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Towards Real-Life Applications: Reactivity of Biomimetic Iron *N*-Heterocyclic Carbene Complexes in Homogeneous Catalysis

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„Stets findet Überraschung statt

Da, wo man's nicht erwartet hat."

Wilhelm Busch (1908)

Mein ganz besonderer Dank gilt meinem Doktorvater

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für die unkomplizierte Aufnahme in seinen Arbeitskreis, das mir entgegengebrachte Vertrauen und die spannenden Forschungsmöglichkeiten. Vielen Dank für die Betreuung während der letzten Jahre in Form von vielen konstruktiven aber auch unterhaltsamen Gesprächen sowie die großzügigen Freiräume, die zu einem angenehmen und produktiven Forschungsumfeld beigetragen haben.

KURZZUSAMMENFASSUNG

Im Rahmen dieser Arbeit wird die katalytische Anwendung von Eisen(II) *N*-heterozyklischen Carben (NHC) Komplexen untersucht, wobei reale Fragestellungen der chemischen Synthese im Vordergrund stehen.

Die selektive Oxidation nicht-aktivierter Aromaten ist eine zentrale Reaktion in der Synthese von Basis- und Feinchemikalien sowie in biologischen Prozessen. Dennoch bereitet diese aufgrund der Inertheit der Substrate und Reaktivität der Produkte in der Praxis oft Schwierigkeiten, sodass auf mehrstufige Syntheseprozesse zurückgegriffen werden muss. Inspiriert durch die hohe Effizienz, mit der natürlich vorkommende Enzyme derartige Reaktionen katalysieren, wurde in den letzten Jahrzehnten intensiv an der Entwicklung von biomimetischen Oxidationskatalysatoren geforscht. Im Rahmen dieser Arbeit wird ein Eisen(II) Komplex, der durch einen donorsubstituierten bis-NHC Liganden stabilisiert wird, als Katalysator für die Oxidation von Alkylaromaten (*p*-Xylol und Pseudocumol) mit Wasserstoffperoxid als umweltfreundliches Oxidationsmittel eingesetzt. Dabei werden die Reaktionsbedingungen im Hinblick auf Temperatur, Oxidationsmittel und Konzentration der Reaktanden optimiert und mechanistische Aspekte der katalytischen Hydroxylierung von aromatischen C–H Bindungen durch Eisen-NHC Komplexe beleuchtet. Mittels katalytischer Modellreaktionen, Isotopenmarkierungsexperimente, kinetischer Isotopeneffekte und dichtefunktionaltheoretischer Berechnungen wird der vorherrschende Reaktionsverlauf bestimmt. In diesem Zusammenhang werden Ähnlichkeiten bezüglich der Reaktivität des synthetischen Katalysators und eisenbasierten Enzymen, wie beispielsweise das Auftreten von „NIH Shift" Reaktionen, identifiziert.

Zudem werden Modifizierungen der Axialliganden durchgeführt, um deren Einfluss auf die elektronischen Eigenschaften des Eisenzentrums zu evaluieren. Zu diesem Zweck werden labile Solvensmoleküle durch Isocyanid Liganden substituiert. Weiterhin werden Eisen-NHC Komplexe erfolgreich als Katalysatoren für Aldehydolefinierungsreaktionen eingesetzt, wobei hohe Olefinausbeuten und sehr gute Selektivität beobachtet werden. Mechanistische Studien ermöglichen Einsicht in die Details der katalytischen Reaktion und zeigen, dass der zentrale Schritt der Reaktion die Bildung eines Phosphorylids ist.

ABSTRACT

Catalytic applications of iron(II) *N*-heterocyclic carbene (NHC) complexes are explored focusing on bridging the gap between academic model reactions and real-life chemical problems relevant to organic synthesis and the industry.

The selective oxidation of non-activated arenes is central for the production of both fine and bulk chemicals, however, it remains a challenge and often multi-step processes are required. Inspired by the high efficiency of naturally occurring enzymes, which often bear iron in their active sites, extensive research efforts have been performed in the past decades to develop biomimetic oxidation catalysts. In this work an iron(II) complex bearing a donorsubstituted bis-NHC ligand is applied as catalyst for the oxidation of alkylarenes (e.g. *p*-xylene and pseudocumene) with hydrogen peroxide as environmentally benign oxidant. The optimization of the reaction conditions is conducted including the variation of temperature, oxidant and concentration and mechanistic details of the hydroxylation of aromatic C−H bonds by Fe-NHC complexes are investigated. Using catalytic probe reactions, isotope labelling studies, kinetic isotope effects and density functional theory calculations the predominant reaction pathway is determined. Moreover, close similarities between the reactivity of the synthetic catalyst and iron-based enzymes are identified including the occurrence of NIH shifts.

Modifications of the apical ligands are introduced to evaluate their influence on the electronic properties of the respective complexes. For this purpose, substitution reactions of the axially coordinating solvent molecules by isocyanides are performed. Furthermore, iron-NHC complexes are successfully applied as catalysts for Wittig-type aldehyde olefination reactions exhibiting high olefin yields and very good selectivity. Mechanistic studies allow to gain detailed insights into the catalytic reactions revealing that the key step of the reaction is the formation of a phosphorous ylide.

LIST OF ABBREVIATIONS

AAAH	aromatic amino acid hydroxylase
BHT	2,6- bis(1,1-dimethylethyl)-4-methylphenol
BTX	benzene, toluene and xylene
Cpd	compound
CYP	cytochrome P450
DFT	density functional theory
DMBQ	dimethyl-1,4-benzoquinone
DMP	dimethylphenol
EDA	ethyl diazoacetate
Fc	ferrocene
Fe(btsa)$_2$	iron(II) bis(trimethylsilyl)amide
GC	gas chromatography
HOMO	highest occupied molecular orbital
KIE	kinetic isotope effect
LUMO	lowest unoccupied molecular orbital
MeCN	acetonitrile, CH_3CN
min	minute
MS	mass spectrometry
MTO	methyltrioxorhenium
NCCN	bis(*o*-imidazol-2-ylidenepyridine)alkane
NHC	*N*-heterocyclic carbene
NIH	National Institute of Health
PheOH	phenylalanine hydroxylase
pXy	*p*-xylene
RO	Rieske oxygenase
SCXRD	single crystal x-ray diffraction
TMB	1,2,4-trimethylbenzene, pseudocumene
TMBQ	trimethyl-1,4-benzoquinone
TMHQ	trimethyl-1,4-hydroquinone
TMP	trimethylphenol
TPA	tris(2-pyridylmethyl)amine
TrpOH	tryptophan hydroxylase
TyrOH	tyrosine hydroxylase

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1 INTRODUCTION

1.1 BTX Aromatics as Valuable Feedstock for the Chemical Industry

For the chemical industry basic aromatic compounds like benzene, toluene and xylenes (BTX) are important raw materials for the synthesis of a wide range of secondary products and are produced on a scale of 10 megatons per year (Western Europe, 2015).[1] The primary sources of these compounds nowadays are the catalytic reforming of naphtha and steam cracking of pyrolysis gas.[2, 3] In order to meet the high demand for benzene, processes have been developed to interconvert for instance toluene, which is the major product of catalytic reforming, to benzene by hydrodealkylation. Other aromatic components of reformate and cracking streams are 1,2,4-trimethylbenzene (TMB, pseudocumene) and 1,2,4,5-tetramethylbenzene (durene).[2] Based on BTX aromatics a great variety of other bulk chemicals, polymers and consumer products can be obtained as depicted in Figure 1.[4]
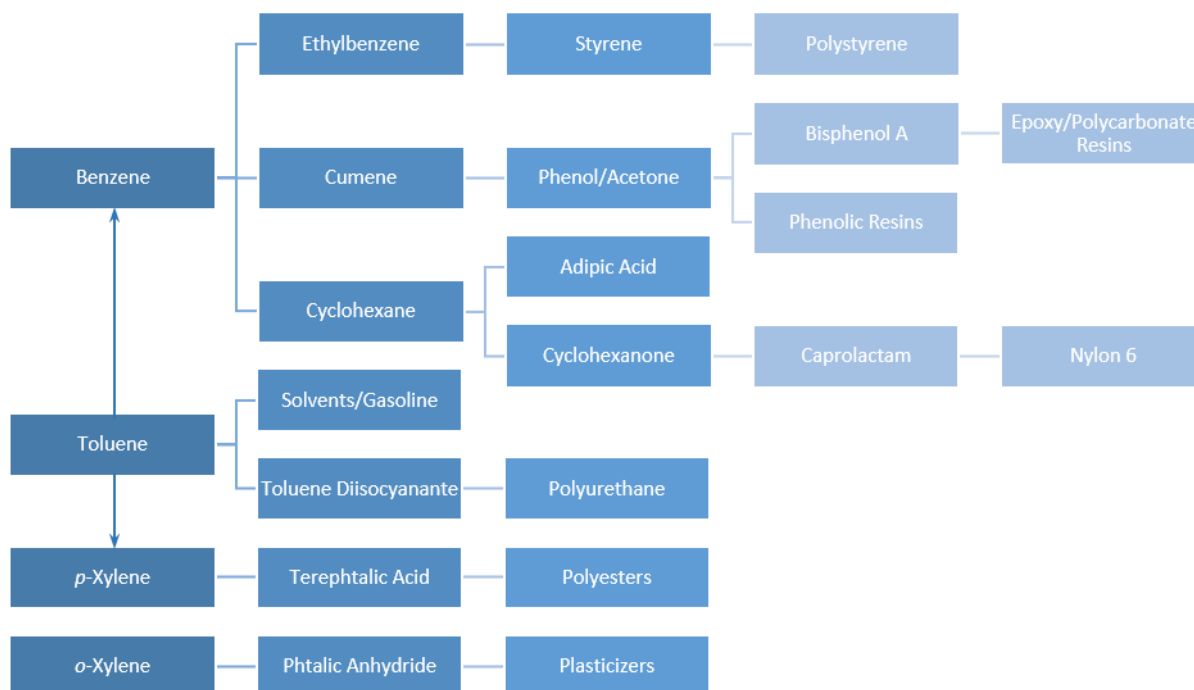
Figure 1. Secondary chemical products obtained from BTX aromatics (adopted from [4]).

A significant proportion of these BTX derivatives are ring oxidation products, such as phenols, cresols, xylenols, dihydroxybenzenes and quinones. Phenol, for instance, can be produced industrially from benzene *via* different intermediates (Scheme 1).[2, 3] In the classical process benzene is firstly sulfonated to benzenesulfonic acid followed by reaction of the corresponding sulfonate salt with alkali. Alternatively, chlorobenzene is formed by reaction of benzene with Cl_2, which is subsequently hydrolyzed by aqueous alkaline solution. The most important phenol production route, however, is the Hock process: Firstly, benzene is alkylated with propylene *via* acid catalysis and in the presence of

oxygen from the air it is further oxidized to cumene hydroperoxide. Finally, the hydroperoxide is cleaved to form phenol and acetone. All these processes have in common that they are indirect procedures. Direct oxidation of benzene to phenol would be desirable, however selectivity issues arise as the phenolic product is more activated, i.e. easier to oxidize, than the non-activated substrate. Therefore, overoxidation is likely to occur.
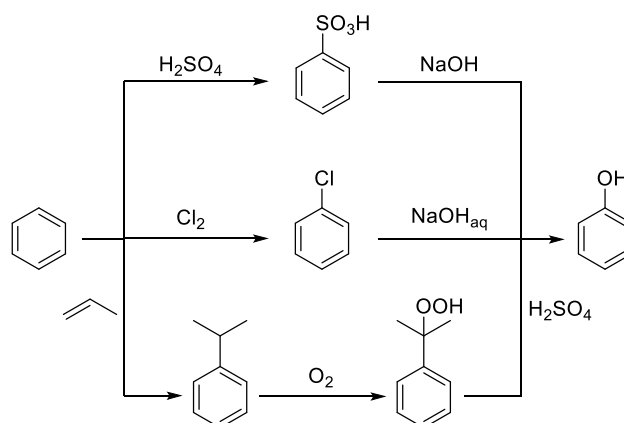
Scheme 1. Industrially relevant synthetic routes to phenol from benzene.[2, 3]

However, in some cases quinones may also be the desired oxidation products as they serve as building blocks for many biologically active compounds such as vitamins (Scheme 2).[5] Vitamin E, for instance, comprises a group of eight compounds derived from a 6-chromanol scaffold bearing either an unsaturated (tocotrienols) or a saturated C_{16} side chain (tocopherols).[6-9] Of these, (all-*rac*)-α-tocopherol is produced on a scale exceeding 30,000 tons per year and presents the industrially most important fat-soluble antioxidant. One of the key building blocks for its large-scale synthesis is trimethyl-1,4-hydroquinone (TMHQ), which is reacted with isophytol in a condensation reaction. The main starting material for TMHQ synthesis is 2,3,6-timethylphenol, which is typically oxidized to trimethyl-1,4-benzoquinone (TMBQ) in the presence of copper chloride and several co-catalysts. TMBQ can then be hydrogenated to TMHQ in the presence of a noble metal catalyst. Another synthetic approach uses α-isophorone as a starting material converting it to TMHQ in a multi-step process comprising isomerization, oxidation, rearrangement and saponification steps. An appealing alternative to these processes would be the direct oxidation of pseudocumene to TMBQ in a single step.[10] However, reports on this reaction are scarce in literature. Besides organic peracids, there is a series of catalytic systems, which can mediate this challenging reaction.[11-18] Yet the reported TMBQ yields are generally rather low (< 20%) as the selectivity is corrupted by the inherent asymmetrical substitution pattern of the substrate. Furthermore, catalytic systems often use expensive transition metals such as rhenium or palladium and require high catalyst loadings and/or amounts of oxidant.
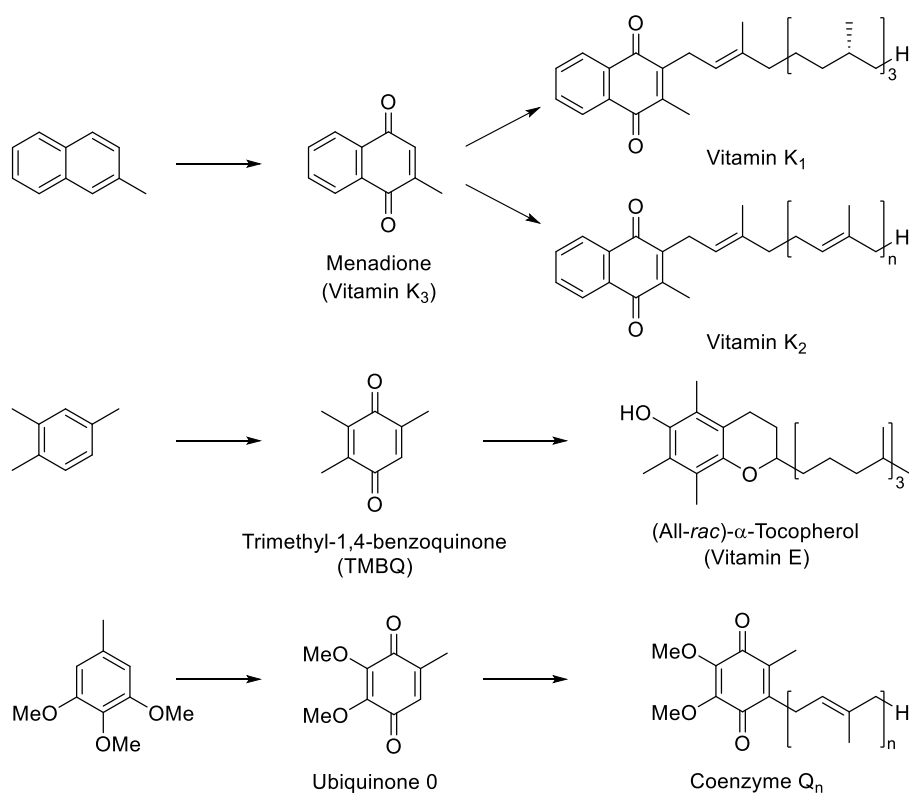
Scheme 2. Examples of nuclear aromatic oxidations in the synthesis of biologically active compounds.[5]

As it can be seen from the examples presented above, the selective oxidation of non-activated arenes to phenolic and quinoid products is a central reaction in the production of bulk and fine chemicals as well as organic synthesis. However, it also ranges among the most challenging ones and single-step synthetic procedures still remain largely infeasible. Extensive research is being performed to realize such reactions by developing suitable catalysts on the basis of inexpensive and non-toxic materials.[19, 20] Additionally, considering the growing demand for environmentally benign chemical processes, the nature of the oxidant has become an important aspect. Molecular oxygen (ideally from air) and hydrogen peroxide are generally considered to be the most environmentally friendly oxidants as their use is highly atom-efficient and involves a minimum amount of byproducts.[21, 22]

Furthermore, in the prospect of a limited availability of fossil fuels, which are the primary source of BTX aromatics for the chemical industry, the search for alternative resources has become increasingly important. In this context lingocellulosic biomass has emerged as a valuable source for the sustainable production of both fuels and chemicals.[23-25] One of its major components is lignin, an amorphous three-dimensional polymer consisting of methoxylated phenylpropane units. In plants it accounts for structural strength and rigidity and protects the other major components cellulose and hemicellulose from microbial attack. Currently it is already produced in large quantities as a byproduct of the pulp and paper industry, however, most of it is only burned as a low-value fuel. Due to its aromatic nature lignin can potentially serve as a feedstock for simple arene compounds and various routes have been

explored for its depolymerization yielding monomeric aromatic compounds.[23, 25] These are usually highly functionalized with alcohol, aldehyde or other substituent groups so that they can either be reduced to classical BTX aromatics or directly used for the synthesis of valuable bulk and fine chemicals. The latter would avoid the demanding oxidative activation of non-activated arenes.[23] Yet the complex lignin structure, exhibiting various distinct and chemically different binding motifs, renders this task particularly challenging and research is still ongoing in order to develop effective, sustainable and feasible valorization strategies.[25]

1.2 Biochemical Inspirations: Enzymatic Oxidation of Arenes

Nature has solved the problem of the selective oxofunctionalization of aromatic substrates under mild conditions by employing metalloenzymes, which mediate such reactions with very high chemo-, regio- and stereoselectivity.[26, 27] Overoxidation of phenols, for example, is avoided as the active sites of many enzymes are located in a hydrophobic pocket. This allows lipophilic substrates to approach the active site, but simultaneously promotes the release of the more hydrophilic oxidation products.[5] Prominent examples of enzymes, which catalyze the oxidation of aromatic C−H bonds are the heme-containing monooxygenases of the cytochrome P450 (CYP) family, the Rieske dioxygenases, and the aromatic amino acid hydroxylases (AAAHs). A common structural feature of these enzymes is their iron-containing active site. Moreover, they all use molecular oxygen as the terminal oxidant forming a peroxo intermediate, which is subsequently transformed into a high-valent iron-oxo species. Electrons are usually supplied by a NAD(P)H cofactor. In the following sections, each of these enzyme families will be presented in more detail regarding their structure and reactivity.

1.2.1 Cytochrome P450

Cytochrome P450 enzymes play a key role in the oxidative transformation of both endogenous and exogenous molecules in all kinds of organisms (plants, bacteria and mammals).[28-30] They constitute a large family of heme enzymes with more than 2000 members. Their active site contains an iron(III) porphyrin cofactor, which is axially coordinated by a cysteine residue (Scheme 3, left).
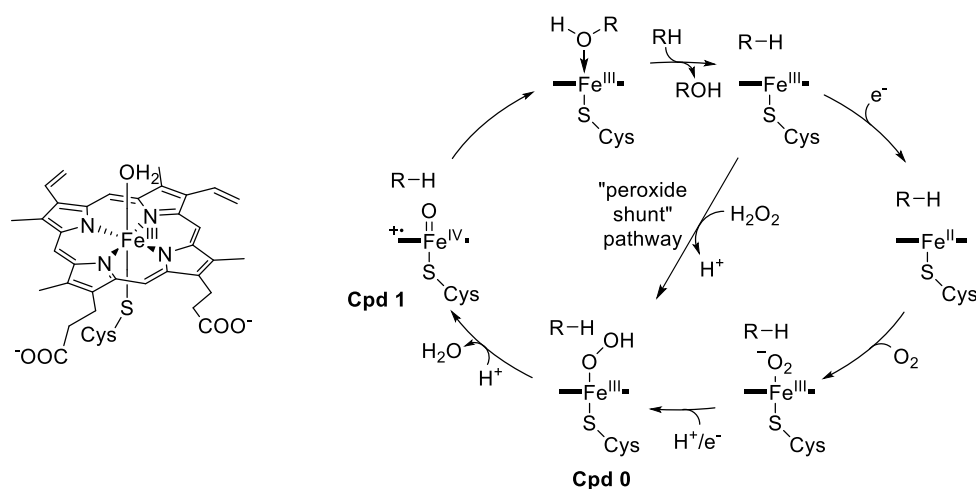
Scheme 3. Active site of cytochrome P450 enzymes (left) and proposed catalytic cycle for the hydroxylation of hydrocarbons (right).[31, 32]

Due to their almost ubiquitous nature, the mode of action by which they catalyze the oxidation of hydrocarbon substrates has been studied extensively and a consensus mechanism is presented in Scheme 3 (right). Key features of this catalytic cycle are the formation of a ferric hydroperoxo intermediate (Cpd 0) and the subsequent heterolytic cleavage of the O−O bond to a formal iron(V)-oxo species (Cpd 1), which is considered to be the active oxidant. The porphyrin ligand helps to stabilize this high-valent intermediate by delocalization of the positive charge so that Cpd 1 is better described as an oxoiron(IV) porphyrin radical $[(Por^\bullet)Fe(IV)=O]^+$. Instead of molecular oxygen, hydrogen peroxide may also serve as the oxidant forming Cpd 0 through the so-called "peroxide shunt" pathway.

Scheme 4 presents mechanistic pathways, which have been proposed for the hydroxylation of benzene by Cpd 1.[28, 33, 34] In contrast to the oxidation of aliphatic substrates, the C−H bond activation of arenes proceeds by an initial electrophilic attack yielding an iron-arene σ-complex instead of a hydrogen atom abstraction. This is owed to the comparatively high bond dissociation energy of aromatic C−H bonds (benzene: BDE_{C-H} = 112.9 kcal mol^{-1}; cyclohexane: BDE_{C-H} = 99.5 kcal mol^{-1}) and was confirmed by observation of low kinetic isotope effects (KIEs).[35-37] The arene unit of this intermediate may be either radical or cationic and *via* a 1,2-proton shift a keto-species is formed. Theoretical calculations further indicate that a proton shuttle mechanism might be relevant, where the proton temporarily binds to one of the nitrogen atoms of the porphyrin ligand.[33] The keto-intermediate further isomerizes yielding the phenol with the ferric resting state of the active site being recovered.
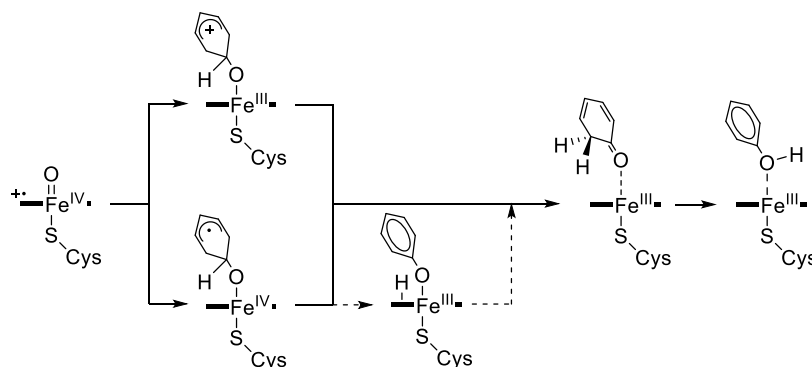
Scheme 4. Mechanistic pathways for the hydroxylation of benzene by Cpd 1.[28, 33, 34]

Within the framework of this mechanism the occurrence of so-called "NIH shifts" – named after the National Institute of Health where they were first discovered in 1967[38] – may be rationalized. This term describes the "intramolecular migration or shift of the group displaced by hydroxyl to an adjacent position of the aromatic ring"[38] where the migrating group is usually a small substituent like a deuterium, halogen or methyl group. Originally these shift reactions were associated with the intermediate formation of an arene oxide, however regarding CYP enzymes, the mechanism presented above involving an iron-arene σ-complex was soon proposed and supported by theoretical calculations.[33, 34, 36, 37, 39] So far, NIH shifts have been observed for both enzymatic as well as non-enzymatic hydroxylation reactions catalyzed by heme and non-heme molecular iron complexes.

1.2.2 Rieske Dioxygenases

Rieske dioxygenases are multicomponent, non-heme iron enzymes, which catalyze the aerobic *cis*-dihydroxylation of aromatic hydrocarbons in bacteria initiating the biodegradation of aromatics in the soil.[26, 40] Their active site, which is located in the oxygenase subunit (RO), consists of mononuclear iron(II) bound to a 2-His-1-carboxylate facial triad motif, where the iron center is coordinated by two histidines and a bidentate aspartate (Scheme 5, left). Resembling the mechanism of arene hydroxylation by CYP enzymes, firstly dioxygen is activated forming a hydroperoxo species, which is further transformed into a high-valent iron-oxo intermediate. However, in case of ROs, both oxygen atoms are transferred simultaneously to the aromatic substrate (Scheme 5, right).
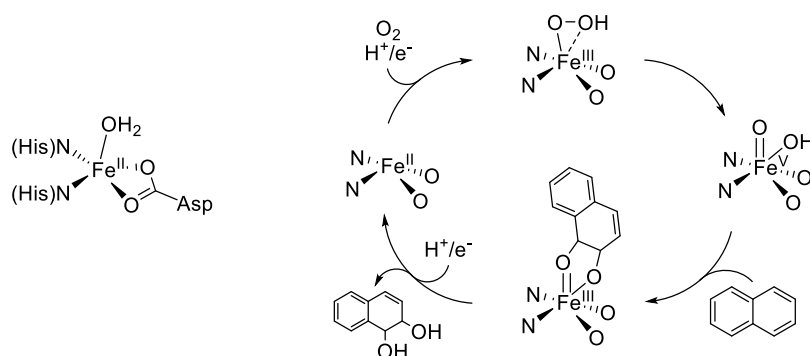
Scheme 5. Active site (left) and proposed catalytic cycle (right) for the dihydroxylation of naphthalene by naphthalenedioxygenase, a Rieske oxygenase enzyme.[26]

1.2.3 Aromatic Amino Acid Hydroxylases

The aromatic amino acid hydroxylases are a group of three pterin-dependent enzymes: phenylalanine hydroxylase (PheOH), tyrosine hydroxylase (TyrOH), and tryptophan hydroxylase (TrpOH).[41, 42] Each enzyme is designed to catalyze the hydroxylation of the aromatic side chain of a specific amino acid, which is a key step in the biosynthesis of compounds relevant to the nervous system of multicellular organisms, such as dopamine or epinephrine. Yet they share many physical, structural and catalytic properties. They are all non-heme iron enzymes bearing a ferrous iron center coordinated by two histidine residues and a glutamate (2-His-1-carboxylate facial triad). Moreover, they are monoxygenases and rely on molecular oxygen and a tetrahydropterin cofactor providing electrons for the reduction of the second oxygen atom to water. The mechanism proposed for the catalytic hydroxylation of phenylalanine by PheOH is presented in Scheme 6.[43, 44]
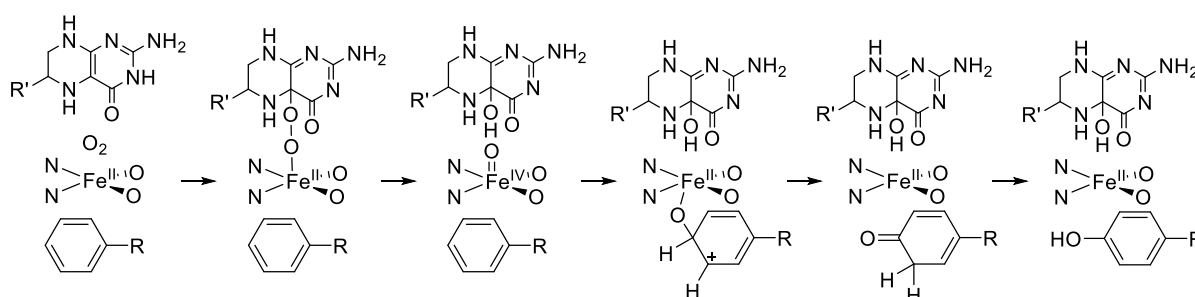
Scheme 6. Mechanism proposed for the hydroxylation of phenylalanine by PheOH in the presence of molecular oxygen and tetrahydropterin.[43, 44]

Binding of all substrates to the active site of the enzyme triggers the activation of molecular oxygen to form a high-valent iron(IV)-oxo intermediate. This reacts with the side chain of the respective amino acid to a cationic iron-arene σ-complex, which is converted to a ketone *via* a proton shift. Thus, the ferrous form of the iron center is regenerated and the phenolic product is formed by isomerization of the ketone. This mechanism has been confirmed theoretically as well as by the observation of NIH shifts and inverse KIEs, which are associated with a hybridization change from sp^2 to sp^3 at the position of deuteration upon interaction with the iron oxidant.[38, 43, 45-47]

1.3 Biomimetic Oxidation by Molecular Iron Catalysts[a]

The selective oxidative activation of hydrocarbons by enzymes has been a source of inspiration for the development of biomimetic catalysts. This approach does not only serve the need for effective and sustainable oxidation catalysts but has also aided the mechanistic understanding of biological processes.[31, 48] For instance, the stability of reactive intermediates based on synthetic model complexes may be higher compared to their enzymatic prototypes and the spectroscopic or crystallographic characterization is facilitated outside the enzymatic surrounding.

As it has been demonstrated in section 1.2 for the oxygenation of aromatic C−H bonds, iron-based enzymes are predominantly employed by nature for this type of reaction. Therefore, iron has often been chosen as central metal for the development of biomimetic catalysts. Besides, it is readily available as it is the most abundant transition metal on earth, inexpensive, and considered to be environmentally benign.[49-51] However, the latter should not be taken for granted when discussing the application of coordination compounds of iron but also other first row transition metals like copper and nickel in real-life processes. The leaching of metal ions or nanoparticles into products, solvents and waste may pose significant toxicity problems depending on the bioavailability, valence state, particle size or nature of the ligands.[52]

Since the late 1970s tremendous efforts have been directed towards the development of biomimetic iron catalysts for the oxygenation of both aliphatic and aromatic C−H bonds. They can be divided into two major classes: heme and non-heme compounds. The first group comprises iron complexes, which are supported by porphyrin or closely related ligands. The second group includes all other ligands bearing mainly *N*- and *O*-donor units. In the following sections, firstly some generally applicable mechanistic aspects will be discussed followed by an overview of important examples of biomimetic iron-based oxidation catalysts according to the two classes.

1.3.1 Iron-based Oxidation Catalysis: Mechanistic Considerations

Inspired by the work of Henry Fenton in the late 1800s the first example of the iron catalyzed direct oxidation of benzene to phenol was reported in 1900.[53, 54] What nowadays is known as the famous Fenton's reagent is a combination of a simple iron salt (e.g., $FeSO_4$) and hydrogen peroxide, which has proven to be capable of oxidizing a large variety of organic compounds.[55] It was Haber and Weiss who unraveled that the hydroxyl radical is the actual oxidant in these reactions, which is formed by the reaction of the iron cation with peroxide (equations (1) and (2)).[56] This initiates a series of radical chain

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[a] This research area has been reviewed comprehensively as part of this thesis (A. C. Lindhorst, S. Haslinger, F. E. Kühn, "Molecular Iron Complexes as Catalysts for Selective C−H Bond Oxygenation Reactions", *Chem. Commun.* **2015**, 51, 17193-17212) and a summary of the respective article is provided in section 3.1.

reactions involving the formation of long-lived alkyl radicals, which upon recombination or reaction with molecular oxygen form a mixture of different products. In the case of benzene these are, in addition to phenol, also biphenyl, catechol and dihydroquinone.

$$\text{Fe}^{\text{II}} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{\text{III}} + \text{HO}^{\bullet} + \text{HO}^{-} \tag{1}$$

$$\text{Fe}^{\text{III}} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{\text{II}} + \text{HOO}^{\bullet} + \text{H}^{+} \tag{2}$$
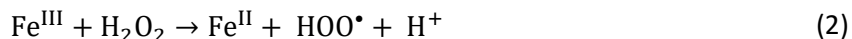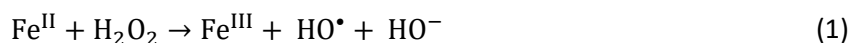
In light of the high selectivity observed for enzyme catalyzed oxidation reactions, one major goal in the development of biomimetic iron catalysts is to inhibit the occurrence of Fenton-type radical reactions.[57, 58] A common feature of both heme and non-heme based catalysts is the formation of a ferric peroxide intermediate upon reaction with a peroxide oxidant (Scheme 7).[59, 60] This may either interact directly with the substrate or undergo homolytic or heterolytic O−O bond cleavage to form a high-valent iron-oxo species. Homolytic O−O bond fission produces hydroxyl radicals, which can enter radical chain reactions rendering the reaction less selective. Therefore, as a strategy for rational catalyst design, this reaction pathway should ideally be inhibited.
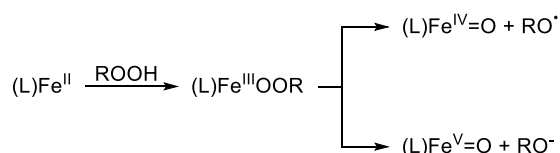
Scheme 7. Reactivity of biomimetic iron compounds with peroxides.[59, 60]

Furthermore, unselective radical reactions can be avoided by opening a metal-centered reaction pathway. Regarding the oxygenation of aliphatic C−H bonds, this implies the abstraction of a hydrogen atom by the oxidizing iron species forming a short-lived alkyl radical, which is quickly trapped by transfer of the OH group forming the alcohol product ("oxygen rebound mechanism", Scheme 8, left).[59]
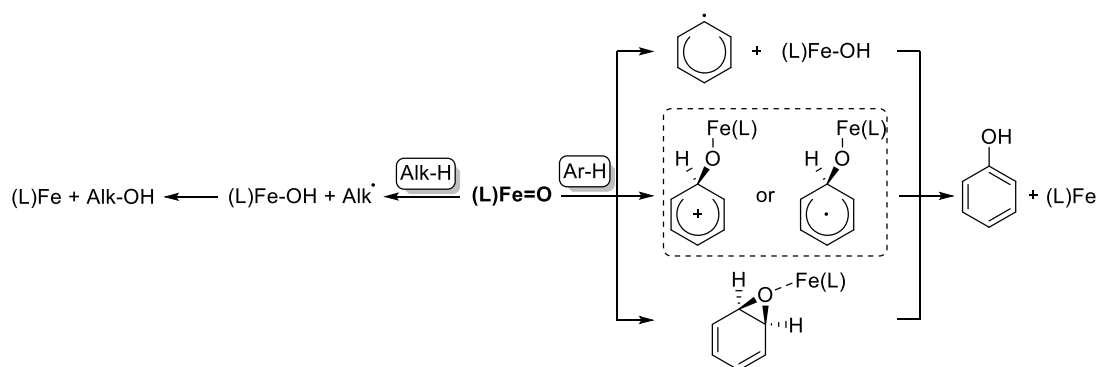
Scheme 8. Reaction pathways of the hydroxylation of aliphatic (left) and aromatic (right) C−H bonds by a high-valent iron-oxo compound.[59, 61, 62]

Considering the oxidation of arene compounds by biomimetic iron catalysts, alternatively to an oxygen rebound mechanism, electrophilic metal-centered reaction pathways have been proposed (Scheme 8, right).[61, 62] They involve either the formation of an iron-arene σ-complex analogous to the intermediate

formed in the oxidation of arenes by CYP enzymes, or an arene oxide intermediate. As the isolation or spectroscopic characterization of these intermediates is often very difficult due to their short lifetime, mechanistic probe reactions have been established to determine, which reaction pathway is prevalent. Addition of radical scavengers or the determination of Hammett ρ values and KIEs have proven to be useful tools in this context. While an inverse KIE is generally associated with the occurrence of an iron-arene σ-complex intermediate, a normal KIE points either towards the formation of an arene oxide (KIE ≈ 1.2) or a hydrogen abstraction mechanism (higher KIE).[45, 63] Moreover, both electrophilic reaction pathways help to rationalize the occurrence of NIH shift reactions, which have also been observed during the hydroxylation of (substituted) arenes by synthetic iron catalysts, thus closely resembling the reactivity of naturally occurring enzymes (cf. section 1.2).[64-69] To detect NIH shift reactivity, 1,3,5-D_3-benzene has been introduced as a useful test substrate (Scheme 9).[68] By GC-MS the relative amounts of mono- and trideuterated 1,4-benzoquinone products can be determined, which originate from a 1,2-deuterium shift reaction. Additionally, an intramolecular KIE isotope effect can be determined from the ratio of di- and trideuterated phenolic products.
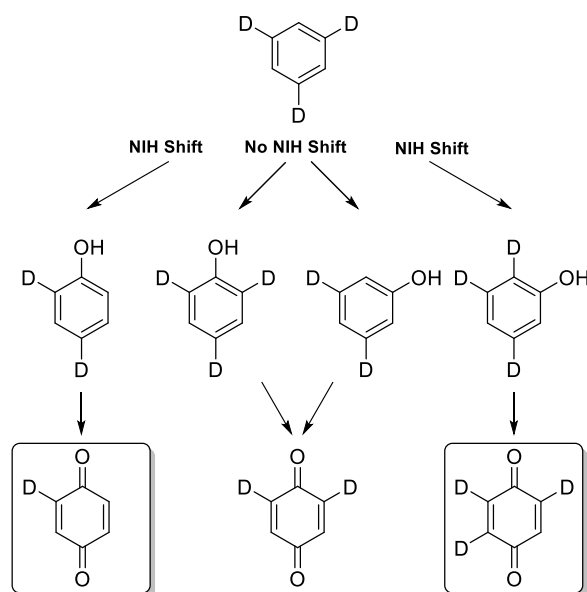
Scheme 9. 1,3,5-D_3-Benzene as a test substrate for NIH shift reactivity as described by Kudrik and Sorokin.[68]

In order to provide better comparability of different catalytic systems, benchmark substrates have been established. Regarding the oxygenation of aliphatic C−H bonds, cyclohexane and adamantane are the most widely used substrates. Their use enables the determination of certain key indicators, which help to draw conclusions about mechanistic aspects of the reaction.[59, 60, 70] Most importantly, the alcohol-to-ketone ratio (A/K) is usually provided, which indicates whether an unselective radical based reaction pathway (A/K close to unity) or a metal-centered reaction mechanism (high A/K) is predominant. The regioselectivity of the reaction is usually determined as the ratio of tertiary and secondary oxidation products of adamantane.

Concerning the oxidation of arenes, the choice of substrate is often governed by the purpose of the respective investigation. If a certain reaction product is desired, the corresponding substrate is largely predetermined. For instance, for the synthesis of menadione (Vitamin K_3) 2-methylnaphtalene is the most sensible substrate and TMBQ can potentially be obtained directly from 1,2,4-trimethylbenzene (Scheme 2). However, for mechanistic studies, mostly non-substituted arenes like benzene or anthracene are chosen as selectivity issues are less likely, facilitating the determination of kinetic parameters as well as computational modelling.

1.3.2 Biomimetic Iron-Heme Catalysts

Pioneering work on the oxidation of hydrocarbons by mononuclear iron porphyrin complexes was published by Groves et al. in 1979.[71] They applied a ferric tetrakis(phenyl)porphyrin complex to oxidize adamantane and cyclohexane with iodosylbenzene. Since then a fast evolution regarding the ligand substituents could be observed as oxidative degradation of the porphyrin structure was identified as a main catalyst degradation pathway.[72, 73] Bulky substituents in the *meso* positions of the ligand and electron withdrawing groups in the β-pyrrolic position were installed to increase the stability under oxidative conditions and the electrophilicity of the iron center. Analogous to Cpd 1 in the CYP catalyzed mechanism, an oxoiron(IV) porphyrin radical intermediate is believed to be the active oxidizing species, which is formed by reaction with peroxides according to the peroxide shunt pathway.[72, 73] Further ligand scaffolds, which are closely related to porphyrin, are depicted in Figure 2. They share a rigid, planar structure, which is induced by a continuously conjugated aromatic system, and four *N*-donor moieties facing into the ring cavity. There are several examples of iron phthalocyanine, but also corrole and porphyrazine complexes, which have been applied as catalysts for the oxidative activation of C−H bonds.[74-77]
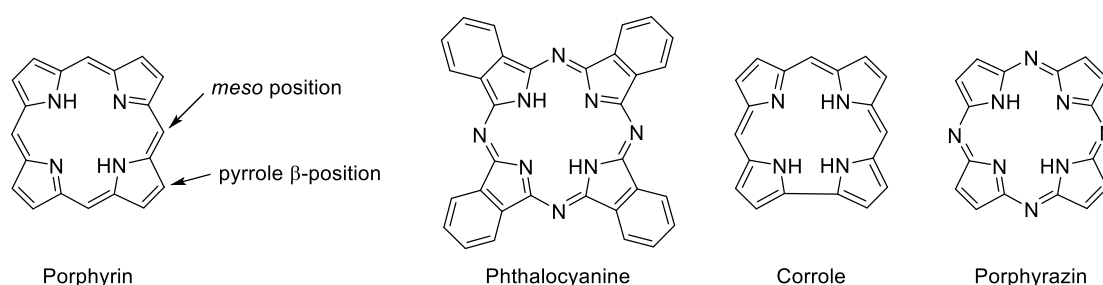
Figure 2. Basic structural motifs of heme-type ligands used for the synthesis of iron-based oxidation catalysts.

In further analogy to the CYP enzymes, the nature of the anionic axial ligand has proven to be decisive for the reactivity of synthetic metalloporphyrins.[73] It was found that the electron donating ability of the axial ligand strongly influences the basicity of the iron center. In alkane hydroxylation reactions, the activation energy for the initial C−H bond fission is reduced for porphyrin complexes bearing

electron-donating axial ligands and the Fe=O bond of the oxidizing species is weakened. This increases the reactivity of the oxidizing species towards oxygen transfer.

1.3.3 Biomimetic Iron-Non-heme Catalysts

To date the most extensively studied and also most successful non-heme iron oxidation catalysts are based on tetradentate *N*-donor ligands. As a common structural feature, they share a coordination geometry exhibiting two *cis* labile sites, which enable the formation of a high-valent oxoiron compound by a water- or acid-assisted mechanism.[57] Some prominent examples are summarized in Figure 3.

1
[Fe(TPA)Cl$_2$](ClO$_4$)

2
[Fe(BPMEN)(OTf)$_2$]

3
[Fe(PyTACN)(OTf)$_2$]

4
[Fe(*S,S*-PDP)(MeCN)$_2$](SbF$_6$)$_2$
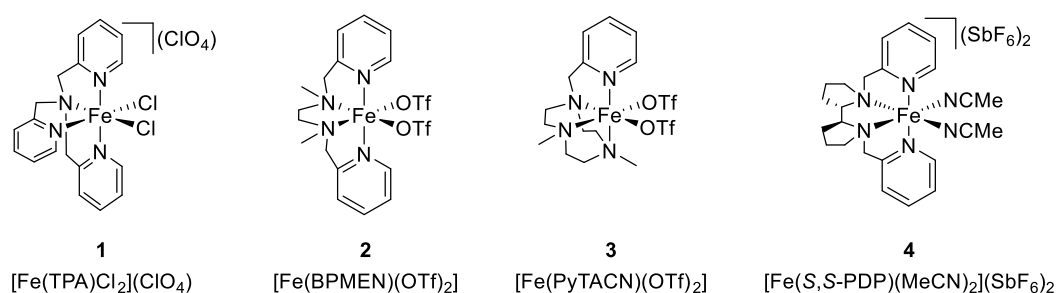
Figure 3. Examples of non-heme iron oxidation catalysts bearing two *cis* labile coordination sites.[78-81]

In the early 1990s Que and coworkers were the first to use non-heme iron complexes based on tris(2-pyridylmethyl)amine (TPA) ligands for the selective oxidation of hydrocarbons.[78] In the following years this approach was further extended resulting in a large number of new catalysts of which **2** and **3** were among the most active ones. For instance, using **2** a yield of 65% and an A/K ratio of 9.5 in the oxidation of cyclohexane with hydrogen peroxide were reported, which suggests a largely metal-centered reaction mechanism.[80] A similar catalyst bearing the same ligand but a different anion was also reported to catalyze the hydroxylation of benzene.[64] However, in this reaction a ferric hydroperoxide derivative was suggested to be the active oxidant. A milestone was reached by Chen and White in 2007 when they reported on the application of **4** as selective catalyst for the oxidation of complex functionalized organic molecules with hydrogen peroxide under synthetically feasible conditions.[81] Bearing a chiral ligand, even the oxidation of natural products is catalyzed by **4** with a high degree of stereoselectivity.

In comparison to enzymes, synthetic catalysts bear important advantages in terms of flexibility regarding substrates, reaction conditions and controllable selectivity.[57] However, despite all efforts, most biomimetic iron catalysts still lack behind the performance of their naturally occurring role models regarding catalytic efficiency and selectivity as they tend to suffer from degradation under oxidative conditions. This demonstrates that there is still significant room for improvement in terms of both inhibiting oxidative degradation and enhancing catalyst activity and selectivity.

1.4 *N*-Heterocyclic Carbenes and their Metal Complexes in Oxidation Catalysis

The first *N*-heterocyclic carbene (NHC) metal complexes were reported by Wanzlick[82] and Öfele[83] in 1968, however, NHCs were only regarded as lab curiosities at that time. It was not until the isolation of the first thermally stable carbene by Arduengo[84] in 1991 (Figure 4) that they started to gain increasing importance as ligands in organometallic chemistry. Since Herrmann and coworkers[85] first used NHC complexes in homogeneous catalysis a wide range of catalytic applications for this compound class has been explored including oxidations, reductions, cross-coupling reactions, hydrogenation and olefin metathesis.[86, 87] But what is the essential difference between NHCs and other, traditionally used ligands?

Generally, the term *N*-heterocyclic carbene refers to a heterocyclic compound containing a carbene carbon and at least one nitrogen atom within the ring.[88] There are several different classes of NHCs but the most widely used ones are based on an imidazole scaffold. In contrast to other carbene species, which usually possess a triplet ground-state electronic configuration, NHCs exhibit a singlet configuration, which can be attributed to the stabilizing effect of the adjacent nitrogen atom (Figure 4).[88-90] The highest occupied molecular orbital (HOMO) is therefore best described as sp^2-hyrbidized and the lowest unoccupied molecular orbital (LUMO) has the properties of an empty π-orbital. On the one hand the nitrogen stabilizes the HOMO by withdrawing σ-electron density and on the other hand it donates electron density into the empty LUMO. Experimentally this electronic configuration is confirmed by the bond length of the C−N bond, which possesses significant double bond character.
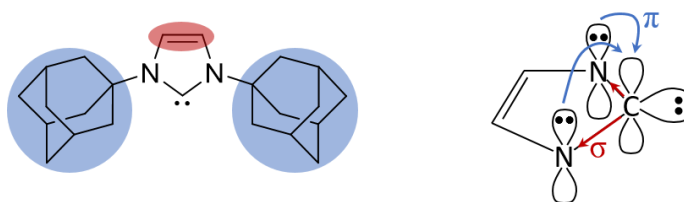
Figure 1. Left: First stable, isolated *N*-heterocyclic carbene described by Arduengo et al in 1991.[84] Right: Electronic stabilization of the carbene singlet state in imidazole-based NHCs.

Due to this electronic configuration NHCs are nucleophiles and being strong σ-donor ligands they can stabilize metal ions even in high oxidation states, which is highly relevant for catalytic applications. In fact, in comparison to other σ-donor ligands such as phosphines the metal-ligand bond of many NHC coordination compounds is remarkably strong.[87] As the LUMO is partly occupied by electron density donated by the adjacent nitrogen atoms the degree of backbonding in NHC-metal complexes is usually low so that the M−C bond has significant σ-character.[91]

The exact electronic and steric properties of a particular NHC can be tuned by variation of the wingtip and backbone substituents.[92, 93] Most synthetic routes comprise the deprotonation of the respective

azolium salt and their synthesis is therefore based on long-known organic reactions. Consequently, NHCs comprise a group of highly flexible and synthetically feasible ligands capable of forming coordination compounds with a wide range of metallic and non-metallic species.

These unique properties are the basis for the success story of *N*-heterocyclic carbenes as ligands for organometallic compounds and, as indicated above, opened the door to a wide range of catalytic applications of transition metal NHC complexes including oxidation catalysis. Obviously, the catalyst stability under oxidative conditions is a key aspect for this reaction type. The suitability of NHCs as stable ligands for high-valent metal complexes was demonstrated by Herrmann and coworkers, who reacted a sterically unhindered NHC with methyltrioxorhenium (MTO).[94] Despite the oxidizing properties of MTO, at -60 °C an adduct complex was formed without oxidation of the NHC to the cyclic urea derivative. In contrast, phosphines react readily with MTO to the corresponding phosphine oxides.[95] Moreover, there are several examples of transition metal NHC complexes that are capable of activating dioxygen and of these first row transition metal NHC complexes are particularly interesting in the context of bioinspired catalysis. For instance, in 2013 Meyer and coworkers reported on the first isolation of an NHC supported oxoiron(IV) complex, which was formed by reaction of iron(II) complex **5** with a iodosobenzene derivative.[96] Reaction with molecular oxygen on the other hand yielded an oxygen bridged Fe-O-Fe dimer, which was characterized spectroscopically and by SCXRD (Figure 5). The cobalt-NHC complex **6**, bearing a tripodal tris-NHC ligand, also shows a distinct reactivity towards oxygen.[97] At room temperature it forms an octahedral adduct species where the dioxygen molecule is coordinated in a side-on fashion. According to DFT calculations the oxygen adduct complex possesses nucleophilic character, which was confirmed experimentally by reaction with electrophilic organic substrates such as benzoyl chloride and tetracyanoethylene. Furthermore, the exposure of nickel-NHC complexes **7** to an oxygen atmosphere affords dimeric hydroxide-bridged nickel complexes and oxygenated allyl byproducs.[98] The proposed reaction mechanism involves the initial end-on coordination of a dioxygen molecule to nickel followed by transfer of one of the oxygen atoms to the allylic ligand.
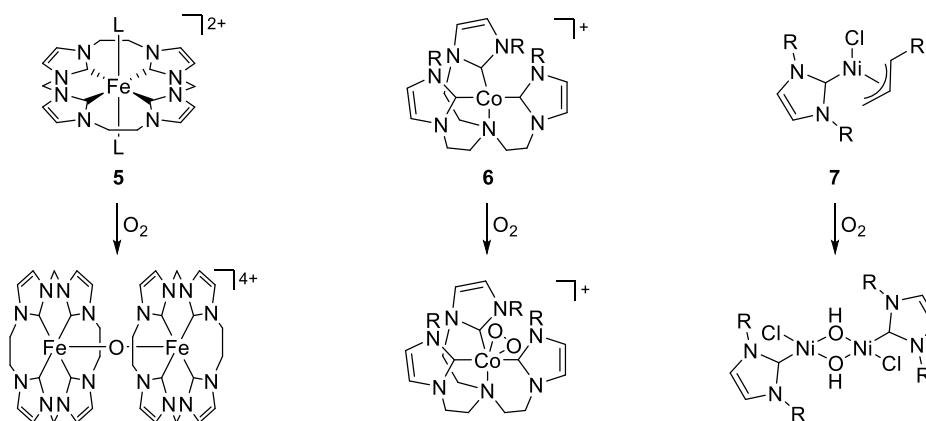
Figure 5. Examples for the reactivity of first row transition metal NHC complexes towards molecular oxygen.[96-98]

With respect to catalytic oxidations, mostly palladium-NHC catalysts have been applied so far. Scheme 10 summarizes types of oxidation reactions that have been reported to be catalyzed by transition metal NHC complexes.
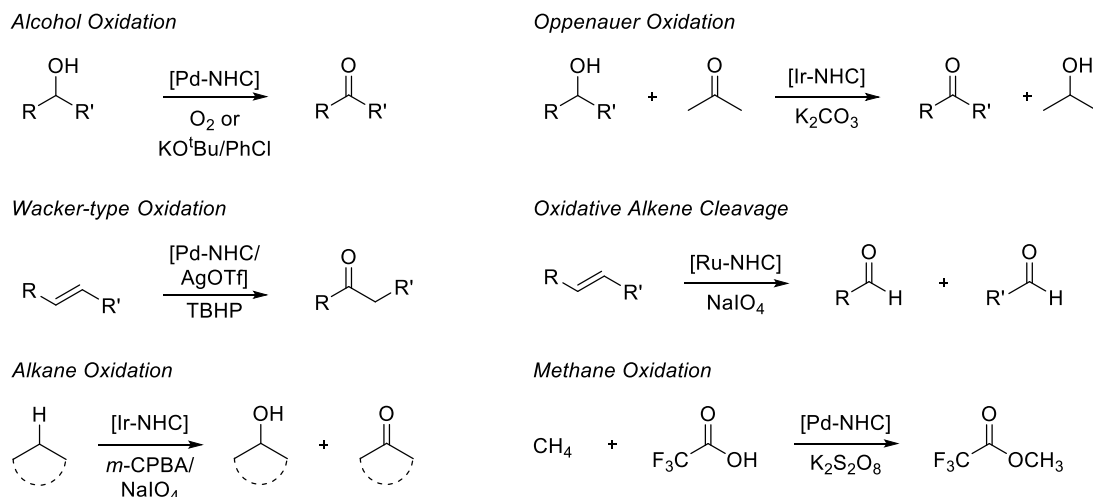
Scheme 10: Oxidation reactions catalyzed by transition metal NHC complexes.[99, 100]

Of these, methane oxidation is the most challenging as the direct transformation of methane to methanol under mild conditions is still considered as one of the "dream reactions" of the chemical industry.[101] As Strassner and coworkers demonstrated, methane can be converted to methyl trifluoroacetate by Pd-bis-NHC complexes with potassium persulfate as the oxidant.[102] The ester product is unlikely to be overoxidized and can be transformed into methanol by hydrolysis. The palladium catalysts possess bridged bis-NHCs as ancillary ligands and the square planar coordination sphere is completed by two halogen atoms. They are stable under strongly acidic conditions (trifluoroacetic acid) and at elevated temperatures, so that turnover numbers of up to 30 were reached.

Interestingly, Sarkar and coworkers recently reported on the use of iridium 1,2,3-triazolydene complexes as alkane oxidation catalysts.[103] 1,2,3-triazolydenes are mesoionic *N*-heterocyclic carbenes

based on a 1,2,3-triazole scaffold.[104-107] As they have only one nitrogen atom adjacent to the carbene carbon, the inductive stabilization of the HOMO is reduced compared to imidazolylidene NHCs, which results in an increase of the σ-donor capability. Therefore, these ligands are highly promising candidates for the stabilization of high-valent metal species and an increasing number of catalytic applications is currently being explored. Iridium complexes thereof bearing bidentate 1,2,3-triazolydene ligands have been shown to mediate the oxidation of cyclooctane with *m*-chloroperbenzoic acid (*m*-CPBA) or NaIO$_4$ as oxidant.[103] Depending on the oxidant, different product distributions of alcohol, ketone and diketones were observed and under optimized conditions a conversion of ~70% was reached at 1 mol% catalyst loading.

Recently Kühn and coworkers reported on the use of iron complexes bearing tetradentate NHC ligands as catalysts for oxidation reactions. These will be treated in more detail in section 1.4.1.

Similar to the oxidation reactions catalyzed by biomimetic iron complexes, there is still the need for improvement of the performance of transition metal NHC complexes. One major issue in this context is the catalyst degradation under oxidative conditions.[108, 109] For porphyrin-based catalysts the cleavage of the ligand ring structure has been identified as the major degradation pathway and also for other biomimetic *N*-donor ligands the oxidation of ligand C−H bonds has been reported to be involved in the catalyst deactivation process.[110] This can possibly proceed *via* a bimolecular autoxidation mechanism where one catalyst molecule mediates the ligand oxidation of another. Restriction of these bimolecular degradation pathways can be achieved either by introduction of bulky substituents to the ligand framework, eliminating basic C−H bonds by replacing them with heteroatoms or C−X bonds (X = F, Ar, …), or by spacial separation of the catalyst molecules. The latter involves the immobilization of the catalyst molecule on a suitable support. Generally speaking, the heterogenization of homogeneous catalysts is an attractive tool to combine the advantages of two worlds as it permits the synthesis of well-defined molecular catalysts, which are easy to separate from the reaction mixture and ideally recyclable. Especially the recycling of transition metal catalysts is of increasing importance due to both ecological and economic reasons.

Considering the growing impact of NHCs as ligands in coordination chemistry and their structural flexibility, the immobilization of NHC compounds[a] appears as a reasonable approach to create active, robust and recyclable catalysts.[111-113] There are three basic strategies, by which immobilization of NHC compounds can be achieved: suitable functionalization of i) the NHC backbone, ii) the wingtips or iii) the use of an immobilized ancillary ligand coordinated to the metal center (Figure 6). Furthermore, the

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[a] This research area has been reviewed comprehensively as part of this thesis (R. Zhong, A. C. Lindhorst, F. J. Groche and F. E. Kühn, "Immobilization of *N*-Heterocyclic Carbene Compounds: A Synthetic Perspective", *Chem. Rev.* **2017**, 117, 1970-2058) and a summary of the respective article is provided in section 3.6. Therefore, only a short overview of the topic will be provided here.

immobilization method itself is decisive for the catalyst characteristics. Covalent grafting, solid synthesis and self-support methods are the three predominant ones as they involve the covalent linkage between the NHC and the support and thus lead to lower leaching rates compared to non-covalent immobilization techniques such as absorption or electrostatic methods. Due to their high flexibility in terms of functionalization and good stability under various reaction conditions, the most frequently used supporting materials are organic polymers and silica materials.[111] The range of catalytic applications for immobilized NHC compounds is just as broad as for molecular NHC catalysts, but the most thoroughly studied reaction types are olefin metathesis and cross coupling reactions.[112, 113] Therefore, the majority of published immobilized NHC-metal complexes contains either ruthenium or palladium metal centers and some representative structures are presented in Figure 6.
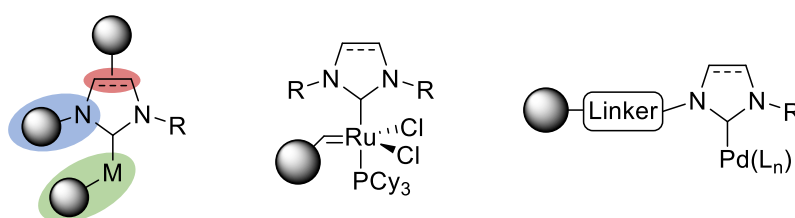
Figure 6. Strategies for the immobilization of NHC metal complexes (*via* backbone (red) or wingtip (blue) substituents or immobilized ancillary ligands (green)) and representative structures of immobilized olefin metathesis (ruthenium) and cross coupling (palladium) catalysts.

1.4.1 Iron *N*-Heterocyclic Carbene Complexes

Since the first report on the synthesis of an iron-NHC complex in 1969[114] and the resurgence of NHCs as ligands for organometallic compounds, the number of publications on iron *N*-heterocyclic carbene complexes has been increasing steadily.[115] In general, iron NHC complexes can be accessed by a number of different routes (Scheme 11). Nowadays the most widely used ones are i) the *in situ* generation of a free carbene by reacting an imidazolium salt with a suitable base followed by addition of an iron halide, ii) the transmetalation of easily accessible silver- or magnesium-NHC complexes with an iron precursor and iii) the direct synthesis from an imidazolium salt and iron(II) bis(trimethylsilyl)amide (Fe(btsa)$_2$). The latter route is particularly appealing as the iron precursor contains an internal base, which deprotonates the imidazolium salt and thus enables a single-step synthesis with the corresponding amine as the only byproduct.[116]
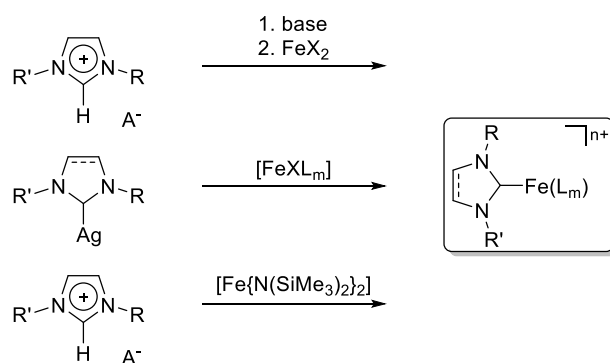
Scheme 11. Synthetic access routes to iron-NHC complexes.[115]

Traditionally, most iron-NHC complexes are based on mono- or bidentate carbene ligands, however, more recently chelating polydentate ligand motifs have gained increasing interest. Those comprise pincer- and scorpionato-type as well as acyclic and macrocyclic ligands containing varying numbers of NHC moieties. In the past five years, our group has focused on the synthesis, characterization and catalytic application of iron complexes bearing tetradentate NHC ligands. These efforts were inspired by the work of Cramer and Jenkins,[117] who synthesized the first macrocyclic tetracarbene iron complex and applied it as catalyst for the aziridination of olefins, and Meyer and coworkers,[96] who isolated the first oxoiron(IV) complex bearing a tetra-NHC ligand. Both reports demonstrate that this ligand class is capable of stabilizing high-valent iron intermediates and might also be a promising candidate for use in oxidation catalysis.

In 2012 our group reported on the preparation of three novel iron(II) complexes **8**, **11** and **12** bearing tetradentate bis(*o*-imidazol-2-ylidenepyridine)alkane (NCCN) ligands.[118] It was found that the coordination geometry of the ligand strongly depends on the length of the bridge between the two carbene moieties. While a square planar coordination is observed for the methylene and ethylene bridged NCCN ligands (**8**, **11**), a sawhorse-type coordination mode is adopted in case of the propylene bridged ligand (**12**). Substitution of the pyridine moieties of the NCCN ligand by other donors such as furan and thiophene units results in the formation of iron complexes **13** and **14** where the ligand binds to the metal in a bidentate fashion while the octahedral coordination sphere is saturated by four solvent molecules (Figure 7).[119]
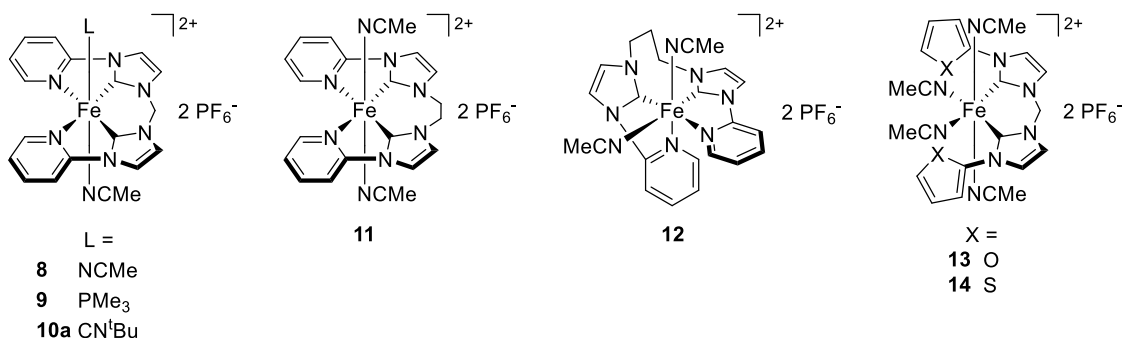
Figure 7. Iron(II) complexes bearing donor-substituted bis-NHC ligands connected by bridges of 1-3 carbon atoms.[118, 119]

Complex **8** proved to be catalytically active in a range of different oxidation reactions (Scheme 12). It was the first organometallic iron complex to be used as catalyst for olefin epoxidation, which is among the most common reactions for the functionalization of olefins.[120, 121] With *cis*-cyclooctene as a model substrate and hydrogen peroxide as oxidant a conversion of 92% was reached within two minutes at room temperature and a very high selectivity for the desired cyclooctene oxide of >99% was observed (2 mol% catalyst). The initial turnover frequency amounts to 2624 h^{-1} under these conditions, which highlights the good catalyst performance, however, it was found that the iron-NHC complex suffers from oxidative degradation in the presence of the oxidant. By lowering the reaction temperature the conversion could be further increased to 100% at -10 °C, which was attributed to an enhanced deceleration of the catalyst degradation opposed to the productive epoxidation pathway. In addition to *cis*-cyclooctene other olefins could also be oxidized with high selectivity including linear and allylic double bonds.
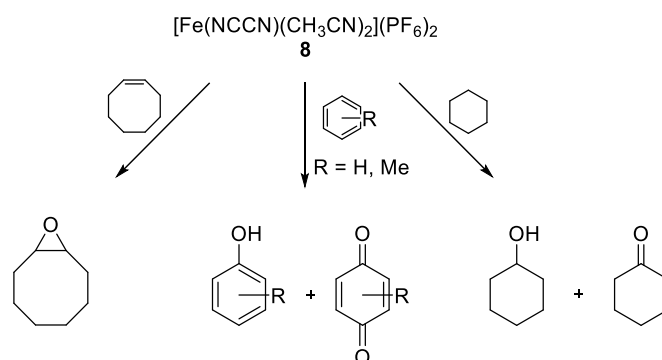
Scheme 12. Application of iron(II)-NHC complex **8** as catalyst for various oxidation reactions.[120, 122, 123]

Complex **8** was further applied as catalyst for the hydroxylation of benzene and toluene with hydrogen peroxide.[122] In the oxidation of benzene conversions range below 10% and in addition to phenol 1,4-benzoquinone is observed as a byproduct. Here, the degree of overoxidation is strongly dependent on the reaction conditions, i.e. the relative amount of oxidant and the temperature. Toluene, being the more electron-rich substrate, is converted more easily (~15% conversion) and a very high selectivity for the oxidation of ring protons of about 80% is reported. Concerning the reaction mechanism, a high-

valent iron-oxo intermediate is suspected to be the active oxidizing species, which reacts with the substrate *via* an electrophilic attack, as indicated by an inverse intermolecular KIE. However, at higher temperatures a Fenton-type reactivity could not be entirely excluded and in addition to an iron-arene σ-complex intermediate, the formation of an arene oxide would also be a possible reaction pathway (cf. section 1.3.1). Therefore, more detailed investigations are required to fully understand the mechanism by which the aromatic hydroxylation by iron(II) complex **8** proceeds.

The third catalytic application, which was so far explored for complex **8**, is the oxygenation of aliphatic C−H bonds.[123] The oxidation of cyclohexane yields the corresponding alcohol and ketone as well as cyclohexyl hydroperoxide, which is converted to cyclohexanol by the addition of triphenylphosphine. Thus, a high A/K ratio of 15 and up to 21 catalytic turnovers were observed at 0.5 mol% catalyst loading. Furthermore, the effect of the bioinspired substitution of axial ligands was investigated. It has been shown that the electronic properties of the iron center of **8** can be tuned by substitution of the axially coordinating acetonitrile molecules by pyridine and phosphine ligands.[124] Cyclic voltammetry measurements in combination with DFT calculations revealed a linear correlation of the experimental half-cell potentials and the HOMO energies, allowing to predict electronic properties of the complexes depending on the π-backbonding ability of the respective ligand. In light of this two monosubstituted complexes **9** and **10a** bearing a trimethylphosphine and a *tert*-butylisocyanide ligand were also tested as catalysts in cyclohexane oxidation. It was found that they are more stable under oxidizing conditions, which translates into increased turnover numbers, whereas the selectivity was not affected significantly.

Structural variation of the tetradentate ligand further allows the precise control of electronic as well as steric properties. Thus, a series of acyclic tetradentate imidazolium salts with varying numbers of NHC and pyridine units and different degrees of structural flexibility in terms of bridge length was synthesized.[125-127] They were used as ligand precursors for the preparation of transition metal NHC complexes *via* the transmetalation route (Scheme 11) exhibiting great flexibility with regard to the stabilized metal centers (Cu, Ag, Au, Ni, Pd, Pt, Fe) and the respective coordination geometries.

Even closer structural resemblance of the active site of heme-based enzymes was intended with the synthesis of iron complexes **15** and **16** bearing cyclic tetradentate NHC ligands (Scheme 13).[128, 129] Just as in porphyrin complexes the iron center is coordinated in a square-planar fashion with the two axial positions being occupied by labile solvent ligands. The reactivity of **16** with small molecules was investigated in detail and it was found that the acetonitrile ligands can be readily replaced. Reactions with CO, NO and DMSO all yielded the corresponding mono- or disubstituted iron(II) complexes. Upon exposure to molecular oxygen, however, a different reactivity was observed. Depending on the solvent either the oxidized iron(III) complex can be obtained or an oxo-bridged Fe(III)-O-Fe(III) dimer is formed

(Scheme 13).[130] As an intermediate species an iron(III) superoxide is suspected to be formed, which is supported by spectroscopic evidence.
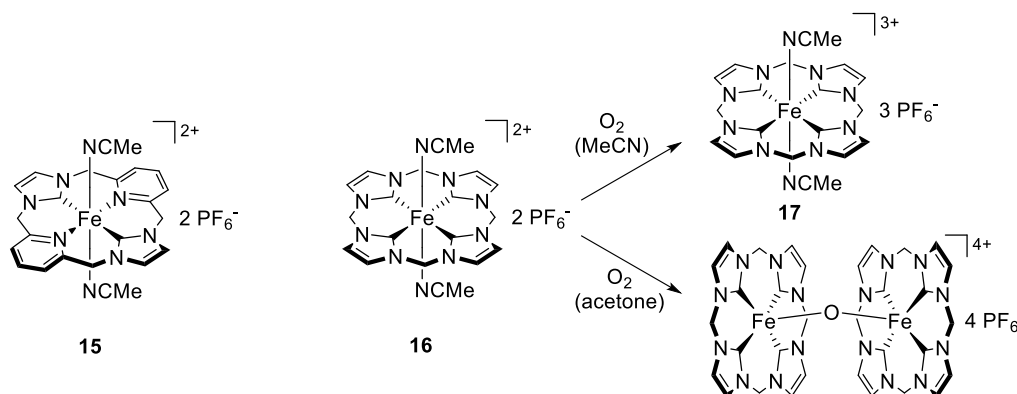
Scheme 13. Synthesis and reactivity of iron(II) complexes bearing cyclic tetradentate NHC ligands.[128-130]

Complexes **16** and **17** were further used as olefin epoxidation catalysts and especially the iron(III) derivative **17** shows a high catalytic activity under mild conditions.[131] Both complexes range among the most active homogeneous epoxidation catalysts known to date with turnover frequencies of up to $50\,000\ h^{-1}$ for **16** and $183\,000\ h^{-1}$ for **17**. The different performance of the two catalysts can be attributed to the higher oxidation state of **17**, rendering the initial oxidation of the catalyst by the oxidant obsolete.

In summary, a considerable number of iron complexes bearing tetradentate NHC ligands has been synthesized and thoroughly characterized. Some of these have been applied successfully in the oxidation of aromatic and aliphatic substrates as well as the epoxidation of olefins. In particular complexes **8** and **16/17** have proven to be efficient and promising catalysts. However, some mechanistic understanding remains elusive and the range of applications needs to be extended. The latter is particularly important in order to bridge the gap between model substrates used in academia and real-life problems of organic synthesis and industrially relevant processes.

2 OBJECTIVE

As outlined in the introduction, iron complexes have gained increasing interest as catalysts for various reaction types due to their rich structural and electronic flexibility as well as the high availability and low toxicity of the central metal. Building on previous work on the synthesis and use of iron *N*-heterocyclic carbene complexes, the applicability of these catalysts in reactions, which are relevant to industrial and organic synthesis, are explored.

The main focus is placed on the oxidation of non-activated aromatic substrates in order to develop new routes for the synthesis of trimethyl-1,4-benzoquinone, a key intermediate in the synthesis of Vitamin E. This part of the thesis is conducted in collaboration with the company DSM. Using the previously described iron-NHC complex **8** and preferentially benign oxidants a suitable catalytic system is to be designed and optimized. Moreover, mechanistic details on the catalytic oxidation of aromatic hydrocarbons by iron-NHC complexes with hydrogen peroxide as oxidant have to be considered. This is particularly important as a better mechanistic understanding helps to identify critical reaction steps and possibly allows the rational design of more active and/or more stable catalysts. As indicated by previous studies, the modification of the axial ligands of iron complexes bearing tetradentate, equatorially coordinating ligands is a powerful way to tune the electronic properties of the central metal and thus adjust the reactivity.

To further extent the scope of applications of iron-NHC complexes, their use as catalysts for aldehyde olefination reactions is investigated. In organic synthesis they present a useful tool to form C−C bonds from carbonyl motifs, however, only few applicable catalytic systems have been established so far.

3 RESULTS - PUBLICATION SUMMARIES

3.1 Molecular Iron Complexes as Catalysts for Selective C−H Bond Oxygenation Reactions

Anja C. Lindhorst, Stefan Haslinger, and Fritz E. Kühn

This feature article reviews key developments achieved in the last decade in the field of hydrocarbon oxygenation reactions catalyzed by molecular iron complexes. In this context two basic reaction types are considered: The oxidation of aliphatic and the oxidation of aromatic C−H bonds.

In biological systems the oxidation of hydrocarbons is often mediated with high efficiency by iron-containing enzymes, which serve as source of inspiration for the design of biomimetic catalysts. In line of this, the first mononuclear iron complex to be used as catalyst for the hydroxylation of non-activated alkanes was a based on a porphyrin ligand mimicking the heme unit of CYP enzymes.[71] Since then extensive research has been performed in order to design catalysts acting *via* a metal-centered rather than a radical-based reaction mechanism, which is associated with higher selectivity.

Adjustment of the nature and topology of the ligand(s) allows tuning of the catalytic performance as well as the selectivity towards specific products. Non-heme iron complexes bearing tetradentate *N*-donor ligands have demonstrated high potential for the oxidation of aliphatic hydrocarbons. A coordination geometry exhibiting two *cis*-labile sites proved to be crucial to mediate the oxidation of C−H bonds with hydrogen peroxide by a metal-centered reaction pathway. In some cases, the predictable reactivity even allowed the oxidation of complex organic molecules, such as natural products, with high regio- and stereoselectivity and under reaction conditions feasible for organic synthesis. Compared to alkane oxidation, the number of molecular iron catalysts reported for the oxidative functionalization of arene substrates is much lower. This is mainly due to selectivity problems arising from the inertness of the non-activated substrates compared to the phenolic products. Furthermore, one of the main challenges in this field remains the limited catalyst lifetime of most catalysts under oxidative conditions, which is reflected by low turnover numbers (TON < 100). Thus, only a few practical applications have been realized so far and further research is necessary in order to develop efficient, iron-based catalysts for the oxidation of C−H bonds with environmentally friendly oxidants as an alternative to traditional systems.

3.2 Catalytic Oxidation of Aromatic Hydrocarbons by a Molecular Iron-NHC Complex

Anja C. Lindhorst, Jan Schütz, Thomas Netscher, Werner Bonrath, and Fritz E. Kühn

The catalytic oxidation of the non-activated arene substrates *p*-xylene and pseudocumene by iron(II) complex **8** bearing the previously described NCCN ligand (section 1.4.1) is presented. Hydrogen peroxide is used as an environmentally friendly oxidant to yield phenolic as well as quinoid reaction products (Scheme 14).
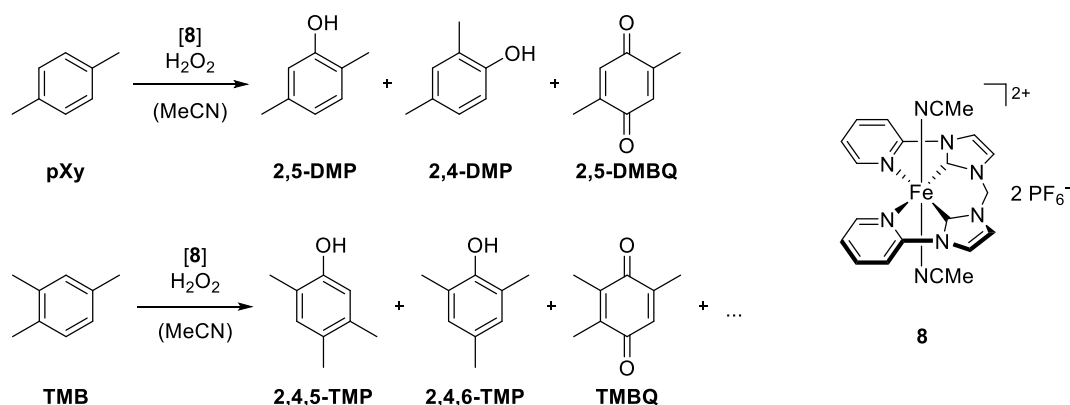

Scheme 14. Catalytic Oxidation of *p*-xylene and pseudocumene by iron(II) complex **8** and hydrogen peroxide.

It was found that in accordance with earlier studies the catalyst exhibits a high selectivity towards the oxidation of ring protons compared to benzylic protons. Systematic evaluation of the reaction conditions showed that for both reactions the highest conversions and product yields are obtained at lower temperatures (-10 °C), which is attributed to an enhanced catalyst lifetime, i.e. an increased number of catalytic turnovers. Furthermore, the relative amount of oxidant proved to have significant impact on the reaction as at high hydrogen peroxide concentrations (>2 equiv.) the selectivity towards the desired products, particularly TMBQ, is reduced. On the other hand, control experiments revealed that at lower concentrations the oxidant is the limiting reagent. By continuous addition of a hydrogen peroxide solution *via* a syringe pump this problem can be circumvented resulting in conversions of up to 86% while keeping the TMBQ selectivity almost constant.

Unexpectedly, 2,4-dimethylphenol and 2,4,6-trimethylphenol were detected as by-products. They are formed by a methyl shift reaction, which is mediated by the iron catalyst. This so-called "NIH shift" has earlier been reported for iron-containing enzymes as well as several molecular heme and non-heme iron complexes.[33, 38, 45, 47, 64, 65, 67, 69] According to literature, it may proceed either *via* an iron-arene σ-complex intermediate or the formation of an arene oxide (Scheme 15). As it has been demonstrated

before that the isomerization of *p*-xylene-1,2-oxide to the two phenolic products 2,4-DMP and 2,5-DMP is highly sensitive towards the pH,[132] different acids and bases were applied as additives in the catalytic oxidation of *p*-xylene by **8**/H_2O_2. However, no influence on the product distribution was observed, which led to the conclusion that the present reaction most likely proceeds *via* an iron-arene σ-complex intermediate (path a, Scheme 15).
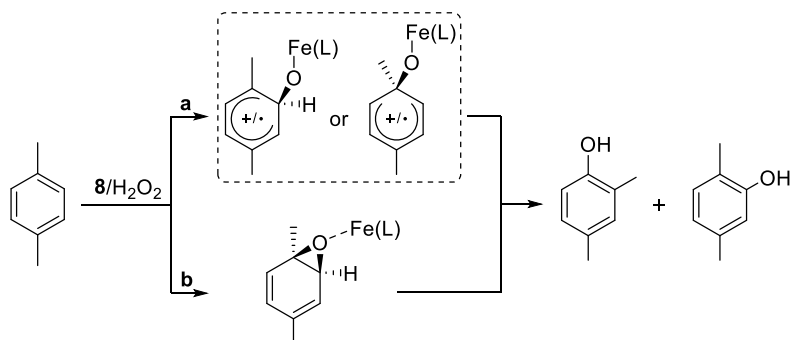
Scheme 15. Possible NIH shift reaction pathways during the iron-mediated oxidation of *p*-xylene including either an iron-arene σ-complex intermediate (path **a**) or the formation of an arene oxide (path **b**).

3.3 Mechanistic Insights into the Biomimetic Catalytic Hydroxylation of Arene Substrates by a Molecular Fe(NHC) Complex

Anja C. Lindhorst, Markus Drees, Werner Bonrath, Jan Schütz, Thomas Netscher, and Fritz E. Kühn

Initiated by the observation of NIH-shift products in the catalytic oxidation of methyl substituted arenes by iron(II) complex **8** and hydrogen peroxide, which closely resembles the reactivity of naturally occurring enzymes (cf. section 3.2), investigations into the reaction mechanism of the catalytic hydroxylation of aromatic substrates are presented.

A high-valent iron(IV)oxo species is assumed to be the terminal oxidizing species and based on previous reports on iron-catalyzed arene hydroxylation, three different reaction pathways are considered: The first involves the abstraction of a hydrogen atom followed by the transfer of the hydroxyl group to the arene radical (path a). Alternatively, either a tetrahedral iron-arene σ-complex intermediate may be generated (path b) or the aromatic oxidation proceeds *via* an arene oxide species (path c).
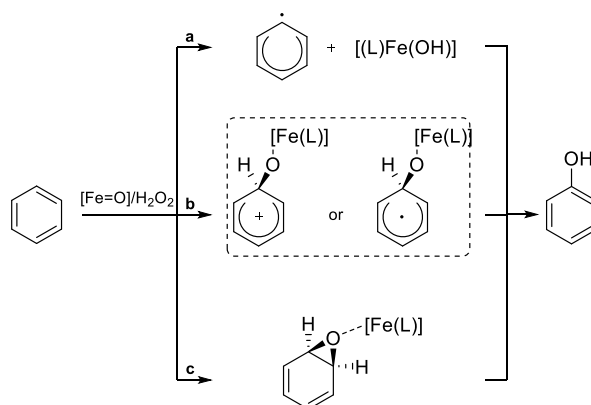
Scheme 16. Alternative mechanistic pathways for the iron catalyzed hydroxylation of benzene.

The addition of 2,6- bis(1,1-dimethylethyl)-4-methylphenol (BHT) as a radical scavenger proved to have no effect on the catalytic performance of iron-NHC complex **8** and an inverse intermolecular kinetic isotope effect (KIE) was determined. Thus, the hydrogen abstraction pathway (a) could be excluded. Furthermore, the inverse KIE indicates a hybridization change from sp^2 to sp^3 at a deuterium substituted carbon atom to be involved in the rate determining step, which is consistent with an electrophilic addition of an iron-oxo species to the benzene ring. Using 1,3,5-D_3-benzene as a model substrate, the degree of substituent migration during the catalytic hydroxylation reaction was quantified and an intramolecular KIE could be determined. Taking into account all experimental evidence it was concluded that the prevalent reaction mechanism most likely involves the formation of an iron-arene σ-complex (path b), which is supported by DFT calculations.

3.4 Isocyanide Substitution Reactions at the Trans Labile Sites of an Iron(II) *N*-Heterocyclic Carbene Complex

Stefan Haslinger, Anja C. Lindhorst, Jens W. Kück, Mirza Cokoja, Alexander Pöthig, and Fritz E. Kühn

Following the reactivity of CYP enzymes, the axially coordinating ligands of biomimetic iron complexes have been identified as a handle to alter the electronic properties of these compounds.[73, 124] Starting from iron(II) complex **8**, a variety of isocyanide-substituted complexes **10** and **18** (Scheme 17) has been synthesized and characterized.
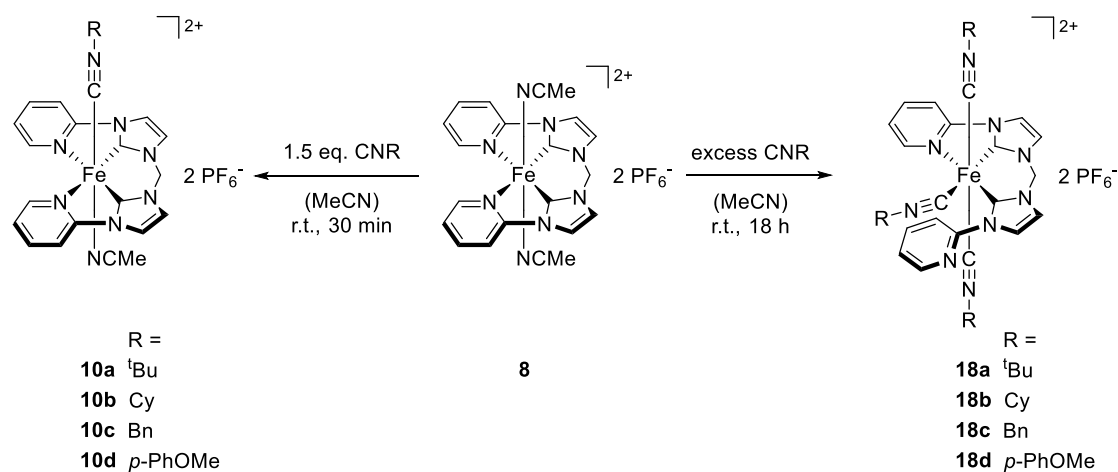
Scheme 17. Synthesis of isocyanide-substituted iron(II) complexes **10** and **18** by reaction of complex **8** and various isocyanides (^tBu = *tert*-butyl; Cy = cyclohexyl; Bn = benzyl; *p*-PhOMe = 4-methoxyphenyl).

Depending on the relative amount of isocyanide used, either the mono- or the trisubstituted complexes were obtained in high yields. In case of the trisubstituted complexes the NCCN ligand adopts a meridional tridentate coordination geometry. Interestingly, no disubstituted complexes bearing two isocyanide ligands in *trans* position could be isolated. Following the formation of **18a** in the presence of CN^tBu by ^{1}H-NMR spectroscopy revealed that as intermediate a disubstituted species is formed, bearing two isocyanide ligands in *cis* coordination positions.

The influence of the differently substituted isocyanides on the electronic properties of the iron complexes was evaluated by determination of the half-cell potentials referenced against Fc/Fc$^+$ by cyclic voltammetry. As isocyanides are known to be strong π-acceptors, the oxidation potential corresponding to the Fe(II)/Fe(III) redox couple of the monosubstituted complexes **10a**-**10d** is increased by 116-150 mV compared to that of the starting complex **8**. In case of the trisubstituted complexes **18a**-**18d** even higher potentials of 994-1092 mV are required and the oxidation was found to be no longer reversible.

3.5 Iron(II) *N*-Heterocyclic Carbene Complexes in Catalytic One-Pot Wittig Reactions: Mechanistic Insights

Özden Karaca, Markus R. Anneser, Jens W. Kück, Anja C. Lindhorst, Mirza Cokoja, and Fritz E. Kühn

In this study two iron(II) complexes **8** and **16** (cf. section 1.4.1) are tested as catalysts for the olefination of aldehydes with ethyl diazoacetate in the presence of triphenylphosphine (Scheme 18). Using benzaldehyde as substrate, with both catalysts high aldehyde conversions were observed, however only **8** successfully directs the reaction towards the desired product *E*-ethyl cinnamate. Under optimized reaction conditions (70 °C, catalyst/benzaldehyde/EDA/PPh$_3$ = 0.1/1/1.2/2) yields of up to 90% *E*-ethyl cinnamate after 2 h could be obtained. The selectivity of this reaction amounts to 95% as only 2% of the (usually unwanted) azine byproduct are formed.
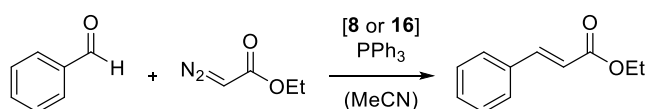
Scheme 18. One-pot Wittig reaction of benzaldehyde and ethyl diazoacetate (EDA) catalyzed by molecular iron complexes **8** and **16**.

In order to rationalize the observed catalytic behavior, investigations on the mode of action of **8** were performed. Using a cyclopropanation reaction as an indirect detection method, the presence of a metal carbene intermediate (NHC)Fe=CH(CO$_2$Et) formed from **8** and EDA was proven. This may serve as a carbene donor to PPh$_3$ to form a phosphorous ylide, which subsequently undergoes a Wittig reaction (pathway 1, Scheme 19). Furthermore, evidence was found that in an alternative pathway a phosphazine compound may be generated in a first step from EDA and PPh$_3$, which is transformed to a phosphorous ylide by iron complex **8** or the triphenylphosphine-substituted analogue. However, this reaction only occurs if an additional equivalent of PPh$_3$ is added and a reaction pathway was proposed where PPh$_3$ acts as a nucleophile during the conversion of the phosphazine to the ylide (pathway 2, Scheme 19). In both cases a two-step mechanism is suggested to be present: i) the catalytic formation of a phosphorous ylide and ii) a Wittig-type conversion with the aldehyde to the olefin.
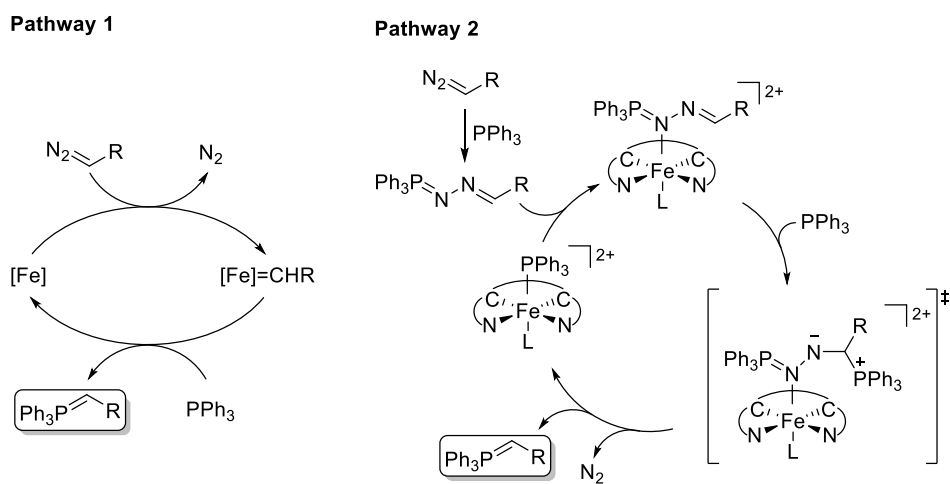
Scheme 19. Possible mechanistic pathways proposed for the catalytic generation of a phosphorous ylide by iron complex **8**.

3.6 Immobilization of *N*-Heterocyclic Carbene Compounds: A Synthetic Perspective

Rui Zhong, Anja C. Lindhorst, Florian J. Groche, and Fritz E. Kühn

This review article presents synthetic strategies and methods for the immobilization of NHC compounds on various supporting materials. Since NHCs are very versatile in terms of steric and electronic tunability and allow the formation of comparatively stable carbon-metal bonds, they have emerged as powerful ligands stabilizing metal coordination compounds for a plethora of catalytic applications (cf. section 1.4). Furthermore, the heterogenization of homogeneous catalysts is an attractive method to obtain well-defined and recyclable catalyst materials. However, combining those two aspects can be synthetically challenging. Therefore, this review article aims to provide a synthetic toolkit by summarizing and evaluating published examples of immobilized NHC compounds. Special focus is laid on each of three correlative steps involved in the synthesis of an immobilized NHC compound: i) the formation of a suitable NHC moiety, ii) the heterogenization and iii) the metalation.

The most frequently applied immobilization strategy is the covalent grafting method, where a functionalized NHC precursor is coupled to a support *via* a well-defined organic reaction. Other methods, like self-support, are less often reported, even though they bear certain advantages in terms of the product properties. Regarding the supporting material organic polymers and silica-based materials have traditionally been used, however, a growing interest in carbon-based materials and nanoparticles can be observed. Furthermore, methods for the in-depth characterization of immobilized NHC compounds are presented, which in most cases deviate strongly from the techniques applied for molecular compounds. A combination of various methods is required to thoroughly characterize the NHC unit in interaction with the supporting material. This is particularly important in the context of catalytic applications. Here, the determination of the nature of the catalytically active species is one of the major challenges. So far a broad range of possible catalytic applications of immobilized NHC compounds has been presented, among which cross coupling and metathesis reactions are the most prominent ones. However, especially for those two reaction types there is still a large gap to be overcome between the performance of state-of-the-art homogeneous systems and their immobilized analogues. Therefore, even though a broad range of synthetic approaches towards the preparation of immobilized NHC compounds is available, careful consideration of various aspects, such as metal-support interactions or accessibility of the active sites, is required in order to create catalysts, which combine the advantages of both homogeneous and heterogeneous catalysis.

4 CONCLUSION AND OUTLOOK

In this thesis catalytic applications of iron(II) complex **8** bearing a tetradentate bis-NHC ligand have been explored focusing on bridging the gap between academic model reactions and real-life chemical problems relevant to organic synthesis and the industry.

Therefore, the applicability of **8** as catalyst for the direct oxidation of pseudocumene to trimethyl-1,4-benzoquinone (TMBQ) with environmentally friendly oxidants was explored, a reaction, which is highly desirable for the chemical industry as TMBQ is a key compound in the synthesis of (all-*rac*)-α-tocopherol (section 3.2). Under optimized reaction conditions almost quantitative conversion of pseudocumene could be reached, however, the selectivity for the desired product amounts only up to 15%. As alternative approach towards the valorization of non-activated arenes, *p*-xylene was chosen as a substrate as the corresponding 2,5-dimethylphenol can be methylated under industrially feasible conditions and thus also serve as a resource for TMBQ production. In this case the selectivity could be directed successfully to the phenolic products, however, unexpectedly a mixture of 2,5-dimethylphenol and 2,4-dimethylphenol was obtained. This finding was the starting point for further investigations into the reaction mechanism of the catalytic hydroxylation of aromatic substrates by complex **8** and hydrogen peroxide (section 3.3). An oxoiron(IV) compound is assumed to the be the oxidizing species, however, this intermediate could not be isolated nor unambiguously characterized spectroscopically. Therefore, further investigations into the true nature of the intermediates formed upon reaction of iron-NHC complex **8** and analogous compounds with oxidants would help to increase the understanding and the predictability of their catalytic behavior not only in arene hydroxylation. Well-established catalytic probe reactions in combination with density functional theory calculations were employed to rule out a hydrogen abstraction pathway (cf. Scheme 8). Furthermore, evidence was found that the reaction proceeds *via* an iron-arene σ-complex intermediate closely resembling the reactivity pattern of CYP and AAAH enzymes (cf. section 1.2). This is also reflected by the occurrence of NIH shift products during the oxidation of both methylated arenes (pseudocumene and *p*-xylene) and deuterated benzene.

As the axial ligands of biomimetic iron complexes have proven to be an effective way of tuning the electronic properties of the iron center, isocyanide substituted iron(II) complexes were synthesized (section 3.4). Upon substitution, the oxidation potential of the iron center was found to have increased which can be attributed to the pronounced π-acceptor properties of the isocyanide ligands. Concerning the oxidation of aliphatic C−H bonds this proved to have a positive effect on the catalyst stability under oxidizing conditions.[123]

Yet, the oxidative degradation of the catalyst remains an important issue restricting the feasibility of real-life applications of many biomimetic iron complexes. There are several strategies, which may be

employed in the future to further improve the stability of iron-NHC complexes in the presence of oxidants like hydrogen peroxide. Firstly, the NHC and/or pyridine units of the tetradentate ligand could be replaced by 1,2,3-triazolydene moieties, an approach, which is currently being followed within the scope of a Master's thesis in our laboratories. These mesoionic abnormal NHC ligands form even stronger metal-carbon bonds than classical imidazolydenes and some of their complexes have proven to be stable even under strongly oxidizing conditions and capable of stabilizing transition metals in high oxidation states.[103, 133] Therefore, they are promising ligand candidates for the synthesis of iron-based oxidation catalysts. Secondly, as indicated in the introduction (section 1.4), the spacial separation of the catalyst molecules might also contribute to their lifetime as by this means bimolecular degradation pathways could potentially be inhibited. The heterogenization of the catalyst molecules could be achieved by grafting a suitably functionalized iron complex onto a supporting material (section 3.6). In this context special attention should be paid to the properties of the supporting material and the grafting conditions. Potential positions for a functionalization of the iron-NHC complex would either be the imidazolydene backbone or the bridging methylene units. Modification of the latter would additionally bear the advantage of replacing acidic protons, which are prone to oxidation. In addition to immobilization purposes, a functionalization of the tetradentate ligand could open the door towards the introduction of further donor moieties. In case of metalloporphyrins the introduction of a pendant group ("hangman metallophorphyrins") proved to be beneficial for the activity and stability during the activation of O−O bonds.[134] Likewise, substitution of a labile acetonitrile ligand by another donor bound to the NCCN scaffold, could help to enhance catalyst stability by providing a reversibly coordinating, yet spatially close axial ligand.

In addition to oxidation reactions, the catalytic Wittig olefination was explored as a useful application of iron-NHC complexes. Under optimized reaction conditions remarkable conversions and high E/Z selectivity were observed with complex **8** as catalyst. The cyclic tetracarbene complex **16** on the other hand did not catalyze the Wittig reaction or more precisely the formation of a phosphorous ylide. This underlines the difference in reactivity between these two complexes and raises the question of structure-reactivity relationships. Further investigations into the electronic and structural features of the library of tetradentate iron-NHC complexes synthesized by our group and the identification of critical attributes responsible for high performance in a particular catalytic reaction would certainly aid the rational design of highly efficient catalysts.

5 REPRINT PERMISSIONS

5.1 RSC Journals

"Molecular Iron Complexes as Catalysts for Selective C−H Bond Oxygenation Reactions"

Chemical Communications **2015**, 51 (97), 17193-17212, DOI: 10.1039/c5cc07146a

"Catalytic Oxidation of Aromatic Hydrocarbons by a Molecular Iron-NHC Complex"

Catalysis Science & Technology **2017**, 7, 1902-1911, DOI: 10.1039/c7cy00557a

"Isocyanide Substitution Reactions at the Trans Labile Sites of an Iron(II) *N*-Heterocyclic Carbene Complex"

RSC Advances **2015**, 5 (104), 85486-85493, DOI: 10.1039/C5RA18270K

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"Mechanistic Insights into the Biomimetic Catalytic Hydroxylation of Arenes by a Molecular Fe(NHC) Complex"

Journal of Catalysis **2017**, 352, 599-605, DOI: 10.1016/j.jcat.2017.06.018

"Iron (II) *N*-Heterocyclic Carbene Complexes in Catalytic One-Pot Wittig Reactions: Mechanistic Insights"

Journal of Catalysis **2016**, 344, 213-220, DOI: 10.1016/j.jcat.2016.09.029

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Chemical Reviews **2017**, 117 (3), 1970-2058, DOI: 10.1021/acs.chemrev.6b00631

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Title: Immobilization of N-Heterocyclic Carbene Compounds: A Synthetic Perspective

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Publisher: American Chemical Society

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Title: Immobilization of N-Heterocyclic Carbene Compounds: A Synthetic Perspective

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6 Bibliographic Data of Complete Publications

6.1 Molecular Iron Complexes as Catalysts for Selective C−H Bond Oxygenation Reactions

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Chair of Inorganic Chemistry/Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85747 Garching bei München, Germany.

6.2 Catalytic Oxidation of Aromatic Hydrocarbons by a Molecular Iron-NHC Complex

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6.3 Mechanistic Insights into the Biomimetic Catalytic Hydroxylation of Arenes by a Molecular Fe(NHC) Complex

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6.4 Isocyanide Substitution Reactions at the Trans Labile Sites of an Iron(II) *N*-Heterocyclic Carbene Complex

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6.5 Iron(II) *N*-Heterocyclic Carbene Complexes in Catalytic one-pot Wittig Reactions: Mechanistic Insights

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6.6 Immobilization of *N*-Heterocyclic Carbene Compounds: A Synthetic Perspective

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8 COMPLETE LIST OF PUBLICATIONS

8.1 Journal Articles

Aroma-Active Compounds in the Fruit of the Hardy Kiwi (Actinidia arguta) Cultivars Ananasnaya, Bojnice, and Dumbarton Oaks: Differences to Common Kiwifruit (Actinidia deliciosa 'Hayward')

A. C. Lindhorst, M. Steinhaus

European Food Research and Technology **2015**, 1-9.

Molecular Iron Complexes as Catalysts for Selective C−H Bond Oxygenation Reactions

A. C. Lindhorst, S. Haslinger, F. E. Kühn

Chemical Communications **2015**, 51 (97), 17193-17212.

Isocyanide Substitution Reactions at the Trans Labile Sites of an Iron(II) *N*-Heterocyclic Carbene Complex

S. Haslinger, **A. C. Lindhorst**, J. W. Kück, M. Cokoja, A. Pöthig, F. E. Kühn

RSC Advances **2015**, 5 (104), 85486-85493.

Iron (II) *N*-Heterocyclic Carbene Complexes in Catalytic One-Pot Wittig Reactions: Mechanistic Insights

Ö. Karaca, M. R. Anneser, J. W. Kück, **A. C. Lindhorst**, M. Cokoja, F. E. Kühn

Journal of Catalysis **2016**, 344, 213-220.

Immobilization of *N*-Heterocyclic Carbene Compounds: A Synthetic Perspective

R. Zhong, **A. C. Lindhorst**, F. J. Groche, F. E. Kühn

Chemical Reviews **2017**, 117 (3), 1970-2058.

Catalytic Oxidation of Aromatic Hydrocarbons by a Molecular Iron-NHC Complex

A. C. Lindhorst, J. Schütz, T. Netscher, W. Bonrath, F. E. Kühn

Catalysis Science & Technology **2017**, 7, 1902-1911.

Mechanistic Insights into the Biomimetic Catalytic Hydroxylation of Arenes by a Molecular Fe(NHC) Complex

A. C. Lindhorst, Markus Drees, Werner Bonrath, Jan Schütz, Thomas Netscher, Fritz E. Kühn

Journal of Catalysis **2017**, 352, 599-605.

8.2 Conference Contributions

Substitution of Labile Solvent Ligands of an Iron(II) NHC Complex by Isocyanides

A. C. Lindhorst, S. Haslinger, J. W. Kück, M. Cokoja, A. Pöthig, F. E. Kühn

Conference talk, 251st ACS National Meeting & Exposition, San Diego, CA, United States, March **2016**.

Oxidative Activation of Aromatic C−H Bonds by an Iron(NHC) Complex

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