Flavins as Biomimetic Catalysts for Sulfoxidation by H_2O_2

Catalyst Immobilization in Ionic Liquid for H_2O_2 Oxidations

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Abstract

This thesis deals with the development of catalytic oxidation reactions utilizing hydrogen peroxide as terminal oxidant. The main focus has been to find flavin catalysts that are easy to handle and stable to store but still able to perform the desired reaction. A variety of dihydroflavins were prepared and the electrochemical oxidation potentials were measured and compared with their catalytic activity.

A flavin catalyst was applied in the sulfoxidation of allylic and vinylic sulfides by H_2O_2. This transformation was highly chemoselective and the sulfoxides were obtained without formation of other oxidation products. The scope of the reaction was demonstrated by applying the method on substrates with a wide range of functional groups such as a tertiary amine. Another flavin catalyst was immobilized in the ionic liquid [BMIm]·PF_6 and used for sulfoxidations by H_2O_2. The chemoselectivity was maintained in this system and the catalyst-ionic liquid system could be recycled several times.

Finally two bimetallic catalyst systems for the dihydroxylation of alkenes by H_2O_2 were immobilized in the ionic liquid. These systems employed either vanadium acetylacetonate $VO(acac)_2$ or methyl trioxorhenium (MTO) as co-catalysts together with the substrate-selective osmium catalyst. Good to excellent yields of the diols were obtained.

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List of Publications

The papers are in the text referred to by their roman numerals **I-IV**.

I. **Highly Selective Sulfoxidation of Allylic and Vinylic Sulfides by Hydrogen Peroxide Using a Flavin as Catalyst.** Auri A. Lindén, Lars Krüger, and Jan-E. Bäckvall *J. Org. Chem.* **2003**, *68*, 5890-5896.

II. **Preparation and Redox Properties of *N,N,N*-1,3,5-Trialkylated Flavin Derivatives and Their Activity as Redox Catalysts.** Auri A. Lindén, Nina Hermanns, Sascha Ott, Lars Krüger, and Jan-E. Bäckvall *Chem. Eur. J.* **2005**, *11*, 112-119.

III. **Osmium-Catalyzed Dihydroxylation of Alkenes by H_2O_2 in Room Temperature Ionic Liquid co-Catalyzed by $VO(acac)_2$ or $MeReO_3$.** Mikael Johansson, Auri A. Lindén, and Jan-E. Bäckvall *J. Organomet. Chem.* **2005**, *690*, 3614-3619.

IV. **Efficient and Selective Sulfoxidation by Hydrogen Peroxide Using Recyclable Flavin-Catalyst-[BMIm]·PF_6 System.** Auri A. Lindén, Mikael Johansson, Nina Hermanns, and Jan-E. Bäckvall *Submitted for publication.*

Preface

My ambition has been to summarize all the results in papers I-IV listed on the preceding page so that it would help the reader to better understand the chemistry that has been performed. I also want to emphasize the work I am responsible of.

In paper **I** Dr. L. Krüger and I collaborated equally. In paper **II** Dr. N. Hermanns and I are responsible for the synthesis and Dr. S. Ott performed the electrochemical measurements. In paper **III** I performed the MTO mediated reactions and M. Johansson performed the reactions mediated by $VO(acac)_2$. In paper **IV** I am responsible for the synthesis of the catalyst and development of the system. The catalysis and recycling reactions were performed by me and M. Johansson.

Abbreviations

Abbreviations and acronyms are in agreement with the standard ones.[1,2] Only the nonstandard ones that appear in the thesis are listed here.

Enz	Enzyme
K_a	Ionization constant
n.d.	not determined

1 Introduction

Hydrogen peroxide, which is composed of two hydrogen atoms and two oxygen atoms (H_2O_2), can be found in medical cupboards as dilute solutions and is used for disinfection of small cuts. It can also be found in hair products as a bleaching agent. It is an environmentally benign oxidant that is finding more and more practical applications in catalysis. As a stoichiometric oxidant it has relatively high atom economy and the only "waste" formed, after formally loosing an oxygen atom, is water. The energy barrier for the direct oxidation of organic substrates with hydrogen peroxide is often very high and the reactions are generally too slow for industrial purposes. By applying a catalyst, which is not consumed even though it may adopt different states during a reaction, the energy barrier can be decreased and the reaction rate thus increased.

More than 120 years ago A. Wynter Blyth, an English chemist, isolated a yellow pigment from cow milk that he named lactochrome.[3,4] It took a few years before scientists became interested in the use and properties of this pigment, after it had been isolated from several sources. It received a variety of names depending on the source (*e.g.* urochrome when isolated from urine). The real interest in this compound arouse when it was found to be a constituent of vitamin B complex (vitamin B_2).

The groups of Richard Kuhn[5] and Paul Karrer[6] determined and confirmed the structure of the pigment by synthesis almost concurrently in the middle of 1930's. It was named "riboflavin" (Figure 1) and all the other names it had before were disregarded. The name was derived from its ribityl side chain on the N(10) and the Latin word *flavus* (eng. yellow), for its characteristic color. Flavin is used as a generic term for yellow compounds that have the heterocyclic alloxazine chromophore in common (Figure 1).

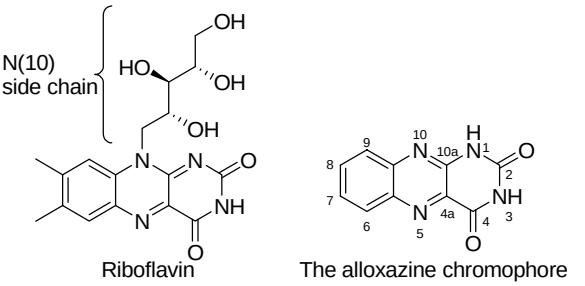


Figure 1. Riboflavin and the alloxazine chromophore with numbering.

1.1 The Role of Flavins in Nature

In nature flavin can be found as flavin mononucleotide (FMN) or flavin adenosine dinucleotide (FAD) and these compounds function as enzyme cofactors (Figure 2). They are in most cases non-covalently bound to the enzymes through the N(10) side chain. This leads to that only one of the two forms can bind to a certain enzyme.

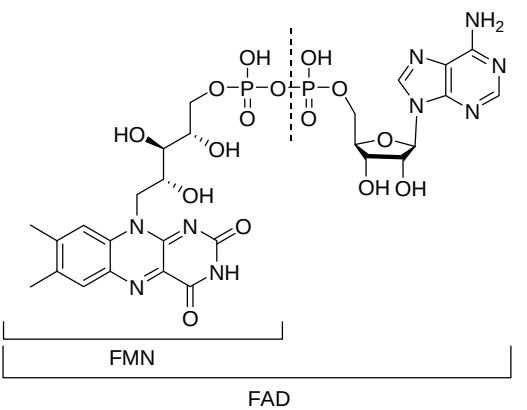
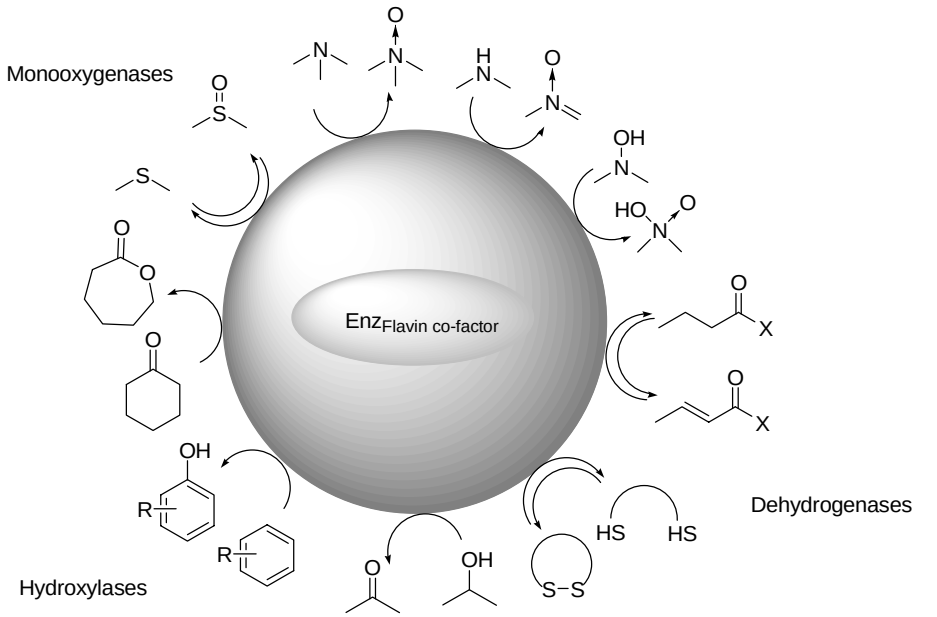


Figure 2. Flavin mononucleotide (FMN) and flavin adenosine dinucleotide (FAD)

There are a great number of enzymes reported to date that use a flavin cofactor. Examples of such enzymes are some monooxygenases, hydroxylases, and some dehydrogenases.[4,7-9] The enzymes in these classes catalyze a variety of reactions (Scheme 1). Monooxygenases catalyze the transfer of one oxygen atom to a substrate, whereas hydroxylases catalyze the hydroxylation of for example aromatic rings and

dehydrogenases catalyze hydrogen abstraction from various substrates. These enzymes can be found in the human body.



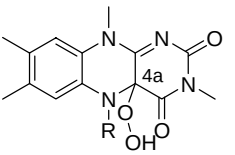
Scheme 1. Examples of reactions catalyzed by flavo-enzymes.

Baeyer-Villiger monooxygenases (BVMOs) constitute a group of enzymes that catalyzes Baeyer-Villiger oxidations of ketones and sulfoxidation of some sulfides.[9] The cyclohexanone monooxygenase (CHMO),[10] cyclopentanone monooxygenase (CPMO)[11] and 4-hydroxyacetophenone monooxygenase (HAPMO)[12] are examples of BVMOs that catalyze the oxidation of thioanisole to the corresponding sulfoxide with high enantioselectivity.[9]

1.2 Mechanism of the Oxidation of Sulfides

The Groups of Thomas Bruice and Vincent Massey have intensively studied the mechanism for oxidation of flavins and oxidations by flavins. The 4a-hydroperoxy species of a flavin was first proposed by Massey *et al.* already in 1969 (Figure 3).[13] At the time they had no direct evidence for its existence, only implications from the different reactivity of flavo-enzymes towards the addition of sulfite or molecular oxygen. In 1973 they reported on “conventional support” for this species through kinetic studies on the reaction between a range of reduced flavins and O_2 and the

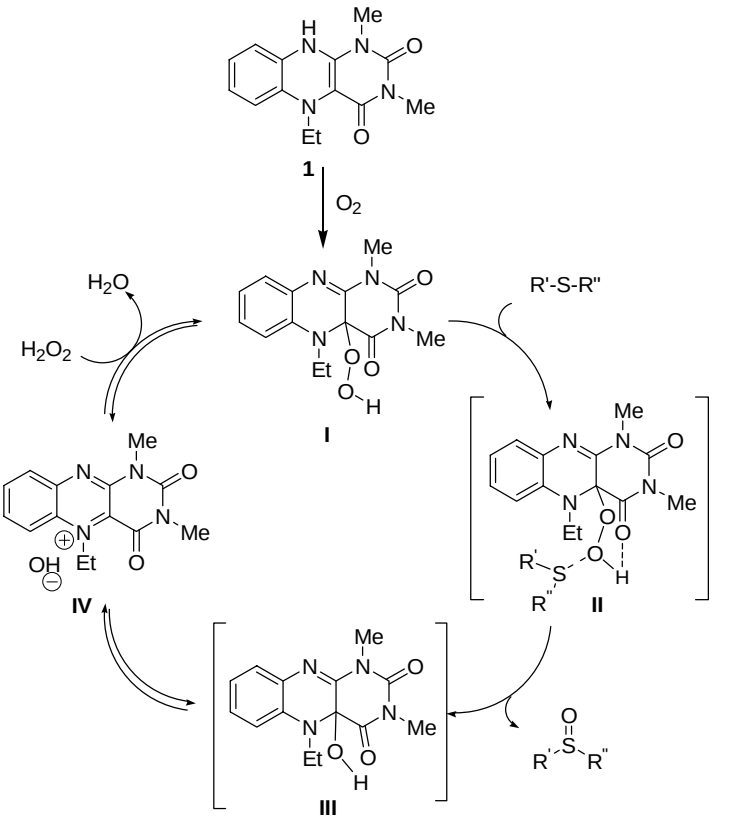
observed formation of the oxygen radical $O_2^{-\bullet}$.[14] The group of Bruice could in 1976 synthesize and characterize the 4a-hydroperoxy-adducts of some 1,5-dihydroflavins (Figure 3).[15] It should be noted, however, that Gibson and Hastings postulated a hydroperoxy-intermediate already in 1962 without suggesting any particular structure for it.[16]



R = CH_3, CD_3, C_2H_5

Figure 3. Hydroperoxyflavins characterized by Bruice and coworkers.

On the basis of these reports, the catalytic cycle for the oxidation of sulfides to sulfoxides using flavin **1** and H_2O_2 was proposed, and is depicted in Scheme 2.[17] The active flavin hydroperoxide **I** is generated *in situ* from the catalyst precursor **1** by reaction with molecular oxygen. The nucleophilic sulfide reacts with the electrophilic oxygen of the active catalyst via transition state **II**. The oxygen is transferred to the substrate, releasing the sulfoxide together with the hydroxy flavin intermediate **III**. Subsequently, the hydroxyl group is eliminated from **III** by the lone-pair on N(5), to give the aromatic 1,4-diazine resting state **IV**. Intermediate **IV** can now react with hydrogen peroxide to regenerate the active catalyst, thus completing the catalytic cycle.



Scheme 2. The proposed catalytic cycle for the oxidation of sulfides to sulfoxides by flavin **1** and H_2O_2.

1.3 Applications

Since their discovery flavins have been used in oxidations of a variety of organic substrates. Initially they were used as stoichiometric oxidants and later together with an oxidant. The developed chemical processes that utilize flavins as catalysts mimic Nature's way of performing catalysis. This is why they are often referred to as biomimetic catalysts.

Mager and co-workers reported on the reaction between phenylalanine and a dihydroflavin in the presence of O_2 and H_2O_2 in 1976. Since then 4a-hydroperoxyflavins have been reported to oxidize aldehydes,[15] sulfides,[18-20] and tertiary amines.[21,22]

Before the work reported in this thesis there were only a few examples on the

catalytic use of flavins. Oxidation of secondary amines to nitrones[23] as well as oxidation of sulfides[23-25] had been reported and Furstoss *et al.* had performed Baeyer-Villiger oxidations of some activated cyclic ketones[26] using a flavin as catalyst (Figure 4).

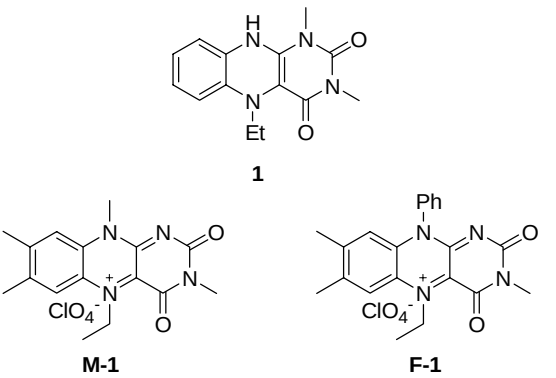


Figure 4. Flavin catalysts used for oxidation reactions.

Flavin **1** was synthesized in our laboratory in 1998 and it exhibited superior activity compared to the ones reported thus far in the flavin catalyzed oxidation reactions.[17] It has been used in the oxidation of tertiary amines to *N*-oxides,[17] and sulfides to sulfoxides[27] using hydrogen peroxide as terminal oxidant. A few years ago flavin catalyst **1** was successfully incorporated into the triple-catalytic system for the dihydroxylation of olefins by H_2O_2 by our group.[28-30] Recently Murahashi *et al.* reported on the use of flavin **M-1** with molecular oxygen as terminal oxidant in the oxidation of organic sulfides and amines employing hydrazine as the reducing agent, mimicking the role of NADPH.[31]

It is important to note that flavin **1** and all the other flavins, which will be presented later in the thesis, need molecular oxygen for activation (see Scheme 2). This is not necessary for flavins **M-1** and **F-1** that can directly react with hydrogen peroxide.

1.4 Objectives of the Thesis

It is highly desirable to develop catalytic systems that are robust and can react with a large number of substrates. A catalyst should also be selective towards the transformation it is designed for. Flavins have shown good potential as selective catalysts for sulfoxidation, but a major drawback has been their limited lifetime. The

development of flavin catalysts that can withstand oxidative degradation is of great importance. In Chapter 2 the structure-reactivity relationship of eight different catalyst precursors is discussed.

The second goal of this thesis was to broaden the scope of substrates to allylic and vinylic sulfides in the sulfoxidation reaction employing hydrogen peroxide and catalyst precursor **1**. The chemoselectivity and scope of this reaction is discussed in Chapter 3. As the atom economy of chemical transformations is becoming more important catalyst recycling is highly desirable. This inspired us to develop a system to reuse the flavin catalyst. The immobilization of a flavin in ionic liquid [BMIm]·PF_6 is presented in Chapter 4.

The last chapter deals with osmium-catalyzed dihydroxylation of alkenes by hydrogen peroxide. Since osmium is toxic, the catalyst loading needs to be low and the demand to recycle this catalyst is high. Two bimetallic, triple-catalytic oxidation systems immobilized in ionic liquid [BMIm]·PF_6 are presented.

2 Preparation and Redox Properties of Flavins

(Paper II)

2.1 Introduction

There have been many reports on the preparation and chemistry of different lumiflavins and flavins. Most of these studies were conducted with the purpose to elucidate the mechanism of the flavo-enzyme-catalyzed reactions occurring in nature as well as the binding of the flavin cofactor. The early work on structure-reactivity studies was made by the groups of Mager,[32,33] Lambooy[34] and Bruice.[18,35,36] Subsequent studies focused on broadening the range of substituents on the flavins and studies of their effect.[27,37-47] Systems using metal ligation[48] and hydrogen bonded motifs[49-55] around the flavin nucleus has also been investigated. All these studies were based on flavins with substituents on N(3), N(5) and N(10) (Figure 4).

The auto-oxidative behavior of the *N*,*N*,*N*-1,3,5-trialkylated dihydroflavin was reported by Mager *et al*..[33] No other reports of oxidation potentials or chemical properties of this type of flavins have been published. As mentioned above a very stable and efficient flavin catalyst was discovered by our group in 1998.[17] It was found that catalyst **1** is more robust and has a superior catalytic activity in the oxidation of tertiary amines than all the previously reported flavin catalysts. It activates hydrogen peroxide (and molecular oxygen) efficiently and an important feature of the proposed catalytic cycle (Scheme 2) is the driving force for the elimination of OH^- from **III** *i.e.* the formation of the aromatic intermediate **IV** rendering the formation of **I** faster. An understanding of the relationship between structure and reactivity is important in order to find an optimal catalyst for a desired transformation.

In a previous study by our group it was shown that electron-withdrawing fluorine substituents on the 7- and 8- positions of the flavin **2**[56] result in a catalyst precursor that is more stable than flavin **1** (Figure 5).[27] This is rationalized by the fact that the dihydroflavin needs to be oxidized by molecular oxygen in order to enter the catalytic cycle (Scheme 2). This process has higher energy barrier for electron deficient catalyst precursors, leading to a longer activation time. In this chapter the properties of flavins **1** and **2** together with six other flavin derivatives are discussed.

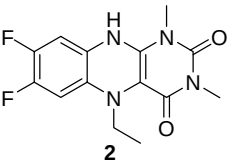


Figure 5. Dihydroflavin **2**.

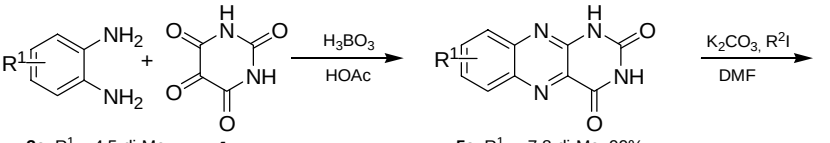
2.2 Results and Discussion

2.2.1 Synthesis of the Catalyst Precursors

To study the effect of substituents on the flavin, seven different catalyst precursors were designed and flavins **1**, **7a-e** and **8** were prepared (Scheme 3 and 4). The synthesis of the catalyst precursors followed the previously described path starting from the diamines **3a-e**, which were either commercially available (**3a**, **d**, **e**) or synthesized from 3,4-diaminobenzoic acid through acid-catalyzed esterification with the corresponding methyl- or butylalcohol (**3b**, **c**) (Scheme 3).[17] The diamines **3a-e** were condensed with alloxane (**4**) resulting in the tricyclic alloxazine ring systems **5a-e** in good yields. Unsymmetrically substituted compounds **5b-d** were obtained as mixtures of the 7- and 8-regioisomers, in ratios of 1:1 (**5b**, **c**) and 5:1 (**5d**), which were not separable due to poor solubility. Products **5a-e** were subsequently alkylated by methyl- or ethyl iodide on N(1) and N(3) leading to *N*,*N*-1,3-dimethyl- or diethyl alloxazines **6a-e**. Substrates **5b** and **5c** gave 1:1 mixtures of 7- and 8-regioisomer of **6b** and **6c**. When the 7/8-trifluoromethyl alloxazine **5d** was reacted with ethyl iodide the 1,3-diethyl-7-trifluoromethyl alloxazine **6d** was obtained in 57% yield. The other regioisomer surprisingly did not react to form any product.

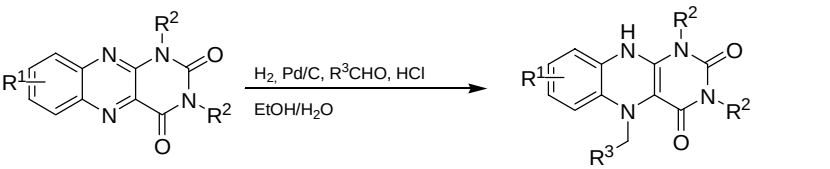
The final step involved reduction of the 1,4-diazine ring of the alloxazines and alkylation on N(5). This was realized through a reductive alkylation with acetaldehyde or butyraldehyde and H_2, using a catalytic amount of Pd on activated charcoal. In the final reductive alkylation step, the methoxy- and butoxy carbonyl substrates **6b** and **6c** reacted somewhat differently. The dihydroflavin **7b** was obtained from **6b** mainly as the 7-isomer, with only about 10% contamination from the 8-isomer, in 64% combined yield. The analogous reaction of **6c** afforded **7c** as a 1.7:1 mixture of the 7- and 8-isomers in 29% combined yield. The regioisomeric mixtures of **7b** and **7c** were used

as such for the oxidation potential measurements and catalysis since the separation of the isomers was very difficult.



3a: R^1 = 4,5-di-Me
3b: R^1 = 4-COOMe
3c: R^1 = 4-COOBu
3d: R^1 = 4-CF_3
3e: R^1 = 4,5-di-H

5a: R^1 = 7,8-di-Me, 99%
5b: R^1 = 7/8-CO_2Me, 66%, 44:56
5c: R^1 = 7/8-CO_2Bu, 75%, 45:55
5d: R^1 = 7/8-CF_3, 53%, 84:16
5e: R^1 = 7,8-di-H, 95%

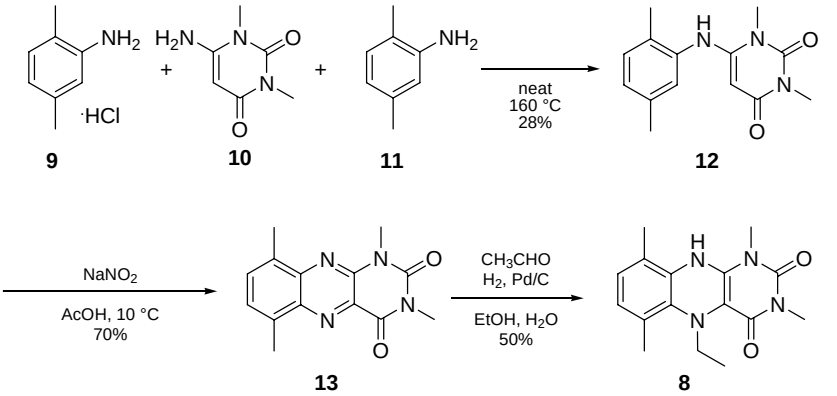


6a: R^1 = 7,8-di-Me; R^2 = Me, 77%
6b: R^1 = 7/8-CO_2Me; R^2 = Me, 76%, 54:46
6c: R^1 = 7/8-CO_2Bu; R^2 = Me, 96%, 1:1
6d: R^1 = 7-CF_3; R^2 = Et, 57%
6e: R^1 = 7,8-di-H; R^2 = Me, 89%

7a: R^1 = 7,8-di-Me; R^2 = R^3 = Me, n.d.
7b: R^1 = 7/8-CO_2Me; R^2 = R^3 = Me, 64%, 9:1
7c: R^1 = 7/8-CO_2Bu; R^2 = R^3 = Me, 29%, 1.7:1
7d: R^1 = 7-CF_3; R^2 = Et; R^3 = Me, 54%
7e: R^1 = 7,8-di-H; R^2 = Me; R^3 = Pr, 64%
1: R^1 = 7,8-di-H; R^2 = R^3 = Me, 47%

Scheme 3. Synthesis of the catalyst precursors **1** and **7a-e**.

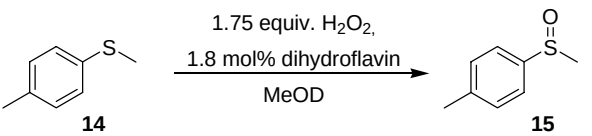
The preparation of dihydroflavin **8** required a different synthetic strategy, since 2,5-dimethyl-1,2-diaminobenzene is not commercially available (Scheme 4). 2,5-Dimethylaniline hydrochloride (**9**) was reacted with 1,3-dimethyl-6-aminouracil (**10**) in 2,5-dimethylaniline (**11**) at 160 °C to give the product **12** in moderate yield. Compound **12** was cyclized with $NaNO_2$ to give the tri-cyclic alloxazine **13** in 70% yield. Subsequently the standard reductive alkylation procedure was applied on **13**, which afforded the desired dihydroflavin **8** in 50% yield.



Scheme 4. Synthesis of pre-catalyst **8**.

2.2.2 Catalytic Activity of Substituted Flavins

Flavins **1**, **2**, **7a-e** and **8** were subsequently used in a kinetic study of the oxidation of sulfide **14**, depicted in Scheme 5.



Scheme 5. The reaction used in the kinetic study.

To compare dihydroflavins **1** and **2**, the conversion of **14** was monitored over 80 min and plotted in Figure 6a. As previously observed in our group,[27] the conversion curves for the reactions catalyzed by **1** and **2** were shaped differently, indicating an induction period in the oxidation of **14** with **2**.

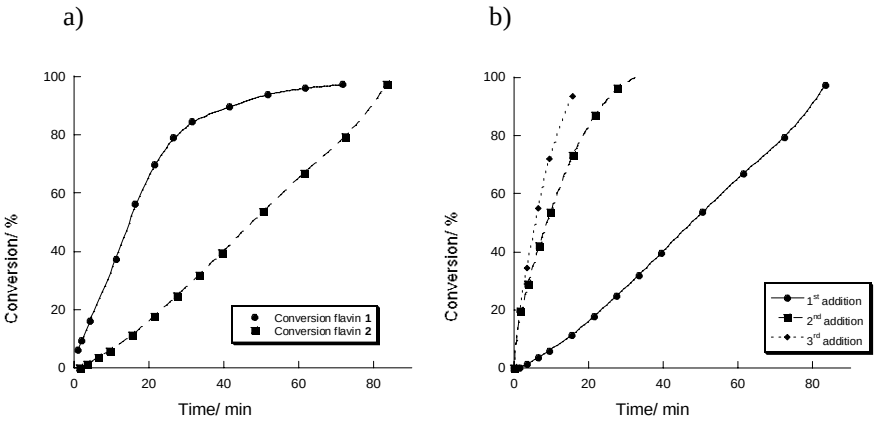


Figure 6. a) Oxidation of **14** by H_2O_2 with flavins **1** and **2** as catalysts. b) Oxidation with flavin **2** in three consecutive runs.

To confirm this assumption a reaction was run where the substrate was added in three portions, each of which corresponded to ca. 50:1 substrate to catalyst ratio. The conversion to **15** was followed by ^{1}H NMR and the kinetic curves are presented in Figure 6b. A dramatic enhancement of the reaction rate was observed in the second addition; the initial lag period disappeared and a fast conversion of the starting material to product took place. This is a strong indication that the induction period in the first run is caused by slow formation of the active catalyst from **2** with molecular oxygen. Once the active species is formed in an adequate concentration the reaction becomes fast, adapting the typical first order rate expression. This also suggests that the active catalyst, which is formed *in situ* from **2** is more efficient than the active species formed from **1**, since the reaction in the second addition is twice as fast as that with **1**. This in turn means that dihydroflavin **2** is more stable toward oxidation by molecular oxygen and can therefore be stored longer.

Next, the catalytic activity of precursors **7a-e** was studied in the oxidation of **14** to **15** (Table 1). Dihydroflavin **7a** gave low conversion of **14**,[27] which is most likely due to oxidative degradation of the catalyst (entry 3). Dihydroflavin **7b** showed good catalytic activity (entry 4) whereas dihydroflavin **7c** proved to be only partially soluble in methanol and could not be used in this study. An induction period was observed also for dihydroflavin **7b** analogous to dihydroflavin **2** whereas **7d** showed very poor

catalytic activity (entry 5). The N(5) butyl substituted catalyst precursor **7e** had a comparable activity to that of **1** and compound **8** was inactive (entries 6, 7).

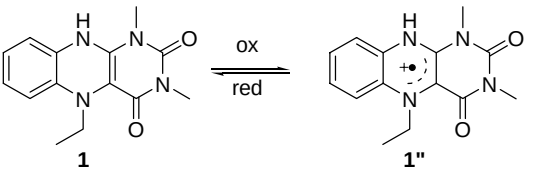
Table 1. Dihydroflavin activity in oxidation of **14** to **15**.[a]

Entry	Dihydroflavin	Time (min)	Conversion (%)
1	**1**	60	95
2	**2**	60	65
3[b]	**7a**	60	40
4	**7b**	60	90
5	**7d**	60	9
6	**7e**	60	99
7	**8**	-	n. r.[c]

[a)] The reactions were run with 0.223 mmol of the substrate **14** using 1.8 mol% of the catalyst and 1.75 equiv. of H_2O_2 in 0.6 mL CD_3OD. [b)] Taken from reference 25. [c)] n. r.= no reaction detected.

2.2.3 Redox Potentials for the Flavin Derivatives

The results from the kinetic study intrigued us to look deeper into the redox behavior of these catalyst precursors, to reach a better understanding of the relationship between electronic properties and different substitution pattern of the dihydroflavins. As described above, the dihydroflavin catalyst precursors are oxidized to the corresponding active hydroperoxyflavin catalysts *in situ*. Since it is difficult to make direct observations of this process a simple one-electron oxidation of the dihydroflavins was studied. The redox process taking place is shown in Scheme 6. The half-wave potentials of flavins **1**, **2**, **7a-e** and **8** were measured by cyclic voltammetry. The acquired data reflect the thermodynamics for the activation step of the flavin catalyst precursor.



Scheme 6. Electrochemical oxidation / reduction of flavin **1** (model catalyst).

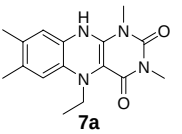
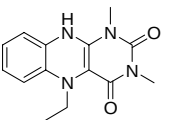
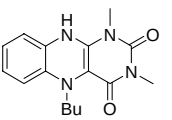
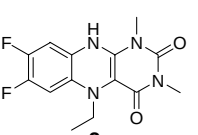
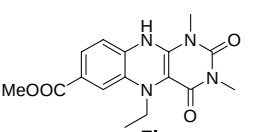
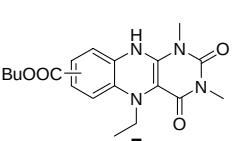
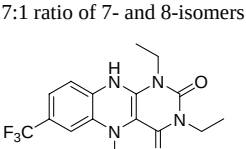
The electrochemical oxidation of all the dihydroflavins proved to be fully reversible (see Appendix). It is a one-electron oxidation process, which was evident from a peak split (larger than 60 mV) as well as the bulk electrolysis of dihydroflavin **1**. The acquired potentials are in line with the observed catalytic activity of the dihydroflavins studied (Table 1).

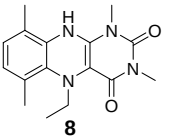
The catalyst precursor **7a** (Table 2, entry 1), having electron donating methyl groups in positions 7 and 8, is most susceptible towards oxidation, which is apparent from the most negative oxidation potential. When its catalytic activity was studied in the oxidation of **14** it showed a good initial activity, but the reaction slowed down and practically stopped at around 40% conversion.[27] This is most likely due to its sensitivity towards auto-oxidative degradation.

As electron withdrawing group(s) are introduced on C(7) and C(8) (entries 4-7), the oxidation potential shifts to less negative. This means that the precursors become less prone to oxidation and activation of the pre-catalyst becomes slower. This is in agreement with the observed lag period for catalyst precursor **2** (Figure 6).

The effect of the 7-trifluoromethyl substituent is not clear, since the oxidation potential measured for dihydroflavin **7d** (entry 7) suggests it to have higher activity than it turned out to have. It has only marginally lower oxidation potential than pre-catalyst **7b** (entry 5) but is much less efficient in catalyzing the oxidation of sulfide **14** to sulfoxide **15** (Table 1, entries 3 and 4). It could be that trifluoromethyl group plays a larger role elsewhere in the catalytic cycle, *e.g.* lower the ability of the N(5) to donate its electron pair to eliminate the OH^- from intermediate **III** (Scheme 2), thereby making this step slower and rate determining.

Table 2. Half-wave potentials for Dihydroflavins **1**, **2**, **7a-e** and **8**.

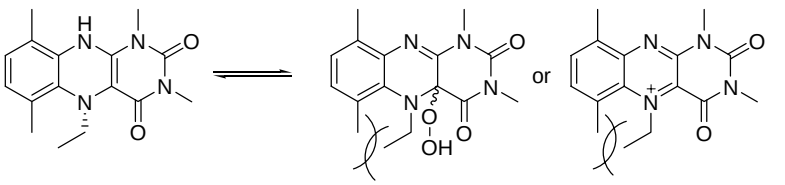
Entry	Dihydroflavin	E_0 (V)[a]
1	 **7a**	-0.414
2	 **1**	-0.305
3	 **7e**	-0.304
4	 **2**	-0.207
5	 **7b** Main isomer 9:1 ratio of 7- and 8-isomers	-0.182
6	 **7c** 1.7:1 ratio of 7- and 8-isomers	-0.182
7	 **7d**	-0.176

8	 **8**	-0.162

[a] Cyclic voltammograms were recorded using a Autolab Potentiostat (Ecochimie, Netherlands), controlled by GPES software (version 4.8). A glassy carbon disc electrode (diameter 3 mm) was used as the working electrode and was polished prior to each experiment using an aqueous alumina powder slurry. A platinum wire served as a counter electrode and a non-aqueous Ag/Ag^{+} was used as reference electrode. All potentials are half-wave potentials and are given vs. the $Fc^{+/0}$ couple. Cyclic voltammograms were obtained for 1 mM solutions of the analyte in dry acetonitrile, containing 0.1 M tetrabutylammonium hexafluorophosphate as supporting electrolyte.

Some evidence for the conformation of oxidized and reduced flavins has been presented by Vázquez *et al.* using theoretical calculations.[57] The reduced dihydroflavins have significant anti-aromatic character, which leads to distortion of the middle ring rendering the molecule non-planar.

The 6,9-dimethyl-substituted dihydroflavin **8** had the highest oxidation potential. This was expected from the results in the reaction with **14**, where no catalysis could be observed (Table 1, entry 5). If the oxidation potential of this catalyst precursor is compared to that of the 7,8-dimethyl substituted dihydroflavin **7a** the difference is about 0.25 V. This large difference cannot solely be explained by the electronic effect of the 6,9-substitution pattern, but other factors need to be considered. The steric effect of the methyl substituent on carbon 6 is thought to play a role in making flavins **7a** and **8** so different in their redox behavior as illustrated in Scheme 7. The non-planarity of the reduced form of the 6,9-dimethyl-substituted flavin makes it more stable compared to the oxidized form due to that the *N*-5-ethyl group and the 6-methyl group are not in the same plane.



8, bent **8'**, nearly planar **8",** planar

Scheme 7. Illustration of the steric effect of the 6-methyl group.

The oxidized form **8”** on the other hand is planar and aromatic introducing steric repulsion between the N(5) and N(6) substituents, thereby increasing the free energy of **8”**. In the active hydroperoxy species **8’** the C(4a) position is sp^3-hybridized and not part of the aromatic system. However, the double bond between N(10) and C(10a) together with the free electron pair on N(5), which is conjugated to the π-system, makes the molecule essentially planar, analogous to **8”**.

2.2.4 The Linear Free-energy Relationship

To find out if the relationship between the rate of a reaction and the reaction conditions is linear, one can construct a Hammet plot. In 1937 Hammet assigned a σ_{meta} and σ_{para} value for a range of substituents by comparing the K_a’s of *para*- and *meta*-substituted benzoic acids with the K_a of benzoic acid. They were established through measurement of their respective ionization constants. It was found that electron donating groups decrease the ionization constant leading to a negative σ value and electron withdrawing groups through increasing the ionization constant received a positive σ value. These values are constructed so that when plotting the proper σ values against the logarithm of the ratio of physical quantities (*e.g.* log K_x/K_0) gives a straight line. The slope of the line, denoted as Hammet ρ value, reflects the sensitivity of a substrate to electronic effects from the substituents in a given reaction.[58]

The log $[E^{ox}/E_0{}^{ox}]$ was plotted against the respective Hammet σ values to correlate the oxidation potentials of dihydroflavins **1**, **2** and **7a-e** with the electronic effect of the substituents. E^{ox} is the oxidation potential of the catalyst precursors and $E_0{}^{ox}$ is the oxidation potential of dihydroflavin **1**, which was set as the standard. In the catalytic cycle the deprotonation occurs at N(10), so substituent at C(8) was set as *meta* and at C(7) as *para* substituent, respectively. This assignment was used in the calculation of the σ values. Since the oxidation potentials reflect the free energy of the reaction for the different substrates, we can use them directly in the Hammett plot. The Hammet σ values and log $[E^{ox}/E_0{}^{ox}]$ are presented in Table 3 and the plot is shown in Figure 7.

Table 3. The Hammet σ values and log [$E^{ox}/E_0{}^{ox}$] values for the dihydroflavins.

Dihydroflavin	σ	Log [$E^{ox}/E_0{}^{ox}$]
1	0	0
2	0.4	-0.17
7a	-0.24	0.13
7b	0.45	-0.22
7c	0.45	-0.22
7d	0.54	-0.24
7e	0	0

A linear correlation with R = 0.997 was obtained between the log [$E^{ox}/E_0{}^{ox}$] and σ values as can be seen from Figure 7. A Hammet ρ value of -0.48 was obtained in this study, which indicates that electron donating groups make the electrochemical oxidation of the dihydroflavins easier. This value is consistent with the catalyst activity study as well as with the conclusion drawn from the half-wave potentials directly.

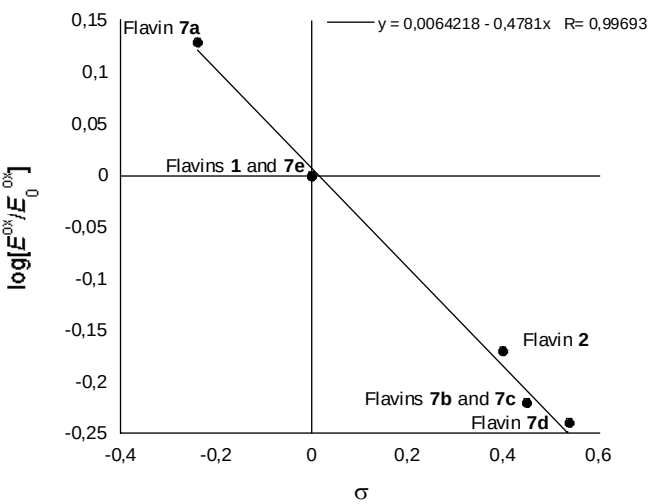


Figure 7. The Hammett plot of log [$E^{ox}/E_0{}^{ox}$] against Hammett σ values**.**

2.3 Conclusions

The properties of eight different dihydroflavins were studied. The results obtained from these studies suggest that the electron deficient dihydroflavins are, as expected, more difficult to oxidize and hence exhibit an induction period in the beginning of the reaction. This makes them more stable towards auto-oxidative degradation. A linear free-energy relationship was obtained for oxidation potentials against the Hammet σ values using flavin **1** as standard.

The electron-rich dihydroflavin **7a** suffers from sensitivity toward auto-oxidative degradation albeit performing well in the initial reaction. We have prepared pre-catalysts that are more tolerant towards this behavior and still able to perform the catalysis efficiently. The flavins functionalized with an ester group (**7b** and **7c**) provide opportunities for further derivatization of the catalysts.

3 Flavin-Catalyzed Biomimetic Oxidation of Sulfides to Sulfoxides

(Paper I)

3.1 Introduction

Sulfoxides and other organosulfur compounds are important synthetic intermediates in organic chemistry and are valuable in the preparation of biologically and pharmaceutically important materials.[59,60] Esomeprazole, which is used in treatment of gastric acid related diseases, is an example of a sulfoxide-containing drug (Figure 8). As sulfoxides bearing two different R-groups are chiral, enantioselective oxidation of dialkylsulfide to give only one sulfoxide-enantiomer has attracted considerable attention and has been applied on large scale at AstraZeneca.[61] When there are several different functional groups present in a molecule, as in esomeprazole, chemoselective transformations are important. This has often been difficult in sulfoxidation chemistry, and oxidations of other functional groups can take place simultaneously.[62] Furthermore, sulfoxides can undergo overoxidation to sulfones and therefore it is important that the catalyst has a low reactivity towards the sulfoxides.

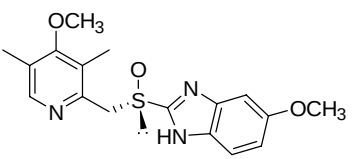


Figure 8. Esomeprazole.

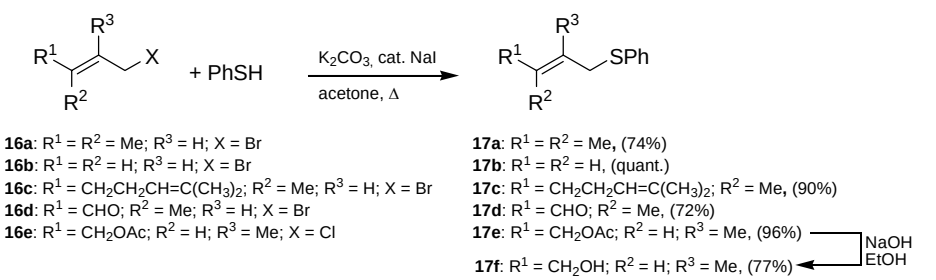
There are examples of selective sulfoxidations[63] and catalyst complexes such as $Fe(NO_3)_3$-$FeBr_3$,[64] oxodiperoxo molybdenum complexes absorbed on silica,[65] $LiNbMoO_6$,[66] $FeCl_3$ with periodic acid as stoichiometric oxidant,[67] and iron tetrakis(pentafluorophenyl) porphyrin[68] have been employed. These methods, however, suffer from drawbacks like toxic solvents and/or expensive catalysts and in most of the cases overoxidation to the sulfone cannot be avoided.

H_2O_2 is a mild and environmentally friendly oxidant. As it is a nucleophilic oxidant, the direct oxidation of sulfides, which are also nucleophilic, is slow. To increase the rate the use of an appropriate catalyst is required. As discussed in Chapter 2, flavins have previously been used in our group as catalysts for oxidation of sulfides, yielding the corresponding sulfoxides with high chemoselectivity. The method was, however, only tested on simple aromatic and aliphatic sulfides.[27] To broaden the scope of the method, allylic sulfides were studied as substrates in order to provide information concerning chemoselectivity of sulfide *versus* alkene oxidation. To avoid overoxidation and byproducts like epoxides, it was necessary to find suitable conditions for the flavin-H_2O_2 oxidation.

To obtain a good chemoselectivity towards the sulfoxide in the oxidation of allylic sulfides, a moderately electrophilic catalyst that does not react with the double bond or the formed product is required. Therefore, flavin **1** was chosen as catalyst for the oxidation of a range of allylic and vinylic sulfides.

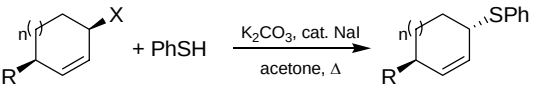
3.2 Preparation of Starting Materials

Most of the sulfides used in the present study were prepared from the corresponding allyl halides **16a-e** and thiophenol.[69] With this method the linear sulfides **17a-e** (Scheme 8) were obtained in good yields. Sulfide **17f** was obtained via ester hydrolysis of sulfide **17e** in 77% yield (Scheme 8).



Scheme 8. Preparation of sulfides **17a-f**.

The cyclic allyl halides **18a-c** reacted to the corresponding sulfides **19a-c** in good to excellent yields.

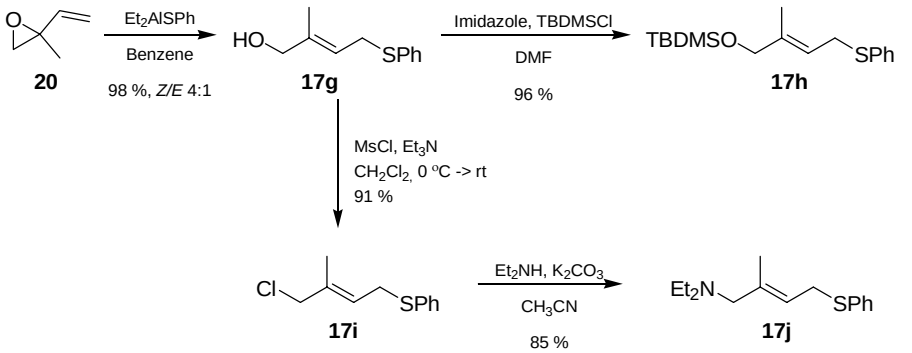


18a: R = OAc; X = Cl
18b: R = H; X = Br; n = 1
18c: R = H; X = Br; n = 3

19a: R = OAc, (81%)
19b: R = H; n = 1, (quant.)
19c: R = H; n = 3, (62%)

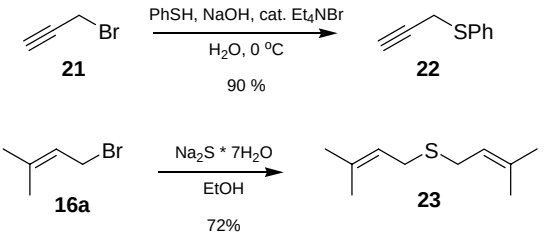
Scheme 9. Preparation of sulfides **19a-c**.

The regioisomer of sulfide **17f** *i.e.* **17g** was formed via a reaction of 1-methyl-1-vinyloxirane (**20**) with diethyl aluminum phenyl sulfide giving sulfide **17g** in excellent yield and with an *Z:E* ratio of 4:1 (Scheme 10).[70,71] Protection of **17g** with TBDMSCl resulted in compound **17h**. Alternatively treatment of **17g** with MsCl yielded the allyl chloride **17i** in almost quantitative yield instead of the expected mesylate. Chloride **17i** was then transformed to the corresponding amine **17j** in good yield.



Scheme 10. Preparation of sulfides **17g-j**.

Using propargyl bromide **21** with a modified method of Donkervoort *et al.*, the sulfide **22** was formed in a phase transfer reaction (Scheme 11).[72] The diprenyl sulfide **23** was prepared from prenyl bromide **16a** by reacting it with $Na_2S{\cdot}7H_2O$ in ethanol (Scheme 11).



Scheme 11. Preparation of sulfides **22** and **23**.

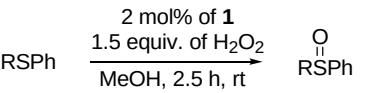
3.3 Results and Discussion

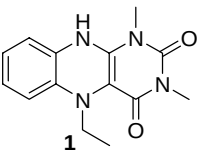
3.3.1 Oxidation of Allylic Sulfides

The previously established conditions for sulfide oxidation were applied to electron-rich sulfide **17a**. With 2 mol% of **1** and 1.5 equiv. of H_2O_2 in MeOH in an open flask, **17a** was oxidized to the corresponding sulfoxide **24a** in 92% yield (Table 4, entry 1). The chemoselectivity was complete both with respect to the sulfur moiety and the double bond, *i.e.* neither sulfone nor epoxide was detected. It was not necessary to strictly control the amount of hydrogen peroxide, which indicates that the chemoselectivity of the flavin-catalyst system is high.

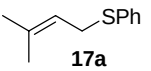
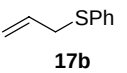
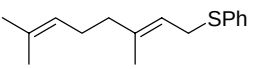
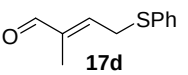
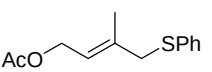
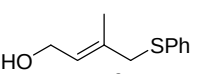
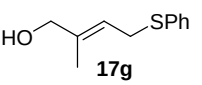
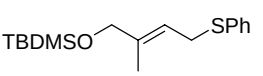
To demonstrate the scope and limitations of the developed system a range of sulfides with different electronic properties and various functional groups were oxidized to the corresponding sulfoxides. Also allyl sulfide **17b** (entry 2) and geranyl sulfide **17c** (entry 3) were oxidized to their corresponding sulfoxides **24b** and **24c**, respectively, in good yields. It is noteworthy that neither of the fairly nucleophilic double bonds on sulfide **17c**, bearing electron-donating substituents, underwent epoxidation under these conditions.

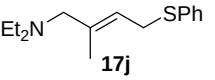
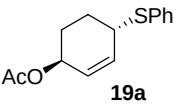
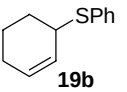
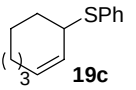
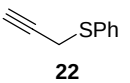
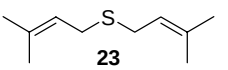
Table 4. Oxidation of the sulfides with the flavin catalyst-H_2O_2 system.[a]





1

Entry	Sulfide	Sulfoxide	Yield[b] of Sulfoxide (%)
1	 **17a**	**24a**	92
2	 **17b**	**24b**	88
3	 **17c**	**24c**	76
4	 **17d**	**24d**	65
5[c,d]			77
6	 **17e**	**24e**	96
7	 **17f**	**24f**	74
8	 **17g**	**24g**	77
9	 **17h**	**24h**	87

10	 **17j**	**24j**	86
11	 **19a**	**25a**	80[e]
12	 **19b**	**25b**	84[e]
13 14[c,f]	 **19c**	**25c**	72[e] 86[e]
15[c]	 **22**	**26**	75
16[g]	 **23**	**27**	85

[a)] Unless otherwise noted, the reactions were performed using 1.8 mol% of **1**, 1.5 equiv. H_2O_2 in MeOH at rt for 2.5-3 h. [b)] Isolated yields. [c)] The reaction was run overnight. [d)] The reaction was run with 4 mol% of **1** and 4 equiv. H_2O_2. [e)] Diastereomeric mixture. [f)] The reaction was run with 4 mol% of **1** and 2 equiv. H_2O_2. [g)] The reaction was run at 0 °C; 1.5% sulfone was formed.

The electron deficient sulfide **17d**, with an electron-withdrawing carbonyl moiety in conjugation with the double bond afforded sulfoxide **24d** in only 65% yield using standard conditions (entry 4). Therefore, modified conditions were needed for sulfide **17d** to react efficiently (entry 5). Thus the catalyst loading was increased to 4 mol% and the amount of hydrogen peroxide to 4 equivalents. When the reaction was run overnight, sulfoxide **24d** was obtained in 77% yield. Interestingly the electron-deficient double bond of **17d** was unaffected, although it could be susceptible to direct epoxidation by hydrogen peroxide.

Sulfides **17e-h** and **19a** (entries 6-9 and 11) with more electron-rich double bonds compared to **17a-c**, were also cleanly oxidized to the corresponding sulfoxides **24e-h** and **25a** without affecting the double bonds. These substrates contain an oxygen atom that could hydrogen bond to the active catalyst, thereby directing the catalyst to the double bond. Even if hydrogen bonding occurs, it apparently does not affect the

selectivity of the reaction, since no epoxide was detected with ^{1}H NMR.

Also the cycloalkenyl sulfides **19b** and **19c** (entries 12 and 13) were cleanly oxidized to sulfoxides **25b** and **25c**. The yield of **19c** was improved by increasing the amount of catalyst and hydrogen peroxide (entry 14).

With propargyl sulfide **22** a full conversion could not be reached even after prolonged reaction time (entry 15). Sulfoxide **26** was isolated in 75% yield without formation of any other oxidation products, and the rest of the crude product was unreacted starting material, which was not isolated.

As expected, the electron-rich sulfides reacted faster than the electron deficient ones. This can be exemplified by diprenyl sulfide (**23**), which was efficiently oxidized under the standard conditions, giving a high yield of sulfoxide **27** in short time (entry 16). Lowering the reaction temperature to 0 °C and with a catalyst loading of 1 mol% still gave a fast reaction and improved the selectivity and the sulfoxide to sulfone ratio was 98.5:1.5.

It has previously been shown in our group that flavins are good catalysts also for the oxidation of tertiary amines.[17,27] It is well known that tertiary amines are oxidized faster than secondary amines. However, there is little knowledge about the competitive behavior of tertiary amines *vs.* thioethers. To investigate the relative rate of oxidation the amino sulfide **17j** was exposed to the reaction conditions. Gratifyingly, sulfoxide **24j** was the only product and was isolated in 86% yield after 3 h (entry 16). To make sure that no *N*-oxide that may have been reduced in the work-up, was formed during the reaction, the reaction was monitored by ^{1}H NMR. No oxidation of the amine moiety was detected, which shows that the selectivity of the catalyst is high.

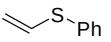
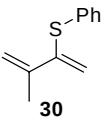
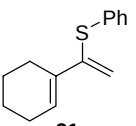
3.3.2 Oxidation of Vinylic Sulfides

The oxidation of vinylic sulfides was subsequently investigated using 2 mol% of **1**. The reaction with these substrates turned out to be much less efficient, as vinyl sulfide **28** gave only 24% conversion to the corresponding sulfoxide **29** after 3 h (Table 5, entry 1). Increasing the catalyst loading to 4 mol% and using 4 equiv. of hydrogen peroxide resulted in 75% conversion and 60% yield of sulfoxide **29** (entry 2).

When applying the method to the 1,3-dienic vinylic sulfides **30** and **31** the reactivity decrease is even more pronounced. Conversions of only 11 and 12% for sulfides **30**

and **31**, respectively, were reached after 3 h (entries 3 and 5). Also the yields of **32** and **33** were improved by increasing the amount of catalyst and hydrogen peroxide. Changing the oxidant source from aq. H_2O_2 to urea·H_2O_2-adduct gave better results for sulfides **30** and **31** (entries 4 and 6), which could be due to higher solubility and increased stability of the oxidant.

Table 5. Oxidation of vinylic sulfides with the flavin catalyst-H_2O_2 system.

Entry	Sulfide	Sulfoxide	H_2O_2 (equiv)	Conv. (%)	Yield (%)
1	 **28**	**29**	1.5	24[a]	n.d.[b]
2			4	75[c]	60
3	 **30**	**32**	1.5	11[a]	n.d.
4			10	74[d]	53
5	 **31**	**33**	1.5	12[a]	n.d.
6			10	80[d,e]	60

[a)] The reactions were performed using 2 mol% of **1** in MeOH at rt For 2.5-3 h. [b)] n.d. = not determined. [c)] The reaction was run for 24 h using 4 mol% of **1**. [d)] The reaction was run for 48 h using 4 mol% of **1**, and H_2O_2·urea complex. [e)] The reaction was run at 35 °C.

No sulfone or epoxide formation was detected in any of the above oxidations. The moderate yields in Table 5 can be a result of longer reaction times (and elevated temperature for sulfide **31**) required for these reactions, during which decomposition of the catalyst can occur. The reactivity of the vinylic sulfides compared to that of allylic sulfides can be explained by the frontal orbital theory; the HOMO of vinylic sulfides is significantly lower than that of allylic sulfides, due to conjugation of the sulfide lone pair with the double bond. This leads to a weaker interaction between the HOMO of the sulfide and the LUMO of the hydroperoxyflavin **1'** as well as lower nucleophilicity of the vinylic sulfides and some of the chemoselectivity obtained for the allylic sulfides is lost going to vinylic sulfides. This effect is even more prominent with the 1,3-dienic sulfides, since the electrons are even more dispersed over the conjugated system.

3.4 Conclusions

We have shown that the oxidation protocol using flavin catalyst **1** and hydrogen peroxide can be applied to the oxidation of allylic sulfides and some vinylic sulfides. The reaction is efficient and highly chemoselective. A wide range of functional groups are tolerated, including tertiary amines, which demonstrates the mildness of the procedure. The allylic sulfoxides were obtained in high yields without any overoxidation in most of the cases, whereas vinylic sulfoxides required slightly modified conditions, to reach acceptable yields.

4 Recyclable Flavin-[BMIm]·PF_6 Catalyst System Sulfoxidation by H_2O_2

(Paper IV)

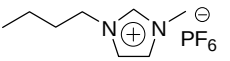
4.1 Introduction

As shown in the previous chapter, a flavin catalyst can be used in highly chemoselective oxidation of organic sulfides to sulfoxides even in the presence of double bonds and tertiary amines. The third objective of this thesis was to reuse the flavin catalyst to further improve the system.

A catalyst can be recycled in a number of ways and many of them involve immobilization on a solid support. This often requires tedious synthetic work and the amount of catalyst on the surface is many times difficult to quantify. In recent years ionic liquids have attracted a lot of attention as good, reusable reaction media for organic reactions.[73] The reusability arises from the fact that the ionic liquids have practically no vapor pressure and that it is fairly easy to extract the products from the medium. They have good solvent properties and are able to dissolve organic compounds as well as a wide range of inorganic materials such as metal catalysts.[74]

A number of reactions have been reported using ionic liquids, and among them one can find metal-, bio- and organo-catalyzed reactions.[73] The oxidation of sulfides to sulfoxides in ionic liquid has so far only been reported by two groups. Hardacre and co-workers have reported on sulfoxidation using mesoporous Ti or Ti/Ge[75] and mesoporous titanium-containing silica[76] as catalysts. Therisod and coworkers have used ionic liquids as reaction media in enzyme-catalyzed sulfoxidation.[77]

Very recently our group showed that the triple catalytic system for dihydroxylation of alkenes, including a flavin catalyst, could be immobilized in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIm]·PF_6, Figure 9).[78] This inspired us to develop a reusable flavin catalyst/ionic liquid system for oxidation of sulfides to sulfoxides.



[BMIm]PF_6

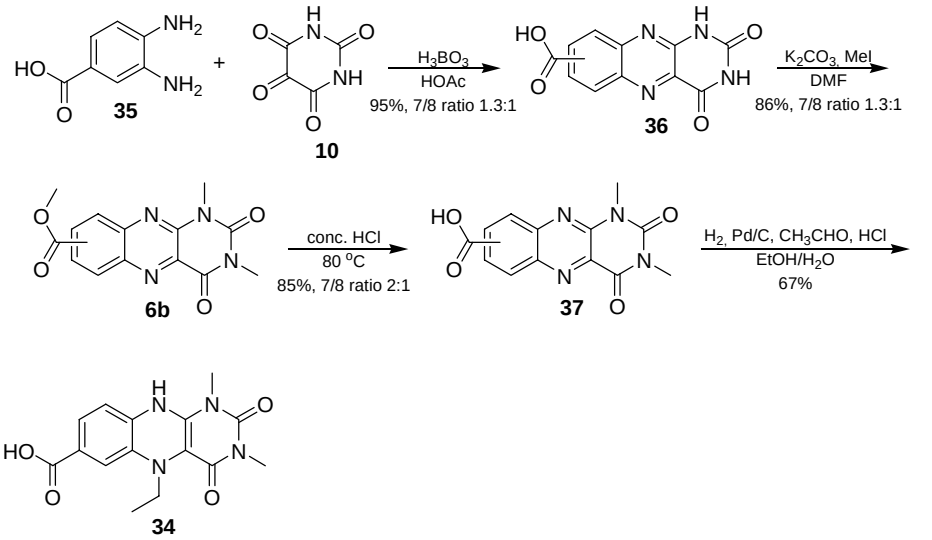
Figure 9. The ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate.

4.2 Results and Discussion

Ionic liquids are easy to use and many of them are commercially available. Since we had used [BMIm]·PF_6 earlier in the immobilization of the triple catalytic system[78] it was chosen for the sulfoxidation reactions as well. Diethyl ether was used for the extractions, since it is essentially immiscible with the [BMIm]·PF_6 ionic liquid. The flavin catalyst **1** previously used in our group was initially used in these reactions, but its solubility in diethyl ether was too high, which resulted in catalyst leaching and loss of activity. As presented in Chapter 2, a good catalytic activity was observed for the methyl ester flavin **7b**. It was therefore decided to investigate the catalytic activity of the corresponding carboxylic acid derivative **34** as it is a more polar catalyst that should be less soluble in diethyl ether at the same time as the solubility in the ionic liquid should be increased.

4.2.1 Synthesis of the Flavin Catalyst

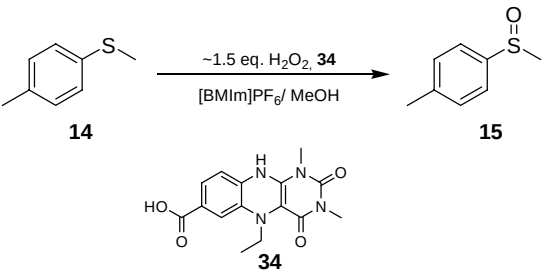
The synthesis of flavin **34** is similar to those discussed in Chapter 2. The first step of the synthesis is a condensation between 3,4-diaminobenzoic acid (**35**) and alloxane (**10**) forming the tricyclic alloxazine ring system **36** (Scheme 12). In the second step the nitrogens in positions 1 and 3 together with the carboxylic acid moiety were methylated, to give the methyl ester **6b**. The ester was subsequently deprotected and the free carboxylic acid **37** isolated in good yield. The reductive amination of **37** in the last step yields the catalyst precursor **34** in good yield which was used as such in the oxidation reactions.



Scheme 12. Synthesis of the catalyst precursor **34**.

4.2.2 Oxidation of Sulfides

The model substrate methyl *p*-tolyl sulfide (**14**) was used in the optimization of the reaction conditions (Scheme 13). It was found that using the method published earlier but using methanol/ ionic liquid [BMIm]·PF_6 as solvent and replacing flavin **1** with **34**, the sulfide **14** was efficiently oxidized to sulfoxide **15**. The reaction time was comparable with the previous method and no overoxidation was detected. This system was applied to several other sulfides and the results are given in Table 6.

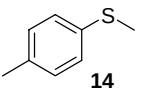
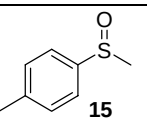
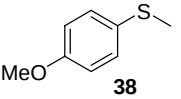
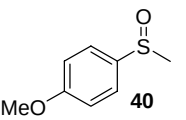
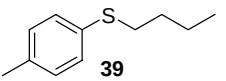
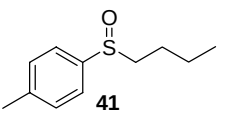
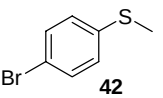
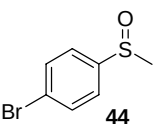
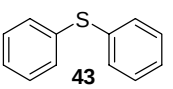
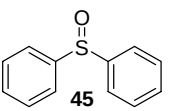
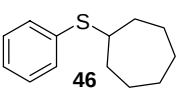
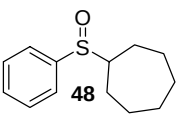
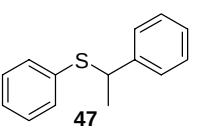
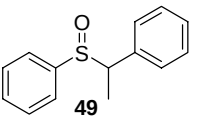


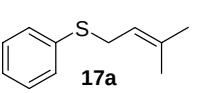
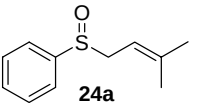
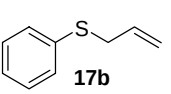
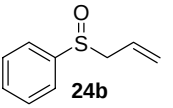
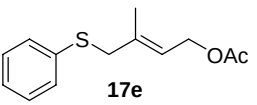
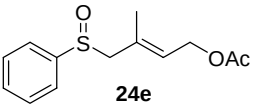
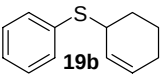
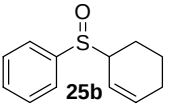
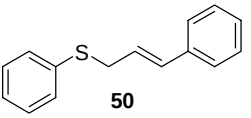
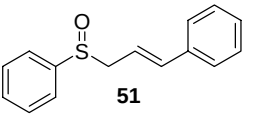
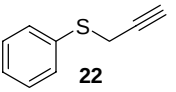
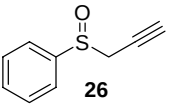
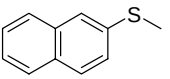
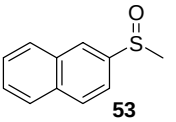
Scheme 13. Oxidation of the model substrate methyl *p*-tolyl sulfide **14**.

All the sulfides were oxidized chemoselectively in good to high yields. Both electron rich and electron poor substrates were tolerated. The electron rich sulfides **14**, **38** and **39** gave the corresponding sulfoxides **15**, **40** and **41** in 84%, 87% and 95%

yield, respectively, within 2.5 hours (Table 6, entries 1-3). The electron-deficient sulfides **42** and **43** required longer reaction times to reach acceptable yields of the sulfoxides **44** and **45** (entries 4 and 5). Sulfides **46** and **47** gave an efficient reaction even though they are more sterically crowded, and the sulfoxides **48** and **49** were isolated in 99% and 79% yield, respectively.

Table 6. Oxidation of sulfides in [BMIm]·PF_6/MeOH using **34** and hydrogen peroxide.[a]

Entry	Substrate	Product	Time (h)	Yield[b] (%)
1	 **14**	 **15**	1	78
2	 **38**	 **40**	1.5	87[c]
3	 **39**	 **41**	2.5	95
4	 **42**	 **44**	5	83[d]
5	 **43**	 **45**	5	60[d]
6	 **46**	 **48**	3.5	99
7	 **47**	 **49**	4.5	79

8	 **17a**	 **24a**	2	91
9	 **17b**	 **24b**	2	78
10	 **17e**	 **24e**	4.5	82
11	 **19b**	 **25b**	4.5	76
12	 **50**	 **51**	4	80
13	 **22**	 **26**	6	66
14	 **52**	 **53**	7	87

[a] Unless otherwise noted: The reactions were run using 1 mmol of sulfide in 0.5 mL [BMIm]·PF_6 and 3.2 mL MeOH. Flavin **34** (2 mol%) and H_2O_2 (1.5 equiv.) were added and reaction stirred for 1.5-7 h. [b] Unless otherwise noted: isolated yields. [c] An average yield of 1 run, the products of 6 runs were combined and chromatographed together. [d] NMR yield.

It was important to maintain the chemoselectivity established for the flavin-catalyzed sulfoxidation, and to investigate this a few allylic sulfides were oxidized to their corresponding sulfoxides. We were pleased to find that the system was compatible with substrates bearing a double bond and no epoxidation occurred (entries 8-12). Even sulfide **17a**, with two electron donating methyl groups on the double bond, and sulfide **17e** with an acyl group that can hydrogen bond to the catalyst and direct it to the double bond, gave clean reactions without formation of either epoxide or sulfone (entries 8 and 10). The oxidation of propargyl sulfide **22** was stopped after 6 hours having reached 86% conversion and product **26** was isolated in

66% yield (entry 13). Naphthyl methyl sulfide (**52**) reacted slowly due to poor solubility in the reaction media and sulfoxide **53** was isolated in good yield after 7 hours.

The isolated yields were slightly lower for the more polar substrates, which is due to incomplete extraction of the sulfoxide from the ionic liquid. The background reactions *i.e.* oxidation without pre-catalyst **34**, was measured on sulfide **14**. The reaction was monitored by GC and a comparison between the catalyzed and uncatalyzed reactions was made. The results are presented in Figure 10 and show that the background reaction is negligible compared to the catalyzed reaction.

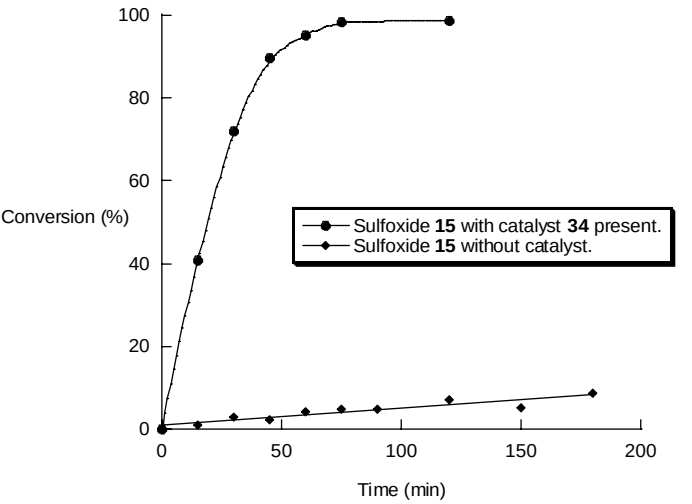
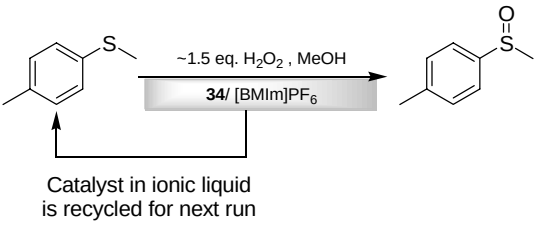


Figure 10. The amount of sulfoxide **15** with and without pre-catalyst **34** present.

4.2.3 Recycling of the flavin catalyst in ionic liquid [BMIm]·PF_6

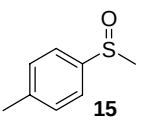
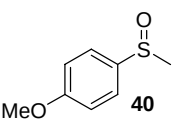
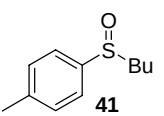
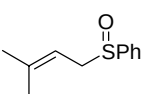
Methyl *p*-tolyl sulfide (**14**) was used as the model substrate in the development of the recycling system. The principle of the system is depicted in Scheme 14. The reactions were run as above, but after the reaction was complete (followed by TLC) the methanol co-solvent was evaporated and the residual ionic liquid was extracted with diethyl ether. The combined ether phases were treated with sodium dithionite to destroy residual hydrogenperoxide and extracted with water.



Scheme 14. A representative reaction for the catalyst recycling system.

The ionic liquid catalyst system was recycled up to 7 times (with **38**) and no significant loss of activity or selectivity was observed (Table 7). The recycling of the catalyst system was performed with four different sulfides and high yields were obtained through 3-7 runs.

Table 7. Recycling of the flavin catalyst in ionic liquid.[a,b]

Entry	Product	Yield[b] (%)					
		Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	 **15**	78	84	80	88	91	89
2[c]	 **40**	87[d]	87[d]	87[d]	87[d]	87[d]	87[d]
3	 **41**	95	98	89	86	92	94
4[e]	 **24a**	91	94	88	-	-	-

[a)] Unless otherwise noted: The reactions were run using 1 mmol of sulfide in 0.5 mL [BMIm]·PF_6 and 3.2 mL MeOH. Flavin (2 mol%) and H_2O_2 (1.5 equiv.) were added and the reaction was stirred for 1-2.5 h. [b)] Isolated yields. [b)] Conversion determined by ^{1}H-NMR and was 96-99%. [c)] Seven runs were run for this substrate and the 7th run gave 88% yield. [d)] The crude products of runs 1-6 were combined to give 482% isolated yield converted on one run, which gives in average 87% yield per run. [e)] Only three runs were run due to lack of substrate.

The system retains its activity throughout the runs. When the allylic sulfide **17a** was subjected to recycling the chemoselectivity did not decrease, as neither epoxide nor sulfone was detected in any of the runs made with the recycled catalyst. The flavin-catalyst ionic liquid system could be stored in the freezer for days between the runs without any significant deactivation of the catalyst, even though the flavin catalysts are known to be sensitive towards auto-oxidative degradation, which is generally fast in solution. The flavin-catalyst **34** seems to be stable in the ionic liquid.

4.3 Conclusions

A range of sulfides have been oxidized selectively using a flavin-catalyst ionic liquid system. The reusability of the catalyst system was demonstrated using four different sulfides and the activity was retained in at least 7 runs. Recycling the catalyst system did not affect the selectivity of the system.

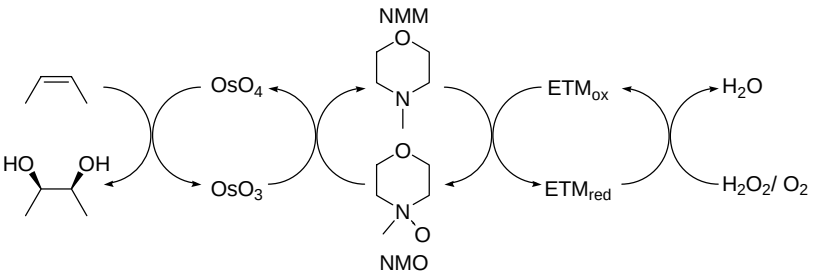
5 Bimetallic Catalyst System for H_2O_2-based Dihydroxylation of Olefins Immobilized in [BMIm]·PF_6

(Paper III)

5.1 Introduction

The osmium-catalyzed dihydroxylation of alkenes is a very important transformation leading to useful building blocks for further modifications of the molecule (*e.g.* transforming one of the hydroxyl groups into a leaving group and reacting it with a nucleophile).[79,80] The dihydroxylation is very specific and easy to perform, during the past years many systems have been developed for this reaction. Since osmium is extremely toxic it is desirable to use it in catalytic amounts. Typical reoxidants are 4-methylmorpholine *N*-oxide (NMO), used in the Upjohn reaction[81] and potassium ferricyanide, often employed in the asymmetric version of the reaction.[82] From an environmental point of view, molecular oxygen or hydrogen peroxide, are preferred since they produces no waste products.

The main focus of our group has been to develop systems utilizing hydrogen peroxide in the osmium-catalyzed dihydroxylation reaction.[28-30,78,83,84] These systems are triple-catalytic and the energy-barriers are lowered by the use of different electron transfer mediators (ETM's) like in nature (Scheme 15). This results in a mild and selective reaction. NMO is used to reoxidize the formed osmium(VI) back to osmium(VIII). The formed 4-methylmorpholine (NMM) in turn is oxidized back to NMO using an ETM. This ETM can be a metal catalyst such as vanadium(V)oxide (V_2O_5),[84] vanadyl acetylacetonate ($VO(acac)_2$) **54**[84] or methyltrioxorhenium (MTO) **55**[83,85] or it can be an organo-catalyst like flavin **1**.[28-30]



Scheme 15. The triple catalytic system for dihydroxylation of olefins.

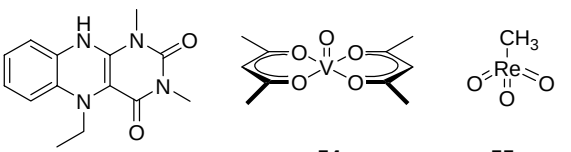


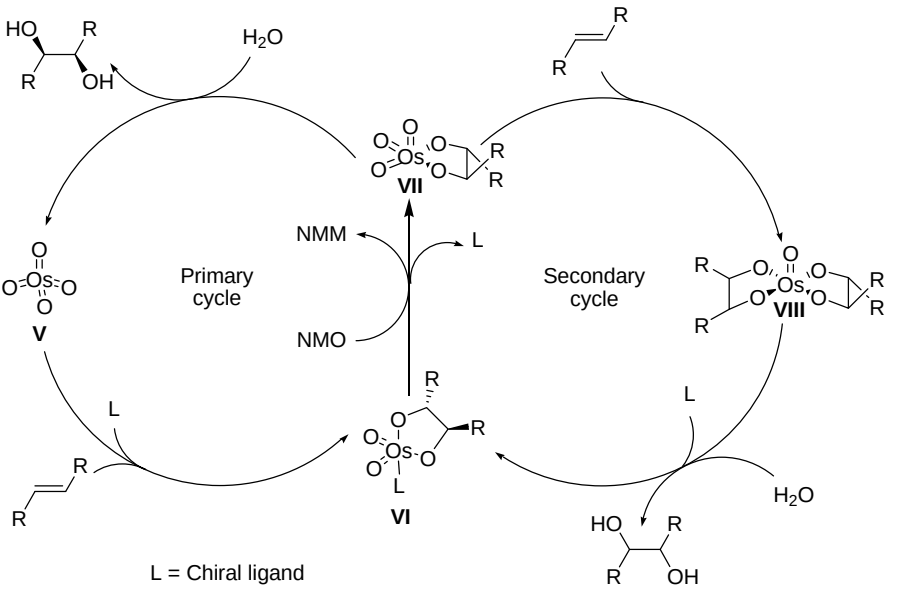
Figure 11. Different ETMs for the oxidation of NMM.

Several methods for immobilization of OsO_4 have been reported in the literature and they have been recently reviewed.[80] They have concerned chemical anchoring of osmium to a solid support,[86-88] polymer encapsulation of osmium tetroxide,[89-91] and dissolving osmium tetroxide in ionic liquid.[92-95] Very recently it was shown by our group that the triple-catalytic system using flavin **1** as hydrogen peroxide activator could be immobilized in [BMIm]·PF_6.[78] We wanted to immobilize also the bimetallic triple-catalytic systems in the ionic liquid.

5.2 Mechanism of the Osmium Catalyzed Dihydroxylation

The mechanism in Scheme 16 was first proposed by Sharpless and co-workers,[96,97] and it is widely accepted in the chemical community. The cycle starts with the addition of OsO_4 (**V**) to the alkene (osmylation) forming the osmium(VI) monoglycolate-amine complex **VI**. The chiral ligand **L** contains an amine functionality, which coordinates to osmium. Subsequent oxidation to form osmium(VIII) trioxoglycolate **VII** takes place. To release the enantiopure product intermediate **VII** is hydrolysed and this step is often rate limiting. If the latter step is too slow a second alkene molecule can coordinate, thus entering the secondary cycle. Osmium(VI) oxodiglycolate **VIII** is

then formed and since no chiral ligand is present there is no face selection and a racemic product is obtained.



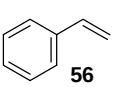
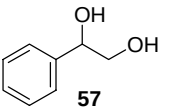
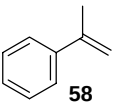
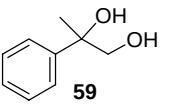
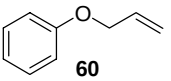
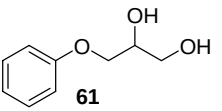
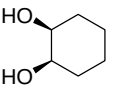
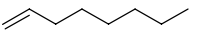
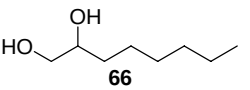
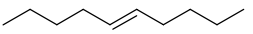
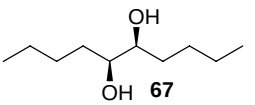
Scheme 16. The catalytic cycles for the osmium-catalyzed dihydroxylation.

5.3 Results and Discussion

5.3.1 $VO(acac)_2$ as co-catalyst

The protocol established earlier in our group for the $VO(acac)_2$-mediated dihydroxylation of olefins was used with 0.5 mL of $[BMIm]\cdot PF_6$ added (Table 8). The reaction of styrene **56** afforded the diol **57** in 81% yield (entry 1). Also α-methylstyrene (**58**) reacted well and gave the corresponding diol **59** in high yields (entry 2). Olefin **60** was converted to the corresponding diol **61** in good yield (entry 3). Cyclohexene (**62**) and acyclic aliphatic olefins **63** and **64** gave good to high yields of the corresponding diols **65**-**67** (entries 4-6). All the yields reported here were in similar range as those reported for the previous method, which shows that the catalyst system is compatible with the ionic liquid.

Table 8. Osmium-catalyzed dihydroxylation of alkenes in ionic liquid using $VO(acac)_2$ as co-catalyst[a]

Entry	Olefin	Product	Yield[b] (%)
1	 **56**	 **57**	81
2	 **58**	 **59**	91
3	 **60**	 **61**	81
4	 **62**	 **65**	91
5	 **63**	 **66**	81
6	 **64**	 **67**	87

[a] Selected results; Experimental conditions: $K_2OsO_4 \cdot 2H_2O$ (2 mol%), $VO(acac)_2$ (2 mol%), NMM (23 mol%), and $Et_4N^+OAc^-$ (TEAA, 2 equiv.) were stirred in $[BMIm] \cdot PF_6$ (0.5 mL). Acetone (3.8 mL) and H_2O (1.2 mL) were added as co-solvents together with the olefin (1 mmol). H_2O_2 (30% aq., 1.5 mmol) was added over 8 h with syringe pump followed by 8 h of reaction at rt. [b] Isolated yields.

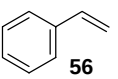
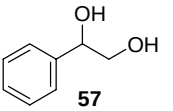
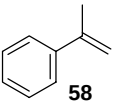
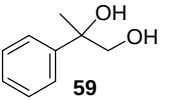
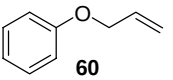
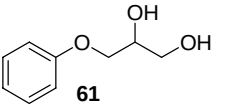
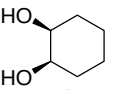
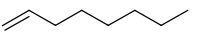
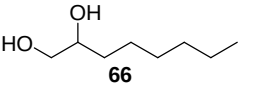
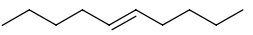
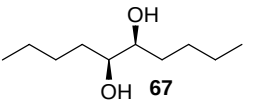
5.3.2 MTO as co-catalyst

MTO is known to undergo decomposition to methanol and catalytically inactive perrhenic acid by H_2O_2 at alkaline pH.[98] It has therefore been problematic to utilize it as H_2O_2–activating catalyst in the osmium-catalyzed dihydroxylation, which generally operates at a pH around 10. This problem was solved by using small amounts of citric acid together with MTO in the dihydroxylation.[85]

Reacting styrene (**56**) with hydrogen peroxide in $[BMIm] \cdot PF_6$/acetone catalyzed by $K_2OsO_4 \cdot 2H_2O$ (2 mol%) and MTO (2 mol%) in the presence of citric acid afforded the corresponding diol **57** in excellent yield (Table 9, Method A, entry 1). Olefins **58** and **60** gave the corresponding diols **59** and **61** in good yields (entries 2 and 3). This less

basic protocol worked well for some olefins. However, especially the aliphatic olefins with internal double bonds gave a lot of cleaved product (entries 4 and 6). It is well-known that the cleavage is faster at lower pH. The only aliphatic olefin that gave a clean reaction and high yield of the corresponding diol using 5 mol% of citric acid was 1-octene (**63**) (entry 5).

Table 9. Osmium-catalyzed dihydroxylation of alkenes in ionic liquid using MTO as co-catalyst.[a]

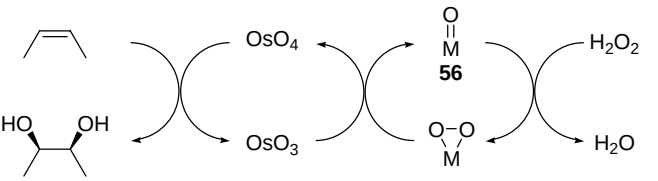
Entry	Substrate	Product	Method A[b] Yield (%)[d]	Method B[c] Yield (%)[d]
1	 **56**	 **57**	95	74[e]
2	 **58**	 **59**	99	86
3	 **60**	 **61**	86	68
4	 **62**	 **65**	41	72
5	 **63**	 **66**	78	90
6	 **64**	 **67**	18	85

[a] Selected results. [b] Method A: $K_2OsO_4 \cdot 2H_2O$ (2 mol%), MTO (2 mol%), NMM (20 mol%) and citric acid (5 mol%) were stirred in [BMIm]·PF_6 (0.5 mL). Acetone (1 mL) and H_2O (0.2 mL) were added as co-solvents together with the olefin (1 mmol). H_2O_2 (30% aq., 1.5 mmol) was added over 4 h followed by 4-16 h of reaction. [c] Method B: As method A apart from TEAA (2 equiv.) instead of citric acid, 3 mL acetone and 8 h addition of H_2O_2 with syringe pump and 8 h additional reaction. [d] Isolated yields. [e] H_2O_2 was added over 4 h followed by an additional 16 h of stirring. [f] Not determined due to poor conversion.

Since the method based on citric acid did not give satisfactory results for all the olefins, citric acid was replaced by tetraethyl ammonium acetate (TEAA). This proved

to be more successful and high yields were obtained for all the aliphatic olefins. (Method B, entries 4-6). Also the aromatic olefins gave satisfactory results although the yields were better with the citric acid-assisted method (Mehtod A, entries 1-3).

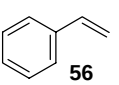
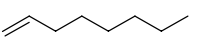
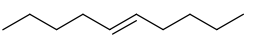
The OsO_3 can be oxidized directly with MTO, thus the significance of this reaction in the TEAA-based method was investigated (Scheme 17). Six different olefins were oxidized without any NMM present (selected examples in Table 10).



Scheme 17. Coupled bimetallic catalytic system for dihydroxylation of olefins without NMM.

Styrene **56** was oxidized in good yield even without NMM (entry 1). Also cyclohexene (**62**) gave the corresponding diol **65** in good yield (entry 2). Olefin **63** reacted highly efficiently yielding 95% of diol **66** (entry 3), whereas **64** gave the diol **67** in only 75% yield (entry 4). The results show that direct oxidation of OsO_3 to OsO_4 by MTO works well but in some cases the presence of NMM improves the outcome of the dihydroxylation.

Table 10. Osmium-catalyzed dihydroxylation of alkenes in ionic liquid using MTO as co-catalyst without NMM.[a]

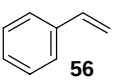
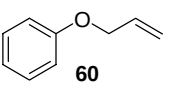
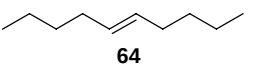
Entry	Olefin	Yield of diol (%)[b]
1	 **56**	74
2	 **62**	88
3	 **63**	95
4	 **64**	75

[a] Selected results; $K_2OsO_4 \cdot 2H_2O$ (2 mol%), MTO (2 mol%), and TEAA (2 equiv.) were stirred in [BMIm]·PF_6 (0.5 mL). Acetone (3 mL) and H_2O (0.2 mL) were added as co-solvents together with the olefin (1 mmol). H_2O_2 (30% aq., 1.5 mmol) was added over 8 h with syringe pump followed by 8 h of reaction. [b] Isolated yields.

5.3.3 Recycling of the Bimetallic Systems

The results presented above were encouraging and the attention was turned to recycling these systems in the ionic liquid. To find out if the catalytic activity of the system could be maintained, the catalysts in ionic liquid (the "catalytic soup"[78]) was reused. For the initial experiments styrene (**56**) and allyl phenyl ether (**60**) were used as model olefins (Table 11, entries 1 and 2). There was practically no loss of catalytic activity over five cycles using the OsO_4/NMM/$VO(acac)_2$/H_2O_2 triple-catalytic system, which shows that it is possible to recycle this system. However, the aliphatic olefin (*E*)-5-decene (**64**) gave only a moderate yield in the second use of the catalytic soup. This could be due to the fact that the hydrolysis of the osmate ester is slower for this substrate, causing loss of catalyst during the extraction.

Table 11. Recycling of the bimetallic OsO_4-$VO(acac)_2$ catalytic system.[a]

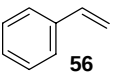
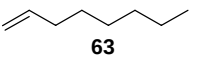
Entry	Olefin	Yield (%)[b]				
		Run 1	Run 2	Run 3	Run 4	Run 5
1	 **56**	81	83	84	78	83
2	 **60**	81	88	74	80	82
3	 **64**	87	43	n.d.[c]	-	-

[a] Selected results; $K_2OsO_4 \cdot 2H_2O$ (2 mol%), $VO(acac)_2$ (2 mol%), NMM (20 mol%) and TEAA (2 equiv.) were stirred in [BMIm]·PF_6 (0.5 mL). Acetone (3.8 mL) and H_2O (1.2 mL) were added as co-solvents together with the olefin (1 mmol). H_2O_2 (30% aq., 1.5 mmol) was added over 8 h with syringe pump followed by 8 h of reaction. [b] Isolated yields. [c] Not determined.

Recycling of the MTO-mediated dihydroxylation system was also attempted, but turned out to be less productive compared to the $VO(acac)_2$ system. Severe contamination of product from carbon-carbon bond cleavage in the citric acid-based method was detected already in the third run for styrene (**56**) (Table 12, entry 1). Thus, the method utilizing TEAA together with MTO (method B) was chosen instead, since

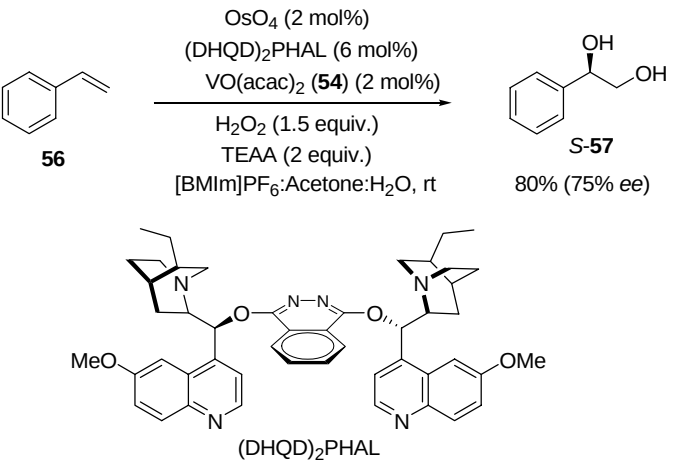
it gave better yields for the aliphatic olefins. The oxidation of **62** resulted in good yield of diol **65** through 3 runs and dropped in the fourth run (entry 2). The yield of diol **66**, resulting from the aliphatic olefin **63**, dropped steadily for each reuse of the ionic liquid-catalyst system (entry 3).

Table 12. Recycling of the OsO_4-MTO catalytic system.[a]

Entry	Olefin	Yield (%)[b]			
		Run 1	Run 2	Run 3	Run 4
1[c]	 **56**	81	38[d]	n.d.[e]	-
2	 **62**	72	70	84	46
3	 **63**	98	76	59	n.d.[e]

[a)] Selected results; Method B: $K_2OsO_4 \cdot 2H_2O$ (2 mol%), MTO (2 mol%), NMM (20 mol%) and TEAA (2 equiv.) were stirred in 0.5 mL of [BMIm]·PF_6. Acetone (3 mL) and H_2O (0.2 mL) were added as co-solvents together with the olefin (1 mmol). H_2O_2 (30% aq., 1.5 equiv.) was added over 8 h with syringe pump followed by 8 h of reaction. [b)] Isolated yields. [c)] $K_2OsO_4 \cdot 2H_2O$ (0.5 mol%), MTO (2.5 mg, 1 mol%), NMM (20 mol%) and Citric acid (75 mol%) were stirred in [BMIm]·PF_6 (0.5 mL). Acetone (3 mL) and H_2O (0.2 mL) were added as co-solvents together with the olefin (1 mmol). H_2O_2 (30% aq., 1.5 mmol) was added over 4 h with syringe pump followed by 8 h of reaction. [d)] H_2O_2 was added over 8 h with syringe pump and the reaction stirred for additional 8 h. [e)] Not determined due to poor conversion.

An important issue was to find out whether the hydrogen peroxide-based dihydroxylation in ionic liquid was compatible with chiral ligands. In a test reaction with styrene (**56**) using the chiral ligand $(DHQD)_2PHAL$ and the osmium-$VO(acac)_2$ catalytic system diol *S*-**57** was obtained in 80% yield and 75% *ee* (Scheme 18). In this reaction no NMM was needed, because the chiral ligand works as an electron transfer mediator in itself.[83] Further optimization of this system is necessary to improve the *ee*.



Scheme 18. Asymmetric dihydroxylation using $(DHQD)_2PHAL$ in the osmium-$VO(acac)_2$ catalytic system.

5.4 Conclusions

Two bimetallic catalytic dihydroxylation systems operating in ionic liquid $[BMIm]\cdot PF_6$ using hydrogen peroxide as terminal oxidant has been investigated. These systems utilize either $VO(acac)_2$ or MTO as ETMs working together with Osmium. The two bimetallic catalytic systems were tested with a variety of aromatic and aliphatic olefins and gave the corresponding 1,2-diols in good to excellent yields. NMM can be used as an additional ETM to facilitate a more selective reaction. It was demonstrated that in some cases direct electron transfer from MTO to osmium is efficient without added NMM.

No or moderate loss of catalytic activity by reusing the system was observed, thereby demonstrating the immobilization and recycling of the catalytic system. The bimetallic catalytic system in room temperature ionic liquid gives a simple and reusable “catalytic soup”, which is environmentally benign as hydrogen peroxide is the terminal oxidant and the only by-product formed is water.

6 Concluding Remarks

The properties of eight different flavins were studied and their catalytic activity was measured in sulfoxidation. The electrochemical potentials of the flavins were also presented and compared to the catalytic activities. It was shown that electron-deficient flavins require longer activation times and are more stable towards auto-oxidative degradation. Some fairly stable flavins were prepared and a few of them were shown to have good catalytic activity. A linear free-energy relationship between the electrochemical oxidation potentials and the respective Hammett σ values was obtained with seven of the prepared flavins.

An environmentally benign and selective system for sulfoxidation by H_2O_2 has been developed. A flavin-catalyst was applied in the chemoselective oxidation of allylic and vinylic sulfides. The sulfoxides were obtained in good to excellent yields and no overoxidation was detected except for the most electron-rich allylic sulfide. The amount of the formed sulfone was very low even in that case. No epoxide formation was detected in any of the cases nor was the tertiary amine present in sulfide **17j** oxidized. The flavin **34** was successfully immobilized in an ionic liquid and used for sulfoxidations of various sulfides including some allylic sulfides. The chemoselectivity established in the oxidation of allylic substrates was maintained and the catalyst system was recycled up to seven times.

Immobilization of two bimetallic systems for dihydroxylation of olefins by H_2O_2 was presented. $VO(acac)_2$ was used together with osmium and TEAA to give good to high yields of the diols. Two complementary methods for the MTO-catalyzed dihydroxylation with osmium and hydrogen peroxide were developed. The catalyst system utilizing $VO(acac)_2$ as ETM was applicable for recycling. However, the MTO-mediated dihydroxylation system, even though it worked to a certain extent, was not as productive.

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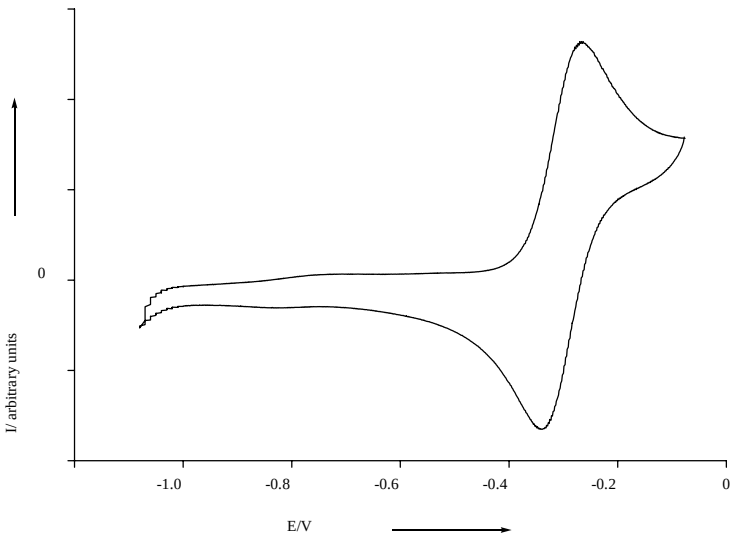
Appendix



A representative cyclic voltammogram for *N*,*N*-1,3-dimethyl-*N*-5-butyl-5,10-dihydroalloxazine (**7e**).

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