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学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称 博士（薬科学） 氏 名 劉 強

学 位 論 文 題 名

Enantioselective Synthesis of Planar-Chiral Metallocenes and Their Application in Asymmetric Catalysis

（面不斉メタロセン類のエナンチオ選択的合成法の開発と不斉触媒反応への応用）

Planar-chiral metallocenes are widely used chiral building-blocks in organometallic chemistry, and have been applied as asymmetric catalysts and chiral ligands in many ways. Notable examples of utilizing the architectures of planar-chiral metallocenes are a series of planar-chiral ferrocene-fused 4-dialkylaminopyridine derivatives (Fc^* -DAAPs), which were developed by G. C. Fu since 1996, and planar-chiral *ansa*-zirconocene species developed by Brintzinger. In my doctoral studies, I have developed the novel and efficient methods of preparing three types of planar-chiral metallocenes, and catalytic applications of these planar-chiral compounds were examined.

The specific compounds I have examined are following three: (i) ferrocene- and cymantrene-fused planar-chiral pyridones and 4-dialkylaminopyridines, (ii) ferrocene-fused planar-chiral cyclic phosphonic acids, and (iii) planar-chiral *ansa*-zirconocene dichlorides.

Applications of these planar-chiral complexes in asymmetric catalysis have also been demonstrated.

Chapter 1. Enantioselective Synthesis of Metallocene-Fused Planar-Chiral

4-(Dialkylamino)pyridine Derivatives and Their Application in Asymmetric Catalysis

Planar-chiral ferrocene-fused 4-dimethylaminopyridine derivatives (Fc^* -DAAPs) were developed by G. C. Fu in 1996. Fu has demonstrated the usefulness of these compounds, however, applications of these elegant molecules have been limited probably due to the complicated synthesis as well as necessity of the enantiomeric resolution. In 2015, our group reported the enantioselective synthesis of Fc^* -DAAPs. Although our synthesis could provide a series of Fc^* -DAAPs in enantiomerically pure forms, the synthetic sequence is somewhat lengthy and needs to use expensive noble metal catalysts. In addition, the method only works with ($\eta^5\text{-C}_5\text{H}_5$)Fe or ($\eta^5\text{-C}_5\text{Me}_5$)Fe substructures, and the corresponding ($\eta^5\text{-C}_5\text{Ph}_5$)Fe derivatives could not be prepared by the same method. In Chapter 1 of my thesis, I have developed an improved method of preparing various Fc^* -DAAPs as single-enantiomers. The new synthetic sequence does not need the expensive metal catalysts and shows shorter synthetic sequence and higher yields. Furthermore, the improved method is applicable to the preparation of Fc^* -DAAPs with a sterically demanding cyclopentadienide (such as $\eta^5\text{-C}_5\text{Ph}_5$ or $\eta^5\text{-C}_5\text{Bn}_5$) as well as cymantrene-fused DAAPs. Some of these compounds are prepared for the first time by our research group.

The newly prepared library of Fc^* -DAAP derivatives was examined in the asymmetric addition reaction of 2-*t*-Bu-phenol to ethyl(*p*-tolyl)ketene and in the kinetic resolution/acetylation of *rac*-secondary alcohols, and some newly prepared Fc^* -DAAP derivatives showed better enantioselectivity than the known Fc^* -DAAPs.

Chapter 2. Enantioselective Synthesis of Metallocene-Fused Planar-Chiral Cyclic Phosphonic Acids

Binaphthyl-based chiral phosphoric acids were developed by Akiyama et al. and Terada et al. independently. These unique molecules catalyze various reactions in excellent enantioselectivity, and their applications have grown considerably over the last decade. For example, the chiral phosphoric acid-catalyzed Mannich reaction or Friedel-Crafts reaction provide attractive ways to construct carbon-nitrogen/ carbon-carbon bonds in the enantioselective fashions.

In Chapter 2, synthesis and characterization of new ferrocene-fused cyclic phosphonic acid derivatives are described. Our strategy for the enantioselective synthesis of cyclic phosphonic acids consists of two features: (i) chiral substituent-directed *ortho*-lithiation on the ferrocene platforms takes place in high diastereoselectivity (>99% de) to induce the planar chirality in the ferrocenes, (ii) after the appropriate conversions of the two substituents at the 1- and 2-positions of the ferrocene core, a cyclization process affords the planar-chiral cyclic phosphonic acid as a single-enantiomer in high to excellent yield.

Chapter 3. Catalytic Asymmetric Synthesis of Planar-Chiral Zirconocenes by Asymmetric Ring-Closing Metathesis and Their Applications in Asymmetric Carbometalations

Over the past two decades, organozirconium derivatives have emerged as synthetically useful reagents and catalysts. Typical methods of providing single-enantiomeric planar-chiral zirconocenes are resolution of the racemates. The first enantioselective synthesis of planar-chiral zirconocenes was reported in 2004 by Jordan, however, this method requires a stoichiometric or more than a stoichiometric amount of chiral reagents. To the best of our knowledge, there have been no previous reports on the *catalytic asymmetric synthesis* of planar-chiral zirconocene derivatives. In Chapter 3, I have established that planar-chiral zirconocene derivatives could be obtained by the asymmetric ring-closing metathesis (ARCM) reaction in extremely high enantioselectivity of up to 98% ee and in 96% yields.

The application of planar-chiral zirconocene derivatives was examined in the two prototypical asymmetric carbometalation reactions. The first one is enantioselective carbomagnesation of 2,5-dihydrofuran in the presence of the catalytic zirconocene showing high yield and moderate enantioselectivity. The second asymmetric reaction examined is ZACA reaction giving the corresponding carboalumination product in moderate yield and enantioselectivity.