THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

N-Heterocyclic Carbene Catalysis in Organic Synthesis – A Green Chemistry Approach

Method development using ionic liquid as carbene precursors and aerobic oxidative NHC catalysis

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CHALMERS UNIVERSITY OF TECHNOLOGY

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Cover: The utilization of green chemistry and NHC catalysis in method development for the synthesis of various compounds presented in this thesis from readily available starting materials.

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Abstract

The twelve principles of green chemistry were created as a response to the multiple environmental issues caused by the release of waste from the chemical industry. The principles acts as a guide in the development of sustainable chemical processes for the syntheses of important molecules needed to sustain our living standards. This thesis will focus on the most important principle, catalysis, which can aid in making reactions more efficient and atomeconomic, hence reducing the formation of chemical waste. One type of catalyst is the *N*-heterocyclic carbene (NHC), a type of organocatalyst that has become an attractive tool for the synthesis of various interesting compounds. Two different methods of using NHC catalysis are presented.

The first method uses an imidazolium-based ionic liquid as an NHC-precatalyst for the synthesis of oxo triphenylhexanoates (OTHOs) in a highly stereo- and regioselective manner. The scope of the reaction is broad, with multiple functional groups tolerated. With this method, the selective modification of complex polyols, such as carbohydrates is possible. The reaction operates under mild conditions, can be performed in a one-pot multicomponent reaction without the use of protecting groups, and omits the use of solvent-demanding chromatography by a simple filtration work-up procedure.

The second method employs oxidative NHC catalysis for the synthesis of various α,β unsaturated esters, lactones, and acylated *N*-heterocyclic compounds such as indoles and oxazolidinones. An aerobic protocol was developed with the help of electron transfer mediators (ETMs) enabling the use of molecular oxygen as the terminal oxidant. This aerobic protocol allows for the substitution of a high molecular weight oxidant frequently associated with oxidative NHC catalysis. The developed method facilitates scale-up reactions and reduction of the chemical waste generated. The obtained products were also applied in further functionalization towards commercially interesting compounds.

This thesis demonstrates the use of catalysis for the development of reactions that are atomeconomic, energy efficient and avoid the creation of chemical waste. Moreover, with NHC catalysis readily available reagents could be utilized as starting materials, thus avoiding hazardous substrates. By the guidance of the principles of green chemistry more sustainable and benign reactions can be designed.

Keywords: Organocatalysis, NHC catalysis, green chemistry, aerobic oxidation, sustainability, oxidative NHC catalysis, OTHO, ionic liquid

List of publications

This thesis is based on the work contained in the following papers. Reprints were made with permission from the publishers.

I. *Ionic liquids as precatalysts in the highly stereoselective conjugate addition of α,β-unsaturated aldehydes to chalcones*
Linda Ta*, Anton Axelsson*, Joachim Bijl, Matti Haukka, Henrik Sundén
Chem. Eur. J., **2014**, *20*, 13889–13893

II. *Ionic liquids as carbene catalyst precursors in the one-pot four-component assembly of Oxo Triphenylhexanoates (OTHOs*)
Anton Axelsson*, Linda Ta*, Henrik Sundén
Catalysts, **2015**, *5*, 2052–2067

III. *Direct highly regioselective functionalization of carbohydrates: A three-component reaction combining the dissolving and catalytic efficiency of ionic liquids*
Anton Axelsson, Linda Ta, Henrik Sundén
Eur. J. Org. Chem. **2016**, *2016*, 20, 3339–3343

IV. *Attractive aerobic access to the α,β-unsaturated acyl azolium intermediate: Oxidative NHC catalysis via multistep electron transfer*
Linda Ta*, Anton Axelsson*, Henrik Sundén
Green Chem, **2016**, *18*, 686–690

V. *Asymmetric aerobic oxidative NHC-catalysed synthesis of dihydropyranones utilising a system of electron transfer mediators*
Anton Axelsson, Emmelie Hammarvid, Linda Ta, Henrik Sundén
Chem. Commun. **2016**, *52*, 77, 11571–11574

VI. *Oxidative organocatalytic chemoselective N-acylation of heterocycles with aromatic and conjugated aldehydes*
Linda Ta, Henrik Sundén
Chem. Commun. **2018**, *54*, 5, 531–534

VII. *N-acylation of oxazolidinones via aerobic oxidative NHC catalysis*
Linda Ta*, Anton Axelsson*, Henrik Sundén
Manuscript

*These authors contributed equally

Contribution report

The author's contribution to the papers presented in this thesis:

Paper **I** Contributed to the outline of the study. Performed half of the experimental work. Contributed to the interpretation of the results. Wrote parts of the manuscript.

Paper **II** Contributed to the outline of the study. Performed half of the experimental work. Contributed to the interpretation of the results. Wrote parts of the manuscript.

Paper **III** Contributed to the outline of the study. Performed half of the experimental work. Contributed to the interpretation of the results. Wrote parts of the manuscript.

Paper **IV** Contributed to the outline of the study. Performed half of the experimental work. Contributed to the interpretation of the results. Wrote parts of the manuscript.

Paper **V**. Contributed to the experimental work. Contributed to the interpretation of the results.

Paper **VI**. Outlined the study. Performed all the experimental work and analyses. Performed the interpretation of the results. Wrote parts of the manuscript.

Paper **VII**. Outlined the study. Performed half of the experimental work. Contributed to the interpretation of the results. Wrote the majority of the manuscript.

Related publications not included in this thesis

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
Henrik Sundén, Linda Ta, Anton Axelsson
J. Vis. Exp. **2015**, *105*, e53213

Biomimetic oxidative carbene catalysis: Enabling aerial oxygen as a terminal oxidant
Anton Axelsson, Linda Ta, Henrik Sundén
Synlett, **2017**, *28*, 873–878

List of abbreviations

BMIMCl	1-butyl-3-methylimidazolium chloride
Bn	benzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
ee	enantiomeric excess
EMIMAc	1-ethyl-3-methylimidazolium acetate
EMIMCl	1-ethyl-3-methylimidazolium chloride
ETM	electron transfer mediator
Et	ethyl
eq.	equivalents
FePc	iron(II)phthalocyanine
HFIP	hexafluoro-2-propanol
IL	ionic liquid
MCR	multi-component reaction
MeCN	acetonitrile
MEK	methyl ethyl ketone
n.d.	not determined
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Termal Ellipsoid Plot
OTHO	oxo triphenylhexanoate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TPAP	tetrapropylammonium perruthenate

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Chapter 1

Introduction and background

The achievements made by the pharmaceutical and chemical industry during the last century have with no doubt helped us to transform our society as we know it today. The dark side of this fast development has been environmental pollution threatening the future of the planet due to the release of toxic chemical waste into nature. With an increased pressure and awareness from both governments and public, there are now demands for more sustainable productions in the chemical industry.

In the future, chemistry will play an even more central role in order to meet the needs of the world population without further damaging our planet for food production, cleaner energy and engineering of new materials and chemicals. It is not only a matter of *what* we synthesize, but also *how* it should be synthesized.

1.1. Sustainability and green chemistry

In the dawn of the modern chemical industry, little concerns were made about the release of chemical waste into the nature. The belief that chemical waste could be diluted to a point where it was no longer harmful shifted as the effects from the pollution became noticeable.[1] With growing concerns for the human impact on the environment, the United Nations founded The World Commission for Environment in 1983 aiming to create a report on the world-scale perspectives of a long term, sustainable and environmentally friendly development. The report, also known as the *Brundtland report*, defined sustainable development as: "Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs".[2]

In the 1990s, the U.S. government issued a pollution prevention act,[3] hence the idea of creating a more sustainable chemical industry became more and more important. The concept of *green chemistry* was proposed by Anastas and Warner in the early 90s and is established as its own field today.[4] The heart

of green chemistry entails processes and products to be *benign by design*.[5] To aid this aim, there are a set of guidelines, called *the twelve principles of green chemistry*, which can be listed as the following:

1. Waste prevention
2. Atom economy
3. Less hazardous chemical syntheses
4. Safer products by design
5. Safer solvents and auxiliaries
6. Design for energy efficiency
7. Use of renewable feedstock
8. Shorter syntheses (reduce derivatives)
9. Catalysis instead of stoichiometric reagents
10. Design products for degradation
11. Analytical methodologies for pollution prevention
12. Inherently safer chemistry for accident prevention

These twelve principles can essentially be summarized as creating more sustainable ways of performing chemistry. The methods and processes should be **efficient** (principle 2. 6, 8 and 9), **safe** (principle 3, 4, 5, 10, 11 and 12) and generate as **little waste** as possible (principle 1, 2, 7, 8, 9, 10, and 11).

In order to measure the "greenness" of a reaction, several metrics has been devised. There are two important concept related to this thesis: the *atom economy* devised by Trost and the *environmental factor (E-factor)* developed by Sheldon.[6] Atom economy measures the amount of starting atoms that are incorporated into the final product (atom economy = (molecular mass of desired product/molecular mass of all reactants) × 100%). An ideal reaction therefore has a high atom economy with all atoms incorporated into the desired product. It does not, however, take other substrates used in the reaction into account, such as the use of stoichiometric amounts of reagents or solvents. The E-factor on the contrary, calculates the amount of waste generated per kilogram of product (E = waste (kg)/kg product), which can be useful in deciding whether or not a technology could be helpful in green chemistry innovations.

The quest for sustainable reactions and technologies requires the development of new methodologies under the guidance of the principles of green chemistry.

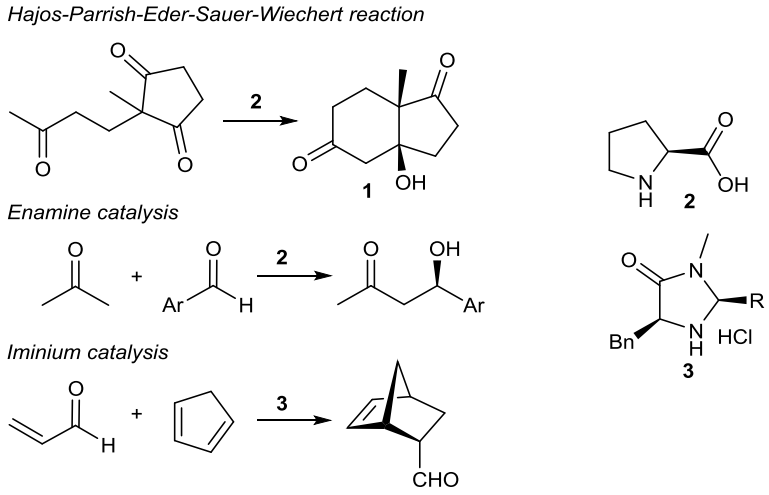
1.2. Catalysis

One of the most important concepts of the *principles of green chemistry* is catalysis. The term catalysis, was coined by Berzelius in 1835, who hypothesized that some substances had a certain *catalytic force*, which could *awaken* sleeping substances by their mere presence.[7] A catalyst is a compound that takes part in a reaction and increases the reaction rate without being consumed at the end of the reaction.[8] From the early history of civilization, humans have used catalysis with the introduction of yeast for the fermentation of wine and beer.

Catalysis is traditionally divided into two categories: heterogeneous and homogeneous catalysis. Heterogeneous catalysts perform the reaction in a different phase than the reactants; homogeneous catalysts, on the other hand, operate in the same phase. It is estimated that catalysis accounts for about 90% of all chemical processes in the industry and is thus essential for the production of compounds of interest in agricultural, pharmaceutical and materials industries.[9] The importance of catalysis has been acknowledged with the awarding of at least 15 Nobel prizes.[10] With the help of catalysis it is possible to prevent waste, enhance atom economy, have more energy efficient reactions, and reduce the amount of derivatives needed for synthesis.

1.3. Organocatalysis

The field of homogeneous catalysis has long been dominated by metal-based catalysts, however, the use of small organic molecules as catalysts has gained a widespread attention in the last decade. This field is known as organocatalysis.[11] The use of organic molecules as catalysts, however, has been reported sporadically over the last century. In 1971, the use of L-proline in the Hajos-Parrish-Eder-Sauer-Wiechert reaction for the formation of **1** (Scheme 1), demonstrated the potential of organic molecules for the first asymmetric synthesis without metal-complexes.[12] The actual use of organic molecules as catalysts did not gain momentum until the year 2000 by the seminal works of List *et al*. and MacMillan and co-workers, who both independently introduced the field of organocatalysis.[13] Using L-proline, List *et. al*. demonstrated an asymmetric aldol reaction between acetone and various aldehydes *via* enamine catalysis, while MacMillan and co-workers utilized catalyst **3** for an asymmetric Diels-Alder reaction *via* iminium catalysis (Scheme 1).



Scheme 1. Top: the Hajos-Parrish-Eder-Sauer-Wiechert reaction. Middle: aldol reaction by *List et al.* Bottom: asymmetric Diels-Alder by MacMillan and co-workers.

Organocatalysis offers several benefits and has enabled a wide range of transformations under mild reaction conditions with high enantioselectivities in comparison with classical metal-based catalysis. The absence of metals combines the advantages of green chemistry and low costs of production. Organocatalysts are generally less toxic and can be synthesized from readily available starting materials, often also accessible from a natural chiral pool, thereby avoiding environmentally challenging mining industry. Being metal-free removes any possibility of metal leaching from the catalyst and contamination of the end-product. Moreover, organocatalysts are quite easy to handle in contrast to metal-catalysts that often require rigorous anhydrous and/or anaerobic conditions.

The field of organocatalysis can itself be divided into two types of catalysis, covalent and non-covalent. Non-covalent catalysis uses interactions such as hydrogen bonding,[14] exemplified by the used of thiourea catalysts or ionic interactions,[15] such as by phase transfer catalysts. Covalent catalysis involves the formation of a covalent bond between the catalyst and the substrate, such as enamine and iminium catalysis.[16] One type of covalent catalysts that has gained wide attention is *N*-heterocyclic carbenes (NHCs).[17]

1.4. *N*-heterocyclic carbenes

For a long time carbenes, molecules with a neutral divalent carbon atom with six electrons in its valence shell, were considered too unstable to be isolated. The breakthrough came with the isolation of persistent phosphinocarbenes in the late 80's and the first NHC was isolated in the early 90's.[18]

Contrary to classical carbenes that exists in a triplet state, NHCs are in a singlet ground state (Figure 1). They are uncharged compounds, with sp^2 hybridization at the carbene carbon, incorporated into a nitrogen-containing ring. This cyclic structure helps to favor the singlet state, which stabilizes the NHC. The carbene center is further stabilized by two effects: 1) the mesomeric effects by the π-electron donation from adjacent heteroatoms, such as nitrogen, into the empty p-orbital of the carbene, 2) inductive effect by σ-electron withdrawal of the heteroatoms, which reduces the electron density at the carbene center and favors the singlet state.[17c, 19]

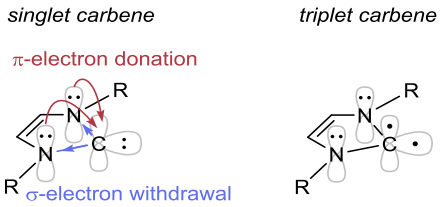
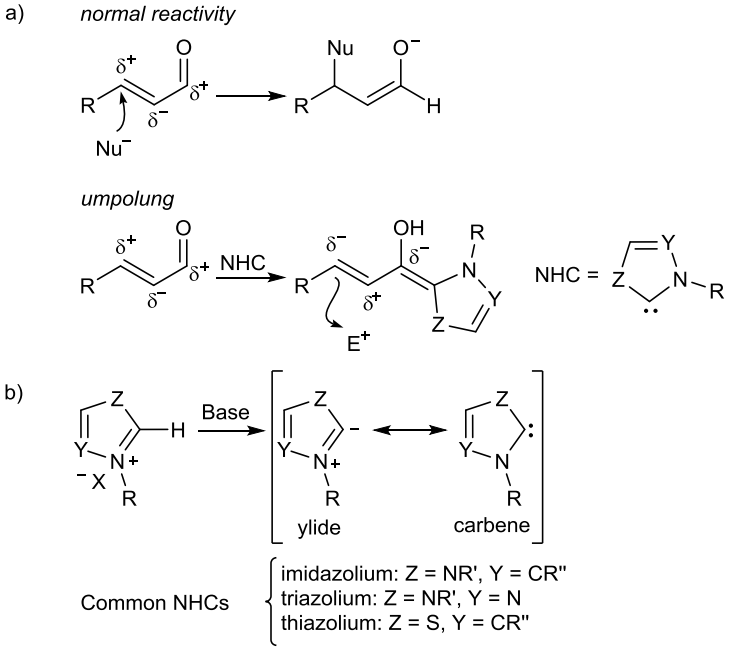


Figure 1. Left: Singlet carbene, stabilization of singlet carbenes *via* π-electron donation and σ-electron withdrawal. Right: triplet carbene.

NHCs are nucleophilic by nature and are capable of reversing the polarity in a substrate – through *umpolung*, thus turning electrophilic species into nucleophilic species.[20] In NHC catalysis, this strategy is mostly applied for aldehydes, creating acyl anion equivalents (Scheme 2a). The most convenient way of generating the active carbene species is by deprotonation of the corresponding salt using a base *in situ* and can be represented either as an ylide or as a carbene. The most common NHCs are imidazolium, triazolium or thiazolium-based salts (Scheme 2b).[17d]



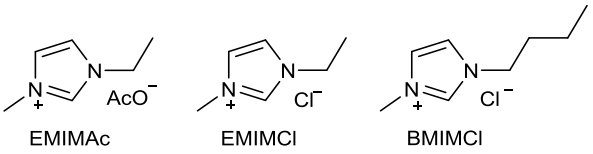
Scheme 2 a) Umpolung of a substrate. b) Generation of the active carbene.

Early reports of NHC-catalyzed reactions can be found in the work of Ukai in 1943, who demonstrated that 3-ethylthiazolium bromide could catalyze the formation of benzoin in the presence of a base.[21] The active catalytic species was later found to be a carbene, in the works of Breslow, who showed that the coenzyme thiamine (vitamin B1) – a thiazolium-based compound, could catalyze the formation of benzoin.[22] However, the field of NHC catalysis did not gain attention until half a century later by the seminal works of the groups of Bode,[23] Rovis[24] and Glorius,[25] demonstrating the use of α-

functionalized aldehydes as acylating reagents using NHC catalysis. Since the beginning of the 2000s the field of NHC catalysis has rapidly grown with multiple reports for the application in organic synthesis.[17d, 26]

1.4.1. Ionic liquids

An ionic liquid (IL) has been defined as being a salt that is liquid below 100 °C.[27] These substrates have become an appealing alternative as green solvents due to their low volatility, high recyclability and good ability to dissolve carbohydrates (e.g. cellulose).[28] In this context, imidazolium-based ionic liquids (Figure 2) are particularly important as they, in the presence of a base, can be used as NHC precursors. Aggarwal *et. al.* noted that with the use of 1-butyl-3-methylimidazolium chloride (BMIMCl) as solvent in a Baylis–Hillman reaction lower yields were obtained due to side-reactions of the aldehyde and the IL.[29] Chen and co-workers used 1-ethyl-3-methylimidazolium (EMIMAc) as catalyst for the synthesis of 5,5'-dihydroxymethyl furoin (DHMF) as a promising jet fuel intermediate.[30]



EMIMAc EMIMCl BMIMCl

Figure 2. Three imidazolium-based ionic liquids.

Chapter 2

Objectives and aims

The overall aim of this thesis has been to design and develop synthetic methods using NHC catalysis under the guidance of green chemistry.

More specific aims of this thesis are to:

- Demonstrate the use of commercially available imidazolium-based ionic liquids as precatalysts in NHC catalysis.
- Replace the use of a high molecular weight oxidant frequently used in NHC catalysis with aerial oxygen.
- Investigate the reaction scope of the developed protocols and the application of the synthesized products.

To achieve these aims, the following will be presented:

In chapter 4.1, the use of ionic liquids as NHC precatalysts for the formation of oxo triphenylhexanoates (OTHOs) is described. This project was performed in a one-pot multi-component reaction (MCR) (principle 2) using a simple filtration work-up procedure (principle 1). A wide range of substrates were incorporated, which showed the possibility to regioselectively modify complex polyols without the need for protecting groups (principle 6, principle 7). In chapter 4.2, development of an oxidative synthetic protocol that utilizes oxygen from the air as a terminal oxidant, which could replace a stoichiometric oxidant using of catalysis was demonstrated. Various useful and interesting compounds could be synthesized with this method. Both these methods were developed accordingly to the one of the most important principle of green chemistry – catalysis (principle 9).

Chapter 3

Theory and methodology

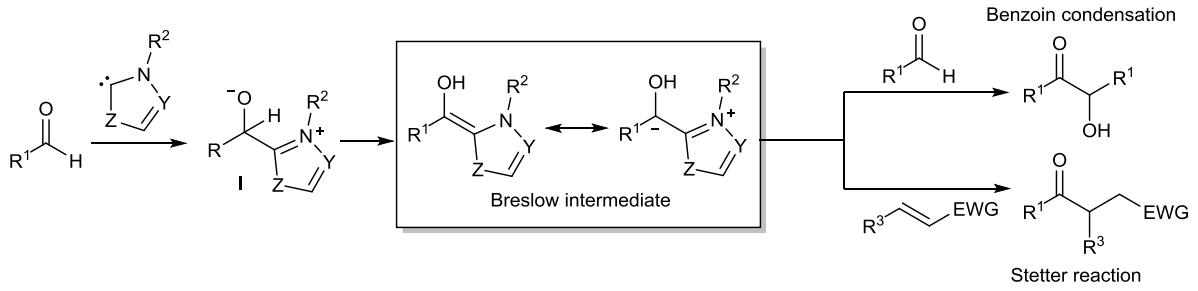
3.1. Catalytic intermediates generated by NHC catalysis

Nature has long served as an inspiration for chemists in the design of reactions and catalysts. After Breslow's discovery of thiamine being a carbene, many chemists have tried to imitate the function of thiamin as a carbene.[22, 26a] Today, a wide range of NHC-catalysts are available, which has enabled the synthesis of new and interesting compounds. The following sections aim to give a short overview of some important key intermediates related to this thesis.

3.1.1. The Breslow intermediate and the homoenolate

The key intermediate in NHC catalysis is the Breslow intermediate (Scheme 3), proposed by Breslow in 1958.[22] The Breslow intermediate is an acyl anion analogue and can be obtained through the reaction between an electrophilic aldehyde and an NHC-catalyst. It has mostly been studied in the benzoin condensation and the Stetter reaction (Scheme 3). The first step for these reactions is the nucleophilic addition of the active carbene species to an aldehyde which generates the tetrahedral intermediate **I**. The Breslow intermediate is then formed through proton transfer, which can further react with other species to form either benzoin product *via* an 1,2-addition to another aldehyde or a Stetter product *via* an 1,4-addition to a Michael acceptor.

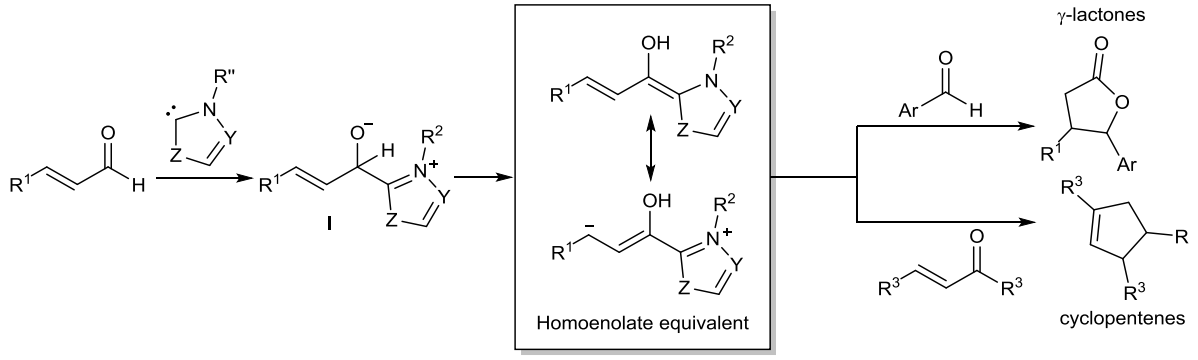
The benzoin condensation and Stetter reaction are two of the classic reactions in NHC catalysis and have become a reference point for the evaluation of chiral NHCs. Several examples of asymmetric homo-benzoin, cross-benzoin and Stetter reactions have been reported.[31]



Scheme 3. Formation of the Breslow intermediate.

The use of NHC-catalyst in combination with an α,β-unsaturated aldehydes gives access to an extended Breslow intermediate, also known as the homoenolate intermediate (Scheme 4). The homoenolate was first reported in 1962 but were not explored due to the lack of suitable routes for directly generating these intermediates.[32] With the emergence of NHC catalysis, the homoenolate intermediates have now been reported in the synthesis of several compounds.[33]

The generation of homoenolates is similar to the generation of the Breslow intermediate. The NHC adds to an α,β-unsaturated aldehyde giving the zwitterionic intermediate **I** (Scheme 4). After proton transfer, the homoenolate is formed. The β-carbon which is normally electrophilic is now nucleophilic through a conjugate umpolung. It can then react with an electrophile to form cyclic products such as γ-lactones and cyclopentenes



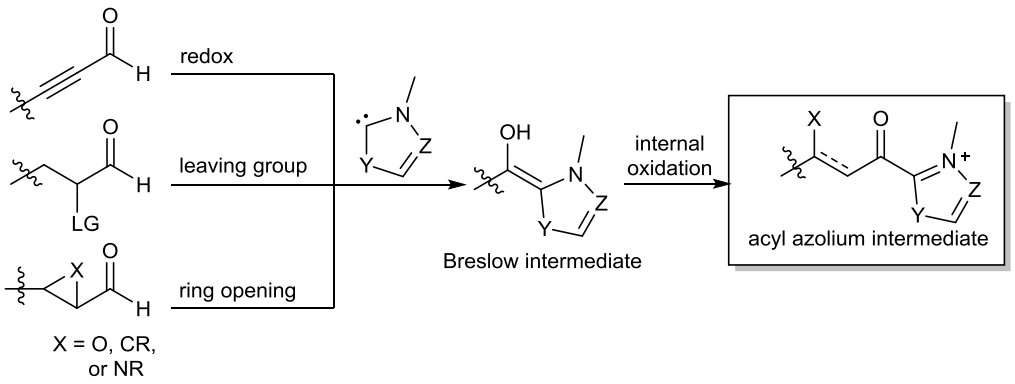
Scheme 4. Generation of the homoenolate equivalent.

3.1.2. The acyl azolium intermediate

Under oxidative conditions, the electrophilic acyl azolium intermediate can be accessed through oxidation of the Breslow intermediate or homoenolate *via* either an internal redox process or by addition of an external oxidant.

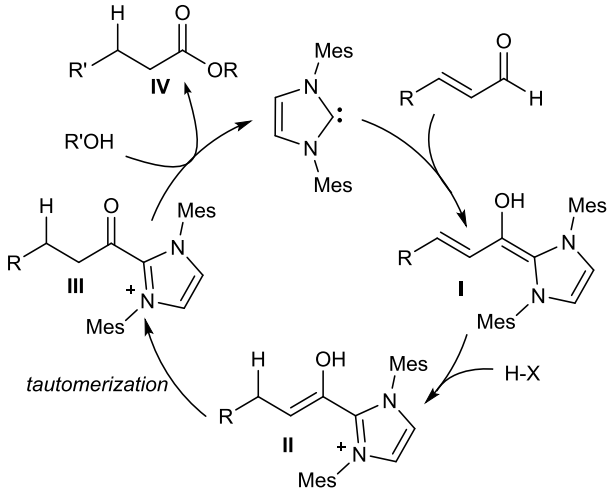
3.1.2.1. Internal redox

The acyl azolium generated from internal redox processes have been reported with several different α-functionalized aldehydes (enals,[34] ynals,[35] α-haloaldehydes,[24] epoxyaldehydes,[23] cyclopropanyl aldehydes,[36] aziridine aldehydes[23]) (Scheme 5). Addition of the NHC forms the Breslow intermediate, which undergoes an internal redox reaction, either *via* redox isomerization, loss of a leaving group, or ring-opening forming the acyl azolium.



Scheme 5. Generation of acyl azolium through internal redox.

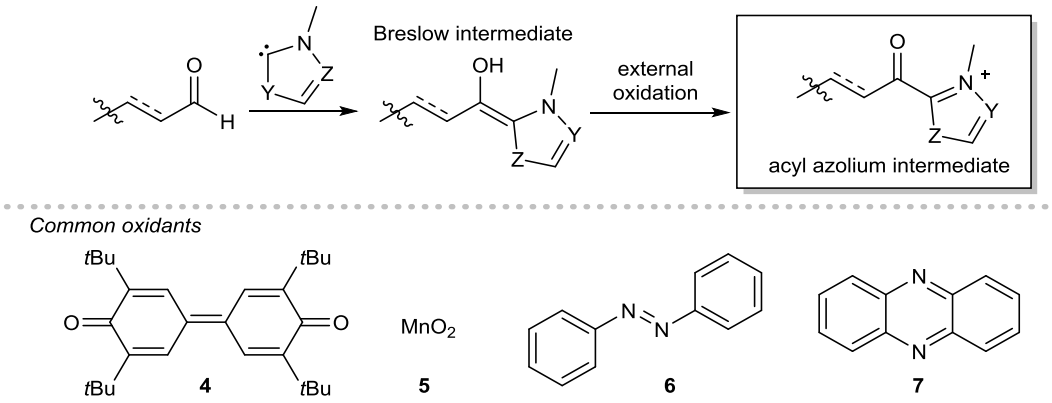
In the groups of Scheidt[34a] and Bode,[34b] α,β-unsaturated aldehydes were used for the synthesis of saturated esters (Scheme 6). By protonation of the homoenolate **I** at the β-position, the acyl azolium **III** was obtained after tautomerization of enol **II**. In the last step, the saturated ester **IV** is obtained after a nucleophilic attack of the alcohol regenerating the NHC at the same time. Bode and colleagues noted that the choice of base could alter the outcome of the reaction. With stronger bases such as *t*-BuOK, formation of C-C bonds is preferred, *via* reaction with a second aldehyde forming γ-lactones. Weaker bases, on the contrary, such as *N*,*N*-diisopropylethylamine (DIPEA), acts like a proton shuttle and protonation at the β-carbon of the homoenolate will occur instead, leading to the saturated ester **IV**.



Scheme 6. Postulated catalytic cycle for the formation of saturated ester **IV**.

3.1.2.2. External redox

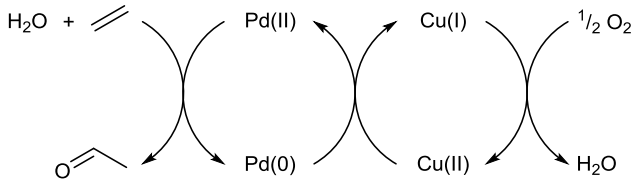
Addition of an external oxidant for the oxidation of the Breslow intermediate into the acyl azolium intermediate opens up the possibility of using other types of starting materials (Scheme 7). This removes the restriction of α-reducible aldehydes. The oxidants can both be inorganic and organic. The Kharasch oxidant[37] 3,3',5,5'-tetra-tert-butyldiphenoquinone **4** is the most frequently employed. Other oxidants commonly employed in oxidative NHC catalysis are, for example, manganese dioxide **5**, azobenzene **6** and phenazine **7**. These oxidants are often added in stoichiometric quantities which generate a stoichiometric amount of waste to be taken care of at the end of the reaction, which correspond to a poor atom economy. Therefore, greener oxidation alternatives are desirable.



Scheme 7. Generation of the acyl azolium intermediate *via* external oxidation. Common oxidants used.

3.1.2.3. Greener oxidation alternatives

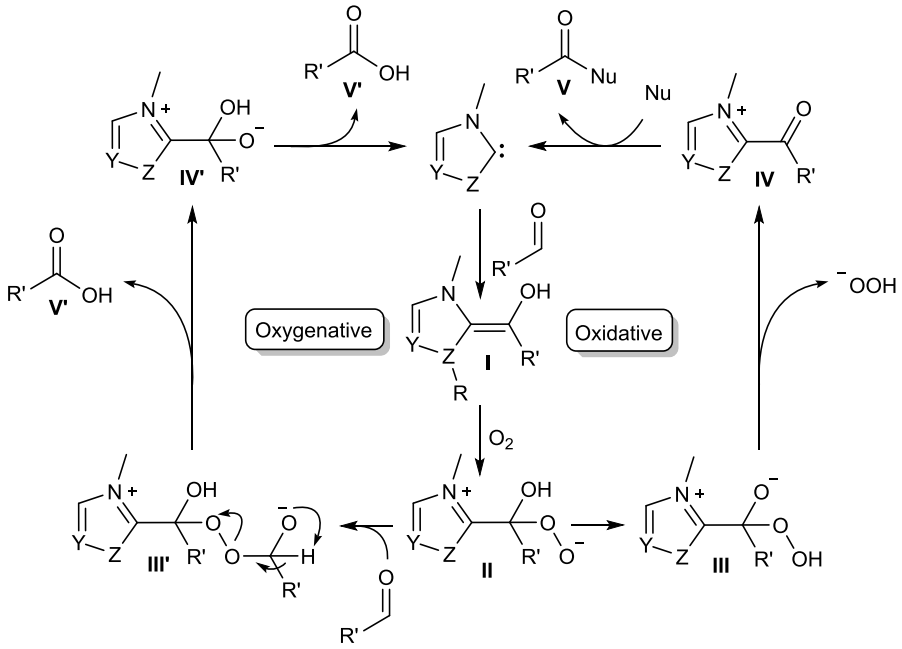
Attractive environmentally friendly oxidants which show high efficiency per weight of oxidant and with water as the generated by-product are hydrogen peroxide and molecular dioxygen. Both oxidants have their advantages and disadvantages. Using dioxygen is inexpensive as it is readily available from the air; however, it requires rigorous safety measures for large scale operations (as oxygen/organic solvent can spontaneously ignite). This can be circumvented by, for example, flow reactors. Hydrogen peroxide on the other hand, is easier to handle as it is a liquid, but can undergo radical induced decomposition to water and oxygen which can be catalyzed by traces of metal. It is also not readily available and the production of hydrogen peroxide is energy demanding.[38] The attractive features of dioxygen make it an ideal choice as oxidant, from both economic, availability and a sustainable point of view. However, the direct oxidation using molecular oxygen is difficult due to the high energy barrier between oxygen and the substrate, which leads to unfavorable reaction conditions requiring high temperatures for an efficient reaction. This can be circumvented by the introduction of electron transfer mediators (ETMs) which creates a lower energy barrier allowing the flow of electrons from the substrate to oxygen. The use of ETMs can, for example, be found in the Wacker process that uses a palladium-catalyst for the synthesis of acetaldehyde from ethylene.[39] For the regeneration of the Pd-catalyst, $CuCl_2$ is typically added as an ETM. The Cu-salt is then re-oxidized by aerobic dioxygen as a terminal oxidant (Scheme 8). Direct oxidation using molecular dioxygen in NHC catalysis has been limited to the formation of carboxylic acids.[40] The groups of Studer and Gois have also with the help of a catalytic oxidant been able to form esters.[41] The limitations of these protocols are the use of high reaction temperatures and/or narrow substrate scope.



Scheme 8. The Wacker process.

Aerobic oxidations of the Breslow intermediate can undergo two different pathways, oxygenative or oxidative (Scheme 9).[42] The NHC adds to the aldehyde forming Breslow intermediate **I**. The zwitterionic peroxide **II** is then formed after addition of O_2. This intermediate form the acyl azolium **IV** after liberation of hydroperoxy anion from intermediate **III** in the oxidative pathway, which can react further with a nucleophile to form various products (**V**) in form of esters, amides etc. Alternatively, through the oxygenative pathway, the peroxide **II** adds to a second molecule of

aldehyde to form intermediate **III'** which forms the first molecule of acid **V'**. The final step is the release of an additional molecule of acid **V'** from intermediate **VI'** with regeneration of the catalyst. Because of this bifurcated reaction pathway, aerobic oxidation of the Breslow intermediate often leads to unselective reactions forming both the carboxylic acid and the ester. The ratio of the products is dictated by the substitution pattern of the R'-group.[42c]

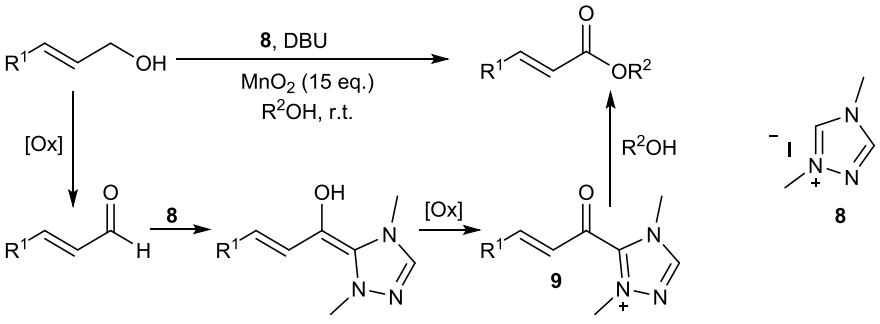


Scheme 9. The oxygenative vs the oxidative pathway for aerobic oxidation.

3.1.3. Reactions of α,β-unsaturated acyl azolium through external redox

3.1.3.1. Esterification with acyl azolium

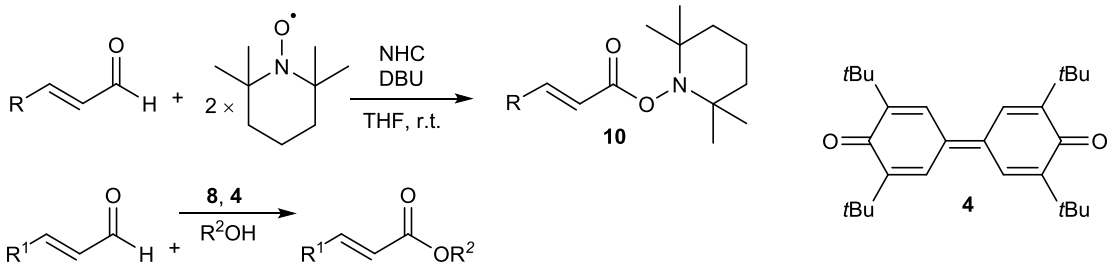
The simplest reaction involving the α,β-unsaturated acyl azolium intermediate **9** (Scheme 10) is esterification reactions. Esters, which can serve as protecting groups in organic synthesis, can be made by activation of an acid followed by a nucleophilic substitution. Oxidative NHC catalysis, offers an alternative route to conventional methods. In 2007, Scheidt and co-workers reported the use of MnO_2 (in 15 eq.) as the terminal oxidant for the conversion of allylic alcohols *via* a tandem oxidation and α,β-unsaturated aldehydes to the α,β-unsaturated acyl azolium for the synthesis of various esters (Scheme 10).[43]



Scheme 10. Tandem oxidation of allylic alcohols.

Other examples include, for example, the use of TEMPO,[44] and the Kharasch oxidant **4** (Scheme 11).[45] In the case of using TEMPO, Studer and co-workers obtained the TEMPO-ester **10** which obstructed

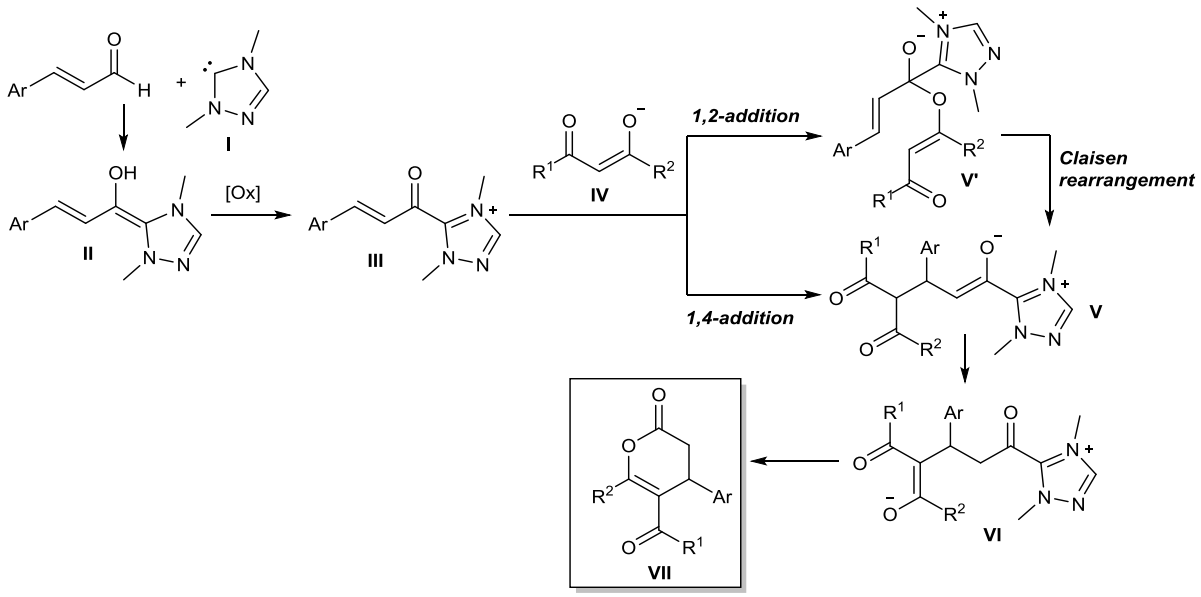
other attempts of using any other nucleophiles, limiting the scope of the method. Thus, **4** is the most versatile choice of oxidant for esterification of aldehydes. Quinone **4** has become the most commonly employed oxidant in oxidative NHC catalysis for accessing α,β-unsaturated acyl azolium.



Scheme 11. Synthesis of various esters with external oxidants TEMPO and Kharasch oxidant.

3.1.3.2. β-carbon reactivity of acyl azolium intermediate

The α,β-unsaturated acyl azolium can serve as a Michael acceptor. Exploiting the electrophilicity at the β-carbon by reactions with *bis*-nucleophiles such as diketone-derivatives has allowed the formation of more complex products such as dihydropyranones (Scheme 12). There are multiple routes accessing these important structures. Lupton and co-workers were the first to generate dihydropyranones *via* the α,β-unsaturated acyl azolium from acyl fluorides in combination with silyl enol ethers. After desilylation, the unmasked nucleophile adds to the β-position of the acyl azolium to form dihydropyranones.[46] Both Chi and colleagues[47] and Studer and co-workers[48] employed readily available aldehydes to generate the α,β-unsaturated acyl azolium by oxidation of the homoenolate intermediate using an excess of oxidant **4**. Chi et al. were able to utilize saturated aldehydes, which are usually less reactive, as starting materials by using 4 equivalents of **4**. Alternative routes also involves the use of α-bromoenals[49] and β-bromoenals,[50] which eliminates HBr for the generation of the α,β-unsaturated acyl azolium, the use of sacrificial reagents[51] and coupling reagents.[52]



Scheme 12. Postulated mechanism for the formation of dihydropyranones.

The proposed mechanism for the formation of dihydropyranones starts with a nucleophilic addition of the carbene **I** to an aldehyde forming homoenolate **II** (Scheme 12). The α,β-unsaturated acyl azolium intermediate **III** is obtained after oxidation and is then reacted with **IV** in an 1,4-addition yielding intermediate **V**. After proton transfer and lactonization of intermediate **VI**, the dihydropyranone **VII** is

obtained regenerating the NHC catalyst. The alternative mechanism proposal for similar systems involves an initial oxa-1,2-addition to the carbonyl, forming the hemiacetal **V'** followed by Claisen rearrangement to the intermediate **V**.[53]

3.1.3.3. Amidations with acyl azolium

The amide bond, ubiquitous in life, is one of the more important functionalities in organic chemistry and can be found in polymers, peptides, complex molecules and pharmaceuticals. Although prevalent in many areas there are, however, few catalytic methods for making amides from simple starting materials. The direct condensation from a carboxylic acid and amine results in formation of a stable salt due to unfavorable thermodynamics for amide bond formation. Condensation of the salt can be achieved but at high temperatures, which can be incompatible with other functional groups present.[54] Addition of Lewis acids[55] or boronic acid derivatives[56] can lower the high reaction temperatures, but are limited to a few types of amines, with scavenging of water necessary by addition of molecular sieves.[57] The other way for making amide bonds is through aminolysis using activated carboxylic acid derivatives, such as halides, anhydrides, azides or activated esters, that requires a pre-functionalization step using waste-generating, highly reactive and expensive reagents. The general synthesis of amides is by *in situ* activation of the carboxylic acid relying on stoichiometric quantities of coupling reagents for the generation of an activated carboxylate. However, this strategy has a poor atom economy, generating a stoichiometric waste by-product to be taken care of.[58] The American Chemical Society Green Chemistry Institute Roundtable has therefore identified "amide formation avoiding poor atom economy reagents" as the most urgent challenge for sustainable organic synthesis.[59]

The use of NHC catalysis can provide an alternative route to conventional synthesis for amide bonds, granting access to reactive intermediate in a catalytically fashion, thereby avoiding the use of stoichiometric reagents. This allows the use of aldehydes for the direct acylation of amines. The acyl azolium intermediate appears to show a preference for acylation of *O*-nucleophiles forming esters and carboxylic acids. The formation of amides through acyl azolium, however, has remained elusive. The intrinsic lack of reactivity of the acyl azolium towards amines has been demonstrated by Studer et al. where chemoselective acylation of alcohols in the presence of amines were possible. This study did, however, indicate that the acyl azolium is capable of acylation of *N*-nucleophiles.[45] The difficulties of employing amines as nucleophiles could stem from the incompatibility between the starting aldehyde used in NHC catalysis and amines by formation of an inactive imine as well as water-formation from the condensation to act as a competing nucleophile, forming the carboxylic acid instead. Studies have also indicated coordination of alcohols to the carbene center by H-bonding, thereby increasing the nucleophilicity of the alcohol, which has not been observed for amines.[60] The groups of Bode and Rovis have both independently overcome such problems by using co-catalytic additives and non-aldehyde substrates (e.g. α'-hydroxyenones) for amidations through internal redox.[61] The use of external oxidants for amidations were first demonstrated by Studer *et al.* where quinone **4** was used in combination of hexafluoroisopropanol (HFIP) for the formation of the active ester, which was subsequently reacted with an amine for the formation of amides.[62] The protocol was limited to primary amines and pyrrolidine. Biju and co-workers employed the same quinone but in a two-fold excess for the amidation of aldehydes with 2-aminobenzothiazoles.[63] Brown and co-workers on the other hand, used anodic oxidation in flow process with stoichiometric amounts of a thiazolium based NHC precatalyst for the synthesis of several amides.[64]

Chapter 4

Results and discussions

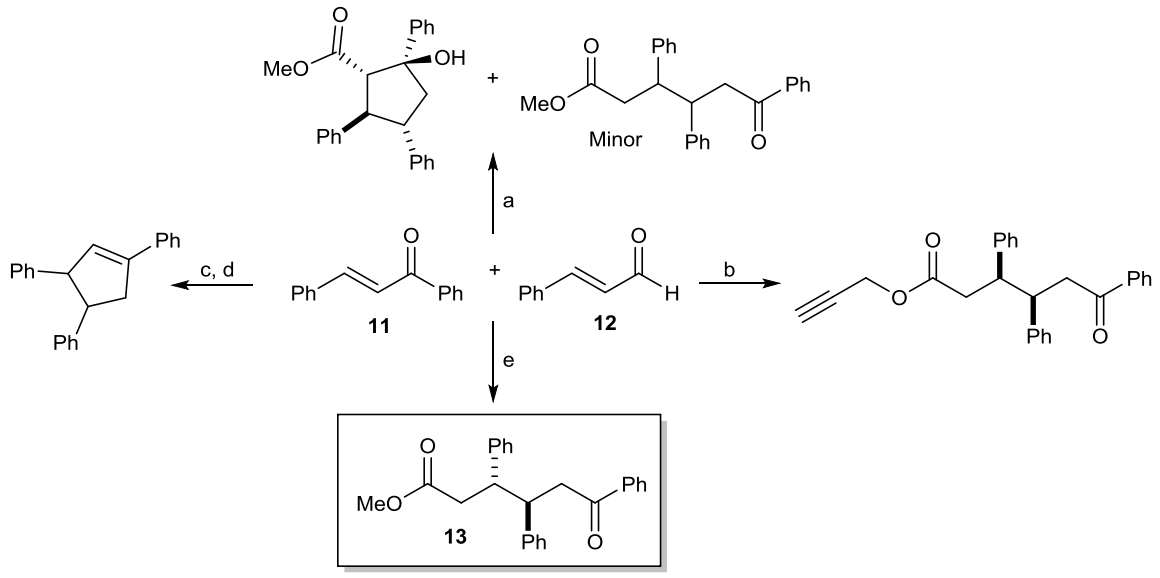
The following chapter will give a brief introduction of the different articles discussed in this thesis.

4.1. Functionalized OTHOs with ionic liquid NHC-precursor (Paper I, II, III)

4.1.1. Synthesis of OTHOs with ionic liquids as precatalysts (Paper I)

The use of ILs as NHC precursors, although being a relatively inexpensive method of accessing active carbenes, has not been thoroughly explored yet. Given the attractive properties of both ILs and NHC catalysis, uniting these two would allow the discovery of powerful and novel chemistry.

The groups of Bode,[65] Chi,[66] Nair,[67] and Scheidt[68] have previously demonstrated that α,β-unsaturated aldehydes and chalcones together with NHC catalysis can give annulation products (Scheme 13 a,c,d). The linear compound **13** can be obtained in the combination with an alcohol providing a highly functionalized acyclic 1,6-ketoester (oxo triphenylhexanoates) (Scheme 13 a, b) although in low yields.[67b, 69] The vicinal diphenyl ethylene moiety, found in **13** is a rare synthetic motif. A new pathway for its synthesis is therefore very important, not at least for the pharmaceutical industry where the exploration of new chemical entity are of utmost importance in the quest of finding new drugs. Therefore a more selective method to synthesize these compounds would be desirable and the use of IL as NHC precursors for the selective synthesis of oxo triphenylhexanoates (OTHOs) was explored.

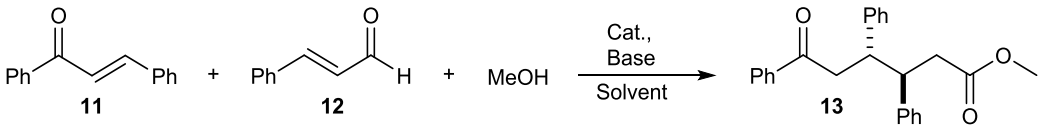


Scheme 13. a-d) Reported products of the combination of aldehydes with chalcones with NHC catalysis. e) Our synthesis of OTHOs.

4.1.1.1. Optimization of the reaction conditions

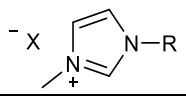
Preliminary results indicated that EMIMAc in combination with chalcone **11**, cinnamaldehyde **12**, methanol (MeOH) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) could form OTHO **13**. However, running the reaction neat with EMIMAc as solvent, the product was only obtained in moderate yields due to the insolubility of **13**, disturbing the homogeneity of the reaction. Different co-solvents capable of dissolving both **13** and EMIMAc were investigated (Table 1, entry 1, 2 and 5).

Table 1. Optimization of the reaction conditions.[a]



Entry	Solvent	Base	Precatalyst	MeOH (eq.)	t (h)	Yield (%)[f]
1.	MeCN	DBU	EMIMAc	10	3	60
2.	MeOH	DBU	EMIMAc	-	21	32
3.	DCM	DBU	EMIMAc	10	5	72[b]
4.	DCM	DBU	EMIMAc	10	5	82[c]
5.	**DCM**	**DBU**	**EMIMAc**	**10**	**3**	**92 (86[d])**
6.	DCM	DBU	EMIMAc	10	16	9[e]
7.	DCM	DBU	EMIMAc	1	26	27
8.	DCM	DBU	EMIMAc	15	4	59
9.	DCM	*t*-BuOK	EMIMAc	10	1.5	65
10.	DCM	Cs_2CO_3	EMIMAc	10	1.5	72
11.	DCM	TEA	EMIMAc	10	24	4
12.	DCM	DIPEA	EMIMAc	10	48	5
13.	DCM	DBU	EMIMCl	10	3	72
14.	DCM	DBU	BMIMCl	10	3	62

[a)] Reaction conditions unless otherwise noted: chalcone (0.25 mmol, 1 eq.), cinnamaldehyde (3 eq.), precatalyst (2.5 eq.), base (0.5 eq), MeOH (see table), solvent (0.083 M) at room temperature. [b)] With cinnamaldehyde (1 eq.). [c)] With cinnamaldehyde (2 eq.). [d)] Gram-scale synthesis yielding 1.1 g. [e)] With EMIMAc (0.25 eq.). [f)] Isolated yield of **13**



EMIMAc, R = Et, X = AcO
EMIMCl, R = Et, X = Cl
BMIMCl, R = Bu, X = Cl

Whereas compound **13** remained insoluble in acetonitrile (MeCN) and MeOH, it was able to dissolve in dichloromethane (DCM). Running the reaction with MeOH as solvent highlighted the importance of the amount of MeOH used. For optimal results, 10 equivalents were required. Using less MeOH resulted in longer reaction time and using more gave lower yields (entry 2, 7 and 8). With the optimal solvent in hand, different bases were investigated and DBU proved to be the most effective base (entry 5). Inorganic bases such as *t*-BuOK and Cs_2CO_3 did increase the rate of the reaction but also resulted in lower yields, due to unidentified side-reactions (entry 9 and 10). Organic bases such as triethylamine (TEA) and *N*,*N*-diisopropylethylamine (DIPEA), slowed down the reaction significantly (entry 11 and 12) and only trace amounts of 10 was detected. With substoichiometric amount of EMIMAc (0.25 eq.) the reaction time increased with decreased yield (entry 6). Moreover, when other ILs were tested, 1-ethyl-3-methylimidazolium chloride (EMIMCl) and BMIMCl (entry 13 and 14) good yields were obtained, though not surpassing the yields using EMIMAc, indicating a potential anion effect on the reactivity.[53, 70]

4.1.1.2. Scope of the reaction

Different α,β-unsaturated aldehydes and chalcones bearing different substituents on the aromatic rings and different alcohols were investigated. In all cases, the reaction proceeded in a highly stereoselective fashion giving >20:1 d.r. for the *anti*-product, confirmed by X-ray crystallography (Figure 3).

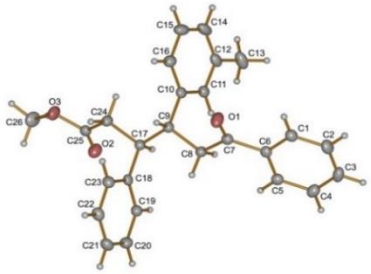


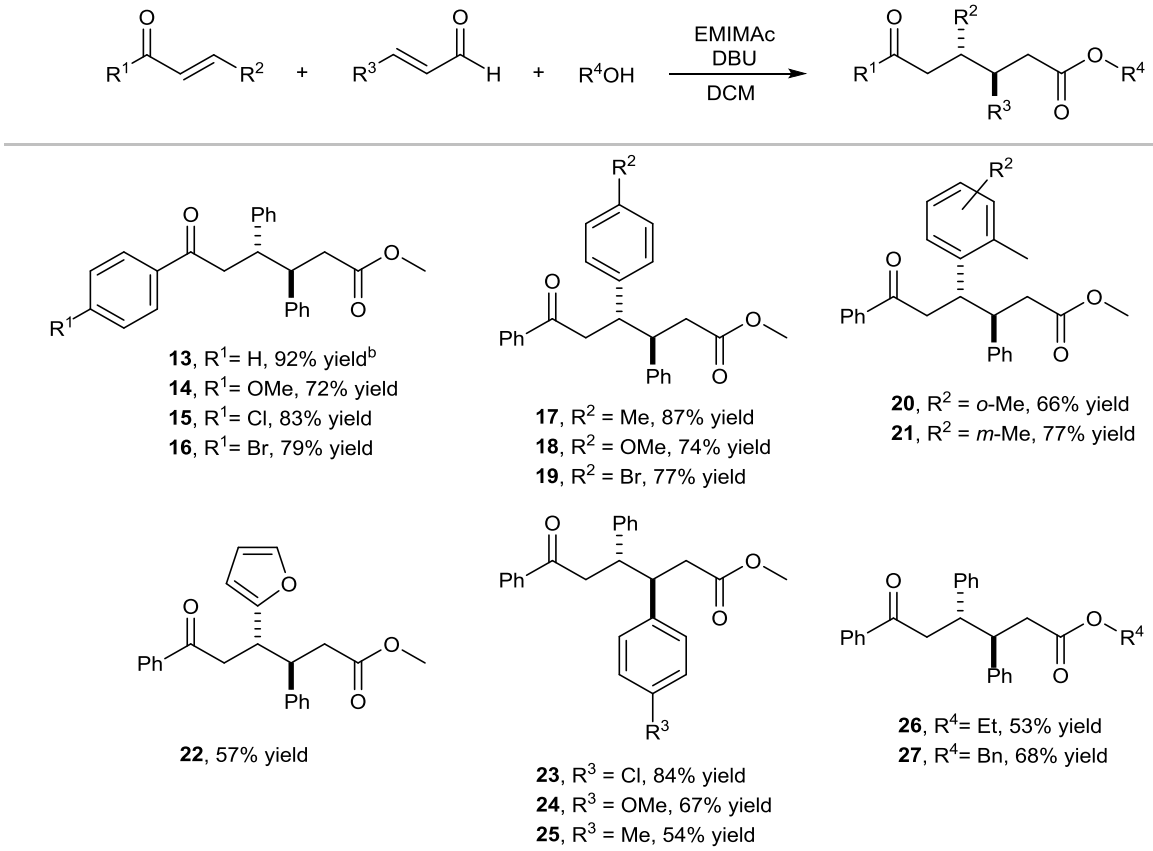
Figure 3. ORTEP-drawing showing the *anti*-configuration of the vicinal diphenyl groups.

For the chalcone substrate, both electron donating groups and electron withdrawing groups (Scheme 14, compounds **14**–**22**) were well tolerated on both of the aromatic rings. Both *orto*-, *meta*- and *para*-substitution patterns on the aromatic rings could be incorporated into the products in good yields (compounds **17**, **20**, **21**). Moreover, a furan substituent (**22**) was also integrated in good yields.

The investigation of different α,β-unsaturated aldehydes revealed that electron withdrawing groups (**23**) gave higher yields (84%) in comparison with electron donating substituents (compounds **24** and **25**). This electronic effect has been previously described in Cope rearrangements.[71]

Two different alcohol nucleophiles were tested; ethanol and benzyl alcohol, resulting in the corresponding esters in 53% and 68% yields, respectively (compound **26** and **27**). Experiments with other potential nucleophiles (ethanolamine, pyrrolidine, ethanethiol) showed chemoselectivity towards primary alcohols. Using secondary (2-propanol, HFIP, cyclohexanol) or tertiary alcohols (*tert*-butanol) did not yield any products, possibly due to steric effects hindering access to the acyl azolium carbonyl.

The synthesized OTHOs were also shown to be a low molecular weight gelator, forming organogels in a wider range of organic solvents.[72]



[a)] Unless otherwise stated the reactions were performed with chalcone (0.25 mmol, 1 eq.), aldehyde (3 eq.), EMIMAc (2.5 eq.), DBU (0.5 eq.), alcohol (10 eq.), DCM (3 mL) at r.t. [b)] Yields refer to isolated yields after purification, d.r. of compounds (>20:1).

Scheme 14. Scope of the reaction.[a]

4.1.1.3. Recycling of the catalyst

In order to make this reaction more sustainable and since ILs are known to be recyclable,[28c] investigations to reuse the ILs were performed. The IL was initially extracted from the reaction mixture with water and then washed with DCM to remove any organic compounds. The water was removed under reduced pressure and the recovered IL was used in subsequent reactions. A decreased reactivity of the catalyst was observed and a different extraction protocol was adopted. This time, the solvent was first evaporated *in vacuo* after reaction completion. The resulting solid was washed with MeOH, and filtered off to give pure compound **13**. The IL was then recovered after removal of MeOH under reduced pressure and could be reused in consecutive five experiments with no loss in selectivity or reactivity (Table 2). With this straightforward work-up protocol, the reaction was subjected to a large scale synthesis of **13**, giving 1.1 gram (86% yield) (Table 1, entry 5).

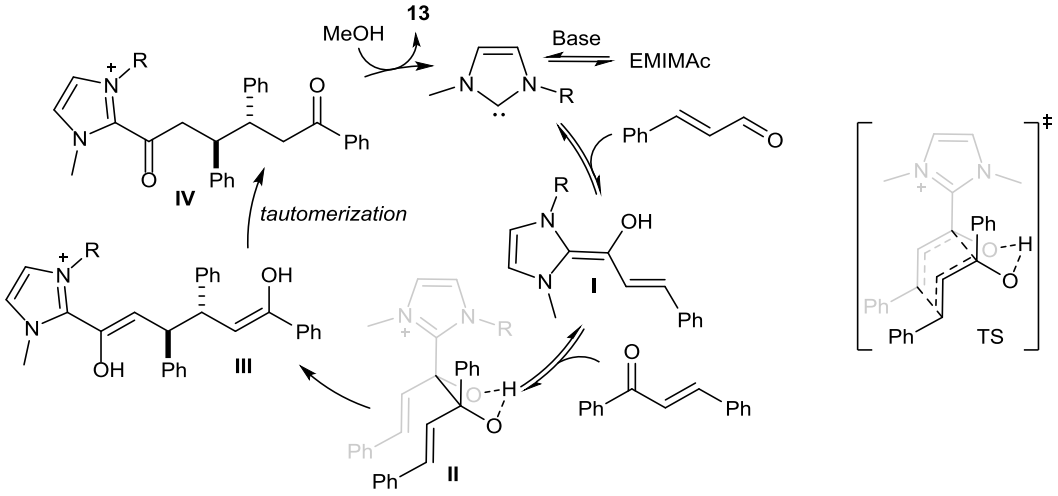
Table 2. Recycling of the IL.

Times recycled[a]	Yield (%)[b]
1	85
2	82
3	83
4	89
5	81

[a)] To each new run with recovered IL was added: DCM (3 ml) chalcone (0.25 mmol, 1 eq.), cinnamaldehyde (3 eq.), DBU (0.5 eq.), MeOH (10 eq.). [b)] Yields referred to isolated yields.

4.1.1.4. Mechanism

The postulated mechanism for this reaction, based on the *anti*-configuration obtained, is proposed as the following: The start of the cycle begins with the generation of the active carbene species through deprotonation with a base (Scheme 15). Nucleophilic addition of the carbene to cinnamaldehyde generates the Breslow intermediate **I**, which further reacts with the chalcone forming diene **II**. This intermediate undergoes an oxy-Cope rearrangement *via* a boat-transition state that sets the *anti*-oriented stereogenic centers (**III**). The acyl azolium **IV**, formed after tautomerization, is then intercepted by methanol delivering the OTHO with regeneration of the catalyst.



Scheme 15. Proposed catalytic cycle for formation of OTHO.

4.1.1.5. Summary

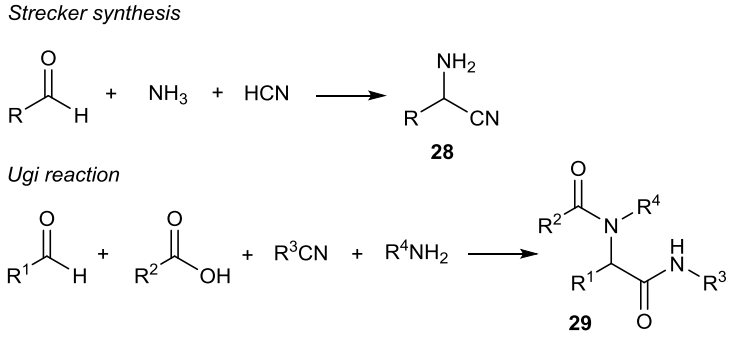
The use of a commercially available imidazolium-based IL as NHC-precursor was successfully demonstrated. Various types of OTHOs bearing different substituents were synthesized with excellent diastereoselectivity. The work-up of the reaction is swift and allows gram-scale synthesis, omitting the use of chromatography purification and making it possible to recycle and reuse the IL-catalyst.

4.1.2. Synthesis of OTHOs by a four-component reaction (Paper II)

The environmental impact of a reaction is assessed by the contribution from all the added inputs in the form of reactants, solvents and energy, and outputs in the form of product, waste and hazards. Thus, designing a reaction with the *principles of green chemistry* as guiding lines, the reaction should ideally have high atom economy, low E-factor with non-hazardous starting materials and performed in as few reaction steps as possible. The amount of reaction steps will determine the amount of waste generated after the synthesis as well as the practicality of the reaction. Therefore by decreasing the amount of reaction steps, the waste generating and time consuming factors will also be reduced. In the synthesis of pharmaceuticals and fine chemicals, solvents are the major source of waste generation accounting for about 80% of the total waste generated.[73]

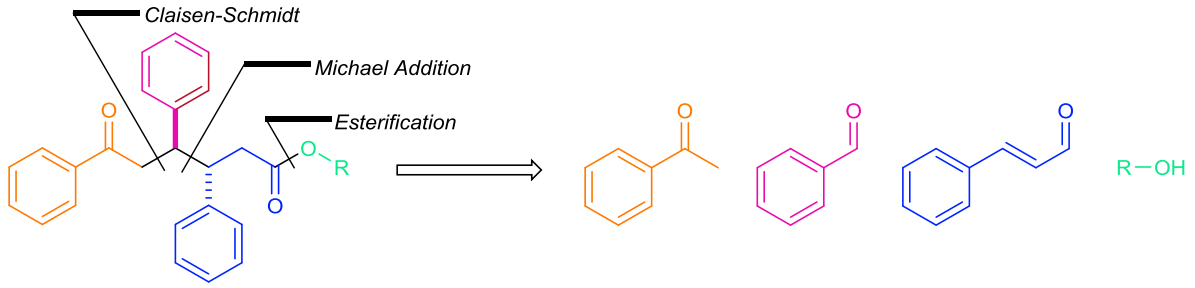
One strategy for a more efficient synthesis is the use of a multi-component reaction (MCR). An MCR approach is where three or more starting materials reacts in one-pot, contrasting with the traditional approach where reactions are performed in sequence, often requiring isolation and purification of reaction intermediates. Thus, performing the reaction in one-pot, results in less waste generated per bond-forming reaction as essentially all of the atoms from the starting materials are incorporated into the product. Omitting the purification of reaction intermediates also eliminates time-consuming separation processes, such as solvent-demanding chromatography, which saves time and resources.

Furthermore, careful selection of reaction conditions allows the generation of complex structures by the formation of several bonds in one-pot with less effort. Famous examples of MCRs include, for example, the Strecker synthesis of α-aminonitriles **28** for the synthesis of amino acids and the Ugi reaction forming *bis*-amides **29** (Scheme 16).[74]



Scheme 16. Examples of multi-component reactions.

As the OTHOs had shown to be potential gelators, further development of greener synthesis of the previously devised method seemed like an attractive sustainable approach for the easy creation of a library of functionalized OTHOs. The assembly of OTHOs was envisioned starting from simple, inexpensive and commercially available acetophenones, benzaldehydes, unsaturated aldehydes and alcohols (Scheme 17). As the MCR method could potentially lead to some undesired side reactions (such as benzoin condensation, cross-reactions between aldehydes) and build-up of water in the reaction mixture, sequencing the addition of reagents, by first forming the chalcone *via* a Claisen-Schmidt condensation, and thereafter synthesize the OTHO in the same pot would be a solution to circumvent the above mentioned side-reactions.



Scheme 17. Retrosynthesis of the OTHOs.

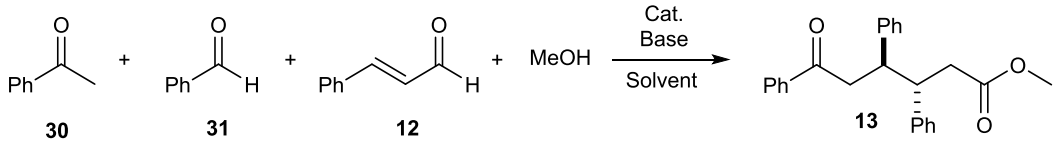
4.1.2.1. Optimization of reaction conditions

Investigations of different bases was the starting point of the study as the base has here a dual purpose; deprotonation of the acetophenones to form the chalcone component and deprotonation of the IL precatalyst to generate the active catalyst. With bases such as *t*-BuOK and NaOMe, quantitative formation of chalcone was observed on ^{1}H NMR against an internal standard in MeCN. However, for the subsequent synthesis of **13**, these bases resulted in low yields (Table 3, entry 1 and 2). With DBU, no formation of chalcone was observed (entry 5). Both Cs_2CO_3 and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) showed promising results, forming **13** in moderate yield (entry 3 and 4).

However, with both Cs_2CO_3 and TBD, the formation of chalcone required rather long reaction times (up to 72 h). In order to decrease these reaction times, the amount of solvent used in the formation of the chalcone was reduced. Full conversion was possible within 5 h by using only the MeOH-component as solvent for the chalcone synthesis and with these conditions, TBD appeared to be the

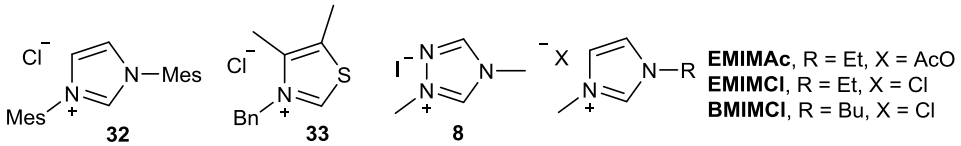
best base (entry 6). Investigation of solvents used for the subsequent synthesis of OTHO showed that both MeCN and DCM gave similar results (entry 6 and 7), but as MeCN is considered less hazardous and more environmentally friendly, it became the solvent of choice.[75] Other ILs as precatalysts, such as BMIMCl and EMIMCl (entry 10 and 11) were also capable of yielding **13** in good yields. Interestingly, the most commonly employed non-IL NHC precursors failed to generate any product at all (entry 12–14).

Table 3. Optimization of reaction conditions.[a]



Entry	Solvent	Base	Precatalyst	Yield (%)[b]
1.	MeCN	NaOMe	EMIMAc	35
2.	MeCN	*t*-BuOK	EMIMAc	38
3.	MeCN	Cs_2CO_3	EMIMAc	45
4.	MeCN	TBD	EMIMAc	54
5.	MeCN	DBU	EMIMAc	0
6.[c]	**MeCN**	**TBD**	**EMIMAc**	**66**
7.[c]	DCM	TBD	EMIMAc	65
8.[c]	1,4-dioxane	TBD	EMIMAc	20
9.[c]	MeCN	TBD	EMIMAc	31
10.[c]	MeCN	TBD	BMIMCl	56
11.[c]	MeCN	TBD	EMIMCl	52
12.[c]	MeCN	TBD	8	0
13.[c]	MeCN	TBD	32	0
14.[c]	MeCN	TBD	33	0

[a)] Reaction conditions unless otherwise state: acetophenone (0.25 mmol), benzaldehyde (1.1 eq.), cinnamaldehyde (3 eq.), base (0.5 eq.), MeOH (10 eq.), precatalyst (2.5 eq.), solvent (3 ml) at r.t. [b)] Yields determined by ^{1}H NMR against durene as internal standard. [c)] With reduced amount of solvent for the chalcone formation.

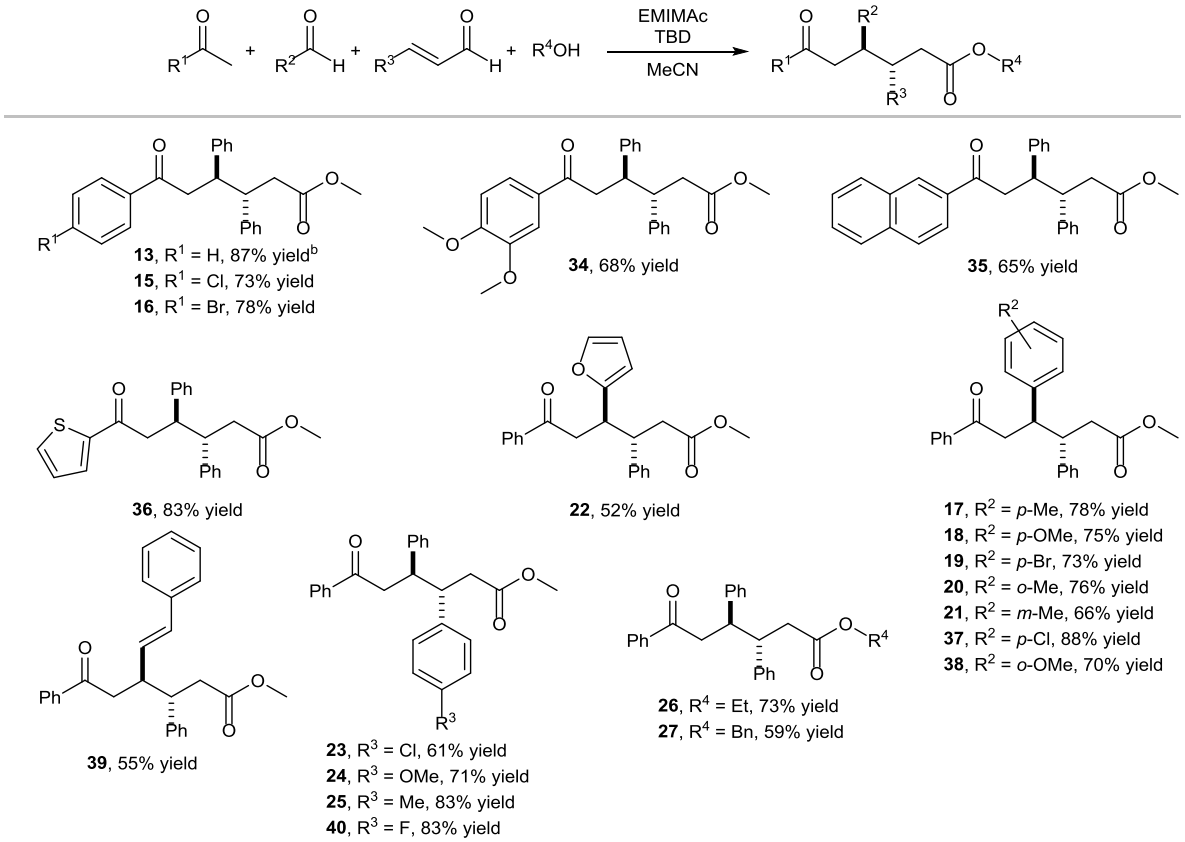


4.1.2.2. Scope of the reaction

The scope of the reaction was investigated with respect to the four different components (acetophenone, benzaldehyde. α,β-unsaturated aldehyde and alcohol) (Scheme 18). Acetophenone with both electron donating and electron withdrawing substituents on the aromatic rings was well tolerated and the products were obtained in good to very good yields. Both *orto*-, *meta*- and *para*-substitution on the chalcone aromatic rings worked well. Important handles for further transformations, such as halogen-groups, could be incorporated into the synthesis to yield the products in very good yields (compounds **15**, **16**, **19**, **37**). A thiophene and furan containing chalcone could also give the corresponding esters in moderate to very good yields (compounds **22** and **36**). By replacing benzaldehyde in the chalcone-synthesis with cinnamaldehyde, compound **39** was synthesized, thereby introducing a double-bond functionality into the OTHO-scaffold. Experiments with differently substituted α,β-unsaturated aldehydes gave good results (compound **23**–**25**, **40**).

Replacing MeOH with ethanol and benzyl alcohol gave the respective esters **26** and **27**, in 73% and 59% yield, respectively. The one-pot four-component approach for the synthesis of OTHOs was especially advantageous for the compounds **22**, **38**, and **39**. With this method, the pre-formation of the chalcones

is avoided, thus omitting purification through column chromatography avoiding waste-generating and time-consuming work-up.



[a)] Unless otherwise stated the reactions are performed with acetophenone (0.25 mmol), benzaldehyde (1.1 eq.), TBD (0.5 eq.), alcohol (10 eq.), cinnamaldehyde (3 eq.), EMIMAc (2.5 eq.), solvent (3 mL) at room temperature. [b)] All yields referred to isolated yield, d.r. of products (>20:1).

Scheme 18. Scope of the reaction.[a]

4.1.2.3. Recycling experiments

Recycling experiments of the IL catalyst were made in an effort to make the reaction more sustainable. The initial trials with recovering the IL were conducted by first removing the volatiles under reduced pressure once the reaction had reached completion (Table 4). Then the resulting solid was subjected to a MeOH/water mixture that causes the OTHO product to precipitate out from the mixture and can be filtered off. The IL can subsequently be recovered from the filtrate by evaporation of the solvents. However, this method showed deactivation of the catalyst already after two subsequential runs, possibly due to the longer times and higher temperatures required to remove water from the filtrate. By omitting water from the work-up procedure, the reaction could be applied in five consecutive runs using the recovered IL with retained activity

Table 4. Recycling experiments.[a,b]

Run	1	2	3	4	5
MeOH/Water (3:1)	83%	54%	0	0	0
MeOH	76%	82%	76%	82%	80%

[a)] Procedure of recovery: after completion of the reaction evaporation of the volatiles under reduced pressure. The resulting solid is then washed with MeOH/water mixture, causing the OTHO product to precipitate out which can be filtered off. The IL was subsequently recovered from the filtrate by evaporation of the solvents. [b)] All yields refer to isolated yields.

Investigations for the deactivation of IL were made; mixtures of EMIMAc/water, EMIMAc/water/TBD and pure EMIMAc were subjected to the same temperature and time used for the removal of water in the initial recovery studies. No degradation or deactivation of the IL was observed, which indicates that other deactivation routes must be active. Analysis of the deactivated EMIMAc-mixtures by ^{1}H and ^{13}C NMR showed the presence of several imidazolium species. Imidazolium-based ILs have been reported to degrade *via* a number of different pathways, such as dealkylation, hydrolysis or rearrangements.[76] Thus, it is possible that some unidentified IL deactivation processes caused the loss of reactivity in the trials using MeOH/water wash.

4.1.2.4. Summary

The MCR one-pot strategy for synthesis of OTHOs demonstrated a facile methodology for the creation of a library of OTHOs. The yields are excellent per bond forming steps (up to >95%) and various functional groups were tolerated. The ease of isolation omits the need for any solvent and time-demanding chromatography. The devised method can be used for the synthesis of a library of functionalized OTHOs for the investigation of their gelating properties.

4.1.3. Regioselective acylation of carbohydrates (Paper III)

Carbohydrates and sugar alcohols are biologically significant and important polyols that can be easily accessed from biomass. Simpler carbohydrates, such as mono- and oligosaccharides, are common structures in drug discovery,[77] and more complex ones (e.g. cellulose, polysaccharides) are important for the synthesis of new materials.[78] Regioselective functionalization of carbohydrates has been a long-standing challenge in organic synthesis as they contain several hydroxyl-groups with similar reactivity. To selectively manipulate these polyhydroxylated compounds protection strategies are often employed.[79] This is not only tedious, as two extra steps are required (protection followed by deprotection) but also waste generating. Catalytic regioselective functionalization of polyls has been reported employing Lewis acid catalysis[80] and organocatalysis.[81] However, the uses of NHC catalysis in combination with polyols are limited in literature, especially for unprotected carbohydrates.[82]

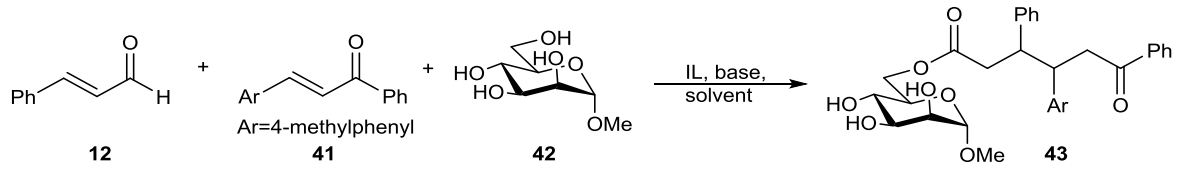
In the synthesis of OTHOs, a preference of the reaction for primary alcohols over secondary or tertiary alcohols was observed and thus offers a potential strategy to incorporate more complex polyhydroxyl-containing compounds into the OTHO-scaffold. Being able to directly modify carbohydrates without the use of protecting groups is interesting from a green chemistry perspective. Since ILs have also been known to dissolve carbohydrates, the methodology could offer a dual purpose of using IL for both dissolving the carbohydrates and as NHC precursor for the synthesis of OTHOs with carbohydrates.

4.1.3.1. Optimization of reaction conditions

To optimize the reaction conditions, cinnamaldehyde, chalcone **41** and methyl α-D-mannopyranoside **42** were selected as model compounds (Table 5). By using a methylated mannopyranoside on the anomeric hydroxyl group, isomerization of the carbohydrate from α to the β-form is prevented. In DCM together with DBU and EMIMAc, the reaction was shown to proceed with total selectivity towards the primary alcohol, with no reaction on the secondary alcohols observed, giving 72% yield with both of the two *anti*-diastereomers obtained in 1:1 dr. (entry 1). Running the reaction in 2-propanol could deliver the product in 54% yield (entry 12), showcasing the excellent selectivity towards primary alcohols. Running the reaction with NHC-precursors that are not ILs failed to deliver any product at all (entry 4–6). Since ILs have the ability to dissolve carbohydrates this can help in enabling a homogenous phase reaction. The best reaction conditions were by using EMIMAc in 2.5 equivalents. With less EMIMAc (entry 7) lower yields were obtained with prolonged reaction time. Lower yields were also obtained when using other ILs such as EMIMCl and BMIMCl (entry 2–3).

The different bases tested showed that the weaker organic base TEA or inorganic bases such as *t*-BuOK and Na_2CO_3 were not suitable (entry 7–9) whereas the organic base DBU worked well. Running the reaction with MeCN further increased the yield to 83% (entry 11) and was therefore chosen as the optimized reaction conditions.

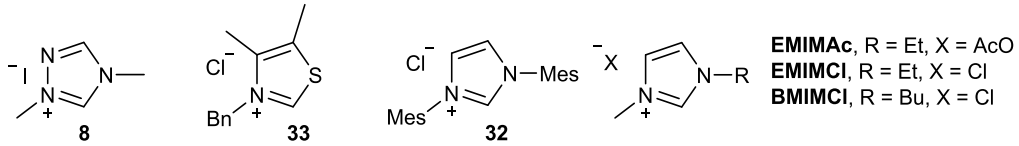
Table 5. Optimization of reaction conditions.



12 41 42 43

Entry	Solvent	Base	NHC	Yield (%)[b]
1.	DCM	DBU	EMIMAc	72
2.	DCM	DBU	EMIMCl	45
3.	DCM	DBU	BMIMCl	56
4.	DCM	DBU	8	0
5.	DCM	DBU	32	0
6.	DCM	DBU	33	0
7.	DCM	DBU	EMIMAc	20
8.	DCM	*t*-BuOK	EMIMAc	52
9.	DCM	TEA	EMIMAc	0
10.	DCM	Na_2CO_3	EMIMAc	0
11.	**MeCN**	**DBU**	**EMIMAc**	**83**
12.	2-propanol	DBU	EMIMAc	54

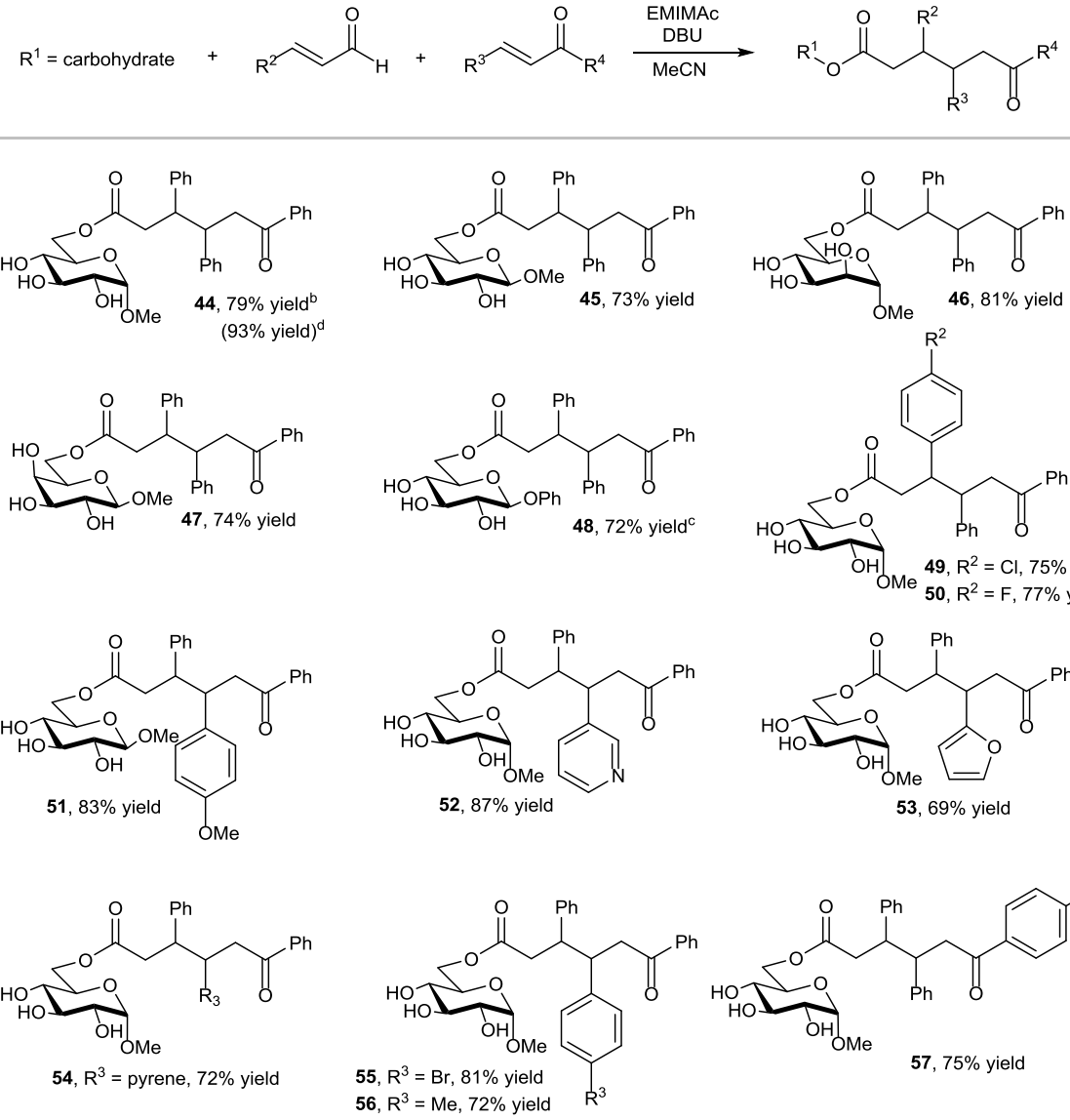
[a)] Reaction conditions unless otherwise stated: chalcone (0.25 mmol, 1. eq.), cinnamaldehyde (3 eq.), methyl α-D-mannopyranoside (3 eq.), base (0.5 eq.), NHC (2.5 eq.), solvent (0.08 M), 24 h at room temperature. [b)] Yield (d.r. anti-products, 1:1) determined against durene as internal standard. [c)] EMIMAc (0.25 eq) for 72 h.



4.1.3.2. Scope of the reaction

With the optimized reaction conditions in hand the scope of the reaction was investigated. Different hexopyranosides were studied (Scheme 19). The products obtained showed total regioselectivity towards the primary hydroxyl group. Both α- and β-anomers of hexopyranosides worked well with both methyl and phenyl substituents at the anomeric position. The products were all obtained in very good yields. For example using methyl-α-D-glucopyranoside the corresponding OTHO **44** was obtained in 79% yield and with methyl-β-D-galactopyranoside **47** the product was obtained in 74% yield.

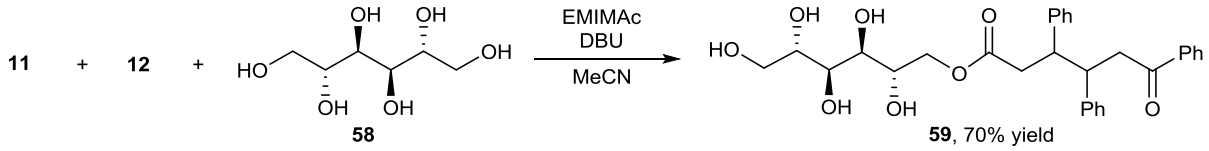
Variation of the OTHO-backbone was also explored using different chalcones and α,β-unsaturated aldehydes. Electron withdrawing groups on the chalcone and aldehyde aromatic rings could yield compound **49**, **50**, **55**, and **57** in very good yields. For chalcones bearing an electron donating group compounds **51** and **56** were obtained in 72% and 83% yield respectively. Heteroaromatic chalcones (compounds **52** and **53**) were also possible substrates.



[a] Unless otherwise stated the reactions are performed with chalcone (1 eq. 0.08 M), DBU (0.5 eq.), cinnamaldehyde (3 eq.), carbohydrate (3 eq.), EMIMAc (2.5 eq.), MeCN, 24 h at room temperature. [b] Yield (d.r. *anti*-products, 1:1) refers to isolated yields [c] gram-scale synthesis [d] with DCM as solvent.

Scheme 19. Scope of the reaction.

Having investigated only cyclic polyols, the attention was turned to acyclic alcohols containing multiple reaction sites. Using acyclic sugar alcohol, such as mannitol **58**, (Scheme 20), could deliver product **59** in 70% yield (1:1 dr) with only acylation at the primary alcohol. Mannitol is interesting because of its biological activity and is used as a drug.[83]



Scheme 20. Functionalization of mannitol using NHC catalysis.

The acylated polyols were isolated using extraction and filtration of the precipitated product, which enables recycling of the IL catalyst. Recycling experiments showed that product **44** could be generated in 77%, 79% and 72% yields in three consecutive runs with the recycled IL. The reaction is robust, as it can be run without the need to exclude moisture or air. The scalability of the reaction was tested in a scale-up of the reaction, giving 1.5 gram (93% yields) of compound **44**.

4.1.3.4. Summary

With the help of an IL NHC-precursor highly regioselective mono-functionalized carbohydrates were obtained. The products can be isolated in a 1:1 d.r. of the two anti-products in high to excellent yields. The method is run at room temperature, using standard laboratory equipment without the exclusion of air or moisture. The polyols can be modified directly without the use of protecting groups, thus fulfills some of the principles of green chemistry. It was also possible to recycle the catalyst. The success of the reaction was the use of IL, demonstrating their solvating and catalytic properties.

4.2. Oxidative NHC catalysis (Paper IV, V, VI, VII)

4.2.1. Introduction

Oxidation reactions are one of the fundamental reactions in the organic chemist's toolbox. Conventional methods are often powerful, but lack the selectivity needed for transformations of compounds with multiple functional groups. Thus, the ability to selectively oxidize a functional group is a great challenge. Traditional oxidation reaction often suffers from high loadings of oxidants and toxicity of the oxidation reagents used (such as chromium or osmium-based reagents) and are therefore not in accordance with the principles of green chemistry.[84] To directly utilize O_2, readily available from the atmosphere, would be desirable. As O_2 has a high reaction barrier introduction of ETMs can circumvent the unfavorable kinetics.

4.2.1.1. Aerobic oxidation by NHC catalysis (Paper IV)

Esterification of α,β-unsaturated aldehydes was chosen as a model reaction in order to implement oxidation by aerobic oxygen in combination with oxidative NHC catalysis. In NHC catalysis, α,β-unsaturated aldehydes are well-reported to undergo several different reactions yielding compounds such as cinnamic acid **60**, saturated esters **61** and γ-butyrolactone **62**[25] (Figure 4). Therefore, development of a system that only forms the unsaturated methyl cinnamate would give an indication of the selectivity for the oxidation.

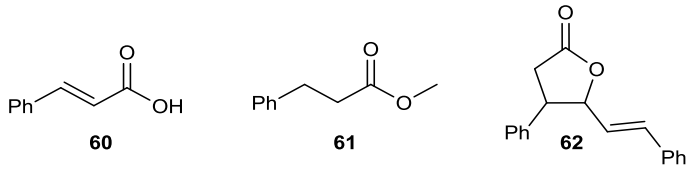


Figure 4. Possible side-products.

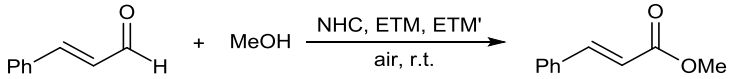
4.2.1.2. Optimization of reaction conditions

The reaction conditions were at first studied using a stoichiometric amount of oxidant **4**, for the oxidative esterification between cinnamaldehyde and MeOH (Table 6, entry 1). Methyl cinnamate was obtained in good yield (74%) after 4 h. By lowering the amount of oxidant to 1 mol%, in combination with an open reaction vessel, the yield dropped to 24% after 7 h but since the reaction still proceeded, it was a good indication that the amount of oxidant could be lowered (entry 2). In this case, it turned out that the formation of competing side-products was faster than the oxidation step, which led to an investigation of ways to increase the oxidation rate.

Addition of iron(II)phthalocyanine (FePc), showed major improvement of the yield (entry 3). Replacing quinone **4** with its precursor, 2,6-di-*tert*-butyl phenol **63**,[37] gave similar results (entry 4). Oxidant **4** appeared to be formed *in situ* from phenol **63** under our reaction conditions, thus **63** became the ETM-precursor of choice, as it is less expensive than quinone **4**.[*] Screening of other NHC-catalysts (entry 5–7) showed that **8** was the best catalyst. The loadings of the NHC-catalyst also proved to be important; loadings of more than 2 mol% gave lower reaction efficiency (entry 4, 8 and 9) with increased formation of side products.

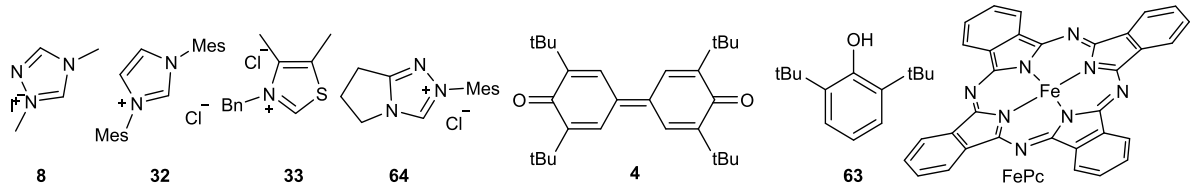
[*] Sigma-Aldrich, phenol **63** (CAS 128-39-2) 1 kg, $44.3, quinone **4** (CAS 2455-14-3) 50 mg, $125.

Table 6. Optimization of reaction conditions.



Entry	NHC	ETM (mol%)	ETM' (mol%)	t (h)	Yield (%)[b]	Selectivity (%)[c]
1.	8	4 (100)	-	4	74	78
2.	8	4 (1)	-	7	24	40
3.	8	4 (1)	FePc (0.55)	4	80	88
4.	**8**	**63 (2)**	**FePc (0.55)**	**4**	**85**	**89**
5.	33	63 (2)	FePc (0.55)	-	-	-
6.	32	63 (2)	FePc (0.55)	22	65	65
7.	64	63 (2)	FePc (0.55)	4	68	68
8.	8[d]	63 (2)	FePc (0.55)	4	19	19
9.	8[e]	63 (2)	FePc (0.55)	4	67	74

[a)] Reaction conditions unless otherwise noted: NHC (1 mol%), aldehyde (0.5 mmol, 1 eq.), TBD (0.5 eq.), MeOH (4 eq.), ETM (see table), FePc (see table), in MeCN (0.5 M) with open reaction vessels exposed to the atmosphere at room temperature. [b)] Yields determined with ^{1}H NMR against durene as internal standard. [c)] Yields over conversion. [d)] NHC (20 mol%). [e)] NHC (5 mol%).

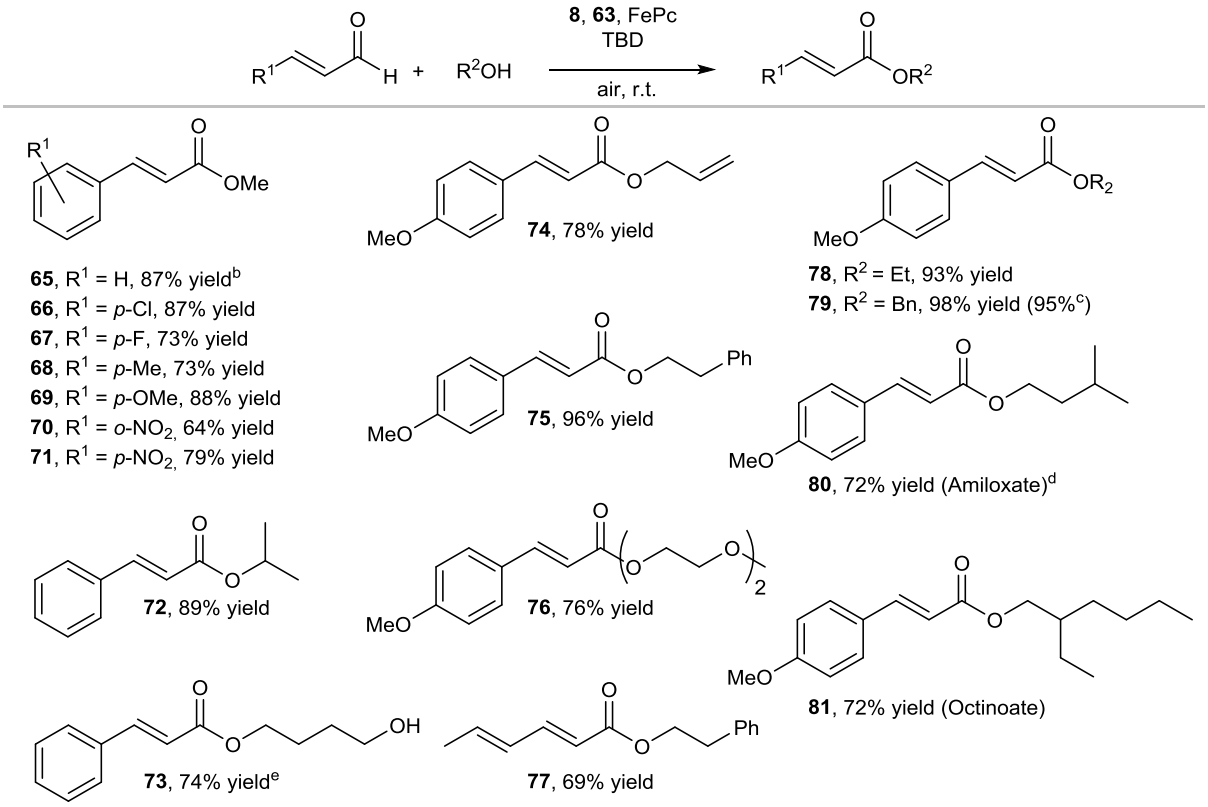


4.2.1.3. Scope of the reaction

With the optimal reaction conditions in hand, the scope of the reaction was investigated (Scheme 21). The resulting esters were isolated in good to excellent yields. Multiple functional groups were tolerated; electron withdrawing groups such as *p*-chloro and *p*-fluoro (compounds **66** and **67**) could deliver the corresponding ester in 87% and 73% yield, respectively. Electron donating groups were also possible giving *p*-methoxy cinnamate **69** in 88% yield. Different alcohols tested showed formation of the corresponding ester in high to excellent yields. For example, allyl alcohol and benzyl alcohol gave ester **74** and **79** in 78% and 98% yields, respectively.

Running the reaction with deactivated aliphatic α,β-unsaturated aldehydes, such as 2-hexenal and citral, resulted in longer reactions times. However, more reactive aliphatic conjugated aldehydes, such as sorbic aldehyde, could deliver ester **77** in 69% yield.

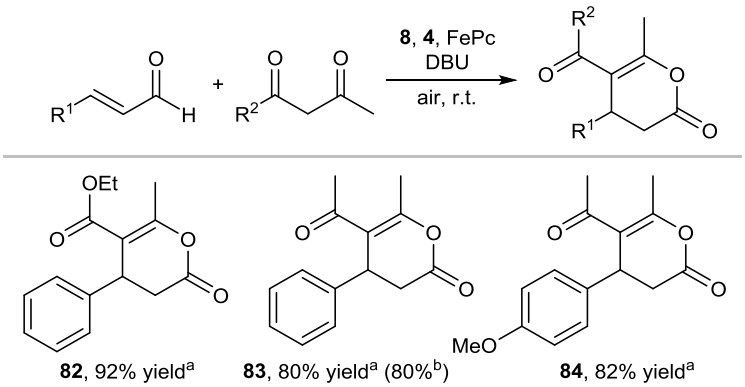
A scale-up experiment generated **79** in 1.5 g, in 95% yield, demonstrating the feasibility of substituting the stoichiometric high molecular weight oxidant with ETMs and oxygen as the terminal oxidant. Two sun-screening agents, amiloxate (**80**) and octinoxate (**81**) could both be synthesized and isolated with this one-step procedure in 72% yield.[85] Diols, such as 1,4-butanediol gave only the corresponding mono-ester **73** in 74% yield



[a] Unless otherwise stated the reactions are performed with in open reaction vessels at room temperature with aldehyde (0.5 mmol, 1 eq.), TBD (0.5 eq.), alcohol (4 eq.), **8** (0.02 eq), FePc (0.0055 eq.), **63** (0.02 eq.) in MeCN (1 mL). [b] Yields refer to isolated yields. [c] 1.5 g isolated yield. [d] Performed with the alcohol as solvent. [e] Performed with MeCN (4 mL).

Scheme 21. Scope of the reaction.[a]

The developed aerobic oxidation method was also applied in conjugated additions (Scheme 22). Using *bis*-nucleophiles such as 1,3-diketones and 1,3-ketoesters, dihydropyranones **82**, **83** and **84** could be isolated in 92%, 80% and 82% yield, respectively, demonstrating the wide utility of the method.



Reaction conditions: [a] aldehyde (0.5 mmol, 1 eq.), DBU (0.1 eq.). 1,3-dicarbonyl (1.1 eq.), **8** (0.05 eq.), FePc (0.05 eq.), **4** (0.05 eq.) in THF (0.5 M) in open reaction vessels. All yields refer to isolated yields. [b] Gram-scale synthesis, 1.4 grams isolated.

Scheme 22. Synthesis of dihydropyranones.

4.2.1.4. Background reactions

Experiments with open reaction vessels, but without the addition of phenol **63** and FePc, showed that these two ETMs were important for the reaction efficiency. Removing phenol **63**, the reaction reached the maximum conversion after 100 minutes with 40% yield (Figure 5). Removal of FePc also showed similar results. Eliminating phenol **63** and FePc altogether, the reaction only reaches 30% yield. In all

of these experiments, the full consumption of the starting materials was observed, indicating competing parasitic side-reactions. In the experiments without FePc, cinnamic acid was obtained as side-product after an aqueous work-up, which suggests formation of a peracid compound as a possible background reaction.

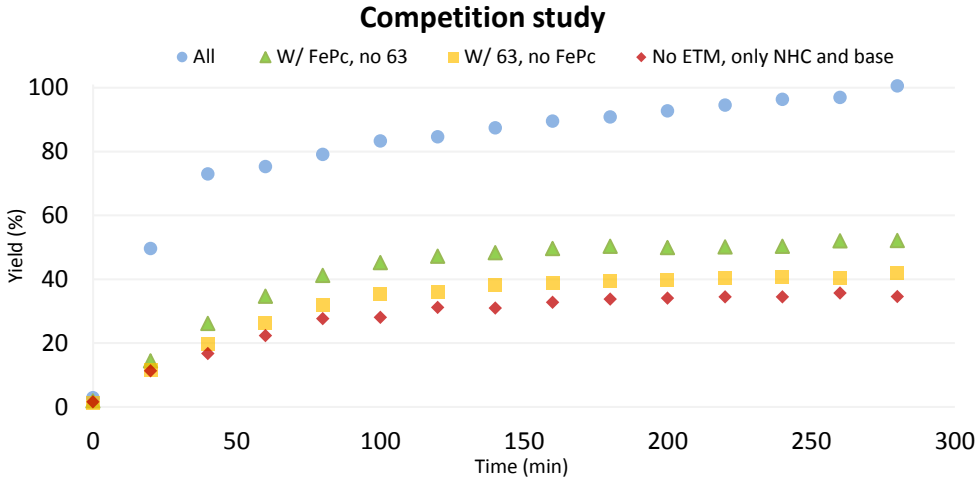
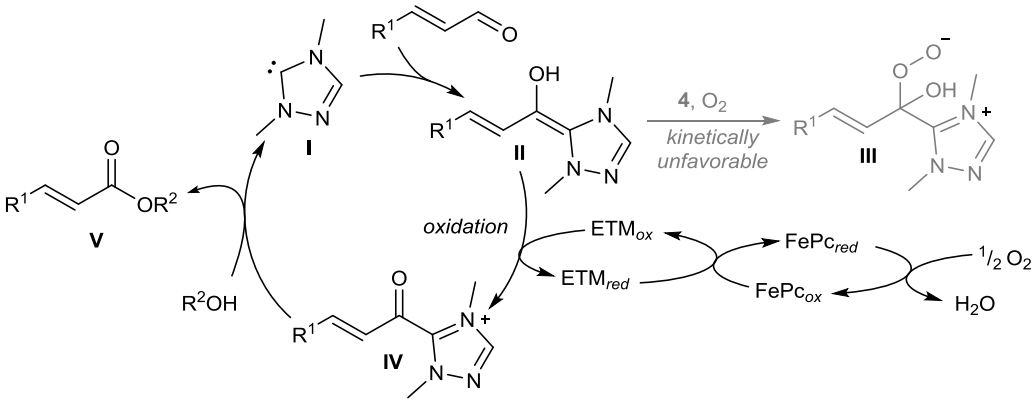


Figure 5. Kinetic study of the reaction.

The formation of the peracid has been previously reported in the literature (Scheme 23).[40]

The following mechanism is proposed: In the presence of O_2, homoenolate **II** is oxidized to the peroxo-species **III** instead of the acyl azolium **IV**. Phenol **63**, in combination with FePc creates a lower energy pathway, which enables the oxidation of homoenolate to acyl azolium. In the last step of the catalytic cycle the ester **V** is formed after a nucleophilic substitution of methanol on acyl azolium, regenerating the catalyst.



Scheme 23. Proposed catalytic cycle.

4.2.1.5. Summary

Aerobic oxidation with NHC catalysis using O_2 as terminal oxidant *via* a coupled ETM-system was proven successful. The reactions have a broad substrate scope and the products were obtained in good to excellent yields. The protocol uses low loadings of NHC-catalyst and ETMs, and by using O_2 as oxidant the reaction offers a sustainable and inexpensive way for scaling up important reactions using oxidative NHC catalysis.

4.2.2. Asymmetric synthesis of dihydropyranones (Paper V)

The acyl azolium intermediate can in combination with 1,3-diketones, give access to dihydropyranones. The dihydropyranone skeleton is a privileged structure found in many biologically active compounds and several natural products. For example, nepetalactone, the active molecule found in catnip and deoxyloganin are two members of the irioids, a diverse family of natural products founds in both marine and terrestrial origins.[86] Aspyrone, another molecule with the dihydropyranone functionality, isolated from the *Aspergillus ochraceus* and *Aspergillus mellus* molds, has shown antibiotic activity (Figure 6).[87]

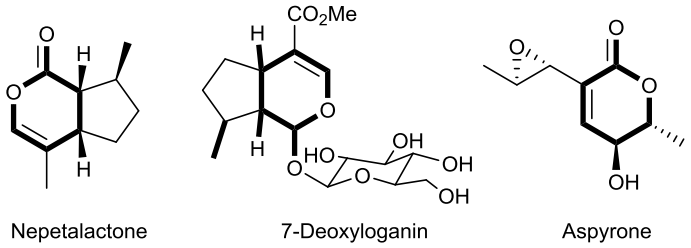


Figure 6. Examples of dihydropyranones scaffolds found in nature.

The dihydropyranone-moiety also form a versatile synthetic handle for the synthesis of other types of functional compounds such as, benzonoids,[88] 1,5-diketones,[89] 2-cyclohexanones[90] and pyrones.[91] Several syntheses of the dihydropyranone-scaffold using NHC catalysis have been reported but are not very sustainable because of their generation of waste, poor atom economy, use of derivatives and the use of stoichiometric reagents.[47-52] Thus a more convenient and sustainable enantioselective synthesis of dihydropyranones is desirable.

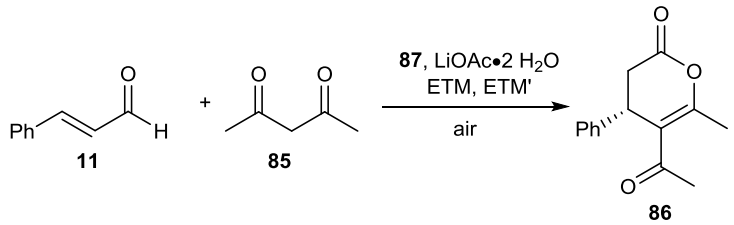
4.2.2.1. Optimization of reaction conditions

To replace oxidant **4** with oxygen, initial experiments focused on finding suitable reaction conditions that could be performed in an open vessel and without dry solvents. The model reaction, using cinnamaldehyde, acetylacetone **85**, and stoichiometric amounts of **4**, indicated that NHC catalyst **87** and lithium acetate in toluene were needed for the reaction. Different ETMs were then tested for the compatibility between the aerobic system with and the enantioselective synthesis of dihydropyranones.

Using **89** together with oxidant **4** delivered the product in poor yields, but with excellent enantiomeric excess (ee) (Table 7, entry 1). Changing oxidant **4** to **88** gave better yields (entry 2). Using FePc together with **88**, a minor improvement of yield was achieved, however, with prolonged reaction time (72 h) (entry 3). By switching back to oxidant **4**, the reaction time was shortened (48 h) with retained yield. Further reduction of reaction time could be made by increasing the reaction temperature to 40 °C (25 h), with maintained selectivity (entry 5)

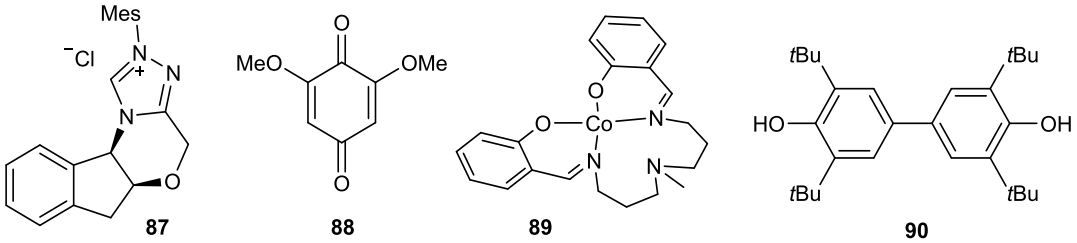
The reaction requires all the components involved; without one of any of the ETMs (**4** or FePc), the reaction only yields traces of product (entry 7 and 8). Elimination of both ETMs completely shuts down the reaction (entry 9). Under an atmosphere of N_2, only small amounts of products were isolated (entry 10). In an attempt to improve the yield, the reaction was run under an atmosphere of pure O_2. However, this did not result in any product formation (entry 6), possibly as a consequence of an inactivation somewhere in the electron transfer chain. Since the FePc component has been shown to form a dimeric μ-oxo-species together with oxygen that is possibly catalytically inactive under our reaction conditions,[92] experiments to investigate the stability of FePc during the course of the reaction were made.

Table 7. Optimization of the reaction conditions.[a]



Entry	Temp. (°C)	t (h)	ETM (mol%)	ETM' (mol%)	Yield (%)	ee (%)
1.	r.t.	46	89 (2)	4 (10)	29	94
2.	r.t.	48	89 (2)	88 (10)	58	n.d.
3.	r.t.	72	FePc (2)	88 (10)	62	95
4.	r.t.	48	FePc (2)	4 (10)	62	95
5.	40	22	FePc (2)	4 (10)	69	95
6.[b]	r.t.	48	FePc (2)	4 (10)	0	-
7.[c]	r.t.	48	FePc (2)	-	6	n.d.
8.[c]	r.t.	48	-	4 (10)	7	n.d.
9.[c]	r.t.	48	-	-	0	-
10.[d]	r.t.	48	FePc (2)	4 (10)	17	n.d.
11.[e]	**40**	**25**	**FePc (2)**	**4** (2)	**79**	**94**

[a)] Reaction conditions unless otherwise noted: aldehyde (0.125 mmol, 1 eq), acetylacetone (3 eq.), LiOAc•2 H_2O (0.65 eq.), ETM (see table), ETM' (see table). [b)] Performed under an atmosphere of pure O_2. [c)] Yield determined with ^{1}H NMR against durene as internal standard. [d)] Performed under an atmosphere of N_2. [e)] Sequential addition of FePc (see ESI for details).

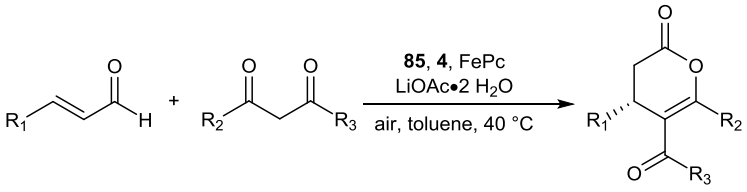


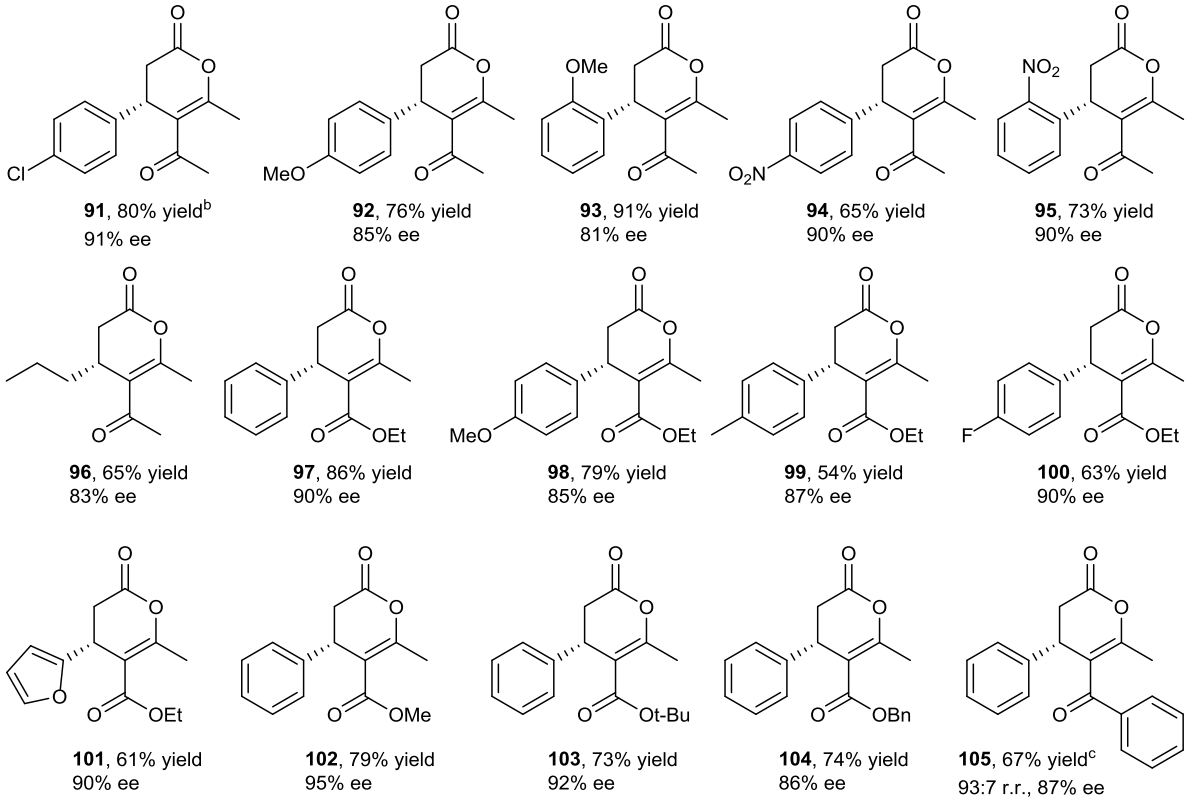
Monitoring oxidant **4** and its reduced form **90** on a gas chromatography mass-spectrometry (GC-MS) showed that after around 3 h, only the reduced form of the oxidant could be detected in the reaction mixture. With addition of an additional portion of FePc after 3 h, the reduced form could be re-oxidized again. This result strengthened the hypothesis of a catalytically inactive dimeric μ-oxo form of the FePc. This inactivation could be circumvented by adding FePc sequentially and dihydropyranone **86** could be obtained in 79% yield and 94% ee (entry 11).

4.2.2.2. Scope of the reaction

With the optimal reaction conditions in hand, the scope of the reaction was tested (Scheme 24). In combination with acetylacetone, different α,β-unsaturated aromatic aldehydes with both electron donating and electron with drawing groups, in both *orto*- and *para*-position could be obtained in good to excellent yields with generally very good ee values (81–91%). For example, *para*-chlorocinnamaldehyde was converted into its corresponding dihydropyranone **91** in 80% yield with 91% ee, while the yield of the corresponding dihydropyranone to *orto*-methoxycinnmaldehyde **93** was 91% with 81% ee. Aliphatic α,β-unsaturated aldehydes were also possible starting reagents giving the analogous product **96** in 65% yield with 83% ee. Switching from the diketone to a ketoester resulted in the corresponding ester derivative. This reagent was well accommodated by the reaction and esters **97**–**102** could be isolated in good to very good yields with ee values ranging from 85 to 95%. For example, ethyl 3-oxobutanoate and furanylacrylaldehyde gave the compound **101** in 61% yield and 90%

ee. Asymmetrical diketones gave compound **105** in 67% yield in a 93:7 regioisomeric ratio, with 87% ee of the major isomer.

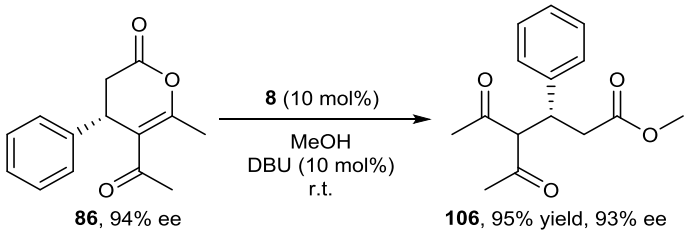




[a)] Reaction conditions unless otherwise noted: in open reaction vessels at 40 °C with aldehyde (0.125 mmol, 1 eq), 1,3-dicarbonyl (3 eq.), LiOAc•2 H_2O (1 eq.), **4** (0.2 eq.), FePc (0.006 eq.). [b)] Isolated yields. [c)] Major isomer combined yield r.r. determined by ^{1}H NMR of the crude reaction mixture.

Scheme 24. Scope of the reaction.[a]

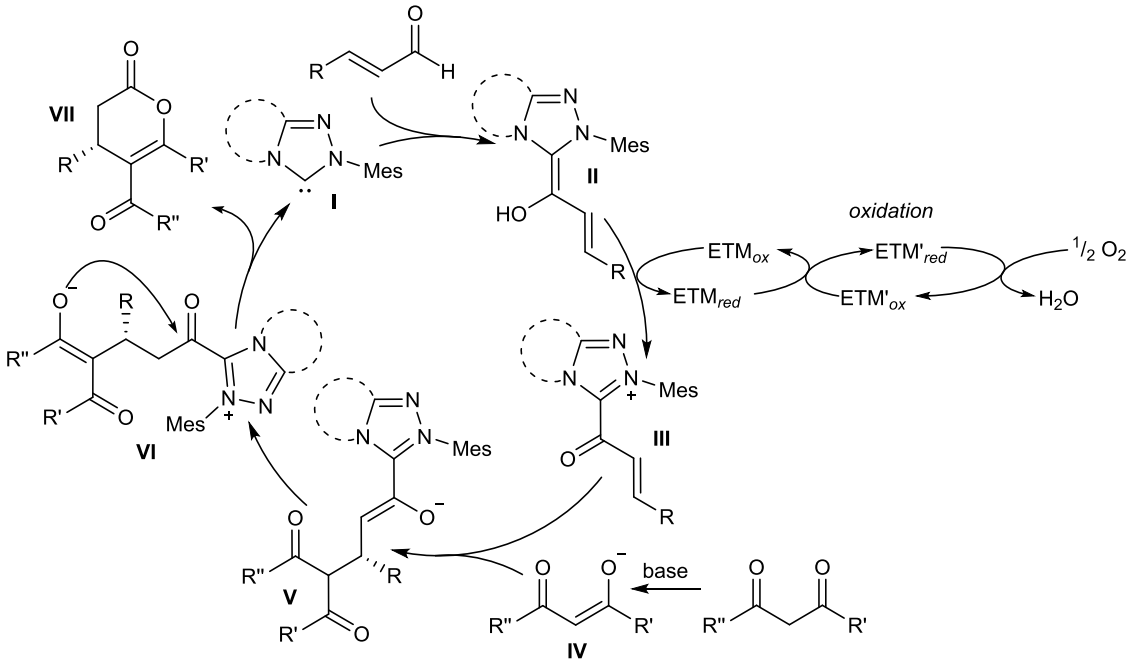
As the synthesized dihydropyranones are highly functionalized, they are good precursors for further modifications. The dihydropyranone **86**, was subjected to an NHC/base-catalyzed transesterification with MeOH resulting in 95% yield of ester **106** with retained optical purity (Scheme 25). The obtained products are difficult to form *via* a direct Michael addition of acetylacetone to cinnamates demonstrating the usefulness of the dihydropyranones as starting materials.[93]



Scheme 25. Transesterification of dihydropyranone **86** for the formation of ester **106**.

4.2.2.3. Mechanism

Deprotonation of the chiral triazolium salt forms the active carbene **I** (Scheme 26). The NHC then adds in a 1,2-fashion to the α,β-unsaturated aldehyde forming homoenolate **II**. Intermediate **II** is subsequently oxidized by O_2 through a multistep electron transfer mediated by the ETMs to the acyl azolium intermediate **III**. The 1,3-keto compound **IV** then adds onto the acyl azolium **III** in 1,4-fashion.[46, 48, 94] After tautomerization and cyclization of intermediate **VI**, product **VII** is obtained with regeneration of the NHC catalyst.



Scheme 26. Postulated catalytic cycle.

4.2.2.4. Summary

The use of aerobic oxidative NHC catalysis has enabled an enantioselective and convenient synthesis of dihydropyranones. The scope of the reaction is wide with multiple functional groups incorporated. The obtained yields of the products are good with good to excellent enantioselectivities. The usefulness of the dihydropyranone moiety was shown in a transesterification reaction yielding a diketoester. The protocol is mild, with low loadings of catalyst and efficient using air as the terminal oxidant, complying with principle 1, 2, 3, 6 and 9 of green chemistry.

4.2.3. Chemoselective acylation of indoles with oxidative NHC catalysis (Paper VI)

The ability of selectively modify heterocycles containing multiple reactive sites is an important but challenging task. Heterocycles are a common structural motif in medicinal chemistry, especially nitrogen containing heterocycles, and make up about 59% of all the marketed drugs.[95] These structures are therefore important compounds for further modifications. The indole-scaffold is a privileged structure that is common to many natural compounds and synthetic drugs. Acylated indoles are especially important as several *N*-acylated indoles can be found in commercially available drugs, such as indomethacin, oxamethacin, acemetacin and imaging agents for β-amyloid plaques (Figure 7).[96]

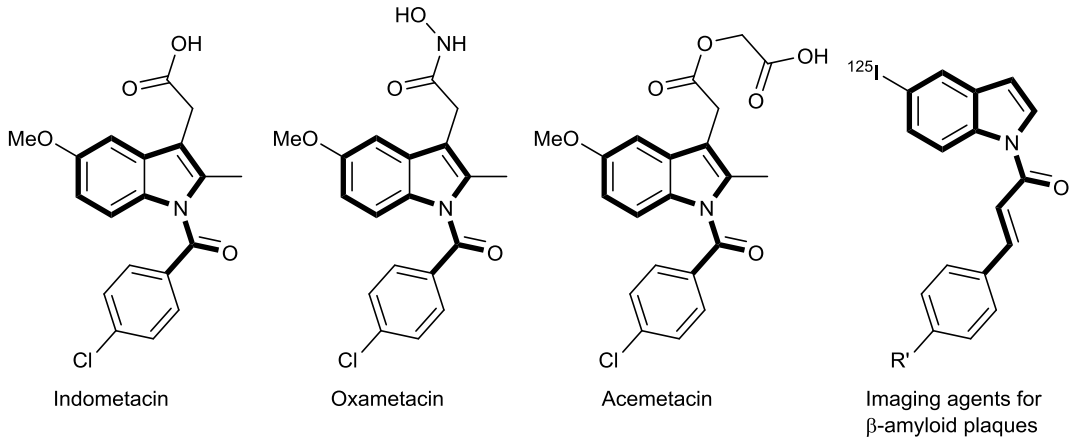
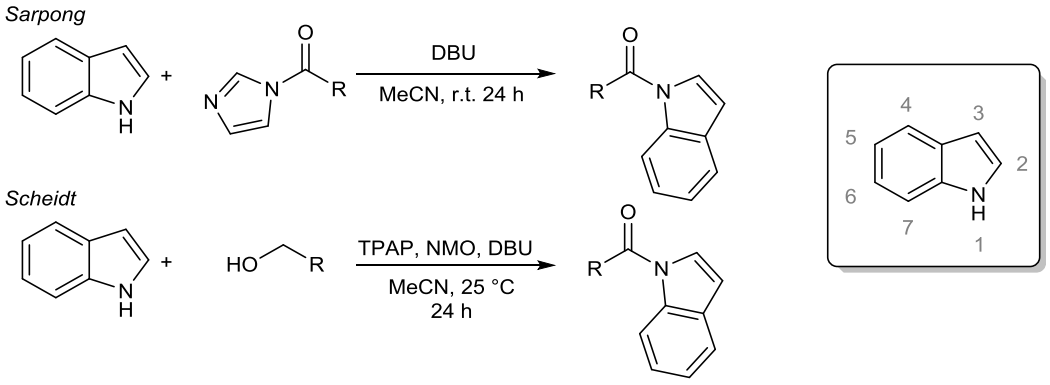


Figure 7. Examples of *N*-acylated indoles.

The preferred site for acylation of indoles is at the C-3 position, usually performed with a carboxylic acid derivative together with a Lewis acid,[97] or *via* the Vilsmeier–Haack reaction,[98] making selective *N*-acylations challenging. Conventional synthesis of *N*-acylated indoles uses reactive electrophiles, such as acyl chlorides with stoichiometric amount of base or carboxylic acids that needs to be activated with coupling reagents.[99] These methodologies require the use of reactive starting reagents and inorganic bases that might not be compatible with different functional groups; thus limiting the further development of these methods. In an attempt to circumvent the harsh reaction conditions the group of Sarpong reported the synthesis of *N*-acylated indoles with stoichiometric amounts of carbonylazoles.[100] Scheidt and co-workers, have on the other hand demonstrated a dehydrogenative coupling protocol of alcohols using tetrapropylammonium perruthenate (TPAP) as catalyst (Scheme 27).[101]



Scheme 27. Synthesis of *N*-acylated indoles.

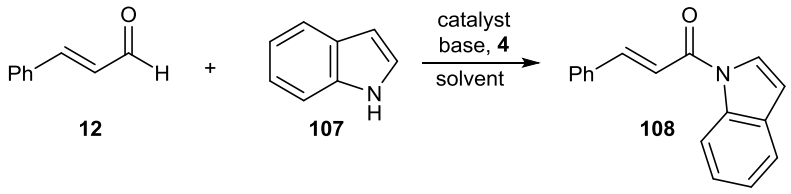
In the field of NHC catalysis readily available aldehydes can be converted into latent acyl donors *via* the acyl azolium intermediate, which offers a mild method for the acylation of indoles. Previous studies indicate that it is possible to use NHC catalysis for the *N*-functionalization of indoles *via* an intramolecular reaction cascade[102] or an imination reaction together with isocyanides.[103] Therefore, investigation of the selectivity of the acyl azolium intermediate towards the acylation of heterocycles with multiple functional sites was an interesting target.

4.2.3.1. Optimization of reaction conditions

The starting point for the study was the choice of the NHC-precatalyst. Both imidazolium and triazolium salts could yield the *N*-acylated product together with DBU, cinnamaldehyde and oxidant **4** in DCM. The triazolium catalyst **62** appeared to be the most active (Table 8, entry 1–3). The base

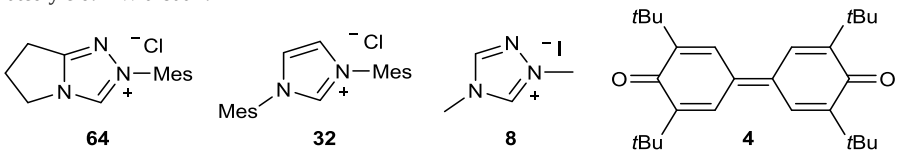
DBU was shown to be the superior option, while milder bases, such as TEA, failed to generate any product and inorganic bases, such as Cs_2CO_3, only gave trace amounts (entry 4 and 5). Investigation of different solvents showed that MeCN, toluene and THF did not perform as well as DCM. The best condition found was the combination of DCM with increased base-loadings (entry 9). Since water can pose as a competing nucleophile, the addition of molecular sieves (MS, 4 Å) proved important. Systematic exclusion of the NHC-precursor, the oxidant **4** and the base for checking background reactions, showed that without NHC or oxidant the reaction does not work (entry 10–12) which means that the reaction is indeed operates under oxidative NHC catalysis.

Table 8. Optimization of reaction conditions.[a]



Entry	Solvent	Cat.	Base	Additive	Yield (%)[b]
1.	DCM	64	DBU	-	54
2.	DCM	32	DBU	-	31
3.	DCM	8	DBU	-	25
4.	DCM[c]	64	Cs_2CO_3	-	4
5.	DCM[c]	64	TEA	-	0
6.	MeCN[d]	64	DBU	-	46
7.	Toluene[d]	64	DBU	-	36
8.	THF[d]	64	DBU	-	17
9.	**DCM**[d]	**64**	**DBU**	**MS 4 Å**	**81/71**[f]
10.	DCM[d]	-	DBU	-	0
11.	DCM[d]	-	-	-	0
12.[g]	DCM[d]	64	DBU	MS 4 Å	0

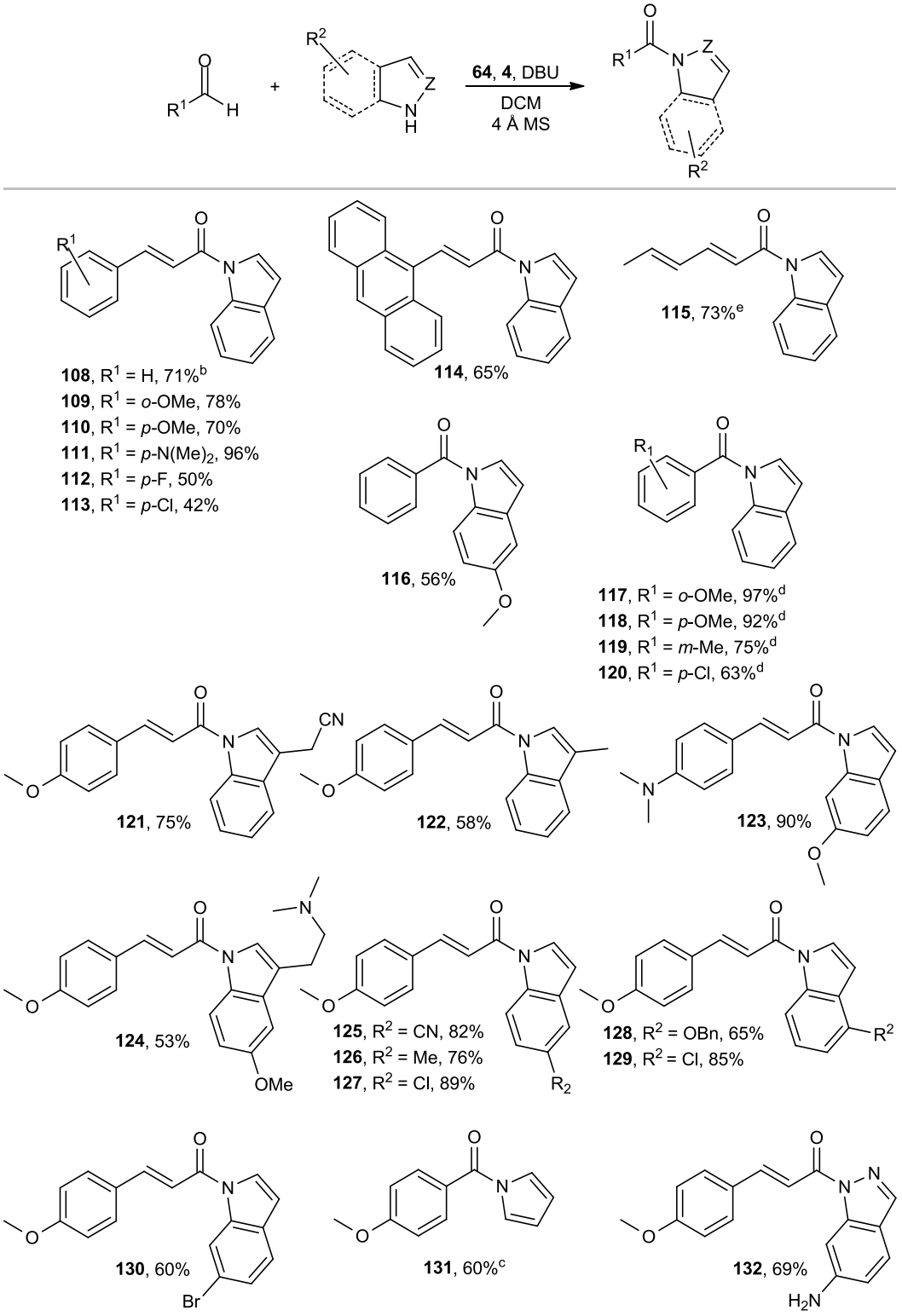
[a)] Reaction conditions unless otherwise stated: indole (0.14 mmol, 1 eq.), cinnamaldehyde (2 eq.), base (0.5 eq.), precatalyst (10 mol%), solvent (1 ml), and **4** (1 eq.). [b)] Yields determined by ^{1}H NMR against durene as internal standard. [c)] Solvent (1.5 ml). [d)] Solvent (0.8 ml). [e)] DBU (1 eq.). [f)] Isolated yield. [g)] Without **4**.



4.2.3.2. Scope of the reaction

Having found the optimal reaction conditions the scope of the reaction was investigated (Scheme 28). Different α,β-unsaturated aldehydes containing both electron withdrawing groups and electron donating groups were viable in the synthesis of *N*-acylated indoles. These useful indoles can be further modified with different metal-catalyzed reactions.[104] The electron donating substituents were more efficient in comparison with the electron withdrawing counterpart. For example, *orto*- and *para*-methoxycinnamaldehydes and *para*-dimethylamino, gave the corresponding acylated indoles in 70–96% yields (compound **109**–**111**). With electron withdrawing halogen groups the corresponding products resulted in slightly lower yields with longer reaction times (compound **112** and **113**). The benzaldehydes, being less activated than their unsaturated counterparts, required longer reaction times and slightly higher loadings of catalyst for the synthesis of the benzoylated indoles. Similar electronic effects of the aromatic substituents as for the α,β-unsaturated aldehydes were observed for the benzaldehydes; electron donating groups could deliver the products in excellent yields (compound

117–**119**), whereas the electron withdrawing groups was less efficient giving compound **120** in 63% yield.



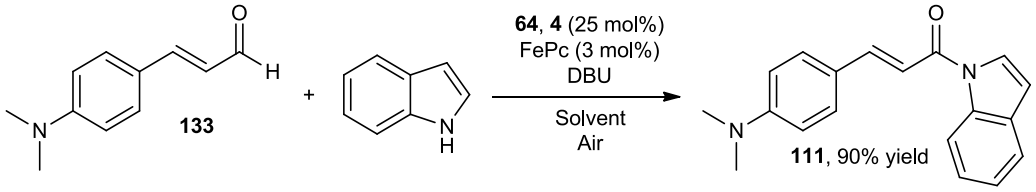
a) Reaction conditions unless otherwise stated: indole (1 eq.), cinnamaldehyde (see ESI), base (0.5 eq.), **64** (5 mol%), solvent (1 ml), and **4** (1 eq.). b) Yields refer to isolated yields. c) As footnote a, but with aldehyde (1 eq.), pyrrole (1.5 eq), **64** (10 mol%).

Scheme 28. Scope of the reaction.[a]

The next step was to investigate different substituted indoles. Overall, substituents on the indole in various positions worked well, incorporating a wide range of different types of functional groups. However, substitution on C-2 and C-7 position did not lead to any reaction. Experiments using 2-

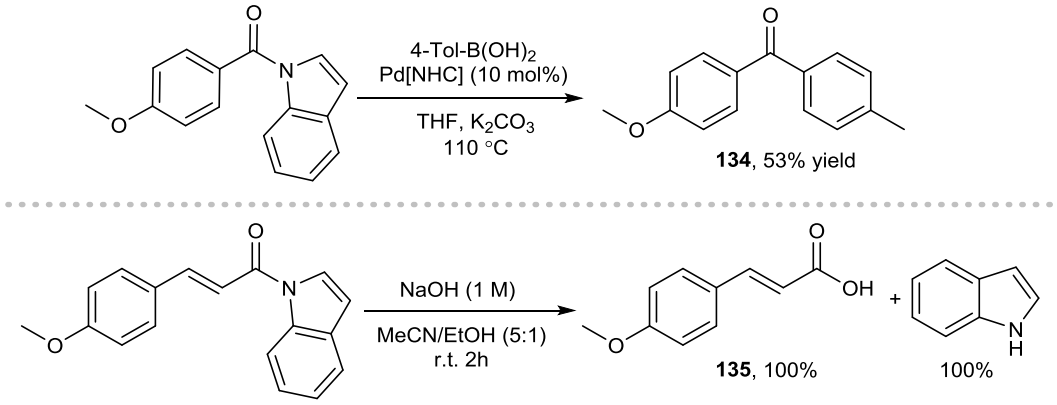
methylindole, 7-methylindole and 7-chloroindole with cinnamaldehyde failed to give any product. A plausible explanation is steric effects caused by the substituents when the indole reacts with the acyl azolium intermediate. For the other positions on the indole ring, products were obtained in good to excellent yields (53–90%, compound **121**–**130**). For example, compounds **116**, **123**, **126** and **128**, with electron donating groups were obtained in 56–90% yields. Furthermore, tryptamine analogues, incorporating a tertiary amine (compound **124**), and functional groups such as nitriles were also viable (compound **125**). Incorporation of other heterocycles containing nitrogen was also possible; pyrrole and indazole could deliver the products in good yields (compounds **131** and **132**), with selective acylation of the indazole in presence of an unprotected amine. In all experiments, selectivity towards *N*-acylation was observed with no observation of acylation at the C-3 position. In control experiments with protected *N*-site of the indole using 1-methylindole, no conversion of starting materials could be observed.

In order to further improve the E-factor of the reaction, the developed aerobic oxidative NHC catalysis methodology, using molecular dioxygen as terminal oxidant was applied (Scheme 29). Aldehyde **133** and indole in combination with catalyst **64**, FePc and substoichiometric amount of oxidant **4** using an open reaction vessel, delivered compound **111** in 90% yield, showing a possibility of using an aerobic protocol for oxidation.



Scheme 29. Aerobic oxidative NHC catalysis for the synthesis of *N*-acylated indoles.

The synthesized acyl indoles are good synthetic building blocks, which can be used for further modifications (Scheme 30). For instance, compound **118** can be converted to benzophenone **134** using a Suzuki-Miyaura reaction with a Pd-catalyst, in 53% yield.[105] The acylated indoles were also subjected to hydrolysis using NaOH giving carboxylic acid **135** and regenerating the indole in quantitative yields. This showcases that acylindoles could function as protecting groups for both carboxylic acids and indoles.

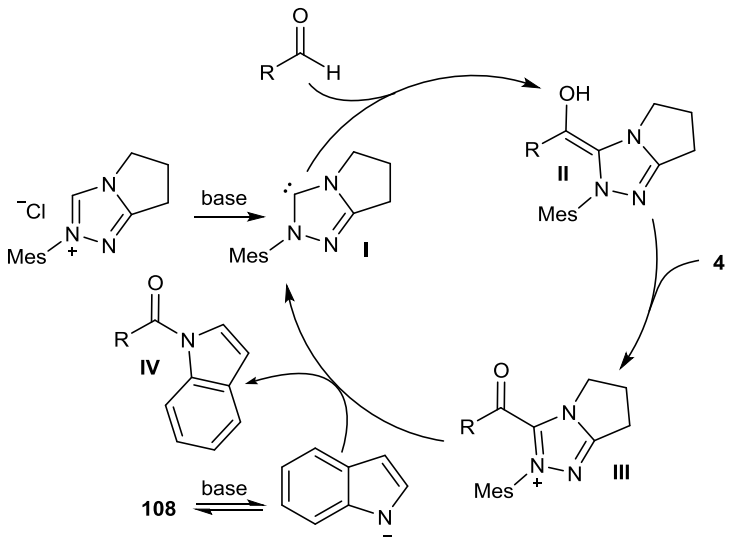


Scheme 30. Synthetic modifications of *N*-acylated indoles.

4.2.3.3. Mechanism

The catalytic cycle starts with deprotonation of the NHC salt giving the active carbene catalyst **I** (Scheme 31). This then adds to the aldehyde forming the Breslow intermediate **II**. Oxidation with **4**

delivers the acyl azolium intermediate **III** which after a nucleophilic substitution with the deprotonated indole, forms product **IV** and regenerates the NHC.



Scheme 31. Proposed catalytic cycle.

4.2.3.4. Summary

Selective *N*-acylation of indoles, indole and pyrrole was shown using oxidative NHC catalysis. The developed protocol offers a broad scope, with multiple functional groups incorporated. The products were obtained in good to excellent yields. The *N*-acylated indoles were subjected to further reactions in a Suzuki-Miyaura coupling and hydrolysis showing their usefulness. Moreover, the reaction could also be run following the aerobic oxidative protocol indicating the possibility of performing this reaction in a more sustainable fashion. The developed methodology offers a mild alternative to the harsh conditions normally associated with these transformations.

4.2.4. *N*-Acylated oxazolidinones *via* aerobic oxidative NHC catalysis (Paper VII)

Functionalized oxazolidinones are a class of useful molecules that also exhibit interesting biological activities. The oxazolidinone-skeleton can be found in many pharmaceutical drugs, such as locostatin, a Raf-kinase inhibitor, linezolid, a synthetic antibiotic and natural products (Figure 8).[106] Synthetically, *N*-acylated oxazolidinones, are mostly known as Evans' auxiliaries, and have been employed in asymmetric synthesis, for example, in aldol,[107] alkyl,[108] Diels–Alder reactions[109] and Michael additions.[110]

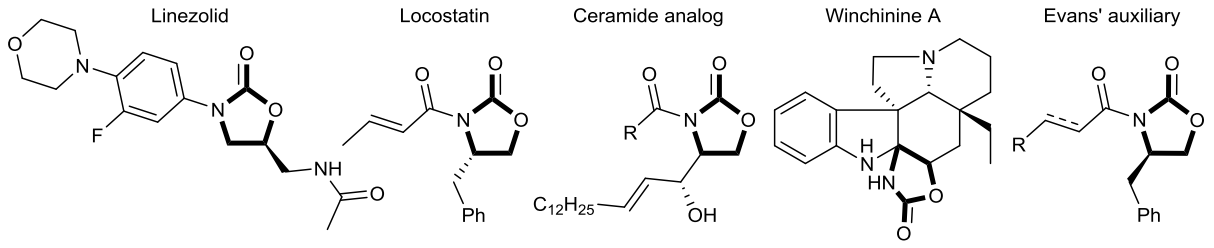


Figure 8. Examples of useful oxazolidinone-containing compounds.

The conventional synthesis of *N*-acylated oxazolidinones uses strong base for deprotonation together with reactive reagents such as acid chlorides.[111] This strategy can, however, limit the practicality of the reaction as it uses reactive substrates that require special precautions and strong bases are also capable

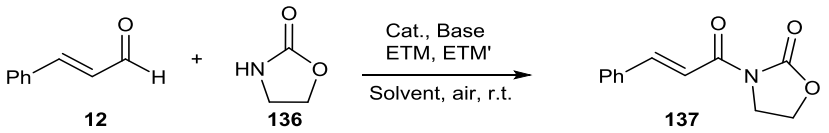
of epimerizing chiral oxazolidinones at the C-5 position.[112] Alternative procedures for the formation of *N*-acylated oxazolidinones include acyl fluorides,[113] carbonylazoles,[100] DMAP,[114] coupling reagents,[115] metal catalysis[116] and electrochemistry.[117] However, these protocols still requires the use of sensitive reagents as starting materials, coupling reagents and high reaction temperatures to drive the reaction to completion. Therefore, in accordance to the principles of green chemistry, these methods are not sustainable in terms of atom economy, energy efficiency, less hazardous synthesis and catalysis.

Given that NHC catalysis has the ability to generate latent acyl donors, it became the starting point for developing a strategy for acylation of oxazolidinones in mild conditions. Oxidative NHC catalysis with oxidant **4** have demonstrated numerous novel reaction pathways involving mostly *O*-nucleophiles and annulation reaction. However, *N*-nucleophiles are not as common and the combination of an aerobic protocol, where O_2 serves as the terminal oxidant, for the *N*-acylation of oxazolidinones has not been reported. Thus, this became the starting point for our investigations.

4.2.4.1. Optimization of reaction conditions

The starting point of the study was to identify suitable NHC-precatalysts. Triazolium salt **64** and **8** in combination with MeCN, TBD, FePc and oxidant **4**, seemed to be promising choices with catalyst **8** giving slightly better results (Table 9, entry 1 and 2). Imidazolium salt **32** was less efficient whereas thiazolium salt **135** did not work at all (entry 3 and 4). Investigations of different solvents showed that using EtOAc, acylated oxazolidinone **137** was obtained in comparable yields to MeCN (entry 6).

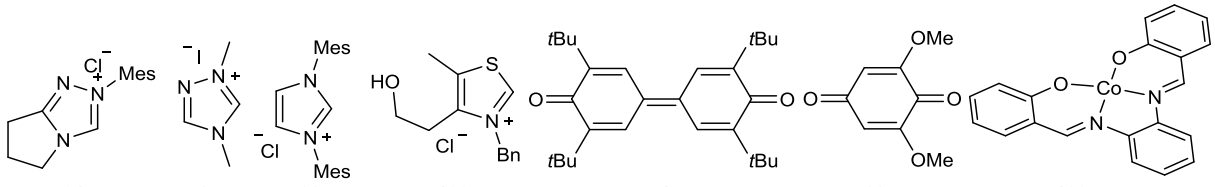
Table 9. Optimization of reaction conditions.



12 **136** **137**

Entry	Cat.	Solvent	Base	ETM	ETM'	Yield (%)[d]
1.[a]	64	MeCN	TBD	4	FePc	47
2.[a]	8	MeCN	TBD	4	FePc	53
3.[a]	32	MeCN	TBD	4	FePc	32
4.[a]	138	MeCN	TBD	4	FePc	0
5.[a]	8	Anisole	TBD	4	FePc	24
6.[a]	8	EtOAc	TBD	4	FePc	55
7.[a]	8	DCM	TBD	4	FePc	35
8.[a]	8	MEK	TBD	4	FePc	32
9.[b]	**8**	**EtOAc**	**DBU**	**4**	**FePc**	**90/89[e]**
10.[c]	8	EtOAc	TEA	4	FePc	0
11.[c]	8	EtOAc	DBU	4	139	39
12.[c]	8	EtOAc	DBU	88	FePc	78
13.[f]	8	EtOAc	DBU	4	-	84

[a)] Reaction conditions unless otherwise stated: cinnamaldehyde (1 eq.), oxazolidinone (1.5 eq.) cat (5 mol%), ETM (5 mol%), ETM' (3 mol%), solvent (0.16 M). [b)] As footnote a, but with cat (1 mol%), base (0.2 eq.), ETM (3 mol%), ETM' (2 mol%), solvent (0.31 M). [c)] As footnote a, but with cat (1 mol%). [d)] Yield is determined by ^{1}H NMR against durene as internal standard. [e)] Isolated yields. [f)] As footnote b, but performed under N_2 with **4** (1 eq.).



64 **8** **32** **138** **4** **88** **139**

The solvents DCM and methyl ethyl ketone (MEK) both resulted in lower yields in comparison with MeCN (entry 7 and 8). Since EtOAc is considered to be a more sustainable and greener solvent than MeCN, it became our solvent of choice.[118] At this point, the reaction was still not efficient enough and isolation of three side-products, cinnamic acid **60**, γ-butyrolactone **62** and the saturated *N*-acyloxazolidinone **140** (Figure 9), indicated a slow oxidation step of the Breslow intermediate to the acyl azolium intermediate. Thus, further optimization for a more efficient oxidation was made by investigating different bases and ETM-systems. The best base was once again DBU (entry 9) capable of delivering the product in 90% yield, while weaker organic bases such as TEA (entry 10) failed to form any product at all. Investigation of different ETM-systems (entry 11–12) showed oxidant **4** in combinations with FePc to be the best ETM-pairs. When running the reaction with a stoichiometric amount of **4** the *N*-acylated oxazolidinone was obtained in 84% yield (entry 13), which is less efficient in comparison with the developed aerobic system. Experiments excluding the ETMs and O_2 resulted in slow reactions and low yields, the ETMs are thus needed for the reaction to be efficient. It was also possible to lower the amount of catalyst, base and ETM-loadings of the reaction but further on, the reaction appeared to be sensitive towards changes in concentration; with lower concentrations lower yields were obtained.

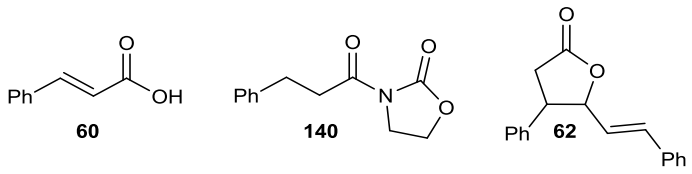
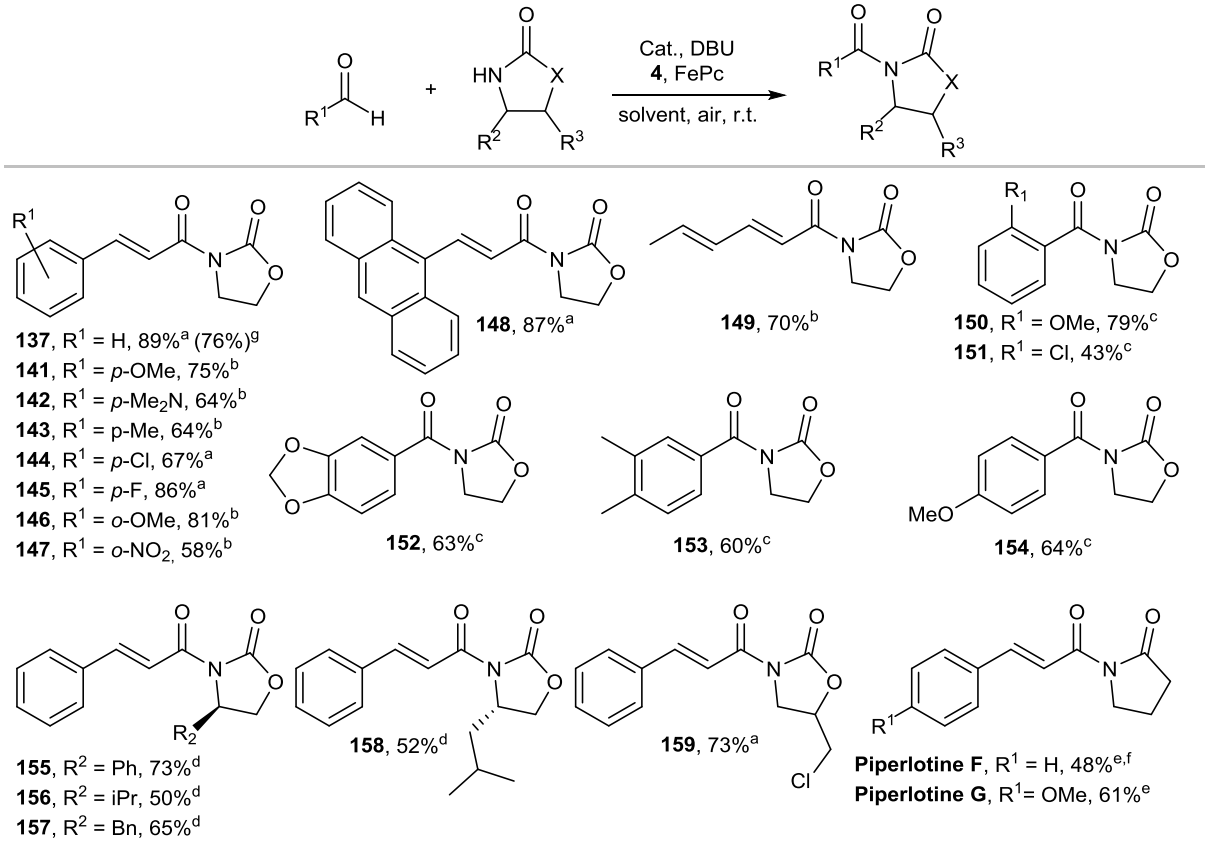


Figure 9. Side-products isolated from the reaction.

4.2.4.2. Scope of the reaction

Having optimized the reaction conditions the scope of the reaction was investigated using α,β-unsaturated aldehydes and benzaldehydes with different functional groups. Both electron withdrawing and electron donating groups with *orto*- and *para*-substitution pattern were tolerated (compounds **141**–**153**). A gram-scale synthesis of **137** was possible and the product could be isolated in a pure form without the use of chromatography. Non-aromatic α,β-unsaturated aldehyde delivered the corresponding acylated product **149** in good yields. Both benzaldehydes and the α,β-unsaturated aldehydes bearing aromatic electron donating functional groups required a more electron-rich catalyst **64** for the reaction to work efficiently. The benzaldehydes being less activated required slightly higher loadings of catalyst **64**. Good yields were obtained for the benzaldehydes with electron donating groups (**150**, **152**–**154**) whereas compound **151** with a Cl-group was obtained in an acceptable yield. For benzaldehydes with electron withdrawing groups, the lower yields are the consequence of benzoic acids formation *via* direct oxygenative oxidation of the Breslow intermediate with O_2.

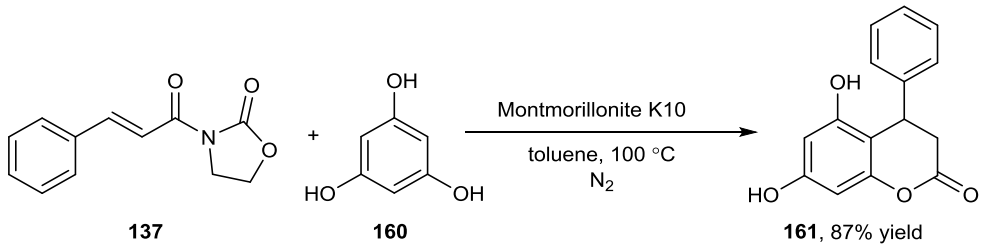
Different oxazolidinones were investigated. Both *N*-acylation of chiral and achiral oxazolidinones gave good yields. Chiral groups at the C-4 position of the oxazolidinone could deliver their acylated counterpart in good yields (compounds **155**–**158**) but because of the steric nature of the substituents, an elevation of reaction temperature (60 °C) and a slight increase of base was required. With C-5 substituted oxazolidinone, the product **159** was obtained in 73% yield under normal reaction conditions, leaving the primary alkyl chloride intact. Moreover, it was also possible to use 2-pyrrolidinone as nucleophiles for the synthesis of two natural products, piperlotine F and piperlotine G, an Nrf2 activator, in moderate to good yields.[119]



[a] Reaction conditions unless otherwise stated: with **8** (5 mol%). [b] With **64** (1 mol%). [c] With **64** (4 mol%). [d] With **8** (1 mol%), DBU (0.4 eq), 60 °C. [e]With **8** (5 mol%), DBU (1.5 eq.), aldehyde (1 eq.), 2-pyrrolidinone (2 eq.). [f] With molecular sieves (4 Å, 0.5 g). [g] Gram-scale synthesis.

Scheme 32. Scope of the reaction.

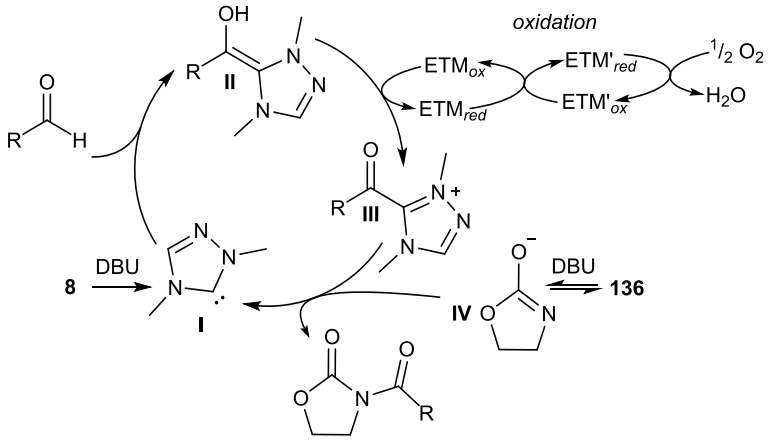
The synthesized *N*-acylated oxazolidinones were used in the synthesis of a 2-chromanon-scaffold found in natural products of the calomelanol family (Scheme 33). Compound **137** and phloroglucinol **160** were reacted in toluene at 100 °C using montmorillonite K10 as catalyst to give compound **161** in 87% yield, through a Friedel-Craft alkylation followed by lactonization.



Scheme 33. Synthesis of 2-chromanone using *N*-acylated oxazolidinones.

4.2.4.3. Scope of the reaction

The proposed catalytic cycle begins with the deprotonation of the precatalyst salt by DBU forming the active carbene **I** (Scheme 34). The catalyst then adds to cinnamaldehyde forming the Breslow intermediate **II**. The Breslow intermediate is subsequently oxidized by O_2 through a multistep electron transfer step *via* the ETMs forming the acyl azolium **III**. Lastly, the product is formed upon interception by **IV** of the acyl azolium, regenerating the NHC catalyst.



Scheme 34. Proposed catalytic cycle.

4.2.4.4. Summary

With the help of a coupled ETM-system it was possible to use O_2 from the air as a terminal oxidant for the synthesis of various *N*-acylated oxazolidinones and pyrrolidinone. The functional group tolerance is high, giving products with good to excellent yields. The usefulness of the acylated oxazolidinones was shown with the synthesis of a chromanone. The developed protocol enables a sustainable way of using readily available starting materials for the synthesis of valuable compounds, circumventing the need for a separate activation step.

Chapter 5

Concluding remarks and future outlooks

In this thesis, the development of synthetic methodologies mediated by NHC catalysis under the guidance of green chemistry has been addressed. The developed methods can utilize readily available reagents, such as aldehydes and molecular oxygen from air as starting materials for the synthesis of complex molecular architectures. The generality of the protocols has been investigated with further functionalization of the derived products.

In the first part of this thesis, commercially available and relatively inexpensive ILs based on the imidazolium-scaffold were used as NHC-precursors. Access to the homoenolate intermediate can be achieved by the use of enals. In combination with chalcones and a nucleophile, the synthesis of highly functionalized OTHOs was enabled with high yields, stereo- and regioselectivity. The substrate scope of the reaction is broad with both electron withdrawing and electron donating groups. The reaction can also be performed in a one-pot reaction, with no purification techniques other than filtration, omitting the use of solvent-demanding chromatography and enabling scale-up of the reaction. Furthermore, the solvating properties of the IL were also demonstrated in the regioselective acylation of carbohydrates, yielding multiple monoacylated compounds without the use of protecting groups. The developed protocols are robust, mild and can be executed without the exclusion of moisture or air, demonstrating the benefits of NHC catalysts.

Additional mechanistic studies are needed to fully understand the high stereoselective formation of the *anti*-product and dependency of the equivalences of MeOH. This could be achieved by, for example, computational studies. As the obtained OTHOs were shown to be potent gelators for the formation of both organogels and hydrogels, further characterizations and studies for possible applications of the obtained products are needed. Modifications of the OTHO-scaffold, by an enantioselective synthesis or by incorporation of other types of nucleophiles, can further give a direction of the usefulness of the products as gelators.

The second part of this thesis has demonstrated the used of oxidative NHC catalysis, accessing the acyl azolium intermediate for the synthesis of various useful compounds. The developed protocols were also able to replace the use of a stoichiometric high molecular weight oxidant. The usage of a coupled system of ETMs lowers the high reaction barrier of oxygen, and enables the utilization of molecular oxygen from the atmosphere as a terminal oxidant.

The aerobic method has allowed the synthesis of various α,β-unsaturated esters, including two sun screening agents, amiloxate and octinoxate. The products were obtained in high yields with a wide range of functional groups. The use of ETMs was essential for being able to use O_2 as a terminal oxidant. The method was also applied in the enantioselective synthesis of several dihydropyranones in high yields, and good to excellent ee. During the course of the project, inactivation of FePc could be noted, by the formation of an μ-oxo-FePc-species, which required the sequential addition of FePc for the success of the reaction.

The use of oxidative NHC catalysis allowed the selective acylation of *N*-nucleophiles such as indoles. The products were obtained in good to high yields with multiple functional groups tolerated. The potential of using an aerobic system for the synthesis of *N*-acylated indoles was demonstrated. The synthesized products were applied in a Suzuki-Miyaura reaction generating benzophenone **131**. Further development for the use of the aerobic system led to *N*-acylation of oxazolidinones and pyrrolidinones, giving products in good to excellent yields. Two of the obtained substrates are natural products. The obtained products were also subjected to further manipulations demonstrating their usefulness.

The use of aerobic oxygen facilitates scale-up reactions and reduces the quantities of chemical waste generated. Furthermore, the use of oxidative NHC catalysis allows the use of readily available aldehyde as acylation reagents and circumvents the need for a separate activation step and use of harsh reaction conditions.

Future work to study the ETMs is needed to be able to understand what governs the stability of the system in order to develop more reactions compatible with aerobic oxidative NHC catalysis. The acyl azolium intermediate have demonstrated to readily participate in acylation of *O*-nucleophiles and in annulation reactions but have been somewhat limited in the case of *N*-nucleophiles. Overcoming the difficulties of using amines as nucleophiles would present a convenient and more sustainable method for the synthesis of amides. Further examination of the reactivity of the α- and γ-carbons could lead to development of new products with oxidative NHC catalysis.

The use of NHC catalysis is a powerful alternative to conventional metal based catalyzed reactions and with the appropriate reaction design, the principles of green chemistry can be accomplished.

Chapter 6

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Chapter 7

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