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学位の種類 博士 (ナノメディシン科学)

学位記番号 博第1187号

学位授与の日付 2020年12月16日

学位授与の条件 学位規則第4条第1項該当 課程博士

学位論文題目 Development of Novel Methodologies for Synthetic Transformation of Fluorine-containing Compounds  
(含フッ素化合物を合成変換するための新手法の開発)

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## 論文内容の要旨

In the last few decades, an interest in fluorine chemistry in pharmaceuticals and agrochemicals has significantly bloomed mainly due to discovering the unusual or even extreme physical and chemical properties exhibited by organofluorine compounds. Notably, the biological characteristics, including stability, lipophilicity, and bioavailability, are dramatically altered by fluorine incorporation into the parent molecules. These miraculous phenomena mainly root in the strongest electronegativity of the fluorine atom. However, developing methodologies to synthesize complex organofluorine compounds remains crucial. In this thesis, we described our contribution to developing facile protocols to fulfill the transformation of fluorine-containing molecules under mild conditions.

In chapter 1, we disclosed Pd-catalyzed decarboxylative cyclization of 4-CF<sub>3</sub>-4-vinyl benzoxazinanes with sulfur ylides to deliver biologically attractive CF<sub>3</sub>-containing 1,2-dihydroquinolines via zwitterionic CF<sub>3</sub>-Pd- $\pi$ -allyl intermediates. A mechanistic study shows that the CF<sub>3</sub> group plays a significant role in obtaining the corresponding dihydroquinolines via a rare C<sub>3</sub>-terminal attack of the zwitterionic  $\pi$ -allyl intermediate. On the other hand, the CH<sub>3</sub>-substituted analogs afford different products that should proceed via another rare C<sub>2</sub>-attack of the zwitterionic-

$\pi$ -allyl intermediate.

In chapter 2, we developed a Cu-catalyzed annulation reaction of 4-CF<sub>3</sub>-4-propargyl-benzoxazinones with sulfur ylides that delivers 3-CF<sub>3</sub> indoles in good to high yield via an unexpected  $\alpha$ -attack at the Cu-allenylidene intermediates. In contrast, when the 4-CH<sub>3</sub>-variants were used instead of 4-CF<sub>3</sub>-4-propargyl-benzoxazinones, very different, 3-CH<sub>3</sub>-3-propargyl-indolines having a stereogenic carbon center were obtained with high enantioselectivity via Cu-catalyzed decarboxylative [4+1] annulation, which proceeds predominantly through a  $\gamma$ -attack at the Cu-allenylidene intermediates. Control over the  $\alpha/\gamma$ -attack at the Cu-allenylidene intermediates by the same interceptors was achieved for the first time.

In chapter 3, the synthesis of unstable aryl difluorovinyl pinacolboronates was achieved by the dehydrofluorination of  $\alpha$ -trifluoromethyl arylmethyl pinacolboronates with LDA. These aryl difluorovinyl pinacolboronates can be used for Suzuki-Miyaura coupling with various aryl halides under Pd-catalysis to furnish diaryl gem-difluorovinyl compounds.

In chapter 4, we developed a base-promoted defluoroetherification of unactivated fluoroarenes with the efficient alkoxy source alkoxyboronic acid pinacol esters (ROBpin) via C(<sub>sp</sub><sup>2</sup>)-F bond cleavage, which surely obviates the need for transition metals or specific cost ligands. The C-F bond cleavage of fluoroarenes is, in general, significantly more challenging due to their high bond dissociation energy. This base-mediated defluoroetherification of aryl and heteroaryl fluorides with alkoxy source under transition-metal-free conditions could selectively forge C-O bonds and accomplished a wide variety of aryl ethers efficiently and safely in high yield. Therefore, compared to the previously reported etherification method of aryl halides, the simple synthetic nucleophiles, mild conditions, easy accessibility, and broad substrate scope advantages of this method successfully enables the access to the late-stage etherification of structurally complex aryl fluorides and natural bioactive alcohols, such as  $\beta$ -estradiol, calciferol, and tocopherol.

In chapter 5, we disclosed a nickel catalyzed difunctionalization of electron-neutral alkenes with fluoroarenes via cleavage of unactivated C-F bonds to form arylsilylated products, accompanied with good to excellent yields and exclusive regioselectivity. This protocol could be a breakthrough, provided easy access to the difunctionalized arylsilylated products with fluoroarenes and alkenes as easily accessible starting materials, and might be a useful pharmaceutical research tool.

In chapter 6, a summary of the thesis was described.

## 論文審査結果の要旨

In the last few decades, an interest in fluorine chemistry in pharmaceuticals and agrochemicals has significantly bloomed mainly due to discovering the unusual or even extreme physical and chemical properties exhibited by organofluorine compounds. Notably, the biological characteristics, including stability, lipophilicity, and bioavailability, are dramatically altered by fluorine incorporation into the parent molecules. These miraculous phenomena mainly root in the strongest electronegativity of the fluorine atom. However, developing methodologies to synthesize complex organofluorine compounds remains crucial. In this thesis, we described our contribution to developing facile protocols to fulfill the transformation of fluorine-containing molecules under mild conditions.

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以上のように、本論文では含フッ素化合物を合成するための新手法の開発に成功した。これらは、3編の有審査論文（うち、第1著者1編）としてまとめられている。よって、本論文は、学位論文として十分価値あるものと認められる。