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A b s t r a c t

Title	Highly Chemo- and Stereoselective Carbene Transfer Reactions Catalyzed by Ru(II) Complexes
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(800 words)

The decomposition of α -diazocarbonyl compounds by transition-metal complexes to generate Fischer-type metal carbene intermediates has received considerable attention because of their ability to subsequently undergo diverse transformations, including cyclopropanation, X-H (X= N, O, C, etc.) insertion and ylide formation. Among the various transformations, the cyclopropanation of olefins with diazo reagents is one of the most important reactions because the corresponding optically active cyclopropanes have been recognized as useful building blocks for biologically active compounds. These factors will be described in detail in chapter 1. Therefore, during the past two decades, various catalytic systems have been developed for the highly diastereo- and enantioselective cyclopropanation of diazoacetates. In particular, highly effective and stereocontrolled syntheses of cyclopropanes have been achieved with catalyst based on copper, rhodium, ruthenium and recently, cobalt, which will be discussed in more detail in chapter 2. Despite these considerable advances, only a few catalytic systems are able to catalyze asymmetric cyclopropanation of vinylcarbamates, α,β -unsaturated carbonyl compounds and allenes. For this regard, the development of a general and efficient catalytic system for cyclopropanation of these olefins is highly desirable. Initially, we focused our efforts on functionalized diazoacetates because we envisioned that the carbonyl groups on the functional groups could play an important role as an electron-donating group for electrophilic Ru-carbene complex intermediate increasing steric hindrance and nucleophilicity of the intermediate, which were expected to be efficient for highly stereoselective cyclopropanation and the reaction of electron-deficient olefins. This thesis describes the synthesis of the functionalized diazo compounds such as succinimidyl diazoacetate (SDA), acetyl diazoacetate (ADA) and methyl (diazoacetoxy)acetate (ADA) and the evaluation of them as carbene sources in cyclopropanation of various olefins including vinylcarbamates, α,β -unsaturated carbonyl compounds and allenes catalyzed by Ru(II)-Pheox complex.

Chapter 3 presents a protocol for the highly stereoselective Ru(II)-Pheox catalyzed cyclopropanation of terminal olefins with succinimidyl diazoacetate (SDA). The reaction can be carried out smoothly under practically desirable conditions, and succinimidyl cyclopropylcarboxylates can be obtained in significantly enhanced yields, diastereoselectivity, and enantioselectivity. Subsequent reduction of these cyclopropane products readily afforded the corresponding cyclopropylmethanol derivatives with superior enantioselectivity.

Chapter 4 describes the development of the first highly enantioselective cyclopropanation of vinylcarbamate derivatives with diazoesters, using the Ru(II)-Pheox complex as a catalyst. The simple ethyl diazoester was found to be an efficient carbene precursor than the functionalized diazoacetates and the reaction proceeded smoothly under mild conditions, giving the corresponding protected cyclopropylamine products in high yields, with excellent diastereoselectivities (up to 96:4) and enantioselectivities (up to 99% ee). Furthermore, the utility of the present asymmetric cyclopropanation is highlighted in the stereoselective and

straightforward synthesis of enantioenriched 2-((*tert*-butoxycarbonyl)-amino)-cyclopropylmethanol, which is a key intermediate in the synthesis of the antitumour antibiotic belactosin A.

Chapter 5 presents a Ru(II)-Pheox catalyzed asymmetric cyclopropanation of α,β -unsaturated carbonyl compounds with ketone- or ester-functionalized diazoacetates. The use of methyl (diazoacetoxy)acetate (MDA) was found to be crucial to the cyclopropanation of electron-deficient olefins, to give the corresponding dicarbonyl cyclopropane products in high yields with excellent diastereoselectivities (up to >99:1) and enantioselectivities (up to 99% ee). In addition, we have successfully used the dicarbonyl cyclopropane product to synthesize the optically active 1,2-cyclopropane dicarboxylic acid and 1,2-cyclopropane dimethanol, which are useful as key intermediates in the synthesis of various bioactive compounds. Moreover, the present method also confirms the synthetic value of the spiral cyclopropane oxindole as a HIV-1 non-nucleoside reverse transcriptase inhibitor.

Chapter 6 describes the development of an efficient protocol for the synthesis of optically active alkylidenecyclopropane derivatives (ACPs) via the Ru(II)-Pheox catalyzed asymmetric cyclopropanation of allenes with succinimidyl diazoacetate (SDA). This catalytic system gives direct access to ACPs in high yields (up to 90%) with high enantioselectivities (up to 98% ee) and high diastereoselectivities (up to 99:1).

Chapter 7 presents the development of an efficient water-soluble Ru(II)-*hm*-Pheox catalyst. The aqueous catalyst delivered excellent reactivities up to 99% yield and enantioselectivities up to 98% ee in intramolecular cyclopropanation of *trans*-allylic diazoacetates and alkenyl diazoketone in a water/ether biphasic medium. The easily separation of the ether-phase, which contains the cyclopropane product, allows the simple reuse of the catalyst in the water-phase at least five times without significant decrease in reactivity or enantioselectivity.

Chapter 8 describes an efficient protocol for the preparation of *N*-substituted α -aminoamides through the Ru(II)-*dm*-Pheox catalyzed N-H insertion reaction of various diazoacetamides into several amines, including aniline. This method gives easy access to α -aminoamide derivatives, which are important building blocks for the synthesis of natural products and pharmaceuticals. In addition, we successfully used this catalytic N-H insertion reaction to obtain 2-(2-methylquinolin-4-ylamino)-*N*-phenylacetamide, a potential antileishmanial agent, in high yield (96%) within 5 min under mild reaction conditions.

Chapter 9 provides the experimental and analytical data for chapters 3 to 8.