THESIS FOR THE DEGREE OF LICENTIATE OF PHILOSOPHY

Organocatalytic Transformations with *N*-Heterocyclic Carbenes

An Investigation of Ionic Liquids as NHC Precatalysts and Aerobic Oxidative Esterifications

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Department of Chemistry and Chemical Engineering

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Gothenburg, Sweden 2016

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ABSTRACT

The call for more sustainable processes in the chemical society has led to the development of the field of green chemistry. The *Twelve Principles of Green Chemistry* serve as guidelines for the design of processes. With the rise of organocatalysis and *N*-heterocyclic carbenes (NHCs), the NHCs have become powerful alternatives *in lieu* of traditional metal-catalysts; being inexpensive and non-toxic. In this thesis, two different applications of NHC catalysis are presented.

In the first part of the thesis an imidazole-based ionic liquid is used as an NHC-precursor, forming oxo triphenylhexanoates (OTHOs) in a highly stereo- and regioselective manner. The reaction negates the requirements for laborious work-up procedures usually required for the isolation of products.

The second part of the thesis have demonstrated the use of molecular oxygen as a terminal oxidant, combined with coupled electron transfer mediators for oxidative NHC catalysis enabling access to various α,β-unsaturated esters and lactones. The catalytic protocol permits the substitution of stoichiometric high molecular weight oxidants, thereby facilitating scale-up reactions as well as reducing the amount of chemical waste generated.

Both of these routes have been designed according to the principles of green chemistry in an attempt to meet the demands for more environmentally benign synthetic strategies.

Keywords: Organocatalysis, *N*-heterocyclic carbene, green chemistry, ionic liquid, multi-component reaction, aerobic oxidation, OTHO

List of Publications

This thesis is based on the following papers and will be referred to their Roman numerals in the text. Reprints were made with permission from the publishers.

Paper I. *Ionic Liquids as Precatalysts in the Highly Stereoselective Conjugate Addition of a,β-Unsaturated Aldehydes to Chalcones*
Linda Ta, Anton Axelsson, Joachim Bijl, Matti Haukka, Henrik Sundén
Chem. Eur. J., **2014**, *20* 13889–13893

Paper 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

Paper 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
Manuscript.

Paper IV. *Attractive Aerobic Access to the a,β-Unsaturated Acyl Azolium Intermediate: Oxidative NHC Catalysis via Multistep Electron Transfer*
Linda Ta, Anton Axelsson, Henrik Sundén
Green Chem., **2016**, *18*, 686**–**690

List of Abbreviations

BMIMCl	1-butyl-3-methylimidazolium chloride
Bn	benzyl
DIPEA	*N,N*-diisopropylethylamine
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
E	electrophile
EMIMAc	1-ethyl-3-methylimidazolium acetate
EMIMCl	1-ethyl-3-methylimidazolium chloride
ETM	electron transfer mediator
Eq	equivalents
FePc	iron(II) phthalocyanine
IL	ionic liquid
MCR	multi-component reaction
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
OTHO	oxo triphenylhexanoate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TEA	triethylamine
THF	tetrahydrofuran

Table of Contents

1. Introduction and Background

With increasing demands for more sustainable industrial processes in chemical production, the needs to develop cleaner, alternative reaction protocols has become important. It is now not only just a matter of *what* w synthesize but also *how* it should be synthesized. This has led to the development of a new field with the introduction of green chemistry as a concept together with the publication of the *Twelve Principles of Green Chemistry.*[1] The principles are a set of guidelines for a safer and more environmentally benign way of designing chemical synthesis. Currently, the chemical industry mostly relies on non-renewable resources. Therefore, finding alternative renewable resources is important. Also of importance is the prevention of chemical waste with the help of, for example, catalysis as well as being able to re-use or eliminate the use of solvents and reagents.

Several metrics for to measure how green a reaction is have been devised. One such measure is the atom economy of a reaction, presented by Trost,[2] which measures the amount of the starting atoms being incorporated into the final product. However, the atom economy does not take the other substrates used in the reaction into account, such as the use of a stoichiometric amount of catalysts or solvents. The environmental-factor (E-factor) by Sheldon,[3] on the other hand, calculates the amount of waste generated per kilogram of product.

To meet the ever increasing demands for more sustainable syntheses the efforts put into developing greener and more suitable methods is essential. In this thesis I will present work related to several of the principles of green chemistry. In chapter 3 the formation of oxo triphenylhexanoates (OTHOs) using a catalytic protocol (principle 9, catalysis) is presented. This protocol combines the use of a one-pot, multi-component procedure (principle 2, atom economy), together with a recoverable catalyst, and a simple isolation by filtration (principle 1, prevention). In a related study, on *Regioselective Acylation of Carbohydrates with IL precatalysts,* a method for the regioselective modification of carbohydrates without the requirement for protecting groups (principle 6, reduced derivatives and principle 7, renewable feedstock) is highlighted. In chapter 4, an aerobic oxidation protocol is presented where a stoichiometric oxidant is replaced by molecular oxygen (principle 1, prevention and principle 9, catalysis). With the help of the *Twelve Principles of Green Chemistry* as guidelines for the design of experiments it is possible to make significant steps towards a more sustainable world.

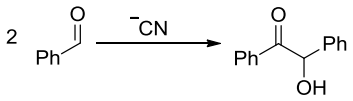
1.1 Catalysis

One of the concepts in the *Twelve Principles of Green Chemistry* is the use of catalysis. With the help of catalysis we can not only eliminate the use of stoichiometric amounts of reagents, but also have cleaner and more efficient synthetic processes. A catalyst is a compound that takes part in a reaction and will increase the reaction rate but is itself not consumed at the end of the reaction.[4] Ideally a catalyst should be stable enough to be handled without any special equipment, be both selective and efficient so that it can convert the reactants to the desired products without generating any side products.

Catalysts are usually divided into two categories; heterogeneous catalysts and homogenous catalysts. Heterogeneous catalysts operate in a different phase from the reactants, whereas a homogeneous catalyst operates in the same phase as the reactants. One field of homogeneous catalysis that has received widespread attention in the last decade is organocatalysis.

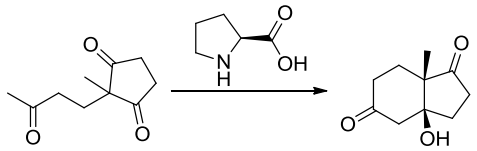
1.2 Organocatalysis and *N*-Heterocyclic Carbenes

Catalysis employing small organic molecules has been known for more than a century. In 1832 Liebig and Wöhler showed that the benzoin condensation could be catalyzed by cyanide anions (Scheme 1).[5] This field is now more known as organocatalysis but received little attention for a long time in organic chemistry.



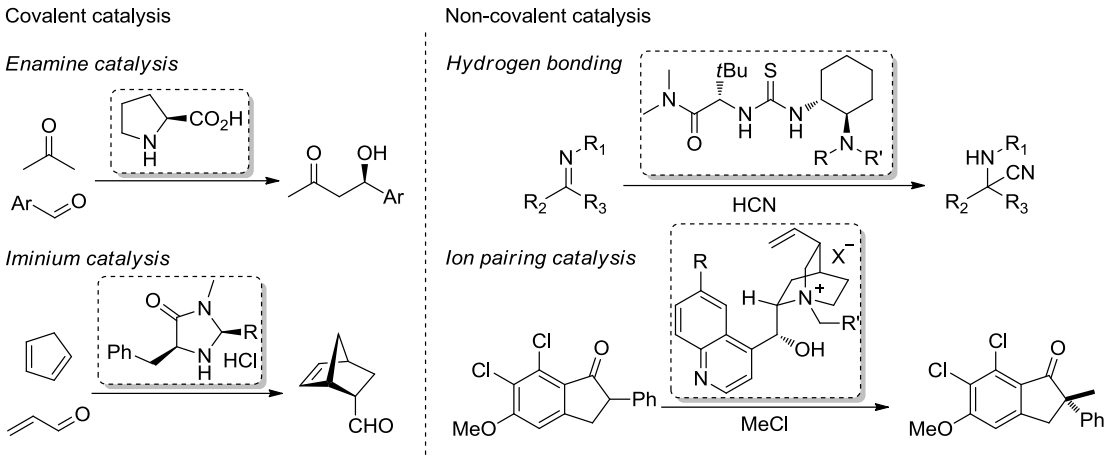
Scheme 1. Benzoin condensation using cyanide anions.

In 1971, two groups reported the Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 2), which uses L-proline as a catalyst.[6] This reaction demonstrates the first synthetic asymmetric synthesis without the use of metal-complexes highlighting the potential for the use of small organic molecules as catalysts. However, the use of organic molecules as catalysts still remained dormant for decades, and it was not until the late 90's that interest for organocatalysis was rekindled.[7]



Scheme 2. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

The field of organocatalysis was introduced in the year 2000 independently by List *et al.* and MacMillan and co-workers.[8] There are several benefits of using organic molecules as catalysts; being metal-free they are generally inexpensive, usually less toxic, and do not require the need to be handled under rigorously anhydrous or anaerobic conditions. In addition, organocatalysis allows easy access to chiral catalysts, readily available from the natural chiral pool (e.g. amino acids, carbohydrates).[7, 9] Organocatalysis can be divided into covalent and non-covalent catalysis (Scheme 3). Covalent catalysis involves the formation of a covalent bond to the substrate; examples of covalent organocatalysis include enamine and iminium catalysis.[10] Non-covalent organocatalysis uses other interactions than covalent bonding for catalysis such as hydrogen bonding, for example, with thiourea catalysts or ionic interactions with ion pairing catalysis utilized by ionic catalysts.[11] More recently, *N*-heterocyclic carbene (NHC) relying on a covalent activation, has also become an important topic of organocatalysis.[12]



Scheme 3. Examples of covalent and non-covalent organocatalysis.

1.3 *N*-Heterocyclic Carbenes (NHCs)

One of the early reports of NHC-catalyzed reactions was published by Ukai in 1943.[13] With the help of a thiazolium salt benzoin was formed in a homodimerization of aldehydes. However, the active catalyst species was unknown. It was not until the work of Breslow in 1958, in which he presented the mechanism of a thiamine catalyzed benzoin condensation, that the active catalyst was identified to be a carbene.[14] Carbenes were long thought to be too instable to isolate, which was invalidated by the isolation of stable phosphinocarbenes by Bertrand as well as the isolation of stable imidazol-2-ylidene by Arduengo in the 90's (Figure 1).[15] Even so, the field of NHC catalysis did not receive any interest until 2004 when Bode,[16] Rovis[17] and Glorius[18] demonstrated that α-functionalized aldehydes could be turned into acylation reagents *via* an internal redox process catalyzed by NHCs. Since then, the area has grown rapidly; NHCs are now no longer only curiosities in the lab but also useful tools for organic synthesis.[12b, 12c]

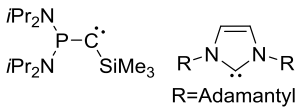


Figure 1. Stable carbenes isolated by Bertrand and Arduengo.

The easiest way to generate NHCs *in situ* is by deprotonation of an imidazolium, triazolium or thiazolium salt using a base. This can be represented as either an ylide or the carbene (Figure 2). After generation of the active carbene it can add to an electrophilic species, often aldehydes.

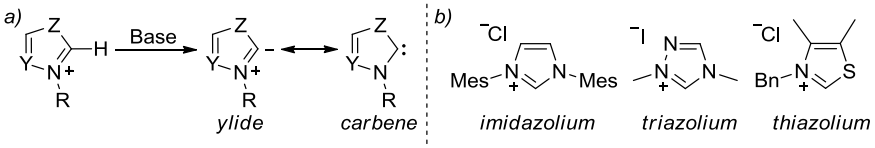
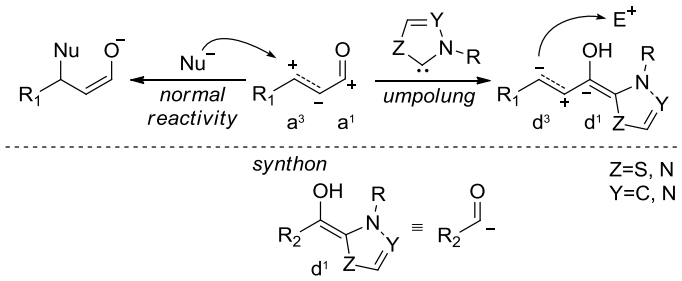


Figure 2. a) Deprotonation using a base for the active carbene. b) Common NHC precursor salts.

A key step in transformations involving NHCs is umpolung, a termed coined by Seebach,[19] which refers to the polarity-reversal of an electrophile (acceptor, a) to a nucleophile (donor, d). In the terms of Seebach, an a^1-synthon is converted to a d^1-synthon (Scheme 4).



Scheme 4. Electrophilic aldehyde turned into a nucleophilic species by umpolung.

1.3.1 Ionic Liquids (ILs)

Ionic liquids (ILs) are salts that are liquid below 100 °C and have received a lot of attention over the last decade. With properties such as low volatility, recyclability and the ability to dissolve carbohydrates (e.g. cellulose), ILs have become an appealing green reaction medium.[20] One type of ILs, based on the imidazolium-structure (for selected examples see Figure 3), is capable of forming NHCs after deprotonation by a base.[21]

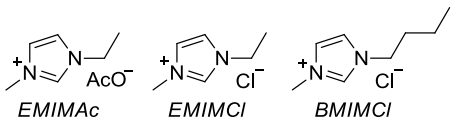
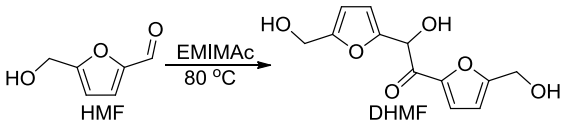


Figure 3. Three imidazolium-based ILs.

The use of imidazolium-based ILs as NHC-precatalysts has previously been demonstrated in, for example, the benzoin condensation.[22] Recently, Chen and co-workers used 1-ethyl-3-methylimidazolium acetate (EMIMAc) (Figure 3) for the formation of 5,5'-di(hydroxymethyl)furoin (DHMF) from 5-hydroxymethyl furfural (HMF) *via* a benzoin-type condensation (Scheme 5).[23] Although generating NHCs from ILs is an easy and inexpensive method, this strategy has not been utilized to a large extent in organic synthesis. Given the attractive features of both ILs and NHCs it would be valuable to unite these two groups to create powerful and novel chemistry.

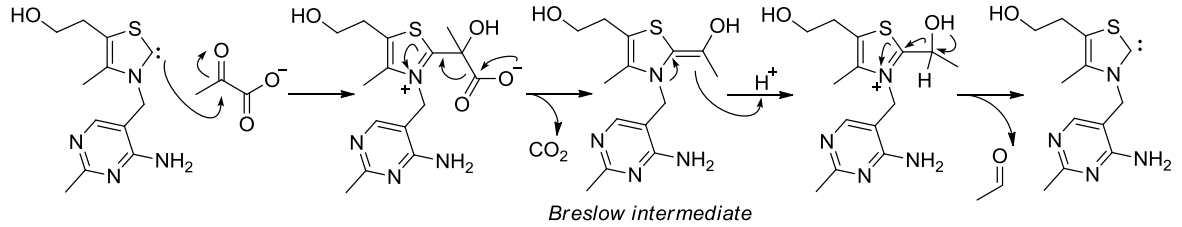


Scheme 5. EMIMAc as precatalyst for the formation of DHMF.

2. Theory and Methodology

2.1 Activation Modes of *N*-Heterocyclic Carbenes

Thiamine (vitamin B1) is a coenzyme that is essential for a variety of biological processes. The active part of thiamine was discovered to be a carbene, capable of generating the Breslow intermediate biochemically, for example, in the decarboxylation of pyruvic acid (Scheme 6).[24]



Scheme 6. The decarboxylation of pyruvic acid by thiamine.

For a long time chemists have turned to nature for inspiration for design of reactions and catalysts. In nature, the formation of carbon-carbon (C-C) bonds almost always proceeds *via* an enol or enolate intermediate. The enols or enolates can be generated by the removal of an α-hydrogen from a carbonyl compound in the presence of a base.[25]

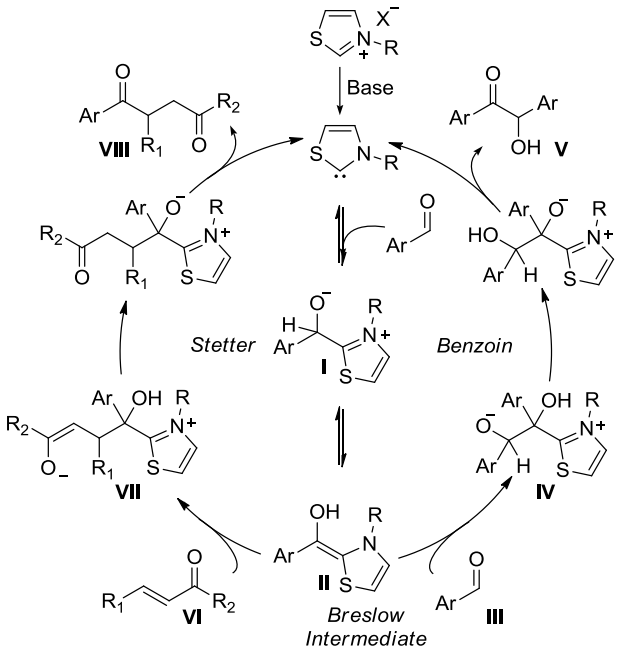
Following on from the discovery of the resemblance in both structure and reactivity between thiamine and NHCs by Breslow, many chemists have tried to imitate the thiamine reaction mode.[12a, 14] Currently, NHC-structures not only based on the thiazole-scaffold exist but have also been extended to include imidazole- and triazole-based catalysts as well. This has helped to improve both yield and selectivities in NHC-catalyzed reactions. With the help of NHC catalysis, new reaction protocols can be accessed, which allows for the synthesis of new and interesting compounds. The following sections will give a short overview of some important key intermediates connected to NHC catalysis.

2.1.1 Breslow Intermediate

The acyl anion equivalent formed between an NHC and simple aldehydes is commonly referred to as the Breslow intermediate **II** (Scheme 7) and is named after Breslow who proposed this enaminol intermediate in his seminal report in 1958.[14] The two most studied reactions involving the Breslow intermediate are the benzoin condensation (or acyloin condensation to include aliphatic aldehydes) and the Stetter reaction.[26] Both reactions start with the nucleophilic addition of the NHC, formed *in situ* after deprotonation of the precursor salt using a base, to an aldehyde, which forms the tetrahedral intermediate **I**. After proton transfer, the nucleophilic Breslow intermediate **II** is formed, which can further react with other substrates. If the reaction partner is, for example, another aldehyde **III**, a nucleophilic attack on the aldehyde by the Breslow will generate the alkoxide intermediate **IV**. After proton transfer and regeneration of the carbene, the final α-hydroxy ketone **V** is obtained.

The Stetter reaction on the other hand, has a different reaction partner with the Breslow intermediate. The reaction also begins in the same manner as for the benzoin condensation,

however, the Breslow intermediate **II** in this case reacts with a Michael acceptor **VI** to deliver the alkoxide intermediate **VII**. The carbene is regenerated after the tautomerization of intermediate **VII** followed by collapse of the tetrahedral intermediate, reforming the carbonyl and delivering **VIII**.

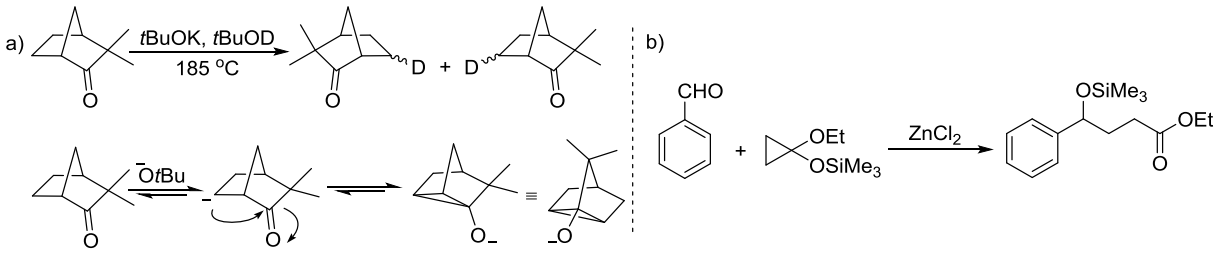


Scheme 7. The mechanism of the benzoin and the Stetter reaction.

The benzoin condensation with NHC has attracted wide attention since its discovery and has since become a reference point for the evaluation of chiral NHCs. Several examples of both asymmetric homo-benzoin reaction and cross-benzoin reactions have been reported.[27] The first asymmetric Stetter reaction was reported by Enders *et al.* in 1996 allowing access to enantiomerically enriched chromanones,[28] and other examples soon followed.[29]

2.1.2 Homoenolate

The first report of a homoenolate anion was in 1962 by Nickon and Lambert (Scheme 8a).[30] However, the chemistry of homoenolates was again left unexplored for a long time due to a lack of suitable routes for generating these types of intermediates directly. Severaö approaches to circumvent this problem have been reported such as the utilization of homoenol silyl ethers in the form of the cyclopropane ketal (Scheme 8b).[31]

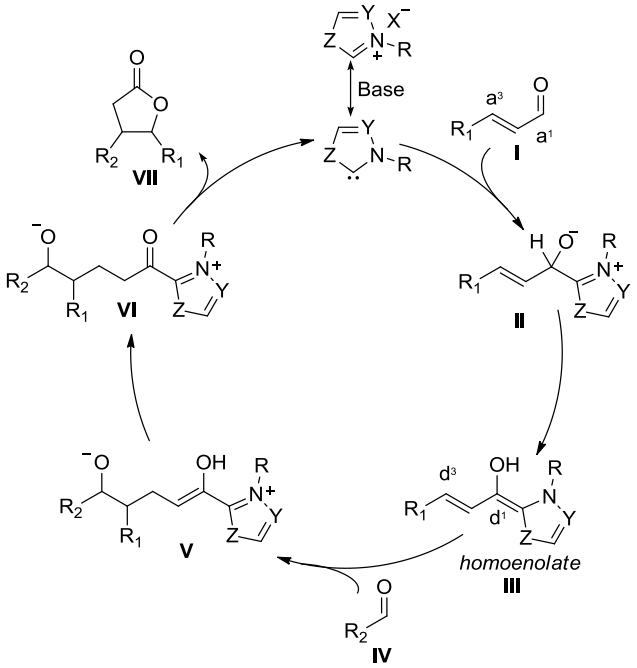


Scheme 8. a) Nickon and Lambert's homoenolate. b) Homoenolate equivalent masked as a cyclopropane ketal.

The combination of NHCs with α,β-unsaturated aldehydes can give homologous intermediates to enolates called homoenolates (Scheme 9, **III**), which can also be seen as an extended Breslow intermediate. Through a conjugate umpolung, this intermediate turns nucleophilic at the β-carbon, which normally would be electrophilic (**I→III**). With this umpolung, interesting synthesis pathways are opened up.

In 2004 Glorius[18] and Bode[16b] independently reported the catalytic generation of homoenolates from readily available starting materials yielding γ-lactones **VII** (Scheme 9). This led to an increase of activity in the area of homoenolate chemistry. The mechanism for the catalytic formation of the homoenolate is similar to the formation of the Breslow intermediate. The proposed catalytic cycle starts with the nucleophilic addition of NHC to the electrophilic α,β-aldehyde which forms the zwitterionic intermediate **II**. The homoenolate **III** is formed following proton transfer, and have at this stage undergone an umpolung where the previously electrophilic centers (a^1 and a^3) are now nucleophilic (d^1 and d^3). The β-carbon can then react with an electrophile **IV** forming the alcoholate **V**. Intermediate **V** then tautomerizes, forming intermediate **VI**. The catalytic cycle is ended with an intramolecular attack of the alkoxide at the carbonyl leading to formation of γ-lactones **VII** and regeneration of the catalyst.

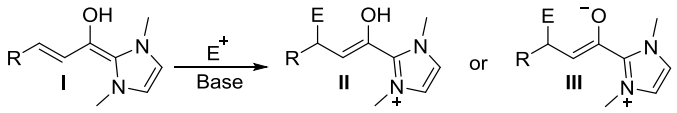
The research groups of Nair and Bode have exploited homoenolates for the synthesis of a number of cyclopentenes and cyclopentanes.[32] Bode and co-workers reported an asymmetric version of this reaction, postulating an intramolecular crossed-benzoin condensation followed by an oxy-Cope rearrangement for the formation of the stereocenters.[32c]



Scheme 9. Formation of γ-lactones through conjugate umpolung, reversing the electrophilic carbon to a nucleophilic carbon.

2.1.3 Azolium Enolates and Azolium Enols

Other key intermediates that can be generated through NHC catalysis are the azolium enolates and azolium enols, which can be seen as a d^2-synthons. Either the enolate or enol species can be generated after the elimination of a leaving group attached in the α-position of an aldehyde. Other ways of accessing these intermediates (Scheme 10, **II** and **III**) include trapping the homoenolate **I** with an electrophile, for example, by protonation at the β-position. This has allowed for the rapid access to a number of oxygen and nitrogen containing heterocycles.

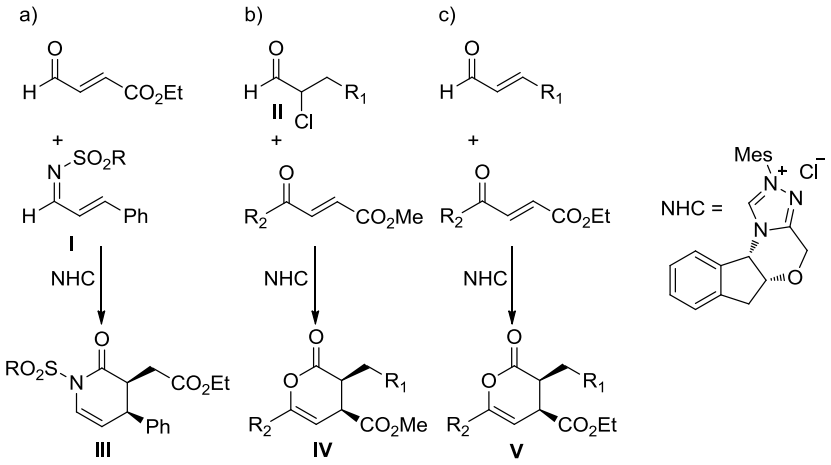


Scheme 10. Generation of the azolium enol and azolium enolate intermediate.

For instance, Bode and co-workers have reported an enantioselective NHC-catalyzed Diels-Alder reaction of dihydropyridinones (**III**)[33] and dihydropyranones (**IV** and **V**)[34] (Scheme 11). Together with *N*-sulfonyl imines **I** and electrophilic α,β-unsaturated aldehydes Bode and co-workers also reported the formation of dihydropyridinones **III** *via* an azadiene Diel-Alder reaction catalyzed by a chiral NHC under mild conditions (Scheme 11a, **III**). The reaction requires the use of enals with electron-withdrawing groups. With less electrophilic enals (such as cinnamaldehyde) the NHC catalyst was observed to react with the electrophilic imine instead.

For the generation of dihydropyranones *via* an inverse-electron demand oxodiene Diels-Alder, Bode and co-workers used racemic α-chloroaldehydes (Sheme 11b, **II)** as the dienophile precursor together with enones. For this reaction they found that the catalysts loading could be

reduced to 0.5 mol% with retention of reactivity and selectivity. To assess if the stereochemistry of the α-chloroaldehyde could influence the stereochemical outcome of the products, enantioenriched chloroaldehyde was treated with both enantiomers of the NHC precatalyst. The products formed were be isolated in identical yields, diastereomeric ratio and enantioenrichment with the only difference being their absolute configurations.[34a] The same type of chiral enolates can be generated from enals using a weak amine base (Scheme 11c). It was noted that weak amine bases, such as *N*-methyl morpholine, were crucial to promote the formation of the enolate equivalents. With stronger bases or an excess of moderate bases, such as triethylamine (TEA), the homoenolate route dominates. The enolate equivalent is only formed if the conjugate acid of the base, which is generated after deprotonation of the NHC-precursor, is acidic enough to protonate the homoenolate at the β-position. It was also noted that the use of triazolium-derived catalysts seem to aid in protonation and thus lead to enolate formation. A wide range of enals and enones have been shown to undergo annulations under these conditions giving the desired products in excellent yields and enantioselectivity.[34b]



Scheme 11. Generation of dihydropyridinones and dihydropyranones.

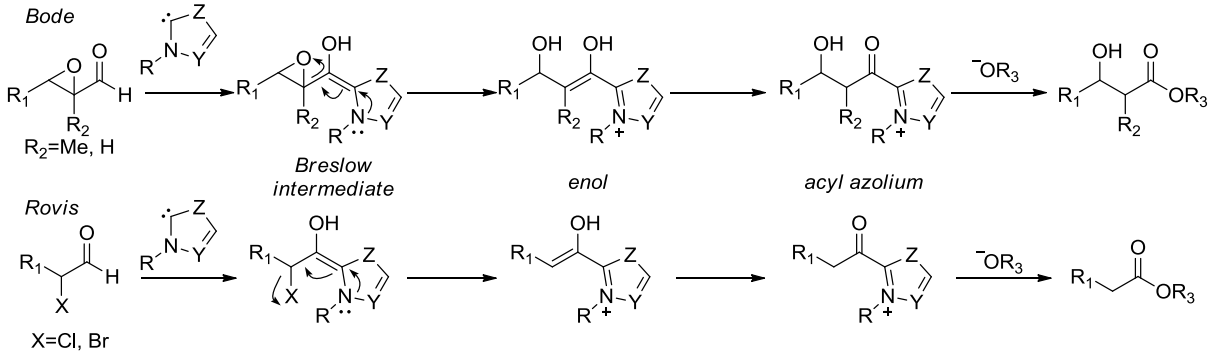
2.1.4 Acyl Azolium

As well as the nucleophilic intermediate species generated with NHCs, electrophilic intermediate species are also possible. The Breslow intermediate can, for example, be converted into the electrophilic acyl azolium intermediate *via* redox reactions either externally or internally, and can be seen as an activated carboxylate species. Selected examples are described in the following sections.

2.1.4.1 Internal Redox

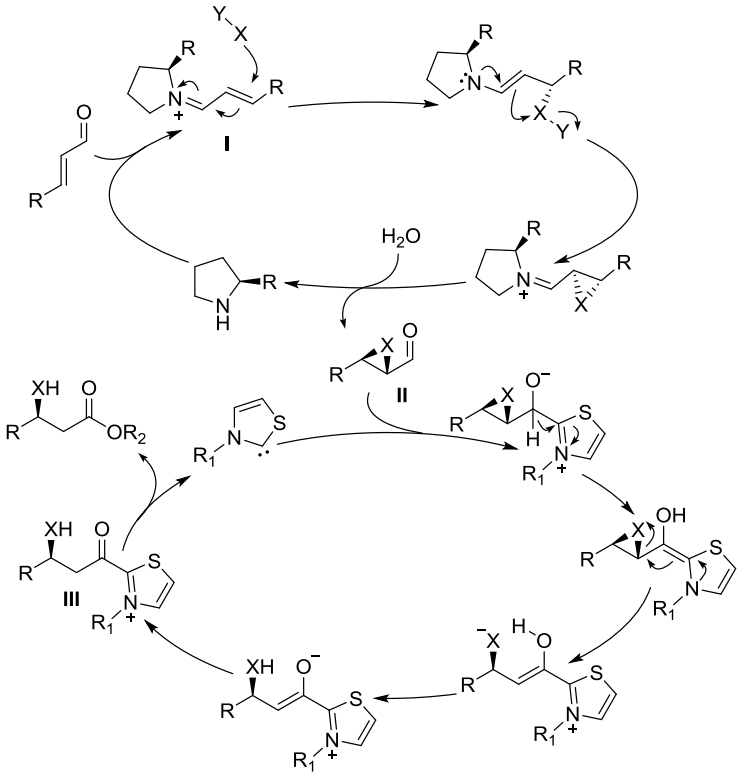
Acyl azoliums generated from internal redox chemistry can be prepared from α-functionalized aldehydes (such as enals, ynals,[35] α-haloaldehydes, epoxyaldehydes, cyclopropanyl aldehydes,[36] and aziridine aldehydes[16a]). In 2004 Bode[16a] and Rovis[17] reported the catalytic generation of acyl azolium in redox esterifications using an aldehyde with an α-leaving group (Scheme 12). Mechanistically the nucleophilic carbene adds to the α-reducible aldehyde and forms the Breslow intermediate, which then undergoes an internal redox reaction to form the enol, either through ring-opening of the epoxide or by loss of the α-leaving group. After tautomerization, the acyl

azolium intermediate is obtained, and after a nucleophilic attack of an alcohol generates the ester-product releasing the NHC-catalyst.



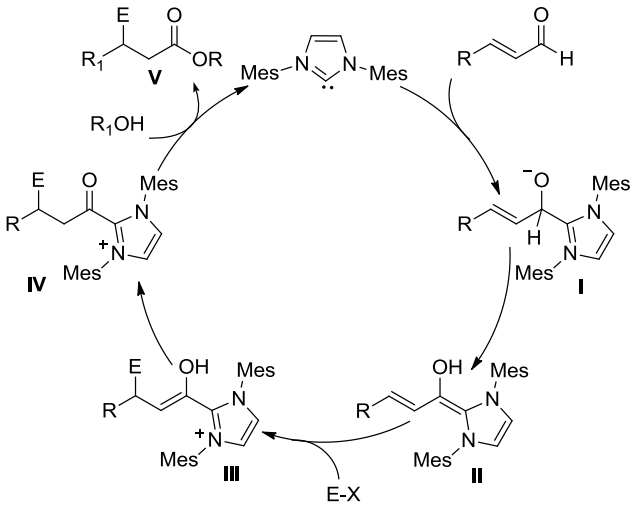
Scheme 12. Catalytic generation of acyl azolium *via* internal redox.

A different approach, using a combination of amine and NHC catalysis, for the generation of β-hydroxy esters has been developed by Zhao and Córdova.[37] First the β-epoxyaldehyde is generated *via* iminium activation of the α,β-unsaturated aldehyde, which then undergoes conjugate addition with a nucleophile (Scheme 13, **I**). The *in situ* formed β-epoxyaldehyde **II** is then subjected to NHC catalysis, which catalyzes the ring opening. The acyl azolium **III** is obtained after an internal redox, which forms the ester after a nucleophilic attack by the alcohol.



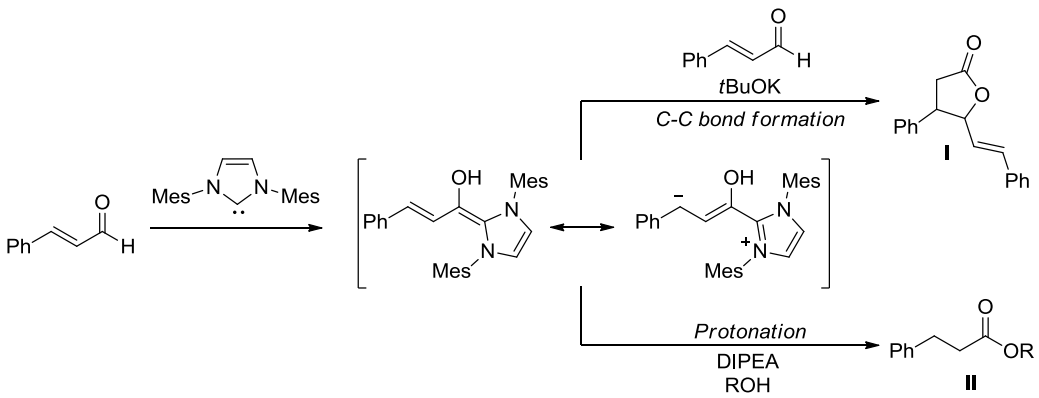
Scheme 13. The combination of amine and NHC catalysis for the generation of β-functionalized esters.

Scheidt and co-workers[38] and Bode and co-workers[39] also used α,β-unsaturated aldehydes to afford saturated esters. The homoenolate **II** (Scheme 14) is protonated at the β-position and through an internal redox the enol **III** is formed. After tautomerization the acyl azolium intermediate **IV** is obtained, which after a nucleophilic attack of the alcohol generates the ester product **V**.



Scheme 14. Formation of acyl azolium *via* protonation of the homoenolate intermediate.

Bode and co-workers observed that the choice of base could play an important part in the protonation of the homoenolate. Using strong bases such as *t*BuOK will promote the formation of C-C bonds and yield, for example, a lactone dimer **I** (Scheme 15). On the other hand, weaker bases, such as *N,N*-diisopropylethylamine (DIPEA), will instead function as a proton shuttle. The homoenolate will be protonated at the β-carbon instead, which will give the saturated ester **II**.

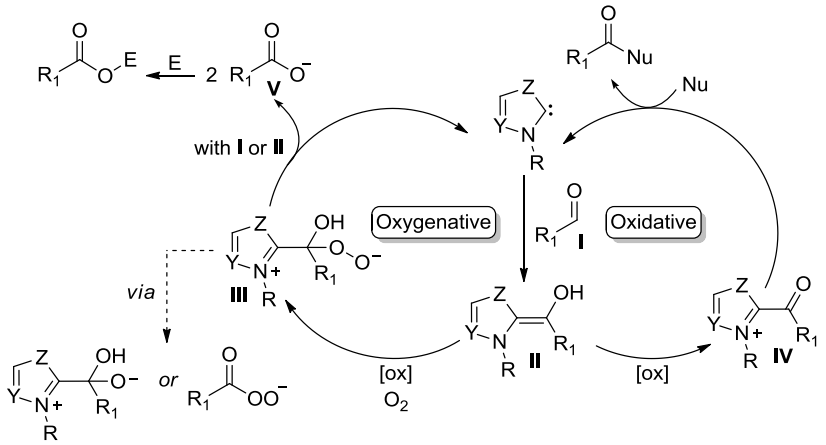


Scheme 15. The role of the base.

2.1.4.2 External Redox

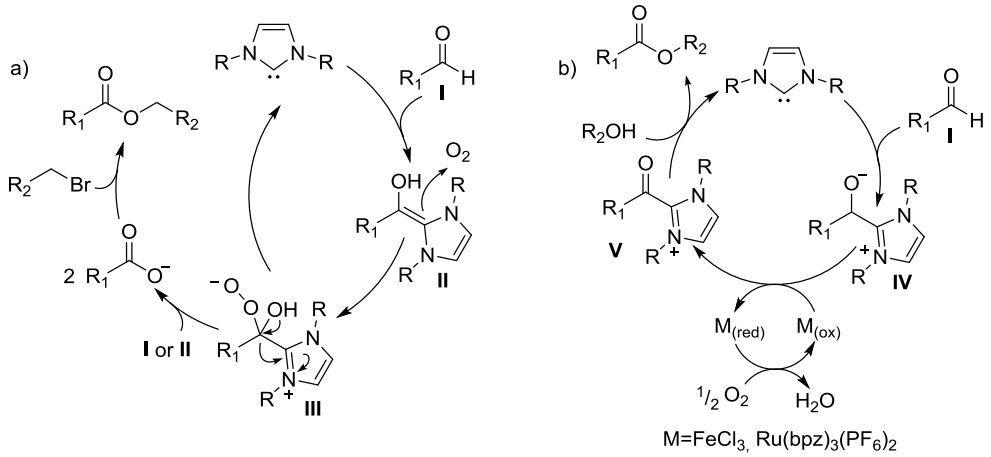
Another method of generating the acyl azolium is by addition of an external oxidant, which opens up the possibility of using other types of starting materials without being restricted to α-reducible aldehydes. Oxidative carbene catalysis can be carried out with both inorganic and organic oxidants. An extremely attractive oxidant would be molecular oxygen (O_2) which is readily available from the air, inexpensive and does not generate any toxic byproducts.

The oxidation pathway can occur *via* two routes. One operates through an oxidative pathway where two electrons are transferred to the oxidant from the substrate, generating the electrophilic acyl azolium intermediate **IV**. The other route goes through an oxygenative pathway that proceeds through a zwitterionic peroxide **III**, formed from O_2, generating a carboxylate **V** that can further react with an electrophile (Scheme 16).[40]



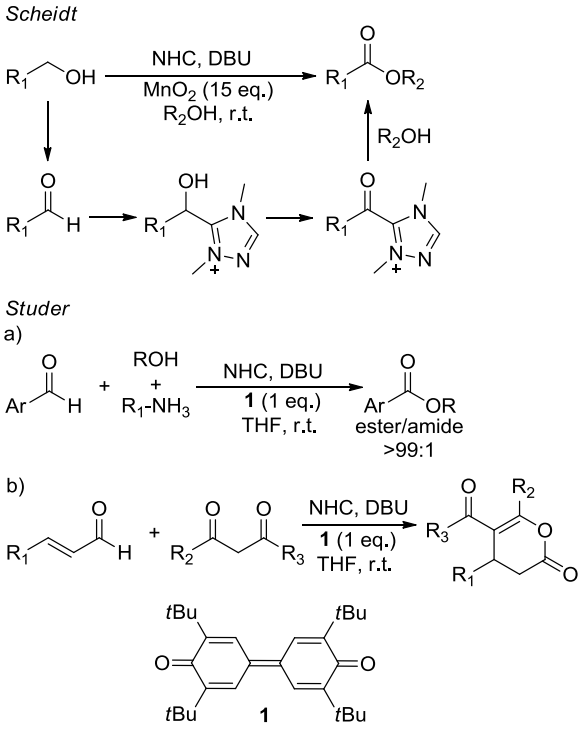
Scheme 16. Oxidative esterification vs. oxygenative esterification.

The direct oxidation using O_2 has, for instance, been noted by the groups of Liu,[41] Hui[42] and Bode[43] forming a carboxylic acid (Scheme 17a). By introducing a catalytic oxidant, Gois[44] and Studer[45] the possibility of using O_2 as the terminal oxidant to form esters (Scheme 17b), however, these protocols suffer from high reaction temperatures, long reaction times or low reactivity. Aerobic oxidation offers an attractive route for green chemistry; however, the use of O_2 as oxidant suffers from high energy barriers for the oxidation of the NHC-aldehyde-adduct.



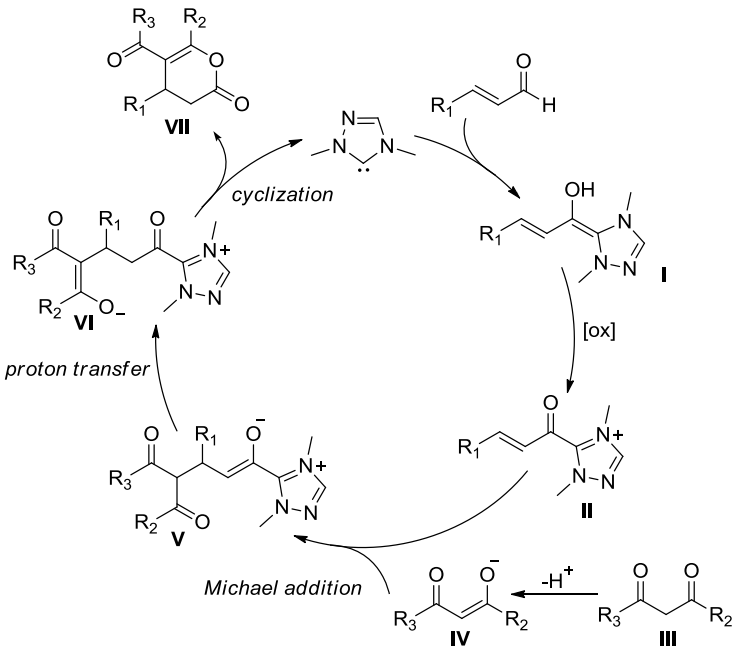
Scheme 17. a) Direct oxidation with O_2. b) Oxidation with a catalytic oxidant and O_2 as terminal oxidant.

Other oxidants that have frequently been employed in oxidative NHC catalysis include MnO_2 and the Kharasch quinone, 3,3',5,5'-tetra-*tert*-butyldiphenoquinone **1** (Scheme 18). Scheidt and co-workers reported the tandem oxidation of alcohols as well as the oxidation of deactivated aldehydes to various esters.[46] The organic Kharasch oxidant is the frequently used oxidant in oxidative NHC catalysis compared to inorganic and other organic oxidants.[47] For example, Studer and co-workers reported the conversion of various aldehydes to the corresponding esters.[48] They also demonstrated that the reaction was chemoselective towards alcohols and selective acylation of alcohols in the presence of amines were achieved (Scheme 18a). The selectivity was attributed to the carbene, which forms hydrogen bonds to the alcohol that increases the nucleophilicity. Furthermore, quinone **1** has been applied to the synthesis of functionalized dihydropyranones *via* catalytically generated α,β-unsaturated acyl azoliums and 1,3-dicarbonyls (Scheme 18b).[49]



Scheme 18. Examples of external oxidants used.

One proposed catalytic cycle for the formation of the dihydropyranones starts with the nucleophilic addition of the NHC catalyst to the α,β-unsaturated aldehyde forming the Breslow intermediate **I** (Scheme 19). The Breslow intermediate is then oxidized by the Kharasch oxidant **1** leading to the acyl azolium intermediate **II**. The acyl azolium intermediate undergoes a Michael addition with the deprotonated 1,3-dicarbonyl compound **IV** affording the intermediate **V**, which forms **VI** after a proton transfer. Finally, cyclization leads to the dihydropyranone **VII** and regenerates the carbene.



Scheme 19. Proposed catalytic cycle for the formation of dihydropyranones.

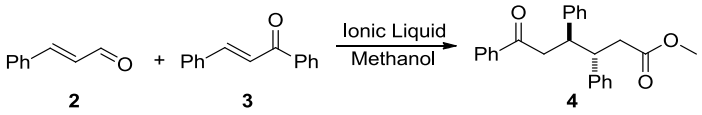
The oxidants used in oxidative carbene catalysis are usually added in stoichiometric quantities, which leads to poor atom economy. An excess of 15 equivalents (eq.) of the inorganic oxidant, MnO_2, is required for the oxidation step. The Kharasch oxidant has a high molecular weight therefore, the use of stoichiometric amounts leads to an increase in chemical waste. This results in a high E-factor and increased costs for the separation of byproducts which are problematic for large scale reactions. Replacing these traditionally used oxidants with lower molecular weight, more efficient oxidants are therefore highly desirable.

3. Ionic Liquid Mediated Generation of Functionalized Ketoesters (Paper I, II, III)

3.1 Ionic Liquids as Precatalysts (Paper I)

3.1.1 Introduction

Despite being a relatively inexpensive and easy way of generating catalytically active carbenes, the utilization of IL as NHC precursors has not been thoroughly explored. This would therefore be an attractive way of accessing NHCs to explore the possibilities of NHC-catalyzed reactions. Within the field of NHC catalysis, previous reports of reactions involving α,β-unsaturated aldehydes and chalcones in combination with different types of NHC catalysts exist from the research groups of Bode,[32c] Chi,[50] Nair,[32a, 32b] and Scheidt[51] yielding annulation products. In combination with an alcohol these reactions are reported to give acyclic products albeit with rather low yields.[32b, 32c, 52] A more selective method to generate these highly functionalized products would therefore be desirable. Pursuant to our interest in this area to improve the before mentioned reaction, our investigations led to the discovery that 1-ethyl-3-methylimidazolium acetate (EMIMAc) could be used as a precatalyst for a three-component synthesis of 1,6-ketoesters or oxo triphenylhexanoates **4** (OTHOs) (Scheme 20).



Scheme 20. Formation of OTHOs using IL as a precatalyst.

3.1.2 Ionic Liquid as Precatalyst in the synthesis of OTHOs

Our preliminary attempts to synthesize ketoester **4** using only EMIMAc as solvent gave **4** in only moderate yields. This was because **4** turned out to be insoluble in IL, which affected the homogeneity of the reaction. A solvent screening for possible co-solvents capable of dissolving EMIMAc, showed that dichloromethane was the most promising solvent, as it could also dissolve **4**. Other interesting solvents included acetonitrile and methanol, which in comparison to dichloromethane, are more environmentally friendly solvents.[53] However, these two solvents were unfortunately unable to dissolve **4** (Table 1, entry 1, 2, and 5).

Further studies have shown that the number of equivalents of methanol required also proved to be important. For optimal results, 10 equivalents were required. With fewer equivalents of methanol resulted in longer reaction times, whereas more than 10 equivalents gave lower yields (Table 1, entry 2, 7 and 8). The base 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), was found to be the optimal choice; stronger inorganic bases such as *t*BuOK and Cs_2CO_3 resulted in a faster reaction, however, it was accompanied by an as yet unidentified side reaction, which consumed the limiting reagent (the chalcone)(Table 1, entry 9 and 10). With weaker organic bases such as TEA and DIPEA, the reaction was slowed down and only trace amounts of **4** were isolated (Table 1, entry 11 and 12). Attempts to reduce the amount of cinnamaldehyde resulted in lower yields (Table 1, entry 3 and 4). Substoichiometric quantities of EMIMAc increased the reaction times significantly (Table 1, entry 6). Further attempts to screen other types of ILs as precatalysts,

such as 1-ethyl-3-methylimidazolium chloride (EMIMCl) and 1-butyl-3-methylimidazolium chloride (BMIMCl) (Table 1, entry 13 and 14) also resulted in lower yields compared with when EMIMAc was used, which indicate that the anion could have an effect on the reactivity.[35b, 54]

Table 1. Screening of reaction conditions[a]

Entry	Solvent	Base (0.5 eq.)	Precatalyst	MeOH (eq.)	*t* (h)	Yield (%)
1.	acetonitrile	DBU	EMIMAc	10	3	60
2.	methanol	DBU	EMIMAc	—	21	32
3.	dichloromethane	DBU	EMIMAc	10	5	72[b]
4.	dichloromethane	DBU	EMIMAc	10	5	82[c]
5.	dichloromethane	DBU	EMIMAc	10	3	92 (86[d])
6.	dichloromethane	DBU	EMIMAc	10	16	9[e]
7.	dichloromethane	DBU	EMIMAc	1	26	27
8.	dichloromethane	DBU	EMIMAc	15	4	59
9.	dichloromethane	*t*BuOK	EMIMAc	10	1.5	65
10.	dichloromethane	Cs_2CO_3	EMIMAc	10	1.5	72
11.	dichloromethane	TEA	EMIMAc	10	24	4
12.	dichloromethane	DIPEA	EMIMAc	10	48	5
13.	dichloromethane	DBU	EMIMCl	10	3	72
14.	dichloromethane	DBU	BMIMCl	10	3	62

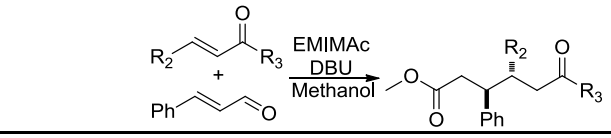
[a] Unless otherwise stated the reactions are performed with chalcone (0.25 mmol, 1 eq.), cinnamaldehyde (3 eq.), precatalyst (2.5 eq.), base (0.5 eq.), MeOH (see table), solvent (3 mL) at room temperature.[b] with cinnamaldehyde (1 eq.), [c] with cinnamaldehyde (2 eq.), [d] gram-scale synthesis, [e] with EMIMAc (0.25 eq.)

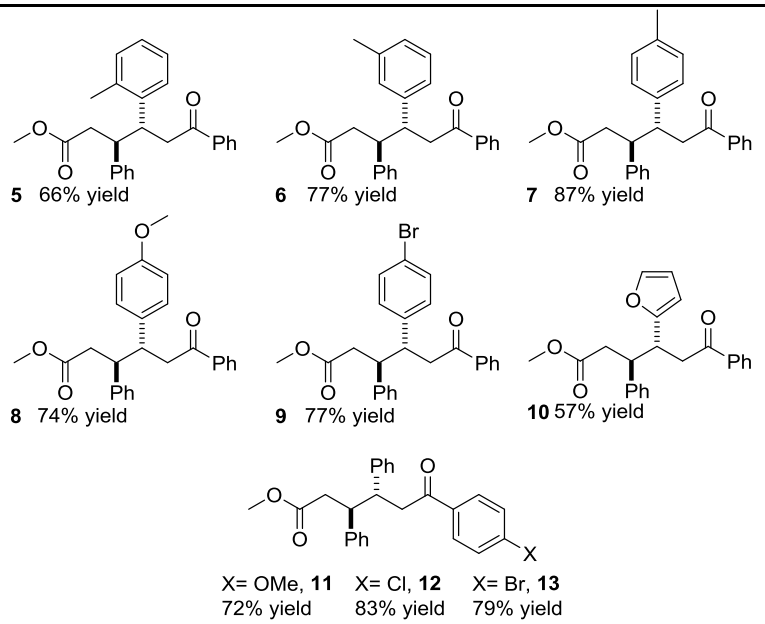
To investigate the formation of the OTHOs, a variety of substituted chalcones (Table 2), α,β-unsaturated aldehydes and alcohols were used. In all cases highly stereoselective reactions were observed. Aromatic chalcones with electron-donating groups (Table 2, compound **5**–**8**) as well as electron-withdrawing groups (Table 2, compound **9**, **12** and **13**) were well tolerated on both chalcone aromatic rings. It was also possible to incorporate a heteroaromatic substituent in the OTHOs (Table 2, compound **10**).

Using *p*-chlorocinnamaldehyde the OTHO (Table 3, compound **14**) was formed relatively faster than with electron-donating groups on the α,β-unsaturated aldehyde (Table 3, compound **15** and **16**). The *p*-methoxy substituted OTHO **15**, required longer reaction time compared with the others. This electronic effect has previously been described in Cope rearrangements.[55]

When investigating the alcohol nucleophile, ethanol and benzyl alcohol, resulted in the corresponding esters in 53% and 68% yields respectively (Table 3, compound **17** and **18**). A screening of other compatible nucleophiles showed that the reaction was chemoselective; only primary alcohols gave the desired product, secondary and tertiary alcohols did not participate in the reaction. One explanation could be that the secondary and tertiary alcohols are too sterically hindered to access the active reaction site.

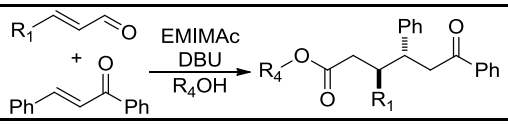
Table 2. Scope of chalcones[a][b]

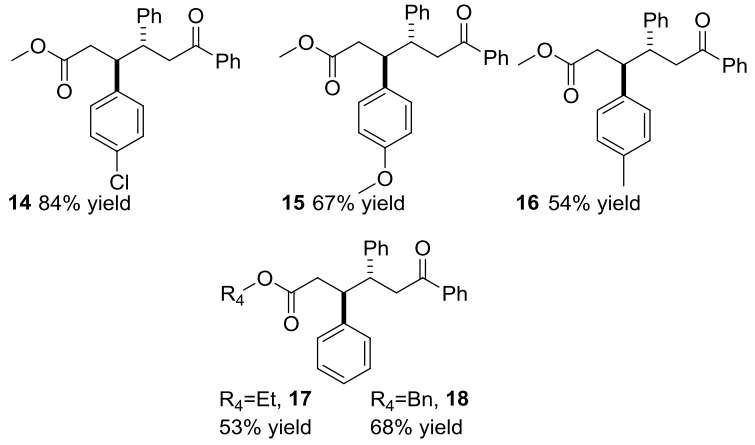




[a] Unless otherwise stated the reactions are performed with chalcone (0.25 mmol, 1 eq.), aldehyde (3 eq.), EMIMAc (2.5 eq.), DBU (0.5 eq.), methanol (10 eq.), dichloromethane (3 mL) at room temperature. [b] Yields refer to isolated yields after purification.

Table 3. Scope of the α,β-unsaturated aldehyde and alcohol.[a][b]





[a] Unless otherwise stated the reactions are performed with chalcone (0.25 mmol, 1 eq.), aldehyde (3 eq.), EMIMAc (2.5 eq.), DBU (0.5 eq.), methanol (10 eq.), dichloromethane (3 mL) at room temperature. [b] Yields refer to isolated yields after purification.

The assembly of OTHOs was found to be highly stereoselective, resulting in only the *anti*-1,6-ketoester with a d.r. (>20:1). The stereochemistry was confirmed by X-ray crystallography (Figure 4).

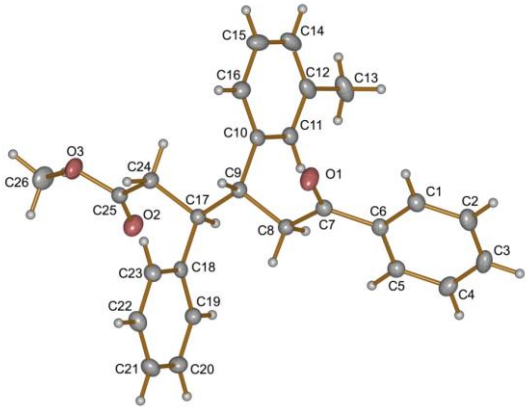


Figure 4. ORTEP drawing of the *anti*-configuration of the vicinal diphenyl-groups.

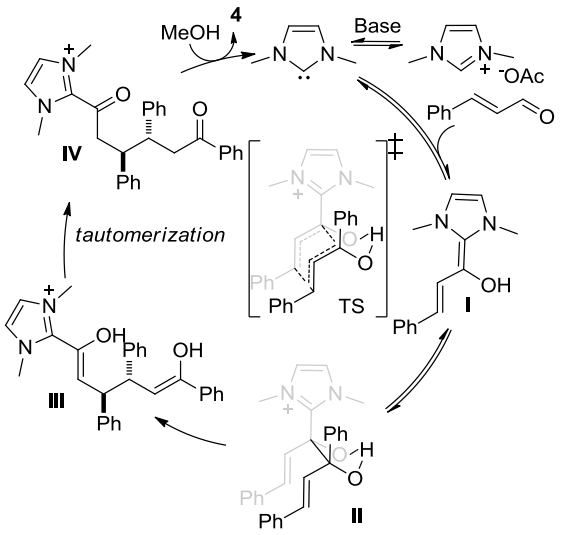
Since ILs are known for their recyclability, it was interesting from a green chemistry point of view, to see whether or not the catalyst could be recovered and reused. Initially the IL was extracted from the reaction mixture using water and then washed with dichloromethane to remove the organic compounds. The water was removed under reduced pressure and the recovered IL was used for subsequent reactions. However, a decrease in reactivity for the catalyst was observed for the subsequent reactions. A different protocol for the catalyst's recycling therefore developed. First the volatiles were removed under reduced pressure after the reaction had reached completion. The resulting solid was then washed with methanol, and filtered off, yielding the pure OTHO. The IL could be recovered from the methanol phase by evaporation under reduced pressure. The recovered IL could be reused up to five consecutive experiments with no loss in selectivity and reactivity (Table 4). Additionally, with this facile work-up protocol the reaction could be performed on a larger scale and 1.1 gram (86% yield) of compound **4** was successfully synthesized and isolated (Table 1, entry **5**).

Table 4. Recycling of the IL[a]

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

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

The following mechanism was proposed for the formation of the OTHOs (Scheme 21): A 1,2-nucleophilic addition of NHC to the α,β-unsaturated aldehyde will form the Breslow intermediate **I**, which reacts with the chalcone reversibly in a cross-benzoin reaction forming diene **II**. Intermediate **II** then undergoes an oxy-Cope rearrangement *via* a boat-transition state (TS), which sets the *anti*-oriented stereogenic center (**III**). After tautomerization nucleophilic substitution of the acyl azolium **IV** with methanol forms the desired compound OTHO and the catalysts is regenerated.



Scheme 21. Proposed catalytic cycle for the formation of OTHOs

3.1.3 Summary

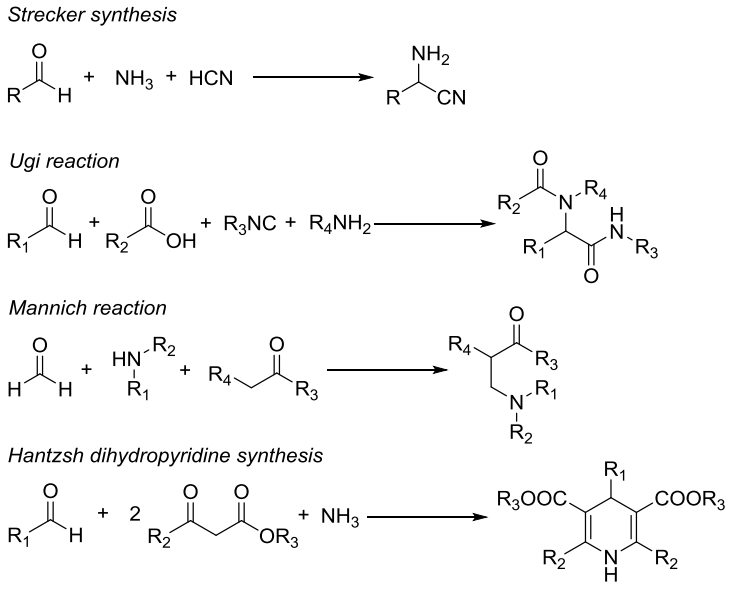
With the help of a commercially available and inexpensive IL as NHC-precatalyst, a highly stereoselective addition of α,β-aldehyde to chalcones was achieved. The reaction is an easy access to OTHOs with high yields and excellent diastereoselectivity. Both electron-withdrawing and electron-donating substituents were introduced on the backbone, with no reactivity loss. The synthesized OTHOs include a rare *anti*-oriented vicinal diphenyl moiety, which are difficult to obtain by other approaches. As a green chemistry approach, the OTHOs can be easily isolated from the reaction mixture, which allows gram-scale synthesis, no need for solvent-demanding chromatography purification and recycling and reusability of the IL-catalyst.

3.2 One-Pot Four-Component Synthesis of OTHOs (Paper II)

3.2.1 Introduction

Designing synthesis with the *Twelve Principles of Green Chemistry* in mind ideally implies to have a high atom economy and a low E-factor using environmentally benign starting materials with a few steps as possible. The number of steps in a synthesis will eventually determine the practicability and labor force required for the reaction, as well as the amount of waste and side and byproducts generated. Reducing the amount of synthetic steps help to eliminate time consuming and waste generating factors.[56] The major source of chemical waste produced by the chemical industry is solvents. A multi-component reaction (MCR) strategy is one way of minimizing the amount of waste generated. An MCR is a convergent synthesis with three or more starting materials that reacts to form product in a one pot strategy. There are several benefits of using a convergent MCR in contrast to a sequential synthesis. Firstly, since MCRs do not require the isolation of intermediates, time-consuming and lengthy separation processes can be avoided, such as solvent-demanding chromatography purification, hence saving both time and resources. Secondly, with careful selection of reaction conditions, it allows for the generation of complex structures by formation of several bonds in one pot procedure with less effort. An MCR is less laborious with less waste formed per bond-forming step. The MCR approach can yield a wide variety of products, thus often applied in combinatorial synthesis.

Synthesis featuring MCRs have been used since the early times of chemistry. For instance, the Strecker synthesis of α-aminonitriles for the synthesis of amino acids was documented in 1850.[57] One of the most famous MCR is probably the Ugi reaction – a four-component reaction combining a ketone or aldehyde with an amine, an isocyanide and a carboxylic acid to form a bis-amide.[58] Other famous examples of MCRs are the Mannich reaction[59] and the Hantzsch dihydropyridine synthesis of heterocycles[60] (Scheme 22).

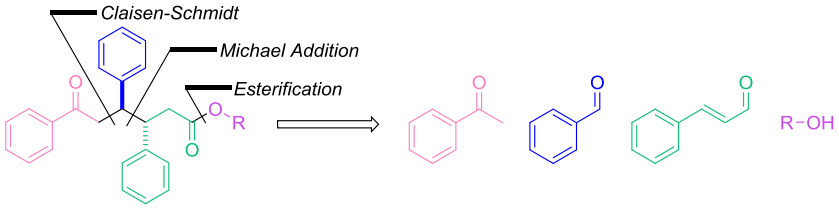


Scheme 22. Examples of some MCR.

In our continuous efforts to extend the possibilities of using ILs as NHC precatalysts to form OTHOs, assembling OTHOs via an MCR appeared as a promising approach.

3.2.2 Multi-Component Reaction for Assembly of OTHOs

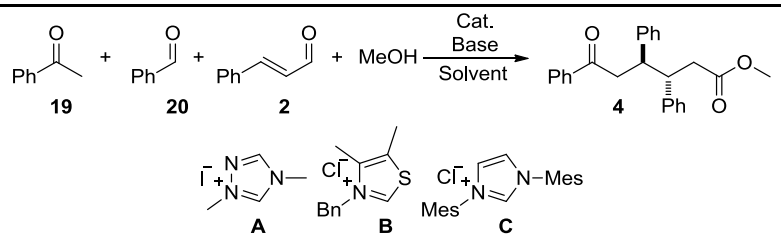
It was imagined that the OTHOs could be assembled from simple, inexpensive and commercially available acetophenones, benzaldehydes, unsaturated aldehydes and alcohols (Scheme 23). The MCR strategy could lead to some possible undesired side reactions such as benzoin condensation, and cross-reactions between aldehydes. An additional potential problem is the build-up of water in the reaction mixture. By sequencing the reagents in the right order it was anticipated that such issues could be circumvented.



Scheme 23. Retrosynthesis of OTHOs.

A base screening became the starting point of our investigations since the base serves two purposes; catalyst for the formation of the chalcone *via* a Claisen-Schmidt condensation and then used for deprotonation of the IL precatalyst to form the active carbene (Scheme 24). With strong bases such as *t*BuOK and NaOMe, quantitative formation of chalcone was observed (seen on ^{1}H NMR using an internal standard), however, for the sequential formation of OTHOs these bases only gave **4** in low yields (Table 5, entry 1 and 2). With DBU, no chalcone formation was observed (Table 5, entry 5). Both Cs_2CO_3 and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) showed promising results (Table 5, entry 3 and 4) giving product **4** in moderate yields. However, formation of the chalcone required long reaction times (up to 72 h). To decrease the reaction times, the amount of solvent used for the formation of chalcone was reduced. Full conversion was achieved within 5 h by only using the alcohol component for the MCR (methanol in this case) as solvent. With these conditions, TBD appeared to be the best base (Table 5, entry 6). The solvent screening showed that both acetonitrile and dichloromethane gave similar results; however, since acetonitrile is considered more environmentally friendly,[53] the rest of the experiments were performed in acetonitrile (Table 5, entry 6 and 7). Investigation on the NHC precatalyst showed that both BMIMCl and EMIMCl were capable of giving good yields (Table 5, entry 10 and 11). Interestingly, with the most commonly used non-IL precatalysts no product formation has been observed (Table 5, entry 12–14).

Table 5. Screening of reaction conditions.[a]

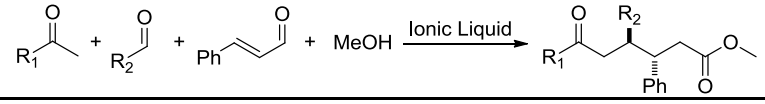


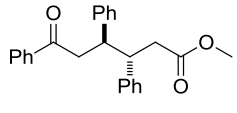
Entry	Solvent	Base	Precatalyst	Yield (%)[b]
1.	acetonitrile	NaOMe	EMIMAc	35
2.	acetonitrile	*t*BuOK	EMIMAc	38
3.	acetonitrile	Cs_2CO_3	EMIMAc	45
4.	acetonitrile	TBD	EMIMAc	54
5.	acetonitrile	DBU	EMIMAc	0
6. [c]	acetonitrile	TBD	EMIMAc	66
7. [c]	dichloromethane	TBD	EMIMAc	65
8. [c]	1,4-dioxane	TBD	EMIMAc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

[a] Unless otherwise stated the reactions are performed with acetophenone (0.25 mmol), benzaldehyde (1.1 eq.), base (0.5 eq.), methanol (10 eq.), cinnamaldehyde (3 eq.), precatalyst (2.5 eq.), solvent (3 mL) at room temperature. [b] Yields determined by ^{1}H NMR against an internal standard (1,2,4,5-tetramethylbenzene), [c] With reduced amount of solvent for the chalcone formation.

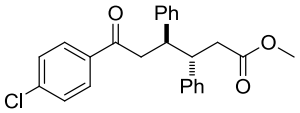
The scope of the reaction was also investigated with respect to the four different components (acetophenone, benzaldehyde, α,β-unsaturated aldehyde and alcohol) (Table 6 and Table 7). Differently substituted acetophenones with both electron-withdrawing and electron-donating groups were well tolerated. For example, the di-methoxy substituted ketoester **22** resulted in good yields. Halogen-functionalities, which could be used as a synthetic handle for potential cross-coupling reactions were obtained in high yields (compound **12** and **13**). Other functionalities, such as 1-(thiophen-2-yl)ethan-1-one yielded the corresponding ketoester **21** in 83% yield. (Table 6) Modifications by both electron-rich and electron-deficient benzaldehydes were successful giving compounds **5–10** and **24–26**. Incorporation of heteroaromatic components was also possible (Table 6, compound **10**) as well as replacing benzaldehyde with cinnamaldehyde (**26**), thereby introducing a double bond functionality in the OTHO scaffold. Both electron-withdrawing and electron-donating substituents on the α,β-unsaturated aldehydes gave good results (Table 7 compound **14–16** and **27**). Variation of the alcohol component was also possible; ethanol and benzyl alcohol delivered the products **17** and **18** in 73% and 59% yield respectively. The MCR approach was especially advantageous for the synthesis of **10**, **24**, and **26**. The chalcones need to be purified by column chromatography, hence the one-pot MCR procedure could omit the isolation of the chalcone, thus avoiding time-consuming and waste-generating workup.

Table 6. Scope of acetophenones and benzaldehydes.

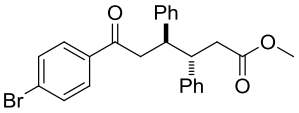




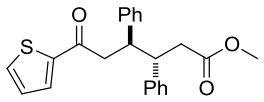
4 87% yield



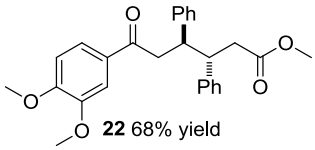
12 73% yield



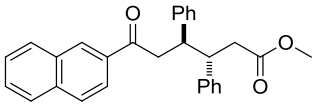
13 78% yield



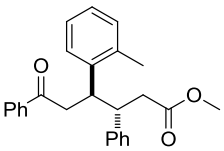
21 83% yield



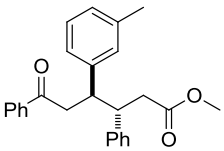
22 68% yield



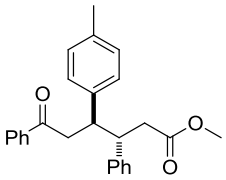
23 65% yield



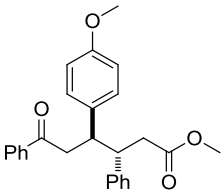
5 76% yield



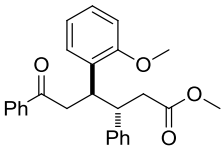
6 66% yield



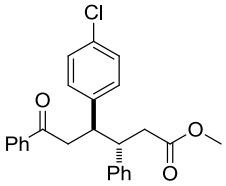
7 78% yield



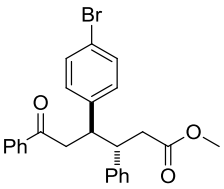
8 75% yield



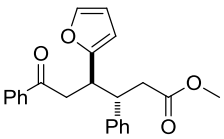
24 70% yield



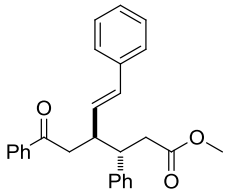
25 88% yield



9 73% yield



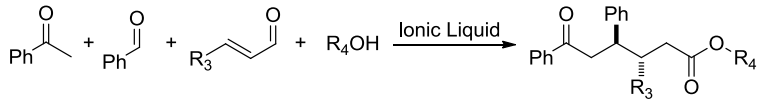
10 52% yield

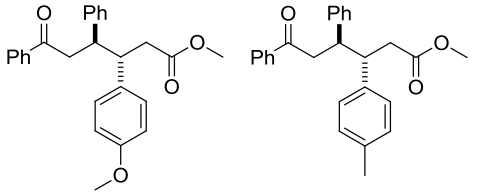


26 55% yield

[a] Unless otherwise stated the reactions are performed with acetophenone (0.25 mmol), benzaldehyde (1.1 eq.), TBD (0.5 eq.), methanol (10 eq.), cinnamaldehyde (3 eq.), EMIMAc (2.5 eq.), solvent (3 mL) at room temperature. [b] Yields referred to isolated yields

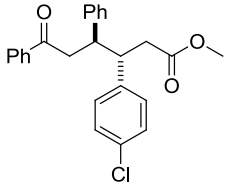
Table 7. Scope of α,β-unsaturated aldehydes and alcohols.



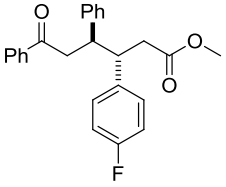


15 71% yield

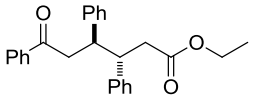
16 83% yield



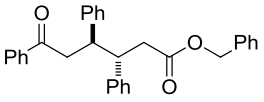
14 61% yield



27 72% yield



17 73% yield



18 59% yield

[a] Unless otherwise stated the reactions are performed with acetophenone (0.25 mmol), benzaldehyde (1.1 eq.), TBD (0.5 eq.), methanol (10 eq.), cinnamaldehyde (3 eq.), EMIMAc (2.5 eq.), solvent (3 mL) at room temperature. [b] Yields referred to isolated yields

To further improve the sustainability of the MCR approach, efforts directed towards IL catalyst recycling were made. After completion of the reaction, volatiles were removed under reduced pressure. The resulting solid was then subjected to a methanol-water (3:1) mixture which caused the OTHOs to precipitate out as a white solid which could be filtered off. The IL could then be recovered from the filtrate after evaporation of the solvents. However, this initial workup method showed deactivation of the IL catalyst after two runs (Figure 5). A long period of time and higher temperature were required to be able to remove all the solvents, especially water, which was suspected to be negative for the activity of the catalysts. By removing water from the workup procedure, the reaction could be run up to five times with the recovered IL (Figure 5). Experiments to investigate the inactivation of the IL were performed. Mixtures of EMIMAc/water, EMIMAc/water/TBD and pure EMIMAc were subjected to the same temperature and time as for solvent evaporation of the reaction mixture. However, no degradation or deactivation could be observed. Hence, other deactivation routes must be taking place. Analysis of the deactivated EMIMAc-mixture by ^{1}H and ^{13}C NMR showed the presence of several imidazolium species. As imidazolium-based ILs have been shown to degrade *via* a number of different pathways, such as dealkylation, hydrolysis or rearrangements some unidentified IL deactivation reactions probably caused the loss of reactivity.[61]

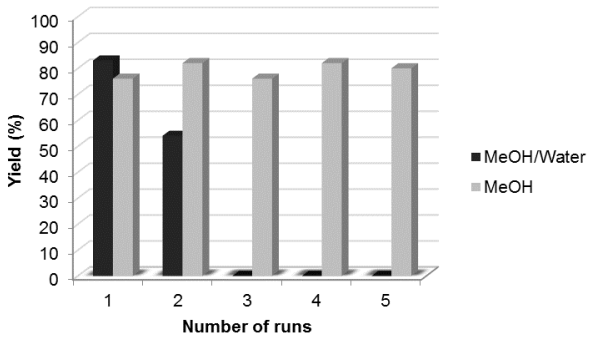
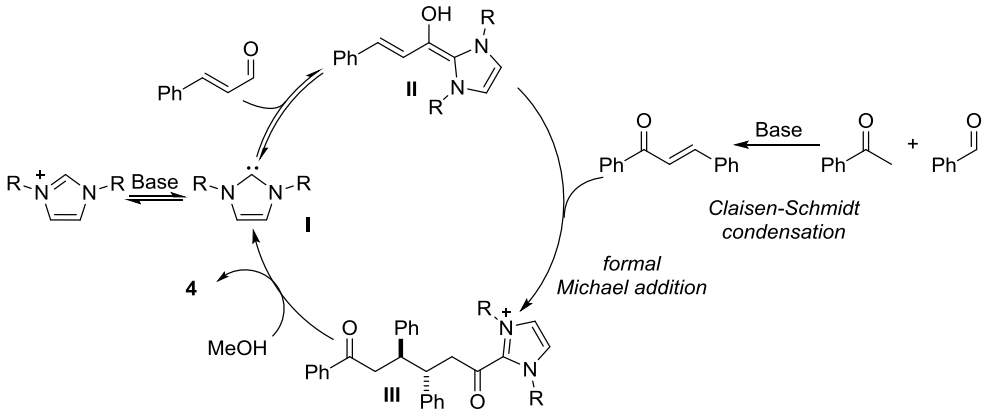


Figure 5. Recycling of the EMIMAc.

The proposed mechanistic cycle for the formation of the OTHOs *via* a four-component reaction is the following: The deprotonated EMIMAc gives the active carbene species **I** that reversibly adds to cinnamaldehyde forming the Breslow intermediate **II** (Scheme 24). The Breslow intermediate **II** undergoes a formal Michael addition with the previously *in situ* formed chalcone, *via* a base-catalyzed Claisen-Schmidt condensation between acetophenone and benzaldehyde, leading to the acyl azolium intermediate **III**. Finally, after a nucleophilic substitution with methanol on intermediate **III**, leads to the formation of product **4** and regeneration of the NHC.



Scheme 24. Proposed catalytic cycle for the MCR of OTHOs.

3.2.3 Summary

The use of IL as a NHC-precursor for the assembly of OTHOs *via* a one pot four-component reaction has been disclosed. By careful selection of reaction conditions and through the sequential addition of starting materials the OTHOs were generated in excellent yields per bond-forming steps (up to >95%). The synthesis of OTHOs also contributes to the green chemistry aspect in many ways. The MCR strategy avoids the need to isolate the chalcone, thereby saving both time and resources. We have shown that it was possible to substitute dichloromethane with acetonitrile which had been the previous solvent of choice. Furthermore, the OHTOs can be isolated by filtration, thus preventing the use of chromatography purification. The IL-catalyst can be recovered for additional reuse. This method allows the access to a platform for the synthesis of a large library of functionalized OTHOs.

3.3 Regioselective Acylation of Carbohydrates with IL-precatalysts (Paper III)

3.3.1 Introduction

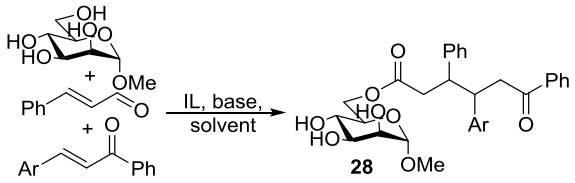
Carbohydrates and sugar alcohols are an important class of polyhydroxyl-containing compounds that are biologically relevant raw materials easily accessible from biomass. The simpler carbohydrates (e.g. mono- and oligosaccharides) are common motifs in drug discovery,[62] while more complex carbohydrates (e.g. cellulose and other polysaccharides) are important for the development of new materials.[63] However, regioselective modifications of these complex structures are often difficult as they contain several hydroxyl-groups with similar reactivity. Strategies for selective manipulation of carbohydrates often involve laborious protecting group strategies.[64] Recently, the regioselective functionalization of polyols using catalysis have been reported,[65] using, for example, Lewis acid catalysis[66] or organocatalysis[67]. The combination of NHC and polyols are limited in the literature, especially for unprotected carbohydrates.[68]. More recently Studer reported the regioselective acylation of methyl glucosides using oxidative NHC catalysis.[69]

In previous work we had observed a preference of primary alcohols over secondary alcohols in the IL-mediated synthesis of OTHOs. This became an intriguing possibility for testing whether or not carbohydrates could be directly modified without the use of protecting groups. Moreover, since ILs have been known to be able to dissolve carbohydrates we also envisioned that the use of ILs could have a dual purpose of both dissolving the carbohydrates and acting as precatalysts for the assembly of the OTHOs.

3.3.2 Combining the Dissolving and Catalytic Efficiency of ILs

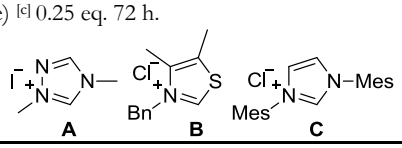
In the initial screening for reaction conditions, methyl α-D-mannopyranoside was subjected to IL, chalcone and cinnamaldehyde. The use of a methylated anomeric hydroxyl group will prevent the isomerization of the carbohydrate to the β-form. The reaction proceeded with total selectivity for the primary hydroxyl with a yield of 72% (Table 8, entry 1). No reaction was observed on the secondary hydroxyls and a 1:1 dr of the two *anti*-diastereomers was obtained. Screening of solvents showed that the reaction could be run in 2-propanol, which shows the excellent selectivity of the reaction towards primary alcohols (Table 8, entry 9). The IL-based precatalysts promoted the formation of **28** (Table 8, entry 1–3) whereas the non-IL-based precatalysts failed to give any product at all (Table 8, entry 4–6). The explanation can be attributed to the ability of ILs to dissolve carbohydrates, thus enabling a homogeneous phase reaction. The best reaction efficiency was obtained with EMIMAc-loadings of 2.5 eq. Reducing the amount of EMIMAc (Table 8, entry 7) resulted in a lower yield even after a prolonged reaction time. The base DBU appeared to be more suitable than *t*BuOK or TEA (Table 8, entry 1, 7–9). Using acetonitrile as solvent, **28** could be obtained in 83% yield (Table 8, entry 11) and acetonitrile was chosen as the optimal solvent for the reaction.

Table 8. Screening of reaction conditions.[a]



Entry	Solvent	Base	NHC-precatalyst	Yield (%)[b]
1.	dichloromethane	DBU	EMIMAc	72
2.	dichloromethane	DBU	EMIMCl	45
3.	dichloromethane	DBU	BMIMCl	56
4.	dichloromethane	DBU	**A**	0
5.	dichloromethane	DBU	**B**	0
6.	dichloromethane	DBU	**C**	0
7.	dichloromethane	DBU	EMIMAc[c]	20
8.	dichloromethane	*t*BuOK	EMIMAc	52
9.	Dichloromethane	TEA	EMIMAc	0
10.	dichloromethane	Na_2CO_3	EMIMAc	0
11.	acetonitrile	DBU	EMIMAc	83
12.	2-propanol	DBU	EMIMAc	54

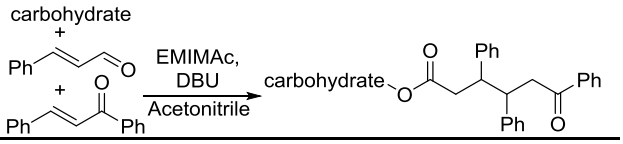
[a] Unless otherwise stated the reactions are performed with chalcone (1 eq. 0.08 M), base (0.5 eq.), cinnamaldehyde (3 eq.), methyl α-D-mannopyranoside (3 eq.), NHC-precatalyst (2.5 eq.), solvent, 24 h at room temperature. [b] Yield (d.r. *anti*-products, 1:1) determined against internal standard (1,2,4,5-tetramethylbenzene) [c] 0.25 eq. 72 h.

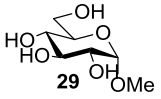
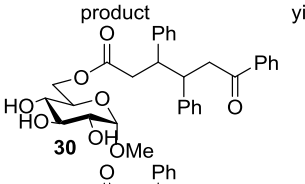
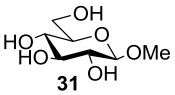
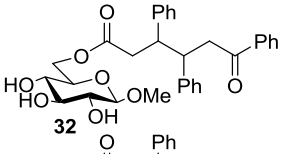
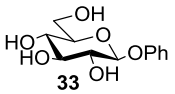
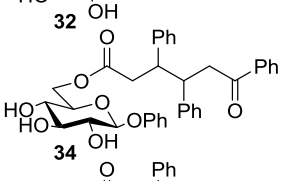
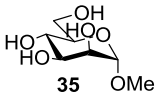
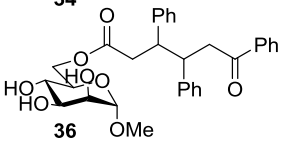
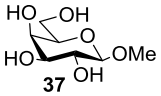
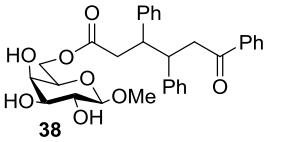


The scope of the reaction was then investigated. A wide range of hexopyranosides was studied (Table 9) and for all cases a total regioselectivity towards the primary hydroxyl was observed.

Hexopyranosides with both α- and β-anomers and phenyl-substituent at the anomeric position were well tolerated and did not affect the selectivity or yield (Table 9, compound **30**, **32** and **34**). Reactions with methyl α-D-mannopyranoside **35** and methyl β-D-galactopyranoside **37** were also successful delivering **36** and **38**. Having shown that the carbohydrate unit could be altered without affecting the selectivity or the yield, the scope of the OTHO-backbone was investigated with different chalcones and α,β-unsaturated aldehydes(Table 10).

Table 9. Scope of the carbohydrates.[a][b]

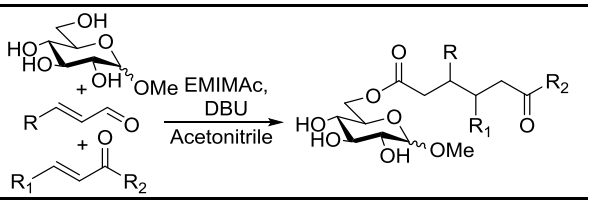


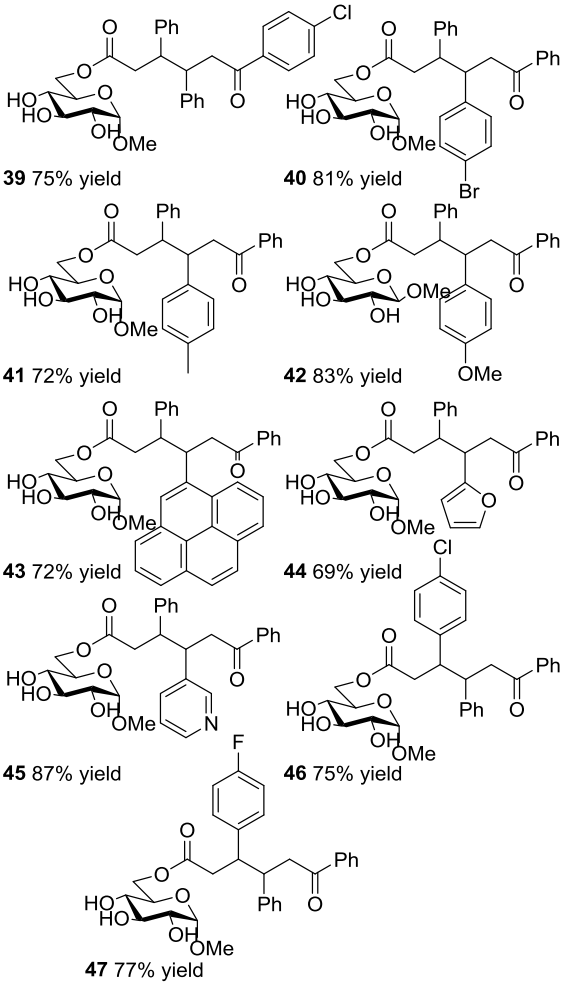
carbohydrate	product	yield %[b]
 **29**	 **30**	79 93[c]
 **31**	 **32**	73
 **33**	 **34**	72[d]
 **35**	 **36**	81
 **37**	 **38**	74

[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 dichloromethane as solvent.

Both electron-withdrawing and electron-donating substituents on the aromatic rings of the chalcones could successfully be incorporated (Table 10). Substituents such as chloro- (**39**, 75% yield), bromo (**40**, 81% yield) and methyl-substituents (**41**, 72% yield) are well tolerated. Heteroaromatic substituents were also successfully incorporated to form compounds **44** and **45** in 69% and 87% yield, respectively.

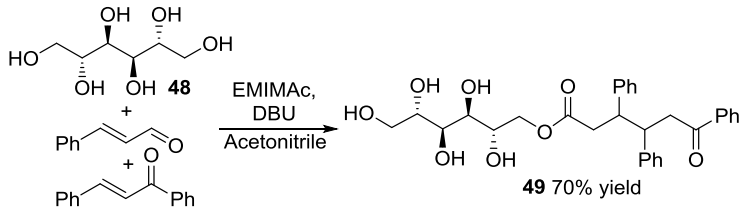
Table 10. Scope of the α,β-unsaturated aldehydes and chalcones.[a][b]





[a] Unless otherwise stated the reactions are performed with chalcone (1 eq. 0.08 M), DBU (0.5 eq.), α,β-unsaturated aldehyde (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.

As the reaction displayed a high regioselective preference for primary alcohols over secondary alcohols with hexopyranosides, it was also interesting to investigate acyclic sugar alcohols, such as mannitol **48** (Scheme 25). Mannitol is a biologically relevant sugar alcohol that is used as a drug.[70] The reaction proceeded with 70% yield with 1:1 d.r. and only the primary alcohol was observed to be acylated.



Scheme 25. Functionalization of mannitol with NHC catalysis.

All the functionalized carbohydrate-derivatives were isolated by extraction followed by a filtration of the precipitated product, enabling recycling of the IL. The recycling of ILs showed that **30** could be afforded in 77%, 79% and 72% yields in three consecutive runs using the recycled IL. The reaction can also be scaled-up to gram-scale, 1.5 g (93% yields) of **30** were isolated demonstrating the scalability of these reactions.

3.3.3 Summary

We have shown that NHC catalysis can be used to form highly regioselective mono-functionalized carbohydrates. The reaction is performed at room temperature, under non-inert atmosphere, using standard laboratory equipment showing the robustness of the protocol. The desired products can be isolated in a 1:1 d.r. of the two *anti*-products in high to excellent yields, with observed regioselectivity on the primary alcohol. Notably, the hexopyranosides can directly be modified without the use for protecting groups. The synthesis of modified carbohydrates fulfills the principles of green chemistry enabling recycling of the IL, avoiding chromatography purification techniques, as well as reducing the number of reaction steps by preventing the use of protecting groups. The key component for the reaction success was using ILs, non-IL-based NHC precatalysts indeed showed no formation of the product, demonstrating the IL's solvating and catalytic properties.

4. Aerobic Oxidative Carbene Catalysis *via* Redox Reaction (Paper IV)

4.1 Introduction

Selective function oxidation of organic molecules is an important transformation in organic chemistry. However, oxidation reactions often suffer from high loadings of oxidants as well as from the toxicity of oxidation reagents (such as chromium- or osmium-based reagents). Most oxidation reactions do not fulfill the principles of green chemistry due to the generation of chemical waste and toxic byproducts. The development of alternative ways for milder and safer oxidations is therefore highly desirable. During recent years oxidative NHC catalysis has become more attractive, allowing the formation of α,β-unsaturated acyl azoliums from the homoenolate intermediate *via* oxidation. The acyl azolium intermediate has been used in different reactions such as oxidative esterifications,[48, 71] annulations reactions[49] and cyclo-additions.[72] For the oxidation of the homoenolate to the acyl azolium intermediate several of these reactions rely on the addition of a high molecular weight oxidant (**1**) (Figure 6) in stoichiometric amounts, which is problematic in terms of green chemistry.

A more ideal and atom efficient oxidant would be to use molecular oxygen (O_2), available from air, which is non-toxic, inexpensive and only form water as a byproduct. Direct oxidations using O_2 have been demonstrated yielding carboxylic acids.[41-43] In combination with an added catalytic oxidant and O_2 as the terminal oxidant, esters have been generated.[44-45] However, these reactions often have high reaction temperatures, long reaction times or low reactivity, which limits the use of aerobic oxidations using O_2. Catalytic oxidation using O_2 often faces high activation energy barriers, conducting to unselective reactions yielding kinetic side products.[73] A way to circumvent this high energy barrier is by introducing a low energy pathway for the electrons to be shuttled from the substrate to oxygen. In transition metal-catalysis this has been achieved by adding electron transport mediators (ETMs) between the substrate specific catalyst and O_2. For example, the Wacker process, uses $CuCl_2$ as an ETM to regenerate the palladium-catalyst by transporting the electrons to O_2.[74] Inspired by this approach, we investigated if the introduction of a coupled system of ETMs would be a viable strategy for oxidative NHC catalysis.

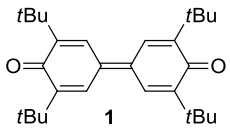


Figure 6. The Kharasch oxidant, 3,3',5,5'-tetra-*tert*-butyldiphenoquinone.

4.2 Oxidation *via* Redox Reaction

Esterification of α,β-unsaturated aldehydes was elected to investigation aerobic oxidative NHC catalysis. The combination of NHC and α,β-unsaturated aldehydes is well known to undergo several distinct reactions to form several compounds such as saturated esters **50**, unsaturated carboxylic acids **51**, and γ-butyrolactones **52** (Figure 7). Thus selectivity of the reaction towards methyl cinnamate **53** would indicate the selectivity of the oxidation.

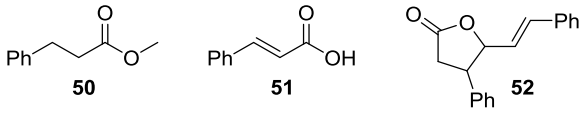
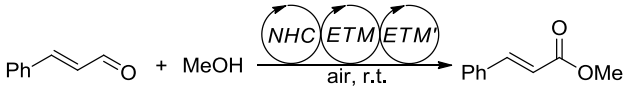


Figure 7. Possible side products.

To investigate the oxidative esterification of cinnamaldehyde quinone **1** was employed as the oxidant (Table 11, entry 1). With one equivalent of quinone **1**, methyl cinnamate **53** was obtained in a 74% yield after 4 h. Performing the reaction with 0.01 equivalent of **1** in an open reaction vessel yielded **53** in a 24% yield after 7 h. This demonstrated that lowering the amount of oxidant **1** in the reaction was possible; however, the rate of competing side-reactions pathways was increased due to a low oxidation rate (Table 11, entry 2). We then hypothesized that a higher oxidation rate could prevent the formation of side products.

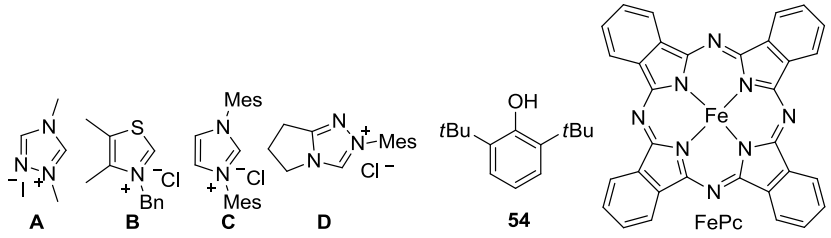
As a proof of concept, a coupled ETM system with NHC catalysis, iron(II) phthalocyanine (FePc) was added to the reaction mixture. The combination of **1** and FePc showed a major improvement in yield, with almost full conversion after 4 h (entry 3). It was possible to replace quinone **1** with 2,6-di-*tert*-butyl phenol **54** (precursor of quinone **1**)[75] with equivalent efficiency (entry 4). Since quinone **1** could be formed *in situ* with the used reaction conditions, phenol **54** became the preferred ETM-precursor, being less expensive* than quinone **1**. Other NHC precursors were also screened (Table 11, entry 5–7) with **A** giving **53** in higher yields. Moreover, the equivalents of the NHC precatalysts proved to be important; loadings above 0.02 eq. resulted in lower reaction efficiency (Table 11, entry 4, 8 and 9) leading to an increased formation of side products.

Table 11. Screening of reaction conditions for the oxidative esterification reaction.[a]



Entry	NHC	ETM	ETM' (FePc)	Time (h)	Yield (%)[b]	Selectivity (%)[c]
1.	**A**	**1** (1 eq.)	—	4	74	78
2.	**A**	**1** (0.01 eq.)	—	7	24	40
3.	**A**	**1** (0.01 eq.)	0.0055 eq.	4	80	88
4.	**A**	**54** (0.02 eq.)	0.0055 eq.	4	85	89
5.	**B**	**54** (0.02 eq.)	0.0055 eq.	—	—	—
6.	**C**	**54** (0.02 eq.)	0.0055 eq.	22	65	65
7.	**D**	**54** (0.02 eq.)	0.0055 eq.	4	68	68
8.	**A** (0.2 eq.)	**54** (0.02 eq.)	0.0055 eq.	4	19	19
9.	**A** (0.05 eq.)	**54** (0.02 eq.)	0.0055 eq.	4	67	74

[a] Unless otherwise stated the reactions were performed in open reaction vessels at room temperature with aldehyde (0.5 mmol, 1 eq.), TBD (0.5 eq.), MeOH (4 eq.), NHC (0.01 eq), FePc (see Table), ETM' (see Table) in acetonitrile (1 mL). [b] yields refer to isolated yields. [c] yield over conversion.



* Sigma-Aldrich, phenol **54** (CAS 128-39-2) 1 kg, $44.3, quinone **1** (CAS 2455-14-3) 50 mg, $125.

In order to test the applicability of the aerobic oxidative esterification of aldehydes, the reaction scope was investigated. A good reactivity of unsaturated aldehydes was observed and the esters have been isolated in good to excellent yields, tolerating both electron-withdrawing and electron-donating groups (Table 12, entry 1–7).

For example, *p*-chloro cinnamate (entry 2) and *p*-fluoro cinnamate (entry 3) can be isolated in 87% and 73% yield, respectively, and *p*-methoxy cinnamate (entry 5) can be obtained in 88% yield. The reaction is also compatible with different alcohols providing the corresponding ester in high to excellent yields (Table 12, entry 8–16). For instance, allyl alcohol and benzyl alcohol gave their corresponding esters **63** and **64** in 78% and 98% yield, respectively. The method showed to be an easy access to the synthesis of two sun-screening agents, amiloxate **66** and octinoxate **67** could be isolated in 72% yield.[76] Moreover, diols such as 1,4-butanediol could be used to yield the corresponding mono-ester **69** in 74% yield. The use of deactivated aliphatic α,β-unsaturated aldehydes proved to be difficult, substrates such as 2-hexenal and citral gave sluggish reactions. However, aliphatic conjugated α,β-unsaturated aldehydes worked well; sorbic aldehyde provided the ester **70** in 69% yield.

With the low equivalents of the two ETMs used in this reaction, a scale-up to gram scale was also performed, yielding 1.5 g of **53** (95% yield). The reaction only requires 26.7 mg of phenol **54** and 18.9 mg of FePc. In comparison, if quinone **1** had been used in a stoichiometric fashion this would have required 2.48 g (Figure 8).

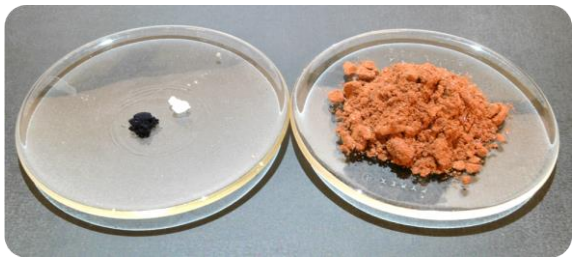
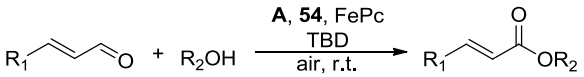
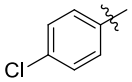
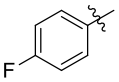
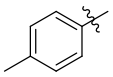
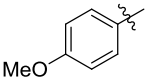
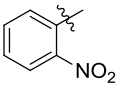
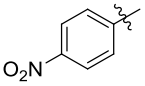
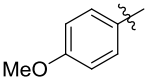
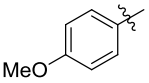
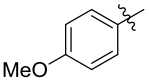
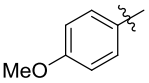
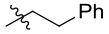
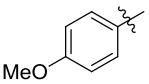
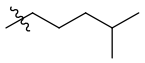
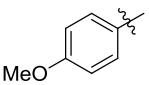
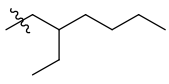
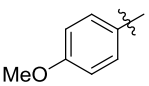
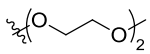
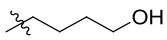
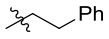


Figure 8. Comparison of the amount of ETMs needed for a gram-scale synthesis.

Table 12. Reaction scope for the oxidative esterifications.[a]



Entry	Product	R_1	R_2	Yield (%)[b]
1.	**53**			87
2.	**55**			87
3.	**56**			73
4.	**57**			73
5.	**58**			88
6.	**59**			64
7.	**60**			79
8.	**61**			89
9.	**62**			93
10.	**63**			78
11.	**64**			98, 95[c]
12.	**65**			96
13.	**66**			72[d]
14.	**67**			72
15.	**68**			76
16.	**69**			74[e]
17.	**70**			69

[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.), A (0.02 eq), FePc (0.0055 eq.), **54** (0.02 eq.) in acetonitrile (1 mL). [b] Yields refer to isolated yields. [c] 1.5 g isolated yield. [d] Performed with the alcohol as solvent. [e] Performed with acetonitrile (4 mL).

Experiments without ETMs showed that both phenol **54** and FePc were essential the reaction. By removing phenol **54**, the reactions reached its maximum conversion after 100 minutes with a 40% yield (Figure 9). The same trend was observed when FePc was removed. Without phenol **54** or FePc, the reaction only reaches 30% yield. In all these experiments, the full consumption of the starting material was observed, which proves that competing reactions are in operation. In the experiment with no addition of FePc, the carboxylic acid was isolated after an aqueous workup and could be an evidence for the formation of a peracid compound as a possible background reaction. This peracid formation has been previously reported in literature, where it is suggested that in the presence of O_2 the homoenolate intermediate **II** (Scheme 26) is oxidized to the peroxo-species **III** and not to the acyl azolium **IV**.[41-43] Both phenol **54** and FePc contributed to create a lower energy pathway, enabling the oxidation of the homoenolate **II** by quinone **1** to the acyl azolium intermediate **IV**. The unsaturated ester **V** is formed after a nucleophilic substitution by methanol on acyl azolium **IV**, releasing the NHC.

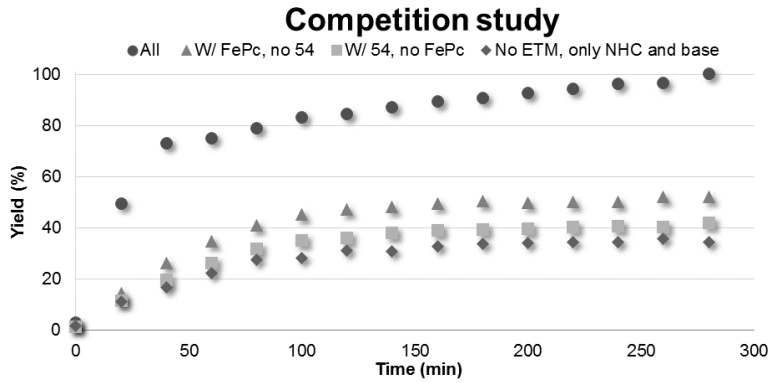
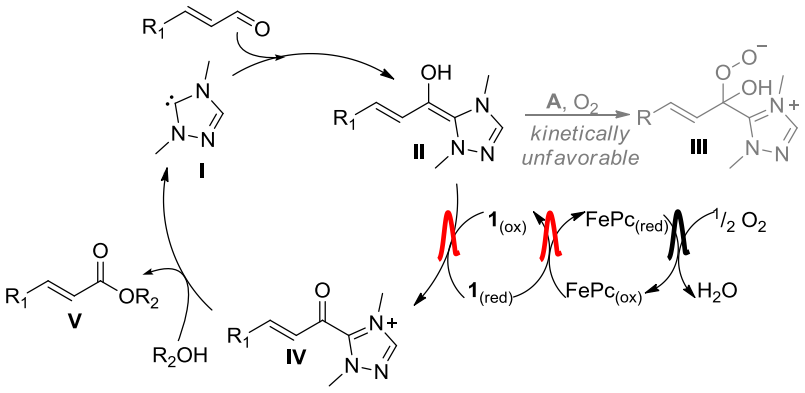


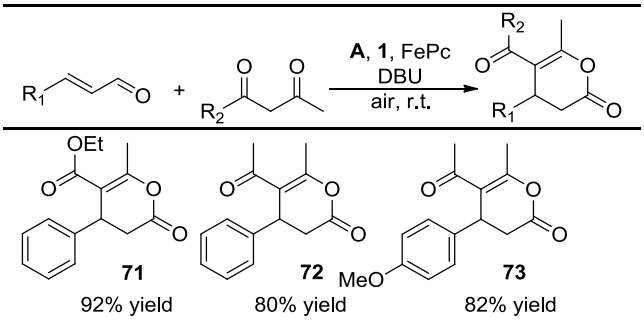
Figure 9. Kinetic profile for the oxidative esterification of cinnamaldehyde to methyl cinnamate.



Scheme 26. Mechanism for aerobic oxidation

The aerobic oxidation with a coupled ETM system was also tested on conjugate additions. The use of 1,3-ketoesters and 1,3-diketones as nucleophiles, required a slightly higher loading of the ETMs and NHC, however, the base amount could be lowered and provided the lactones **71–73** which could then be isolated in 92, 80 and 82% yield, respectively (Table 13).

Table 13. Scope of lactones. [a][b]



[a] Unless otherwise stated the reactions are performed with in open reaction vessels at room temperature with aldehyde (0.5 mmol, 1 eq.), DBU (0.1 eq.), 1,3-dicarbonyl (1.1 eq.), **A** (0.05 eq), FePc (0.05 eq.), **1** (0.05 eq) in THF (1 mL). [b] yields refer to isolated yields.

4.3 Summary

Combination of the coupled system of ETMs with oxidative NHC catalysis proved to be a valuable approach to aerobic esterification reactions. A good selectivity towards the formation of the α,β-unsaturated ester over the other known side products was observed. With the low equivalents of NHC and ETMs, this system can successfully be applied to aerobic oxidative esterifications of several α,β-unsaturated aldehydes as well as Michael-additions of 1,3-dicarbonyl compounds to α,β-unsaturated aldehydes. The reaction shows a broad substrate scope and the products have been isolated in good to excellent yields. This strategy, using O_2 as the terminal oxidant offers a sustainable and inexpensive way to scale-up important reactions with oxidative NHC catalysis.

5. Concluding Remarks

This thesis has demonstrated two synthetic routes using NHC catalysis as a mean to address some of the principles related to the *Twelve Principles of Green Chemistry*.

We have demonstrated that commercially available and relatively inexpensive ILs can be used as precatalysts for several reactions. Together with α,β-unsaturated aldehydes, they give access to the extended Breslow intermediate, which with further reaction with a chalcone and a nucleophile, can form functionalized OTHOs, with high yields and stereo- and regioselectivity. The reaction has a wide substrate scope and can tolerate both electron-withdrawing and electron-donating groups. It is also possible to incorporate heteroaromatic functional groups. Moreover, the dissolving and catalytic properties of IL were demonstrated in a regioselective acylation of carbohydrates, accessing several different functionalized carbohydrate-structures. These robust protocols can be run at room temperature under ordinary atmosphere, showing the power of NHC-catalyzed reactions. Additionally, these reactions are performed in a one-pot strategy, either *via* a three-component or a four-component reaction, without the need for intensive solvent-demanding chromatography purifications.

In a different approach, aerobic oxidations using molecular oxygen from the air allows access to α,β-unsaturated acyl azolium intermediates. The system relies on generating a lower energy barrier for the transportation of electrons from the substrate to oxygen *via* a coupled ETM system. The reaction has proven to be efficient giving high yields and a large substrate scope has been investigated. Two reactions have been studied with this method showing the utility of oxidative NHC catalysis. Furthermore, the use of a catalytic amount of the coupled ETM system, substitution of a stoichiometric high molecular weight oxidant, frequently associated with oxidative NHC catalysis, is possible. Scale-up reaction is then facilitated and the amount of chemical waste generated is reduced.

With the use of NHC catalysis and the proper reaction design the realms of green chemistry can be reached.

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