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Abstract (Doctor)

Title of Thesis	Catalytic Asymmetric Cyclopropanations of Diazo Phosphonates and Designed Diazo Ketones (ジアゾリン酸エステルとデザインジアゾケトンの触媒的不斉シクロプロパン化反応)
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Approx. 800 words

The cyclopropane subunit is present in many biologically important compounds including terpenes, pheromones, fatty acid metabolites, and unusual amino acids, and it shows a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumor, and antiviral activities. This fact has inspired chemists to find novel and diverse approaches to their synthesis, and thousands of cyclopropane compounds have been prepared. In particular, naturally occurring cyclopropanes bearing simple or complex functionalities are chiral compounds; thus, the cyclopropane motif has long been established as a valuable platform for the development of new asymmetric technologies. Asymmetric synthesis constitutes the main strategy to gain access to enantioenriched compounds, involving the use of either chiral auxiliaries or catalysts that in turn can be metal-centered, small organic asymmetric molecules or enzymes. New and more efficient methods employing all these methodologies to gain enantiomerically enriched cyclopropanes are still evolving. Transition metal-catalyzed cyclopropanation involving carbene intermediate is powerful and useful methods for constructing important substructures of targeted molecules, and therefore they have been extensively studied for the past couple of decades.

Although Ruthenium complex is newcomer in the field of catalytic cyclopropanation, it has emerged as the third important catalyst metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium. Therefore, future developments should try to find catalysts that give ruthenium carbene intermediates electrophilic enough to react with a wide range of olefinic substrates and that at the same time give high levels of dia- and enantioselectivity. This prompted us to explore the asymmetric cyclopropanation of various diazo compounds which are potentially building blocks and expectant to be applied in pharmaceutical and medicinal fields.

Chapter 1. Describes the history of the carbene transfer reactions. A brief review of the most successful metal carbene intermediates in asymmetric cyclopropanations over the past ten years are provided. Furthermore, the application of metal carbene complexes in the synthesis of biologically-active

or natural product-like compounds are also mentioned.

Chapter 2. Recently, our research group reported that the complex, Ru(II)-pheox, has been completely efficient in carbene transfer reactions, particularly the cyclopropanation of diethyl diazomethylphosphonates with various electron-deficient olefins such as α,β -unsaturated carbonyl compounds or vinyl carbamates in excellent yields and with high enantioselectivity. Thus, here in, novel catalysis involving phosphonomethylation of *N*-methylaniline and asymmetric cyclopropylphosphonation reactions of *N,N*-diethylaniline derivatives with diazomethylphosphonates are reported. Optically active cyclopropylphosphonate derivatives were directly synthesized from diazomethylphosphonates and *N,N*-diethylaniline derivatives catalyzed by a 3,4,5 methoxy-Ru(II)-pheox complex in one step in good yields and high diastereoselectivities (up to trans/cis = > 99:1<) and enantioselectivities (up to 99% ee). D labeling mechanistic studies of phosphonomethylation and cyclopropylphosphonation suggested that an enamine or iminium intermediate was generated in the reaction process.

Chapter 3. Continuously, the 3,4,5 methoxy-Ru(II)-Pheox-catalyzed cyclopropanation of styrene with diaceptor diazo compound is initially reported in the corresponding cyclopropylphosphonate product in excellent yield (up to 99%) and good enantioselectivity (up to 68% ee).

Chapter 4. Furthermore, finding catalysts which can cyclopropanate with various diazo compounds to enrich stereoselectivity also have been developed during the last decades. In our previous researches, Ru(II)-pheox-catalyzed asymmetric cyclopropanation of succinimidyl diazoacetate with olefins and allenes resulted in high yields and excellent enantioselectivities and of α,β -unsaturated carbonyl compounds with acetyl diazoacetate in much higher stereoselectivities (diastereoselectivity >99:1 and enantioselectivity up to 99%). Consequently, herein, The diazo derivative of acetyl acetate is a useful basic skeleton for the synthesis of cyclopropyl ketones. The intermolecular cyclopropanations of diazo acetoxy acetone with olefins are accomplished by using a novel *p*-nitro-Ru(II)-diphenyl-Pheox catalyst to give the corresponding optically active cyclopropane derivatives in good yields (up to 95%) with excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 98% ee).

Chapter 5. Finally, all the experimental and analytical data as the evidence for chapter 2 to 4 are described.

In summary, the Ru(II)-Pheox catalyzed asymmetric cyclopropanation reaction proved to be an efficient and straightforward method for the preparation of chiral cyclopropylphosphonates, diaceptor cyclopropylphosphonates, ketone cyclopropanes, which are important intermediates in the synthesis of many biologically active compounds. We believe that Ru(II)-Pheox derivatives will contribute to the progress of not only asymmetric cyclopropanation but also other asymmetric carbene transfer reactions.

List of publications and experimental supporting information are included in the appendices.