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学 位 論 文 題 名

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 are strongly preferred and get 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 catalyst. Five types of Lewis acid catalytic systems are developed for synthesis of amide and imide with a wide substrate scope.

In chapter 2, various Lewis and Brønsted acid catalysts including water tolerant $\text{Sc}(\text{OTf})_3$, 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 for the above reaction. This simple and atom-efficient method tolerates various functional groups and is applicable to challenging substrates such as anilines and α -hydroxycarboxylic acids. I investigated the reusability of catalyst and general applicability of the present catalytic system. Kinetics studies showed 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 used catalyst.

In chapter 3, I examined various Lewis and Brønsted acid catalysts including some effective homogeneous catalysts ($\text{La}(\text{OTf})_3$, NaOMe) for direct amidation of methyl benzoate with aniline. I found that Nb_2O_5 showed the highest catalytic activity for this reaction. I investigated the reusability of catalyst and general applicability of the present catalytic system. This Lewis acid catalyst is effective for various functionalities and is applicable to challenging substrates such as anilines and α -hydroxyesters. This result demonstrates the first successful example of heterogeneous catalysis for direct amidation of esters with amines.

For chapter 4, I examined various Lewis and Brønsted acid catalysts, water tolerant homogeneous and heterogeneous catalysts and commercial acidic resins for direct imidation of succinic acid with *n*-octylamine. Among those used catalyst Nb_2O_5 showed highest catalytic activity to the corresponding *n*-octylsuccinimide. The catalyst was reusable and easily separable from the mixture. Preliminary mechanistic studies suggested

that Lewis acid site of Nb₂O₅ has higher tolerance to basic molecules (amines and water) than other used catalyst. These results demonstrate the first heterogeneous Lewis acid catalytic system for imidation of dicarboxylic acid with amines and ammonia.

In chapter 5, for condensation reaction of carboxylic anhydride and amine, I investigated several Lewis acid catalysts including some metal oxide and water tolerant homogeneous Lewis acid catalysts. Nb₂O₅ showed the best catalytic activity for the imidation of succinic anhydride with aniline than other screened catalyst. I investigated the reusability of catalyst and general applicability of the present catalytic system. These results demonstrate the first reusable Lewis acid catalysis to synthesize cyclic imide from carboxylic anhydrides with amines and ammonia.

In chapter 6, I examined different types of catalyst for transamidation of benzamide with *n*-octyl amine. Among them Fe-mont acts as an effective heterogeneous catalyst for the transamidation of benzamide with *n*-octyl amine. I investigated the reusability of catalyst and general applicability of the present catalytic system. Catalytic cycle showed that carbonyl oxygen is activated by Fe³⁺ Lewis acid. This results shows that Fe-mont is an efficient catalyst for the transamidation reaction.

Chapter 7 is the general conclusion. Chapters 2-6 show the precise examples of heterogeneous Lewis acid catalysis for the direct synthesis of amide and imide from various substrates. By using these simple methodologies, I synthesized various important amides and 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 makes it highly effective for amidation and imidation reaction. These heterogeneous Lewis acid catalysts can be applied to other reactions involving activation of carbonyl groups in the presence of amines.