

## Summary

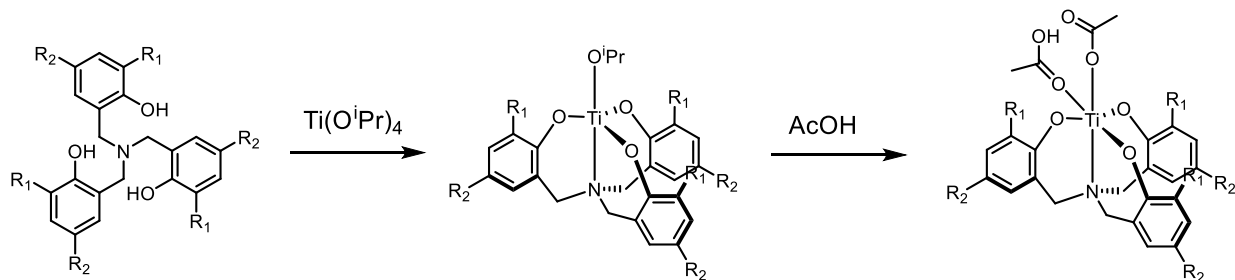
The ester bond is an important structural motif in organic molecules, that among others find application as pharmaceuticals, fragrances or coatings. Although the direct coupling of carboxylic acids and alcohols is known for more than a century, it is still the most prominent route to synthesize the ester moiety. This chemical transformation affords the desired ester bond and water as the only by-product. However, the unfavorable equilibrium conditions of this reaction require a non-equimolar stoichiometry of substrates or a dehydration technique to drive the reaction to completion. Dehydration via evaporation or azeotropic distillation is often, especially at an industrial scale, the preferred route to obtain (poly)esterification products. This method allows equimolar ratios of substrates, but high reaction temperatures are still required. Therefore, the use of a catalyst that can lower the reaction temperature and enable mild reaction conditions is highly desirable. Strong Brønsted acids are well-known to efficiently catalyze the direct esterification reaction, but their application has several disadvantages since they are highly corrosive and facilitate unwanted side reactions. In contrast, Lewis acidic metals are less corrosive and exclusively catalyze the desired esterification reaction. As a result, Lewis acidic metals have been intensively explored as catalysts in the direct esterification reaction. Although a wide variety of different metal salts were found to be effective catalysts, understanding the origin of their catalytic activity is still limited. Mechanistic studies are severely complicated due to *in situ* transformation of the catalyst, since all reaction components (carboxylic acid, alcohol and ester) have the ability to coordinate to the Lewis acidic metal center. This transformation does not exclusively lead to monomeric species but also dimeric and multinuclear complexes have been identified.

Besides the direct (poly)esterification, many other ester-forming reactions have been explored by chemists. One notable example is the nickel-catalyzed carbon-oxygen bond forming reaction between an organic (pseudo)halide and a carboxylic acid, which has received much attention in recent years. Also here, mechanistic understanding of the catalytic cycle is hindered by many side reactions, either by reaction with one of the reaction components, or by other (deactivation) reactions.

In this thesis, we have shed light on the structure of various *in situ* formed catalysts, potential intermediates and have provided deeper mechanistic understanding of the catalytic cycle. This knowledge contributes to the development of novel efficient esterification catalysts based on abundant and non-toxic metals.

In **Chapter 1** an overview of different Lewis acidic homogeneous catalysts applied in the direct (poly)esterification reactions is provided. Studies that have attempted to elucidate the structure of the *in situ* formed catalytically active complex and investigations that provide mechanistic insights are discussed. Moreover, new routes for ester synthesis are reviewed with a focus on the nickel-catalyzed cross-coupling of aryl halides and carboxylic acids.

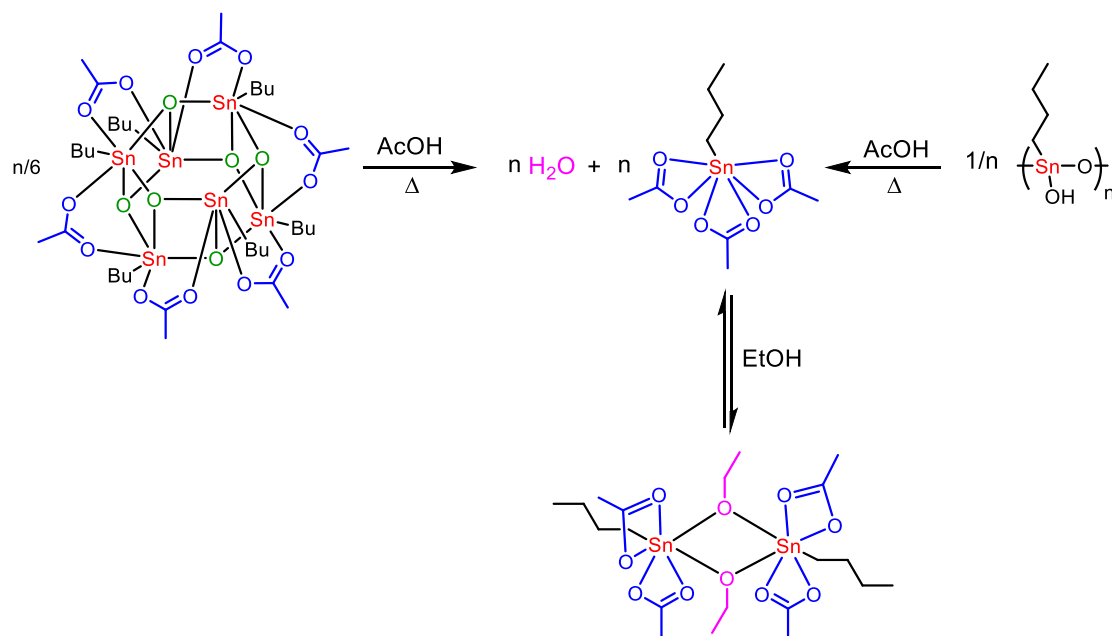
In **Chapter 2** a mechanistic study into titanium(IV)-catalyzed direct esterification reactions is described. Since mechanistic investigations into common titanium alkoxides (poly)esterification catalysts are troublesome due to uncontrolled ligand exchange reactions, we selected the class of titanium-aminotriphenolate complexes for our investigations. The combination of the tetradentate aminotriphenolate ligand and  $\text{Ti}(\text{iOPr})_4$  afforded a variety of robust  $C_3$ -symmetric titanium complexes with only an exchangeable isopropoxide group in the apical position (Figure S1). During catalytic studies we found that steric bulk in the *ortho*-position was hampering catalysis. As a result, the titanium-aminotriphenolate complex lacking steric bulk in this position was found to be the most active catalyst, albeit with a lower activity than  $\text{Ti}(\text{iOPr})_4$ . Based on *in situ* and stoichiometric experiments, we concluded that the amphoteric octahedral titanium-aminotriphenolate acetic acid/acetate complex is the resting state during catalysis. With the help of kinetic experiments and DFT calculations a mononuclear reaction mechanism was proposed, which revealed three essential prerequisites for an active catalyst: Lewis acidity of the titanium(IV) metal, favorable hydrogen bonding interactions between both reactants and the ligand, and a Brønsted basic group to facilitate proton transfer.



**Figure S1.** Synthesis of titanium aminotriphenolate complexes.

In **Chapter 3**, we have investigated *n*-butyltin(IV) complexes using a variety of spectroscopic techniques (ATR-FTIR,  $^{119}\text{Sn}$  NMR,  $^1\text{H}$  NMR) under catalytically relevant conditions. The profound activity of this class of (poly)esterification catalyst was demonstrated in a model esterification reaction. Here, the mono-alkylated tin(IV)

complexes readily outperformed other tin(IV)-based catalysts (e.g.  $\text{SnCl}_4$  and  $\text{Sn}(\text{OAc})_4$ ). In order to elucidate the structure of various mono-alkylated tin(IV) complexes (polymeric  $n\text{-BuSnOOH}$  and hexameric  $[\text{n-BuSn}(\text{O})\text{OAc}]_6$ ) in solution we studied their transformation in acetic acid at various temperatures. At an elevated temperature ( $90\text{ }^\circ\text{C}$ ), all complexes formed monomeric  $n\text{-BuSn}(\text{OAc})_3$  (Figure S2), while at reduced temperatures also water adducts of this complex were detected. In ethanol monomeric  $n\text{-BuSn}(\text{OAc})_3$  was partially converted into dimeric  $(n\text{-BuSnOAc}_2\text{OEt})_2$  (Figure S2). During catalytic experiments using a 1:1 mixture of acetic acid and ethanol, an equilibrium between the previously identified monomeric  $n\text{-BuSn}(\text{OAc})_3$  and dimeric  $(n\text{-BuSnOAc}_2\text{OEt})_2$  emerged. These findings reveal that while the stoichiometric chemistry of  $n$ -butyltin(IV) carboxylates is dominated by the formation of multinuclear tin assemblies, during catalysis only monomeric and dimeric complexes are present. Additional DFT calculations provided support for a mononuclear mechanism, where  $n\text{-BuSn}(\text{OAc})_3$  and dimeric  $(n\text{-BuSnOAc}_2\text{OEt})_2$  are regarded as off-cycle species, and suggested that carbon-oxygen bond breaking is the rate determining step.

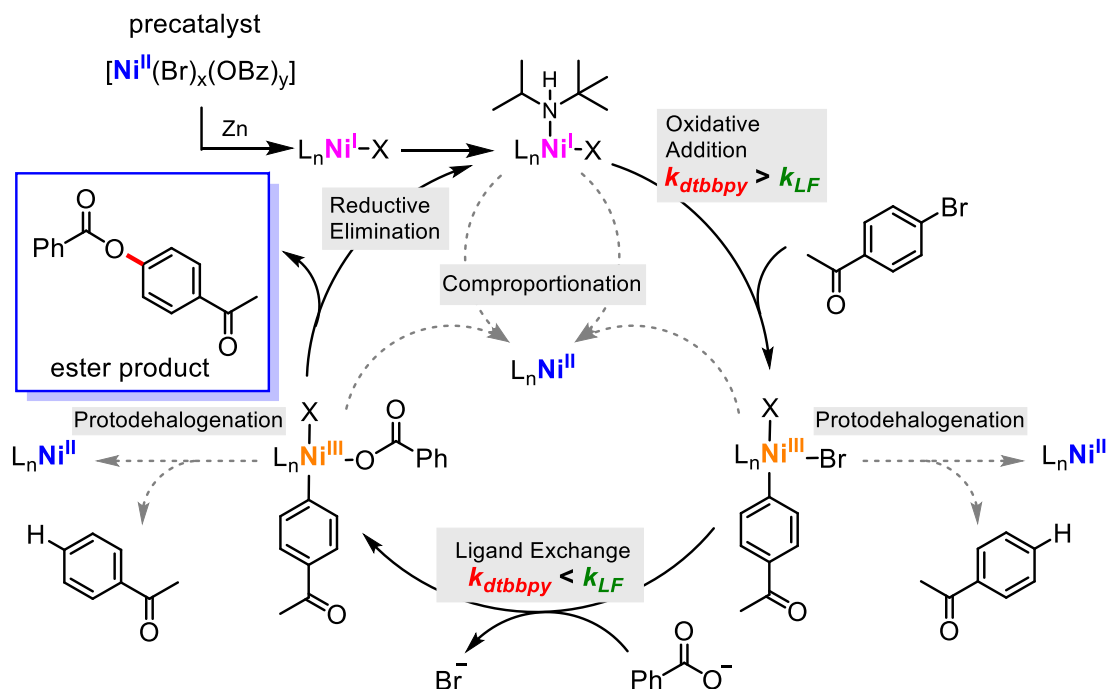


**Figure S2.** Reaction of mono-alkyltin complexes with acetic acid and ethanol.

In **Chapter 4**, the reaction kinetics of titanium- and tin-catalyzed polyesterification are studied under different reaction conditions. Under neat conditions (polyesterification of 1,6-hexanediol and adipic acid at  $170\text{ }^\circ\text{C}$ , with removal of water via evaporation) the  $n\text{-BuSnOOH}$  catalyst displayed remarkable activity. Moreover, under these reaction conditions catalyst deactivation was not observed for  $n\text{-BuSnOOH}$ . In contrast, both the titanium-based catalysts ( $\text{Ti}(\text{O}^i\text{Pr})_4$  and Ti-atrane complex) performed comparable to the

reaction without metal catalyst. We also performed the same polyesterification reaction under azeotropic conditions (via the addition of xylene). At a reaction temperature of 140 °C, *n*-BuSnOOH still has the highest activity, but is outperformed in the initial phase of the reaction (first 2 hours) by the Ti-atrane complex. Further elevation of the temperature (to 150 °C) provided an effective azeotropic reflux over the whole reaction period and the water concentrations were significantly diminished. Under these conditions, Ti(OiPr)<sub>4</sub> was the most active catalyst and no catalyst deactivation was observed. These findings show that the catalytic performance is crucially determined by the robustness of the catalyst against hydrolytic degradation.

In **Chapter 5**, we focused on the cross-coupling reaction of aryl halides and carboxylic acids. This reaction is a prime example of a challenging C-heteroatom bond formation that has been enabled by nickel catalysis. Similar to other nickel-catalyzed protocols for the synthesis of C-heteroatom bonds also this reaction is hampered by off-cycle pathways. In order to suppress these unwanted side reactions non-equimolar ratios of coupling partners are typically required. To gain mechanistic insight, including off-cycle pathways, we performed the nickel-catalyzed carboxylate *O*-arylation reaction in the presence and absence of an exogenous 2,2'-bipyridine-ligand. We demonstrate that for the reaction in the absence of an exogenous ligand, facile ligand exchange and reductive elimination steps exists (Figure S3).



**Figure S3.** Mechanistic hypothesis for nickel-catalyzed carboxylate *O*-arylation.

Moreover, deleterious off-cycle protodehalogenation and comproportionation pathways are circumvented. Thereby this strategy enabled the formation of *O*-aryl esters from equimolar amounts of carboxylic acid and aryl halides. In contrast, for the (dtbbpy)NiBr<sub>2</sub>-catalyzed reaction an excess of the carboxylic acid substrate is required to enhance the rate for ligand exchange and prevent unproductive comproportionation of Ni<sup>I</sup> and Ni<sup>III</sup>. Our subsequent spectroscopic investigation of the novel ligand-free (no exogenous dtbbpy-ligand) catalytic system revealed that during catalysis the bulk of Ni<sup>II</sup> is present in the form of [Ni(Br)<sub>x</sub>(OBz)<sub>y</sub>], yet for catalysis an alkylamine base was essential. Therefore the catalytically active complex is likely a minor nickel complex where the base functions as ligand. For the reduction of the Ni<sup>II</sup>-precursor, in the absence of aryl halides, we identified a Ni<sup>I</sup>-Ni<sup>II</sup> dimer as the reaction product. Moreover, this bimetallic complex was found to be reactive towards aryl bromides.

In **Chapters 2, 3** and **4** we performed spectroscopic, computational and kinetic studies to unveil the relationship between catalytic activity and structure of the *in situ* formed catalyst in direct esterification reactions. Our investigations show that catalytic performance is not solely determined by the Lewis acidity of the metal center. Ligands proved to play an important role in catalysis since they were found to function as an internal base and to form hydrogen bonds with substrates. Even ligands that are considered spectators have a distinct effect on the *in situ* formation of the active catalyst, as was demonstrated for the *n*-butyltin(IV) complexes, where the alkyl tail enforces a favorable seven-coordinate environment around the tin center. In the case of the titanium-based catalyst, the application of a multidentate ligand affords a catalyst that has a slight improved ability to withstand hydrolytic degradation. However, for these type of complexes the catalytic activity was generally lower because the ligand effectively shields the active metal center. Although it remains challenging to provide clear design rules for the development of novel Lewis acid catalyst based on abundant and non-toxic materials, we identified the following factors as requisite: 1) Lewis acidity of the metal center; 2) Facile ligand exchange reactions, hence a sterically uncongested metal center; 3) Robustness of the catalyst, particularly the ability to withstand hydrolytic degradation. Similar to the preceding chapters, **Chapter 5** provides fundamental insight into the catalytic cycle of an esterification reaction. Our studies uncover the competition between productive catalysis and deleterious off-cycle reaction pathways that exist for all fundamental elementary steps. These findings provide a better understanding of the commonly proposed self-sustained Ni<sup>I</sup>/Ni<sup>III</sup> catalytic cycle and are therefore relevant to many nickel-catalyzed C-heterobond formation reactions.