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Direct Synthesis of Amides and Imides by using Heterogeneous Lewis Acid Catalysts

(不均一系 Lewis 酸触媒によるアミド・イミドの直接合成)

Amide bond formation avoiding poor atom economy reagents is strongly preferred and gets one of the highest attention as a priority area in organic synthesis and pharmaceutical industry. Conventionally, amides are prepared from carboxylic acids and amines via activated carboxylic acid derivatives such as carboxylic acid anhydrides or acyl chlorides or via activation with stoichiometric amount of a dehydrating agent. Lewis acid promoted amidation reaction is also developed. These methods have some limitations of low atom efficiency and production of byproducts. Lewis acid catalyzed amidation have additional drawbacks, such as limited substrate scope and high catalyst loading. These drawbacks may be caused by the suppression of Lewis acid by basic molecules (amines and water as byproduct), present in the reaction mixture. The author hypothesized that water and base-tolerant Lewis acid catalyst may catalyze the amidation of carboxylic acid with amines more effectively. This thesis focuses on direct synthesis of amide bond by using base-tolerant heterogeneous Lewis acid catalysts. Five types of Lewis acid catalytic systems are developed for synthesis of amides and cyclic imides.

In chapter 2, various Lewis and Brønsted acid catalysts including well known water tolerant catalysts, $\text{Sc}(\text{OTf})_3$ and Cs-exchanged heteropoly acid, were investigated for the amidation of *n*-dodecanoic acid with aniline. Among them, Nb_2O_5 showed the highest catalytic activity. This simple and atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as anilines and α -hydroxycarboxylic acids. The catalyst was reusable. Kinetics studies show that the Lewis acid site of Nb_2O_5 , as the active site for the amidation is more tolerant to the co-present basic molecules than other catalysts.

Chapter 3 studies direct amidation of methyl benzoate with aniline by various Lewis and Brønsted acid catalysts including reported catalysts ($\text{La}(\text{OTf})_3$, NaOMe). Nb_2O_5 showed the highest catalytic activity for this reaction. Reusability of the Nb_2O_5 catalyst was shown. The Lewis acid catalysis of Nb_2O_5 was effective for the amidation of various substrates, including challenging substrates such as anilines and α -hydroxyesters. This is the first successful example of heterogeneous catalysis for direct amidation of esters with amines.

Chapter 4 studies direct imidation of succinic acid with *n*-octylamine by various Lewis and Brønsted acid catalysts.

Among the catalyst screened, Nb₂O₅ showed the highest catalytic activity. The catalyst was reusable and easily separable from the mixture. Mechanistic studies suggested that Lewis acid site of Nb₂O₅ has higher tolerance to basic molecules (amines and water) than other Lewis acid catalysts such as TiO₂. This is the first catalytic system for cyclic imidation of dicarboxylic acids with amines (and ammonia).

Chapter 5 studies condensation of carboxylic anhydrides and amines by several Lewis acid catalysts. Nb₂O₅ showed the higher catalytic activity for the imidation of succinic anhydride with aniline than other catalysts tested. Reusability and general applicability of the catalytic system with Nb₂O₅ were shown. The results demonstrate the first reusable catalysis to synthesize cyclic imides from carboxylic anhydrides with amines and ammonia.

Chapter 6 studies transamidation of benzamide with *n*-octylamine. Among the catalysts tested, Fe-mont clay acts as the most effective heterogeneous catalyst. The reusability of the catalyst and general applicability of the catalytic system were shown. Catalytic cycle showed that carbonyl oxygen is activated by Fe³⁺ Lewis acid.

Chapter 7 is the general conclusion. Chapters 2-6 show new heterogeneous Lewis acid catalysts for direct synthesis of amides and cyclic imides from non-activated substrates. By using the simple methodology, the author synthesized various important amides and cyclic imides from readily available starting materials. Mechanistic studies suggested that the Lewis acid site of Nb₂O₅ is tolerant to base present in the reaction mixture, which results in effective catalysis for amidation and imidation reactions. The heterogeneous Lewis acid catalysts developed in this study would be applied to other reactions involving activation of carbonyl groups in the presence of amines.

Considering these research achievements, we conclude that the author is eligible to have a Doctor degree of engineering.