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## Abstract (Doctor)

Title of Thesis	Development of Polymer Microsphere-immobilized Chiral Pyrrolidine Catalyst and Its Application to Multistep One-pot Asymmetric Synthesis
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Approx. 800 words

Transformation reaction with chiral catalyst is of increasing importance in process chemistry in organic synthesis. The most crucial challenge is developing a suitable synthesis procedure, that can produce the desired optically active compounds with low environmental impact, high economic feasibility, and high efficiency. If multiple transformation reactions using chiral catalysts can be consecutively carried out in a one reaction vessel, in that case, a highly efficient organic synthetic process can be realized. Unfortunately, one of the limitations is that multiple catalysts with contrary properties (e.g., acidic, and basic, oxidative, and reductive) cannot be used simultaneously.

"Site isolation" is an effective way to allow multiple catalysts to operate independently. Several site isolating materials are available, but their synthesis methods are complicated. Therefore, developing a general method that can smoothly perform one-pot catalytic reactions based on site isolation is strongly desired.

Polymer microspheres can be one of the promising candidates as the site isolating material. They possess exciting features such as large specific surface area, high mechanical strength, high dispersibility, insolubility, a simple separation process, low swelling tendency, and easy preparation. In this research, we have tried to establish a one-pot reaction system based on site isolation using crosslinked polymer microsphere as a new site isolating material, which leads to a highly efficient one-pot organic synthetic process.

Chapter I describes the general introduction and background of the thesis.

Chapter II describes the synthesis of crosslinked polymer microsphere-immobilized chiral pyrrolidine catalysts and their application to asymmetric Michael addition reactions. The polymer microsphere-immobilized chiral pyrrolidine catalysts have been prepared via the precipitation polymerization using divinylbenzene, a comonomer, and a methacrylate monomer bearing a chiral *N*-Boc pyrrolidine moiety, followed by the removal of the *N*-Boc group. The resulting polymeric

catalysts were characterized by scanning electron microscopy, Fourier transform infrared spectroscopy, and elemental analysis. After the successful preparation of the polymeric catalyst, the catalytic performances of the polymeric catalysts were evaluated by carrying out asymmetric Michael addition reactions between aldehydes and alkyl vinyl ketones. The reaction proceeded with excellent yield and enantioselectivity when the polymeric catalysts were hydrophobic because the hydrophobic nature of the catalysts provided the suitable microenvironment for the reaction to occur. The effect of the molar ratios within the catalyst, catalyst loading, temperature, solvent, and substrate on the reaction yield and enantioselectivity were investigated in detail. Polar and non-polar organic solvents significantly affected the reaction yield and enantioselectivity. In the presence of polar solvents, the yield of the Michael adduct decreased significantly due to the restricted dispersion of hydrophobic polymeric catalysts in the reaction medium. On the other hand, the presence of non-polar organic solvents the yield of the reaction slightly increased but not satisfactorily due to the insolubility of the cocatalyst in non-polar solvents. The solvent-free condition was best suited for this reaction system. The recovery and reuse of a polymer microsphere-immobilized catalyst were performed, and the catalysts retained its original catalytic activity up to five cycles.

Chapter **III** describes the development of one-pot asymmetric two steps reaction system based on site isolation using crosslinked polymer microsphere as the site isolating precursor. The site isolation potential of the crosslinked polymer microspheres was demonstrated by carrying out a one-pot two steps deacetalization-asymmetric Michael addition reaction using crosslinked polymer microsphere-immobilized sulfonic acid and chiral pyrrolidine catalysts. The first step of the one-pot reaction sequence is the deacetalization of propionaldehyde diethyl acetal catalyzed by the acid catalyst to produce the intermediate compound propionaldehyde. The second step is the asymmetric Michael addition between the produced intermediate compound propionaldehyde and methyl vinyl ketone using chiral basic pyrrolidine catalyst. The pair of low-molecular-weight acid and base catalysts cannot catalyze the reaction due to the neutralization reaction among them. The final product was obtained with good yield and enantioselectivity when the acid and base organocatalysts are crosslinked polymer microsphere-immobilized. This result indicating that using crosslinked polymer microspheres site isolation can be achieved. The best catalytic activity was found for the hydrophobic chiral pyrrolidine catalyst and polymer microsphere-immobilized sulfonic acid catalysts pair with a good yield (82%) and enantioselectivity (91%). The recovery and reusability of the best catalysts pair were also performed, and they retained their original catalytic activity in the next cycles.

Chapter **IV** describes development of one-pot three steps asymmetric reaction based on site isolation using heterogeneous acid and base catalysts. The first step of the reaction, i.e., the asymmetric Michael addition reaction between the *tert*-butyl acetoacetate and *trans*-cinnamaldehyde was catalyzed by the chiral pyrrolidine catalyst. Then, the acid catalyst sequentially catalyzed the remaining two steps, i.e., hydrolysis and decarboxylation reactions. The low-molecular-weight acid and base catalysts pair even linear polymer-immobilized acid and base catalyst cannot afford the final product due to the deactivation of the catalytic sites by

neutralization reaction. Using the polymer microsphere-immobilized chiral pyrrolidine catalyst and silica gel immobilized acid catalyst pair, good yield and excellent enantioselectivity were obtained. Using the combination of polymer microsphere and silica gel, site isolation was achieved due to the insolubility and the 3-dimensional structure of the crosslinked polymer microsphere and silica gel microsphere. The active sites of acid and base cannot diffuse into each other and thus site isolation accomplished.

Chapter V describes the general summary of the thesis work.