Syntheses and Applications of Ionic Liquids as Solvents and Reactants

-- Natural Substances Dissolution, Esterification & Ionic Tagging

vorgelegt von

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- Bin Zhao, Lasse Greiner, Walter Leitner;
  “Esterification of carboxylate-based ionic liquids with alkyl halides”
  *Chemical Communications*, **2011**, 47, 2973-2975.

- Bin Zhao, Lasse Greiner, Walter Leitner;
  “Cellulose solubilities in carboxylate-based ionic liquids”

- Anna K. Ressmann, Katharina Strassl, Peter Gaertner, Bin Zhao, Lasse Greiner, Katharina Bica;
  “New aspects for biomass processing with ionic liquids: towards the isolation of pharmaceutically active betulin”
The present thesis deals with the applications of ionic liquids (ILs), especially carboxylate-based ILs. The first part describes the syntheses and uses of ILs as solvents for natural compounds to dissolve cellulose and to extract betulin. The second part reveals their applications as reactants for esterification and ionic tagging.

Dissolution of cellulose allows easier processing of this important biogenic feedstock. For this, ILs have been proposed. To foster understanding of the structure activity relationship of IL and cellulose and to provide mandatory data for computer-aided cellulose solvent design, a systematic approach towards the synthesis and experimental determination was carried out and is described in Chapter 2. Three homologous series of all 27 combinations of the three cations: 1,3-dimethylimidazolium ([DMIm]), 1-ethyl-3-methylimidazolium ([EMIm]), and \(N,N\)-diethyl-\(N,N\)-dimethylammonium ([DEDMN]) with nine carboxylate anions were synthesized and characterized. Cellulose solubilities in seventeen synthesized ILs were determined. Alternatives were found to the most widely studied cellulose solvent [EMIm]Ac. Generally, the cellulose solubilities for carboxylate-based ILs with imidazolium cations were found to be in the same range, whereas those with the quaternary ammonium cation were found to be poor solvents for cellulose. Anions with an internal hydrogen bond had no detectable cellulose solubility. Moreover, anions with high \(\beta\) values exhibited good solubilities, which confirmed that anion basicity was an important factor for dissolving cellulose. After addition of water to the cellulose-IL solution, the cellulose precipitated and the IL was readily recovered. The pretreated cellulose was shown to be more degradable with organic acid. Furthermore, the regenerated IL showed no apparent change when compared to the fresh one, showing good thermal and chemical stability. Moreover, carboxylate-based ILs were shown to be good solvents for the extraction of betulin from birch bark.

Based on the unexpected reaction of [EMIm]Ac with dichloromethane, ILs as reactants for esterification and ionic tagging were developed, detailed in Chapter 3. The esterification of carboxylate-based ILs and alkyl halides was performed with moderate to excellent yields (33-99 \%) for a large substrate scope under neat conditions. Its S\(_N\)2 mechanism provided a potential application in the configuration inversion of chiral alcohols. Additionally, chiral carboxylate-based ILs were tested for stereoselective esterifications with racemic electrophiles by kinetic resolution. In the preliminary results,
2-octyl lactate was obtained with a diastereoselectivity ($d.r. = 57/43$). Due to the high polarity of ILs, weakly polar products were readily separated via decantation or extraction. Furthermore, it was demonstrated that the ILs could be recovered into the reactants by three processes (the anion exchange resin method, the recyclable base DBU process, and the anion metathesis method).

The disclosed reaction of 1-ethyl-3-methylimidazolium cation and chloromethyl acetate, which was yielded from the esterification of acetate and dichloromethane, offered a possibility to functionalize imidazolium cation at the 2-position with formaldehyde or ROCH$_2$X compounds. A series of $N$-alkyl-$N'$-alkyl-2-hydroxymethylimidazolium cations was synthesized including a polymer containing ionic liquid-type structures. When a zwitterion $N$-alkyl-$N'$-alkylimidazolium-2-carboxylate as the starting material was employed, 2-hydroxymethylimidazolium-based ILs with various anions were obtained easily and products were separated readily. Furthermore, the resulting $N$-alkyl-$N'$-alkyl-2-hydroxymethylimidazolium cations were successfully grafted on two phosphorus ligands as ionic tags to facilitate catalyst separation in transition metal catalysis in ILs. Their effectiveness to reduce metal leaching was demonstrated.
I sincerely acknowledge the assistance and contributions from many people to complete this dissertation, without you, it would not have been possible.

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Last but not least my parents, my sister and brother in law as well as relatives for their consistent support.
Abbreviations

3-HQD 3-hydroxyquinuclidine
Ac acetate
AMIm 1-allyl-3-methylimidazolium
Amm110 AMMOENG™ 110
AdMIm 1-allyl-2,3-dimethylimidazolium
BMIm 1-butyl-3-methylimidazolium
BdMIm 1-butyl-2,3-dimethylimidazolium
BMPy 1-butyl-3-methylpyridinium
BTA bis(trifluoromethylsulfonyl)imide
COD 1,5-cyclooctadiene
COSMO-RS conductor-like screening model for realistic solvation
DABCO 1,4-diazabicyclo[2.2.2]octane
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCA dicyanamide
DCM dichloromethane
DEDMN N,N-diethyl-N,N-diethylammonium
DMAc N,N-dimethyl acetamide
DMAP 4-dimethylaminopyridine
DMF N,N-dimethyl formamide
DMI dimethyl itaconate ester
DMIm 1,3-dimethylimidazolium
DMSO dimethyl sulfoxide
d.r. diastereomeric ratio
DSC differential scanning calorimetry
ECOENG 1,3-dimethylimidazolium dimethylphosphate
EdMIm 1-ethyl-2,3-dimethylimidazolium
EMIm 1-ethyl-3-methylimidazolium
Et ethyl
HMIm 1-hexyl-3-methylimidazolium
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>ICP</td>
<td>inductively coupled plasma</td>
</tr>
<tr>
<td>IL</td>
<td>ionic liquid</td>
</tr>
<tr>
<td>MCC</td>
<td>microcrystalline cellulose</td>
</tr>
<tr>
<td>MDL</td>
<td>method detection limit</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Ms</td>
<td>mesylate</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>OMIm</td>
<td>1-methyl-3-octylimidazolium</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>PILs</td>
<td>poly(ionic liquid)s</td>
</tr>
<tr>
<td>PMIm</td>
<td>1-methyl-3-propylimidazolium</td>
</tr>
<tr>
<td>Pr</td>
<td>1-propyl</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>scCO₂</td>
<td>supercritical carbon dioxide</td>
</tr>
<tr>
<td>TGA</td>
<td>thermogravimetric analysis</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>tosylate</td>
</tr>
</tbody>
</table>
# Table of Content

Abstract ...................................................................................................................................... III  
Acknowledgement ......................................................................................................................... V  
Abbreviations ............................................................................................................................... VII  

1 Introduction ................................................................................................................................ 1  
1.1 Syntheses of Ionic Liquids ................................................................................................. 1  
1.2 Applications of Ionic Liquids ............................................................................................ 3  
1.2.1 Biomass Processing ........................................................................................................ 3  
1.2.2 Reactivities of Ionic Liquids .......................................................................................... 9  
1.2.2.1 Reaction of the cation ............................................................................................... 9  
1.2.2.2 Reaction of the anion .............................................................................................. 12  
1.3 Objective ............................................................................................................................ 15  

2 Applications of Ionic Liquids as Solvents .............................................................................. 17  
2.1 Results and Discussion ....................................................................................................... 17  
2.1.1 Syntheses of Carboxylate-based Structures .................................................................. 17  
2.1.1.1 Synthesized carboxylate-based structures .............................................................. 18  
2.1.1.2 Removing residual carboxylic acid from ionic liquids ........................................... 19  
2.1.2 Thermal Properties of Synthesized Structures ............................................................ 20  
2.1.3 Cellulose Solubilities in Carboxylate-based Ionic Liquids ........................................... 21  
2.1.3.1 General methodology of investigations .................................................................. 21  
2.1.3.2 Influence of ionic liquid structures ....................................................................... 23  
2.1.3.3 Water content and halide content influences ......................................................... 24  
2.1.3.4 Modelling cellulose solubilities in ionic liquids using COSMO-RS ....................... 24  
2.1.3.5 Investigation of regenerated ionic liquids .............................................................. 28  
2.1.3.6 Degradation of precipitated cellulose ..................................................................... 28  
2.1.4 Betulin Extraction Using Carboxylate-based Ionic Liquids .......................................... 30  

2.2 Experimental ....................................................................................................................... 31  
2.2.1 Preparation of Proposed Structures ............................................................................. 32  
2.2.1.1 Synthesis of 1,3-dimethylimidazolium carboxylate ............................................... 32  
2.2.1.2 Synthesis of 1-ethyl-3-methylimidazolium carboxylate ........................................... 36  
2.2.1.3 Synthesis of N,N-diethyl-N,N-dimethylammonium carboxylate ............................ 40  
2.2.1.4 Removing residual carboxylic acid from ionic liquids ......................................... 44
2.2.2 Dissolving Cellulose in Ionic Liquids ..................................................... 44
2.2.3 Regeneration of Cellulose and Ionic Liquid ........................................ 44
2.2.4 Cellulose Degradation Using Oxalic Acid .......................................... 45
2.2.5 Betulin Extraction Using Carboxylate-based Ionic Liquids .................. 45

2.3 Interim Summary ....................................................................................... 46

3 Applications of Ionic Liquids as Reactants ............................................. 48

3.1 Esterification Reactant ................................................................................ 48
3.1.1 Background ............................................................................................ 48
3.1.2 Results and Discussion ......................................................................... 51
  3.1.2.1 Reaction of [EMIm]Ac with dichloromethane ..................................... 51
  3.1.2.2 Reaction of [EMIm]Ac with chloroform ........................................... 52
  3.1.2.3 Esterification of carboxylate-based ionic liquids with primary alkyl halides ................................................................. 53
  3.1.2.4 Esterification of carboxylate-based ionic liquids with chiral secondary substituted alkanes ........................................................................ 56
  3.1.2.5 Esterification of racemic electrophiles with chiral ionic liquids .......... 57
  3.1.2.6 Recovery of ionic liquids for esterification ........................................ 58
3.1.3 Experimental .......................................................................................... 60
  3.1.3.1 General ............................................................................................. 60
  3.1.3.2 Typical procedures for the reaction of [EMIm]Ac with dichloromethane or chloroform ................................................................. 61
  3.1.3.3 Esterification of carboxylate-based ionic liquids and alkyl halides ....... 62
  3.1.3.4 Esterification of carboxylate-based ionic liquids with chiral secondary substituted alkanes ................................................................. 66
  3.1.3.5 Esterification of racemic electrophiles with chiral ionic liquids .......... 68
  3.1.3.6 Recycling processes of ionic liquids for esterification ....................... 76
3.1.4 Interim Summary .................................................................................... 79

3.2 Ionic Tagging ............................................................................................. 80
3.2.1 Background ............................................................................................ 80
3.2.2 Results and Discussion ......................................................................... 83
  3.2.2.1 Functionalization of imidazolium cations at the 2-position ............... 83
  3.2.2.2 Syntheses of and catalysis with ionic-tagged phosphorus ligands ....... 88
3.2.3 Experimental .......................................................................................... 92
  3.2.3.1 General ............................................................................................. 92
  3.2.3.2 Procedures for functionalizing imidazolium cations at the 2-position .. 94
3.2.3.3 Syntheses of and catalysis with ionic-tagged phosphorus ligands......... 100
3.2.4 Interim Summary.............................................................................. 108

4 Summary and Outlook................................................................................ 110
Appendices .................................................................................................... 113
References....................................................................................................... 119
Curriculum Vitae.............................................................................................. 129
1 Introduction

The term “ionic liquid” (IL) is now commonly accepted for salts with a melting point temperature below 373 K. They generally have negligible vapor pressure, high thermal and chemical stability, wide liquidus range, and good solvation behavior. Therefore they are considered to be potential environmentally friendly alternatives to conventional volatile organic solvents. One of their impressive features is the wide variation in their physicochemical properties, including viscosity, polarity, density, melting point and solubility. These properties are related to their ionic structures, which provide numerous possibilities to modify cation and anion structures for specific properties.\footnote{1}

1.1 Syntheses of Ionic Liquids

Most ILs can be easily synthesized with common methods, which are outlined in Figure 1-1.

![Synthesis paths for ionic liquids](image)

\textbf{Figure 1-1.} Typical synthesis paths for ionic liquids.\footnote{1a}

Generally, their synthesis includes two steps, the first to obtain the wanted cation by protonation or alkylation and the second to get the desired anion by either directly treating with Lewis acids or exchanging anions. Anion exchange can be further divided into the anion metathesis method, with metal salts or protic acids, and the anion exchange resin method.\footnote{1a-f}

In 2003, Robin Rogers \textit{et al.} reported a zwitterion, 1,3-dimethylimidazolium-2-carboxylate, which was obtained at a high yield from the reaction of dimethyl carbonate and 1-methylimidazole.\footnote{2} The zwitterion is readily neutralized with protic acid and is accompanied by CO\textsubscript{2} release. An imidazolium-based IL with a protic acid anion is obtained (Scheme 1-1). This method to prepare ILs offers a halide-free protocol, easy
purification and avoids the use of expensive metal salts for the anion metathesis.\[^3\] In addition, this kind of zwitterions can also be synthesized via depronation of imidazolium cations with a strong base to form carbenes, and a subsequent addition of CO\(_2\).\[^4\]

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{N} & \quad \text{O} \\
\text{+} & \quad \Delta & \quad \text{N} & \quad \text{N} & \quad \text{O} \\
\text{+ HX} & \quad - \quad \text{CO}_2 & \quad \text{X} & \quad \text{-}
\end{align*}
\]

Scheme 1-I. Syntheses of imidazolium-based ionic liquids from the zwitterion
1,3-dimethylimidazolium-2-carboxylate

As new techniques (e.g. microwave and ultrasonic sound) are integrated into reactors, IL preparation is improved. New reactors significantly reduce the reaction time from hours to minutes, avoid the use of solvents and large excesses of alkyl halides, and improve qualities as well as yields.\[^{1a-f}\]

Typically, impurities in ILs from preparations are traces of water, residual solvents, halides, acids, unreacted starting materials, or metal salts. These impurities have strong impacts on the physical and chemical properties of ILs.\[^{1b-d,5}\] Seddon and co-workers first systematically studied the effect of impurities, water, chloride and co-solvent on the physical properties of ILs. Chloride contamination increases the viscosity of [BMIm]BF\(_4\), while water or other co-solvent decrease the viscosity.\[^5\] Halide impurity, normally from anion metathesis, could deactivate transition metal catalysts and enzymes, when ILs are used as reaction media.\[^{1b-d,6}\] Removal of impurities from ILs is difficult, due to their high viscosity, negligible vapor pressure and ion characteristic. To date, ILs can be purified only partially with traditional methods, like decolorization with activated charcoal, column chromatography with alumina or silica gel, crystallization or distillation.\[^7\] Therefore synthetic routes to avoid impurities are preferable.

ILs, considered to be “green solvents”, must be efficient in their preparation and purification. Seddon and co-worker reported the first critical assessment of the sustainability of IL preparations using SWOT (Strengths, Weaknesses, Opportunities, Threats) analyses. By this method, researchers can measure the balance between good and bad for some common preparations and purifications, and choose the preferred process to optimize the production routes for ILs.\[^8\]
1.2 Applications of Ionic Liquids

Due to the unique properties of ILs, they have been investigated for applications in many fields, not only traditional fields such as inorganic chemistry, organic chemistry and electrochemistry, but also new fields like engineering and analytics (Figure 1-2). In these applications, the most focused is placed on solvent characteristics. There are several excellent, extensive and detailed reviews about this in the literature.\textsuperscript{[1b-f, 9]} Within the scope of this thesis, their applications as solvents for biomass processing and as reactants are of primary interest.

![Figure 1-2. Investigated applications of ionic liquids.](image)

1.2.1 Biomass Processing

Cellulose is the most widespread natural organic compound on earth (about $7.5 \times 10^{10}$ tons produced annually). Therefore, it is considered the most important bio-renewable resource to overcome challenges resulting from the depletion of the fossil fuels via its transformation into tailored biofuels or chemical products.\textsuperscript{[1d, 10]}
The intermolecular and intramolecular hydrogen bonds (Figure 1-3) give cellulose excellent mechanical properties, but also make it insoluble in most solvents. Its poor solubility in solvents limits its utilization. Furthermore, most conventional cellulose solvents have severe drawbacks (Table 1-1). Generally, these solvent systems require relatively harsh conditions and the use of expensive, toxic or non-reusable solvents.\textsuperscript{[12]}

\begin{table}[h]
\centering
\begin{tabular}{|c|l|}
\hline
Entry & Solvent systems & Problems \tabularnewline
\hline
1 & Sulfuric, phosphoric, nitric, hydrochloric or trifluoroacetic acid & Insoluble, no solvent recovery, polymer degradation \tabularnewline
2 & Calcium thiocyanate and zinc chloride & Poor fiber properties, high salt concentrations \tabularnewline
3 & Potassium hydroxide and hydrazine & High temperatures and pressures, polymer degradation, toxicity \tabularnewline
4 & Triton bases, amines, amine oxides and dimethyl sulfoxide/methylamine & Incomplete dissolution, solvent instability \tabularnewline
5 & Cuam,\textsuperscript{[a]} Cuen,\textsuperscript{[b]} Codoxen,\textsuperscript{[c]} Nioxen\textsuperscript{[d]} & No solvent recovery, poor fiber properties, polymer degradation \tabularnewline
6 & Bis(\(\beta\)-\(\gamma\)-dihydroxypropyl)-disulfide & High temperature, limited solubility range \tabularnewline
7 & Lithium chloride/dimethyl acetamide & Difficult and expensive recycling \tabularnewline
\hline
\end{tabular}
\caption{Conventional cellulose solvents.\textsuperscript{[12a]}}
\end{table}

\textsuperscript{[a]} Cuam: cuprammonium hydroxide, ([Cu(NH\textsubscript{3})\textsubscript{4}][OH\textsubscript{2}]). \textsuperscript{[b]} Cuen: cupriethylenediamine or bis(ethylenediamine)copper bihydroxide, ([Cu(NH\textsubscript{2}(CH\textsubscript{2})\textsubscript{2}NH\textsubscript{2})\textsubscript{2}][OH\textsubscript{2}]). \textsuperscript{[c]} Codoxen: cobalt ethylenediamine or tris(ethylenediamine)cobalt bihydroxide, ([Co(NH\textsubscript{2}(CH\textsubscript{2})\textsubscript{2}NH\textsubscript{2})\textsubscript{3}][OH\textsubscript{2}]). \textsuperscript{[d]} Nioxen: nickel ethylenediamine or tri(ethylenediamine)nickel bihydroxide, ([Ni(NH\textsubscript{2}(CH\textsubscript{2})\textsubscript{2}NH\textsubscript{2})\textsubscript{3}][OH\textsubscript{2}]).
The first report of cellulose dissolution in molten salts, alkyl pyridinium chlorides, came in a patent by Graenacher in 1934. However, these salts have melting points above 373 K and are therefore out of the common definition of ILs.\[^{13}\] In 2002, Robin Rogers and co-workers first used ILs to dissolve cellulose. Due to the high polarity of ILs, it successfully destroyed the hydrogen bonds within the cellulose. In addition, it could be recovered after dissolution.\[^{14}\] This ignited the widespread interest in this field. Many papers have been published using ILs as cellulose solvents, as well as carbohydrate solvents. The ILs that are used to dissolve cellulose are listed in Table 1-2. Some of them have already been applied for functionalizing cellulose,\[^{15}\] extracting carbohydrate,\[^{16}\] hydrolyzing cellulose.\[^{17}\]

**Table 1-2:** Cellulose solubilities in ionic liquids.\[^{[a]}\]

<table>
<thead>
<tr>
<th>Ionic liquid</th>
<th>Cellulose</th>
<th>Water content /wt.%</th>
<th>Temp/K</th>
<th>Time/h</th>
<th>Solubility /wt.%</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[BMIm]BTA</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>&lt; 0.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>([P_{6,6,6,14}])DCA[^{[e]}]</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>&lt; 0.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[BMIm]HCO(_2)</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>8</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[BU(_4)N]HCO(_2)</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>1.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[BU(_4)P]HCO(_2)</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>6</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[BMIm]Cl</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>10</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[BMIm]DCA</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>1</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[EMIm]Ac</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>15</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[OMIm]Ac</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>&lt; 1</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Amm110]Cl</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>0.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Amm110]DCA</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>&lt; 0.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Amm110]HCO(_2)</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>0.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Amm110]Ac</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>0.5</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Me(OEt)(_2)]EIm]Cl</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>2</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Me(OEt)(_3)]EIm]Ac</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>12</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Me(OEt)(_3)]EIm]Cl</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>12</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Me(OEt)(_4)]EIm]Cl</td>
<td>Avicel (DP 225)</td>
<td>n.d.</td>
<td>383</td>
<td>-</td>
<td>10</td>
<td>[^{15c}]</td>
</tr>
<tr>
<td>[Me(OEt)(_3)]MeOEtOMe-I</td>
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*DP* stands for degree of polymerization.
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<td>12 5</td>
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Generally, there are a few external factors influencing the cellulose solubility of ILs, like water content, dissolving time, temperature, heating method and the degree of polymerization (DP). Cellulose solubility is favored by low water content, low DP, long time, high temperature and microwave heating.\(^{[1j, 14, 22]}\)

Based on NMR spectra, the dissolution mechanism of cellulose in ILs has been proposed as shown in Figure 1-4.\(^{[1j, 18]}\) In ILs, cations and anions separate from each other at a certain temperature, individually forming hydrogen bonds with cellulose, which destroy the intermolecular or intramolecular hydrogen bonds within the cellulose and disperse the cellulose molecules in the ILs. Thus, the anion and cation structure of the IL both play roles in dissolving cellulose. Previous studies provide several hints for exploring new ILs to dissolve cellulose:

![Proposed dissolution mechanism of cellulose in ionic liquids.](image)

For cations, compared to quaternary ammonium or phosphonium, imidazolium and pyridinium are more favorable for dissolving cellulose. Cellulose solubility decreases with increases in the alkyl chain length in the imidazolium cation; even numbers of carbon atoms in the side chain of imidazolium chloride show higher cellulose solubility than that with odd numbers in the series C2 to C10. However, when the bromide anion is used, there is no obvious difference observed.\(^{[10a]}\) Usually, a longer alkyl chain gives the IL higher viscosity, which correlates with lower cellulose solubility.

For anions, ILs with NO\(_3^-\), F\(_3\)CSO\(_3^-\), EtSO\(_4^-\), BTA\(^-\), BF\(_4^-\), PF\(_6^-\) or DCA\(^-\) as the anion, exhibit low cellulose solubility or even no solubility. In contrast, acetate, phosphate and formate are favorable for dissolving cellulose. Different anions exert dramatic differences on cellulose solubility.
As the hydrogen bond formation between the IL and cellulose hydroxyl group is the key to dissolving cellulose\textsuperscript{[1]} and hydrogen-bonding characteristics of ILs can be empirically estimated using Kamlet-Taft parameters\textsuperscript{[1g, 23]} a correlation between Kamlet-Taft parameters with cellulose solubility was proposed\textsuperscript{[19-20, 24]} Parameters of the Kamlet–Taft solvatochromic relationship, which measure separately the hydrogen bond donor ($\alpha$), hydrogen bond acceptor ($\beta$), and dipolarity / polarizability ($\Pi^*$) properties of solvents, contribute to the overall solvent polarity\textsuperscript{[25]} Brandt and co-workers found that anion basicity described by parameter $\beta$ correlated with the ability to expand and dissolve pine lignocellulose and the anion was the most important determinant for $\beta$\textsuperscript{[24]}

Recently, ILs as solvents to dissolve and process other biomass, like chitin, wood, and other carbohydrates, have been explored. Also, the ability of ILs to swell or dissolve biomass can be used to extract valuable ingredients embedded in the biopolymers. In 2006, Lapkin and co-workers first reported that artemisinin, an anti-malaria drug, could be extracted with ILs\textsuperscript{[26]} In the past years, IL extraction, combined with either ultrasound or microwave techniques, have been used for several active pharmaceutical ingredients\textsuperscript{[27]} However, compared to the large number of valuable substances in nature, this application is still in its infancy. Moreover, most of the explored processes are restricted to studies at an analytical scale. A scalable isolation process, as well as a practical recovery strategy, is still a challenging issue.

1.2.2 Reactivities of Ionic Liquids
ILs do not always act as inert solvents; sometimes they are also involved in catalysis as catalysts or ligands, even in reactions as reagents\textsuperscript{[1b, c, 1h]} Considering that ILs catalyzed reactions have been fully discussed in recent reviews and books and that comparatively little attention is paid to the use of ILs as reagents, efforts to review this area are currently being made.

1.2.2.1 Reaction of the cation
Due to the acidity of the hydrogen at the 2-position of 1,3-dialkylimidazolium-based ILs, it is easily deprotonated by a mild base to form an active intermediate NHC (N-heterocyclic carbene), which can effectively catalyze organic reactions, coordinate with transition metal catalysts, or attack electrophiles. Several examples of various organic reactions have been reported\textsuperscript{[28]} Although the undesired reactivity of ILs is a
drawback in most known cases, a few applications of the reactivity have been explored in the modification of metal catalysts for high activity and selectivity.\cite{29} In the meanwhile, several examples from stoichiometric reactions of the formed carbenes with electrophiles have been reported.

\[ \text{Scheme 1-2. Reaction of an imidazolium cation with benzaldehyde.} \]

Aggarwal and co-workers discovered a side reaction of 1-butyl-3-methylimidazolium cation with benzaldehyde (Scheme 1-2), revealing the incorrect assumption reported by Afonso et al. that [BmIm]PF\textsubscript{6} catalyzed the Baylis-Hillman reaction of benzaldehyde and methyl acrylate 33 times faster than acetonitrile.\cite{28a} Specifically, the cation is first deprotonated by the mild base 3-HQD or DABCO to form a NHC, which subsequently attacks the electrophile benzaldehyde. The formed imidazolium derivative is not stable and easily decomposes. In other words, the formation is reversible. The yield and separation of this imidazolium derivative were therefore not mentioned in their report.

Nair et al. used in situ formed carbenes from imidazolium cations to synthesize furanone derivatives (Scheme 1-3).\cite{30} Six substituted benzaldehydes were tested and gave moderate to good yields (25 to 79\%).

\[ \text{Scheme 1-3. Multicomponent reaction of 1,3-dimesitylimidazol-2-ylidene, dimethyl acetylenedicarboxylate and benzaldehyde.} \]
In 1975, Begtrup reported the alkylation of imidazolium cations at the 2-position (Scheme 1-4).[31] In their report, 1,3-dimethylimidazolium tosylate was chosen as the starting material. With ethyl iodide as the electrophile, ethyl-substituted imidazolium cation was observed exclusively as the product, based on $^1$H-NMR measurements. However, when it was replaced with methyl iodide, only iso-propyl-substituted imidazolium cation was obtained. This was due to further methylation on the initatively formed methyl group in the imidazolium. In the alkylation of 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene with alkyl bromide (1-bromohexane, 1-bromoocatane, or 2-bromopropane), Alder et al. mentioned that there was minor elimination of the alkyl halide competing with substitution.[31a]

Scheme 1-4. Alkylation of imidazolium cations at the 2-position.

Handy and Okello conducted similar reactions to Begtrup’s work.[32] They used 3-butyl-4(5)-hydroxymethyl-1-methylimidazolium iodide, derived from fructose, for the alkylation. Due to further methylation on the initatively formed methyl group, only an ethyl-substituted product was observed, which was different from Betrup’s iso-propyl-substituted product. It indicated that the substituted products were affected by different cation structures. Ennis and Handy continued the alkylation of imidazolium cations to obtain 2-substituted imidazolium-based ILs.[33] In their case, large excesses of base and alkyl halides were needed to achieve complete alkylation. They successfully isolated products with good to excellent yields (67 to 99 %) and further synthesized other ILs with different anions via the anion exchange method. In their investigations, primary alkyl halides were good substrates, without further alkylation of the formed 2-substituent, but secondary alkyl halide, 2-chloropropane or 2-bromopropane failed to give any alkylated products; thus, elimination was assumed as the sole reaction pathway. Other functionalized alkyl groups were tested; no pure compounds were separated due to competing side reactions, such as multi-alkylation and elimination.

The reactivity of imidazolium cations is not always caused by the NHC formation, but is also related to their aromatic ring. Laali et al. observed the nitration of the imidazolium
ring at the 4- or 5-postion, when the nitration of toluene was carried out in [EMIm]BF₄ or [EMIm]PF₆ (Scheme 1-5).[34]

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{X} & \quad \text{NO}_2\text{BF}_4 \\
\text{BF}_4^- & \\
\end{align*}
\]

\[X = \text{BF}_4^-, \text{PF}_6^-\]

\[\text{Scheme 1-5. Nitration of [EMIm]X (X=BF}_4, \text{ PF}_6) \text{ with [NO}_2\text{][BF}_4].[34]\]

In all these reactions, the reactivity of the cations is always considered to be undesired and has not been explored for its benefit. Due to the similar ion characteristics of imidazolium cations and their derivatives, separations are often difficult to be conducted in practice. Hitherto, successful examples only result from the reactions with full conversion, high selectivity, or non-ionic products.

**1.2.2.2 Reaction of the anion**

In the field of phase transfer catalysis, which was introduced to tackle the heterogeneity problem in biphasic systems,[35] the phase transfer agent, often a quaternary ammonium salt, works as a shuttle for transporting the reactant anion from one phase across the interface into the other phase. During the process, it increases the activity of the nucleophile, since it is less tightly bound to the catalyst cation than to the metal cation. Indeed, several phase transfer catalysts conform to the definition of IL. To some extent, ILs could replace phase transfer catalysts in conventional substitution systems, while simultaneously acting as a solvent to replace conventional organic solvents. However, some ILs may not be as effective as most phase transfer catalysts. Nevertheless, as a solvent, its high concentration would overcome the limitation, yielding a fast reaction. Through kinetic investigations of the activity of the nucleophile in ILs, nucleophilicity is generally determined by the combination of cations and anions.[16, 1h, i, 36] Increasing the cation hydrogen bonding donor effect decreases the activity of the nucleophile through the direct interaction. The effect of the anion is more complicated due to the hydrogen bond formation with nucleophiles and competition with nucleophiles for the interaction with the cation. To some extent, every IL is unique and thus, the influences on nucleophilicity are different. Wheeler et al. reported a cyanide replacement of benzyl chloride in [BMIm]PF₆ instead of volatile organic solvents, without additional phase transfer catalysts.[37] Based on the neglectable solubility of IL in scCO₂,[38] they proposed
a recyclable IL system for this reaction (Figure 1-5). Firstly, reactants are added to the IL and reaction processes. After reaction, the organic reactants and products are removed via vaporization or scCO$_2$ extraction, inorganic salts are washed out with water, followed by decantation, the purified IL is obtained and available for the next run.

Afonso and co-workers demonstrated that nucleophilic substitutions of azide and cyanide could be carried out in an aqueous-[BMIm]PF$_6$ biphasic system. The recycling of the IL was also demonstrated. Fluorination of mesylate with KF (potassium fluoride) in several ILs was addressed by Kim and co-workers (Scheme 1-6). In their report, ILs not only enhanced the reactivity of KF, but also reduced the formation of side products. Co-solvent, even water, added to system, had positive effects on the reaction.

However, in most cases, ILs are just used as the solvent for reactions. The IL anion is not always innocent during the reaction; it competes with the nucleophiles, even suppresses their nucleophilicity for the displacement. The “non-nucleophilic” anion BTA (bis(trifloromethylsulfonyl)imide), which was always considered an innocent stable anion, was found to be surprisingly more reactive than nucleophilic bromide and chloride anions in the dediazoniation of PhN$_2^+$BF$_4^-$ when associated with a [BMIm] cation (Scheme 1-7).

**Figure 1-5.** Proposed recyclable ionic liquid solvent system for cyanide substitution.$^{[37]}$

**Scheme 1-6.** Fluorination of mesylate with KF.$^{[40]}$

**Scheme 1-7.** Dediazoniation of PhN$_2^+$BF$_4^-$ in [BMIm]Br – [BMIm]BTA.$^{[41]}$
To date, [BMIm]BF$_4$ and [BMIm]PF$_6$ are commonly used as solvents for these reactions. However, hydrolysis of these anions (BF$_4^-$ and PF$_6^-$) under either acidic or basic conditions has also been unveiled.$^{[42]}$ To avoid the influence of hydrolyzed anions, a promising method is using the IL anion simultaneously as the nucleophile. At present, there is one example published. Kemal and Chouhan reported the thiocyanation of alkyl halide with task-specific IL [BMIm]SCN into alkyl thiocyanate (Scheme 1-8).$^{[43]}$ [BMIm]SCN was not only used as the solvent, but also acted as the starting material. The reaction had high reactivity and high selectivity at r.t.: α-chloroacetophenone was quantitatively converted into the corresponding product in 10 min. Without side products, there was no need for further product purification. The product [BMIm]X could be converted back into [BMIm]SCN just via the simple anion metathesis method with KSCN.

![Scheme 1-8](attachment:image.png)

**Scheme 1-8.** Thiocyanation of alkyl halide with [BMIm]SCN.$^{[43]}$

Furthermore, several IL anions can react with Lewis acids to form coordinated metal anions (e.g., Cl$^-$/AlCl$_3$), which could be used as catalysts for certain reactions, namely Friedel-Crafts alkylation and acylation, isomerization and hydrogenation.$^{[1b-f, 9]}$

In ILs, both anions and cations are reactive. When applied as a solvent in the system, their reactivity should not be ignored. Compared with tens of thousands of papers about ILs as catalysts or ligands, their role as a reactant to favor organic synthesis is still in its infancy.
1.3 Objective

Although many ILs have been tested for dissolving cellulose and certain guidelines about the structure-activity relationships have been proposed, further understanding of the factors controlling the solubility is still needed. To efficiently investigate this relationship and to obtain effective data for computer-aided solvent design, a systematic approach towards the synthesis and experimental determination was proposed in Chapter 2. Considering that the anion basicity of ILs is an important factor for dissolving cellulose, carboxylate anions (formate, acetate, $n$-propionate, $n$-butyrate, iso-butyrate, mono-maleate, maleate, mono-succinate, and succinate), which have high $\beta$ value, are selected (Table 1-3). To highlight the anion influence, three small cations without functional groups (1,3-dimethylimidazolium, 1-ethyl-3-methylimidazolium, and $N,N$-diethyl-$N,N$-dimethylammonium) are chosen. Compared to the large number of valuable substances in nature, applications of employing ILs as solvents to dissolve or to extract natural products needs to be explored. Therefore, extracting pharmaceutically active betulin from birch bark is also targeted.

ILs are not inert as they were considered before. However, their reactivity is rarely used for organic syntheses. Therefore, employing ILs as reactants is aimed, to synthesize organic compounds in Chapter 3.1. Carbenes, which are produced from deprotonation at the 2-position of imidazolium cations by a base, have high reactivity, and thus are considered to be reactants for organic reactions in Chapter 3.2.
**Table 1-3:** Proposed structures to study the cellulose solubility.

<table>
<thead>
<tr>
<th>Anion</th>
<th>1,3-Dimethylimidazolium</th>
<th>1-Ethyl-3-methylimidazolium</th>
<th>N,N-Diethyl-N,N-dimethylammonium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formate</td>
<td>○[44]</td>
<td>○[44]</td>
<td>-</td>
</tr>
<tr>
<td>Acetate</td>
<td>○[45]</td>
<td>○[15c]</td>
<td>×[46]</td>
</tr>
<tr>
<td>n-Propionate</td>
<td>○[45]</td>
<td>○[47]</td>
<td>-</td>
</tr>
<tr>
<td>n-Butyrate</td>
<td>-</td>
<td>○[44]</td>
<td>-</td>
</tr>
<tr>
<td>iso-Butyrate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>mono</strong>-Maleate</td>
<td>-</td>
<td>×[48]</td>
<td>×[49]</td>
</tr>
<tr>
<td>Maleate</td>
<td>-</td>
<td>×[50]</td>
<td>-</td>
</tr>
<tr>
<td><strong>mono</strong>-Succinate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Succinate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- The structure has not been reported. ○ The structure has been mentioned to dissolve cellulose, but the data was not given except [EMIm]Ac (15 wt%[15c]). × The structure has been reported, but has not been used to dissolve cellulose.
2 Applications of Ionic Liquids as Solvents

Cellulose is the major carbohydrate produced by plant photosynthesis and therefore an important biogenic feedstock.\cite{1d, 1j, 12a, 14, 20, 22, 51} However, poor solubility in conventional solvent systems limits its processing. IL having low volatility, low flammability, high thermal stability and tunable physicochemical properties is considered an alternative to dissolve cellulose.\cite{1b, 1d, 1j, 14, 22, 51-52}

To foster understanding of the structure activity relationship, a systematic approach towards the synthesis and experimental determination was carried out. This data is mandatory for the future design of novel and superior solvent systems, the synthesis of a set of IL was carried out and used for the experimental determination of cellulose solubility at different temperatures.

In addition, another abundant natural product betulin (lup-20(29)-en-3β,28-diol) is broadly found in birch bark, but also in the roots or leaves of some ash trees.\cite{53} It and its derivatives exhibit versatile pharmaceutical activity, including antitumor, anti-HIV, antiviral, antibacterial, anti-inflammatory, and antimalarial properties.\cite{54}

Until now, betulin has been industrially extracted using traditional organic solvents.\cite{54d, 55} This not only leads to safety constraints, but also economic and environmental issues.\cite{56} Most importantly, the current technology co-extract many impurities, requiring additional column chromatography or other purification methods in order to obtain pharmaceutically pure betulin, resulting in lengthy processing times and limited yields.

ILs have demonstrated higher solubilities and higher extraction efficiencies for natural substances than traditionally-used molecular solvents.\cite{1b-d, 1j, 16d, 22b, 27, 51, 52d, 57} Efforts to extract betulin from birch bark using synthesized ILs were made.

2.1 Results and Discussion

2.1.1 Syntheses of Carboxylate-based Structures

Considering the dramatic influence of impurities on the physical properties of ILs,\cite{1b, 5, 58} a straightforward route was chosen to get pure [RMI m] Carboxylate (R=Me or Et). The method is the zwitterion method, which only needs two steps: carboxylate-type
zwitterion formation and neutralization with acid. Compared with the classic method, which requires three steps (quaternization with alkyl halide, anion exchange, neutralization with corresponding acid), the applied method has many advantages (e.g. free halide, low impurity content, and environmentally benign.).\(^2\)\(^{-3}\, 4b,\, 59\) Since quaternary ammonium type zwitterions are difficult to form, the traditional method was used to obtain the target quaternary ammonium molecules.

### 2.1.1.1 Synthesized carboxylate-based structures

<table>
<thead>
<tr>
<th>Anion</th>
<th>Cation</th>
<th>1,3-Dimethylimidazolium</th>
<th>1-Ethyl-3-methylimidazolium</th>
<th>N,N-Diethyl-N,N-dimethylyl ammonium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formate:</td>
<td></td>
<td></td>
<td>2a</td>
<td>3a</td>
</tr>
<tr>
<td>Acetate:</td>
<td></td>
<td>1b</td>
<td>[DEDMN]Formate</td>
<td>white solid</td>
</tr>
<tr>
<td>n-Propionate:</td>
<td></td>
<td>1c</td>
<td>[DEDMN]Formate</td>
<td>yellowish solid</td>
</tr>
<tr>
<td>n-Butyrate:</td>
<td></td>
<td>1d</td>
<td>[DEDMN]Formate</td>
<td>yellowish solid</td>
</tr>
<tr>
<td>iso-Butyrate:</td>
<td></td>
<td>1e</td>
<td>[DEDMN]Formate</td>
<td>yellowish solid</td>
</tr>
<tr>
<td>mono-Maleate:</td>
<td></td>
<td>1f</td>
<td>[DEDMN]Formate</td>
<td>yellowish solid</td>
</tr>
<tr>
<td>Maleate:</td>
<td></td>
<td>1g</td>
<td>[DEDMN]Formate</td>
<td>yellowish solid</td>
</tr>
<tr>
<td>Succinate:</td>
<td></td>
<td>1h</td>
<td>[DEDMN]Formate</td>
<td>yellowish solid</td>
</tr>
</tbody>
</table>

**Table 2-1:** Overview of the carboxylate-based compounds synthesized for the study
Three homologous series of cation structures: [DMIm]Carboxylate, [EMIm]Carboxylate and [DEDMN]Carboxylate were synthesized, and are listed in Table 2-1. The appearances of these compounds are shown in Table 5-1 in Appendices.

Although these small cations (molecular weight less than 120) increased the percentage of anion in ILs, they also increased the melting point of the compounds. Therefore, only seventeen compounds actually turned out to be ILs as defined by fluids below 373 K. In the [EMIm]Carboxylate and [DMIm]Carboxylate, the halide content was less than MDL of ion chromatography (MDL: method detection limit, 10 ppm for all halide).  For [DEDMN]Carboxylate, there was only chloride in the product, the chloride contents in these compounds are listed in Table 2-2. Fifteen compounds: 1d, 1e, 1g, 1h, 1i, 2e, 2h, 2i, 3a, 3c, 3d, 3e, 3g, 3h, 3i, have not been previously reported in the literature.

Table 2-2: Chloride content of [DEDMN]Carboxylate

<table>
<thead>
<tr>
<th>Ionic liquid</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>3d</th>
<th>3e</th>
<th>3f</th>
<th>3g</th>
<th>3h</th>
<th>3i</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride content/ppm</td>
<td>&lt; 10</td>
<td>1678</td>
<td>29</td>
<td>&lt; 10</td>
<td>119</td>
<td>104</td>
<td>&lt; 10</td>
<td>1683</td>
<td>2625</td>
</tr>
</tbody>
</table>

2.1.1.2 Removing residual carboxylic acid from ionic liquids

In the preparation of carboxylate-based ILs, residual carboxylic acids were difficult to be removed from products. Although small molecular carboxylic acids did not have high boiling points, they could not be removed under reduced pressure. Actually, the excess carboxylic acids formed hydrogen bonds with carboxylate anions, which mad their removal difficult. Due to the interaction between the carboxylate anion with the residual carboxylic acid, there was no difference between these two kinds of anions and only one set of peaks could be assigned to them in the $^1$H-NMR. But if there was carboxylic acid left in the ILs, the integration of the carboxylate signal would be higher than expected. Recently, ILs catalyzing the esterification of carboxylic acid and alcohol has been reported.$^{[60]}$ In contrast to the carboxylic acid, its corresponding ester exhibits a lower

![Scheme 2-1](image-url).
boiling point and can not form hydrogen bonds with ILs. Therefore, the investigation of the method for purifying IL was carried out. \(N,N\)-Diethyl-\(N,N\)-dimethylammonium propionate was taken as a model (Scheme 2-1) and mixed with methanol for esterification. After a certain time, a sample was taken, dried, and then dissolved in \(\text{D}_2\text{O}\) for \(^1\text{H}\)-NMR measurement. The integration of peak A (assigned to methyl group of propionate, referenced peak B assigned to methyl group of the cation) decreased over time in \(^1\text{H}\)-NMR spectra, due to esterification (Figure 2-1).

![Figure 2-1](image_url) Integration in \(^1\text{H}\)-NMR spectra decreasing during the esterification of the residual carboxylic acid with methanol.

This method not only was feasible for the quaternary ammonium-based ILs, but also worked for purifying imidazolium-based ILs. For imidazolium-based ILs, normally the esterification needed higher temperature.

### 2.1.2 Thermal Properties of Synthesized Structures

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) techniques were used to characterize phase behaviors and thermostabilities, respectively. The results are summarized in Table 2-3.

Only nine compounds (\(1\text{a}, 1\text{b}, 1\text{f}, 1\text{h}, 2\text{a}, 2\text{e}, 3\text{b}, 3\text{d}, 3\text{f}\)) had melting temperatures determined. According to the DSC and TGA results, eight compounds (\(1\text{d}, 1\text{e}, 2\text{b}, 2\text{c}, 2\text{d}, 2\text{f}, 2\text{g}, 2\text{h}\)) showed glass transition at temperatures of 190 to 240 K. Decomposition temperatures for all compounds were above 430 K. In comparison to the reported decomposition temperatures of [EMIm]Acetate (\(2\text{b}, 523\) K),\(^{[61]}\) [DMIm]Formate (\(1\text{a}, 523.9\) K) and [DMIm]Acetate (\(1\text{b}, 544.6\) K),\(^{[62]}\) the measured results for these three
compounds were more conservative (2b: 492 K, 1a: 494 K, 1b: 490 K). As onset decomposition temperatures were given instead of their midpoint decomposition temperatures, this was explained easily. With the same anion (except \textit{n}-butyrate and \textit{iso}-butyrate), there were almost no difference between imidazolium cations in thermal stability. Obviously quaternary ammonium cation was less stable than imidazolium cations, except for structures with maleate anions. With the same cation, anions with only one carboxylate had similar decomposition temperature, and dicarboxylates anions with an internal hydrogen bond were more stable than those without internal hydrogen bonds.

In imidazolium-based structures, \textit{mono}-succinate anion had the highest decomposition temperature, and maleate anion had the lowest. Anions without C=C double bond were more stable. However, in quaternary ammonium-based structures, anions with C=C double bond were more stable. Moreover, \textit{mono}-maleate anion provided the most stable structure.

In imidazolium-based structures, \textit{mono}-succinate anion had the highest decomposition temperature, and maleate anion had the lowest. Anions without C=C double bond were more stable. However, in quaternary ammonium-based structures, anions with C=C double bond were more stable. Moreover, \textit{mono}-maleate anion provided the most stable structure.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|c|c|c|c|}
\hline
 & 1a & 1b & 1c & 1d & 1e & 1f & 1g \textsuperscript{[e]} & 1h & 1i \textsuperscript{[e]} \\
\hline
T\textsubscript{m} \textsuperscript{[a]/K} & 363 & 296 & - & - & - & 394 & - & 384 & - \\
\hline
T\textsubscript{g} \textsuperscript{[b]/K} & - & - & - & 197 & 215 & - & - & - & - \\
\hline
T\textsubscript{d} \textsuperscript{[c]/K} & 494 & 490 & 486 & 487 & 485 & 472 & 441 & 508 & 495 \\
\hline
2a & 2b & 2c \textsuperscript{[e]} & 2d & 2e & 2f & 2g & 2h & 2i \textsuperscript{[e]} \\
\hline
T\textsubscript{m} \textsuperscript{[a]/K} & 329 & - & - & - & 209 & - & - & - & - \\
\hline
T\textsubscript{g} \textsuperscript{[b]/K} & - & 203 \textsuperscript{[d]} & 200 & 195 & - & 193 & 216 & 236 & - \\
\hline
T\textsubscript{d} \textsuperscript{[c]/K} & 495 & 492 & 488 & 511 & 499 & 468 & 438 & 511 & 499 \\
\hline
3a & 3b & 3c & 3d & 3e & 3f & 3g \textsuperscript{[e]} & 3h & 3i \\
\hline
T\textsubscript{m} \textsuperscript{[a]/K} & - & 357 & - \textsuperscript{[f]} & 356 & - \textsuperscript{[f]} & 277 & - \textsuperscript{[f]} & - \textsuperscript{[f]} & - \textsuperscript{[f]} \\
\hline
T\textsubscript{g} \textsuperscript{[b]/K} & - & - & - & - & - & - & - & - & - \\
\hline
T\textsubscript{d} \textsuperscript{[c]/K} & 450 & 459 & 455 & 454 & 452 & 501 & 463 & 485 & 464 \\
\hline
\end{tabular}
\caption{Thermal properties of synthesized structures obtained by DSC & TGA.}
\end{table}

\textsuperscript{[a]} T\textsubscript{m}: melting temperature. \textsuperscript{[b]} T\textsubscript{g}: onset glass transition temperature. \textsuperscript{[c]} T\textsubscript{d}: onset decomposition temperature. \textsuperscript{[d]} In line with results reported previously.\textsuperscript{[63]} \textsuperscript{[e]} No phase transitions in the inspected temperature range. \textsuperscript{[f]} Phase transitions in the compound are most probably crystal structure rearrangements.

\subsection*{2.1.3 Cellulose Solubilities in Carboxylate-based Ionic Liquids}

\subsubsection*{2.1.3.1 General methodology of investigations}

At present, visual observation is commonly used to investigate the cellulose solubility in
Although some researchers applied NMR techniques to measure the cellulose content in ILs at high temperature with $^{13}$C-NMR, the high viscosity of the solution makes it difficult to apply for high concentration cellulose-IL solutions. Polarizing light microscope has also been used to observe the small cellulose particles dissolution. Two cellulose addition methods have been reported. One is adding a certain amount of cellulose to the system and varying the temperature, and then recording the lowest temperature, at which it is a clear solution; the other is at a certain temperature, adding new small portions cellulose to the system until the complete dissolution is observed. Here, considering its further application, simplicity and feasibility, visual observation and the second cellulose addition method were used for the study. The flow scheme and setup for dissolving cellulose with IL are shown in Figure 2-2.

**Figure 2-2.** Flow scheme and setup for dissolving cellulose with ionic liquid.
2.1.3.2 Influence of ionic liquid structures

The cellulose solubilities of these compounds are given in Figure 2-3. *mono*-Succinate (2h) or *mono*-maleate (2f, 3f) effectively blocked the hydrogen bond formation between cellulose and anion resulting in no detectable cellulose solubility. In comparison, 2g and 2i having two carboxylate groups showed some solubility for cellulose at elevated temperatures. Generally, dicarboxylate anions gave lower solubility. Comparing succinate to maleate, the C=C double bond decreased the solubility.

![Figure 2-3. α-Cellulose solubilities of carboxylate-based ionic liquids at 333, 353&373K.](image)

Alternative to the commonly used cellulose solvent [EMIm]Ac (2b), other carboxylate-based ILs (2a, 2c, 2d, 2e) had similar cellulose solubility. Considering their similar β value (β value of formate, acetate, propionate, n-butyrate are 1.01, 1.09, 1.10, 1.10, respectively),[22a, 24] and different anion concentrations per gram IL (anion concentration of 2a, 2b, 2c, 2d, 2e were: 6.4, 5.9, 5.4, 5.0, 5.0 mmol g⁻¹, respectively), the similar results with [EMIm]Ac were not out of the expectation. With the same anion, [EMIm] as the cation (2a-e) had higher cellulose solubility than that of [DMIm] (1a-e). Quaternary ammonium as the cation (3b, 3d, 3f) showed lower cellulose solubility. Although the influence of the cation on cellulose solubility was usually considered to be less important than anion, it could not be neglected.
2.1.3.3 Water content and halide content influences

Water content in ILs significantly affects cellulose solubility.\textsuperscript{[10a, b, 21]} Swatloski \textit{et al.} reported that 1 wt.% water can dramatically decrease the cellulose solubility and make cellulose precipitate from its IL solution.\textsuperscript{[14]} To avoid the water influence, the dissolution was carried out under argon atmosphere, and cellulose and IL were dried for at least 12 hours under reduced pressure prior to use. Due to the high hydrophilicity of carboxylate-based ILs, typical water contents of $10^3$ ppm were obtained.

Results of [EMIm]Ac (2b) for the dissolution of cellulose showed that water contents of less than 2500 ppm did not affect the cellulose solubility (Table 2-4). Since chloride ion may severely affect the properties of ILs even in trace amounts,\textsuperscript{[5, 65]} the effect of the chloride content on dissolution was investigated. Results indicated that chloride contents less than 1200 ppm did not have influence on the cellulose solubility (entries 3-5).

\begin{table}[h]
\centering
\begin{tabular}{lcccccc}
\hline
Entry & Compounds & 333 K /wt.\% & 353 K /wt.\% & 373 K /wt.\% & Water Content /ppm & Chloride Content /ppm \\
\hline
1 & [EMIm]Ac \textsuperscript{[b]} & - \textsuperscript{[e]} & 11 & - \textsuperscript{[e]} & 889 & 1200 \\
2 & [EMIm]Ac \textsuperscript{[b]} & 9 & 11 & 16 & 1262 & 1200 \\
3 & [EMIm]Ac \textsuperscript{[b]} & 10 & 12 & 16 & 1423 & 1200 \\
4 & [EMIm]Ac \textsuperscript{[c]} & - \textsuperscript{[e]} & 11 & - \textsuperscript{[e]} & 1981 & 44 \\
5 & [EMIm]Ac \textsuperscript{[d]} & 9 & 13 & 15 & 2513 & < 10 \textsuperscript{[a]} \\
\hline
\end{tabular}
\caption{Investigation of water content and chloride content effects on $\alpha$-cellulose solubility of [EMIm]Ac.}
\end{table}

\textsuperscript{[a]} Chloride method detection limit of Ion Chromatography is 10 ppm. \textsuperscript{[b]} Purchased from Iolitec Co. \textsuperscript{[c]} [EMIm]Ac as synthesized according to the literature\textsuperscript{[45]}. \textsuperscript{[d]} [EMIm]Ac was synthesized according to the synthetic route described. \textsuperscript{[e]} Not determined.

2.1.3.4 Modelling cellulose solubilities in ionic liquids using COSMO-RS

To find a great cellulose solvent from hundreds of thousands of combinations of cations and anions in short time, Kai Leonhard and co-workers used the COSMO-RS (Conductor-like Screening Model for Realistic Solvation) method, which gains full predictivity from an underlying quantum chemical calculation of molecular surface charges in an ideal conductor and also has high working speed. A screening of more than 2000 ILs has been done and is shown in Figure 2-4 (The lower ln $\gamma^{\infty}$ value, the higher cellulose dissolving power.).\textsuperscript{[52a]} The data indicates that anion has the dominating effect
Figure 2-4. Graphical representation of the contributions to the activity coefficients of cellulose in 2272 different ILs at infinite dilution.\textsuperscript{[52a]}
on dissolving cellulose. This correlates with experimental data. It also shows that carboxylates (acetate and decanoate) are favored anions, 1-ethyl-3-methylimidazolium cation, 1,3-dimethylimidazolium cation and small quaternary ammonium cation are also good candidates.

Prof. Dr. Kai Leonhard and Jens Kahlen helped me calculate the cellulose solubilities in the synthesized structures using COSMO-RS model. The qualitative trend of the solubilities is shown in Table 2-5.

Table 2-5: Calculated trend of cellulose solubilities in the synthesized structures.

<table>
<thead>
<tr>
<th>X</th>
<th>Compound</th>
<th>X</th>
<th>Compound</th>
<th>X</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>[DEDMN]Acetate</td>
<td>12</td>
<td>[EMIm]Acetate</td>
<td>21</td>
<td>[EMIm]Formate</td>
</tr>
<tr>
<td>4</td>
<td>[DEDMN]Propionate</td>
<td>13</td>
<td>[DMIm]Propionate</td>
<td>22</td>
<td>[DEDMN]mono-Maleate</td>
</tr>
<tr>
<td>5</td>
<td>[DEDMN]Butyrate</td>
<td>14</td>
<td>[EMIm]Propionate</td>
<td>23</td>
<td>[DMIm]mono-Maleate</td>
</tr>
<tr>
<td>6</td>
<td>[DEDMN]i-Butyrate</td>
<td>15</td>
<td>[EMIm]Butyrate</td>
<td>24</td>
<td>[EMIm]mono-Maleate</td>
</tr>
<tr>
<td>7</td>
<td>[DMIm]Succinate</td>
<td>16</td>
<td>[DMIm]Butyrate</td>
<td>25</td>
<td>[DEDMN]mono-Succinate</td>
</tr>
<tr>
<td>8</td>
<td>[DMIm]Maleate</td>
<td>17</td>
<td>[EMIm]i-Butyrate</td>
<td>26</td>
<td>[EMIm]mono-Succinate</td>
</tr>
<tr>
<td>9</td>
<td>[EMIm]Succinate</td>
<td>18</td>
<td>[DMIm]i-Butyrate</td>
<td>27</td>
<td>[DMIm]mono-Succinate</td>
</tr>
</tbody>
</table>

[a] X is the number in the sequence. 1 has the highest cellulose solubility, 27 has the lowest.

The result indicated that, in each cation series, the cellulose solubility decreased with the sequence of the anions: succinate > maleate > acetate > n-propionate > n-butyrate > iso-butyrate > formate > mono-maleate > mono-succinate. In experimental results, low cellulose solubilities were also observed in ILs with mono-succinate anion and mono-maleate anion. However, the trend in other anions, in the experimental results, did not match the calculated result (Table 2-6).
Table 2-6: Comparison of cellulose solubilities in [EMIm]Carboxylates between calculated results and experimental results.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Calculated trend</th>
<th>Experimental trend $^{[c]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[EMIm]Succinate</td>
<td>[EMIm]Propinate (18 wt%)</td>
</tr>
<tr>
<td>2</td>
<td>[EMIm]Maleate</td>
<td>[EMIm]iso-Butyrate (17 wt%)</td>
</tr>
<tr>
<td>3</td>
<td>[EMIm]Acetate</td>
<td>[EMIm]Butyrate (16 wt%)</td>
</tr>
<tr>
<td>4</td>
<td>[EMIm]Propinate</td>
<td>[EMIm]Acetate (16 wt%)</td>
</tr>
<tr>
<td>5</td>
<td>[EMIm]Butyrate</td>
<td>[EMIm]Formate (15 wt%)</td>
</tr>
<tr>
<td>6</td>
<td>[EMIm]iso-Butyrate</td>
<td>[EMIm]Succinate (11 wt%)</td>
</tr>
<tr>
<td>7</td>
<td>[EMIm]Formate</td>
<td>[EMIm]Maleate (4 wt%)</td>
</tr>
<tr>
<td>8</td>
<td>[EMIm]mono-Maleate</td>
<td>[EMIm]mono-Maleate $^{[b]}$</td>
</tr>
<tr>
<td>9</td>
<td>[EMIm]mono-Succinate</td>
<td>[EMIm]mono-Succinate $^{[b]}$</td>
</tr>
</tbody>
</table>

[a] 1 has the highest cellulose solubility, 9 has the lowest. [b] Both have no cellulose solubility. [c] The experimental cellulose solubility in IL at 373 K is shown in parentheses.

In each anion series, the trend of cellulose solubilities in three cations varied with anions, and also differed from the experimental result. Even in the acetate-based ILs, the experimental data exhibited an opposite trend with the calculated result (Table 2-7).

Table 2-7: Comparison of cellulose solubilities in acetate-based ILs between calculated results and experimental results.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Calculated trend</th>
<th>Experimental trend $^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[DEDMN]Ac</td>
<td>[EMIm]Ac (16 wt%)</td>
</tr>
<tr>
<td>2</td>
<td>[DMIm]Ac</td>
<td>[DMIm]Ac (11 wt%)</td>
</tr>
<tr>
<td>3</td>
<td>[EMIm]Ac</td>
<td>[DEDMN]Ac (2 wt%)</td>
</tr>
</tbody>
</table>

[a] 1 has the highest cellulose solubility, 3 has the lowest. [b] Experimental cellulose solubilities in ILs at 373 K is shown in parentheses.

In a word, although modeling cellulose solubilities in ionic liquids using COSMO-RS offered a fast way to optimize IL structures, the predicted result only provided a guideline. Therefore, the experimental determination remained inevitable for IL screening.
2.1.3.5 Investigation of regenerated ionic liquids

Several cellulose-IL solutions (1b, 1d, 2b, 2d, 2i,) were chosen as representatives to investigate the changes of ILs through cellulose dissolution. Water was added to the solution to precipitate cellulose, the IL-water solution was collected through filtration. After removing water under reduced pressure and drying overnight at 333 K, $^1$H-NMR and $^{13}$C-NMR spectra showed no apparent difference. The spectra of 1b ([DMIm]Ac) are shown in Figure 2-5. Other spectra can be found in Appendices.

2.1.3.6 Degradation of precipitated cellulose

During the regeneration of IL from cellulose-IL solution, the precipitated cellulose was collected. It is reported that precipitated cellulose has almost the same DP as the initial one, but the morphology changes significantly and makes the cellulose more accessible for degradation. Having experiences in depolymerizing cellulose, colleagues Dr. Pablo Domínguez de María and Philipp Grande helped me degrade the precipitated cellulose from a series of ILs ([DMIm]Ac, [DMIm]Butyrate and [EMIm]Butyrate) using oxalic acid. The concentration of formed monosaccharides during cellulose degradation was measured for analysis.

In comparison with untreated cellulose, cellulose pretreated with either [EMIm]Butyrate or [DMIm]Butyrate both exhibited faster degradation rates and higher yields (Figure 2-6).
30 wt.% Sodium chloride as co-catalyst significantly increased the degradation rate (Figure 2-7). Furthermore, the pretreated cellulose using [DMIm]Ac was more accessible for degradation.

**Figure 2-6.** Degradation of precipitated cellulose using oxalic acid.

**Figure 2-7.** Degradation of precipitated cellulose using 30 wt.% NaCl as co-catalyst.
2.1.4 Betulin Extraction Using Carboxylate-based Ionic Liquids

Dr. Katharina Bica and co-workers, from Vienna University of Technology, compared the extraction efficiencies of conventional solvents and IL ([EMIm]Ac) for betulin extraction from birch bark (Table 2-8). Obvious differences were observed when [EMIm]Ac was used in place of conventional solvents (e.g., water, toluene, methanol, ethanol or chloroform) (entries 1-6). [EMIm]Ac provided higher extraction yields (entries 6-7). Microwave irradiation drastically reduced extraction time, such that a yield of about 32 wt.% extraction yield was achieved in 15 minutes (entry 8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yield/wt.% [d]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>5 wt.%, 373 K, 24 h</td>
<td>9.8 ± 1.0</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>5 wt.%, reflux, 24 h</td>
<td>21.6 ± 1.2</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>5 wt.%, reflux, 24 h</td>
<td>23.4 ± 0.6</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>5 wt.%, 373 K, 24 h</td>
<td>25.4 ± 0.7</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃</td>
<td>5 wt.%, 373 K, 24 h</td>
<td>26.7 ± 1.3</td>
</tr>
<tr>
<td>6</td>
<td>[EMIm]Ac</td>
<td>5 wt.%, 373 K, 24 h</td>
<td>30.0 ± 1.0</td>
</tr>
<tr>
<td>7</td>
<td>[EMIm]Ac</td>
<td>10 wt.%, 373 K, 24 h</td>
<td>31.0 ± 1.6</td>
</tr>
<tr>
<td>8</td>
<td>[EMIm]Ac</td>
<td>10 wt.%, MW, 373K, 15 min</td>
<td>31.7 ± 2.8</td>
</tr>
</tbody>
</table>

[a] Mean ± STD, n = 3. [b] Performed using a Biotage Microwave unit. [c] 5 wt.% means that 5 parts birch bark is extracted using 95 parts solvent. [d] Determined via HPLC using 1-methylcyclohexene as the internal standard. The yield is based on the mass of the birch bark.

Considering the high cellulose solubilities of carboxylate-based ILs and the strong extraction performances of ILs for natural substances, [1b-d, 1j, 16d, 22b, 27, 51, 52d, 57] selected carboxylate-based ILs ([DMIm]Ac, [DMIm]Butyrate, [EMIm]Ac, [EMIm]Propionate, [EMIm]Butyrate and [EMIm]i-Butyrate) were investigated with regard to betulin extraction. (Figure 2-8).
All the selected carboxylate-based ILs, with the exception of [DMIm]Ac, exhibited good abilities to extract betulin, with yields of 30 to 31%. The extraction efficiencies of these ILs exhibited a similar trend to their cellulose solubilities. With the same anion, the [EMIm] cation demonstrated higher extraction efficiency than the [DMIm]. With [DMIm] as the cation, the n-butyrate anion gave a better result than the acetate anion. However, with [EMIm] as the cation, there was no obvious difference between these two carboxylate anions.

A scale-up process and recovery method were developed using [EMIm]Ac as the extraction solvent. More details of the procedures, results, scale-up strategy and recovery of ILs can be found in Ref.[68].

2.2 Experimental

α-Cellulose and anion exchange resins IRA-400(OH) were purchased from Sigma-Aldrich. All other chemicals were obtained from Alfa Aesar and were used as received unless stated otherwise. High vacuum is always carried out under 5 Pa pressure.

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a AV400 MHz NMR or AV300 MHz NMR (Bruker BioSpin) at r.t.. Chemical shifts are given in ppm relative to tetramethylsilane ($^1$H- and $^{13}$C-NMR) or the residual solvent peak. For the description of multiplicity of the signal following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad.

Water content was determined by coulometric Karl-Fischer-titration (Metrohm).
Ion chromatography was carried out using ICS-1500 (Dionex). The detection threshold is 10 ppm for all halides.

Mass spectra were recorded on a Varian Model 500-Mass Spectrometer equipped with electrospray ion source (ESI), Positive mode (80 volts) or negative mode (1 volt).

Melting and glass transition temperatures were recorded with differential scanning calorimeter (DSC) (NETZSCH DSC 204). Samples were placed in a sealed aluminum pan with a pinhole. An empty pan was used as the reference. Measurements were carried out by heating from 173 K to 423 K with the rate of 10 K min\(^{-1}\) under nitrogen atmosphere. Decomposition temperatures were measured by NETZSCH TG 209. All samples were run in aluminum oxide pans under nitrogen atmosphere with heating rate of 10 K min\(^{-1}\).

### 2.2.1 Preparation of Proposed Structures

#### 2.2.1.1 Synthesis of 1,3-dimethylimidazolium carboxylate

![Synthesis of 1,3-dimethylimidazolium carboxylate](image)

To synthesize the intermediate 1,3-dimethylimidazolium-2-carboxylate, a few modifications were made to the literature procedure\cite{2}. 10 mL 1,3-dimethylimidazole, 15 mL dimethylcarbonate and 20 mL methanol were added to a 75 mL autoclave, then heated up to 373 K for 24 hours. After removing low-boiling compounds under vacuum and washing with acetone (3×10 mL), 10.5 g 1,3-Dimethylimidazolium-2-carboxylate was obtained, yield: 60 %. For transformation into the carboxylates, 2.8 g intermediate was dissolved with 20 mL water or ethanol-water (10 mL-10 mL) as the solvent, then 20 mmol carboxylic acid was added dropwise. At 343 K, the solution was stirred over 3 hours. After removal of the solvent, pure product was obtained quantitatively.

1,3-Dimethylimidazolium-2-carboxylate

![1,3-Dimethylimidazolium-2-carboxylate](image)
1H-NMR(400 MHz; D₂O; δ/ppm) : 3.97 (s, 6H, NCH₃), 7.35 (s, 2H, NCHCHN). It conforms with the literature[2].

1,3-Dimethylimidazolium formate (1a):

\[
\text{H-NMR (400 MHz; DMSO-d₆; δ/ppm): 3.86 (s, 6H, NCH₃), 7.79 (d, } \text{J(H4,H2)=1.6 Hz, 2H, NCHCHN), 8.60 (s, 1H, HCO₂), 9.70 (br, 1H, NCHN).}
\]

\[
\text{ESI-MS: Cation ([C₃H₅N₂]⁺, calc.: 97.1) m/z=97.1.}
\]

1,3-Dimethylimidazolium acetate (1b):

\[
\text{H-NMR (400 MHz; DMSO-d₆; δ/ppm): 1.57 (s, 3H, O₂CCH₃), 3.83 (s, 6H, NCH₃), 7.80 (d, } \text{J(H4,H2)=J(H5,H2)=1.6 Hz, 2H, NCHCHN), 10.02 (br, 1H, NCHN).}
\]

\[
\text{ESI-MS: Cation ([C₃H₅N₂]⁺, calc.: 97.1) m/z=97.1; Anion ([C₂H₃O₂]⁻, calc.: 59.0) m/z=59.0.}
\]

1,3-Dimethylimidazolium n-propionate (1c):

\[
\text{H-NMR (400 MHz; DMSO-d₆; δ/ppm): 0.87 (t, } \text{J(H,H)=7.6 Hz, 3H, CH₃CH₂), 1.82 (q, J(H,H)=7.6 Hz, 2H, CH₂CH₂), 3.87 (s, 6H, NCH₃), 7.84 (s, 2H, NCHCHN), 10.17 (s, 1H, NCHN).}
\]

\[
\text{ESI-MS: Cation ([C₃H₅N₂]⁺, calc.: 97.1) m/z=97.1; Anion ([C₃H₅O₂]⁻, calc.: 73.0) m/z=73.0.}
\]
1,3-Dimethylimidazolium \textit{n}-butyrate (1d):

\[ \text{1H-NMR (400 MHz; DMSO-\textit{d}_6; \delta/ppm): 0.79 (t, }^3J(\text{H,H})=7.2 \text{ Hz, 3H, CH}_2\text{CH}_3\text{), 1.40 (sextet, 2H, CH}_3\text{CH}_2\text{), 1.79 (t, }^3J(\text{H,H})=7.2 \text{ Hz, 2H, CO}_2\text{CH}_2\text{), 3.87 (s, 6H, NCH}_3\text{), 7.76 (d, }^4J(\text{H4,H2})=-^4J(\text{H5,H2})=1.6 \text{ Hz, 2H, NCHCHN)}\text{, 10.14 (br, 1H, NCHN).} \]

\[ \text{13C-NMR (100 MHz; DMSO-\textit{d}_6; \delta/ppm): 14.6 (CH}_3\text{CH}_2\text{), 19.9 (CH}_3\text{CH}_2\text{), 35.4 (NCH}_3\text{), 41.4 (O}_2\text{CCH}_2\text{), 123.3 (NCHCHN), 138.2 (NCHN), 175.3 (CH}_2\text{CO}_2\text{).} \]

ESI-MS: Cation ([C\textsubscript{5}H\textsubscript{9}N\textsubscript{2}]\textsuperscript{+}, calc.: 97.1) m/z=97.1; Anion ([C\textsubscript{4}H\textsubscript{7}O\textsubscript{2}]\textsuperscript{-}, calc.: 87.1) m/z=87.1.

1,3-Dimethylimidazolium \textit{iso}-butyrate (1e):

\[ \text{1H-NMR (400 MHz; DMSO-\textit{d}_6; \delta/ppm): 0.90 (d, }^3J(\text{H,H})=6.8 \text{ Hz, 6H, CH(CH}_3\text{)_2)}\text{, 1.97 (septet, }^3J(\text{H,H})=6.8 \text{ Hz, 1H, CHCO}_2\text{), 3.87 (s, 6H, NCH}_3\text{), 7.80 (d, }^4J(\text{H4,H2})=-^4J(\text{H5,H2})=1.6 \text{ Hz, 2H, NCHCHN)}\text{, 10.14 (br, 1H, NCHN).} \]

\[ \text{13C-NMR (100 MHz; DMSO-\textit{d}_6; \delta/ppm): 21.0 (CH(CH}_3\text{)_2)}\text{, 35.4 (NCH}_3\text{), 36.8 ((CH}_3\text{)_2CH)}\text{, 123.3 (NCHCHN), 138.5 (NCHN), 179.0 (CHCO}_2\text{).} \]

ESI-MS: Cation ([C\textsubscript{5}H\textsubscript{9}N\textsubscript{2}]\textsuperscript{+}, calc.: 97.1) m/z=97.0; Anion ([C\textsubscript{4}H\textsubscript{7}O\textsubscript{2}]\textsuperscript{-}, calc.: 87.1) m/z=87.1.

1,3-Dimethylimidazolium \textit{mono}-maleate (1f):

\[ \text{1H-NMR (400 MHz; DMSO-\textit{d}_6; \delta/ppm): 3.85 (s, 6H, NCH}_3\text{), 6.02 (s, 2H, CHCH), 7.68 (s, 2H, NCHCHN), 9.05 (s, 1H, NCHN).} \]

\[ \text{13C-NMR (100 MHz; DMSO-\textit{d}_6; \delta/ppm): 35.7 (NCH}_3\text{), 123.5 (NCHCHN), 136.2 (CHCH), 137.1 (NCHN), 167.2 (CHCO}_2\text{).} \]

ESI-MS: Cation ([C\textsubscript{5}H\textsubscript{9}N\textsubscript{2}]\textsuperscript{+}, calc.: 97.1) m/z=97.0; Anion ([C\textsubscript{4}H\textsubscript{3}O\textsubscript{4}]\textsuperscript{-}, calc.: 115.0) m/z=115.0.
Bis(1,3-dimethylimidazolium) maleate (1g):

\[
\text{\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{maleate_structure.png}
\end{center}
\end{figure}}
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 3.89 (s, 12H, NCH$_3$), 5.46 (s, 2H, CHCH), 7.72 (s, 4H, NCH$\text{CH}_2$N), 9.98 (s, 2H, NCH$_2$N).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 35.4 (NCH$_3$), 123.1 (NCH$\text{CH}_2$N), 130.6 (CHCH), 139.1 (NCH$_2$N), 171.2 (CH$\text{CO}_2$).

ESI-MS: Cation ([C$_5$H$_9$N$_2$]$^+$, calc.: 97.1) m/z=97.0; Anion ([C$_4$H$_2$O$_4$]$^-$, calc.: 114.0) m/z=115.0 ([M+H$^+$]$^+$].

1,3-Dimethylimidazolium mono-succinate (1h):

\[
\text{\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{succinate_structure.png}
\end{center}
\end{figure}}
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 2.23 (s, 4H, CH$_2$CH$_2$), 3.85 (s, 6H, NCH$_3$), 7.69 (s, 2H, NCH$\text{CH}_2$N), 9.08 (s, 1H, NCH$_2$N).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 32.9 (CH$_2$CH$_2$), 35.6 (NCH$_3$), 123.5 (NCH$\text{CH}_2$N), 137.1 (NCH$_2$N), 175.4 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_5$H$_9$N$_2$]$^+$, calc.: 97.1) m/z=97.0; Anion ([C$_4$H$_2$O$_4$]$^-$, calc.: 117.0) m/z=117.1.

Bis(1,3-dimethylimidazolium) succinate (1i):

\[
\text{\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{bis succinate_structure.png}
\end{center}
\end{figure}}
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.97 (s, 4H, CH$_2$CH$_2$), 3.87 (s, 12H, NCH$_3$), 7.75 (s, 4H, NCH$\text{CH}_2$N), 9.99 (s, 2H, NCH$_2$N).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 35.5 (NCH$_3$), 37.0 (CH$_2$CH$_2$), 123.3 (NCH$\text{CH}_2$N), 138.4 (NCH$_2$N), 176.8 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_5$H$_9$N$_2$]$^+$, calc.: 97.1) m/z=97.2; Anion ([C$_4$H$_2$O$_4$]$^-$, calc.: 116.0) m/z=117.0 ([M+H$^+$]$^+$].
2.2.1.2 Synthesis of 1-ethyl-3-methylimidazolium carboxylate

According to the method of synthesizing 1,3-dimethylimidazolium carboxylate and the literature, 1-ethyl-3-methylimidazolium carboxylate was prepared. 10 mL 1-Ethylimidazole, 20 mL dimethylcarbonate, and 20 mL methanol were added to a 75 mL autoclave. Then the solution was heated up to 393 K for 24 hours. After the reaction, the solvent was removed under reduced pressure at temperature less than 313 K. After washing with acetone (3×10 mL), the intermediate 1-ethyl-3-methylimidazolium-2-carboxylate was obtained, 8.1 g, yield: 51 %.

3.08 g Intermediate was dissolved in 20 mL water or ethanol-water (10 mL-10 mL), subsequently 20 mmol carboxylic acid was added. At 343 K, the solution was stirred over 3 hours. After removal of the solvent, pure product was obtained quantitatively.

Target molecules were also prepared by replacing the intermediate with 1-ethyl-3-methylimidazolium hydrogen carbonate, which was synthesized with the following procedure: 1-Ethylimidazolium-2-carboxylate was dissolved in 20 mL water, and stirred at 313 K overnight. After removing water under reduced pressure and washing with acetone (3×10 mL), pure product 1-ethyl-3-methylimidazolium hydrogen carbonate was obtained.

1-Ethylimidazolium-2-carboxylate

$^1$H-NMR (400 MHz; D$_2$O; δ/ppm) : 1.40 (t, $^3$J(H,H)=7.2 Hz, 3H, CH$_2$CH$_3$), 3.92 (s, 3H, NCH$_3$), 4.37 (q, $^3$J(H,H)=7.2 Hz, 2H, NCH$_2$), 7.35 (d, $^3$J(H,H)=1.6 Hz, 1H, NCH), 7.41 (d, $^3$J(H,H)=1.6 Hz, 1H, NCH).
$^{13}$C-NMR (100 MHz; D$_2$O; δ/ppm): 15.0 (CH$_2$CH$_3$), 36.4 (NCH$_3$), 45.1 (NCH$_2$), 121.2 (NCH), 123.1 (NCH), 139.6 (NCHN), 158.3 (CHCO$_2$).

1-Ethyl-3-methylimidazolium hydrogen carbonate:

\[
\text{HO-}^+\text{N-}\text{N-}\text{N-}\text{CH}_3
\]

$^1$H-NMR (400 MHz; D$_2$O; δ/ppm) : 1.43 (t, $^3$J(H,H)=7.2 Hz, 3H, CH$_2$CH$_3$), 3.82 (s, 3H, NCH$_3$), 4.15 (q, $^3$J(H,H)=7.2 Hz, 2H, NCH$_2$), 7.35 (d, $^3$J(H,H)=1.6 Hz, 1H, NCH), 7.42 (d, $^3$J(H,H)=1.6 Hz, 1H, NCH), 8.65 (s, 1H, NCHN).

$^{13}$C-NMR (100 MHz; D$_2$O; δ/ppm): 14.4 (CH$_2$CH$_3$), 35.5 (NCH$_3$), 44.7 (NCH$_2$), 121.7 (NCH), 123.3 (NCH), 160.2 (HCO$_2$).

1-Ethyl-3-methylimidazolium formate (2a):

\[
\text{H-COO-}^+\text{N-}\text{N-}\text{N-}\text{CH}_3
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm) : 1.39 (t, $^3$J(H,H)=7.2 Hz, 3H, CH$_2$CH$_3$), 3.87 (s, 3H, NCH$_3$), 4.21 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_3$CH$_2$), 7.82 (dd, $^3$J(H-H$_5$)=4$^3$J(H$_4$,H$_2$)=1.6 Hz, 1H, NCH), 7.92 (dd, $^3$J(H$_5$,H$_4$)=4$^3$J(H$_5$,H$_2$)=1.6 Hz, 1H, NCH), 8.63 (s, 1H, HCO$_2$), 9.86 (br, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 15.2 (CH$_2$CH$_3$), 35.5 (NCH$_3$), 44.0 (NCH$_2$), 122.0 (NCH), 123.6 (NCH), 137.2 (NCHN), 165.5 (HCO$_2$).

1-Ethyl-3-methylimidazolium acetate (2b):

\[
\text{O-}^+\text{N-}\text{N-}\text{N-}\text{CH}_3
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm) : 1.38 (t, $^3$J(H,H)=7.2 Hz, 3H, CH$_2$CH$_3$), 1.58 (s, 3H, O$_2$CCH$_3$), 3.89 (s, 3H, NCH$_3$), 4.23 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_3$CH$_2$), 7.90 (d, $^3$J(H,H)=1.6 Hz, 1H, NCH), 8.01 (d, $^3$J(H,H)=1.6 Hz, 1H, NCH), 10.37 (s, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 15.3 (CH$_2$CH$_3$), 26.3 (O$_2$CCH$_3$), 35.4 (NCH$_3$), 43.9 (NCH$_2$), 122.1 (NCH), 123.6 (NCH), 138.0 (NCHN), 173.4 (CH$_3$CO$_2$).

ESI-MS: Cation ([C$_6$H$_{11}$N$_2$]$^+$, calc.: 111.1) m/z=111.0; Anion ([C$_2$H$_3$O$_2$]$^-$, calc.: 59.0) m/z=58.9.
1-Ethyl-3-methylimidazolium n-propionate (2c):

![Structure](image)

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 0.87 (t, $^3$J(H,H)=7.6 Hz, 3H, CH$_3$CH$_2$), 1.40 (t, $^3$J(H,H)=7.2 Hz, 3H, NCH$_2$CH$_3$), 1.79 (q, $^3$J(H,H)=7.6 Hz, 2H, O$_2$CCH$_2$), 3.88 (s, 3H, NCH$_3$), 4.22 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_2$CH$_2$), 7.78 (dd, $^3$J(H4,H5)=4$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 7.88 (dd, $^3$J(H4,H5)=4$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 10.11 (br, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 11.6 (CH$_2$CH$_3$), 15.3 (NCH$_2$CH$_3$), 31.8 (O$_2$CCH$_2$), 35.5 (NCH$_3$), 43.9 (NCH$_2$), 121.9 (NCH), 123.5 (NCH), 137.6 (NCHN), 176.0 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_6$H$_{11}$N$_2$]$^+$, calc.: 111.1) m/z=111.0; Anion ([C$_3$H$_5$O$_2$]$^-$, calc.: 73.0) m/z=73.0.

1-Ethyl-3-methylimidazolium n-butyrate (2d):

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 0.79 (t, $^3$J(H,H)=7.2 Hz, 3H, CH$_2$CH$_2$CH$_3$), 1.40 (m, 5H, NCH$_2$CH$_3$ & O$_2$CCH$_2$CH$_2$), 1.79 (t, $^3$J(H,H)=7.2 Hz, 2H, O$_2$CCH$_2$), 3.88 (s, 3H, NCH$_3$), 4.22 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_2$CH$_2$), 7.82 (dd, $^3$J(H4,H5)=4$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 7.92 (dd, $^3$J(H4,H5)=4$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 10.25 (br, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 14.6 (CH$_2$CH$_2$CH$_3$), 15.2 (NCH$_2$CH$_3$), 35.4 (NCH$_3$), 41.4 (O$_2$CCH$_2$), 43.9 (NCH$_2$), 122.0 (NCH), 123.5 (NCH), 137.8 (NCHN), 175.4 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_6$H$_{11}$N$_2$]$^+$, calc.: 111.1) m/z=111.1; Anion ([C$_3$H$_7$O$_2$]$^-$, calc.: 87.0) m/z=87.0.

1-Ethyl-3-methylimidazolium iso-butyrate (2e):

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 0.89 (d, $^3$J(H,H)=6.8 Hz, 6H, CH(CH$_3$)$_2$), 1.41 (t, $^3$J(H,H)=7.2 Hz, 3H, NCH$_2$CH$_3$), 1.95 (septet, 1H, (CH$_3$)$_2$CH), 3.87 (s, 3H, NCH$_3$), 4.22 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_2$CH$_2$), 7.76 (dd, $^3$J(H4,H5)=4$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 7.86 (dd, $^3$J(H4,H5)=4$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 10.03 (br, 1H, NCHN).
13C-NMR (100 MHz; DMSO-d6; δ/ppm): 15.2 (NCH2CH3), 21.1 (CH(CH3)2), 35.5 (NCH3), 36.9 ((CH3)2CH), 43.9 (NCH2), 121.9 (NCH), 123.5 (NCH), 137.5 (NCHN), 178.8 (CHCO2).

ESI-MS: Cation ([C6H11N2]⁺, calc.: 111.1) m/z=111.1; Anion ([C4H7O2]⁻, calc.: 87.0) m/z=87.1.

1-Ethyl-3-methylimidazolium mono-maleate (2f):

![Structural formula of 1-Ethyl-3-methylimidazolium mono-maleate (2f)](image)

1H-NMR (400 MHz; D2O; 1,4-dioxane; δ/ppm) : 1.44 (t, 3J(H,H)=7.2 Hz, 3H, NCH2CH3), 3.84 (s, 3H, NCH3), 4.16 (q, 3J(H,H)=7.2 Hz, 2H, CH3CH2), 6.21 (s, 2H, CCH=CH2), 7.36 (dd, 3J(H4,H5)=4J(H4,H2)=1.6 Hz, 1H, NCH), 7.43 (dd, 3J(H4,H5)=4J(H4,H2)=1.6 Hz, 1H, NCH), 8.66 (br, 1H, NCHN).

13C-NMR (100 MHz; D2O; 1,4-dioxane; δ/ppm): 15.1 (NCH2CH3), 36.2 (NCH3), 45.4 (NCH2), 122.5 (NCH), 124.1 (NCH), 134.5 (CH=CH), 136.2 (NCHN), 172.2 (CHCO2).

ESI-MS: Cation ([C6H11N2]⁺, calc.: 111.1) m/z=111.1; Anion ([C4H7O4]⁻, calc.: 115.0) m/z=115.0.

Bis(1-ethyl-3-methylimidazolium) maleate (2g):

![Structural formula of Bis(1-ethyl-3-methylimidazolium) maleate (2g)](image)

1H-NMR (400 MHz; DMSO-d6; δ/ppm) : 1.38 (t, 3J(H,H)=7.2 Hz, 6H, NCH2CH3), 3.89 (s, 6H, NCH3), 4.25 (q, 3J(H,H)=7.2 Hz, 4H, CH3CH2), 5.41 (s, 2H, CH=CH), 7.67 (d, 3J(H,H)=1.6 Hz, 2H, NCH), 7.75 (d, 3J(H,H)=1.6 Hz, 2H, NCH), 9.80 (s, 2H, NCHN).

13C-NMR (100 MHz; DMSO-d6; δ/ppm): 15.3 (NCH2CH3), 35.5 (NCH3), 43.8 (NCH2), 121.5 (NCH), 123.2 (NCH), 130.4 (CH=CH), 138.1 (NCHN), 171.1 (CHCO2).

ESI-MS: Cation ([C6H11N2]⁺, calc.: 111.1) m/z=111.0; Anion ([C4H7O4]⁻, calc.: 114.0) m/z=115.0 ([M+H⁺]).
$^1$H-NMR (400 MHz; DMSO-$d_6$; $\delta$/ppm): 1.41 (t, $^3$J(H,H)=7.2 Hz, 3H, NCH$_2$CH$_3$), 2.28 (t, 4H, CH$_2$CH$_2$), 3.85 (s, 3H, NCH$_3$), 4.19 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_3$CH$_2$), 7.71 (dd, $^3$J(H4,H5)=$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 7.80 (dd, $^3$J(H4,H5)=$^4$J(H4,H2)=1.6 Hz, 1H, NCH), 9.22 (br, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; $\delta$/ppm): 15.1 (NCH$_2$CH$_3$), 35.0 (NCH$_3$), 35.7 (CH$_2$CH$_2$), 44.1 (NCH$_2$), 122.0 (NCH), 123.6 (NCH), 136.4 (NCHN), 175.5 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_6$H$_{11}$N$_2$]$^+$, calc.: 111.1) m/z=111.1; Anion ([C$_4$H$_5$O$_4$]$^-$, calc.: 117.0) m/z=117.0.

Bis(1-ethyl-3-methylimidazolium) succinate (2i):

$^1$H-NMR (400 MHz; DMSO-$d_6$; $\delta$/ppm): 1.39 (t, $^3$J(H,H)=7.2 Hz, 6H, NCH$_2$CH$_3$), 1.97 (s, 4H, CH$_2$CH$_2$), 3.88 (s, 6H, NCH$_3$), 4.23 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_3$CH$_2$), 7.79 (dd, $^3$J(H4,H5)=$^4$J(H4,H2)=1.6 Hz, 2H, NCH), 7.88 (dd, $^3$J(H4,H5)=$^4$J(H4,H2)=1.6 Hz, 2H, NCH), 10.24 (br, 2H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; $\delta$/ppm): 15.3 (NCH$_2$CH$_3$), 35.4 (NCH$_3$), 37.3 (CH$_2$CH$_2$), 43.9 (NCH$_2$), 121.9 (NCH), 123.5 (NCH), 137.9 (NCHN), 177.0 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_6$H$_{11}$N$_2$]$^+$, calc.: 111.1) m/z=111.0; Anion ([C$_4$H$_5$O$_4$]$^-$, calc.: 116.0) m/z=117.0 ([M+H$^+$]).

### 2.2.1.3 Synthesis of N,N-diethyl-N,N-dimethylammonium carboxylate

![Chemical reaction diagram]

According to the literature,$^{[27d, 46]}$ a few modifications were made to get pure products. Under argon atmosphere, 7.0 g N,N-diethylammonium chloride, and 11 mL dimethylcarbonate were added to a 75 mL autoclave, then heated up to 383 K overnight. After removing the low-boiling compounds under reduced pressure and washing with acetone (3×10 mL), 8.5 g pure intermediate N,N-diethyl-N,N-dimethyl ammonium...
chloride was obtained in 91 % yield. Then the intermediate passed over a stacked column of anion exchange resin IRA-400 (OH), to obtain the corresponding hydroxide. Subsequently, the hydroxide was neutralized with a stoichiometric amount of carboxylic acid. After removal of the solvent under reduced pressure, the target molecule was obtained.

\[ \text{N,N-Diethyl-N,N-dimethylammonium chloride:} \]

\[ \text{\text{C\text{H}_2}\text{C\text{H}_3}} \times 6\text{H}, \text{N\text{C\text{H}_3}} \times 3\text{.40 (q,} \text{^3J(H,H)=7.2 Hz,} \text{4H, N\text{C\text{H}_2})}. \text{^* Here,} \text{^1H-}^{14}\text{N coupling constant was measurable, because the highly symmetric} \text{^{14}N made the quadrupolar coupling constant much smaller and the relaxation much slower.}^{[69]} \]

\[ \text{N,N-Diethyl-N,N-dimethylammonium formate (3a):} \]

\[ \text{^1H-NMR (400 MHz; DMSO-}d_6; \text{\text{\delta/ppm}}: 1.37 (t,} \text{^3J(H,H)=7.2 Hz,} \text{^3J(H,N)=2.0 Hz,} \text{6H,} \text{CH_2CH_3}, \text{3.05 (s, 6H, NCH_3), 3.40 (q,} \text{^3J(H,H)=7.2 Hz,} \text{4H, NCH_2).} \text{^*} \]

\[ \text{^1^3C-NMR (100 MHz; DMSO-}d_6; \text{\text{\delta/ppm}}): 7.8 \text{ (CH_2CH_3), 48.7 (NCH_3), 57.7 (NCH_2), 165.0 (HCO_2).} \]

\[ \text{N,N-Diethyl-N,N-dimethylammonium acetate (3b):} \]

\[ \text{^1H-NMR (400 MHz; DMSO-}d_6; \text{\text{\delta/ppm}}: 1.19 (tt,} \text{^3J(H,H)=7.2 Hz,} \text{^3J(H,N)=2.0 Hz,} \text{6H,} \text{CH_2CH_3), 1.54(s, 3H, O_2CCH_3), 3.00(s,} \text{6H, NCH_3), 3.37(q,} \text{^3J(H,H)=7.2 Hz,} \text{4H, NCH_2).} \text{^*} \]

\[ \text{^1^3C-NMR (100 MHz; DMSO-}d_6; \text{\text{\delta/ppm}}): 7.7 \text{ (CH_2CH_3), 25.9 (O_2CCH_3), 48.7 (NCH_3), 57.5 (NCH_2), 172.5 (CH_3CO_2) \text{ ESI-MS: Cation ([C_8H_16N]^+, calc.: 102.1) m/z=102.1; Anion ([C_2H_3O_2]^-, calc.: 59.0) m/z=58.9.} \]

\[ \text{N,N-Diethyl-N,N-dimethylammonium n-propionate (3c):} \]

41
ESI-MS: Cation ([C₆H₁₆N]+, calc.: 102.1) m/z=102.1; Anion ([C₅H₃O₂]⁻, calc.: 73.0) m/z=73.0.

**N,N-Diethyl-N,N-dimethylammonium n-butyrate (3d):**

\[\text{CH}_{3}\text{CCH}_2\text{N},\text{CH}_2\text{CH}_3\]

1H-NMR (400 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 0.78 (t, \(3J(\text{H},\text{H})=7.2\) Hz, 3H, \(\text{CH}_2\text{CH}_3\)), 1.20 (tt, \(3J(\text{H},\text{H})=7.2\) Hz, 6H, \(\text{NCH}_2\text{CH}_3\)), 1.73 (t, \(3J(\text{H},\text{H})=7.2\) Hz, 2H, \(\text{O}_2\text{CCH}_2\text{CH}_2\)), 3.00 (s, 6H, \(\text{NCH}_3\)), 3.35 (q, \(3J(\text{H},\text{H})=7.2\) Hz, 4H, \(\text{NCH}_2\)).

13C-NMR (100 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 7.7 (\(\text{NCH}_2\text{CH}_3\)), 11.6 (\(\text{CH}_2\text{CH}_3\)), 31.6 (\(\text{CH}_3\text{CH}_2\)), 48.7 (\(\text{NCH}_3\)), 57.6 (\(\text{NCH}_2\)), 175.5 (\(\text{CH}_2\text{CO}_2\)).

ESI-MS: Cation ([C₆H₁₆N]+, calc.: 102.1) m/z=102.1; Anion ([C₅H₃O₂]⁻, calc.: 87.0) m/z=87.1.

**N,N-Diethyl-N,N-dimethylammonium iso-butyrate (3e):**

\[\text{CH}\_3\text{CCH}_2\text{N},\text{CH}_2\text{CH}_3\]

1H-NMR (400 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 0.87 (d, \(3J(\text{H},\text{H})=6.8\) Hz, 6H, \(\text{CH(}\text{CH}_3\text{)}_2\)), 1.20 (t, \(3J(\text{H},\text{H})=7.2\) Hz, 6H, \(\text{NCH}_2\text{CH}_3\)), 1.92 (septet, \(3J(\text{H},\text{H})=6.8\) Hz, 1H, \(\text{CH(}\text{CH}_3\text{)}_2\text{CH})

13C-NMR (100 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 7.7 (\(\text{CH}_2\text{CH}_3\)), 21.1 (\(\text{CH(}\text{CH}_3\text{)}_2\)), 36.7 (\(\text{CH(}\text{CH}_3\text{)}_2\text{CH})

ESI-MS: Cation ([C₆H₁₆N]+, calc.: 102.1) m/z=102.1; Anion ([C₄H₇O₂]⁻, calc.: 87.0) m/z=87.0.

**N,N-Diethyl-N,N-dimethylammonium mono-maleate (3f):**

\[\text{HO}\text{C}\text{CH}_2\text{N},\text{CH}_2\text{CH}_3\]
$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.22 (t, $^3$J(H,H)=7.2 Hz, 6H, CH$_2$CH$_3$), 2.96 (s, 6H, NCH$_3$), 3.30 (q, $^3$J(H,H)=7.2 Hz, 4H, NCH$_2$), 6.04 (s, 2H, CH=CH).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 7.7 (CH$_2$CH$_3$), 48.9 (NCH$_3$), 57.9 (NCH$_2$), 136.0 (CH=CH), 167.2 (CHCO$_2$)

ESI-MS: Cation ([C$_6$H$_{16}$N]$^+$, calc.: 102.1) m/z=102.1; Anion ([C$_4$H$_5$O$_4$]$^-$, calc.: 115.0) m/z=115.0.

Bis(N,N-diethyl-N,N-dimethylammonium) maleate (3g):

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.19 (t, $^3$J(H,H)=7.2 Hz, 12H, CH$_2$CH$_3$), 3.01 (s, 12H, NCH$_3$), 3.38 (q, $^3$J(H,H)=7.2 Hz, 8H, NCH$_2$), 5.27 (s, 2H, CH=CH).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 7.8 (CH$_2$CH$_3$), 48.7 (NCH$_3$), 57.5 (NCH$_2$), 130.2 (CH=CH), 170.5 (CHCO$_2$)

ESI-MS: Cation ([C$_6$H$_{16}$N]$^+$, calc.: 102.1) m/z=102.1; Anion ([C$_4$H$_5$O$_4$]$^{2-}$, calc.: 114.0) m/z=115.0 ([M+H$^+$]).

$N,N$-Diethyl-$N,N$-dimethylammonium mono-succinate (3h):

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.22 (tt, $^3$J(H,H)=7.2 Hz, 3.01 (s, 6H, NCH$_3$), 2.22 (s, 4H, CH$_2$CH$_2$), 2.96 (s, 6H, NCH$_3$), 3.30 (q, $^3$J(H,H)=7.2 Hz, 4H, NCH$_2$).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 7.7 (CH$_2$CH$_3$), 33.0 (CH$_2$CH$_2$), 48.8 (NCH$_3$), 57.9 (NCH$_2$), 175.4 (CH$_2$CO$_2$)

ESI-MS: Cation ([C$_6$H$_{16}$N]$^+$, calc.: 102.1) m/z=102.1; Anion ([C$_4$H$_5$O$_4$]$^-$, calc.: 117.0) m/z=117.1.

Bis(N,N-diethyl-N,N-dimethylammonium) succinate (3i):

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.19 (t, $^3$J(H,H)=7.2 Hz, 12H, CH$_2$CH$_3$), 1.86 (s, 4H, CH$_2$CH$_2$), 3.01 (s, 12H, NCH$_3$), 3.37 (q, $^3$J(H,H)=7.2 Hz, 8H, NCH$_2$).
$^{13}$C-NMR (100 MHz; DMSO-$d_6$; $\delta$/ppm): 7.8 (CH$_2$CH$_3$), 37.6 (CH$_2$CH$_2$), 48.6 (NCH$_3$), 57.5 (NCH$_2$), 176.4 (CH$_2$CO$_2$).

ESI-MS: Cation ([C$_6$H$_{16}$N]$^+$, calc.: 102.1) m/z=102.1; Anion ([C$_4$H$_4$O$_4$]$^{2-}$, calc.: 116.0) m/z=117.0 ([M+H$^+$]$^+$).

2.2.1.4 Removing residual carboxylic acid from ionic liquids

1.0 g Crude IL (containing residual carboxylic acid) and 5.0 mL methanol were added to a 25 mL flask, and heated to reflux. A sample was taken every 1 hour to check whether there was still free residual acid in the system with $^1$H-NMR, until the integration ratio was reduced to that as expected. After evaporation of the solvent and the ester, pure IL was obtained.

2.2.2 Dissolving Cellulose in Ionic Liquids

$\alpha$-Cellulose was dried at 373 K and ILs at 333 K under reduced pressure of 5 Pa for 12 hours. The water content of ILs was measured with an automated Karl-Fisher titration. 1.0 g IL was kept in a Schlenk tube immersed in an oil bath. Starting at 333 K, $\alpha$-cellulose was added with an increment of 10 mg under argon atmosphere. After stirring for 30 min, the solution was either clear and another 10 mg cellulose was added; otherwise the temperature was increased by 20 K, up to the maximum temperature of 373 K.

2.2.3 Regeneration of Cellulose and Ionic Liquid

10 mL Water was added to the cellulose-IL solution to precipitate the cellulose. After filtration, the aqueous solution of the IL was obtained. After removing water under reduced pressure and drying overnight at 333 K, $^1$H-NMR and $^{13}$C-NMR measurements were used to characterize the recovered IL. The filter cake or the precipitated cellulose was dried and stored for further investigations.
2.2.4 Cellulose Degradation Using Oxalic Acid

Slurries of cellulose (20 g L\(^{-1}\)) were suspended in water, in which 0.1 M oxalic acid (and 30 wt.% NaCl) was aggregated. Then the mixture was magnetically stirred and heated to 398 K for 6 hours. Samples were taken every one hour for analysis. Colorimetric method PAHBAH was used for measuring produced reducing-end sugars. A calibration curve was recorded taking glucose as the standard substrate. Before determination, the sample was diluted until absorbance values within the linear region of the calibration curve. Equation for linear region: \[ \text{Absorbance} = 0.66 \times [\text{oligomers}] + 0.028 \] (\(r^2=0.997\)).

2.2.5 Betulin Extraction Using Carboxylate-based Ionic Liquids

Extraction and analyzing procedures were as follows: A 5 ml microwave vial was charged with birch bark (0.1000 ± 0.0090 g) in IL (0.9000 ± 0.0150 g), sealed with a Teflon septum and heated for 15 min at 373 K by microwave irradiation (high absorption level). The resulting dark solution was diluted to 50 mL MeOH. A sample of 1 mL was taken from the solution and 0.2 mL of a 1-methyl-1-cyclohexene stock solution (50.0 mg in 100 mL methanol) was added. The samples were centrifuged for 10 min at 13000 rpm and the supernatant was directly analyzed by HPLC.
2.3 Interim Summary

1. All 27 combinations of three cations (1,3-dimethylimidazolium, 1-ethyl-3-methylimidazolium, and 
   \(N,N\)-diethyl-\(N,N\)-dimethylammonium) with nine carboxylate anions (formate, acetate, 
   \(n\)-propionate, \(n\)-butyrate, \(iso\)-butyrate, \(mono\)-maleate, maleate, \(mono\)-succinate, and succinate) were synthesized and characterized.
   - Fifteen compounds of them (1d, 1e, 1g, 1h, 1i, 2e, 2h, 2i, 3a, 3c, 3d, 3e, 3g, 3h, and 3i) were first reported here. Imidazolium-based carboxylates were synthesized by a simple, halide-free, environmentally benign method.
   - Residual carboxylic acid in the product was easily transformed into an ester via esterification with methanol without any additional catalyst. The resulting ester, which had no hydrogen bond to the carboxylate anion, and had a lower boiling point, was readily removed by evaporation.
   - Seventeen compounds (1a, 1b, 1c, 1d, 1e, 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 3b, 3d, and 3f) could be defined as ionic liquids. Decomposition temperatures for all compounds were above 430 K.

2. Cellulose solubilities in synthesized ILs were measured at three different temperatures (333K, 353K and 373K).
   - High temperature led to high cellulose solubility.
   - At low concentrations, chloride content (less than 1200 ppm) and water content (less than 2500 ppm) in ILs had no obvious influence on the cellulose solubility.
   - Anions with an internal hydrogen bond had no detectable cellulose solubility. Moreover, other anions with high \(\beta\) values, exhibited good cellulose solubilities. These results confirmed that the anion basicity was an important factor for dissolving cellulose. In addition, the existence of a C=C double bond in anion structures was not favorable.
   - Alternative to the common cellulose solvent [EMIm]Ac, other carboxylate-based ILs (2a, 2c, 2d, 2e) with similar cellulose solubilities were found. This provided more options for dissolving cellulose.
   - With the same anion, [EMIm] as the cation facilitated a higher cellulose solubility than that of [DMIm]. Quaternary ammonium as the cation showed a poor ability to dissolve cellulose. The influence of the cation on cellulose solubility was usually considered to be less important, but its role could not be neglected.
• These carboxylate-based ILs had good stabilities, and did not show any difference after dissolving cellulose at high temperature.

3. Cellulose solubilities predicted by the COSMO-RS method indicated that anion had the dominating effect and carboxylate anions were favorable. Generally, it was consistent with the experimental results. However, there were still mismatches between the calculated result and the experimental data, especially for the trend in cations. Therefore, the experimental determination remained inevitable for IL screening.

4. After the pretreatment using ILs, cellulose was easier to degrade by oxalic acids. Moreover, the addition of sodium chloride significantly accelerated the degradation.

5. Carboxylate-based ILs also demonstrated good abilities to extract betulin from birch bark. The extracting efficiencies in the selected ILs exhibited a similar trend to their cellulose solubilities.
3 Applications of Ionic Liquids as Reactants

During a trial in which water was used to wash potassium chloride residue from [EMIm]Ac-dichloromethane solution, a facile reaction involving [EMIm]Ac and DCM (dichloromethane) was observed. After mixing the [EMIm]Ac and DCM, chloride anion concentration increased and new species were detected (methylene diacetate and 2-(acetoxyethyl)-1-ethyl-3-methylimidazolium cation). The proposed pathways are as follows: the acetate anion (as a nucleophile) first attacks the carbon center of the DCM and forms an intermediate chloromethyl acetate ester; this intermediate is then attacked by acetate producing methylene diacetate, or by N-heterocyclic carbene (NHC), which is formed via deprotonation of the imidazolium by the acetate, producing a derivative of imidazolium (2-(acetoxyethyl)-1-ethyl-3-methylimidazolium) (Figure 3-1). Through investigation of these side reactions, the high reactivity of ILs was discovered and employed for esterification and ionic tagging.

![Figure 3-1. Proposed pathways for the formation of methylene diacetate and 2-(acetoxyethyl)-1-ethyl-3-methylimidazolium cation from the reaction of [EMIm]Ac with DCM.](image)

3.1 Esterification Reactant

3.1.1 Background

Esterification is one of the most important reactions in organic synthesis, providing a large number of important esters in a variety of chemical areas, such as pharmaceutical, food, perfume. As it is one of the oldest chemical processes, various synthetic methods have been reported. The reaction of alcohol with carboxylic acid or its derivatives, as the primary method for ester production, is an equilibrium process. To shift the reaction system to the product side to the greatest degree, one reactant is commonly added in excess, and the simultaneous removal of by-product is thus required. Catalysts are usually
necessary, and a variety (including acid, base, organometal and enzyme) are employed to improve ester yields. Nevertheless, the compatibility of catalyst and substrate is another critical issue, since high value added esters commonly have additional functional groups, which are often sensitive to the acidic or basic nature of catalysts. To promote esterification, carbodiimide and azodicarbonamide compounds are often used to activate carboxylic acid. Alternatively, organotin is commonly employed to activate alcohol. However, at least one equivalent activator is needed and consumed in these techniques. Unfortunately, although enzyme catalysts exhibit excellent selectivity, most of enzymes have very narrow tolerances to most functional groups.\textsuperscript{[70b]}

Inexpensive alkyl halide is considered another good substrate for esterification. Alkyl halide can react directly with carboxylate salt in polar solvents with or without catalysts,\textsuperscript{[71]} or work with carboxylic acid together with catalysts, which are always bases, (e.g. KOH,\textsuperscript{[72]} Et\textsubscript{3}N,\textsuperscript{[73]} KHCO\textsubscript{3},\textsuperscript{[74]} DBU\textsuperscript{[75]} and Cu\textsubscript{2}O\textsuperscript{[76]}), to produce ester. Large amounts of the base, often more than one equivalent, are always required. As a result of the acidity of carboxylic acid and the basicity of the catalyst, carboxylate salt can form during the neutralization. Consequently, the reaction is considered to be adapted from the reaction of alkyl halide with carboxylate salt. Unlike the alcohol and carboxylic acid process, the alkyl halide and carboxylate salt process is more tolerable, highly-selective and even quantitative. It is, therefore, considered a good complement to the alcohol process.

Due to the low solubilities of carboxylate salts in common organic solvents, polar aprotic solvents (e.g. DMSO, DMF and HMPA) and ILs are employed to dissolve them. In comparison to carboxylate metal salt, quaternary ammonium salt has a higher solubility in organic solvents, and thus drives the reaction faster. Recently, Cao and co-workers reported a solvent-free esterification of alkyl halides and sodium carboxylate or thioacetates catalyzed by PEG 400.\textsuperscript{[77]} In their case, 3 mol\% PEG 400 was employed. Following the reaction, the resultant mixture was washed with water, and the organic phase was distilled to obtain the product.

Alkyl halide and carboxylate salt perform an S\textsubscript{N}2 nucleophilic substitution for the esterification. Due to backside attack, alkyl halide undergoes a Walden inversion to form its corresponding ester. Kunz and Lerchen reported important intermediate \textit{D-}\textalpha-hydroxy carboxylic acids could be obtained from \textit{N}-protected \textit{L}-amino acids, which are inexpensive and abundant components of protein.\textsuperscript{[78]} The amine group is converted into chloride through diazotization and deazotization with chloride. The chloride compounds
are attacked by cesium carboxylate salts via $S_{N}2$ substitution. The resultant esters are hydrolyzed with sodium hydroxide solution to produce $D$-$\alpha$-hydroxy carboxylic acids.

![Scheme 3-1. $D$-$\alpha$-hydroxy carboxylic acids synthesized from $L$-amino acids.][78]

The esterification of carboxylate salts and other electrophiles (e.g., alkyl mesylate or alkyl tosylate) is also considered an $S_{N}2$ substitution. It has thus been used for the synthesis of chiral alcohol from its enantiomer via mesylation or tosylation, esterification with carboxylate cesium and hydrolysis (Scheme 3-2).[79] Normally, $S_{N}2$ substitution is applied for secondary substituted electrophiles, as $S_{N}1$ substitution is always involved in tertiary substituted substrates. In comparison with alkyl halide, alkyl mesylate and alkyl tosylate have higher activities with carboxylate salt, due to their good leaving groups. Thus, esterification can proceed under milder conditions. Kruizinga and co-workers investigated a series of propionate metal salts (including Na, K, Rb, and Cs) for the esterification of alkyl mesylate.[79a] Cesium propionate proved to be the best choice, owing to its high solubility in the polar aprotic solvent DMF, which is considered to be one of the best solvents for this substitution, and broadly used in spite of its toxicity and instability in base or acid conditions.

![Scheme 3-2. Inversion of the configuration of secondary alcohols.][80]

Desirable goals of esterification are:

- The two reactants should be stoichiometric;
- Catalyst is not needed or neutral;
- Yield is 100 \%;
- No solvent is needed.

Until now, there have been no satisfactory results meeting all these requirements.

50
3.1.2 Results and Discussion

3.1.2.1 Reaction of [EMIm]Ac with dichloromethane

During a trial in which water was used to wash potassium chloride residue from [EMIm]Ac-dichloromethane solution, a facile reaction involving [EMIm]Ac and DCM was observed. When the [EMIm]Ac and DCM mixture was stirred at r.t., chloride was detected after only 5 min, by the addition of 0.1 mol L\(^{-1}\) AgNO\(_3\)-HNO\(_3\) solution. The \(^1\)H-NMR indicated the existence of a derivative of the imidazolium ring and changes in both the chemical shift and the integration of the acetate anion (Figure 3-2). According to the result of Isleyen and Dogan, methylene diacetate can be prepared using tetrabutylammonium acetate with DCM.\(^{[80]}\) Consequently, the signals at 5.64 ppm and 2.06 ppm can be readily assigned to methylene diacetate. Analysis by LC-MS gave the main peak at m/z=183.2, in line with 2-(acetoxymethyl)-1-ethyl-3-methylimidazolium cation.

\[\text{Figure 3-2. } \text{\(^1\)H-NMR differences of pure [EMIm]Ac and a mixture of [EMIm]Ac and DCM.} \]
Based on these findings, the reaction products can be explained by the intermediate formation of chloromethyl acetate in an $S_N2$ reaction and the subsequent nucleophilic attack of this intermediate by either acetate anion or imidazolium ring (Figure 3-3).

![Figure 3-3](image.png)

**Figure 3-3.** Proposed pathways for the formation of methylene diacetate and 2-(acetoxyethyl)-1-ethyl-3-methylimidazolium cation from the reaction of [EMIm]Ac with DCM.

When commercial [EMIm]Ac was replaced with the one described in Chapter 2.2.1.2, in which neither chloride nor other anions were detectable by ion chromatography, the same result with DCM was observed. This eliminated any suspicion that trace amounts of residue catalyzed the reaction.

Since [EMIm]Ac is highly hygroscopic, the inhibitory effect of water was tested. With 10 wt.% water, chloride from the reaction between [EMIm]Ac and DCM remained below the detectable limit after stirring for 14 hours with AgNO$_3$-HNO$_3$. There was also no change in acetate in $^1$H-NMR after 5 days.

### 3.1.2.2 Reaction of [EMIm]Ac with chloroform

Chloroform also reacted with [EMIm]Ac, although at a relatively slower rate. When a mixture of [EMIm]Ac and chloroform was heated to reflux, the colour gradually changed. After 2 hours stirring at 343 K under argon atmosphere, a colour change was apparent (Figure 3-4), and the integration of acetate anion in $^1$H-NMR decreased obviously after 5 days heating at 343 K (Figure 3-5). Unfortunately, new species was not captured.

Considering the fact that chloroform and DCM are often chosen as solvents for IL synthesis, or as one component of liquid-liquid biphasic systems with ILs, and that deuterated chloroform is commonly used to dissolve ILs for NMR characterization, attention should be paid to their side reactions in their further applications.
Figure 3-4. The color change of the [EMIm]Ac and chloroform reaction mixture.

Figure 3-5. $^1$H-NMR of the [EMIm]Ac and chloroform mixture after 5 days stirring at 343K. (The integration of the peak 7 should be 3.00.)

3.1.2.3 Esterification of carboxylate-based ionic liquids with primary alkyl halides

Following the observations of [EMIm]Ac with DCM and with chloroform, an experimental study was conducted to see whether this could be applied to synthetic applications. Compared with other methods of esterification, access via alkyl halide and carboxylate salts is attractive, especially since alkyl halides are cost-effective starting
materials. Until now, its industrial application is limited by its low conversion, low yield, solid state, and the low solubility of metal carboxylate salts in organic solvents. As an alternative to metal carboxylate salts, quaternary ammonium carboxylates must be conducted in organic solvents, as these salts are solid at reaction temperature. Toxic organic solvents with high boiling points, such as DMSO, DMF, and HMPA, are usually used.\textsuperscript{[71a, b, 71d, e, 71g, h, 72, 75a]} By substituting them with carboxylate-based IL, these shortcomings could be overcome.

![Scheme 3-3. Esterification of [EMIm]Ac and 1-chlorobutane.](image)

Kinetic investigations were undertaken on the esterification of [EMIm]Ac and 1-chlorobutane (Scheme 3-3). The reaction was stoichiometric, without catalyst or solvent, but still ran to completion within 3 hours at 343K, producing ester exclusively (Figure 3-6). The yield was calculated from $^1\text{H}$-NMR spectra, based on the methylene group adjacent to the O-atom. In comparison with the result of Cao et al.,\textsuperscript{[77]} which reached 89% yield after 5 hours reaction time at the same temperature with 3 mol% PEG 400 as a catalyst, this positive result encouraged further investigations.

![Figure 3-6. Conversion-time profile of the esterification of [EMIm]Ac with 1-chlorobutane](image)

In addition, $N,N$-diethyl-$N,N$-dimethylammonium acetate gave a 53% yield of 1-butyl acetate at r.t. after 12 hours. Thereby, the predominant role of the imidazolium cation could be excluded.
To assess the scope of the reaction, a series of ester syntheses with alkyl halides and carboxylate-based ILs, was undertaken (Table 3-1). For the primary alkyl halides, the selectivity towards the corresponding ester was higher than 99 % as no side product was detected. At r.t., the esterification of 1-chlorobutane had a limited reaction rate (entry 1). although at a slightly elevated temperature, quantitative conversion was achieved (entry 2). Interestingly, when 30 mmol sodium acetate, 30 mmol 1-chlorobutane and 3 mmol [EMIm]Ac were mixed and stirred at 343 K for 6 hours, they produced around 9.3 mmol ester. On the contrary, no chloride was detectable with 0.1 mol L\(^{-1}\) AgNO\(_3\)-HNO\(_3\) solution, regardless of sodium acetate mixed with DCM at r.t., or with 1-chlorobutane at 343 K, prior to overnight stirring. However, around 5 % ester was detected when 1.5 mmol [EMIm]Cl was added to a mixture of 0.5 g (6.1 mmol) sodium acetate and 0.5 g (5.4 mmol) 1-chlorobutane and stirred overnight at 343 K. Thus, IL could act as a mediator for the delivery of the acetate anion from solid sodium acetate.

Employing bromide or iodide instead of chloride resulted in shorter reaction times, in accordance with the trends of S\(^{\text{N}}\)\(_2\) nucleophilic substitution (entries 3, 4, and 8). Yields decreased with increasing chain length of the alkyl halide, which could be counteracted to some extent by increasing the temperature (entries 6 and 7). The reaction tolerated double bonds in both alkyl halide and carboxylate (entries 8 and 12). Furthermore, a range of carboxylates could be employed with moderate to good yields (entries 9 through 13). In addition, the phenolic hydroxy group in 4-hydroxybenzoic acid exhibited no side reactions (entry 13).

In case of tertiary and secondary alkyl halides (2-chloro-2-methylhexane and 2-bromoheptane), alkenes formed during the reaction. For tertiary alkyl halide, alkene was the main product. An interesting result was obtained by mixing [EMIm]Ac with \(\alpha\)-chlorodesoxybenzoin (entry 14). The reaction finished in just a few minutes, during the dissolution of solid \(\alpha\)-chlorodesoxybenzoin in [EMIm]Ac, and was accompanied by a large release of heat.

Notably, the esterification mixture was biphasic throughout (entries 1 through 12), which facilitated product separation by decantation. For homogeneous reaction systems (entries 13 and 14), products were easily extracted from solution using low-polar solvents, such as ethyl acetate.
Table 3-1: Esterification between carboxylate-based ionic liquids and alkyl halide.\(^\text{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R' - X)</th>
<th>Carboxylate anion of IL</th>
<th>Temp./K</th>
<th>Time/h</th>
<th>Product</th>
<th>Yield/% by NMR(^\text{[b]}) isolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\alpha)</td>
<td>CH(_3)CO(^{-})</td>
<td>r.t.</td>
<td>16</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>(\alpha)</td>
<td>CH(_3)CO(^{-})</td>
<td>343</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>(\beta)</td>
<td>CH(_3)CO(^{-})</td>
<td>343</td>
<td>2</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>(\gamma)</td>
<td>CH(_3)CO(^{-})</td>
<td>343</td>
<td>1</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>(\alpha)</td>
<td>CH(_3)CO(^{-})</td>
<td>323</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>(\alpha)</td>
<td>CH(_3)CO(^{-})</td>
<td>373</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>(\alpha)</td>
<td>CH(_3)CO(^{-})</td>
<td>373</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>(\beta)</td>
<td>CH(_3)CO(^{-})</td>
<td>343</td>
<td>1</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>(\alpha)</td>
<td>CH(_3)CH(_2)CO(^{-})</td>
<td>343</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>87</td>
</tr>
<tr>
<td>10</td>
<td>(\alpha)</td>
<td>CH(_3)(CH(_2))(_2)CO(^{-})</td>
<td>343</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>(\alpha)</td>
<td>(CH(_3))(_2)CHCO(^{-})</td>
<td>343</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>(\alpha)</td>
<td>CH(_2)=CHCO(^{-})</td>
<td>343</td>
<td>3</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>78</td>
</tr>
<tr>
<td>13</td>
<td>(\alpha)</td>
<td>CH(_3)CH(_2)=CHCO(^{-})</td>
<td>353</td>
<td>6</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>69</td>
</tr>
<tr>
<td>14</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>CH(_3)CO(^{-})</td>
<td>r.t.</td>
<td>0.15</td>
<td>![esterification product]((\text{(R')-esterification product}))</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

[a] [EMIm] was chosen as the cation in the ionic liquids. Reactants: 3 mmol IL, 3 mmol alkyl halide.
[b] Yield calculated from \(^1\)H-NMR integration based on the methylene group adjacent to the O-atom.

3.1.2.4 Esterification of carboxylate-based ionic liquids with chiral secondary substituted alkanes

\[\text{Scheme 3-4.} \quad \text{Esterification of (R)-2-chlorooctane and [EMIm]Ac.}\]
To demonstrate that the reaction is an $S_N2$ nucleophilic substitution, (R)-2-chlorooctane was synthesized and used as the substrate. Although the reaction occurred at 343 K, it was too slow, with only 30% yield being achieved after 19 hours and around 5% alkene formed. A Finkelstein reaction is an $S_N2$ reaction that involves the exchange of one halogen atom for another.\cite{81} To avoid a Finkelstein reaction involving the produced chloride during the long reaction time, a high temperature 393 K with excess [EMIm]Ac was employed (Scheme 3-4). After 3 hours reaction time, around 15% alkene formed. (S)-2-octyl acetate was obtained from (R)-2-chlorooctane with a yield of 79%. This proved that the displacement actually occurred through the backside attack of the acetate anion via Walden inversion.

![Scheme 3-5](image)

**Scheme 3-5.** Inversion of the configuration of (S)-2-octanol.

The $S_N2$ nucleophilic substitution mechanism offers this esterification an opportunity to invert the configuration of chiral alcohol. To demonstrate this, (S)-2-octanol was chosen as the starting material. As an excellent leaving group, tosylate was used as the electrophile to ensure the reaction occurred under mild conditions. Through tosylation, substitution and hydrolysis, (S)-2-octanol was successfully converted into (R)-2-octanol with an excellent isolated yield (Scheme 3-5). Notably, the substitution of alkyl tosylate and 3 eq. [EMIm]Ac reached 90% yield (1H-NMR) in 3 hours at r.t., with a small amount of alkene formed. In addition, acetate ester was readily extracted with pentane. Compared with literature reports, which always indicate the need for harsh conditions and have separation problems,\cite{79} this application is believed to be a good alternative. Mild reaction temperatures also provide possibilities for the syntheses of sensitive drug intermediates.

### 3.1.2.5 Esterification of racemic electrophiles with chiral ionic liquids

Maruotka et al. reported the preparation of an optically active ester via alkylation of carboxylic acid using chiral ammonium fluoride generated in situ as the catalyst (Scheme 3-6).\cite{82} The esterification took 42 hours to reach 98% yield with 58% ee at r.t.. Inspired
by this work, the possibility of using chiral carboxylate-based ILs for esterification with kinetic resolution was investigated.

Scheme 3-6. Esterification via alkylation of carboxylic acid using a chiral catalyst.\textsuperscript{[82]}

Three chiral carboxylate-based ILs (CIL-1, CIL-2 and CIL-3) were successfully synthesized. Their structures are listed in Scheme 3-7.

\begin{align*}
\text{CIL-1} & \quad \text{CIL-2} & \quad \text{CIL-3} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{HO} & \quad \text{CO}_2^- & \quad \text{CH}_3 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 & \quad \text{CH}_2\text{OH} \\
\text{Cat.} & \quad \text{Ar} & \quad \text{CF}_3 \\
\text{N} & \quad \text{Ar} & \quad \text{CF}_3 \\
\text{HSO}_4^- & \quad & \text{O} \\
\end{align*}

Scheme 3-7. Synthesized chiral carboxylate-based ionic liquids.

To facilitate the reaction under mild conditions, 2-octyl mesylate was chosen as the substrate for the investigations. The best result was provided by CIL-1, which has a chiral anion and was readily prepared from \textit{L}-lactic acid. Due to the limit of the analytical method, the lactate produced was hydrolyzed into 2-octanol for \textit{ee} determination. Esterification was carried out at 313 K for 2 hours, \textsuperscript{1}H-NMR yield reached 67 \% and isolated yield was 59 \%. Following hydrolysis, enantioenriched alcohol (57 \% (S)-configuration and 43 \% (R)-configuration) was obtained. Unfortunately, the other two chiral ILs both resulted in an \textit{ee} of just 2 \%. Considering that the cation had a limited influence on reaction rate in \textit{S}\textsubscript{N}2 displacement, the low enantioselectivity was not unexpected.

3.1.2.6 Recovery of ionic liquids for esterification

Recycling ILs not only lowers the cost of ILs, but also reduces waste production. Three processes for recycling ILs for esterification were explored: the anion exchange resin me-
method, the recyclable DBU process and the anion metathesis method.

The anion exchange resin method is a frequently-used way of preparing ILs from corresponding halide ILs, and was successfully performed in the esterification of [EMIm]Ac with 1-chlorobutane for the recovery of the IL (Figure 3-7). The reaction system of the esterification was biphasic: the upper phase was 1-chlorobutane and the lower phase was [EMIm]Ac. Following the reaction, the ester product accumulated in the upper phase and was decanted. The lower phase enriched with by-product [EMIm]Cl was washed with pentane. Subsequently, the mixture of unreacted [EMIm]Ac and produced [EMIm]Cl was dried and dissolved with methanol. The solution was introduced to a stacked column of anion exchange resin to obtain [EMIm]OH, which was subsequently neutralized with a stoichiometric amount of acetic acid to acquire [EMIm]Ac for the next esterification run. A yield of 91 % [EMIm]Ac was recovered, which in turn produced a yield of 95 % 1-butyl acetate. There was no obvious difference between this and the 96 % 1-butyl acetate yield obtained using fresh [EMIm]Ac.

![Figure 3-7](image) Recycling process of IL using the anion exchange resin method.

The drawback of the anion exchange resin method, however, is that large amounts of sodium hydroxide (at least 5 eq.) are required to recover the resin.

![Figure 3-8](image) Recycling process of IL using recyclable DBU.
This could be improved by using a base, which could be neutralized with carboxylic acid to form a carboxylate-based IL with high esterification activity. Three bases (tributylamine, 1-ethylimidazole, and DBU) were tested with acetic acid. While DBU provided a promising result, the other two exhibited no activity. The reactivity of [DBUH]Ac was lower than [EMIm]Ac, with an 85 % \(^1\)H-NMR yield achieved after 3 hours at 343 K. However, following esterification, the [DBUH]Cl was dissolved using methanol and neutralized with 1 eq. sodium hydroxide, resulting in a DBU yield of 91 %.

![Figure 3-9. Recycling process of IL using the anion metathesis method.](image)

Zhang and Xu reported the preparation of acetate-based ILs using the anion metathesis method.\(^{[83]}\) During preparation, chloride-based ILs exchanged the anion with metal or ammonium acetate salts in the ethanol solution. The drawback of this method is the poor purity of the ILs formed. High chloride content is unavoidable, and its influence limits the applications of the synthesized ILs.\(^{[1b, c, 5, 7c]}\) However, in this esterification, the influence of chloride is minor. Considering the sodium acetate, [EMIm]Ac and 1-chlorobutane result presented in Chapter 3.1.2.3, the dissolved potassium acetate residue could even be involved in the reaction to provide acetate anion. As a result, the [EMIm]Ac yield was 90 %, at 97 % purity (Figure 3-9). Using recovered [EMIm]Ac for esterification, the 1-butyl acetate was obtained in 95 % yield.

### 3.1.3 Experimental

#### 3.1.3.1 General

a) Chemicals

[EMIm]Ac (1-ethyl-3-methylimidazolium acetate) was purchased from Ionic Liquid Technologies GmbH&Co. KG. Carboxylate-based IL were synthesized in section 2.2.1.2. Dichloromethane, chloroform, and 1-chlorobutane were purified according to the
All other chemicals were obtained from Alfa Aesar and used as received unless stated otherwise. Before using, ILs were dried under reduced pressure around 5 Pa overnight. High vacuum is always carried out under 5 Pa pressure. Typically, the water content was less than 0.6 %.

b) Analysis

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on a AV400 MHz NMR or AV300 MHz NMR (Bruker BioSpin) at r.t.. Chemical shifts were given in ppm relative to tetramethylsilane ($^1$H- and $^{13}$C-NMR) or the residual solvent peak. For the description of multiplicity of the signal following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad.

Water content was determined by an automated Karl-Fischer-titration (Metrohm).

Ion chromatography was carried out using ICS-1500 (Dionex). The detection limit of ion chromatography is 10 ppm for all halides.

Optical rotation was measured on a JASCO P-1020 Polarimeter using a thermo-controlled glass cuvette of 1 dm.

For column chromatography, columns were hand-packed with silica gel 60. TLC was carried out with 0.2 mm thick silica gel plates. TLC visualization was accomplished by UV light, I$_2$ staining, or phosphomolybdic acid staining.

Gas Chromatography, the enantioselectivity determination of chiral 2-octanol was carried out with GC column: 25 m Ivadex 7 (inner diameter 0.25 mm, film thickness 0.25 µm). Temperature program: 50-80 °C, 5min isothermal, heating rate 3 °C min$^{-1}$ and then to 160 °C with heating rate 15 °C min$^{-1}$ and 15 min holding at the end temperature. Carrier: H$_2$, 2.0 mL min$^{-1}$ constant flow; Inlet: 250 °C; Split flow: 80 mL min$^{-1}$; FID: 250 °C.

3.1.3.2 Typical procedures for the reaction of [EMIm]Ac with dichloromethane or chloroform

0.51 g [EMIm]Ac and 2.00 g DCM (or chloroform) were added to a 20 mL Schlenk tube. Then the mixture was stirred at r.t. or 343 K. 0.1 mol L$^{-1}$ AgNO$_3$-HNO$_3$ solution was employed to test the chloride anion every one hour. A sample was taken for $^1$H-NMR every 24 hours until there was no differences observed between the last two samples.
3.1.3.3 Esterification of carboxylate-based ionic liquids and alkyl halides

3.0 mmol IL and 3.0 mmol alkyl halide were added to a 25 ml flask, and heated to the desired temperature for a certain time. After the reaction, in most cases the ester was in the upper phase. The yield was based on the $^1$H-NMR of the upper phase. Then the upper phase was decanted, the lower phase was extracted with pentane (3x5 mL). After evaporating the solvent of the combined extracting solution with the upper phase, the product was purified with column chromatography. For homogeneous reaction systems, the product was extracted with ethyl acetate (3x5 mL) and purified with column chromatography (pentane: ethyl acetate, 19:1).

1-Ethyl-3-methylimidazolium acrylate:

\[
\text{N}^+\text{N}^-\text{O} \quad \text{O} \quad \text{CH}_2=\text{CH}_2
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.40 (t, $^3$J(H,H)=7.2 Hz, 3H, NCH$_2$CH$_3$), 3.86 (s, 3H, NCH$_3$), 4.20 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_3$CH$_2$), 5.13 (dd, $^3$J(H,H)=3.4 Hz, $^3$J(H,H)=10.0 Hz, 1H, CHCH$_2$), 5.65 (dd, $^3$J(H,H)=3.4 Hz, 1H, CHCH$_2$), 5.94 (dd, $^3$J(H,H)=10.4 Hz, 3J(H,H)=17.4 Hz, 1H, CH$_2$CH), 7.74 (br, 1H, NCH), 7.83 (br, 1H, NCH), 9.65 (s, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 15.2 (NCH$_2$CH$_3$), 35.6 (NCH$_3$), 44.0 (NCH$_2$), 119.8 (CHCH$_2$), 121.9 (NCH), 123.5 (NCH), 136.9 (NCHN), 140.2 (CH$_2$CH), 168.9 (CHCO$_2$).

1-Ethyl-3-methylimidazolium 4-hydroxybenzoate:

\[
\text{N}^+\text{N}^-\text{O} \quad \text{OH} \quad \text{C}_6\text{H}_4\text{OH}
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.39 (t, $^3$J(H,H)=7.2 Hz, 3H, NCH$_2$CH$_3$), 3.84 (s, 3H, NCH$_3$), 4.18 (q, $^3$J(H,H)=7.2 Hz, 2H, CH$_3$CH$_2$), 6.67 (d, $^3$J(H,H)=4.0 Hz, 2H, Ph), 7.65 (d, $^3$J(H,H)=4.0 Hz, 2H, Ph), 7.70 (br, 1H, NCH), 7.79 (br, 1H, NCH), 9.51 (s, 1H, NCHN).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 15.1 (NCH$_2$CH$_3$), 35.6 (NCH$_3$), 44.0 (NCH$_2$), 121.9 (NCH), 123.5 (NCH), 136.8 (NCHN), 113.8, 130.4, 159.1 (Ph), 169.3 (PhCO$_2$).
n-Butyl acetate

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (400 MHz; CDCl}_3; \delta/\text{ppm}}: & \quad 0.93 (t, J(\text{H,H})=7.2 \text{ Hz, } 3\text{H, CH}_2\text{CH}_3), 1.37 \text{ (sextet, } 2\text{H, CH}_2\text{CH}_2), 1.60 \text{ (pentet, } 2\text{H, OCH}_2\text{CH}_2), 2.04 \text{ (s, } 3\text{H, O}_2\text{CCH}_3), 4.06 \text{ (t, J(\text{H,H})=6.8 Hz, } 2\text{H, OCH}_2) \\
\text{\textsuperscript{13}C-NMR (100 MHz; CDCl}_3; \delta/\text{ppm}}: & \quad 13.8 \text{ (CH}_2\text{CH}_3), 19.3 \text{ (CH}_3\text{CH}_2), 21.1 \text{ (O}_2\text{CCH}_3), 30.8 \text{ (OCH}_2\text{CH}_2), 64.5 \text{ (OCH}_2), 171.4 \text{ (CH}_3\text{CO}_2).
\end{align*}
\]

n-Propyl acetate:

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (400 MHz; CDCl}_3; \delta/\text{ppm}}: & \quad 0.93 (t, J(\text{H,H})=7.6 \text{ Hz, } 3\text{H, CH}_2\text{CH}_3), 1.64 \text{ (sextet, } 2\text{H, CH}_3\text{CH}_2), 2.04 \text{ (s, } 3\text{H, O}_2\text{CCH}_3), 4.02 \text{ (t, J(\text{H,H})=6.8 Hz, } 2\text{H, OCH}_2) \\
\text{\textsuperscript{13}C-NMR (100 MHz; CDCl}_3; \delta/\text{ppm}}: & \quad 10.5 \text{ (CH}_2\text{CH}_3), 21.1 \text{ (O}_2\text{CCH}_3), 22.1 \text{ (CH}_3\text{CH}_2), 66.2 \text{ (OCH}_2), 171.4 \text{ (CH}_3\text{CO}_2).
\end{align*}
\]

n-Pentyl acetate:

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (400 MHz; DMSO}-\text{d}_6; \delta/\text{ppm}}: & \quad 0.87 \text{ (t, J(\text{H,H})=6.8 Hz, } 3\text{H, CH}_2\text{CH}_3), 1.28 \text{ (m, } 4\text{H, CH}_2\text{(CH}_2\text{)})_2), 1.55 \text{ (pentet, } 2\text{H, OCH}_2\text{CH}_2), 1.99 \text{ (s, } 3\text{H, O}_2\text{CCH}_3), 3.98 \text{ (t, J(\text{H,H})=6.8 Hz, } 2\text{H, OCH}_2) \\
\text{\textsuperscript{13}C-NMR (100 MHz; DMSO}-\text{d}_6; \delta/\text{ppm}}: & \quad 13.8 \text{ (CH}_2\text{CH}_3), 18.6 \text{ (CH}_3\text{CH}_2), 20.7 \text{ (O}_2\text{CCH}_3), 21.7 \text{ (O(CH}_2\text{)})_2\text{CH}_2), 27.5 \text{ (O(CH}_2\text{)})_2\text{CH}_2), 27.8 \text{ (OCH}_2\text{CH}_2), 63.8 \text{ (OCH}_2), 170.4 \text{ (CH}_3\text{CO}_2).
\end{align*}
\]

n-Decyl acetate:

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR (400 MHz; CDCl}_3; \delta/\text{ppm}}: & \quad 0.87 \text{ (t, J(\text{H,H})=6.8 Hz, } 3\text{H, CH}_2\text{CH}_3), 1.30 \text{ (m, } 14\text{H, CH}_3\text{(CH}_2\text{)})_2), 1.61 \text{ (pentet, } 2\text{H, OCH}_2\text{CH}_2), 2.04 \text{ (s, } 3\text{H, O}_2\text{CCH}_3), 4.04 \text{ (t, J(\text{H,H})=6.8 Hz, } 2\text{H, OCH}_2) \\
\text{\textsuperscript{13}C-NMR (100 MHz; CDCl}_3; \delta/\text{ppm}}: & \quad 14.24 \text{ (CH}_2\text{CH}_3), 21.15 \text{ (O}_2\text{CCH}_3), 22.81, 26.05, 28.75, 29.39, 29.44, 29.66, 32.03\text{ (OCH}_2\text{CH}_2\text{)}_8, 64.81 \text{ (OCH}_2), 171.37 \text{ (CH}_3\text{CO}_2).
\end{align*}
\]
3-Butenyl acetate:

![3-Butenyl Acetate structure]

$^1$H-NMR (400 MHz; CDCl$_3$; δ/ppm): 2.03 (s, 3H, O$_2$CCCH$_3$), 2.37 (m, 2H, OCH$_2$CH$_2$), 4.10 (t, $^3$J(H,H)=6.8 Hz, 2H, OCH$_2$), 5.05-5.13 (m, 2H, CH=CH$_2$), 5.77 (m, 1H, CH$_2$=CH$_2$).

$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 21.1 (O$_2$CCH$_3$), 33.2 (OCH$_2$CH$_2$), 63.6 (OCH$_2$), 117.3 (CH=CH$_2$), 134.1 (CH$_2$=CH), 171.2 (CH$_3$CO$_2$).

$n$-Butyl propionate:

![n-Butyl Propionate structure]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 0.88 (t, $^3$J(H,H)=7.6 Hz, 3H, O$_2$CCH$_2$CH$_3$), 1.02 (t, $^3$J(H,H)=7.2 Hz, 3H, O(CH$_2$)$_3$CH$_3$), 1.32 (sextet, 2H, O(CH$_2$)$_2$CH$_2$), 2.29 (q, $^3$J(H,H)=7.6 Hz, 2H, O$_2$CCH$_2$), 4.00 (t, $^3$J(H,H)=6.8 Hz, 2H, OCH$_2$).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; δ/ppm): 9.0 (O$_2$CCH$_2$CH$_3$), 13.5 ((CH$_2$)$_3$CH$_3$), 18.6 (O(CH$_2$)$_3$CH$_3$), 26.8 (O$_2$CCH$_2$), 30.2 (OCH$_2$CH$_2$), 63.4 (OCH$_2$), 173.6 (CH$_2$CO$_2$).

$n$-Butyl $n$-butyrate:

![n-Butyl Butyrate structure]

$^1$H-NMR (400 MHz; CDCl$_3$; δ/ppm): 0.91-0.96 (m, 6H, O(CH$_2$)$_3$CH$_3$&O$_2$C(CH$_2$)$_2$CH$_3$), 1.37 (sextet, 2H, O(CH$_2$)$_2$CH$_2$), 1.56-1.69 (m, 4H, CH$_2$), 2.27 (t, $^3$J(H,H)=7.2 Hz, 2H, O$_2$CCH$_2$), 4.06 (t, $^3$J(H,H)=6.8 Hz, 2H, OCH$_2$).

$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 13.8 (CH$_2$CH$_3$), 18.6 (O$_2$CCH$_2$CH$_2$), (O(CH$_2$)$_3$CH$_3$), 30.9 (OCH$_2$CH$_2$), 36.4 (O$_2$CCH$_2$), 64.2 (OCH$_2$), 172.0 (CH$_2$CO$_2$).

$n$-Butyl $t$-butyrate:

![n-Butyl Tertiary Butyrate structure]

$^1$H-NMR (400 MHz; CDCl$_3$; δ/ppm): 0.93 (t, $^3$J(H,H)=7.4 Hz, 3H, CH$_2$CH$_3$), 1.16 (d, $^3$J(H,H)=7.0 Hz, 6H, CH(CH$_3$)$_2$), 1.38 (sextet, 2H, CH$_2$CH$_2$), 1.61 (pentet, 2H, OCH$_2$CH$_2$), 2.53 (septet, $^3$J(H,H)=7.0 Hz, 1H, O$_2$CCH), 4.06 (t, $^3$J(H,H)=6.6 Hz, 2H, OCH$_2$).
$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 13.7 (CH$_2$CH$_3$), 19.0 (CH(CH$_3$)$_2$), 19.1 (CH$_2$CH$_2$), 30.7 (OCH$_2$CH$_2$), 34.0 (CH$_3$OCH), 64.1 (OCH$_2$), 177.3 (CHCO$_2$).

$n$-Butyl acrylate:

\[ \begin{align*}
&\text{H-NMR (400 MHz; CDCl$_3$; δ/ppm): 0.94 (t, }^{3}J(H,H)=7.2 \text{ Hz, 3H, CH$_2$CH$_3$), 1.40} \\
&\text{(sextet, 2H, O(CH$_2$)$_2$CH$_2$), 1.65 (pentet, 2H, OCH$_2$CH$_2$), 4.15 (t, }^{3}J(H,H)=6.8 \text{ Hz, 2H,} \\
&\text{OCH$_2$), 5.80 (dd, }^{3}J(H,H)=1.4 \text{ Hz, }^{3}J(H,H)=10.4 \text{ Hz, 1H, CH=CH$_2$), 6.11 (dd,} \\
&\text{ }^{3}J(H,H)=10.4 \text{ Hz, }^{3}J(H,H)=17.3 \text{ Hz, 1H, CH$_2$=CH$H$), 6.39 (dd, }^{3}J(H,H)=1.4 \text{ Hz,} \\
&\text{ }^{3}J(H,H)=17.3 \text{ Hz, 1H, CH=CH$_2$).} \\
\end{align*} \]

$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 13.8 (CH$_2$CH$_3$), 19.3 (O(CH$_2$)$_2$CH$_2$), 30.8 (OCH$_2$CH$_2$), 64.5 (OCH$_2$), 128.8 (CHCH$_2$), 130.5 (CH$_2$CH), 166.5 (CHCO$_2$).

$n$-Butyl 4-hydroxybenzoate:

\[ \begin{align*}
&\text{H-NMR (400 MHz; CDCl$_3$; δ/ppm): 0.97 (t, }^{3}J(H,H)=7.2 \text{ Hz, 3H, O$_2$CHCH$_2$CH$_3$), 1.47} \\
&\text{(sextet, 2H, O(CH$_2$)$_2$CH$_2$), 1.74 (pentet, 2H, OCH$_2$CH$_2$), 4.30 (t, }^{3}J(H,H)=6.8 \text{ Hz, 2H,} \\
&\text{OCH$_2$), 6.54(b, 1H, COH), 6.89 (d, }^{3}J(H,H)=4.4 \text{ Hz, 2H, Ph), 7.95(d, }^{3}J(H,H)=4.4 \text{ Hz,} \\
&\text{2H, Ph).} \\
\end{align*} \]

$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 13.9 ((CH$_2$)$_3$CH$_3$), 19.4 (O(CH$_2$)$_2$CH$_2$), 30.9 (OCH$_2$CH$_2$), 65.0 (OCH$_2$), 115.4, 122.7, 132.1, 160.4 (Ph), 167.2 (PhCO$_2$).

2-Oxo-1,2-diphenylethyl acetate

\[ \begin{align*}
&\text{H-NMR (400 MHz; CDCl$_3$; δ/ppm): 2.21 (s, 3H, O$_2$CCH$_3$), 6.88 (s, 1H, OCH),} \\
&\text{7.34-7.95(10H, Ar).} \\
\end{align*} \]

$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 20.9 (O$_2$CCH$_3$), 128.8, 129.3, 129.5, 133.6, 134.7 (Ar), 170.6 (CH$_3$CO$_2$), 193.8 (OCH).
3.1.3.4 Esterification of carboxylate-based ionic liquids with chiral secondary substituted alkanes

a) Synthesis of (R)-2-chloroocetane

According to the literature,[85] to a solution of 204 mg (1.57 mmol) (S)-2-octanol in 20 mL DCM at 273 K was added 374 mg (3.07 mmol) DMAP, followed by 389 mg (2.00 mmol) tosyl chloride. The reaction mixture was allowed to warm up to r.t., and kept overnight, adsorbed onto silica and purified with silica gel column chromatography (ether : petroleum ether, 1:4) to give colorless liquid (S)-2-octyl tosylate (395 mg, 88 %). Then the formed ester was dissolved in 5 mL acetone, and 389 mg lithium chloride was added. The mixture was heated to reflux until no 2-octyl tosylate detectable with TLC. Then the solution was cooled down to r.t., diluted with pentane, and filtered through a plug of silica. After removal of the solvent, the product was purified with column chromatography (pentane as eluent). A colorless liquid (R)-2-octyl chloride was obtained in 97 % yield (202 mg). Optical purity was 98 %.

(R)-2-octyl chloride

$^1$H-NMR (300 MHz; CDCl$_3$; δ/ppm): 0.89 (t, $^3$J(H,H)=7.2 Hz, 3H, CH$_2$CH$_3$), 1.25-1.47 (m, 8H, (CH$_2$)$_4$), 1.50 (d, $^3$J(H,H)=6.5 Hz, 3H, CHCH$_3$), 1.66-1.74 (m, 2H, CHCH$_2$), 4.03 (sextet, 1H, CICH).

b) Esterification of [EMIm]Ac and (R)-2-octyl chloride

The mixture of 0.12 mmol (R)-2-octyl chloride and 1.20 mmol [EMIm]Ac was stirred at 393 K for 3 hours. After the reaction, a sample from the upper phase was taken for
The result indicated that the reaction had 94 % conversion and 79 % yield (2-octyl acetate). The side product was alkene from the elimination of 2-chlorooctane. Then the GC result of the sample showed that ester was composed of 98 % (S)-configuration and 2 % (R)-configuration.

c) Inversion of the configuration of (S)-2-octanol

To a solution of 208 mg (1.6 mmol) (S)-2-octanol in 20 mL DCM at 273 K was added 393 mg DMAP, followed by 403 mg tosyl chloride. The reaction mixture was allowed to warm up to r.t., and kept overnight, adsorbed onto silica and purified with silica gel column chromatography (ether: pentane, 1:4) to give a colorless liquid (S)-2-octyl tosylate (417 mg, 92 % yield). 282 mg (1.0 mmol) (S)-2-octyl tosylate and 534 mg (3.1 mmol) [EMIm]Ac were mixed and stirred at r.t. for 3 hours. The upper phase was decanted and the lower phase was extracted with (3×5 mL) pentane. The pentane extracting solution was combined with the upper phase, and the solvent was evaporated. Then the product was purified with column chromatography (pentane as eluent). 151 mg A colorless liquid 2-octyl acetate was obtained in 88% yield. A sample was taken for GC measurement, the result indicated that the formed 2-octyl acetate was composed of 99 % (R)-configuration and 1 % (S)-configuration. 120 mg (0.7 mmol) 2-Octyl acetate was dissolved in 2 mL ethanol and 1 mL 10 % sodium hydroxide was added. The mixture was heated to reflux and kept for two hours. Ethanol was removed with a rotary evaporator. The residue was extracted with (3×3 mL) pentane. After removal of pentane, the colorless liquid 2-octanol was obtained in 89 % yield (80 mg).

(S)-2-Octyl tosylate
1H-NMR (400 MHz; CDCl₃; δ/ppm): 0.85 (t, 3J(H,H)=7.2 Hz, 3H, CH₂CH₃), 1.15-1.24 (m, 8H, (CH₂)₄), 1.25 (d, 3J(H,H)=6.2 Hz, 3H, CHCH₃), 1.40-1.68 (m, 2H, CHCH₂), 2.44 (s, 3H, PhCH₃), 4.59 (sextet, 1H, CH₃CH), 7.32 (d, 3J(H,H)=8.1 Hz, 2H, Ph), 7.79 (d, 3J(H,H)=8.1 Hz, 2H, Ph).

13C-NMR (100 MHz; CDCl₃; δ/ppm): 14.2 (CH₂CH₃), 21.0 (PhCH₃), 21.8 (CH₂C₃H₃), 22.6 (CH₃CH₂), 25.9 (CH₃(CH₂)₂CH₂), 29.5 (CH₃(CH₂)₂CH₂), 32.0 (CH₃CH₂CH₂), 39.5 (CHCH₂), 80.86 (CH₃CH), 127.9, 129.8, 134.8, 144.5 (Ph).

(R)-2-Octanol

1H-NMR (300 MHz; CDCl₃; δ/ppm): 0.87 (t, 3J(H,H)=7.2 Hz, 3H, CH₂C₃H₃), 1.19 (d, 3J(H,H)=6.2 Hz, 3H, CHC₃H₃), 1.23-1.60 (m, 10H, (CH₂)₅), 3.79 (sextet, 1H, HOCH).

13C-NMR (100 MHz; CDCl₃; δ/ppm): 14.2 (CH₂CH₃), 22.7 (CHCH₃), 23.6 (CH₃CH₂), 25.9 (CH₃(CH₂)₂CH₂), 29.5 (CH₃(CH₂)₂CH₂), 32.0 (CH₃CH₂CH₂), 39.5 (CHCH₂), 69.4 (CH₃CH).

3.1.3.5 Esterification of racemic electrophiles with chiral ionic liquids

a) Preparation of CIL-1

3.01 g (20 mmol) [EMIm]Cl was dissolved in 5 mL methanol and passed over a stacked column of anion exchange resin IRA-400(OH), to get [EMIm]OH. The hydroxide was neutralized with a stoichiometric amount of lactic acid. After removal of the solvent, the
product was dried overnight under 5 Pa vacuum at 333 K. 3.8 g colourless viscous liquid was obtained in 95 % yield.

1-Ethyl-3-methylimidazolium lactate (CIL-1):

\[
\text{N} \quad \text{N}^+ \quad \text{CO}_2^- \\
\text{CH}_3
\]

\(^1\text{H-NMR}\) (300 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 1.05 (d, \(^3\text{J(H,H)}=6.7\) Hz, 3H, CH(OH)CH\(_3\)), 1.41 (t, \(^3\text{J(H,H)}=7.3\) Hz, 3H, CH\(_2\)CH\(_3\)), 3.45 (q, \(^3\text{J(H,H)}=6.8\) Hz, 1H, O\(_2\)CCH\(_3\)), 3.86 (s, 3H, NCH\(_3\)), 4.20 (q, \(^3\text{J(H,H)}=7.3\) Hz, 2H, CH\(_3\)CH\(_2\)), 7.73 (br, 1H, NCH), 7.82 (br, 1H, NCH), 9.43 (s, 1H, NCHN).

\(^1\text{C-NMR}\) (75 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 15.1 (CH\(_2\)CH\(_3\)), 21.6 (HOCHCH\(_3\)), 35.6 (NCH\(_3\)), 44.1 (CH\(_3\)CH\(_2\)), 67.0 (HOCH), 122.0 (NCH), 123.6 (NCH), 136.7 (NCHN), 176.7 (HOCHCO\(_2\)).

\([\alpha]^{26}_D = -12.3\) cm\(^2\) g\(^{-1}\) dm\(^{-1}\) (c = 2.1 g cm\(^{-1}\) in ethanol).

b) Preparation of CIL-2

(R)-\(N,N\)-Dimethyl-1-phenylethylamine was synthesized according to a literature procedure,\(^{[86]}\) which is described as follows:

2.78 g (23 mmol) (R)-1-Phenylethylamine was added to 90 % formic acid (7.08 g) cooled with ice bath. Subsequently, 5.74 g 37 % aqueous formaldehyde was added. Then the mixture was heated to 373 K and kept overnight. After that, the mixture was cooled down to r.t. and acidified with 4 M HCl and evaporated to dryness. The residue solid was dissolved in 10 mL water and rendered basic with 40 % aqueous NaOH to pH 11. After the extraction with 3×20 mL diethyl ether and removal of the solvent, the residue was distilled to give liquid (R)-\(N,N\)-dimethyl-1-phenylethylamine (2.70 g, 18 mmol, yield 79 %), at 343 K, 10 mbar. Then the amine was mixed with 6.18 mL (54 mmol) 1-iodobutane. A clear solution was obtained, but the solution became cloudy after a few minutes. The
solution was stirred at 333 K overnight. After removing the unreacted 1-iodobutane, (R)-N-butyl-N,N-dimethyl-N-(1-phenylethyl)ammonium iodide was obtained quantitatively. Then it was dissolved in 5 mL methanol and passed over a stacked column of anion exchange resin IRA-400(OH) to get its hydroxide. The hydroxide was neutralized with a stoichiometric amount of acetic acid. After removal of methanol, the product was dried overnight under 5 Pa vacuum at 333 K. A red viscous liquid was obtained in 89 % yield, 4.24 g.

(R)-N,N-Dimethyl-1-phenylethylamine

\[
\text{N} \quad \text{r}
\]

\(^1\)H-NMR (300 MHz; CDCl\(_3\); \(\delta/\text{ppm}\)): 1.37 (d, \(^3\)J(H,H)=6.6 Hz, 3H, CH\(_2\)CH\(_3\)), 2.19 (s, 6H, N(CH\(_3\)_2)), 3.24 (q, \(^3\)J(H,H)=6.6 Hz, 1H, NCH), 7.21-7.34 (5H, Ph).

\([\alpha]^{26}_D = +56.1 \text{ cm}^2 \text{ g}^{-1} \text{ dm}^{-1} \) (c = 2.8 g cm\(^{-3}\) in CHCl\(_3\)) [lit.\(^{[86]}\) \([\alpha]^{22}_D = +62.5 \text{ cm}^2 \text{ g}^{-1} \text{ dm}^{-1}\) (neat)].

(R)-N-Butyl-N,N-dimethyl-N-(1-phenylethyl)ammonium iodide

\[
\text{N} \quad \text{r}
\]

\(^1\)H-NMR (400 MHz; CDCl\(_3\); \(\delta/\text{ppm}\)): 0.94 (t, \(^3\)J(H,H)=7.4 Hz, 3H, CH\(_2\)CH\(_3\)), 1.40 (sextet, 2H, CH\(_3\)CH\(_2\)), 1.76-1.85 (m, 5H, CH\(_3\)CH\(_2\)CH\(_2\))&CH\(_2\)), 3.15 (s, 3H, NCH), 3.20 (s, 3H, NCH), 3.45-3.54 (m, 2H, NCH\(_2\)), 5.27 (q, \(^3\)J(H,H)=7.0 Hz, 1H, NCH), 7.40-7.62 (5H, Ph).

\(^{13}\)C-NMR (100 MHz; CDCl\(_3\); \(\delta/\text{ppm}\)): 13.8 (CH\(_2\)CH\(_3\)), 15.7 (CH\(_2\)CH\(_3\)), 19.8 (CH\(_2\)CH\(_2\)), 24.9 (CH\(_3\)CH\(_2\)CH\(_2\)), 48.1 (NCH\(_3\)), 48.7 (NCH\(_3\)), 62.4 (NCH\(_2\)), 72.8 (NCH), 129.3-132.3 (Ph).

(R)-N-Butyl-N,N-dimethyl-N-(1-phenylethyl)ammonium acetate (CIL-2)

\[
\text{N} \quad \text{r}
\]

\(^1\)H-NMR (300 MHz; CDCl\(_3\); \(\delta/\text{ppm}\)): 0.93 (t, \(^3\)J(H,H)=7.4 Hz, 3H, CH\(_2\)CH\(_3\)), 1.32 (sextet, 2H, CH\(_3\)CH\(_2\)), 1.54 (s, 3H, CO\(_2\)CH\(_3\)), 1.65-1.78 (m, 5H, CH\(_3\)CH\(_2\)CH\(_2\))&CH\(_2\)\(_3\)), 2.89 (s,
3H, NCH$_3$), 3.04 (s, 3H, NCH$_3$), 3.45-3.54 (m, 2H, NCH$_2$), 4.86 (q, $^3$$J$(H,H)=7.0 Hz, 1H, NCH$_3$), 7.47-7.66 (5H, Ph).

$^{13}$C-NMR (75 MHz; CDCl$_3$; δ/ppm): 13.5 (CH$_3$CH$_3$), 14.5 (CHCH$_3$), 19.3 (CH$_2$CH$_2$), 23.7 (CH$_3$CH$_2$CH$_2$), 25.9 (CO$_2$CH$_3$), 47.1 (NCH$_3$), 47.9 (NCH$_3$), 61.6 (NCH$_2$), 70.9 (NCH), 128.7-133.4 (Ph), 172.3 (CH$_3$CO$_2$).

[α]$_{D}^{26}$ = +20.4 cm$^3$ g$^{-1}$ dm$^{-1}$ (c = 2.0 g cm$^{-3}$ in ethanol).

c) Preparation of CIL-3

To synthesize the intermediate (S)-1-ethyl-3-(1′-hydroxyl-2′-propyl)imidazolium bromide, a literature procedure$^{[87]}$ was used with a few modifications. Formalin solution (37 %, 2.93 g) and glyoxal aqueous solution (40 %, 5.10 g) were mixed and heated to 323 K. To the solution was added a mixture of 3.13 g (35 mmol) alanine, 2.39 g of a 25 % ammonia solution and 15 mL of a 10 % sodium hydroxide solution in small portions during half an hour. The solution changed from colorless into yellow. After stirring for 4 hours at 323 K, the water was evaporated. The residue was dissolved into 10 mL methanol and cooled in an ice bath. Then 5.11 mL (70.4 mmol) thionyl chloride was added dropwise to the solution. After stirring at r.t. overnight, the solvent was removed under reduced pressure and the oil-like residue was treated with a saturated aqueous sodium carbonate solution to adjust the pH (~9). The product was extracted with ethyl acetate and purified by column chromatography (ethyl acetate : pentane, 8:2). A orange solid (S)-methyl 2-(1-imidazolyl)propionate was obtained in 42 % yield, 2.30 g. 1.89 g (12 mmol) obtained ester was dissolved in 60 mL ethanol and cooled with an ice bath. 1.99 g Sodium borohydride was added in small portions during half an hour. After addition, the mixture was heated to reflux and kept overnight. When the solution was cooled to r.t., ethanol was removed with reduced pressure, and 50 mL saturated aqueous
potassium carbonate solution was added. The mixture was heated to 333 K for 3 hours and cooled down to r.t.. Then the mixture separated into a biphasic system, and the organic phase was decanted. The aqueous phase was extracted with (3×10 mL) ethyl acetate. The extracting solution and the organic phase were combined and dried with anhydrous sodium sulfate. After removal of the solvent, the product was purified with column chromatography (DCM: methanol, 4:1), and (S)-2-(1-Imidazolyl)-propanol was obtained in 90 % yield (1.36 g). 1.26 g (10 mmol) Synthesized imidazole and 3.8 mL (51 mmol) bromoethane were mixed and a clear solution was observed. The solution was heated to 313 K and kept overnight. Once no more unreacted imidazole was detectable with TLC, the mixture was dried under high vacuum at 353 K for an hour. Yellow viscous liquid (S)-1-Ethyl-3-(1′-hydroxy-2′-propyl)imidazolium bromide was obtained quantitatively. Then it was dissolved into 5 mL methanol and passed over a stacked column of anion exchange resin IRA-400(OH) to get its hydroxide. The hydroxide was neutralized with a stoichiometric amount of acetic acid. After removal of methanol, the product was dried overnight under 5 Pa vacuum at 333 K. Orange viscous liquid (S)-1-ethyl-3-(1′-hydroxy-2′-propyl)imidazolium acetate was obtained in 91 % yield, 1.95 g.

(S)-Methyl 2-(1-imidazolyl)propionate

\[
\text{N} \quad \text{N} \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_3
\]

\(^1\)H-NMR (300 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 1.64 (d, \(^3\)J(H,H)=7.2 Hz, 3H, CH\(\text{CH}_3\)), 3.67 (s, 3H, CO\(_2\)CH\(_3\)), 5.22 (q, \(^3\)J(H,H)=7.2 Hz, 1H, CH\(_3\)CH), 6.90 (br, 1H, NCH), 7.23 (br, 1H, NCH), 7.71 (s, 1H, NCHN).

\(^{13}\)C-NMR (75 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 18.0 (CHCH\(_3\)), 52.5 (CO\(_2\)CH\(_3\)), 53.9 (NCH), 118.5 (NCH), 128.2 (NCH), 136.7 (NCHN), 171.1 (CH\(_3\)CO\(_2\)).

(S)-2-(1-Imidazolyl)-propanol

\[
\text{N} \quad \text{N} \quad \text{CH}_2\text{OH} \\
\text{H}_3\text{C}
\]

\(^1\)H-NMR (400 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 1.35 (d, \(^3\)J(H,H)=7.2 Hz, 3H, CH\(\text{CH}_3\)), 3.55 (m, 2H, HOCH\(_2\)), 4.23 (sextet, 1H, CH\(_3\)CH), 6.86 (br 1H, NCH), 7.20 (br, 1H, NCH), 7.63 (br, 1H, NCHN).
13C-NMR (100 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 17.7 (CHCH\(_3\)), 54.5 (CH\(_3\)CH), 65.1 (HOCH\(_2\)), 117.6 (NCH), 127.9 (NCH), 136.3 (NCHN).

\(\text{(S)}\)-1-Ethyl-3-(1'-hydroxyl-2'-propyl)imidazolium bromide

\[\text{C}=\text{N}^-\text{N}^+\text{H}_2\text{CH}_2\text{CH}_2\text{Br}\]

\(^1\)H-NMR (300 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 1.40–1.45 (m, 6H, CH\(_2\)CH\(_3\)&CHCH\(_3\)), 3.33–3.70 (m, 2H, HOCH\(_2\)), 4.21 (q, \(^3\)J(H,H)=7.5 Hz, 2H, CH\(_3\)CH\(_2\)), 4.49 (m, 1H, CH\(_3\)CH), 5.22 (t, \(^3\)J(H,H)=5.4 Hz, 1H, CH\(_2\)OH), 7.84 (dd, \(^3\)J(H5,H4)=1.9 Hz, \(^4\)J(H5,H2)=1.6 Hz, 1H, NCH), 7.85 (dd, \(^3\)J(H4,H5)=1.9 Hz, \(^4\)J(H4,H2)=1.6 Hz, 1H, NCH), 9.28 (dd, \(^4\)J(H5,H2)=\(^4\)J(H4,H2)=1.6 Hz, 1H, NCHN).

13C-NMR (75 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 15.1 (CH\(_2\)CH\(_3\)), 16.3 (CHCH\(_3\)), 44.1 (CH\(_3\)CH\(_2\)), 58.1 (CH\(_3\)CH), 63.7 (HOCH\(_2\)), 121.1 (NCH), 121.9 (NCH), 135.2 (NCHN).

\(\text{(S)}\)-1-Ethyl-3-(1'-hydroxyl-2'-propyl)imidazolium acetate (CIL-3)

\[\text{C}=\text{N}^-\text{N}^+\text{H}_2\text{CH}_2\text{CH}_2\text{OAc}\]

\(^1\)H-NMR (400 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 1.40–1.44 (m, 6H, CH\(_2\)CH\(_3\)&CHCH\(_3\)), 1.57 (s, 3H, CO\(_2\)CH\(_3\)), 3.52–3.70 (m, 2H, HOCH\(_2\)), 4.19 (q, \(^3\)J(H,H)=7.3 Hz, 2H, CH\(_3\)CH\(_2\)), 4.54 (m, 1H, CH\(_3\)CH), 7.80 (dd, \(^3\)J(H5,H4)=\(^4\)J(H5,H2)=1.6 Hz, 1H, NCH), 7.87 (dd, \(^3\)J(H5,H4)=\(^4\)J(H5,H2)=1.6 Hz, 1H, NCH), 9.70 (br, 1H, NCHN).

13C-NMR (100 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\)): 15.1 (CH\(_2\)CH\(_3\)), 16.4 (CHCH\(_3\)), 25.7 (CO\(_2\)CH\(_3\)), 44.0 (CH\(_3\)CH\(_2\)), 58.1 (CH\(_3\)CH), 63.6 (HOCH\(_2\)), 121.0 (NCH), 121.6 (NCH), 135.9 (NCHN), 173.4 (CH\(_3\)CO\(_2\)).

\([\alpha]^{26}_{D} = +6.4 \text{ cm}^3 \text{ g}^{-1} \text{ dm}^{-1} \) (c = 3.0 g cm\(^{-3}\) in ethanol).

d) Synthesis of 2-octyl mesylate

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} & \quad \xrightarrow{\text{CH}_3\text{SO}_2\text{Cl}, \text{Et}_3\text{N}} \quad \xrightarrow{\text{Et}_2\text{N}\text{HCl}} \\
\text{CH}_3\text{SO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} & \quad \xrightarrow{\text{CH}_3\text{SO}_2\text{Cl}, \text{Et}_3\text{N}} \quad \xrightarrow{\text{Et}_2\text{N}\text{HCl}}
\end{align*}
\]

2-Octyl mesylate (or 2-octyl methanesulfonate) was synthesized in the usual manner by the reaction of alcohol with mesyl chloride. To a mixture of 13.1 g (0.10 mol) 2-octanol...
and 21.6 mL (0.15 mol) triethylamine was added mesyl chloride (8.5 mL) with stirring in an ice bath. After addition, the mixture was stirred for another one hour and stopped for filtration. The filtrate was collected and condensed with a rotary evaporator. The product was separated by column chromatography (ethyl acetate: pentane, 1:49), whereby phosphomolybdic acid staining was used to aid the visualization of the product in TLC. After removal of the solvent, 19.92 g of a colorless liquid was obtained in 95 % yield.

2-Octyl mesylate or 2-octyl methanesulfonate

\[
\text{O} \quad \text{SO}_3 \quad \text{O}
\]

\(^1\text{H}-\text{NMR} (300 \text{ MHz; CDCl}_3; \delta/\text{ppm}): 0.86 (t, \ ^3\text{J}(\text{H,H})=6.5 \text{ Hz}, 3\text{H}, \text{CH}_2\text{CH}_3), 1.15-1.76 (10\text{H}, (\text{CH}_2)_5), 1.39 (d, 3\text{H}, \ ^3\text{J}(\text{H,H})=6.3 \text{ Hz}, \text{OCHCH}_3), 2.97 (s, 3\text{H}, \text{O}_3\text{SCCH}_3), 4.76 (\text{sextet, 1H, OCH}).
\]

\(^{13}\text{C}-\text{NMR} (75 \text{ MHz; CDCl}_3; \delta/\text{ppm}): 14.1 (\text{CH}_2\text{CH}_3), 21.3 (\text{CHCH}_3), 22.6 (\text{CH}_2\text{CH}_2), 25.2 (\text{CH}_3(\text{CH}_2)_2\text{CH}_2), 29.0 (\text{CH}_3(\text{CH}_2)_2\text{CH}_2), 31.7 (\text{CH}_3\text{CH}_2\text{CH}_2), 36.8 (\text{CHCH}_3), 38.7 (\text{SO}_3\text{CH}_3), 80.5 (\text{OCH}).

\(e\) Esterification of CIL-1 with 2-octyl mesylate

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{CH}_3 & \quad \text{CO}_2^- \\
\text{HO} & \quad \text{H} \\
\end{align*}
\]

\[
\text{O} \quad \text{SO}_3 \quad \text{O}
\]

\[
\begin{align*}
\text{313 K} & \\
\end{align*}
\]

0.99 g (4.8 mmol) 2-Octyl mesylate and 1.03 g (5.1 mmol) CIL-1 were mixed and stirred at 313 K for 2 hours forming a homogeneous mixture. After the reaction, the ester and the unreacted mesylate were extracted with ethyl acetate (3×5 mL), and condensed with a rotary evaporator for column chromatography (DCM as eluent). Phosphomolybdic acid staining was used to aid the visualization of the product in TLC. After removal of the solvent, 0.60 g colorless liquid was obtained in 47 % yield.

To a 10 mL ethanol solution of 0.50 g 2-octyl lactate was added a 2 M sodium hydroxide aqueous solution. After refluxing for 2 hours, ethanol was evaporated and 2-octanol was
extracted with DCM (3×5 mL). The solvent was evaporated and the colorless 2-octanol was obtained quantitatively.

Then 10 mg 2-octanol was dissolved in DCM and mixed with 0.2 mL N-methyl-N-(trimethylsilyl)trifluoroacetamide. After half an hour reaction at 353 K, the solution was analyzed with GC. Enantioenriched 2-octanol (57 % (S)-configuration and 43 % (R)-configuration) was detected.

2-Octyl lactate

\[
\text{HO}_2\text{C} - \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3
\]

\(^1\text{H-NMR}\) (300 MHz; CDCl\(_3\); δ/ppm): 0.87 (t, 3\(^1\)J(H,H)=6.9 Hz, 3H, CH\(_2\)CH\(_3\)), 1.19-1.27 (11H, CHCH\(_3\)&(CH\(_2\))\(_4\)), 1.39 (dd, J(H,H)=2.6 Hz, 3\(^3\)J(H,H)=6.8 Hz, 3H, HOCHCH\(_3\)), 1.47-1.60 (m, 2H, CHCH\(_2\)), 2.86 (t, 3\(^1\)J(H,H)=5.1 Hz, 1H, OH), 4.22 (m, 1H, HOCH), 4.97 (sextet, 1H, CH\(_2\)CH).

\(^13\text{C-NMR}\) (100 MHz; CDCl\(_3\); δ/ppm): 14.2 (CH\(_2\)CH\(_3\)), 20.1, 20.6, 22.7, 25.4, 29.2, 31.8, 35.9, 66.9 (HOCH), 73.0 (CH\(_3\)CH), 175.6 (CO\(_2\)).

\([\alpha]^{23}\)\(_D\) = -1.7 cm\(^3\) g\(^{-1}\) dm\(^{-1}\) (c = 1.5 g cm\(^{-3}\) in CHCl\(_3\)).

f) Esterification of CIL-2 or CIL-3 with 2-octyl mesylate

A mixture of 255 mg (1.22 mmol) 2-octyl mesylate and 238 mg (1.20 mmol) CIL-2 (a biphasic system) was heated to 343 K and kept for half an hour. After the reaction, the upper phase was decanted, and the lower phase was extracted with ethyl acetate (3×5 mL). The extracting solution and the upper phase were combined and the solvent was evaporated. A sample was taken for \(^1\)H-NMR and GC measurements. \(^1\)H-NMR result indicated that the yield of 2-octyl acetate reached 83 %. The GC result showed that 2 % ee ((S)-2-octyl acetate) was achieved.
A mixture of 233 mg (1.12 mmol) 2-octyl mesylate and 238 mg (1.11 mmol) CIL-3 (a biphasic system) was heated to 313 K and kept for 7 hours. After the reaction, the upper phase was decanted, and the lower phase was extracted with ethyl acetate (3×5 mL). The extracting solution and the upper phase were combined and the solvent was evaporated. A sample was taken for $^1$H-NMR and GC measurements. $^1$H-NMR result indicated that 2-octyl acetate ester was formed in 34 % yield. Based on the GC result, 2 % ee ((S)-2-octyl acetate) was observed.

3.1.3.6 Recycling processes of ionic liquids for esterification

a) Anion exchange resin method

\[
\text{[EMIm]Ac} + \text{BuCl} \xrightarrow{\text{BuO}_2\text{CCH}_3} \text{[EMIm][Cl]}
\]

5.11 g (30 mmol) [EMIm]Ac and 2.76 g (30 mmol) 1-chlorobutane were mixed and heated to 343 K for 3 hours. When the reaction was cooled down to r.t., the upper phase was decanted. The lower phase was washed with pentane (3×10 mL) and dried. Then the lower phase was dissolved in 5 mL methanol and passed over a stacked column of anion exchange resin IRA-400(OH) to obtain [EMIm]OH. The hydroxide was neutralized with a stoichiometric amount of acetic acid, and the methanol was evaporated. An orange liquid [EMIm]Ac was obtained (4.65 g, 27 mmol, yield 91 %). $^1$H- and $^{13}$C-NMR did not show differences between recovered [EMIm]Ac and the original one. Then the recovered [EMIm]Ac was mixed with 2.55 g (28 mmol)1-chlorobutane. After 3 hours reaction at 343 K, 95 % yield ($^1$H-NMR) of 1-butyl acetate was achieved.

b) Recyclable DBU process

\[
\text{[EMIm]Cl} + \text{CH}_2\text{CO}_{\text{H}} \xrightarrow{\text{DBU}, 343 K} \text{[EMIm]Ac}
\]

\[
\text{NaOH / MeOH} \xrightarrow{\text{DBU}, 343 K} \text{[EMIm]Cl}
\]
1.00 g (6.6 mmol) DBU was neutralized with 0.39 g (6.6 mmol) acetic acid. The solution was stirred for half an hour at r.t., and white solid [DBUH]Ac was obtained quantitatively. Then 0.65 g (3.0 mmol) [DBUH]Ac and 0.28 g (3.0 mmol) 1-chlorobutane were mixed and heated to 343 K. [DBUH]Ac melted into liquid, and the reaction was carried out in this biphasic system. After 3 hours, 85 % $^1$H-NMR yield of 1-butyl acetate was achieved. The upper phase was decanted; the lower phase was washed with pentane (3×5 mL). The unreacted [DBUH]Ac was extracted with ethyl acetate (3×5 mL), white solid [DBUH]Cl was obtained and dried. 0.48 g (2.6 mmol) [DBUH]Cl was dissolved into 5 mL methanol and neutralized with 0.11 g (2.7 mmol) sodium hydroxide. After evaporating methanol, the remaining mixture was extracted with DCM (3×5 mL). The extracting solution was collected and DCM was evaporated. 0.36 g DBU was obtained in 91 % yield.

[DBUH]Ac

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\]

$^1$H-NMR (300 MHz; DMSO-$d_6$; δ/ppm): 1.55-1.65 (m, 9H), 1.86 (m, 2H), 2.73 (m, 2H), 3.21 (t, $^3$J(H,H)=5.4 Hz, 2H), 3.40 (t, $^3$J(H,H)=5.7 Hz, 2H), 3.47 (m, 2H).

[DBUH]Cl

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{H} & \quad \text{Cl}
\end{align*}
\]

$^1$H-NMR (400 MHz; CDCl$_3$; δ/ppm): 1.59-1.1.82 (m, 6H), 2.00 (m, 2H), 2.95 (m, 2H), 3.40 (t, $^3$J(H,H)=5.6 Hz, 2H), 3.46-3.61 (m, 4H), 11.54 (br, NH).

$^{13}$C-NMR (100 MHz; CDCl$_3$; δ/ppm): 19.6, 24.1, 26.9, 29.1, 32.2, 38.0, 48.8, 54.5, 166.3 (NCN).

DBU

\[
\begin{align*}
\text{N} & \quad \text{N}
\end{align*}
\]

$^1$H-NMR (400 MHz; DMSO-$d_6$; δ/ppm): 1.49-1.57 (m, 6H), 1.65 (m, 2H), 2.26 (m, 2H), 3.07 (t, $^3$J(H,H)=5.6 Hz, 2H), 3.13-3.16 (m, 4H).
In a 25 mL round-bottom flask, 4.036 g (23.7 mmol) recovered [EMIm]Ac and 1.572 g (17.0 mmol) 1-chlorobutane were added. After 3 hours stirring at 343 K, the upper phase was decanted; the lower phase was extracted with pentane (4×5 mL). The extract solution was combined with the upper phase, and the solvent was evaporated with a rotary evaporator. Then the ester was collected. The lower phase or IL phase was dried under vacuum for half an hour and weighed. $^1$H-NMR result indicated that 3.547 g IL was composed of 7.0 mmol [EMIm]Ac and 16.2 mmol [EMIm]Cl.

Under argon atmosphere, the IL phase was dissolved in 2 mL ethanol and heated up to 343 K. 1.590 g potassium acetate was dissolved in 12 mL ethanol and warmed up at 343 K. Then the potassium acetate-ethanol solution was added dropwise into the IL-ethanol solution at 343K. White solid precipitated immediately. After another one hour of stirring, the solution was kept in the freezer at 255 K for 1 hour and filtered through a Büchner Funnel with glass frits. The filtrate was collected and ethanol was evaporated. After drying overnight at 333 K under 5 Pa vacuum, 3.540 g [EMIm]Ac was obtained in 90 % yield, 97 % purity.
3.1.4 Interim Summary

1. Esterification between carboxylate-based ILs and alkyl halides was unveiled.
   - When carboxylate-based ILs come in contact with common halocarbons, such as DCM and chloroform, they are not innocent, as was previously believed.
   - The reactivity could be exploited for a facile esterification procedure that could be performed under neat conditions with stoichiometric reactants.
   - A series of substrates was investigated, all of which provided moderate to excellent yields (33-99%).
   - Due to the high polarity of ILs, the resultant alkyl carboxylate esters were isolated without difficulty by decantation or extraction.

2. The $S_N2$ mechanism of the esterification of alkyl halides and carboxylate-based ILs was demonstrated, offering potential applications for the configuration inversion of chiral alcohol.

3. Chiral ILs were tested for stereoselective esterification with racemic electrophiles. In the case of [EMIm]Lactate, hydrolysis of the ester produced enantioenriched alcohol ($57\%$ (S)-configuration and $43\%$ (R)-configuration). With chiral cations, only $2\%$ ee 2-octyl acetate ester was observed.

4. Three processes were demonstrated for the recycling of the by-product ILs, to be readily converted back into reusable reactant ILs.
   - The commonly-used anion exchange resin method was applicable for the recovery of ILs.
   - DBU was a good reagent for the recyclable base process, and avoided the use of large quantities of sodium hydroxide for regenerating the exchange resin.
   - The anion metathesis method avoided the use of additional bases and acids.
3.2 Ionic Tagging

3.2.1 Background

Due to their interesting properties, ILs have been employed as solvents for transition metal catalysis, and provide potential advantages over traditional solvents, in terms of activity, stability and reusability of catalysts.\cite{1b-f, 9a, b} Catalyst leaching often causes a decrease in catalyst activity, and is an important criterion for the reusability of catalysts. To decrease catalyst leaching, ionic tags have been successfully introduced. The ionic tagging technique incorporates an ionic moiety into the catalyst structure. After modification, catalysts have an ionic character, and thus can be better immobilized in ILs for their further recovery and reuse.\cite{88}

The ionic tagging technique is mainly employed to prepare cationic phosphorus ligands, as P-ligands (phosphorus ligands) are broadly used in transition metal catalysis.\cite{88d, 88f, 89} When ILs were successfully employed as reaction media for transition metal catalysis at the end of the last century, a large number of cationic P-ligands were developed. Following early quaternary ammonium or phosphonium tagged P-ligands, imidazolium or pyridinium tagged P-ligands are focused on at the moment, due to their better stability and accessibility. To obtain these ligands, two synthetic strategies are commonly applied, distinguished by the number of steps required for the introduction of the ionic tag (Figure 3-10). Method A normally requires three steps to obtain the targeted cationic P-ligands: grafting with a tertiary amine (or phosphine, imidazole), quaternization (to form a cation) and anion exchange (due to the negative influence of the halide anion on transition metal catalysis). Even though this is the main method employed, it has several critical drawbacks. Quaternization requires long reaction time, and its selectivity is often critical due to side alkylation of the undesired phosphine. Moreover, the basicity of alkylimidazoles or amines limits the existence of sensitive functional groups in the ligands. Furthermore, the last step of anion exchange is not always easy to conduct, as trace amounts of halide may deactivate metal catalysts. Method B involves direct grafting of the preformed ionic group. However, successful processes have been achieved only rarely, because the separation of ionic compounds is very difficult in practice.
To graft phosphorus groups onto specific structures, the facile reaction of P-Cl compounds with alcohols to form phosphite (or phosphinite, phosphonite) ligands is commonly used. However, in the preparation of cationic P-ligands, separation becomes a severe problem due to the same ionic characters of the by-product and the product. So far, there are only four reported structures (Figure 3-11).\cite{88e, 90} In all of them, the formed by-products are readily removed by washing, owing to the good stability of the target ligands in water.

![Figure 3-10. Synthetic strategies for cationic P-ligands.](image)

**Figure 3-10.** Synthetic strategies for cationic P-ligands.

Feng and co-workers reported a modified Josiphos ligand with an imidazolium tag.\cite{91} The imidazolium cation was attached to the phosphine ligand via amide formation (Scheme 3-8).

![Figure 3-11. Cationic P-ligands prepared via the reaction of the hydroxyl group and the P-Cl compounds.](image)

**Figure 3-11.** Cationic P-ligands prepared via the reaction of the hydroxyl group and the P-Cl compounds.\cite{88e, 90}
Tagged phosphines were prepared by Consorti et al. for Grubbs-type catalysts. The imidazolium cation was introduced by one-step radical chain addition of secondary phosphines to allyl or vinyl imidazolium salts (Scheme 3-9). Prepared metal catalysts were immobilized in ILs and showed good activity and stability for the RCM (ring-closing metathesis) reaction of octa-1,7-diene in the biphasic system of [BMIm]PF$_6$-toluene.

In 2010, Beller’s group synthesized a class of cationic imidazolium phosphines for palladium-catalyzed coupling reactions. The ligands were synthesized via methylation at the 2-position of the imidazolium cation, followed by deprotonation of this methyl group and grafting with a P-Cl compound (Scheme 3-10). The catalysts were stable towards air and water, and active in palladium-catalyzed coupling reactions. In addition, the catalysts were recycled several times without a significant activity loss due to their ionic nature.
Another class of cationic P-ligands are 2-imidazolium phosphines, which are normally synthesized in two steps, \textit{i.e.} deprotonation at the 2-position of the imidazolium cation and addition of the P-Cl compound. Recently, Hintermair \textit{et al.} reported that this kind of ligand also could be prepared via NHC-transfer. In this case, the bis-NHC Ag (I) complex was first synthesized through the reaction of [EMIm]BTA, silver oxide and KOH. The formed complex could transfer one carbene to the P-Cl compound with halide abstraction (Scheme 3-11). Unfortunately, several attempts to isolate the pure P-ligands failed.

\begin{align*}
\text{Scheme 3-11.} & \quad \text{Carbene-halide exchange reaction of bis-NHC Ag(I) complex with P-Cl compounds.}
\end{align*}

3.2.2 Results and Discussion

3.2.2.1 Functionalization of imidazolium cations at the 2-position

a) Functionalization of imidazolium cations via deprotonation with bases

During the investigations of the reaction of [EMIm]Ac and DCM, the formation of 2-(acetoxymethyl)-1-ethyl-3-methylimidazolium cation was observed. It was proposed
that the imidazolium cation was deprotonated by acetate to form carbene, which subsequently attacked the chloromethyl acetate (Scheme 3-12).\textsuperscript{[195]} When [EMIm]Ac was directly mixed with chloromethyl acetate without any solvent, the functionalized imidazolium cation was also found in a small amount. Additionally, Aggarwal \textit{et al.} reported a similar phenomenon through the mixture of the imidazolium cation and benzaldehyde under mild basic conditions (DABCO or 3-HQD).\textsuperscript{[28a]} However, acetate anion or these mild bases was not basic enough to render these transformations synthetically useful. In DMSO, the pKa of acetic acid and the imidazolium salt are 12.6 and ~24, respectively.\textsuperscript{[31a, 96]} Therefore, addition of external base was considered.

![Scheme 3-12. Proposed pathway for the formation of the 2-(acetoxy)methyl)-1-ethyl-3-methylimidazolium cation.](image)

With [EMIm]Ac as the starting material, functionalizing the imidazolium cation was not favorable due to nucleophilicity of the acetate anion. Therefore [EMIm]Cl was used as the starting material instead of [EMIm]Ac and potassium carbonate was chosen as the base. Four electrophiles (1-chlorobutane, 2-butanone, benzaldehyde and butanal) were investigated for functionalization. Only the aldehydes were found to be reactive to form the secondary alcohols (Scheme 3-13). For benzaldehyde and butanal, 27 \% and 14 \% \textsuperscript{1}H-NMR formation of the alcohols were observed, respectively, after one hour of reaction at 353 K (Figure 5-5 and Figure 5-6 in Appendices). When the reaction time was extended to 3 hours, the conversion did not change. Pure products could not be isolated due to separation issues.

![Scheme 3-13. Reaction of [EMIm]Cl and benzaldehydes (or butanal).](image)

When paraformaldehyde was used, the reaction ran to completion within 2 hours at 353 K. The target molecule 1-ethyl-2-hydroxymethyl-3-methylimidazolium chloride was
easily extracted with 1-butanol and obtained quantitatively. When potassium carbonate was replaced with potassium tert-butoxide, the reaction ran to completion in one hour at r.t. (Scheme 3-14). Biedroń and Kubisa reported the reaction of imidazolium-based ILs with paraformaldehyde to form 2-hydroxymethylimidazolium cations without the use of a base. The long reaction time and uncompleted reaction (96 hours for [BMIIm]Cl and 22 days for [OMIm]Cl to reach 95% yield at 353 K) limited the separation and application. These authors also reported that there was no reaction observed between [BMIIm]BF₄ and paraformaldehyde even after 30 days at 353 K. Here, the reaction for [BMIIm]BF₄ was successfully accomplished (¹H-NMR yield > 90%, Figure 5-7 in Appendices) in 4 hours at 353 K; but the pure product was not isolated. However, the reaction for [BMIIm]BTA had full conversion, and was successfully isolated.

![Scheme 3-14](image)

**Scheme 3-14.** Syntheses of 2-hydroxymethylimidazolium cations via base deprotonation.

b) Modification of imidazolium cations from PILs

The functionalization of the imidazolium cation is also applicable for imidazolium-type PILs (poly(ionic liquid), refers to polymers containing ionic liquid-type structures), which have been intensely investigated in the PILs field. The functionalization of poly-[(N-vinyl-pyrrolidone)-co-(1-vinyl-3-butylimidazolium bromide)] with paraformaldehyde was chosen as a model (Scheme 3-15).

After the reaction, there were new peaks at 3099, 1202, 1037 cm⁻¹ and the peak at 1159 cm⁻¹ disappeared in the IR spectrum (Figure 3-12). Also, a new broad peak (~ 4.7 ppm) appeared in the ¹H-NMR spectrum (Figure 3-13). All these new peaks could be assigned to a new hydroxymethyl group at the 2-position of the imidazolium cation.

![Scheme 3-15](image)

**Scheme 3-15.** Functionalization of poly-[(N-vinyl-pyrrolidone)-co-(1-vinyl-3-butylimidazolium bromide)] with paraformaldehyde.
Figure 3-12. IR spectra before and after modification of the PILs, pink line: before modification, blue line: after modification.

Figure 3-13. $^1$H-NMR spectra before and after modification of the PILs, red line: before modification, blue line: after modification.
This technique not only blocks the 2-position of the imidazolium of PILs, but also provides a good functional group, \textit{i.e.} a hydroxyl group, into the PILs structure for further modifications.

c) Reaction of N-alkyl-N′-alkylimidazolium-2-carboxylate with electrophiles

The zwitterion N-alkyl-N′-alkylimidazolium-2-carboxylate is considered to be a good precursor for synthesizing pure ILs. Normally the zwitterion is treated with one equivalent of protic acid, then it undergoes decarboxylation, leading to the formation of the corresponding IL and the evolution of gaseous CO$_2$.$^{[2-3, 99]}$ To synthesize pure 2-hydroxymethylimidazolium-based ILs in the present work, 1,3-dimethylimidazolium-2-carboxylate was employed as starting material. It was dissolved in methanol and mixed with 1.1 equivalent of paraformaldehyde. After stirring for 2 hours at 353 K, one equivalent of hydrochloric acid was added. Upon evaporating the solvent and drying overnight, 1,3-dimethyl-2-hydroxymethylimidazolium chloride was obtained quantitatively without the need for further purification. By this method, functionalized ILs with various anions could be generated \textit{via} their conjugate protic acid. 1,3-Dimethyl-2-hydroxymethylimidazolium cation with different anions (BF$_4^-$, BTA$^-$, Cl$^-$) and 1-ethyl-2-hydroxymethyl-3-methylimidazolium chloride were successfully synthesized (Scheme 3-16).

\[ \begin{align*}
\text{N}^+ & \text{N}^- \quad \text{R} \quad \text{O} \\
& \text{O} \\
\text{N}^+ & \text{N}^- \\
& \text{R} \\
\end{align*} \]

\[ + (\text{CH}_2\text{OH})_n \quad \Delta \quad + \text{HX} \]

\[ \begin{align*}
\text{N}^+ & \text{N}^- \quad \text{R} \quad \text{HO}^- \\
& \text{X} \\
\end{align*} \]

\[ \text{R}=\text{Me}, \text{Et}, \text{X}=\text{Cl}, \text{BF}_4^-, \text{BTA}^-, \text{Cl}^- \]

\textit{Scheme 3-16.} Synthetic route of 2-hydroxymethylimidazolium cations from zwitterions.

With 1,3-dimethylimidazolium-2-carboxylate as the starting material, the same methodology was tested also for the reaction with other electrophiles (Figure 3-14). Only the electrophiles ROCH$_2$X showed a promising reactivity.

\[ \begin{align*}
\text{Cl} & \text{O} \quad \text{X} \quad \text{Cl}, \text{Br}, \text{I} \\
\text{Cl} & \text{O} \quad \text{Br} \\
\text{Cl} & \text{O} \quad \text{CO} \\
\text{R} & \text{O} \quad \text{X} \\
\text{R} & \text{O} \quad \text{CO} \\
\end{align*} \]

\textit{Figure 3-14.} Investigated electrophiles for the functionalization of 1,3-dimethylimidazolium-2-carboxylate.
For chloromethyl acetate and chloromethyl ethyl ether, moderate conversions of 50 % and 66 % were observed based on $^1$H-NMR (Figure 5-8 and Figure 5-9 in Appendices), Several efforts to separate the products failed, and only a small amount of target molecules (purity > 92 %) was obtained. To facilitate separation of the product, chloromethyl butyrate, which has a longer alkyl chain and thus provides different polarity for reactants and products, was employed. Its product was successfully purified through recrystallization, and the isolated yield reached 50 % (Figure 3-15).

![Figure 3-15](image)

**Figure 3-15.** Functionalized imidazolium cations from alkyl halide and 1,3-dimethylimidazolium-2-carboxylate.

### 3.2.2.2 Syntheses of and catalysis with ionic-tagged phosphorus ligands

**a) A bis(phenyl)phoshine ligand**

The hydroxymethyl substituted imidazolium cations obtained in Chapter 3.2.2.1 were tested as synthons for the syntheses of ionic-tagged P-ligands. Firstly, a bis(phenyl)phoshine ligand was targeted similar to the imidazolium phosphine structures reported by the Beller group.$^{[92]}$ Under the conditions of Scheme 3-17, the new ligand **IPL** was isolated in 78 % yield. Ion chromatography verified the iodide anion in the isolated species. The ligand showed a resonance at $\delta=-18.2$ ppm in the $^{31}$P-NMR. It is soluble in methanol and DMSO, slightly soluble in acetonitrile, and insoluble in pentane, diethyl ether, toluene, DCM, THF and water.

![Scheme 3-17](image)

**Scheme 3-17.** Synthetic route of the ionic phosphine ligand (IPL).

The synthesized ionic phosphine ligand **IPL** was tested in the catalytic hydroxylation of 2-bromomesitylene with a palladium catalyst (Scheme 3-18). Under typical reaction
conditions, only 5 % conversion (1H-NMR) was reached. This was in sharp contrast to the related ligands reported by Beller,[92] which gave moderate to excellent yield (31-96 %). Presumably, this was due to the reduced steric bulk of IPL as compared to the previously reported structures.

![Scheme 3-18. Hydroxylation of 2-bromomesitylene with IPL.](image)

Next, the ligand was applied in the hydroformylation of 1-octene with a rhodium catalyst. Here, more promising result (conv. 47 %, l/b=2.1, TOF=59 h⁻¹) was obtained, under the conditions: Rh(CO)₂acac: 1mg, L/Rh=4, S/Rh=1000, 0.2 mL [EdMIm]BTA as the solvent, 30 bar Syngas (H₂:CO=1:1), 8 h, 373 K (Scheme 3-19).

![Scheme 3-19. Hydroformylation of 1-octene with IPL.](image)

b) A BINOL-derived chiral phosphite ligand
In 2000, Reetz’s group reported chiral monophosphite ligands and chiral ionic phosphites for highly enantioselective rhodium-catalyzed hydrogenation reactions, their ligands are shown in Figure 3-16.[90a, 100] The rhodium complex with the cationic monophosphite ligand could be readily immobilized via ionic interaction with a negatively charged support (H₃PW₁₂O₄₀/SiO₂) and its application for asymmetric catalysis was demonstrated.

![Figure 3-16. Monophosphite structures reported by Reetz’s group](image)
monophosphite ligand **CIPL** was moisture-sensitive. Therefore, water washing was not suitable for purifying the new ligand. To avoid the difficulty of removing triethylammonium chloride, "BuLi was employed to get the lithium alcoholate for the addition of the P-Cl compound (Scheme 3-20). Thus, **CIPL** could be isolated in 81 % yield, and showed a resonance at δ=132.0 ppm in the $^{31}$P-NMR. The ligand was soluble in THF, DCM, chloroform and acetonitrile, insoluble in pentane, slightly soluble in toluene and diethyl ether, and sensitive to alcohol and water.

![Scheme 3-20](image)

**Scheme 3-20.** Preparation of the chiral ionic phosphite ligand (**CIPL**).

With this new ligand, asymmetric hydrogenation of dimethyl itaconate ester (DMI), methyl acetamidoacrylate and N-(1-phenylethylidene)aniline were investigated (Figure 3-17). The hydrogenation of dimethyl itaconate resulted in a good yield and enantioselectivity (full conversion, 72 % ee (S-)) under the following reaction conditions: 1 mmol DMI, [Rh(COD)(**CIPL**)$_2$][BTA]$_3$ (preformed), S/C=100, 40 bar H$_2$, 2 mL DCM, r.t., overnight. Under the same condition, the rhodium catalyzed hydrogenation of methyl acetamidoacrylate resulted in full conversion and 48 % ee (S-). For N-(1-phenylethylidene)aniline, an iridium-based system was used, but only 54 % conversion and 3 % ee were achieved, under the following reaction conditions: [Ir(COD)Cl]$_2$, P/Ir=2, S: 0.5 mmol, S/C=50, r.t., 40 bar H$_2$, 2 mL DCM, overnight.

![Figure 3-17](image)

**Figure 3-17.** The structures of substrates for asymmetric hydrogenation.

As good results were achieved in the asymmetric hydrogenation of DMI (Scheme 3-21), parameters were varied to investigate the influence of the reaction conditions (Table 3-2).
When the preformed catalyst \([\text{Rh(COD)}(\text{CIPL})_2][\text{BTA}]_3\) was replaced with an \textit{in situ} formed catalysts from \([\text{Rh(COD)}_2]\text{BF}_4\) with two equivalents of \text{CIPL}, the enantioselectivity was increased by 10\% (entries 1-2). When 14.1 mg of the additive \([\text{BMIm}]\text{BF}_4\) was added to the system, enantioselectivity did not change (entry 3). Due to the limited solubility of the ligand, only one other solvent (THF) was tested, but showed poor enantioselectivity (4 \%, entry 4). This was in line with the result of mass spectroscopy. For mass spectroscopy, the complex \([\text{Rh(COD)}(\text{CIPL})_2][\text{BTA}]_2\text{BF}_4\) from \([\text{Rh(COD)}_2]\text{BF}_4\) and two equivalents of \text{CIPL} was preformed and dissolved in organic solvents. In ESI-MS positive mode, the THF solution did not show the expected peak for the coordinated metal catalyst in the spectra. In contrast, the DCM solution exhibited a main peak at 686.9 for \([\text{Rh(COD)}(\text{CIPL})_2][\text{BTA}]_2^{2+}\). Under 1 bar of hydrogen pressure, the catalysis reaction did not occur. Pressure variation between 10-100 bar did not give different enantioselectivities (entries 5-7). When the ratio of substrate to catalyst was increased to 10000, conversion reached 50 \% (TOF= 5000 h\(^{-1}\)) and 79 \% ee was obtained after one hour of reaction under the following conditions: 10 mmol DMI, 40 bar \(\text{H}_2\), 2 mL DCM, preformed complex \([\text{Rh(COD)}(\text{CIPL})_2][\text{BTA}]_2\text{BF}_4\).

\textit{Scheme 3-21.} Asymmetric hydrogenation of DMI with \text{CIPL}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>(\text{H}_2/\text{bar})</th>
<th>Additive</th>
<th>Conv./%</th>
<th>ee/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{[b]})</td>
<td>DCM</td>
<td>40</td>
<td>-</td>
<td>(&gt;99)</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>DCM</td>
<td>40</td>
<td>-</td>
<td>(&gt;99)</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>DCM</td>
<td>40</td>
<td>14.1 mg ([\text{BMIm}]\text{BF}_4)</td>
<td>(&gt;99)</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>40</td>
<td>-</td>
<td>(&gt;99)</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>100</td>
<td>-</td>
<td>(&gt;99)</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>DCM</td>
<td>10</td>
<td>-</td>
<td>(&gt;99)</td>
<td>82</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction conditions: 1 mmol DMI, \([\text{Rh(COD)}_2]\text{BF}_4\), P/Rh=2, S/C=100, 2mL DCM, r.t., overnight; full conversion was observed except entry 5. \(^{[b]}\) Catalyst: \([\text{Rh(COD)}(\text{CIPL})_2][\text{BTA}]_3\) (preformed).
Next, it was attempted to carry out the asymmetric hydrogenation of DMI in pure \([\text{BMIIm}]\text{BF}_4\) as IL solvent to study catalyst recycling. Catalysis was conducted with \textbf{CIPL} and with a neutral monophosphite ligand (\textbf{PL}), which was synthesized according to Scheme 3-22.

![Scheme 3-22: Preparation of the neutral monophosphite ligand PL.](image)

After each run of catalysis, toluene (3×1 mL) was used to extract the hydrogenated product and the unreacted substrate out of the IL phase. Then, fresh substrate was added to the IL phase for the next run. The extracted solution was used for further analysis. The recycling results are listed in Table 3-3. Compared with the neutral monophosphite ligand \textbf{PL}, \textbf{CIPL} showed good activity and reduced rhodium leaching. Unfortunately, the good enantioselectivity was achieved in DCM could not be retained in the IL phase.

### Table 3-3: Asymmetric hydrogenation of DMI in [BMIIm]BF$_4$\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Run</th>
<th>Conv./%</th>
<th>eel/%</th>
<th>Rh/ppm\textsuperscript{[b]}</th>
<th>Run</th>
<th>Conv./%</th>
<th>eel/%</th>
<th>Rh/ppm\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>36</td>
<td>1</td>
<td>1</td>
<td>87</td>
<td>34</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>19</td>
<td>2</td>
<td>2</td>
<td>39</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>24</td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>12</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 1 mL [BMIIm]BF$_4$, 0.9 mmol DMI, S/C=300, 333K, 40 bar H$_2$, 2 h. \textsuperscript{[b]} Rh leaching, the concentration in the toluene extracting solution, measured by ICP.

### 3.2.3 Experimental

#### 3.2.3.1 General

**a) Chemicals**

[EMIm] Ac, [EMIm]Cl, [BMIIm]BF$_4$, [BMIIm]BTA were purchased from Ionic Liquid Technologies GmbH&Co. KG and dried overnight under high vacuum (5 Pa) before use. Zwitterions (1-ethyl-3-methylimidazolium-2-carboxylate, 1,3-dimethylimidazo-
lium-2-carboxy-late) were synthesized in Chapter 2.2.1. All other chemicals were obtained from Alfa Aesar and used as received unless stated otherwise.

b) Analysis

NMR spectra were recorded on a AV400 MHz NMR or AV300 MHz NMR (Bruker BioSpin) at r.t.. Chemical shifts are given in ppm relative to tetramethylsilane (\(^1\)H- and \(^{13}\)C-NMR) or the residual solvent peak and 85% phosphoric acid (\(^{31}\)P-NMR). For the description of multiplicity of the signal following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quadruplet, m=multiplet, br=broad. \(^{11}\)B, \(^{19}\)F-NMR spectra were referenced externally to BF\(_3\)-Et\(_2\)O at 0 ppm and CF\(_3\)CO\(_2\)H at -78.5 ppm relative to CFCl\(_3\) at 0 ppm, respectively.

Water content was determined by an automated Karl-Fischer-titration (Metrohm).

ICP (inductively coupled plasma) was used to measure Rh and P leaching and carried out by M.Sc. Yvonne Brunsch (Group of Prof. Dr. Arno Behr, Lehrstuhl Technische Chemie A, TU Dortmund).

IR spectroscopy was measured on Bruker Alpha FT-IR spectrometer. ATR spectra were measured with a platinum/diamond P-module. Sample spectra were collected with 2 cm\(^{-1}\) resolution as the sum of 100 scans from 500 to 4500 cm\(^{-1}\).

Ion chromatography was carried out using ICS-1500 (Dionex). The detection limit of ion chromatography is 10 ppm for all halides.

Mass spectra were recorded on a Varian Model 500-Mass Spectrometer equipped with electrospray ion source (ESI).

Optical rotation was measured on a JASCO P-1020 Polarimeter using a thermo-controlled glass cuvette of 1 dm.

Gas Chromatography:

The enantioselectivity determination of the hydrogenation of DMI was carried out with GC conditions: 25 m Ibadex-1 chiral phase capillary column (dimethylpentyl-cyclodextrine, id=0.25 mm) isothermally at 80 °C with 0.8 mL min\(^{-1}\) H\(_2\) flow and a flame ionization detector at 250 °C.

The enantioselectivity determination of the hydrogenation of N-(1-phenylethylidene)aniline was carried out with GC conditions: 25 m Chirasil-Dex-CB column (inner diameter 0.25 mm, film thickness 0.25 µm); Temperature program: 100-160 °C 5min isothermal, heating rate 5 °C min\(^{-1}\) and 15 min holding time at end temperature; Carrier: H\(_2\), 2.0 mL min\(^{-1}\) constant flow; Inlet: 250 °C; Split Flow: 70 mL min\(^{-1}\); FID: 250 °C.
The enantioselectivity determination of the hydrogenation of methyl 2-acetamidoacrylate was carried out with GC conditions: 25 m Ivadex 7 column (inner diameter 0.25 mm, film thickness 0.25 µm); Temperature program: 90-160 °C 10 min isothermal, heating rate 5 °C min\(^{-1}\) and 15 min holding at end temperature; Carrier: H\(_2\), 2.0 mL min\(^{-1}\) constant flow; Inlet: 250 °C; Split Flow: 80mL min\(^{-1}\); FID: 250 °C.

3.2.3.2 Procedures for functionalizing imidazolium cations at the 2-position

a) Procedures for the reactions between [EMIm]Cl and electrophiles

1 mmol [EMIm]Cl, 1.1 eq. K\(_2\)CO\(_3\), and 2 mL Methanol were added to a 10 mL flask. After 5 min stirring, 1.1 eq. electrophile (1-chlorobutane, 2-butanone, benzaldehyde or butanal) was added. The mixture was heated to 353 K and kept stirring for one hour. Then 0.1 mL solution was taken, and neutralized with 1 M HCl solution. After evaporating the solvents, the residue was dissolved in DMSO-\(d_6\) for NMR analysis.

b) Functionalization of [EMIm]Cl using K\(_2\)CO\(_3\)

0.146 g (1 mmol) 1-Ethyl-3-methylimidazolium chloride, 0.152 g (1.1 mmol) potassium carbonate and 2 mL methanol were added to a 10 mL flask. After 5 min stirring, 0.03 g (1 mmol) paraformaldehyde was added. Then the mixture was heated to 353 K for 1 hour. When the reaction was cooled down to r.t., the solution was neutralized with 1 M hydrochloric acid. After removal of the solvent, the product was extracted with 1-butanol (3×1 mL). Then the solvent of the collected extracting solution was evaporated, and the residue was dried under vacuum overnight. As a white solid, 1-ethyl-2-hydroxymethyl-3-methylimidazolium chloride was obtained quantitatively.

1-Ethyl-2-hydroxymethyl-3-methylimidazolium chloride
H-NMR (400 MHz; DMSO-\textit{d}_6; \delta/\text{ppm}) : 1.38 (t, \textit{J}(H,H)=7.2 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 3.89 (s, 3H, NCH\textsubscript{3}), 4.27 (q, \textit{J}(H,H)=7.2 Hz, 2H, CH\textsubscript{2}CH\textsubscript{2}), 4.74(d, \textit{J}(H,H)=6.3 Hz, 2H, CH\textsubscript{2}O), 6.52 (t, \textit{J}(H,H)=6.3 Hz, 1H, O\textsubscript{H}), 7.73 (d, \textit{J}(H,H)=1.9 Hz, 1H, NCH), 7.79 (d, \textit{J}(H,H)=1.9 Hz, 1H, NCH).

\textsuperscript{13}C-NMR (100 MHz; DMSO-\textit{d}_6; \delta/\text{ppm}): 15.5 (CH\textsubscript{2}CH\textsubscript{3}), 35.9 (NCH\textsubscript{3}), 43.0 (NCH\textsubscript{2}), 50.1 (C\textsubscript{H}2OH), 121.0 (NCH), 123.1 (NCH), 145.0 (NCHN).

White solid.

c) Functionalization of [EMIm]Cl using \textit{tert}-BuOK

\[
\begin{align*}
\text{N} & \text{N} \quad \text{O} \quad \text{Cl}^+ \\
\text{N} & \text{N} \\
& \text{O} \\
\end{align*}
\]

0.304 g (2 mmol) 1-Ethyl-3-methylimidazolium chloride, 0.236 g (2.1 mmol) potassium \textit{tert}-butoxide and 2 mL 1-butanol were added to a 10 mL flask. After 5 min stirring at r.t., 0.064g (2.1 mmol) paraformaldehyde was added. Then the mixture was stirred at r.t. for 1 hour. Subsequently, 0.1 g water was added to quench the unreacted potassium \textit{tert}-butoxide, and the solution was neutralized with 1 M hydrochloric acid. After removal of the solvent, the product was extracted with 1-butanol (3×2 mL). Then the solvent of the collected extracting solution was evaporated, and the residue was dried under vacuum overnight. 1-Ethyl-2-hydroxymethyl-3-methylimidazolium chloride was obtained quantitatively.

d) Synthesis 1-butyl-2-hydroxymethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide using K\textsubscript{2}CO\textsubscript{3}

\[
\begin{align*}
\text{N} & \text{N} \quad \text{O} \\
\text{N} & \text{N} \\
& \text{O} \\
\text{BTA}^- & \\
\end{align*}
\]

A 10 ml flask was charged with 0.469 g (1.12mmol) 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 0.170 g (1.23 mmol) potassium carbonate and 5 ml methanol. After 5 min stirring, 0.037 g (1.23 mmol) paraformaldehyde was added. Then the mixture was heated to 353 K, and turned into clear solution in a few minutes.
After 4 hours stirring, 2 mL water was added to the solution. Methanol was evaporated resulting in formation of a liquid-liquid biphasic system. The upper aqueous phase was decanted. The lower phase (organic phase) was washed with water (2×2 mL), and dried overnight under vacuum at 333 K. 0.412 g 1-Butyl-2-hydroxymethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide was obtained, as a colourless liquid in 82% yield.

1-Butyl-2-hydroxymethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide

\[
\begin{align*}
\text{OH} & \quad \text{N} \quad \text{N} \quad \text{O} \\
\text{F} & \quad \text{C} \quad \text{S} \quad \text{O} \\
\text{S} & \quad \text{O} \quad \text{CF}_3
\end{align*}
\]

1H-NMR (300 MHz; DMSO-\textit{d}_6; δ/ppm): 0.90 (t, 3J(H,H)=7.4 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 1.29 (sextet, 2H, CH\textsubscript{3}CH\textsubscript{2}), 1.73 (pentet, 2H, NCH\textsubscript{2}CH\textsubscript{2}), 3.84 (s, 3H, NCH\textsubscript{3}), 4.19 (t, 3J(H,H)=7.4 Hz, 2H, CH\textsubscript{3}CH\textsubscript{2}), 4.76 (s, 2H, CH\textsubscript{2}O), 7.68 (d, 3J(H,H)=1.9 Hz, 1H, NCH), 7.73 (d, 3J(H,H)=1.9 Hz, 1H, NCH).

13C-NMR (75 MHz; DMSO-\textit{d}_6; δ/ppm): 13.4 (CH\textsubscript{2}CH\textsubscript{3}), 18.9 (CH\textsubscript{3}CH\textsubscript{2}), 31.8 (NCH\textsubscript{2}CH\textsubscript{2}), 34.9 (NCH\textsubscript{3}), 47.5 (NCH\textsubscript{2}), 50.4 (CH\textsubscript{2}OH), 117.4 (CF\textsubscript{3}), 121.6 (NCH), 123.1 (NCH), 145.0 (NCN).

19F-NMR (282 MHz; DMSO-\textit{d}_6; δ/ppm): -78.7.

e) Syntheses of 2-hydroxymethylimidazolium-based ILs from N-alkyl-N′-alkylimidazolium-2-carboxylate

\[
\begin{align*}
\text{N} \quad \text{N} \quad \text{O} & \quad \text{C} \\
\text{O} & \quad \text{OH} & \quad \text{HA}
\end{align*}
\]

In a typical procedure, 28 mmol paraformaldehyde, 3.5 g (25 mmol) 1,3-Dimethylimidazolium-2-carboxylate and 15 mL methanol or water were added to a 25 mL flask. The mixture was heated to 353 K and kept for 2 hours. Then 25 mmol of the required acid was added dropwise, and carbon dioxide release was observed immediately. After removal of solvents, the residue was dried under vacuum overnight. 1,3-Dimethyl-2-hydroxymethylimidazolium cation with the corresponding anion was obtained quantitatively.
1,3-Dimethyl-2-hydroxylimidazolium chloride

\[
\text{N} \quad \text{N} \\
\text{OH} \\
\text{Cl}^-
\]

\(^1\)H-NMR (400 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\) : 3.86 (s, 6H, NCH\(_3\)), 4.68 (s, 2H, OCH\(_2\)), 7.67 (s, 2H, NCH).

\(^{13}\)C-NMR (100 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\): 34.8 (NCH\(_3\)), 50.8 (OCH\(_2\)), 122.4 (NCH), 146.5 (NCHN).

Yellowish solid.

1,3-Dimethyl-2-hydroxylimidazolium bis(trifluoromethylsulfonyl)imide

\[
\text{N} \quad \text{N} \\
\text{OH} \\
\text{F}_2\text{C} \quad \text{SO}_2 \quad \text{N} \\
\text{OF}_3
\]

\(^1\)H-NMR (300 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\) : 3.85 (s, 6H, NCH\(_3\)), 4.75 (s, 2H, OCH\(_2\)), 7.66 (s, 2H, NCH).

\(^{13}\)C-NMR (75 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\): 34.9 (NCH\(_3\)), 50.5 (OCH\(_2\)), 113.1, 117.4, 121.7, 125.9 (CF\(_3\)), 122.8 (NCH), 145.2 (NCHN).

\(^{19}\)F-NMR (282 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\): -78.7.

Brown liquid.

1,3-Dimethyl-2-hydroxylimidazolium tetrafluoroborate

\[
\text{N} \quad \text{N} \\
\text{OH} \\
\text{BF}_4^-
\]

\(^1\)H-NMR (300 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\) : 3.85 (s, 6H, NCH\(_3\)), 4.75 (s, 2H, OCH\(_2\)), 7.65 (s, 2H, NCH).

\(^{13}\)C-NMR (75 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\): 34.9 (NCH\(_3\)), 50.5 (OCH\(_2\)), 122.8 (NCH), 145.2 (NCHN).

\(^{19}\)F-NMR (282 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\): -148.3.

\(^{11}\)B-NMR (96 MHz; DMSO-\(d_6\); \(\delta/\text{ppm}\): -1.3.

Yellow solid.

**f) Reaction of 1,3-dimethylimidazolium-2-carboxylate and electrophiles**

1 mmol 1,3-dimethylimidazolium-2-carboxylate, 1.1 eq. electrophile and 2 mL methanol were mixed, heated to 353 K and kept stirring for three hours. Then 0.1 mL
solution was taken, and neutralized with 1 M HCl solution. After evaporating solvents, the residue was dissolved in DMSO-$d_6$ for NMR analysis.

**g) Reaction between 1,3-dimethylimidazolium-2-carboxylate and the electrophile ROCH$_2$X**

0.70 g (5 mmol) 1,3-dimethylimidazolium-2-carboxylate, 0.7 ml (6 mmol) chloromethyl butyrate and 2 mL acetonitrile were added to a 10 mL flask. Then the mixture was heated to 333 K, and stirred for one hour. After removing the solvent and the unreacted chloromethylbutyrate, the product was recrystallized from a mixture of ethyl acetate and dichloromethane (ethyl acetate:DCM, 6:4). A white solid 2-(butyryloxymethyl)-1,3-dimethylimidazolium chloride was obtained in 50 % yield (0.59 g).

2-(Butyryloxymethyl)-1,3-dimethylimidazolium chloride

$^1$H-NMR (400 MHz; DMSO-$d_6$; $\delta$/ppm): 0.86 (t, $^3$J(H,H)=7.3 Hz, 3H, CH$_2$CH$_3$), 1.53 (sextet, 2H, CH$_3$CH$_2$), 2.37 (t, $^3$J(H,H)=7.3 Hz, 2H, O$_2$CCH$_2$), 3.91 (s, 6H, NCH$_3$), 5.43 (s, 2H, OCH$_2$), 7.81 (s, 2H, NCH).

$^{13}$C-NMR (100 MHz; DMSO-$d_6$; $\delta$/ppm): 11.3 (CH$_2$CH$_3$), 17.6 (CH$_2$CH$_2$), 34.6 (O$_2$CCH$_2$), 35.2 (NCH$_3$), 52.2 (OCH$_2$), 123.5 (NCH), 140.8 (NCHN), 172.5 (CO$_2$).

For chloromethyl acetate and chloromethyl ethyl ether, the same procedure was used. Although above 50 % $^1$H-NMR yield was observed, only small amount of products (purity > 92 %) were obtained, due to separation issues.

2-(Ethyloxymethyl)-1,3-dimethylimidazolium chloride
\( ^1 \text{H-NMR} \) (400 MHz; DMSO-\( d_6 \); \( \delta \)/ppm): 1.16 (t, \( ^3 J(\text{H},\text{H})=7.0 \text{ Hz} \), 3H, CH\(_2\)CH\(_3\)), 3.56 (q, \( ^3 J(\text{H},\text{H})=7.0 \text{ Hz} \), 2H, CH\(_3\)CH\(_2\)), 3.86 (s, 6H, NCH\(_3\)), 4.81 (s, 2H, OCH\(_2\)), 7.74 (s, 2H, NCH).

2-(Acetoxymethyl)-1,3-dimethylimidazolium chloride

\( ^1 \text{H-NMR} \) (400 MHz; DMSO-\( d_6 \); \( \delta \)/ppm): 2.09 (s, 3H, OCOCH\(_3\)), 3.89 (s, 6H, NCH\(_3\)), 5.39 (s, 2H, OCH\(_2\)), 7.76 (s, 2H, NCH).

**h) Modification of PILs**

\[
\text{Poly-}[(\text{N-vinyl-pyrrolidone})\text{-co-(1-vinyl-3-butylimidazolium bromide})] + (\text{CH}_2\text{O})_n \xrightarrow{\text{K}_2\text{CO}_3, 353 \text{ K} \text{, 1h}} \text{1M HCl}
\]

To the solution of Poly-[(N-vinyl-pyrrolidone)-co-(1-vinyl-3-butylimidazolium bromide)] 0.102 g in 1 mL methanol, were added 45 mg potassium carbonate, 1 mL methanol solution of 12 mg paraformaldehyde. Then the mixture was heated to 353 K and kept for an hour. 1 M HCl solution was added to neutralize the solution. After removal of the solvent, the solid residue was extracted with (3×5 mL) methanol. Methanol was evaporated from the methanol extract, and a white solid was obtained. \(^1\text{H-NMR}\) and IR data are shown in **Appendices** as Figure 5-10 and Figure 5-11, respectively.
3.2.3.3 Syntheses of and catalysis with ionic-tagged phosphorus ligands

a) Preparation of IPL

\[
\text{[Pd(cinnamyl)Cl]}_2 \quad \text{L, CsOH+H}_2\text{O} \quad 1\text{,}4\text{-dioxane, 373 K, 20 h} \quad \text{OH}
\]

Under argon atmosphere, 1,3-dimethyl-2-hydroxymethylimidazolium chloride 1.63 g (10 mmol), 2.99 g (20 mmol) sodium iodide, and 6 mL acetonitrile were added into a 20 mL Schlenk flask. 3 mL (24 mmol) Chlorotrimethylsilane was added dropwise to the mixture. After 10 min stirring at r.t., 3.88 g (21 mmol) diphenylphosphine was added. Then the mixture was heated to 333 K for 40 hours. When the reaction was cooled down to r.t., the mixture was filtered through frit. The filter cake was sequentially washed with pentane (3×10 mL) and degassed water (3×10 mL). The white solid 2-((diphenylphosphino)methyl)-1,3-dimethylimidazolium iodide was obtained in 78 % yield, 2.57 g.

2-((Diphenylphosphino)methyl)-1,3-dimethylimidazolium iodide (IPL)

\[
^1\text{H}\{^{31}\text{P}\}\text{-NMR (400 MHz; DMSO-}_d^6; \delta/\text{ppm}): \quad 3.44 \text{ (s, 6H, NCH}_3\text{), 4.07 (s, 2H, CH}_2\text{P), 7.44-7.50 (m, 10H, Ar), 7.57 (s, 2H, NCH).}
\]

\[
^{13}\text{C}\text{-NMR (100 MHz; DMSO-}_d^6; \delta/\text{ppm): 23.0 (PCH}_2\text{), 34.6 (NCH}_3\text{), 122.8 (NCH), 128.9, 130.0, 132.8, 134.7 (Ar), 143.6 (NCN).}
\]

\[
^{31}\text{P}\{^1\text{H}\}\text{-NMR (162 MHz; DMSO-}_d^6; \delta/\text{ppm): -18.2.}
\]

ESI-MS: Cation ([C}_{18}\text{H}_{20}\text{N}_3\text{P}]^+, \text{calc.: 295.1) m/z=295.2.}

b) Hydroxylation of 2-bromomesitylene

\[
\text{Br} \quad \text{[Pd(cinnamyl)Cl]}_2 \quad \text{L, CsOH+H}_2\text{O} \quad 1\text{,}4\text{-dioxane, 373 K, 20 h} \quad \text{OH}
\]
A 10 mL Schlenk tube was filled with 5.2 mg (10 μmol) [Pd(cinnamyl)Cl]₂, 13.0 mg (40 μmol) ligand IPL, 504 mg (3 mmol) CsOH·H₂O and molecular sieves. Subsequently 0.199 g (1 mmol) 2-bromomesitylene and 1.2 mL dried 1,4-dioxane were added. The mixture was heated to 373 K and kept for 10 hours. After acidifying with 1 M HCl aqueous solution, a sample was taken for ¹H-NMR measurement. The result indicated that 5 % conversion was reached.

c) Hydroformylation of 1-octene

\[
\text{RH}(\text{CO})_2\text{acac} \quad \text{L/Rh=4} \quad \text{30 bar CO/H}_2 \quad 373 \text{ K} \quad \text{H CO} \quad \text{O} \quad \text{H} \\
\]

Under argon atmosphere, 1 mg (4 μmol) Rh(CO)₂acac, 6.6 mg (16 μmol) IPL and 0.2 mL [EdMIm]BTA were added to a 10 mL Schlenk tube. After stirring for half an hour, 0.63 mL (4 mmol) degassed 1-octene was added. Then the mixture was transferred into a 10 mL finger autoclave. 30 bar Syngas (H₂:CO=1:1) was charged into the autoclave. Subsequently, the autoclave was heated to 373 K and kept stirring for 8 hours. When the autoclave was cooled down to r.t., gas was released and a sample was taken for ¹H-NMR. ¹H-NMR result indicated that the conversion was 47 % (l/b=2.1, TOF=59 h⁻¹).

d) Preparation of CIPL

According to a literature procedure, under argon atmosphere, a mixture of 4 g (14 mmol) (S)-2,2′-dihydroxybinaphthyl, 18.5 mL fresh distilled PCl₃ and 1 drop of N-methyl-2-pyrrolidone was heated to 348 K and stirred for 30 min. Excess PCl₃ war removed largely evaporated under vacuum. The final trace amount of PCl₃ were removed by azeotropic distillation with toluene (40 mL) in vacuo. White solid (11bS)-4-chlorodinaphtho[2,1-d:1′,2′-f][1,3,2]dioxaphosphepine was obtained quantitatively.
(11bS)-4-Chlorodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphine

\[
\begin{align*}
\text{H}^{31}\text{P}\text{-NMR (300 MHz; CDCl}_3; \delta/\text{ppm}): & \quad 7.18-7.48 \text{ (m, 8H, Ar), 7.87-7.95 \text{ (m, 4H, Ar).}} \\
\text{13C-NMR (75 MHz; CDCl}_3; \delta/\text{ppm}): & \quad 121.3, 121.7, 123.2, 124.5, 125.6, 125.8, 126.63, 126.8, 127.1, 127.2, 128.6, 130.2, 131.1, 131.7, 132.1, 132.6, 132.9, 147.4, 148.0. \\
\text{31P{\text{(1H)}}-NMR (126 MHz; CDCl}_3; \delta/\text{ppm}): & \quad 178.3. \\
\left[\alpha\right]^{26}_D & = +754.7 \, \text{cm}^{-1} \, \text{g}^{-1} \, \text{dm}^{-1} \, (c = 0.4 \, \text{g cm}^{-3} \text{ in DCM}), \text{Ref.}^{[101]} \left[\alpha\right]^{20}_D = +709.3 \, \text{cm}^{-1} \, \text{g}^{-1} \, \text{dm}^{-1} \, (c = 1.135 \, \text{g cm}^{-3} \text{ in DCM}).
\end{align*}
\]

Under argon atmosphere, 580.4 mg 1,3-dimethyl-2-hydroxymethylimidazolium bis(trifluoromethylsulfonyl)imide was dissolved in 5 mL THF and cooled down to 195 K. 0.9 mL n-Butyllithium (1.6 M in hexane) was added dropwise. When the mixture was warmed up to r.t., 499.8 mg (11bS)-4-chlorodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphine was added to the solution. The solution colour changed from yellow to pink. The mixture was kept stirring for 1 hour at r.t.. Then THF was evaporated and 5 mL dichloromethane was added to dissolve the product. The reaction mixture was passed over a 3 cm celite pad to remove the lithium chloride from the reaction.

After evaporating dichloromethane, the crude product was washed with the mixture of 12 mL toluene and 8 mL pentane three times and dried under vacuum overnight. A slightly yellow amorphous product 2-(((11bS)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yloxy)methyl)-1,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide was obtained in 81 % yield, 834.1 mg.
2-(((11bS)-Dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yloxy)methyl)-1,3-dimethylimidazolium bis(trifluoromethylsulfonyl)amide (CIPL)

\[
\text{H}^{31}\text{P}\text{-NMR (400 MHz; CDCl}_3; \delta/\text{ppm}): \ 3.46 \ (s, \ 6\text{H, NCH}_3), \ 4.87 \ (m, \ 2\text{H, CH}_2\text{O}), \ 7.01 \ (s, \ 2\text{H, NCH}), \ 7.22-7.98 \ (m, \ 12\text{H, Ar}).
\]

\[
\text{C}-\text{NMR (100 MHz; CDCl}_3; \delta/\text{ppm}): \ 35.4, \ 52.5, \ 114.9, \ 118.1, \ 120.5, \ 121.3, \ 122.5, \ 123.4, \ 123.8, \ 124.5, \ 125.9, \ 126.5, \ 127.0, \ 127.3, \ 128.7, \ 128.9, \ 131.3, \ 131.5, \ 132.0, \ 132.5, \ 132.8, \ 141.4, \ 146.5, \ 147.7.
\]

\[
\text{P}^{1}\text{H}\text{-NMR (162 MHz; CDCl}_3; \delta/\text{ppm}): \ 132.0.
\]

\[
\text{F}-\text{NMR (376 MHz; DMSO}-\text{d}_6; \delta/\text{ppm}): \ -79.1.
\]

ESI-MS: Cation ([C_{26}H_{22}N_2O_{13}P]^+, calc.: 441.1) m/z=441.1; Anion ([C_{2}F_{6}NO_{4}S_{2}]^-, calc.: 279.9) m/z=280.0.

\([\alpha]^{26}_{\text{D}} = +395.5 \ \text{cm}^{-1} \ \text{g}^{-1} \ \text{dm} \ (c = 0.87 \ \text{g} \ \text{cm}^{-3} \ \text{in DCM}).
\]

e) Synthesis of PL

According to the literature,\textsuperscript{100, 102} 105 mg (0.3 mmol) (11bS)-4-chlorodinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine was dissolved in 2 mL diethyl ether under argon atmosphere, and 0.05 mL triethylamine was added. The mixture was cooled to 273 K with an ice bath. Then 13.0 mg degassed and dried methanol was added dropwise to the mixture. After stirring for an hour, the mixture was filtered with a syringe filter. The filtrate was collected and the solvent was evaporated. A white solid was obtained in 69 % yield, 72 mg.
(11bS)-4-Methoxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine (PL)

\[
\text{\begin{tikzpicture}
    ...%
\end{tikzpicture}}
\]

\( ^1\text{H}\{^{31}\text{P}\}\text{-NMR (400 MHz; CDCl}_3; \delta/\text{ppm): 3.55 (s, 3H, OCH}_3\}, 7.24-7.99 (m, 12H, Ar). \)

\( ^{31}\text{P}\{^{1}\text{H}\}\text{-NMR (162 MHz; CDCl}_3; \delta/\text{ppm): 140.0.} \)

ESI-MS: ([C\textsubscript{21}H\textsubscript{15}O\textsubscript{3}P], calc.: 346.0) m/z=347.0 for [M+H\textsuperscript{+}]\textsuperscript{+}.

f) Preparation of rhodium complex

Under argon atmosphere, 39 mg (126 \(\mu\text{mol}) \) Rh(acac)(COD) and 36 mg (128 \(\mu\text{mol}) \) solid bis(trifluoromethyl)sulfonamide (HBTA) were dissolved in 6 mL DCM, a yellow solution was obtained. After 30 min stirring, a solution of 191 mg (264 \(\mu\text{mol}) \) CIPL in 4 mL DCM was added dropwise. The solution turned orange and was kept stirring for an hour. Then the solvent was evaporated under reduced pressure, the residue was washed with a mixture of DCM and pentane (3\times10 \text{mL, DCM:Pentane 2:8). Then it was dried overnight under vacuum. A yellow solid was obtained in 64 % yield, 156 mg.

\[\text{[Rh(COD)(CIPL\textsubscript{2})]BTA}_3\]

\( ^1\text{H}\{^{31}\text{P}\}\text{-NMR (300 MHz; CD}_2\text{Cl}_2; \delta/\text{ppm): 1.80-2.56 (m, 8H, COD), 3.45 (s, 12H, N CH}_3\}, 5.03 (m, 2H, COD), 5.43 (m, 4H, OCH}_2\), 5.98 (m, 2H, COD), 7.00 (s, 4H, NCH), 7.06-8.25 (m, 12H, Ar). \)

\( ^{31}\text{P}\{^{1}\text{H}\}\text{-NMR (121 MHz; CD}_2\text{Cl}_2; \delta/\text{ppm): 124.4 (d, }^{1}\text{J}_{\text{P-Rh}}=265 \text{ Hz).} \)

ESI-MS: Cation ([(Rh(COD)(CIPL\textsubscript{2})]^{3+}, calc.: 1093.3, m/z=687.0 ([Rh(COD)(CIPL\textsubscript{2})(BTA)]^{2+}, 53 %), m/z=1544.9 ([Rh(CIPL\textsubscript{2})(BTA)]^{+}, 71 %); Anion ([C\textsubscript{2}F\textsubscript{6}NO\textsubscript{4}S\textsubscript{2}])\textsuperscript{-}, calc.: 279.9, m/z=279.9.
Under argon atmosphere, 21 mg (52 µmol) [Rh(COD)₂]BF₄ and 74 mg (103 µmol) **CIPL** were dissolved in 2 mL DCM. After 3 hours stirring at r.t., the solvent was evaporated under reduced pressure. After washing with (3×2 mL) pentane, the residue was dried under vacuum for two hours. A yellow solid was obtained (68 mg, 75 % yield).

\[
[Rh(COD)(CIPL)₂][BF₄][BTA]₂
\]

\[
{^1}H\{^{31}P\}\text{-NMR (300 MHz; CD}_2\text{Cl}_2; \delta/\text{ppm})\text{: 1.80-2.56 (m, 8H, COD), 3.45 (s, 12H, NCH}_3\text{), 5.03 (m, 2H, COD), 5.43 (m, 4H, OCH}_2\text{), 5.98 (m, 2H, COD), 7.00 (s, 4H, NCH}, 7.06-8.25 (m, 12H, Ar).}
\]

\[
{^{31}P}\{^{1}H\}\text{-NMR (121 MHz; CD}_2\text{Cl}_2; \delta/\text{ppm})\text{: 124.1 (d, }^{1}J_{P-Rh}=265 \text{ Hz).}
\]

ESI-MS: Cation ([Rh(COD)(CIPL)₂]³⁺, calc.: 1093.3), m/z=686.9 ([Rh(COD)(CIPL)₂(BTA)]²⁺, 100 %), m/z=1544.6 ([Rh(CIPL)₂(BTA)]⁺, 20 %);

Anion ([C₂F₆NO₄S₂]⁻, calc.: 279.9) m/z=279.9.

Under argon atmosphere, 20 mg (49 µmol) [Rh(COD)₂]BF₄ and 35 mg (101 µmol) **PL** were dissolved in 2 mL DCM. After 3 hours stirring at r.t., the solvent was evaporated under reduced pressure. After washing with pentane (3×2 mL), the residue was dried under vacuum for two hours. A yellow solid was obtained (33 mg, 68 %).

\[
[Rh(COD)(PL)₂] \text{ BF}_4
\]
$^1$H-$^{31}$P-NMR (300 MHz; CD$_2$Cl$_2$; δ/ppm): 1.80-2.56 (m, 8H, COD), 3.76 (s, 6H, OCH$_3$), 4.42 (m, 2H, COD), 5.84 (m, 2H, COD), 7.11-8.20 (m, 24H, Ar).

$^{31}$P-$^1$H-NMR (121 MHz; CD$_2$Cl$_2$; δ/ppm): 123.0 (d, $^1$J$_{P-Rh}$=259 Hz).

ESI-MS: Cation ([Rh(COD)(HOC)$_1$]$_2$)$^+$, calc.: 903.2, m/z=903.2 ([Rh(COD)(PL)$_2$]$^+$, 100 %), m/z=1487 ([Rh(PL)$_4$]$^+$, 19 %); Anion ([BF$_4$]$^-$, calc.: 87) m/z=87.0.

**g) Procedures for asymmetric hydrogenation with CIPL**

A typical procedure for hydrogenation of dimethyl itaconate ester was performed: under argon atmosphere, 10 μmol Rh(COD)$_2$BF$_4$, 20 μmol CIPL and 2 mL DCM were mixed and stirred for half an hour. Then 1 mmol dimethyl itaconate was added to the mixture.

When the clear solution was observed, the solution was transferred into a dry 10 mL finger autoclave. Hydrogen was introduced into the autoclave with a certain pressure. Hydrogenation was subsequently carried out overnight at r.t. After releasing the pressure, a sample was taken directly for conversion determination with $^1$H-NMR. The remaining solution was passed through a pad of silica gel prior to GC analysis for enantioselectivity determination.

A typical procedure for hydrogenation of methyl acetamidoacrylate was performed: under argon atmosphere, 10 μmol [Rh(COD)(CIPL)$_2$]BTA$_3$, 1 mmol methyl acetamidoacrylate and 2 mL DCM were mixed and stirred for an hour. Then the solution was transferred into a dry 10 mL finger autoclave. 40 bar Hydrogen was introduced into the autoclave. Hydrogenation was subsequently carried out overnight at r.t.. After releasing the pressure, a sample was taken directly for conversion determination with $^1$H-NMR. The remaining solution was passed through a pad of silica gel prior to GC analysis for enantioselectivity determination.
A typical procedure for hydrogenation of N-(1-phenylethylidene)aniline was performed: under argon atmosphere, 5 µmol [Ir(COD)Cl]₂, 20 µmol CIPL and 2 mL DCM were mixed and stirred for an hour. Then 0.5 mmol substrate was added to the mixture. When the clear solution was observed, the solution was transferred into a dry 10 mL finger autoclave. 40 bar Hydrogen was introduced into the autoclave. Hydrogenation was subsequently carried out overnight at r.t.. After releasing the pressure, a sample was taken directly for conversion determination with ¹H-NMR. Product was purified with silica gel column chromatography (ethyl acetate: pentane, 1:50). Then 10 mg product was dissolved into 1.5 mL DCM for enantioselectivity determination with GC.

h) Procedure for asymmetric hydrogenation of DMI in [BMI][BF₄]

Under argon atmosphere, 3 µmol preformed Rh complex and 0.9 mmol DMI were dissolved into 1 mL [BMI][BF₄]. When the clear solution was observed, the solution was transferred into a dry 10 mL finger autoclave. 40 bar Hydrogen was introduced into the autoclave. Hydrogenation was subsequently carried out overnight at 333 K. After releasing the pressure, (3×1 mL) toluene was used to extract the hydrogenated product and unreacted substrate out of the IL phase. Then 0.9 mmol fresh DMI was charged for the next run. The extracting solution was used for the further analysis. A sample was taken directly for the conversion determination with ¹H-NMR. 0.5 mL toluene solution was passed through a pad of silica gel prior to GC analysis for enantioselectivity determination. 1.5 mL toluene solution was taken for Rh leaching measurement with ICP.
3.2.4 Interim Summary

1. A facile reaction to functionalize imidazolium cations at the 2-position was developed (Scheme 3-23).

   - Imidazolium cations were deprotonated at the 2-position by a base to form the corresponding carbenes, which subsequently attacked paraformaldehyde. As a result, 2-hydroxymethylimidazolium cations were obtained quantitatively.
   - The method was also applicable to functionalize the imidazolium cations of poly(ionic liquid)s.
   - The zwitterion $N$-alkyl-$N'$-alkylimidazolium-2-carboxylate as the starting material should be highlighted. During the reaction, protic acid was added and accompanied by the release of carbon dioxide. Thus 2-hydroxymethylimidazolium-based ILs with various anions were readily synthesized. After evaporating the solvents, pure products were easily obtained quantitatively.
   - In addition to aldehydes, ROCH$_2$X was found able to functionalize the 2-position of imidazolium cations. Due to separation issues, only the product from chloromethyl butyrate with a longer alkyl chain was isolated, however.

2. An ionic-tagged phosphine ligand (IPL) was synthesized from 2-hydroxymethyl-1,3-dimethylimidazolium chloride. It was not active for the hydroxylation of 2-bromomesitylene with a palladium catalyst, it showed some activity (conv.: 47 %, l/b=2.1, TOF=59 h$^{-1}$) for the hydroformylation of 1-octene with a rhodium catalyst.
3. A chiral ionic phosphite ligand (CIPL) was successfully prepared from 2-hydroxymethyl-1,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide. With this ligand, asymmetric hydrogenation of C=C and C=N were investigated.

- In the hydrogenation of N-(1-phenylethylidene)aniline, the ligand with an iridium catalyst gave a moderate yield (54 %), but unsatisfactory enantioselectivity (3 %).
- For the hydrogenation of methyl 2-acetamidoacrylate and dimethyl itaconate, excellent yields (>99 %) and moderate enantioselectivities (48 % and 82 %, respectively) were observed using a rhodium catalyst with this ionic phosphite ligand.
- Hydrogenation of dimethyl itaconate in [BMIm]BF$_4$ led to reduced rhodium leaching, compared with the neutral monophosphite ligand PL. Nevertheless, significant decreases in the conversion and enantioselectivity were observed.
4 Summary and Outlook

To foster understanding of the structure activity relationship of IL and cellulose for cellulose dissolution, a systematic approach towards IL synthesis and experimental determination of cellulose solubility was carried out in Chapter 2 (Scheme 4-1). Three homologous series of all 27 combinations of three cations (1,3-dimethylimidazolium, 1-ethyl-3-methylimidazolium, and N,N-diethyl-N,N-dimethylammonium) with nine carboxylate anions (formate, acetate, n-propionate, n-butyrate, iso-butyrate, mono-maleate, maleate, mono-succinate, succinate) were synthesized and characterized. Cellulose solubilities in synthesized ILs were determined at three different temperatures: 333 K, 353 K and 373 K. Several alternatives ([EMIm]Formate, [EMIm]Propionate, [EMIm]Butyrate and [EMIm]-Butyrate) to the most preferred cellulose solvent [EMIm]Ac were found. Results also verified that the anion basicity of ILs is an important factor for dissolving cellulose. However, the cation influence can not be neglected. Although modeling cellulose solubilities in ILs using COSMO-RS offers a fast way to optimize IL structures, the predicted result only provides a guideline. Therefore, the experimental determination remains inevitable at present for IL screening. Cellulose pretreated with ILs was much easier to degrade by oxalic acid into its monomeric units; further investigation should be carried out. Carboxylate-based ILs also exhibited a good ability to extract betulin from birch bark. Thus, further applications of ILs in pretreating, dissolving, and extracting natural compounds seem promising to be explored.

Scheme 4-1. Cellulose dissolution of carboxylate-based ionic liquids.

Reaction of [EMIm]Ac (an excellent cellulose solvent) and DCM (a common organic solvent) was observed and exploited for the esterification of carboxylate-based ILs and
alkyl halides in a large substrate scope under neat conditions in Chapter 3.1 (Scheme 4-2). \( S_N 2 \) mechanism of the esterification was demonstrated, and so was its potential application for the configuration inversion of chiral alcohol. Additionally, with chiral carboxylate-based ILs, stereoselectivity was obtained in the esterification from racemic starting materials by kinetic resolution. Due to the high polarity of ILs, weakly polar products could be simply separated via decantation or extraction. Considering the poor solubility of ILs in scCO\(_2\),\(^{37-38} \) it is very promising that scCO\(_2\) could be employed to extract the product out of the IL phase. Three strategies for regenerating ILs were demonstrated. With the anion metathesis method, the recovery of ILs is very simple and environmentally benign. Recently, Wasserscheid et al. reported that the esterification of [EMIm][Me(Me)PO\(_3\)] with R'-X to form Me(Me)PO\(_2\)OR', which is a useful alkylating agent to quaternize amines with the R' group into ammonium.\(^{103} \) This is another good example of using the high nucleophilicity of IL anions. Therefore, the nucleophilic substitution reactions of IL anions can offer new possibilities to synthesize high value-added compounds, especially with the simple and environmentally friendly recovery techniques.

\[
\text{[Cation]}^+ \cdot \text{OR} \quad + \quad \text{X-R} \quad \xrightarrow{\Delta} \quad \text{R'}\cdot\text{OR} \quad + \quad \text{[Cation]}^+ \cdot \text{X}^- \quad (S_N 2 \text{ mechanism})
\]

**Scheme 4-2.** Esterification of carboxylate-based ionic liquids with alkyl halides.

Based on the observation that an imidazolium derivative was produced during the reaction of [EMIm]Ac and DCM, a facile reaction to functionalize imidazolium cations at the 2-position with formaldehyde or ROCH\(_2\)X compounds was unveiled in Chapter 3.2 (Scheme 4-3). A series of N-alkyl-N'2-alkyl-2-hydroxymethylimidazolium cations was synthesized including a polymer bound ionic liquid-type structures. When the zwitterion N-alkyl-N'2-alkylimidazolium-2-carboxylate was used as the starting material, 2-hydroxymethylimidazolium-based ILs with various anions were easily synthesized, and products were separated readily. The new readily accessible N-alkyl-N'2-alkyl-2-hydroxymethylimidazolium cations were successfully grafted onto phosphorus ligands as ionic tags to facilitate catalyst separation in transition metal catalysis. The effectiveness of the tag to reduce metal leaching could be demonstrated. However, the performance of the catalysts in pure IL solvent did not retain promising results obtained in conventional solvents. Moreover, the broad and general synthetic
possibilities offered by the hydroxymethyl group provide many opportunities to make ionic-tagged phosphorus ligands available for multiphase catalysis to enhance this traditional catalysis field.

Scheme 4-3. Functionalization of imidazolium cations at the 2-position.
**Appendices**

*Table 5-1:* Appearances of synthesized carboxylate-based structures.

| Cation       | Anion | 1a  | 1b  | 1c  | 1d  | 1e  | 1f  | 1g  | 1h  | 1i  | 1j  | 1k  | 1l  | 1m  | 1n  | 1o  | 1p  | 1q  | 1r  | 1s  | 1t  | 1u  | 1v  | 1w  | 1x  | 1y  | 1z  | 1aa | 1ab | 1ac | 1ad | 1ae | 1af | 1ag | 1ah | 1ai | 1aj | 1ak | 1al | 1am | 1an | 1ao | 1ap | 1aq | 1ar | 1as | 1at | 1au | 1av | 1aw | 1ax | 1ay | 1az | 1ba | 1bb | 1bc | 1bd | 1be | 1bf | 1bg | 1bh | 1bi | 1bj | 1bk | 1bl | 1bm | 1bn | 1bo | 1bp | 1bq | 1br | 1bs | 1bt | 1bu | 1bv | 1bw | 1bx | 1by | 1bz |
|--------------|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| *Not IL as m.p. > 373 K.*

**Figure 5-1.** $^1$H- and $^{13}$C-NMR of fresh [DMIm]Butyrate (the upper one) and the regenerated one (the lower one).
Figure 5-2. $^1$H- and $^{13}$C-NMR of fresh [EMIm]Ac (the upper one) and the regenerated one (the lower one).

Figure 5-3. $^1$H- and $^{13}$C-NMR of fresh [EMIm]Butyrate (the upper one) and the regenerated one (the lower one).

Figure 5-4. $^1$H- and $^{13}$C-NMR of fresh [EMIm]Succinate (the upper one) and the regenerated one (the lower one).
Figure 5-5. $^1$H-NMR of the reaction mixture of [EMIm]Cl and benzaldehyde after evaporating volatile compounds ($^1$H-NMR yield: $\sim$27 %).

Figure 5-6. $^1$H-NMR of the reaction mixture of [EMIm]Cl and butanal after evaporating volatile compounds ($^1$H-NMR yield: $\sim$14 %).
Figure 5-7. \(^1\)H-NMR of the reaction mixture of [BMIm]BF\(_4\) and paraformaldehyde (\(^1\)H-NMR yield: \(\sim 90\%\)).

Figure 5-8. \(^1\)H-NMR of the reaction mixture of 1,3-dimethylimidazolium-2-carboxylate and chloromethyl acetate after evaporating volatile compounds (\(^1\)H-NMR yield: \(\sim 50\%\)).
Figure 5-9. $^1$H-NMR of the reaction mixture of 1,3-dimethylimidazolium-2-carboxylate and chloromethyl ethyl ether after evaporating volatile compounds ($^1$H-NMR yield: ~66 %).

Figure 5-10. $^1$H-NMR of functionalized PILs.
Figure 5-11. IR of functionalized PILs.
References


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