Dissertation

Homo- and Heterobimetallic Complexes of the PDIxCy ligand system; Synthesis, Characterization and Reactivity

Andreas Joseph Hofmann

Technische Universität München

Fachgebiet Bioanorganische Chemie

Homo- and Heterobimetallic Complexes of the PDIxCy ligand system; Synthesis, Characterization and Reactivity

Andreas Joseph Hofmann

Vollständiger Abdruck der von der Fakultät Chemie der Technischen Universität München zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften (Dr. rer. nat.)

genehmigten Dissertation.

Vorsitzende(r):   Prof. Dr. Roland A. Fischer

Prüfer der Dissertation: 1. Prof. Dr. Corinna R. Hess

                            2. Hon.-Prof. Dr. Richard W. Fischer

Die Dissertation wurde am 15.02.2021 bei der Technischen Universität München eingereicht und durch die Fakultät für Chemie am 30.03.2021 angenommen.

Die vorliegende Arbeit wurde im Fachgebiet Bioanorganische Chemie der Technischen Universität München in der Zeit von Juni 2017 bis Februar 2021 angefertigt.

Teile dieser Arbeit wurden bereits veröffentlicht:

Andreas J. Hofmann, Christian Jandl, Corinna R. Hess "Structural Differences and Redox Properties of Unsymmetric Diiron PDIxCy Complexes" *European Journal of Inorganic Chemistry* **2020**, *2020*, 499-505.

Andreas J. Hofmann, Lukas Niederegger, Corinna R. Hess "Neighbouring effects on catalytic epoxidation by Fe-cyclam in M_2-PDIxCy complexes" *Dalton Transactions* **2020**, *49*, 17642-17648.

Mein besonderer Dank gilt meiner Doktormutter

Frau Prof. Dr. Corinna R. Hess

für die Aufnahme in ihren Arbeitskreis und die Möglichkeit, an dieser interessanten Themenstellung zu arbeiten. Außerdem möchte ich Frau Prof. Hess für die wissenschaftliche Betreuung und das mir entgegengebrachte Vertrauen danken.

1.1 Danksagung

Mein Dank gilt:

Lukas Niederegger, der mich in der ganzen Zeit meiner Promotion unterstützt hat, für seine hilfreichen Tipps und sein großes Engagement, das er für jedes Thema aufbrachte. Seine Freude an der Forschung bereicherte den ganzen Arbeitskreis.

Dr. Ruth Haas, welche mich in den ersten Monaten unter ihre Fittiche nahm, für ihre Vorarbeit in diesem Thema und für zahlreiche Tipps auch nach Verlassen unseres Arbeitskreises.

Allen Mitarbeitern des AK Hess, mit denen ich stets die Mittagspause genoss und die meinen Gesang im Labor ertragen mussten. Vielen Dank für die gute Zusammenarbeit.

Stuart Boyce und Ceren Tok, welche stets bemüht waren mein Englisch zu verbessern.

Meinen Bacheloranten, Praktikanten und Masteranten, Ümit, Matthias, Tjark, Mykhaylo, Kara und Julian, welche sich erfolgreich in dieses schwierige Thema eingearbeitet haben und gute Arbeit leisteten.

Dr. Christian Jandl und Dr. Alexander Pöthig, für die Unterweisungen in der Kristallographie und das Beantworten meiner Fragen diesbezüglich.

Allen Mitarbeitern der anderen Lehrstühle, sowie den Technikern der TUM, welche zu zahlreich wären, um sie alle zu nennen, ohne die Gefahr jemanden zu vergessen. Vielen Dank für die Einweisungen, Messungen und Unterstützung in den letzten Jahren.

Deutscher Abstract

Diese Arbeit handelt über das Ligandsystem PDIxCy (PDI: Pyridin diimin, x: linker, Cy: Cyclam) und seine homo- und heterobimetallischen Komplexe. Das zuvor entworfene PDIpCy (p: Propyl) wurde durch Verkürzen der Linkerlänge zum PDIeCy (e: Ethyl) modifiziert. Mehrere PDIxCy Komplexe wurden synthetisiert und auf ihre spektroskopischen, strukturellen und redoxaktiven Eigenschaften untersucht. Des Weiteren wurden sie auf ihre katalytische Aktivität in Oxidationsreaktionen getestet.

Auswirkungen durch die modifizierte Linkerlänge auf die Komplexe wurden anhand der bimetallischen Eisenkomplexe beider Liganden untersucht. Hierbei zeigten die PDIxCy Komplexe simultane Resultate in ihren spektroskopischen und redoxaktiven Eigenschaften. Beide Systeme zeigten Temperaturabhängigkeit sowohl in ihren elektronischen Spektren, als auch in ihrer magnetischen Suszeptibilität.

Strukturelle Unterschiede durch den verkürzten Linker, wie die Ausbildung eines verbrückenden Triflates zwischen den Eisenatomen des PDIeCy Komplexes und einem verkürzten Metall−Metall Abstand von 5.6 Å anstatt 8.0 Å, wurden mittels Kristallstrukturen gezeigt. Anhand ^{19}F-NMR konnte die Existenz der verbrückten Triflate auch in nicht-koordinierenden Lösemittel bewiesen werden.

Des Weiteren konnte die bereits für reduzierte PDIpCy Komplexe bewiesene Ladungstrennung innerhalb des Komplexes bestätigt werden, jedoch erstmals an einem zweifach reduzierten Komplex. Hierbei ergab die chemisch oder elektrochemisch zweifach reduzierte Spezies des dinuklearen Eisen PDIeCy Komplexes, einen zweivalenten Komplex mit einem formalen Fe^0 im PDI-Teil und einem Fe^{2+} in der Cy-Seite.

Im zweiten Teil dieser Arbeit wurden weitere homo- und heterobimetallische Komplexe des PDIeCy Liganden synthetisiert. Strukturelle Untersuchungen verifizierten die Ausbildung der Brückentriflate unter Verwendung des kürzeren Linkers. Auch konnte für heterobimetallische Komplexe eine Methode zur gezielten Positionierung der unterschiedlichen Metalle in die jeweiligen Bindungsstellen des Liganden entwickelt werden. Mittels selektiver Metallierung konnten so gezielt die Stereoisomeren der Eisen-Zink PDIeCy Komplexe synthetisiert werden. Die unterschiedlichen Positionierungen der Metalle äußerten sich in ihren spektroskopischen Eigenschaften, wie auch in der katalytischen Aktivität für die Epoxidation von Olefinen. So wurde gezeigt, dass nur Komplexe mit einem im Cylam gebundenen Eisenatom eine katalytische Aktivität aufweisen. Als aktive Spezies wird ein Fe(IV)−oxo Cylam vermutet, welches durch Zugabe von Wasserstoffperoxid zu den $[Zn_{PDI}Fe_{Cy}(PDIeCy)(OTf)_4]$ bei -80 °C beobachtet wurde. Der Einfluss durch das zweite, in dem PDI gebundene Metall konnte für α,β-ungesättigte Ketone nachgewiesen werden. So wurden unter gleichen Bedingungen mit den bimetallischen PDIxCy Komplexen bessere Umsätze erzielt als mit dem mononuklearen Eisen Cyclam Komplex. Aufgrund nur geringer Abweichungen zwischen dem mononuklearen und der dinuklearen Komplexe in ihrer Aktivität für Olefinoxidation in Abwesenheit einer elektronenziehenden Carboxyl-Gruppe am Olefin postulieren wir einen aktivitätssteigernden Einfluss der PDI-Seite durch Aktivierung des Substrates in räumlicher Nähe zur aktiven Eisen Cyclam Seite.

English Abstract

This work focuses on the ligand system PDIxCy (PDI: pyridine diimine, x: linker, Cy: cyclam) and its homo- and heterobimetallic complexes. The previously designed PDIpCy (p: propyl) was modified by shortening the linker length to the PDIeCy (e: ethyl). Complexes from both, PDIpCy and PDIeCy were synthesized and their spectroscopic, structural and redox properties, such as their catalytic activity in oxidation reactions were characterized.

For the investigation of how the modified linker length affects the system the two homobimetallic iron complexes of both ligands were compared to each other. Similar results were observed in both cases for their spectroscopic and redox properties. Both complexes exhibit temperature dependency in their electronic spectra and magnetic susceptibility.

Differences between the complexes were observed in their molecular structure in the form of a bridging μ-triflate between the metal ions, which was only present in the PDIeCy complex. The ethyl linker further causes a smaller metal-to-metal distance of 5.6 Å compared to 8.0 Å using the propyl linker. Based on ^{19}F-NMR it was verified that the μ-triflate also persists in non-coordinating solvents.

Similar to the PDIpCy complexes, charge separated species were generated with complexes using the PDIeCy ligand. The dinuclear PDIeCy complex was two-electron reduced by chemical and electrochemical methods. The electronic spectra indicated that reduction occurred at the PDI site. Thus, the reduced complex contains a formal PDI-Fe^0 beside an Fe^{2+} in the cyclam site.

For the second part of this work other homo- and heterobimetallic complexes were synthesized with the PDIeCy ligand. The series demonstrated that the bridging μ-

triflate is a typical structural feature of PDIeCy complexes. The selective positioning of metals into the binding sites of the PDIeCy could be achieved. Controlled selective metalation enables the synthesis of the respective stereoisomers of iron-zinc complexes. Variation of the metal positions led to differences in their spectroscopic behavior and in the catalytic activity with respect to olefin epoxidation. Herein, we demonstrate that only complexes containing iron in the cyclam site possess catalytic activity towards epoxidation. We propose an iron(IV)-oxo cyclam as active species, which we obtained in the treatment of [$Zn_{PDI}Fe_{Cy}$(PDIeCy)$(OTf)_4$] with hydrogen peroxide at -80 °C. An influence by the PDI bound metal was observed for the epoxidation of α,β-unsaturated ketones. Our dinuclear iron complexes possess a higher conversion of enones to epoxides than the monometallic iron cyclam complex under the same conditions.

Because of the similar results obtained in the reactivity of mono- and dinuclear complexes toward olefins without the electron deficient carboxyl group, and the lack of activity for complexes with a zinc cyclam, we propose that the enhanced reactivity toward enones is caused by the PDI-site, which activates the enones in close proximity of the active iron.

List of Abbreviations

ADO	aldehyde deformylating oxygenase
AMO	alkene monooxygenase
Ar	Aryl
Cy	Cyclam
DCM	dichlormethane
DFT	density functional theory
e	ethyl
EPR	electron paramagnetic resonance
eq.	equivalent
EXAFS	extended X-ray absorption fine-structure spectroscopy
FDH	formate dehydrogenase
h	hour
H_2pydic	pyridine-2,6-dicarboxylic acid
H_4MPTP	methylene tetrahydromethanopterin pathway
HAA	hydrogen atom abstraction
HAT	hydrogen atom transfer
His	histidine
HRP	horseradish peroxidase
m/z	mass-to-charge ratio
MDH	methanol dehydrogenase
Me_3NTB	tris((*N*-methylbenzimidazol-2-yl)methyl)amine)
MeCN	acetonitrile
MMO	methane monooxygenase
M^{n+}	metal ions
MS	mass spectroscopy
nm	nanometer
NMR	nuclear magnetic resonance
p	propyl

P450	cytochromes P450
PDI	pyridine diimine
PhIO	iodosylbenzene
pMMO	particulate methane monooxygenase
Por	porphyrin
PPh_3	triphenylphosphane
PQQ	pyrroloquinoline quinone
sMMO	soluble methane monooxygenase
sPhIO	soluble iodosylbenzene
SQUID	superconducting quantum interference device
TauD	Taurine α-KG dioxygenase
TauDJ	active iron(IV)−oxo species of Taurine α-KG dioxygenase
TMC	1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane
TMP	meso-tetramesityl porphinate anion
ToMO	toluene/o-xylene monooxygenase
TON	turnover number
TPA*	tris((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amine)
TQA	tris(2-quinolyl-methyl)amine)
UV/Vis	ultraviolet-visible light

TABLE OF CONTENTS

1 INTRODUCTION

Life, in even its simplest form, has been estimated to have originated 3.5 billion years ago.[1] Since then, all species have appeared to follow, to a certain degree, a path of evolution supported by the concept of natural selection. This path, guided by nature, has provided the required chemically and biologically optimized materials.[2] Our understanding of the first step, which connects biology with the synthetic chemistry, can be traced to 200 years ago. Until 1820 the theory of vis vitalis (lat. vital force) was common, postulating that organic compounds could not be produced without this force. In 1828 Friedrich Wöhler was able to produce urea by treating silver cyanate with ammonium chloride.[3] This successful synthesis of urea was regarded as the first organic compound artificially produced from inorganic starting materials, without the involvement of living organisms. This was evidence enough to discredit the theory that chemicals of living organisms are fundamentally different from those of inanimate matter.[3]
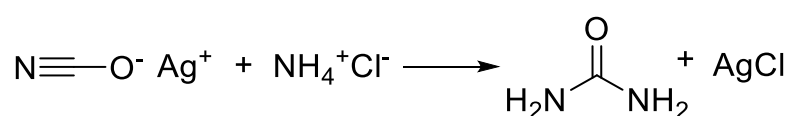
Scheme 1   Synthesis of urea from inorganic starting materials, without the involvement of living organism.[3]

This discovery is widely regarded as the birth of modern biochemistry. Five years later Payen and Persoz isolated the first enzyme, called diastase, and went on to formulate some basic principles of enzyme action.[4] However, initial insight into the mechanisms of such complex systems was only acquired in 1894 when Emil Fischer introduced the lock-key-principle.[5] As interest in understanding the mechanistic pathways of enzymes grew, so did that in mimicking these complex systems, spawning the field of

biomimicry.[6-12] Traditionally, biomimicry concerns novel structural and functional breakthrough technologies that are inspired by nature. One example is given by the selective oxidation of organic molecules. This reaction is an essential step of many biological processes and further is important for industrial processes.[13-14] Epoxides represent a particularly useful class of intermediates in this field, since they are valuable for the synthesis of fine chemicals and pharmaceuticals due to the multiplicity of modifications they can undergo (Figure 1).[15-20]
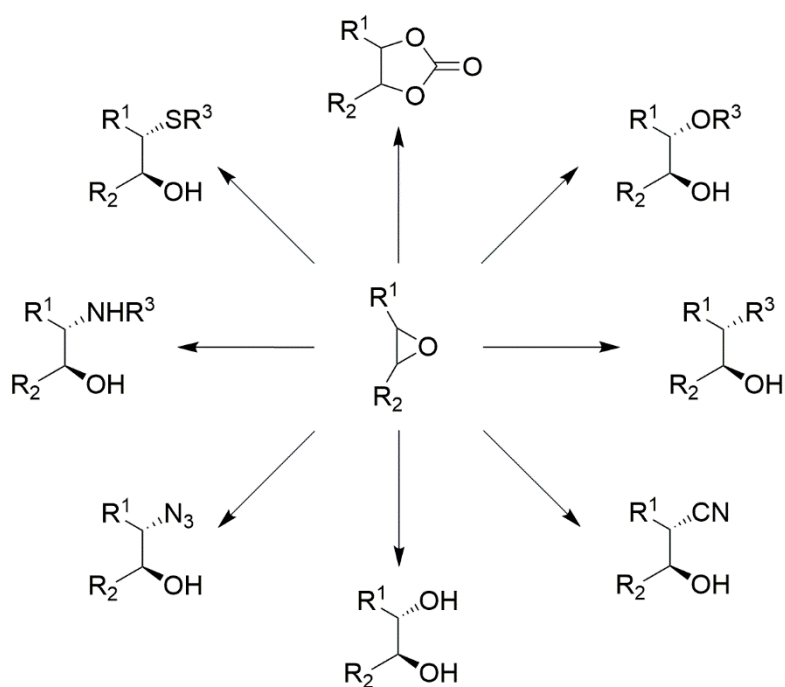

Figure 1   Examples of products that can be derived from epoxides.[18]

Therefore, oxygen activating enzymes were studied to understand their mechanism and to likewise develop synthetic complexes with high selectivity and efficiency in catalysis.

1.1 Enzymes for oxygen activation

The oxygen activation mechanisms for hydrocarbon oxidations by metalloenzymes have fascinated chemists and biochemists since Mason and Hayaishi´s independently published papers in the *Journal of the American Chemical Society* in 1955, which established the important role O_2 plays in oxidative metabolism.[21-22] The most commonly found metal at the active site of metalloenzymes that participate in metabolic O_2 activation and oxygenation reactions is iron, because of its high abundance, its inherent electronic properties and accessible redox potentials.[23-24]
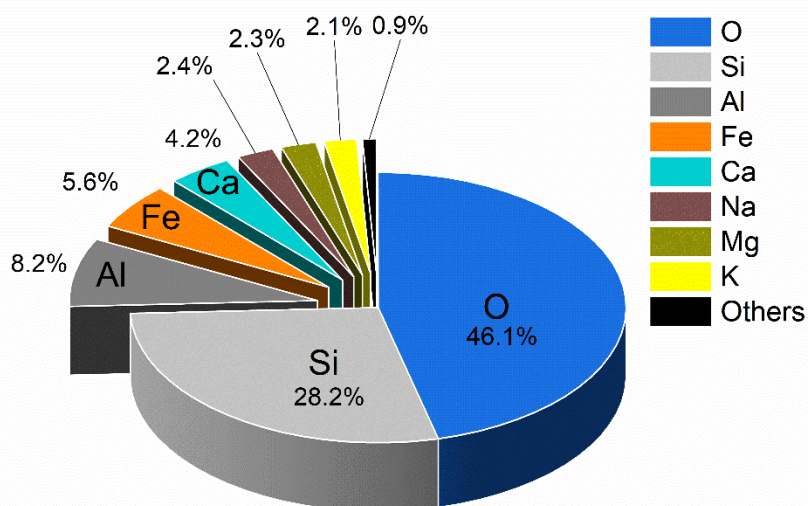

Figure 2   Abundance of elements in the geosphere.[25]

The most extensively studied oxygen-activating iron enzymes are cytochromes P450, which play a key role in oxidative transformations in a variety of organisms and constitute powerful catalysts in the oxidation of several substrates including alkenes, alkanes or aromatic compounds with molecular oxygen.[26-30] Another well-studied enzyme is the horseradish peroxidase (HRP), which catalyze a wide variety of organic and inorganic compounds utilizes hydrogen peroxide.[31] Similar to P450, HRP is a heme enzyme, characterized by the presence of an iron ion coordinated to a porphyrin or a closely related system which in turn acts as a tetradentate ligand, with one or two

additional axial ligands.[32] In contrast to heme sites where the porphyrin macrocycle leaves only one axial position for oxygen activation, the non-heme sites have additional, exchangeable positions that can also allow the possibility of substrate binding to the iron center.[33] Furthermore, other coordination modes for oxygen activation are possible.[10]
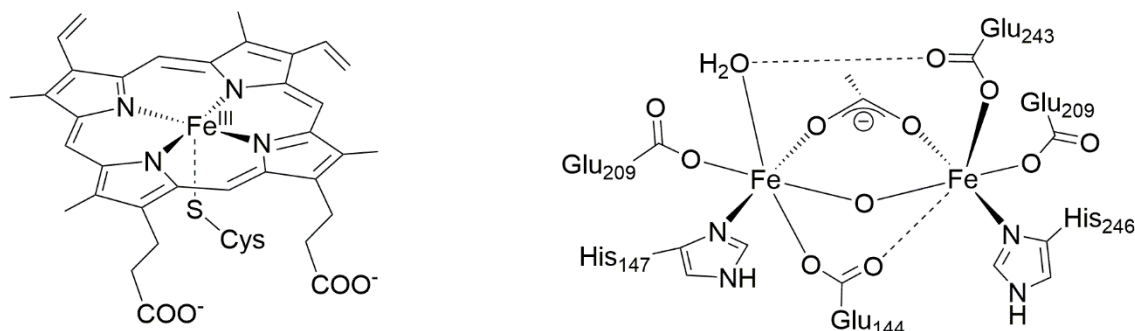

Figure 3   Representative structures for heme and non-heme active sites. Left: cytochrome P450 (heme)[26, 34] Right: methane monooxygenases (non-heme)[35]

Despite the size and mechanistic variety of mononuclear non-heme iron enzymes, the majority presents a common structural arrangement. There the iron center is octahedral coordinated by two histidines (His) and a carboxyl group, forming the characteristic 2-His/1-Carboxylate facial triad.[33] Ligands in non-heme enzymes, such as histidine, carboxylate and H_2O are also much less covalently ligated, with more limited π-interactions with the iron compared to porphyrin, which can greatly modify the electronic structure of the active site and, hence, its activation of oxygen.[36]

Typically, these enzymes contain mono- or binuclear iron sites and catalyze a variety of oxidation reactions including hydrogen atom abstraction (HAA) for hydroxylation, halogenation, desaturation, peroxidation, epoxidations, ring closure, electrophilic aromatic substitution for mono or dioxygenation, or even phosphate-bond hydrolysis.[9, 37-46]

4

Rieske oxygenases are examples for mononuclear non-heme enzyme. They catalyze the cis-dihydroxylation of arenes to cis-dihydrodiol products.[46] In the last decade, Rieske oxygenases have also been shown to play important roles in natural product biosynthesis by catalyzing oxidative carbocyclisation, N-oxygenation, C-hydroxylation and C–C desaturation.[46] Another example for a mononuclear non-heme iron enzyme is lipoxygenase, which catalyzes the addition of oxygen to polyunsaturated fatty acids to form hydroperoxides.[47] Lipoxygenases have food-related applications in bread making and aroma production.[48]

As mentioned before non-heme enzymes can also contain binuclear iron sites. Commonly they feature histidine and carboxylate as bridging ligands.[41, 49] Enzymes, such as soluble methane monooxygenase (sMMO)[9, 38-39, 45], alkene monooxygenase (AMO)[40], aldehyde deformylating oxygenase (ADO)[41] and toluene/o-xylene monooxygenase (ToMO)[42] are examples of non-heme dinuclear iron moieties in biology. They are involved in numerous metabolic functions but also catalyze a variety of chemical reactions, which are relevant for industry. Table 1 shows heme and non-heme mono- and binuclear iron enzymes with their reactions and proposed biological functions. In particular, the methane monooxygenases (MMO), the most studied dinuclear enzymes, are responsible for both the methane metabolism and carbon fixation in methanotrophic bacteria.[35] The diiron center catalyzes the conversion of methane to methanol using dioxygen as oxidant.[9, 38-39, 45] Its ability to oxidize a wide range of hydrocarbons including $C_1 − C_8$ n-alkanes, alkenes and molecules such as benzene, styrene, naphthalene, ethylbenzene, and cyclohexane,[50-55] makes it attractive for synthetic applications.[54] Methanotrophic bacteria using the unique isoenzymes of MMO (particulate methane monooxygenase (pMMO); sMMO, soluble methane monooxygenase (sMMO)), can produce biomass in the form of formaldehyde

or formate by utilizing C_1 sources more reduced than formic acid as sources of carbon and energy.[56-59] In this regard MMOs have attracted intense attention in recent years as potential targets for new gas-to-liquid methane bioconversion processes (see Figure 4).[54]
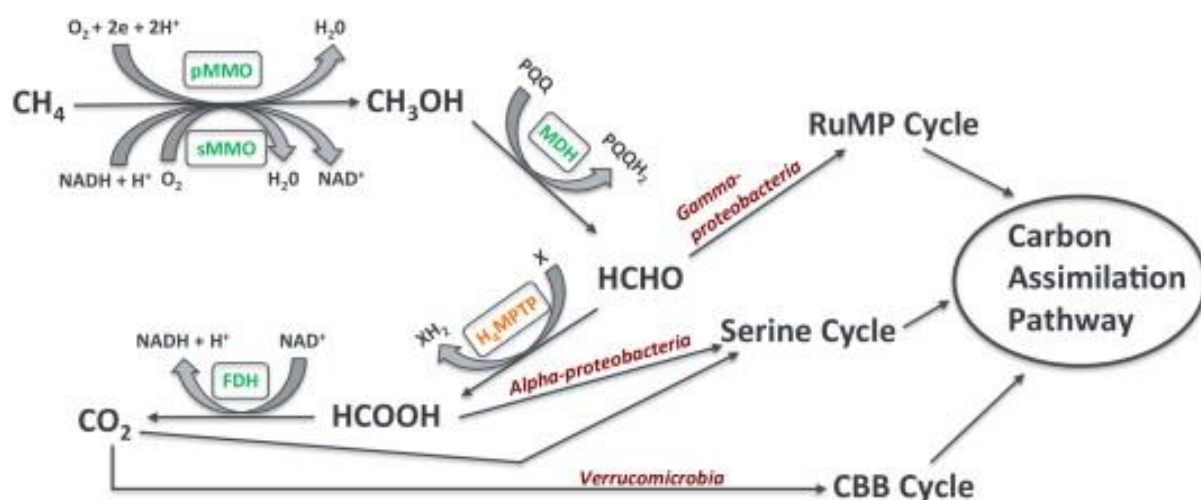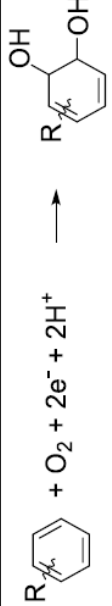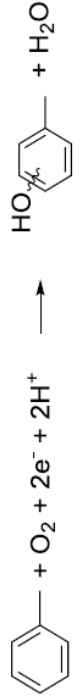

Figure 4   Simplified pathway for the oxidation of methane and assimilation of formaldehyde. Major enzymes are presented in green. Abbreviations: PQQ, pyrroloquinoline quinone; MDH, methanol dehydrogenase; H_4MPTP, methylene tetrahydromethanopterin pathway; FDH, formate dehydrogenase. Reprint with permission.[54]

Non-heme diiron enzymes are also of industrial interest due to their involvement in important metabolic pathways. For example, AMO constitutes the first step in alkene metabolism through which it catalyzes the epoxidation of aliphatic alkenes. AMO is also known to catalyze the oxidation of $C_3 - C_4$ chain length 1- and 2-alkenes, styrenes and even chloroalkenes.[60-61] The tendency to form predominantly R enantiomers has attracted increasing attention in recent years, since optically active epoxides are of interest in the development of pharmaceutical compounds.[62-63] Therefore synthetic complexes bearing chiral backbones were investigated to enhance the enantioselectivity.[64-68]

Table 1   Examples of oxygen activating enzymes.

Enzyme	Active center	Catalytic reaction	Metabolism role
Cytochrome P450	Heme iron	$RH + O_2 + 2e^- + 2H^+ \longrightarrow ROH + H_2O$	Fat metabolism
Horseradish peroxidase	Heme iron	$2RH + H_2O_2 \longrightarrow 2R^{\bullet} + 2H_2O$	Detoxification of H_2O_2
Rieske oxygenase	Non-heme iron	(aromatic ring)$R \cdots + O_2 + 2e^- + 2H^+ \longrightarrow$ (cyclohexadiene-diol with OH, OH)	Hydrocarbon biodegradation
Lipoxygenase	Non-heme iron	(diene R/R') $+ O_2 \longrightarrow$ (HOO-diene R/R')	Fat metabolism
methane monooxygenase	Non-heme diiron	$CH_4 + O_2 + 2e^- + 2H^+ \longrightarrow CH_3OH + H_2O$	Carbon fixation, Methane metabolism
alkene monooxygenase	Non-heme diiron	$RCH{=}CH_2 + O_2 + 2e^- + 2H^+ \longrightarrow$ (R-epoxide) $+ H_2O$	Alkene metabolism
aldehyde deformylating oxygenase	Non-heme diiron	$R{-}C(O)H + O_2 + 4e^- + 3H^+ \longrightarrow R{-}H +$ (formate) $+ H_2O$	Alkane metabolism
toluene/o-xylene monooxygenase	Non-heme diiron	(benzene ring) $+ O_2 + 2e^- + 2H^+ \longrightarrow$ (phenol, HO-) $+ H_2O$	Toluene, o-xylene hydroxylation

1.2 Biomimicking catalyst for epoxidation

Since epoxides can undergo a variety of modifications, they are effective intermediates for the synthesis of fine chemicals and pharmaceuticals.[15-20, 62-63] Methodologies for selective oxidation of alkane C−H bonds are numerous because they enable novel straightforward synthetic strategies.[69-71] This, and the rich chemistry of the iron oxidases and oxygenases, inspired the development of hydrocarbon catalysts in the last decades.[23, 72-77] The aim is to understand the high activities and selectivities of enzymes and to be able to develop environmentally friendly and efficient systems using this knowledge. Key features such as mild activation conditions, found in biological systems are also a target for synthetic catalysts, because less decomposition occurs at lower temperature. Regarding to industrial application a lot of money can be saved through lower energy consumption. Also the choice of oxidant plays a key role, since oxygen and hydrogen peroxide generate no environmentally unfriendly side products and are easier to produce than alkyl peroxides.[78] Therefore, this exposes a key feature for the development of industrial catalysts regarding green chemistry and low cost production. Even organometallic compounds, containing palladium, rhodium, iridium and ruthenium are well established catalysts for a broad spectrum of reactions, the precious metals bear several disadvantages like toxicity and rareness leading to high costs, which make them unattractive for large scale applications in industry.[24, 79] The low cost of iron and its non-toxicity makes iron not only relevant for biology but also for biomimicry catalysts.[24, 80] As an inexpensive and relatively nontoxic metal, iron meets the economic and environment requirements the community requests.[24]

The first application of iron in oxidation chemistry has already been known for more than a century. The oxidation of tartaric acid in the presence of iron salts was described by Henry Fenton.[81] Decades later Haber and Weiss were able to identify the hydroxyl

radical as the actual oxidant for Fenton-type reactions, generated by the reaction of peroxide with iron cations.[82]

$$Fe^{II} + H_2O_2 \longrightarrow Fe^{III} + OH^- + \dot{O}H$$

$$Fe^{III} + H_2O_2 \longrightarrow Fe^{II} + \dot{O}OH + H^+$$

$$\dot{O}H + H_2O_2 \longrightarrow H_2O + \dot{O}OH$$

$$Fe^{II} + \dot{O}H \longrightarrow Fe^{III} + OH^-$$

Scheme 2   Fenton-type reaction of hydrogen peroxide in the presence of iron cations.[82]

Nowadays this kind of oxidation process finds applications in water cleaning among other purposes.[83] Because Fenton-type radical reactions result in a drastic loss in selectivity, researchers aim to develop catalyst that can suppress such processes and perform selective oxidation reactions.[23, 84]

The first biomimetic iron catalyst exhibiting selective oxidation was published in 1979 by Groves *et al.*, mimicking the enzyme P450.[85] The heme iron catalyst was able to transfer an oxygen from to cyclohexene but with a low selectivity towards the epoxide. Only 55% of the consumed PhIO was used to generate the epoxide and 15% led to formation of cyclohexenol. Higher selectivities were obtained using stilbene where a conversion of even 82% to the respective epoxide was achieved. Metalloporphyrins without protecting steric groups was discarded due to their very fast oxidative degradation.[86] Modification of heme iron catalysts was carried out on the meso position of the porphyrin sites. Functionalization of the meso position with bulky groups hindered the self-oxidation of the highly reactive position. The use of steric groups also inhibits the formation of the catalytically inactive oxo-bridged dimer.[87] Further modifications were made to influence the electronic properties of the porphyrin by

introducing electron withdrawing groups, such as halides[87-89] or nitro groups,[90] to the ligand.
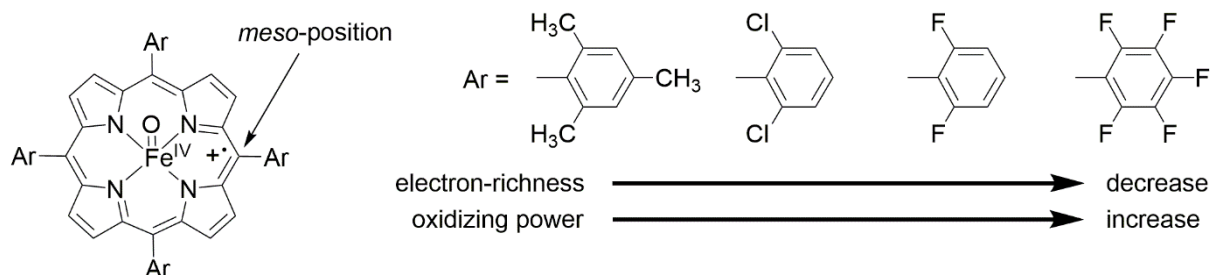

Figure 5 Stereo-electronic influence on the catalytic reaction progression via porphyrin modification on its meso position.[89]

Because non-heme complexes reveal more possibilities for their ligand structure than heme and related systems, the field of non-heme iron complexes is considerably broader. Furthermore, the inherent modular nature of non-heme iron complexes enables a simple manipulation of their structure, enabling their fine-tuning for different oxidation reactions. In synthetic metal complexes, the active oxygen-transferring intermediates can be more stable than in their enzymatic prototypes, which enables more detailed insight to the reactivity of active species and clarification regarding their role in catalysis.[91] Unravelling the key features of the mechanisms of iron oxygenases due to synthetic iron systems advances the synthetic strategy for biomimicking catalyst itself. Substantial improvements with respect to the breadth of activities, yields and selectivities of bioinspired mononuclear non-heme complexes were made, demonstrating the potential for oxidative catalysis at a single metal center.[11, 23, 73-77] In 1991 Nam and coworkers reported the catalytic activity of olefin epoxidation by iron complexes with the tetratendate ligand cyclam (cyclam = 1,4,8,11-tetraazacyclotetradecane) and related ligands.[92] Their work showcased high turnover

numbers (TON; up to 20), high percent yields based on hydrogen peroxide, stability against water, stereospecifity and only small amounts of side products.
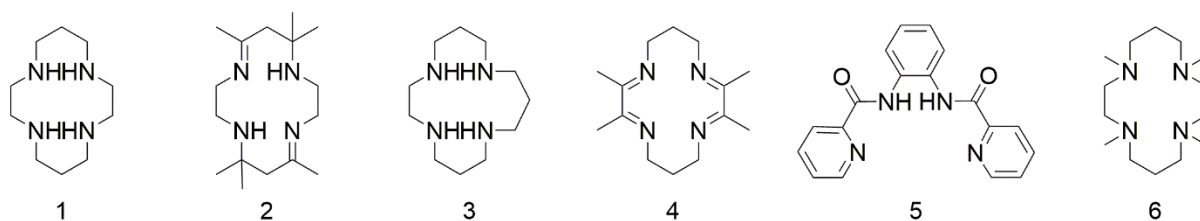

Figure 6   Ligands for iron complexes bearing firstly catalytic activities towards olefin epoxidation with high TONs, reported by Nam *et al.*[92]

The highest TON was achieved by complexes of cyclam itself, while the complexes with the ligand 2 - 4 only achieved TONs of 10, 5 and 2 respectively. With ligands 5 and 6 no epoxidation was observed, suggesting a participation of N−H in the catalysis of iron cyclam. Nowadays, iron complexes with tetratendate ligands are still regarded as valuable functional models of natural non-heme oxygenases. They form a large group of efficient and selective catalysts, mediating highly challenging reactions such as stereospecific hydroxylation and (cis)- dihydroxylation and the epoxidation of olefins with hydrogen peroxide.[23, 91, 93-99]

The most relevant epoxidation systems regarding applicability are simple systems that utilize pyridine-2,6-dicarboxylic acid (H_2pydic).[100-103] A variety of olefins could be epoxidised by hydrogen peroxide and complex generated in situ from H_2pydic and different amines (pyrrolidine, benzylamines, imidazoles) or formamidines with $FeCl_3 \cdot 6H_2O$, under mild conditions.[100-103] Further studies showed that complexes achieved by the combination of chiral diamines with H_2pydic and $FeCl_3 \cdot 6H_2O$ are able to catalyze asymmetric epoxidation. The use of the respective diamine enantiomer results in the opposite asymmetric epoxides.[104-105]

11

Asymmetric epoxidation of olefins is a very interesting reaction in synthetic organic chemistry, because chiral epoxides can be easily converted to further chiral products and building blocks.[15-20] Therefore, new iron complexes bearing chiral backbones were investigated to enhance the enantioselectivity.[62, 67-68] Sun *et al.* discovered that the enantioselective induction of their complexes can be enhance by using carboxylic acids. Bulkier acids provide higher enantioselectivities for diverse substrates. Although they achieve high conversion, the substrate scope for high enantioselectivity is limited to chalcone and its derivatives.[67]
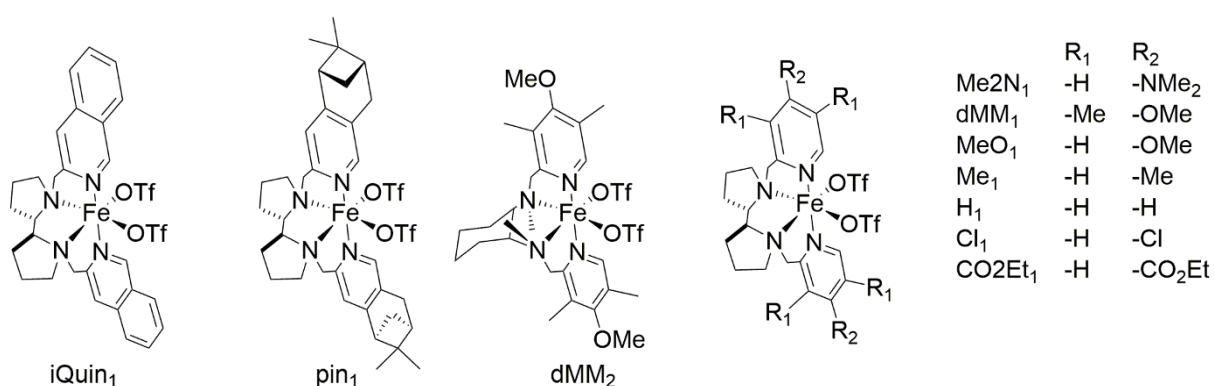

	R_1	R_2
Me2N$_1$	-H	-NMe$_2$
dMM$_1$	-Me	-OMe
MeO$_1$	-H	-OMe
Me$_1$	-H	-Me
H$_1$	-H	-H
Cl$_1$	-H	-Cl
CO2Et$_1$	-H	-CO$_2$Et

iQuin$_1$ pin$_1$ dMM$_2$

Figure 7   Non-heme iron complexes utilize by Costas *et al.* for investigation of electronic effects towards catalytic performance regarding to epoxidation.[106]

A non-heme iron complex that catalyzes highly enantioselective epoxidation of a broader range of olefins is described by Costas *et al.*, who investigated the impact of varying the electronic properties of the catalyst on their catalytic performance. Electronic effects, induced to the iron center by the ligand, in combination with catalytic amounts of carboxylic acids promoting efficient O−O cleavage and generate epoxides with high chemo- and enantioselectivity in high yields.[106] The more electron-rich catalysts providing the better yields and enantioselectivities. For instance, complex Me2N$_1$ achieved 87% yield with 62% enantiomer excess (ee) for the epoxidation of cis-β-methylstyrene, while CO2Et$_1$ only achieved yields of 31% with 21% ee. This

tendency was observed for several classes of substrates, such as electron-deficient cyclohexenone, chromene and tetralone derivatives.

The practical use is only one of the major targets of biomimicry. The understanding of the mechanism and the associated characterization of intermediates are also essential. The insight gained in this way can in turn be used for the further development of new systems.

This work investigates the intramolecular communication of two metals in a biomimicking complex. The well-studied Cy site was combined with a PDI unit. This work summarizes advances in biomimicry and reveals the role of cyclam. The following section provides an overview of iron-oxygen intermediates, their characterization, their catalytic activities, and strategies for improving these in bio-inspired compounds with a focus on the role of cyclam complexes.

1.3 Iron oxygen intermediates

Bioinspired systems are indispensable in the understanding of the mechanism of enzymes. The high reactivity of enzymes goes hand in hand with the short life of their active intermediates. This impedes the isolation and characterization of the active species in the original form of enzymes. This problem motivates one major target of biomimicry: the investigation of the active site of the enzymes by synthesizing their simplified replica with similar structural properties, but without their protein part.[107] Research on the structural properties and reactivities of oxidase and oxygenase replicas has yielded a large extended understanding of iron oxygen intermediates. Stabilization by macrocyclic and acyclic ligands, has resulted in the isolation and characterization of iron oxygen species, such as metal−superoxo, −peroxo,−hydroperoxo, and −oxo.[10, 89, 93, 108-110] The different binding modes of oxygen are a main factor in determining the reactivity of the intermediates.[10]

end-on   side-on   end-on/end-on   side-on/side-on   end-on/side-on
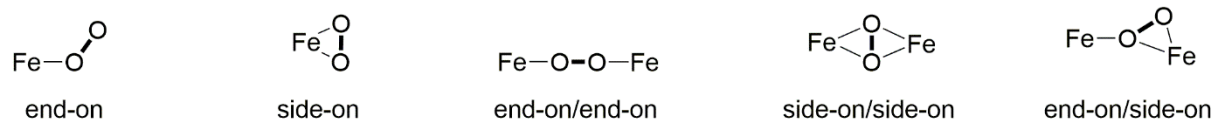
Figure 8   Different binding modes observed for iron-oxygen intermediates.

The reduced size of synthetic bioinspired compounds, enables more accessible strategies to isolate and spectroscopically study the active intermediates. Furthermore, steric and electronic modifications of the ligand environments are more simplified and lead to insights into the catalytic mechanisms and structural properties of biological systems.[111] Also biomimicry could be employed for the development of better catalysts with potential applications due their simplified modification.[112]

1.3.1 Iron−superoxo

Compared to the high valent iron oxygen intermediates, lower valent superoxo complexes are only modestly studied, with few reports of synthetic non-heme iron superoxo compounds. So was the structure of a non-heme superoxo not reported until thirty years after the structure of its heme counterpart.[113-114] The structural and spectroscopic characterization of the iron(III)−superoxo in heme containing proteins and synthetic iron porphyrins revealed that these species bind the O_2 unit in an end-on manner.[113, 115-116] It is assumed that the reduced accessible surface of iron due to the planar heme group caused the end-on binding of oxygen.[117] Superoxo species of hemes is rarely proposed as a reactive species in oxygenase reactions unless the substrate is highly activated as, for example, in the final step of the nitric oxide synthase cycle.[118] Dey *et al.* report the first synthetic heme iron−superoxo, which is able to perform hydrogen atom transfer (HAT) in 2019.[119] It is generally thought that the heme superoxo is first converted to a peroxo, hydroperoxo, or high-valent oxo intermediate.
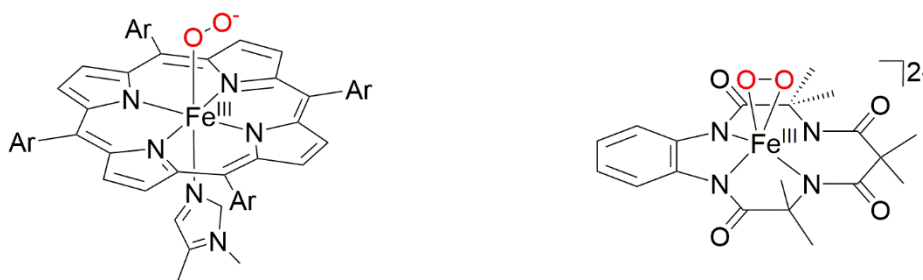

Figure 9   Right: End-on superoxo of an iron porphyrin complex.[113] Left: Side-on superoxo of the non-heme iron complex [Fe^{III}(O$_2$)(TAML)]$^{2-}$.[114]

In contrast to heme, the crystal structure of the non-heme iron complex proposed to be in a side-on mode such as published by Nam *et al.*[114] The presented [Fe^{III}(O$_2$)(TAML)]$^{2-}$ showed reactivity in both electrophilic as well as nucleophilic reactions. Also the superoxo iron complexes published by Lee *et al.* such as that from

Hikichi *et al.* show electrophilic reactions.[120-121] In general, iron−superoxo complexes undergo electrophilic reactions such as C−H and O−H bond activation.[122-123]

Metal−superoxo species can participate directly in substrate oxidation reactions, or can be one-electron reduced by either an exogenous reductant or a second reduced metal center to form a metal−peroxo.

1.3.2 Iron−peroxo

Iron−peroxo complexes are commonly cited as the key intermediates in heme and non-heme iron enzyme catalyzed oxidation reactions, carrying out a variety of nucleophilic and electrophilic reactions.[116, 124-125] Iron−peroxo species act as the active oxidant in many cytochromes P450.[126-128] Mechanistic studies of the reactions of enzymes and biomimicking iron−peroxo porphyrin compounds reveal the nucleophilic character for this iron−oxygen species in heme compounds.[116, 129] Iron−peroxo species was also proposed to be the active oxidant in non-heme enzymes, such as in the catalysis of aromatic cis-dihydroxylation by Rieske dioxygenase.[124, 130] The first crystal structure of a synthetic $Fe^{III}(O_2)^{2-}$ was reported by Nam *et al.* with a non-heme iron system.[131] The iron complex with the TMC (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane) ligand bound the oxygen in a side-on mode and shows sluggish activity towards nucleophilic deformylation. The lower activity compared to its corresponding hydroperoxo complex is caused by the binding of the oxygen, since the end-on mode is more reactive.[129, 132] In a further report Nam *et al.* were able to tune the reactivity in electron-transfer, electrophilic, and nucleophilic reactions of $[(TMC)Fe^{III}(O_2)]^+$ by binding of redox-inactive metal ions (M^{n+}) in a side-on/side-on manner to the oxygen.[133] The Lewis acidity of the redox-inactive metal ions affect the reactivities of the iron(III)−peroxo complex in electron-transfer, electrophilic, and nucleophilic reactions.

1.3.3 Iron−hydroperoxo

Protonation the iron(III)−peroxo species could be generated into iron(III)−hydroperoxo species.[16] Another formation of iron(III)−hydroperoxo is generated from an iron(III)−superoxo species by HAA from substrates.[10, 114, 134] The reaction of iron(II)/(III) with hydrogen peroxide as oxidant directly forms iron−hydroperoxo.[135-136]

While there is a general consensus that heme iron(III)−superoxo systems are sluggish oxidants,[137-138] debate still exists as to the "typical" reactivity of these compounds.[107] It has been shown that, for example, while synthetic low-spin Fe(III)−OOH complexes behave as sluggish oxidants for sulfides, olefins, and aldehydes,[139] a high-spin $[(TMC)Fe^{III}(O_2H)]^{2+}$ compound showed comparably good reactivity in nucleophilic and electrophilic oxidative reactions.[131]
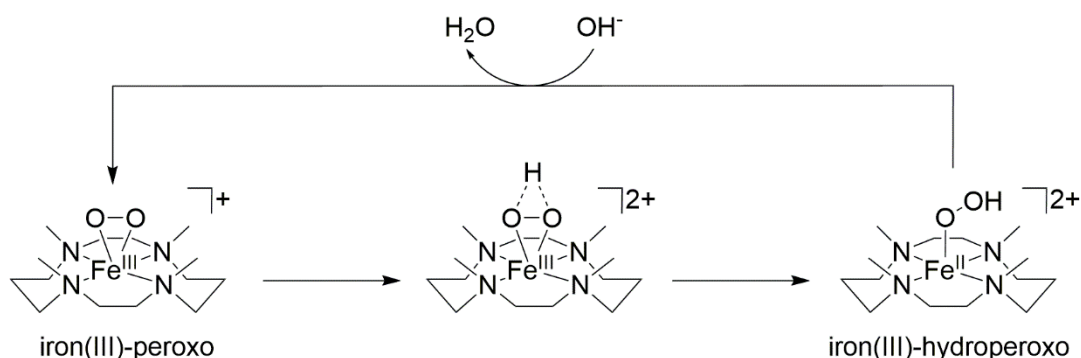

Figure 10   Formation of iron−hydroperoxo from iron−superoxide via protonation and vice versa utilizing base.[131]

Another debate of iron(III)−hydroperoxides is the heterolysis versus homolysis cleavage of the O−O bond, leading to the more reactive iron−oxo. Despite extensive investigation of the O−O bond cleavage mechanisms in heme systems,[89, 124, 140-141] such mechanistic studies in non-heme iron(III)−hydroperoxo species have been conducted only recently.

1.3.4 Iron−oxo

High-valent oxoiron species have been proposed, and identified, as key reactive intermediates in enzymes, which combine the activation of dioxygen with the oxidation of substrates.[108] The reactions range from hydroxylation, halogenation, cyclization, epoxidation and desaturation to vital processes like respiration, catabolism and angiogenesis.[12, 36-37, 142-144] Iron−oxo species have been trapped in enzymes with heme and non-heme monometallic and bimetallic active sites. In 1986 the first evidence of high-valent oxoiron species involved in enzymatic activity was reported for the heme peroxidases.[145-146]
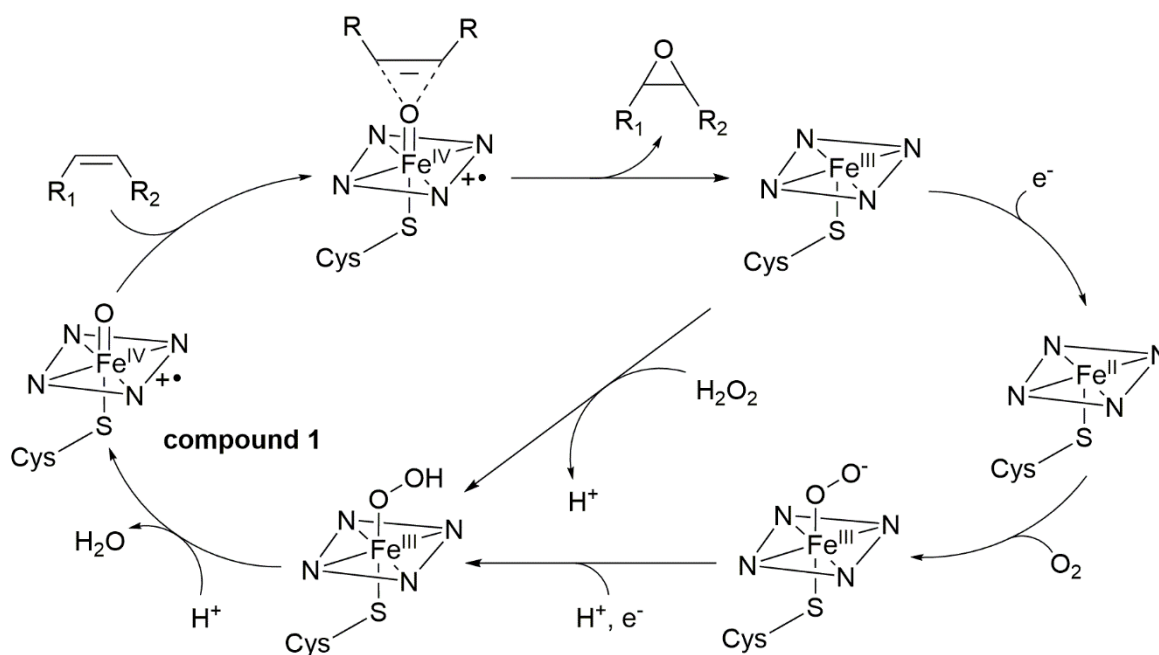

Figure 11 Epoxidation mechanism of cytochrome P450 enzymes using O_2 and H_2O_2 as oxidant.[26, 34, 147]

Nowadays crystal structures of the active sites of various heme-enzymes are known, including horseradish peroxidase, cytochrome P450 and catalase.[148] The detected iron−oxo intermediates consist of an iron(IV) center, with an intermediate spin S = 1, coupled to a cationic radical, either located in the porphyrin ring or in the amino acid

residue near the heme ring.[26, 34, 148] For example, for Cytochrome P450 the active species is to an $Fe^{IV}=O$ porphyrin radical $[(por^{\bullet})Fe^{IV}=O]^{+}$ (Figure 11, compound 1).[26, 34, 147, 149-150]

When the iron(IV) center is coupled ferromagnetically or antiferromagnetically to the radical, the overall spin is S = 3/2 or S = 1/2, respectively.[108] Vast attempts have been made to model these crucial intermediates in the last few decades. In 1981 Groves *et al.* reported the first fully characterized synthetic iron−oxo complex.[151] The oxidation of $[(TMP)Fe^{III}(Cl)]$ (TMP = meso-tetramesityl porphinate anion) with meta-choroperbenzoic acid at −78 °C yielded the iron(IV)−oxo porphyrin cation radical $[(TMP^{\bullet+})Fe^{IV}(O)(X)]^{+}$ with a spin state of S = 1 for iron. The complex was active in olefin epoxidation and alkane hydroxylation reactions.[85] A great number of iron(IV)−oxo porphyrin radicals followed this, which have been synthesized, spectroscopically characterized and exhaustively researched in a variety of oxidation reactions.[152] The oxidizing power of iron–oxo porphyrins is controlled by the electronic nature of porphyrin ligands. Iron–oxo species with electron-deficient porphyrins are better oxidants in the oxygenation of organic substrates.[153] While in the active species of heme compounds iron shows spin intermediate S = 1, in all of the non-heme enzymes the iron center has been found to be in the high-spin S = 2 state.[142] It has been suggested that this is due to weak ligand field from the ligands histidine and carboxylate.[93, 108] Taurine α-KG dioxygenase (TauD) was the first non-heme iron enzyme revealing the active iron(IV)−oxo species (TauDJ), as an active oxidizing species.[154] Mössbauer measurements for TauDJ exhibited a high spin iron center S = 2.[144]
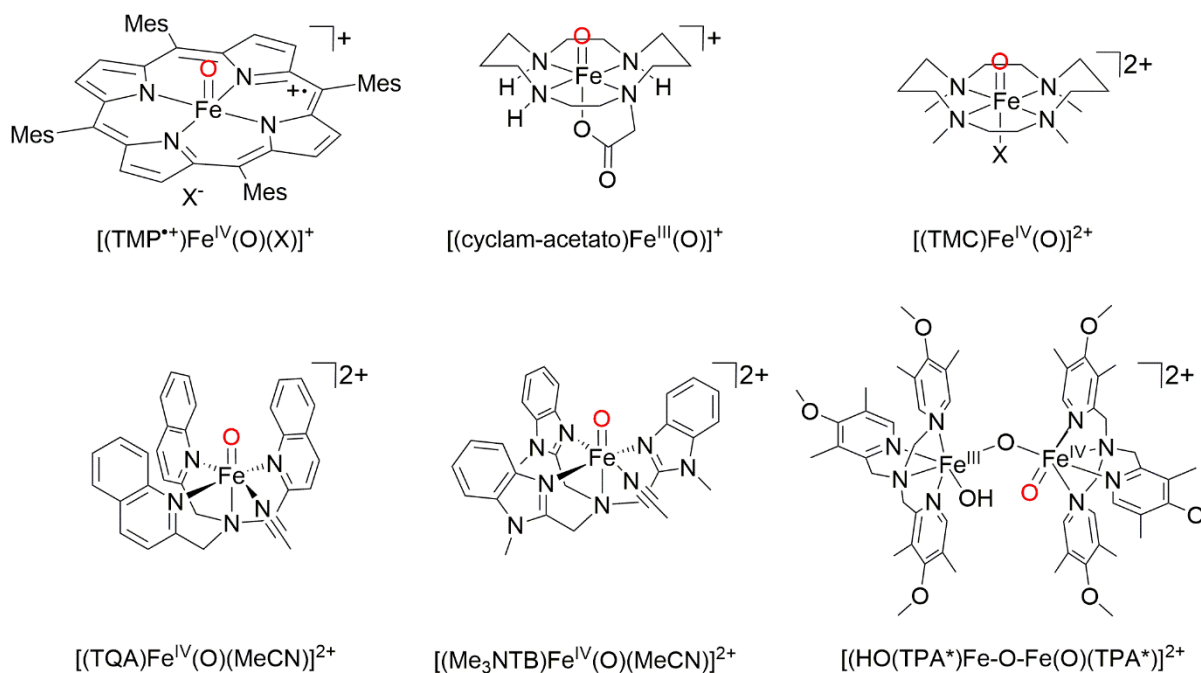
Figure 12 Examples of heme and nonheme intermediates containing iron−oxo cores in synthetic model systems, discussed in this section.[151, 155-159]

Studies of synthetic non-heme iron−oxo turned out to be more difficult, compare to the iron−oxo complexes with porphyrin, since non-heme iron−oxo species exhibit a lack of suitable spectroscopic signatures detectable with routine spectroscopy techniques.[89, 93] This is reportedly the reason why the first non-heme iron−oxo was characterized decades after the heme analogue.[151, 155] The first evidence was demonstrated by Wieghardt *et al.* by treating [(cyclam-acetato)Fe^{III}(O$_3$SCF$_3$)]$^+$ with ozone at -78 °C.[155] Another milestone was set by Nam *et al.* three years later with the first crystal structure of this species.[158] Again the starting compound was an iron cyclam complex [(TMC)Fe]$^{2+}$, which was trapped in its active species after the oxidation with PhIO in acetonitrile at -40 °C. Beside crystallographic also spectroscopic characterization, such as UV/Vis, EPR, Mössbauer, and mass spectrometry were done to study the active species [(TMC)Fe^{IV}(O)]$^{2+}$. Characterization reveals the spin state of S = 1 for iron, unlike the imitated iron−oxo found in enzymes. Despite this the complex from

Nam *et al.* found also to be active for the oxidation of substrates, such as PPh₃, but not for epoxidation or HAT. The non-methylated iron cylam complex, was already known to be active for epoxidation and HAT in 1991,[92] however its iron−oxo intermediate was demonstrated as the active species in 2019.[160]

Many new iron−oxo complexes have been synthesized and characterized in the last twenty years.[75, 89, 93, 108, 142, 156-157, 160-167] Such as for Fe-TMC the majority of the bioinspired Fe(IV)−oxo cores have S = 1 ground state, unlike the enzymatic intermediates. But recent efforts have also led to the characterization of iron(IV)−oxo complexes with spin S = 2.[157, 163] Iron(IV)−oxo complexes with spin S = 2 have been proposed by density functional theory (DFT) calculations to be much more reactive towards C−H bond activation than compounds with S = 1.[108, 168-170] This agrees with nature's preference for non-heme enzymes that utilize high-spin iron centers.

This factor is also obvious for synthetic complexes. The [(Me₃NTB)Fe^{IV}(O)(MeCN)]$^{2+}$ (Me₃NTB = tris((*N*-methylbenzimidazol-2-yl)methyl)amine)) and [(TQA)Fe^{IV}(O)(MeCN)]$^{2+}$ (TQA = tris(2-quinolyl-methyl)amine)) are the most reactive iron−oxo models synthesized and completely characterized.[156-157] Indeed [(Me₃NTB)Fe^{IV}(O)(MeCN)]$^{2+}$ has an intermediate-spin S = 1, but has a highly accessible S = 2 high-spin state.[156] Thus it has extremely low activation barriers and high reactivity. [(TQA)Fe^{IV}(O)(MeCN)]$^{2+}$ reveal a high-spin (S = 2) quintet ground state.[171] Its reactivity rates are comparable to those of the natural intermediate TauD-J.[157] The trapping of the highly reactive [(TQA)Fe^{IV}(O)(MeCN)]$^{2+}$ complex was achieved by the use of bulky tripodal ligand, with weaker-field donors such as quinolones.[172] The enforcement of the trigonal-bipyramidal geometry by bulky tripodal ligand were shown to stabilize species with high-spin configurations such as the use of weaker ligand field environments.[173-174] This example reveals the advantage of

bioinspired compounds, to be more accessible for modification to tune the activity to be either less active, enabling characterization, or to enhance the activity for catalytic applications.

Other than in mononuclear enzymes, where the iron(III)−superoxo species forms an iron(III)−hydroperoxo intermediate by consuming a proton and an electron followed by the subsequent O−O bond cleavage yields the reactive iron−oxo species,[12, 37, 144] in dinuclear enzymes no proton or electron is necessary to form the active species. The oxygen is directly activated at a diiron(II) center to form either closed bis(μ-oxo)diiron(^{IV}) or open O=Fe^{IV}−O−Fe^{IV}=O forms, without the necessity of any additional proton or electron donors.[12, 45, 175-176]
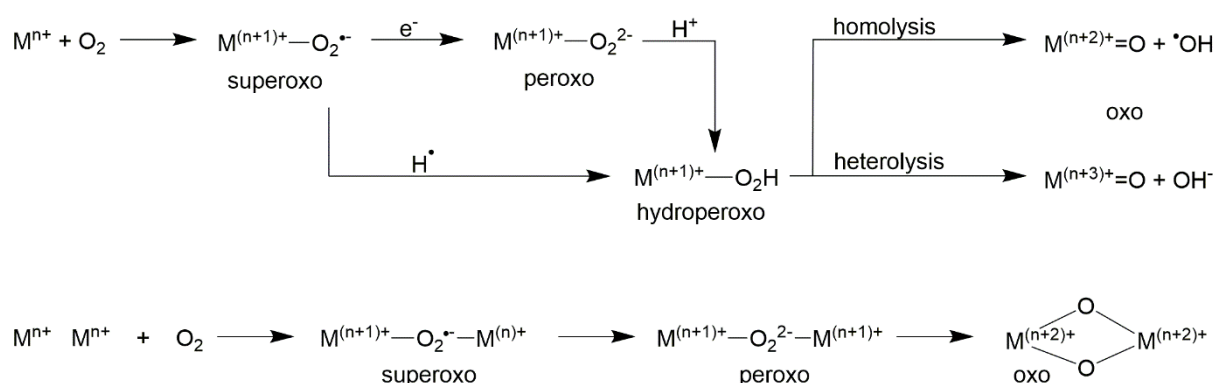

Figure 13   Unified mechanisms for dioxygen activation at mononuclear and dinuclear active sites.[10]

In the conversion of methane to methanol with MMO the formation of the catalytically active diiron(IV) di-oxo intermediate was also observed.[45] Altogether dinuclear iron enzymes bind dioxygen very similar but activate it for different catalytic purposes.[39, 73] The first characterization of a diiron(IV) di-oxo synthetic intermediate was investigated on dinuclear iron complexes [(HO(TPA*)Fe–O–Fe(O)(TPA*)] with TPA* = tris((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)amine), reveals a valence-delocalized [Fe$^{3.5}$(μ-O)$_2$Fe$^{3.5}$]$^{3+}$ diamond core.[177] The dinuclear complex is 100-fold less effective

in carrying out HAT of DHA than its mononuclear analogue. Conversion from the diamond core complex into a complex with a valence-localized [HO−Fe^{III}−O−Fe^{IV}=O]$^{2+}$ open core, changed the spin state from low spin S = 1 into high spin S = 2, resulting in a million-fold higher reactivity for the C−H cleavage.[159] Similar to mononuclear examples dinuclear non-heme biomimicries also reveal the tendency for higher activity for compounds with high spin S = 2.[159, 170, 177-178]

1.4 Fe-cyclam complexes

Cyclam and its derivates are well-studied and play a great role in bioinspired chemistry. Crystal structures of iron oxygen intermediates in non-heme complexes were first reported for iron complexes which utilized TMC, as a ligand.[131, 158] Subsequent studies with cyclam derivates helps unravelling the debate between homolytic and heterolytic cleavage in the formation of non-heme iron−oxo.[109, 179-182] Valentine and coworkers discovered the potential of iron complexes, with cyclam and cyclam related ligands catalyzing the epoxidation of alkenes in the presence of hydrogen peroxide in 1991.[92] Before this discovery no complexes were known, that could convert olefins into the corresponding epoxides with high product yields and stereospecificity. The observed color change in the catalytic reaction initially led to the conclusion that several intermediates are involved in this reaction. An iron(III)−hydroperoxo was mistakenly proposed as the active species without any strong spectroscopic evidence. The lack of activity with alkyl peroxides led to this conclusion, since the O−O bond is stronger in H_2O_2 than in ROOH.[183] In 2019 Ray, Nam and coworkers were able to trap and characterize spectroscopically the actual active species responsible for olefin epoxidation.[160] They synthesized the active species $[(cyclam)Fe^{II}(O)(CH_3CN]^{2+}$ by oxidizing $[(cyclam)Fe^{II}]^{2+}$ with 1.5 eq. sPhIO in acetonitrile at -40 °C. Characterization was completed through means of: (1) UV/Vis spectroscopy, which revealed a typical peak at 737 nm; (2) MS, with point a signal at m/z = 421.08 with the right isotope pattern for the complex with an additional oxygen, shifting two mass units by using $sPhI^{18}O$; (3) ^{1}H-NMR spectroscopy, which exhibited a cis-V cyclam configuration; (4) EXAFS, which demonstrated results typical for S = 1 iron(IV)−oxo complexes; and finally (5) Mössbauer spectroscopy, which was used to validate the S = 1 iron(IV)−oxo species. Addition of cyclohexene to $[(cyclam)Fe^{II}(O)(CH_3CN]^{2+}$ at -20 °C caused a

decrease in the intensity of the peak at 737 nm in the electronic spectra, thus confirming the iron(IV)−oxo as the active species.
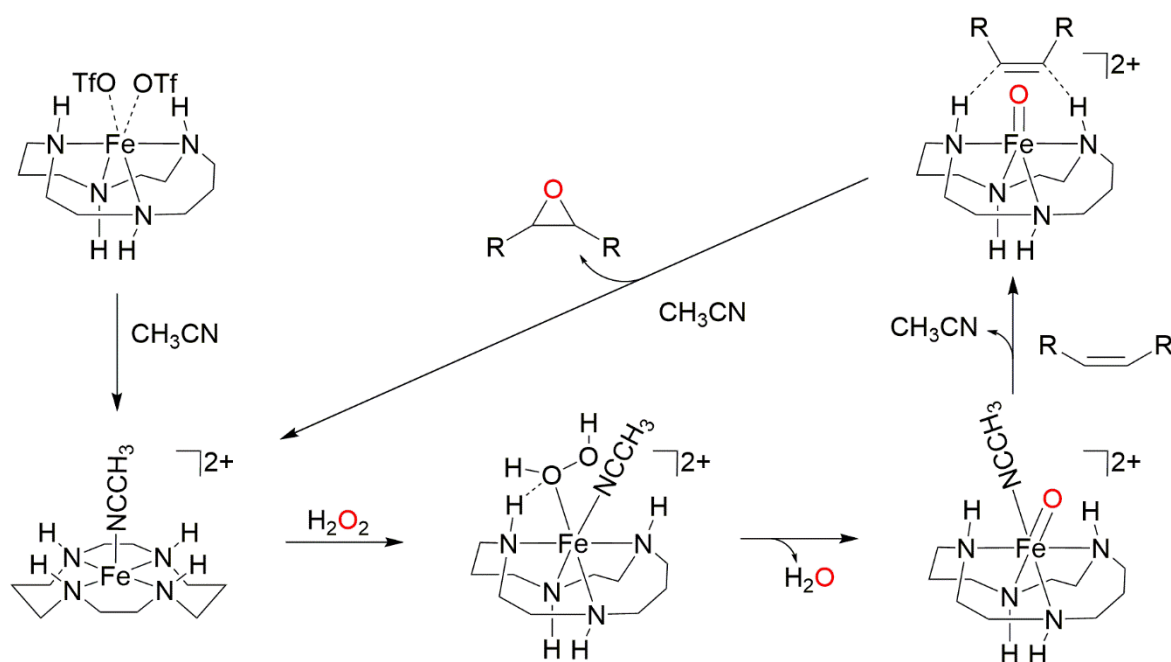

Figure 14   Formation of an iron(IV)−oxo cyclam complex with hydrogen peroxide and epoxidation of alkene showing interaction with N−H.[160]

Normally synthetic iron(IV)−oxo compounds prefer allylic oxidation over epoxidation of cyclohexene[184-188] and are often not kinetically competent to perform the rapid oxidation observed in iron-catalyzed epoxidation and hydroxylation reactions such as in biological catalysts.[10, 75, 142, 170, 189-193] Thus, cyclam represents a key ligand for the investigation of nature chemistry. In a more recent paper, Ray *et al.* were able to crystallize [(cyclam)Fe^{II}(O)(CH$_3$CN]$^{2+}$ in trans configuration.[194] Although both species represent an iron(IV)−oxo with the same ligand, the trans configuration exhibits worse reactivity towards oxygen atom transfer (OAT) and HAA than the cis-configuration. Therefore, the cis-configuration can be described as an essential feature for the reactivity in olefin epoxidation. Complexes with TMC exhibit greater stability for the iron(IV)−oxo species than complexes with the non-methylated cyclam.
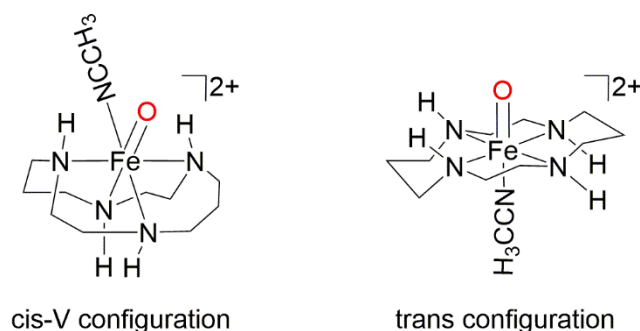
cis-V configuration   trans configuration

Figure 15   Different configurations observed for [(cyclam)Fe^{II}(O)(CH$_3$CN]$^{2+}$.[160, 194]

This enables the synthesis of this oxo complex with H$_2$O$_2$ at -40 °C, stable for at least 1 month at this temperature. Compared to this, the synthesis of [(cyclam)Fe^{II}(O)(CH$_3$CN]^2 with hydrogen peroxide instead of sPhIO was only feasible at -80 °C due to spontaneous decay to bis-(hydroxo)diiron(III) at higher temperatures.[160]

Differences are also observed at the formation of the iron−oxo complexes with hydrogen peroxide. Compare to the formation of the cyclam iron−oxo complex the [(TMC)Fe^{IV}=O]$^{2+}$ is very slow with 4 h. The slower formation depends on the absence of H-bonding interaction between N−H and H$_2$O$_2$, which is proposed as an intermediate to the formation of the iron(IV)−oxo species in [(cyclam)Fe^{II}(O)(CH$_3$CN]$^{2+}$. It was shown by Que *et al.* that addition of base encourages the hemolytic cleavage to form [(TMC)Fe^{II}(O)(CH$_3$CN]$^{2+}$.[195-196] The slower formation with the TMC complexes simplifies the exploration of the mechanism behind this. Nam and coworkers were able to demonstrate the formation of the iron(IV)−oxo via heterolysis after the one-electron reduction from iron(III)− to iron(II)−hydroperoxo.[180]
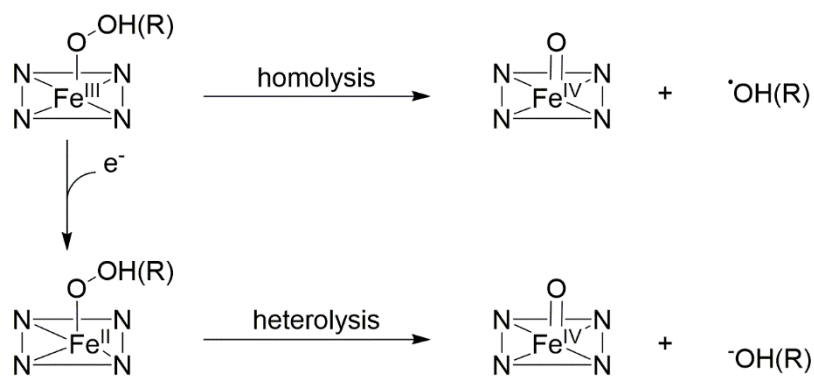
Figure 16   Homolytic and heterolytic cleavage of iron−hydroperoxo in the formation of iron(IV)−oxo.[180]

Notably, the differences in reactivity between the methylated versus non-methylated forms is striking. The HAT performed by iron TMC complexes also proceeds two orders of magnitude slower than the cyclam analogue. Olefin epoxidation was only observed for $[(cyclam)Fe^{II}(O)(CH_3CN]^{2+}$ - the higher reactivity may arise from kinetic and thermodynamic factors.[197]

1.5 PDIxCy system

Cyclam and its related derivates with late transition metals have been used in a variety of biomimetic systems. [109, 179-182] Ligand system bearing a pendant arm on the macrocyclic ring offers additional application.[195, 198-199] In 2017 Haas and coworkers presented the first generation of the PDIxCy ligand, which expanded the macrocyclic cyclam by another binding site.[200] The pincer site is able to bind a second metal physically connected via the propyl linker to the metal in the cyclam site, but electronically uncoupled. The homobimetallic dinickel and dizinc complexes and the heterobimetallic Ni-Zn, containing Ni in the PDI-site, were synthesized and characterized in this study. (see Figure 17)
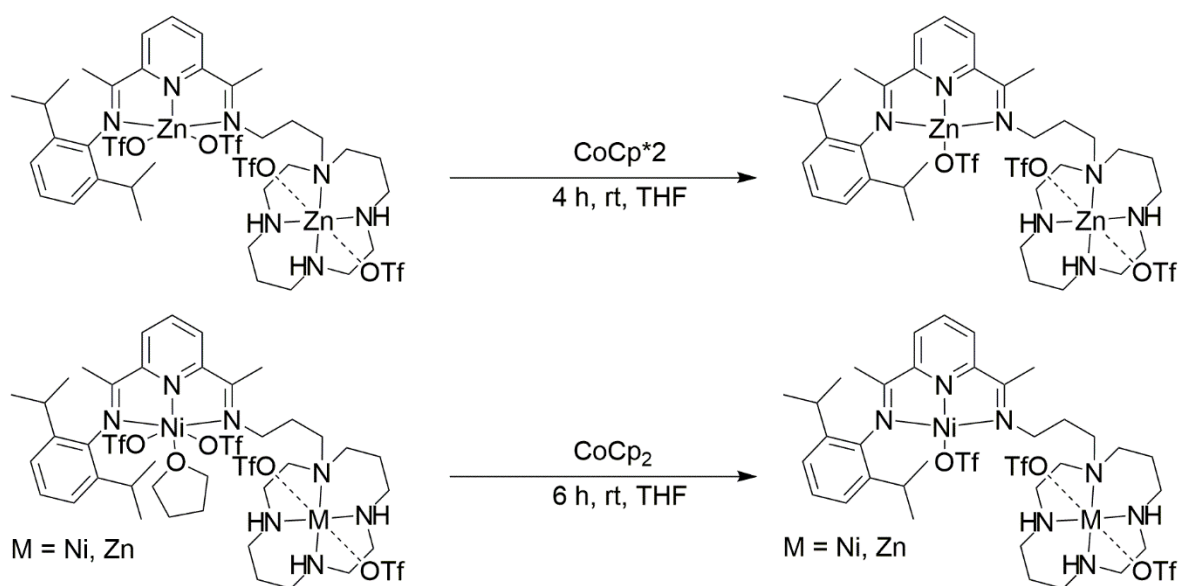
Figure 17   Reduction of the PDIpCy complexes to the charge seperated species.[200]

Haas and coworkers demonstrated the ability to store electrons close to the cyclam site by the redox-active PDI unit in the bimetallic system. Investigation concerning the redox properties involved the one-electron reduction of the complexes chemically. Characterization of the reduced species by UV/Vis- and EPR-spectroscopy showed that the one electron reduction of the complexes takes place on the PDI site, and either

as metal-centered or ligand centered reduction can occur with formation of the PDI$^{\cdot-}$ radical. This study demonstrated that the unique sites are electronically uncoupled, suggesting the function of either site would not be influenced by the adjacent metal site.

1.6 Pyridine diimine

PDI´s represent a well-known class of "non-innocent" ligands that confer additional redox activity to coordination complexes beyond metal-centered oxidation/reduction.[201] It was shown that PDI can accept up to four electrons via its diimine π* orbitals, associated with the electron-transfer series, [PDI]^0 → [PDI]$^{4-}$.[202]

Haas *et al.* have already shown that this feature is transferable to the PDIxCy system for the one electron reduction.[200] This enhances the redox inactive cyclam with a redox active feature for PDIxCy complexes. Since the reduction of [(TMC)Fe^{III}(O$_2$H)]$^{2+}$ influences the formation of the iron−oxo species, it is conceivable that the formation of an iron−oxygen intermediate might be influenced by the redox active site, for example activating substrates.

The application of binding a high variety of elements, such as main group elements, transition metal ions, lanthanides and actinides, makes it a versatile supplement in the PDIxCy system,[202] offering the possibility for a wide range of dinuclear complexes. Furthermore, it was already shown for cyclam complexes that the coordination of a second metal to the iron-peroxo center affects the catalytic activity for this complex in electron-transfer, electrophilic, and nucleophilic reactions.[133] Perhaps forced proximity of the two metals could influence the reactivity further. Also it seems feasible to use the additional metal as anchor for substrates to bind/activate the substrate in close proximity to the active center. Such a system is already reported for dinuclear titan complexes, where one site binds the substrate and the other site activates the oxidant to form the respective epoxide from enones.[203]

Complexes of the PDI ligand exhibit a wide range of catalytic activity,[204-212] which might support or might be supported by the activity of the Cy site. The system of PDIxCy was developed in our group to combine the applications of PDI and Cy complexes. Modification in the linker length was carried out to connect both sites in a more compact fashion.

2 RESULTS – PUBLICATIONS

2.1 Structural Differences and Redox Properties of Unsymmetric Diiron PDIxCy Complexes

Andreas J. Hofmann, Christian Jandl, Corinna R. Hess

This publication presents the synthesis and characterization of homobimetallic complexes [Fe$_2$(PDIeCy)(OTf)$_4$] (**1**) and [Fe$_2$(PDIpCy)(THF)(OTf)$_4$] (**2**). Herein we introduce our modified ligand system PDIeCy, which connecting the unique binding sites Cy and PDI with an ethyl- instead of a propyl- unit as utilize in PDIpCy. The use of the smaller linker leads to a significant structural change, revealed by crystal structure and ^{19}F-NMR.

Unlike **2** and other PDIpCy complexes,[200] **1** exhibits a bridging μ-triflate between the iron ions, observable in the crystal structure shown in Figure 18. The existence of the μ-triflate appearing also in non-coordinating solvents was verified by ^{19}F-NMR. The use of the smaller linker further leads to a smaller metal-to-metal distance of 5.6 Å compare to 8.0 Å, which was observed for **2**. The smaller distance and the performance of the bridging μ-triflate, clearly demonstrates the potential for cooperative substrate interactions for **1**.

The iron centers of **1** and **2** are high-spin, which are electronically uncoupled as verified by Mössbauer and magnetic susceptibility measurements (SQUID) in the solid. Based on Evan´s method the magnetic susceptibilities of **1** and **2** in solution decrease with lower temperature from 7.0 μ_B (**1**) and 7.1 μ_B (**2**) to 5.8 μ_B (**1**) and 5.7 μ_B (**2**). Also the

electronic spectra of **1** and **2** show temperature dependency in acetonitrile (MeCN), noticeable by a significant increase of the extinction coefficient at lower temperature. Since the magnetic susceptibilities are constant between -20 °C and 90 °C, the origin of the spectral changes could not be due to that.
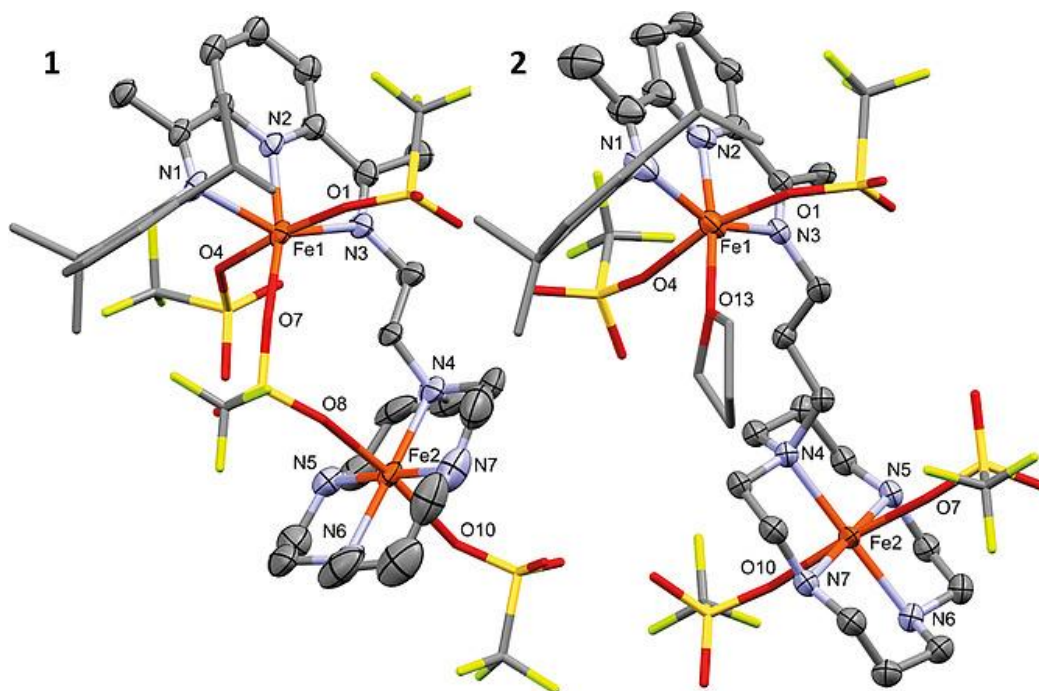

Figure 18   Molecular structure of **1** (left) and **2** (right) in the solid state (50 % probability ellipsoids). Hydrogen atoms, solvent molecules and partial disorder are omitted for clarity. Reprint with permission.[213]

Additionally, redox properties were determined for both complexes. Two electron reduction of **1** was carried out chemically and electrochemically. The similarity in the electronic spectra towards two electron reduced monometallic iron complexes with PDI ligand[214] indicate that a formal "Fe_{PDI}^0" site exists alongside an Fe_{Cy}^{II} center. This property might be helpful for reactivity toward multi-electron processes.

2.2 Neighbouring effects on catalytic epoxidation by Fe-cyclam in M₂-PDIxCy complexes

Andreas J. Hofmann, Lukas Niederegger and Corinna R. Hess

Three more complexes with the PDIeCy ligand were synthesized and characterized, [Zn$_{PDI}$Fe$_{Cy}$(PDIeCy)(OTf)$_4$], [Fe$_{PDI}$Zn$_{Cy}$(PDIeCy)(OTf)$_4$] and [Zn$_2$(PDIeCy)(OTf)$_4$] (Figure 18; **3**, **4** and **5**, respectively). Based on the synthesis of Fe-Zn-PDIeCy we were able to demonstrate, for the first time, the ability to control the metalation of the individual coordination sites in this system. Crystal structures obtained for **4** and **5** proves that the bridging ligand is a common feature of all PDIeCy structures.[213]
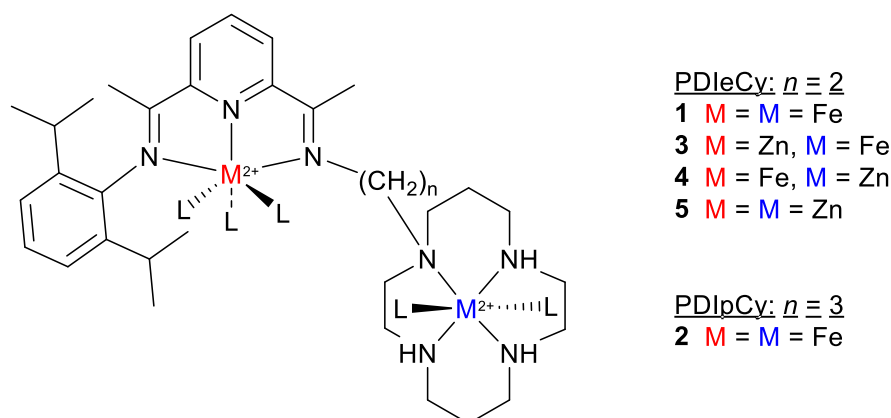
Figure 19 PDIxCy complexes used for oxidation catalysis. Reprint with permission.[215]

The reactivity of **1** - **5** toward olefin epoxidation was examined and compared to the monometallic complex [Fe(Cy)(OTf)$_2$].[92] **1** – **3**, containing iron in the cyclam site, show activity towards olefin epoxidation, while **4** and **5** are inactive for this kind of oxidation chemistry. This indicates that the iron cyclam unit is the active center and that the PDI-site alone is inert. Treatment of **3** with two equivalents of hydrogen peroxide at -80 °C in acetone leads to a band in the electronic spectrum similar to the bands for

[Fe^{IV}O(Cy)(OTf)$_2$],[160] indicate an iron(IV)−oxo at the cyclam site to be the active species. This explains the similar behavior to [Fe(Cy)(OTf)$_2$] towards olefin epoxidation. The bimetallic PDIxCy complexes show an increase in activity toward α,β-unsaturated ketones. Since neither **4** nor **5** show any activity towards epoxidation, the enhancement is not due to activity of the PDI site. Our current hypothesis for the greater activity of the bimetallic PDIxCy complexes toward α,β-unsaturated ketones is that the adjacent M-PDI unit likewise binds the substrate carbonyl group, bringing the alkene group in close proximity to an iron(IV)−oxo at the cyclam site.

3 CONCLUSION AND OUTLOOK

In conclusion we modified the PDIpCy ligand system by its linker length to the more compact PDIeCy. Characterization of homo- and heterobimetallic complexes of both systems reveals significant differences between the complexes of PDIeCy and PDIpCy. The smaller distance in the ligand backbone enables triflate to perform as additional bridging ligand between the metal ions, which was observed in the crystal structures of the PDIeCy complexes. Based on ^{19}F-NMR it was verified that the µ-triflate also persist in non-coordinating solvents. This demonstrates the potential for cooperative substrate interactions in complexes containing the smaller linker.

The influence of the second site could be already shown for PDIxCy complexes towards the epoxidation of α,β-unsaturated ketones. Hereby the PDI site operates as anchor for the electron deficient substrates, while the Cy act as oxidant. Further it was shown that the PDI site on its own is inert to oxidation reaction.

The selective metalation developed in this work was beneficial to understand the different roles played by the Cy and PDI site in oxidation catalysis.

This method could be used to synthesize a series of heterobimetallic complexes by placing different metals in the PDI site. This opens the door for more complexes with a wide range of activity and enables us to determine trends and unravel the mechanism behind these reactions.

It seems feasible that in other PDIxCy systems the PDI site could interact with the iron−oxygen intermediate directly, which would affects the catalytic activity as shown for [(TMC)Fe^{III}(O$_2$)]$^+$,[133] or could enhance the formation of the iron−oxo species by contributing an electron.[180] The close proximity of the two metals might affect the activity further.

Access to a wide range of redox states through the combination of the redox active PDI with the redox inactive Cy part enables the formation of a two-electron separated species, and bodes promise for reactivity toward other multi-electron processes, such as CO_2 and hydrogen activation.[211-212] In this case the PDI site acts as an active center and the Cy part would play a supporting role, for example as a Lewis acid.

4   REPRINT PERMISSIONS

4.1 John Wiley and Sons Journals

"Structural Differences and Redox Properties of Unsymmetric Diiron PDIxCy Complexes"

European Journal of Inorganic Chemistry **2020**, *2020*, 499-505.

DOI: 10.1002/ejic.201901173

Reproduced with permission from Elsevier.

Authors contributing to Elsevier (Journal of Catalysis) publications (journal articles) do not need to formally request permission to reproduce material contained in this article provided that the correct acknowledgement is given with the reproduced material

4.2 RSC Journals

"Neighbouring effects on catalytic epoxidation by Fe-cyclam in M$_2$-PDIxCy complexes"

Authors contributing to RSC publications (journal articles, books or book chapters) do not need to formally request permission to reproduce material contained in this article provided that the correct acknowledgement is given with the reproduced material.

If you are the author of this article you do not need to formally request permission to reproduce figures, diagrams etc. contained in this article in third party publications or in a thesis or dissertation provided that the correct acknowledgement is given with the reproduced material.

Sharing rights	Accepted manuscript	Version of record
Share with individuals on request, for personal use	✓	✓
Use for teaching or training materials	✓	✓
Use in submissions of grant applications, or academic requirements such as theses or dissertations*	✓	✓
Share with a closed group of research collaborators, for example via an intranet or privately via a scholarly communication network	✓	✓
Share publicly via a scholarly communication network that has signed up to STM sharing principles	⧗	✕
Share publicly via a personal website, institutional repository or other not-for-profit repository	⧗	✕
Share publicly via a scholarly communication network that has not signed up to STM sharing principles	✕	✕

*You may include your article in the electronic version of your thesis or dissertation as long as it is not made available as a separate document.

5 REFERENCES

1. Dodd, M. S.; Papineau, D.; Grenne, T.; Slack, J. F.; Rittner, M.; Pirajno, F.; O'Neil, J.; Little, C. T. S., Evidence for early life in Earth's oldest hydrothermal vent precipitates. *Nature* **2017,** *543* (7643), 60-64.

2. Darwin, C.; Murray, J.; Tatham, R. G. E.; Lacaita, C. C.; Edmonds; Remnants; Harcourt, B.; William, C.; Sons; Bradbury; Evans, *On the origin of species by means of natural selection, or, The preservation of favoured races in the struggle for life.* John Murray, Albemarle Street: London, 1859.

3. Wöhler, F., Ueber künstliche Bildung des Harnstoffs. *Annalen der Physik* **1828,** *88* (2), 253-256.

4. Seetharaman, K.; Bertoft, E., Perspectives on the history of research on starch Part II: On the discovery of the constitution of diastase. *Starch - Stärke* **2012,** *64* (10), 765-769.

5. Fischer, E., Einfluss der Configuration auf die Wirkung der Enzyme. *Berichte der deutschen chemischen Gesellschaft* **1894,** *27* (3), 2985-2993.

6. Zhang, M.; Gu, Z.-Y.; Bosch, M.; Perry, Z.; Zhou, H.-C., Biomimicry in metal–organic materials. *Coordination Chemistry Reviews* **2015,** *293-294,* 327-356.

7. Breslow, R., Biomimetic Chemistry and Artificial Enzymes: Catalysis by Design. *Accounts of Chemical Research* **1995,** *28* (3), 146-153.

8. Olivo, G.; Cussó, O.; Borrell, M.; Costas, M., Oxidation of alkane and alkene moieties with biologically inspired nonheme iron catalysts and hydrogen peroxide: from free radicals to stereoselective transformations. *JBIC Journal of Biological Inorganic Chemistry* **2017,** *22* (2), 425-452.

9. Wang, V. C. C.; Maji, S.; Chen, P. P. Y.; Lee, H. K.; Yu, S. S. F.; Chan, S. I., Alkane Oxidation: Methane Monooxygenases, Related Enzymes, and Their Biomimetics. *Chemical Reviews* **2017,** *117* (13), 8574-8621.

10. Ray, K.; Pfaff, F. F.; Wang, B.; Nam, W., Status of Reactive Non-Heme Metal–Oxygen Intermediates in Chemical and Enzymatic Reactions. *Journal of the American Chemical Society* **2014,** *136* (40), 13942-13958.

11. Vicens, L.; Olivo, G.; Costas, M., Rational Design of Bioinspired Catalysts for Selective Oxidations. *ACS Catalysis* **2020,** *10* (15), 8611-8631.

12. Jasniewski, A. J.; Que Jr., L., Dioxygen Activation by Nonheme Diiron Enzymes: Diverse Dioxygen Adducts, High-Valent Intermediates, and Related Model Complexes. *Chemical Reviews* **2018,** *118* (5), 2554-2592.

13. Arakawa, H., Catalysis Research of Relevance to Carbon Management: Progress, Challenges, and Opportunities. *Chemical Reviews* **2001,** *101* (4), 953-996.

14. Punniyamurthy, T.; Velusamy, S.; Iqbal, J., Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chemical Reviews* **2005,** *105* (6), 2329-2364.

15. Valery V. Fokin, P. W., Epoxides and Aziridines in Click Chemistry. In *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed. Wiley-VCH: Weinheim, Germany, 2006; pp 443-477.

16. Nachbauer, L.; Brückner, R., Synthesis of a C^n–C^{n+6} Building Block Common to Important Polyol,Polyene Antibiotics from a Divinylcarbinol by a Desymmetrizing Sharpless Epoxidation. *European Journal of Organic Chemistry* **2013,** *2013* (29), 6545-6562.

17. Piontek, A.; Bisz, E.; Szostak, M., Iron-Catalyzed Cross-Couplings in the Synthesis of Pharmaceuticals: In Pursuit of Sustainability. *Angewandte Chemie International Edition* **2018,** *57* (35), 11116-11128.

18. Fingerhut, A.; Serdyuk, O. V.; Tsogoeva, S. B., Non-heme iron catalysts for epoxidation and aziridination reactions of challenging terminal alkenes: towards sustainability. *Green Chemistry* **2015,** *17* (4), 2042-2058.

19. Sunohara, K.; Mitsuhashi, S.; Shigetomi, K.; Ubukata, M., Discovery of N-(2,3,5-triazoyl)mycophenolic amide and mycophenolic epoxyketone as novel inhibitors of human IMPDH. *Bioorganic & Medicinal Chemistry Letters* **2013,** *23* (18), 5140-5144.

20.   Weiß, K. M.; Tsogoeva, S. B., Enantioselective epoxidation of electron-deficient olefins: an organocatalytic approach. *The Chemical Record* **2011,** *11* (1), 18-39.

21.   Mason, H. S.; Fowlks, W. L.; Peterson, E., Oxygen transfer and electron transport by the phenolase complex1. *Journal of the American Chemical Society* **1955,** *77* (10), 2914-2915.

22.   Hayaishi, O.; Katagiri, M.; Rothberg, S., Mechanism of the pyrocatechase reaction. *Journal of the American Chemical Society* **1955,** *77* (20), 5450-5451.

23.   Que Jr., L.; Tolman, W. B., Biologically inspired oxidation catalysis. *Nature* **2008,** *455* (7211), 333-340.

24.   Enthaler, S.; Junge, K.; Beller, M., Sustainable Metal Catalysis with Iron: From Rust to a Rising Star? *Angewandte Chemie International Edition* **2008,** *47* (18), 3317-3321.

25.   Haynes, W. M.; Lide, D. R.; Bruno, T. J., *CRC handbook of chemistry and physics : a ready-reference book of chemical and physical data*. 2016.

26.   Denisov, I. G.; Makris, T. M.; Sligar, S. G.; Schlichting, I., Structure and Chemistry of Cytochrome P450. *Chemical Reviews* **2005,** *105* (6), 2253-2278.

27.   Ortiz de Montellano, P. R., *Cytochrome P450: Structure, mechanism, and biochemistry*. 4 ed.; Springer International Publishing: Switzerland, 2015.

28.   Meunier, B.; de Visser, S. P.; Shaik, S., Mechanism of Oxidation Reactions Catalyzed by Cytochrome P450 Enzymes. *Chemical Reviews* **2004,** *104* (9), 3947-3980.

29.   Guengerich, F. P., Common and Uncommon Cytochrome P450 Reactions Related to Metabolism and Chemical Toxicity. *Chemical Research in Toxicology* **2001,** *14* (6), 611-650.

30.   Ortiz de Montellano, P. R., Hydrocarbon Hydroxylation by Cytochrome P450 Enzymes. *Chemical Reviews* **2010,** *110* (2), 932-948.

31.   Veitch, N. C., Horseradish peroxidase: a modern view of a classic enzyme. *Phytochemistry* **2004,** *65* (3), 249-259.

32.   Moss, G. P.; Smith, P. A. S.; Tavernier, D., Glossary of class names of organic compounds and reactivity intermediates based on structure (IUPAC Recommendations 1995). *Pure and Applied Chemistry* **1995,** *67* (8-9), 1307-1375.

33.   Hegg, E. L.; Que Jr., L., The 2-His-1-Carboxylate Facial Triad — An Emerging Structural Motif in Mononuclear Non-Heme Iron(II) Enzymes. *European Journal of Biochemistry* **1997,** *250* (3), 625-629.

34.   McQuarters, A. B.; Wolf, M. W.; Hunt, A. P.; Lehnert, N., 1958–2014: After 56 Years of Research, Cytochrome P450 Reactivity Is Finally Explained. *Angewandte Chemie International Edition* **2014,** *53* (19), 4750-4752.

35.   Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J.; Nordlund, P.; auml, Crystal structure of a bacterial non-haem iron hydroxylase that catalyses the biological oxidation of methane. *Nature* **1993,** *366* (6455), 537-543.

36.   Solomon, E. I.; Decker, A.; Lehnert, N., Non-heme iron enzymes: Contrasts to heme catalysis. *Proceedings of the National Academy of Sciences* **2003,** *100* (7), 3589-3594.

37.   Solomon, E. I.; Goudarzi, S.; Sutherlin, K. D., O2 Activation by Non-Heme Iron Enzymes. *Biochemistry* **2016,** *55* (46), 6363-6374.

38.   Banerjee, R.; Jones, J. C.; Lipscomb, J. D., Soluble Methane Monooxygenase. *Annual Review of Biochemistry* **2019,** *88*, 13.1–13.23.

39.   Wallar, B. J.; Lipscomb, J. D., Dioxygen Activation by Enzymes Containing Binuclear Non-Heme Iron Clusters. *Chemical Reviews* **1996,** *96* (7), 2625-2658.

40.   Miuran, A.; Dalton, H., Purification and Characterization of the Alkene Monooxygenase from Nocardia corallina B-276. *Bioscience, Biotechnology, and Biochemistry* **1995,** *59* (5), 853-859.

41.   Das, D.; Eser, B. E.; Han, J.; Sciore, A.; Marsh, E. N. G., Oxygen-Independent Decarbonylation of Aldehydes by Cyanobacterial Aldehyde Decarbonylase: A New Reaction of Diiron Enzymes. *Angewandte Chemie International Edition* **2011,** *50* (31), 7148-7152.

42.   Bochevarov, A. D.; Li, J.; Song, W. J.; Friesner, R. A.; Lippard, S. J., Insights into the Different Dioxygen Activation Pathways of Methane and Toluene Monooxygenase Hydroxylases. *Journal of the American Chemical Society* **2011,** *133* (19), 7384-7397.

43.   Stenkamp, R. E., Dioxygen and Hemerythrin. *Chemical Reviews* **1994,** *94* (3), 715-726.

44. Nordlund, P.; Reichard, P., Ribonucleotide Reductases. *Annual Review of Biochemistry* **2006,** *75* (1), 681-706.

45. Tinberg, C. E.; Lippard, S. J., Dioxygen Activation in Soluble Methane Monooxygenase. *Accounts of Chemical Research* **2011,** *44* (4), 280-288.

46. Perry, C.; de los Santos, Emmanuel L. C.; Alkhalaf, L. M.; Challis, G. L., Rieske non-heme iron-dependent oxygenases catalyse diverse reactions in natural product biosynthesis. *Natural Product Reports* **2018,** *35* (7), 622-632.

47. Göbel, C.; Feussner, I.; Rosahl, S., Lipid Peroxidation during the Hypersensitive Response in Potato in the Absence of 9-Lipoxygenases*. *Journal of Biological Chemistry* **2003,** *278* (52), 52834-52840.

48. Whitehead, I. M.; Muller, B. L.; Dean, C., Industrial use of soybean lipoxygenase for the production of natural green note flavor compounds. *Cereal foods world.* **1995,** *40* (4), 193-194.

49. Nordlund, P.; Eklund, H., Di-iron—carboxylate proteins. *Current Opinion in Structural Biology* **1995,** *5* (6), 758-766.

50. Brusseau, G. A.; Tsien, H.-C.; Hanson, R. S.; Wackett, L. P., Optimization of trichloroethylene oxidation by methanotrophs and the use of a colorimetric assay to detect soluble methane monooxygenase activity. *Biodegradation* **1990,** *1* (1), 19-29.

51. Green, J.; Dalton, H., Substrate specificity of soluble methane monooxygenase. Mechanistic implications. *The Journal of Biological Chemistry* **1989,** *264 30*, 17698-703.

52. Colby, J.; Stirling, D. I.; Dalton, H., The soluble methane mono-oxygenase of Methylococcus capsulatus (Bath). Its ability to oxygenate n-alkanes, n-alkenes, ethers, and alicyclic, aromatic and heterocyclic compounds. *Biochemical Journal* **1977,** *165* (2), 395-402.

53. Burrows, K. J. A.; Cornish, A.; Scott, D.; Higgins, I., Substrate Specificities of the Soluble and Particulate Methane Mono-oxygenases of Methylosinus trichosporium OB3b. *Microbiology-sgm* **1984,** *130*, 3327-3333.

54. Fei, Q.; Guarnieri, M. T.; Tao, L.; Laurens, L. M. L.; Dowe, N.; Pienkos, P. T., Bioconversion of natural gas to liquid fuel: Opportunities and challenges. *Biotechnology Advances* **2014,** *32* (3), 596-614.

55. Ng, K.-Y.; Tu, L.-C.; Wang, Y.-S.; Chan, S. I.; Yu, S. S. F., Probing the Hydrophobic Pocket of the Active Site in the Particulate Methane Monooxygenase (pMMO) from Methylococcus capsulatus (Bath) by Variable Stereoselective Alkane Hydroxylation and Olefin Epoxidation. *ChemBioChem* **2008,** *9* (7), 1116-1123.

56. Jiang, H.; Chen, Y.; Jiang, P.; Zhang, C.; Smith, T. J.; Murrell, J. C.; Xing, X.-H., Methanotrophs: Multifunctional bacteria with promising applications in environmental bioengineering. *Biochemical Engineering Journal* **2010,** *49* (3), 277-288.

57. Hanson, R. S.; Tsien, H. C.; Tsuji, K.; Brusseau, G. A.; Wackett, L. P., Biodegradation of low-molecular-weight halogenated hydrocarbons by methanotrophic bacteria. *FEMS Microbiology Reviews* **1990,** *7* (3-4), 273-278.

58. Arfman, N.; Vries, K.; Moezelaar, H.; Attwood, M.; Robinson, G.; Geel, M.; Dijkhuizen, L., Environmental regulation of alcohol metabolism in thermotolerant methylotrophic Bacillus strains. *Archives of microbiology* **1992,** *157*, 272-8.

59. Buswell, A. M.; Mueller, H. F., Mechanism of Methane Fermentation. *Industrial & Engineering Chemistry* **1952,** *44* (3), 550-552.

60. Leahy, J. G.; Batchelor, P. J.; Morcomb, S. M., Evolution of the soluble diiron monooxygenases. *FEMS Microbiology Reviews* **2003,** *27* (4), 449-479.

61. Saeki, H.; Akira, M.; Furuhashi, K.; Averhoff, B.; Gottschalk, G., Degradation of trichloroethene by a linear-plasmid-encoded alkene monooxygenase in Rhodococcus corallinus (Nocardia corallina) B-276. *Microbiology* **1999,** *145* (7), 1721-1730.

62. Lin, H.; Liu, J.-Y.; Wang, H.-B.; Ahmed, A. A. Q.; Wu, Z.-L., Biocatalysis as an alternative for the production of chiral epoxides: A comparative review. *Journal of Molecular Catalysis B: Enzymatic* **2011,** *72* (3), 77-89.

63. Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Keßeler, M.; Stürmer, R.; Zelinski, T., Industrial Methods for the Production of Optically Active Intermediates. *Angewandte Chemie International Edition* **2004,** *43* (7), 788-824.

64.   Lyakin, O. Y.; Ottenbacher, R. V.; Bryliakov, K. P.; Talsi, E. P., Asymmetric Epoxidations with H_2O_2 on Fe and Mn Aminopyridine Catalysts: Probing the Nature of Active Species by Combined Electron Paramagnetic Resonance and Enantioselectivity Study. *ACS Catalysis* **2012,** *2* (6), 1196-1202.

65.   Wu, M.; Miao, C.-X.; Wang, S.; Hu, X.; Xia, C.; Kühn, F. E.; Sun, W., Chiral Bioinspired Non-Heme Iron Complexes for Enantioselective Epoxidation of α,β-Unsaturated Ketones. *Advanced Synthesis & Catalysis* **2011,** *353* (16), 3014-3022.

66.   Wang, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W., Bioinspired Manganese and Iron Complexes with Tetradentate N Ligands for the Asymmetric Epoxidation of Olefins. *ChemCatChem* **2013,** *5* (8), 2489-2494.

67.   Wang, B.; Wang, S.; Xia, C.; Sun, W., Highly Enantioselective Epoxidation of Multisubstituted Enones Catalyzed by Non-Heme Iron Catalysts. *Chemistry – A European Journal* **2012,** *18* (24), 7332-7335.

68.   Mitra, M.; Cusso, O.; Bhat, S. S.; Sun, M.; Cianfanelli, M.; Costas, M.; Nordlander, E., Highly enantioselective epoxidation of olefins by H_2O_2 catalyzed by a non-heme Fe(II) catalyst of a chiral tetradentate ligand. *Dalton Transactions* **2019,** *48* (18), 6123-6131.

69.   Labinger, J. A.; Bercaw, J. E., Understanding and exploiting C–H bond activation. *Nature* **2002,** *417* (6888), 507-514.

70.   Godula, K.; Sames, D., C–H Bond Functionalization in Complex Organic Synthesis. *Science* **2006,** *312* (5770), 67-72.

71.   Chen, K.; Baran, P. S., Total synthesis of eudesmane terpenes by site-selective C–H oxidations. *Nature* **2009,** *459* (7248), 824-828.

72.   Bruijnincx, P. C. A.; van Koten, G.; Klein Gebbink, R. J. M., Mononuclear non-heme iron enzymes with the 2-His-1-carboxylate facial triad: recent developments in enzymology and modeling studies. *Chemical Society Reviews* **2008,** *37* (12), 2716-2744.

73.   Trehoux, A.; Mahy, J.-P.; Avenier, F., A growing family of O_2 activating dinuclear iron enzymes with key catalytic diiron(III)-peroxo intermediates: Biological systems and chemical models. *Coordination Chemistry Reviews* **2016,** *322*, 142-158.

74.   Kal, S.; Xu, S.; Que Jr., L., Bio-inspired Nonheme Iron Oxidation Catalysis: Involvement of Oxoiron(V) Oxidants in Cleaving Strong C−H Bonds. *Angewandte Chemie International Edition* **2020,** *59* (19), 7332-7349.

75.   Engelmann, X.; Monte-Pérez, I.; Ray, K., Oxidation Reactions with Bioinspired Mononuclear Non-Heme Metal–Oxo Complexes. *Angewandte Chemie International Edition* **2016,** *55* (27), 7632-7649.

76.   Cussó, O.; Ribas, X.; Costas, M., Biologically inspired non-heme iron-catalysts for asymmetric epoxidation; design principles and perspectives. *Chemical Communications* **2015,** *51* (76), 14285-14298.

77.   Kovaleva, E. G.; Lipscomb, J. D., Versatility of biological non-heme Fe(II) centers in oxygen activation reactions. *Nature Chemical Biology* **2008,** *4* (3), 186-193.

78.   Hermans, I.; Spier, E. S.; Neuenschwander, U.; Turrà, N.; Baiker, A., Selective Oxidation Catalysis: Opportunities and Challenges. *Topics in Catalysis* **2009,** *52* (9), 1162-1174.

79.   Bolm, C.; Legros, J.; Le Paih, J.; Zani, L., Iron-Catalyzed Reactions in Organic Synthesis. *Chemical Reviews* **2004,** *104* (12), 6217-6254.

80.   Hölzl, S. M.; Altmann, P. J.; Kück, J. W.; Kühn, F. E., Speciation in iron epoxidation catalysis: A perspective on the discovery and role of non-heme iron(III)-hydroperoxo species in iron-catalyzed oxidation reactions. *Coordination Chemistry Reviews* **2017,** *352*, 517-536.

81.   Fenton, H. J. H., LXXIII.—Oxidation of tartaric acid in presence of iron. *Journal of the Chemical Society, Transactions* **1894,** *65* (0), 899-910.

82.   Haber, F.; Weiss, J.; Pope, W. J., The catalytic decomposition of hydrogen peroxide by iron salts. *Proceedings of the Royal Society of London. Series A - Mathematical and Physical Sciences* **1934,** *147* (861), 332-351.

83.   Brillas, E.; Sirés, I.; Oturan, M. A., Electro-Fenton Process and Related Electrochemical Technologies Based on Fenton's Reaction Chemistry. *Chemical Reviews* **2009,** *109* (12), 6570-6631.

84. Gamba, I.; Codolà, Z.; Lloret-Fillol, J.; Costas, M., Making and breaking of the O-O bond at iron complexes. *Coordination Chemistry Reviews* **2017,** *334*, 2-24.

85. Groves, J. T.; Nemo, T. E.; Myers, R. S., Hydroxylation and epoxidation catalyzed by iron-porphine complexes. Oxygen transfer from iodosylbenzene. *Journal of the American Chemical Society* **1979,** *101* (4), 1032-1033.

86. Chang, C. K.; Kuo, M.-S., Reaction of iron(III) porphyrins and iodosoxylene. The active oxene complex of cytochrome P-450. *Journal of the American Chemical Society* **1979,** *101* (12), 3413-3415.

87. Meunier, B., Metalloporphyrins as versatile catalysts for oxidation reactions and oxidative DNA cleavage. *Chemical Reviews* **1992,** *92* (6), 1411-1456.

88. Dolphin, D.; Traylor, T. G.; Xie, L. Y., Polyhaloporphyrins: Unusual Ligands for Metals and Metal-Catalyzed Oxidations. *Accounts of Chemical Research* **1997,** *30* (6), 251-259.

89. Nam, W., High-Valent Iron(IV)–Oxo Complexes of Heme and Non-Heme Ligands in Oxygenation Reactions. *Accounts of Chemical Research* **2007,** *40* (7), 522-531.

90. Bartoli, J.-F.; Le Barch, K.; Palacio, M.; Battioni, P.; Mansuy, D., Iron polynitroporphyrins bearing up to eight β-nitro groups as interesting new catalysts for H_2O_2-dependent hydrocarbon oxidation: unusual regioselectivity in hydroxylation of alkoxybenzenes. *Chemical Communications* **2001,** (18), 1718-1719.

91. Bryliakov, K. P.; Talsi, E. P., Active sites and mechanisms of bioinspired oxidation with H_2O_2, catalyzed by non-heme Fe and related Mn complexes. *Coordination Chemistry Reviews* **2014,** *276*, 73-96.

92. Nam, W.; Ho, R.; Valentine, J. S., Iron-cyclam complexes as catalysts for the epoxidation of olefins by 30% aqueous hydrogen peroxide in acetonitrile and methanol. *Journal of the American Chemical Society* **1991,** *113* (18), 7052-7054.

93. Que Jr., L., The Road to Non-Heme Oxoferryls and Beyond. *Accounts of Chemical Research* **2007,** *40* (7), 493-500.

94. White, M. C.; Doyle, A. G.; Jacobsen, E. N., A Synthetically Useful, Self-Assembling MMO Mimic System for Catalytic Alkene Epoxidation with Aqueous H_2O_2. *Journal of the American Chemical Society* **2001,** *123* (29), 7194-7195.

95. Chen, M. S.; White, M. C., A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis. *Science* **2007,** *318* (5851), 783-787.

96. Chen, M. S.; White, M. C., Combined Effects on Selectivity in Fe-Catalyzed Methylene Oxidation. *Science* **2010,** *327* (5965), 566-571.

97. Company, A.; Gómez, L.; Fontrodona, X.; Ribas, X.; Costas, M., A Novel Platform for Modeling Oxidative Catalysis in Non-Heme Iron Oxygenases with Unprecedented Efficiency. *Chemistry – A European Journal* **2008,** *14* (19), 5727-5731.

98. Gómez, L.; Garcia-Bosch, I.; Company, A.; Benet-Buchholz, J.; Polo, A.; Sala, X.; Ribas, X.; Costas, M., Stereospecific C-H Oxidation with H_2O_2 Catalyzed by a Chemically Robust Site-Isolated Iron Catalyst. *Angewandte Chemie International Edition* **2009,** *48* (31), 5720-5723.

99. Gómez, L.; Canta, M.; Font, D.; Prat, I.; Ribas, X.; Costas, M., Regioselective Oxidation of Nonactivated Alkyl C–H Groups Using Highly Structured Non-Heme Iron Catalysts. *The Journal of Organic Chemistry* **2013,** *78* (4), 1421-1433.

100. Anilkumar, G.; Bitterlich, B.; Gelalcha, F. G.; Tse, M. K.; Beller, M., An efficient biomimetic Fe-catalyzed epoxidation of olefins using hydrogen peroxide. *Chemical Communications* **2007,** (3), 289-291.

101. Schröder, K.; Tong, X.; Bitterlich, B.; Tse, M. K.; Gelalcha, F. G.; Brückner, A.; Beller, M., Novel biomimetic iron-catalysts for environmentally benign epoxidations of olefins. *Tetrahedron Letters* **2007,** *48* (36), 6339-6342.

102. Bitterlich, B.; Schröder, K.; Tse, M. K.; Beller, M., An Improved Iron-Catalyzed Epoxidation of Aromatic and Aliphatic Olefins with Hydrogen Peroxide as Oxidant. *European Journal of Organic Chemistry* **2008,** *2008* (29), 4867-4870.

103. Enthaler, S.; Schröder, K.; Inoue, S.; Eckhardt, B.; Junge, K.; Beller, M.; Drieß, M., Formamidines – Versatile Ligands for Zinc-Catalyzed Hydrosilylation and Iron-Catalyzed Epoxidation Reactions. *European Journal of Organic Chemistry* **2010,** *2010* (25), 4893-4901.

104. Gelalcha, F. G.; Anilkumar, G.; Tse, M. K.; Brückner, A.; Beller, M., Biomimetic Iron-Catalyzed Asymmetric Epoxidation of Aromatic Alkenes by Using Hydrogen Peroxide. *Chemistry – A European Journal* **2008,** *14* (25), 7687-7698.

105. Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M., Iron-Catalyzed Asymmetric Epoxidation of Aromatic Alkenes Using Hydrogen Peroxide. *Angewandte Chemie International Edition* **2007,** *46* (38), 7293-7296.

106. Cussó, O.; Garcia-Bosch, I.; Ribas, X.; Lloret-Fillol, J.; Costas, M., Asymmetric Epoxidation with H_2O_2 by Manipulating the Electronic Properties of Non-heme Iron Catalysts. *Journal of the American Chemical Society* **2013,** *135* (39), 14871-14878.

107. Dhuri, S. N.; Harmalkar, S. S., Chapter 22 - Iron-oxygen intermediates and their applications in biomimetic studies. In *Advances in Biological Science Research*, Meena, S. N.; Naik, M. M., Eds. Academic Press: 2019; pp 363-380.

108. Hohenberger, J.; Ray, K.; Meyer, K., The biology and chemistry of high-valent iron–oxo and iron–nitrido complexes. *Nature Communications* **2012,** *3* (1), 720.

109. Cho, J.; Sarangi, R.; Nam, W., Mononuclear Metal–O_2 Complexes Bearing Macrocyclic N-Tetramethylated Cyclam Ligands. *Accounts of Chemical Research* **2012,** *45* (8), 1321-1330.

110. Nam, W.; Lee, Y.-M.; Fukuzumi, S., Tuning Reactivity and Mechanism in Oxidation Reactions by Mononuclear Nonheme Iron(IV)-Oxo Complexes. *Accounts of Chemical Research* **2014,** *47* (4), 1146-1154.

111. Siewert, I.; Limberg, C., Low-Molecular-Weight Analogues of the Soluble Methane Monooxygenase (sMMO): From the Structural Mimicking of Resting States and Intermediates to Functional Models. *Chemistry – A European Journal* **2009,** *15* (40), 10316-10328.

112. Xiao, D. J.; Bloch, E. D.; Mason, J. A.; Queen, W. L.; Hudson, M. R.; Planas, N.; Borycz, J.; Dzubak, A. L.; Verma, P.; Lee, K.; Bonino, F.; Crocellà, V.; Yano, J.; Bordiga, S.; Truhlar, D. G.; Gagliardi, L.; Brown, C. M.; Long, J. R., Oxidation of ethane to ethanol by N_2O in a metal–organic framework with coordinatively unsaturated iron(II) sites. *Nature Chemistry* **2014,** *6* (7), 590-595.

113. Collman, J. P.; Gagne, R. R.; Reed, C. A.; Robinson, W. T.; Rodley, G. A., Structure of an Iron(II) Dioxygen Complex; A Model for Oxygen Carrying Hemeproteins. *Proceedings of the National Academy of Sciences* **1974,** *71* (4), 1326-1329.

114. Hong, S.; Sutherlin, K. D.; Park, J.; Kwon, E.; Siegler, M. A.; Solomon, E. I.; Nam, W., Crystallographic and spectroscopic characterization and reactivities of a mononuclear non-haem iron(III)-superoxo complex. *Nature Communications* **2014,** *5* (1), 5440.

115. Phillips, S. E. V.; Perutz, M. F., Structure of Oxymyoglobin. *Biochemical Society Transactions* **1978,** *6* (2), 368-368.

116. Momenteau, M.; Reed, C. A., Synthetic Heme-Dioxygen Complexes. *Chemical Reviews* **1994,** *94* (3), 659-698.

117. Karlsson, A.; Parales, J. V.; Parales, R. E.; Gibson, D. T.; Eklund, H.; Ramaswamy, S., Crystal Structure of Naphthalene Dioxygenase: Side-on Binding of Dioxygen to Iron. *Science* **2003,** *299* (5609), 1039-1042.

118. Jousserandot, A.; Boucher, J.-L.; Henry, Y.; Niklaus, B.; Clement, B.; Mansuy, D., Microsomal Cytochrome P450 Dependent Oxidation of N-Hydroxyguanidines, Amidoximes, and Ketoximes: Mechanism of the Oxidative Cleavage of Their CN(OH) Bond with Formation of Nitrogen Oxides. *Biochemistry* **1998,** *37* (49), 17179-17191.

119. Singha, A.; Dey, A., Hydrogen atom abstraction by synthetic heme ferric superoxide and hydroperoxide species. *Chemical Communications* **2019,** *55* (39), 5591-5594.

120. Oddon, F.; Chiba, Y.; Nakazawa, J.; Ohta, T.; Ogura, T.; Hikichi, S., Characterization of Mononuclear Non-heme Iron(III)-Superoxo Complex with a Five-Azole Ligand Set. *Angewandte Chemie International Edition* **2015,** *54* (25), 7336-7339.

121. Chiang, C.-W.; Kleespies, S. T.; Stout, H. D.; Meier, K. K.; Li, P.-Y.; Bominaar, E. L.; Que Jr., L.; Münck, E.; Lee, W.-Z., Characterization of a Paramagnetic Mononuclear Nonheme Iron-Superoxo Complex. *Journal of the American Chemical Society* **2014,** *136* (31), 10846-10849.

122. Noh, H.; Cho, J., Synthesis, characterization and reactivity of non-heme 1st row transition metal-superoxo intermediates. *Coordination Chemistry Reviews* **2019,** *382*, 126-144.

123. Fukuzumi, S.; Lee, Y.-M.; Nam, W., Structure and reactivity of the first-row d-block metal-superoxo complexes. *Dalton Transactions* **2019,** *48* (26), 9469-9489.

124. Costas, M.; Mehn, M. P.; Jensen, M. P.; Que Jr., L., Dioxygen Activation at Mononuclear Nonheme Iron Active Sites: Enzymes, Models, and Intermediates. *Chemical Reviews* **2004,** *104* (2), 939-986.

125. Girerd, J.-J.; Banse, F.; Simaan, A. J., Characterization and Properties of Non-Heme Iron Peroxo Complexes. In *Metal-Oxo and Metal-Peroxo Species in Catalytic Oxidations*, Meunier, B., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2000; pp 145-177.

126. Vaz, A. D. N.; Roberts, E. A.; Coon, M. J., Olefin formation in the oxidative deformylation of aldehydes by cytochrome P-450. Mechanistic implications for catalysis by oxygen-derived peroxide. *Journal of the American Chemical Society* **1991,** *113* (15), 5886-5887.

127. Akhtar, M.; Calder, M. R.; Corina, D. L.; Wright, J. N., Mechanistic studies on C-19 demethylation in oestrogen biosynthesis. *Biochemical Journal* **1982,** *201* (3), 569-580.

128. Swinney, D. C.; Mak, A. Y., Androgen Formation by Cytochrome P450 CYP17. Solvent Isotope Effect and pL Studies Suggest a Role for Protons in the Regulation of Oxene versus Peroxide Chemistry. *Biochemistry* **1994,** *33* (8), 2185-2190.

129. Wertz, D. L.; Valentine, J. S., Nucleophilicity of Iron-Peroxo Porphyrin Complexes. In *Metal-Oxo and Metal-Peroxo Species in Catalytic Oxidations*, Meunier, B., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2000; pp 37-60.

130. Wolfe, M. D.; Lipscomb, J. D., Hydrogen Peroxide-coupled cis-Diol Formation Catalyzed by Naphthalene 1,2-Dioxygenase*. *Journal of Biological Chemistry* **2003,** *278* (2), 829-835.

131. Cho, J.; Jeon, S.; Wilson, S. A.; Liu, L. V.; Kang, E. A.; Braymer, J. J.; Lim, M. H.; Hedman, B.; Hodgson, K. O.; Valentine, J. S.; Solomon, E. I.; Nam, W., Structure and reactivity of a mononuclear non-haem iron(III)–peroxo complex. *Nature* **2011,** *478* (7370), 502-505.

132. Selke, M.; Valentine, J. S., Switching on the Nucleophilic Reactivity of a Ferric Porphyrin Peroxo Complex. *Journal of the American Chemical Society* **1998,** *120* (11), 2652-2653.

133. Bae, S. H.; Lee, Y.-M.; Fukuzumi, S.; Nam, W., Fine Control of the Redox Reactivity of a Nonheme Iron(III)–Peroxo Complex by Binding Redox-Inactive Metal Ions. *Angewandte Chemie International Edition* **2017,** *56* (3), 801-805.

134. van der Donk, W. A.; Krebs, C.; Bollinger, J. M., Substrate activation by iron superoxo intermediates. *Current Opinion in Structural Biology* **2010,** *20* (6), 673-683.

135. B. Jensen, K.; J. McKenzie, C.; Preuss Nielsen, L.; Zacho Pedersen, J.; Molina Svendsen, H., Deprotonation of low-spin mononuclear iron(III)–hydroperoxide complexes give transient blue species assigned to high-spin iron(III)–peroxide complexes. *Chemical Communications* **1999,** (14), 1313-1314.

136. Bukowski, M. R.; Comba, P.; Limberg, C.; Merz, M.; Que Jr., L.; Wistuba, T., Bispidine Ligand Effects on Iron/Hydrogen Peroxide Chemistry. *Angewandte Chemie International Edition* **2004,** *43* (10), 1283-1287.

137. Shaik, S.; de Visser, S. P.; Kumar, D., One oxidant, many pathways: a theoretical perspective of monooxygenation mechanisms by cytochrome P450 enzymes. *JBIC Journal of Biological Inorganic Chemistry* **2004,** *9* (6), 661-668.

138. Wang, B.; Li, C.; Cho, K.-B.; Nam, W.; Shaik, S., The $Fe^{III}(H_2O_2)$ Complex as a Highly Efficient Oxidant in Sulfoxidation Reactions: Revival of an Underrated Oxidant in Cytochrome P450. *Journal of Chemical Theory and Computation* **2013,** *9* (6), 2519-2525.

139. Park, M. J.; Lee, J.; Suh, Y.; Kim, J.; Nam, W., Reactivities of Mononuclear Non-Heme Iron Intermediates Including Evidence that Iron(III)−Hydroperoxo Species Is a Sluggish Oxidant. *Journal of the American Chemical Society* **2006,** *128* (8), 2630-2634.

140. Nam, W., Dioxygen Activation by Metalloenzymes and Models. *Accounts of Chemical Research* **2007,** *40* (7), 465-465.

141. Baldwin, J. E.; Bradley, M., Isopenicillin N synthase: mechanistic studies. *Chemical Reviews* **1990,** *90* (7), 1079-1088.

142.   Guo, M.; Corona, T.; Ray, K.; Nam, W., Heme and Nonheme High-Valent Iron and Manganese Oxo Cores in Biological and Abiological Oxidation Reactions. *ACS Central Science* **2019,** *5* (1), 13-28.

143.   Bollinger, J. M.; Krebs, C., Stalking intermediates in oxygen activation by iron enzymes: Motivation and method. *Journal of Inorganic Biochemistry* **2006,** *100* (4), 586-605.

144.   Krebs, C.; Galonić Fujimori, D.; Walsh, C. T.; Bollinger, J. M., Non-Heme Fe(IV)–Oxo Intermediates. *Accounts of Chemical Research* **2007,** *40* (7), 484-492.

145.   Penner-Hahn, J. E.; McMurry, T. J.; Renner, M.; Latos-Grazynsky, L.; Eble, K. S.; Davis, I. M.; Balch, A. L.; Groves, J. T.; Dawson, J. H.; Hodgson, K. O., X-ray absorption spectroscopic studies of high valent iron porphyrins. Horseradish peroxidase compounds I and II and synthetic models. *Journal of Biological Chemistry* **1983,** *258* (21), 12761-4.

146.   Berglund, G. I.; Carlsson, G. H.; Smith, A. T.; Szöke, H.; Henriksen, A.; Hajdu, J., The catalytic pathway of horseradish peroxidase at high resolution. *Nature* **2002,** *417* (6887), 463-468.

147.   Jin, S.; Makris, T. M.; Bryson, T. A.; Sligar, S. G.; Dawson, J. H., Epoxidation of Olefins by Hydroperoxo−Ferric Cytochrome P450. *Journal of the American Chemical Society* **2003,** *125* (12), 3406-3407.

148.   Hersleth, H.-P.; Ryde, U.; Rydberg, P.; Görbitz, C. H.; Andersson, K. K., Structures of the high-valent metal-ion haem–oxygen intermediates in peroxidases, oxygenases and catalases. *Journal of Inorganic Biochemistry* **2006,** *100* (4), 460-476.

149.   Rittle, J.; Green, M. T., Cytochrome P450 Compound I: Capture, Characterization, and C-H Bond Activation Kinetics. *Science* **2010,** *330* (6006), 933.

150.   Yosca, T. H.; Rittle, J.; Krest, C. M.; Onderko, E. L.; Silakov, A.; Calixto, J. C.; Behan, R. K.; Green, M. T., Iron(IV)hydroxide pK_a and the Role of Thiolate Ligation in C–H Bond Activation by Cytochrome P450. *Science* **2013,** *342* (6160), 825.

151.   Groves, J. T.; Haushalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J., High-valent iron-porphyrin complexes related to peroxidase and cytochrome P-450. *Journal of the American Chemical Society* **1981,** *103* (10), 2884-2886.

152.   Fujii, H., Electronic structure and reactivity of high-valent oxo iron porphyrins. *Coordination Chemistry Reviews* **2002,** *226* (1), 51-60.

153.   Goh, Y. M.; Nam, W., Significant Electronic Effect of Porphyrin Ligand on the Reactivities of High-Valent Iron(IV) Oxo Porphyrin Cation Radical Complexes. *Inorganic Chemistry* **1999,** *38* (5), 914-920.

154.   Price, J. C.; Barr, E. W.; Tirupati, B.; Bollinger, J. M.; Krebs, C., The First Direct Characterization of a High-Valent Iron Intermediate in the Reaction of an α-Ketoglutarate-Dependent Dioxygenase: A High-Spin Fe(IV) Complex in Taurine/α-Ketoglutarate Dioxygenase (TauD) from Escherichia coli. *Biochemistry* **2004,** *43* (4), 1134-1134.

155.   Grapperhaus, C. A.; Mienert, B.; Bill, E.; Weyhermüller, T.; Wieghardt, K., Mononuclear (Nitrido)iron(V) and (Oxo)iron(IV) Complexes via Photolysis of [(cyclam-acetato)Fe^{III}(N$_3$)]$^+$ and Ozonolysis of [(cyclam-acetato)Fe^{III}(O$_3$SCF$_3$)]$^+$ in Water/Acetone Mixtures. *Inorganic Chemistry* **2000,** *39* (23), 5306-5317.

156.   Seo, M. S.; Kim, N. H.; Cho, K.-B.; So, J. E.; Park, S. K.; Clémancey, M.; Garcia-Serres, R.; Latour, J.-M.; Shaik, S.; Nam, W., A mononuclear nonheme iron(IV)-oxo complex which is more reactive than cytochrome P450 model compound I. *Chemical Science* **2011,** *2* (6), 1039-1045.

157.   Biswas, A. N.; Puri, M.; Meier, K. K.; Oloo, W. N.; Rohde, G. T.; Bominaar, E. L.; Münck, E.; Que Jr., L., Modeling TauD-J: A High-Spin Nonheme Oxoiron(IV) Complex with High Reactivity toward C–H Bonds. *Journal of the American Chemical Society* **2015,** *137* (7), 2428-2431.

158.   Rohde, J.-U.; In, J.-H.; Lim, M. H.; Brennessel, W. W.; Bukowski, M. R.; Stubna, A.; Münck, E.; Nam, W.; Que Jr., L., Crystallographic and Spectroscopic Characterization of a Nonheme Fe(IV)=O Complex. *Science* **2003,** *299* (5609), 1037-1039.

159.   Xue, G.; De Hont, R.; Münck, E.; Que Jr., L., Million-fold activation of the [Fe$_2$(μ-O)$_2$] diamond core for C-H bond cleavage. *Nature chemistry* **2010,** *2* (5), 400-405.

160.   Engelmann, X.; Malik, D. D.; Corona, T.; Warm, K.; Farquhar, E. R.; Swart, M.; Nam, W.; Ray, K., Trapping of a Highly Reactive Oxoiron(IV) Complex in the Catalytic Epoxidation of Olefins by Hydrogen Peroxide. *Angewandte Chemie International Edition* **2019,** *58* (12), 4012-4016.

161.   de Visser, S. P.; Rohde, J.-U.; Lee, Y.-M.; Cho, J.; Nam, W., Intrinsic properties and reactivities of mononuclear nonheme iron–oxygen complexes bearing the tetramethylcyclam ligand. *Coordination Chemistry Reviews* **2013,** *257* (2), 381-393.

162.   Hong, S.; So, H.; Yoon, H.; Cho, K.-B.; Lee, Y.-M.; Fukuzumi, S.; Nam, W., Reactivity comparison of high-valent iron(IV)-oxo complexes bearing N-tetramethylated cyclam ligands with different ring size. *Dalton Transactions* **2013,** *42* (22), 7842-7845.

163.   Kleespies, S. T.; Oloo, W. N.; Mukherjee, A.; Que Jr., L., C–H Bond Cleavage by Bioinspired Nonheme Oxoiron(IV) Complexes, Including Hydroxylation of n-Butane. *Inorganic Chemistry* **2015,** *54* (11), 5053-5064.

164.   Wilson, S. A.; Chen, J.; Hong, S.; Lee, Y.-M.; Clémancey, M.; Garcia-Serres, R.; Nomura, T.; Ogura, T.; Latour, J.-M.; Hedman, B.; Hodgson, K. O.; Nam, W.; Solomon, E. I., $[Fe^{IV}=O(TBC)(CH_3CN)]^{2+}$: Comparative Reactivity of Iron(IV)-Oxo Species with Constrained Equatorial Cyclam Ligation. *Journal of the American Chemical Society* **2012,** *134* (28), 11791-11806.

165.   Kaizer, J.; Klinker, E. J.; Oh, N. Y.; Rohde, J.-U.; Song, W. J.; Stubna, A.; Kim, J.; Münck, E.; Nam, W.; Que Jr., L., Nonheme $Fe^{IV}O$ Complexes That Can Oxidize the C−H Bonds of Cyclohexane at Room Temperature. *Journal of the American Chemical Society* **2004,** *126* (2), 472-473.

166.   Mitra, M.; Nimir, H.; Demeshko, S.; Bhat, S. S.; Malinkin, S. O.; Haukka, M.; Lloret-Fillol, J.; Lisensky, G. C.; Meyer, F.; Shteinman, A. A.; Browne, W. R.; Hrovat, D. A.; Richmond, M. G.; Costas, M.; Nordlander, E., Nonheme Fe(IV) Oxo Complexes of Two New Pentadentate Ligands and Their Hydrogen-Atom and Oxygen-Atom Transfer Reactions. *Inorganic Chemistry* **2015,** *54* (15), 7152-7164.

167.   Wang, D.; Ray, K.; Collins, M. J.; Farquhar, E. R.; Frisch, J. R.; Gómez, L.; Jackson, T. A.; Kerscher, M.; Waleska, A.; Comba, P.; Costas, M.; Que Jr., L., Nonheme oxoiron(IV) complexes of pentadentate N5 ligands: spectroscopy, electrochemistry, and oxidative reactivity. *Chemical Science* **2013,** *4* (1), 282-291.

168.   Shaik, S.; Hirao, H.; Kumar, D., Reactivity of High-Valent Iron–Oxo Species in Enzymes and Synthetic Reagents: A Tale of Many States. *Accounts of Chemical Research* **2007,** *40* (7), 532-542.

169.   Cho, K.-B.; Shaik, S.; Nam, W., Theoretical predictions of a highly reactive non-heme Fe(IV)=O complex with a high-spin ground state. *Chemical Communications* **2010,** *46* (25), 4511-4513.

170.   Puri, M.; Que Jr., L., Toward the Synthesis of More Reactive S = 2 Non-Heme Oxoiron(IV) Complexes. *Accounts of Chemical Research* **2015,** *48* (8), 2443-2452.

171.   Biswas, A. N.; Das, P.; Agarwala, A.; Bandyopadhyay, D.; Bandyopadhyay, P., Selective hydroxylation of alkanes catalyzed by iron(IV)corrole. *Journal of Molecular Catalysis A: Chemical* **2010,** *326* (1), 94-98.

172.   Paine, T. K.; Costas, M.; Kaizer, J.; Que Jr., L., Oxoiron(IV) complexes of the tris(2-pyridylmethyl)amine ligand family: effect of pyridine α-substituents. *JBIC Journal of Biological Inorganic Chemistry* **2006,** *11* (3), 272-276.

173.   England, J.; Martinho, M.; Farquhar, E. R.; Frisch, J. R.; Bominaar, E. L.; Münck, E.; Que Jr., L., A Synthetic High-Spin Oxoiron(IV) Complex: Generation, Spectroscopic Characterization, and Reactivity. *Angewandte Chemie International Edition* **2009,** *48* (20), 3622-3626.

174.   Pestovsky, O.; Stoian, S.; Bominaar, E. L.; Shan, X.; Münck, E.; Que Jr., L.; Bakac, A., Aqueous $Fe^{IV}=O$: Spectroscopic Identification and Oxo-Group Exchange. *Angewandte Chemie International Edition* **2005,** *44* (42), 6871-6874.

175.   Tinberg, C. E.; Lippard, S. J., Revisiting the Mechanism of Dioxygen Activation in Soluble Methane Monooxygenase from M. capsulatus (Bath): Evidence for a Multi-Step, Proton-Dependent Reaction Pathway. *Biochemistry* **2009,** *48* (51), 12145-12158.

176.   Castillo, R. G.; Banerjee, R.; Allpress, C. J.; Rohde, G. T.; Bill, E.; Que Jr., L.; Lipscomb, J. D.; DeBeer, S., High-Energy-Resolution Fluorescence-Detected X-ray Absorption of the Q Intermediate of Soluble Methane Monooxygenase. *Journal of the American Chemical Society* **2017,** *139* (49), 18024-18033.

177.   Xue, G.; Wang, D.; De Hont, R.; Fiedler, A. T.; Shan, X.; Münck, E.; Que Jr., L., A synthetic precedent for the [Fe^{IV2}(μ-O)$_2$] diamond core proposed for methane monooxygenase intermediate Q. *Proceedings of the National Academy of Sciences* **2007,** *104* (52), 20713-20718.

178.   Kodera, M.; Itoh, M.; Kano, K.; Funabiki, T.; Reglier, M., A Diiron Center Stabilized by a Bis-TPA Ligand as a Model of Soluble Methane Monooxygenase: Predominant Alkene Epoxidation with H$_2$O$_2$. *Angewandte Chemie International Edition* **2005,** *44* (43), 7104-7106.

179.   Li, F.; Meier, K. K.; Cranswick, M. A.; Chakrabarti, M.; Van Heuvelen, K. M.; Münck, E.; Que Jr., L., Characterization of a High-Spin Non-Heme Fe^{III}−OOH Intermediate and Its Quantitative Conversion to an Fe^{IV}=O Complex. *Journal of the American Chemical Society* **2011,** *133* (19), 7256-7259.

180.   Bang, S.; Park, S.; Lee, Y.-M.; Hong, S.; Cho, K.-B.; Nam, W., Demonstration of the Heterolytic O-O Bond Cleavage of Putative Nonheme Iron(II)-OOH(R) Complexes for Fenton and Enzymatic Reactions. *Angewandte Chemie International Edition* **2014,** *53* (30), 7843-7847.

181.   Comba, P.; Gahan, L. R.; Hanson, G. R.; Mereacre, V.; Noble, C. J.; Powell, A. K.; Prisecaru, I.; Schenk, G.; Zajaczkowski-Fischer, M., Monoesterase Activity of a Purple Acid Phosphatase Mimic with a Cyclam Platform. *Chemistry – A European Journal* **2012,** *18* (6), 1700-1710.

182.   Hubin, T. J.; McCormick, J. M.; Collinson, S. R.; Buchalova, M.; Perkins, C. M.; Alcock, N. W.; Kahol, P. K.; Raghunathan, A.; Busch, D. H., New Iron(II) and Manganese(II) Complexes of Two Ultra-Rigid, Cross-Bridged Tetraazamacrocycles for Catalysis and Biomimicry. *Journal of the American Chemical Society* **2000,** *122* (11), 2512-2522.

183.   CRC Handbook of Chemistry and Physics, 2009−2010, 90th ed. *Journal of the American Chemical Society* **2009,** *131* (35), 12862-12862.

184.   Cho, K.-B.; Hirao, H.; Shaik, S.; Nam, W., To rebound or dissociate? This is the mechanistic question in C–H hydroxylation by heme and nonheme metal–oxo complexes. *Chemical Society Reviews* **2016,** *45* (5), 1197-1210.

185.   Kwon, Y. H.; Mai, B. K.; Lee, Y.-M.; Dhuri, S. N.; Mandal, D.; Cho, K.-B.; Kim, Y.; Shaik, S.; Nam, W., Determination of Spin Inversion Probability, H-Tunneling Correction, and Regioselectivity in the Two-State Reactivity of Nonheme Iron(IV)-Oxo Complexes. *The Journal of Physical Chemistry Letters* **2015,** *6* (8), 1472-1476.

186.   Dhuri, S. N.; Cho, K.-B.; Lee, Y.-M.; Shin, S. Y.; Kim, J. H.; Mandal, D.; Shaik, S.; Nam, W., Interplay of Experiment and Theory in Elucidating Mechanisms of Oxidation Reactions by a Nonheme Ru^{IV}O Complex. *Journal of the American Chemical Society* **2015,** *137* (26), 8623-8632.

187.   Suh, Y.; Seo, M. S.; Kim, K. M.; Kim, Y. S.; Jang, H. G.; Tosha, T.; Kitagawa, T.; Kim, J.; Nam, W., Nonheme iron(II) complexes of macrocyclic ligands in the generation of oxoiron(IV) complexes and the catalytic epoxidation of olefins. *Journal of Inorganic Biochemistry* **2006,** *100* (4), 627-633.

188.   Bae, S. H.; Seo, M. S.; Lee, Y.-M.; Cho, K.-B.; Kim, W.-S.; Nam, W., Mononuclear Nonheme High-Spin (S=2) versus Intermediate-Spin (S=1) Iron(IV)–Oxo Complexes in Oxidation Reactions. *Angewandte Chemie International Edition* **2016,** *55* (28), 8027-8031.

189.   Rohde, J.-U.; Stubna, A.; Bominaar, E. L.; Münck, E.; Nam, W.; Que Jr., L., Nonheme Oxoiron(IV) Complexes of Tris(2-pyridylmethyl)amine with cis-Monoanionic Ligands. *Inorganic Chemistry* **2006,** *45* (16), 6435-6445.

190.   Chen, J.; Jiang, Z.; Fukuzumi, S.; Nam, W.; Wang, B., Artificial nonheme iron and manganese oxygenases for enantioselective olefin epoxidation and alkane hydroxylation reactions. *Coordination Chemistry Reviews* **2020,** *421*, 213443.

191.   Chen, Z.; Yin, G., The reactivity of the active metal oxo and hydroxo intermediates and their implications in oxidations. *Chemical Society Reviews* **2015,** *44* (5), 1083-1100.

192. Baglia, R. A.; Zaragoza, J. P. T.; Goldberg, D. P., Biomimetic Reactivity of Oxygen-Derived Manganese and Iron Porphyrinoid Complexes. *Chemical Reviews* **2017,** *117* (21), 13320-13352.

193. Huang, X.; Groves, J. T., Oxygen Activation and Radical Transformations in Heme Proteins and Metalloporphyrins. *Chemical Reviews* **2018,** *118* (5), 2491-2553.

194. Kass, D.; Corona, T.; Warm, K.; Braun-Cula, B.; Kuhlmann, U.; Bill, E.; Mebs, S.; Swart, M.; Dau, H.; Haumann, M.; Hildebrandt, P.; Ray, K., Stoichiometric Formation of an Oxoiron(IV) Complex by a Soluble Methane Monooxygenase Type Activation of O_2 at an Iron(II)-Cyclam Center. *Journal of the American Chemical Society* **2020,** *142* (13), 5924-5928.

195. Li, F.; England, J.; Que Jr., L., Near-Stoichiometric Conversion of H_2O_2 to Fe^{IV}=O at a Nonheme Iron(II) Center. Insights into the O−O Bond Cleavage Step. *Journal of the American Chemical Society* **2010,** *132* (7), 2134-2135.

196. Hirao, H.; Li, F.; Que Jr., L.; Morokuma, K., Theoretical Study of the Mechanism of Oxoiron(IV) Formation from H_2O_2 and a Nonheme Iron(II) Complex: O–O Cleavage Involving Proton-Coupled Electron Transfer. *Inorganic Chemistry* **2011,** *50* (14), 6637-6648.

197. Decker, A.; Rohde, J.-U.; Klinker, E. J.; Wong, S. D.; Que Jr., L.; Solomon, E. I., Spectroscopic and Quantum Chemical Studies on Low-Spin Fe^{IV}O Complexes: Fe−O Bonding and Its Contributions to Reactivity. *Journal of the American Chemical Society* **2007,** *129* (51), 15983-15996.

198. Lau, Y. H.; Clegg, J. K.; Price, J. R.; Macquart, R. B.; Todd, M. H.; Rutledge, P. J., Molecular Switches for any pH: A Systematic Study of the Versatile Coordination Behaviour of Cyclam Scorpionands. *Chemistry – A European Journal* **2018,** *24* (7), 1573-1585.

199. David, T.; Kubíček, V.; Gutten, O.; Lubal, P.; Kotek, J.; Pietzsch, H.-J.; Rulíšek, L.; Hermann, P., Cyclam Derivatives with a Bis(phosphinate) or a Phosphinato–Phosphonate Pendant Arm: Ligands for Fast and Efficient Copper(II) Complexation for Nuclear Medical Applications. *Inorganic Chemistry* **2015,** *54* (24), 11751-11766.

200. Haas, R. M.; Hern, Z.; Sproules, S.; Hess, C. R., An Unsymmetric Ligand Framework for Noncoupled Homo- and Heterobimetallic Complexes. *Inorganic Chemistry* **2017,** *56* (24), 14738-14742.

201. Knijnenburg, Q.; Gambarotta, S.; Budzelaar, P. H. M., Ligand-centred reactivity in diiminepyridine complexes. *Dalton Transactions* **2006,** (46), 5442-5448.

202. Römelt, C.; Weyhermüller, T.; Wieghardt, K., Structural characteristics of redox-active pyridine-1,6-diimine complexes: Electronic structures and ligand oxidation levels. *Coordination Chemistry Reviews* **2019,** *380*, 287-317.

203. Bhadra, S.; Akakura, M.; Yamamoto, H., Design of a New Bimetallic Catalyst for Asymmetric Epoxidation and Sulfoxidation. *Journal of the American Chemical Society* **2015,** *137* (50), 15612-15615.

204. Boudier, A.; Breuil, P.-A. R.; Magna, L.; Olivier-Bourbigou, H.; Braunstein, P., Ethylene oligomerization using iron complexes: beyond the discovery of bis(imino)pyridine ligands. *Chemical Communications* **2014,** *50* (12), 1398-1407.

205. Zhang, W.; Sun, W.-H.; Redshaw, C., Tailoring iron complexes for ethylene oligomerization and/or polymerization. *Dalton Transactions* **2013,** *42* (25), 8988-8997.

206. Chirik, P. J., Iron- and Cobalt-Catalyzed Alkene Hydrogenation: Catalysis with Both Redox-Active and Strong Field Ligands. *Accounts of Chemical Research* **2015,** *48* (6), 1687-1695.

207. Tondreau, A. M.; Atienza, C. C. H.; Weller, K. J.; Nye, S. A.; Lewis, K. M.; Delis, J. G. P.; Chirik, P. J., Iron Catalysts for Selective Anti-Markovnikov Alkene Hydrosilylation Using Tertiary Silanes. *Science* **2012,** *335* (6068), 567-570.

208. Russell, S. K.; Lobkovsky, E.; Chirik, P. J., Iron-Catalyzed Intermolecular [2π + 2π] Cycloaddition. *Journal of the American Chemical Society* **2011,** *133* (23), 8858-8861.

209. Biernesser, A. B.; Delle Chiaie, K. R.; Curley, J. B.; Byers, J. A., Block Copolymerization of Lactide and an Epoxide Facilitated by a Redox Switchable Iron-Based Catalyst. *Angewandte Chemie International Edition* **2016,** *55* (17), 5251-5254.

210.   Qi, M.; Dong, Q.; Wang, D.; Byers, J. A., Electrochemically Switchable Ring-Opening Polymerization of Lactide and Cyclohexene Oxide. *Journal of the American Chemical Society* **2018,** *140* (17), 5686-5690.

211.   Thammavongsy, Z.; Seda, T.; Zakharov, L. N.; Kaminsky, W.; Gilbertson, J. D., Ligand-Based Reduction of CO_2 and Release of CO on Iron(II). *Inorganic Chemistry* **2012,** *51* (17), 9168-9170.

212.   Arevalo, R.; Chirik, P. J., Enabling Two-Electron Pathways with Iron and Cobalt: From Ligand Design to Catalytic Applications. *Journal of the American Chemical Society* **2019,** *141* (23), 9106-9123.

213.   Hofmann, A. J.; Jandl, C.; Hess, C. R., Structural Differences and Redox Properties of Unsymmetric Diiron PDIxCy Complexes. *European Journal of Inorganic Chemistry* **2020,** *2020* (5), 499-505.

214.   Bart, S. C.; Lobkovsky, E.; Chirik, P. J., Preparation and Molecular and Electronic Structures of Iron(0) Dinitrogen and Silane Complexes and Their Application to Catalytic Hydrogenation and Hydrosilation. *Journal of the American Chemical Society* **2004,** *126* (42), 13794-13807.

215.   Hofmann, A. J.; Niederegger, L.; Hess, C. R., Neighbouring effects on catalytic epoxidation by Fe-cyclam in M_2-PDIxCy complexes. *Dalton Transactions* **2020,** *49* (48), 17642-17648.