Drug development, Organic electronic materials

Carbon–fluorine bond scission & reconstruction: new synthetic method for organofluorine compounds by insertion reaction of C1 unit into C–F bond

Department of Applied Chemistry, Graduate School of Engineering / Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI)

Associate Professor Yoshihiro Nishimoto Researchmap https://researchmap.jp/nishimoto123

Professor Makoto Yasuda Researchmap https://researchmap.jp/read0185253

Abstract

We have established the first synthetic method for fluorine compounds by insertion reaction of a C1 unit into a carbon–fluorine bond. This reaction is a new synthetic method for fluorine compounds, in which the innovative concept of *carbon-fluorine bond scission & reconstruction* is the key. Quantum chemical calculations revealed that the two functions of boron trifluoride, *scission & reconstruction carbon-fluorine bond*, are important. Boron trifluoride abstracts fluoride ions from alkyl fluorides (*scission of C-F bond*) and then returns fluoride ions to the intermediate (*reconstruction of C-F bond*) to complete the insertion reaction.

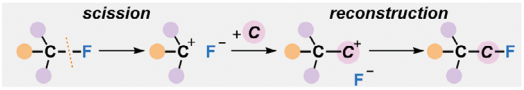
Background & Results

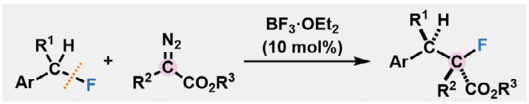
Fluorine is an important substituent in high value products that support modern society, such as pharmaceuticals, agrochemicals, lubricants, surfactants, and organic electronic materials. In pharmaceuticals and agrochemicals, the introduction of fluorine atom dramatically increases drug activity, including metabolic stability and the mimic effect for recognition by enzymes. For this reason, the development of new synthetic methods for organofluorine compounds is of great significance in modern society. However, conventional methods are limited to the introduction of fluorine substituents into organic compounds, which is problematic because it requires expensive, corrosive, and highly toxic fluorinating reagents. Therefore, the establishment of a new methodology for the synthesis of fluorinated compounds is an urgent issue. In this context, this research established the first method for the synthesis of fluorine compounds by insertion reaction of a C1 unit into a carbon–fluorine bond. This reaction is a new synthetic method for fluorine compounds, in which the innovative concept of *carbon-fluorine bond scission & reconstruction* is the key. The reaction of alkyl fluorides with diazo compounds in the presence of boron trifluoride catalyst yielded a product in which a C1 unit from the diazo compound was inserted into the carbon–fluorine bond of the alkyl fluoride. Quantum chemical calculations for the reaction mechanism revealed that the two functions of boron trifluoride, *carbon-fluorine bond scission & reconstruction*, are important. Boron trifluoride abstracts fluoride ions from alkyl fluorides (*scission of C-F bond*) and then returns fluoride ions to the intermediate (*reconstruction of C-F bond*) to complete the insertion reaction. By utilizing this reaction, we have also succeeded in synthesizing fluorine analogues of TRPC channel inhibitors.

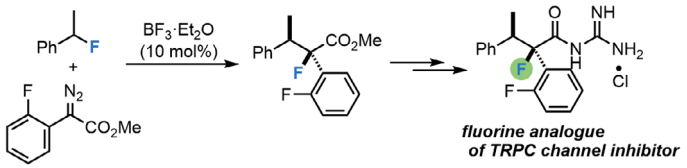
Significance of the research and Future perspective

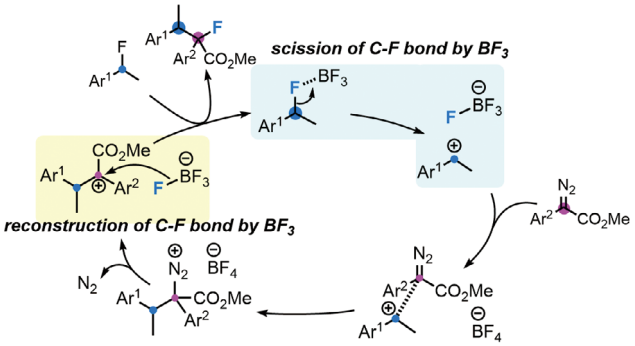
This innovative *scission & reconstruction of carbon-fluorine bond* method developed enables the construction of libraries for complex fluorine compounds, which is expected to create novel chemical spaces. Fluorine compounds are an important group of compounds that have practical applications in pharmaceuticals, agrochemicals, functional resins, organic electronic materials, etc. Therefore, this research will have a great impact on the development of next-generation pharmaceuticals and functional materials.

innovative concept of carbon–fluorine bond scission & reconstruction









Patent

Treatise Wang, Fei; Nishimoto, Yoshihiro; Yasuda, Makoto. Insertion of Diazo Esters into C–F Bonds toward Diastereoselective One-Carbon Elongation of Benzylic Fluorides: Unprecedented BF_3 Catalysis with C–F Bond Cleavage and Re-formation. Journal of the American Chemical Society. 2021, 143 (49), p. 20616–20621, doi: 10.1021/jacs.1c10517

URL

Keyword lewis acid, fluorine compound, C–F bond activation, insertion reaction