

Date of Submission (month day, year) : March 27, 2020

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Abstract (Doctor)

Title of Thesis	Catalytic Intramolecular Carbene Transfer Reactions into σ and π Bonds (σ 及び π 結合への触媒的分子内カルベン移動反応)
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Approx. 800 words

A carbene known as an most active intermediate is complexed with a transition metal, which afford the corresponding metal-carbene complex and catalytically insert into σ and π bonds of organic compound. Even though there are many reports on the carbene transfer process to develop a new approach for the synthesis of medicine and other bioactive compounds, the regio-, stereo- and chemoselective approaches are still limited and remained as a main subject in the filed of synthetic organic chemistry. For these background, I developed an efficient catalytic intramolecular carbene transfer reactions by using originally developed ruthenium catalyst into σ and π bonds and successfully applied for the synthesis of γ -lactam ring fused aromatics (oxindoles), γ -lactone ring fused cyclopropanes, and γ -lactam ring fused seven member rings via Buchner reaction.

Although ruthenium complex is a newcomer in the field of catalytic carbene transfer reaction, it has emerged as a useful transition metal for the carbenoid chemistry of diazo compounds, besides copper and rhodium. And recently, we have developed a Ru(II)-Pheox complex, which is efficient for carbene transfer reactions, in particular, asymmetric cyclopropanation, N-H insertion, C-H insertion and Si-H insertion reactions.

Therefore, driven by my interests in the catalytic asymmetric carbene transfer reaction and the efficiency displayed by the Ru(II)-Pheox catalyst, I started to explore the asymmetric cyclopropanation, C-H insertion, Buchner reactions of various diazo compounds, which are potentially building blocks and expectant to be applied in pharmaceutical and medicinal fields.

In my thesis, **Chapter 1** describes the importance of carbene transfer reactions. And a short review of the metal carbene intermediates in C-H insertion, asymmetric cyclopropanations, and Buchner reaction have been also illustrated in this chapter. In addition, the application of metal carbene complexes in the synthesis of biologically-active or natural product-like compounds is also mentioned.

Chapter 2 is for the synthesis of oxindoles. The oxindole ring is prevalent as an important scaffold found in numerous natural products and pharmaceutically active compounds. Over the past few decades, the emerging therapeutic potential of structural motif of oxindole has encouraged the medicinal chemists to synthesize novel oxindole derivatives. I report Ru(II)-Pheox was found to be a highly efficient catalyst for the synthesis of oxindole derivatives in excellent yields. We developed the efficient synthesis of oxindole derivatives via intramolecular ArC_{sp2}-H insertion reaction of diazo acetamides derived from the corresponding anilines by using Ru(II)-Pheox catalyst. The reaction proceeds smoothly under mild conditions, providing the corresponding oxindole derivatives in excellent yield (up to 99%). No other side reactions related to metal-carbene reactivity such as dimerization, aromatic ring expansion and C_{sp3}-H on amide nitrogen insertion reaction were observed.

On the other hand, the cyclopropane subunit is also present in many biologically important compounds and it shows a large spectrum of biological properties. 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. Thus, **Chapter 3** presents the development of asymmetric catalysts based

on Ru(II)-Pheox complexes, I developed a new series of Ru-C_{olefin}(sp²) bond-containing organometallic complexes and successfully applied them to the catalytic asymmetric inter- and intramolecular cyclopropanations, which are carbene transfer reaction. It is noteworthy that high yields and stereoselectivity were achieved for *trans*-cyclopropane carboxylates even with a low catalyst loading. Catalytic asymmetric cyclopropanations of diazoesters with olefins in the presence of the Ru-C_{olefin}(sp²)-phenyloxazoline complexes (Ru-C_{olefin}(sp²)-Ru(II)-Pheox) proceeded smoothly to give the corresponding optically active cyclopropanes in high yields, with a *trans/cis* ratio 97/3 to >99/1 and 97% to >99% ee (*trans*). The enantioselectivities were affected by the geminal substituent on the Ru-C_{olefin}(sp²) bond; the highest enantioselectivities were obtained when using Ru(II)-Prox catalyst with no substituent at the germinal position of the metal.

Furthermore, medium ring-containing organic molecules, such as seven-membered rings, are also the cornerstone of many bioactive natural compounds such as guaiane sesquiterpenes, guaianolide sesquiterpene lactones. However, there are few reports on their synthesis. Thus, the development of an efficient method to prepare these scaffolds has attracted a significant amount of research attention. This unique strategy toward seven-membered carbocycles has been utilized in natural product synthesis. In **Chapter 4**, I report the development of an intramolecular Buchner reaction of a variety of *N*-benzyl diazoamide derivatives in the presence of a chiral Ru(II)-Pheox catalyst. The aromatic rings are converted into the corresponding γ -lactam ring fused seven-membered ring system with high regio- and stereoselectivity. A variety of γ -lactam fused 5,7-bicyclic-heptatriene derivatives have been prepared from diazoacetamides in up to 99% yield with high enantioselectivity (up to 99% ee) using a chiral Ru(II)-Pheox catalyst under mild reaction conditions.

In conclusion, **Chapter 5**, the Ru(II)-Pheox catalyzed C-H insertion reaction and asymmetric Buchner reaction proved to be the efficient and straightforward methods for the preparation of oxindole and seven-membered ring which are important intermediates in the synthesis of many biologically active compounds. Moreover, we have successfully designed and synthesized a novel Ru-Prox type catalyst. This catalyst showed excellent reactivities and selectivities in asymmetric cyclopropanation reactions. And it is expected to provide many further opportunities in asymmetric catalysis.

In **Chapter 6**, all the experimental and analytical data as the evidence for Chapter 2 to 4 are described.