



HOKKAIDO UNIVERSITY

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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 游 震生

学位論文題名

Defluorinative Synthesis of Organophosphorus Compounds

(有機リン化合物の脱フッ素的合成法)

Organophosphorus compounds exist widely in pharmaceuticals, bioactive compounds, chemical materials, and ligands for catalysis. Although synthetic methodologies toward organophosphorus compounds have attracted the interest of organic chemists for decades, preparation of complex organophosphorus compounds still faces great challenges. On the other hand, aryl fluorides have been incorporated in a wide range of complex molecules due to its unique fluorine impact on pharmaceutical and chemical material performance. The C(sp²)-F bond is one of the strongest chemical bonds in nature, remaining stable during general chemical transformations. Hence, the late-stage derivation from abundant aryl fluoride building blocks could be a convenient approach to complex organophosphorus compounds. However, cleaving C-F bonds to construct significantly less stable C-P bonds is thermodynamically unfavorable. The current methods are largely relying on preactivation of aryl fluorides, which limits the practical application.

The author has developed a series of protocols for preparing various organophosphorus compounds from non-activated aryl fluorides through C(sp²)-F cleavage. Those protocols have been applied to the preparation of electroluminescent materials and *P*-chirogenic bisphosphine scaffolds, direct derivation of drug molecules and so on. Experimental and computational investigations were carried out to reveal the mechanistic insights of those reactions.

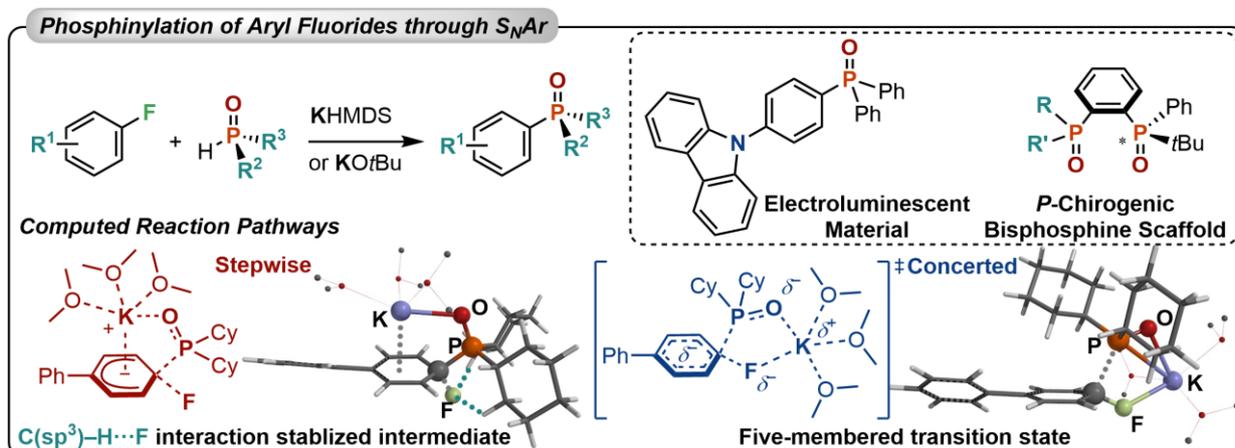
◆ Chapter 1: General Introduction

Chapter 1 discusses the synthetic methodologies for C-P bond construction through a manner of different mechanisms, focusing the role of organophosphorus compounds in those mechanism. Besides, C-F bond functionalization protocols are reviewed and discussed, and the author briefly summarizes the reported protocols for C-P bond formation through C-F cleavage. In the end of this chapter, the major contents of this thesis are introduced.

◆ Chapter 2: Phosphinylation of Aryl Fluorides through Nucleophilic Aromatic Substitution

Chapter 2 describes the author's finding that nucleophilic aromatic substitution (S_NAr) of non-activated or even electron-rich aryl fluorides occurred efficiently with potassium diorganophosphinites, which was *in situ* generated from bench-stable secondary phosphine oxides. This S_NAr reaction produced a variety of tertiary phosphine oxides, including a blue electroluminescent material obtained through the

reaction of an electron-rich *p*-fluoroaniline derivative, and enantioenriched *P*-chirogenic phosphorus scaffolds obtained through stereoretentive reaction with *P*-chirogenic secondary phosphine oxides. Quantum chemical calculations suggested unusual nucleophile-dependent features of this S_NAr reaction, showing both concerted and stepwise S_NAr reaction pathways are feasible. This is due to noncovalent interactions and ambiphilic nature of the potassium diorganophosphinite nucleophiles.



◆ Chapter 3: Nickel-Catalyzed Defluorophosphonylation of Aryl Fluorides

Chapter 3 describes a Ni-catalyzed cross-coupling reaction between aryl fluorides and dialkyl phosphonates $[HP(O)(OR)_2]$ in the presence of potassium *tert*-butoxide as a stoichiometric base. The reaction uses commercially available Ni complexes as catalyst precursors and requires no exogenous ligands. A wide range of aryl fluorides were successfully converted into the corresponding aryl phosphonates. Defluorophosphonylation of *N*-methyl paroxetine, an antidepressant, was successfully achieved. Interestingly, the reaction proceeds specifically with di-*sec*-alkyl phosphonates. Mechanistic studies suggested that the catalytic cycle involves turnover-limiting oxidative addition of the aryl fluoride to a Ni(0) complex coordinated with potassium dialkyl phosphites $[(RO)_2PO-K^+]$ through a cooperative action of a Ni(0)-K⁺ bimetallic system.

