Development of sustainable esterification reactions and the transformation of carbohydrates into applicable building blocks
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Chapter 1 - Introduction
**1.1 Green Chemistry and the Objectives of this Thesis**

In 1990s, the concept of green chemistry was formulated in order to reduce pollution and energy consumption resulting from chemical synthesis and engineering. Green chemistry is defined as the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances. Green chemistry is an approach to achieve sustainability at the molecular level, which has been applied to diverse industry sectors such as aerospace, automobile, cosmetics, electronics, energy, household products, pharmaceuticals, and agriculture.[1] In this thesis, we aim to design chemical processes and syntheses that avoid waste production and result in sustainable (commercially interesting) products. The included topics are studies on (poly)esterification with non-toxic Lewis acid catalysts, site-selective modification of common mono-sugars, and the development of fructose-based surfactants.

**1.2 Sustainability in Esterification**

Esterification is the condensation of carboxylic acids and alcohols to yield esters. In principles, this condensation reaction has a high atom economy since an equivalent of water is formed as the only side product. Esters are commercially interesting products for diverse industries such as the automotive, pharmaceutical, and coatings industry.[2] Some polyester-based plastics are good alternatives to petroleum-based plastics like PE and PP because the ester linkages can undergo hydrolysis which assists biodegradation.[3] However, uncatalyzed esterification is an energy-consuming reaction requiring high temperature. Therefore, several esterification methods focusing on the activation of carboxylic acids have been developed. In the synthesis lab, some common name reactions such as the Mitsunobu and Steglich reactions are used to obtain esters in the synthesis of complex molecules.[4,5] Those methods are particularly advantageous for the synthesis of acid-sensitive and thermo-labile compounds since they efficiently produce esters at ambient temperature. However, those methods require stoichiometric amounts of harmful chemical reagents which sometimes are difficult to separate from the product. Hence, catalytic methods to obtain esters are favored. Fischer esterification is the esterification reaction performed
in the presence of Brønsted acids (the classic Fischer esterification uses sulfuric acid). This method efficiently reduces the energy profile of esterification, but the use of acids requires post-neutralization leading to the production of (salt) waste.\[^6\] Furthermore, side reactions such as elimination and ether formation are common under the acidic conditions. To this end, Lewis acids are often preferred catalysts since, in principle, they efficiently activate carboxylic acids for esterification only producing minimal waste. Nevertheless, some of the most active Lewis acid catalysts for esterification are based on toxic organometallics,\[^7,8\] and sustainable alternatives are required for industrial applications. In this thesis, we will illustrate the development of esterification methods and our studies on (poly)esterification with non-toxic Bi(III) compounds aiming to develop a sustainable esterification system.

### 1.3 Site Selective Modification of Common Mono-Saccharides

The transformation of biomass-derived feedstocks such as polysaccharides, sugars, and their derived polyols provides a sustainable way for the production of commercially interesting chemicals. However, selective modification of those polyol derivatives is challenging since they bear multiple hydroxyl groups presenting similar reactivity.\[^9\] To achieve a "simple" modification, epimerization for example, several steps including protection-deprotection are required leading to low atom economy in the entire conversion.\[^10\] In this thesis, a catalytic method to achieve epimerization of common mono-sugars into their counterparts is presented. We combined palladium-catalyzed site-selective oxidation with heterogeneous hydrogenation resulting in an efficient epimerization of mono-sugars (Scheme 1). Furthermore, column chromatography is not included in the entire epimerization preventing excessive solvent waste, thus achieving a more sustainable epimerization.

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\text{Scheme 1. The designed epimerization of common mono-sugars through site-selective oxidation and heterogeneous hydrogenation}
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Another difficulty for direct exploitation of common saccharides is their high degree of functionality, or more precise; high oxidation degree. Usually, the excess hydroxyl groups have to be removed by biological, chemical, or thermochemical treatment to transform the polyols into simpler building blocks for further utilization.\[^{11}\] Deoxydehydration carried out either in a stoichiometric or a catalytic fashion converts vicinal diols into alkenes and alkanes is therefore potentially a versatile method to reduce the degree of functionality. In particular, Re-based catalyzed DODH reactions under reductive conditions are extensively explored. Other DODH methods such as V(V) and Mo(VI)-catalyzed reactions are also studied, but these usually require very high temperature compared to the Re-catalyzed DODH reaction.\[^{12}\] In this thesis, we exploited Re-based heterogeneous catalyst to achieve the DODH reaction of methyl mannopyranoside.\[^{13}\] This type of “dehydration” selectively eliminates the \textit{cis}-diol on the pyranose ring resulting in the deoxy-pyranoside, which is an interesting building block for polyesterification. Furthermore, we also implemented the reaction conditions in the flow system to study the activity of the catalyst over time.

![Scheme 2. The studied Re-based heterogeneous catalyzed DODH reaction of methyl mannopyranoside](image)

**1.4 Development of Fructose-based Surfactants**

Surfactants are amphiphilic compounds composed of a hydrophilic head and hydrophobic tail. Due to their surface tension-active properties, surfactants are essential compounds in the chemical industry and daily commodities.\[^{14}\] The synthesis of surfactants conventionally includes sulfonation, sulfation, ethoxylation, alkylation, and esterification. The synthesis of surfactants is mainly based on petrochemicals and harsh acidic conditions contribute to environmental pollutants and hazards.\[^{15,16}\] In this thesis, we present the synthesis of fructose-based surfactants from sustainable starting materials. Direct exploitation of
fructose for synthesis, glycosidation for example, is not trivial since it usually results in a complicated mixture of α/β-furanosides and pyranosides. To achieve an efficient fructose-based surfactant synthesis, we used a glycosidation method in 3-hydroxypropionitrile to selectively obtain cyanoethyl-β-fructopyranoside as a solid. The subsequent heterogeneous hydrogenation of the cyano group and amidation of the resulting amine with fatty acid methyl esters (FAME) led to a series of fructose-based surfactants. The proposed synthesis avoids the use of non-renewable starting materials and column chromatography. Furthermore, the proposed synthesis is scalable. Hence, the developed synthesis of fructose-based surfactants can be an interesting production method for the surfactant industry.

Scheme 3. The designed synthesis of fructose-based surfactant including glycosidation of fructose, hydrogenation of the cyano group, and amidation with FAME

1.5 Thesis Outline

This thesis provides studies on Bi(III)-catalyzed esterification reactions aiming at the development of an efficient (poly)esterification method for industrial application. Furthermore, site-selective modification of common mono-sugars including DODH reaction and epimerization are studied in order to obtain uncommon sugar-based moieties. Finally, to provide a sustainable surfactant synthesis, the synthesis of fructose-based surfactants from D-fructose is presented. In Chapter 2, the study of a series of commercially available Bi(III) salts in esterification reactions is reported. Furthermore, together with the industrial partner AkzoNobel, Bi$_2$O$_3$ and Bi(OTf)$_3$-catalyzed polyesterification is studied. In Chapter 3, Re-catalyzed DODH reaction on methyl mannopyranoside and several other cis-diol bearing sugars is studied. To monitor the reactivity of the Re-based catalyst over time, the reaction in a continuous setup is illustrated. In Chapter 4,
we show the epimerization of common mono-sugars into their counterparts by consecutive site-selective oxidation and heterogeneous hydrogenation. Initially, the oxidation step includes the Pd-based complex as the catalyst and 2-tert-butyl-1,4-benzoquinone as the oxidant. To eliminate the stoichiometric organic oxidant, site-selective oxidation under oxygen is studied. In Chapter 5, in connection with the development of fructose-based surfactants, the scalable synthesis of cyanoethyl-β-fructopyranoside by the glycosidation of D-fructose in 3-hydroxypropionitrile is reported. In Chapter 6, the development of fructose-based surfactants from cyanoethyl-β-fructopyranoside is presented. With a series of fructose-based surfactants available, the physical properties of the surfactants are also studied.
1.6 References
