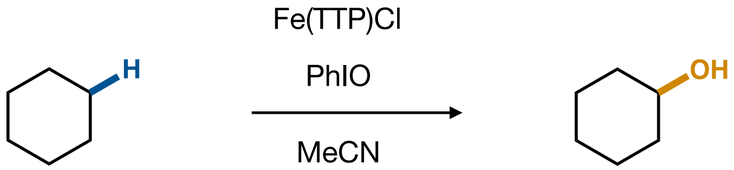
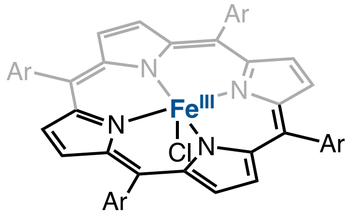


Groves (1983)



24% yield



Fe(TTP)Cl (Ar = *p*-Tol)

Groves *J. Am. Chem. Soc.* **1976**, *98*, 5290–5297; Groves *J. Am. Chem. Soc.* **1983**, *105*, 6243–6248; Mansuy *J. Chem. Soc., Chem. Commun.* **1986**, 341.

First steps in mimicking enzymatic rebound

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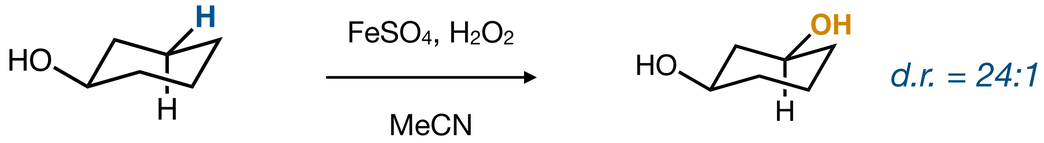

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modification of Fenton's reaction

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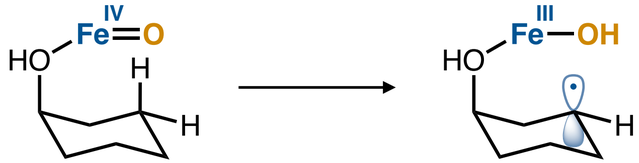
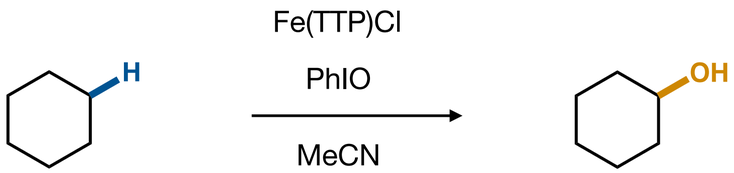
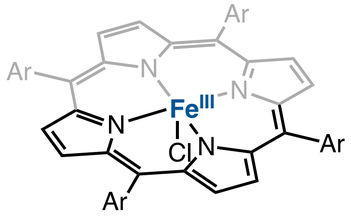


Groves (1983)

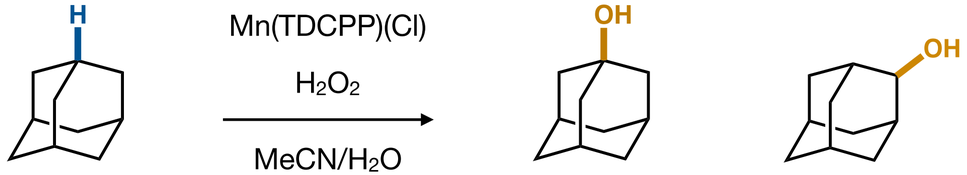


24% yield

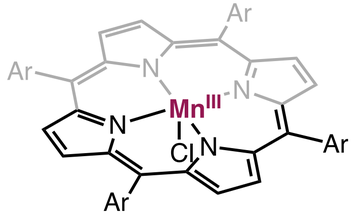


Fe(TTP)Cl (Ar = *p*-Tol)

Mansuy (1986)



63% yield *19% yield*



Mn(TDCPP)(Cl) (Ar =2,6-Cl-Ph)

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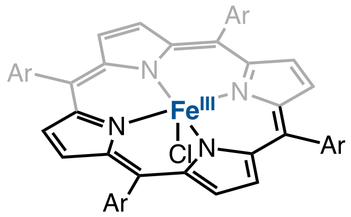
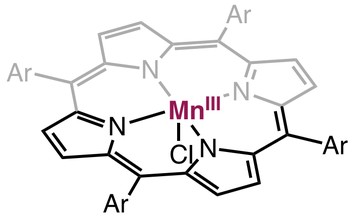
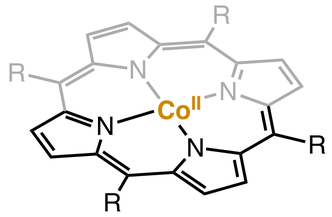
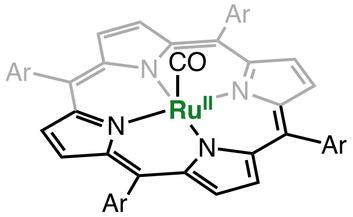
Metalloporphyrins for synthetic rebound

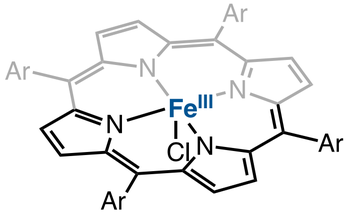


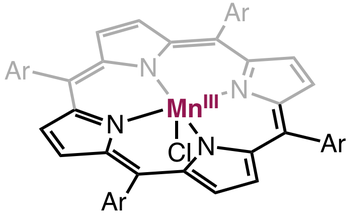


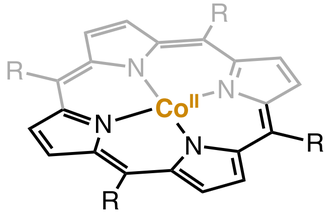


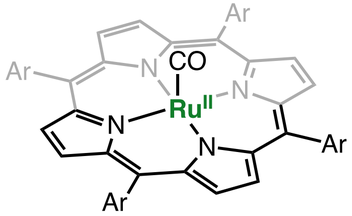


Metalloporphyrins for synthetic rebound









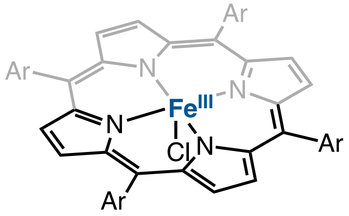
rigid coordination environment

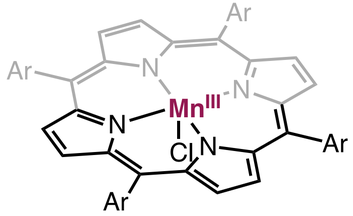
flexible redox system

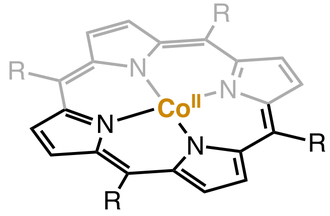
stabilizing high-valent metal-oxo species

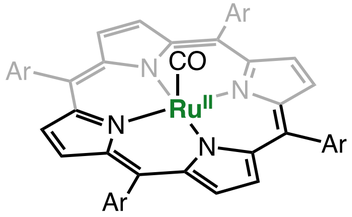
balance between strong metal–oxo bonds to generate radicals and tunable M–OH BDE

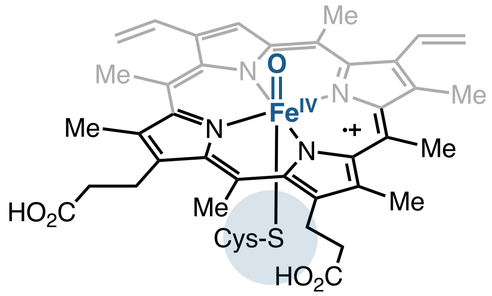
Influence of axial ligand on reactivity







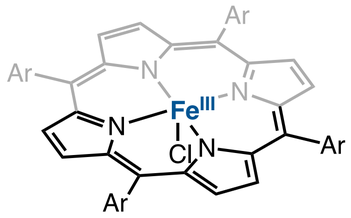


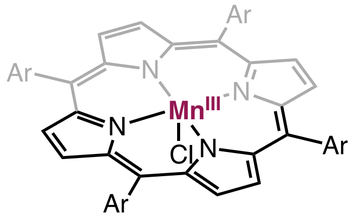


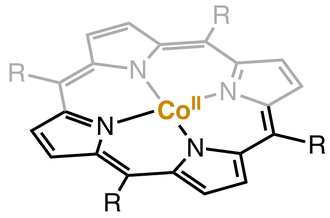
axial ligand crucial for rebound

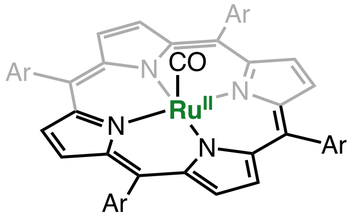
Kang, Y.; Chen H.; Jeong, Y. J.; Lai, W.; Bae, E. H.; Shaik, S.; Nam, W. *Chem. Eur. J.* **2009,** *15*, 10039.

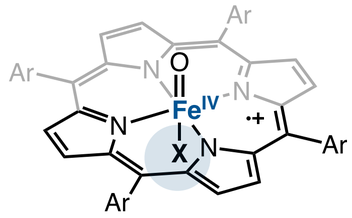
Influence of axial ligand on reactivity











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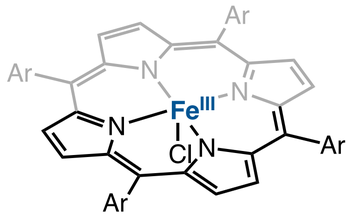

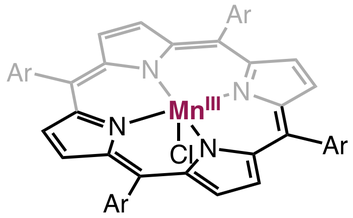

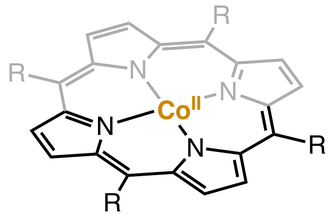

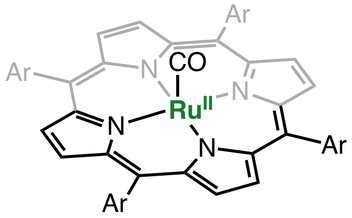

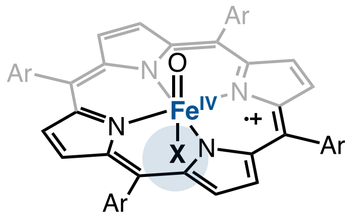

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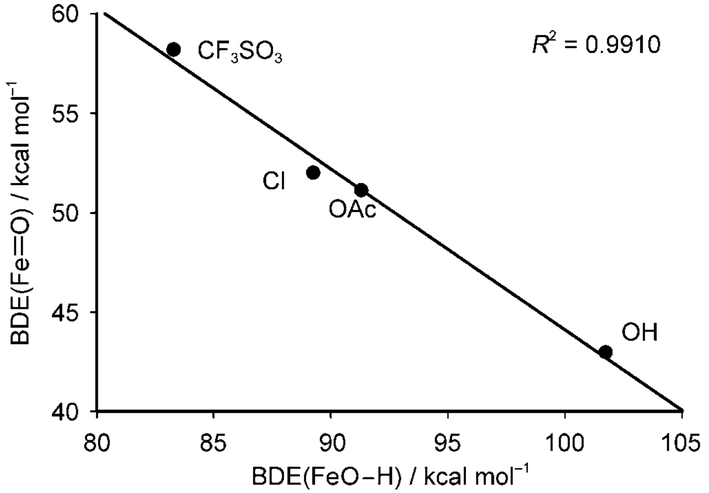

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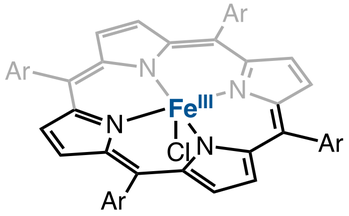
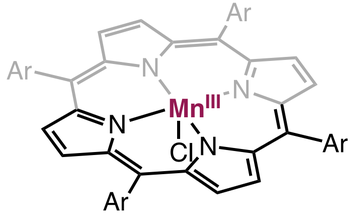
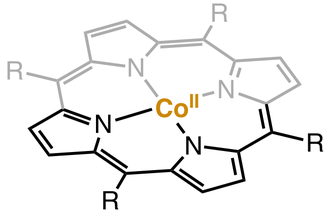
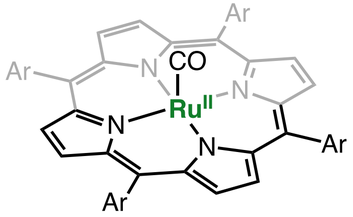
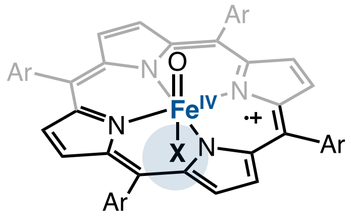










axial ligand crucial for rebound

axial ligand X

electron donation

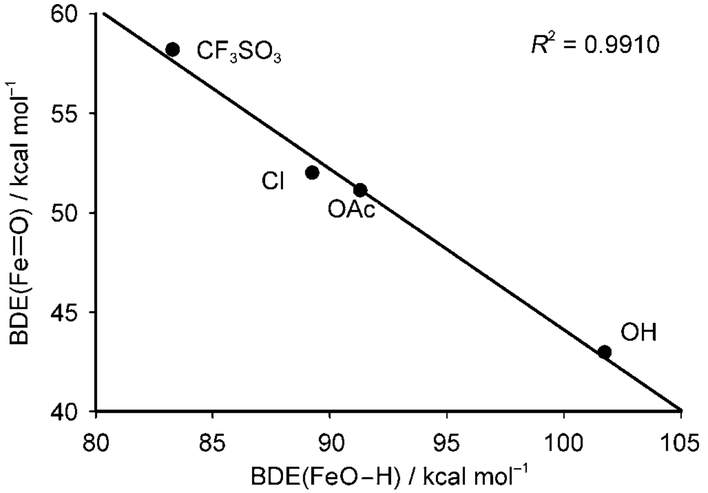
CF_3SO_3

Cl

OAc

OH

increasing rate of oxo-transfer



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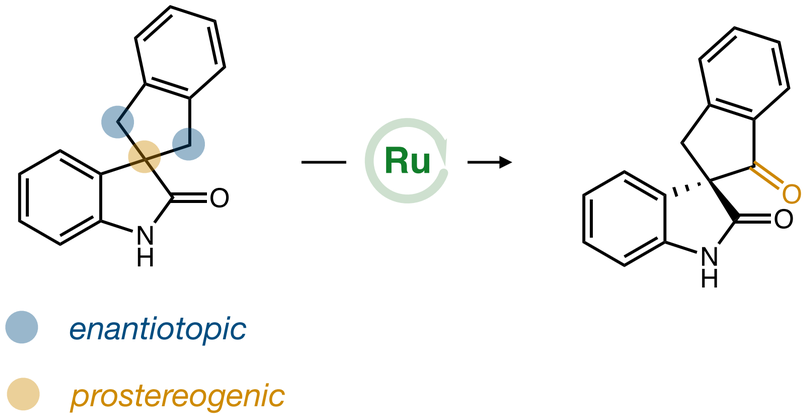
Use of chiral porphyrins for C–H oxidation

Bach (2014)



Frost, J. R.; Huber, S.; Breitenlechner, S.; Bannwarth, C.; Bach, T. *ACIE* **2015,** *54*, 691.

DCPNO: 2,6-Cl-pyridine-*N*-oxide

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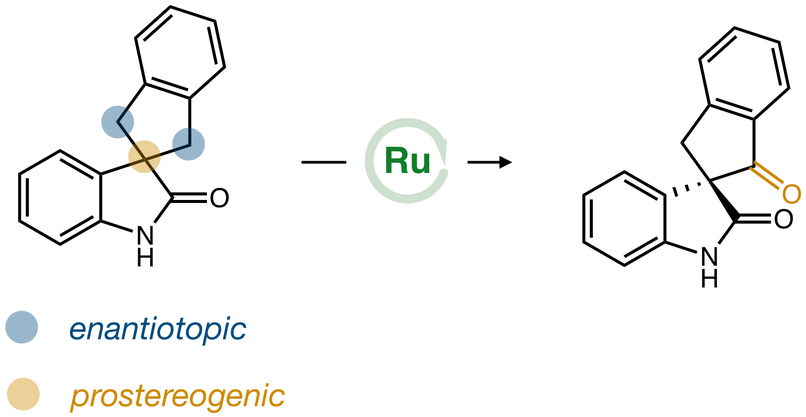
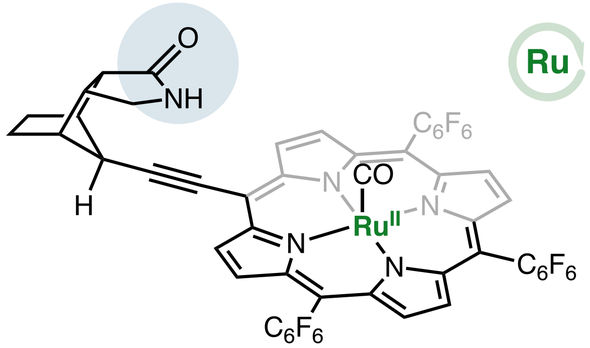


lactam binding unit



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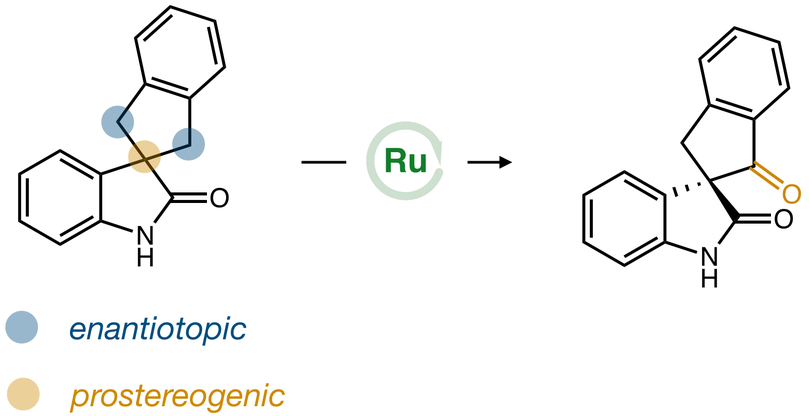

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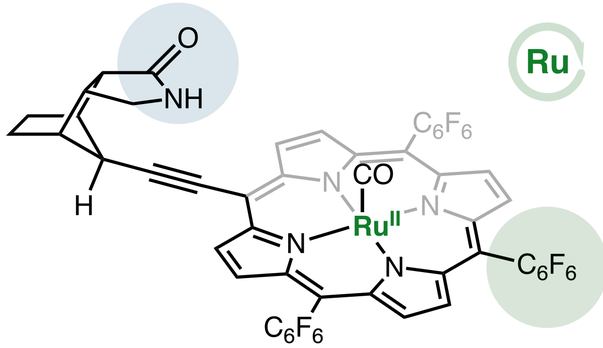

increased
electrophilicity at Ru

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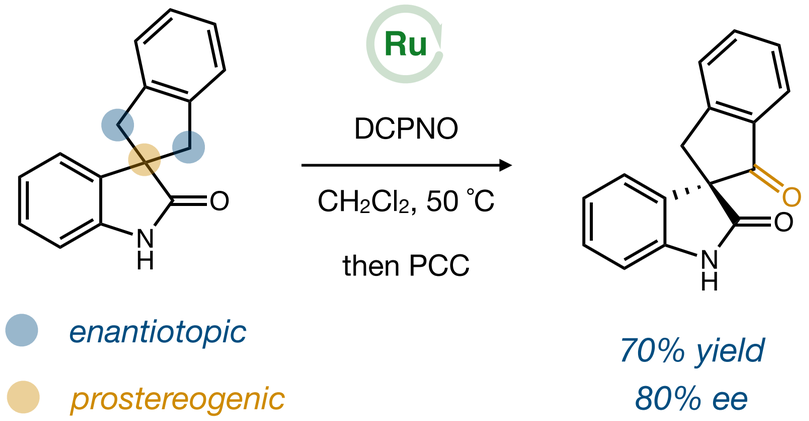


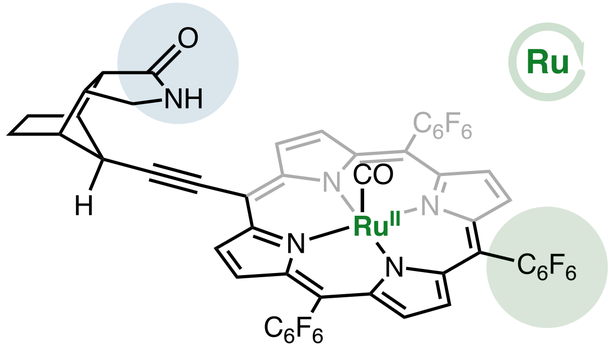
enantiotopic

prostereogenic

70% yield

80% ee

lactam binding unit



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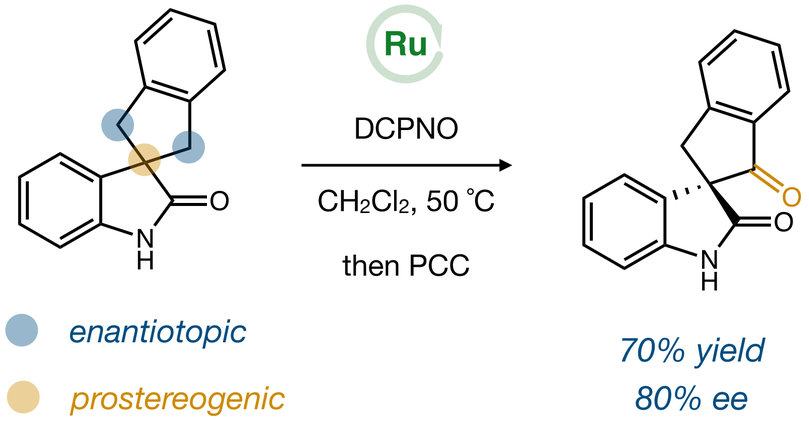

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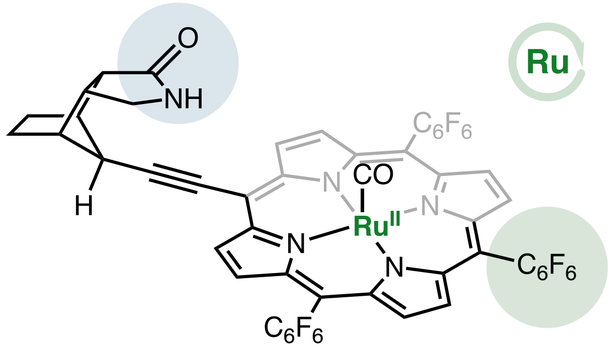
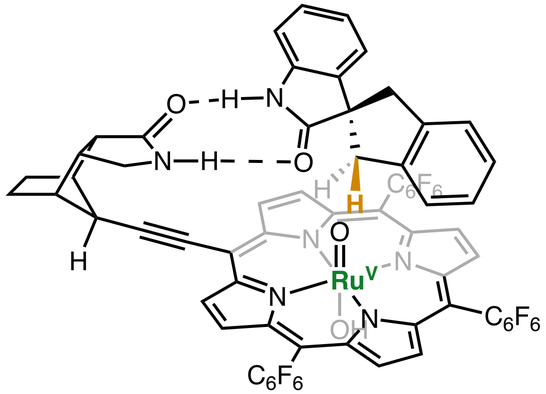


increased
electrophilicity at Ru

proposed intermediates

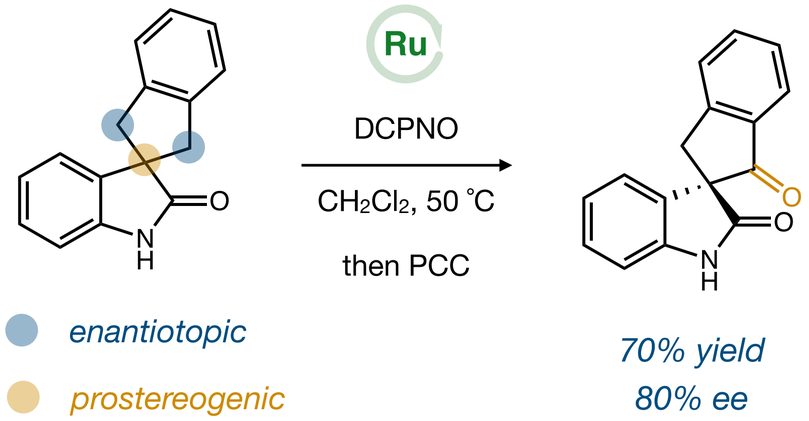


Frost, J. R.; Huber, S.; Breitenlechner, S.; Bannwarth, C.; Bach, T. *ACIE* **2015,** *54*, 691.

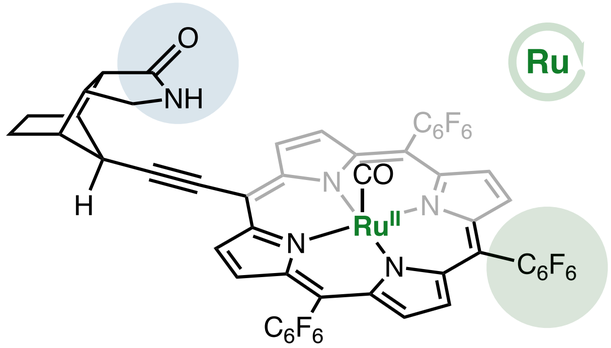
DCPNO: 2,6-Cl-pyridine-*N*-oxide

Use of chiral porphyrins for C–H oxidation

Bach (2014)

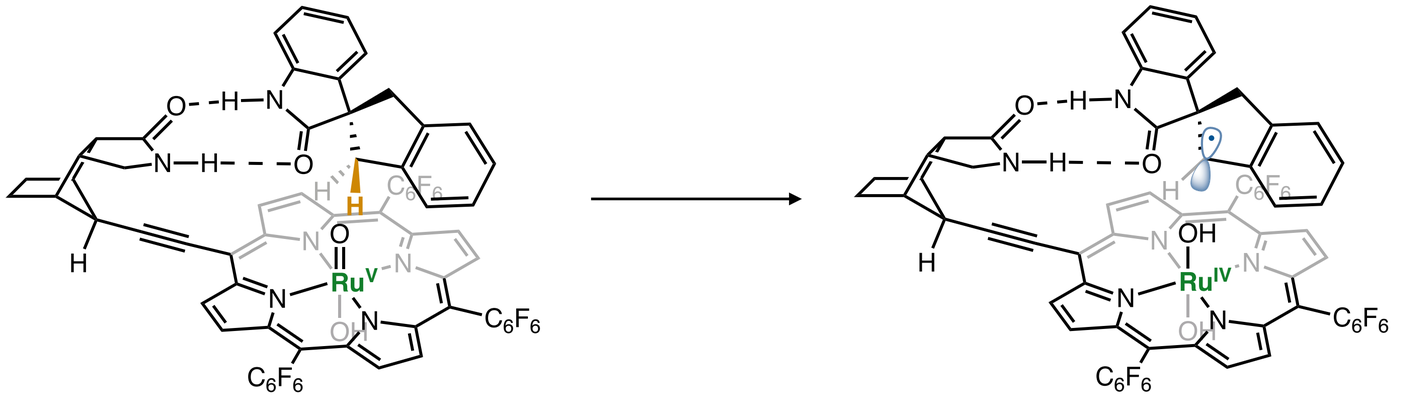


lactam binding unit



increased
electrophilicity at Ru

proposed intermediates



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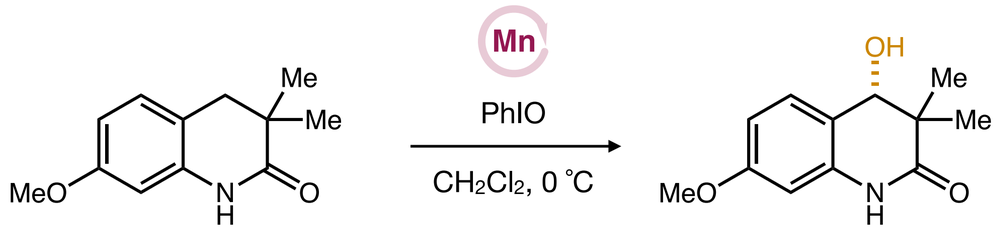
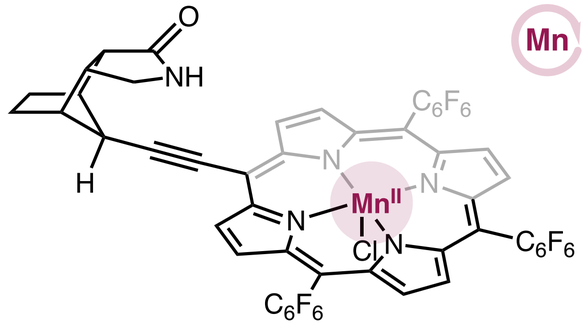


68% yield
99% ee

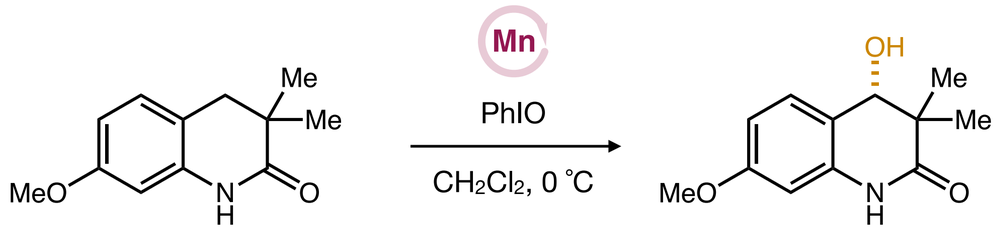


lower reactivity of Mn prevents over-oxidation + improves selectivity

Burg, F.; Gicquel, M.; Breitenlechner, S.; Pöthig, A.; Bach, T. *ACIE* **2018,** *57*, 2953.

Use of chiral porphyrins for C–H oxidation

Bach (2018)



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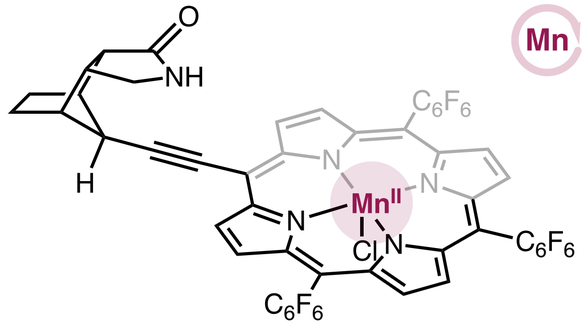
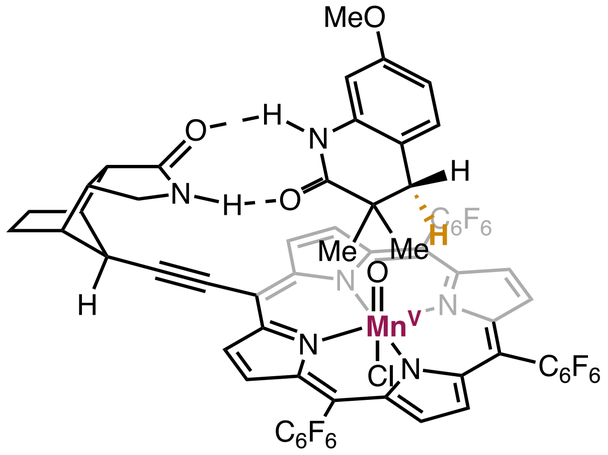


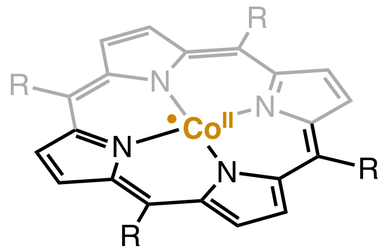
lower reactivity of Mn prevents over-oxidation + improves selectivity

proposed intermediates



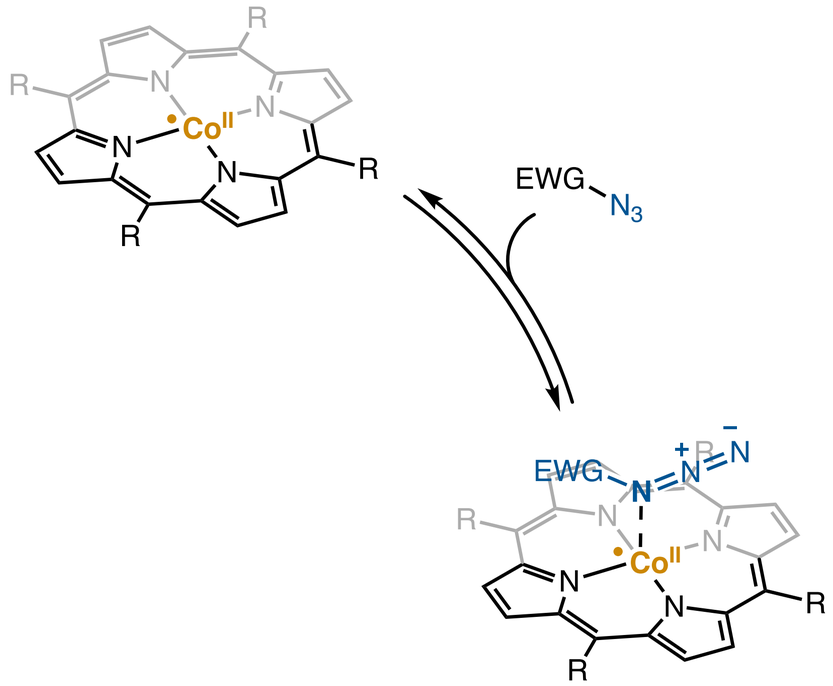
Burg, F.; Gicquel, M.; Breitenlechner, S.; Pöthig, A.; Bach, T. *ACIE* **2018,** *57*, 2953.

C–H aminations by radical rebound with cobalt porphyrins



Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011,***133*, 12264.

C–H aminations by radical rebound with cobalt porphyrins



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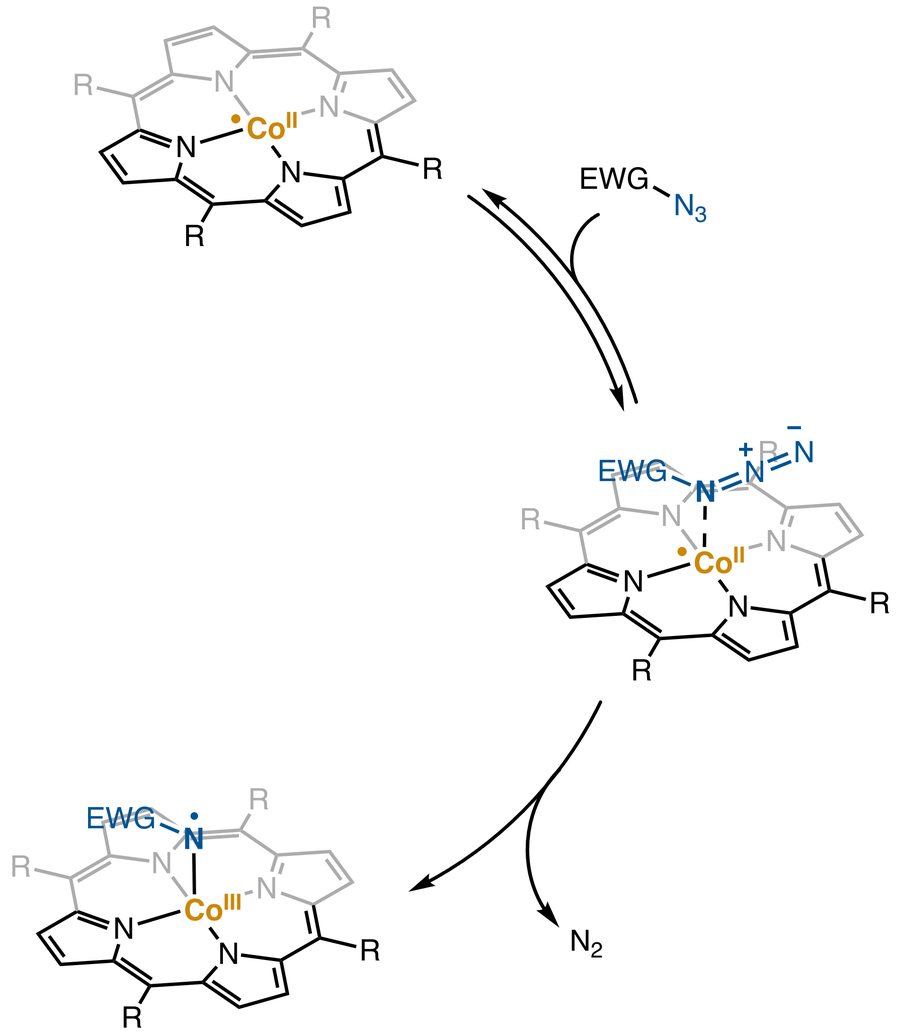
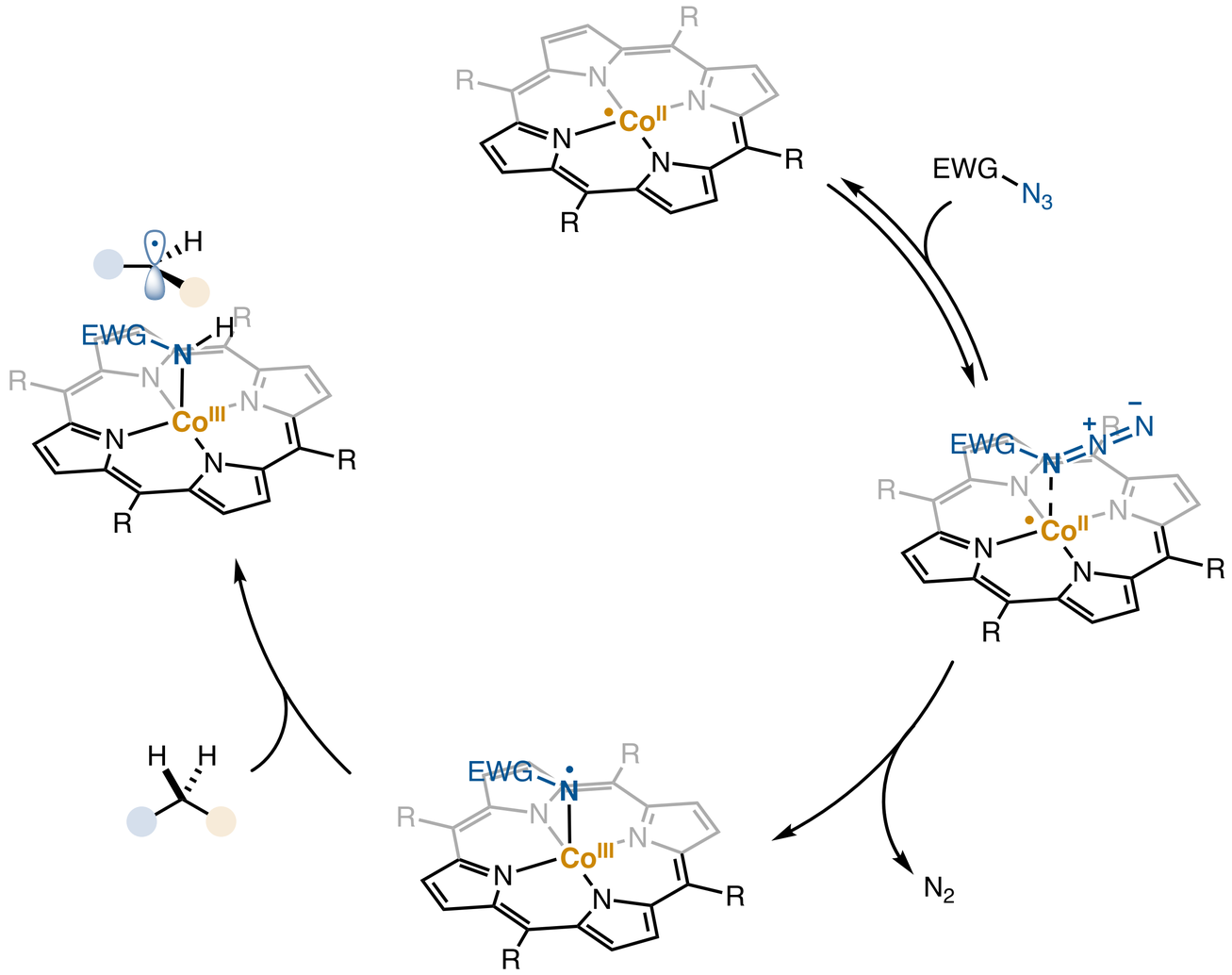


16 e⁻ d_6-complex with nitrene radical ligand (non-redox innocent)

Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011,***133*, 12264.

C–H aminations by radical rebound with cobalt porphyrins



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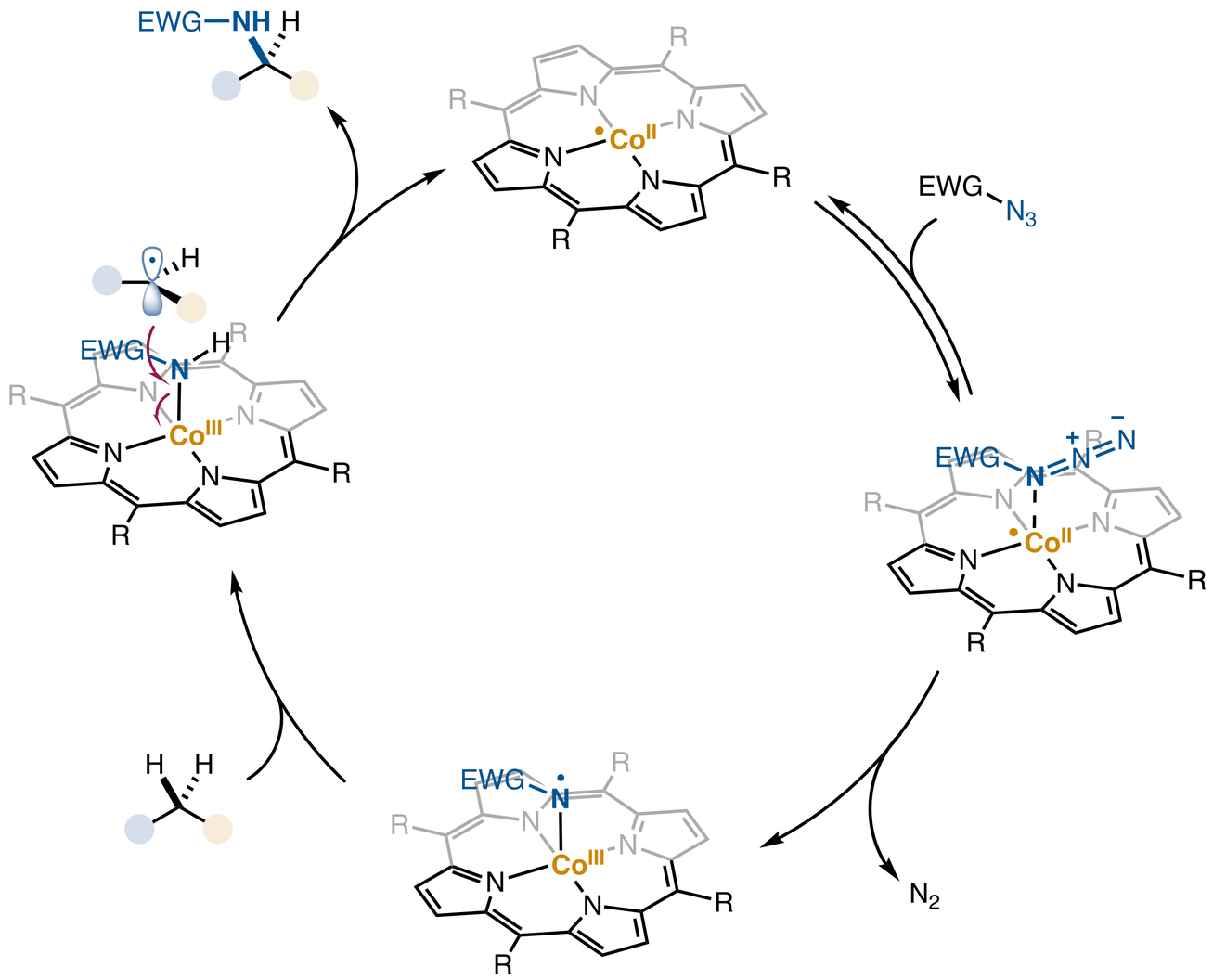

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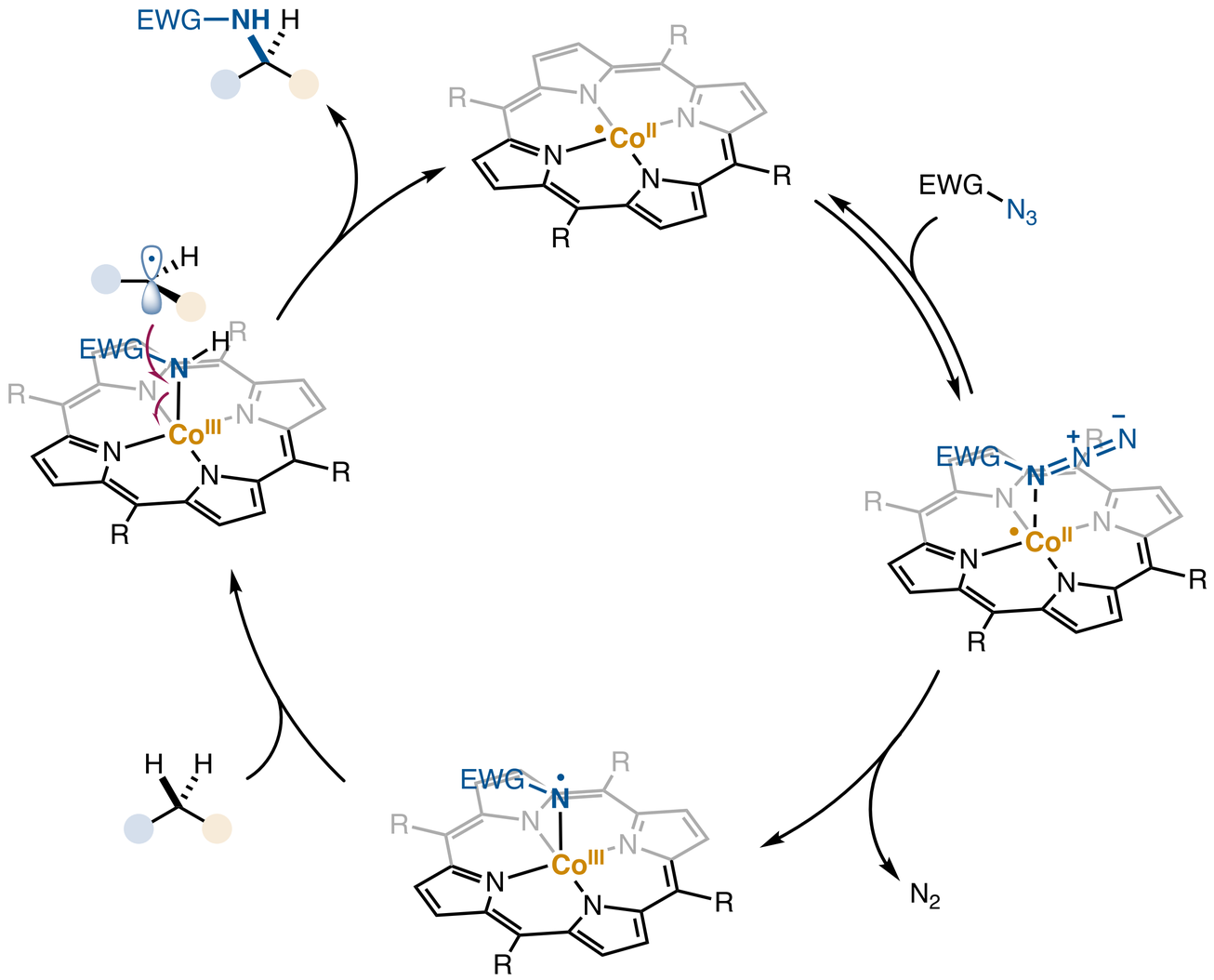

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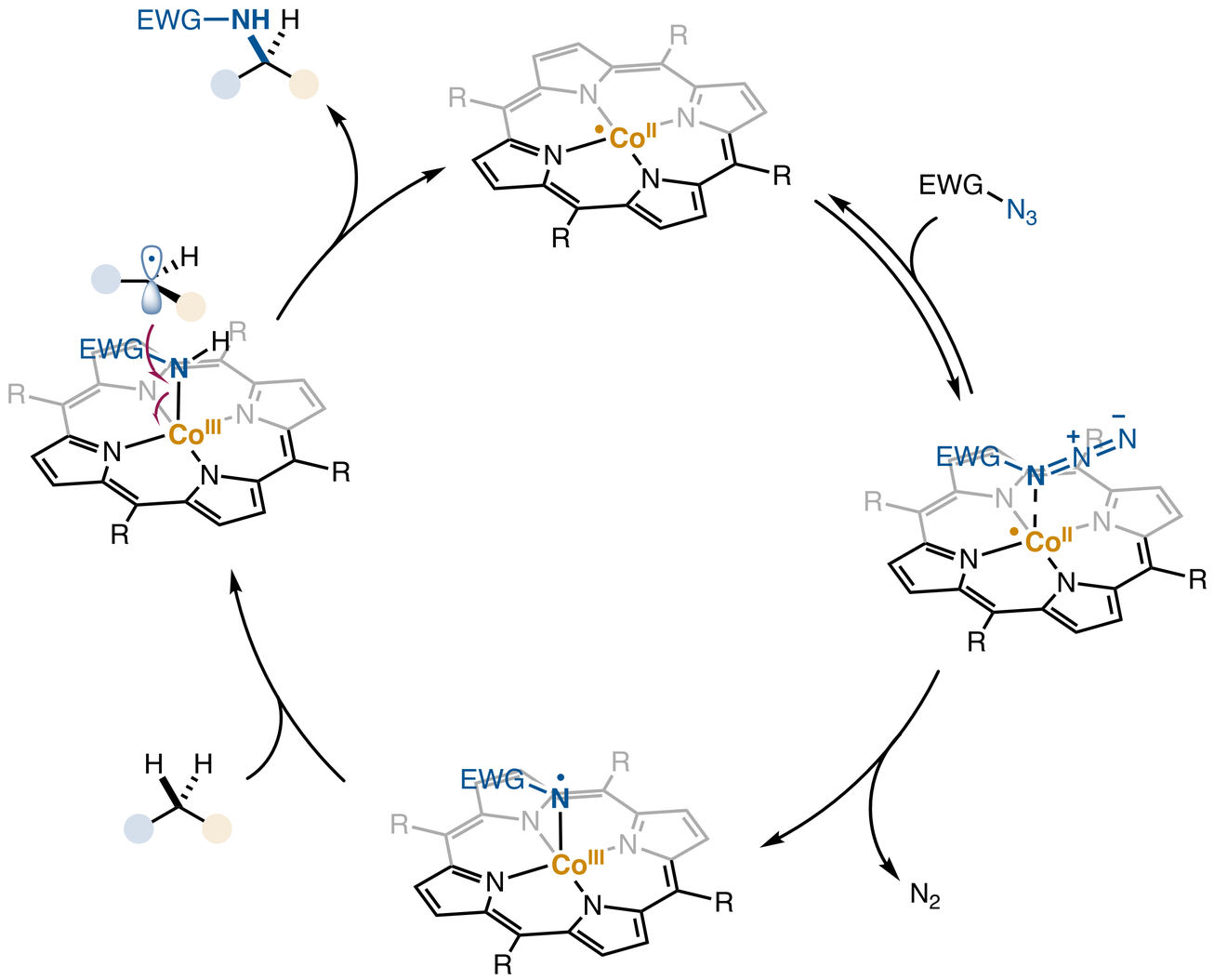
highly reactive nitrene intermediates involved

requires fast C–H abstraction

Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011,***133*, 12264.

C–H aminations by radical rebound with cobalt porphyrins



16 e⁻ d_6-complex with nitrene radical ligand (non-redox innocent)

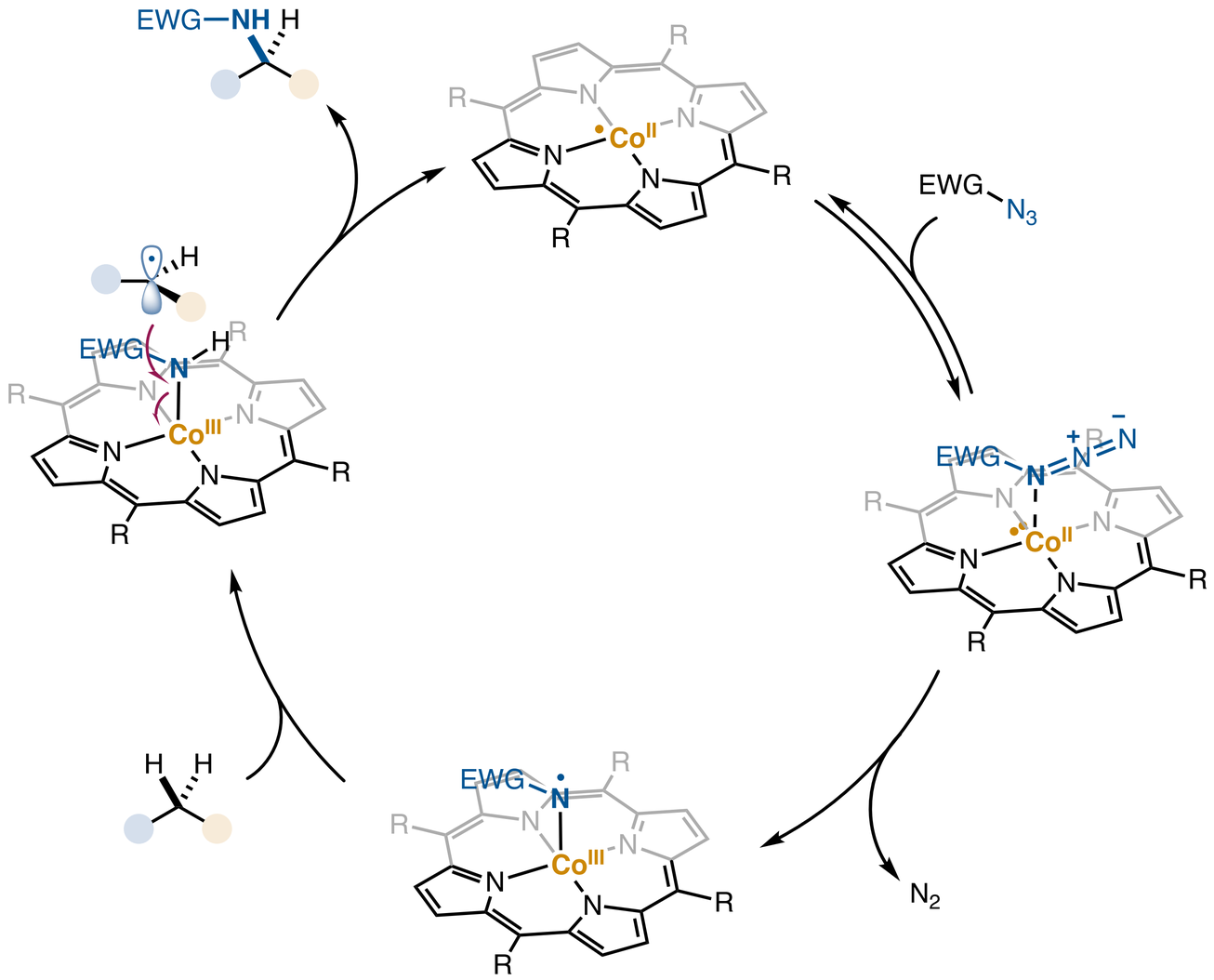
highly reactive nitrene intermediates involved

requires fast C–H abstraction

intramolecular C–H amination preferred / intermolecular challenging

Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011,***133*, 12264.

C–H aminations by radical rebound with cobalt porphyrins



nitrogen extrusion is RDS

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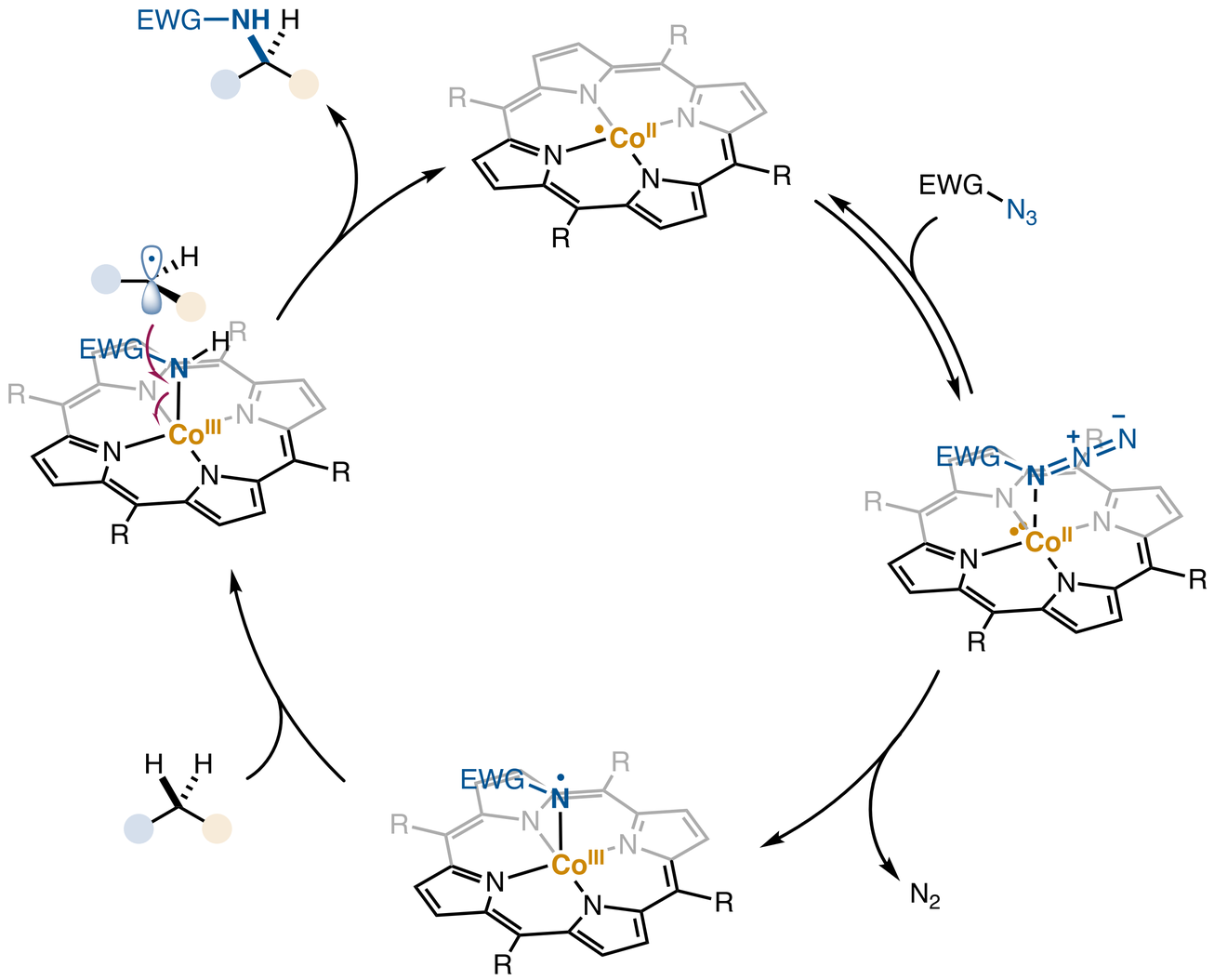
Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011,***133*, 12264.

C–H aminations by radical rebound with cobalt porphyrins



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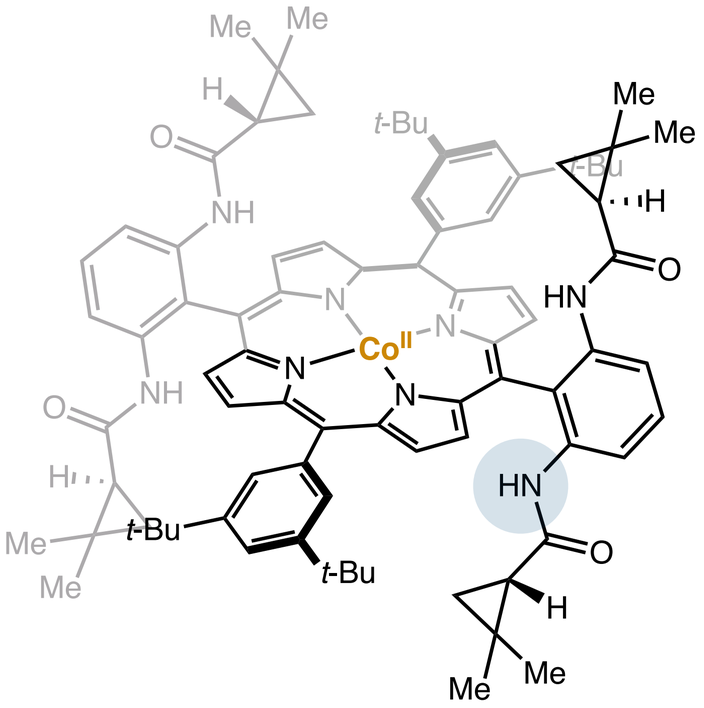


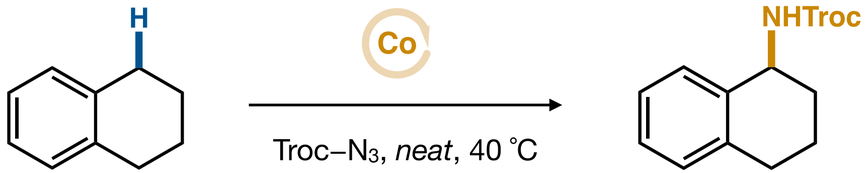
16 e⁻ d_6-complex with nitrene radical ligand (non-redox innocent)

H-bonds with EWG ➡ *improved N_2 evolution rate*

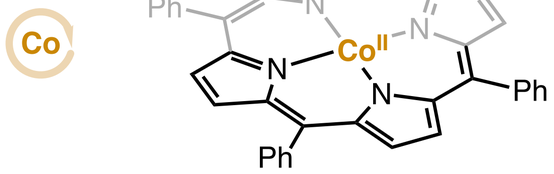
Lyaskovskyy, V.; Suarez, A. I. O.; Lu, H.; Jiang, H.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2011,***133*, 12264.

C–H aminations by radical rebound with cobalt porphyrins

Zhang (2009)



85% yield

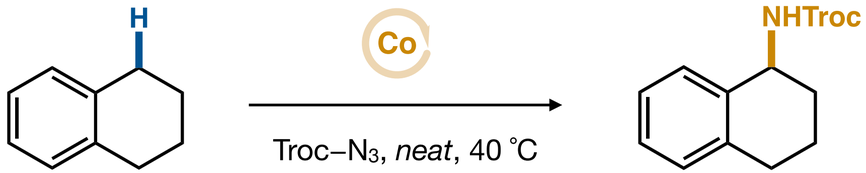


Co(TPP)

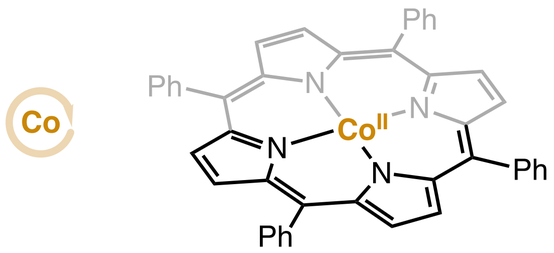
Zhang *Organometallics* **2010,** *29*, 389; de Bruin *Chem. J. Eur.* **2017**, *23*, 7945.

C–H aminations by radical rebound with cobalt porphyrins

Zhang (2009)

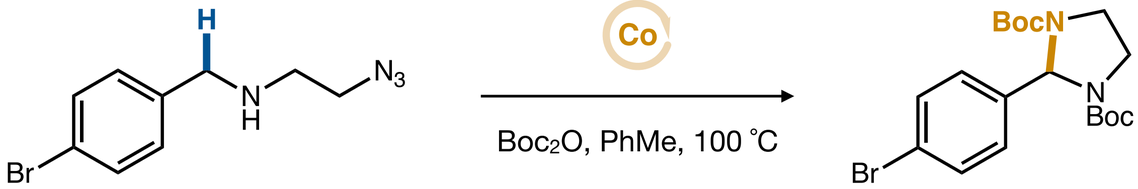


85% yield

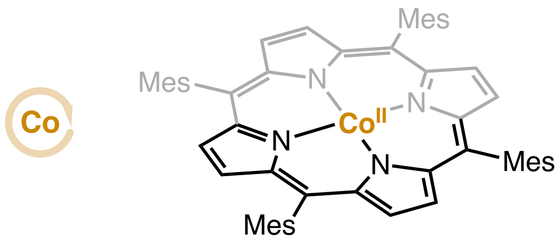


Co(TPP)

de Bruin (2017)



95% yield

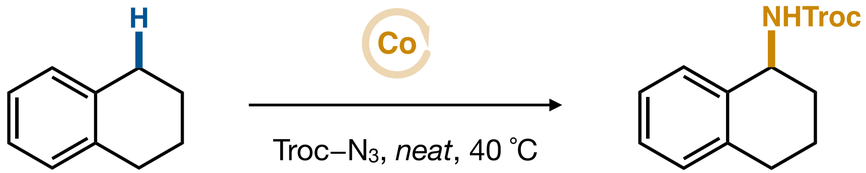


Co(TMP)

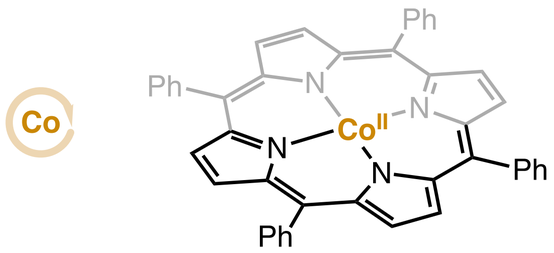
Zhang *Organometallics* **2010,** *29*, 389; de Bruin *Chem. J. Eur.* **2017**, *23*, 7945.

C–H aminations by radical rebound with cobalt porphyrins

Zhang (2009)

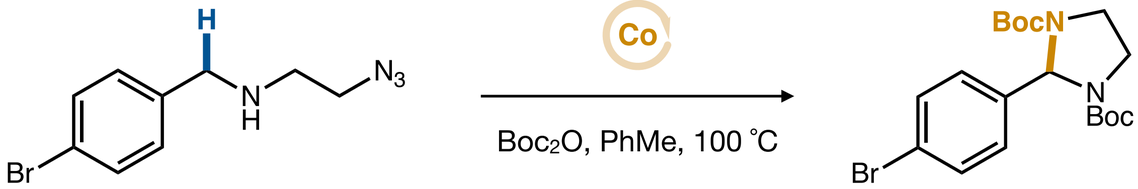


85% yield

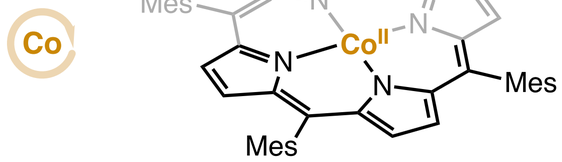


Co(TPP)

de Bruin (2017)



95% yield



Co(TMP)

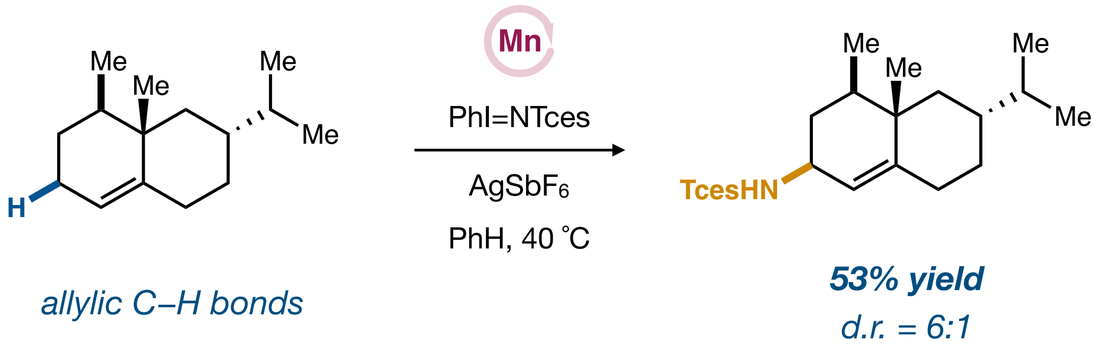
cobalt: C–H amination occurs via rebound

other metals: rebound vs. C–H insertion

Zhang *Organometallics* **2010,** *29*, 389; de Bruin *Chem. J. Eur.* **2017**, *23*, 7945.

Allylic C–H aminations by radical rebound

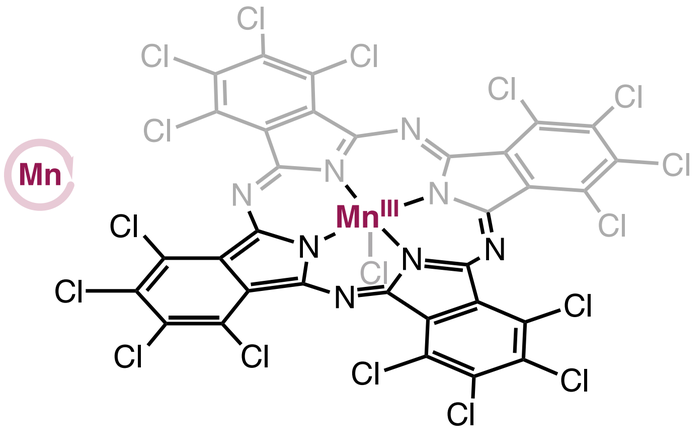
White (2018/2021)



allylic C–H bonds

53% yield

d.r. = 6:1



Mn(ClPc)Cl

White *Nat. Chem.* **2018**, *10,* 583; White *J. Am. Chem. Soc.* **2021**, *143*, 14969.

Allylic C–H aminations by radical rebound

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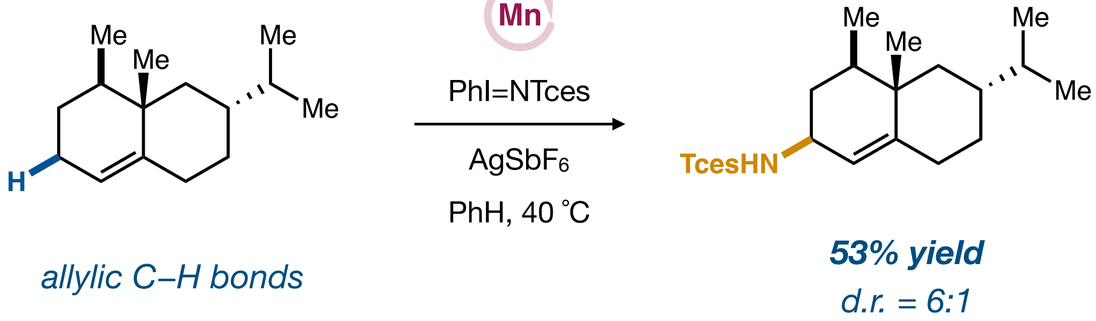

allylic C–H bonds

53% yield

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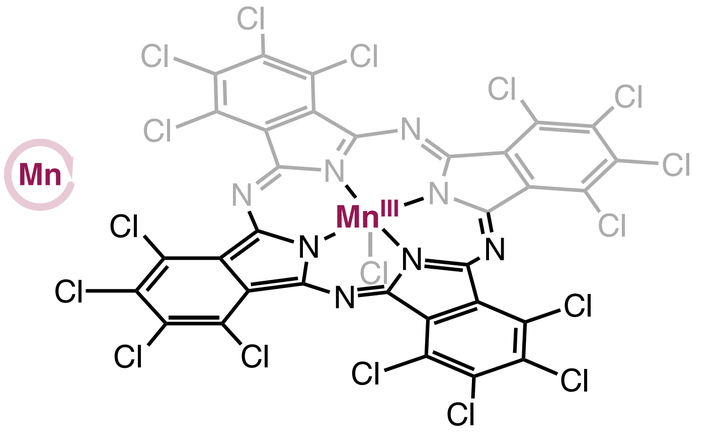

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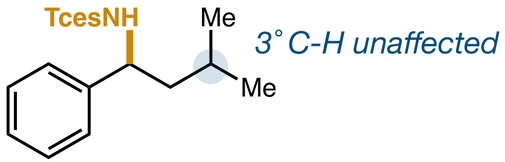


3° C-H unaffected

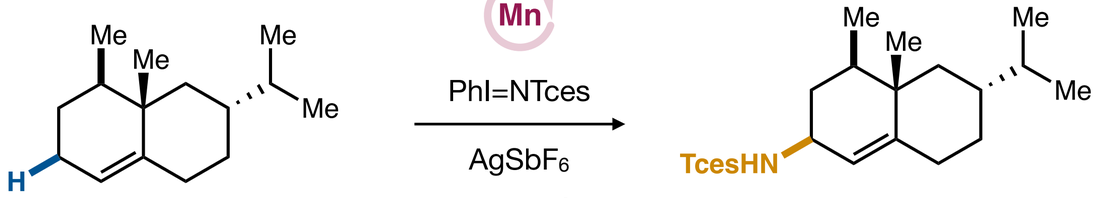
53% yield

Exceptional selectivity for benzylic position over tertiary amination

White *Nat. Chem.* **2018**, *10,* 583; White *J. Am. Chem. Soc.* **2021**, *143*, 14969.

Allylic C–H aminations by radical rebound

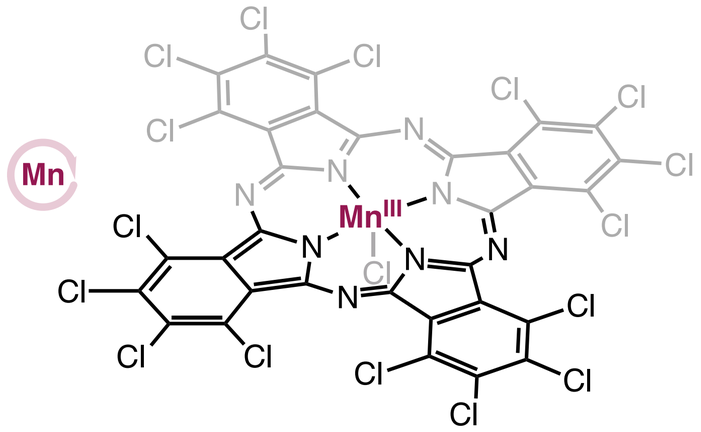
White (2018/2021)



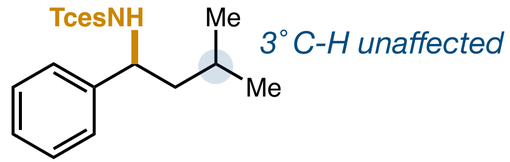
allylic C–H bonds

53% yield

d.r. = 6:1

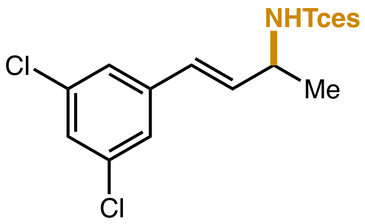


Mn(ClPc)Cl



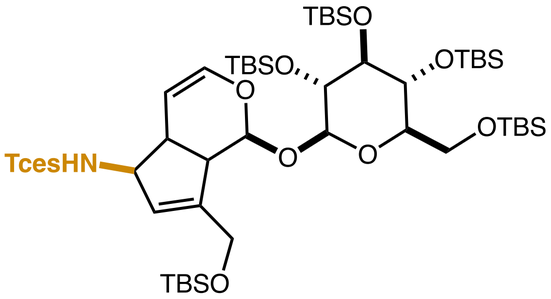
3° C-H unaffected

53% yield



44% yield

8% aziridine

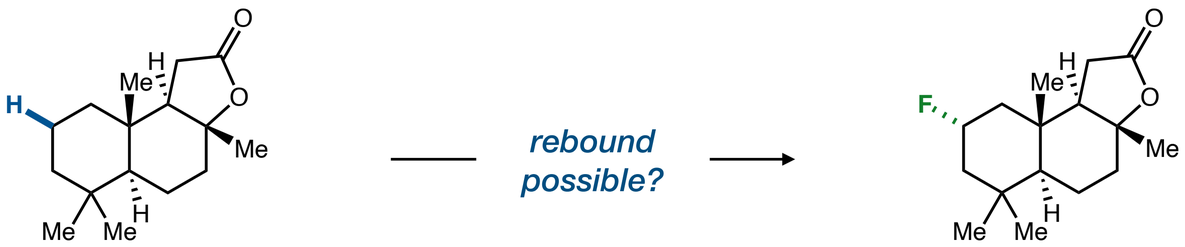


53% yield

r.r > 20:1; d.r. > 20:1

White *Nat. Chem.* **2018**, *10,* 583; White *J. Am. Chem. Soc.* **2021**, *143*, 14969.

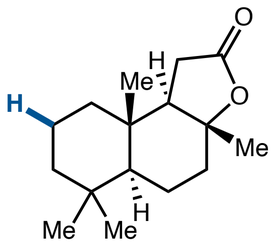
Aziridination using manganese catalysts



fluorination by radical rebound mimics unnatural halogenase activity

Aziridination using manganese catalysts

Groves (2012)

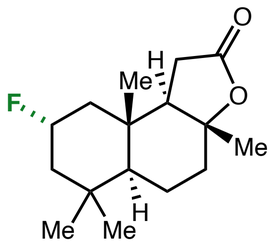


AgF (3 equ.),TBAF (0.3 equ.)

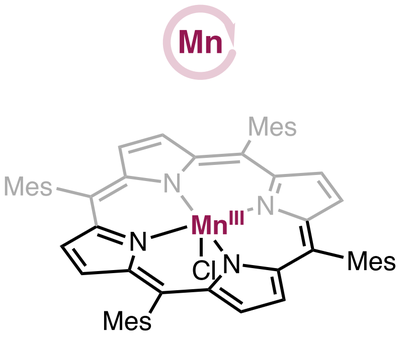
PhIO (3–6 equ.)

Mn(TMP)Cl

$MeCN/CH_2Cl_2$, 50 °C



42% yield

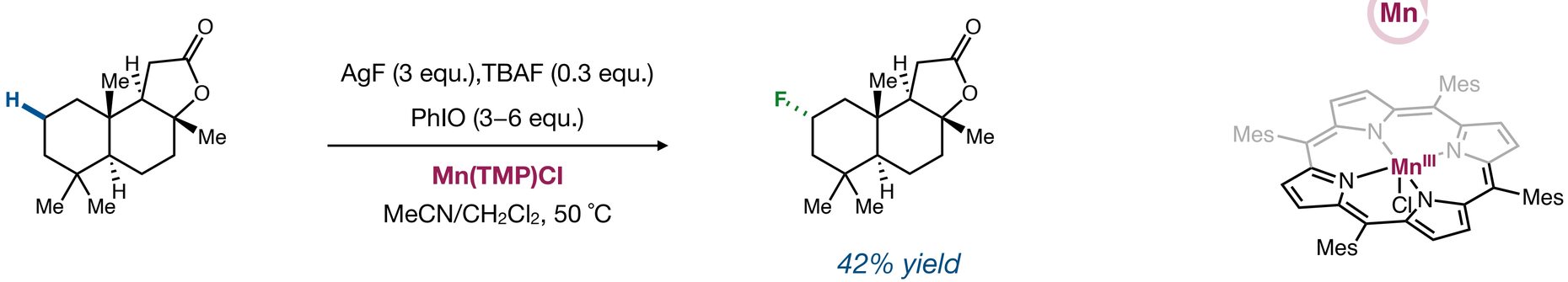


Mn(TMP)Cl

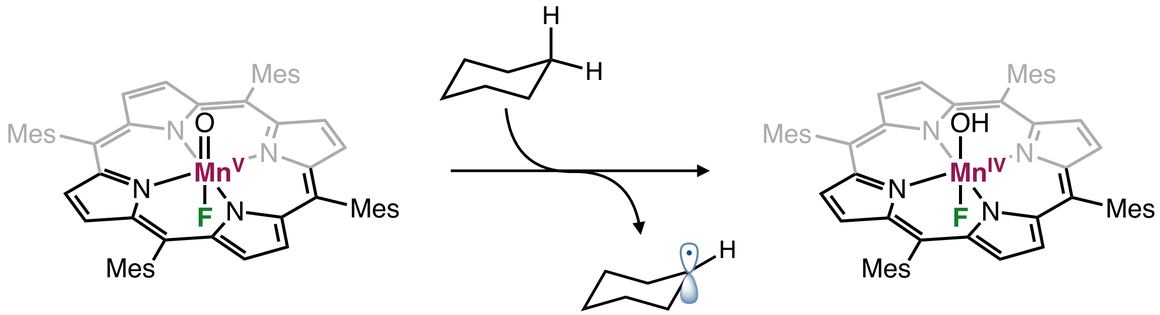
Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A.; Groves, J. T. *Science* **2012,** *337*, 1322.

Aziridination using manganese catalysts

Groves (2012)



proposed mechanism:



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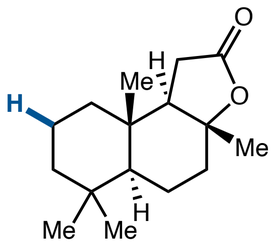
Aziridination using manganese catalysts

Groves (2012)

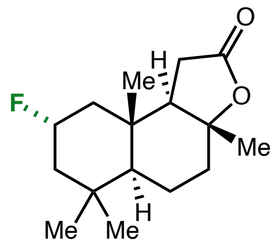


AgF (3 equ.),TBAF (0.3 equ.)

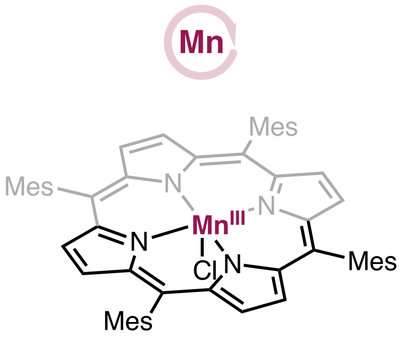
PhIO (3–6 equ.)

Mn(TMP)Cl

$MeCN/CH_2Cl_2$, 50 °C

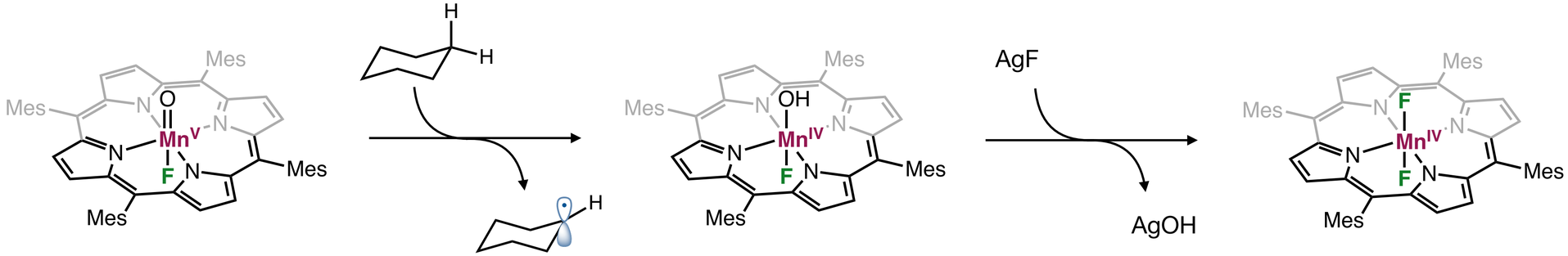


42% yield



Mn(TMP)Cl

proposed mechanism:

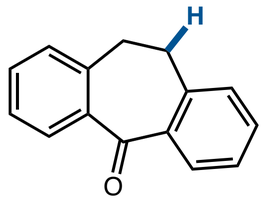


hydroxy/fluoride exchange allows for selective fluorine-atom transfer

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

Aziridination using manganese catalysts

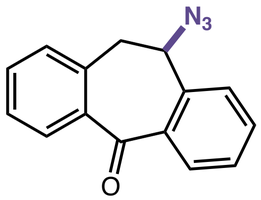
Groves (2015)



NaN_3 (aq.,4 equ.), PhIO (3–6 equ.)

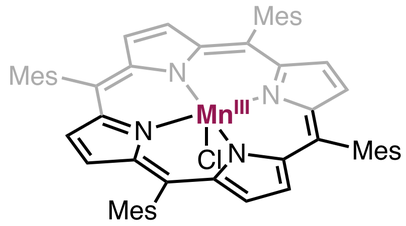
Mn(TMP)Cl or Mn(salen)Cl

EtOAc, r.t.

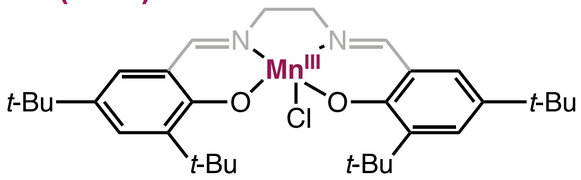


56% yield

Mn(TMP)Cl



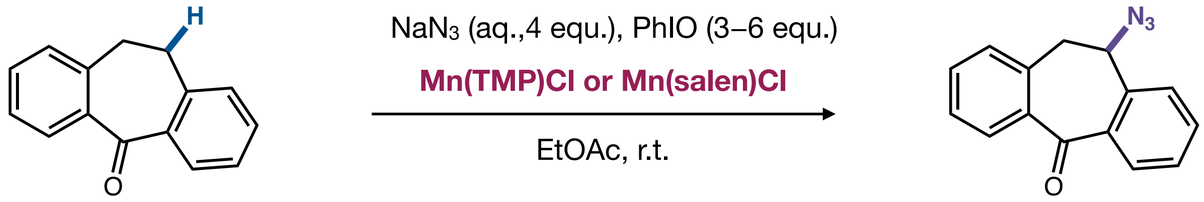
Mn(salen)Cl



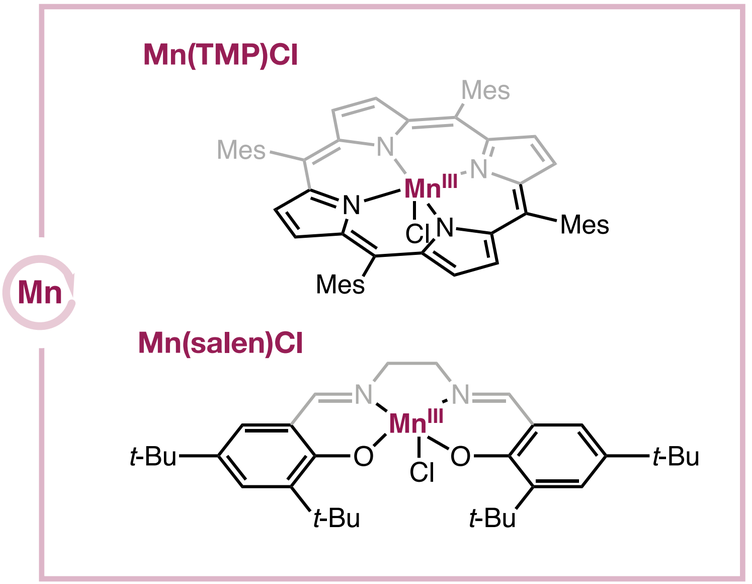
Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015,** *137*, 5300.

Aziridination using manganese catalysts

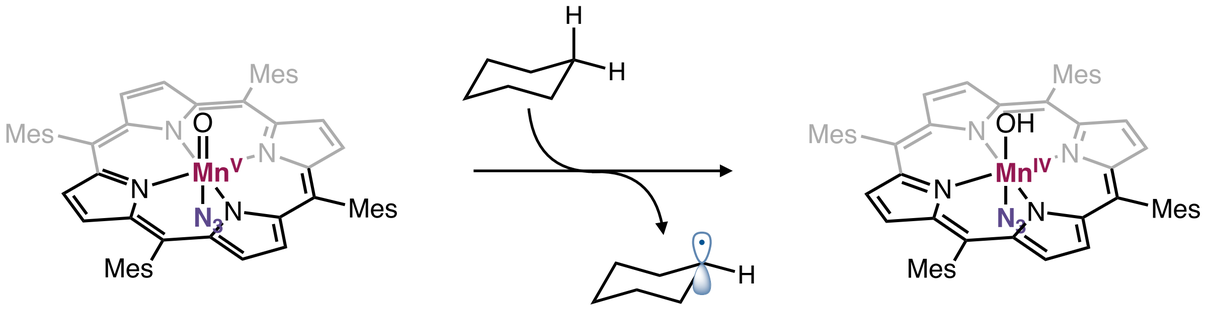
Groves (2015)



56% yield



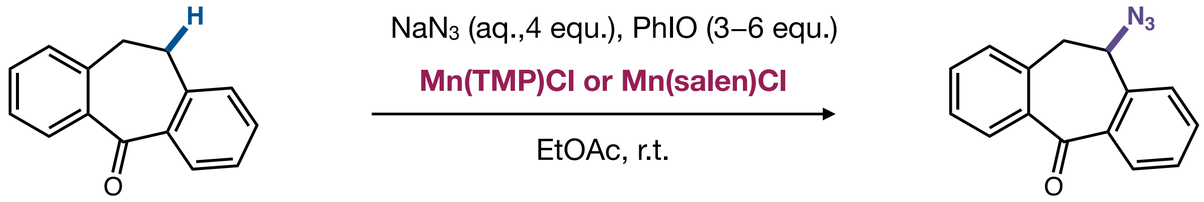
proposed mechanism:



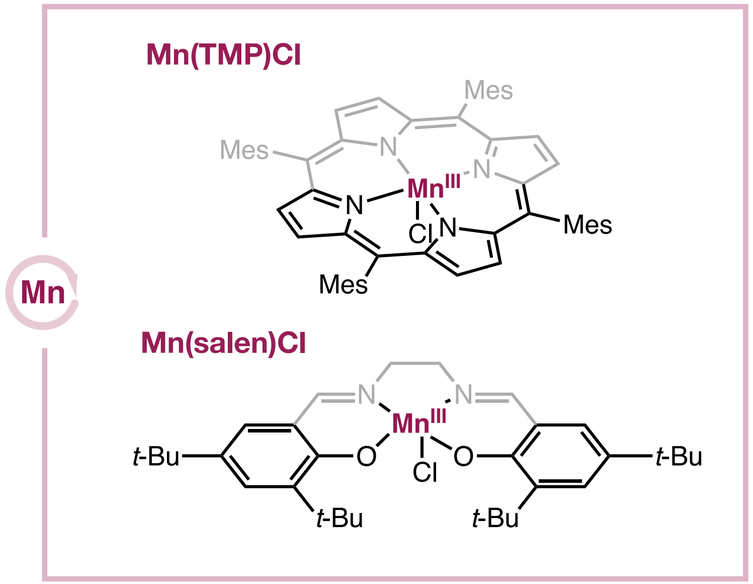
Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015,** *137*, 5300.

Aziridination using manganese catalysts

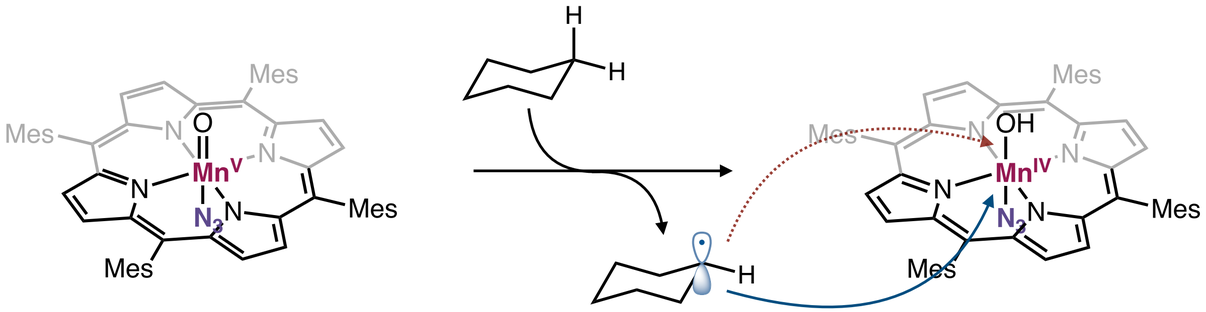
Groves (2015)



56% yield



proposed mechanism:



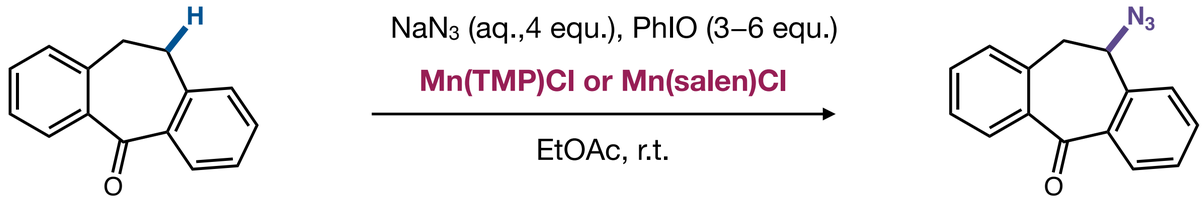
relative rebound rates

N_3 > NCS > NCO > Cl > OH

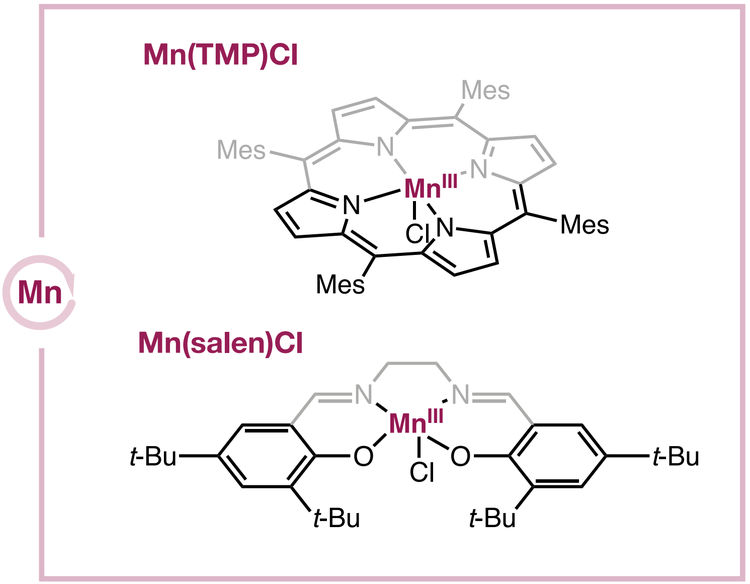
Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015,** *137*, 5300; Goldberg **2023**, *62*, 17830.

Aziridination using manganese catalysts

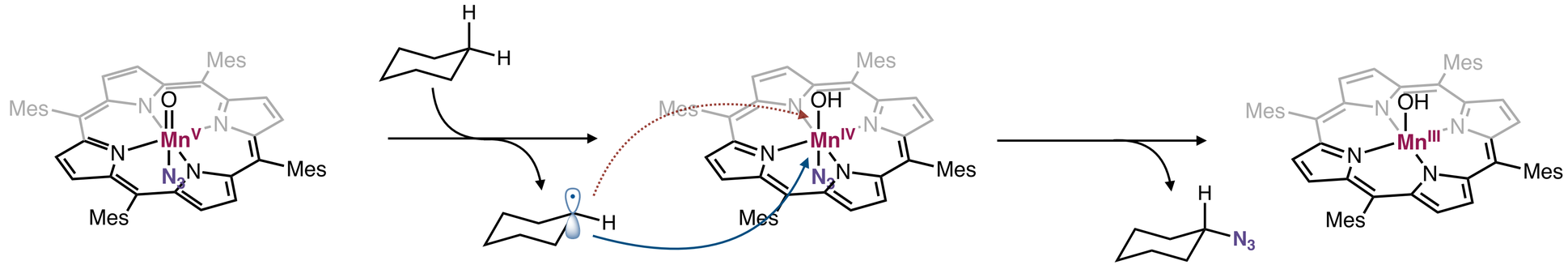
Groves (2015)



56% yield



proposed mechanism:



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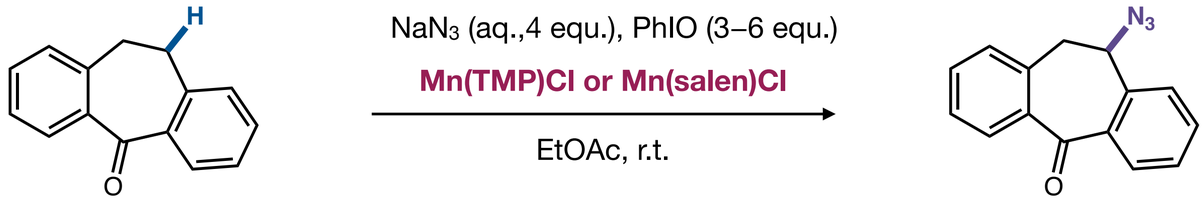
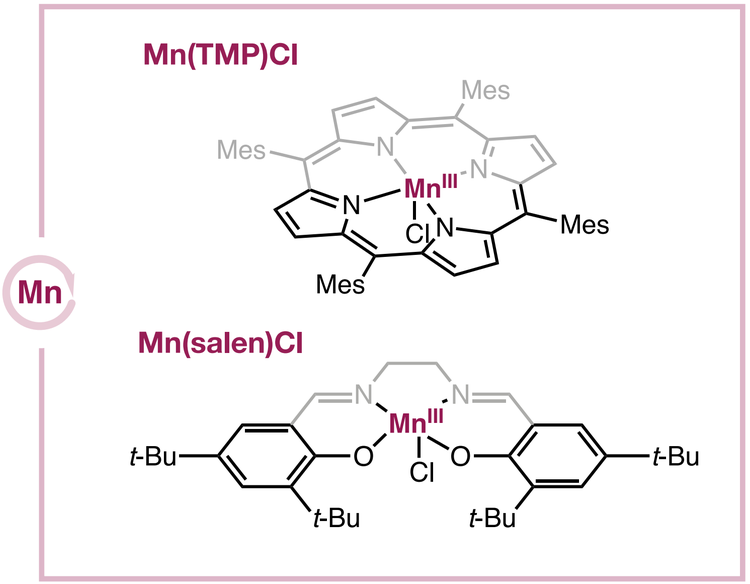
Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015,** *137*, 5300; Goldberg **2023**, *62*, 17830.

Aziridination using manganese catalysts

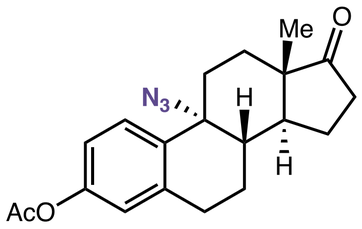
Groves (2015)



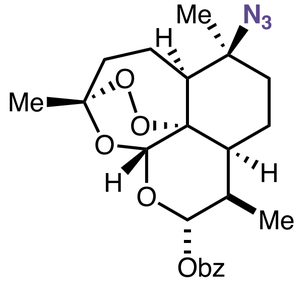
56% yield



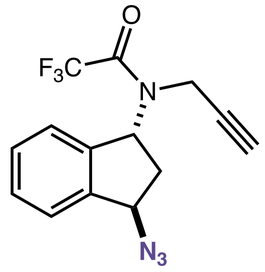
late-stage aziridination



38% yield
from estrone



20% yield
from artemisinin

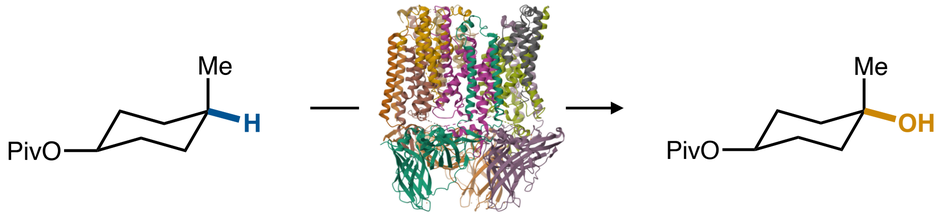


45% yield
from rasagiline

Huang, X.; Bergsten, T. M.; Groves, J. T. *J. Am. Chem. Soc.* **2015,** *137*, 5300.

Development of non-heme catalytic systems

How can we mimic non-heme hydroxylases?



Chen, M. S.; White, M. C. Science **2007**, 381, 783.

Development of non-heme catalytic systems

How can we mimic non-heme hydroxylases?

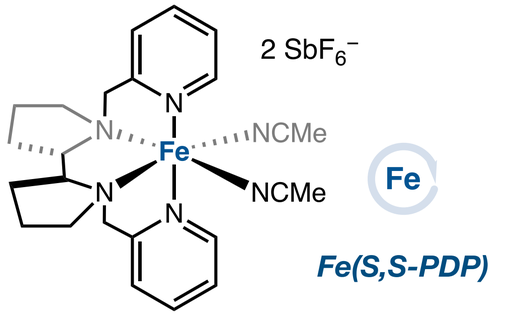
Chen, M. S.; White, M. C. Science **2007**, 381, 783.

Development of non-heme catalytic systems

White (2007)

51% yield

d.r. > 99:1



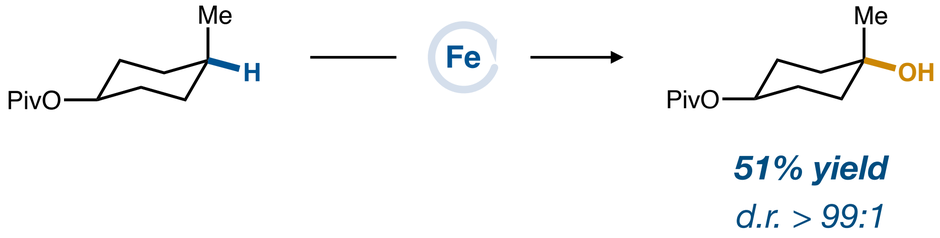
Fe(S,S-PDP)

non-heme catalyst

Chen, M. S.; White, M. C. Science **2007**, 381, 783.

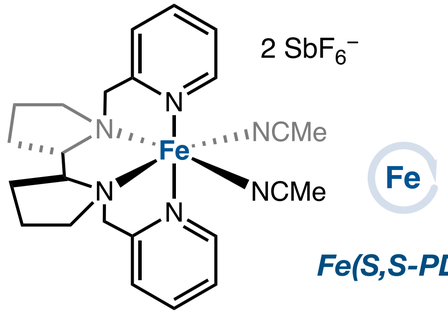
Development of non-heme catalytic systems

White (2007)



51% yield

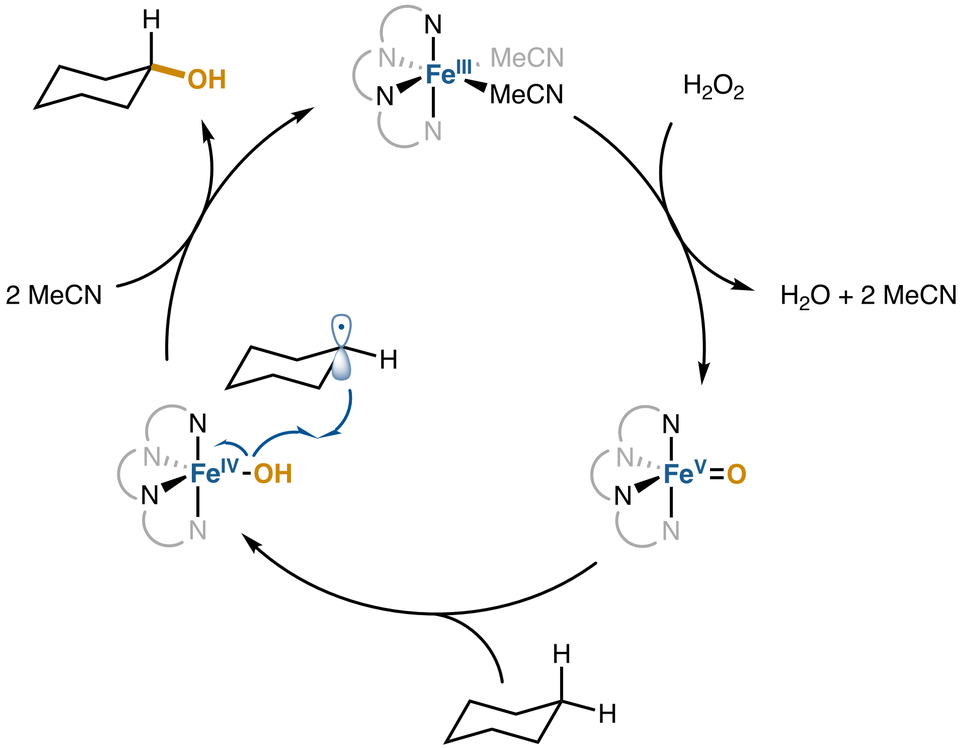
d.r. > 99:1



Fe

Fe(S,S-PDP)

non-heme catalyst



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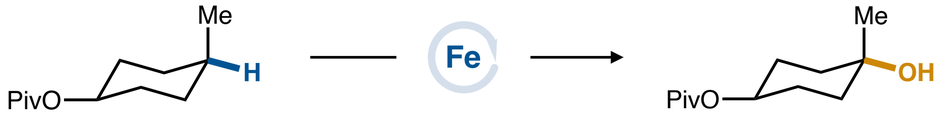
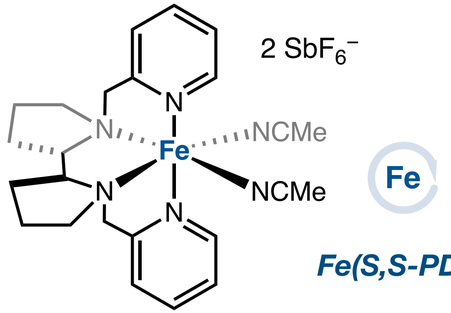
Development of non-heme catalytic systems

White (2007)



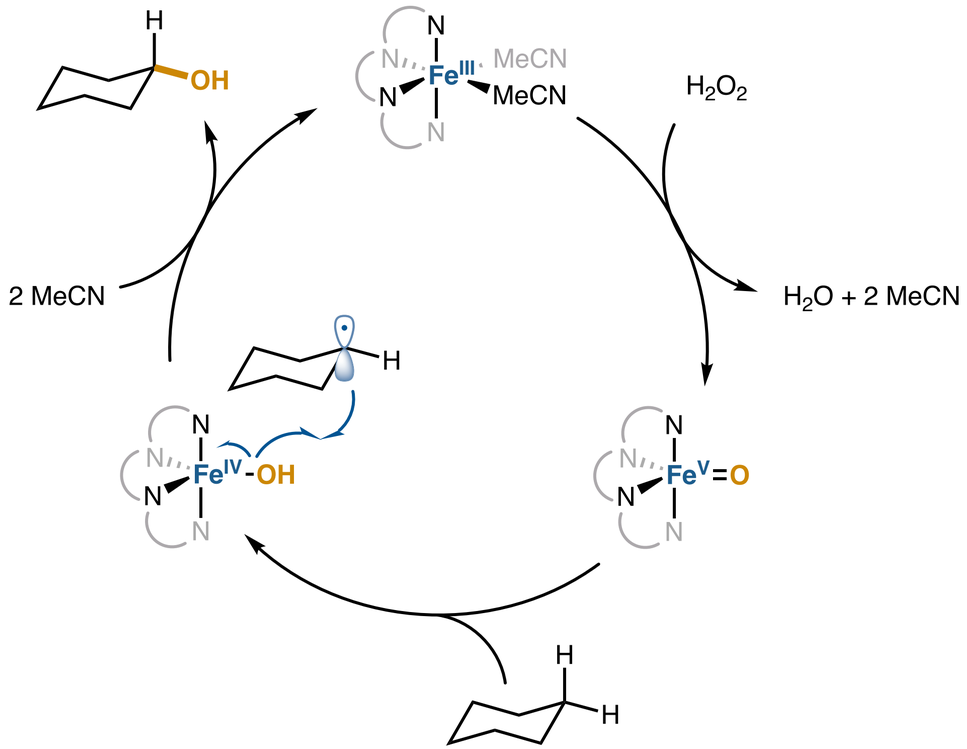
51% yield

d.r. > 99:1



Fe(S,S-PDP)

non-heme catalyst

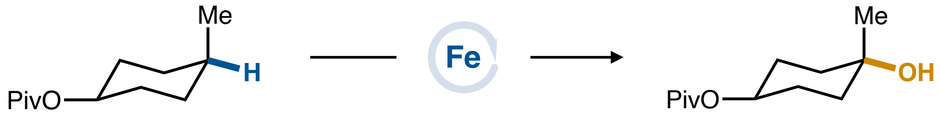


Mechanistically similar to metalloporphyrin oxidation

Chen, M. S.; White, M. C. Science **2007**, 381, 783.

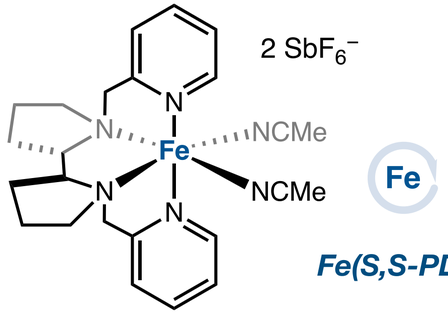
Development of non-heme catalytic systems

White (2007)



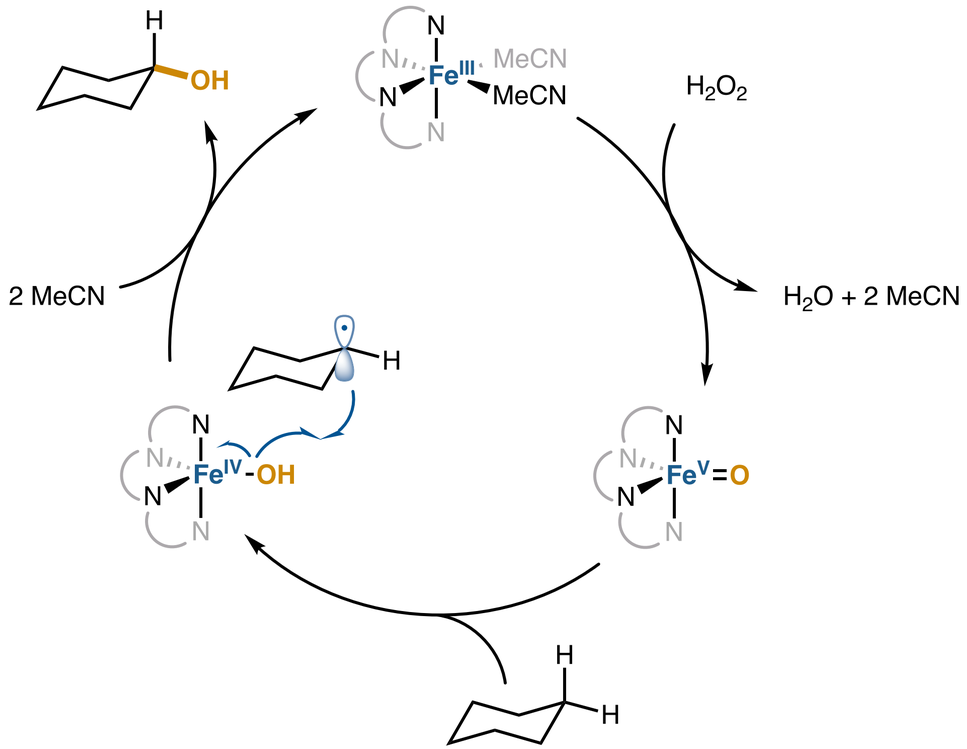
51% yield

d.r. > 99:1



Fe(S,S-PDP)

non-heme catalyst



1 equiv. of C–H substrate

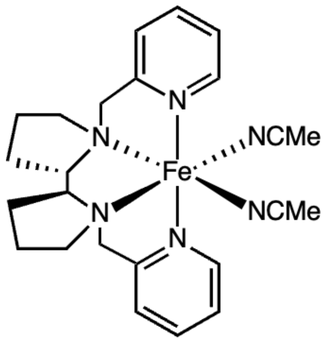
lower oxidant loading

improved TON

higher site selectivities

Chen, M. S.; White, M. C. Science **2007**, 381, 783.

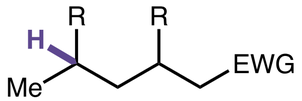
Catalyst Design for Selective C–H Oxidation



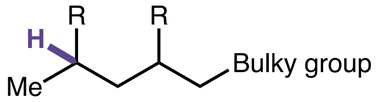
Fe(PDP)

Factors for selectivity:

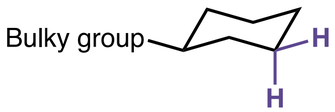
i) electronic



ii) steric

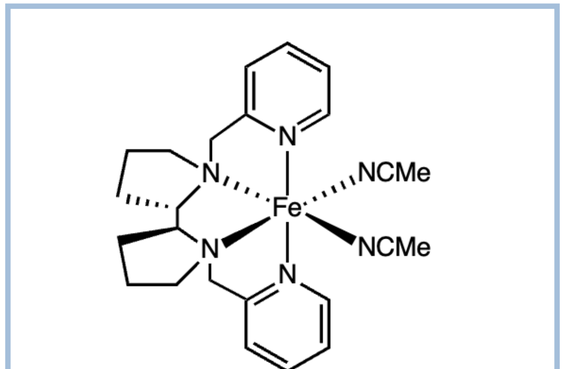


ii) stereo-electronic

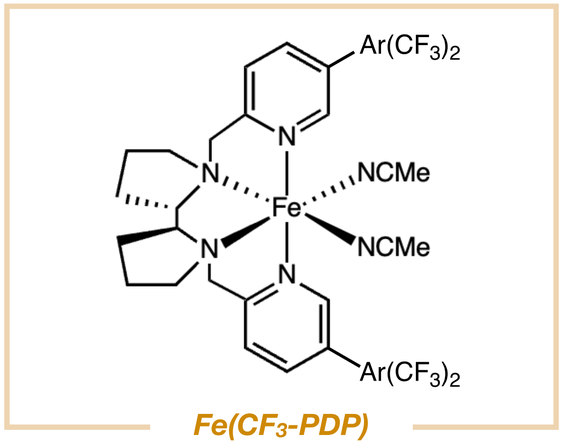


Howell, J.; Feng, K.; Clark, J.; Trzepkowski, L.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590.

Catalyst Design for Selective C–H Oxidation



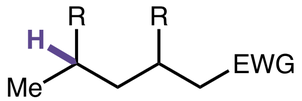
Fe(PDP)



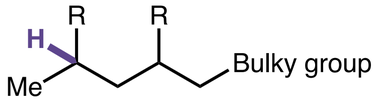
Fe(CF_3-PDP)

Factors for selectivity:

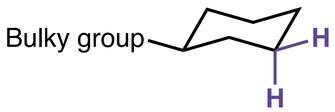
i) electronic



ii) steric



ii) stereo-electronic



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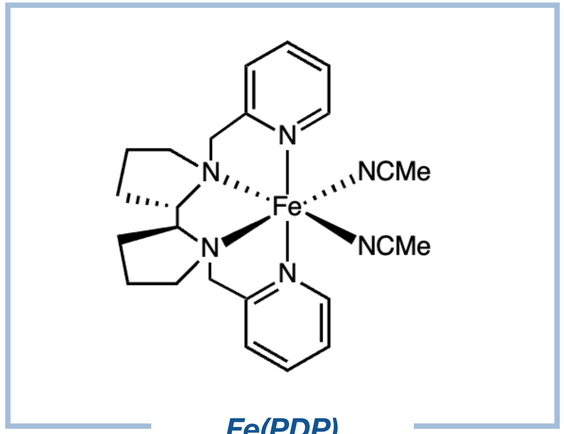
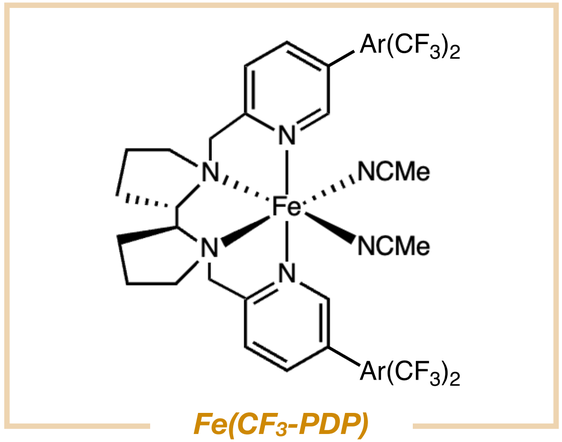


Fe(PDP)



Fe(CF$_3$-PDP)

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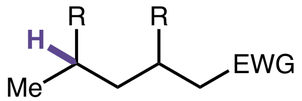

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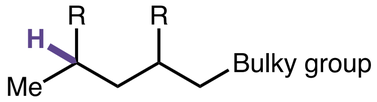

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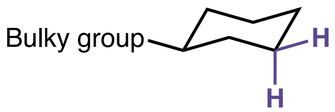
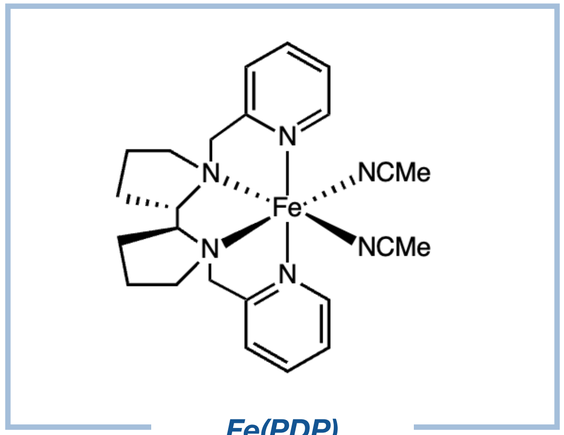


Main factor for selectivity:

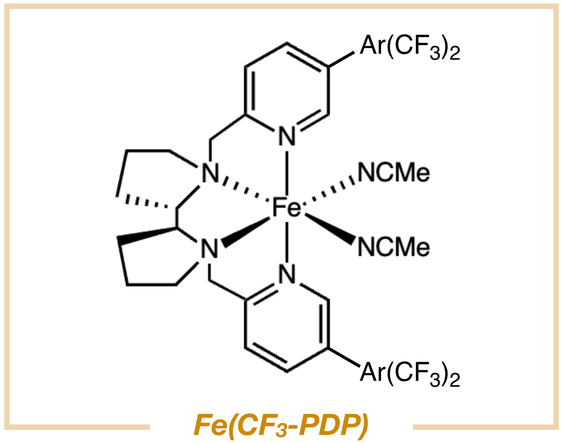
primarily sterics

Howell, J.; Feng, K.; Clark, J.; Trzepkowski, L.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590.

Catalyst Design for Selective C–H Oxidation



Fe(PDP)



Fe(CF$_3$-PDP)

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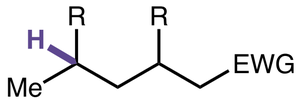
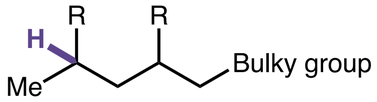
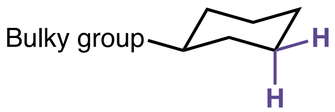
i) electronic



ii) steric

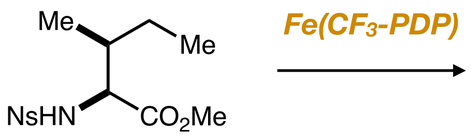


ii) stereo-electronic

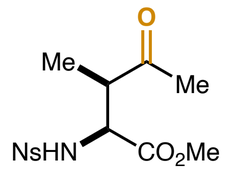


Main factor for selectivity:

primarily sterics



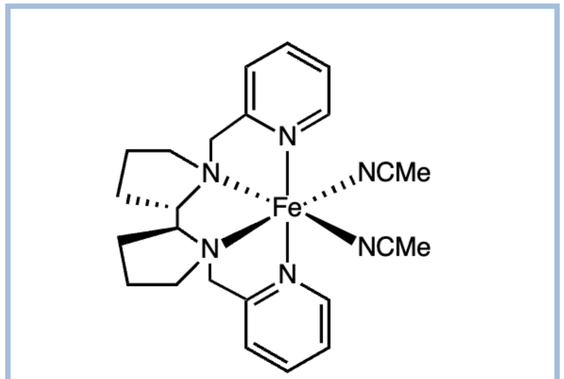
Fe(CF$_3$-PDP)



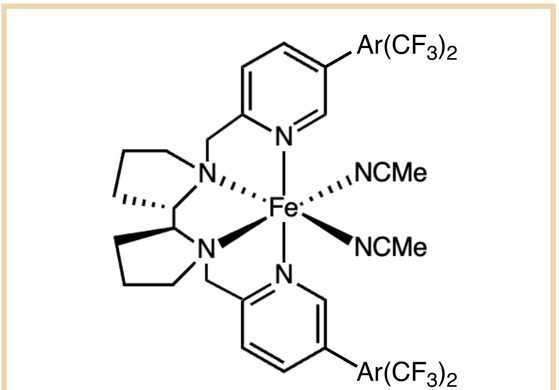
56% yield ketone
15% yield alcohol

Howell, J.; Feng, K.; Clark, J.; Trzepkowski, L.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590.

Catalyst Design for Selective C–H Oxidation

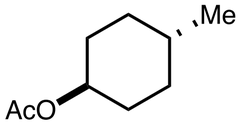


Fe(PDP)



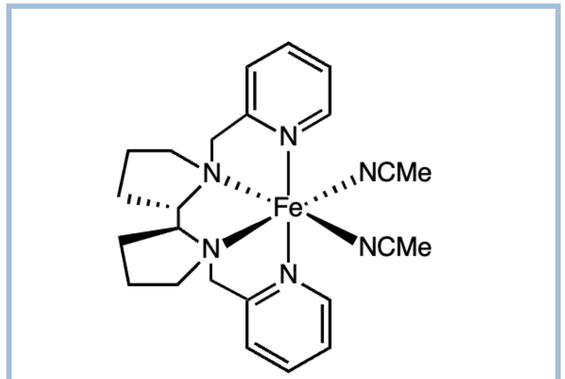
Fe(CF_3-PDP)

Site-selectivity for Fe(PDP) vs. Fe(CF_3-PDP)

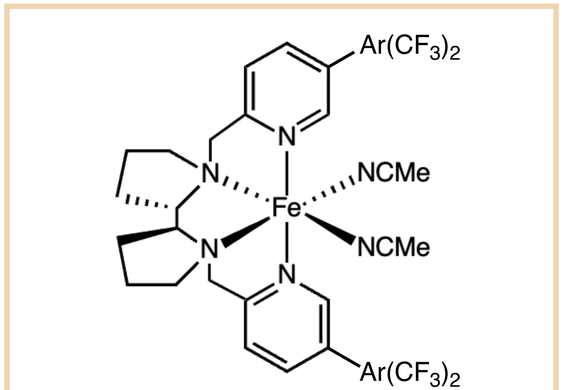


Gormisky, P.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.

Catalyst Design for Selective C–H Oxidation



Fe(PDP)



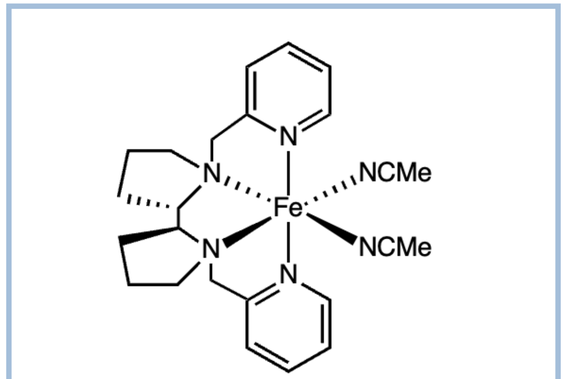
Fe(CF$_3$-PDP)

Site-selectivity for Fe(PDP) vs. Fe(CF$_3$-PDP)

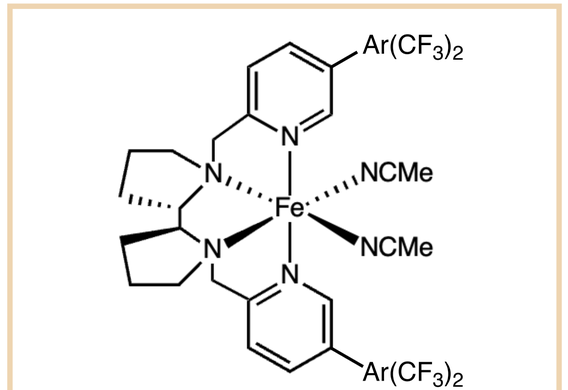
66% yield alcohol
19% yield ketone

Gormisky, P.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.

Catalyst Design for Selective C–H Oxidation

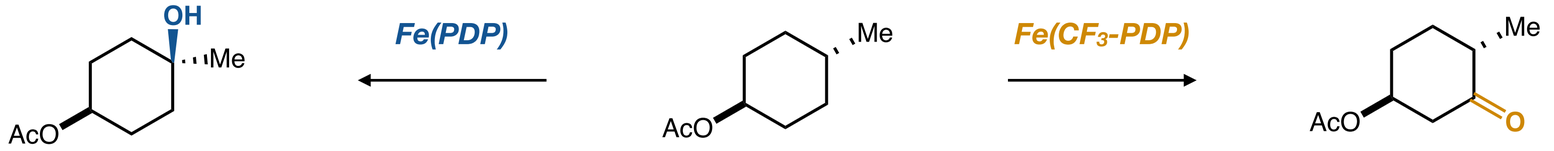


Fe(PDP)



Fe(CF$_3$-PDP)

Site-selectivity for Fe(PDP) vs. Fe(CF$_3$-PDP)

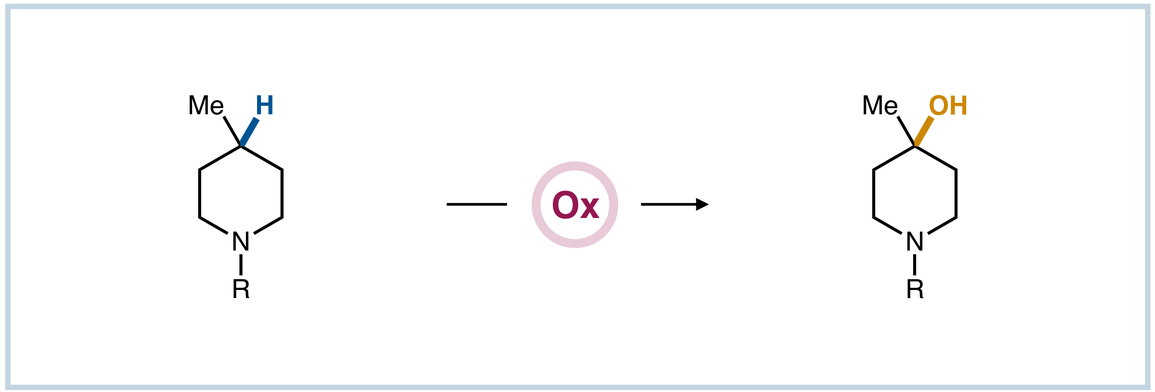


66% yield alcohol
19% yield ketone

51% yield ketone
28% yield alcohol

Gormisky, P.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.

Strategies for Overcoming Substrate Control: N–Complexation

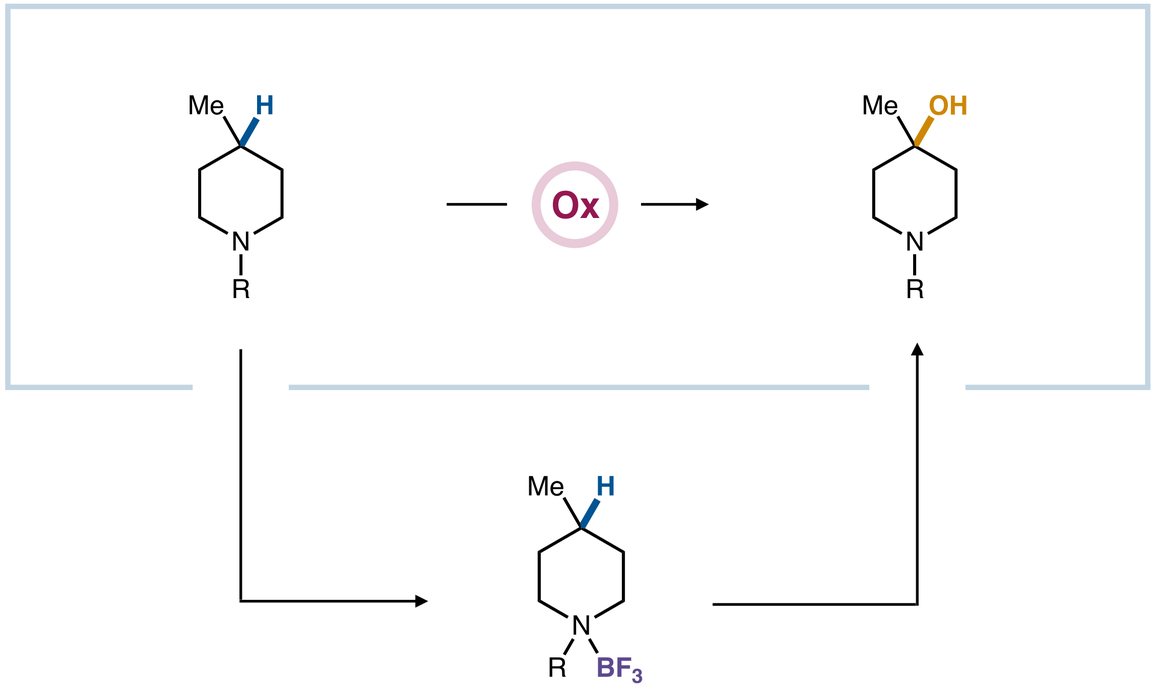


Challenges of N-Heterocycle Remote Oxidation

N-heterocycles prone to catalyst complexation and/or oxidation to N-oxide

C–H bonds adjacent to nitrogen are activated toward functionalization

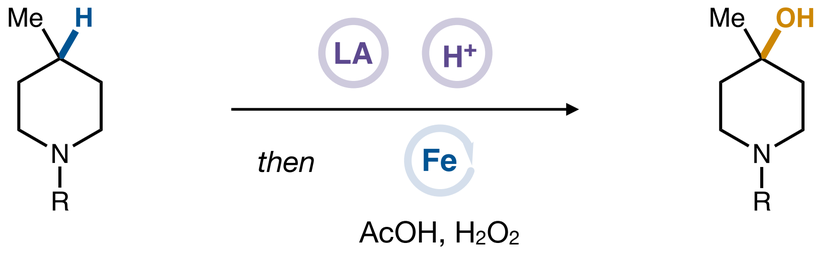
Strategies for Overcoming Substrate Control: N–Complexation

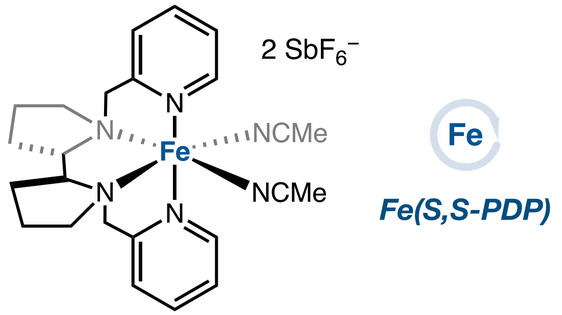


Lewis acid complexation renders basic nitrogen strongly withdrawing

Strategies for Overcoming Substrate Control: N–Complexation

White (2015)





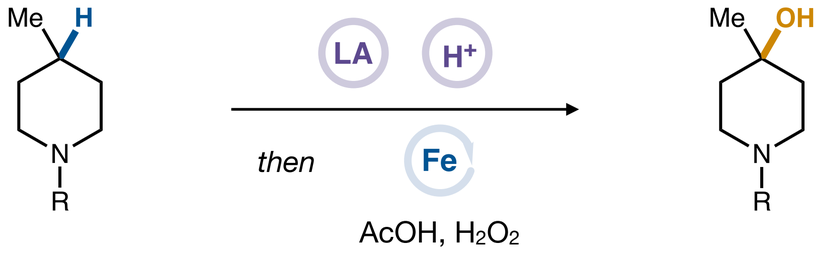
Fe

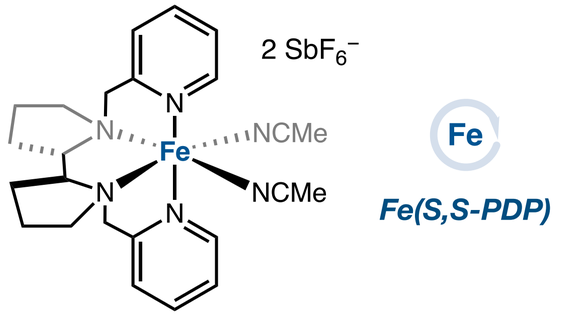
Fe(S,S-PDP)

Howell, J.; Feng, K.; Clark, J.; Trzepkowski, L.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590.

Strategies for Overcoming Substrate Control: N–Complexation

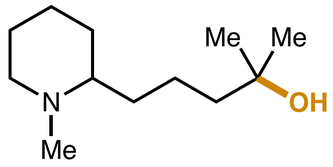
White (2015)



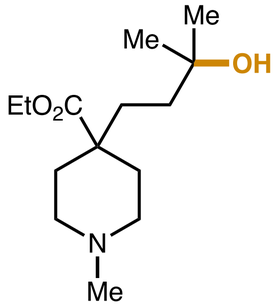


Fe

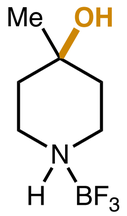
Fe(S,S-PDP)



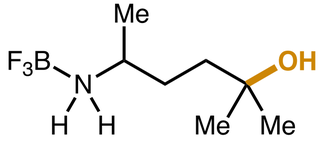
52% yield



55% yield



65% yield

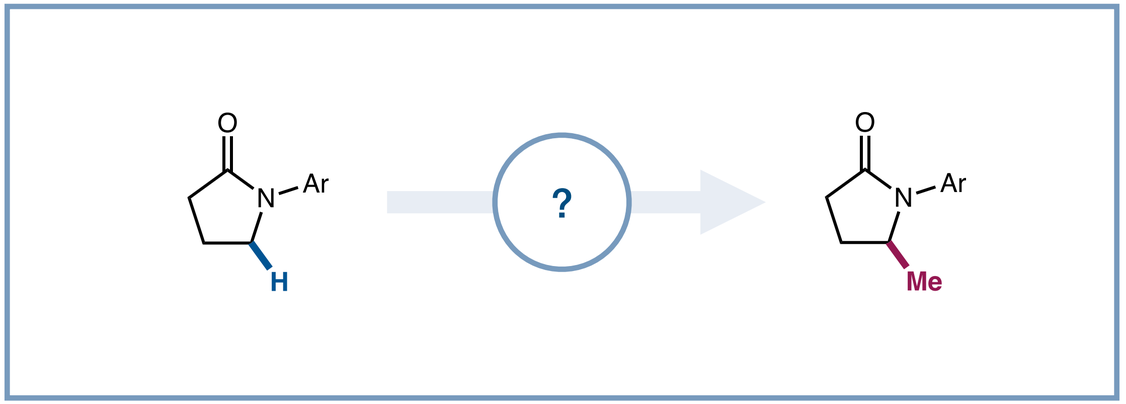


56% yield

Howell, J.; Feng, K.; Clark, J.; Trzepkowski, L.; White, M. C. *J. Am. Chem. Soc.* **2015**, *137*, 14590.

Late-stage C–H methylation via radical rebound

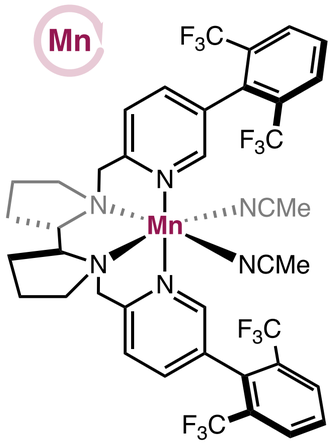
How can a selective, late-stage C–H methylation be achieved via an Fe-oxidation?



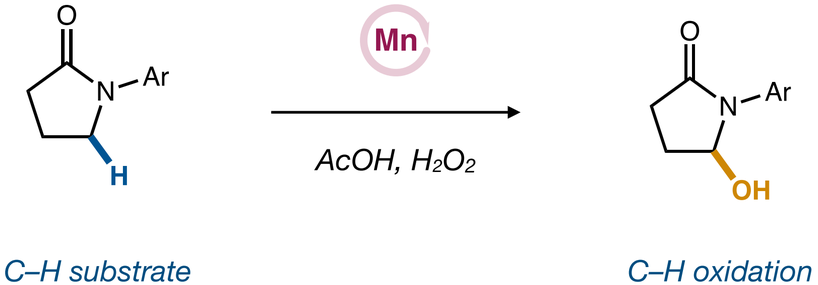
Gormisky, P.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.

Late-stage C–H methylation via radical rebound

White (2020)



Mn(CF$_3$-PDP)



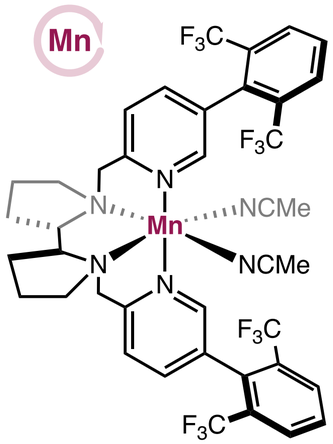
C–H substrate

C–H oxidation

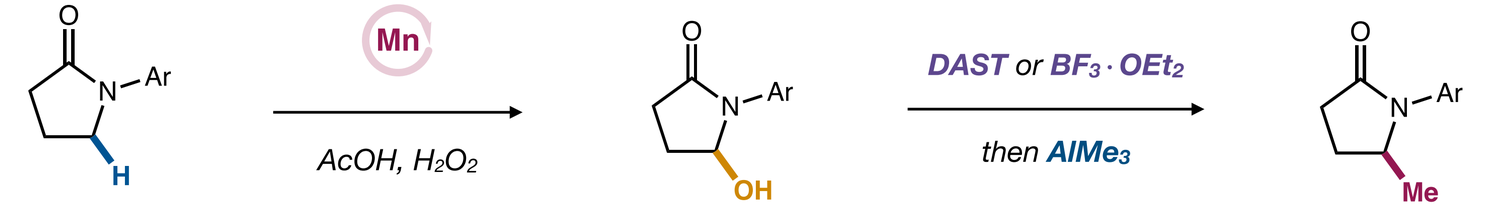
Feng, K.; Quevedo, R.; White, M. C. *Nature* **2020**, *580*, 621.

Late-stage C–H methylation via radical rebound

White (2020)



Mn(CF$_3$-PDP)

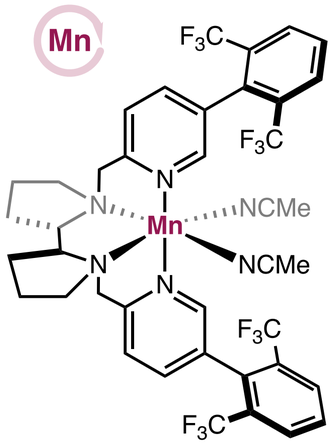


C–H substrate *C–H oxidation* *methylated product*

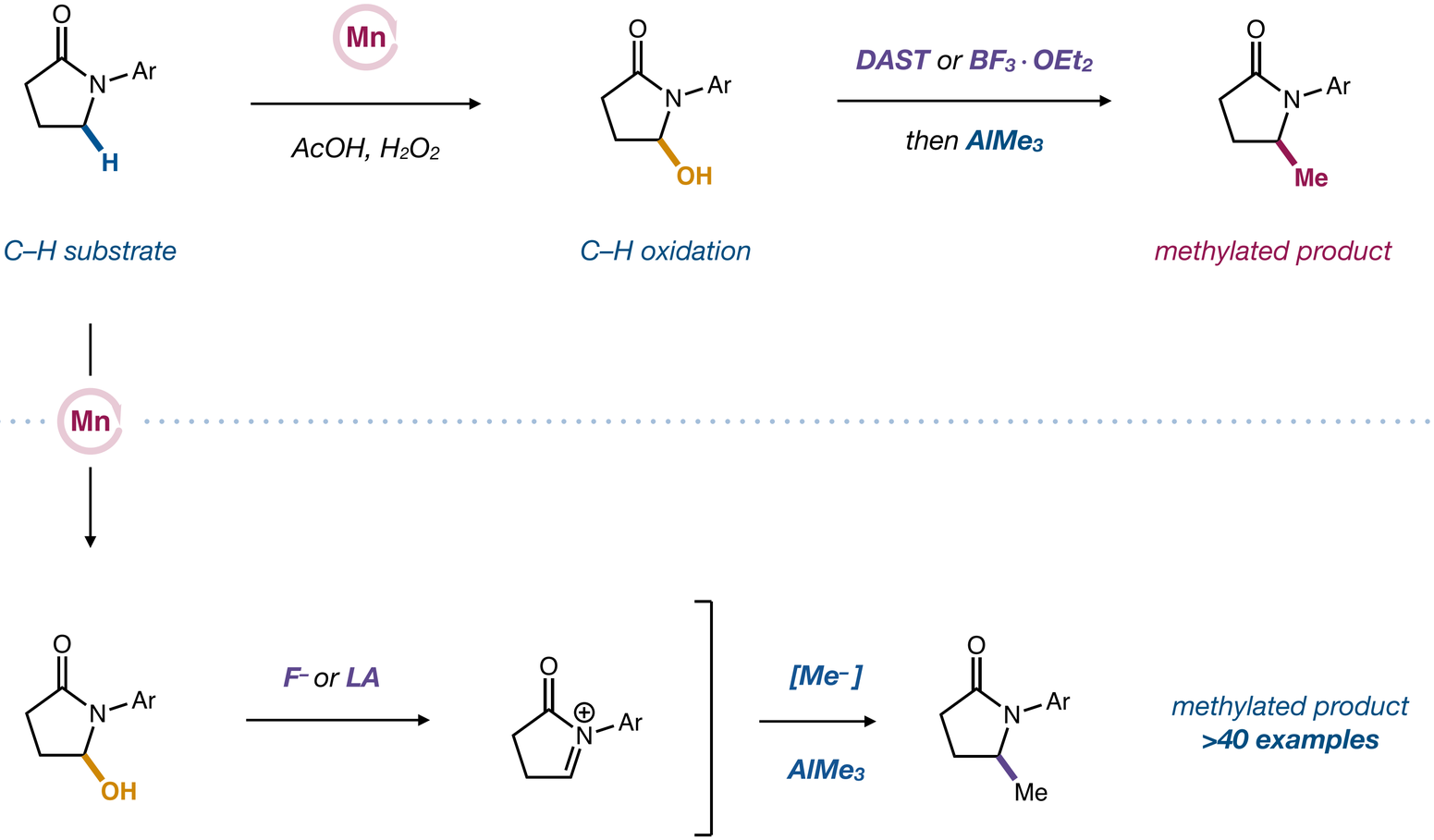
Feng, K.; Quevedo, R.; White, M. C. *Nature* **2020**, *580*, 621.

Late-stage C–H methylation via radical rebound

White (2020)



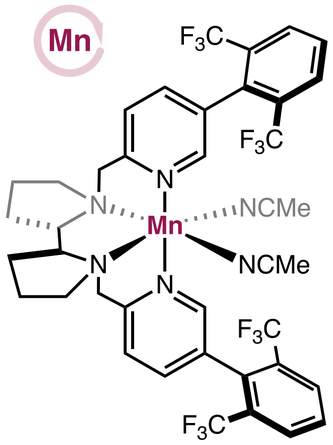
Mn(CF$_3$-PDP)



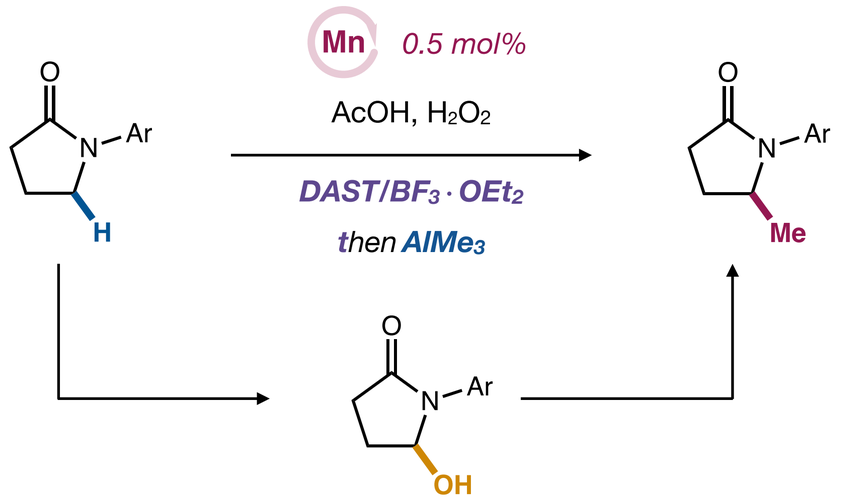
Feng, K.; Quevedo, R.; White, M. C. *Nature* **2020**, *580*, 621.

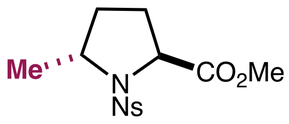
Late-stage C–H methylation via radical rebound

White (2020)



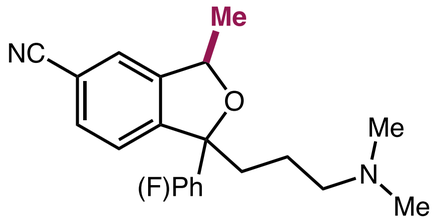
Mn(CF$_3$-PDP)





68% yield

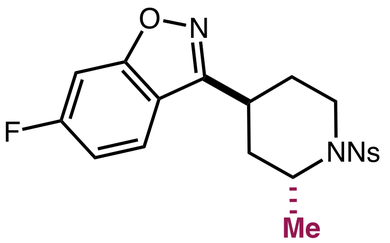
88% yield/step



36% yield

71% yield/step

from citalopram



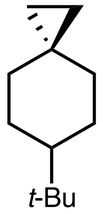
37% yield

72% yield/step

Feng, K.; Quevedo, R.; White, M. C. *Nature* **2020**, *580*, 621.

Catalyst control over rebound pathways

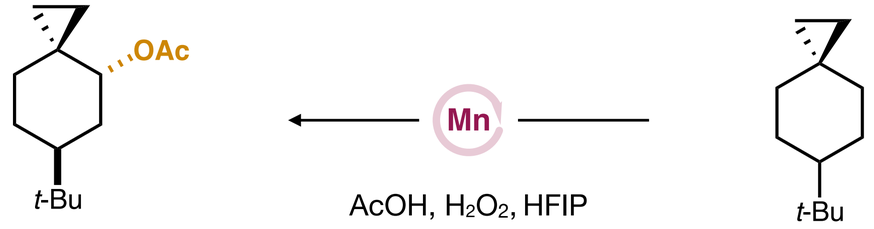
Costas (2024)



Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

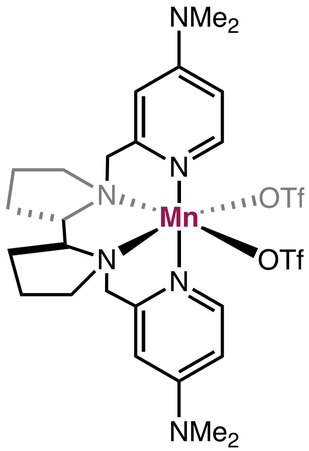
Catalyst control over rebound pathways

Costas (2024)



72% yield

73:27 cyclopropane:cyclobutane

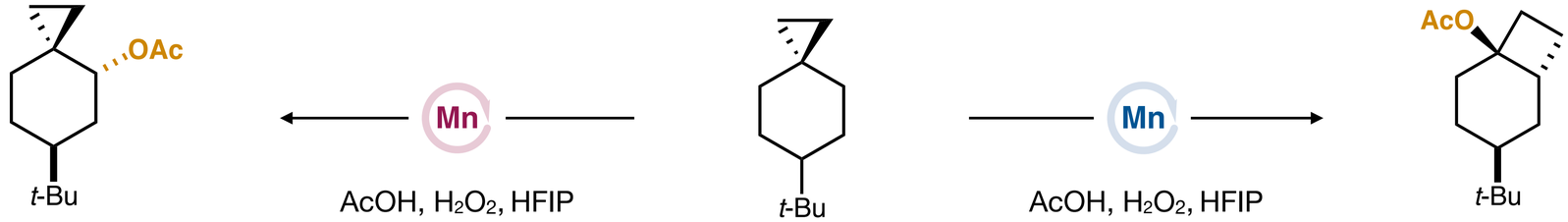


Mn

Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

Catalyst control over rebound pathways

Costas (2024)

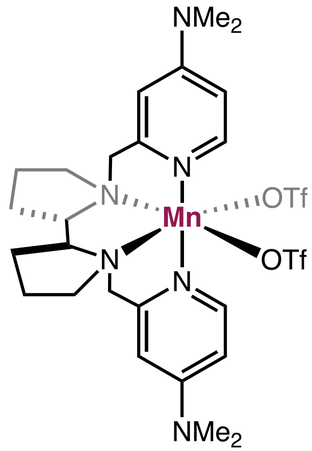


72% yield

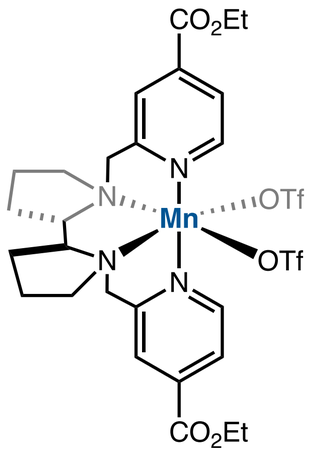
73:27 cyclopropane:cyclobutane

40% yield

20:80 cyclopropane:cyclobutane



Mn

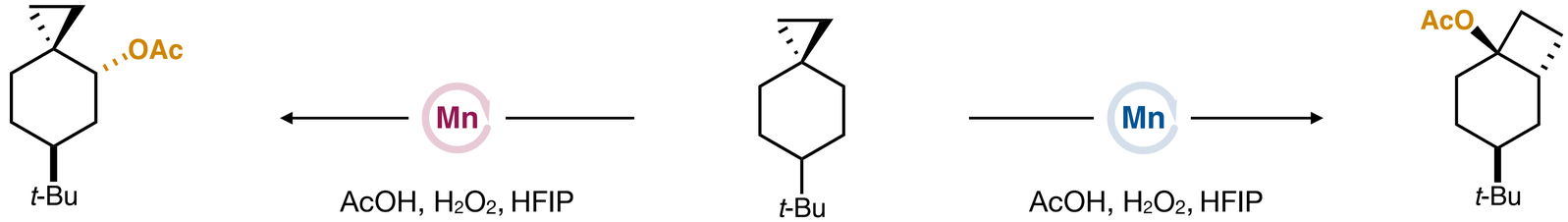


Mn

Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

Catalyst control over rebound pathways

Costas (2024)



72% yield

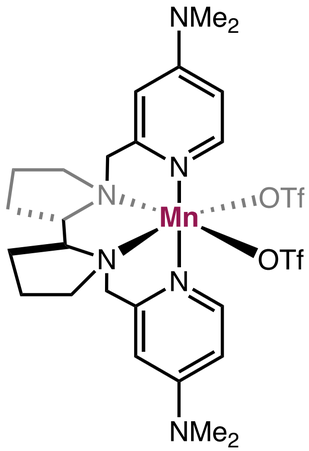
73:27 cyclopropane:cyclobutane

40% yield

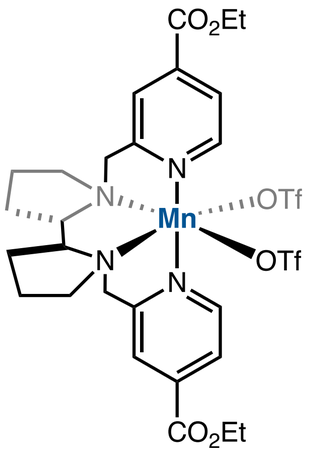
20:80 cyclopropane:cyclobutane

more nucleophilic

less oxidizing



Mn

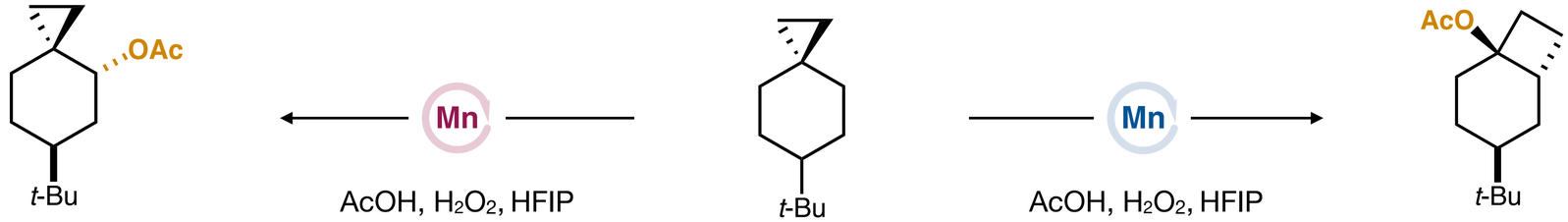


Mn

Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

Catalyst control over rebound pathways

Costas (2024)



72% yield

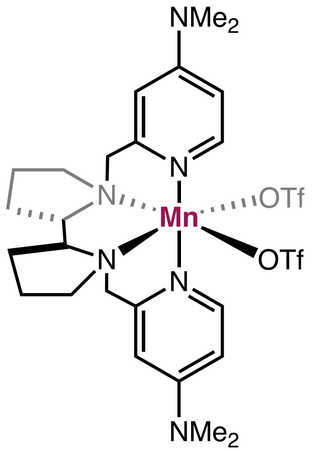
73:27 cyclopropane:cyclobutane

40% yield

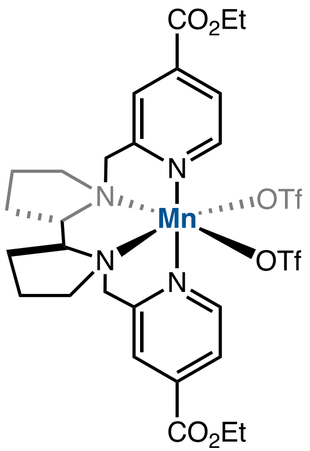
20:80 cyclopropane:cyclobutane

more nucleophilic

less oxidizing



Mn



Mn

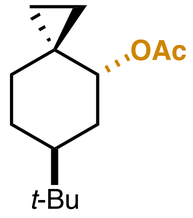
more electrophilic

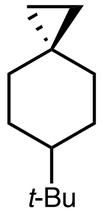
stronger oxidizing

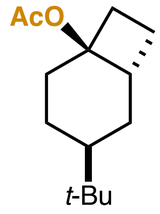
Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

Catalyst control over rebound pathways

Costas (2024)







72% yield

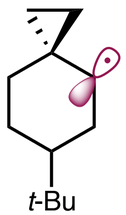
73:27 cyclopropane:cyclobutane

40% yield

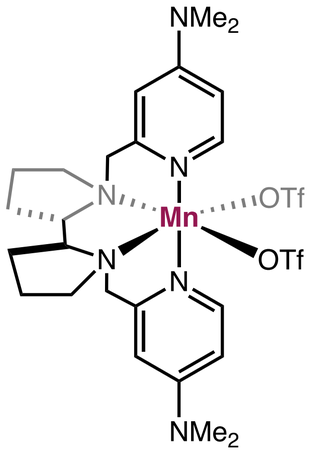
20:80 cyclopropane:cyclobutane

more nucleophilic

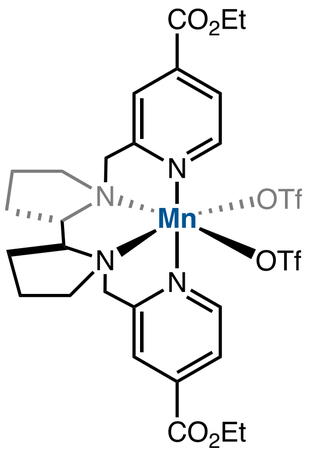
less oxidizing



radical rebound dominates



Mn

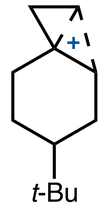


Mn

more electrophilic

stronger oxidizing

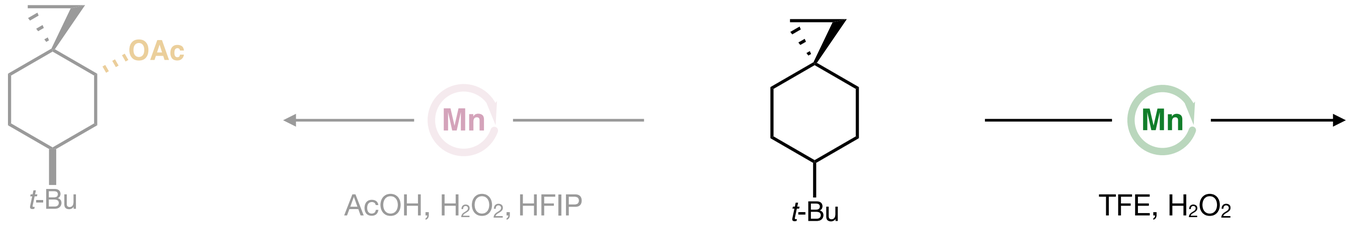
cationic pathway dominates



Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

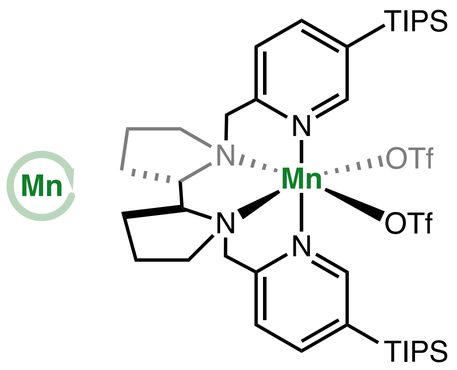
Catalyst and medium control over rebound pathways

Costas (2024)



72% yield

73:27 cyclopropane:cyclobutane



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Catalyst and medium control over rebound pathways

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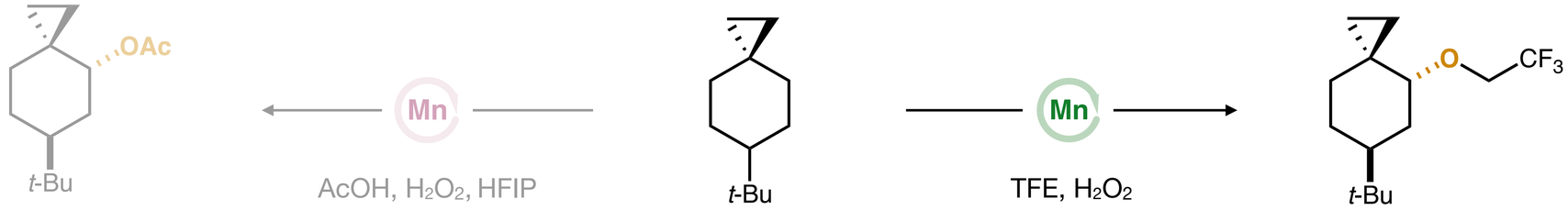


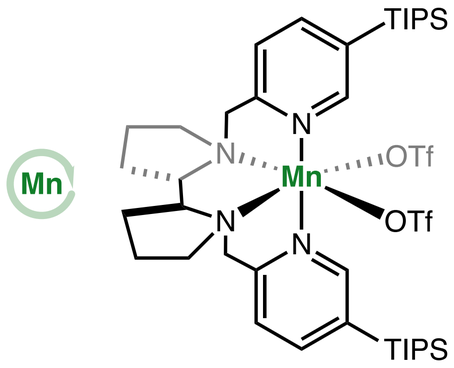
72% yield

73:27 cyclopropane:cyclobutane

60% yield

57:43 cyclopropane:cyclobutane

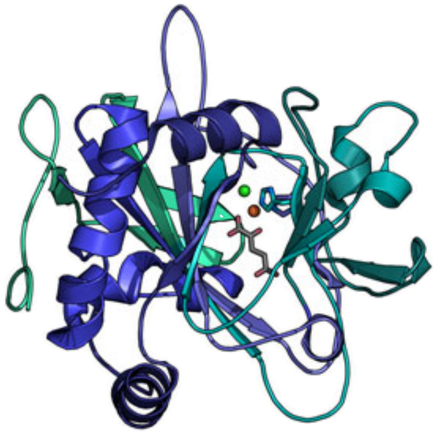
rare use of alcohols in radical rebound



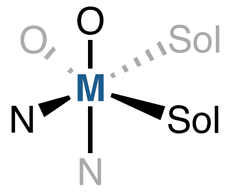
Galeotti, M.; Bietti, M; Costas, M. *J. Am. Chem. Soc.* **2024**, *146*, 8904.

Radio fluorination of C–H bonds

Can we mimic halogenase activity?



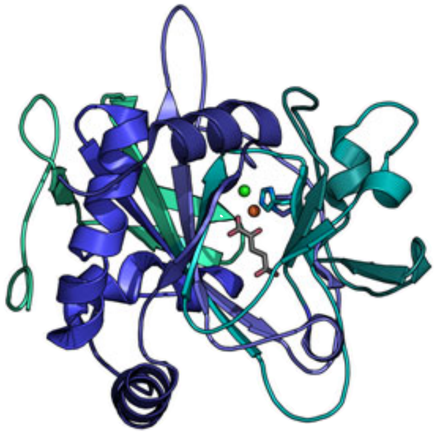
SyrB2



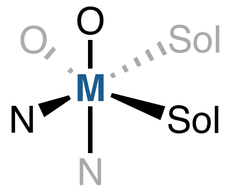
synthetic catalyst

Radio fluorination of C–H bonds

Can we mimic halogenase activity?



SyrB2

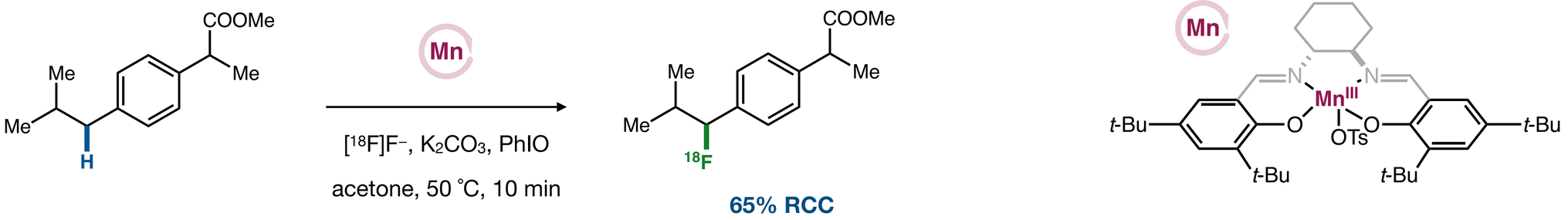


synthetic catalyst

hydroxylation often preferred over halogenation in catalytic non-heme systems

Radio fluorination of C–H bonds

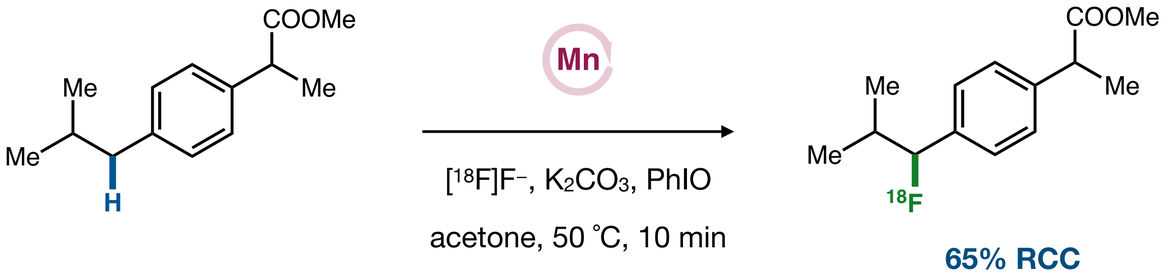
Groves (2024)



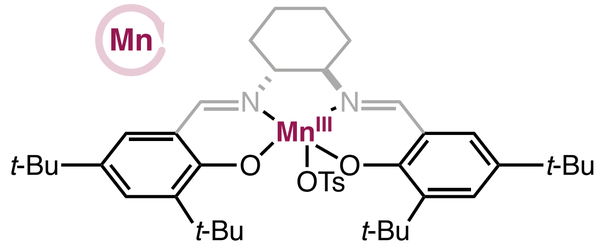
Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

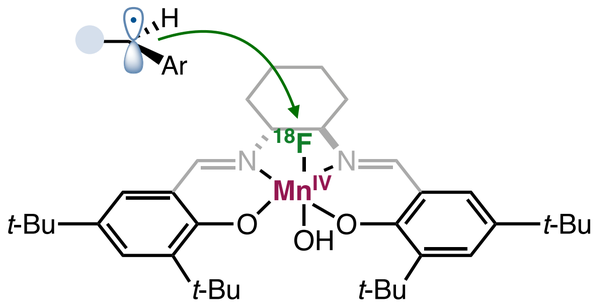
Radio fluorination of C–H bonds

Groves (2024)



65% RCC





lower TS for fluorine vs. oxygen rebound

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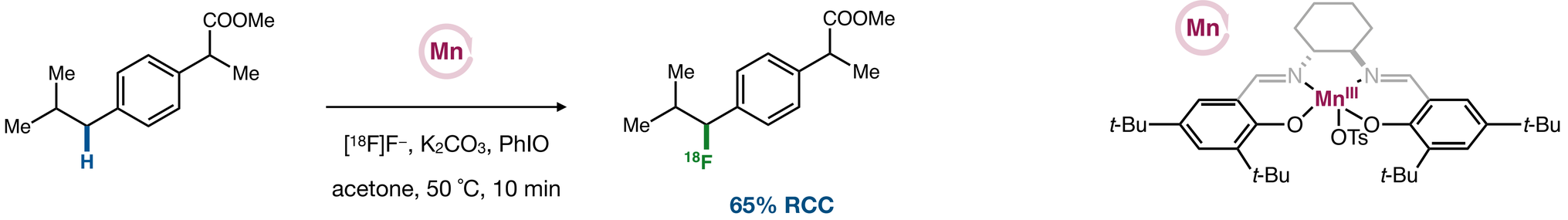
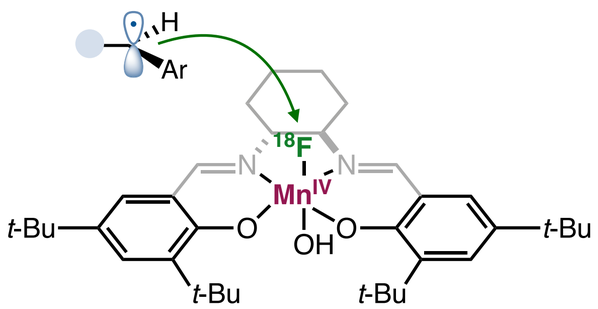
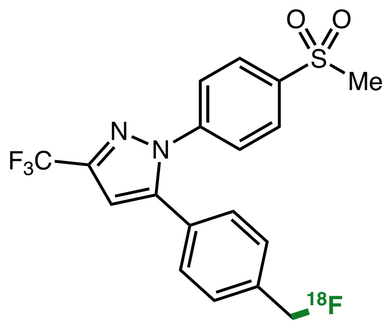
Radio fluorination of C–H bonds

Groves (2014)



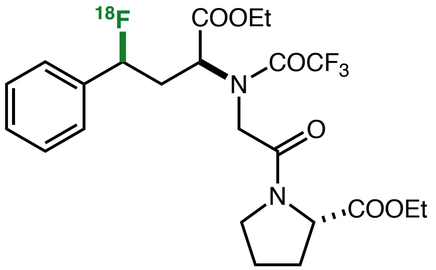


lower TS for fluorine vs. oxygen rebound



23% RCC

from celecoxib



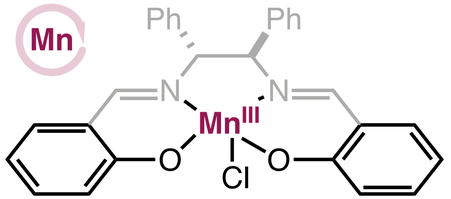
46% RCC

from enableprilat

Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 6842.

Electrochemically induced radical rebound

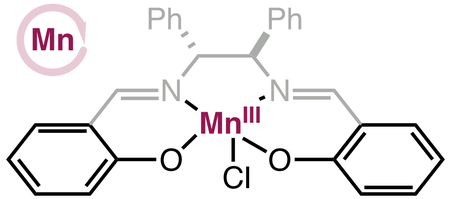
Ackermann (2018)

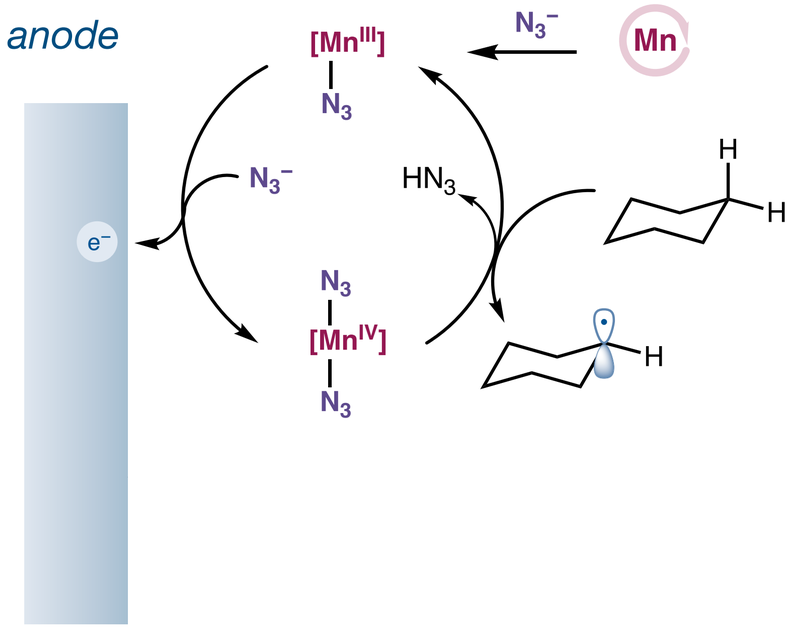


Meyer, T. H.; Samanta, R. C.; del Vecchio, A.; Ackermann, L. *Chem. Sci.* **2021,** *12*, 2890.

Electrochemically induced radical rebound

Ackermann (2018)





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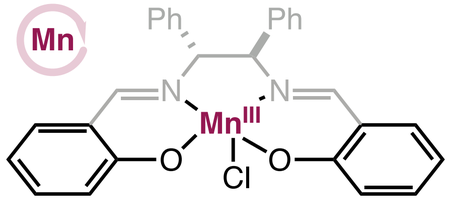

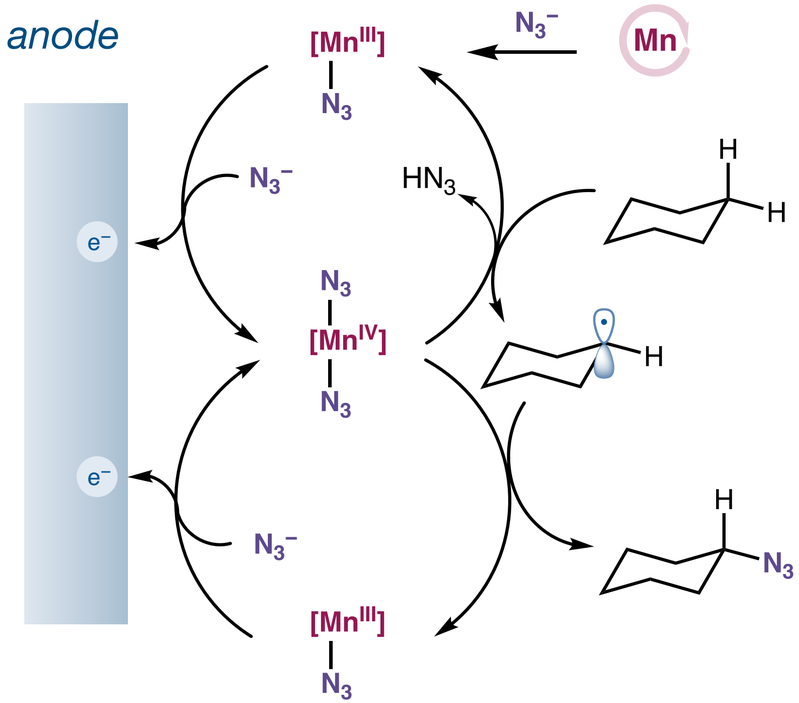

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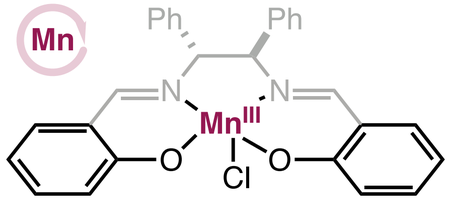
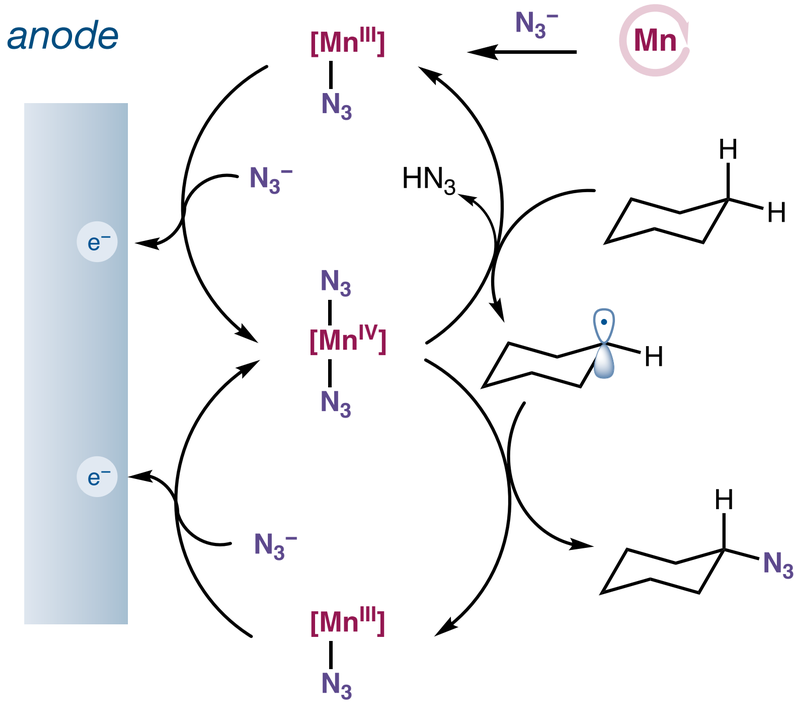
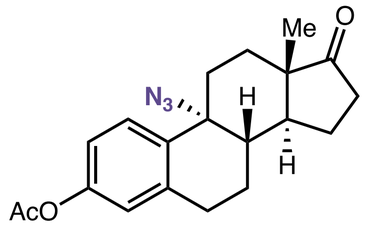
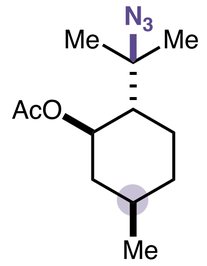






75% yield
from estrone



48% yield (r.r. = 3:1)
from (–)-menthol

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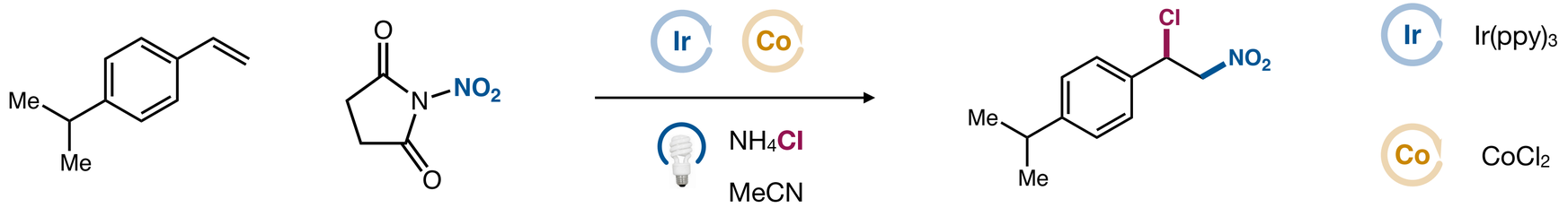
Radical ligand transfer by photoredox

Katayev (2023)



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Radical ligand transfer by photoredox

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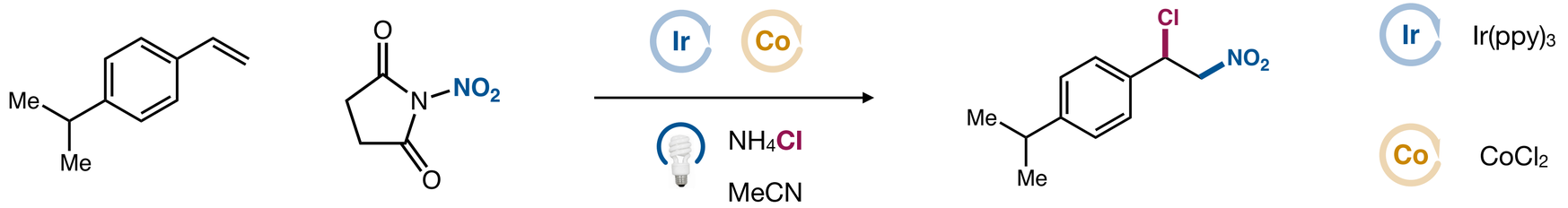
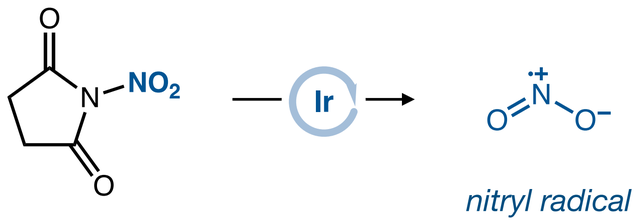


proposed mechanism



nitryl radical

Patra, S.; Giri, R.; Katayev, D. *ACS Catal.* **2023,** *13*, 16136.

Radical ligand transfer by photoredox

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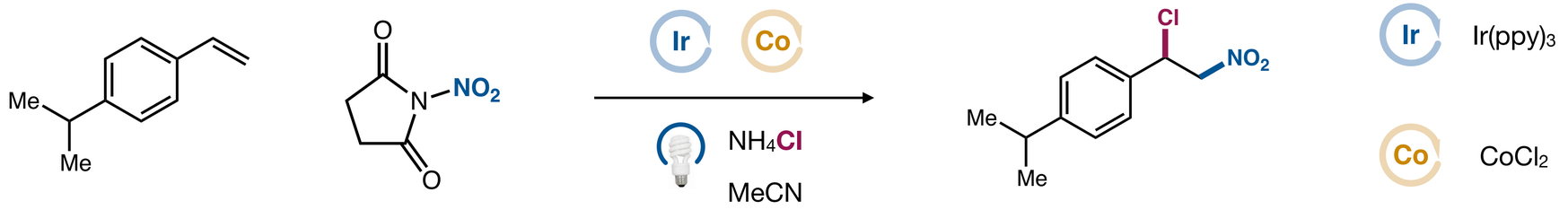
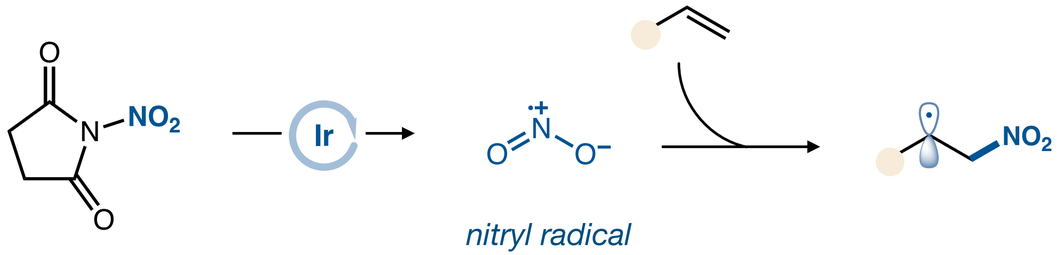


proposed mechanism



nitryl radical

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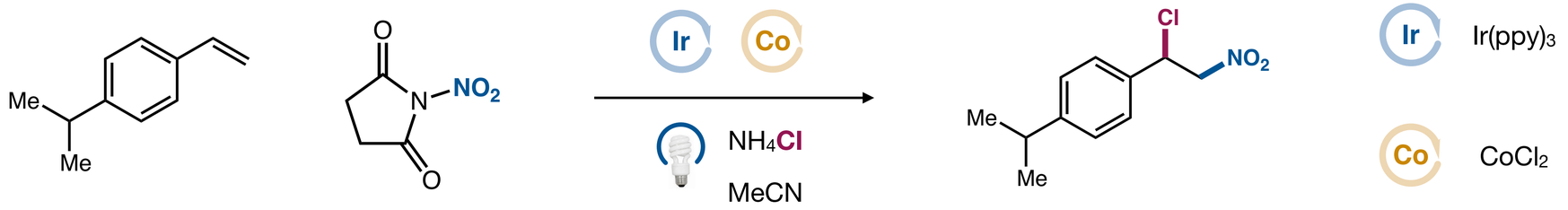
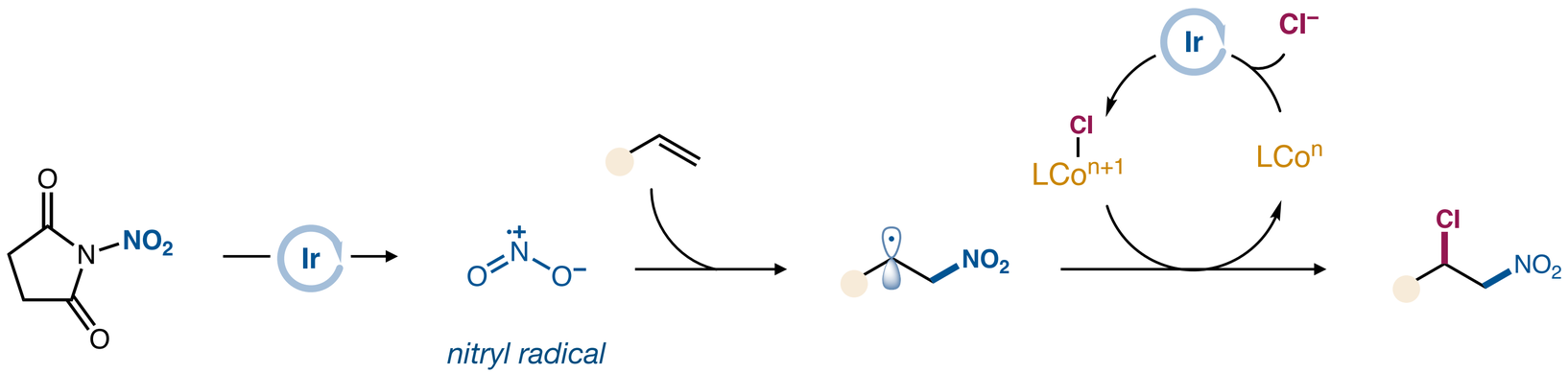
Katayev (2023)



proposed mechanism



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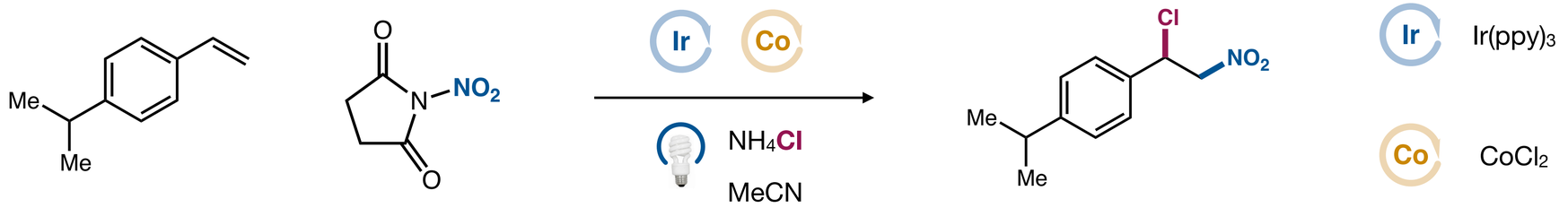
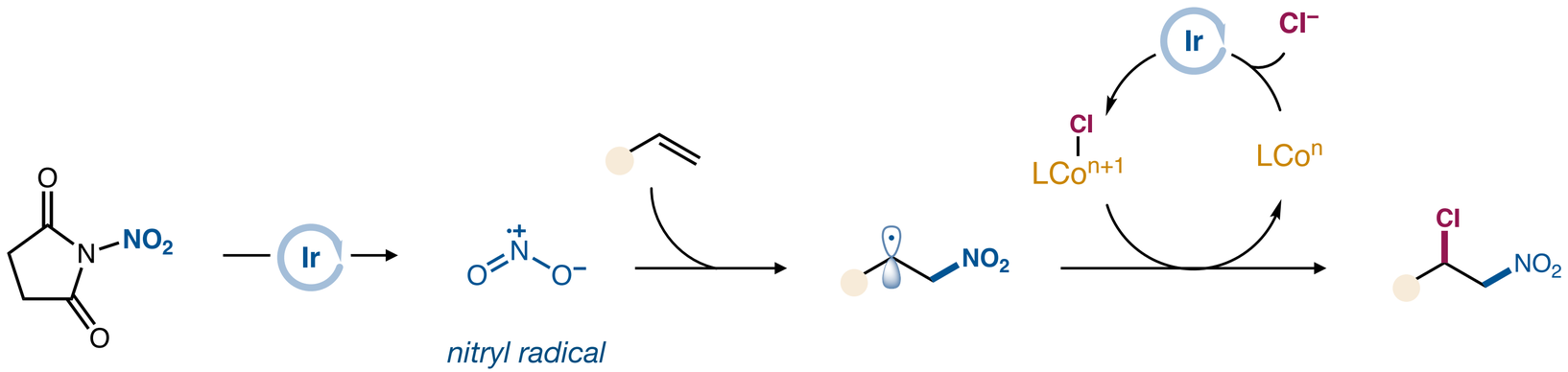


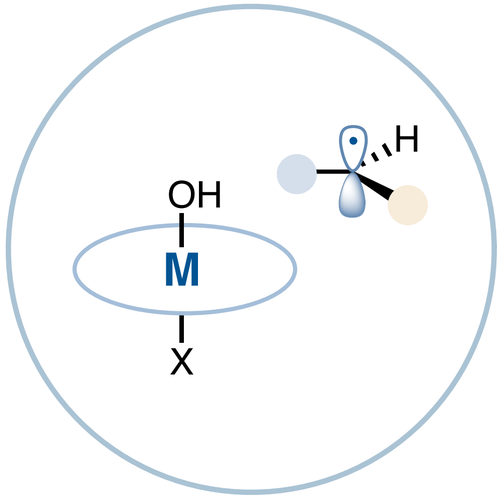
proposed mechanism



not radical rebound, but radical ligand transfer operative

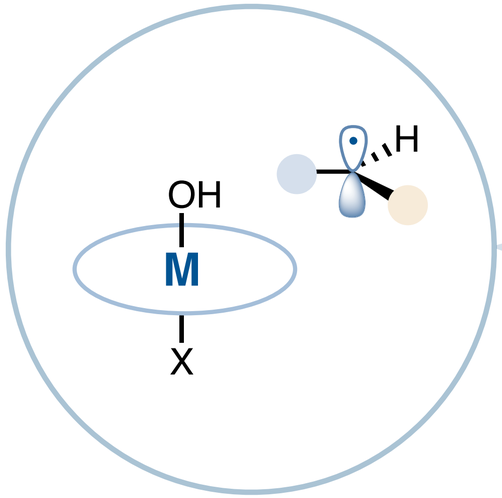
Patra, S.; Giri, R.; Katayev, D. *ACS Catal.* **2023,** *13*, 16136.

Radical rebound: bio-inspiredversatility and precision

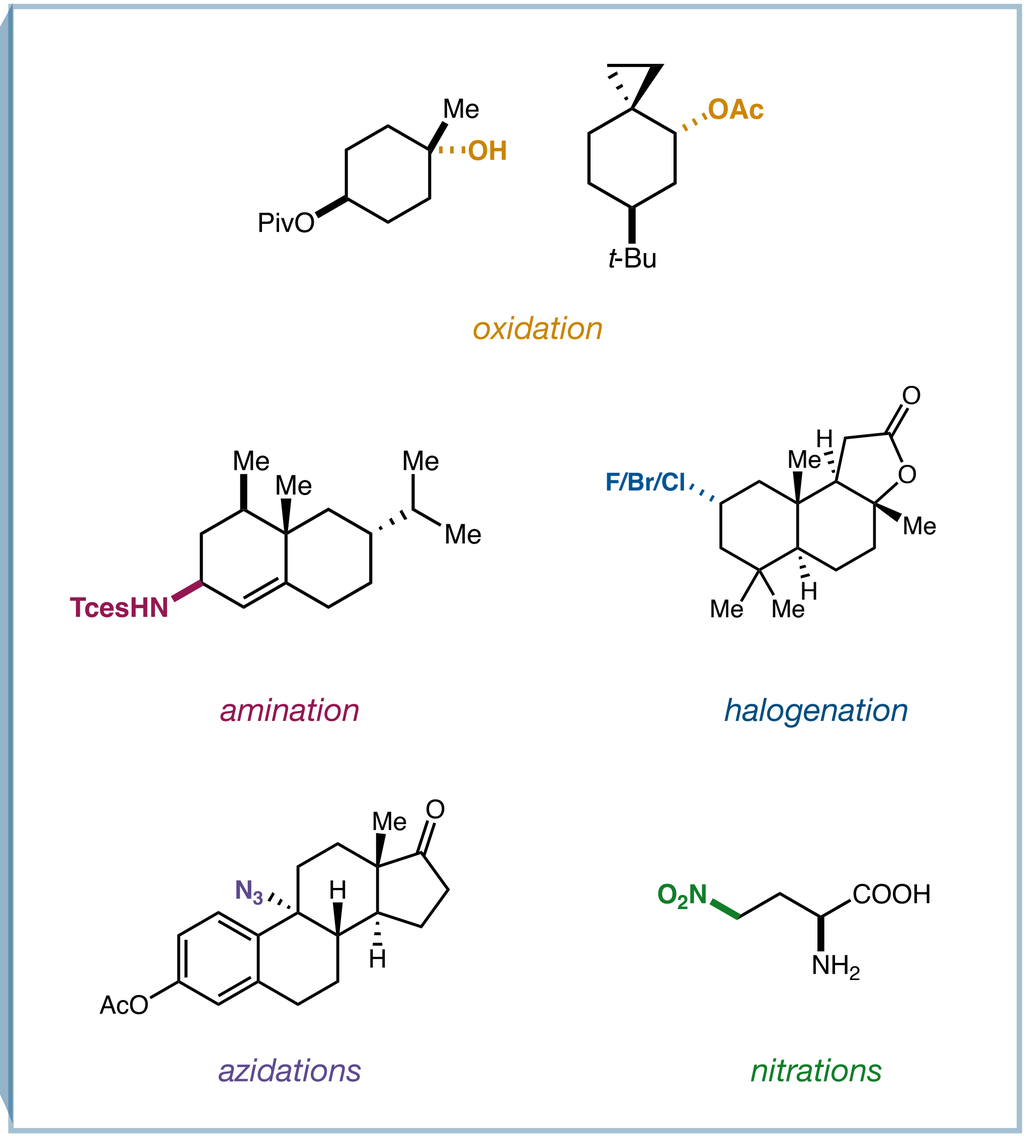


1 mechanism, multiple application

Radical rebound: bio-inspiredversatility and precision



1 mechanism, multiple application



Thank you!

Any Questions?