Technische Universität München
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TRANSITION METAL NHC COMPLEXES IN OXIDATION CATALYSIS AND MEDICINAL CHEMISTRY

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Dissertation

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„Sic parvis magna."

Sir Francis Drake

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ABSTRACT

The synthesis, electrochemical properties and performance of homogeneous iron epoxidation catalysts bearing tetradentate *N*-heterocyclic carbene (NHC) ligands are described. A series of complexes with a mixed NHC/1,2,3-triazole ligand shows high activity and selectivity in the epoxidation of olefins while tolerating a variety of functional groups. The catalytic performance is tunable by the 1,2,3-triazole substituents and considerably improved in presence of Brønsted and Lewis acidic additives.

When applying strong Lewis acids as additives in *cis*-cyclooctene epoxidation catalyzed by iron complexes bearing an imidazole based macrocyclic tetra-NHC ligand, unprecedented turnover frequencies up to 410,000 h^{-1} are achieved. The iron carbene bond is identified as the weak spot. Consequently, related complexes based on a ligand derived from the different heterocycle benzimidazole show significantly higher turnover numbers for more intricate substrates than *cis*-cyclooctene.

A cobalt(II) complex of the imidazole based tetra-NHC is synthesized and capable of dioxygen activation at ambient conditions. The subsequent addition of Brønsted acids results in hydrogen peroxide formation. Applying the same macrocyclic ligand, the first copper(III) carbene complex is obtained. Upon addition of acetic acid, a mono-oxidized ligand is formed *via* reductive elimination.

The copper(I), silver(I) and gold(I) complexes of this ligand show anticancer and antibacterial properties *in vitro*. Additionally, a series of palladium(II) and platinum(II) complexes bearing differently substituted mixed NHC/1,2,3-triazole ligands in two different coordination modes (bidentate, tetradentate) is reported showing promising antiproliferative activity and selectivity for cancer cell lines as well as luminescence properties. According to fluorescence microscopy the compounds are located in late endosomes or lysosomes.

KURZZUSAMMENFASSUNG

Die Synthese von homogenen Epoxidationskatalysatoren mit tetradentaten *N*-heterozyklischen Carben (NHC) Liganden und deren elektrochemischen und katalytischen Eigenschaften werden beschrieben. Dabei weisen Komplexe mit gemischten NHC/1,2,3-Triazolliganden eine hohe Aktivität und Selektivität, sowie eine hohe Toleranz gegenüber einer Vielzahl funktioneller Gruppen auf. Durch Modifikation der 1,2,3-Triazolsubstituenten, sowie durch Zugabe von Brønsted- und Lewis-sauren Additiven können die katalytischen Eigenschaften signifikant verbessert werden.

In Gegenwart starker Lewis-Säuren werden mit Eisenkomplexen eines Imidazol-basierten makrozyklischen tetra-NHC Liganden bislang unerreichte Aktivitäten von bis zu 410.000 h^{-1} in der Epoxidation von *cis*-Cycloocten erreicht. Als Schwachstelle der Komplexe stellt sich die Eisen-Carben Bindung heraus. Daher werden durch Verwendung eines Benzimidazol-basierten NHC-Komplexes in der Epoxidation von anspruchsvolleren Olefinen deutlich höhere Umsatzzahlen als mit dem verwandten Imidazol-basierten Katalysator erzielt.

Ein analoger Kobalt(II)-Komplex des Imidazol-basierten tetra-NHC Liganden aktiviert molekularen Sauerstoff aus Luft. Durch anschließende Zugabe von Brønsted-Säuren entsteht Wasserstoffperoxid. Darüber hinaus wird mit dem gleichen makrozyklischen Liganden der erste bekannte Kupfer(III)-Carbenkomplex gewonnen. Dieser bildet nach Zugabe von Essigsäure durch reduktive Eliminierung einen mono-oxidierten makrozyklischen Liganden.

Die Kupfer(I)-, Silber(I)- und Gold(I)-Komplexe dieses Liganden zeigen *in vitro* antitumorale und antibakterielle Eigenschaften. Des Weiteren werden Palladium(II)- und Platin(II)-Komplexe gemischter NHC/1,2,3-Triazolliganden mit zwei verschiedenen Substituenten und Koordinationsmodi (bidentat, tetradentat) beschrieben. Diese besitzen eine vielversprechende antiproliferative Aktivität und Selektivität für Krebszelllinien, sowie Lumineszenzeigenschaften. Mit Hilfe von Fluoreszenzmikroskopie werden die Verbindungen in späten Endosomen bzw. Lysosomen lokalisiert.

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ABBREVIATIONS

A	Adenine
aNHC	Abnormal/mesoionic *N*-heterocyclic carbene
Bn	Benzyl
BPMEN	*N,N*-dimethyl-*N,N*-bis(2-pyridylmethyl)-1,2-diaminoethane
C	Cytosine
cCCCC	16-Membered macrocyclic methylene bridged tetra-NHC ligand
CV	Cyclic voltammetry
Cy	Cyclohexyl
CYP 450	Cytochrome P450
Cys	Cysteine
Dipp	2,6-Diisopropylphenyl
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
E. coli	*Escherichia coli*
$E_{1/2}$	half-cell potential
Fc	Ferrocene
FDA	United States Food and Drug Administration
G	Guanine
GSH	Gluthathione
His	Histidine
HOMO	Highest occupied molecular orbital
HPPO	Hydrogen peroxide to propylene oxide
HSA	Human serum albumin
IC_{50}	Half maximal inhibitory concentration
L	Ligand
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
Mes	Mesityl
MIC	Minimum inhibitory concentration
MMC	4-Methoxycoumarin
MS	Mass spectroscopy
MTO	Methyltrioxorhenium
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
$NADP^+$	Nicotinamide adenine dinucleotide phosphate

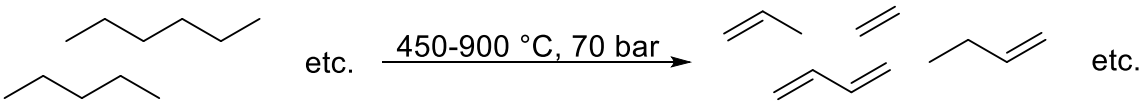
NADPH	Dihydronicotinamide adenine dinucleotide phosphate
NCI	US National Cancer Institute
NER	Nucleotide excision repair
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
Np	Neopentyl
Ph	Phenyl
POR	Cytochrome P450 oxidoreductase
Prx	Peroxiredoxin
PyTACN	1-(2-Pyridylmethyl)-4,7-dimethyl-1,4,7-triazacyclononane
r.d.s	Rate determining step
SC-XRD	Single crystal X-ray diffraction
Sec	Selenocysteine
sMMO	Soluble methane monooxygenase
T	Thymine
TBHP	*tert*-Butyl hydroperoxide
TMC	Tetramethylcyclam
TPA	Tris(2-pyridylmethyl)amine
Trx	Thioredoxin
TrxR	Thioredoxin reductase
TS-1	Titanium silicate 1
UV	Ultraviolet
Vis	Visible
w.a.p.	Water-assisted pathway

1 INTRODUCTION

1.1 CARBON FEEDSTOCKS FOR CHEMICAL INDUSTRY

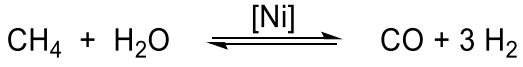
The synthesis of various bulk and fine chemicals largely relies on easily accessible and abundant carbon feedstocks.[1, 2] The production of polymers, pharmaceuticals, flavors, fragrances and coatings, amongst other important industrial and consumer goods, is based on the functionalization and converting of basic carbon building blocks, primarily obtained by refining of mineral oil and natural gas.[1-5]

The former mainly consists of alkanes with various chain lengths alongside olefins, aromatics and acetylene as minor, but easier to functionalize components.[1] In its refining process, after desalting, the crude oil is distilled into fractions: gaseous fuel, naphta, kerosine, diesel, fuel oil and heavier compounds (increasing order of boiling range).[6] Thermal steam cracking of naptha, the fraction mainly containing liquid alkanes with a low boiling point, results in the formation of smaller, often unsaturated hydrocarbons, including ethylene and propylene with an annual production scale of 1.5×10^8 t and 8×10^7 t, respectively.[2, 6, 7] In this process, C–C bond breaking and dehydrogenation take place at temperatures of 450-900 °C and pressures up to 70 bar (Scheme 1).[2, 6, 8] The composition of the product mixture is essentially dependent on the reaction temperature, *i.e.* higher temperatures favor ethylene formation, whereas lower temperatures produce higher relative amounts of propylene and unsaturated C_4-hydrocarbons.[8] The so obtained olefins represent crucial intermediates towards more complex and valuable molecules.[1, 2, 8]



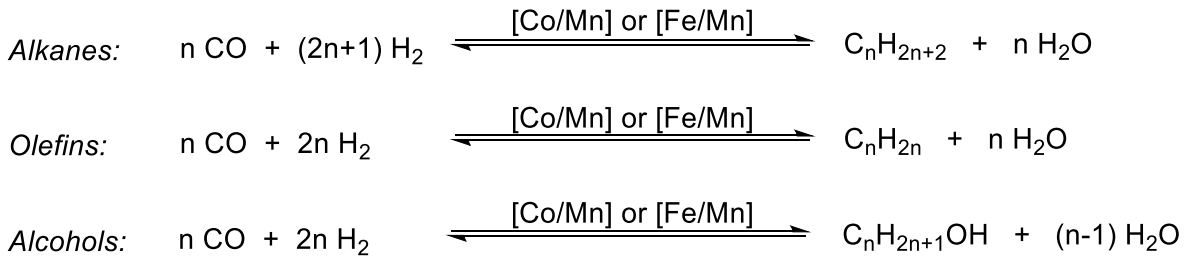
Scheme 1. Thermal steam cracking.[1, 6, 8, 9]

Another route for the synthesis of carbon based building blocks starts from syngas, a mixture of carbon mono-oxide and hydrogen produced by catalytic steam reforming of natural gas, one of the largest sources of hydrocarbon (Scheme 2).[11]



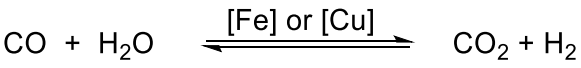
Scheme 2. Catalytic steam reforming.[11]

In the *Fischer-Tropsch* process syngas is converted to alkanes, alkenes or alcohols applying Co/Mn or Fe/Mn on a partially reduced oxide support as catalyst (Scheme 3).[2,10, 11] The chain length of the products mainly depends on the reaction temperature, with higher temperatures favoring a lower molecular weight, as well as the composition of the catalyst.[12]



Scheme 3. Reaction equations of the *Fischer-Tropsch* synthesis of alkanes, olefins and alcohols.[2,10-12]

In this process, the watergas shift reaction plays an important role to manipulate the CO:H_2 ratio. Herein, H_2O and CO are converted to H_2 and CO_2 utilizing an iron or copper based catalyst. As an additional benefit to the regulation of the CO:H_2 ratio, toxic carbon mono-oxide is converted to carbon dioxide (Scheme 4).[13, 14]

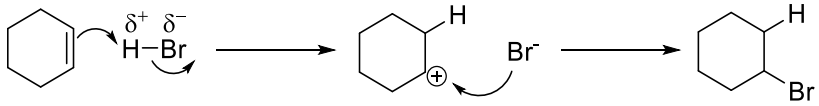


Scheme 4. Watergas shift reaction.[13, 14]

A considerable number of products yielded by the *Fischer-Tropsch* process consists of higher alkanes and alkenes, which are used as raw materials for cracking in order to obtain shorter olefinic building blocks. This process requires an additional step when compared to thermal cracking of naphtha from mineral oil. Thus, converting of natural gas to smaller olefins is more energy demanding and accordingly associated with higher costs. However, syngas is still of high importance for the synthesis of acetic acid, methanol and waxes.[15-17]

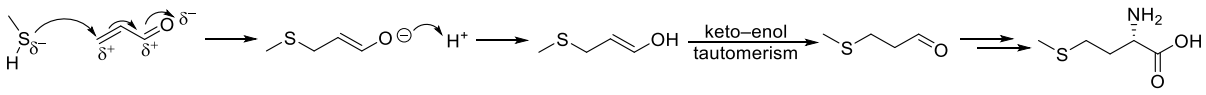
1.2 Olefins as important and versatile building blocks in organic synthesis

When compared to alkanes and alkynes, alkenes are the most versatile hydrocarbons. By nature, C=C double bonds are electron-rich and therefore react as a nucleophile with a variety of electrophiles.[18-20] A prominent organic transformation showcasing this reactivity is the addition of hydrohalogenic acids. Herein the C=C double bond is attacked by a proton, the simplest of all electrophiles, initially, forming a carbocation, which subsequently reacts with the halide (Scheme 5). The regioselectivity of the addition is determined by the stability of the intermediately occurring carbocation.[18-20]



Scheme 5. Mechanism of the electrophilic addition of hydrobromic acid to cyclohexene acting as a nucleophile.[20]

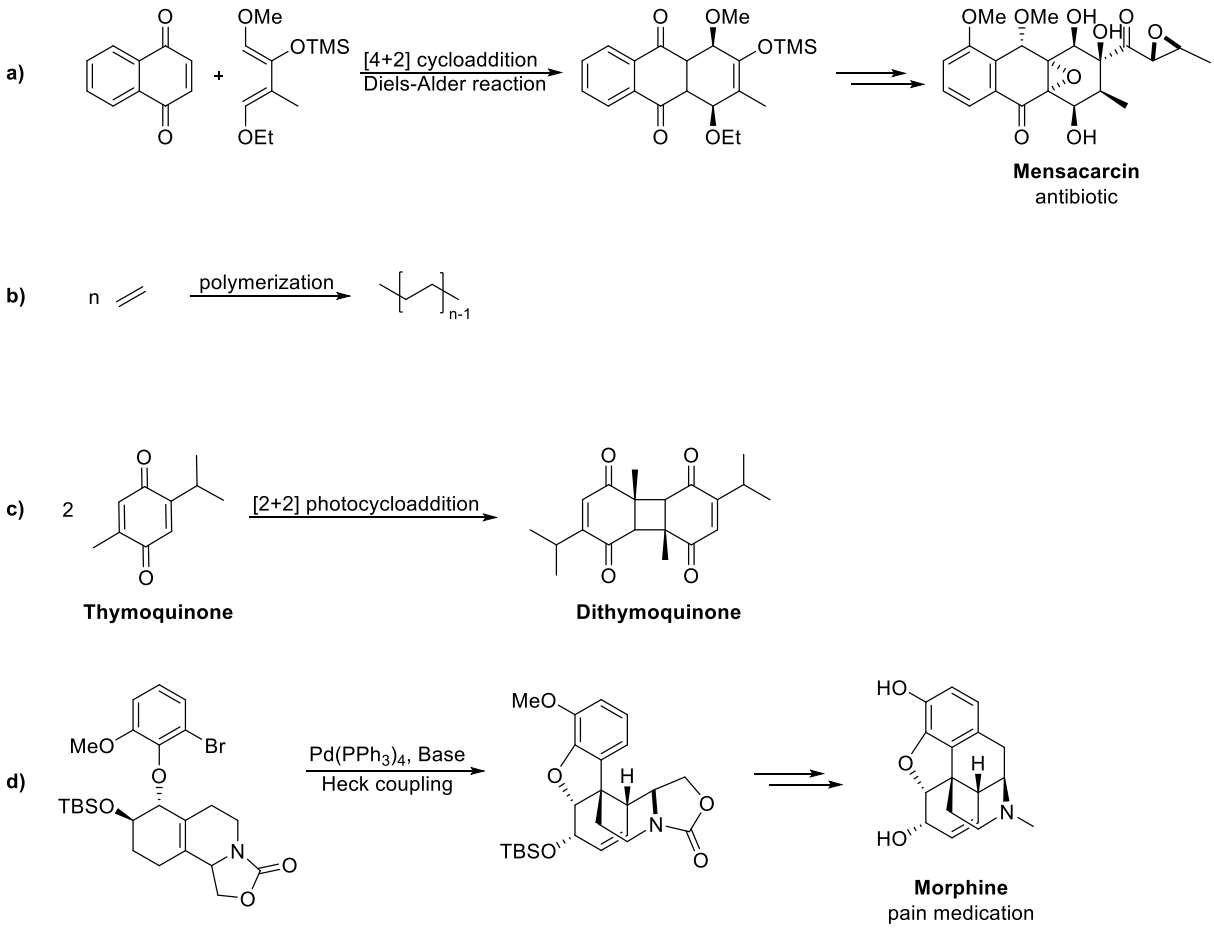
However, olefins can also act as electrophilic *Michael* acceptors – named after the American chemist *Arthur Michael* – and react with nucleophiles, when conjugated to electron accepting substituents, the most prominent example being carbonyls.[18, 20, 21] This reactivity plays an important role in the synthesis of the amino acid methionine. In a *Michael* addition acrolein and methanethiol are converted to methional, yielding the essential proteinogenic amino acid methionine after subsequent *Strecker* synthesis (Scheme 6).[22, 23]



Scheme 6. Mechanism of methional formation from methanethiol and acrolein *via* conjugate *Michael* addition as an important step in the synthesis of L-methionine.[22, 23]

Further important reactions of olefins include cycloadditions (a), polymerizations (b), photoreactions (c) and *Heck*-couplings (d), amongst others, illustrating the versatile reactivity of this compound class (Scheme 7).[6, 10, 18, 20, 24-29] In addition to their vast reactivity, asymmetrically substituted alkenes are prochiral and therefore suitable educts for the synthesis of enantiomeric products, which is of particular interest for the preparation of biologically active compounds like pharmaceuticals.[18-20] Moreover, alkenes are produced in multi-ton scale by cracking processes and distillation of mineral oil, as described above,

rendering them comparably inexpensive. All these characteristics make olefins unique and predestined building blocks for the synthesis of various organic molecules, both in laboratory and industrial scale.[1, 2]

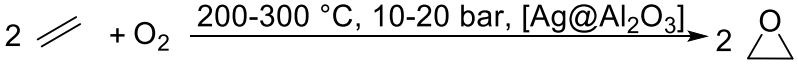


Scheme 7. Selection of important reactions of olefins: a) *Diels-Alder* reaction in the synthesis of Mensacarcin as an example of a cycloadditon;[27] b) polymerization of ethylene;[6] c) formation of Dithymoquinone from Thymoquinone as the first reported example of a [2+2] photocycloaddition;[28] d) intramolecular *Heck* coupling within in the synthesis of Morphine.[29]

1.3 HETEROGENEOUS OLEFIN EPOXIDATION CATALYSIS

Amongst all olefins, ethylene and propylene are produced in the highest quantities by a large margin with an annual production scale of around 1.5 x 10^8 t and 8 x 10^7 t, respectively.[2, 6, 7] Besides their polymerization to yield highly demanded polyethylene and polypropylene, a major share is epoxidized to ethylene oxide and propylene oxide.[1, 2, 7, 30] Both compounds are subsequently converted to glycols, polyglycols, polycarbonates, polyesters and epoxy resins, amongst other products, but can also be used as disinfectants or fumigants without further processing. However, the direct application of ethylene and propylene oxide only accounts for less than 1% of their usage.[1, 2, 7, 30, 31]

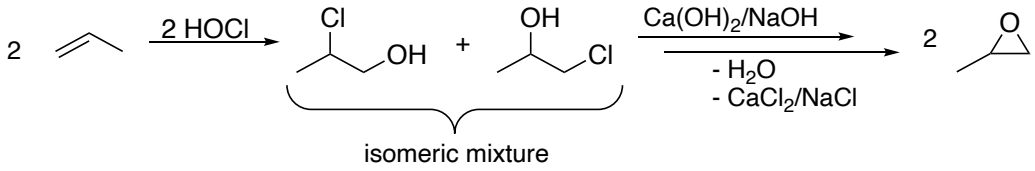
The most common industrially applied ethylene epoxidation process was developed by *Union Carbide* (1937) and *Shell* (1958) and is catalyzed by α-alumina supported silver nanoparticles applying dioxygen from air (*Union Carbide*) or in its pure form (*Shell*) as oxidant with a selectivity of up to 80% (Scheme 8).[32]



Scheme 8. Catalytic ethylene epoxidation.[32]

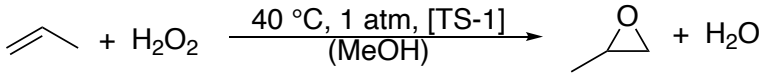
Although this process can successfully be applied to ethylene, higher olefins bearing allylic C–H bonds cannot be epoxidized with sufficient selectivity due to the stabilization of allyl radicals. When reacting propylene under the same reaction conditions as shown in Scheme 8, a large margin is over-oxidized to CO_2 and H_2O.[33] An industrially applicable process to selectively utilize dioxygen to epoxidize propylene in high yield and selectivity has not been developed yet and due to the difficulty been referred to as one of the “holy grails” in chemistry.[34, 35]

Over 90% of propylene oxide is produced in the chlorohydrin and (hydro)peroxide processes.[36] The chlorohydrin route involves two main steps, which are illustrated in Scheme 9. First, propylene is converted with an aqueous chlorine solution resulting in the formation of propylene chlorohydrin in an isomeric mixture, which subsequently reacts with NaOH or $Ca(OH)_2$ to form propylene oxide and NaCl or $CaCl_2$ as byproduct, respectively. Per each ton of propylene oxide, around two tons of chloride salt are produced (Scheme 9). Another disadvantage of this process is the formation of 1,2-dichloropropane as byproduct, which has to be separated from propylene oxide *via* distillation.[36] Therefore, other processes for the synthesis of propylene oxide have become more and more important over the past decades.[37]



Scheme 9. Synthesis of propylene oxide *via* the chlorohydrin route.[36, 37]

These processes involve the application of organic or inorganic peroxides as oxidant, mainly *tert*-butyl hydroperoxide (TBHP) and hydrogen peroxide.[37] Although molybdenum catalysts utilizing TBHP show high activity and selectivity, they depict some major disadvantages. Molybdenum is considered toxic and TBHP is more expensive, environmentally less benign and atom-economic than hydrogen peroxide.[38, 39] The latter can be applied as oxidant, when using a non-toxic titanium silicate (TS-1) as catalyst, which has been developed by *Enichem* in 1983. In a slurry of TS-1, aqueous hydrogen peroxide and methanol, propylene is epoxidized in almost quantitative yields at 40 °C and ambient pressure (Scheme 10, HPPO process).[37, 40]



Scheme 10. Industrial process of propylene oxide synthesis applying hydrogen peroxide as oxidant and TS-1 as catalyst (HPPO process).[37, 40]

1.4 Homogeneous Ti, Mn, Re and Mo Olefin Epoxidation Catalysts

Even though heterogenous catalysts are highly efficient for ethylene and propylene epoxidation, they cannot be applied to obtain epoxides of more intricate olefins in sufficient yields. For their oxidation, homogeneous catalysts are often applied. In general, homogeneous catalysts exhibit a higher activity and selectivity. However, the separation of the product from the catalysts is a major challenge. Therefore, in industry such catalysts are only applied to obtain highly relevant and comparably expensive fine chemicals. A selection of important examples with an epoxide functionality, is illustrated in Figure 1.

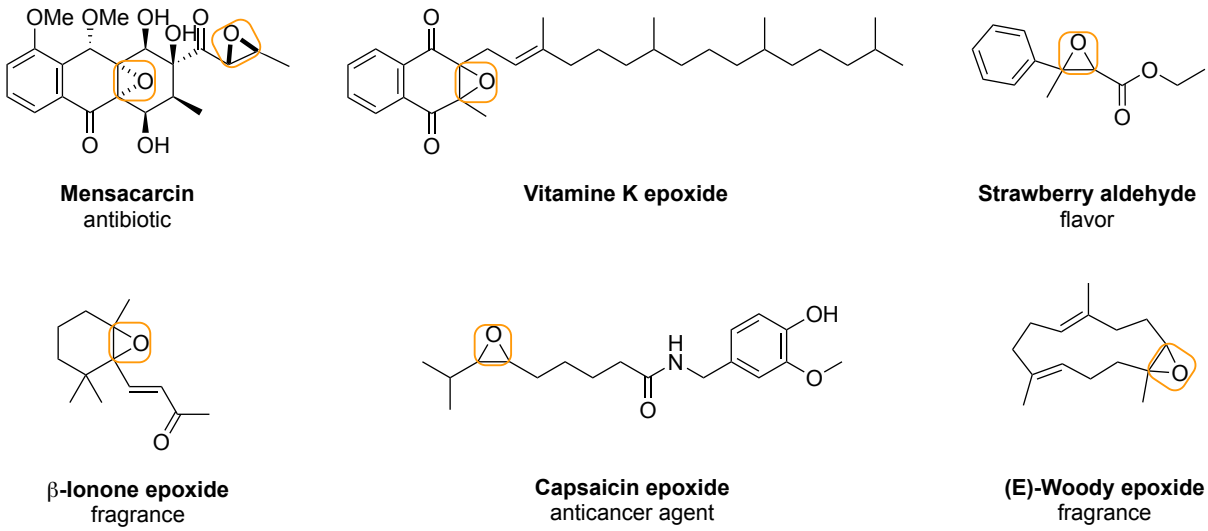


Figure 1. Selection of relevant fine chemicals with epoxide functionalities (highlighted in orange), including pharmaceuticals, flavors and fragrances.[27, 41-44]

In homogeneous epoxidation catalysis, the works of *Sharpless*,[45, 46] *Kochi*,[45, 47] *Jacobsen*,[48, 49] *Katsuki*,[50, 51] *Herrmann*[52, 53] and *Espenson*[54, 55] can be considered as milestones. Due to the significance of his contributions in the field of asymmetric homogeneous epoxidation catalysis, *Sharpless* was awarded the Nobel prize in chemistry in 2001 for a method to epoxidize ally alcohols in over 90% enantiomeric excess.[56] The *in situ* generated catalyst is a dinuclear titanium(IV) complex bearing diethyl tartrate and alkoxy ligands, giving the respective product enantiomer depending on the tartrate configuration [(*S,S*) or (*R;R*)], when applying TBHP as oxidant. Unfortunately, the substrate scope of the *Sharpless* epoxidation is limited to olefins with directing functional groups like allyl alcohols (Figure 2).[45, 46]

A broader range of olefins with aromatic and aliphatic substituents can be epoxidized with high stereoselectivity by manganese(III) salen catalysts, developed by *Kochi*,[47] *Jacobsen*[48, 49] and *Katsuki*.[50, 51] NaOCl is commonly applied as oxidant for these reactions (Figure 2).[47-51] Major disadvantages of such complexes are a lack of functional group tolerance, the inability to

epoxidize terminal olefins, as well as the application of comparably hazardous hypochlorites as oxidant.[57]

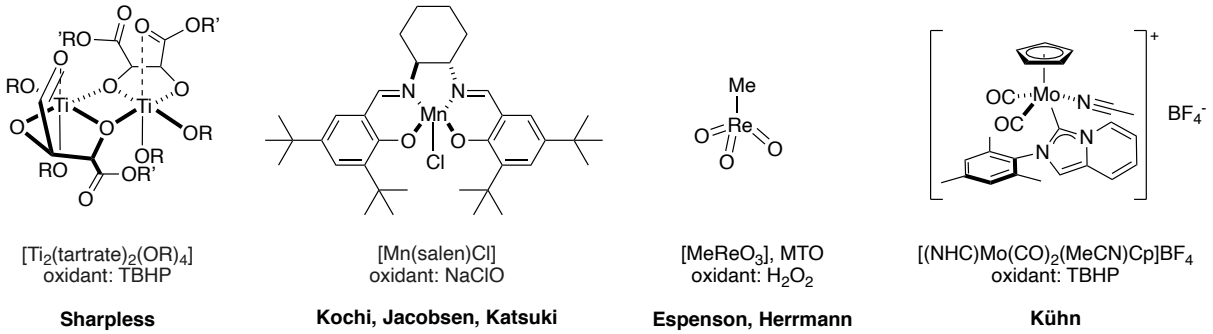
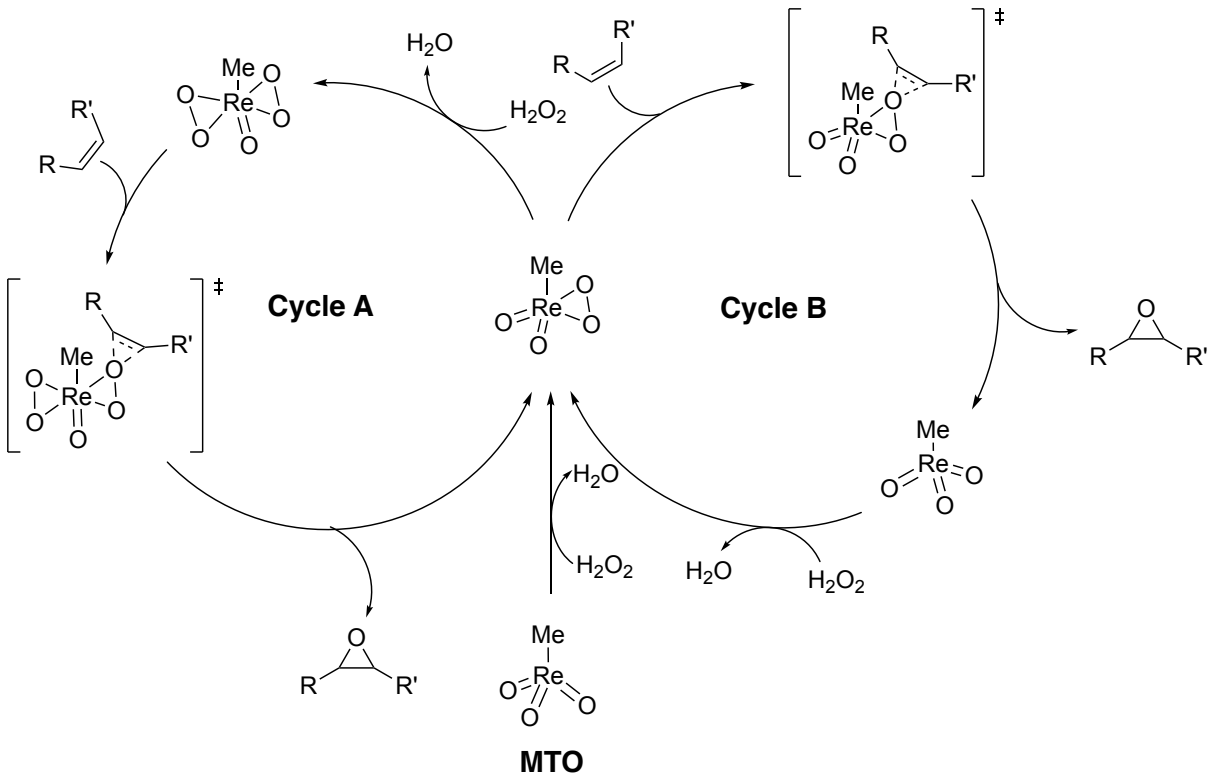


Figure 2. Important molecular epoxidation catalysts studied by *Sharpless*, *Kochi*, *Jacobsen*, *Katsuki*, *Espenson*, *Herrmann* and *Kühn*.[45-56, 58]

All of these disadvantages can be overcome using methyltrioxorhenium (MTO) as catalyst (Figure 2). MTO, originally discovered by *Beattie* and *Jones* in 1979,[59] was later applied as a homogenous epoxidation catalyst by *Herrmann*[52, 53] and *Espenson*.[54, 55, 60] Further optimization by using pyrazole as additive and hexafluoroisopropanol as solvent significantly increases its activity reaching unprecedented turnover frequencies (TOFs) of up to 39 000 h^{-1} at that time.[61] MTO tolerates a variety of functional groups and uses hydrogen peroxide as oxidant, which is considered the most atom-economic and green oxidant besides dioxygen from air.[62 60, 63] However, in contrast to the catalysts developed by *Sharpless, Kochi, Jacobsen* and *Katsuki*, MTO does not have a stereocenter and therefore does not allow for enantioselective epoxidation.[60] The mechanism of MTO catalyzed olefin epoxidation can be divided into two separate catalytic cycles (Scheme 11, cycles A and B), which involve a mono- or bis(η^2-peroxo) intermediate, formed upon reaction with one or two hydrogen peroxide molecules under elimination of water, respectively. In a subsequent concerted step, the respective peroxo moiety attacks the olefin, resulting in the formation of the epoxide (Scheme 11).[53, 55, 64-67]

As rhenium and molybdenum have similar chemical properties, derived from the diagonal relationship in the periodic table of elements and Mo (ca. 20 $/kg) is significantly cheaper than Re (ca. 2 800 $/kg), molecular molybdenum catalysts have been in the focus of research to potentially replace MTO (www.dailymetalprice.com, November 2020).[60, 68] Amongst those compounds, a molybdenum(II) *N*-heterocyclic carbene (NHC) complex reported by *Kühn* in 2014 shows the highest activity reaching TOFs up to 53 000 h^{-1} using TBHP as oxidant (Figure 2). However, the substrate scope is limited, when compared to MTO.[58]



Scheme 11. Mechanism of MTO-catalyzed olefin epoxidation using H_2O_2 as oxidant.[53, 55, 64-67]

As discussed above, all mentioned homogeneous epoxidation catalysts have their advantages and disadvantages, which are summarized in Table 1. None of the complexes combines all of the following requirements for an ideal epoxidation catalyst: low metal cost, lack of toxicity, green oxidant, tolerance towards functional groups and high selectivity.

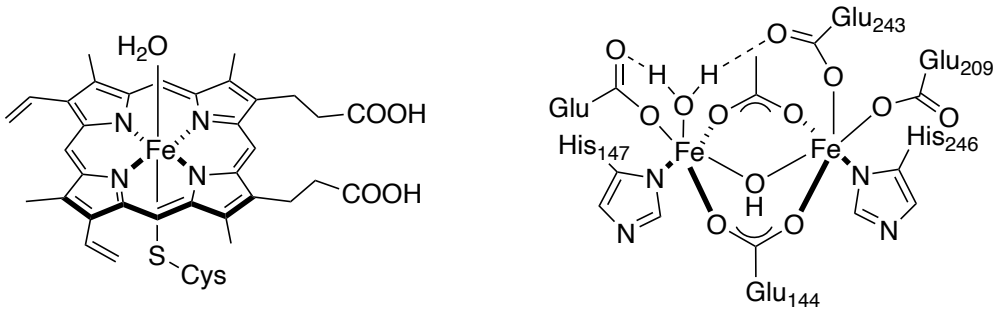
Table 1. Advantages and disadvantages of important homogeneous catalysts.[45-56]*

Catalyst	Substrate scope	Enantioselectivity	Oxidant	Metal cost
Sharpless	only allyl alcohols	✓	H_2O_2	low
Jacobsen-Katsuki	aliphatic, aromatic	✓	NaOCl	low
MTO	highest	**X**	H_2O_2	high
Mo(II) NHC	high	**X**	TBHP	low

*green = advantage, red = disadvantage, yellow = in between.

1.5 BIO-INSPIRED IRON COMPLEXES IN EPOXIDATION CATALYSIS

Metalloenzymes capable of performing the selective oxidation of various substrates fulfill all of the requirements for an ideal catalyst listed above.[39, 60, 69] Processes like alkane hydroxylation and olefin epoxidation/dihydroxylation have been optimized in the course of evolution over billions of years in nature involving iron containing metalloproteins.[70-79] Amongst those, cytochrome P450 (CYP P450; Figure 3, left) and soluble methane monooxygenase (sMMO; Figure 3, right) are the most prominent representatives.[70-79]

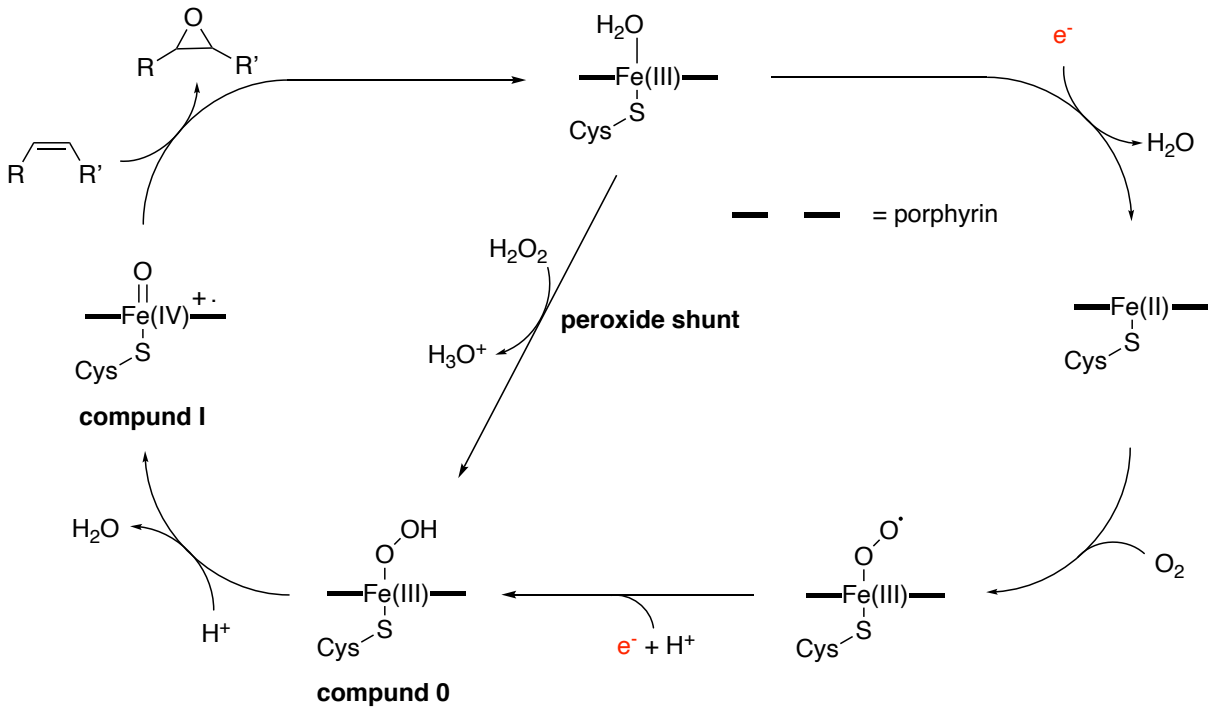


CYP 450 **sMMO**

Figure 3. Active centers of cytochrome P450 (CYP P450, left) and soluble methane monooxygenase (sMMO, right).[76-78]

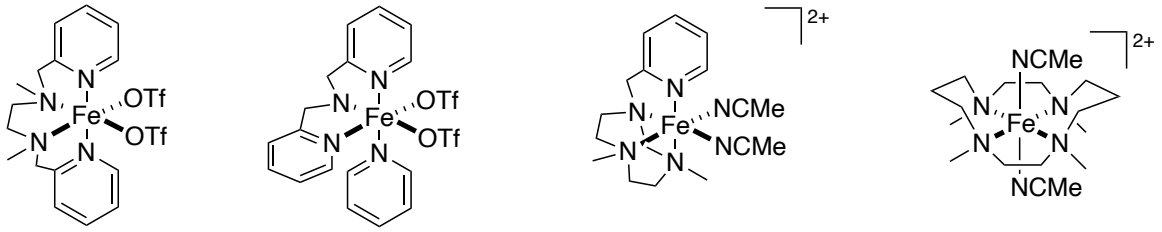
Both enzymes follow a distinctively different epoxidation mechanism than MTO. In contrast to a side-on η^2-peroxo ligated complex formed upon reaction of H_2O_2 with MTO, the species capable of C–H oxidation/epoxidation is a high valent iron oxo species.[71-73, 75] In the case of CYP P450, it is formed from dioxygen.[76] The active center of the enzyme is a heme b cofactor, an iron(III) complex bearing an equatorial porphyrin as well as cysteine and water as axial ligands. In the first reaction step, the Fe(III) center is reduced to Fe(II) by the coenzyme NADPH. Subsequently, the labile water ligand is replaced by dioxygen in a formal redox reaction, resulting in the formation of an iron(III) end-on superoxo species.[76] The superoxo ligand is further reduced and protonated by NADPH forming an end-on η^1-hydroperoxo iron(III) species (compound 0, Scheme 12).[76] Both reduction processes involving cosubstrate NADPH are facilitated by a second enzyme called cytochrome P450 oxidoreductase (POR).[80] Instead of dioxygen and NADPH/H^+, compound 0 can also be obtained directly without the need of POR from H_2O_2 *via* the so called peroxide shunt pathway.[76, 78, 81, 82] In the next step, the O–O bond is cleaved heterolytically, forming a formal Fe(V) oxo species (compound I, Scheme 12). As demonstrated by *Groves* in 1979, compound I is more accurately described as a Fe(IV) oxo complex bearing a cationic radical porphyrin ligand, stabilized by the large conjugated system.[76, 81] In the final step of the reaction, this species transfers the oxygen atom to the olefin,

forming the epoxide and the initial iron(III) catalyst.[76, 78] Alkane hydroxylation undergoes an identical reaction pathway until the formation of compound I. This species then abstracts a hydrogen atom, followed by an attack of the resulting hydroxy ligand to the alkyl radical to obtain the respective alcohol (oxygen rebound mechanism).[76, 78]



Scheme 12. Mechanism of CYP P450 catalyzed olefin epoxidation.[76, 78, 80-82]

A closer look at the reaction mechanism shows, that CYP 450 cannot epoxidize olefins using dioxygen as oxidant without the additional oxidation of the coenzyme NADPH providing two electrons (Scheme 12, red).[76, 78, 80-82] Therefore, bio-inspired/biomimetic catalysts designed to mimic the enzyme's reactivity commonly use hydrogen peroxide as oxidant following the peroxide shunt pathway to avoid the requirement for a comparably expensive cosubstrate.[70-72] Bio-inspired iron catalysts are roughly divided into heme and non-heme complexes. Heme catalysts are all compounds bearing porphyrin ligands, while non-heme catalysts are more diverse and commonly show other tetradentate *N*-donor ligands, as well as two labile ligands like triflate or acetonitrile (Figure 4).[72, 75, 83-88]



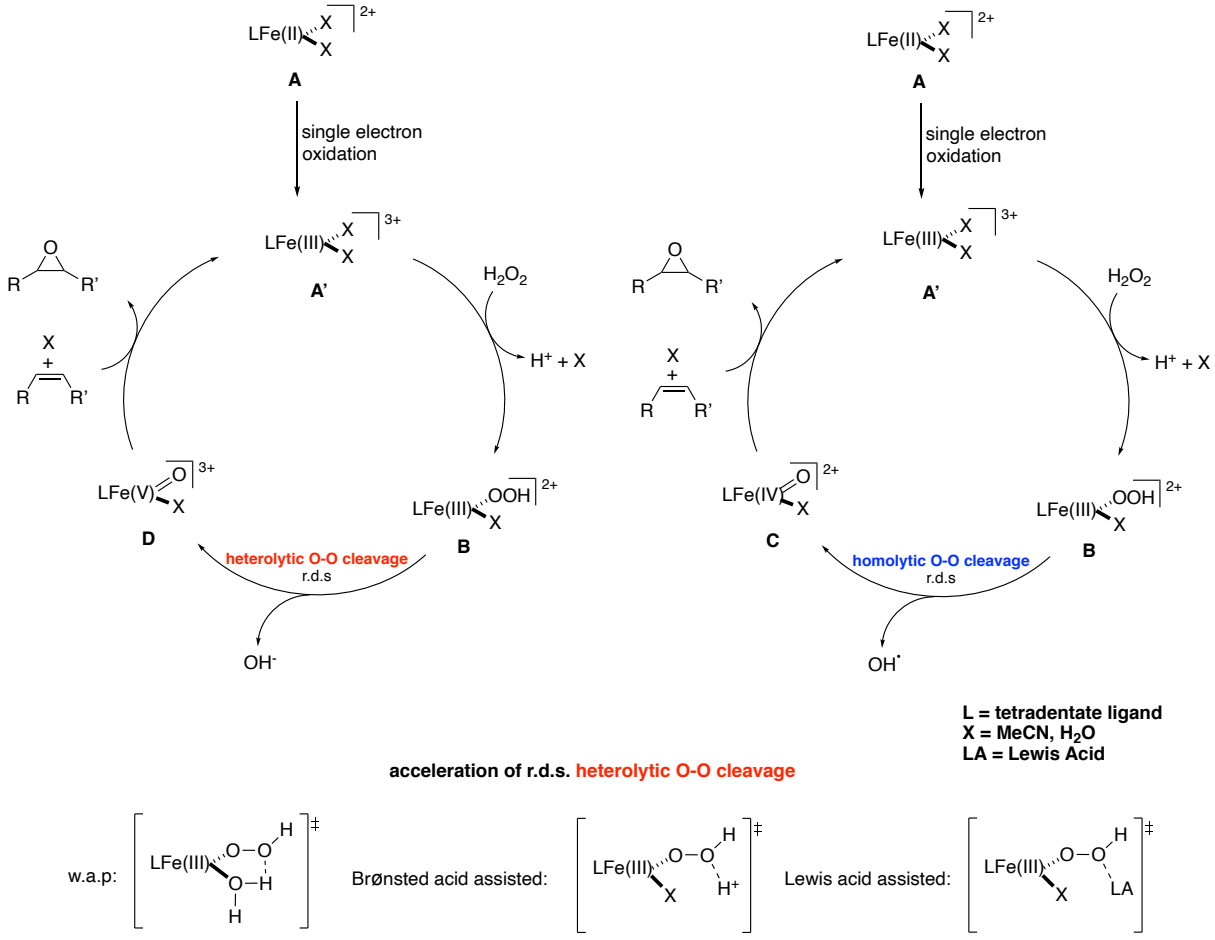
[Fe(BPMEN)(OTf)$_2$] **[Fe(TPA)(OTf)$_2$]** **[Fe(PyTACN)(MeCN)$_2$]$^{2+}$** **[Fe(TMC)(MeCN)$_2$]$^{2+}$**

Figure 4. Important non-heme iron(II) complexes applied in oxidation catalysis.[86-89]

In contrast to heme compounds, where the labile ligands are *trans* oriented, non-heme iron complexes often exhibit *cis* labile sites.[72, 74, 88] The mechanism of non-heme complexes has been studied extensively over the past decades by *Que*, *Costas*, *Christina White*, *Nam* and *Valentine*.[72, 73, 87, 89-92] However, it is still not fully understood. Due to the fact that intermediate species occurring during the catalytic cycle are highly elusive, new mechanistic insights are still reported on a regular basis today.[93-98] The currently accepted mechanisms are shown in Scheme 13 and involve a high valent iron(IV) or iron(V) oxo species transferring the oxygen atom to the olefin (Scheme 13, C and D).[72, 73, 75, 83, 87, 89-92] The preferred oxidation state of this species depends on the electronic and steric properties of the tetradentate spectator ligand (Scheme 13, L).[75] It is formed *via* homolytic or heterolytic O–O cleavage of an iron(III) hydroperoxo intermediate, respectively, formed upon deprotonation of the oxidant hydrogen peroxide and coordination to the iron(III) center (Scheme 13, B).[86, 89, 99, 100] In practice, iron(II) complexes are commonly applied as pre-catalysts, which are oxidized *in situ* by H_2O_2 to form the active iron(III) catalyst (Scheme 13, A and A').[100]

The aforementioned orientation of labile ligands in non-heme catalysts strongly impacts the activity and selectivity.[88, 92, 101, 102] The oxidant hydrogen peroxide is commonly used in an aqueous solution. The present water molecules compete with solvent molecules (usually MeCN) for vacant coordination sites.[75, 100] When water and epoxide coordinate to the iron center in *cis* orientation, the former can attack the epoxide resulting in *cis*-diol formation and therefore decreasing the selectivity for epoxide.[92, 102] In contrast, when the complex exhibits *trans* labile sites, epoxide ring opening does not occur going along with a higher selectivtiy.[75, 102] However, despite of its negative effect on the selectivity, water positively impacts the activity of catalysts bearing *cis* labile sites.[74, 75, 100] The iron(III) hydroperoxide species (B), can interact with a neighboring H_2O molecule *via* hydrogen bonds and accelerate the heterolytic O–O cleavage and iron(V) oxo formation. This process is exclusive for *cis* labile sites and often referred to as the water-assisted pathway (Scheme 13, w.a.p).[100]

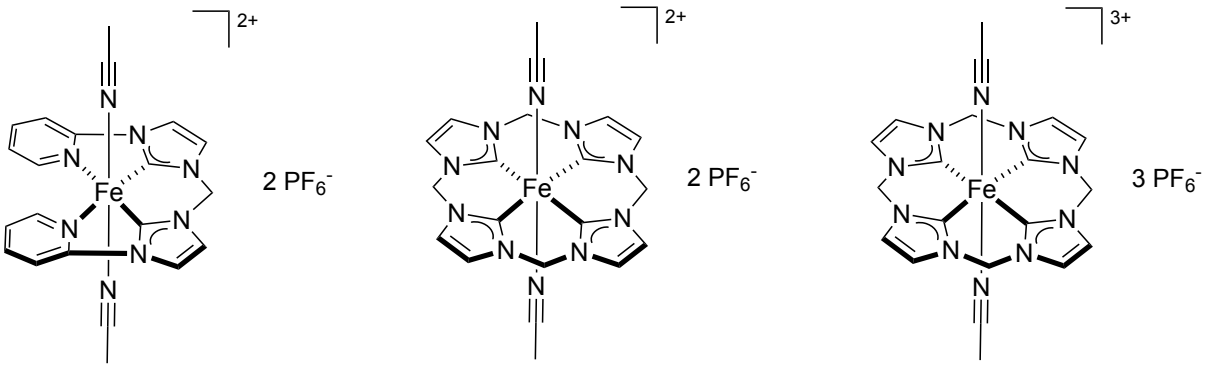
Due to the fact that hydroxide, formed during O–O cleavage, is a bad leaving group, this step is generally considered as rate determining (r.d.s).[75, 100] The r.d.s. is not only accelerated by water, but also (and to a stronger degree) by Brønsted and Lewis acidic additives, making OH^- a better leaving group by protonation or coordination, respectively (Scheme 13).[75, 89, 98] Brønsted acids can be divided into two groups, those having non-coordinating corresponding anions like $HClO_4$ and those having coordinating anions like acetic acid.[89, 98] Acetate is a stronger donating ligand than water and therefore suppresses H_2O coordination to the iron center and thus *cis*-diol formation. As a result, the coordinating Brønsted acid HOAc not only increase the activity of catalysts with *cis* labile sites, but also the selectivity for the epoxide.[89]



Scheme 13. Mechanisms of olefin epoxidation catalyzed by non-heme iron complexes showing *cis* labile sites. Left: *via* iron(V) oxo formed by heterolytic O–O cleavage. Right: *via* iron(IV) oxo formed by homolytic O–O cleavage. Bottom: acceleration of the heterolytic O–O cleavage by water (left), Brønsted (middle) and Lewis acids (right). Generally, the mechanism of iron catalysts with *trans* labile sites follows the same pathways. For those, the homolytic cleavage and iron(IV) oxo seems to be more common.[72-75, 83, 87, 89-98, 100, 102]

A closer look on the transition states for the acceleration of the heterolytic O–O cleavage by water, Brønsted and Lewis acids reveals, that only the water assisted pathway requires *cis* labile sites.[100] Surprisingly, a performance enhancing influence of Brønsted and Lewis acidic additives is barely reported in literature.[75]

Unfortunately, when compared to the enzymes they are supposed to mimic or Ti, Mn, Mo and Re based complexes, most non-heme iron catalysts show poor performance.[75] For instance, [Fe(BPMEN)$(OTf)_2$] reaches a TOF of 17 h^{-1} and a TON of only 8.4.[92]
Recently, significantly better performing iron catalysts have been reported by *Kühn*.[103, 104] These complexes exhibit *trans* labile coordination sites and are both based on tetradentate *N*-heterocyclic carbene ligands. Without applying any additive, iron(II) catalyst **1** with a pyridine/NHC ligand shows a TOF of 800 h^{-1} and TON of 50 in the epoxidation of the benchmark substrate *cis*-cyclooctene (Figure 5, left).[103, 104] The catalyst also selectively facilitates the more challenging hydroxylation of aliphatic and aromatic hydrocarbons.[105-108] A further improvement are iron(II) and iron(III) (pre-)catalysts **2** and **3** featuring a 16-membered macrocyclic tetra-NHC ligand (Figure 5, right).[109, 110] **2** shows an initial TOF of 50 000 h^{-1} in the epoxidation of *cis*-cyclooctene outperforming MTO in terms of activity.[110] As described earlier and shown in Scheme 13, the active catalyst is an iron(III) complex commonly generated *in situ* by oxidation of an iron(II) precatalyst with H_2O_2. Therefore, iron(II) complex **2** shows an induction period and a significantly lower initial TOF than its pre-oxidized iron(III) counterpart **3**. To date, **3** is the most active epoxidation catalyst, exhibiting unprecedented additive free TOFs of up to 183,000 h^{-1} with a selectivity up to 99%.[110] At the same time, **3** also reaches the highest TON for an iron-based epoxidation catalyst reported to date (4,300). It has to be noted, that this value is only obtained at temperatures below -20 °C. At room temperature, the TON is considerably lower.[110] Despite being notably more stable than other non-heme oxidation catalysts (in terms of TON), the stability of **3** is still nowhere near optimized Mo and Re based catalysts and has to be further increased.[60] In addition, **3** lacks functional group tolerance and is limited to simple olefins.[110]
Nevertheless, the significantly better performance of **1**, **2** and **3** in comparison to non-heme catalysts based on tetradentate *N*-donor ligands shows, that chelating *N*-heterocyclic carbenes are highly promising ligands for the design of efficient homogeneous oxidation catalysts, which can be attributed to their unique properties.[75]



1 **2** **3**

Figure 5. Structures of iron NHC oxidation (pre-)catalysts **1**, **2** and **3**.[103, 109, 110]

1.6 *N*-HETEROCYCLIC CARBENE LIGANDS

N-heterocyclic carbenes (NHCs) have been discovered independently by *Wanzlick* and *Öfele* in the 1960s, who reported chromium(0) and mercury(II) complexes bearing an imidazole based ligand (Figure 6, middle).[111, 112] For a long time, these compounds have been considered as mere lab curiosities, in contrast to *Fischer* and *Schrock* carbenes, which found wide applications as ligands in catalysis and organic synthesis.[113-116] In fact, *Schrock* was awarded the Nobel prize in chemistry for his work on catalytic olefin metathesis with transition metal carbene complexes in 2005. [115, 117]

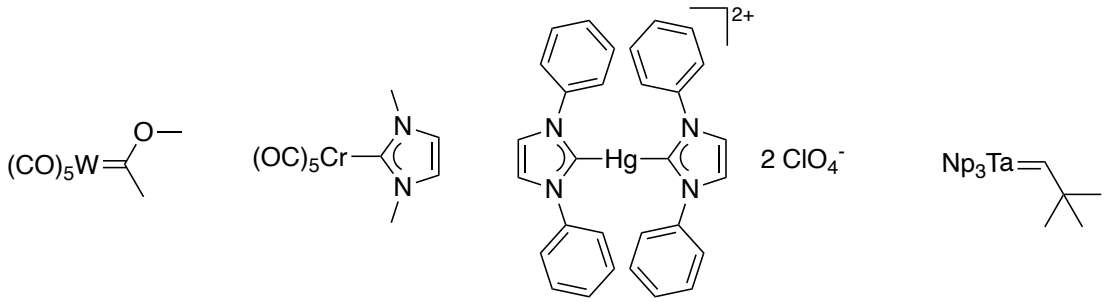
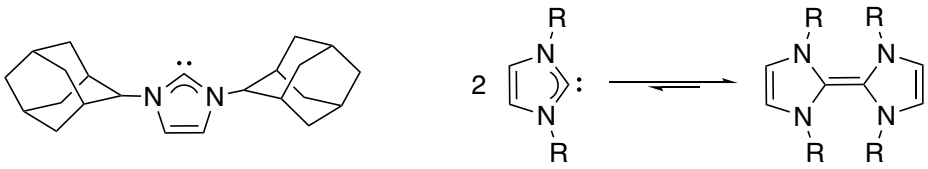


Figure 6. Structures of different carbene complex types.[111-114]

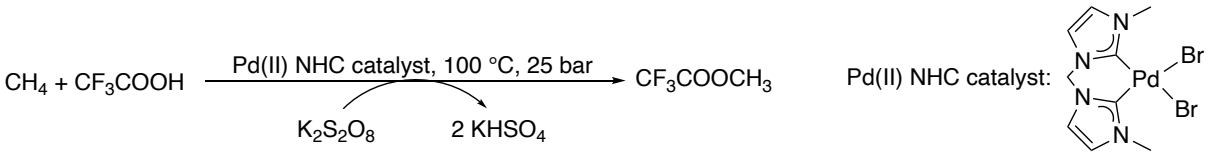
It took about 30 years since their discovery for NHCs to get in the focus of research again. In 1991, *Arduengo* was able to isolate the first imidazol-2-ylidene with two sterically demanding adamantyl wingtips, as the *N*-substituents are often called (Scheme 14, left).[118] Before this report, NHCs have been considered to be highly reactive, unstable and not isolable due to the fact that they tend to dimerize forming a C=C double bond (*Wanzlick* equilibrium, Scheme 14, right).[119] The use of bulky wingtips prevents the dimerization of two carbene molecules.[118]



Scheme 14. Structure of the first isolated stable NHC (left), *Wanzlick* equilibrium (right).[118, 119]

Since *Arduengo's* report on stable NHCs, this compound class has emerged as highly important spectator ligands in organometallic chemistry replacing widely applied phosphines, which they are often compared to.[120-123] Both, NHCs and phosphines can easily be tuned in

terms of steric and electronic properties by substituent variation.[120, 124, 125] However, NHCs are significantly stronger σ-donors and therefore do not dissociate from the metal as easily as phosphines often do.[121, 122] Due to their strong donating properties NHCs can stabilize high oxidation states exceptionally well.[126] These unique properties of *N*-heterocyclic carbenes might explain the unprecedented activity of the aforementioned iron(III) tetra-NHC complex in the catalytic olefin epoxidation, which undergoes a high valent iron oxo intermediate, if it follows the commonly accepted mechanism shown in Scheme 13.[75, 110] Another example showcasing the suitability of NHC ligands in oxidation catalysis is a palladium(II) bis(NHC) compound applicable in methane oxidation which even sustains $K_2S_2O_8$ at 100 °C in CF_3COOH (Scheme 15).[127] Their high robustness against oxidation even under harsh conditions sets NHCs further apart from phosphines which are known to rapidly form phosphine oxides.[120, 127]



Scheme 15. Methane oxidation catalyzed by a Pd(II) NHC complex under harsh conditions.[127]

The high stability of the catalyst can be assigned to the exceptional electronic properties of NHC ligands.[120, 122, 127, 128] In contrast to classical triplet carbenes, NHCs are formally sp^2 hybridized and depict a singlet state.[122-124, 128] The highest occupied molecular orbital (HOMO) is best described as a lone pair, while the lowest unoccupied molecular orbital (LUMO) has a p-orbital character. The adjacent nitrogen atoms donate electron density to the LUMO (+π effect), while at the same time withdrawing electron density on the σ-level due to their high electronegativity (-σ effect).[122-124, 128] This interplay of electron donation and withdrawing is often described as the push-pull effect (Figure 7).[128]

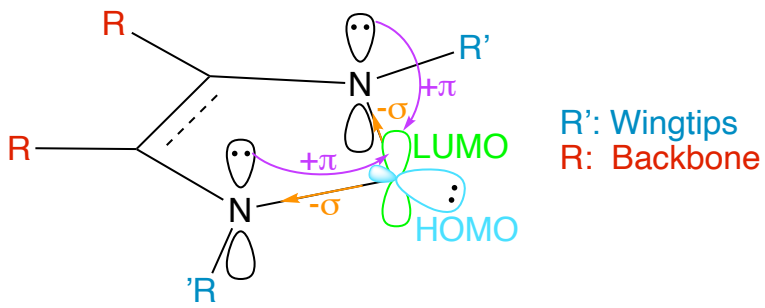
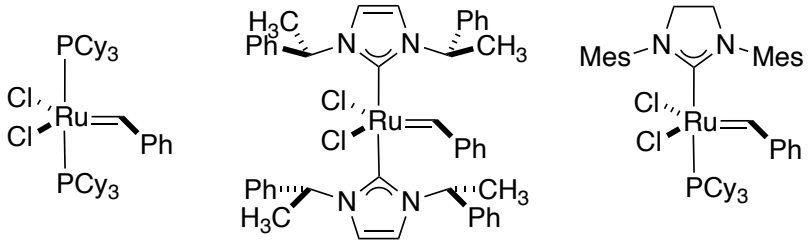


Figure 7. Stabilization of the singlet carbene by the adjacent nitrogen atoms.[122-124, 128]

The electronic and steric properties can be fine-tuned by varying the wingtip and backbone substituents (Figure 7).[124, 128] These modification sites can also support functional groups or other donating moieties, thus allowing for the design of suitable chelating ligands for catalytic

applications including cross-coupling, transfer hydrogenation, oxidation, olefin metathesis and hydrosilylation, amongst others.[120, 129-135]

In 2005, *Grubbs* was awarded the Nobel prize in chemistry alongside *Schrock* and *Chauvin* for his work on catalytic olefin metathesis. *Grubbs* reported a ruthenium complex bearing a NHC ligand in *trans* position to a phosphine as a highly efficient catalyst for olefin metathesis in 1999 (*Grubbs* II, Figure 8).[136, 137] In contrast to its bis(phosphine) ligated counterpart (*Grubbs* I, Figure 7), it is stable towards air and moisture and significantly more active due to a faster phosphine dissociation resulting from the strong *trans* effect induced by the strongly donating NHC ligand.[136, 137] Unlike the previously described NHCs by *Arduengo*, *Wanzlick* and *Öfele,* which are based on imidazole, the Grubbs II catalyst features an imidazoline-based NHC with a saturated backbone – a small structural difference that results in significantly better catalytic performance.[133, 135] In fact, *Herrmann* also reported a similar metathesis catalyst ligated by two imidazole-based NHC ligands in 1999 (Figure 8).[132] Due to the high similarity of the *Grubbs* II catalyst with *Herrmann's* complex a long-lasting patent dispute was fought in the USA which *Herrmann* and *Evonik* have finally won.[138] However, even though *Herrmann* won the patent dispute in court, *Grubbs* maintained the Nobel laureate.[138]



Grubbs I **Herrmann** **Grubbs II**

Figure 8. Ru-based olefin metathesis catalysts by *Grubbs* and *Herrmann*.[132, 133, 135, 136]

This historic dispute in NHC chemistry showcases that small differences in the structure of the heterocycle have a significant impact on the electronic properties and therefore the reactivity.[133, 135] Since *Arduengo's* report on imidazol-2-ylidenes (NHC_{im}), a variety of other NHCs based on different heterocycles has been reported (Figure 9). These can be divided in normal NHCs (in the following: NHCs) and mesoionic or abnormal NHCs (MIC, aNHCs) as they were originally called by *Crabtree* who discovered them in 2001.[139, 140] Both, NHCs and MICs are stabilized by the heteroatom(s) as shown in Figure 8, however to a different extent depending on their number and position. For normal NHCs, a structure without charge separation can be drawn while all aNHCs show a zwitterionic/mesoionic structure.[122, 125] In general, aNHCs are considered stronger σ-donors than normal NHCs (compare *e.g.*

imidazole-2-ylidene vs. imidazol-4-ylidene or 1,2,4-triazol-5-ylidene vs. 1,2,3-triazol-5-ylidene, Figure 9).[122, 125] The donating properties of a ligand (L) can be expressed by the *Tolman* electronic parameter (TEP), derived from the CO stretching frequencies obtained by infrared (IR) vibrational spectroscopy in *cis*-[RhCl(L)$(CO)_2$] or [Ni(L)$(CO)_3$] complexes, *i.e.*, the lower the TEP, the stronger the electron donating capability of the ligand.[122, 125] However, this method has its limitations and needs to be complemented by NMR spectroscopic (^{77}Se) and computational methods to validate the results. Nevertheless, due to its practicability the TEP is still commonly applied today.[141, 142]

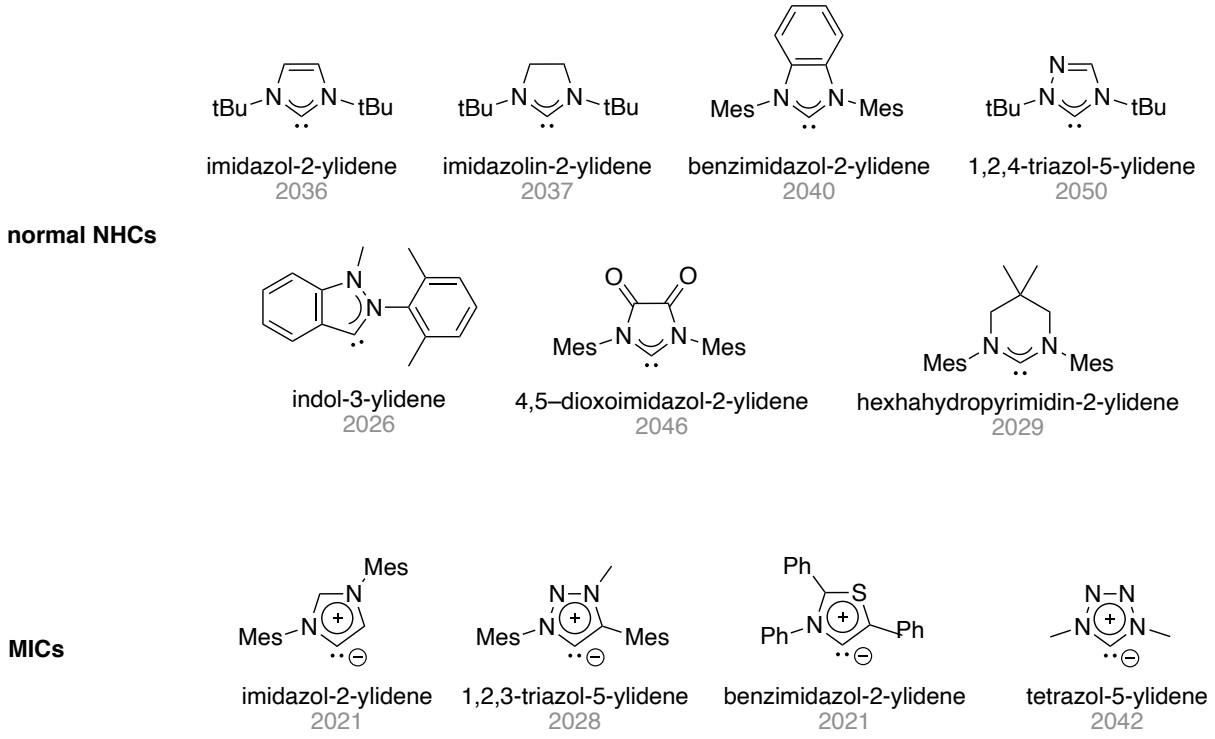
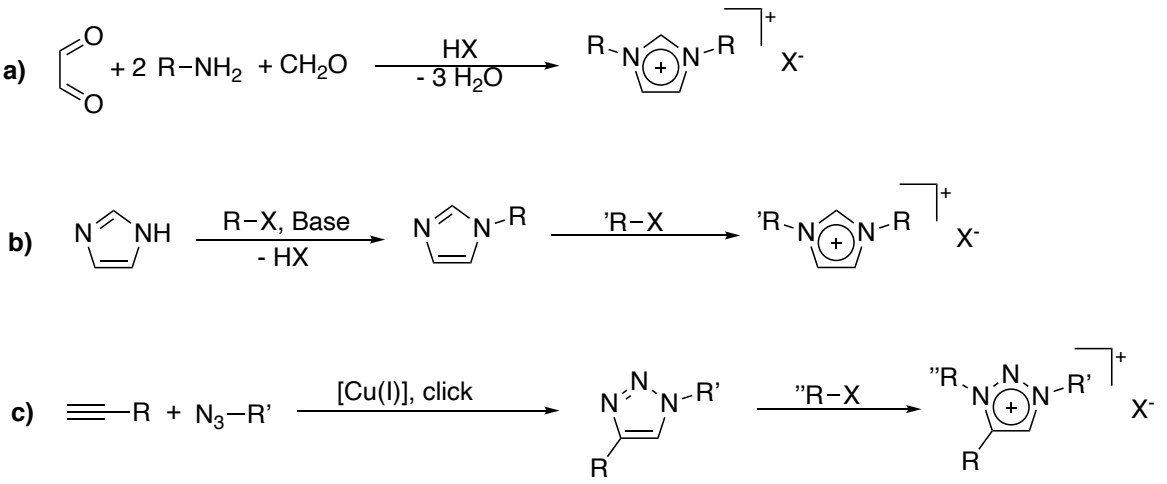


Figure 9. Selection of normal NHCs and MICs. Their corresponding TEP (in cm^{-1}) as a measure of donor strength is given below in grey.[122]

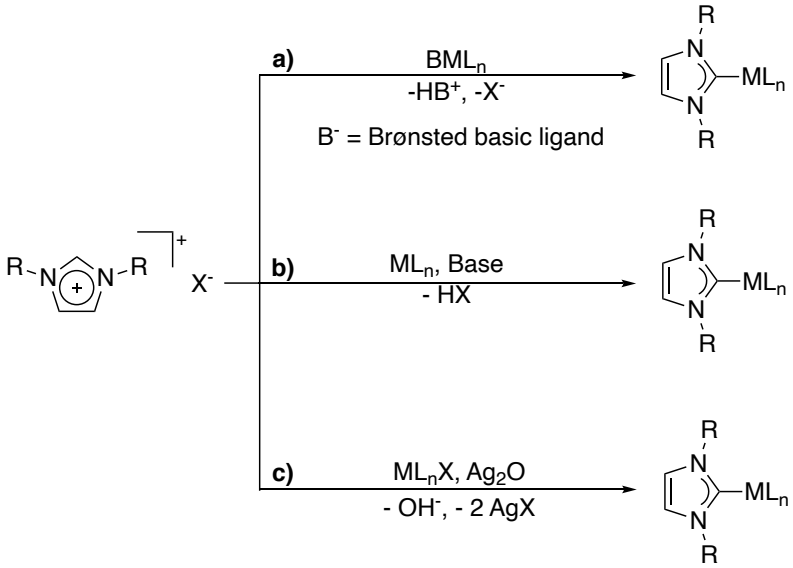
In recent years, 1,2,3-triazol-5-ylidenes (NHC_{trz}) got more and more in the focus of research. First reported by *Albrecht* in 2008, they are now widely applied ligands in homogeneous catalysis and even termed as “rising stars”.[143-148] Since their first report, complexes bearing NHC_{trz} ligands make up the second largest share amongst all *N*-heterocyclic carbene complexes today, while imidazol-2-yildene (NHC_{im}) complexes are the most widely spread.[146] Both, NHC_{trz} and NHC_{im} share a common characteristic, *i.e.*, they are easy to synthesize and modify setting them apart from many other *N*-heterocyclic carbenes shown in Figure 7. NHC_{im} are commonly synthesized from their corresponding imidazolium salts, which can be obtained by condensation reactions (a) or S_N2 reactions (b), allowing for a variety of different ligand precursors (Scheme 16). NHC_{trz} complexes are derived from their corresponding 1,3,4-

substituted 1,2,3-triazolium salts, which are obtained by cycloaddition and subsequent alkylation (c). In 2005, *Sharpless* reported on the simple synthesis of 1,4-substitued 1,2,3-triazoles *via* copper(I) catalyzed cycloaddition of azides and alkynes (CuAAC) in high yield, (regio)selectivity and purity at ambient conditions using non-toxic solvents like water and tolerating various functional groups (c, Scheme 15).[149, 150] As the CuAAC fulfills all criteria of click chemistry, it is often referred to as the click reaction.[149, 150]



R, R' = wingtip; X = halide, PF_6, OTf…

Scheme 16. Synthesis of the two most common NHC/MIC precursors: imidazolium salts *via* condensation (a) and alkylation (b), as well as 1,2,3-triazolium salts *via* click chemistry and subsequent alkylation (c).[120, 151, 152]



R = wingtip; X = halide, PF_6, OTf…

Scheme 17. Synthetic routes to transition metal NHC complexes starting from imidazolium salts: internal base (a), external base (b) and Ag_2O (c). The same methods are also applicable to 1,2,3-triazolium salts.[140, 150, 153, 154]

1.7 TRANSITION METAL *N*-HETEROCYCLIC CARBENE COMPLEXES AS POTENTIAL ANTICANCER AGENTS

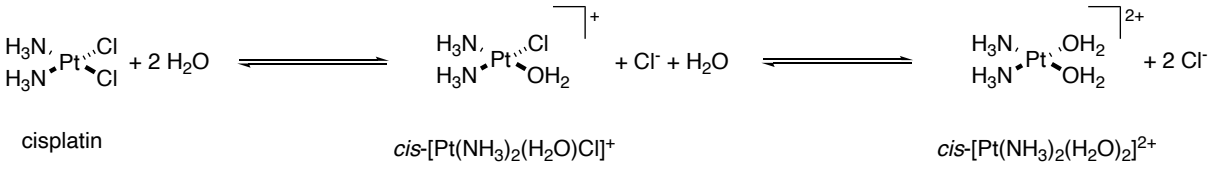
While transition metal NHC complexes have been employed in homogeneous catalysis just shortly after *Arduengo's* breakthrough in 1991, especially in the past decade the number of reports on applications in the field of medicinal chemistry has significantly increased.[118, 120, 155-158] Miscellaneous NHC complexes show promising antibacterial, antiviral and antiproliferative properties.[155-160] The latter are of special interest in cancer therapy.[161]

According to the world health organization (WHO), cancer is the second most common cause of death amounting 9.6 million fatalities and 18.1 million new incidences in 2018.[162] Cancer is a disease in which mutated cells proliferate uncontrolled and excessively which can invade nearby tissues forming tumors.[163-165] In contrast to cancer cells, the growth and replication of non-malignant cells is controlled by diverse mechanisms like apoptosis, a programmed cell death.[163-165] Besides surgery and radiotherapy, the treatment of cancer involves chemotherapy aimed at inhibiting the proliferation of cancer cells and induce apoptosis.[163-166] However, both radio- and chemotherapy are rather unselective and also affect healthy cells, thus inducing severe side-effects including nephrotoxicity, cardiotoxicity, anaphylaxis, neurotoxicity, vomiting and diarrhea.[166, 167]

One of the most prominent chemotherapeutics is *cis*-diamminedichloroplatinum(II) (cisplatin, Scheme 18), first synthesized by *Pyrone* in 1844.[167-169] In 1965, *Rosenberg* accidently discovered its outstanding ability to inhibit cell proliferation in an experiment designed to study the influence of an electric field on the growth of *Escherichia coli* (*E. coli*) bacteria in a common cellular medium.[170] Due to the fact that other metals like copper were already known to have biological functions at that time, *Rosenberg* and his coworkers used platinum electrodes, which have so far been considered inert, to circumvent possible interferences.[170, 171] When applying an electric current the cell growth was fully inhibited.[170] After stopping the power supply the cells started dividing again.[172] At first glance it looked like an electric field indeed controls the proliferation of bacteria.[173] However, when using different electrode materials, the cell culture grew applying otherwise identical conditions.[170] After subsequent studies, the cause of the antiproliferative effect was unequivocally proven to result from a reaction of chloride and ammonium from the cellular medium with the electrode material, originally assumed to be inert, forming small amounts of cisplatin and *cis*-diamminetetrachloroplatinum(IV) as soon as the current is applied (Figure 10).[170, 173-175] Soon after, the antiproliferative effect of both platinum compounds on cancer cells was reported.[176] Further successful studies on mice and clinical trials on humans by the US National Cancer Institute (NCI) have finally led to an approval of cisplatin for cancer treatment by the United States Food and Drug Administration (FDA) in 1978.[167, 169, 172, 175, 177, 178]

These groundbreaking results aroused the interest of scientists to elucidate the mechanism of action underlying cisplatin which could potentially enable the targeted design of even more potent metallodrugs for cancer therapy.[175, 177] The generally accepted predominant mode of action involves several important steps which finally induce apoptosis.[169]

First, cisplatin enters the cell *via* passive transport through the lipophilic membrane. For this process, the neutral nature of the complex is vital as many positively charged complexes are too polar to be imported passively.[169, 179] Due to the lower chloride concentration in the cells (4 mM to 10 mM) in comparison to blood (104 mM), the equilibrium reaction of chloride substitution by water is shifted from cisplatin to its hydrolyzed forms (Scheme 18).[169, 180, 181] Due to the higher polarity of these mono- and dicationic complexes in comparison to cisplatin they can no longer exit the cells *via* passive transport through the lipophilic membrane.[169, 179]



Scheme 18. Equilibrium reaction between cisplatin and its hydrolyzed forms.[169, 179-181]

In the next step, the hydrolyzed form of cisplatin enters the nucleus where it interacts with the DNA.[169] The purine derived DNA bases adenine (A), guanine (G) show a higher basicity and σ-donor strength than the pyrimidine derived bases cytosine (C) and thymine (T).[169, 182] Consequently, the aqua ligands are replaced by adenine or guanine units which coordinate *via* the N7 atom resulting in intra- and interstrand crosslinks (Figure 10).[169, 175, 183] After platination of the DNA, the strands exhibit a bent structure which is recognized by the cell. To prevent the replication of the damaged DNA and avoid mutations the nucleotide excision repair machinery (NER), a series of various proteins and enzymes, tries to correct the damages.[169, 184, 185] However, cisplatin also interacts with many of the involved molecules of the NER, therefore hindering their efficiency.[169, 185] If the NER cannot correct DNA lesions the cell subsequently induces apoptosis.[169]

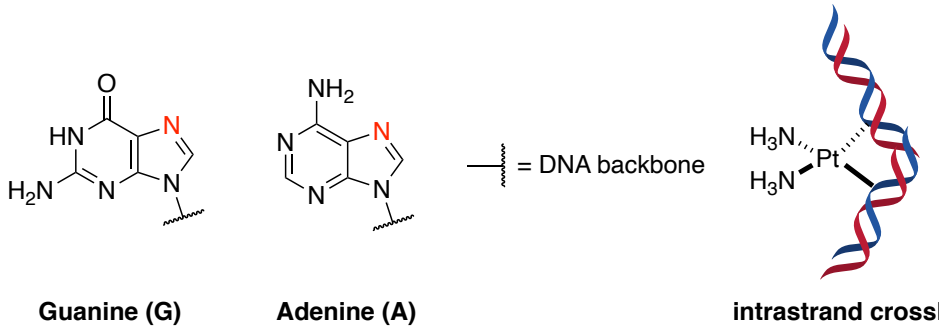


Figure 10. Structures of purine bases guanine (G) and adenine (A) with DNA binding sites marked in red (left); intrastrand crosslink induced by platination of DNA (right).[169, 175]

Unfortunately, due to the mechanism of action described above, the treatment of cancer with cisplatin is associated with disadvantages. Cisplatin is comparably unselective and also affects healthy cells, therefore inducing severe side-effects including vomiting, nausea, nephrotoxicity, cardiotoxicity and diarrhea, amongst others.[167] In addition, cancer cells can develop a resistance against cisplatin, *e.g.* by enhancing the NER activity.[185, 186]
Consequently, research has focused on alternative metallodrugs with different mechanisms of action. Figure 11 shows a variety of transition metal complexes that show potential in the treatment of cancer and are currently in clinical trials.[187-190]

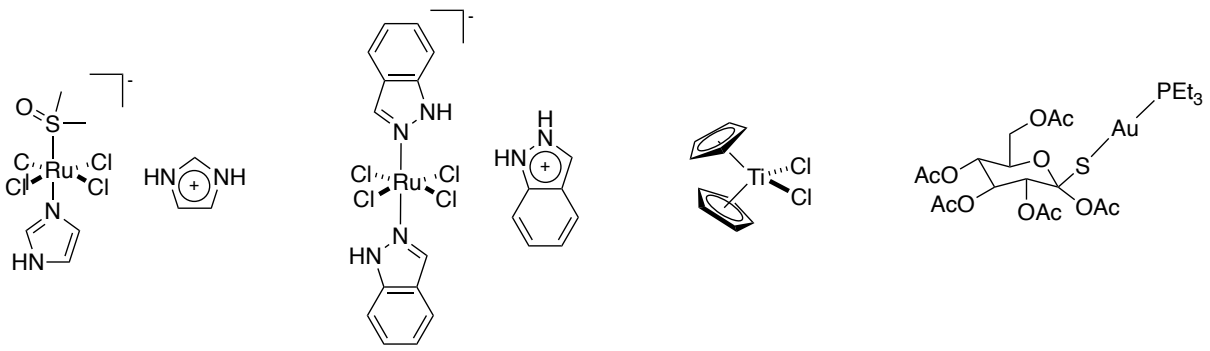
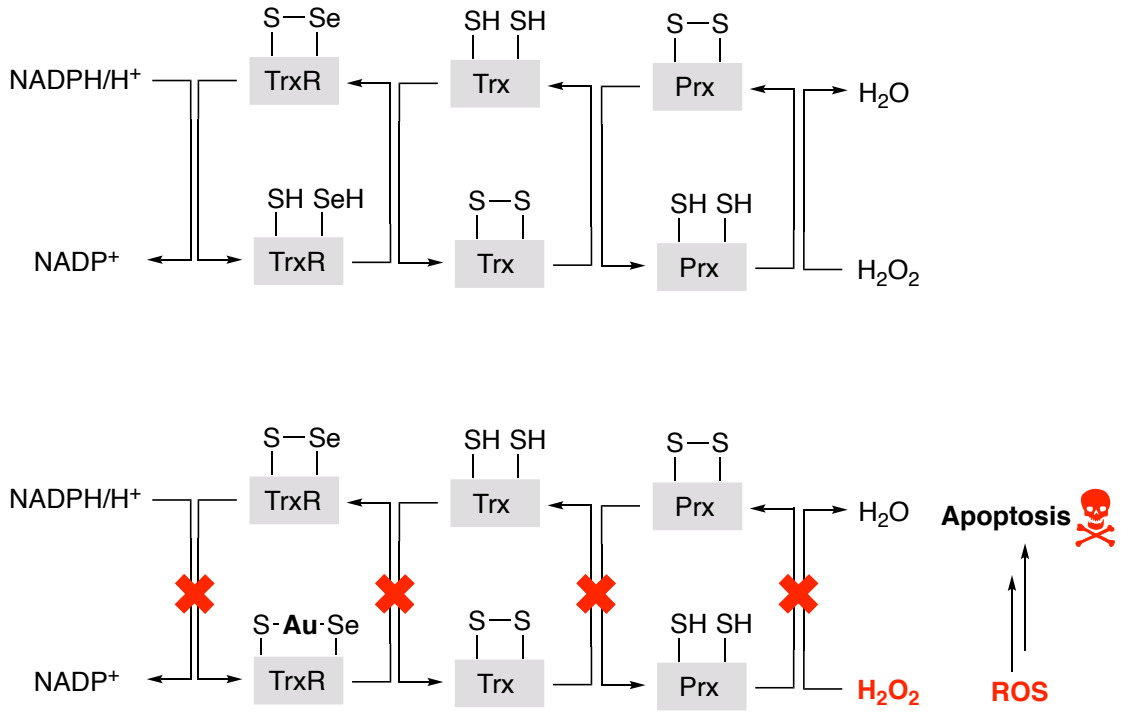


Figure 11. Structures of transition metal complexes in clinical trials for cancer treatment.[187-190]

Out of those, auranofin, originally discovered by *Sutton* in 1972, has already been approved for the treatment of rheumatoid arthritis by the FDA in 1985.[191, 192] Therefore, its side-effects are well studied and less severe than those associated with cisplatin, mainly including diarrhea as well as abdominal cramping.[193] Soon after its approval for the treatment of rheumatoid arthritis, the antiproliferative activity was reported *in vivo* showing promising results in a cervix cancer cell line (HeLa).[194] Consequently, its mechanism of action was studied in detail.[195, 196]

In contrast to cisplatin, auranofin and other related gold(I) complexes do not interact with the DNA. Instead, they interact with the enzyme thioredoxin reductase (TrxR) which is mainly located in the mitochondrion and overexpressed in cancer cells.[196-198] In conjunction with two other enzymes, *i.e.* thioredoxin (Trx), and peroxiredoxin (Prx), TrxR forms the thioredoxin system.[195, 196, 199, 200] Its main purpose is the reduction of reactive oxygen species (ROS) like hydrogen peroxide to harmless water.[196, 199-202] The mechanism of the thioredoxin system is shown in Scheme 19.[196] The active center of TrxR contains a cysteine (Cys) selenocysteine (Sec) bridge.[195, 196, 203] Gold(I) originating from auranofin and other related complexes forms strong bonds with these soft Lewis basic amino acids which replace the ligands of those

compounds.[196, 204, 205] As a result, TrxR is inhibited irreversibly leading to an accumulation of ROS eventually inducing apoptosis *via* the mitochondrial pathway (Scheme 19).[195, 196, 200]



Scheme 19. Thioredoxin system: active (top), inhibited by gold (bottom).[195, 196, 200]

Due to the high thiophilicity of gold(I) its complexes also react with other cysteine containing proteins than TrxR.[204-206] Amongst those, glutathione (GSH) and human serum albumin (HSA) are highly important.[206] HAS can deactivate gold(I) compounds in human blood before reaching cancer cells, while GSH can deactivate them within the cell before reaching.[206, 207] As a result, many gold complexes show insufficient activity *in vivo*. The degree of deactivation is highly dependent on the stability of the gold complex.[195, 206] However, complexes with a higher stability against GSH and HSA are also more robust against their intracellular target TrxR.[157, 195, 208] Therefore, research has focused on finding a sweet spot between activity and stability.[208] As phosphine compounds like auranofin seem to show insufficient stability for *in vivo* applications, more stable gold(I) NHC complexes have attracted attention as potential anticancer compounds. [206, 207, 209-212] The simple modifiability of NHC ligands described in the previous chapter allows for electronic and steric finetuning as well as the tuning of the polarity of the complex.[124] As reported by *Berners-Prize* the latter plays a crucial role in the cellular uptake through the lipophilic cell membrane and correlates with the cytotoxicity which is often expressed by the IC_{50} value determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays (Figure 12). The IC_{50} value is the concentration of complex required to reduce the metabolic activity by 50% *in vitro* (Figure 12).[207, 213, 214]

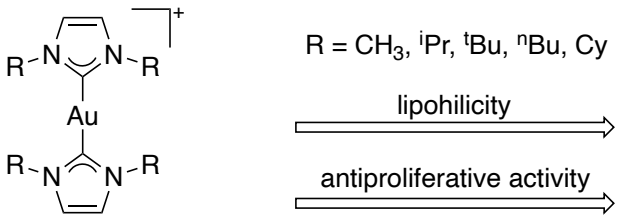


Figure 12. Correlation between antiproliferative activity and lipophilicity of gold(I) bis(NHC) complexes.[214]

The lipophilicity not only correlates with the cytotoxicity of the complexes but also has an impact on the selectivity towards cancer cells in comparison to non-malignant cells.[214, 215] The complexes shown in Figure 12 are active against breast cancer cell lines while they are significantly less toxic to healthy epithelial cells.[206] Out of the series the complex bearing isopropyl wingtips depicts the best selectivity.[206] Similar to auranofin the compound inhibits TrxR by a stepwise replacement and protonation of both NHC ligands by Sec and Cys.[195, 196, 200, 214]

Other recent developments in gold(I) NHC chemistry aiming to achieve both, high selectivity for cancer cells and antiproliferative activity at the same time include the attachment of so-called vectors or targeting ligands to these compounds.[216, 217] Vectors are specifically designed to interact with molecules overexpressed by cancer cells and therefore often facilitate an active transport into the cells.[216] Targeted drug delivery is a common approach used for bioactive organic molecules to avoid side-effects, however still quite uncommon for organometallic compounds.[216, 218] The simple modifiability of NHCs allows for the attachment of vectors to potentially increase the selectivity of their antiproliferative gold(I) complexes (Figure 13).[217, 219] In order to link targeting ligands to NHCs a suitable functional group is required.[216] Those include carboxylic acids, amines, azides and alkynes, amongst others.[216]

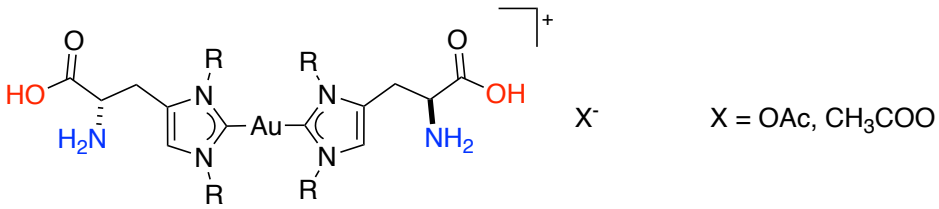


Figure 13. Structure of a histidine derived gold(I) bis(NHC) complex with modifiable amine (blue) and carboxylic acid (red) functionalities as potential modification sites for vectors.[219]

This approach can also be extended to NHC complexes of other transition metals than gold which show a different mechanism of action, *e.g.* palladium, platinum, ruthenium, rhodium, copper.[158, 160, 216]

2 OBJECTIVE

Transition metal complexes bearing NHC ligands have a broad variety of applications ranging from oxidation catalysis where they stabilize high valent intermediates to medicinal chemistry as potential anticancer compounds where they not only stabilize the compounds against deactivating proteins that are present in the blood but also allow for the finetuning of activity, stability and selectivity.

The present thesis can be divided into two parts. The first part covers the stabilization of high valent transition metals in oxidation catalysis and related applications like dioxygen activation by NHC ligands, while the second part covers the application of NHC complexes as potential antiproliferative compounds.

As described in the previous chapters, iron complexes bearing tetradentate NHC ligands are remarkably active olefin epoxidation catalysts that can also be applied in the hydroxylation of alkanes and aromatics. So far, only iron NHC complexes bearing *trans* labile coordination sites have been studied in those catalytic reactions. According to mechanistic studies, iron complexes with purely nitrogen donating ligands and *cis* labile sites show significantly higher activity and stability than those bearing *trans* labile sites. Furthermore, the performance of complexes with *cis* labile sites is reported to be considerably improved by acidic additives.

In the first part of the thesis novel iron complexes bearing a tetradentate NHC/1,2,3-triazole hybrid ligand and *cis* labile sites are described and studied in olefin epoxidation catalysis, also with regard to additive influences. This newly reported additive influence on iron NHC complexes is then applied to the aforementioned iron(III) tetra-NHC complex, the so far most active homogeneous epoxidation catalyst. Due to the fact that bio-inspired iron-based oxidation catalysts suffer from low turnover numbers, first studies regarding the deactivation of the iron(III) tetra-NHC catalyst are described in order to determine its weak spot, serving as a starting point for further improvements. The remarkable trait of the 16-membered tetra-NHC ligand to stabilize high valent iron intermediates is further expanded to cobalt and copper. With copper the first copper(III) NHC complex is obtained. The related cobalt(II) complex bearing the same ligand is applied in the activation of dioxygen from air aiming at potential (co-)catalytic applications.

In the second part of the thesis late transition metal NHC complexes of gold, nickel, palladium and platinum are synthesized and studied with regard to their antiproliferative activity against various cancer cell lines. The compounds bear ligands with functional groups which allow for various modifications. As a proof of concept comparably simple substituents are chosen to show the future potential of linking selectivity enhancing vectors. Additionally, preliminary mechanistic insights are obtained by spectroscopic and enzymatic methods.

3 RESULTS – PUBLICATION SUMMARIES

In this chapter, the publications that originated from this thesis are summarized. The chapter is divided into two sections. The first part covers iron NHC complexes in oxidation catalysis and their related copper and cobalt complexes (3.1). The second part deals with late transition metal NHC complexes and their antiproliferative effects against cancer cells (3.2). The articles in the related chapter are ordered by the date of publication. The publications, bibliographic data and reprint permissions are attached in the appendix.

3.1 Iron NHC Complexes Applied in Epoxidation Catalysis and Their Copper and Cobalt Analogues

3.1.1 A Bench Stable Formal Cu(III) *N*-heterocyclic Carbene Accessible from Simple Copper(II) Acetate

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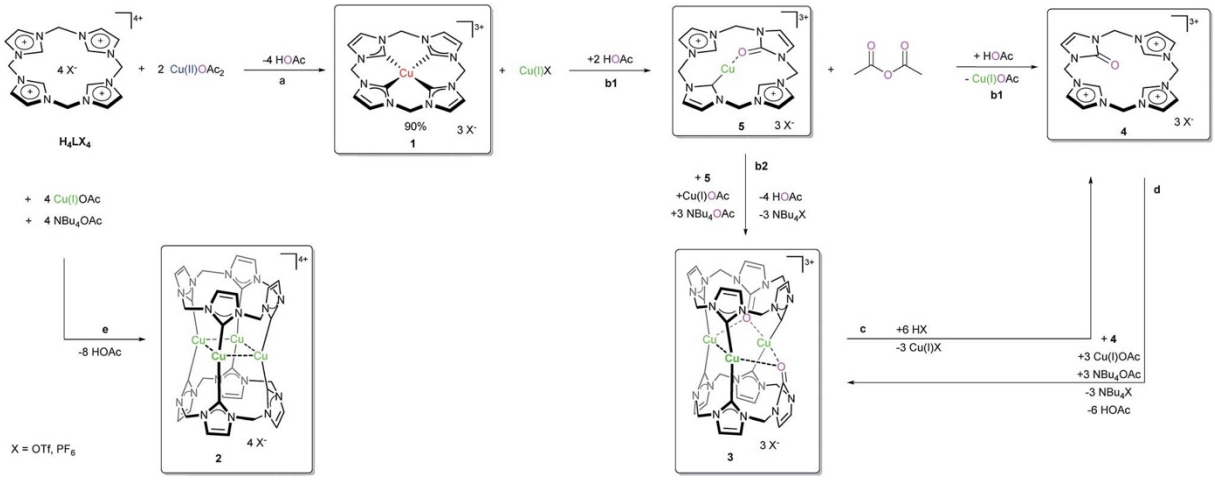
published in *Chem. Sci.*, 2018, **9**, 8307-8314.[220]

In this article, the synthesis and characterization of the first copper NHC complex **1** with copper in the formal oxidation state +III is described. It is formed upon reaction of 16-membered tetra-NHC precursor $\mathbf{H_4LX_4}$ with copper(II) acetate (Scheme 20, a). Thereby, the solvent dimethyl sulfoxide (DMSO) plays a crucial role facilitating the disproportionation of copper(II) to copper(I) and copper(III).



Scheme 20. Synthesis of the first reported copper(III) NHC complex **1** (a) and its reactivity with acetic acid forming acetic anhydride and mono-oxidized and protonated ligand precursor **4** *via* intermediate **5** (b1); synthesis of copper(I) complex **3** ligated by **5** (b2, d).

1 depicts a square planar structure as shown by SC-XRD (Figure 14, left). The average Cu–C distance is 1.88 Å and slightly shorter compared to Cu(I) and Cu(II)–NHC complexes. Despite its high stability towards air, moisture and other Brønsted acids, **1** shows a unique reactivity with acetic acid. *Via* reductive elimination copper(I) acetate, acetic anhydride and the mono-oxidized NHC/urea ligand precursor **4** are formed (Scheme 20, b1; Figure 14, middle). **4** is one of the rarely reported examples where imidazole based NHCs are selectively oxidized. When **4** is converted with copper(I) acetate and tetrabutylammonium acetate as an external base in a 2:3:3 ratio, the trinuclear copper(I) complex **3** is formed (Scheme 20, d). The Cu atoms are linearly coordinated by the NHC donors of two ligands but also show weak electrostatic interactions with the urea moieties (Figure 14, right).

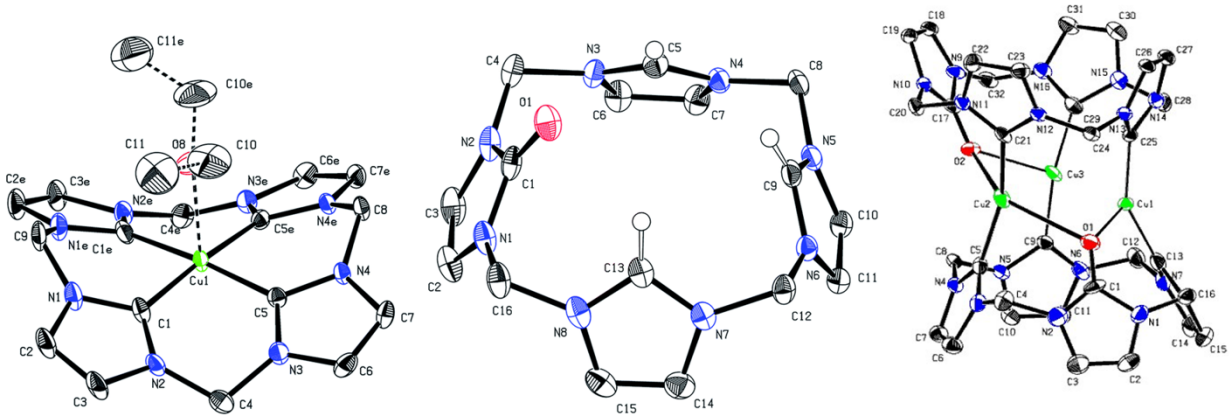


Figure 14. ORTEP-style representations of the cationic fragments of compound **1** (left)**, 4** (middle) and **3** (right). Hydrogen atoms and counterions are omitted for clarity. Thermal ellipsoids are shown at 50% probability level.

3.1.2 Mixed Tetradentate NHC/1,2,3-Triazole Iron Complexes bearing *cis* Labile Coordination Sites as Highly Active Catalysts in Lewis and Brønsted Acid Mediated Olefin Epoxidation

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published in *J. Catal.*, 2020, **383**, 144-152.[221]

In this article, the first mixed tetradentate NHC/1,2,3-triazole iron(II) complexes are synthesized, characterized and studied in olefin epoxidation catalysis. The two compounds depict distorted octahedral structures with a sawhorse coordination of the spectator ligand and two *cis* oriented labile acetonitrile ligands. The structures of the derivatives are shown in Figure 15 and bear different substituents of the 1,2,3-triazole moieties, *i.e.* diisopropylphenyl (Dipp, **3**) and benzyl (Bn, **4**). As demonstrated by cyclic voltammetry (CV), the modification significantly impacts the electronic properties of the iron(II) complexes, with the benzyl substituted complex **4** showing a lower half-cell potential corresponding to the Fe(II)/Fe(III) redox couple ($E_{1/2}$ = 0.37 V vs. Fc/Fc^+) than its Dipp derivative **3** ($E_{1/2}$ = 0.46 V vs. Fc/Fc^+).

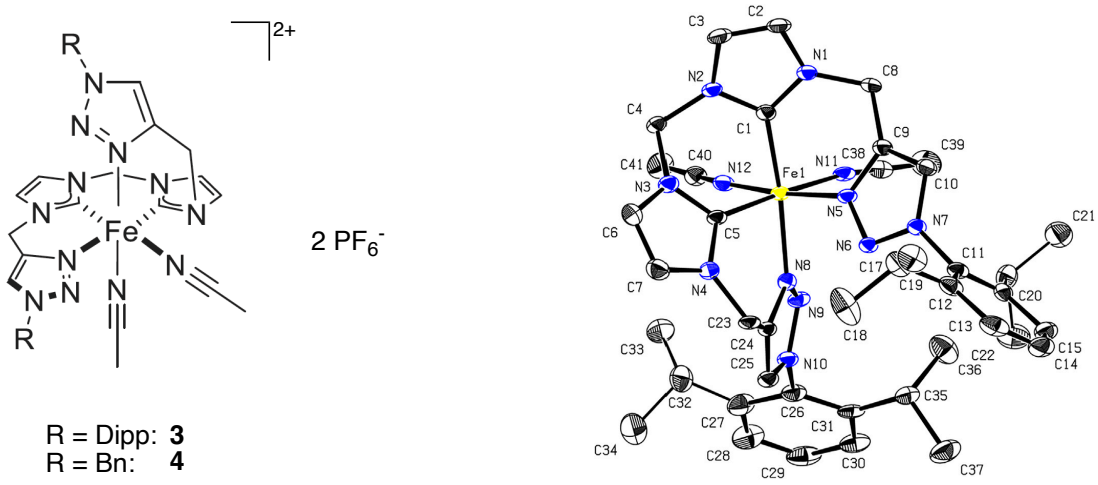

Figure 15. Structure of compounds **3** and **4** (left). ORTEP-style representation of the cationic fragment of compound **3** (right). Thermal ellipsoids are shown at a 50% probability level. Hydrogen atoms and hexafluorophosphate anions are omitted for clarity.[221]

Resulting from the different electronic properties of **3** and **4** the complexes show considerably different catalytic performance in the epoxidation of *cis*-cyclooctene applying H_2O_2 as oxidant. The Bn substituted complex **4** significantly outperforms its Dipp derivative **3** in terms of activity, stability and selectivity (Figure 16, left). Brønsted (HOAc, $HClO_4$) and Lewis acidic ($Sc(OTf)_3$) additives further increase the catalytic performance (Figure 16, right).[221]

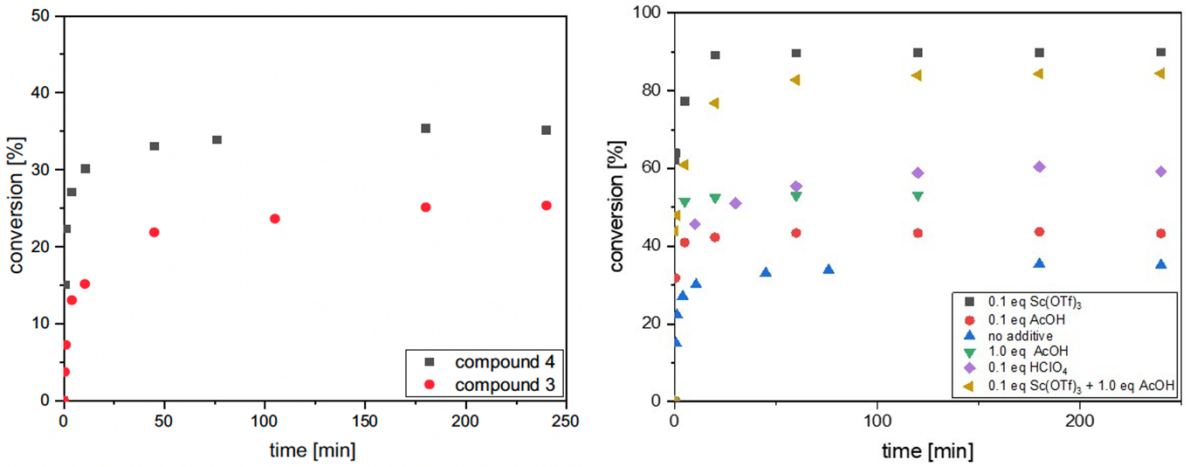

Figure 16. Time-dependent conversion of *cis*-cyclooctene with H_2O_2 applying catalysts (1.0 mol%) **3** (red) and **4** (black) at 20 °C in MeCN (left). Screening of various acidic additives applying catalyst **4** (1.0 mol%) at 20 °C in MeCN (right).[221]

Under optimized conditions, *i.e.* using acetic acid at 20 °C, **4** is one of the most active iron(II) epoxidation catalyst, reaching a TOF of 76,000 h^{-1}, a TON of 200 and selectivity of 98%. In contrast to other iron catalysts **4** also tolerates substrates with functional groups and selectively epoxidizes allyl chloride and allyl alcohol.

3.1.3 Pushing the Limits of Activity and Stability: the Effects of Lewis Acids on Non-heme Iron-NHC Epoxidation Catalysts

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published in *Catal. Sci. Technol.*, 2020, **10**, 3532-3536.[222]

In this article, the aforementioned beneficial effect of acidic additives on the catalytic performance of iron NHC complexes in olefin epoxidation is expanded to iron complexes bearing the same macrocyclic tetra-NHC ligand applied for the synthesis of the first Cu(III) NHC complex (Figure 17).[220, 221] Before this study, the highest activity ever reported in homogeneous olefin epoxidation was achieved with **2** at 25 °C (TOF = 183 000).[110]

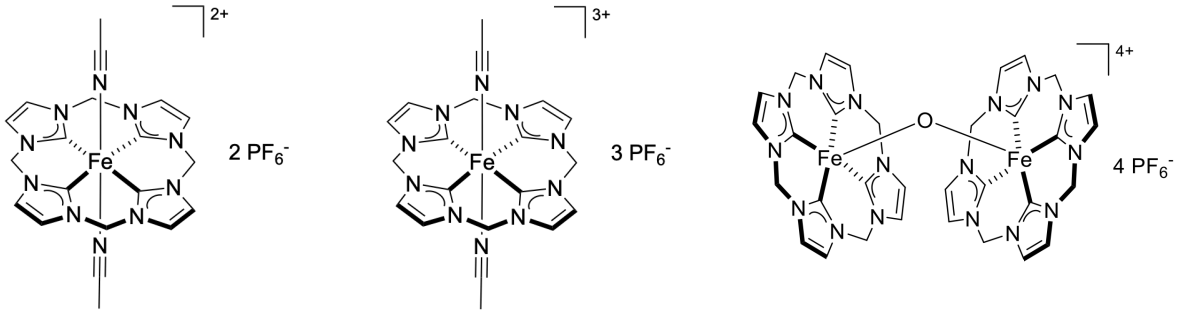

Figure 17. Iron tetra-NHC (pre-)catalysts **1**, **2** and **3**.[222]

When using salts of Sc^{3+}, Fe^{3+}, Y^{+3}, Ce^{4+}, Ce^{3+}, Sm^{3+}, Nd^{3+} and Dy^{3+} with weakly coordinating anions (OTf^- and ClO_4^-) as additives in the catalytic *cis*-cyclooctane epoxidation with H_2O_2 as oxidant, a notable improvement of performance is observed, both in terms of TOF and TON. The most beneficial effect is observed with Ce^{4+}, Sc^{3+} and Fe^{3+} all leading to an unprecedented TOF of 410,000 h^{-1} and a corresponding TON of 1,200 at 20 °C. Interestingly, although (pre-)catalysts **1**, **2** and **3** perform significantly different under additive free reaction conditions they all show the same TOF and TON in presence of strong Lewis acids.

According to UV/Vis spectroscopy the addition of a strong Lewis acid promotes the oxidation of iron(II) complex **1** as well as cleavage of the oxo ligand from Fe(III)–O–Fe(III) dimer **3,**

respectively. Both processes result in an almost instantaneous formation of to the active catalyst **2** (Figure 18).

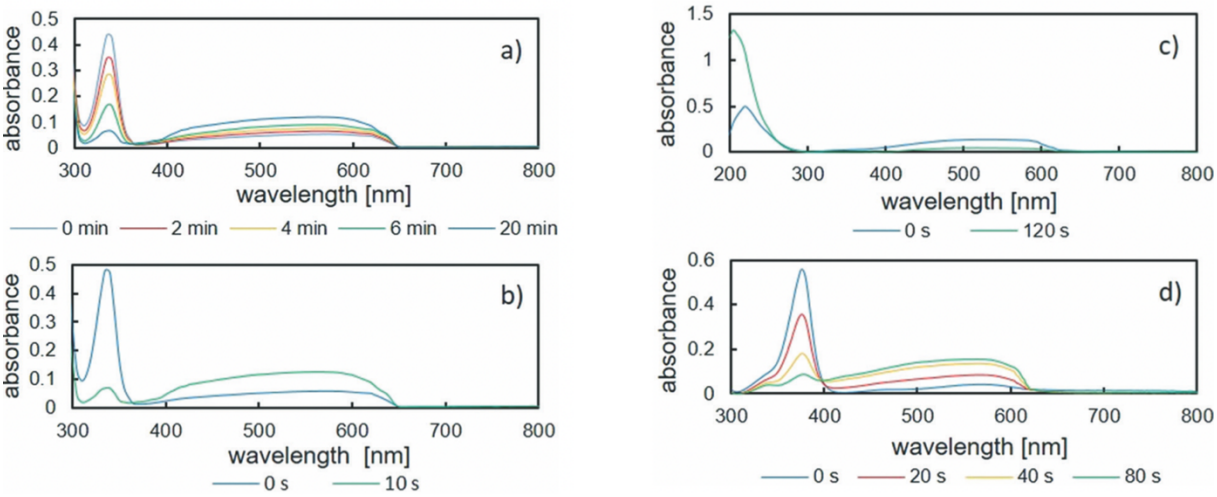

Figure 18. UV/Vis kinetics of the formation of **2** (450 to 650 nm) from **1** (337 nm) in presence of $Sc(OTf)_3$ and air without (a) and with (b) 1.5 eq. H_2O_2; decomposition of **2** with 1.5 eq. H_2O_2 in absence of substrate (c); formation of **2** from **3** (376 nm) in presence of $Sc(OTf)_3$ (d); T = 20 °C.[222]

The oxo-bridged diiron complex **3** has previously been reported to be formed under oxidative conditions from **1** and **2** and considered as a deactivation product.[223] The reformation of catalytically active complex **2** from the deactivation product **3** in presence of strong Lewis acids gives a potential explanation for the significant increase of the TON from 550 to 1 200.[110] Due to the fact that the TON is still limited despite reactivating **3**, another deactivation mechanism still has to be present. The drastic increase in activity is presumably a result of a Lewis acid promoted acceleration of the rate-determining heterogeneous O–O cleavage of the iron(III) hydroperoxo species formed upon reaction of the catalyst with H_2O_2 (Scheme 13, chapter 1.5).[75]

3.1.4 Electronic Finetuning of a Bio-inspired Iron(II) tetra-NHC Complex by *trans* Axial Isocyanide Substitution

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published in *Chem. Asian J.*, 2020, **15**, 1896-1902.[224]

As described in chapter 3.1.2 the electrochemical properties of iron complexes play a vital role for the performance in oxidation catalysis.[106, 221, 225] Therefore, in this article two derivatives of iron(II) tetra-NHC complex **1** are synthesized by replacing one (**1a**) or two *trans* axial acetonitrile with *tert*-butyl isocyanide ligand(s) (Figure 19).

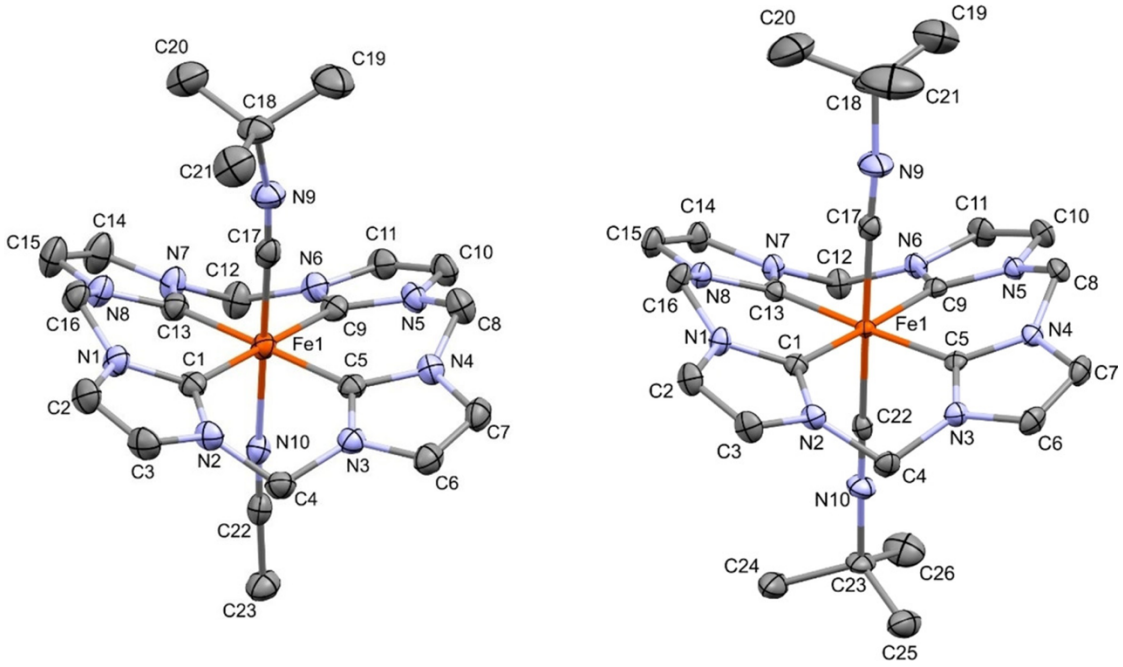

Figure 19. ORTEP-style representation of the cationic fragment of compounds **1a** (left) and **1b** (right). Thermal ellipsoids are shown at a 50% probability level. Hydrogen atoms and hexafluorophosphate anions are omitted for clarity.[224]

The electrochemical properties of **1a** and **1b** are evaluated by CV and compared to parent complex **1** (Figure 19). Due to the π-accepting nature of the isocyanide ligands the electron density of the iron(II) center is decreased with an increasing number of isocyanide ligands (x). Therefore the half-cell potential of the reversible Fe(II)/Fe(III) redox process increases from **1**

(x = 0, $E_{1/2}$ = 0.15 V), over **1a** (x = 1, $E_{1/2}$ = 0.35 V) to **1b** (x = 2, $E_{1/2}$ = 0.44 V) proving that axial ligand substitution is a simple but effective method for fine-tuning the electronic properties of iron NHC complexes.

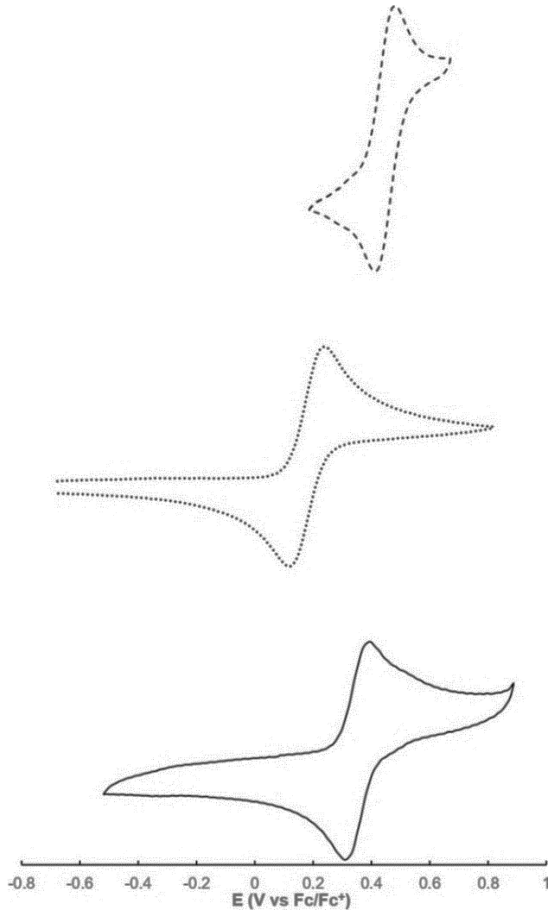

Figure 20. Cyclic voltammograms of **1a** ($E_{1/2}$ = 0.35 V, bottom), **1** ($E_{1/2}$ = 0.15 V, middle) and **1b** ($E_{1/2}$ = 0.44 V, top) measured with a scan rate of 100 mV/s and ferrocene as internal standard in MeCN.[224]

3.1.5 Tuning the Electronic Properties of Tetradentate Iron-NHC Complexes: Towards Stable and Selective Epoxidation Catalysts

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published in *J. Catal.*, 2020, **391**, 548-561.[226]

The imidazole based iron(III) tetra-NHC complex **3b** shows exceptional activity in the catalytic olefin epoxidation. However, even though its stability is rather high for *cis*-cyclooctene epoxidation compared to other homogeneous iron catalysts, the TON drastically decreases for more intricate substrates like linear internal or terminal olefins.[110, 222] As shown for other iron NHC complexes in chapter 3.1.2 electronic finetuning by targeted ligand design is an effective way to improve the catalytic performance.[106, 221] Therefore, in this article the tetra-NHC motif of parent complexes **3a** and **3b** is modified by changing the NHC backbones to methyl groups (**1a**, **1b**) and benzimidazole (**2a**, **2b**). Figure 21 shows the structures, half-cell potentials and crystal structures of the novel compounds.

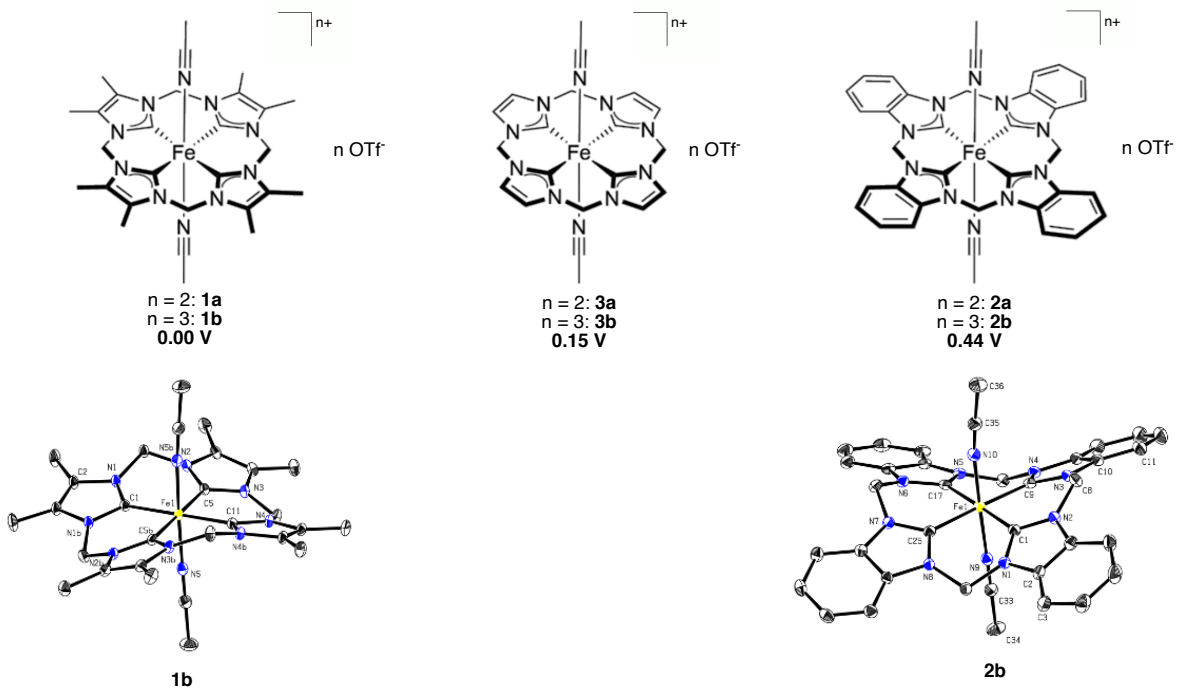

Figure 21. Structures and half-cell potentials (in V) of Fe(II) and Fe(III) derivatives of **3a** and **3b** (middle) with methyl (**1a** and **1b**, left) and benzimidazole groups (**2a** and **2b**, right). ORTEP-style representation of the cationic fragments of compounds **1b** (bottom left) and **2b** (bottom right). Thermal ellipsoids are shown at a 50% probability level. Hydrogen atoms and triflate anions are omitted for clarity.[226]

The electron-rich derivatives **1a** and **1b** show considerably lower activity and stability than parent complexes **3a** and **3b** in the epoxidation of all evaluated substrates (Figure 22, left). The electron deficient derivatives **2a** and **2b** display a comparable stability to **3a** and **3b** (TON up to 1,000 at 20 °C vs. up to 1,200) and significantly lower activity (TOF up to 11,000 h^{-1} vs. 410,000 h^{-1} at 20 °C) with $Sc(OTf)_3$ as additive in *cis*-cyclooctene epoxidation. However, in the epoxidation of the more intricate substrates 2-hexene, 1-hexene and 5-hexen-1-ol, the benzimidazole based complex **3b** significantly outperforms the imidazole based parent complex **2b** (middle) in terms of TON.

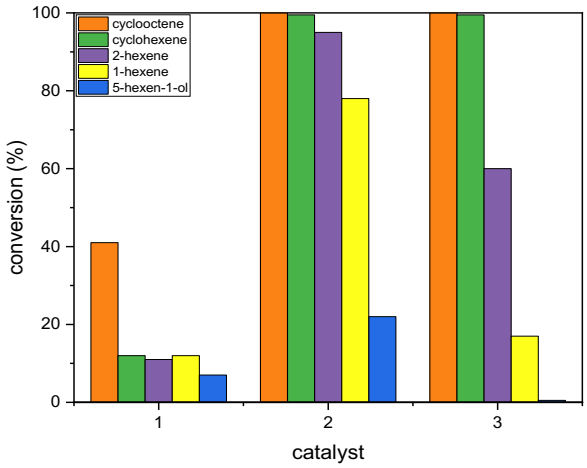

Figure 22. Epoxidation of various cyclic, acyclic and functionalized olefins by catalysts (0.5 mol%) **1b** (left), **2b** (middle) and **3b** (right) at 20 °C with a reaction time of 2 h.[226]

Supporting DFT calculations show notable differences between the new derivatives **1b** and **2b** in comparison to parent complex **3b**. In contrast to the unmodified ligand, the backbone modified ligands allow for significant π-backdonation which might explain the significantly lower activity of **1b** and **2b** compared to **3b**.

3.1.6 Activation of Molecular Oxygen by a Cobalt(II) Tetra-NHC Complex

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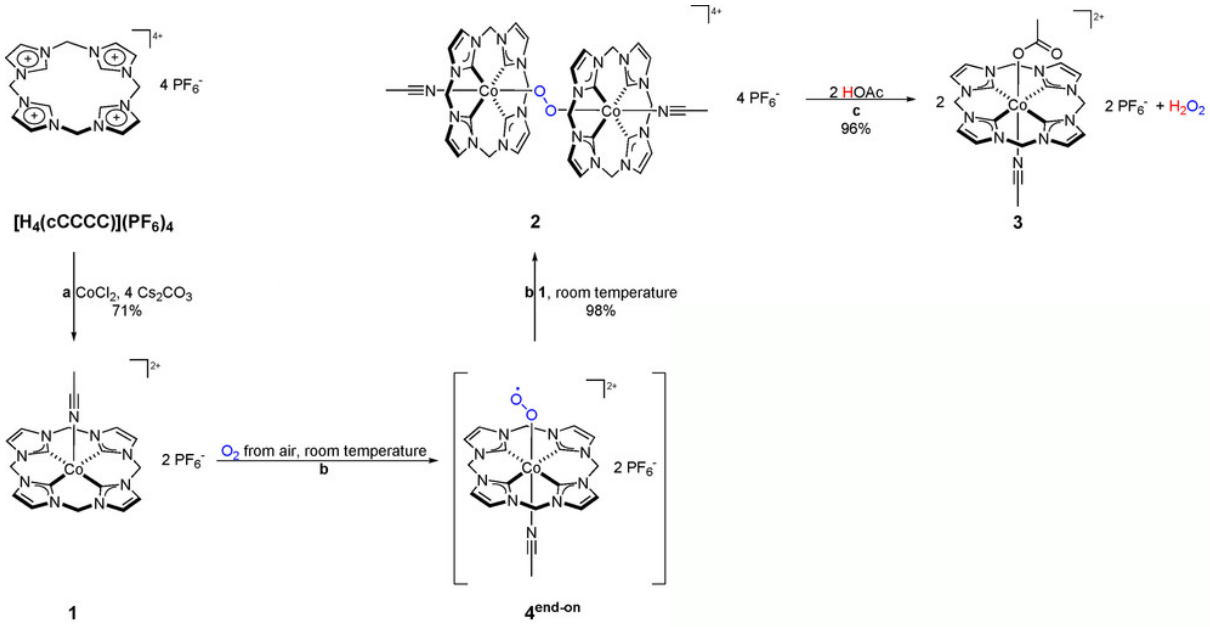
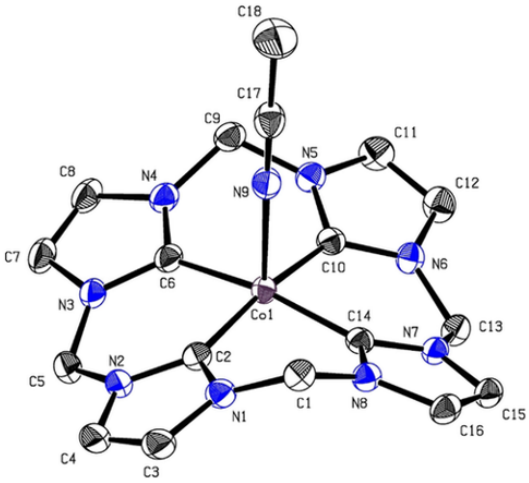
Bio-inspired cobalt complexes have been studied extensively in literature and compared to their iron derivatives in dioxygen activation.[228] The reactivity of the aforementioned iron(II) tetra-NHC complex (chapters 3.1.3 and 3.1.5) with dioxygen has been reported previously resulting in the formation of an oxo-bridged diiron(III) species.[223] In this article the cobalt(II) analogue **1** and its reactivity with molecular oxygen is reported.

Reaction of **1** with dioxygen at ambient conditions results in the quantitative formation of the first reported dicobalt(III) μ_2-peroxo NHC complex **2** *via* the end-on superoxo intermediate $\mathbf{4}^{\text{end-on}}$ which has been characterized by *in situ* EPR spectroscopy (Scheme 21, b). In line with a nucleophilic nature assigned by DFT calculations (Figure 23, bottom right), **2** reacts with electrophiles like protons from acetic acid resulting in quantitative formation of **3** along hydrogen peroxide (Scheme 21, c).

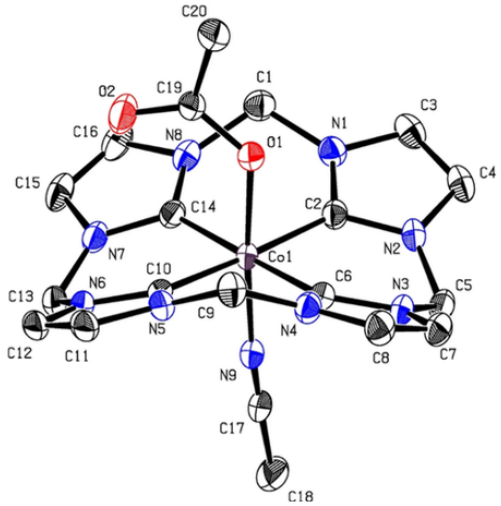


Scheme 21. Synthesis of cobalt tetra-NHC **1** (a); activation of O_2 from air resulting in formation of μ_2-peroxo complex **2** *via* superoxo intermediate $\mathbf{4}^{\text{end-on}}$ (b); reaction of μ_2-peroxo complex **2** with HOAc resulting in formation of **3** and H_2O_2 (c).

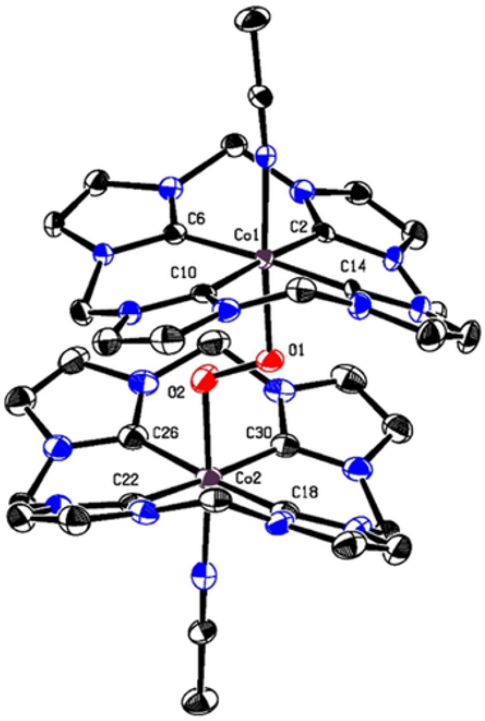
All isolated compounds (**1**, **2**, **3**) have also been characterized by SC-XRD (Figure 23).



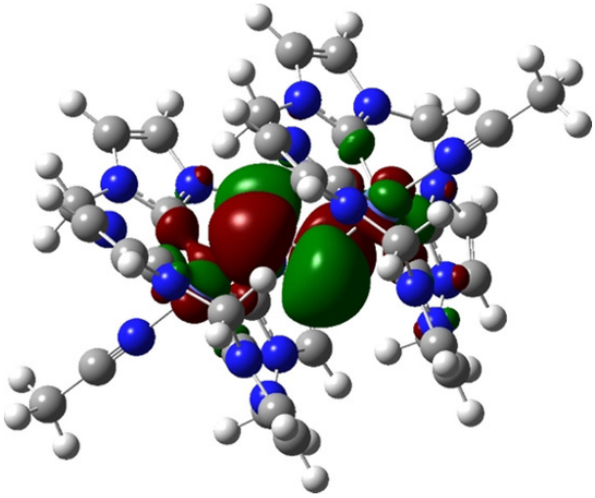
1



3



2



HOMO of 2

Figure 23. ORTEP-style representation of the cationic fragments of compounds **1**, **2** and **3**. Thermal ellipsoids are shown at a 50% probability level. Hydrogen atoms and hexafluorophosphate anions are omitted for clarity. Electronic structure of the HOMO of **2**, with mostly π* character located on the O−O bond (bottom right).

3.1.7 Modification of Bio-inspired Tetra-NHC Iron Complexes with Axial Nitrile Ligands

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published in *Inorg. Chim. Acta*, 2021, **518**, 120228.[229]

As reported previously, the oxo bridged diiron(III) complex described in chapter 3.1.3 is capable of oxidizing acetonitrile.[223] Therefore, during oxidation catalysis MeCN oxidation competes with substrate oxidation when performed in this solvent and used as *trans* axial ligands. Aiming at catalytic experiments in different nitrile solvents bearing less activated C–H bonds, in this article, *tert*-butyl nitrile (*t*-BuCN, **4** and **6**) and benzonitrile (PhCN, **5** and **6**) derivatives of iron(II) and iron(III) tetra-NHC complexes **1** and **2** bearing acetonitrile ligands are reported (Figure 24). According to CV measurements in the respective nitriles as solvent, the derivatives show the desired similar electrochemical properties and are therefore expected to also have similar catalytic activity as their acetonitrile counterparts.

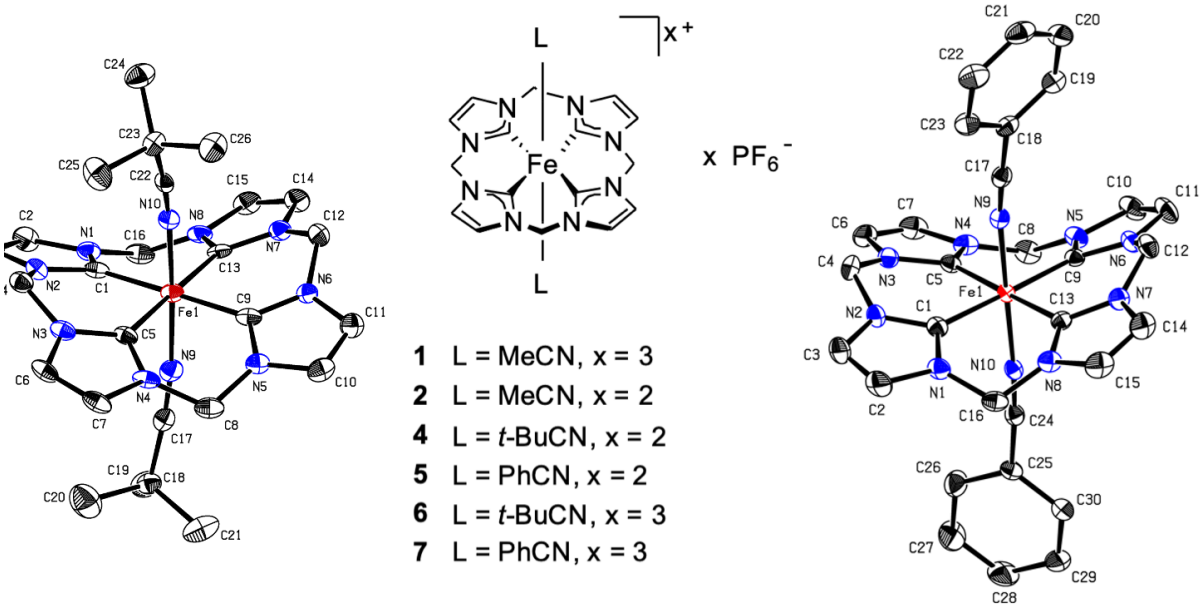

Figure 24. Structures of iron(II) and iron(III) tetra-NHC complexes **1** to **7** bearing different axial nitrile ligands (middle). ORTEP-style representation of the cationic fragments of compounds **4** (left) and **5** (right). Thermal ellipsoids are shown at a 50% probability level. Hydrogen atoms and hexafluorophosphate anions are omitted for clarity.[229]

According to UV/Vis kinetics the change of axial nitrile ligand and solvent has a significant impact on the nitrile oxidation by the diiron(III) oxo complex shown in chapter 3.1.3 (Figure 25). The rate of solvent/ligand oxidation decreases in the order: MeCN < *t*-BuCN << PhCN.

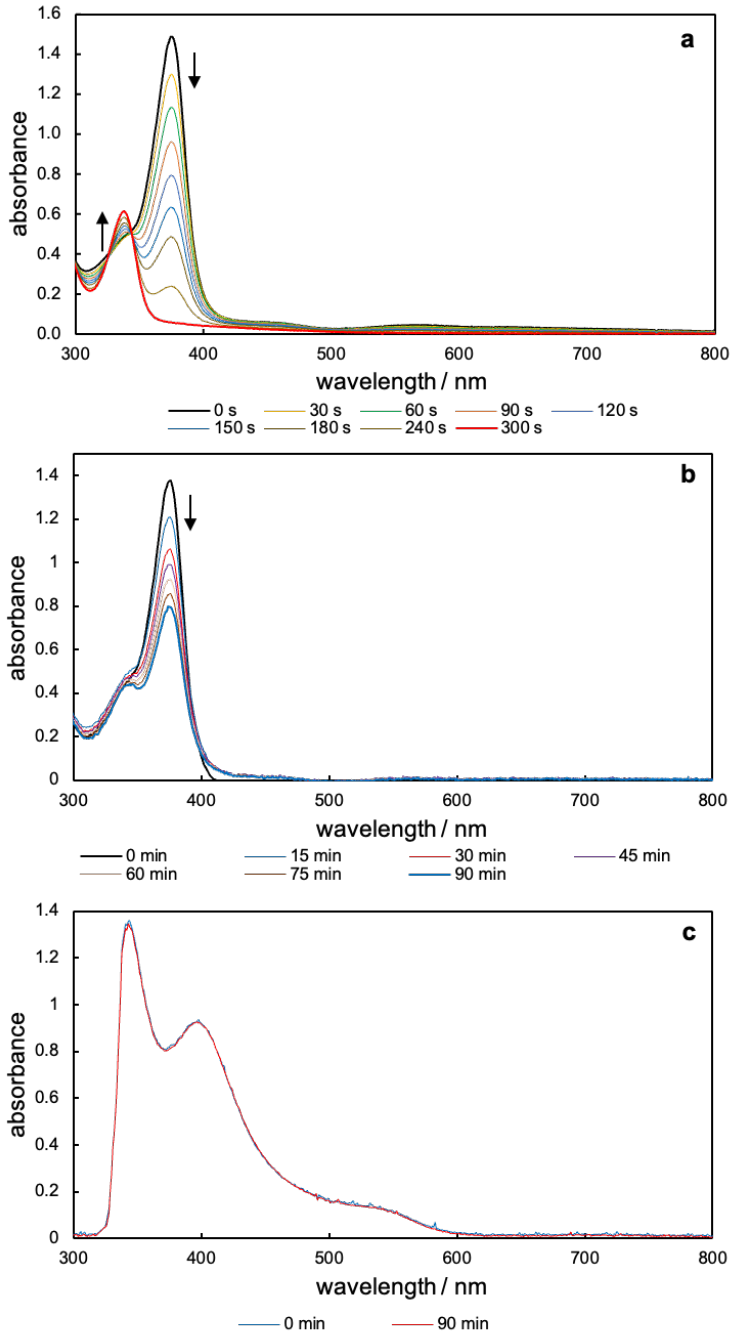

Figure 25. UV/Vis kinetics of the decay of the diiron(III) oxo complex going along with nitrile oxidation in MeCN (a), t-BuCN (b) and PhCN (c); c = 2 · 10^{-4} M, T = 20 °C.

3.1.8 Degradation Pathways of a Highly Active Iron(III) Tetra-NHC Epoxidation Catalyst

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* corresponding author

published in *Catal. Sci. Technol.*, 2021, **11**, 795-799.[230]

As discussed in chapter 3.1.3 the TON of iron(II) and iron(III) tetra-NHC complexes **1** and **2** is significantly improved by Lewis acidic additives *via* reactivation of their catalytically inactive oxo-bridged diiron(III) derivative **3** (Scheme 22, A).[222, 223] However, as the TON is still limited, another relevant deactivation pathway is present. In this article, the deactivation product and weak spot of **1** and **2** is unequivocally identified serving as a starting point for further improvements of the catalyst.

Other homogeneous non-NHC iron oxidation catalysts degrade *via* ligand methylene bridge hydroxylation which has been demonstrated by a significant increase in stability *via* deuteration of the bridges.[231] In contrast to non-NHC catalysts, the bridge-deuterated derivative **2-d$_8$** does not show improved TONs in comparison to **2** (Figure 26). Therefore, bridge hydroxylation can be excluded as a deactivation pathway (Scheme 22, B).

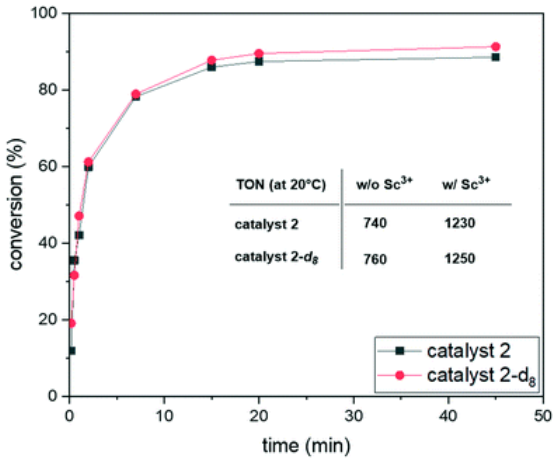
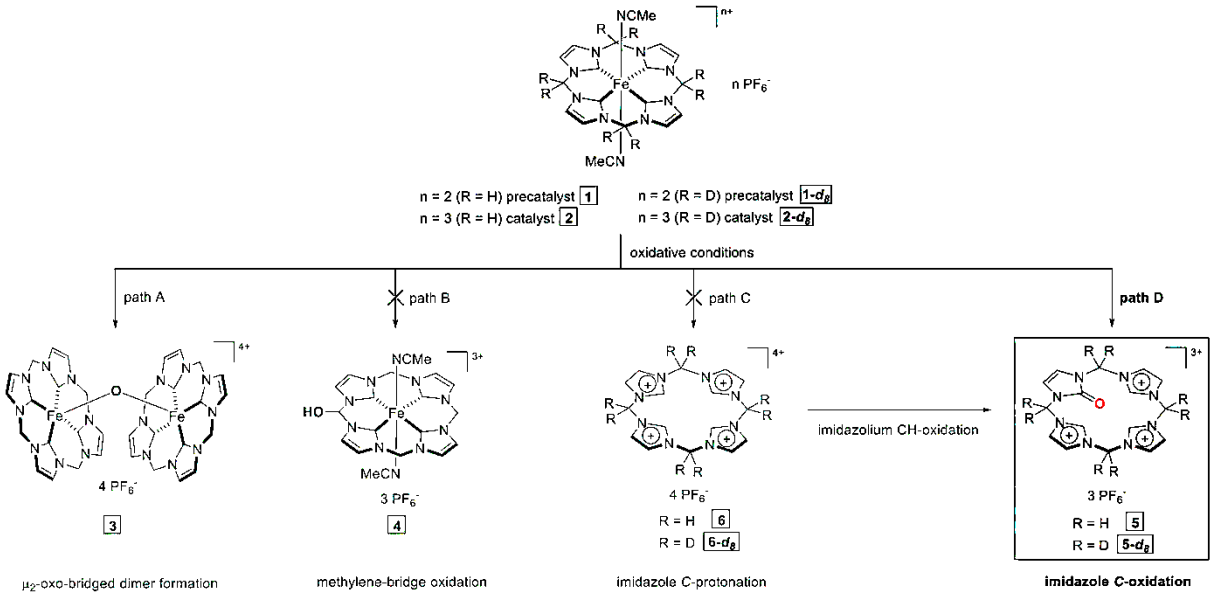


Figure 26. Time-dependent conversions of catalysts (0.05 mol%) **2** and **2-d$_8$** in the epoxidation of *cis*-cyclooctene with H_2O_2 in MeCN at -10 °C.[230]

NMR and ESI-MS experiments after addition of H_2O_2 to **1** and **2** show that the same mono-oxidized and protonated ligand **5** described in chapter 3.1.1 is formed selectively.[220] This deactivation pathway of carbene C oxidation is exclusive to NHC catalysts and has never been reported in literature before.



Scheme 22. Formation of mono-oxidized and three-fold protonated ligand **5** (path D). The other conceivable paths B and C (colored in grey) are unequivocally excluded while A can be circumvented by addition of Lewis acids.[222, 230]

3.2 Late Transition Metal NHC Complexes in Medicinal Chemistry

3.2.1 Exploring Different Coordination Modes of the First Tetradentate NHC/1,2,3-Triazole Hybrid Ligand for Group 10 Complexes

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* corresponding author

published in *Dalton Trans.*, 2019, **48**, 14820-14828.[232]

In this article, the first tetradentate NHC/1,2,3-triazole hybrid ligand and its nickel(II), palladium(II) and platinum(II) complexes are reported. The ligand has two central imidazole-2-ylidene donors connected by a methylene bridge. Both NHCs bear additional Dipp substituted 1,2,3-triazole moieties as wingtips.

Starting from the related imidazolium salt, metal acetate and potassium carbonate as an additional base different complexes are obtained depending on the stoichiometry and reaction conditions. For palladium, two different complexes are obtained. The first complex features the ligand in a tetradentate coordination mode coordinating *via* both NHC and both 1,2,3-triazole moieties (Figure 27, **1**). The second complex bears the ligand in a bidentate coordination mode where only the NHCs donate to the palladium(II) center. As d^8 metals favor a square planar structure, a second ligand coordinates palladium center *via* the NHC moieties (Figure 28, **2**).

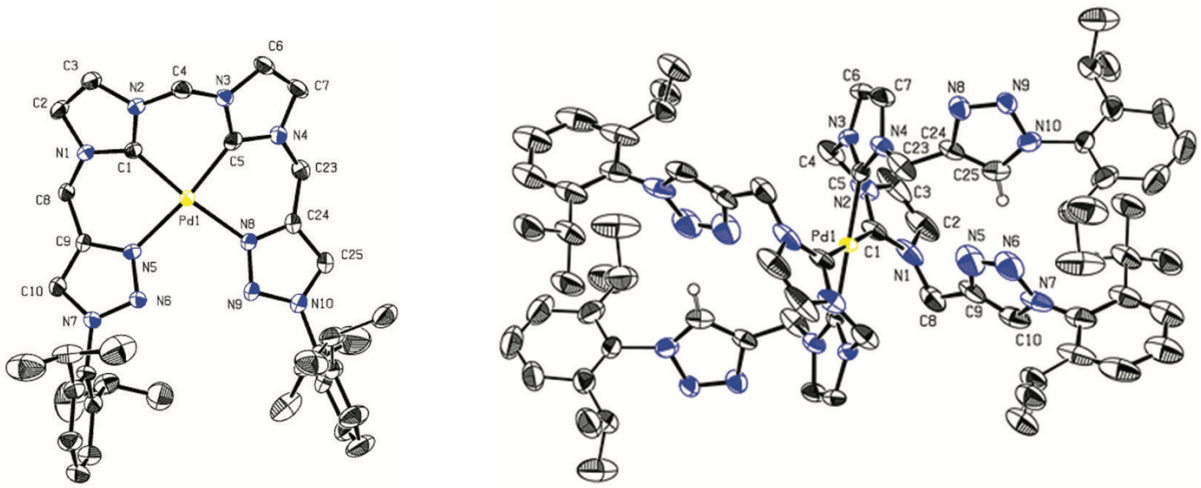

Figure 27. ORTEP-style representation of the cationic fragments of compounds **1** (left) and **2** (right). Thermal ellipsoids are shown at a 50% probability level. Hydrogen atoms and hexafluorophosphate anions are omitted for clarity.[232]

According to VT-NMR spectroscopy the complex bearing two ligands features strong intramolecular hydrogen bonds between the 1,2,3-triazole moieties of two opposing ligands that are also present at elevated temperatures up to 80 °C.

While two different complexes of palladium are accessible when varying the reaction conditions, for nickel and platinum only complexes bearing two ligands in the bidentate coordination mode are obtained when applying the respective acetate salts and external bases regardless of stoichiometry and reaction conditions.

3.2.2 Improved Antiproliferative Activity and Fluorescence of a Dinuclear Gold(I) Bisimidazolylidene Complex *via* Anthracene-Modification

Christian H. G. Jakob,[§] Bruno Dominelli,[§] **Jonas F. Schlagintweit**, Pauline J. Fischer, Franziska Schuderer, Robert M. Reich, Fernanda Marques, João D. G. Correia and Fritz E. Kühn*

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published in *Chem. Asian J.*, 2020, **15**, 4275-4279.[233]

In this article, a previously reported dinuclear gold(I) bis-NHC complex **1** bearing *syn*-oriented hydroxy functionalized methylene bridges is modified with 9-anthracenecarbonyl chloride forming monoester **1** and diester **2** depending on the amount of acyl chloride applied during synthesis (Figure 28). By attaching anthracene (Anth) moieties to the complex the water solubility significantly decreases. Unmodified **1** and monoester **2** are water soluble, while diester **3** is not. Therefore only **2** is used in biological studies and compared to **1**.

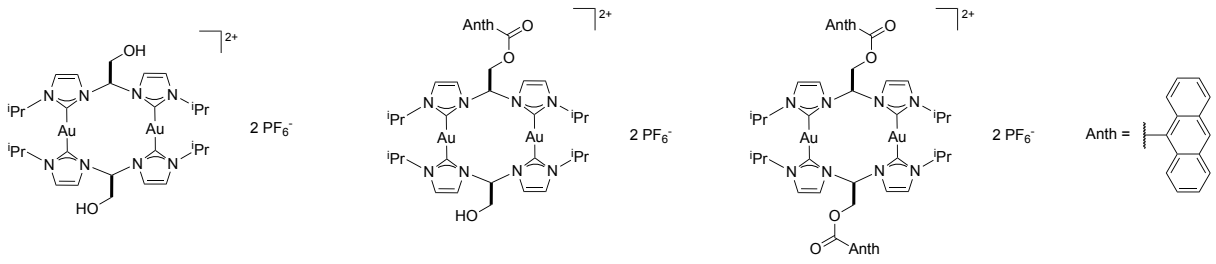


Figure 28. Hydroxyl functionalized Au(I) bis-NHC **1** and its anthracenyl ester modified derivatives **2** and **3**.[233]

In contrast to inactive **1**, monoester **2** shows good antiproliferative activity against cervix (HeLa) and breast (MCF-7) cancer cell lines with IC_{50} values of 7.3 µM and 7.9 µM, respectively. In addition, a comparably high selectivity in comparison to non-malignant V79 cells is observed (selectivity index 8 to 8.8).

The modification with anthracene groups not only increases the lipophilicity, antiproliferative activity and selectivity but also leads to fluorescence properties with quantum yields of 18% (Figure 29). Interestingly, monoester **2** depicts a higher quantum yields than diester **3** (8%) which is a result of a reversible intramolecular [2+2] photocycloaddition (Scheme 23).

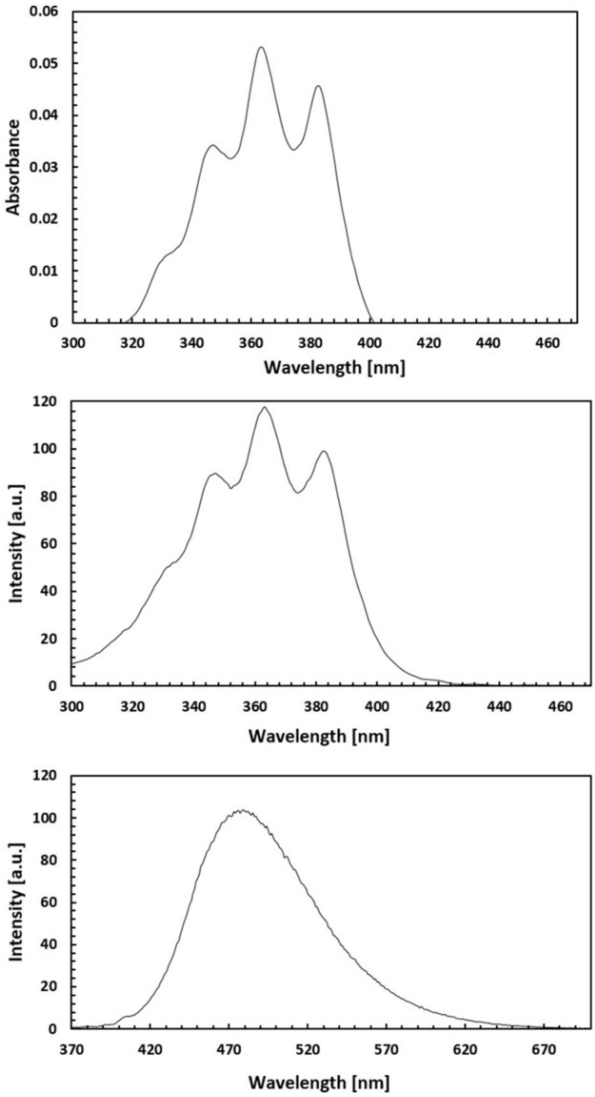
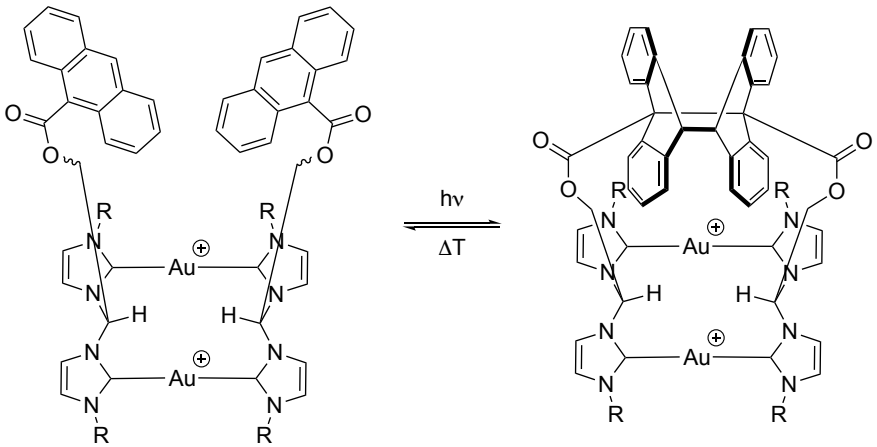


Figure 29. UV/Vis spectrum (top), excitation spectrum at λ = 479 nm (maximum λ_{max} = 363 nm; middle) and emission spectrum at λ = 363 nm (λ max =479 nm; bottom) of **2** in acetonitrile.[233]



Scheme 23. Reversible intramolecular [2+2] photocycloaddition of **2** reducing the quantum yield.[233]

3.2.3 Anticancer and Antibacterial Properties of Trinuclear Cu(I), Ag(I) and Au(I) Macrocyclic NHC/Urea Complexes

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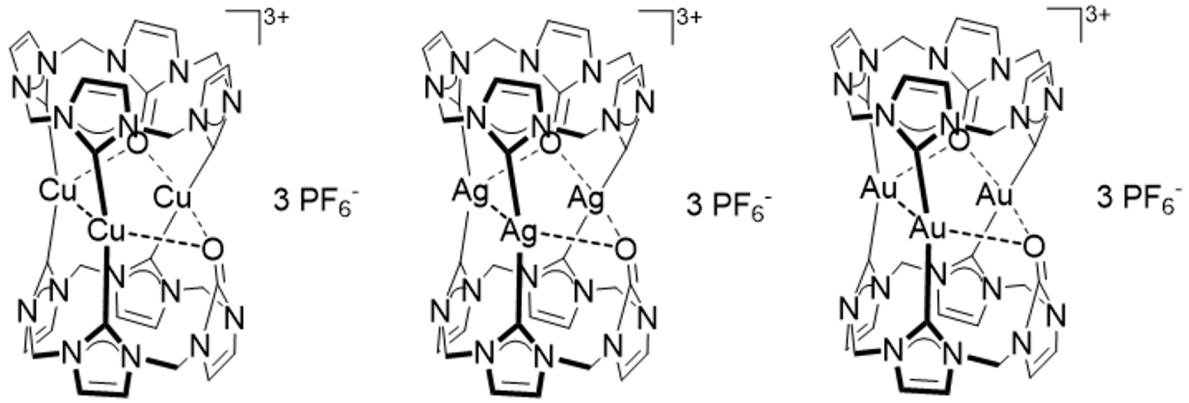
published in *J. Organomet. Chem.*, 2021, **932**, 121643.[234]

As oulined in chapter 3.1.1, the unique reactivity of the first ever reported Cu(III) NHC complex with acetic acid affords a macrocyclic ligand precursor with three imidazolium and one urea moiety.[220] In this work, its trinuclear Cu(I), Ag(I) and Au(I) complexes are synthesized and studied with regard to their antiproliferative and antibacterial properties (Figure 30).



1
MIC > 100 μM
IC_{50} = 12.2 μM to 25.1 μM

2
$\lambda_{em,max}$ = 481 nm
MIC = 30 μM
IC_{50} = 3 μM

3
$\lambda_{em,max}$ = 334 nm
MIC > 100 μM
IC_{50} > 100 μM

Figure 30. Structures, fluorescence emission maxima ($\lambda_{em,max}$) and antiproliferative activity against *E. coli* and *Staphylococcus aureus* bacteria strains (MIC) and cervix (HeLa) and breast (MCF-7) cancer cell lines (IC_{50}) of complexes **1**, **2** and **3**.[234]

Out of the series Au(I) complex **3** is inactive against *E. coli* (Gram negative) and *Staphylococcus aureus* (Gram positive) bacteria strains as well as cervix (HeLa) and breast (MCF-7) cancer cell lines. While the related Cu(I) compound **1** is also inactive against both bacteria strains, it exhibits moderate activity against both cancer cell lines depicting IC_{50} values of 12.2 µM and 25.1 µM, respectively. Out of the series, only Ag(I) complex **3** shows antibacterial activity against *E. coli* and *Staphylococcus aureus* with MIC values of 30 µM. In

addition, it exhibits promising antiproliferative activity against both tested cancer cell lines (IC_{50} values ≈ 3 μM).

As a result of argentophilic and aurophilic interactions Ag(I) complex **2** and Au(I) complex **3** show fluorescence properties with emission maxima at 481 nm and 334 nm, respectively.

3.2.4 Fluorescent Palladium(II) and Platinum(II) NHC/1,2,3-Triazole Complexes: Antiproliferative Activity and Selectivity Against Cancer Cells

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published in *Dalton Trans.*, 2021, **50**, 2158-2166.[235]

In this article derivatives of the palladium(II) and platinum(II) complexes from chapter 3.2.1 are reported.[232] Here, the Dipp substituents are replaced by fluorescent 4-methylene-7-methoxycoumarin (MMC) applying click chemistry.[150] The antiproliferative activity of compounds is studied in cervix (HeLa) and breast (MCF-7) cancer cell lines as well as a non-malignant skin cell line (HaCaT) and compared to their Dipp substituted counterparts (Figure 31).

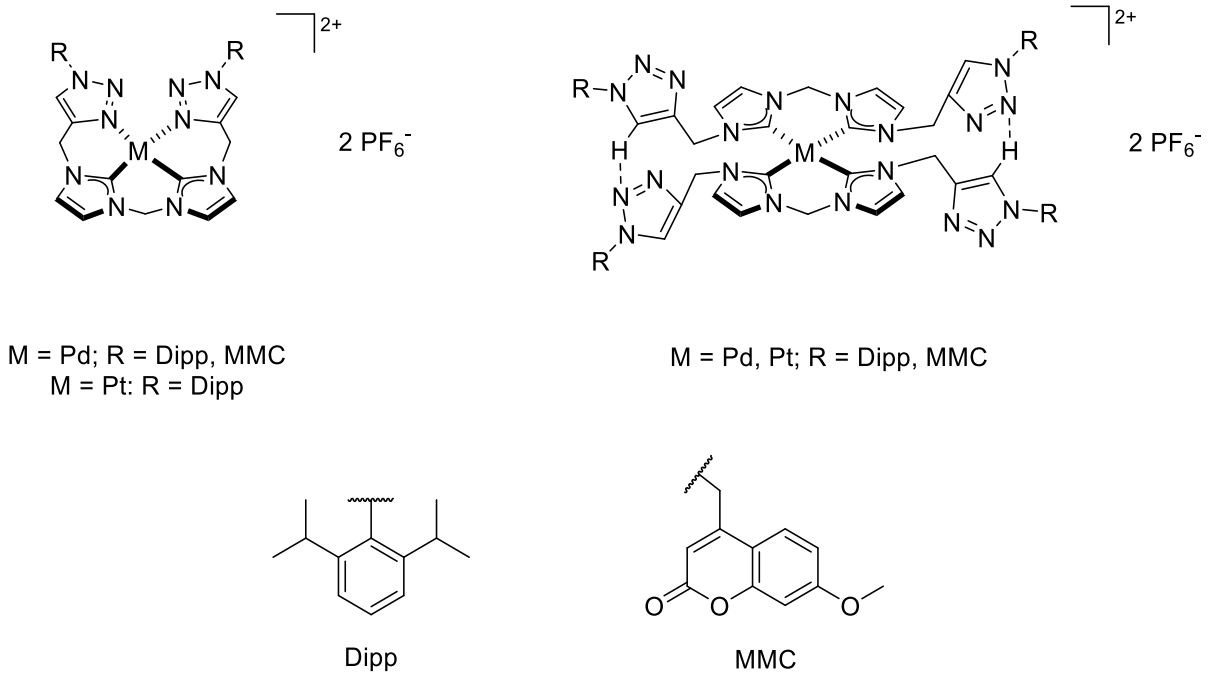

Figure 31. Structures of the Pd(II) and Pt(II) complexes studied with regard to their antiproliferative activity.[235]

The activity against all tested cell lines strongly depends on the 1,2,3-triazole wingtip and coordination mode. The complexes bearing two ligands in the bidentate coordination mode (Figure 31, right) are significantly more active than the compounds featuring one ligand in its

tetradentate coordination mode (Figure 31, left). Related complexes with Dipp substituents are more active than their MMC counterparts. While the activity of the Dipp complexes barely depends on the metal, out of the MMC compounds only the palladium(II) complex bearing two ligands is active with its platinum(II) counterpart not showing antiproliferative activity. The active Pd(II) MMC complex depicts an IC_{50} value of 6.1 µM against HeLa while being inactive against non-malignant HaCaT cells (>100 µM). In contrast to its structurally related Dipp derivative it shows a high selectivity for cancer cells.

Due to the luminescence properties resulting from the MMC substituents the compound is applied in fluorescence microscopy revealing a localization in late endosomes or lysosomes (Figure 32).

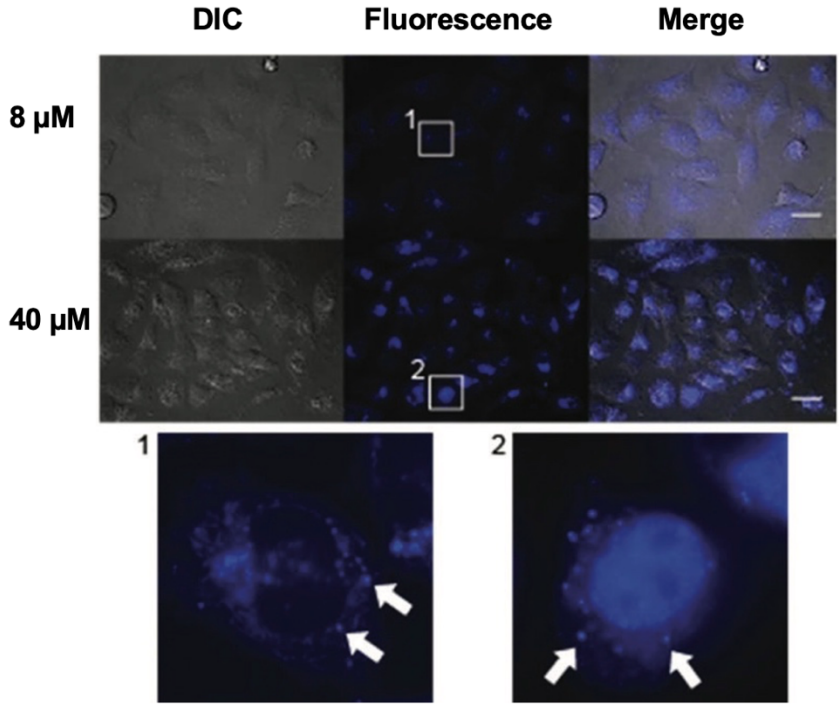

Figure 32. The Pd(II) complex bearing two MMC substituted ligands is readily imported into HeLa cells. Differential interference contrast (DIC) microcopy images and blue fluorescence are shown. Scale bars correspond to 20 µm. Magnifications of areas indicated by white boxes are denoted by numbers and arrows indicate signal specifically produced by the compound and presumably represent late endosomes or lysosomes.

4 CONCLUSION

In this thesis, several different transition metal NHC complexes were synthesized, characterized and applied in oxidation catalysis, dioxygen activation or evaluated as potential anticancer agents *in vitro*.

Tetradentate NHCs prove to be superior to purely *N*-donating ligands in iron catalyzed olefin epoxidation reactions. A mixed NHC/1,2,3-triazole hybrid ligand supported iron(II) complex with *cis* labile sites shows significantly higher activity and stability than *N*-donated iron catalysts while also tolerating a wide variety of functionalized substrates. Here, Brønsted and Lewis acidic additives show a beneficial impact on the catalyst performance which has never been reported for iron NHC oxidation catalysts before.
When applying this approach to macrocyclic tetra-NHC iron epoxidation (pre-)catalysts the TOF and TON can further be improved to values of 410,000 h^{-1} and 1,200, respectively at 20 °C, thereby outperforming all other reported iron-based catalysts in *cis*-cyclooctene epoxidation. However, for more intricate substrates the TON considerably decreases. Therefore, in order to improve the catalyst stability by targeted ligand design its weak spot is identified. Detailed studies reveal that one iron–NHC bond of the macrocyclic tetra-NHC ligand is selectively oxidized before dissociating from the metal. In line, iron catalysts of macrocyclic ligands consisting of NHC subunits derived from differently substituted heterocycles show drastically different catalyst lifetimes. When replacing the imidazole-2-ylidene donors to benzimidazol-2-ylidene, the stability of the catalyst is improved leading to significantly higher TONs in the epoxidation of more intricate substrates than *cis*-cyclooctene.
These results demonstrate that introducing macrocyclic NHC ligands based on heterocycles other than imidazole is a promising way to further enhance the catalytic performance. The study of mesoionic carbene ligands is of particular interest, as MICs are known to form stronger metal–carbene bonds, which have been identified as the weak spot of the most active iron based epoxidation catalyst.

The exceptional properties of the tetra-NHC ligands, studied in this work, to stabilize high valent iron oxo intermediates occurring during oxidation catalysis inspired the study of its copper and cobalt analogues. Using the 16-membered imidazole based tetra-NHC ligand a cobalt(II) compound is synthesized capable of dioxygen activation at ambient conditions resulting in the formation of the first ever reported dicobalt(III) μ_2-peroxo NHC complex. In contrast to high valent iron oxo species which facilitate olefin epoxidation and have an electrophilic nature, the peroxo complex is of nucleophilic nature which enables the formation

of hydrogen peroxide originating from air upon addition of Brønsted acids. A potential co-catalytic application is to be further investigated.
With the same macrocyclic ligand, the first ever reported formal Cu(III) NHC complex is accessible serving as a reference for future upcoming copper(III) complexes. The compound is stable against air, moisture and most Brønsted acids. However, it readily reacts with acetic acid *via* reductive elimination selectively forming the same mono-oxidized ligand species that is identified as the deactivation product of the related iron epoxidation catalyst.

The mono-oxidized NHC ligand gives access to a trinuclear copper(I) complex and its fluorescent silver(I) and gold(I) analogues. While the Au(I) compound does not show biological activity, the Cu(I) and Ag(I) derivatives depict antibacterial (Ag) and/or antiproliferative activity (Cu, Ag).
In contrast to the trinuclear Au(I) complex, a dinuclear Au(I) complex, also studied in this thesis, shows promising antiproliferative activity against cervix (HeLa) and breast (MCF-7) cancer cell lines. *Via* modification of a hydroxy functionalized bridge an anthracenyl ester is introduced which makes the compound fluorescent. Upcoming fluorescence microscopy studies might assist in the understanding of the mechanism involved by locating the compound directly in the cell.
In addition to easily modifiable gold(I) complexes, fluorescent palladium(II) and platinum(II) compounds bearing tetradentate NHC/1,2,3-triazole accessible by click chemistry show a promising antiproliferative activity and selectivity for cancer cells. According to fluorescence microscopic studies late endosomes or lysosomes are identified as the potential target of the compounds.
In the future, the presented simple modification of the synthesized gold(I), palladium(II) and platinum(II) complexes by esterification or click chemistry can potentially be applied to conjugate vectors/targeting ligands in order to further improve the antiproliferative activity and selectivity of the compounds. Those vectors include sugars, antibodies and peptide sequences, specifically designed to address cancer cells.

5 REPRINT PERMISSIONS

5.1 ROYAL SOCIETY OF CHEMISTRY JOURNALS

"A Bench Stable Formal Cu(III) *N*-heterocyclic Carbene Accessible from Simple Copper(II) Acetate"
Chemical Science, 2018, **9**, 8307-8314.
DOI: **10.1039/C8SC01834K**

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5.2 Elsevier Journals

"Mixed Tetradentate NHC/1,2,3-Triazole Iron Complexes bearing cis Labile Coordination Sites as Highly Active Catalysts in Lewis and Brønsted Acid Mediated Olefin Epoxidation"
Journal of Catalysis, 2020, **383**, 144-152.
DOI: **10.1016/j.jcat.2020.01.011**

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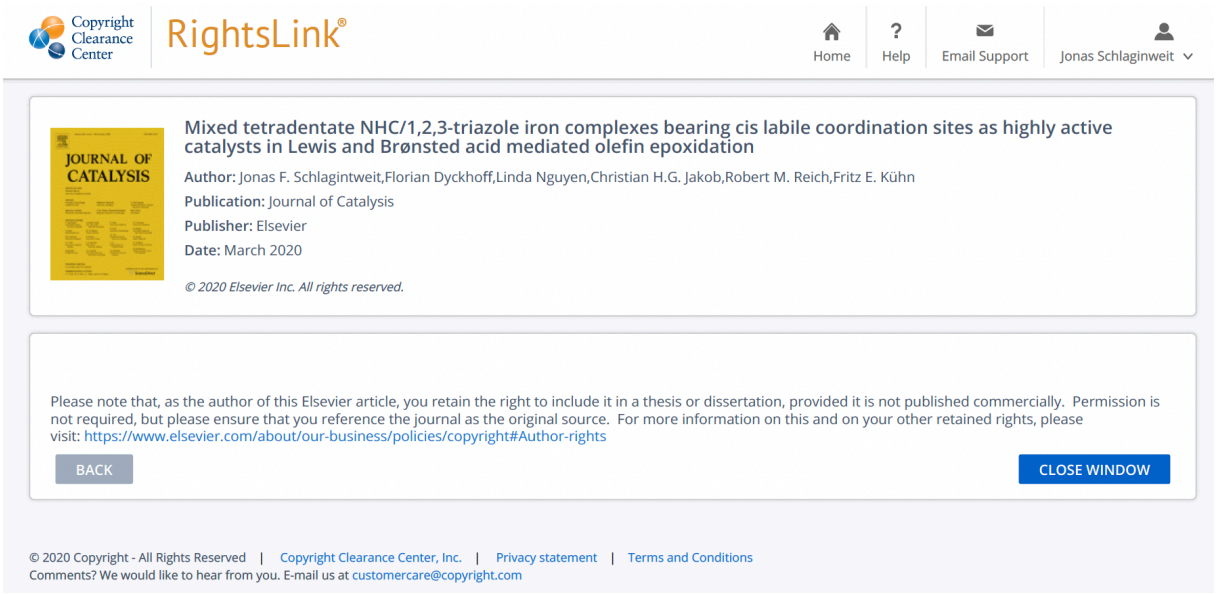

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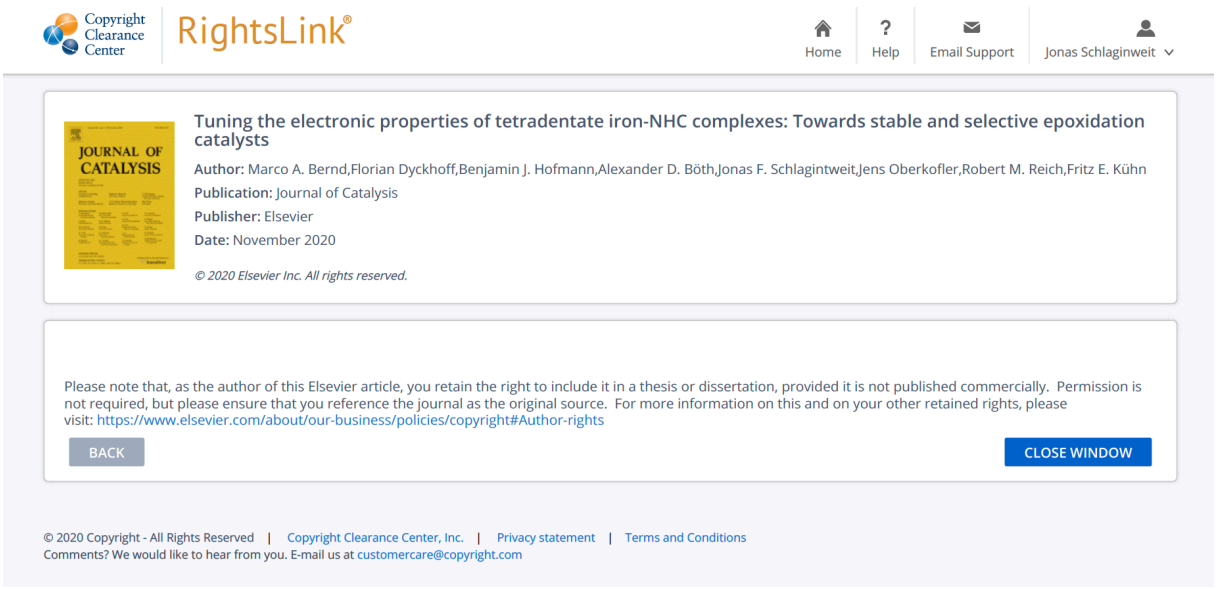

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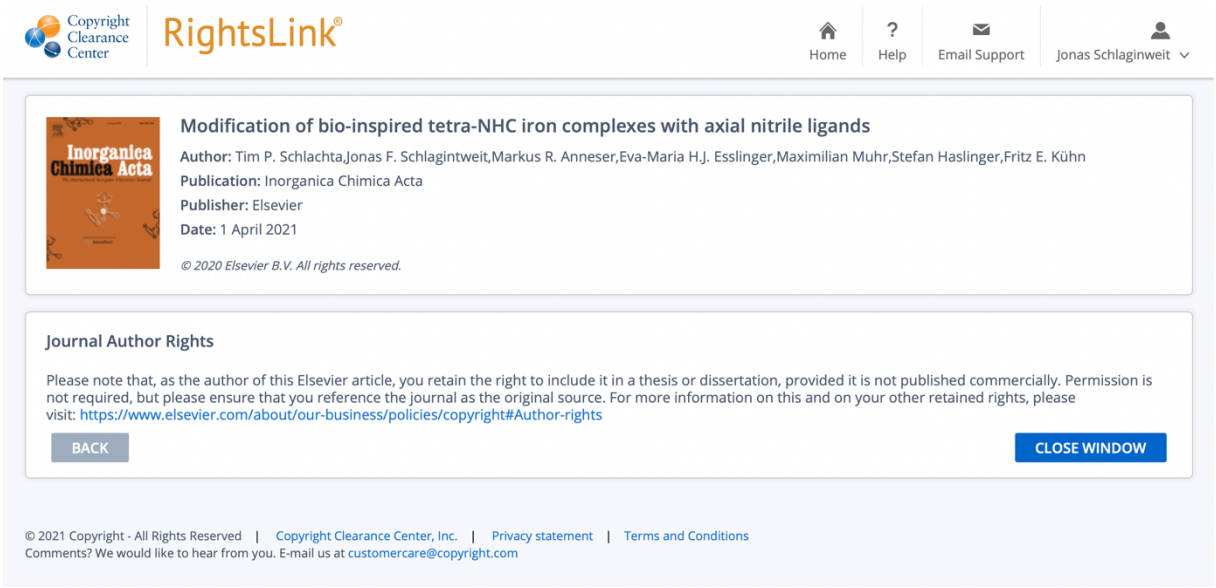

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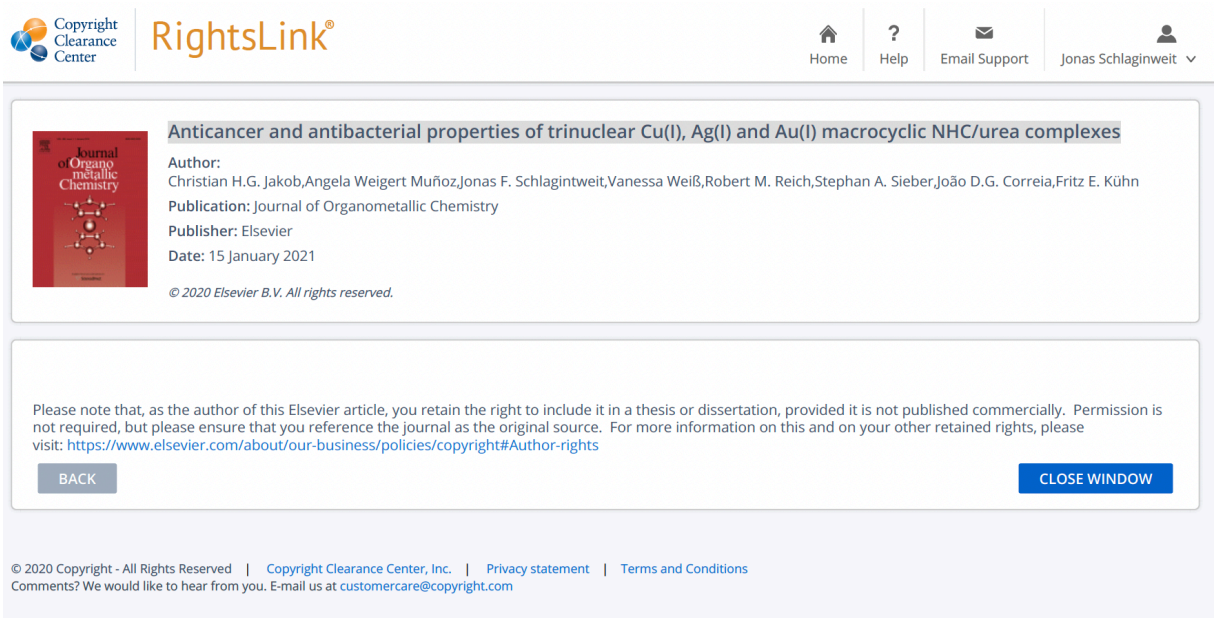

5.3 WILEY-VCH JOURNALS

"Electronic Finetuning of a Bio-inspired Iron(II) tetra-NHC Complex by *trans* Axial Isocyanide Substitution"

Chemistry – An Asian Journal, 2020, **15**, 1896-1902.
DOI: **10.1002/asia.202000214**

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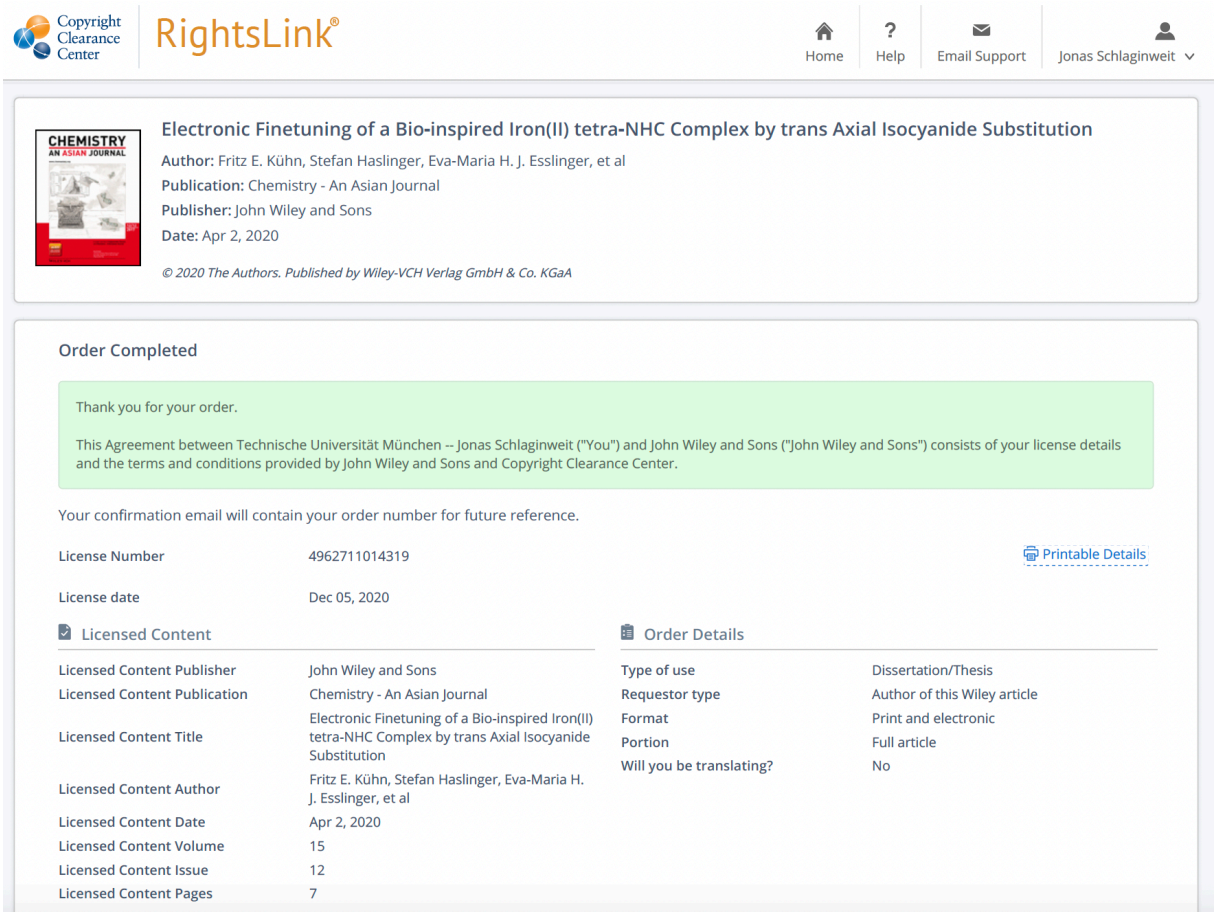

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Electronic Finetuning of a Bio-inspired Iron(II) tetra-NHC Complex by trans Axial Isocyanide Substitution

Author: Fritz E. Kühn, Stefan Haslinger, Eva-Maria H. J. Esslinger, et al
Publication: Chemistry - An Asian Journal
Publisher: John Wiley and Sons
Date: Apr 2, 2020

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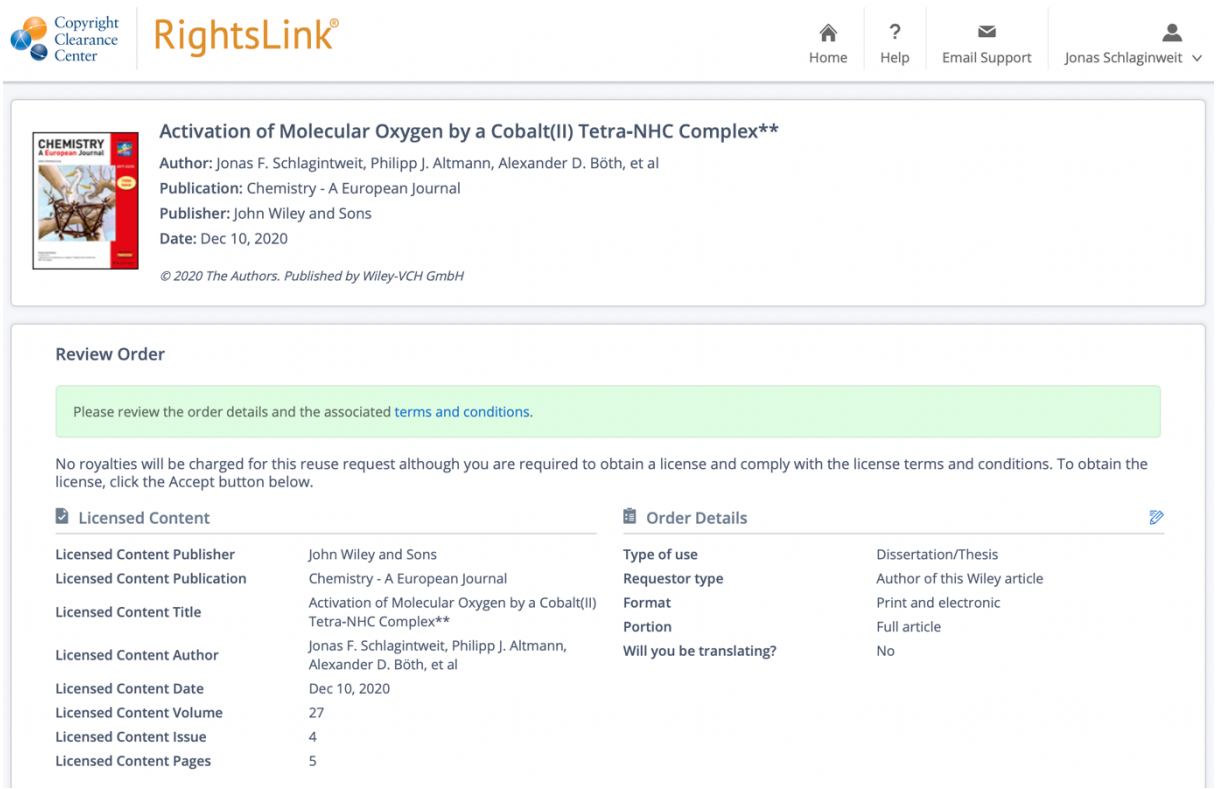

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Activation of Molecular Oxygen by a Cobalt(II) Tetra-NHC Complex**

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Publication: Chemistry - A European Journal

Publisher: John Wiley and Sons

Date: Dec 10, 2020

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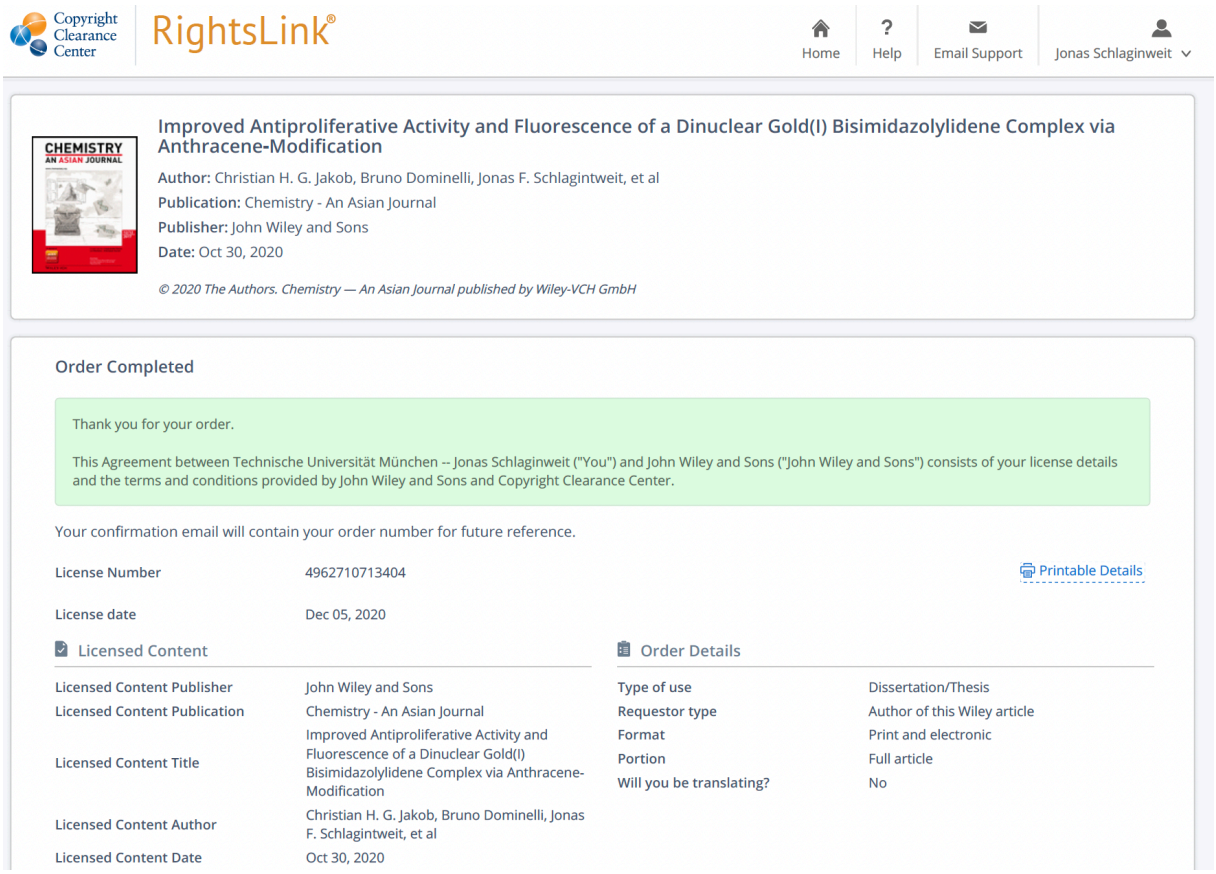
DOI: **10.1002/asia.202001104**



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Improved Antiproliferative Activity and Fluorescence of a Dinuclear Gold(I) Bisimidazolylidene Complex via Anthracene-Modification

Author: Christian H. G. Jakob, Bruno Dominelli, Jonas F. Schlagintweit, et al
Publication: Chemistry - An Asian Journal
Publisher: John Wiley and Sons
Date: Oct 30, 2020

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6 BIBLIOGRAPHIC DATA OF COMPLETE PUBLICATIONS

6.1 A BENCH STABLE FORMAL CU(III) *N*-HETEROCYCLIC CARBENE ACCESSIBLE FROM SIMPLE COPPER(II) ACETATE

Zohreh S. Ghavami,[b,§] Markus R. Anneser,[a,§] Felix Kaiser,[a] Philipp J. Altmann,[a] Benjamin J. Hofmann,[a] Jonas F. Schlagintweit,[a] Gholamhossein Grivani[b] and Fritz E. Kühn[a,*]

[a] Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany
[b] School of Chemistry, Damghan University, Damghan 36715-364, Iran

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Chemical Science, 2018, **9**, 8307-8314.
DOI: **10.1039/C8SC01834K**

Direct link: **https://doi.org/10.1039/C8SC01834K**

6.2 Mixed tetradentate NHC/1,2,3-triazole iron complexes bearing *cis* labile coordination sites as highly active catalysts in Lewis and Brønsted acid mediated olefin epoxidation

Jonas F. Schlagintweit,[§,a] Florian Dyckhoff,[§,a] Linda Nguyen,[a,b] Christian H. G. Jakob,[a] Robert M. Reich[a] and Fritz E. Kühn[a,*]

[a] Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany
[b] Ausbildungszentrum der Technischen Universität München, Lichtenbergstr. 4, D-85748 Garching bei München, Germany

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Journal of Catalysis, 2020, **383**, 144-152.
DOI: **10.1016/j.jcat.2020.01.011**

Direct link: **https://doi.org/10.1016/j.jcat.2020.01.011**

6.3 Pushing the Limits of Activity and Stability: the Effects of Lewis Acids on Non-Heme Iron-NHC Epoxidation Catalysts

Florian Dyckhoff,[§] Jonas F. Schlagintweit,[§] Robert M. Reich and Fritz E. Kühn*

Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany

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Catalysis Science & Technology, 2020, **10**, 3532-3536.
DOI: **10.1039/D0CY00631A**

Direct link: **https://doi.org/10.1039/D0CY00631A**

6.4 Electronic Finetuning of a Bio-inspired Iron(II) tetra-NHC Complex by *trans* Axial Isocyanide Substitution

Jonas F. Schlagintweit,[§] Carolin Hintermeier,[§] Markus R. Anneser, Eva-Maria H. J. Esslinger, Stefan Haslinger and Fritz E. Kühn*

Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany

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[§] equally contributing authors

Chemistry – An Asian Journal, 2020, **15**, 1896-1902.
DOI: **10.1002/asia.202000214**

Direct link: **https://doi.org/10.1002/asia.202000214**

6.5 Tuning the Electronic Properties of Tetradentate Iron-NHC Complexes: Towards Stable and Selective Epoxidation Catalysts

Marco A. Bernd,[§] Florian Dyckhoff,[§] Benjamin J. Hofmann, Alexander D. Böth, Jonas F. Schlagintweit, Jens Oberkofler, Robert M. Reich and Fritz E. Kühn*

Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany

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Journal of Catalysis., 2020, **391**, 548-561.
DOI: **10.1016/j.jcat.2020.08.037**

Direct link: **https://doi.org/10.1016/j.jcat.2020.08.037**

6.6 Activation of Molecular Oxygen by a Cobalt(II) Tetra-NHC Complex

Jonas F. Schlagintweit,[§,a] Philipp J. Altmann,[§,a,b] Alexander D. Böth,[a] Benjamin J. Hofmann,[a] Christian Jandl,[b] Clemens Kaußler,[a] Linda Nguyen,[a,c] Robert M. Reich,[a] Alexander Pöthig,[b] Fritz E. Kühn[a,*]

[a] Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany
[b] Single Crystal XRD Laboratory of the Catalysis Research Center, Technische Universität München, Ernst-Otto-Fischer-Str.185747, Garching bei München, Germany
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Chemistry – A European Journal, 2021, **27**, 1311-1315.
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Direct link: **https://doi.org/10.1002/chem.202004758**

6.7 Modification of Bio-inspired Tetra-NHC Iron Complexes with Axial Nitrile Ligands

Tim P. Schlachta,[§,a] Jonas F. Schlagintweit,[§,a] Markus R. Anneser,[a] Eva-Maria H. J. Esslinger,[a] Maximilian Muhr,[b] Stefan Haslinger[a] and Fritz E. Kühn[a,*]

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Inorganica Chimica Acta, 2021, **518**, 120228.
DOI: **10.1016/j.ica.2020.120228**

Direct link: **https://doi.org/10.1016/j.ica.2020.120228**

6.8 Degradation Pathways of a Highly Active Iron(III) Tetra-NHC Epoxidation Catalyst

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Catalysis Science & Technology, 2021, **11**, 795-799.
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6.9 Exploring Different Coordination Modes of the First Tetradentate NHC/1,2,3-Triazole Hybrid Ligand for Group 10 Complexes

Jonas F. Schlagintweit,[a] Linda Nguyen,[a,b] Florian Dyckhoff,[a] Felix Kaiser,[a] Robert M. Reich[a] and Fritz E. Kühn[a,*]

[a] Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany
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Dalton Transactions, 2019, **48**, 14820-14828.
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6.10 Improved Antiproliferative Activity and Fluorescence of a Dinuclear Gold(I) Bisimidazolylidene Complex *via* Anthracene-Modification

Christian H. G. Jakob,[a,§] Bruno Dominelli,[a,§] Jonas F. Schlagintweit,[a] Pauline J. Fischer,[a] Franziska Schuderer,[a] Robert M. Reich,[a] Fernanda Marques,[a] João D. G. Correia[a] and Fritz E. Kühn[a,*]

[a] Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany
[b] Centro de Ciências e Tecnologias Nucleares and Departamento de Engenharia e Ciências Nucleares, Instituto Superior Técnico, Universidade de Lisboa, Campus Tecnológico e Nuclear, Estrada Nacional N° 10 (km 139,7), 2695-066 Bobadela LRS, Portugal

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Chemistry – An Asian Journal, 2020, **15**, 4275-4279.
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Direct link: **https://doi.org/10.1002/asia.202001104**

6.11 Anticancer and Antibacterial Properties of Trinuclear Cu(I), Ag(I) and Au(I) Macrocyclic NHC/Urea Complexes

Christian H. G. Jakob,[a,§] Angela Weigert Muñoz,[b,§] Jonas F. Schlagintweit,[a] Vanessa Weiß,[a,c] Robert M. Reich,[a] Stephan A. Sieber,[b] João D. G. Correia[d] and Fritz E. Kühn[a,*]

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Journal of Organometallic Chemistry, 2021, **932**, 121643.
DOI: **10.1016/j.jorganchem.2020.121643**

Direct link: **https://doi.org/10.1016/j.jorganchem.2020.121643**

6.12 Fluorescent Palladium(II) and Platinum(II) NHC/1,2,3-Triazole Complexes: Antiproliferative Activity and Selectivity Against Cancer Cells

Jonas F. Schlagintweit,[a,§] Christian H. G. Jakob,[a,§] Kevin Meighen-Berger,[b] Thomas F. Gronauer,[c] Angela Weigert Muñoz,[c] Vanessa Weiß,[a,d] Matthias J. Feige,[b] Stephan A. Sieber,[c] João D. G. Correia[e] and Fritz E. Kühn[a,*]

[a] Molecular Catalysis, Technische Universität München, Department of Chemistry/Catalysis Research Center, Lichtenbergstr. 4, D-85748 Garching bei München, Germany
[b] Cellular Protein Biochemistry, Department of Chemistry and Institute for Advanced Study, Technische Universität München, Lichtenbergstraße 4, D-85748 Garching bei München, Germany
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Dalton Transactions, 2021, **50**, 2158-2166.
DOI: **10.1039/D0DT04114A**

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7 COMPLETE LIST OF PUBLICATIONS

7.1 JOURNAL ARTICLES

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Z. S. Ghavami, M. R. Anneser, F. Kaiser, P. J. Altmann, B. J. Hofmann, **J. F. Schlagintweit**, G. Grivani and F. E. Kühn
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