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Abstract (Doctor)

Title of Thesis	Development of Polymer-immobilized Chiral Organocatalyst for Continuous-flow Synthesis
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Approx. 800 words

Organocatalytic asymmetric reactions represent one of the most powerful methods for the synthesis of chiral molecules, often providing high yields and excellent enantioselectivities. Chiral organocatalysts have attracted considerable attention owing to their environmental compatibility, tolerance toward air and moisture, operational simplicity, and the absence of metal contamination. In addition, they are cost-effective in terms of catalyst design and reproduction, providing an attractive alternative to organometallic catalysts. Among the various classes of chiral organocatalysts, chiral imidazolidine-4-ones and their salts, originally developed by MacMillan and co-workers, are particularly important because of stability, high catalytic performance, and ease of handling.

One limitation of homogeneous organocatalysts is that catalyst separation and recovery from the reaction product often require laborious purification procedures, such as silica gel column chromatography. effective approach to overcoming this limitation is the immobilization of the organocatalysts onto insoluble polymer supports. In particular, polymer microspheres have emerged as attractive support materials because of their large specific surface area, high mechanical strength, good dispersibility, ease of separation, and low swelling behaviour.

In recent years, continuous-flow systems have attracted growing interest, particularly when combined in combination with polymer-immobilized organocatalysts, because of its significant advantages over conventional batch processes. These advantages include simplified product purification, improved catalyst stability, facile automation, and enhanced process controllability. Continuous-flow system also enables safer handling of hazardous reagents and high-pressure conditions, accelerates reaction rates, facilitates scale-up, and provides efficient platforms for photochemical transformations. The integration of organocatalysis with flow chemistry is therefore

highly consistent with the principles of green chemistry, offering safer reaction conditions, reduced waste generation, and improved process efficiency. Furthermore, precise control of reaction parameters such as temperature, pressure, and residence time leads to enhanced reaction efficiency, selectivity, and reproducibility.

Chapter I provides an introduction and background of this thesis, including an overview of polymer-supported chiral organocatalysts and continuous-flow synthesis. The importance of developing highly efficient polymer-supported chiral organocatalysts for improving the performance of continuous-flow asymmetric synthesis is also discussed.

Chapter II describes the synthesis of ionically polymer-immobilized chiral imidazolidinone (MacMillan) catalysts based on crosslinked polymer supports. The catalytic performance of these polymer-supported catalysts was evaluated in the asymmetric Diels-Alder reaction between *trans*-cinnamaldehyde and 1,3-cyclopentadiene under continuous-flow conditions. The ionically immobilized MacMillan catalysts exhibited high catalytic activity and excellent enantioselectivity, affording the desired products in yields of up to 84% with enantiomeric excesses of up to 91% ee for the *exo* isomer and 96% ee for the *endo* isomer. Long-term continuous-flow operation demonstrated excellent catalyst durability; no catalyst leaching was detected even after 180 h of continuous use, and no significant decrease in catalytic activity was observed.

Chapter III describes the development of polymer microsphere-immobilized MacMillan catalyst prepared through the ionic immobilization of a MacMillan catalyst precursor onto polymer microspheres containing sulfonic acid groups in their side chains. A continuous-flow reactor system with reduced pressure loss was successfully constructed by uniformly packing the polymer microspheres together with silica gel in a column reactor. The resulting catalyst system exhibited high catalytic performance in the asymmetric Diels-Alder reaction of *trans*-cinnamaldehyde with 1,3-cyclopentadiene, providing high productivity and excellent enantioselectivity of up to 93% ee for the *endo* isomer. The catalytic performance was significantly influenced by several reaction parameters, including solvent, flow rate, substrate concentration, and polymer particle size. In addition, the durability, reproducibility, and long-term stability of the polymer-supported catalysts were systematically investigated under continuous-flow conditions. The substrate scope was also examined using structurally diverse aldehydes, demonstrating the versatility and robustness of the developed catalytic system.

Chapter IV describes the development of a novel synthetic method for core-corona polymer microsphere-immobilized MacMillan catalysts. Core-corona polymer microspheres bearing sulfonic acid groups were prepared by surface-initiated atom transfer radical polymerization (SI-ATRP) of

phenyl 4-vinylbenzenesulfonate and styrene with benzyl bromide-functionalized polymer microsphere as a macroinitiator, followed by regeneration of the sulfonic acid functionalities. The corresponding catalyst was then synthesized through ionic interaction between the sulfonic acid groups on the polymer support and a MacMillan catalyst precursor.

The catalytic performance of the resulting core-corona polymer-immobilized MacMillan catalyst was evaluated in the continuous-flow asymmetric Diels-Alder reaction between *trans*-cinnamaldehyde and 1,3-cyclopentadiene. The catalyst exhibited excellent catalytic activity, high productivity, and outstanding enantioselectivity, achieving up to 94% ee for the *exo* isomer and 95% ee for the *endo* isomer. Reaction parameters such as monomer composition, solvent, flow rate, and substrate concentration significantly affected the catalytic performance. The particle size of the core polymer microsphere and the length of the polymer corona had a pronounced effect on the catalytic activity. Furthermore, structural factors including the particle size of the core microspheres, graft density, and the molecular weight of the corona chains profoundly influenced catalytic activity by affecting the accessibility of active sites, surface area, and mass transport properties within the polymeric structure. The catalyst also showed excellent durability and broad substrate applicability under continuous-flow conditions.

Chapter V summarizes the results obtained in this study and discusses their scientific significance and future prospects. The findings presented in this thesis establish important design principles for the development of highly efficient heterogeneous chiral catalysts for continuous-flow asymmetric synthesis. Furthermore, the developed ionically polymer-immobilized chiral organocatalysts provide valuable insights into the practical implementation of continuous-flow asymmetric processes and are expected to contribute significantly to the advancement of efficient and sustainable production technologies for pharmaceuticals and fine chemicals.