別紙４－１（課程博士（英文））

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Abstract（Doctor）

Title of Thesis	Catalytic Asymmetric Synthesis of Chiral Halogenated Compounds and Their Stereospecific Transformation （キラルハロゲン化合物の触媒的不斉合成法および立体特異的変換反応の開発）

Approx. 800 words

Stereoselective synthesis of halogenated small organic molecules is highly important in synthetic organic chemistry because resulting chiral organohalides can be easily converted into various chiral molecules by S_N2 reaction. Furthermore, recently, not only fluorinated compounds but also chiral chlorinated and brominated compounds are expected as potent drugs because biologically active natural compounds often contain chlorine or bromine atoms on stereogenic carbon centers. Despite the extraordinary interest in practical synthetic methodologies towards chiral halogenated compounds, the methodology for the construction of chiral halogenated stereogenic carbon center have not established well. Introduction of halogen atoms onto tertiary carbon center have been mostly limited to halogenation of active methylene compounds such as β-keto esters. In this research, highly enatioselective synthesis of tertiary halides was carried out. Furthermore, synthetic utility of resulting tertiary halides was explored by subsequent stereospecific derivatizations.

First, enantioselective synthesis of tertiary fluoride was achieved by fluorination of α-branched aldehydes with a newly developed chiral primary amine catalyst. Enantioselective fluorination of aldehydes with chiral secondary amine catalyst is a highly useful method to introduce a fluorine atom on a stereogenic carbon center. Although this method yields α-fluoroaldehydes with high enantioselectivity when α-alkylaldehydes were employed as substrates, fluorination of α,α-dialkylaldehydes (α-branched aldehydes) with secondary or primary amine catalysts exabits unsatisfactory results. According to these situations, a new chiral primary amine catalyst was developed and used for enantioselective fluorination of α-branched aldehydes. As a result, various tertiary fluorides were synthesized in good yield with high enantioselectivity (up to 95% ee). Resulting tertiary fluorides were converted into chiral 3-fluoropropenes and fluorinated analogue of bioactive compounds such as Flurbiprofen. Furthermore, α-fluoroaldehydes were converted into α-hydrxyacetal *via* Carbon-Fluorine bond cleavage on a stereospecitic manner [up to >99% es, es = enantiospecificity which is calculated by (ee of product)/(ee of substrate)]. After the confirmation of stereochemistry, it was confirmed that this reaction proceeded *via* S_N2 type reaction.

Second, enantioselective synthesis of tertiary chloride was achieved by decarboxylative chlorination of β-keto carboxylic acids in the presence of chiral primary amine catalyst and

electrophilic chlorinating reagent. Although there is no asymmetric halogenation has been achieved, several enantioselective decarboxylative Carbon-Carbon bond formation reactions of β-oxo carboxylic acids have reported till date. According to these successful examples, β-oxo carboxylic acids can work as an enolate equivalent by decarboxylation of carboxylic acid moiety. Herein, enantioselective halogenation was developed by using β-keto carboxylic acids with chiral amine catalyst and electrophilic chlorinating reagent. This reaction afforded various secondary and tertiary α-chloroketones with high enantioselectivity (up to 98% ee). Furthermore, resulting tertiary chloroketone was subjected to S_N2 reactions and this reaction afforded corresponding α-surfenyl or α-azide ketones without loss of enantiopurity (up to >99% es). The absolute configuration of the substrate and the product were determined by X-ray crystallography and it was confirmed that inversion of stereochemistry surely occurred. Decarboxylative chlorination was also applicable to asymmetric synthesis of α-chloro-α-fluoroketones by asymmetric decarboxylative chlorination of α-fluoro-β-keto carboxylic acids in the presence of chiral amine catalyst. This reaction afforded some products with high enantioselectivity (up to 90% ee). However, moderate to low enantioselectivity was observed with indanone-derived and acyclic substrates. Then, resulting α-chloro-α-fluoroketone was subjected to S_N2 reaction and it yielded the corresponding chiral α-functionalized-α-fluoroketones with almost retained enantiopurity (up to >99% es).

Finally, asymmetric synthesis of chiral fluoroalkenes was achieved by S_N2' reaction of chiral 3-chloro-3-fluropropenes. Fluoroalkene is an important substructure especially in medicinally-relevant chemistry because fluoroalkenes sometime act as peptide bioisosters. Therefore, development of efficient methods for the preparation of fluoroalkenes have attracted attention in recent years. Paquin's research group recently reported an efficient synthetic method of chiral fluoroalkenes by S_N2' reaction of 3,3-difluoropropene. On the other hand, our research group previously reported enantioselective synthesis of α-chloro-α-fluoroaldehydes by organocatalytic enantioselective fluorination of α-chloroaldehydes. Inspired by these works, novel synthetic route for chiral fluoroalkenes was designed by using S_N2' reaction of 3-chloro-3-fluoropropens which are prepared by Horner-Wadsworth-Emmons reaction of chiral α-chloro-α-fluoroaldehydes. After screening of reaction conditions, it was revealed that S_N2' reaction afforded the desired chiral fluroalkene in good yield with almost retained enantiopurity (up to >99% es).