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**Abstract (Doctor)**

Title of Thesis	Cinchona alkaloid derivatives and their polymers as efficient catalysts for asymmetric reaction
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Approx. 800 words

Asymmetric synthesis using chiral catalysts plays an important role in synthesizing pharmaceuticals, pesticides, and the total synthesis of natural products. Because of their versatile structural modifications, cinchona alkaloids and their derivatives have been widely used as chiral organocatalysts in various asymmetric reactions.

Despite the various modifications of cinchona alkaloids, cinchona alkaloids with functional groups in the quinoline ring are limited. A nitro (NO<sub>2</sub>) group has strong electron-withdrawing properties and shows steric and electronic interactions with substrate molecules. The introduction of the NO<sub>2</sub> group at the C5' position in cinchona alkaloids causes a steric repulsion between the hydrogen bound to the C9 position and the nitro group, thus fixing the quinuclidine ring at an angle. Due to these characteristics, the NO<sub>2</sub>-modified cinchona alkaloids at the C5' position are expected to exhibit catalytic performance different from the conventional catalysts.

In this study, we investigated the synthesis of novel asymmetric organocatalysts of quinine derivatives with the NO<sub>2</sub> group at the C5' position. The effects of the NO<sub>2</sub> group at the C5' position on asymmetric reactions were investigated in detail. We also examined the difference in the catalytic performance due to the presence or absence of the C5'-NO<sub>2</sub> group. For the well-understanding of the effect of the C5'-NO<sub>2</sub> group on the asymmetric reaction, other types of cinchona organocatalysts possessing C5'-NO<sub>2</sub> moieties were further investigated.

Cinchona alkaloids have been used to design chiral polymeric organocatalysts as a privileged class of chirality inducers. The design of polymeric catalysts is a critical tool for understanding the efficient catalytic process in asymmetric transformations. Although various studies with low-molecular-weight urea or squaramide catalysts derived from cinchona alkaloids have been reported, the variation of the polymeric counterparts is still limited. Cinchona urea, squaramide, or ether-modified polymeric catalysts can be synthesized by suitable polymerization processes under optimal reaction conditions. In our previous reports, we have established the polymerization of cinchona alkaloids by Yamamoto coupling polymerization reaction and Mizoroki-Heck polymerization reaction. Their reactions were a reliable C-C bond-forming reaction to give main-chain type polymers from cinchona alkaloid derivatives. These main-chain chiral polymers were expected to be used successfully as chiral catalysts in various asymmetric reactions.

Chapter 1 provides a broad introduction of chiral catalysts, an outline of the structural features of cinchona alkaloids, chiral organocatalysts, polymeric organocatalysts, and the background of the study. The broad overviews of the several asymmetric reactions catalyzed by low-molecular-weight and polymeric cinchona alkaloids are also included in this chapter.

In Chapter 2, the catalytic performance of C5'-Nitro-dihydroquinine (**Q1**) was investigated in an asymmetric Michael reaction. **Q1** was prepared from dihydroquinine (**HQ**) in 65% yield. The structure of **Q1** was confirmed by nuclear magnetic resonance (NMR), fourier transform infrared spectroscopy (FT-IR), and time-of-flight mass spectrometry (TOF-MS). We found that the NO<sub>2</sub> group at the C5' position of **Q1** was vertically fixed to the quinoline ring by X-ray crystallography study. When **Q1** and **HQ** were applied to the asymmetric Michael addition reaction of methyl 2-oxocyclopentanecarboxylate and trans- $\beta$ -nitrostyrene, **Q1** showed high yield (96%) and high enantioselectivity (99% ee). The ability of asymmetric induction of **Q1** was superior to that of **HQ** in the reaction.

In Chapter 3, Cinchona urea compounds having 3,5-diiodophenyl moieties were subjected to Yamamoto coupling polymerization to afford the chiral urea polymers. Both urea homopolymers and copolymers with and without the NO<sub>2</sub> group were successfully synthesized using Yamamoto coupling polymerization. These polymers showed high activities as heterogeneous catalysts in asymmetric Michael reactions. The catalytic activities were comparable to those of the corresponding monomeric catalyst in solution systems. The polymer without the NO<sub>2</sub> group required a shorter reaction time, whereas the polymer with the NO<sub>2</sub> group had superior enantioselectivity. Furthermore, these polymeric catalysts were easily recovered from their reaction mixtures due to their insolubility and could be reused several times without loss of catalytic activity.

In Chapter 4, chiral polymers having cinchona squaramide repeating units were synthesized and applied in an aza-Michael reaction. Those polymers were synthesized using Mizoroki-Heck polymerization. The polymer organocatalysts showed excellent catalytic performance in the asymmetric aza-Michael reaction between aniline and chalcone to afford the chiral  $\alpha$ -amino ketones in a highly enantioselective manner (up to >99% ee) under solvent-free conditions. The insolubility of the polymer catalyst facilitated the separation of the catalyst from the reaction mixture. The recovered polymer was reused several times without any loss of its catalytic performance.

In Chapter 5, the Yamamoto coupling reaction was applied to the synthesis of ether- and ester-based cinchona alkaloid chiral homopolymers and copolymers. Asymmetric Michael addition reactions with chiral organocatalysts were investigated, and these catalytic performances were discussed. The reactions afforded the enantioselective adducts in excellent yield with 87-89% ee using the ether-based copolymer in toluene at 25 °C, while the corresponding low-molecular-weight catalyst exhibited poor enantioselectivity (21% ee). The reusability of copolymer up to five cycles was satisfactory, with tolerating excellent enantioselective adduct.

Chapter 6 represents the comprehensive summary and conclusion of the thesis. Introducing the C5'-NO<sub>2</sub> group into cinchona alkaloids provided a distinctive structure, which might lead to superior catalytic activity and stereoselectivity. Yamamoto coupling polymerization was effective for the synthesis of cinchona alkaloid polymers. A new cinchona polymer was synthesized by Mizoroki-Heck polymerization. These polymeric catalysts showed high catalytic performance and reusability in the Michael and aza-Michael reactions.