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OXIDATION OF FINE CHEMICALS BY IRON BASED AND METAL-FREE CATALYSIS

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Academic Dissertation

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Afnan Al-Hunaiti, Helsinki, June 2015

Oxidation of Fine Chemicals by Iron based and Metal-Free catalysis

Afnan Al-Hunaiti

University of Helsinki, 2015

Abstract

The catalytic oxidation by using transition metal complexes offers attractive opportunities for industrial applications following environmentally benign manufacturing processes. However, the number of such catalytic methods has substantially decreased. In this thesis, we developed and utilized three iron based catalysts (FeIII/thymine-1-acetic acid, FeIII/Phenanthroline, and FeII/*N*-methylimidazole) and one organic catalysts (1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA)).

The iron/THA catalyst (iron/thymine-1-acetic acid) is efficiently capable of oxidizing both primary and secondary aliphatic alcohols into their corresponding carbonyl compounds, acids and ketones. The system can also oxidize alkanes with different steric and electronic environment. We also presented a new method for the oxidation of benzylic and aliphatic primary and secondary alcohols using iron-based catalyst, which is $[Fe(phen)_2Cl_2]NO_3$ (iron/Phenanthroline), with hydrogen peroxide as a terminal oxidant. The easily accessible catalyst (iron/*N*-methylimidazole) was developed to form dehydrogenative coupling reaction between benzaldehydes and styrenes. The C-H activation to produce α,β–unsaturated ketones has been also developed.

The organic (metal-free) catalyst (1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA)) has shown to be an efficient catalyst for the oxidation of secondary alcohols with *t*-BuOOH as a terminal oxidant. Under mild reaction conditions, a secondary alcohol is converted into its corresponding ketone.

Keywords: C–H activation, alcohol oxidation, organocatalyst, iron.

List of publications

This thesis consists of an introductory review followed by five papers. Papers are reproduced with the kind permission of the journals concerned. Reference to papers of this thesis will be indicated in the text by their roman numbers.

Paper I **A. Al-Hunaiti**, T. Niemi, A. Sibaouih, P. Pihko, M. Leskelä and T. Repo. Solvent Free Oxidation of Primary Alcohols and Diols Using Thymine Iron(III) Catalyst. *Chem. Commun.* **2010**, 46, 9250–9252.

Paper II B. Biswas, **A. Al-Hunaiti**, M.T. Räisänen, S. Ansalone, M. Leskelä, T. Repo, Y.-T. Chen, H.-L. Tsai, A. D. Naik, A. P. Railliet, Y. Garcia, R. Ghosh and N. Kole. Efficient and Selective Oxidation of Primary and Secondary Alcohols Using an Iron(III)/Phenanthroline Complex: Structural Studies and Catalytic Activity. *Eur. J. Inorg. Chem.* **2012**, 28, 4479–4485.

Paper III **A. Al-Hunaiti**, M. T. Räisänen, P. Pihko, M. Leskelä and T. Repo. Organocatalytic Oxidation of Secondary Alcohols Using 1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA). *Eur. J. Org. Chem.* **2014**, 28, 6141–6144.

Paper IV **A. Al-Hunaiti**, M.T. Räisänen and T. Repo. From DNA to Catalysis: Thymine-Acetate Ligated Non-Heme Iron(III) Catalyst for Oxidative Activation of Aliphatic C–H Bonds. *Submitted to Chem. Commun.* **2015**.

Paper V **A. Al-Hunaiti**, K. Lagerblom, F. Al-Qaisi, M. Nieger and T. Repo. Iron-catalyzed Oxidative C-C Bond Formation: Practical Approach to α,β -Unsaturated Ketones from Styrenes and Aldehydes. *Submitted to Chem. Commun.* **2015**.

List of other publications

H. Guo, **A. Al-Hunaiti**, M. Kemell, S. Rautiainen, M. Leskelä and T. Repo. Gold Catalysis Outside Nanoscale: Bulk Gold Catalyzes the Aerobic Oxidation of π-Activated Alcohols. *ChemCatChem.* **2011**, 3, 1872–1875.

H. Guo, M. Kemell, **A. Al-Hunaiti**, S. Rautiainen, M. Leskelä and T. Repo. Gold–Palladium Supported on porous steel fiber matrix: Structured Catalyst for Benzyl Alcohol Oxidation and Benzyl Amine Oxidation. *Catal. Commun.* **2011**, 12, 13, 1260–1264.

M. T. Räisänen, **A. Al-Hunaiti**, M. Kemell, E. Atosuo, M. Leskelä and T. Repo. Mn(II) Acetate: An Efficient and Versatile Oxidation Catalyst for Alcohols. *Catal. Sci. Technol.* **2014**, 4, 2564–2573.

Das B., **Al-Hunaiti A.**, Haukka M., Demeshko S., Meyer S., Shteinman A. A, Meyer F., Repo T., and Nordlander E. Catalytic Oxidation of Alkanes and Alkenes by H_2O_2 with a μ-Oxido Diiron(III) Complex as Catalyst/Catalyst Precursor. *Eur. J. of Inorg. Chem.***2015**, 21, 3590–3601.

List of Abbreviations

Ac	Acetyl
Acac	Acetylacetonate
AIBN	Azobis(isobutyronitrile)
BHT	Butylated hydroxy toluene
Bipy, (bpy)	2,2'-bipyridyl
Bn	Benzyl
Bpmen	*N*,*N*‘-bis(6-*H*-2-pyridylmethyl)-1,2-diaminoethane
BPO	Dibenzoylperoxide
CAN	Ceric ammonium nitrate
Cbz	Carbobenzyloxy
C–C	Carbon carbon bond
CDC	Crossdehydrogenative coupling
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
m-CPBA	*meta*-Chloroperoxybenzoic acid
DAPHEN	9,10-diaminophenanthrene
DBE	dissociation bond energy
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
En	ethylenediamine
GC	Gas chromatography
KIE	Kinetic isotopic effect
Im	Imidazole
Imim	Imidazoluim ionic
IR	Infrared
Mccp	Methyl cyclopentadienyl
Me-AZADO	1-Methyl-2-azaadamantane-*N*-oxyl
MEP	2-methyl-5- ethylpyridine
Me-picH	methylpicoline
MS	Mass spectrometry
MMO	Monooxygenase enzyme
NHPI	*N*-hydroxyphthalimide
NMR	Nuclear magnetic resonance
NMI	*N*-methylimidazole
PDP	2-({(*S*)-2-[(*S*)-1-(pyridin-2-ylmethyl)pyrrolidin-2-yl]pyrrolidin-1-yl}methyl)pyridine.
Phen	Phenantroline
PINO	Phthalimide-*N*-oxyl
PMB	p-Methoxybenzyl
PPTS	Pyridinium p-Toluenesulfonate
Pv	Pivaloyl
Py	Pyridine
OKR	Oxidative kinetic resolution
TauD	Taurine α-ketoglutarate dioxygenase
TAML	Tetraamido macrocycleic ligand
TBN	*tert*-butylnitrite
TBHP	*tert*-butylhdroxide
TCNQ	7,7,8,8-Tetracyanoquinodimethane
Tf	Triflate
TMEDA	*N*,*N*,*N'*,*N'*-Tetramethylethylenediamine
Tpa	Tris(2-pyridylmethyl)amine
Tpoen	N-(2-pyridylmethoxyethyl)-N,N-bis(2-pyridylmethyl)amine
TPP	Tetraphenylporphyrin
Tpy	2,2’,6’,2’-terpyridine
Tol	*p*-Tolyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TON	Turnover number
UV	Ultraviolet
Vis	Visible
ν	Vibration

Table of Contents

1 Introduction

Whether homogenous, heterogeneous or enzyme, a catalyst lowers the energies of the transition states; and thus, increases the reaction rate without itself being consumed. Catalysis is an important field of chemistry because it is implemented in many fields including, industrial, environmental, and life sciences. In particular, catalytic oxidation provides solutions for some economical and environmental problems, especially in pharmaceuticals, petrochemicals, polymer and basic chemicals production by developing efficient, selective, convenient, and environmentally benign synthetic solutions.[1] For instance, converting petroleum-based stocks of chemicals into a high oxidation state chemicals (e.g. alcohols, carbonyl compounds, and epoxides).[2]

Catalytic oxidation can be performed by utilizing transition metals (including palladium, ruthenium, rhodium, iridium, gold, and platinum)[3–8] or in some cases metal-free catalyst (organo-catalysts). However, some catalysts are too expensive to be used or they might have considerable toxicity; and thus, limited their applications in practice or imposed stringent environmental legislation on their use in manufacturing of fine chemicals. Therefore, first row transition metals (such as iron, copper, zinc, and manganese) have been introduced as an efficient alternative catalyst. As a route for “green” oxidation, metal-free catalysts (organo-catalysts) are highly preferred in order to selectively oxidize certain functional groups using non-toxic reagents. These two facts encouraged us to develop iron-based systems and also a metal-free system to be used in catalytic oxidation processes.

In this chapter I will a present a brief literature review on the oxidation reaction using iron and metal-free catalysts. The first section will be devoted to review these processes, mechanism consideration, and applications of iron catalysts in alcohol and alkane oxidation. The second section will focus on metal-free catalyst in alcohol oxidation.

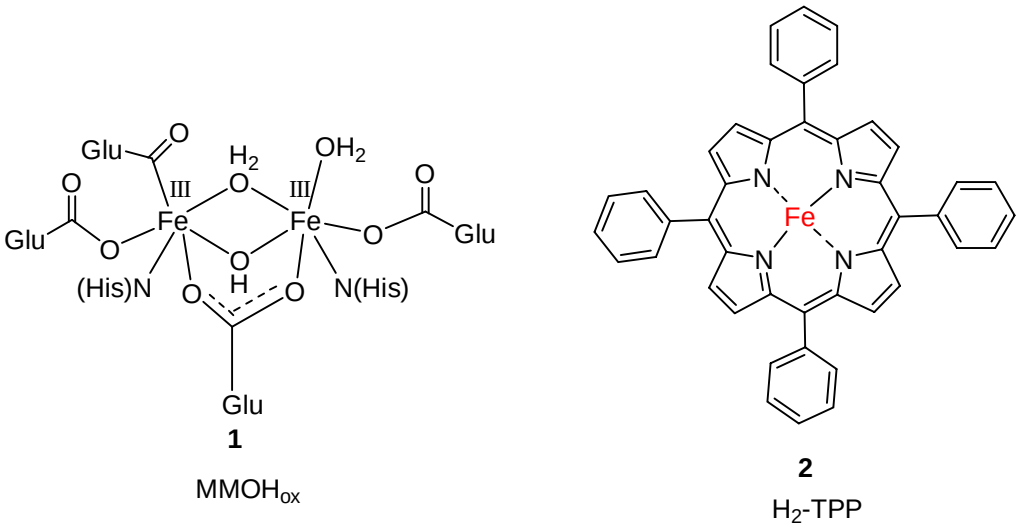


Figure 1.1: Selective examples of non-heme and heme complexes: (**1**) Active site of methane monooxygenase($MMOH_{ox}$) and (**2**) tetraphenylporphyrin ($TPP\text{-}H_2$).

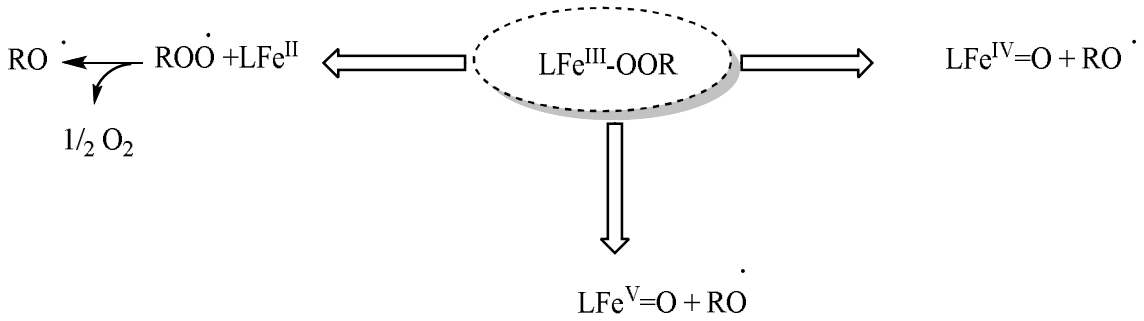
1.1. Iron: an ideal transition metal catalyst

Iron is an effective catalyst that provides inaccessible levels of reactivity.[9] It is the most abundant transition metal on earth, inexpensive, and low in toxicity.[10] Therefore, it is widely used in a vast applications of modern chemistry, especially in oxidation reactions (e.g. oxidation of alcohols and alkanes).

Naturally, iron is an essential element for proper function of nearly all known biological systems (either heme or non-heme). Porphyrine-metalloproteins are well understood heme complexes that have been studied extensively with cytochrome P450 as the prototypical example. Non-heme iron-based enzymes can, in turn, be divided into mononuclear and dinuclear iron enzyme. Methane monooxygenase (MMO), for instance, is a remarkable example of the latter group and catalyzes the selective oxidation of the most difficult hydrocarbon substrates. Figure 1.1 shows the chemical structure of these mentioned examples.[11]

The key active species in numerous biological oxidation reactions in which activation of oxygen is involved are known to be high-valent iron–oxo intermediates of heme and non -heme.[12] As such, significant advancements towards the direct characterization of $Fe^{(IV)}$-O, and $Fe^{(V)}$-O have been made towards detailed knowledge on the structure of model iron complexes.[13] There is no doubt that such basic knowledge is important for the understanding of biologically relevant reactions and the more rational design of artificial catalysts. However, the catalytic performance of most of these model complexes is far away from the

efficiency of biologically active systems and sometimes with model complexes no catalytic behavior is observed at all.



Scheme 1.1: Possible decomposition pathways of the $Fe^{III}OOR$ intermediate.

The mechanism for oxidation by an iron catalyst can be separated into two steps: a C–H bond cleavage followed by a C–O bond formation. At one extreme, these two steps may occur in a concerted fashion so that the oxygen atom is effectively inserted into the C–H bond. Alternatively, the C–H bond is cleaved to form a radical that is very quickly trapped to form the C–O bond. At another extreme, the two steps can be well separated in time so that the long-lived radical can be trapped by other species in the solution. The lifetime of the radical and its consequent reactions is a symptomatic character of the mechanism type.

The long-lived radical formation depends on the fate of $Fe^{III}OOR$ intermediate, which are presumably formed from biomimetic iron complex systems. Such an intermediate can decompose in four distinct pathways and generate five different oxidants, which have been observed spectroscopically in several cases as shown in Scheme 1.1:

1. The Fe–O bond may homolyze to form Fe^{II} and an ROO• Radical. The ROO• radical (ΔH_{DBE} (*t*-BuOO–H) = 89 kcal mol^{-1}, ΔH_{DBE} (HOO–H) = 88 kcal mol^{-1}) can only attack substrates with relatively weak C–H bonds.[14]However, bimolecular self-reaction of the ROO• radical can generate a more powerful oxidant such as an RO• radical, which in turn attacks the stronger C–H bond.[15]

2. The Fe–OOR intermediate may attack the substrate directly in analogy with the reactivity of early transition metal peroxo complexes.[16]

3. The Fe–OOR intermediate may undergo O–O bond homolysis to form Fe^{IV}=O and RO•, which both can attack the substrate.

4. The Fe–OOR intermediate may undergo O–O bond heterolysis to form an Fe^{V}=O species analogous to the high-valent species in cytochrome P450 cycle.

Hydrogen atom transfer (HAT) is an elementary chemical transformation that results in the net transfer of both a proton and an electron. Metal-oxo complexes are widely used to abstract hydrogen atoms from organic compounds through HAT, which leads to the metal hydroxide. In oxidations by cytochrome P450, the mechanism is generally accepted to be HAT to an iron-oxo species (Fe=O) followed by radical formation. Other enzymatic systems such as soluble methane monooxygenas and Tau-D also utilize mechanisms with key HAT steps. Considerable effort has been devoted to synthesizing and studying biomimetic iron oxo complexes in order to help elucidate the enzymatic mechanisms and to develop homogeneous iron-based oxidation catalysts. Studies on heme iron-oxo complexes in the 1980s by Balch, La Mar, and Groves pioneered this field. More recently, Que, Nam, and co-workers have reported isolable non-heme oxoiron$^{(IV)}$ complexes that react with hydrocarbons via HAT. In general, the selectivity of non-enzymatic HAT reactions is thermodynamically controlled, and reaction rates follow a linear correlation with the bond dissociation enthalpy (BDE) of the X-H bond being broken (the Bell-Evans-Polanyi relation); i.e., homolytically weaker substrate bonds react more rapidly.[17]

Based on the lifetime of the radical, the mechanisms of iron oxidation can be divided into two different categories: (1) those that produce short-lived radicals and (2) those that produce long-lived radicals. Whether the oxidant is HO•, RO•, or a metal based oxidant (such as Fe^{III}OOH, Fe^{IV}=O, or Fe^{V}=O species), probing the lifetime of the radical is the key to determine the oxidation mechanism.

It is often very difficult in the catalytic oxidation systems to observe the actual reagent that carries out the key oxidative transformation. Therefore, indirect probes have been useful to adopt the reaction mechanism. These probes provide insight into either the oxidative power of the species that produces the nascent radical or the lifetime of this radical. As one possible mechanistic probe, the kinetic isotope effect (KIE) is used in a competition reaction between proton and deuteron substrate based on the difference of $C_{H/D}$ bond strength (≈1.7 kcal·mol^{-1}). The higher KIE value of *t*-BuO• to HO• is consistent with the lower reactivity of a radical. Metal-based oxidants, on the other hand, may be more selective with moderate KIE values, while in some enzymatic reactions the KIE value is up to 7.[18]

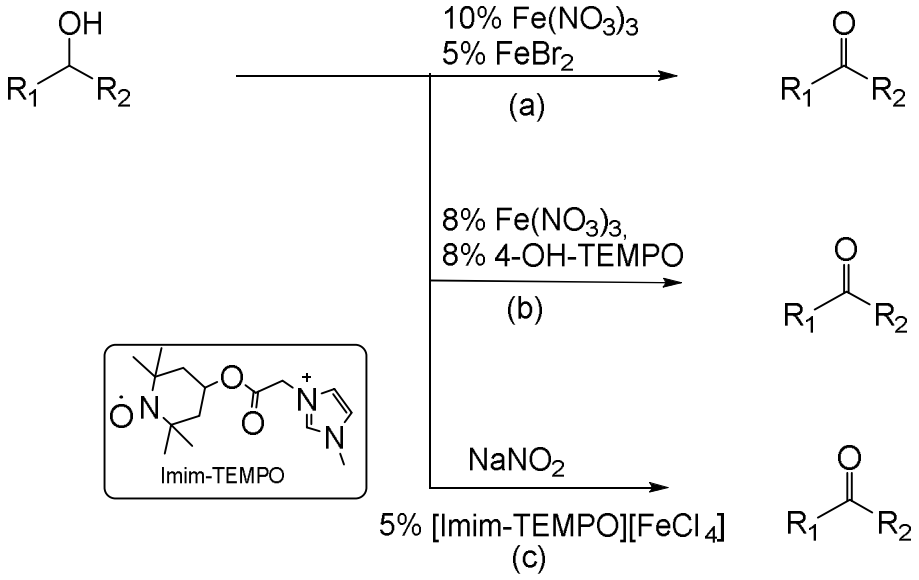
1.1.1. Alcohol oxidation with iron catalysts

Iron-oxo species (e.g. $FeCl_3$ and hydrogen peroxide) are often proposed as catalytic intermediates, which have moderate activity in alcohol oxidations (e.g. 2-cyanoethanol).[19]Although controlled iron-catalyzed oxidation reactions of alcohols with air or hydrogen peroxide is difficult, the oxidation of benzyl and secondary alcohols has been possible under solvent-free conditions in the presence of stoichiometric amounts of iron nitrate.[20] In 2008, it was demonstrated that tuning the absolute pH of the reaction system made it possible to switch between nonselective radical pathways and selective non radical reactions.[21] For instance, the oxidation of benzyl alcohol to give benzaldehyde was studied by various iron salts (mainly $Fe(NO_3)_3$). A constant pH value (close to 1.00) provides a high selectivity towards benzaldehyde, whereas the chemo-selectivity is controlled by changing the pH value (Scheme 1.2).

In the field of non-heme iron complexes, Munck, *et al*. reported the oxidation of benzylic alcohols via stable μ-oxo-bridged diiron$^{(IV)}$ (TAML complexes), which are formed by the reaction of iron-complexes with molecular oxygen.[22] Remarkably, the shown reaction of iron- complexes with molecular oxygen can form non-heme iron complexes (such as benzylic alcohols via stable TAML complexes).[23] Later, Kim and coworkers reported oxidation of alcohols and olefins by using *m*-CPBA as the oxidant.[24]

A biomimetic oxidation with perfluorinated porphyrin complexes [(F_{20}TPP)FeCl] can provide high catalytic activity with secondary alcohols.[25] For example, this catalyst can oxidize a broad range of alcohols under mild conditions with *m*-CPBA as terminal oxidant. Here, a hydroxyalkyl radical species are proposed as central intermediate. Porphyrin complexes can be applied in ionic liquids to oxidize benzyl alcohols with hydrogen peroxide.[26] In addition, TEMPO can be incorporated via a phenyl linker into the porphyrin scaffold (Scheme 1.2c).[27]

A chemoselective oxidation of allylic alcohols to α-β-unsaturated carbonyl compounds can efficiently proceeded using hydrogen peroxide with iron-picolinate catalysts $Fe(OAc)_2$ with Me-PicH or PicH system, which can selectively and efficiently oxidize aliphatic and allylic alcohols was recently reported. Interestingly, this system has tunable regioselctivity toward primary alcohols.[28]



Scheme 1.2: Oxidation of alcohols by iron catalyst using air as oxidant.

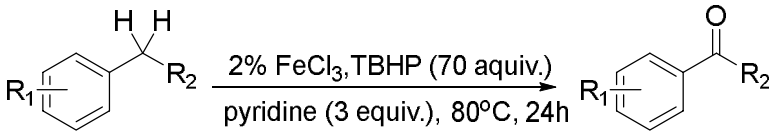
1.1.2. Alkane C–H activation with iron catalysts

Naturally, C–H bond oxidation is one of the most common processes, because alkanes are cheap. Finding effective routes for the selective functionalization of alkane feedstocks remains one the most important contemporary goals in academia and industry, taking into account four major challenges: reactivity, chemoselectivety, regioselectivity, and steroselectivity.[29]

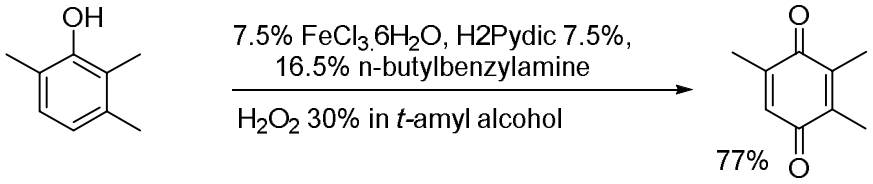
Direct C–H transformation has attracted a great interest since the early 1970s. This is basically due to sustainable requirement of organic transformations and the understanding of the intrinsic features of the C–H bonds in organic molecules. Actually, iron-containing enzyme-catalyzed C–H transformation has suggested a possible application of iron catalysis in C–H transformation.[30] Combining the advantages of both iron chemistry and C–H transformation, the significance of iron-catalyzed C–H transformations and radical reactions based on Fenton chemistry have stimulated the rapid development in the past several years. Although C–H bond oxidation is thermodynamically favored they remain difficult to activate for selective reaction. This is largely because of two main reasons:

(i) The C–H bond energy is high (~ 400 kJ mol^{-1}) and moreover higher than the C–O bond in oxidation products resulting in over-oxidation to mixtures of alcohol, ketone/aldehyde, and carboxylic acid products.

(ii) There are no activating functional groups available in alkanes to direct selective reaction.



Scheme 1.3: Iron –catalyzed benzylic oxidation



Scheme 1.4: Iron-catalyzed oxidation of trimethylphenol.

In the absence of ligands, Fe^{III} perchlorate catalyzes the hydrocarbon oxidation such as methane and ethane into corresponding alkylhydroperoxides with hydrogen peroxide as oxidant in low-moderate yields.[31] Eventually, the alkylhydroperoxide decomposes into alcohol and ketone as the major products. Despite the fact that a simple iron salt can oxidize the strong C–H bond, such as methane, the reaction intermediates and mechanisms are very difficult to define.

In 2007, a protocol was developed to efficiently oxidize benzylic compounds into carbonyl derivatives under mild reaction conditions (Scheme 1.3).[32] This transformation was clean and efficient by using *tert*-butylhydroperoxide (TBHP) aqueous solution as the oxidant. This method was utilized to transform 4-methylanisole and diphenylmethanol to form 4-methoxybenzoic acid and benzophenone, respectively.

It is also possible to have iron-catalyzed selective oxidation of the s_p^2 C–H bond of phenols and arenes as well as direct hydroxylation of benzyl s_p^3 C–H bond.[33] A three component catalyst system consisting of $FeCl_3 \bullet 6H_2O$, pyridine-2,6-dicarboxylic acid (H_2pydic), and different benzylamines was used for the oxidation of 2,3,6- trimethylphenol (TMP) in presence of hydrogen peroxide (Scheme 1.4).[34]

Many different types of ligands were also designed for selective and effective C–H bond oxidation using hydrogen peroxide as an oxidant (Figure 1.2). However, moderate catalytic performances have generally been observed in most cases. The major drawbacks of these reported biomimetic iron catalysts include low reactivity, and oxidative decomposition of the ligand made it difficult to be practically applicable.[35]

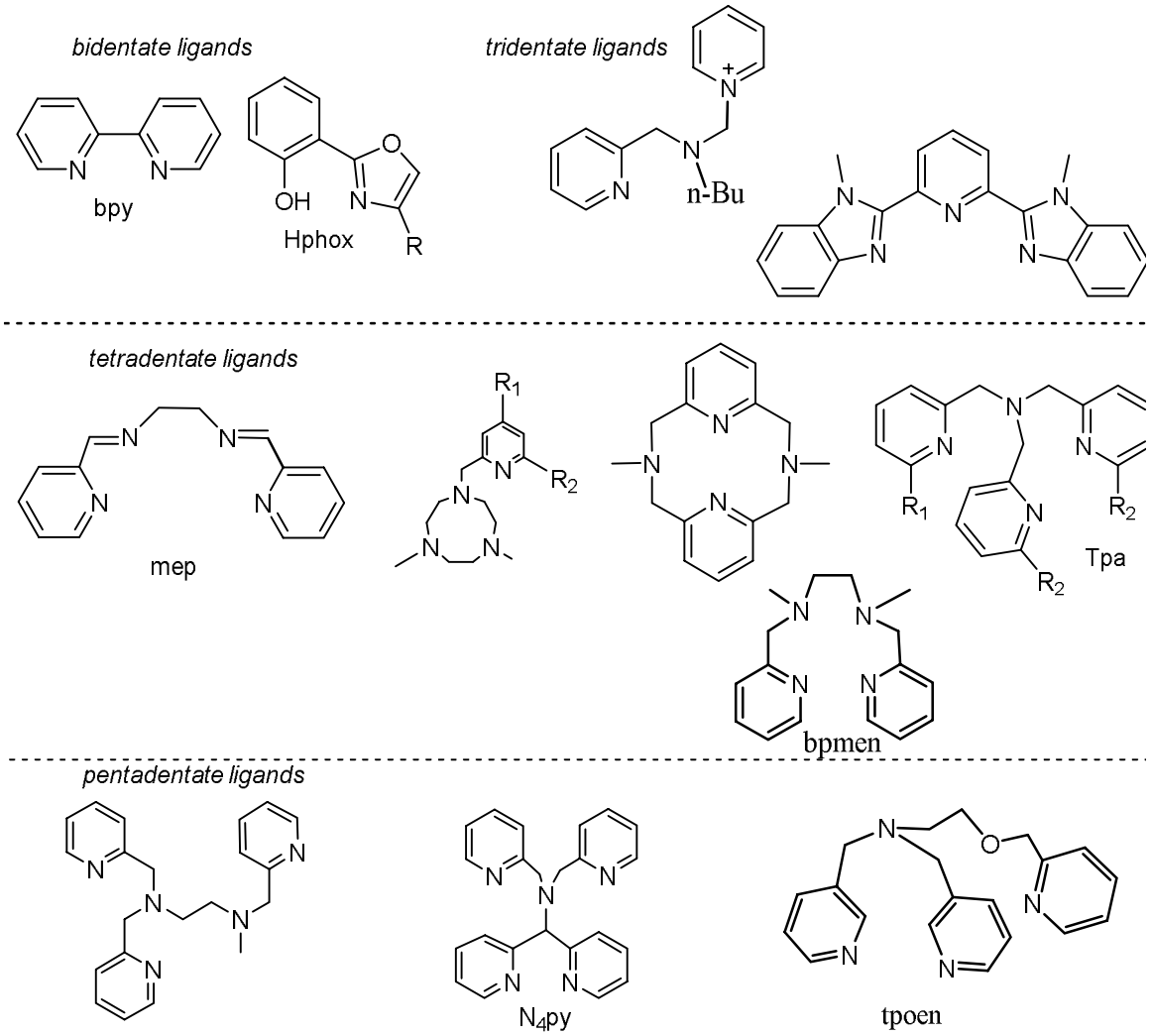
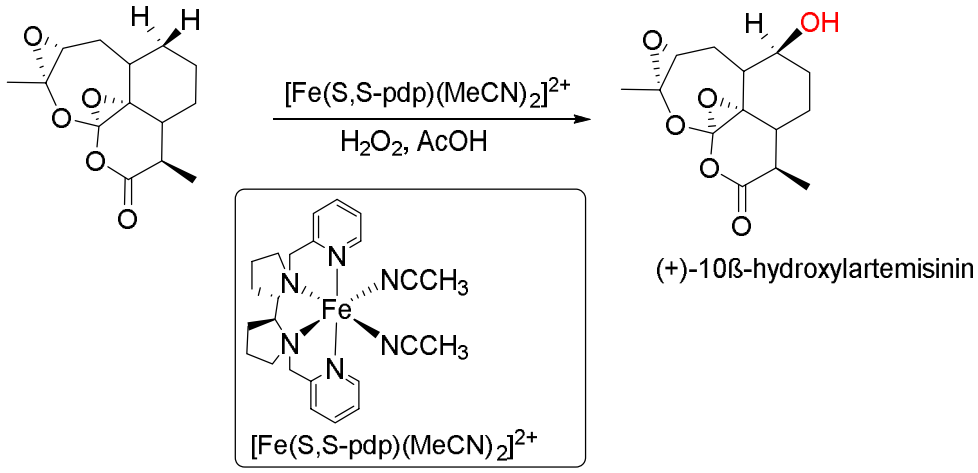


Figure 1.2: Selective examples of ligands used in reported Iron complex catalyzed C-H bond oxidation[38]

Until now, achieving highly selective alcohol formation or effective oxidation of unactivated hydrocarbons remains a difficult task. Chen and coworkers were the first to correlate C–H bond hydroxylation with dioxygen activation involving heme and non-heme iron enzymes such as P-450, and they postulated the involvement of high-valent iron$^{(V)}$-oxo species in the hydrocarbon oxidation with hydrogen peroxide catalyzed by $[Fe^{II}(tpa)(MeCN)_2]^{2+}$ (see Figure 1.2 for ligands).[36–37] The reactivity of $[Fe^{II}(tpa)(MeCN)_2]^{2+}$ complex can be modulated by the electronic and steric properties of the TBA ligand (α and β analogous), resulting in an Fe^{III}–OOH intermediate with different spin states. Isotopic labeling studies by using either $H_2{}^{18}O$ or $H_2{}^{18}O_2$ have proven to be insightful and the mechanistic considerations rely heavily on the results obtained from these experiments. It has been proposed that a Fe^{V}=O species is formed via O–O bond heterolysis of the low spin Fe^{III}–OOH intermediate. The^{18}O incorporation in cyclohexanol from $H_2{}^{18}O$ in isotope

labelling studies. Meanwhile, the high ^{18}O incorporation of alcohol from $^{18}O_2$ gives a clear indication for the participation of radical auto-oxidation through the high spin Fe^{III}–OOH counterpart.[46]



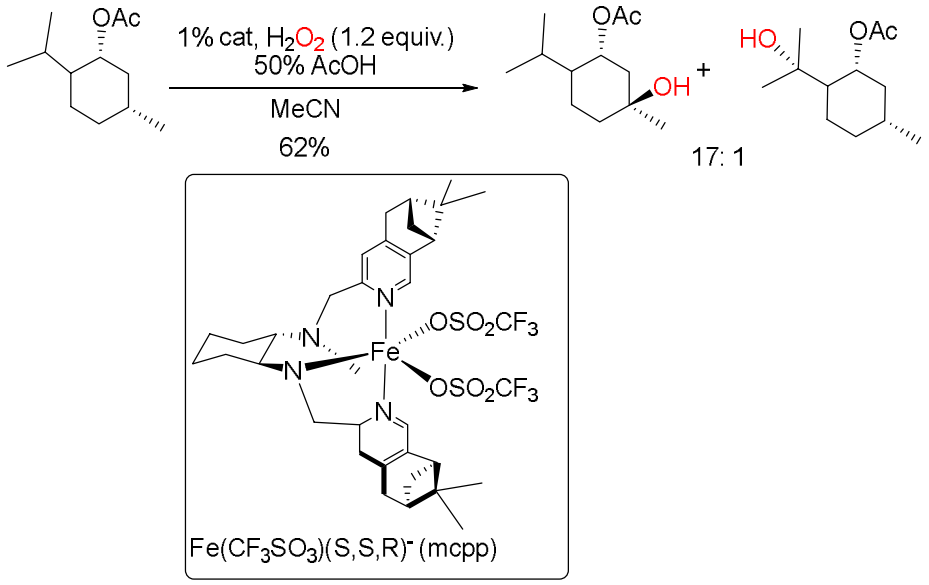
Scheme 1.5: Hydroxylation of (+)-artemisinin by White's system.[40]

Interestingly, the use of peracid can improve the selectivity of alcohol formation in the hydroxylation of C–H bonds. Feringa and co-workers reported that a dramatic enhancement in alcohol selectivity from 1.4 to 4.6-5.6 that was observed in cyclohexane oxidation catalyzed using $[Fe^{II}(N_4Py)(MeCN)]^{2+}$ (see Figure 1.2 for ligand) complex with peracetic acid or *m*-chloroperbenzoic acid (*m*-CPBA) instead of hydrogen peroxide (Figure 1.2).[37] Particular increase in KIE (~ 4.5-6.0) may also imply an involvement of metal-based oxidant (i.e. Fe^{IV}=O) rather than hydroxyl radical in the reaction using *m*-CPBA. Similar observation was also reported by Li and co-workers in alkane oxidation using $[Fe^{II}(tpoen)Cl]^+$ as catalyst with *m*-CPBA as oxidant.[39]

Selective oxidation of unactivated aliphatic C–H bonds of tertiary carbon can be done by using $[Fe^{II}(S,S\text{-}PDP)(MeCN)_2]^{2+}$ catalyst with a combination of hydrogen peroxide and acetic acid.[39] This catalyst incorporated a more rigid pyrrolidine moiety, which provided a promising and predicable C–H bond hydroxylation that can be used for the synthesis of complex natural molecules (Scheme 1.5). With this system, (+)-artemisinin can be specifically oxidized into (+)-10-β-hydroxylartemisinin in comparable yield to the microbial synthesis (Scheme 1.5).[40]

Modifying the ligand at the remote position of the pyridine ring with a more bulky hydrocarbon group forms a robust cavity for iron. This modification leads to higher selectivity and efficiency when compared with the results in the derived catalyst from the

mep ligand.[41] For example, the oxidation of (-)-acetoxy-*p*-menthane by using iron complex [Fe(*S*,*S*,*R*)-mcpp(CF_3SO_3)$_2$] as catalyst a regiospecific oxidation of tertiary C–H was realized in a good yield with only 1% loading of catalyst (Scheme 1.6).[42]



Scheme 1.6: Regiospecific hydroxylation of (-) acetoxy-*p*-menthane.[42]

In spite of the great significance and intense prospects, the studies of iron-catalyzed direct C–H transformations remain challenging. Undoubtedly, the special efficiency, selectivity, and tolerance of functional groups indicated their distinctive and applicability. The experimental observation and the obtained results could provide some suggestion on the mechanism. Further efforts to understand the nature of such transformations is still needed.

1.1.3. Chalcone formation via C–C bond coupling

Chalcones (1,3-diphenylpropenones) constitute to be one of the major classes of flavonoids that are naturally formed in vegetables, fruits, tea, and soy (Figure 1.3).[43] Prehistoric therapeutic applications of chalcones can be associated with the thousand-year old use of plants and herbs for the treatment of different medical disorders.[44] Contemporary studies report a generous variety of naturally occurring and man-made compounds with significant pharmacological activities of chalcones or of compounds possessing an α,β -unsaturated ketone core structure including anti-proliferative, anti-oxidant, anti-inflammatory, antimicrobial, and anti-cancer effects.[45–47]

Chalcones are usually synthesized from acetophenones and benzaldehydes via the Claisen-Schmidt condensation, using base in a polar solvent (Scheme 1.7).[48] In addition, interesting synthetic protocols have been reported, such as the palladium-mediated Suzuki coupling between cinnamoyl chloride and phenyl boronic acids or the carbonylative Heck coupling with aryl halides and styrenes in the presence of carbon monoxide.[49]

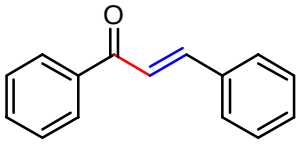
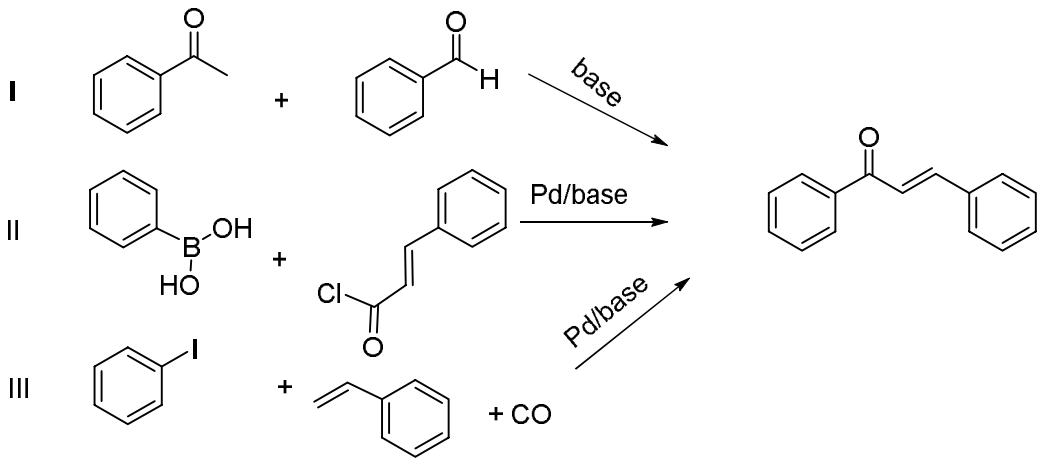


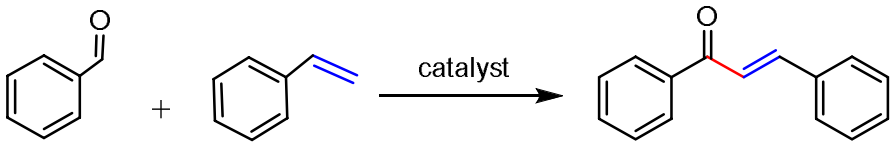
Figure 1.3: The general structure of chalcones.



Scheme 1.7: Examples of synthetic routes toward chalcones. I) Claisen-Schmidt condensation II) Suzuki cross-coupling III) Carbonylative Heck reaction.

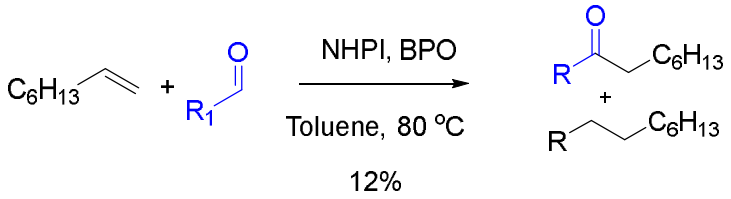
A more subtle and elaborated approach in C-C bond formation in organic synthesis is cross-dehydrogenative coupling (CDC).[50] The advantages of this strategy include high efficiency, environmental benign (avoiding the use of either organohalides/halide surrogates or organometallic reagents), and forming a C-C bond under oxidative conditions. Although some progress has been made in this field, the development of a highly efficient and selective oxidative cross-coupling reaction utilizing two different hydrocarbons as the reagents is still a great challenge. In recent years, significant progress has been achieved, whereby the C_{sp}^2 –H bonds of arenes have been activated for the oxidative coupling with an aldehyde C–H bond to afford ketones.[51] Not only aldehyde was used in such transformation, but also alkenes have been widely used in oxidative transformations.[52]

The functionalization of alkenes is a class of significant synthetic reactions that allows the build-up of molecular complexity in a single procedure. Dihydroxylation[53] and palladium-catalyzed oxidative functionalization of alkenes have demonstrated their high impacts on synthetic chemistry.[54–55] Carbonylation of alkenes has been developed as one of powerful methods for synthesis of carbonyl compounds, including large-scale commodity products and versatile chemical intermediates. The direct oxidative coupling of alkenes with aldehydes would result an inspiring sustainable strategy for the synthesis of α,β-unsaturated ketones (Scheme 1.8).[56] Because this methodology is relatively new, only a few examples in literature are available.

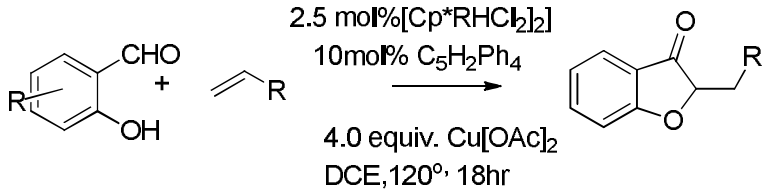


Scheme 1.8: Direct synthesis of α,β-unsaturated ketones.

Early 2001 the first coupling system between an aldehyde and styrene was reported using *N*-hydroxyphthalimide (NHPI) and dibenzoyl peroxide (BPO) in a radical process (Scheme 1.9). Another example, a three-component reaction of alkenes, aldehydes, and hydroperoxides catalyzed by $FeCl_2$ to β-peroxy ketones have been achieved in good to excellent yields. Interestingly, this three-component reaction can be also applied to the synthesis of carbonyl epoxides. Later on a Rh^{III}- based catalyst was developed for regioselective dehydrogenative Heck reaction. This methodology affords another way to complete the Heck reaction on carbonyl groups, as aldehyde C–H bonds was coupled with different classes of olefins in moderate to excellent yields and selectivity (Scheme 1.10). Recently the first copper-catalyzed oxidative coupling of alkenes with aldehydes was reported. A variety of functional groups were tolerated on both the aldehyde and alkene to synthesis of α,β-unsaturated ketones (Scheme 1.10).



Scheme 1.9: NHPI assisted hydroacylation of simple alkenes with aldehydes.



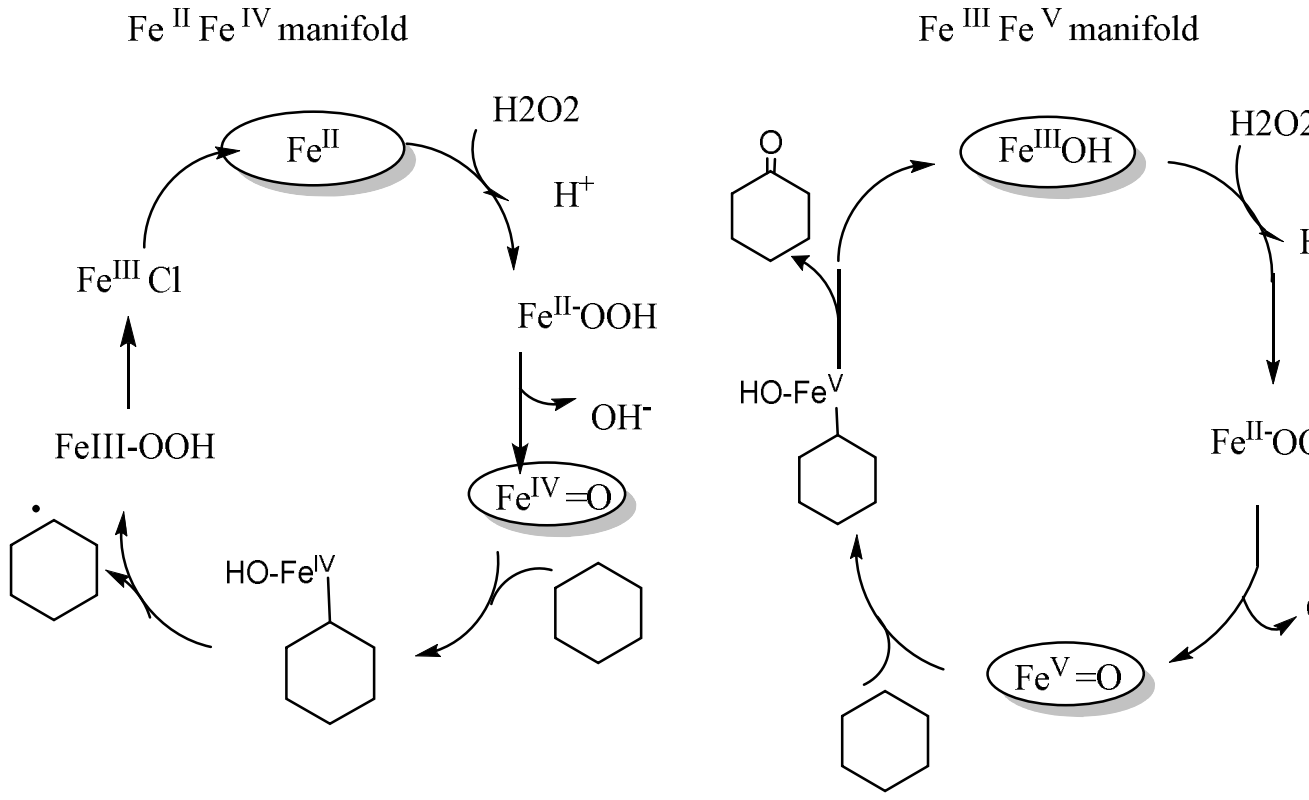
Scheme 1.10: Rh^{III}-catalyzed cyclization of salicylaldehydes and electron deficient olefins.

1.1.4. Nature of high valent iron species

In many of the studies of both the enzymes and the model systems discussed above iron–(hydro) peroxide and/or high valent $iron^{(IV)}$–oxo or $iron^{(V)}$–oxo intermediates are invoked. Several efforts have been specifically devoted to study, isolate, and characterize these species to get more insight into the spectroscopic and chemical properties of these intermediates. The intense spectroscopic and reactivity studies of the last decade have substantially clarified the mechanism of non-heme iron catalyzed oxidations. This section is focused on the mechanism considerations regarding the key active species that participate on the type of catalysis, from Gif chemistry to the current high valent Fe-oxo species (Fe^{IV} and Fe^{V}).

Gif Chemistry (selective C-H activation chemistry)

In the literature, there have been extensive studies on gif chemistry involving variation of the iron source (from iron metal to iron salts), terminal oxidant (from molecular oxygen to hydrogen peroxide or TBHP), pyridine additives (from simple pyridine to substituted pyridine), reducing agent (from hydrogen sulfide to zinc), and acid additive (from acetic acid to 2-picolinic acid).[57] Among the debates on the mechanism of gif oxygenation, Barton and co-workers postulated the concerted addition of a C–H bond to a high valent iron-oxo unit ($iron^{(V)}$-oxo or $iron^{(IV)}$-oxo species) rather than a radical H-atom abstraction mechanism (Scheme 1.11).[58–60]



Scheme 1.11: Proposed mechanism of gif oxygenation by Barton. [57-62]

$$Fe^{III} + H_2O_2 \longrightarrow Fe^{II} + H^+ + HOO^{\cdot} \quad \text{(slow reaction)}$$

$$Fe^{II} + H_2O_2 \longrightarrow Fe^{III} + OH^- + OH^{\cdot} \quad \text{(fast reaction)}$$

$$HO^{\cdot} + RH \longrightarrow R^{\cdot} + H_2O$$

$$R^{\cdot} + O_2 \longrightarrow ROO^{\cdot}$$

$$ROO^{\cdot} + H_2O_2 \longrightarrow ROOH$$

$$FeII + ROOH \longrightarrow FeIII + OH^- + RO^{\cdot}$$

$$RO^{\cdot} + RH \longrightarrow ROH + R^{\cdot}$$

Scheme 1.12: Hydroxyl radical initiated radical autooxidation pathway proposed by Perkin.[63]

In 1983, Barton *et al.* reported adamantane oxidation by simply dissolving metallic iron and hydrogen sulfide or sodium sulfide in pyridine/acetic acid (10:1 v/v) solution, and

in the presence of a small amount of water, affording a mixture of adamantan-1-ol, adamantan-2-ol and adamantanone under aerobic conditions.[61] Although oxidation of hydrogen sulfide is a more favorable reaction, no suppression on C–H bond oxidation was found. It was also claimed that there was extraordinary preference for the oxidation of secondary C–H bond.[62] Similar results were obtained by replacing hydrogen sulfide with other substrates (Ph_2S and PPh_3), further revealing the novelty of this unprecedented chemistry named 'gif paradox'.[62]

Later on, Knight and Perkins proposed the radical auto-oxidation pathway with successful detection of cyclohexyl and hydroxyl radicals in a radical trapping test (Scheme 1.12).[63–65]

Iron$^{(IV)}$-oxo species

The existence of iron$^{(IV)}$-oxo (Fe^{IV}=O) species in biological systems have been postulated for decades. A representative example is iron$^{(IV)}$-oxo porphyrin π-radical cation in cytochrome P-450 catalyzed biological oxidations. Other examples of mononuclear-non-heme-iron enzymes include taurine/α-ketoglutarate dioxygenase (TauD).[66–67] Tyrosine hydroxylase has also been suggested to be involved in iron$^{(IV)}$-oxo reaction.[68]

In 2003, the first X-ray crystal structure of a mononuclear non-heme iron(IV)-oxo complex $[Fe^{IV}(O)(tmc)(MeCN)][OTf]_2$ has been prepared by reacting $[Fe^{II}(tmc)(OTf)_2]$ with PhIO in acetonitrile at -40 °C.[69] The crystal structure reveals the presence of iron$^{(IV)}$-oxo in the synthetic iron porphyrin complexes and heme peroxidase compounds similar to P-450.[70–71] Similar examples including cyclooctene epoxidation by $[Fe^{IV}(O)(tpa)(MeCN)]^{2+}$ and $[Fe^{IV}(O)(Bn\text{-}tpen)]^{2+}$ have been subsequently reported.[72–73]

Iron$^{(IV)}$-oxo intermediate has been suggested to participate in a wide range of iron complex mediated oxidative reactions.[74] It was noticed that cyclohexane hydroxylation can be performed using $[Fe^{IV}(O)(N_4Py)]^{2+}$ and $[Fe^{IV}(O)(Bn\text{-}tpen)]^{2+}$ at room temperature, affording a mixture of cyclohexanone and cyclohexanol.[74] The C–H bond activation was suggested to occur via hydrogen atom abstraction based on the observations of high proton kinetic isotope effects.[75] Such a high KIE value was also measured in hydrogen atom abstraction reactions by iron$^{(IV)}$ intermediate of the mononuclear taurine α-ketoglutarate dioxygenase (TauD).[76]

Recently, Que and coworkers reported the first example of O–H bond activation by (μ-oxo)diiron$^{(IV)}$complex, which was synthesized from electrochemical oxidation of its (μ-oxo)diiron$^{(III)}$ counterpart.[76–77] The diiron complex was found to react much faster with

cyclohexane than the mononuclear iron$^{(VI)}$-oxo complexes of closely related ligand, and very interestingly, it preferentially cleaves the strong O–H bonds of methanol and *tert*-butanol instead of their C–H bonds. The Fe^{III}-O-Fe^{V}=O core, which is from the isomerization of the Fe^{IV}-(μ-O)$_2$-Fe^{IV} species, has been proposed as the reaction intermediate for such an extraordinary observations.[77]

Iron$^{(V)}$-oxo species

Iron$^{(V)}$-oxo species are exceedingly rare. Barton and co-workers were the first to postulate the involvement of iron$^{(V)}$-oxo intermediate in gif chemistry.[60] Later on, based on ^{18}O labelling experiment, assignment of iron$^{(V)}$-oxo hydroxo species (HO-Fe^{V}=O) in the $[Fe^{II}(tpa)(MeCN)_2]^{2+}$ catalyzed alkane hydroxylation has been proposed.[78] Meanwhile, Newcomb and co-workers reported a successful detection of transient iron$^{(V)}$-oxo species in laser flash photolysis experiments involving iron corrole complex and cytochromes P-450 mutant CYP 119.[79–80]

After that, a series of chemical and spectroscopic characterizations including mass spectrometry (ESI-MS), Mossbauer spectroscopy, X-ray absorption spectroscopy, electron paramagnetic resonance spectroscopy (EPR), and density functional theory calculation (DFT) on the iron$^{(V)}$-oxo complex $[Fe^{V}(O)(TMAL)]$ has been extensively studied.[81] Another example of iron $^{(V)}$ oxo complex with tetradendated ligand is $[Fe^{v}(O)(OH)(Pytacn)](CF_3SO_3)]^{+}$.

Oxo-hydroxo tautomerism

The oxo-hydroxo tautamerism can contribute to a better characterization and an improved understanding of chemical reactivities of the high valent metal-oxo species. When oxygenation reaction (hydroxylation or epoxidation) occurs in an organic solvents (usually dichlormethane) with hydrophobic metalloporphyrine catalysts, the oxygen atom incorporated within the substrate originated form the oxidant. This has been evident for hypochlorite or iodosylbenzene. But when this metalloporphyrin catalyzed oxygenation occurs in an aqueous solvent (such as metal-oxo species), an oxygen atom is transferred from either the oxidant or from the bulk water. Since the intramolecular exchange metal oxo with bulk water is slow, an intramolecular exchange of labeled oxygen atom via the so called oxo-hydroxo tautomerism has been proposed.[82]

The nature of the reactive intermediate (such as Fe^{IV}-O) involved in catalytic oxygen transfer reactions can be characterized by using ^{18}O labelling and sources (i.e. $^{18}O_2$, $H_2{}^{18}O$ and $H_2{}^{18}O_2$).[83–86] In the free radicals initiated oxidation, the alkyl radicals can be quenched by ^{18}O labelled oxygen molecule at a diffusion controlled rate to give labelled alkyl peroxide radicals. Rearrangement of such radicals leads to ^{18}O incorporated oxidized products, providing support for a radical pathway. When the oxidation is performed using a metal-based oxidant, the ^{18}O-labelled metal-oxo species can be directly generated from the ^{18}O labelled oxygen source (i.e. $H_2{}^{18}O_2$) and can transfer the corresponding ^{18}O into the organic substrates.

Alternatively, metal-oxo species can exchange its terminal oxo moiety with the ^{18}O labelled water (i.e. $H_2{}^{18}O$) through an 'oxo-hydroxo-tautomerism'. A few decades ago, Meunier and co-workers proposed this mechanism initially for heme model.[86] The work suggested that ^{18}O-labeled water trans to metal-oxo moiety would undergo exchange reactions through a symmetric *trans*-dihydroxometal intermediate such as in trans-dihydroxoiron$^{(IV)}$ porphyrin. An alternative oxo-hydroxo tautomerism is the phenomenon to the non-heme iron system. In such tautomerism, the labelled water, which is coordinated to the iron center and adjacent to the oxo group and the oxygen exchange, occurrs via a two-fold symmetric *cis*-dihydroxoiron$^{(IV)}$ transition state .[88] Although the direct measurements of oxygen atom exchange rate between metal-oxo species and the $H_2{}^{18}O$ in enzymes and biomimetic system are sparse, ^{18}O-labelling remains a popular mechanistic tool in providing evidence for the participation of high-valent metal-oxo intermediate in oxygen atom transfer reactions.

1.2. Metal-free catalysis

Metal-free catalysts (organo-catalysts) are often based on sugar, peptides, or amino acids. They can be linked to a solid support easily; and thus, making them useful for industrial applications. The most attractive property of the metal-free catalysts is simply the fact that they are organic molecule. In general, metal-free catalysts are classified as Lewis bases, Lewis acids, Brønsteted bases, or Brønsted acids. The Lewis base catalyst is introduced in a simplified catalytic cycle to initiate the reaction via nucleophilic addition to the substrate; the resulting complex undergoes a reaction that releases the product along with the catalyst for further turnover. The Lewis acid catalysts activate nucleophilic substrates in a similar manner. The Brønsted base and the Brønsted acid catalytic cycles are initiated via a partial deprotonation or protonation, respectively.

TEMPO is one of the most famous and widely used metal-free catalysts in alcohol oxidation. For example, the use of nitroxyl radicals (Figure 1.4) that are derived from TEMPO are combined with inexpensive, safe, and easy to handle terminal oxidants for alcohol oxidation into aldehydes, ketones, and/or carboxylic acids. Generally, the nitroxyl radicals have important applications such as spin labels in biology and as free radical scavengers (inhibitor of free radical chain processes such as auto-oxidation and polymerization).[89] One of the first metal-free catalysts developed by using nitrox radicals was TEMPO/Br_2/$NaNO_2$ and TEMPO/ (TBN).[90–92] 1-Me-AZADO catalyst is a modified form of nitroxyl radicals that is used as a catalyst not only for oxidation of primary and secondary alcohols, but also in oxidative kinetic resolution (OKR) methods of the recovered alcohols.[93]

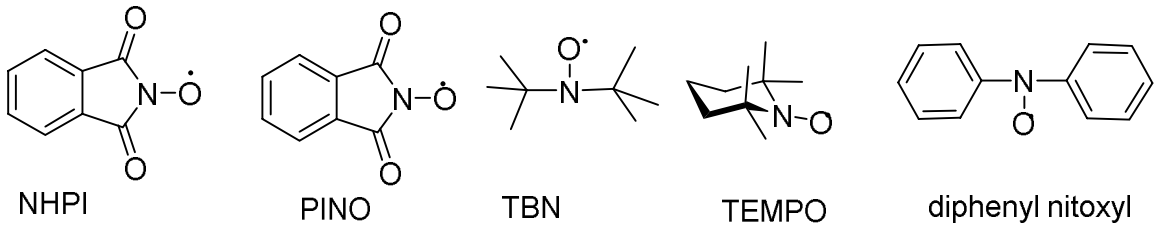
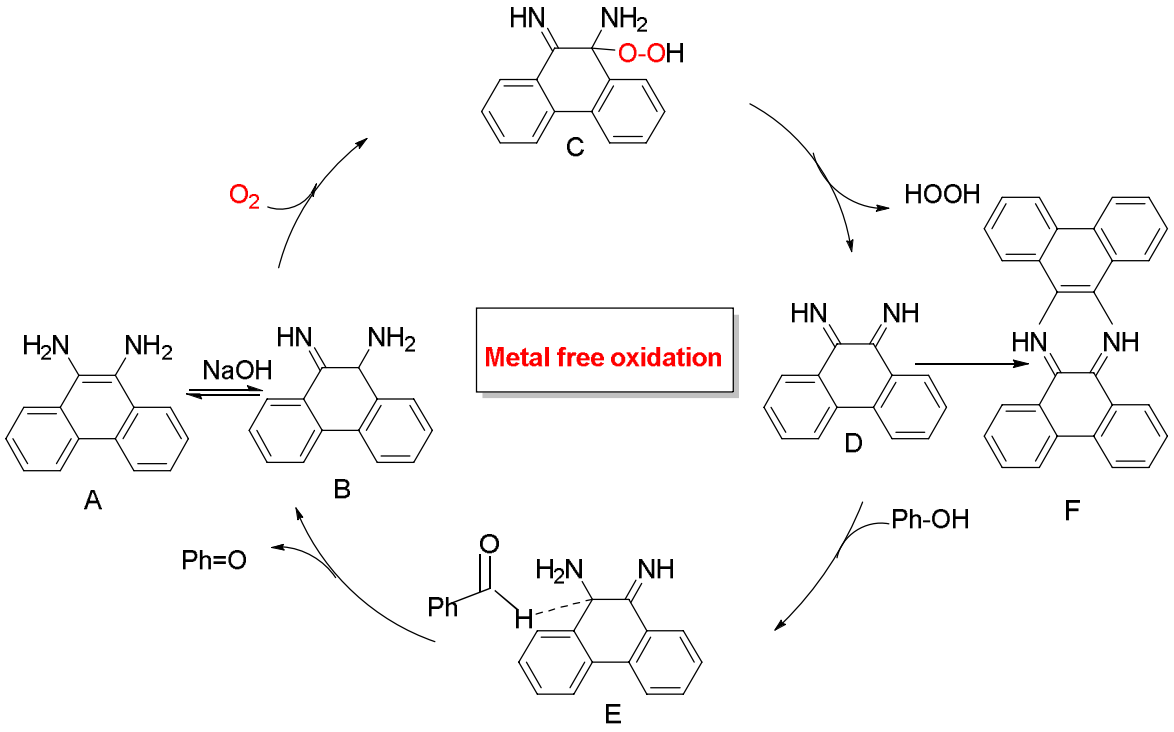


Figure 1.4: Structures of organic nitroxyl radicals.



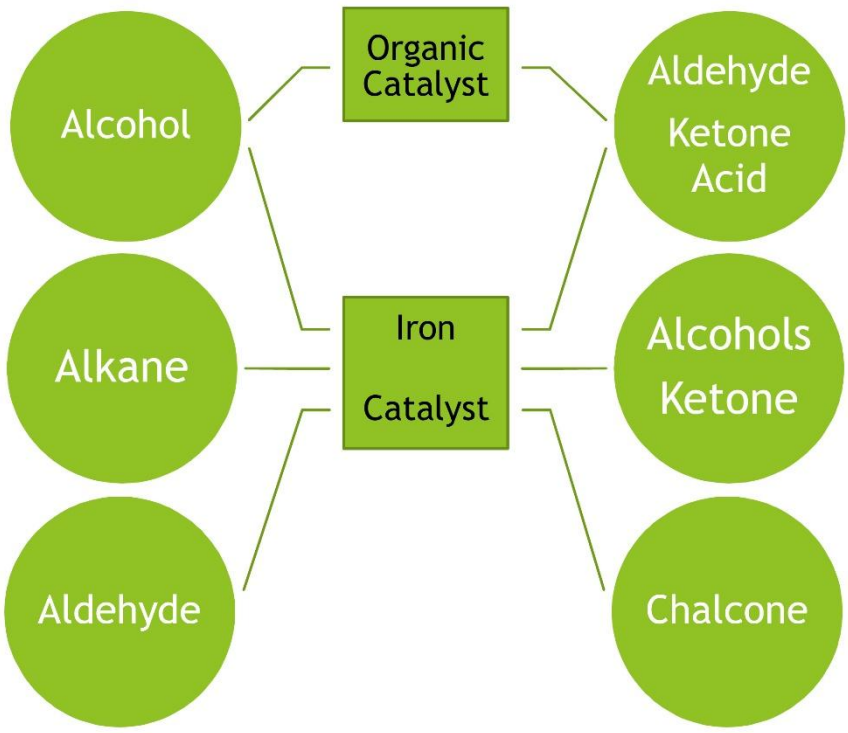
Scheme 1.13: Proposed catalytic cycle for DAPHEN catalyzed alcohol oxidation.

DAPHEN is another example of metal-free catalysts. It has been used previously with copper as a catalyst in the oxidation of veratryl alcohol to veratraldehyde.[94] It also possesses redox–activity and is fully capable of aqueous oxidation catalysis. As an example shown in Scheme 1.13,[95] the imine resonance isomer of DAPHEN provides a reactive H–C bond (**B**) as a metal-free catalyst. In the presence of O_2, it forms a hydroperoxo semi–iminoquinone (**C**) which reacts further to give hydrogen peroxide and an iminoquinone (**D**, 206 m/z). H_2O_2 is formed as a result of the reaction mixture. Iminoquinone is then reduced back to DAPHEN with the help of alcohol in a two–step radical pathway. In this respect, the deactivation of the catalyst by a combination of two molecules of **D**, which eventually resulted in a precipitation of a yellow solid as dimer of DAPHEN. The proposed mechanism shows similarities with flavin based organo-catalytic cycle.[96]

2

Scope of the Thesis

The general goal of this thesis work is to develop new oxidation catalysts that are selective (chemo-, regio- and stereoselective) for different transformations of alcohols, aldehydes, and alkanes (Scheme 2.1). The main features of these catalysts should be: high conversion, stable, inexpensive, and environmental friendly conditions. The catalytic systems developed in this thesis are homogeneous iron and metal-free catalysts .



Scheme 2.1: A general outline that summarizes the catalytic oxidation reactions developed in this thesis.

Keeping this goal in mind, we developed a non-heme iron based complexes that can catalyze a wide variety of alcohols. We also extended their potential utility in challenging applications, such as hydrocarbons C–H bond oxidation and oxidative C–C bond formation. At the same time, we used simple ligands to support the high-valent iron-oxo unit; and thus, characterize and mechanistically investigate these active species in the reaction.

This thesis includes five papers (attached at the end of the thesis) that justify the above mentioned objective. Throughout the course of this thesis, these papers are referred to by their order as **Paper I – V**.

Papers I – II were focused on the oxidation of secondary and primary alcohols by using Fe^{III} based catalysts. In **Paper I**, the catalyst was iron/thymine-1-acetic acid (Fe/THA) that is proven to be efficient system in alcohol oxidation under solvent free conditions when *tert*-butylhydroperoxide (TBHP) is used as an oxidant. In **Paper II** we used an iron/phenanthroline complex as a convenient and efficient catalyst for the oxidation of benzylic and aliphatic primary and secondary alcohols by using hydrogen peroxide as a terminal oxidant.

Paper III was focused on the implementation of a metal-free catalyst (organocatalyst) concept for secondary alcohols in combination with molecular oxygen or peroxides as an emerging alternative to the traditional procedures. Here the metal-free catalyst was 1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA) and *t*-BuOOH was the terminal oxidant.

The results found from the alcohols oxidation in **paper I** prompted further studies along the oxidative activation of aliphatic C–H bonds. Therefore, the same iron-based catalyst (Fe/THA) was used in **Paper IV** for the oxidation of alkanes C–H bonds when H_2O_2 was used as a terminal oxidant.

In **Paper V**, an iron-based catalyst (iron/N-methylimidazole) was used in the C–C bond formation via the reaction between benzaldehydes and styrenes by using TBHP as an oxidant. The cross-dehydrogenative coupling (CDC) reaction by this system produced α,β -unsaturated ketones (Chalcones).

3

Experimental

We developed three iron-based catalysts and one metal-free catalyst (organocatalyst). The iron based catalysts were iron/thymine-1-acetic acid (Fe/THA), iron/Phenanthroline complex, and iron/N-methylimidazole whereas the metal-free catalyst was 1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA). The chapter is dedicated to describe the synthesis and the characterization of the iron based systems.

Before the NMR (^{1}H and ^{13}C) analysis, all solvents (were distilled by employing appropriate drying agents. In addition to the NMR, we also used ESI^{+} TOF-MS, EI-MS, GC-MS, and chiral-HPLC in the analysis of products and catalyst species.

All organic reagents were purchased from Acros Organics, Sigma-Aldrich or Strem and purified by applying conventional methods. The detailed information about the purification of the solvents, peroxides and starting materials, synthesis of catalysts, analyses, as well as metal-free oxidation and oxidation procedures can be found in the "Experimental Part" of the attached original publications (**Papers I – V**).

3.1. Iron/thymine-1-acetic acid (Fe/THA) synthesis and characterization

This research started on early 2009 with the aim to find new iron catalyst that works in benign conditions. At that time, many synthetic complexes and enzymes, with various transition metals had been developed at their reactive core. The experimental work included the development of an efficient and selective iron-based catalyst system to be used in the oxidation of primary and secondary alcohols.

Fe/THA complex

A solution of $FeCl_3 \cdot 6H_2O$ (83.8 mg, 0.31 mmol) in methanol (5 mL) was added to a thymine-1-acetic acid (117 mg, 0.63 mmol)/NaOH(0.63mmol) methanol solution (10 mL). The reaction mixture was stirred for 1 h at 50 ^oC after which diethyl ether was added and a yellow precipitate formed gradually. The crude product was separated by centrifugation and washed twice with diethyl ether (2×40 mL). The product was obtained as a light yellow powder (65% yield). IR (solid): $\bar{\upsilon}$=3160.2, 2906.3, 2851.95, 1711.28, 1612.36, 1449.67, 1408.71, 1351.82, 1326.23, 1230.35, 781.25, 740.19, 595.62 cm^{-1}; ESI-MS: *m/z* = 457.9908 {$[M+H]^+$,calc. 457.992}; solution magnetic moment (Evans' method): μ_{eff}=1.65 B.M.

ESI-MS measurements of the complex

The ESI-MS analysis of the in-situ prepared catalyst solution in MeOH did not show any free ligands. But a prominent ion peak at m/z = 457.99 was assigned for the protonated complex $[Fe(THA)_2Cl]H^+$. A second prominent peak appeared at m/z = 493.96, which was assigned for $[Fe(THA)_2(Cl)_2]^+$ with THA coordinates as a neutral ligand according to the isotope analysis.

3.2. Iron/phenanthroline synthesis and characterization

This complex was synthesized by adding 1,10-phenanthroline into $FeCl_3$ (2:1 molar ratio) in acetic acid/water medium (60/40 v/v). Ammonium ceric nitrate (1 mole) was added into the reaction solution to keep iron in +3 oxidation state. Red colored crystalline hexacoordinated mononuclear complex $[Fe(phen)_2(Cl)_2]NO_3$ was then obtained with a good yield.

The complex was sufficiently stable in air as well as in the presence of moisture. The IR spectrum revealed an interesting sharp and intense band at 1384 cm^{-1}, which reflects the presence of ionic nitrate. The υ(C=N) stretching vibrations of the metal bond 1,10-phenanthroline were observed at 1517 (s) and 1426 (s) cm^{-1}. All other characteristic ligand vibrations were observed between 1600 cm^{-1} and 600 cm^{-1}.

3.3. Iron/N-methylimidazole synthesis

This complex was synthesized by adding *N*-methylimidazole (NMI) into $FeBr_2$ (6:1 molar ratio). The mixture was stirred at room temperature for few hours. A light white

colored crystalline was obtained in a octacoordinated mononuclear complexation of $[Fe(NMI)_6]Br$. The X-ray analysis revealed that the iron(II) complex has NMI as a only ligand and both Br^- anions are shifted to the outer coordination spheres (Figure 3.1).

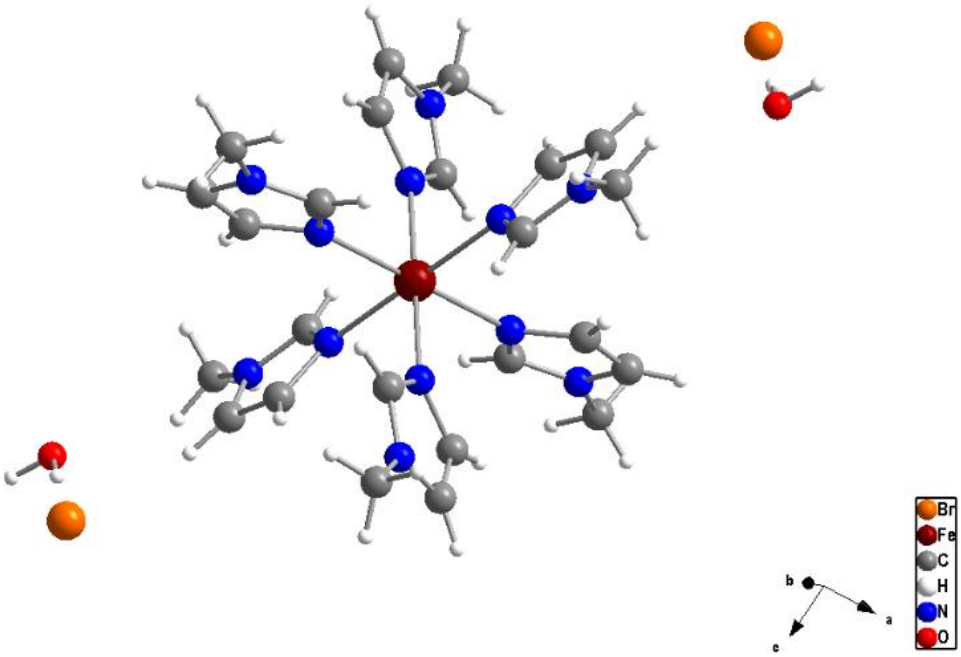


Figure 3.1: A Solid state structure of $Fe(NMI)_6Br_2 \cdot 2H_2O$ which crystallized out from the catalyst solution.

4

Results and Discussions

4.1. Iron/thymine-1-acetic acid (Fe/THA) applications

The Fe/THA system was tested in oxidation of various substrates. Alcohol oxidation perhaps is the most widely used class of oxidation reactions in organic chemistry. Many reagents and catalysts are found for these transformations, but the development of practical benign oxidation methods remains a challenging fact. Therefore, we began our application of this catalyst in oxidizing primary and secondary aliphatic alcohols into their corresponding carbonyl compounds, acids and ketones; even diols are converted to the corresponding acids in mild reaction conditions (**Paper I**). Afterwards, the same system was tested in oxidative alkane activation (**Paper IV**).

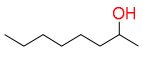
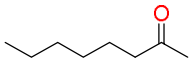
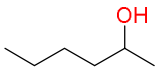
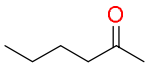
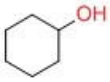
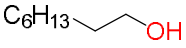
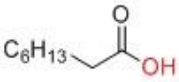
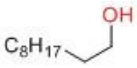
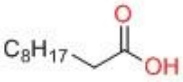
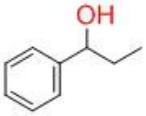
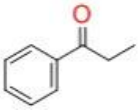
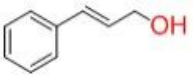
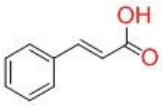
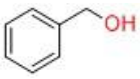
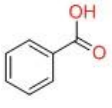
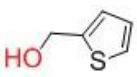
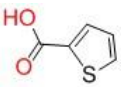
4.1.1. Fe/THA catalyzed alcohol oxidation

The experiments focused on the development of a selective iron-based catalyst for the formation of ketones and carboxylic acids from their corresponding alcohols. This particular reaction is very important and has applications in fine chemical industry (see the introduction section). In order to explore the reactivity and selectivity of the Fe/THA catalyst, 2-octanol was used as a model substrate. Under solvent free conditions, the catalyst converted the substrates such as 2-octanol to 2-octanone with 91.5% isolated yield. Subsequently, various iron precursors were evaluated in solvent free conditions. A control experiment in the absence of Fe/THA complex confirmed the crucial role of iron in this system to oxidize alcohols (**Paper I**).

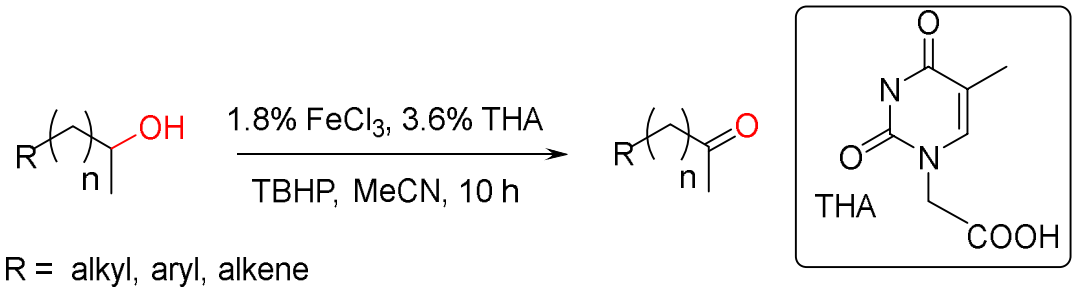
When the optimized conditions were obtained, we tested the efficiency of the in situ-generated Fe/THA in solvent-free conditions to oxidize various secondary and primary alcohols (Scheme 4.1 and Table 4.1). For example, α,β- unsaturated primary alcohols (such as allylic and benzylic alcohols) can be selectively oxidized to the corresponding carboxylic

acids with excellent yields. Similarly, saturated primary alcohol (such as 1-octanol and 1-decanol) produced their corresponding acids with good yield. In addition, the catalyst was capable to oxidize primary aliphatic alcohols into carboxylic acids with very good yield. Furthermore, secondary alcohols were also oxidized to the corresponding ketones with excellent yields (Table 4.1, entries 1-4). Not only sterically hindered secondary alcohols, but also secondary benzylic alcohols (such as phenyl propanol, entry 7) gave almost 100% quantitative yields. Interestingly, 2-thiophenemethanol (entry 10) was also oxidized to give the corresponding acid with a high yield.

Table 4.1: Oxidation of various alcohols with TBHP catalyzed by Fe/THA. [a]

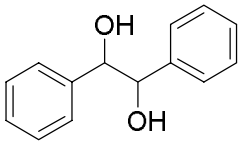
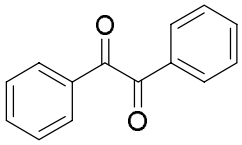
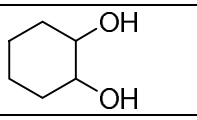
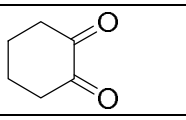
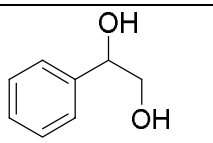
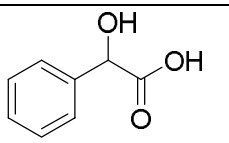
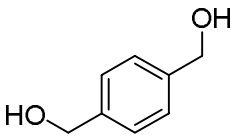
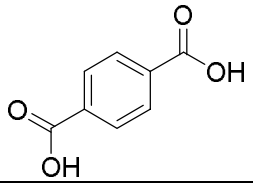
Entry	Substrate	Product	Time	Yield
1			16	99
2			16	91
3			3	94
4			3	70
5 [b]			16	89
6			16	93
7			3	95
8 [b]			6	85
9 [b]			3	98
10			3	74

[a] Reaction conditions: substrate (2.6 mmol), $FeCl_3$ (1.8 mol%), THA (3.6mol%), TBHP (80% solution in decane, 6.5 mmol). [b] The amount of catalyst is 1.5 mol%.



Scheme 4.1: Alcohol oxidation using in-situ Fe/THA complex

Table 4.2: Diol oxidation using in-situ Fe/THA complex. [(a)]

Entry	Substrate	Product	Conversion[%]
1 [(b)]			76
2 [(b)]			80
3 [(a)]			96
4 [(a)]			71

[(a)] Reaction conditions: 2.4 mmol of alcohol, 2.0 mol% of catalyst, 2.5 eq. TBHP, 80 °C for specific time. [(b)] 3 mol% catalysts. The selectivity and the conversion were determined via GC-MS.

Following the success of primary and secondary alcohol oxidation, the catalyst was tested to oxidize a series of diols to acids (Table 4.2). For example, internal vic-diols (such as diphenyl ethandiol) as well as cyclic vic-diols (such as 1,2-cyclohexandiol) were selectively oxidized to diketones with good yields (Table 4.2, entries 1 and 2). Intriguingly, 1-phenyl-1,2-ethanediol was cleanly converted to phenylglyoxylic acid.

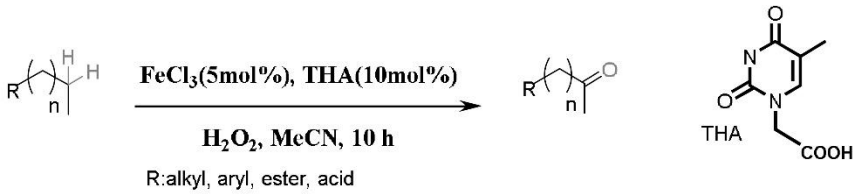
4.1.2. Fe/THA catalyzed alkane oxidation

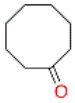
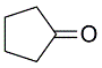
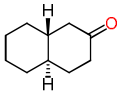
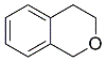
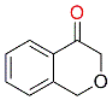
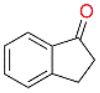
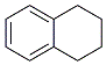
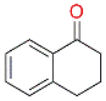
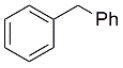
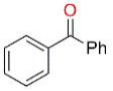
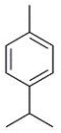
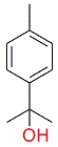
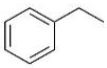
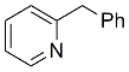
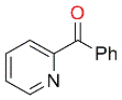
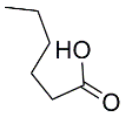
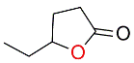
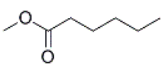
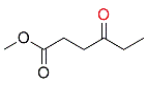
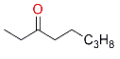
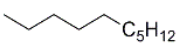
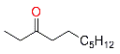
After being an efficient catalyst in alcohol oxidation, we tested the possibility of using Fe/THA in more challenging applications such as C–H oxidation. While screening the solvent effect (such as hexane), the catalyst not only oxidized the alcohols, but also oxidized the solvent residue. Therefore, we investigated the activation of aliphatic C–H bonds (**Paper IV**). After obtaining the optimized conditions, we investigated the substrate scope in these conditions using H_2O_2 as a terminal oxidant. To our delight, a variety of cyclic alkanes were oxidized to ketones with good to excellent yields (Table 4.3 entries 1 and 2).

In the oxidation of *trans*-decalin, the preferential oxidation was observed at a secondary site instead at a tertiary site (Table 4.3 entry 3). In fact, the *trans*-decalin contains sterically more protected tertiary C–H bonds. This leads to a largely dominant secondary site oxidation. Further on, π-activated C–H bonds (both tertiary and secondary ones) were also oxidized with good to excellent conversions and with excellent selectivity (Table 4.3 entries 4–9). As an example, ethylbenzene was oxidized to acetophenone with a high yield. Meanwhile 2-benzylpyridine gives lower yields presumably due to coordination of pyridine to the iron center (Table 4.3 entry 10).

We also investigated the effect of electron-withdrawing groups on the site selectivity of oxidation by using simple substrates (Table 4.3 entries 11 and 12). The carboxylate group on the substrate (such as 4-methylvaleric acid) directed the C–H oxidation site towards a remote site (up to four carbons away from the carboxylic group). Consequently, a five-membered lactone ring was formed and also a terminal ester group formed a ketoester at C_4 as major products. Surprisingly, in the absence of directing groups, aliphatic hydrocarbons (such as *n*- octane and *n*-decane) were oxidized into ketones in a normalized mixture of C_3:C_2:C_4 (8:5:1) with a high combined yields. This indicates that C_2 and C_3 are more reactive than C_4 under these conditions. However, a slight preference towards the oxidation of C_3–carbon was observed (Table 4.3 entries 13 and 14). Very limited examples with similar selectivity can be found in the literature.[41]

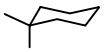
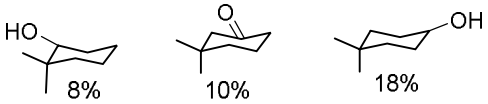
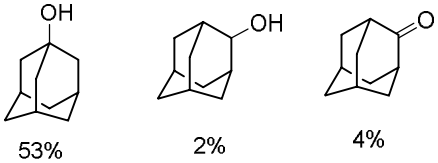
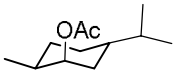
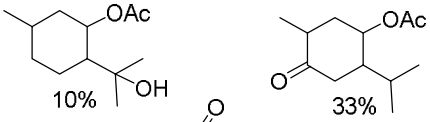
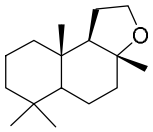
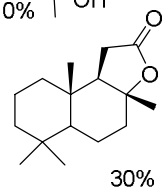
Table 4.3: Oxidation of substituted aliphatic alkanes.[a]



Run	Substrate	Main product	Time [hr]	Yield [%] [b]	Main Product (%): (Isolated Yield) [c]
1			10	86	68:(65)
2			8	83	83
3			10	46	25
4			2	98	98:(94)
5			10	67	67
6			8	80	80:(70)
7			7	95	95:(91)
8			4	89	85
9			6	91	90:(88)
10			10	60	59
11			12	70	63
12			7	72	59
13 [c]			12	68	37
14 [c]			12	62	35

[a] Reaction conditions: substrate 2.0 mmol, iron(III) chloride 5 mol%, THA 10mol%, H_2O_2 6.5 mmol (70% solution in water), MeCN 2 mL and temperature 78 °C. The results were collected via GC-MS (all experiments were repeated at least 3 times). [b] Total yields of all products determined by GC-MS and ^1H NMR using dichlorobenzene as an internal standard [c] The normalized $C_2/C_3/C_4$ selectivity ratio (5:8:1).

Table 4.4: Oxidation of substituted aliphatic alkanes.[(a)]

Entry	Substrate	products yields	Yield [%][b]
15			33
16			36
17			59
18			43
19			30

[(a)] Reaction conditions: substrate 2.0 mmol, iron(III) chloride 5 mol%, THA 10mol%, H_2O_2 6.5 mmol (30% in water), MeCN 2 mL and temperature 60°C. [(b)] The results were collected via 1H NMR using dichlorobenzene as an internal standard and GC-MS (all experiments were repeated at least 3 times) and all products were identified by comparison of their analytical data with those of previous reports or commercial materials.

To assist the selectivity of our iron-based catalyst, the oxidation of substituted cycloalkanes with different 2º and 3º C–H bonds were further investigated (Table 4.4). Several mono and di-substituted cyclohexane derivatives were employed for that purpose. For example, the reactivity of 1,1-dimethylcyclohexane and *tert*-butylcyclohexane were investigated by using that protocol (Table 4.4 entries 15 and 16). For *tert*-butylcyclohexane, the oxidation was observed at the C_3 carbons (3:1 ratio to C_2 carbons). For 1,1-dimethylcyclohexane, the oxidation occurred selectively at the C_3-carbon. Noteworthy, oxidation of the primary carbon was not observed in any of those substrates. Furthermore, the catalyst showed a preferential oxidation to the more accessible secondary site when sterically crowded tertiary C–H bonds were hindered. For adamantane, tertiary C−H bonds were more preferred than the secondary ones (Table 4.4 entry 17). A high ratio of tertiary/secondary C–H bond activation indicates the involvement of highly selective metal centered oxidant. Interestingly, when we tested the catalyst for the oxidation of terpenoid (-

) ambroxide as substrates, which contains two tertiary C–H sites and 14- methylenic sites (Table 4.4, entry 19), the activated methylenic C–H bonds adjacent to the ether moiety were preferentially oxidized (by using 3mol% of catalyst) to sclareolide with moderate yield.

In general, the catalyst prefers tertiary C−H bonds over secondary ones, but the presence of steric congestion can alter the order. Without tertiary C–H bonds the oxidation occurs selectively on secondary C–H bonds at the C_3 and C_2 position as shown with the substituted cyclohexane substrates.

4.1.3. Mechanism prospective

In order to understand the mechanism pathway of the Fe/THA system, we used H_2O_2 as an oxidant and performed several control experiments: kinetic studies, oxygen labelling (^{18}O), kinetic isotopic effect (KIE) studies, and ESI-MS measurements. These experiments were performed from the catalyst solution during the oxidation reaction.

Kinetic studies: A series of substrates were used to study the reaction rate. The catalyst decay followed first-order kinetics with k_{obs} values were linearly dependent on substrate concentration in all cases. This permits us to define the comparable second-order rate constants k_2 (Figure 4.1).

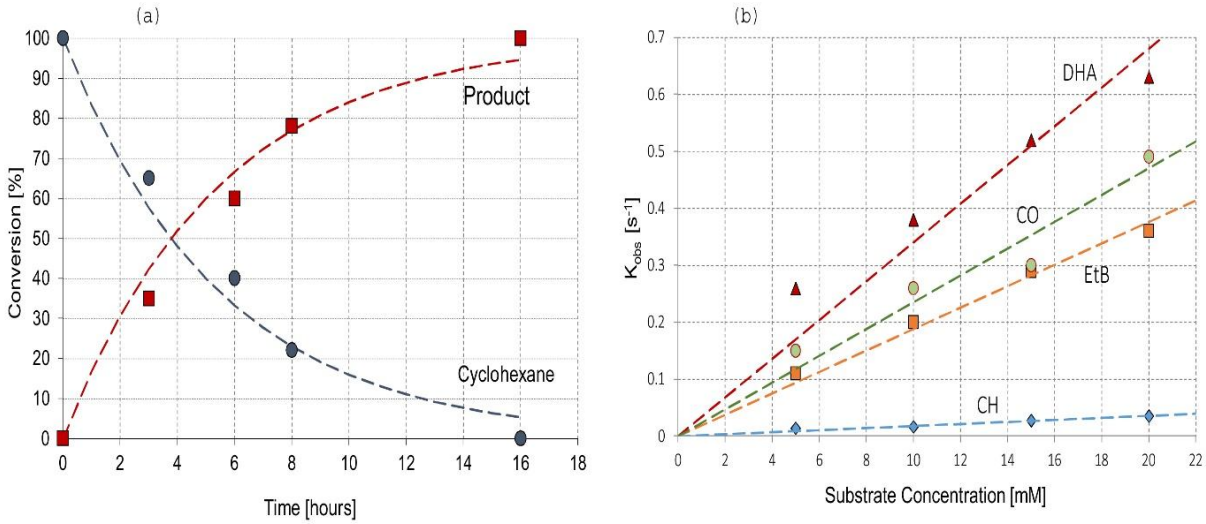


Figure 4.1: (a) Conversion of hexane oxidation (pseudo 1st order kinatics) and (b) Pseudo 1st order oxidation rate constants, k_{obs} [s^{-1}], in CH3CN at 40°C. This is shown for different substrates: 9,10-dihydroantrance (▲, DHA, $k_2 = 3.4\times10^{-2}$ s^{-1}), cyclooctane (x, CO, $k_2 = 2.4\times10^{-2}$ s^{-1}) , ethylbenzene (■, EtBz, $k_2 = 1.9\times10^{-2}$ s^{-1}), and cyclohexane (♦, CH, $k_2 = 1.8\times10^{-3}$ s^{-1}). Reaction conditions: [$FeCl_3(THA)_2$] = 1 mM and [substrate] = 5–30 mM.

^{18}O labeling: Experiments of ^{18}O labeling were used to deduce whether the peroxide O–O bond cleavage occurs prior to the attack of substrates by establishing the source of oxygen atoms incorporated into the products (kindly see introduction section). Cyclohexane was used as a model substrate in this experiment. First the oxidation reaction was carried out in presence of $H_2{}^{18}O$ by using H_2O_2 as a terminal oxidant. The composition of cyclohexanol was then determined from the relative abundances of the peaks at m/z=100 (^{16}O) and 102 (^{18}O) in GC-MS. After 5 min reaction time, 34% of the cyclohexanol product is ^{18}O-labeled. Furthermore, when the oxidation was done in the presence of $H_2{}^{18}O_2$, 42% of the oxygen atoms in the cyclohexanol were ^{18}O-labeled. The results support the mechanism where the iron-oxo species was formed via water-assisted heterolysis of the O–O bond, and the carbonyl bond formed via either the oxygen from H_2O_2 or the oxygen from H_2O.

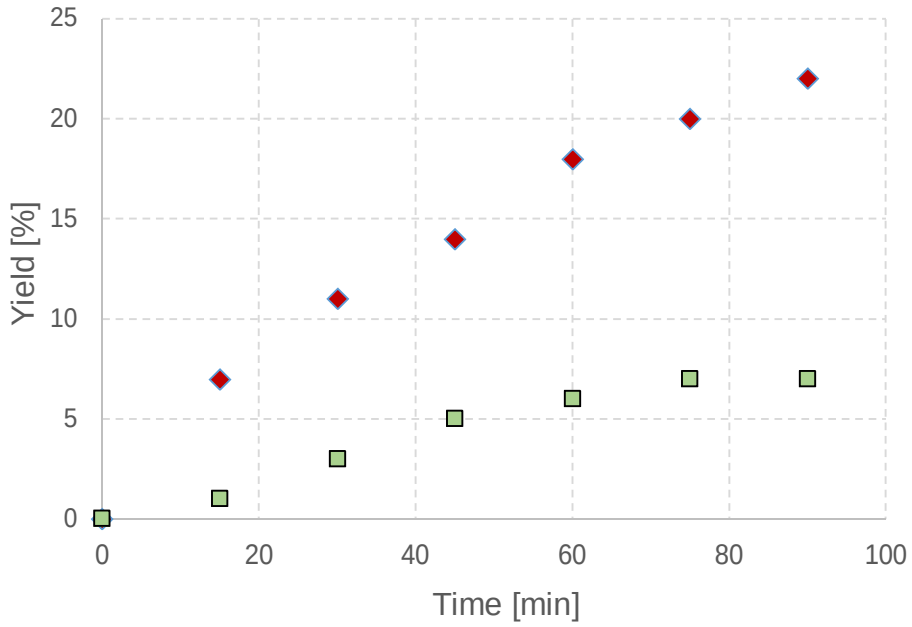


Figure 4.2: Catalytic oxidation yield of c-C_6H_{12} (◊) and c-C_6D_{12} (□).

Kinetic isotopic effect studies (KIE): We performed the kinetic isotopic effect (KIE) studies in order to gain further insight into the mechanism of the reaction and nature of the active species. The determination of intramolecular (KIE) for cyclohexane and [D_{12}]-cyclohexane is a useful method to evaluate the capability of oxidant to discriminate alkanes with different bond strength. The oxidation rate of C_6D_{12} is significantly lower relative to C_6H_{12}. This indicates that H-atom abstraction is an important component of the rate determining step (Figure 4.2). The pseudo-first-order rate constants (k_{obs}) for c-C_6H_{12} and c-C_6D_{12} are 2.26×10^{-2} s^{-1} and 1.15×10^{-2} s^{-1}, respectively. Plotting log(k_2') against the C–H bond

dissociation energy (BDE) of various substrates deduced a linear relation, which indicates that iron-oxo assisted H-atom abstraction as the rate-determining step for the oxidation (Figure 4.3). The linear relation (with a slope -0.12) is comparable to previously reported hydrogen abstraction reactions values mediated by iron catalysts.

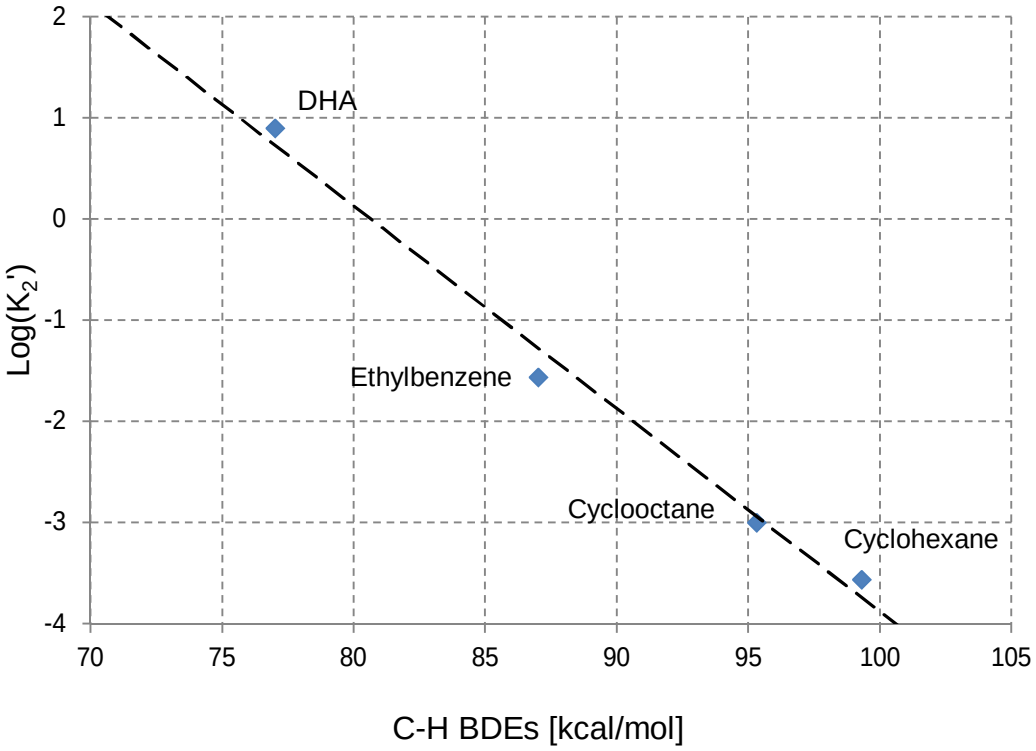


Figure 4.3: K_2' against alkanes C-H BDE in MeCN at 296 K.

In summary, the ESI-MS measurement as well as the kinetic studies confirm the presence of high-valent Fe species, where the iron-oxo species were formed via water-assisted heterolysis of O–O bond. High-valent iron-perxo species were also generated from low spin Fe(III) complex with H_2O_2 as a terminal oxidant. A rapid exchange of FeOOH oxygen atom with $H_2{}^{18}O$ followed a mechanism in which an exogenous water molecule assisted the hydrogen transfer from the coordinated water molecule to the oxo group.

4.2. Iron/phenanthroline catalyzed alcohol oxidation

N-containing ligands, oligopyridine derivatives (such as 2,2'-bipyridine, 1,10-phenanthroline, and 2,2':6',2''- terpyridine) have been given a substantial interest in recent years. Due to the combination of some distinct structural and chemical properties, iron complexes with phenanthroline and phenanthroline-based ligands have been actively studied

for the purpose to better understand their catalytic, redox, photochemical, and photophysical properties.

In order to develop an approach for green oxidation, which involves eco-friendly iron(III) and hydrogen peroxide as terminal oxidant, iron/phenanthroline ($[Fe(phen)_2Cl_2]NO_3$) was used as a catalyst in the oxidation of primary and secondary aliphatic alcohols by using buffer as a solvent (**Paper II**).

The performance of $[Fe(phen)_2Cl_2]NO_3$ in the presence of different oxidants and solvents was investigated by using benzyl alcohol as a model substrate. The combination of an iron complex with molecular oxygen (or hydrogen peroxide) as a terminal oxidant is ideal for green oxidation. This is because iron is generally a very abundant element and less toxic. Furthermore, only H_2O (or basically no toxic waste) is generated from these catalytic reactions. The system worked smoothly with H_2O_2 as an oxidant with short reaction time. As previously reported, a carefully controlled pH solution in iron based oxidation catalysis enhances the selectivity of the target product whether aldehyde or acid.[97] Therefore, acidic aqueous buffer solution (pH = 1) was used as a solvent and indeed both conversion and selectivity of the desired aldehyde product increased without acid formation (Table 4.5).

Table 4.5. Benzyl alcohol optimization of the catalytic system

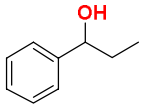
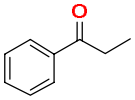
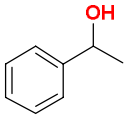
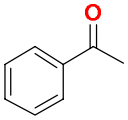
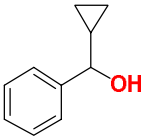
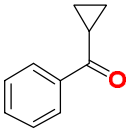
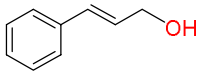
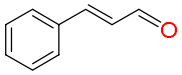
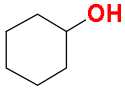
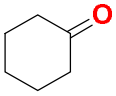
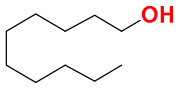
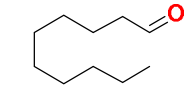
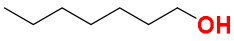
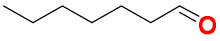
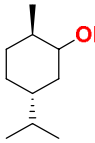
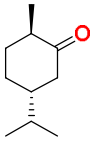
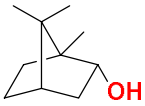
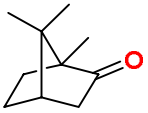
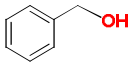
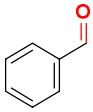
Entry	Solvent	Oxidant	ald:a cid ratio	Conversion [%] [(a)]
1	MeCN	TBHP	10:01	88
2	Toluene	TBHP	10:01	41
3	Alkaline water	TBHP	10:1.4	60
4	MeCN	O_2	10:1.6	8
5	Toluene	O_2	10:03	13
6	Alkaline water	O_2	10:01	24
7	MeCN	H_2O_2	10:01	65
8	MeCN/Acetic acid	H_2O_2	10:03	72
9	Buffer (pH = 1)	H_2O_2	10:0.1	98
10	Buffer (pH = 2)	H_2O_2	10:02	90
11	Buffer (pH = 4)	H_2O_2	10:03	60
12	Buffer (pH = 1)	TBHP	2.5:10	90
13	Buffer (pH = 1)	O_2	10:1	16

[(a)] Conversion were determined by GC analysis; average of 2 runs.

Using the optimized conditions, benzylic, aliphatic primary and secondary alcohols were oxidized (Table 4.6). This methodology can be also applied to more steric compounds (such as endo-fenchyl alcohol, menthol or cyclopropyl-phenyl-methanol) were oxidized to the desired carbonyl compounds with moderate to very good yields (35–98%) and during a

short reaction time. Interestingly, the system is compatible with allylic alcohols, as the system was able to oxidized allylic alcohols to their corresponding aldehydes without epoxide formation. Also iron-catalyzed hydrogen peroxide oxidation of allylic alcohols has rarely been reported, presumably due to the competitive side reaction leading to epoxide.

Table 4.6: Oxidation of alcohols to aldehydes using iron/phenanthroline complex.[a]

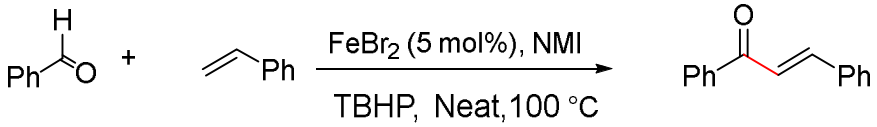
Entry	Substrate	Product	Time [min]	Yield [b] [%]
1			30	95 [c]
2			60	96
3			60	93
4			60	91
5			120	73
6			60	65
7 [b]			60	62
8			120	65
9			120	69
10 [b]			30	98 [c]

[a] Reaction conditions:1mmol substrate,1.5 mol% catalyst, 2.2 equiv. H_2O_2 and buffer solution pH=1. [b] Conversion and yield were determined by GC using decane as internal standard, and ^{1}H NMRspectra analysis; average of 2 runs. [c] Isolated yield.

4.3. Oxidative chalcone formation by using iron/*N*-methylimidazole

We tested the possibility to generate new C–C bonds via simple iron catalyst system and using two nucleophiles as substrates. A new α,β-unsaturated ketone was formed by using unfunctionalized substrates (Scheme 4.2). A wide variety of naturally occurring and

synthetic compounds that exhibit extraordinary biological and pharmaceutical properties (e.g. anticancer, anti-inflammatory, antioxidant, antimicrobial) possess an α,β-unsaturated ketone core structures as explained in the introduction chapter. Various methods for chalcone synthesis have been reported. However only few involves direct catalytic oxidative coupling between aldehydes and alkenes.

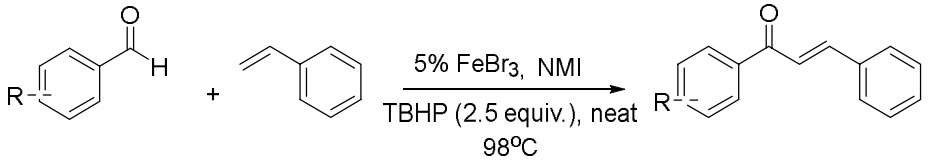


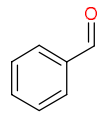
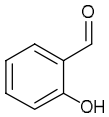
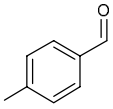
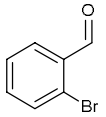
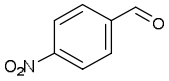
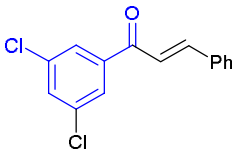
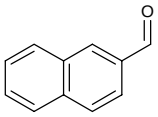
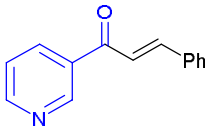
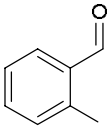
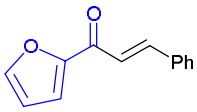
Scheme 4.2: Iron catalyzed unsaturated ketones formation from styrenes and aldehydes.

The reaction conditions were optimized using 4-methylbenzaldehyde and styrene as model compounds in the presence of several metal precursors, solvents, and different oxidants. Interestingly, iron(II) bromide in the presence of TBHP showed good yield for *E*-chalcone and further change of the reaction solvent to pyridine improved the yield up to 69%, which led us to study the other coordinative bases. To our delight *N*-methylimidazol showed the highest reactivity among all bases tested (see original article) Replacing TBHP with H_2O_2 furnished chalcone in a low yield due to the higher stability of t-butyl peroxide. Control experiments in the absence of an iron precursor and with Pd(II) and Cu(II) yielded 0 and 10% conversions, which confirms the crucial role of iron in the C–C coupling. An effect of iron purity was also studied; and as a result, iron precursors with 98 and 99.996% purity gave practically the same activity.

With the optimized conditions (5 mol% catalyst, 2 equiv. TBHP, 100 ^{o}C, NMI 20 mol%, and solvent free conditions), the scope of the Fe-catalyzed C–C coupling reaction was investigated with a variety of aldehydes. The reactivity of various electron deficient and electron-rich aldehydes were also examined (Table 4.7). Electron-donating groups in *ortho*- and *para*-positions enhanced the reaction and afforded the corresponding chalcone products with 25–85% yields. Interestingly, reactions performed with electron-deficient aldehydes gave the desired products but with lower yields (Table 4.7, entries 7-8). Heterocyclic aldehydes such as pyridine-2-carboxaldehyde, and furfural aldehyde were also compatible with the reaction conditions affording the desired α,β–unsaturated ketones in moderate yields without significant side reactions (Table 4.7, entries 9-10). These substrates are considered difficult to utilize for transition metals based oxidation reactions because of their strong coordination ability and susceptibility to oxidation.

Table 4.7: Iron catalyzed direct alkenytion of various aldehydes.[(a)]

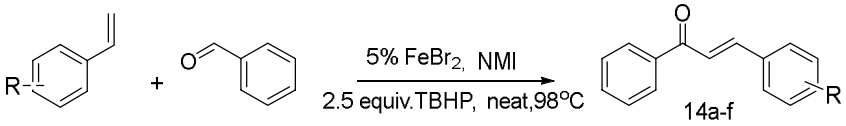


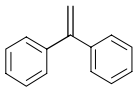
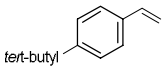
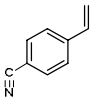
Entry	Substrate	*T* [hr]	Conversion [%]	Entry	Substrate	*T* [hr]	Conversion [%]
1		16	70	6		16	80
2		16	77	7		20	37
3		16	55	8		20	25
4		20	88	9		16	48
5		16	75	10		12	33

[(a)] Reaction condition: styrene (2 mmol), aldehyde (1.0mmol), TBHP (1.0 mmol, 80% in aqueous solution), [$FeBr_2$] (0.05 mmol), NMI (0.1mmol), 98°C, 12 h, Yields is determined by GC and ^1H NMR with CH_2Cl_2 as the internal standard.

Encouraged by these promising results, the substrate scope with styrene derivatives and benzylic aldehyde were also tested (Table 4.8). *Para*-substituted styrene derivatives afforded the desired products in good yields entries 1-3. Intriguingly, α-substitution on the styrene double bond did not affect the reactivity. For example, α-methylstyrene and 1,1-diphenyl methylene coupled with benzylic aldehydes with 72 % and 79% yields (Table 4.8, entries 4 and 5).

Table 4.8: Iron catalyzed direct C-C of various styrene. [a]



Entry	Substrate	*T* [hr]	Conversion [%] [b]	Entry	Substrate	*T* [hr]	Conversion [%] [b]
1		16	60	4		16	72
2		16	68	5[b,d]		16	75
3		16	75	6		16	70

[a] Reaction condition: styrene (2.0 mmol), aldehyde (1.0 mmol), TBHP (1.0 mmol, 80% in aqueous solution), [$FeBr_2$] (0.05 mmol), NMI (0.10 mmol), 98°C. [b] Yields is determined by ^1H NMR with CH_2Cl_2 as the internal standard. [c] 15% diphenyl ketone as byproduct.

To gain insight into the mechanism, we isolated an iron complex that formed in the catalyst solution. The reaction of $FeBr_2$ with an excess amount of *N*-Methylimidazole gave a [$Fe(NMI)_6$] complex as pale yellow crystals. The solid state structure revealed an octahedral coordination sphere wherein iron(II) has six NMI ligands and both Br^- anions are shifted to the outer coordination sphere (Figure 3.1). The complex (5 mol%) was employed as a pre-catalyst for the synthesis of chalcone (70% yield); and thus, oxidant species were thought to be generated via complex in catalyst solution. Furthermore the kinetic progress of the $FeBr_2$-catalyzed coupling between styrene and benzaldehyde was monitored by initial-rate method. The kinetic data disclosed a first order dependence of the rate on p-substituted styrene and pseudo-second-order dependence on [$FeBr_2$]. These results reveal that binuclear iron species were involved in the catalytic reaction (rate constant $k_{obs} = 1.15\times10^2\ s^{-1}$ (Figure 4.4). Moreover, to assess the nature of charge development in transition state of the reaction, a Hammett study was conducted with a series of *para*-substituted styrene derivatives (4-$XPhCH_2CH_2$, where X = CN, CH_3, $(CH_3)C$, or H). A ρ value of -1.53 indicates that the coupling of styrene with aldehyde catalyzed by Fe(II) proceeds through a polar transition state with charge transfer from the substrate to an iron species. Electron-releasing groups were found to promote the cleavage of the O–O bond in the homolysis of $Fe^{(III)}(OOR)$ intermediates.

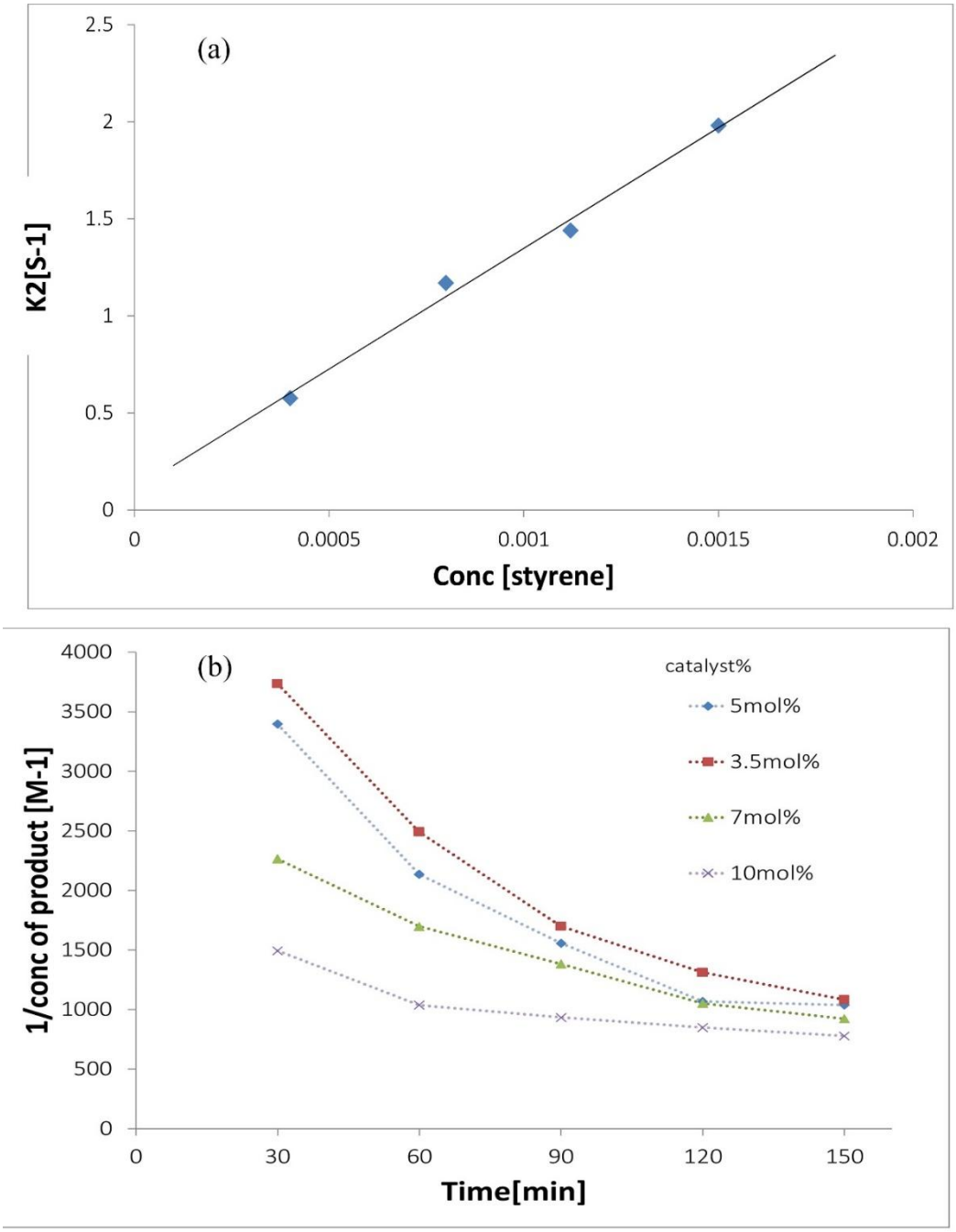


Figure 4.4: Catalyst mol% effect plot of 1/conc of chalcone vs. time.

Iron salts are known catalysts for the decomposition of *t*-BuOOH to radicals, which can further mediate reactions by hydrogen-atom transfer (HAT) or by single-electron transfer (SET). Assuming the intermediacy of radical species, a control experiment with 2,6-di-*tert*-butyl-4-methylphenol (BHT; 3 equiv.) as a radical scavenger was performed. As a result, chalcone was formed with lower yield indicating the presence of a radical mechanism

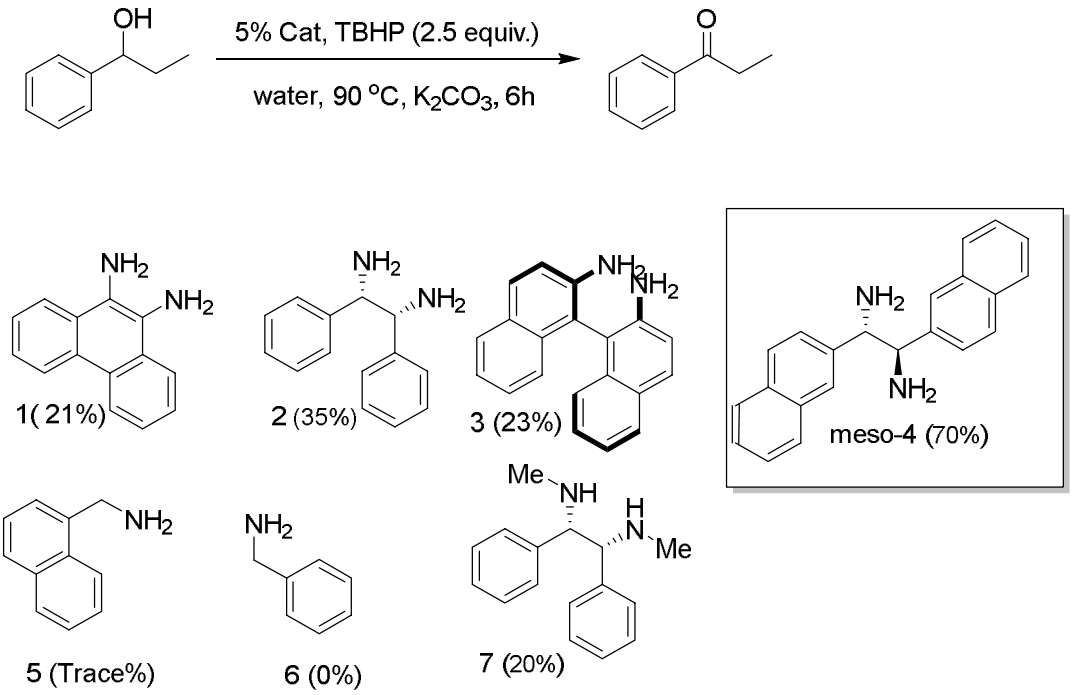
Although the HAT mechanism cannot be excluded, the kinetic and mechanistic studies described above suggest that the reaction proceeds mainly via the SET pathway wherein TBHP oxidizes Fe(II) species to Fe(III) species and the subsequently generated *t*-BuO radical abstract hydrogen from the aldehyde. In turn, the resulting acyl radical adds to styrene and forms a benzyl radical. Next, one-electron oxidation of the benzyl radical by Fe(III) species leads to a benzyl cation and the subsequent deprotonation gives the desired α,β-unsaturated ketone.

4.4. Organocatalyzed alcohol oxidation

Part of our research interest is the implementation of a metal-free catalyst in combination with molecular oxygen or peroxides as an alternative to the traditional procedures. We, therefore, tried to find an organic catalyst suitable for alcohol oxidation, in particular diamines. our group previously reported the activation of molecular oxygen by 9,10-diaminophenanthrene (DAPHEN) for catalytic oxidation of benzylic alcohols with moderate activity.[94] Thus, we focused on similar diamines.

The chemical behavior of DAPHEN was first examined (Scheme 4.3, 1) as a prototypical example of such catalysts. In the model study, the oxidation of propylphen-1-ol was detected with low conversion (Scheme 4.3, 1 21%). Next, structurally related primary diamines were tested, and from those **2** and **3** were found to be reactive. Surprisingly, *meso*-1,2-di(1-napthyl)-1,2-ethanediamine(meso-NEDA) **4**, resulted in a marked improvement of conversion (70%). Catalytic competence of the corresponding ethylenediamine fragment with binaphthyl substituents further evaluated; only trace amount of propiophenone was detected from benzylamine(5) and naphthylmethylamine (6) catalyzed processes. Notably, the synthesized aliphatic secondary amine 7 derived from catalyst 2 shows lower reactivity (20%). Primary diamine centers together with ethanenaphthyl moiety of naphtylethanediamine might be crucial structural moieties for an efficient oxidation catalyst.

Various substrates were studied using this oxidation method under the optimized reaction conditions (Table 4.9). All reactions were carried out under reflux in the presence of 2.2 mol% catalyst and 2.5 equivalent of TBHP in alkaline water. Various benzylic, aliphatic cyclic primary and secondary alcohols were converted to the corresponding ketons in good yields. The secondary benzyl alcohols with different steric and electronic environment were converted in almost quantitative yields (Table 4.9, entries 1-4) demonstrating the generality of the approach used. Interestingly, also cyclohexanol (entry 5) and even tetranol, isoborneol and menthol (entries 6- 8) were viable substrates.

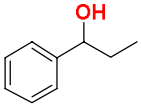
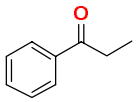
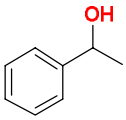
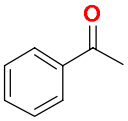
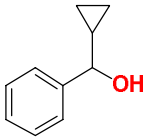
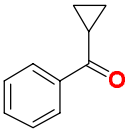
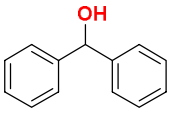
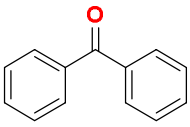
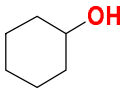
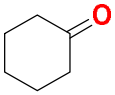
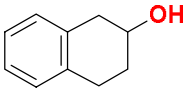
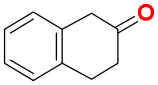
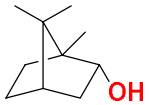
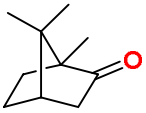
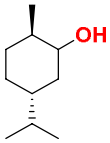
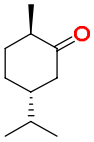
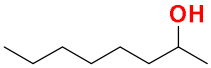
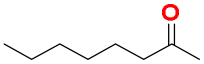
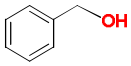
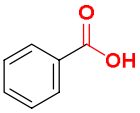
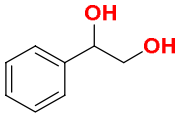
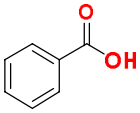
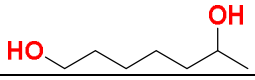
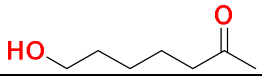


Scheme 4.3: Amines studied as an organocatalyst for oxidation of propylphen-1-ol into propiophenone.

Similar reaction conditions can be employed to the oxidation of primary alcohols. For example, benzyl alcohol was oxidized to benzoic acid with 61% conversion after 23 h (Table 4.9, entry 10). Finally, the catalyst displays interesting regioselectivity for a vicinal diol such as 1-phenyl-1-ethanediol and 1,5-hexandiol; the secondary hydroxyl group is oxidized leaving the primary alcohol function intact (Table 4.9, entry 11 and 12). Only a handful of methods are known for selective oxidation of secondary alcohols in the presence of primary alcohol.

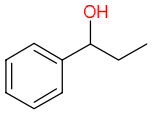
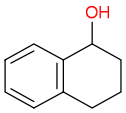
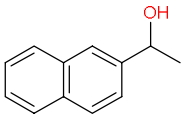
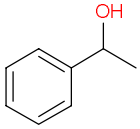
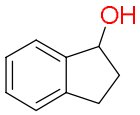
Encouraged by the efficient organocatalyzed oxidations, the possibility to use enantiopure (R,R)-NEDA in kinetic resolution of racemic secondary alcohols was explored. ee value of 98% with yield of 52% were obtained for (R)-1-phenylpropanol. Similarly, the *R*-enantiomer with 99%ee and 46% yield was obtained from the reaction of 1-phenyl-1-propanol at ambient temperature (Table 4.10, entry 3). Similar results were obtained from 1-(2-naphthyl) ethanol, 1-tetranol and 1-indanol which all gave good enantiomeric selectivity (Table 4.10, entry 4-6) This clearly exemplifies the potential of the diamine based organocatalysts NEDA in oxidative kinetic resolution.

Table 4.9: Oxidation of various secondary alcohols into ketones using NEDA catalyst. [a]

Entry	Substrate	Product	Time [hr]	Yield [%]
1			9	97 ©
2			9	94
3			16	72
4			7	98
5			10	87
6			10	91
7 [b]			16	60
8			16	45
9			16	49
10 [b]			16	71
11 [d]			16	74
12 [c]			16	65

[a] Reaction conditions: substrate (2.0 mmol), racemic NEDA (2.2 mol%), TBHP (80% solution in water, 6.2 mmol), alkaline water (pH=9-10) as solvent (2 mL), at 95°C. Yields refer to GC using decane as internal standard, and ^{1}H NMR spectra (average of three experiments). [b] MeCN as solvent. [c] Isolated yield. [d] Side product 20% of aldehyde.

Table 4.10: Oxidative kinetic resolution of racemic secondary alcohols using NEDA as a catalyst in presence of TBHP.[a]

Entry	Substrate	*T* [hr]	Conversion [%] [e]	ee [%] [f],[g]
1 [b]		5	40	52(*R*)
2 [c]		20	52	98(R)
3 [d]		22	53	82(*R*)
4 [d]		22	52	88 (*R*)
5		20	39	83(*R*)
6 [d]		20	55	67 (*R*)

[a] Reaction conditions: substrate (0.5 mmol), NEDA (0.025mmol, 5 mol%), TBHP (70% solution in water, 1.6 mmol), K_2CO_3 (0.020mmol) and CH_2Cl_2 as solvent, rt. [b] Same reaction with prolonged time and higher dilution (0.1M substrate [c] same reaction with high dilution and room temperature. [d] Product conversion was determined by GC or ^1H NMR methods. [e] The ee were determined by GC or HPLC analysis using chiral column [f] Determined by comparison of the optical rotation with literature value.

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Conclusions

The transition metal-complex catalyzed oxidation offers attractive opportunities for industry which seeks to develop more environmentally benign manufacturing processes. So far, most of the oxidation catalysts reported have only academic interest and their true value is to show the way for future research in this area. Although hundreds of different transition metal complexes are capable of acting as catalysts in oxidations of organic substrates the number of such catalytic methods has substantially decreased.

We developed and utilized four catalysts: three of them are iron based and one is organo(metal-free) system. The iron based catalysts were iron/thymine-1-acetic acid (Fe/THA), iron/Phenanthroline complex, and iron/N-methylimidazole whereas the metal-free catalyst was 1,2-Di(1-naphthyl)-1,2-ethanediamine (NEDA).

The iron/THA catalyst is capable of oxidizing alcohols, both primary and secondary aliphatic alcohols were oxidized into their corresponding carbonyl compounds, acids and ketones with good to excellent yields. The system can also oxidize alkanes with different steric and electronic environment. It is an efficient catalyst in terms of product yields and selectivity of the oxidations. Basically, this catalyst can oxidize tertiary C–H bonds and secondary ones, but the presence of steric congest can lead to higher preference to secondary C-H bond . Without tertiary C–H bonds the oxidation occurs selectively on secondary C–H bonds at the C_2 and C_4 position as shown with the substituted cyclohexane substrates. As for the mechanism, high-valent iron-peroxo species are generated from low spin $Fe^{(III)}$ complex with H_2O_2 as a terminal oxidant. A rapid exchange of FeOOH oxygen atom with $H_2{}^{18}O$ follows mechanism in which an exogenous water molecule assists the hydrogen transfer from the coordinated water molecule to the oxo group. The results support the mechanism where the iron-oxo species is formed via water-assisted heterolysis of O–O bond, and the carbonyl bond formed via either the oxygen from H_2O_2 or the oxygen from H_2O.

We also presented a new method for the oxidation of benzylic and aliphatic primary and secondary alcohols using iron-based catalyst, which is $[Fe(phen)_2Cl_2]NO_3$ (iron/Phenanthroline), with hydrogen peroxide as a terminal oxidant. Although there have been enormous number of procedures for conversion of alcohols into aldehydes, this method is a practical alternative because it is simple, environmentally acceptable, and inexpensiveness. Both primary and secondary aliphatic alcohols were oxidized into their corresponding carbonyl compounds, aldehydes and ketones with good to excellent yields during a short reaction time ranging from half an hour to two hours.

An easily accessible iron catalyst (iron/N-methylimidazole) was developed to form dehydrogenative coupling reaction between benzaldehydes and styrenes; and thus, the CH activation to produce α,β–unsaturated ketones has been also developed. The practical advantages of this protocol is the readily available starting materials (aldehydes and styrenes) and the avoidance of any preliminary functionalization or the need for special carbene (or carbenoid) species. Furthermore, this catalyst has a low loading and solvent free reaction conditions that makes it an interesting complementary one for the selective oxidation.

The metal-free catalyst, which is 1,2-Di(1-naphthyl)-1,2-ethandiamine (NEDA), has shown to be an efficient organocatalytic catalyst for the oxidation of secondary alcohols with *t*-BuOOH as a terminal oxidant. Under mild reaction conditions, a wide range of secondary alcohols converted into corresponding ketones with moderate to high yields. Furthermore, the chiral NEDA also has shown a promising enantioselectivity in oxidative kinetic resolution of racemic secondary alcohols with good *ee*-values. However, the main draw-back of this system is that it can't use oxygen as an oxidant and it has low reactivity towards the primary alcohols.

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