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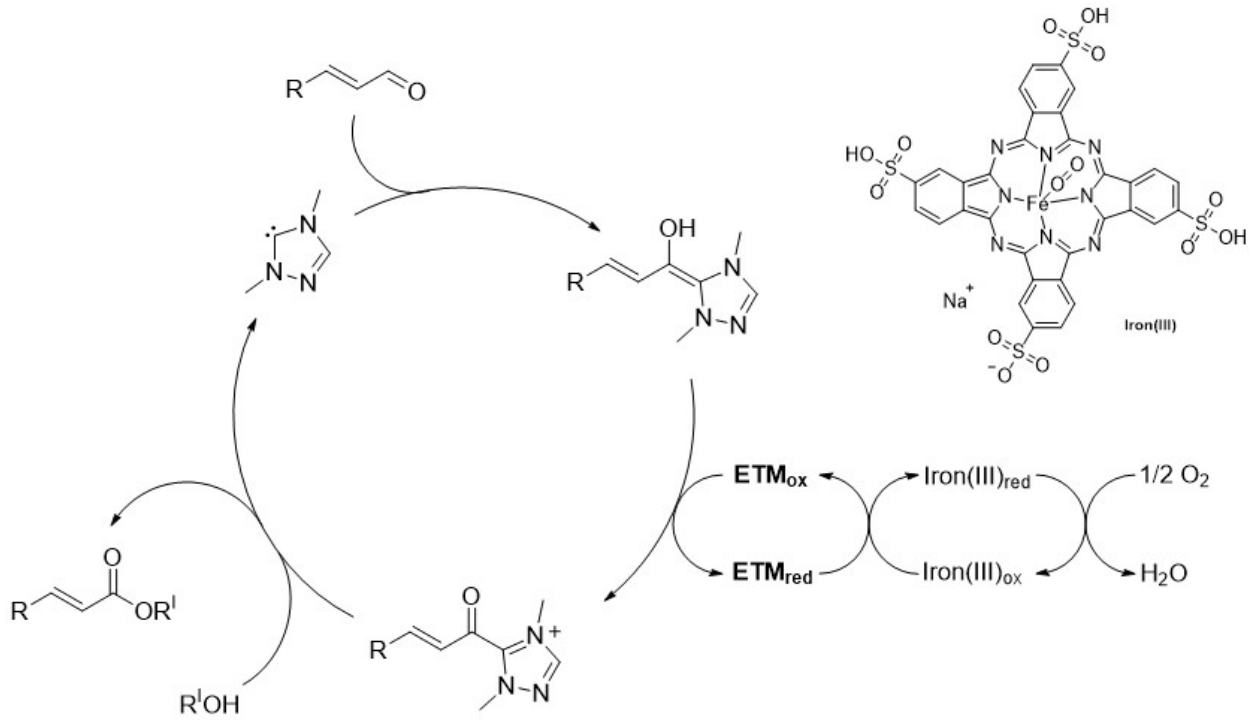

Implementation of water as solvent in aerobic oxidative NHC-catalysis

Method developing using oxidative esterification as model reaction

Master's thesis in Materials Chemistry

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Department of Chemistry and Chemical Engineering
CHALMERS UNIVERSITY OF TECHNOLOGY
Gothenburg, Sweden 2018

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Cover: Aerobic oxidative NHC-catalyzed synthesis of methyl cinnamate from cinnamaldehyde and methanol. Oxidation of acyl azolium intermediate made possible the use of catalytic oxidants, ETMs.

Typeset in LaTeX
Gothenburg, Sweden 2018

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Abstract

Green chemistry works towards making chemistry more benign and environmental friendly. In previously done studies N-heterocyclic carbene catalysis has been used in synthesis creating a range of different molecules. This was done with aerial oxygen as the terminal oxidant and made possible by the help of so called electron transfer mediators, ETMs, creating a low energy path for the oxidation step of the reaction. One way to make this type of reaction even greener would be to use a more benign solvent, like water. This proves to be a problem since organic molecules tends to be hydrophobic. This thesis shows that by changing the used hydrophobic ETM to a more hydrophilic one made the model reaction possible to be carried out in water.

Keywords: N-heterocyclic carbene, Electron transfer mediator, aerobic oxidation, solvent, water, green chemistry.

Acknowledgements

I would like to thank my supervisor **Dr. Henrik Sundén** for giving me the opportunity to learn more about the field of organic- and green chemistry.

I want to give a big thank you to my co-supervisor **Anton Axelsson** for all the help that you gave me throughout my work.

I want to thank my examiner, **Nina Kann**, for taking the time to evaluate my work.

I also want to thank all people on the 9th floor for the help and all of the fun times I've had while doing my thesis.

Last but not least I want to thank **my family** and **my friends** for all of the support and encouragement that they have given me.

Victor Strand, Gothenburg, June 2018

Contents

1 Introduction **1**
1.1 Development towards a Sustainable future 1
1.1.1 The principles of Green Chemistry 1
1.2 Catalysis 4
1.2.1 Organocatalysis 6
1.3 N-heterocyclic carbenes 7
1.4 Electron transfer mediators 8
1.5 Water in organic reactions 10

2 Background **13**
2.1 Oxidative NHC catalysis via multistep electron transfer 13
2.2 Aim 16

3 Result and discussion **17**
3.1 Optimization of reaction 17
3.1.1 Screening of base 17
3.1.2 Screening of ETM 18
3.1.3 Screening of catalyst 19
3.1.4 LiOH and different concentrations of water and nucleophile . . 20
3.1.5 Brine as solvent 21
3.1.6 Reaction in MeOH 23

4 Conclusions **25**

Bibliography **27**

A Appendix 1 **I**
A.1 General procedure I
A.1.1 First general procedure for optimization of reaction conditions I
A.1.2 Second general procedure for optimization of reaction conditions II
A.1.3 Third general procedure for optimization of reaction conditions IV
A.1.4 Representative procedure for isolation of methyl cinnamate . . V
A.1.5 Synthesis of precatalyst, Cat5 VI

B Appendix 2 **IX**
B.1 NMR spectra IX

1
Introduction

1.1 Development towards a Sustainable future

In order to create a sustainable future for us and for generations to come, improvements must be done to the ways industries operate. The chemical industry plays a significant part in this. When developing a more sustainable industry factors like chemical toxicity, energy efficiency and waste production must be taken into account. The sustainable development of the chemical industry is based on the 12 principles of green chemistry which were written in 1998 by Paul T. Anastas and John C. Warner as a reaction to the growing demand of more benign chemistry[1]. The usage of non-green chemistry can have dire consequences if there were to be an accident. In Bhopal 1984 a leakage of methyl isocyanate, approximately 45 tons of toxic gas, led to the death of over 15 000 people. This is an example that is used in today's teaching about green chemistry and sustainability to highlight the importance of safety regulations and safe work environment as well as accident prevention. The incident is called one of the largest disasters that has been caused by the chemical industry[2]. Another focus that green chemistry has is the minimization of the carbon footprint that is currently being left by pollutions from today's society. Factors like these has throughout recent years led to that a lot of focus has been put on making the existing chemistry safer and greener.

1.1.1 The principles of Green Chemistry

The 12 principles sets the foundation of green chemistry, see Table 1.1[1]. This thesis will mainly be focused on including principle 1, 2, 5, 7 and 9. The first principle, Prevention, focuses on the production of waste. It is always more preferable to avoid creating any type of waste instead of cleaning it up after it has been created. If waste products can not be avoided it is of interest to find a use for it instead, an example of an interesting area for this is biofuels[3]. Food waste can, through chemical processes, be turned into fuels such as biodiesel, bioethanol and bio-oil[4]. The production of waste leads to a cost that consists of many different factors. In 1997, John Elkington constructed the Triple bottom line (TBL) which shows the contribution of the social, financial and social strands. This in turn shows that by avoiding the production of waste a number of subsequent costs are avoided, see Figure 1.1[5].

Table 1.1: The 12 principles of green chemistry.

1. Prevention	2. Atom economy	3. Less hazardous chemical synthesis
4. Designing safer chemicals	5. Safer solvents and auxiliaries	6. Design for energy efficiency
7. Use of renewable feedstock	8. Use derivatives	9. Catalysis
10. Design for degradation	11. Real-time analysis for pollution prevention	12. Inherently safer chemistry for accidental prevention

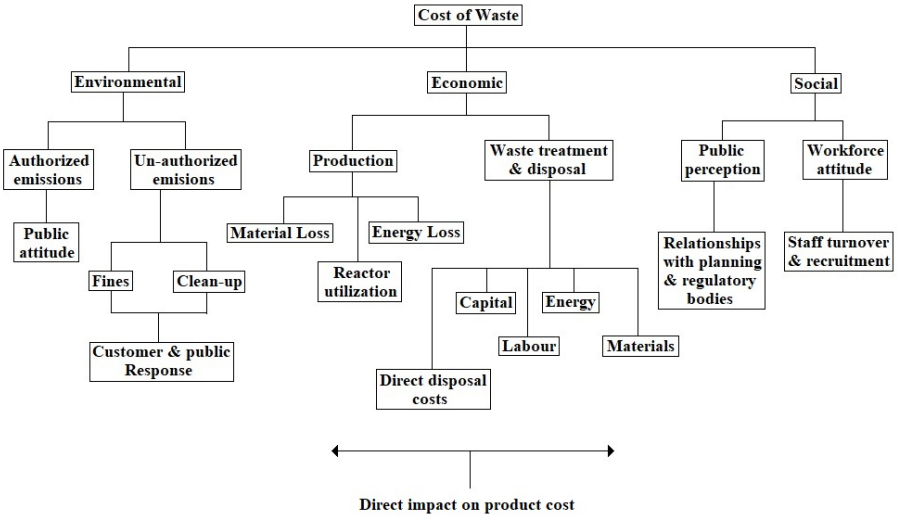


Figure 1.1: The costs of waste expressed in terms of the triple bottom line.

In order for a reaction to be efficient and desirable a substantial amount of product must be achieved per amount of used reactant but also, as said before, not create waste. For this a good atom economy is needed. Atom economy is described by the equation seen in Figure 1.2.

In the given reaction butanol is brominated by sodium bromide and sulfuric acid. As can be seen in the equation in equation 1.1 not only the desired product is formed but also sodium hydrogen sulfate and water. Atom economy calculates the total amount of atoms that ends up in the final, desired, product. Most desirable is an atom economy of 100% where no unwanted side products are created.

$$AtomEconomy = (M_{Product}/M_{Reactants}) * 100\% = (137/275) * 100\% = 50\% \quad (1.1)$$

Figure 1.2: Example calculation of atom economy for a given reaction.

The equation does not take into account the amount of solvent use of the reaction. In order to include it the environmental factor, E-factor, is used, see Equation 1.2. The E-factor describes the ratio between the amount of waste that is created per kg of product created[6]. The E-factor can be calculated with the usage of water both included or excluded. Often the usage of water is excluded due to the fact that if it were to be included the E-factor would be exceptionally larger and thereby making it more difficult to compare different processes[7].

$$E = (\sum m_{waste} / \sum m_{product}) \quad (1.2)$$

As can be seen in Table 1.2 a consistent trend can be seen that the more pure the product needs to be the amount of waste created is also increased. In fine chemical production multi-step reactions is necessary in order to create the desired products. Several clean up steps is also needed in order to purify the products leading to the increased use of solvent and thereby creation of waste[6].

Table 1.2: Different E-factors in the chemical industry.

Industry segment	Product tonnage	E-factor (kg waste/kg product)
Oil refining	10^6-10^8	>0.1
Bulk chemicals	10^4-10^6	<1-5
Fine chemicals	10^2-10^4	5-50
Pharmaceuticals	10-10^3	25-100

Another way to measure the efficiency of a reaction is by calculating the process mass intensity, PMI, which gives the ratio between all materials that is used and the isolated product, see Equation 1.3.

$$PMI = (\sum m_{(materials)} / \sum m_{product}) \quad (1.3)$$

According to studies, done by a couple of pharmaceutical companies and the American Chemical Society Green Chemistry Institute, the avarage amount of solvent used per obtained kg of product was about 55 kg. When all waste was added up it resulted in a PMI of about 77 kg of produced waste per obtained kg of product, excluding the water that was used[8]. Since solvents makes up for a majority of the waste created in the finer chemical area and in the pharmaceutical industry it is of great concern to make this contribution smaller. Solvents makes up for about 85 to 90% of the created waste, excluding water. In order to decrease the usage of solvent existing reactions must be made more efficient or being fully replaced by new and more efficient ones.

In order to avoid depletion of valuable resources, such as oil, it is of interest to use renewable feedstocks to as large extent as possible. In green chemistry this could refer to usage of water as solvent in chemical reactions since it is naturally occuring and recycles in nature. Chemicals that are used in the industry should come from natural resources and should be produced in such a way that they contribute as little as possible to the carbon footprint[9].

1.2 Catalysis

The purpose of catalysis is to enhance the rate of a reaction, this is done by the addition of a so called catalyst. This is due to that the catalyst lowers the activation energy that is required for the reaction. Although it alters the activation energy it does not affect the overall total change in the Gibbs free energy. What makes the catalyst interesting is that while it enhances the reaction it is not consumed by it. This makes it possible, after the reaction is finished, to separate the catalyst and reuse it in the reaction[10].

Catalysis finds uses in many different fields in the chemical industry. A way to create liquid hydrocarbons is through the Fischer-Tropsch process. In this process carbon monoxide and hydrogen gas, or syngas, is used in order to form alkene chains. In this process iron or cobalt based heterogeneous catalysts are used. The mechanism for the catalytic formation of alkene chains can be seen in Figure 1.3.

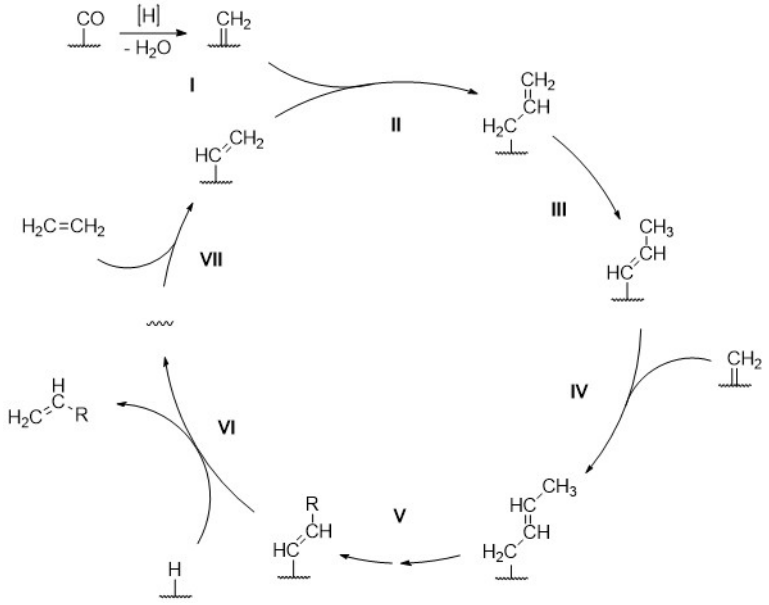


Figure 1.3: Mechanism of the catalytic formation of alkene chains in the Fischer-Tropsch process.

I: Associative adsorption of CO to the metallic surface. Splitting of the C-O bond and dissociative adsorption of 2 H_2 leads to formation of H_2O and surface methylene, water leaves the surface. **II:** The formed methylene groups goes through chain growth polymerization with vinyl group. **III:** Isomerization of alkene chain. **IV,V:**

Repetition of **II** and **III**. **VI:** Termination of chain growth and desorption of formed 1-alkene chain. **VII:** Adsorption of vinyl group to metal surface and initiation of chain growth.

Another process where catalysis is utilized is in the production of ammonia through the Haber-Bosch process, see Figure 1.4. In this reaction ammonia is produced throughout an iron catalyzed reaction between hydrogen and nitrogen gas, see Figure 1.5. Ammonia is mostly used in order to create fertilizer but has found uses in other areas such as the textile industry[13, 14].

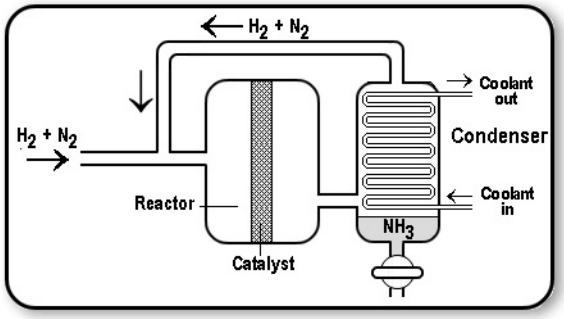


Figure 1.4: Creation of ammonia through the Haber-Bosch process[12].

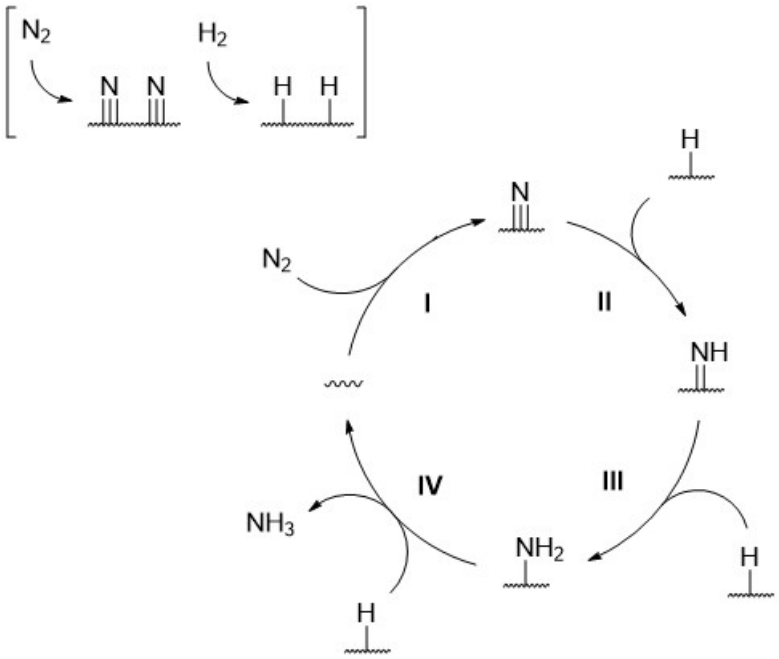


Figure 1.5: Catalytic circle showing the reaction mechanism of the Haber-Bosch process.

I: Adsorption of nitrogen gas to the catalytic metal surface. **II,III:** Adsorbed nitrogen atom forms bond with adsorbed hydrogen atoms. **IV:** NH_2 picks up a third hydrogen atom, ammonia is formed and desorbs from the catalytic surface.

1.2.1 Organocatalysis

The usage of transition metal catalysts has for a long time been of interest and widely used. In order to create these catalysts it is needed to mine for precious metals which leads to unwanted pollution. If possible it would be preferable to decrease the usage of transition metal catalysis. For more then a century it has been known that some small organic molecules can act as potent catalysts. The Knovenagel condensation as it is called today, reported in 1896 by Emil Knovenagel, was one of the first reported organocatalytic reactions, see Figure 1.6[16].

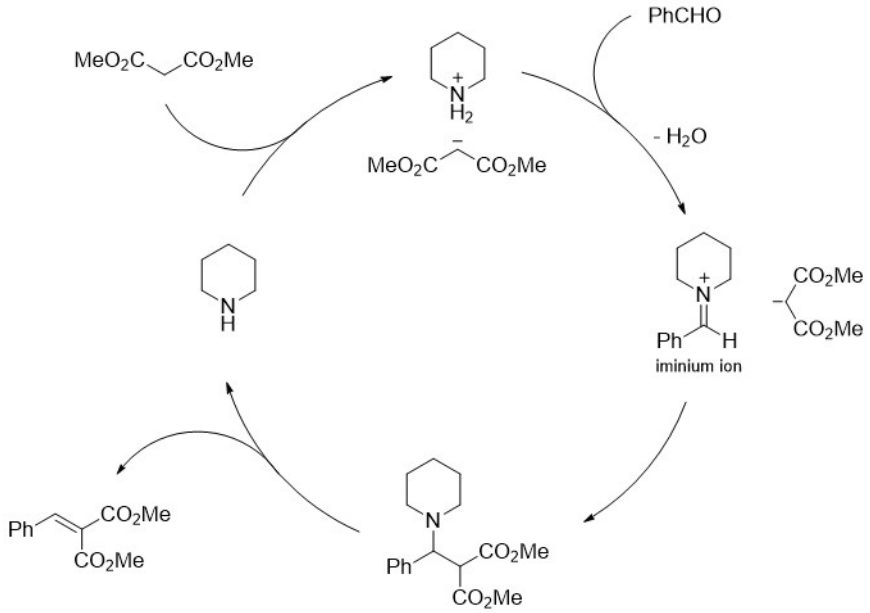


Figure 1.6: The catalytic cycle for Knoevenagel condensation

1.3 N-heterocyclic carbenes

Stable carbenes has over the recent decades received a great deal of attention. The definition of a carbene is that it is a molecule containing a divalent carbon atom with six valence electrons where two are nonbonded. A carbene can have two spin states. The first is where the two valence electrons occupy the same p-orbital leaving a p-orbital unoccupied which is called the singlet state, see Figure 1.7a). The second spin state is where the electrons occupy one degenerate orbital each which is called the triplet state, 1.7b)[17, 18].

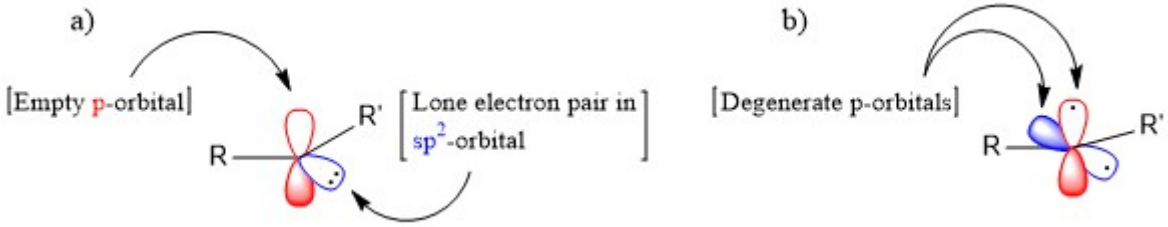


Figure 1.7: a) Singlet state carbene; b) Triplet state carbene.

The triplet state shows to be the more stable state for most carbenes. This is due to that it takes less energy for the electron to be placed in an empty p-orbital than to be placed in a orbital that already contains another electron leading to a repulsive force, Hund's rule[19]. For NHC, containing electron rich nitrogen atoms, the singlet state is the favoured one. This is due to the neighbouring nitrogen decreasing the energy of the highest occupied molecular orbital (HOMO) as well as it increases the energy of the lowest unoccupied molecular orbital (LUMO) which favours the singlet state, see Figure 1.8, and makes the NHC more stable then general carbenes[20, 21].

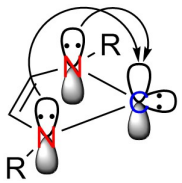


Figure 1.8: The distribution of electrons in a singlet NHC.

Some examples of commmonly used N-heterocyclic carbenes, NHC, are derivates of the imidazole-2-ylide, containing 2 nitrogen atoms. The triazol-5-ylidene, cantaining 3 nitrogen atoms, and the thiazol-2-ylidene, containing a sulfur atom, see Figure 1.9[21].

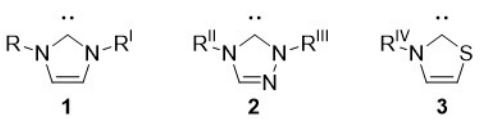


Figure 1.9: Chemical structure of imidazole-2-ylide **1**, triazol-5-ylidene **2** and thiazol-2-ylidene **3**.

One reaction in which NHCs has shown to be successful as a nuchleophilic catalyst is in the Stetter reaction in which a new C-C bond is formed through a 1,4-addition of a aldehyde to a α,β-unsaturated carbonyl compound. The mechanism for this reaction can be seen in Figure 1.10[22, 23].

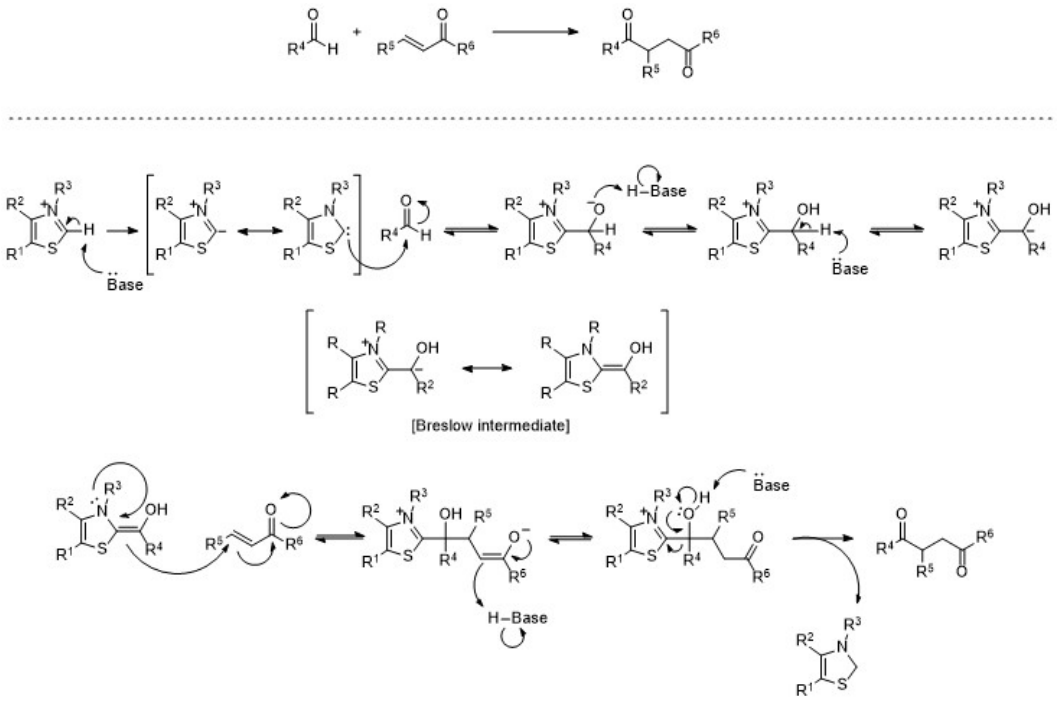


Figure 1.10: The Stetter reaction and reaction mechanism.

The salt of the NHC-catalyst is deprotonated with a base forming the carbene. The carbene will then add to the aldehyde and through deprotonation change the polarity of the electrophilic aldehyde carbon, making it nucleophilic. This is called umpolung. From this the Breslow intermediate is created. The intermediate will add to the α,β-unsaturated carbonylic compound. As the product is formed the NHC-catalyst will be reformed and can be reused in the reaction again.

1.4 Electron transfer mediators

Direct aerobic oxidation of a substrate is rarely occurring in nature due to its high energy barrier. Aerobic oxidation is carried out in the so called respiratory chain that includes a series of proteins that lowers the energy barrier for the transport of electrons. This behaviour is mimicked in synthetic aerobic oxidation by using so called electron transfer mediators, ETM:s.

Palladium complexes are commonly used in aerobic oxidation as the catalyst together with ETM:s. An example of this is the 1,4-oxidation of 1,3-dienes by Bäckvall et al. $Pd(OAc)_2$ in acetic acid acts as the substrate-selective redox catalyst for the diene, turning it into the 1,4-diacetoxy-2-alkene. In Figure 1.11 the energy barriers for the oxidation is shown. In the upper reaction, a), the catalyzed reaction is car-

ried out without any ETM:s leading to a larger energy barrier. In the lower reaction, b), benzoquinone, **BQ**, and a macrocyclic ligand, ML^m, was used as ETM:s and a series of smaller energy barriers was obtained[24]. By introducing the ETM:s and thereby lowering the energy barriers the reaction becomes selective and the rate of reaction is enhanced making it more potent yielding the desired product.

Iron(II)phtalocyanine (FePc)(**4**), Cobalt(II)tetraphenylporphyrin (Co(tpp))(**5**), and Cobalt(II)(salophene)(**6**) are examples of different types of ETMs that were used as ML^m in this reaction, see Figure 1.11 for structures.

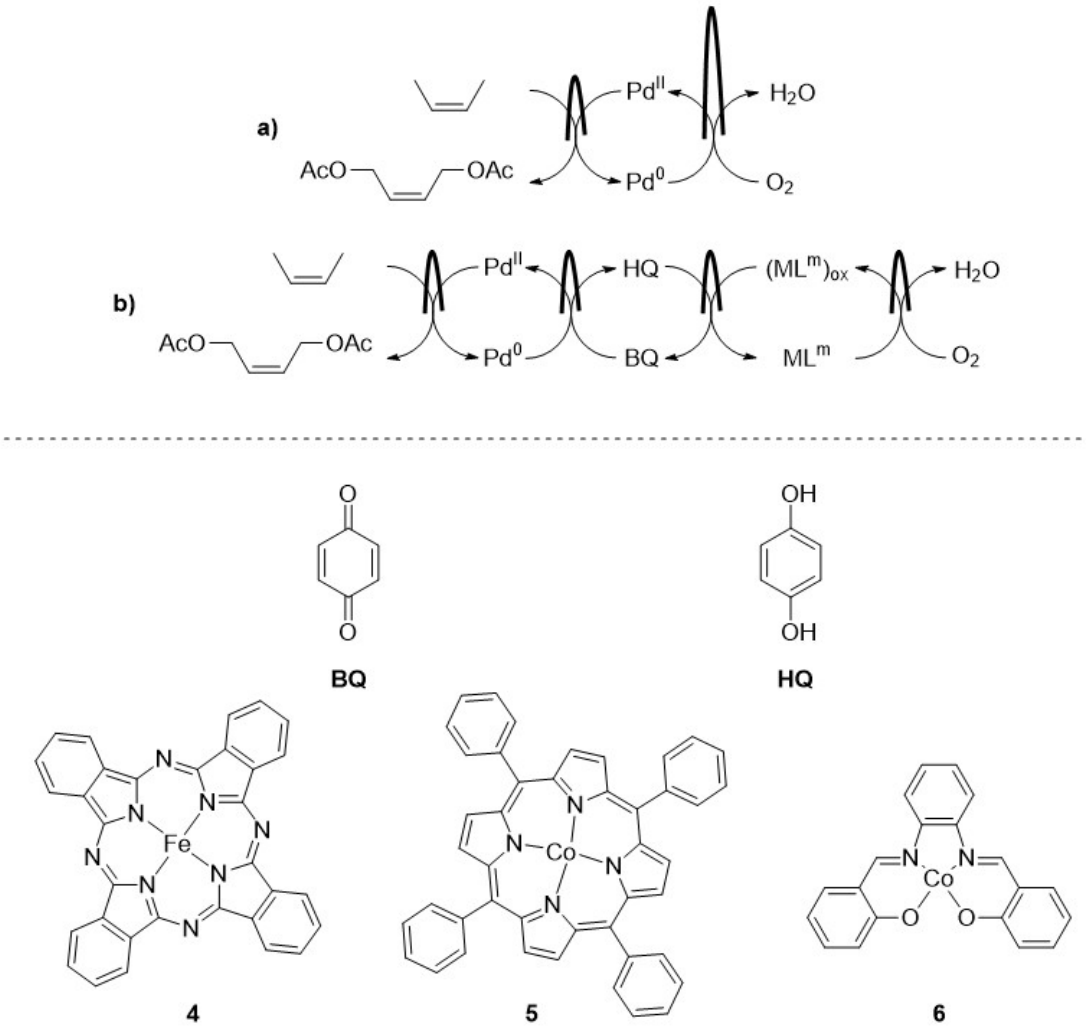


Figure 1.11: The influence of ETMs on the energy barriers in the Pd-catalyzed oxidation of diene to diacetate and structures of some ETMs.

1.5 Water in organic reactions

Water has for a long time been regarded as a contamination when it came to organic synthesis. But studies shows that water can have an enhancing effect on some organic reactions. Using water as solvent in organic reactions is desirable from a green chemistry perspective since it's non-toxic, non-flammable, readily available and cheap. In the 1980:s Breslow discovered that water had an enhancing effect on the rate of reaction and selectivity in Diels-Alder reaction. This has contributed alot to the interest in aqueous synthesis[25, 26]. Using water as solvent showed to create hydrophobic aggregates in order to minimize the contact surface between water and the organic phase. In order for water to maintain its hydrogen bonds it forms networks around the aggregates and acts as an internal pressure, this is called the hydrophobic effect. The resulting effect is that reactions with negative volume of activation, like the Diels-Alder reaction, will be enhanced[27]. Since these discoveries were made there has been significant progress in the field of organic chemistry in aqueous media.

Studies made by Narayan et al., measuring the time of completion for cycloaddition of quadricyclane with azodicarboxylate, see Figure 1.12, shows a significant increase of reaction rate when water is being used as solvent.

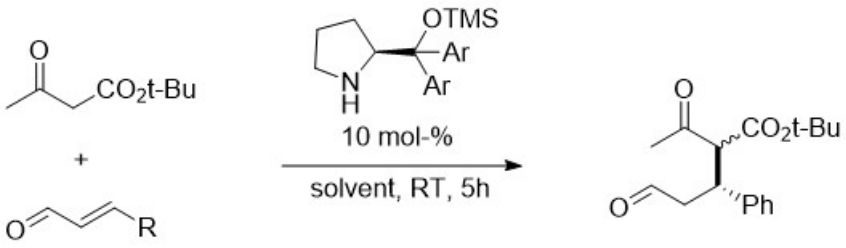
Solvent	Time of completion
Toluene	>120h
Ethyl acetate	>120h
Acetonitrile	84h
Dichloromethane	72h
DMSO	36h
Methanol	18h
Neat	48h
Perflourohexane	36h
D_2O	45min
H_2O	10min

Figure 1.12: Cycloaddition of quadricyclane with azodicarboxylate and the differences in completion time for the cycloaddition of quadricyclane with azodicarboxylate.

In their studies a broad range of solvents were tested in a reaction containing water insoluble reagents. As can be seen in Table 1.12 the time of completion for water, 10 min, is significantly shorter than that for methanol, DMSO as well as under neat condition. This indicates that the heterogeneity of the reaction plays a significant part in the enhancement of the reaction[28]. A difference can be seen between H_2O and D_2O which most likely is because of a isotropic effects and an increase in vis-

cosity leading to a less good mixing of the heterogeneous mixture[29].

In the work of Jørgensen and co-workers where an organocatalytic Michael addition of tert-butyl-3-oxo-butyric esters to α,β-unsaturated aldehydes, see Figure 1.13, it was shown that the reaction could be carried out in seawater as well as in beer[30]. The reaction showed to be equally efficient as the ones carried out in purified water as well as under neat conditions which indicates that initial purification steps of water could be avoided, see Figure 1.13.



Ar = (3,5 CF_3)$_2$$C_6H_4$

Solvent	Yield (%)	ee (%)
Neat	90	94
Water	97	94
Seawater	88	93
Beer	98	96

Figure 1.13: Organocatalyzed asymmetric Michael addition of tert-butyl-3-oxo-butyric esters to α,β-unsaturated aldehyde and solvents used in the organocatalyzed Michael addition, their corresponding yields and enantiomeric excess.

Water has desirable advantages but it also has some disadvantages. Its high energy capacity leads to a high energy demand in order to regulate its temperature when implemented on an industrial scale compared to other solvents like methanol. The high energy demand also becomes a problem when water is to be separated through rotary evaporation.

2
Background

2.1 Oxidative NHC catalysis via multistep electron transfer

The study of this thesis will focus on optimizing the reaction conditions for the aerobic oxidative NHC-catalysed synthesis of methyl cinnamate from cinnamaldehyde and methanol using water as solvent. The generality for the synthesis will also be checked for some similar reagents.

NHC catalysts has been widely used in oxidative reaction paths during recent years. In these reactions much interest is focused on the α,β-unsaturated acyl azolium intermediate, see Figure 2.1.

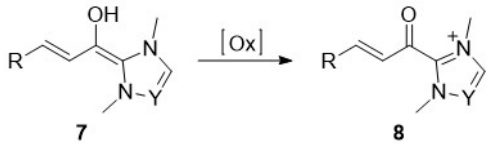


Figure 2.1: 7: Breslow intermediate, **8:** α,β-unsaturated acyl azolium intermediate.

The intermediate is readily used in different reactions like oxidative esterification[31], cyclo-additions[32], macrocyclisations[33], and more, as a reaction intermediate. In most of these reactions a high molecular weight oxidant is needed in order to oxidize the Breslow intermediate and yield the acyl azolium intermediate called the Kharasch oxidant, see Figure 2.2a). In green chemistry it is preferable to not use this high molecular oxidant due to price, separation steps and waste disposal.

In previous work done by L. Ta et al. it was studied if the high molecular oxidant could be replaced by a more suitable one, in this case air, Figure 2.2. Direct oxidation of α,β-unsaturated aldehydes and NHC-catalyst with aerial oxygen gives the carboxylic acid[34]. By introducing an electron transfer mediator that will act as a catalytic oxidant, mimicking the respiratory chain in cells, the ester was formed but the reactivity of the reaction was still low[35]. The low reactivity could be explained by the high energy barrier of the oxidation step. The energy barrier is in general a hindrance for the use of aerial oxygen as a terminal oxidant. By introducing an additional electron transfer mediator a series of lower energy barriers between the substrate and the aerial oxygen could be made[36].

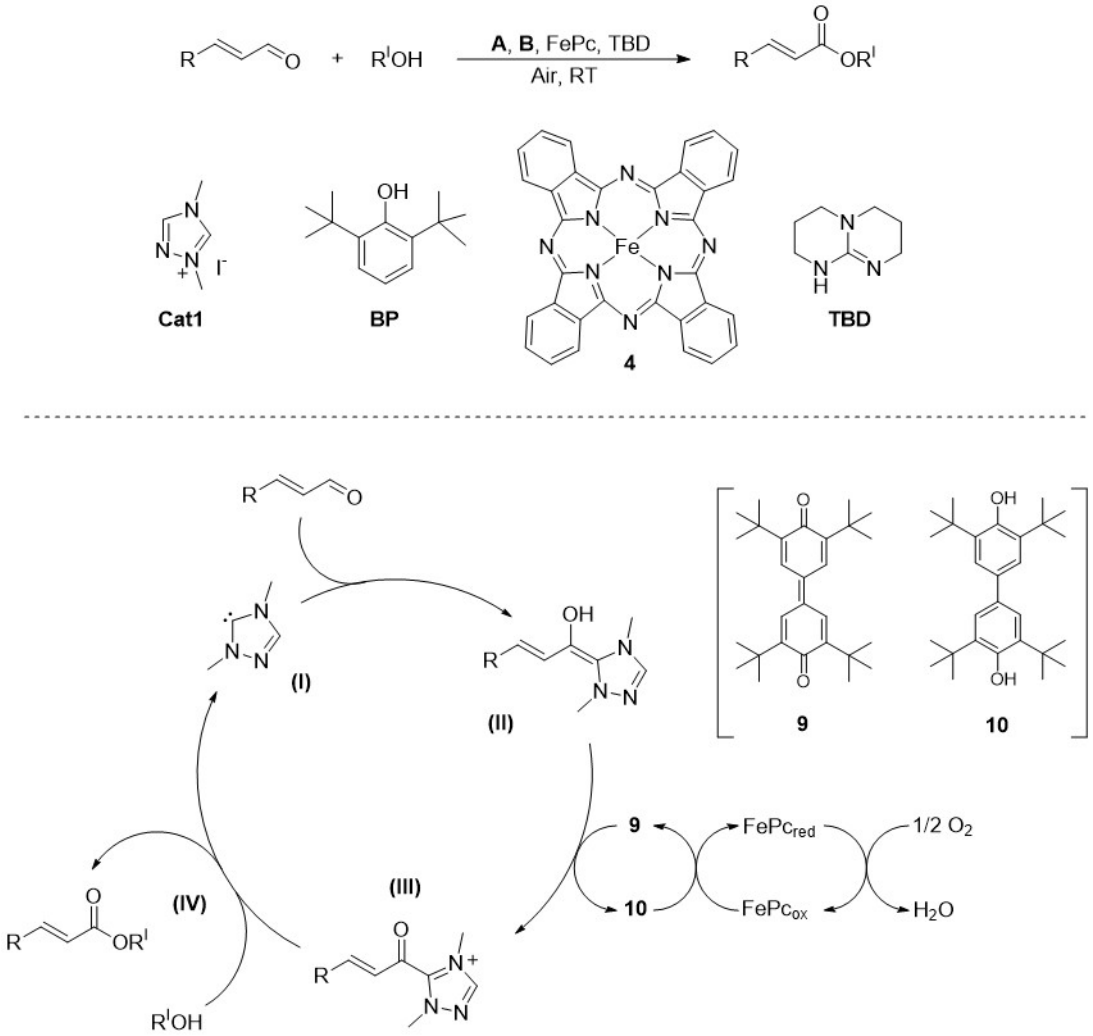


Figure 2.2: Previous reaction and catalytic cycle for aerobic oxidative esterification of aldehydes.

The catalytic cycle starts with the 1,2-addition of the NHC **(I)** to the aldehyde thus forming the Breslow intermediate **(II)**. Oxidation of **(II)** by oxidant **9** leads to the formation of the α,β-unsaturated acyl azolium intermediate **(III)**. The reduced oxidant **10** is oxidized by metal complex FePc$_{ox}$ and **9** is reformed. The reduced metal complex FePc$_{red}$ is then oxidized by the aerial oxygen to reform FePc$_{ox}$ and H_2O. The alcohol does a 1,2-addition to the α,β-unsaturated acyl azolium intermediate to form the ester **(IV)** and the NHC **(I)** is reformed making it possible to react with another aldehyde repeating the cycle.

In a previously reported paper about synthesis of dihydropyranones, utilizing the same principle with ETMs as shown above, it was shown that the presence of aerial oxygen led to that the Iron(II) complex **4** degenerated throughout the course of the reaction, making the reaction ineffective[37]. This is most likely due to that the Iron(II) complex (**4**) forms a oxygen bridge and dimerizes. This leads to a deactivation of the complex and it falls out of solution. A way to circumvent this was to add the Iron(II) complex (**4**) stepwise. Another way to avoid this could be to implement a new complex that would avoid forming this oxygen bridge. A possible way to avoid this could be to implement charged side groups on the metal complex. This could lead to that the repulsive force from the side groups wont allow the complexes to get close enough to each other to form the oxygen bridge. While doing this the charged side group would also make the complex more hydrophilic and easier to solve in water.

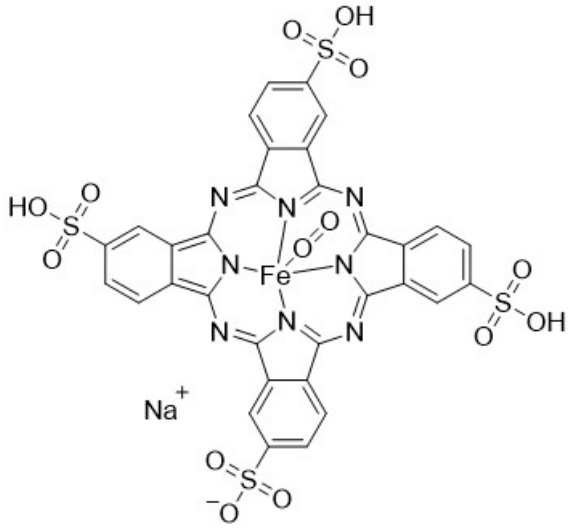


Figure 2.3: Iron(III) phthalocyanine-4,4',4",4"'-tetrasulfonic acid, compound with oxygen monosodium salt hydrate

2.2 Aim

Investigate if the change of electron transfer mediator would lead to no formation of the complex dimer connected by an oxygen bridge.

Investigate if the change of electron transfer mediator to a more water soluble one makes it possible for the NHC-catalytic synthesis to be carried out with water as solvent.

Investigate the effects that an increase of the hydrophobic effect will have on the synthesis by switching out water and use brine as solvent instead.

3

Result and discussion

The major issue with implementing water as solvent in the previously done reaction is the solubility of the non-polar iron complex. In order to avoid this problem a more polar iron complex is implemented. In this case Iron(III) phthalocyanine-4,4',4",4"'-tetrasulfonic acid, compound with oxygen monosodium salt hydrate is used.

3.1 Optimization of reaction

3.1.1 Screening of base

In order to optimize the reaction conditions a series of screenings were made for different types of bases, NHC-catalysts and ETMs. The model reaction can be seen in Figure 3.1.

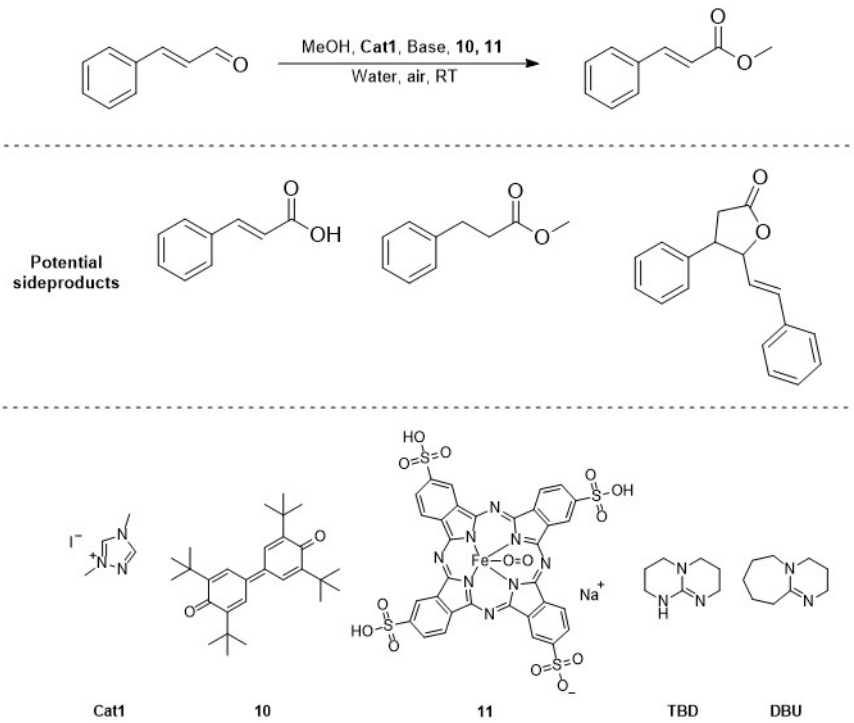


Figure 3.1: Initial reaction conditions for the NHC catalyzed aerobic oxidation of cinnamaldehyde to methyl cinnamate and potential formation of cinnamic acid.

The screening of bases was done according to set reaction conditions, see Table 3.1. Potassium hydroxide (KOH) appeared to be the most promising base (Entry 7), slightly better than the results of using DBU (Entry 2). Comparing this to the results from Entry 5 and 6, where weaker bases are used, would indicate that the reaction needs a strong base.

Table 3.1: Optimization of changed reaction conditions, base screening.
[a](cinnamaldehyde 1 eq (0.2 mmol), MeOH 12.33 eq, NHC 0.09 eq, Base 0.5 eq, **(10)** 0.06 eq, **(11)** 0.03 eq)

Entry[a]	Base	Time(h)	Start Mat.(%)	Product(%)
1	TBD	4	75	25
2	DBU	3	68	32
3	NaOH	3	97	3
4	Et_3N	3	93	7
5	K_2CO_3	4	95	5
6	K_3PO_4	4	80	20
7	KOH	4	67	33

3.1.2 Screening of ETM

Screening of electron transfer mediators, see Table 3.2, showed that the combination of **BP** and **Iron(III)** (Entry 8) and (Entry 27), see Table 3.5, appeared to be the most promising one. In order to validate the choice and combination of ETMs entries were made with less soluble metal complexes like previously used iron(II) phtalocyanine **4** and cobalt salophene **6** (Entry 12 and 13). Both of these entries indicated through their low yields that the solubility of the metal complex is of importance. Entry 11 indicates that the addition of the second ETM is of importance in order to yield the product.

Table 3.2: Screening of ETM.
[a](cinnamaldehyde 1 eq (0.2 mmol), MeOH 12.33 eq, NHC 0.09 eq, Base 0.5 eq, **(10)** 0.06 eq, **(11)** 0.03 eq)

Entry[a]	ETM[1]	ETM[2]	Time(h)	Start Mat.(%)	Product(%)
8	BP	Iron(III)	4	68	32
9	DMT	Iron(III)	4	70	30
10	BQ	Iron(III)	4	86	14
11	no ETM[1]	Iron(III)	4	78	22
12	BP	FePc	4	90	10
13	BP	Co(salophene)	4	91	9

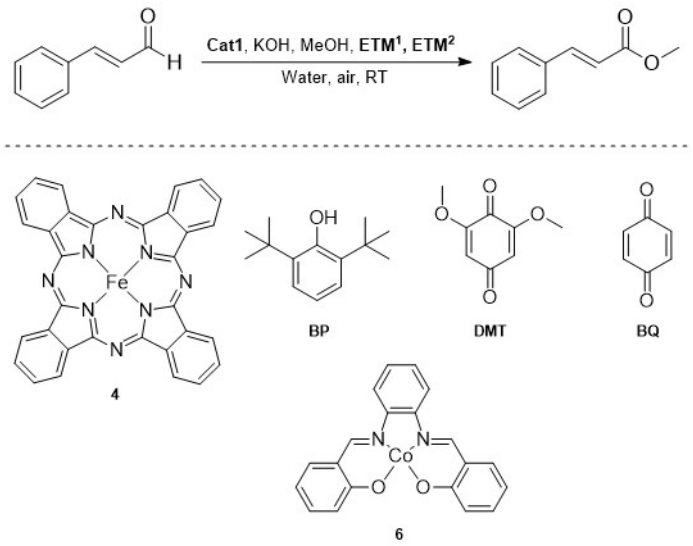


Figure 3.2: Different types of tested electron transfer mediators, ETMs.

3.1.3 Screening of catalyst

Screening of different types of NHC catalyst, see Table 3.3, showed that **Cat5**, containing an electron rich mesityl group was the prefered choice (Entry 25). An explanation for why **Cat5** worked better than **Cat3**, containing an additional electron donating group, could be that **Cat3** is more bulky leading to possible steric hindrances in the reaction. Another factor that can play a part is the difference between the imidazolium and triazolium core of the catalysts giving it different properties.

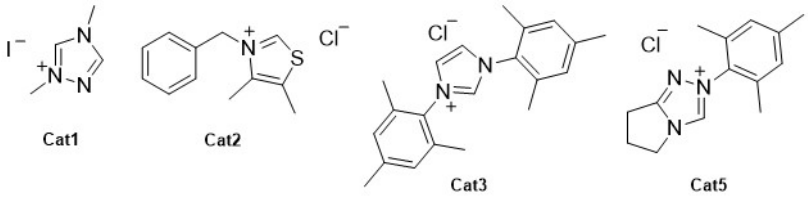


Figure 3.3: Structures of screened catalysts

Table 3.3: Change of catalyst.
[a](cinnamaldehyde 1 eq, MeOH 12.33 eq, NHC 0.09 eq, Base 0.5 eq, BP 0.06 eq, **(11)** 0.03 eq)

Entry[a]	Catalyst	Time(h)	Start Mat.(%)	Product(%)
14	Cat2	3	94	6
15	Cat3	3	60	40
16	Cat5	3	50	50
17	Cat5	6.5	26	74

3.1.4 LiOH and different concentrations of water and nucleophile

Lithium hydroxide was tested and showed greater potential than that of potassium hydroxide which led to the change of base for the experiments to LiOH.

Different concentrations of water and nucleophile were tested, see Table 3.4, in order to see if the ratio between them was of importance. As the concentration of nucleophile was decreased to about half the amount a negative difference in conversion can be seen (Entry 19). This is most likely because the methanol evaporates before reaction has gone to completion. Carrying out the reaction with 1-propanol instead shows a better conversion indicating that the volatility of the methanol matters. Decreasing the concentration of water did not have any impact on the conversion, comparing Entry 18 to Entry 22.

By changing the nucleophile from methanol to acetylacetone the type of reaction is also changed. Instead of forming esters we now form dihydropyranones, see Figure 3.4

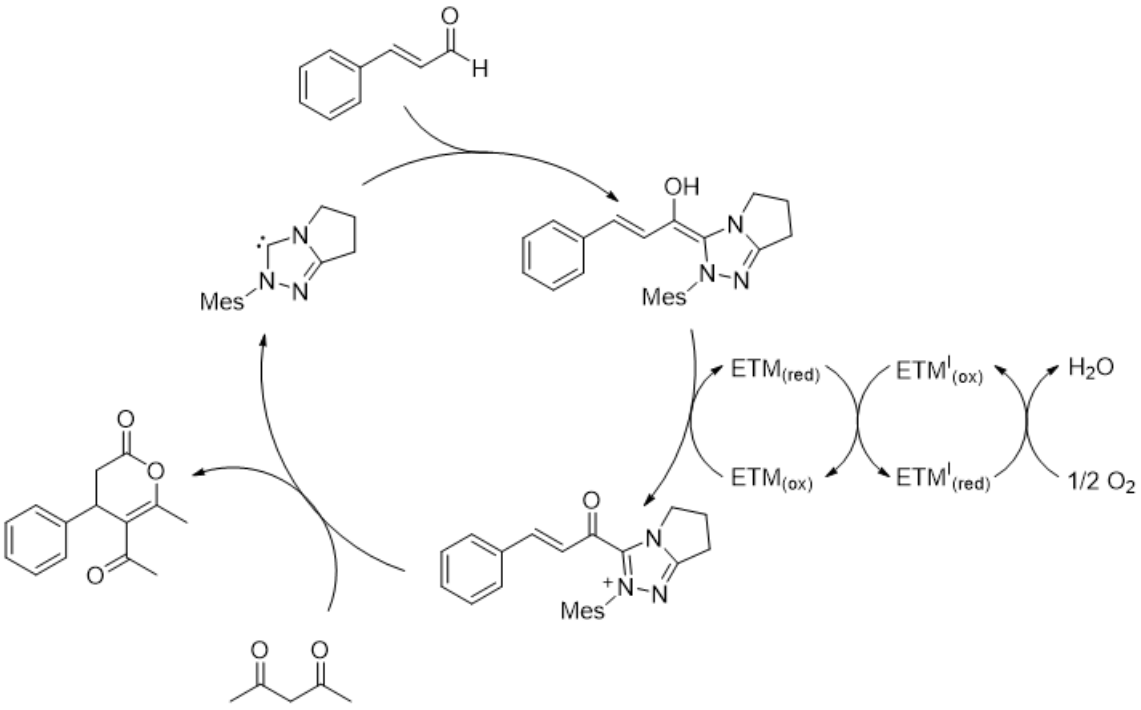


Figure 3.4: Catalytic cycle for the formation of dihydropyranones through aerobic oxidative NHC-catalysis.

In this reaction full conversion was not observed but good selectivity towards the desired product (Entry 23). This indicates that it is possible to run this type of reaction using aerial oxygen as terminal oxidant and water as solvent.

Table 3.4: Concentration changes of water and nucleophile.
[b](cinnamaldehyde 1 eq (0.2 mmol), Nucleophile (see table), Cat5 0.09 eq, LiOH 0.5 eq, BP 0.06 eq, **(11)** 0.03 eq)
[M]:Methanol [P]:1-propanol, [A]:Acetyl acetone.

Entry[b]	H_2O	Nuc.	Time(h)	Start Mat.(%)	Acid(%)	Product(%)
18	600 ul	12.33 eq.[M]	6.5	0	18	82
19	600 ul	6.17 eq.[M]	6.5	49	21	30
20	600 ul	6.17 eq.[P]	3	14	19	67
21	300 ul	6.17 eq.[M]	6.5	4	34	62
22	150 ul	12.33 eq.[M]	6.5	0	20	80
23	600 ul	5 eq.[A]	6	29	0	71

Table 3.5: Change of catalyst concentration and scale of reaction.
[b](cinnamaldehyde 1 eq (0.2 mmol), MeOH (see table), Cat5 0.09 eq, LiOH 0.5 eq, BP 0.06 eq, **(11)** 0.03 eq)
[1]:0.25 eq. Catalyst, [2]:0.5 eq. Catalyst, [3]:0.3 mmol cinnamaldehyde

Entry[b]	H_2O	MeOH	Time(h)	SM(%)	A(%)	P(%)
24[1]	600 ul	12.33 eq.	6.5	69	0	31
25[2]	600 ul	12.33 eq.	6.5	3	21	76
26	600 ul	12.33 eq.	6	26	36	38
27[3]	900 ul	12.33 eq.	6.5	12	6	82

3.1.5 Brine as solvent

When introducing brine as solvent instead of water the rate of the reaction was enhanced so that the time of completion went down from 6 to 2 hours, see Table 3.6. As brine was introduced an increase in the formation of the cis-(E)-4-phenyl-5-styryl-dihydrofuran-2(3H)-one, see Figure 3.5 could be observed through ^{1}H NMR. An explanation for this could be the change in the hydrophobic effect due to the increase of free ions in brine. This will lead to an increased internal pressure pushing the hydrophobic molecules closer together which will favour the reaction between the homoenolate and the α,β-unsaturated aldehyde, forming the lactone.

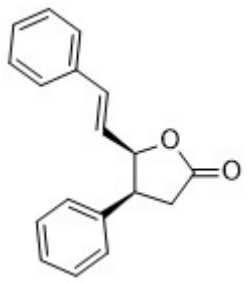


Figure 3.5: Structure of cis-(E)-4-phenyl-5-styryl-dihydrofuran-2(3H)-one

The homoenolate acts as nucleophile and adds to the electrophilic aldehyde. Tautomerization creates the activated carboxylate and an intramolecular ring closure takes place reforming the catalyst as well as creating the lactone.

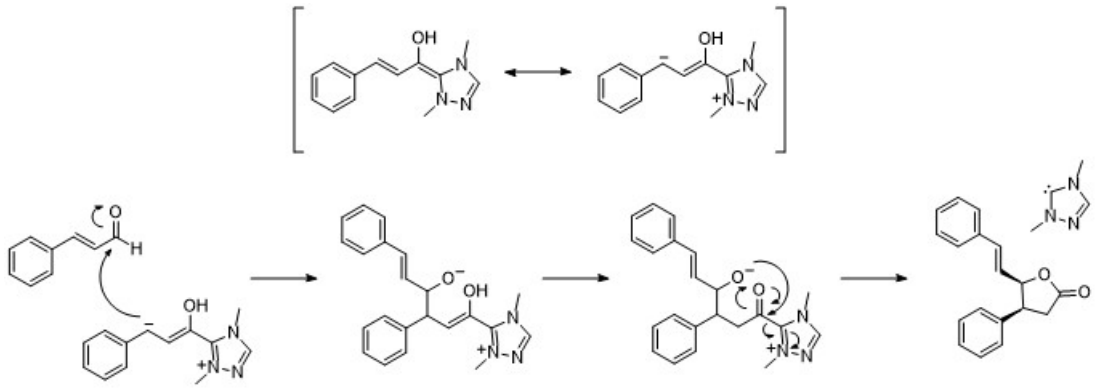


Figure 3.6: Mechanism for the formation of lactone.

Table 3.6: [b](cinnamaldehyde 1 eq (0.2 mmol), Nucleophile 12.33 eq, NHC 0.09 eq, Base 0.5 eq, BP 0.06 eq, **(11)** 0.03 eq)
[4]:4-methoxy-trans-cinnamaldehyde(**12**).

Entry[b]	Nucleophile	Time(h)	SM(%)	A(%)	P(%)	L(%)
28	MeOH	3	21	29	24	26
29	2-propanol	2	0	31	28	40
30	1-propanol	2	0	19	63	18
31[4]	MeOH	2	100	0	0	0

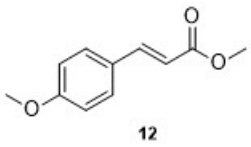


Figure 3.7: 4-methoxy-trans-cinnamaldehyde

The reaction in brine was carried out with 4-methoxy-trans-cinnamaldehyde, see Figure 3.7 instead of cinnamaldehyde. The use of the new aldehyde showed no conversion of the starting material.

3.1.6 Reaction in MeOH

The reaction was carried out with MeOH as the sole solvent, see Table 3.7, 3.8 and 3.9. This was done in order to see if it would make the isolation of product easier. Three different methods where used for this experiment. The first one which were developed through prior optimization done in this thesis. The second and third method had been done in previously done studies. The first and second method gave full conversion of the reaction but isolation was not made. In both cases forming of the saturated ester was also observed as byproduct, see figure 3.8. Using the second method the product could be isolated after purification through chromatography and rotary evaporation at a yield of 38.9%.

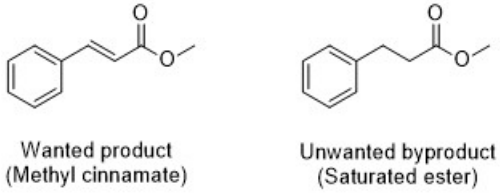


Figure 3.8: The wanted product, Methyl cinnamate, and the unwanted product, saturated ester.

Table 3.7: [c](cinnamaldehyde 1 eq, Cat5 0.09 eq, MeOH 900 ul, LiOH 0.5 eq, BP 0.06 eq, **(11)** 0.03 eq)

Entry[c]	Time(h)	Conversion	Product(%)	Byproduct(%)
32	6	100%	86	14
33	6	100%	71	29

Table 3.8: [d](cinnamaldehyde 1 eq, MeOH 700 ul, Cat1 0.05 eq, TBD 0.5 eq, **(10)** 0.05 eq, **(11)** 0.03 eq)

Entry[d]	Time(h)	Conversion(%)	Product(%)	Byproduct(%)
34	24	100	98	2
35	24	100	97	3

Table 3.9: [e](cinnamaldehyde 1 eq (0.5 mmol), MeOH 1 ml, Cat1 0.02 eq, TBD 0.5 eq, BP 0.02 eq, **(4)** 0.01 eq)

Entry[d]	Time(h)	Starting material(%)	Acid(%)	Product(%)	Byproduct(%)
36	24	31	27	25	16

Using the third method the reaction was carried out with the previously used iron(II) phtalocyanine and BP as ETMs. Using this method also showed signs of the formation of the saturated ester as unwanted byproduct. After 30 minutes the reaction went through a colour change from dark blue to a transparent brownish colour. The

fact that the ^{1}H NMR indicated that full conversion was not achieved and that there was a colour change indicates that something must have happened to the iron complex which gives the mixture its usual blue colour. The hydrophobic iron(II) complexes are pushed together by the hydrophobic effect and forms an oxygen bridge between two complexes, forming dimers. This deactivates the complexes and makes them fall out of the solution, explaining the colour change.

4
Conclusions

Replacing the Iron(II) complex with the Iron(III) complex resulted in that the model reaction, aerobic oxidative esterification, could be done with water as solvent. The replacement also indicated that the addition of charged side groups prevents, or significantly slows down, the formation of an oxygen bridge between two complexes, which otherwise would happen for the hydrophobic iron(II), deactivating them.
The formation of methyl cinnamate indicates that the catalytic cycle works in a water environment meaning that the oxidation of the homoenolate to the acyl azolium intermediate happens, hence the low energy path is taking place.
Using brine as solvent favours the formation of the lactone more than that of the ester due to the increase in the hydrophobic effect meaning that the addition of free ions will not favour the model reaction.
Using acetyl acetone as the nuchleophile showed that synthesis of dihydropyranones can be carried out in a water environment as well.

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A

Appendix 1

A.1 General procedure

A.1.1 First general procedure for optimization of reaction conditions

To a pear shaped flask (10ml) with a magnetic stir bar was added Cat1 (0.07 eq., 3.1 mg), Kharasch oxidant (0.05 eq., 4.2 mg), Iron(III) (0.02 eq., 5.8 mg), TBD (0.5 eq., 14.2 mg), MeOH (5 eq., 40.6 ul) and 700 ul water. After 3 minutes of stirring cinnamaldehyde (1 eq., 25.2 ul) was added and the solution was stirred at ambient temperature. The reaction was monitored by crude ^{1}H NMR. After 4 hours or when the reaction was confirmed to have stopped it was terminated.

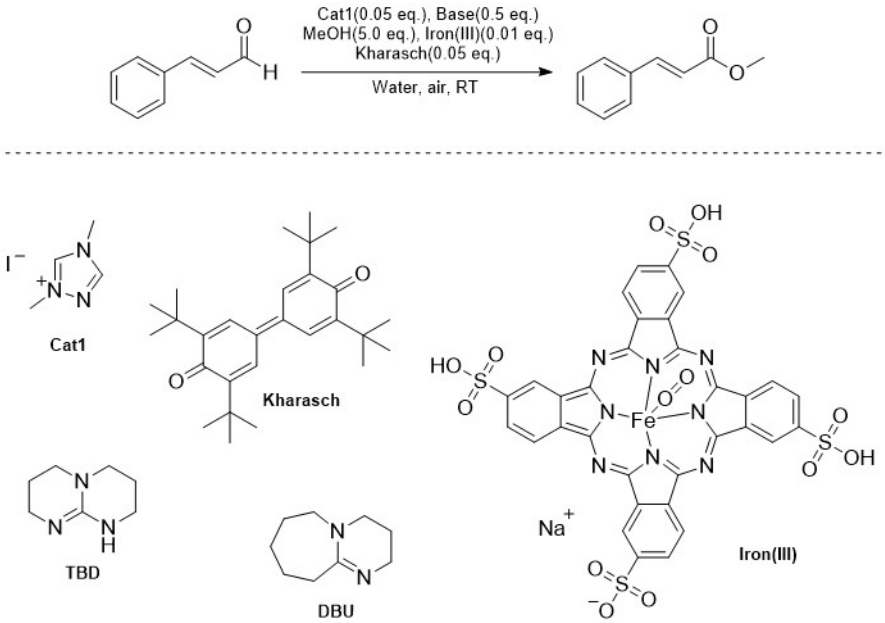


Figure A.1: Reaction conditions for first base screening.

Table A.1: Base screen for reaction condition 1

Entry	Base	Time(h)	Conversion(%)	Yield(%)
1	TBD	2.5	19	3
2	TBD	3	-	-
3	TBD	3	-	-
4	TBD	2	42	6
5	TBD	4	53	23
6	DBU	2.5	12	12
7	DBU	3	-	-
8	DBU	2	37	12
9	NaOH	2.5	2	2
10	NaOH	2.5	-	-
11	NaOH	2	7	7
12	Et_3N	3.5	17	0
13	Et_3N	2	15	0
14	$NaHCO_3$	3	0	0
15	$NaHCO_3$	4	0	0
16	K_2CO_3	4	0	0
17	K_3PO_4	2	3	3
18	KOH	4	8	8
19	KOH	4	0	0

A.1.2 Second general procedure for optimization of reaction conditions

To a pear shaped flask (10ml) with a magnetic stir bar was added Cat1 (0.09 eq., 4 mg), Kharasch oxidant (0.06 eq., 5.1 mg), Iron(III) (0.03 eq., 7.3 mg), TBD (0.5 eq., 14.3 mg), MeOH (12.33 eq., 100 ul) and 600 ul water. After 3 minutes of stirring cinnamaldehyde (1 eq., 25.2 ul) was added and the solution was stirred at ambient temperature. After 4 hours 0.2 ml CDCl3 was added in order to separate the organic phase. ^{1}H NMR sample was taken of the organic phase.

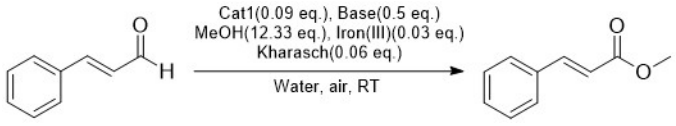


Figure A.2: Reaction conditions for second base screening.

Table A.2: Base screen for reaction condition 2

Entry	Base	Time(h)	SM(%)	P(%)
20	TBD	4	75	25
21	DBU	3	68	32
22	NaOH	3	97	3
23	Et_3N	3	95	5
24	K_2CO_3	4	95	5
25	K_3PO_4	4	85	15
26	KOH	4	67	33

Table A.3: Screening of ETM

Entry	ETM^1	ETM^2	Time(h)	SM(%)	P(%)
27	BP	11	4	68	32
28	DMT	11	4	70	30
29	BQ	11	4	86	14
30	-	11	4	78	22
31	BP	4	4	90	10
32	BP	6	4	91	9

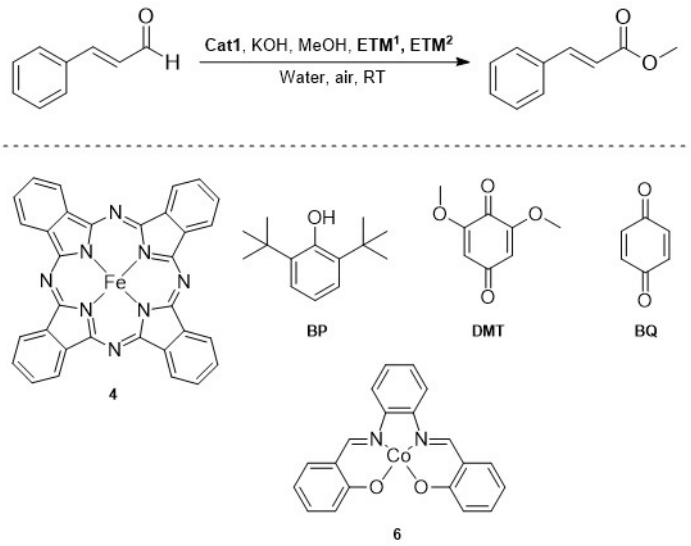


Figure A.3: Different types of tested electron transfer mediators, ETMs.

Table A.4: Screening of Catalyst

Entry	Catalyst	Time(h)	SM(%)	P(%)
33	Cat2	3	94	6
34	Cat3	3	60	40
35	Cat5	3	50	50
36	Cat5	6.5	26	74

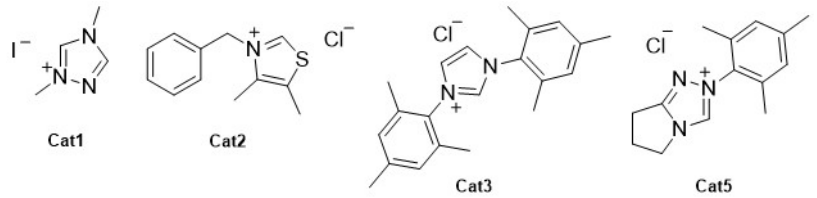


Figure A.4: Screened catalysts

A.1.3 Third general procedure for optimization of reaction conditions

To a pear shaped flask (10ml) with a magnetic stir bar was added Cat5 (0.09 eq., 4.9 mg), BP (0.06 eq., 2.6 mg), Iron(III) (0.03 eq., 7.3 mg), LiOH (0.5 eq., 100 ul), nuchleophile(see table) (12.33 eq., 100 ul) and 600 ul water. After 3 minutes of stirring cinnamaldehyde (1 eq., 25.2 ul) was added and the solution was stirred at ambient temperature. The reaction was monitored by TLC.

Table A.5: LiOH and additional changes.
[1]: 1 eq. LiOH. [2]: 1.2 eq. LiOH. [3]: 0.25 eq. Catalyst. [4]: 0.5 eq. Catalyst.
[M]: MeOH. [P]: 1-propanol. [G]: Glycerol. [A]: Acetyl acetone. [L]: L-serine

Entry	H_2O	Nucleophile	Time(h)	Conversion(%)	Yield(%)
37	600 ul	12.33 eq.[M]	6.5	100	82
38	600 ul	6.17 eq.[M]	6.5	61	24
39	300 ul	12.33 eq.[M]	6.5	92	54
40	300 ul	6.17 eq.[M]	6.5	96	62
41[3]	600 ul	12.33 eq.[M]	6.5	31	31
42[4]	600 ul	12.33 eq.[M]	6.5	97	76
43	150 ul	12.33 eq.[M]	6.5	100	80
44	600 ul	6.17 eq.[P]	3	86	67
45[4]	300 ul	6.17 eq.[M]	2	43	43
46[1,4]	300 ul	6.17 eq.[M]	2	-	-
47	300 ul	12.33 eq.[M]	2	-	-
48	300 ul	12.33 eq.[M]	6	56	33
49	600 ul	12.33 eq.[M]	6	74	38
50	1200 ul	12.33 eq.[M]	6	87	31
51	900 ul	12.33 eq.[M]	6.5	88	82
52	600 ul	10 eq.[G]	6	-	-
53[1]	600 ul	5 eq.[A]	6	71	71
54	600 ul	5 eq.[L]	6	-	-
55	900 ul	12.33 eq.[M]	6	100	39
56	900 ul	12.33 eq.[M]	6	100	56

Table A.6: BRINE, formation of lactone favoured.
[1]: 10 equiv., [2]: 5 equiv. [3]: 4-methoxy-trans-cinnamaldehyde

Entry	Nucleophile	Time(h)	Conversion(%)	Yield(%)
40	MeOH	3	79	24
46	2-propanol	2	100	28
47	1-propanol	2	100	63
48	Glycerol[1]	6	-	-
49	Acetyl acetone[2]	6	62	62
50	1-propanol	2	100	30
51	1-propanol	2	100	46
52[3]	MeOH	2	0	0

A.1.4 Representative procedure for isolation of methyl cinnamate

To a pear shaped flask (10ml) with a magnetic stir bar was added NHC catalyst (0.09 eq., 4 mg), Kharasch (0.06 eq., 5.1 mg), Iron(III) (0.03 eq., 7.3 mg), base (0.5 eq., 14.3 mg), nuchleophile (12.33 eq., 100 ul) and 600 ul water. After 3 minutes of stirring cinnamaldehyde (1 eq., 25.5 ul) was added and the solution was stirred at ambient temperature. After 24 hours the solution was dried through rotary evaporation to remove MeOH. The dried solution was diluted in DCM and moved to a silica column where it was dried under N_2 gas for 1 hour. Running the solution through a biotage with a petroleum ether/ethyl acetate mixture, (10ml/min) 100% petroleum ether $\rightarrow$ 1% $\rightarrow$ 2% $\rightarrow$ 5% $\rightarrow$ ethyl acetate, led to that fractions of the solution was obtained. Through TLC using the mobile phase (1:4, EtOAc:Heptane) the fraction containing the product could be identified. The fractions containing the product was put in a pre-weighed round bottom flask and dried through rotary evaporation. The round bottom flask was weighed and the yield could be calculated. ^{1}H NMR and ^{13}C NMR samples was taken to verify the purity, see Appendix B.

Table A.7: [c](cinnamaldehyde 1 eq, Cat5 0.09 eq, MeOH 900 ul, LiOH 0.5 eq, BP 0.06 eq, **(11)** 0.03 eq)

Entry[c]	Time(h)	Conversion	Product(%)	Byproduct(%)
32	6	100%	86	14
33	6	100%	71	29

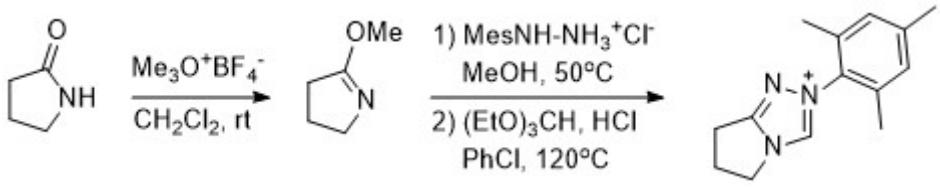
Table A.8: [d](cinnamaldehyde 1 eq, MeOH 700 ul, Cat1 0.05 eq, TBD 0.5 eq, **(10)** 0.05 eq, **(11)** 0.03 eq)

Entry[d]	Time(h)	Conversion(%)	Product(%)	Byproduct(%)
34	24	100	98	2
35	24	100	97	3

Table A.9: [e](cinnamaldehyde 1 eq (0.5 mmol), MeOH 1 ml, Cat1 0.02 eq, TBD 0.5 eq, BP 0.02 eq, **(4)** 0.01 eq)

Entry[d]	Time(h)	Starting material(%)	Acid(%)	Product(%)	Byproduct(%)
36	24	31	27	25	16

A.1.5 Synthesis of precatalyst, Cat5



5-methoxy-3,4-dihydro-2H-pyrrole

To a stirred solution of pyrrolidin-2-one (309 ul, 4.01 mmol, 1 eq.) in anhydrous CH_2Cl_2 (20 ml) was added trimethyloxonium tetraflouroborate (651 mg, 4.41 mmol, 1.1 eq.) in one portion. The colourless mixture was stirred at ambient temperature (16h) and was then diluted with anhydrous diethyl ether. The solution was cooled to 0^oC in a ice bath. Cold saturated aqueous $NaHCO_3$ (30 ml) was added slowly. The layers were separated and the organic layers were washed with cold saturated $NaHCO_3$. The combined organic layers were dried over anhydrous Na_2SO_4. They were then filtered and concentrated through rotary evaporation, this afforded a colourless liquid(VOLATILE COMPOUND!).
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 3.84 (3H, s, O-CH_3), 3.68 (2H, t, CH_2), 2,47 (2H, t, CH_2), 2,04 (2H, m, CH_2) ppm, see Appendix 2.

2-Mesityl-6,7-dihydro-5H-pyrrolo[1,2,4]triazol-2-ium chloride, (Cat5)

To a flame-dried sealed round bottom flask charged with a solution of 5-methoxy-3,4-dihydro-2H-pyrrole (1.01 eq.) in anhydrous MeOH was added mesitylhydrazine hydrochloride (1.0 eq.) as a solid in one portion. The flask was sealed under an atmosphere of nitrogen gas and the mixture was heated to 50 ^oC for 1 hour. The solution was cooled to ambient temperature and concentrated in vacuo to the crude solid. The solid was then triturated several times with anhydrous diethyl ether to afford the hydrazinium chloride (1.477 g) as a white powder. This was suspended in anhydrous chlorobenzene (10 eq., 5,84 ml). Triethyl orthoformate (10 eq., 9.62 ml) and anhydrous 4 M HCl in 1,4-dioxane (1 eq., 1,46 ml) were added. The mixture was heated to 120 ^oC for 1 hour. The tan solution was cooled to ambient temperature and concentrated through rotary evaporation. The resulting oil was azetroped twice with toluene to afford a crude brown solid which was first trituated from anhydrous diethyl ether, dried through rotary evaporation.
^{1}**H NMR** (400 MHz, $CDCl_3$): δ 10,29 (1H, s, iminium CH=N^+), 7,13 (2H, s, MesH), 4.42 (2H, t, CH_2), 3,17 (2H, t, CH_2), 2.74 (2H, m, CH_2), 2,32 (3H, s, para-MesCH_3),

2.04 (6h, s, ortho-MesCH_3) ppm, see Appendix 2.

B

Appendix 2

B.1 NMR spectra

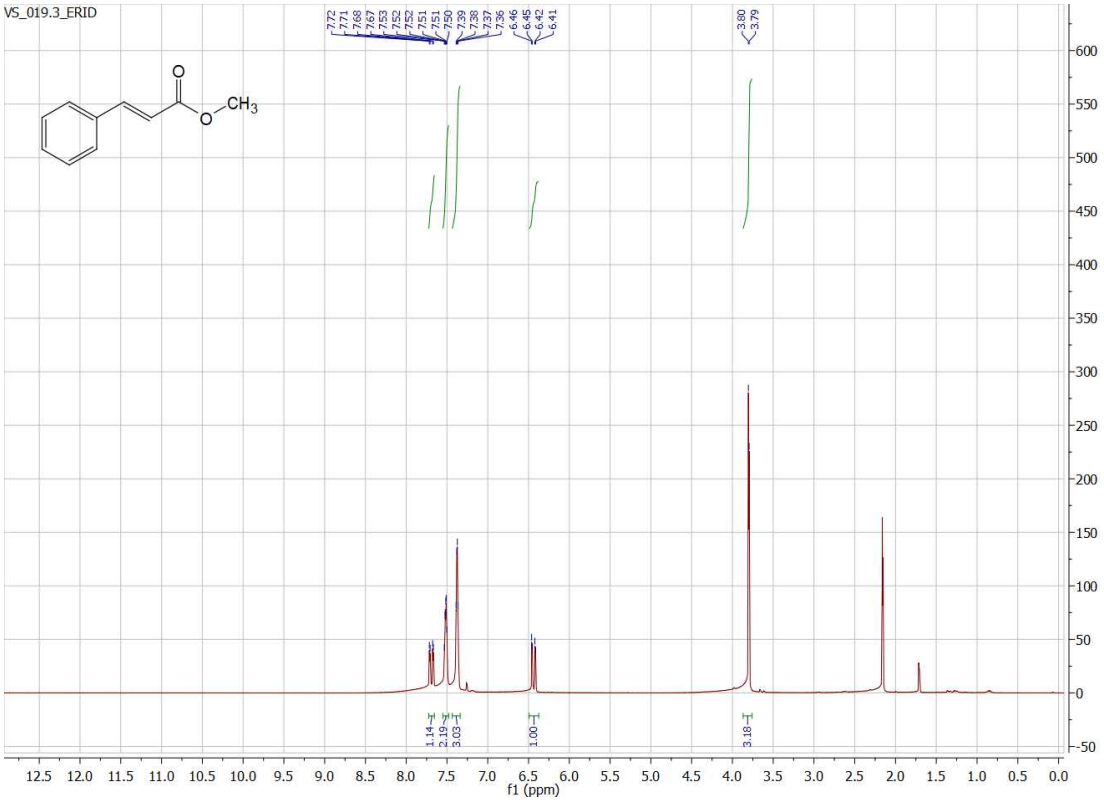


Figure B.1: ^{1}H NMR spectra for isolated Methyl Cinnamate

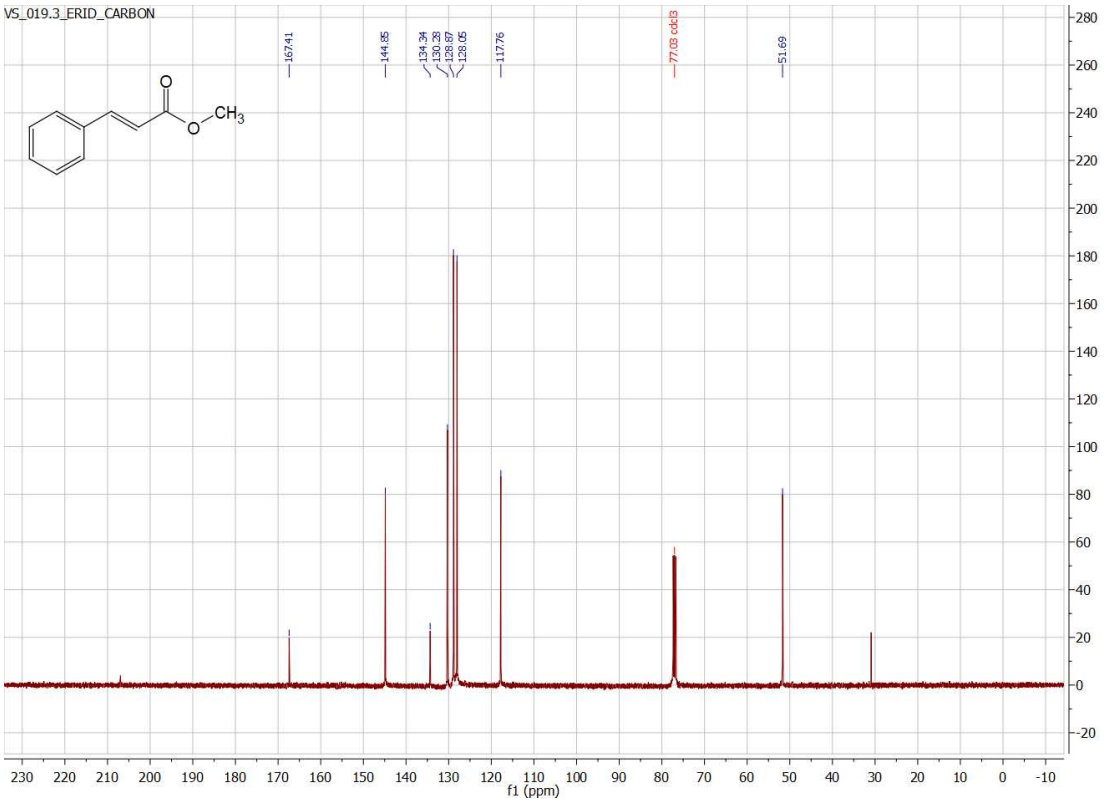


Figure B.2: ^{13}C NMR spectra for isolated Methyl Cinnamate

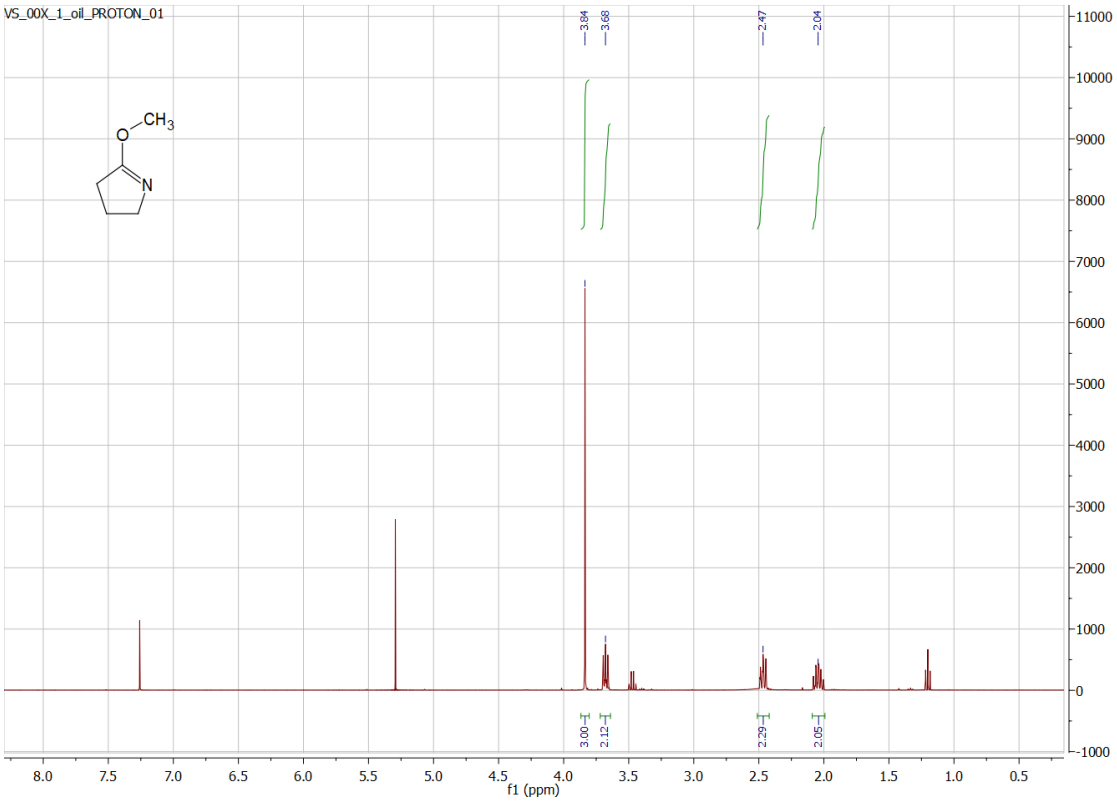


Figure B.3: ^{1}H NMR of 5-methoxy-3,4-dihydro-2H-pyrrole

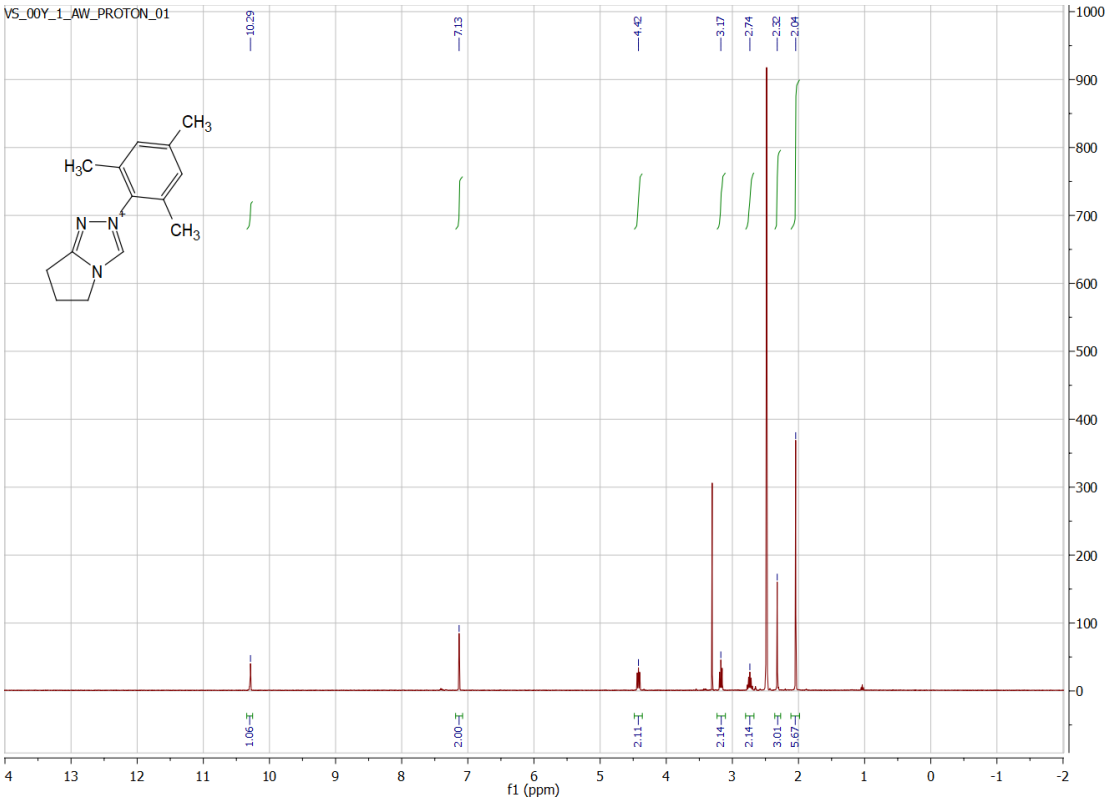


Figure B.4: ^{1}H NMR spectra for 2-Mesityl-6,7-dihydro-5H-pyrrolo[1,2,4]triazol-2-ium chloride, (Cat5)