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| 論文審査委員 | 主査　教授　山下　啓司<br>教授　柴田　哲男<br>教授　林　秀敏<br>（名古屋市立大学） |

# 論文内容の要旨


Organofluorine chemistry has been expanding rapidly to be a promising growth area, including material sciences, agrochemicals, and pharmaceuticals. The introduction of fluorine or fluorinated functional groups into organic molecules often causes significant changes in its physical, chemical, and biological properties of original compounds, which is suitable for biasing the properties of target molecules for their demand. Among a variety of fluorine-containing functional groups, I am interested in trifluoromethylthio ($SCF_3$), pentafluoro-$\lambda^6$-sulfanyl ($SF_5$), trifluoromethoxy ($OCF_3$), and fluorocarbonyl (acyl fluorides, COF) groups, due to their unique properties and reactivities. Although during the last few decades, there are many methods for the preparation of fluorine-containing organic compounds that have been developed, the methods for the preparation of the compounds having $SCF_3$, $SF_5$, $OCF_3$, and COF groups are still challenging. In this thesis, I have developed novel methodologies for the preparation of fluorinated compounds of $SCF_3$, $SF_5$, $OCF_3$, and COF groups.

In chapter 1, the synthesis of cyclic α-$SCF_3$-ketones and lactams via deacylative trifluoromethylthiolation of cyclic 1,3-diketones, lactams, and lactones has been achieved

using $CF_3$-DAST as an electrophilic trifluoromethylthiolation reagent. A wide variety of $SCF_3$-lactams was synthesized in one step. Moreover, we attempted to extend this method to the corresponding pentafluorophenylthiolation of 1,3-diketones and lactams using $C_6F_5$-DAST. Interestingly, lactam substrates gave the desired deacylated pentafluorophenylthiolation products by $C_6F_5$-DAST, while cyclic ketone substrates furnished an α-pentafluorophenylthiolated 1,3-diketones.

In chapter 2, a catalyst-free method on the formation of aryl-tetrafluoro-$\lambda^6$-sulfanyl chloride ($SF_4Cl$) from diaryl disulfide compounds by using trichloroisocyanuric acid (TCCA) and potassium fluoride (KF) under the mild condition as described. The aryl-$SF_4Cl$ is a precursor of aryl-$SF_5$, but the method for the preparation of aryl-$SF_4Cl$ is limited. Our new method has broad applicability for the synthesis of aryl-$SF_4Cl$, and results proceeded well with high yields in the absence of catalysts. We also provided two-step synthesis access to complex $SF_5$-substituted (hetero)aromatics and aryl tetrafluoro-$\lambda^6$-sulfanyl alkenes. The preparation of meta- and para-$SF_4Cl$-substituted pyridines in the presence of TCCA was achieved for the first time.

In chapter 3, we disclose an enantioselective benzylation reaction of α-$OCF_3$-indanones afforded α-benzyl-α-$OCF_3$-indanones with a tetrasubstituted stereogenic carbon center in excellent yield with moderate enantioselectivity under chiral phase-transfer catalysis. The enantioselective allylation reaction of α-$OCF_3$-indanones was also achieved under the same conditions to give the allylation products in moderate yield with good enantioselectivity. Cinchona alkaloid-based chiral phase transfer catalysts were observed to be helpful for this reaction, and two enantiomers of α-benzyl-α-$OCF_3$-indanones and α-allyl-α-$OCF_3$-indanones were accessed by using cinchonidine and cinchonine-derived catalysts.

In chapter 4, we have developed a novel, mild, and efficient method that proceeds for the synthesis of acyl fluorides (R-COF) by Pd-catalyzed cross-coupling reaction of structurally different aryl, alkenyl or heteroaryl iodides using 2-(difluoromethoxy)-5-nitropyridine. This protocol can be a powerful alternative to the existing methodologies for the synthesis of R-COF, which is a crucial intermediate in the process of pharmaceutical synthesis. This system is suitable for the late-stage direct fluorocarbonylation of a variety of substrates containing several natural products and bioactive derivatives molecules. The reaction mechanism was investigated with the assistant of $^{19}F$ NMR and LC-MS analysis. We also showed that acyl fluorides were used as a useful intermediate in a wide range of subsequent transformations.

In chapter 5, the summary of the thesis is described.

# 論文審査結果の要旨

Organofluorine chemistry has been expanding rapidly to be a promising growth area, including material sciences, agrochemicals, and pharmaceuticals. The introduction of fluorine or fluorinated functional groups into organic molecules often causes significant changes in its physical, chemical, and biological properties of original compounds, which is suitable for biasing the properties of target molecules for their demand. Among a variety of fluorine-containing functional groups, I am interested in trifluoromethylthio ($SCF_3$), pentafluoro-$\lambda^6$-sulfanyl ($SF_5$), trifluoromethoxy ($OCF_3$), and fluorocarbonyl (acyl fluorides, COF) groups, due to their unique properties and reactivities. Although during the last few decades, there are many methods for the preparation of fluorine-containing organic compounds that have been developed, the methods for the preparation of the compounds having $SCF_3$, $SF_5$, $OCF_3$, and COF groups are still challenging. In this thesis, I have developed novel methodologies for the preparation of fluorinated compounds of $SCF_3$, $SF_5$, $OCF_3$, and COF groups.

In chapter 1, the synthesis of cyclic α-$SCF_3$-ketones and lactams via deacylative trifluoromethylthiolation of cyclic 1,3-diketones, lactams, and lactones has been achieved using $CF_3$-DAST as an electrophilic trifluoromethylthiolation reagent. A wide variety of $SCF_3$-lactams was synthesized in one step. Moreover, we attempted to extend this method to the corresponding pentafluorophenylthiolation of 1,3-diketones and lactams using $C_6F_5$-DAST. Interestingly, lactam substrates gave the desired deacylated pentafluorophenylthiolation products by $C_6F_5$-DAST, while cyclic ketone substrates furnished an α-pentafluorophenylthiolated 1,3-diketones.

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In chapter 3, we disclose an enantioselective benzylation reaction of α-$OCF_3$-indanones afforded α-benzyl-α-$OCF_3$-indanones with a tetrasubstituted stereogenic carbon center in excellent yield with moderate enantioselectivity under chiral phase-transfer catalysis. The enantioselective allylation reaction of α-$OCF_3$-indanones was also achieved under the same conditions to give the allylation products in moderate yield with good enantioselectivity. Cinchona alkaloid-based chiral phase transfer catalysts were observed to be helpful for this reaction, and two enantiomers of α-benzyl-α-$OCF_3$-indanones and α-allyl-α-$OCF_3$-indanones were accessed by using cinchonidine and cinchonine-derived catalysts.

In chapter 4, we have developed a novel, mild, and efficient method that proceeds for the synthesis of acyl fluorides (R-COF) by Pd-catalyzed cross-coupling reaction of structurally different aryl, alkenyl or heteroaryl iodides using 2-(difluoromethoxy)-5-nitropyridine. This protocol can be a powerful alternative to the existing methodologies for the synthesis of R-COF, which is a crucial intermediate in the process of pharmaceutical synthesis. This system is suitable for the late-stage direct fluorocarbonylation of a variety of substrates containing several natural products and bioactive derivatives molecules. The reaction mechanism was investigated with the assistant of $^{19}F$ NMR and LC-MS analysis. We also showed that acyl fluorides were used as a useful intermediate in a wide range of subsequent transformations.

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以上のように、本博士論文では，様々な含フッ素官能基を有する化合物の新合成手法の開発に成功した。これらの成果は，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。