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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（ 理学 ）　氏名　SUN KAI

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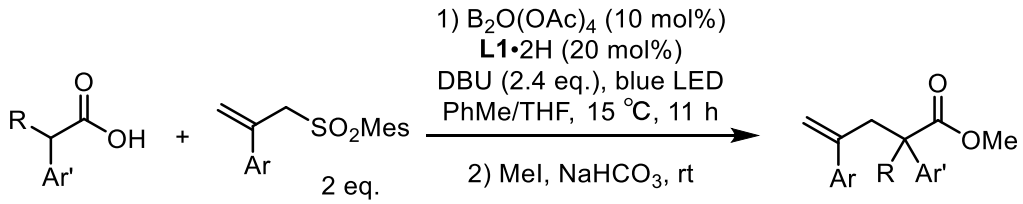
Direct Functionalization of Carboxylic Acids by Boron Catalysis
（ホウ素触媒によるカルボン酸直接修飾反応の開発）

Carboxylic acids exist ubiquitously in natural environment and living bodies. They play important roles in keeping the balance of the world and life. Inspired by naturally generated bioactive molecules, people synthesized pharmaceuticals based on carboxylic acids. They form a category of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs). Functionalization of carboxylic acids can provide us an opportunity to modify them for increasing their bioactivities.

Among functionalization of carboxylic acids, the method of boron catalyzed direct functionalization of carboxylic acid is highlighted because of its numerous advantages. Further development of this method can bring us new transformations and better utilization of carboxylic acids, as well as solve the problem yet unanswered.

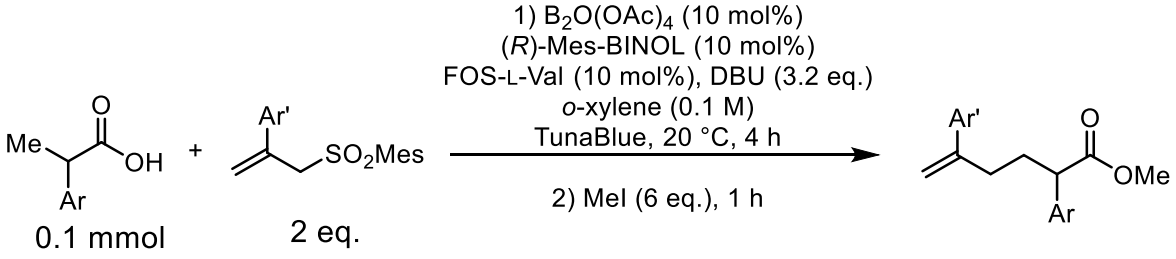
Light-driven α-allylation of carboxylic acids

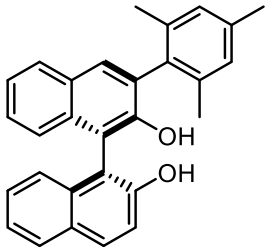
Although nucleophilic α-alkylation had been well known, those reactions require more than two equivalents of very strong base to deprotonate α-proton which has limited the scope. Boron catalysis for α-functionalization of carboxylic acid has been proved to promote the reaction under milder conditions. Meanwhile all the developed reactions are classified as polar reactions. Hence, I conceived that extension of the catalysis to radical reactions may allow distinct transformations. A single-electron transfer (SET) process between a boron enolate and a sulfone was conceived and tested. As a result, blue-light-driven α-allylation of carboxylic acid with allyl sulfone was developed successfully. Sterically demanding quaternary α-carbon was constructed by this transformation. Mechanistic investigation through a variety of experiments indicate that the reaction proceeds in a radical manner.



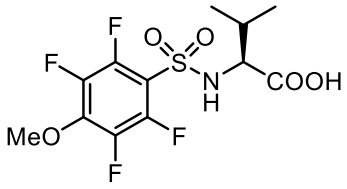
Light-driven β-allylation of carboxylic acids

β-Alkylation of carbonyl compounds are typically difficult to achieve and the most of them require specially designed substrates. The approach that can be applied for easily available substrates remains to be explored. I envisioned that a radical cation intermediate, generated by SET of the boron enolate to the allylsulfone, may allow radical transposition by deprotonation of β-proton to yield β-radical. Subsequent radical-radical coupling would accomplish the β-allylation. Following this idea, a visible-light-induced boron-catalyzed direct β-allylation of carboxylic acids has been developed by using two different ligands simultaneously.





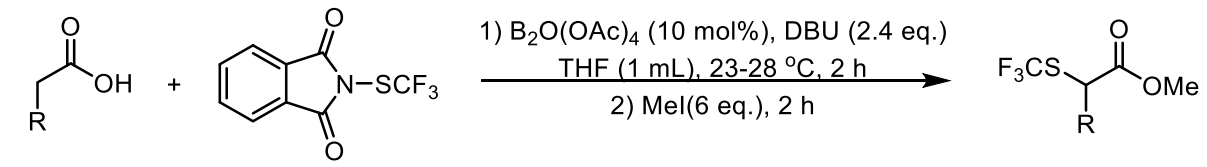
(*R*)-Mes-BINOL



FOS-L-Val

α-Trifluoromethylthiolation of carboxylic acids

Fluorine atom has the highest electronegativity, small van der Waals radius and high lipophilicity. Hence installation of fluorine atom into bioactive molecules has been an attractive method in drug development. In this context, SCF_3 is one of the most attractive among F containing functional groups. It has a Hansch parameter value of 1.44, bestowing high lipophilicity. The progress of installation of this functional group to the molecules has been witnessed in past decades. Some molecules were proved to have great value, such as vanilliprole or cefazaflur. Encouraged by those value-added molecules, a direct α-trifluoromethylthiolation of carboxylic acids by boron catalysis has been developed. Catalytically generated boronenediolates react with an electrophilic SCF_3 reagent, *N*-SCF_3-phtalimide, furnishing the desired product. This method is applicable to various bioactive carboxylic acids. Suitable models for substrate classification or yield prediction were built with data science analyses.



In summary, three direct functionalizations of carboxylic acids are described in this thesis. They feature different types of reaction and methodology while all of them involve a crucial step of carboxylic acid activation by boron catalyst. They are promising to be applied in the synthesis of more value-added compounds. In addition, they can be the fundament of further research in the future.