Aerobic Oxidative N-Heterocyclic Carbene Catalysis via Multistep Electron Transfer
Method Development and Applications

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CHALMERS UNIVERSITY OF TECHNOLOGY

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Cover:
Graphical representation of how the combination of electron transfer mediators and N-heterocyclic carbenes enables the use of oxygen as terminal oxidant in chemical reactions, see section 2.3 Catalytic Aerobic Oxidations.

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Abstract

Oxidation reactions are ubiquitous in synthetic chemistry, but generally suffer from formation of large amounts of potentially toxic byproducts. Aerial oxygen represents an ideal oxidant since it is inexpensive, non-toxic and only forms water as a byproduct. However, aerobic oxidations are characterized by high activation barriers leading to formation of kinetic side products. A common way to circumvent this is by introducing electron transfer mediators (ETMs) to achieve a kinetically useful reaction.

N-heterocyclic carbenes (NHCs) are an important group of organocatalysts that have been used in a wide range of both redox neutral and oxidative transformations. In this thesis, an ETM strategy is used to enable aerobic NHC catalysis. The developed protocol has been employed in aerobic esterifications yielding α,β-unsaturated esters of industrial importance in good to excellent yields. The ETM strategy was also extended to both the racemic and asymmetric synthesis of dihydropyranones.

Lastly, an organocatalytic valorization of the sustainable feedstock glycerol was developed. The reaction furnished several highly functionalized glycerol derivatives in one step from sustainable resources, and could also be extended to the synthesis of 2-oxooxazolidine esters.

To summarize, the combination of ETMs and NHC catalysis enable the use of aerial oxygen as the terminal oxidant in distinct reaction pathways, with water as the only byproduct.

Keywords: Organocatalysis, N-heterocyclic carbene, aerobic oxidation, electron transfer mediator, green chemistry, asymmetric synthesis, esterification, dihydropyranone, glycerol, telescoped reaction.
List of Publications
This thesis is based on the following publications that will be referred to by their Roman numerals in the text. Reprints were made with kind permission from the publishers.

I. Attractive aerobic access to the α,β-unsaturated acyl azolium intermediate: oxidative NHC catalysis via multistep electron transfer
L. Ta,* A. Axelsson,* H. Sunden.
Green Chem., 2016, 18 (3), 686-690

II. Asymmetric aerobic oxidative NHC-catalysed synthesis of dihydropyranones utilising a system of electron transfer mediators
A. Axelsson, E. Hammarvid, L. Ta, H. Sunden.

III. Organocatalytic valorisation of glycerol via a dual NHC-catalysed telescoped reaction
A. Axelsson, A. Antoine-Michard, H. Sunden.

*These authors contributed equally.
Related publications not included in the thesis:

IV. Biomimetic Oxidative Carbene Catalysis: Enabling Aerial Oxygen as a Terminal Oxidant
A. Axelsson, L. Ta, H. Sundén.
*Synlett*, 2017, 28 (08), 873-878

V. Direct Highly Regioselective Functionalization of Carbohydrates: A Three-Component Reaction Combining the Dissolving and Catalytic Efficiency of Ionic Liquids
A. Axelsson, L. Ta, H. Sundén.

VI. Ionic Liquids as Carbene Catalyst Precursors in the One-Pot Four-Component Assembly of Oxo Triphenylhexanoates (OTHOs)
A. Axelsson,* L. Ta,* H. Sundén.

VII. Highly Stereoselective Synthesis of 1,6-Ketoesters Mediated by Ionic Liquids: A Three-component Reaction Enabling Rapid Access to a New Class of Low Molecular Weight Gelators.
H. Sundén, L. Ta, A. Axelsson.
*J. Vis. exp.*, 2015, 105, e53213.

VIII. Ionic Liquids as Precatalysts in the Highly Stereoselective Conjugate Addition of α,β-Unsaturated Aldehydes to Chalcones
L. Ta,* A. Axelsson,* J. Bijl, M. Haukka, H. Sundén.

*These authors contributed equally.*
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DMC</td>
<td>Dimethyl carbonate</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td><em>Et al.</em></td>
<td><em>Et alii</em> (Latin), and others</td>
</tr>
<tr>
<td>Eq.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>ETM</td>
<td>Electron transfer mediator</td>
</tr>
<tr>
<td>FePc</td>
<td>Iron(II) phthalocyanine</td>
</tr>
<tr>
<td>GC-FID</td>
<td>Gas chromatography flame ionization detector</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas chromatography mass spectrometry</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest occupied molecular orbital</td>
</tr>
<tr>
<td>HAT</td>
<td>Hydrogen atom transfer</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>IUPAC</td>
<td>International Union of Pure and Applied Chemistry</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
</tr>
<tr>
<td>N.D</td>
<td>Not determined</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>OCIF</td>
<td>Osteoclastogenesis inhibitory factor</td>
</tr>
<tr>
<td>PEBPLαA</td>
<td>Polyoma enhancer binding protein 2αA</td>
</tr>
<tr>
<td>PCET</td>
<td>Proton coupled electron transfer</td>
</tr>
<tr>
<td>RDS</td>
<td>Rate determining step</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>r.r</td>
<td>Regioisomeric ratio</td>
</tr>
<tr>
<td>SCE</td>
<td>Saturated calomel electrode</td>
</tr>
<tr>
<td>SET</td>
<td>Single electron transfer</td>
</tr>
<tr>
<td>TBD</td>
<td>Triazabicyclo[4.4.0]dec-5-ene</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TMSN₃</td>
<td>Azidotrimethylsilane</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>p-Toluenesulfonic acid</td>
</tr>
<tr>
<td>UN</td>
<td>United Nations</td>
</tr>
</tbody>
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1. Introduction and Background

1.1 Chemistry and Sustainable Development

The term sustainable development was coined in the report *Our Common Future* in 1987 by Brundtland, who defined it as “development that meets the needs of the present without compromising the ability of future generations to meet their own needs”.

The importance of sustainable development was recently reaffirmed by the United Nations (UN) General Assembly’s formal adoption of the 2030 agenda for sustainable development, in which seventeen goals for sustainable development are presented (Figure 1). It is of no surprise that chemistry, sometimes aptly referred to as the central science, lies in the heart of several of these goals. Chemistry is essential to the production of food, water, fuels, medicine and materials, consequently, chemistry has major implications on key aspects such as health and environment. As a testament to chemistry’s contributions to mankind and its role in the transition to sustainable development, the International Union of Pure and Applied Chemistry (IUPAC) and the UN declared 2011 the international year of chemistry, with the banner Chemistry–our life, our future.

1. End poverty in all its forms everywhere
2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture
3. Ensure healthy lives and promote well-being for all at all ages
4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
5. Achieve gender equality and empower all women and girls
6. Ensure availability and sustainable management of water and sanitation for all
7. Ensure access to affordable, reliable, sustainable and modern energy for all
8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
10. Reduce inequality within and among countries
11. Make cities and human settlements inclusive, safe, resilient and sustainable
12. Ensure sustainable consumption and production patterns
13. Take urgent action to combat climate change and its impacts
14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development
15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
17. Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development

*Figure 1. The seventeen sustainable development goals presented in the 2030 agenda for sustainable development.*
Within the field of chemistry, work related to sustainable development is often referred to as green chemistry. The term was coined by Anastas and Warner who initially defined it as the “Design of chemical products and processes to reduce or eliminate the use of hazardous substances”. However, green chemistry is concerned with much more, such as energy conservation, life cycle consideration, waste reduction and the use of renewable feedstock. Anastas and Warner developed a set of twelve principles meant to serve as guidelines to construct a greener chemical process (Figure 2). The principles that are of particular relevance for the work presented in this thesis will be described more thoroughly below.

1. Waste Prevention 7. Use of Renewable Feedstocks
2. Atom Economy 8. Reduce Derivatives
3. Less Hazardous Chemical Syntheses 9. Catalysis
4. Designing Safer Chemicals 10. Design for Degradation
5. Safer Solvents and Auxiliaries 11. Real-time analysis for Pollution Prevention

*Figure 2. The twelve principles of green chemistry.*

The first of the twelve principles states that it is better to prevent the formation of waste than to dispose of it up afterwards. This especially holds true for the fine chemical and pharmaceutical industry, which generate large amounts of waste. A recent survey on 21 compounds, either in phase three clinical trials or already commercially available drugs, showed that every kilogram of product generates on average 76 kg of waste excluding water (range 24–239 kg). Solvents represent the majority of the waste produced, typically ranging between 80–90% for the pharmaceutical industry. Solvent choice is therefore the fifth principle of green chemistry. Several guides for sustainable solvent selection are available.

Waste prevention is also connected to principle two, the design of reactions with high atom economy and to principle nine, the promotion of catalysis over stoichiometric reagents. Atom economy is one of many green chemistry metrics and was introduced by Trost in 1991. It measures the mass efficiency of the transformation of starting materials into products assuming total conversion. It should be noted that atom economy does not take solvent usage in consideration, but other metrics that do so exist, such as the E-factor.
A catalyst is a compound that increases the rate of a reaction without being consumed in the process, so using catalysis is a common way to increase the atom economy of a reaction. Catalysis also enables the reaction to be performed under milder and often more energy efficient conditions, for instance by running the reaction at ambient rather than high temperature. Moreover, sometimes it is also possible to recover and recycle the catalyst, since it is not consumed in the reaction.

Principle seven deals with the use of renewable feedstock. It has been estimated that 95% of all the carbon containing molecules needed to sustain daily life are derived from petrochemical resources, the majority of which are used as fuels.\textsuperscript{11} The building blocks available for the synthetic chemical industry are to a large extent petroleum-based, with roughly 10% of the world production of crude oil used in the manufacturing of industrial chemicals.\textsuperscript{12} Since oil is a depleting and non-sustainable resource, the chemical industry must eventually switch from petroleum based to biobased building blocks. The two largest classes of biomass used as renewable feedstocks are lignocellulosic materials and plant oils.\textsuperscript{13, 14} Plant oils are mostly transformed into biodiesel by transesterification, producing about 10wt% of glycerol as byproduct, making glycerol an attractive renewable feedstock for further manipulation.\textsuperscript{15}
1.2 Organocatalysis

As previously mentioned, a catalyst is a compound that increases the rate, but not the overall standard Gibbs energy change of a chemical reaction, without being consumed.\textsuperscript{16} Catalysis is of fundamental importance to modern society and can be found in numerous aspects of daily life. A famous example is the Haber-Bosch process where ammonia is synthesized from nitrogen and hydrogen through heterogeneous iron catalysis. The produced ammonia is to a large extent used in the manufacturing of fertilizers, enabling us to uphold our food production.\textsuperscript{17} Another example is the use of heterogeneous catalysts based on precious metals such as palladium, platinum and rhodium to purify exhaust from combustion engines found in cars and other vehicles, lessening air pollution.\textsuperscript{18} Catalysts are also used in more delicate chemical processes like the synthesis of sofosbuvir, a drug used together with ledipasvir in Harvoni\textsuperscript{®} for the treatment of hepatitis C, the second most sold drug in 2016.\textsuperscript{19} The synthesis of sofosbuvir entails a telescoped reaction sequence catalyzed by a homogenous palladium(II) complex. Initial borylation of aryl bromide 1 with bis(pinacolato)diboron (2) delivers arylboronic ester 3, which is immediately coupled, using the same catalyst, with aryl bromide 4 via a Suzuki coupling yielding advanced intermediate 5 in 81% yield (Scheme 1).\textsuperscript{20}

\begin{center}
\textit{Scheme 1. Part of the synthesis of sofosbuvir, which is used in the treatment of hepatitis C.}
\end{center}
For a long period of time, the field of catalysis was dominated by the use of transition metal catalysts. However, it has been known for more than a century that small organic molecules can act as potent catalysts. Already in 1896, Knoevenagel reported the condensation of 1,3-dicarbonyl compounds and aldehydes catalyzed by both primary and secondary amines, a reaction nowadays known as the Knoevenagel condensation (Scheme 2 A).\textsuperscript{21, 22} This is one of the first reported organocatalytic reactions. In the early 1900s, it was found that amino acids and secondary ammonium salts catalyzed both the Knoevenagel condensation and the aldol reaction.\textsuperscript{23-25} While aminocatalysis using amino acids has been used for over a hundred years, it was not until the early 1970s that an asymmetric organocatalytic reaction was reported, namely the Hajos-Parrish-Eder-Saur-Wiechert reaction (Scheme 2 B).\textsuperscript{26, 27} In the reaction, S-proline catalyzed an asymmetric intramolecular aldol reaction of triketone 9, which upon acid catalyzed dehydration using \textit{p}-toluenesulfonic acid (\textit{p}-TsOH) yielded diketone 10 in 96:4 enantiomeric ratio (er).

\begin{center}
Scheme 2. An example of a Knoevenagel condensation and the Hajos-Parrish-Eder-Saur-Wiechert reaction.
\end{center}
Although the catalytic abilities of simple amines were well known, the field of organocatalysis was rather dormant during the next 30 years, with some exceptions like the use of R-proline in the total synthesis of Erythronolide A reported by Woodward et al. However, in 2000 two seminal reports laid the foundation of modern organocatalysis. List et al. reported the use of S-proline in the asymmetric aldol reaction between acetone (11) and aldehydes, such as isobutyraldehyde (12) yielding hydroxyketone 13 using an activation strategy now called enamine catalysis. Independently, MacMillan et al. reported the use of S-phenylalanine derived catalyst 16 in the asymmetric Diels-Alder reaction between α,β-unsaturated aldehydes such as cinnamaldehyde (14) and dienes such as cyclopenta-1,3-diene, yielding bridged compound 15 in excellent yield and enantioselectivity, however with poor exo/endo selectivity. The postulated mechanism involves an activation mode now commonly called iminium catalysis.

Organocatalysis have since then developed tremendously and is nowadays a key part of the synthetic chemistry toolbox and a wide range of activation modes in addition to enamine and iminium catalysis have been developed such as chiral Brønsted acids, organic superbases, hydrogen bond donors and phase-transfer catalysts. Moreover, organocatalysts are in general cheaper, more durable and less toxic than the transition metal counterpart. However, organocatalysts often require slightly higher loadings to achieve efficient reactions compared to transition metal catalysts. The use of organocatalysis also circumvents the energy demanding and environment destructing mining of precious metals as well as the metal-scavenging required to remove traces of metal contaminants where they are not tolerated, such as in the pharmaceutical industry. Taken together, these factors make organocatalysis a more sustainable option than transition metal catalysis.

\[
\begin{align*}
\text{Acetone} + \text{PhCHO} &\xrightarrow{\text{S-Proline (30 mol\%)}} \text{PhCH(OH)CHO} \\
\text{PhC} &= \text{endo} \\
\text{PhCHO} &\xrightarrow{\text{MacMillan (10 mol\%)}} \text{exo/endo=1.3:1.0}
\end{align*}
\]

Scheme 3. The organocatalytic asymmetric aldol and Diels-Alder reactions reported by List and MacMillan respectively.
2. Theory and Methodology

2.1 N-Heterocyclic Carbene Catalysis

N-heterocyclic carbenes (NHCs) are a common type of organocatalysts that are characterized by the presence of a neutral bivalent carbon atom with six valence electrons, a so-called carbene, within a N-heterocycle. Carbenes are highly reactive compounds with transient lifetimes. However, it is possible to stabilize carbenes by introducing adjacent heteroatoms enabling resonance stabilization via the corresponding ylide, as in the first persistent carbene (17) reported by Bertrand et al. in 1988 (Figure 3). Three years later Arduengo et al. reported the first stable NHC, which was based on an imidazolium scaffold.

The nitrogen atoms adjacent to the carbene carbon make NHCs more stable than the general carbene. The energy of the highest occupied molecular orbital (HOMO) is decreased while the energy of the lowest unoccupied molecular orbital (LUMO) is increased, hence favoring the singlet state over the triplet state of the carbene. This leads to a thermodynamic stabilization and an increase of the nucleophilicity of the carbene carbon, as seen by the resonance structure (Figure 3 A). The electronic effects of nitrogen atoms in NHCs are sometimes referred to as a push-pull effect, as a result of their σ-withdrawing (inductive) and π-donating (mesomeric, lone pair to vacant p-orbital) nature. The incorporation of the carbene in cyclic structures imposes a sp²-like hybridization of the carbene carbon further favoring the singlet state of the carbene. Lastly, N-substituents stabilize NHCs kinetically by disfavoring the reversible dimerization of carbenes, known as the Wanzlick equilibrium (Figure 3 B). Most NHCs are based on either the imidazolium, triazolium or thiazolium scaffold and are commonly accessed by deprotonation of the corresponding salts.

Figure 3. The structure and stabilization of the first persistent carbene and NHCs.
Although persistent carbenes were not reported until 1989, the catalytic ability of NHCs have been known since 1958 when Breslow proposed a carbene mechanism for the thiamine (vitamin B1) catalyzed decarboxylation of pyruvate by pyruvate dehydrogenase.\(^{48}\) Fifteen years earlier, Ugai et al. had reported that thiamine could replace alkali cyanides as catalysts for the benzoin condensation (Scheme 4).\(^{49}\) In 1976, Stetter reported that thiamine also could replace alkali cyanides in the addition of aldehydes to Michael acceptors, the so called Stetter reaction.\(^{50}\) For both reactions umpolung of aldehyde via the Breslow intermediate is followed by nucleophilic addition to the respective electrophile. Umpolung is the German term for inversion and refers to the inversion of polarity. It was first described by Wittig\(^ {51}\) and later made popular by Seebach,\(^ {52}\) and is a valuable strategy in organic synthesis.\(^ {53}\)

![Scheme 4. The benzoin condensation, the Stetter reaction and the NHC-catalyzed umpolung of aldehydes via formation of the Breslow intermediate.](image)

During the rest of the twentieth century, the field of NHC catalysis was focused around the benzoin condensation and the Stetter reaction.\(^ {54}\) However, in the beginning of the twenty-first century, a surge of activity within the field of NHC catalysis resulted in several distinct reaction modes (Scheme 5). In 2002, Nolan et al. reported a NHC-catalyzed transesterification reaction.\(^ {55}\) Soon thereafter, the groups of Bode and Rovis independently reported the NHC-catalyzed synthesis of esters from epoxyaldehydes (19) and α-haloaldehydes respectively.\(^ {56},\)\(^ {57}\) The reactions proceed via internal oxidation of Breslow intermediate 20 yielding acyl azolium intermediate 21, which can be seen as an activated carboxylic acid that reacts with the alcohol yielding ester 22. Access to the acyl azolium via internal redox forms the basis of many elegant NHC-catalyzed reactions.\(^ {58}\) Bode et al. also reported the first a\(^ 3\)-d\(^ 3\) umpolung of α,β-unsaturated aldehydes for the synthesis of γ-butyrolactones (25), by formation of homoenolate 24 and subsequent addition to various aromatic aldehydes (Scheme 5).\(^ {59}\) Formation of homoenolates is currently one of the most common activation modes in NHC-catalysis.\(^ {60}\) It was not
until 2006 that the first generation of enolate azolium 27, and its use in the asymmetric formal hetero-Diels Alder reaction was reported, with the reaction of \( \alpha \)-chloroaldehydes 26 and enones yielding dihydropyranones 28.\(^{61}\) Enolate azoliums are commonly used to form different heterocycles from readily available starting materials.\(^{58}\) In 2013 Chi et al. reported the \( \gamma \)-activation of \( \beta,\beta \)-disubstituted \( \alpha,\beta \)-unsaturated esters (29) via the formation of vinyl enolate azolium 30, which reacts with an hydrazone to yield unsaturated lactam 31. Besides its uses in fine chemical synthesis, NHC-catalysis is also of increasing importance within the field of polymer science.\(^{62}\)

Scheme 5. Redox neutral activation modes in NHC-catalysis via the acyl azolium, homoenolate, enolate azolium and vinyl enolate azolium.
2.1.1 Oxidative N-Heterocyclic Carbene Catalysis

The Breslow intermediate is electron-rich, which makes it susceptible for oxidation to the corresponding acyl azolium. As noted by Breslow in 1960, acetyl thiazo[li]um salts behave as activated acetates and readily reacts with nucleophiles such as water or methanol (Scheme 6).\textsuperscript{63} Ingraham et al. independently reported a similar reactivity of 2-benzoyl thiazo[li]um salts concurrently with Breslow.\textsuperscript{64} These observations laid the foundation of a prototypical NHC-catalyzed reaction, namely the oxidative esterification of aldehydes, as first reported by Castells et al.\textsuperscript{65} The original report used nitrobenzene as oxidant, but several inorganic\textsuperscript{66} and organic oxidants may be used.\textsuperscript{67, 68} Oxidative esterification gained a lot of interest during the rapid expansion of NHC catalysis in the beginning of the twenty-first century (Scheme 6). In 2005 an oxidative thioesterification of aldehydes was reported.\textsuperscript{69} Soon thereafter, Scheidt reported a NHC-catalyzed oxidation of allylic and benzylic alcohols to esters using MnO\textsubscript{2} as the oxidant.\textsuperscript{70} In 2010, Studer reported the chemoselective O-acylation of aminoalcohols using oxidative NHC catalysis.\textsuperscript{71} The observed selectivity was attributed to activation via carbene–alcohol hydrogen bonding, which increased the nucleophilicity of the alcohol.\textsuperscript{72} In this seminal report Studer also introduced the use of 3,3′,5,5′-tetra-tert-butylidiphenoquinone \textsuperscript{32}, also known as the Kharasch oxidant,\textsuperscript{73} which quickly gained widespread use as oxidant in NHC-catalysis. Studer could also extend this strategy to the oxidative azidation of aldehydes using azidotrimethylsilane (TMSN\textsubscript{3}).

\begin{scheme}
\centering
\begin{tikzpicture}[node distance=1cm,auto]
  \node (a) {$\text{R}_1\text{OH}$};
  \node (b) [right of=a, xshift=1cm] {$\text{Y}^{\text{NR}}\text{R}_2\text{N}$};
  \node (c) [right of=b, xshift=1cm] {$\text{Z}^{\text{CH}}\text{N}$};
  \node (d) [right of=c, xshift=1cm] {$\text{NuH}$};
  \node (e) [below of=a, yshift=-1cm] {$\text{NuH}=\text{MeOH, H}_2\text{O}$};
  \node (f) [right of=a, xshift=3cm] {$\text{R}_1\text{O}^{\text{Nu}}\text{Nu}$};
  \draw [->] (a) -- (b);
  \draw [->] (b) -- (c);
  \draw [->] (c) -- (d);
  \draw [->] (a) -- (f);
\end{tikzpicture}
\caption{Oxidation of the Breslow intermediate yielding the electrophilic acyl azolium intermediate and some of its uses in synthesis.}
\end{scheme}
All of the above-mentioned reactions have in common the direct oxidation of the Breslow intermediate to the electrophilic acyl azolium intermediate, which further reacts with a suitable nucleophile to yield the final product. However, in 2013 Connon et al. reported a novel reaction pathway that led to the first aerobic esterification of aromatic aldehydes (Scheme 7).\textsuperscript{74} Based on the required large excess of alcohol, the observed dependence of steric and \( pK_a \), as well as the identification and isolation of several proposed intermediates, an unconventional mechanism was suggested (Scheme 7).\textsuperscript{75} The reaction commences with deprotonation of triazolium salt 33 with 1,8-diazabicyclo[5.4.0]undec-7-ene (43, DBU) yielding free carbene 34. Breslow intermediate 36 is formed through a nucleophilic 1,2-addition of carbene 34 to benzaldehyde (35) and subsequent proton transfer. Formal acyl anion 36 adds in a 1,2-fashion to another molecule of benzaldehyde and subsequent protonation results in diol 37. Later, 37 collapses to benzoin 38 \textit{via} elimination of carbene 34. \( \alpha \)-Hydroxyketone 38 is then oxidized by aerial oxygen under base catalysis, yielding benzil (39). Nucleophilic addition of the carbene (34) to the diketone yields zwitterion 40, which is rapidly converted into anionic hemiacetal 41 by reacting with methanol, proposedly \textit{via} intramolecular general base catalysis. Scission of the \( \text{C–C} \)-bond fragments unstable intermediate 41, yielding methyl benzoate 42 and regenerating Breslow intermediate 36 and completing the cycle.
Scheme 7. Aerobic esterification of aromatic aldehydes via oxidation of the benzoin product.
The Connon protocol suffers somewhat from a limited scope (only aromatic aldehydes) and the need of high loadings of alcohol. However, its selectivity gives it a large advantage over conventional aerobic NHC-catalyzed reactions. By circumventing direct oxidation of the Breslow intermediate, formation of carboxylic acid as a side product, or sometimes even as the main product, is prevented. This is a consequence of the different paths available for direct aerobic oxidation of the Breslow intermediate, either oxidative or oxygenative (Scheme 8). Both paths begin with the formation of Breslow intermediate 45 via nucleophilic 1,2-addition of carbene 18 to aldehyde 44. Single electron transfer (SET) from electron-rich 45 to dioxygen forms charge-transfer complex 46, which upon radical recombination may yield two tautomeric peroxides, 47 or 51. In the oxidative path, tetrahedral intermediate 47 collapses and expels hydrogen peroxide anion (48) yielding acyl azolium 49, which is further intercepted by methanol yielding ester 50 and regenerating carbene catalyst 18. Even if the desired product is formed through the oxidative pathway, the carboxylic acid side product may still be formed by a NHC-catalyzed side reaction between the aldehyde and the formed hydrogen peroxide.\(^\text{76}\) In the oxygenative pathway, charge-transfer complex 46 recombines to form anionic peroxide 51 that reacts with an additional equivalent of aldehyde yielding intermediate 52. Peroxide 52 fragments, in a similar manner to the Baeyer-Villiger oxidation, yielding carboxylic acid 53 and anionic hemiacetal 54, which then forms another equivalent of carboxylic acid 53 by elimination of carbene 18. Direct formation of the peroxy acid via elimination of the carbene from tetrahedral intermediate 51 and subsequent reduction has also been suggested as a route to the carboxylic acid.\(^\text{77}\) Whether the oxygenative or the oxidative path is predominant is highly dependent on the substitution pattern of the aldehyde, making the development of a general and high-yielding aerobic esterification by direct aerobic oxidation of the Breslow intermediate difficult.\(^\text{78}\)

\textit{Scheme 8. The oxidative and oxygenative path for aerobic oxidation of the Breslow intermediate.}
2.2 The α,β-Unsaturated Acyl Azolium Intermediate

Oxidative NHC catalysis offers several other activation modes besides the use of the acyl azolium as an acylating agent. For instance, enolate azolium reactivity in asymmetric fluorinations and vinyl enolate azoliums in formal [3+3] cycloadditions yielding benzene derivatives. However, the most important intermediate in oxidative NHC catalysis is, arguably, the α,β-unsaturated acyl azolium formed by oxidation of the corresponding homoenolate (Scheme 5, 24). The α,β-unsaturated acyl azolium is a 1,3-biselectrophile and has been isolated and thoroughly characterized by several physical organic chemistry techniques.

The X-ray structure of α,β-unsaturated acyl azolium 56, alongside published values for some physical descriptors for key intermediates in organocatalytic LUMO-activation of Michael acceptors are presented in Figure 4. A comparison of the absorption frequency for the C=O stretch and chemical shift of the β-carbon suggests a similar reactivity of acyl azolium 56 and acyl ammonium 57, which exhibit similar C=O bond strengths but increased polarization at the β-carbon as compared to electron deficient enone 58. A comparison of the electrophilicity parameter $E (\log k = S_N(E + N))$, shows that iminium ion 55 is the most potent electrophile, followed by acyl azolium 56 and quite far behind enone 58. The same trend can also be observed in the chemical shift of the β-carbon. The electrophilicity of 56 is comparable to that of highly activated Michael acceptors such as benzylidenemalononitriles and 2-benzylidene-indan-1,3-ones. In the crystal structure of 56 the C–C double bond and the carbonyl double bond is almost completely coplanar (torsion angle 6.2°), which is the optimal configuration for 1,4-addition. The imidazolium ring of 56 is tilted with respect to the carbonyl group (torsion angle 35.5°) reducing conjugation, which could partly explain the lower electrophilicity compared to 55.
The most characteristic reaction of the α,β-unsaturated acyl azolium is the formal [3+3] cycloaddition with 1,3-dicarbonyl compounds (62) yielding dihydropyranones (63), as first reported by Studer (Scheme 9).88 Since then, a wide range of different heterocycles have been synthesized via this activation mode.89 For instance, a [3+2] cycloaddition with tosylated hydrazine 60 yields pyrazolidine 61 as reported by Chi et al.90 Several different benzothiazepines (66), a privileged structure in medicinal chemistry, is available by formal [4+3] cycloaddition between α-bromoenal 64 and aminothiol 65 that proceeds by internal, and not external oxidation.91 It is also possible to form bicyclic structures, as in the reaction between enal 59 and substituted malonic ester 67 yielding bicyclic enol ester 68.
Scheme 9. Some transformations involving the $\alpha,\beta$-unsaturated acyl azolium intermediate.
2.3 Catalytic Aerobic Oxidations

Oxidation reactions are ubiquitous in synthetic chemistry. Traditional oxidants are often based on either manganese, chromium or iodine and are often of high molecular weight to gain substrate selectivity in the reaction. As a result, oxidation reactions are usually characterized by the formation of large amounts of potentially toxic byproducts, which is not compatible with the concept of green chemistry. Therefore the use of sustainable oxidants such as hydrogen peroxide or molecular oxygen is gaining ground. Hydrogen peroxide is advantageous as it is a liquid, miscible with water, making it relatively easy to handle even on large scale. However, hydrogen peroxide is prone to degradation through a radical process that can be initiated by the presence of impurities such as metallic particles. Molecular oxygen is, on the other hand, abundant and inexpensive since air can often be used directly. Large scale implementation of aerobic oxidations is linked to safety issues, however risks can be reduced in several ways, for instance by the implementation of flow reactors. Both oxygen and hydrogen peroxide present a high efficacy per weight of oxidant and lead to the formation of non-hazardous byproducts (typically water).

Oxygen (O₂) is a peculiar molecule. It has a triplet ground state making it a diradical, but somehow oxygen is stable enough to constitute about 21% of the earth’s atmosphere. Radicals are notorious for their reactivity and typically requires stabilization by either sterical or electronical means to be isolatable, but somehow oxygen persists without steric encumbrance. Another exotic feature of oxygen’s reactivity is that although triplet oxygen is apparently stable under atmospheric conditions singlet oxygen is highly reactive, in stark contrast to general trends, as in the stabilization of NHCs discussed in section 2.1. As a reference, the structure of triplet/singlet oxygen and some carbon centered triplet diradicals and their lifetimes are given in Table 1. Thermodynamic analysis of aerobic oxidations further complicates the issue, it shows that oxygen reacts exothermically with every element except gold. It has even been argued that it is oxygen, and not the hydrocarbon, that should be considered energy-rich in combustion reactions. The reason of the apparent stability of oxygen is clearly not thermodynamic but kinetic, and such species are often referred to as persistent, or long-lived, rather than stable. Hence, aerobic oxidations are generally characterized by favorable thermodynamics and high-activation barriers, requiring high temperatures to be efficient.

<table>
<thead>
<tr>
<th></th>
<th>Lifetime</th>
<th>Persistent</th>
<th>32 µs(^{a})</th>
<th>93 ns(^{b})</th>
<th>390 ns(^{a})</th>
<th>365 ns(^{a})</th>
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</table>

Table 1. Structure and lifetime of some triplet diradicals and singlet oxygen.

\(^{a}\) Measured in benzene at room temperature, values given with a ± 15% interval. \(^{b}\) Measured in benzene at 8 °C, values given with a ± 18% interval.
The high activation barrier for aerobic oxidations is a prerequisite for life as we know it, lessening the extent of oxidative damage. Nonetheless, it complicates the use of oxygen in synthetic transformations, often resulting in the formation of kinetic side products. Inspired by the way nature circumvents these high activation barriers in the respiratory chain, synthetic chemists have started to employ electron transfer mediators (ETMs) in aerobic transformations. The ETMs work in concert, transporting electrons from the substrate to oxygen via a low-energy path thereby circumventing the unfavorable reaction kinetics. This strategy allows the replacement of one large activation barrier by several smaller ones. An industrial application of ETMs is the aerobic oxidation of ethylene to acetaldehyde in the Wacker process (Scheme 10). In this process, ethylene 69 is oxidized by a palladium(II) species, yielding acetaldehyde 70 and palladium(0), which is re-oxidized by a copper(II) salt. The obtained Cu(I) is then readily oxidized back to Cu(II) by aerial oxygen, which completes the redox cycle. The direct oxidation of Pd(0) with oxygen is sluggish, with a kinetic preference for the formation of palladium black instead. However, with the addition of Cu(II) as an ETM the reaction proceeds efficiently.

Scheme 10. The Wacker oxidation of ethylene to acetaldehyde.
The transition metal catalyzed aerobic oxidation of hydroquinones to quinones is a common reaction step in ETM based systems, where the formed quinone later oxidizes either the substrate or another ETM. The cobalt(II) salophen-catalyzed (72) aerobic oxidation of hydroquinone 71 to quinone 73 in methanol has been extensively investigated by a series of kinetic, spectroscopic and computational techniques (Scheme 11). The proposed mechanism begins with the endergonic reaction between oxygen and 72 resulting in production of superoxide 74. Hydroquinone 71 forms the hydrogen bonded complex 75 with the superoxide, which triggers hydrogen atom transfer (HAT) yielding the peroxide intermediate 76. Complex 76 rearranges to hydrogen bonded complex 77 and the hydroquinone radical is further oxidized via proton coupled electron transfer (PCEP) to quinone 73 and Co(II) complex 78. This step has been proposed to be the rate determining step (RDS). The Co(II) complex binds to another molecule of 71 though hydrogen bonding and generates peroxide intermediate 79, which via a second HAT reaction gives water and cobalt(III) hydroxide 80. A third HAT regenerates 72 from 8, releasing water and a second molecule of quinone 73.

_Scheme 11. The mechanism of the Co(salophen) catalyzed aerobic oxidation of quinone 72._
3. Hypothesis and Aim

This thesis is based on the hypothesis that it is possible to develop efficient and general protocols for aerobic NHC catalysis using an ETM strategy. From the hypothesis, three specific aims were formulated:

1. Identify a suitable system of ETMs to enable aerobic NHC-catalyzed reactions.

2. Investigate the generality of the developed system compared to traditional oxidative NHC catalysis.

3. Investigate further use of the developed protocol and the obtained products.
4. Aerobic Access to the α,β-Unsaturated Acyl Azolium Intermediate (Paper I)

4.1 Aerobic NHC Catalysis

The use of stoichiometric amounts of high molecular weight oxidants such as 32 hampers large-scale applications of the rich chemistry associated with oxidative NHC catalysis.68,108 The formation of large amounts of byproducts is accompanied by large costs due to energy demanding separation and disposal of such, which obstructs industrial applications from both a sustainable and an economic perspective. Aerial oxygen is an appealing oxidant since it is non-toxic, cheap and only forms water as a byproduct.

Bäckvall et al. pioneered the use of ETMs in aerobic transformations, and the strategy is amenable for several transition metal catalyzed reactions such as 1,4-oxidation of 1,3-dienes,109 oxidation of alcohols110 and oxidative carbocyclizations.111 Direct aerobic oxidation of the homoenolate is reported to yield the carboxylic acid,112 and early reports using either a Fe(III) or Ru(II) based ETM suffered from restricted scope and high reaction temperatures (Scheme 12).77,113 The limitations of the previously reported aerobic oxidations of the homoenolate could potentially be attributed to inefficient ETM systems, leading to the formation of kinetic side products such as carboxylic acids. It was hypothesized that using two ETMs instead of one would enable a more kinetically potent oxidation of the homoenolate, thereby allowing aerobic access to the α,β-unsaturated acyl azolium.

Scheme 12. Aerobic oxidations of the homoenolate.
4.2 Identification of a Suitable System for Aerobic NHC Catalysis

The aerobic esterification of cinnamaldehyde (14) with methanol (79) was chosen as the model reaction (Table 2). α,β-Unsaturated aldehydes are known to undergo several NHC-catalyzed reactions, such as formation of saturated ester 81, cinnamic acid (82) or γ-butyrolactone 83. Selectivity toward methyl cinnamate 89 would hence be a good indicator of the efficiency in the oxidation of the homoenoate. With stoichiometric amounts of Kharasch oxidant 32, methyl cinnamate was obtained in 74% yield and 78% selectivity, using NHC precatalyst 84 and the base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in acetonitrile (entry 1). When the loading of 32 was decreased to 1 mol% both the yield and the selectivity were drastically reduced, even with prolonged reaction time (entry 2). The result indicates that the direct aerobic oxidation of the formed hydroquinone (Scheme 13, 93) is slow, leading to the formation of kinetic side products. Iron(II) phthalocyanine, FePc, is known to oxidize several hydroquinones to the corresponding quinones in the presence of air.114 In combination with the previously reported selectivity of 32 toward oxidation of the homoenoate, it was theorized that the combination of FePc and Kharasch oxidant would constitute an efficient ETM system. Indeed, by using 1 mol% of 32 and 0.5 mol% of FePc methyl cinnamate was obtained in 80% yield and 88% selectivity (entry 3). Later on, it was shown that 32 could be replaced with phenol 88, maintaining both reactivity and selectivity (entry 4). Phenol 88 is used as a precursor in the synthesis of 32, and under the developed reaction conditions it is rapidly transformed into 32 in situ. Moreover, 88 is a bulk chemical that is considerable cheaper than 32 (88: 538.2 SEK/kg, 32: 1261.67 SEK/50 mg).115 With an efficient ETM system in hand, different NHC precatalysts were examined. Thiazolium based precatalyst 85 proved inactive (entry 5), while imidazolium 86 and bicyclic triazolium 87 formed methyl cinnamate in lower yield and selectivity as compared to 84 (entry 6 and 7). Lastly, the effect of NHC loading was examined and it was found that higher loading gave lower yield with lower selectivity (entry 8 and 9). This effect may be rationalized as follows: increased concentration of the NHC combined with maintained loading of the ETM system leads to an increased average lifetime of the homoenoate, resulting in the formation of kinetic side products.
Table 2. Screening of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>NHC</th>
<th>ETM (eq.)</th>
<th>ETM’ (FePc, eq.)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>84</td>
<td>32 (1.0)</td>
<td>-</td>
<td>4</td>
<td>74</td>
<td>78</td>
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<td>40</td>
</tr>
<tr>
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<tr>
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<td>0.005</td>
<td>4</td>
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<td>89</td>
</tr>
<tr>
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<td>85</td>
<td>88 (0.02)</td>
<td>0.005</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>6</td>
<td>86</td>
<td>88 (0.02)</td>
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<td>65</td>
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<tr>
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<td>88 (0.02)</td>
<td>0.005</td>
<td>4</td>
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<tr>
<td>8</td>
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<td>88 (0.02)</td>
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<td>9</td>
<td>84</td>
<td>88 (0.02)</td>
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<td>67</td>
<td>74</td>
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Potential side products

<table>
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<tr>
<th>Entry</th>
<th>NHC</th>
<th>ETM (eq.)</th>
<th>ETM’ (FePc, eq.)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Selectivity (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<td>32 (1.0)</td>
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<tr>
<td>5</td>
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<td>88 (0.02)</td>
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<td>88 (0.02)</td>
<td>0.005</td>
<td>4</td>
<td>67</td>
<td>74</td>
</tr>
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</table>

a) 14 (0.5 mmol), TBD (0.5 eq.), MeOH (4.0 eq.), NHC (0.02 eq.), ETM (0.02 eq.), ETM’, MeCN (1.0 ml). b) Yield determined by \(^1\)H NMR using durene as internal standard. c) Yield over conversion. d) 0.50 eq. NHC used. e) 0.20 eq. NHC used.

To gain further insight the kinetic profile of the reaction was monitored by gas chromatography equipped with a flame ionization detector (GC-FID) in a series of elimination experiments (Figure 5). In presence of both FePc and 88, cinnamaldehyde is transformed into methyl cinnamate in >90% yield within 5h. Elimination of either FePc or 88 results in about 40% yield within 3h, while exclusion of both FePc and 88 results in about 30% yield. In all reactions, full conversion of cinnamaldehyde is observed and cinnamic acid is obtained as a major side product, indicating that without both FePc and 88 the oxygenative pathway is dominating.
Figure 5. The kinetic profile of the reaction with different ETMs.

Based on the elimination experiments and the decreasing redox potential of FePc ($E^\text{red} = +0.74$ V vs. SCE)$^{116}$ and 32 ($E^\text{red} = -0.52, -0.89$ V vs. SCE)$^{73}$, the following mechanism is proposed (Scheme 13). Deprotonation of the corresponding triazolium salt yields carbene 90 that through a nucleophilic 1,2-addition to cinnamaldehyde yields homoenolate 91. The homoenolate is then rapidly oxidized by 88 to the $\alpha,\beta$-unsaturated acyl azolium 93, by-passing the oxygenative pathways and the formation of peroxy intermediate 92. The acyl azolium is intercepted by methanol yielding methyl cinnamate and carbene 90 is regenerated. Compound 93 is then oxidized back to 32 via FePc-catalyzed aerobic oxidation, yielding water as the sole byproduct and completing the catalytic cycle.

Scheme 13. The proposed mechanism of the aerobic esterification of cinnamaldehyde.

Thereafter, the scope of the reaction was evaluated (Scheme 14). Both electron-poor (96–98) and electron-rich (99–100) cinnamaldehydes were efficiently transformed into the corresponding methyl esters, for instance methyl 4-chlorocinnamate 96 and methyl 4-methoxycinnamate were isolated in 87% and 88% yield respectively. Subsequently, the scope was extended in regard to the alcohol component (102–110). Simple alcohols were well tolerated, and ethanol,
isopropanol and benzyl alcohol delivered esters 102, 103 and 105 in excellent yields. 1,4-Butandiol was also a viable reaction partner yielding monoester 109 in 74% yield. The method also enabled efficient gram-scale reactions, and 1.5 grams of 105 was isolated in 95% yield, using only 26.7 mg of 88 and 18.9 mg of FePc while stoichiometric conditions would have required at least 2.48 grams of 32. The easily oxidizable allyl alcohol was unaffected by the developed oxidative system, and ester 104 could be isolated in 78% yield without any sign of over-oxidation.

The 4-methoxycinnamate motif is common in industrially important antioxidants, and commercial sunscreen agents amiloxate (107) and octinoxate (108) could both be isolated in 72% yield. Aromatic aldehydes could also be employed and methyl benzoate 111 was isolated in 75% yield. Initial attempts with aliphatic enals showed low reactivity and complex reaction mixtures. However, the dienal sorbic aldehyde exhibited good activity and ester 112 was isolated in 69% yield.

Scheme 14. Scope of the NHC-catalyzed aerobic esterification of aldehydes.

---

a) Aldehyde (1 eq.), alcohol (4 eq.), TBD (0.5 eq.), 84 (0.02 eq.) FePc (0.005 eq.), 88 (0.02 eq.) and MeCN (0.2 M). Isolated yields after purification by silica gel chromatography. b) 1.5 grams isolated.
With a rather general method for aerobic access to $\alpha,\beta$-unsaturated acyl azolium intermediates in hand, the possibility of extending the method to other reactions was evaluated. The NHC-catalyzed oxidative annulation between $\alpha,\beta$-unsaturated aldehydes and 1,3-dicarbonyl compounds yielding dihydropyranones was chosen. With light modification of the reaction conditions, dihydropyranones 113–115 could be isolated in good to excellent yields (Scheme 15). The reactions require higher loading of the ETMs and the NHC, while the loading of base could be reduced. This reaction could also be scaled up to 1.4 g, delivering dihydropyranone 114 in 80% yield.

$$\begin{align*}
\text{R}^{1}\text{CH}=\text{O} + \text{R}^{2}\text{CO} & \xrightarrow{84, 32, \text{FePc, DBU}} \text{THF, air, RT} \quad \text{OEt} \\
113, 92\% & \quad 114, 80\%, \ 80\%^{b} \quad 115, 82\% 
\end{align*}$$

\[a) \text{Aldehyde (1 eq.), 1,3-dicarbonyl (1.5 eq.), DBU (0.1 eq., 84 (0.05 eq.) FePc (0.1 eq., 88 (0.05 eq.) and THF (0.1 M). Isolated yields after purification by silica gel chromatography. b) 1.4 Grams isolated.}]

### 4.3 Summary

In conclusion, a catalytic system that enables aerobic access to $\alpha,\beta$-unsaturated acyl azolium intermediates with water as the sole byproduct has been developed. The usage of two ETMs was crucial for achieving a kinetically potent oxidation of the \textit{in situ} formed homoenolate, thereby avoiding the formation of kinetic side products. The method operates at low loadings and at ambient temperature, and has been used in both oxidative esterifications and oxidative annulations. The method exhibits a rather broad scope and drastically reduces the amount of waste formed, making it amenable for scale up from both a sustainability and economic perspective.
5. Asymmetric Aerobic Oxidative NHC-Catalyzed Synthesis of Dihydropyranones (Paper II)

5.1 Synthesis and Natural Occurrence of Dihydropyranones

Dihydropyranones form an intriguing class of compounds and can be found within several natural products and biologically active compounds (Figure 6). For instance, nepetalactone is the principal component responsible for the attractive effect of catnip (*Nepeta cataria*) towards cats.\(^{117}\) Narseronine is found in the flower *Narcissus serotinus* and belongs to a class of compounds that are of interest for their antifungal activities.\(^{118}\) Neocucurbitacin A, isolated from the fruits of *Luffa operculata*, a traditional medicinal plant from South America, inhibits osteogenesis (bone formation) by reducing the amount of polyoma enhancer binding protein 2αA (PEBPLαA) and osteoclastogenesis inhibitory factor (OCIF) mRNA, while neocucurbitacin B shows no effect on osteogenesis.\(^{119}\) A range of dihydropyranones have also been shown to possess cytotoxic activities towards both the SW116 and SGC7901 cell line (colorectal and gastric cancer respectively), with 3ai being the most potent SW116 inhibitor.\(^{120}\)

There is a number of NHC-catalyzed protocols toward the synthesis of the dihydropyranone scaffold.\(^{121}\) However, most of them suffer from poor atom economy due to the use of stoichiometric amounts of oxidants,\(^{88}\) internal leaving groups,\(^{122}\) sacrificial reagents\(^{76}\) or coupling reagents.\(^{123}\) Some protocols based on Ni(II)-catalysis are also available.\(^{124},\, 125\) Based on the recent success in the development of an aerobic method for the racemic synthesis of dihydropyranones, we set out to develop an asymmetric aerobic alternative based on an ETM strategy.

![Figure 6. Natural products and biologically relevant compounds containing the dihydropyranone moiety.](image)
5.2 Screening of Reaction Conditions and Scope

The reaction between cinnamaldehyde 14 and acetylacetone 62 yielding dihydropyranone 116 was chosen as model reaction (Table 3). Initial screening focused on identifying conditions that maintained high efficiency and selectivity when performed with open reaction vessels and using wet solvents, and thus stoichiometric amounts of the Kharasch oxidant were used. This preliminary screen indicated that the use of NHC precatalyst 117 and lithium acetate in toluene was crucial for the development of a robust and effective reaction. Thereafter, attempts to enable aerobic oxidation were initiated by introducing different ETMs.

By using a combination of Kharasch oxidant and Co(II) based ETM 119 dihydropyranone 116 could be isolated in excellent enantiomeric excess (ee), albeit in poor yield (entry 1). Replacing the Kharasch oxidant with quinone 118 resulted in increased yield. Changing to FePc and Kharasch oxidant as the ETM couple resulted in an increased yield and reduced reaction time (entry 4). Running the reaction at higher temperature (40 °C) additionally reduced the reaction time with maintained selectivity (entry 5).

In an attempt to further increase the yield, the reaction was conducted under an atmosphere of oxygen, but, surprisingly, this resulted in no product formation at all (entry 6). It was hypothesized that a catalytically inactive dimeric μ-oxo species, [FePc]₂O, was formed under the oxygen rich conditions. This prompted us to further probe the stability of the ETM couple. Exclusion of either FePc, 32 or both resulted in very low yield (entry 7–9) and performing the reaction under an atmosphere of nitrogen delivered the dihydropyranone in only 17% yield (entry 10). Monitoring the reaction via gas chromatography mass spectrometry, GC-MS, showed that 32 is completely converted into its reduced form 93 after 3h. However, upon addition of one additional portion of FePc 93 is quantitatively re-oxidized to 32. Together these results corroborate that deactivation of FePc is the major inactivation pathway. By adding FePc sequentially, inactivation was circumvented and dihydropyranone 116 was obtained in 79% yield and 94% ee (entry 11).
Table 3. Screening of reaction conditions for the asymmetric synthesis of dihydropyranones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>ETM’ (eq.)</th>
<th>ETM (eq.)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>r.t</td>
<td>46</td>
<td>119 (0.02)</td>
<td>32 (0.1)</td>
<td>29</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>r.t</td>
<td>48</td>
<td>119 (0.02)</td>
<td>118 (0.1)</td>
<td>58</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>r.t</td>
<td>72</td>
<td>FePc (0.02)</td>
<td>118 (0.1)</td>
<td>62</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>r.t</td>
<td>48</td>
<td>FePc (0.02)</td>
<td>32 (0.1)</td>
<td>62</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>22</td>
<td>FePc (0.02)</td>
<td>32 (0.1)</td>
<td>69</td>
<td>95</td>
</tr>
<tr>
<td>6b</td>
<td>r.t</td>
<td>48</td>
<td>FePc (0.02)</td>
<td>32 (0.1)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>7c</td>
<td>r.t</td>
<td>48</td>
<td>FePc (0.02)</td>
<td>-</td>
<td>6%</td>
<td>ND</td>
</tr>
<tr>
<td>8c</td>
<td>r.t</td>
<td>48</td>
<td>-</td>
<td>32 (0.1)</td>
<td>7%</td>
<td>ND</td>
</tr>
<tr>
<td>9c</td>
<td>r.t</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10e</td>
<td>r.t</td>
<td>48</td>
<td>FePc (0.02)</td>
<td>32 (0.1)</td>
<td>17</td>
<td>ND</td>
</tr>
<tr>
<td>11e</td>
<td>40</td>
<td>25</td>
<td>FePc (0.04)</td>
<td>32 (0.2)</td>
<td>79</td>
<td>94</td>
</tr>
</tbody>
</table>

a) The reactions were performed in open reaction vessels at the indicated temperature (see Table) in toluene with cinnamaldehyde 14 (1 eq.), acetylacetone 62 (3 eq.), 117 (0.1 eq.), LiOAc*2H2O (0.65 eq.) ETM (See Table), ETM’ (See Table). b) The reaction was conducted in an atmosphere of pure O2. c) Yield was determined with NMR against internal standard. d) Reaction conducted under an atmosphere of nitrogen. e) Sequential addition of FePc see ESI for details. ND= not determined.

With an efficient protocol finalized, the scope of the transformation was examined (Scheme 16). With acetylacetone as the nucleophile several different dihydropyranones could be isolated in good yields and good to excellent ee (120–125). For instance, 4-chlorocinnamaldehyde and 2-nitrocinnamaldehyde delivered corresponding dihydropyranones 120 and 124 in 80% yield, 91% ee and 73% yield, 90% ee respectively. Aliphatic enals were also reasonably well tolerated in the reaction and 125 was isolated in 65% yield and 83% ee. 1,3-Ketoesters also proved viable reaction partners and several ester-substituted dihydropyranones was obtained in good yield with full regioselectivity and good to excellent ee (126–133). For instance, cinnamaldehyde and methyl acetoacetate yielded dihydropyranone 131 in 79% yield and 95% ee. Asymmetric 1,3-diketones could also be used and compound 134 was obtained in 67% yield, 93:7 r.r. and 87% ee.
a) The reactions were performed in open reaction vessels at 40 °C in toluene (1 mL) with catalyst 117 (0.1 eq.), α,β-unsaturated aldehyde (1 eq.), 1,3-dicarbonyl (3 eq.), LiOAc·2H₂O (1 eq.) FePc (0.06 eq.) and 32 (0.2 eq.). b) Isolated yields after purification with silica gel chromatography. c) major isomer combined yield r.r. determined by ¹H NMR of the crude reaction mixture.

Scheme 16. The scope of the asymmetric aerobic NHC-catalyzed synthesis of dihydropyranones."
The proposed catalytic cycle begins with deprotonation of triazolium salt 117 to form free carbene 135, that further adds in a 1,2-fashion to the enal, forming homoenolate 136 (Scheme 17). The homoenolate is then oxidized by the system of ETMs with oxygen as the terminal oxidant, forming α,β-unsaturated acyl azolium intermediate 137. Acetylacetone 62 is deprotonated forming enolate 138 that upon asymmetric 1,4-addition to 137 gives chiral enolate 139. The more stable enolate 140 is formed through proton transfer and further cyclizes via an internal oxa-1,2-addition of the enolate to the acyl azolium, delivering dihydropyranone 141 and regenerating carbene 135. A mechanism based on initial oxa-1,2-addition of enolate 138 to the α,β-unsaturated acyl azolium and subsequent Claisen rearrangement has also been proposed for a similar system.127

Scheme 17. The proposed mechanism for the aerobic NHC-catalyzed synthesis of dihydropyranones.
Having identified an aerobic system for the asymmetric synthesis of dihydropyranones, further manipulation of the obtained products was investigated. It was found that treating 116 with equimolar amounts of NHC precursor 84 and DBU in methanol yielded acyclic methyl ester 135 in excellent yield and with minimal loss of optical purity (Scheme 18). The obtained product represents the formal asymmetric Michael addition of acetylacetone to methyl cinnamate, a transformation that is nontrivial due to the low electrophilicity of α,β-unsaturated esters.\(^{128}\)

\[
\begin{array}{c}
\text{116, 94\% ee} \\
\text{84, DBU} \\
\text{MeOH} \\
\text{142, 95\%, 93\% ee}
\end{array}
\]

| 116 (1 eq.), DBU (0.1 eq.), 84 (0.1 eq.) and MeOH (0.1M). Isolated yields after purification by silica gel chromatography. |

Scheme 18. NHC/base-catalyzed formation of acyclic ester 135 from dihydropyranone 116.

5.3 Summary

In summary, this report shows that it is possible to extend the use of aerobic NHC catalysis to the synthesis of chiral dihydropyranones. Sequential addition of the ETM FePc was crucial for a successful reaction due to deactivation, possibly via formation of the dimeric µ-oxo species, [FePc]₂O. The reaction has a rather broad scope and dihydropyranones are obtained in good yields with good to excellent enantioselectivities, proving that the aerobic system is compatible with the more delicate chemistry available with oxidative NHC catalysis.
6. Valorization of Glycerol via a Dual NHC-Catalyzed Telescoped Reaction (Paper III)

6.1 Chemical Valorization of Biomass

The valorization of biomass into fuels, fine and commodity chemicals is one of the great challenges within chemistry and is a prerequisite for sustainable development.\textsuperscript{129} Transesterification of vegetable oils into biodiesel yields glycerol as a byproduct (10 wt%), making it an attractive feedstock for various C\textsubscript{3}-chemicals.\textsuperscript{15} Glycerol is currently used as a precursor in the industrial epichlorohydrin synthesis by Solvay,\textsuperscript{129} and glycerol carbonate has gained widespread attention for various uses such as solvent, electrolyte or regent for both fine chemicals and polymers.\textsuperscript{130, 131}

Valorization of glycerol is typically achieved through transition metal catalysis,\textsuperscript{130, 132} organocatalytic transformations of glycerol remaining much scarcer. Organocatalysts are indeed often considered to be less reactive than transition metal catalysts, therefore requiring higher loadings to reach reaction efficiency. However, organocatalysts have many virtues such as low-cost, low toxicity and high stability making them suitable sustainable catalysts with regard to their transition metal counterpart.\textsuperscript{43} Previous reported organocatalytic transformations of glycerol involve transcarboxylation with either dialkyl carbonates or urea using NHCs, quaternary ammonium salts or Brønsted-Lowry bases (Figure 7, A).\textsuperscript{131, 133-135} Organocatalytic acylation of glycerol is possible using either superbases, alkali acetates or sulfonic acids as catalysts (Figure 7, B).\textsuperscript{136-140} Lastly, both homogenous and heterogeneous sulfonic acids have been used to transform glycerol to a variety of different acetals and ethers (Figure 7, C).\textsuperscript{141, 142} Although NHC-catalysis offers several distinct reaction paths, the use of NHC-catalysis in glycerol valorization is currently limited to carbonation reactions. We set out to merge our newly developed system for aerobic NHC catalysis and glycerol upgrading in a telescoped reaction giving access to valuable glycerol derivatives (Figure 7, D). The reaction would furnish esters of glycerol carbonate in a single step from glycerol, and such products have attracted attention for use as surfactants.\textsuperscript{131}
6.2 Design of a Telescoped Reaction for Dual Glycerol Functionalization

Formation of unsaturated glycerol carbonate ester via the initial carbonation of glycerol with dimethyl carbonate followed by aerobic acylation using cinnamaldehyde, was chosen as model reaction (Table 4). A successful reaction would offer several advantages such as direct valorization of glycerol, high atom and pot economy and the incorporation of a carbonate group as a synthetic handle. Moreover, it should be noted that dimethyl carbonate (DMC) is a benign reagent that is non-toxic, biodegradable and is derived from CO₂. The advantages of DMC over other carbonation reagents get especially clear when compared to the highly poisonous phosgene, for instance. Promising initial attempts with triazolium salt TBD and 88/FePc as ETMs yielded 143 in 89% yield using only 1.1 equivalents of glycerol (entry 1). A scan of different NHC precatalysts showed that thiazolium based catalyst 145 was inactive, while catalysts 86 and 87 gave the product in slightly lower yield (entry 2-4). With bicyclic triazolium 87 cinnamic acid was obtained as a side product indicating that the oxygenative pathway is active under these conditions, while imidazolium based catalyst 86 exhibited incomplete consumption of cinnamaldehyde indicating a less robust system as compared to 84.

Replacement of TBD with either K₂CO₃ or Et₃N resulted in no conversion of cinnamaldehyde (entry 5-6). This effect may be rationalized by that the crucial in situ aerobic oxidation of 88 to 32 under FePc catalysis is also base-catalyzed, and
Et₃N is likely a too weak base while K₂CO₃ suffered from poor solvation, hampering the reaction. Realizing this, it was possible to reduce the loading of TBD with maintained yield by replacing 88 with 32, albeit with prolonged reaction time (24h, entry 7). Performing the reaction under an atmosphere of nitrogen delivered the product in only 5% yield, showing that aerial oxygen truly is the terminal oxidant (entry 8).

Direct acylation of glycerol yielding ester 144 is also possible (entry 9). However, these reactions yield several undesired side products, mainly the diester and the secondary ester, which cannot effectively be separated from the main product. The amount of side products formed remained stable around 10% regardless of solvent selection and concentration. For instance, when the reaction was performed in acetone 144 was obtained in 81% yield, due to a competing aldol reaction, in addition to the secondary ester and the diester side reactions (entry 10). Moreover, when the NHC is excluded from the carbonation step, an incomplete conversion of glycerol with subsequent side product formation (14% by ¹H NMR) is noted, suggesting that the carbonation step also is NHC-catalyzed.

Table 4. Screening of reaction conditions for the telescoped valorization of glycerol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat</th>
<th>ETM1</th>
<th>ETM2</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>89</td>
</tr>
<tr>
<td>2.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>86</td>
</tr>
<tr>
<td>3.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>81</td>
</tr>
<tr>
<td>5.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>K₂CO₃</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>6.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>Et₃N</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>7.</td>
<td>84</td>
<td>32</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>88</td>
</tr>
<tr>
<td>8.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>5</td>
</tr>
<tr>
<td>9.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>MeCN</td>
<td>87</td>
</tr>
<tr>
<td>10.</td>
<td>84</td>
<td>88</td>
<td>FePc</td>
<td>TBD</td>
<td>Acetone</td>
<td>81</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by ¹H NMR with durene as internal standard. b) i, Glycerol (1.1 eq.), TBD (0.5 eq), 84 (2 mol%), solvent/dimethyl carbonate 5:2. ii, Cinnamaldehyde (0.5 mmol), FePc (0.5 mol%), 88 (2 mol%). c) As in b), but with 0.2 eq. TBD and 0.01 eq. of 32. d) Last step performed under a nitrogen atmosphere. e) Glycerol (4 eq.), TBD (0.5 eq.), 84 (2 mol%), cinnamaldehyde (0.5 mmol), FePc (0.5 mol%), 88 (2 mol%).
Having found conditions that enable selective functionalization of glycerol (Table 6, entry 1), the scope of the transformation was investigated (Scheme 19). Both electron donating groups (EDG, 146-148, 153) and electron withdrawing groups (EWG, 149-152) were well tolerated on the cinnamaldehyde scaffold providing glycerol carbonate esters in moderate to excellent yields. For instance, 4-chlorocinnamaldehyde and 2-methoxycinnamaldehyde yielded esters 149 and 153 in 90% and 77% yield respectively. Moreover, 4-methoxycinnamaldehyde was efficiently converted to ester 146 in 95% yield, which is worth highlighting since 4-methoxycinnamates are commonly used in sunscreens, and the glycerol ester has been investigated as a more benign sunscreen agent. Aliphatic enals initially showed low reactivity, however using 4 mol% of the more active catalyst 87 enabled the formation and isolation of aliphatic ester 155 in 64% yield. Benzaldehydes appeared to be less reactive than cinnamaldehydes, requiring 4 mol% of catalyst 84 to be successful. With that modification of the reaction protocol, a range of different aromatic aldehydes was used, delivering the products in moderate to good yields (156-162). As an example, piperonal and furfural yielded 160 and 162 in 79% and 63% yield respectively.
Scheme 18. The scope of the NHC-catalyzed dual functionalization of glycerol.

a) i. Glycerol (1.1 eq.), TBD (0.5 eq.), 84 (0.02 eq.), MeCN/DMC 5:2 (0.8 M). ii. Aldehyde (0.5 mmol), FePc (0.005 eq.), 8 (0.02 eq.) and MeCN (0.2 M).

b) 1.6 Grams isolated.

c) As in a, but with 4 mol% of catalyst 87 used.

d) As in a, but with 4 mol% of catalyst 84 used.
The above-mentioned protocol was easily extended to the synthesis of 2-oxooxazolidine esters by replacing glycerol with aminoalcohol 163 (Scheme 20). As for the reaction with glycerol, the reaction tolerated both electron-rich and electron-poor cinnamaldehydes, delivering the products in excellent yields. 2-Methoxycinnamaldehyde and 4-fluorocinnamaldehyde delivered their corresponding oxooxazolidines in 90% and 92% yield respectively.

![Scheme 19. Formation of 2-oxooxazolidine esters via NHC-catalyzed carbonation and aerobic acylation of aminoalcohol 163.](image)

Ring-opening of glycerol carbonates has been used for sustainable synthesis of pharmaceuticals and polymers, and is thus of great interest.\(^{146-148}\) Hence, selective functionalization of the less electrophilic carbonate moiety in presence of the \(\alpha,\beta\)-unsaturated ester function would enable the use of the herein obtained products as sustainable building blocks for further synthesis. Inspired by reports from Kleij \textit{et al.},\(^{149, 150}\) the TBD-catalyzed ring-opening of 143 with piperidine was investigated. At -20 °C, the use of 5 mol% of TBD in dichloromethane (DCM) delivered acyclic carbamate 170 in 83% yield and good regioisomeric ratio (Scheme 21). When higher loading of TBD or other solvents (THF, MeCN) were used, the amide was formed as a side product. Performing the reaction at ambient temperature resulted in decreased regioselectivity.

![Scheme 20. Organocatalytic ring-opening of 143 with piperidine.](image)
Mechanistically, the reaction does not differ much from the one reported in chapter 4. Deprotonation of triazolium salt 84 yields free NHC 90, which after nucleophilic 1,2-addition to the aldehyde forms Breslow intermediate 171 (Scheme 21). The Breslow intermediate is oxidized by the system of ETMs with oxygen as the terminal oxidant, delivering acyl azolium 172 and water. Glycerol and DMC react via NHC/TBD catalysis yielding glycerol carbonate 173, which upon nucleophilic 1,2-addition to 172 gives ester 174, and regenerates the free carbene.

![Scheme 21. Proposed mechanism for the dual functionalization of glycerol by NHC catalysis.](image)

6.3 Summary

To conclude, a telescoped reaction for the NHC-catalyzed carbonation and aerobic acylation of glycerol has been developed. The reaction furnishes highly functionalized glycerol derivatives from sustainable precursors such as glycerol, dimethyl carbonate and aerial oxygen. The reaction occurs under ambient conditions, is high yielding, scalable and tolerates (hetero)aromatic aldehydes and both aromatic and aliphatic α,β-unsaturated aldehydes. The methodology could also be extended to the synthesis of oxooxazolidine esters. Lastly, selective ring-opening of the carbonate in presence of the α,β-unsaturated ester was demonstrated using TBD as a catalyst.
7. Conclusion and Outlook

Herein, a strategy for aerobic NHC-catalysis based on a couple of ETMs has been presented, and the system is amenable for scale-up. The usage of two ETMs was proven crucial in order to achieve a successful reaction, avoiding formation of kinetic side products. The amount of byproduct formed in the reactions is drastically reduced using aerial oxygen as the terminal oxidant, giving water as the sole byproduct.

The strategy could successfully be applied to gain aerobic access to the $\alpha,\beta$-unsaturated acyl azolium intermediates, resulting in the aerobic synthesis $\alpha,\beta$-unsaturated esters such as the industrially important antioxidants amiloxate and octinoxate. Analysis by GC-FID indicated that if one or both of the ETMs are missing the oxygenative pathway is dominating, hence yielding about 30-40% of the desired ester and substantial amounts of the corresponding carboxylic acid.

The system could also be extended to both the racemic and asymmetric synthesis of dihydropyranones. These reactions required higher loadings of both ETMs, and for the asymmetric synthesis a sequential addition of FePc was required to achieve efficient reactions. The need for sequential addition of FePc was attributed to the deactivation of FePc under the reaction conditions, most likely via formation of the dimeric $\mu$-oxo species $[\text{FePc}]_2\text{O}$. However, using these modifications of the reaction protocol a wide range of dihydropyranones could be obtained in good yields and in good to excellent ee.

Lastly, the use of the aerobic system in a telescoped NHC-catalyzed valorization of glycerol was demonstrated. The reaction encompasses carbonation of glycerol and subsequent aerobic acylation using aldehydes, delivering the esters in moderate to excellent yields. A method for the selective activation of the carbonate moiety, in the presence of more electrophilic $\alpha,\beta$-unsaturated ester, was also developed yielding a highly functionalized acyclic carbamate in good yield and regioselectivity.

This thesis highlights that the rich chemistry associated with oxidative NHC-catalysis is viable without the use of high molecular weight oxidants. Future work could be dedicated to the implementation of the developed aerobic system with either $\alpha$- or $\gamma$-activation of aldehydes via oxidative NHC catalysis. Mechanistic studies of the ETM system would also be highly useful for future applications. What factors that govern the stability of the system and through what pathway the oxidation of 93 to 32 proceeds, via a Fe(III)-superoxide mechanism in analogy with the Co-catalyzed reaction or by another pathway, remains to be identified. Lastly, the products obtained in these reactions could be used as sustainable starting materials, and further transformations into valuable compounds should be investigated.
8. Acknowledgement

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9. References

81. CCDC 857879 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [http://www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
87. For the database of reaction parameters see: [http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/](http://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/).
enzymatic oxygen activation, see C.


Such species have been isolated and are believed to have an important role in enzymatic oxygen activation, see C.-W. Chiang, S. T. Kleespies, H. D. Stout, K. K. Meier, P.-Y. Li, E. L. Bominaa, L. Que, E. Münck and W.-Z. Lee, J. Am. Chem. Soc., 2014, 136, 10846-10849.