Abstract of Thesis

Name (Bijan Mohon Chaki)	
Title	Enantioselective Synthesis and Application of Spiro-type Chiral Ligands (スピロ型キラル配位子のエナンチオ選択的合成と応用)

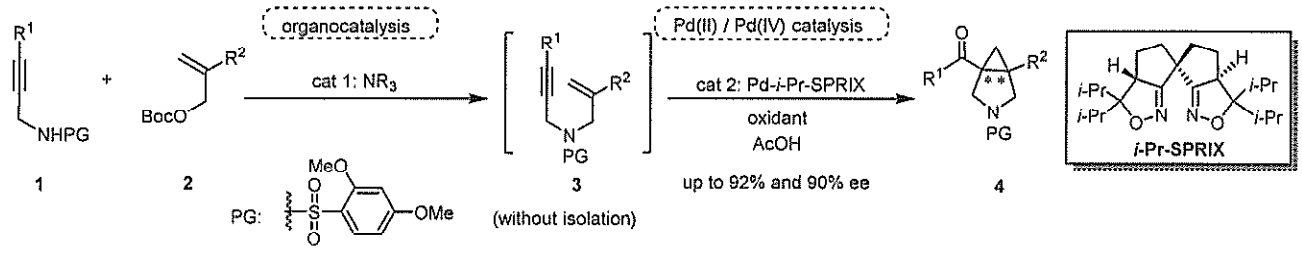
Abstract of Thesis

Chiral catalysts bearing a rigid spiro skeleton can create efficient asymmetric environment because the structural feature of the two perpendicular rings connected through one atom is expected to provide unique chirality and molecular rigidity. Our group has been investigating the development of chiral spiro compounds which already solved formidable synthetic challenges as ligands,[1,2] organocatalyst,[3] and ionic liquids.[4] However, the unavoidable optical resolution during preparation of spiro catalysts limits the development of them in asymmetric catalysis. From the necessity of efficient synthetic application of chiral spiro catalysts and enantioselective synthesis of spiro ligand, two projects were conducted: one is exploration of new application of widely applicable chiral spiro ligand *i*-Pr-SPRIX in enantioselective synthesis of heterocyclic compounds (see project 1); the other is enantioselective desymmetrization of prochiral diol to synthesize optically active precursor subjecting to synthesis of spiro (isoxazole-isoxazoline) hybrid ligand in its optically pure form (see project 2).

Project 1: Enantioselective Synthesis of Bicyclic Pyrrolidine Derivatives *via* One-Pot Sequential Organo and Palladium catalysis.

In addition of diversely developed Pd(0)/Pd(II) catalysis, Pd(II)/Pd(IV) catalysis achieving potential for the unique reactivity of Pd(IV) complex generated *in-situ* during the catalytic transformations. My research group has successfully developed enantioselective Pd(II)/Pd(IV) catalysis by utilizing the unique chiral ligand *i*-Pr-SPRIX, which efficiently produces optically active molecules.[2] Meanwhile, one-pot methodology is now recognized as a potent synthetic approach to target compounds. I, therefore envisaged that a combination of the one-pot strategy and the enantioselective Pd(II)/Pd(IV) catalysis would provide a powerful synthetic method of valuable optically active materials.

The present sequential process consisted of organocatalyzed allylation of propargylamine substrates **1** with allyl carbonates **2** and Pd(II)/Pd(IV)-catalyzed enantioselective oxidative cyclization of the resulting enyne intermediates **3** using *i*-Pr-SPRIX ligand. After extensive screening of reaction parameters, I eventually achieved the efficient formation of enantioenriched bicyclic pyrrolidine products **4** (Scheme 1). Thus, the formation of key intermediate **3** by treatment of **1** with **2** in the presence of Lewis base catalyst and subsequent addition of Pd–*i*-Pr-SPRIX catalyst and oxidant afforded **4** in up to 92% yield with 90% ee.



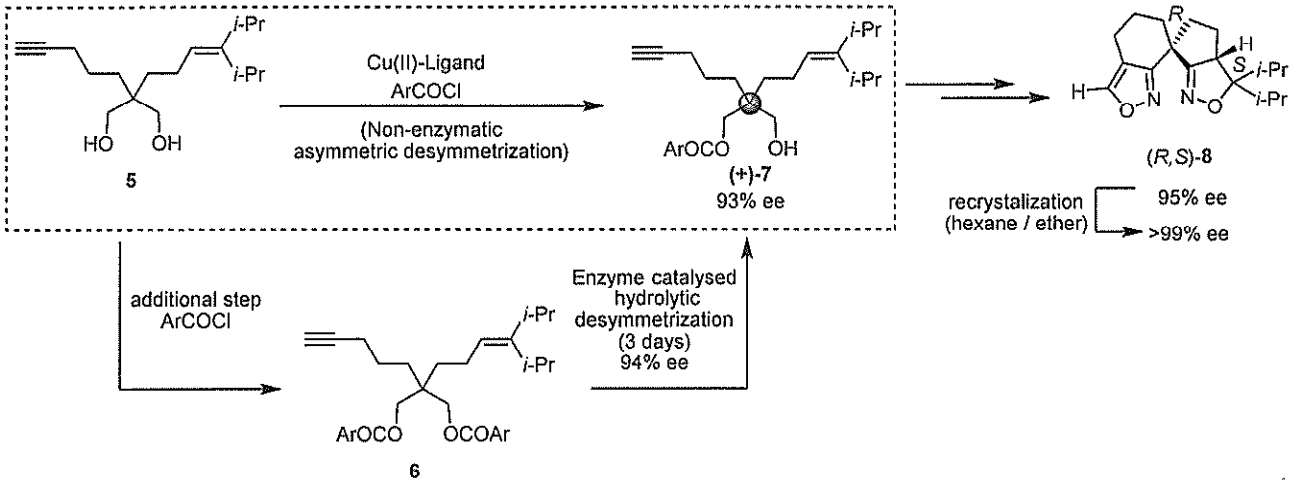
Scheme 1: One-Pot Sequential Synthesis of Enantioenriched Bicyclic Pyrrolidine Products **4** Based on Organocatalysis and Pd(II)/Pd(IV)-Catalysis.

Project 2: Enantioselective Synthesis of Spiro (Isoxazole-Isoxazoline) Hybrid Ligand.

Within the last decades chiral ligands based on a spiro framework have been attracting huge interest in catalytic asymmetric synthesis due to their peculiar nature. Among the various chiral spiro ligands reported, so far, the synthesis of desired spiro compounds in optically pure form is predominant with chiral resolution of

racemates. However, direct enantioselective synthesis of spirocycles as ligands, that could be used for further synthetic manipulation is still rare.

The synthetic utility of spiro-type chiral ligands **8** possessing isoxazole and isoxazoline rings as the coordination site have been demonstrated in enantioselective Pd catalysis.[1,5] Hence, the development of efficient synthetic methods to obtain **8** in optically pure form is thought to be requisite in asymmetric catalysis. Previously, my group member disclosed asymmetric synthesis of **8** with high optical purity from its chiral precursor **7** which was obtained by enzymatic desymmetrization of prochiral diol **5**. As the enzymatic desymmetrization require one more addition step to prepare of diester precursor **6** from diol **5**, this time I attempted non-enzymatic asymmetric desymmterization, a one-step approach to achieving the chiral precursor **7** for enantioselective synthesis of **8**. In this work, Cu-catalyzed enantioselective acylation proceeded into key intermediate **7** up to 80% yield with 93% ee (black circled box).



Scheme 2: Desymmetrization of Prochiral Diol for Enantioselective Synthesis of Spiro (Isoxazole-Isoxazoline) Hybrid Chiral Ligand.

References:

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様式 7

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

Bijan Mohon Chaki 君は、スピロ骨格を持つキラルなイソオキサゾリン—イソオキサゾールハイブリッド配位子のエナンチオ選択的な合成を検討し、ピンサー型キラル配位子と銅触媒を用いる反応ならびに、生体触媒である酵素を利用する二種類の反応により、最高 99% ee の光学純度で目的物が得られることを見出した。また、スピロビスイソオキサゾリン配位子（SPRIX）用いる Pd(II)/Pd(IV)触媒反応により、二環式ピロリジン誘導体を高収率かつ高い光学純度で得ることにも成功している。この反応を、有機触媒と遷移金属触媒を組み合わせた斬新な one-pot 反応へと展開できることも示した。生成物は、多様な生物活性物質合成のためのキラルビルディングブロックとして有用である。よって、本論文は博士（理学）の学位論文として十分価値あるものと認める。