Selective Syntheses of Difluoromethylene Compounds via Difluorocarbene Catalyses

Tatsuya Aono

February 2016
Selective Syntheses of Difluoromethylene Compounds
via Difluorocarbene Catalyses

Tatsuya Aono
Doctoral Program in Chemistry

Submitted to the Graduate School of
Pure and Applied Sciences
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in
Science

at the
University of Tsukuba
Contents

Chapter 1
General Introduction 1

Chapter 2
O-Selective Difluoromethylation of Amides with Free Difluorocarbene 20
2.1. Introduction 21
2.2. Synthesis of Difluoromethyl Imidates 24
2.3. Mechanistic Considerations on O-Selective Difluoromethylation of Amides 31
2.4. Conclusion 33
2.5. Experimental Section 34
2.6. Reference 39

Chapter 3
Regioselective Syntheses of gem-Difluorocyclopentanone Derivatives with Transition Metal Difluorocarbene Complexes 40
3.1. Introduction 40
3.2. Domino Difluorocyclopropanation/Ring Expansion with Nickel Difluorocarbene Complex 46
3.3. [4 + 1] Cycloaddition with Copper Difluorocarbene Complex 59
3.4. Conclusion 67
3.5. Experimental Section 68
3.6. Reference 105

Chapter 4
Conclusion 108

List of Publications 109

Acknowledgement 110
Chapter 1

1. General Introduction

Organofluorine compounds often exhibit unique properties and behaviors in comparison with nonfluorinated parent compounds, playing important roles as pharmaceuticals and agrochemicals. Because of the high bond dissociation energy of C–F bonds, organofluorine compounds are resistant to heat and chemicals, and stable to metabolism. In addition, organofluorine compounds have high lipophilicity. Water has a large Hildebrand’s solubility parameter δ (~48), while organic solvents such as toluene have medium δ values (~20).\(^1\) Having small δ values (~12), fluorous solvents are immiscible to water and organic solvents. The introduction of fluorine atom into molecules thus results in alternation of the behaviors of fluorinated molecules in vivo. Furthermore, being the smallest substituents next to hydrogen, fluorine has been recognized as a mimic of hydrogen.

Among organofluorine compounds, difluoromethylene compounds containing a -CHF\(_2\) group or a -CF\(_2\)- group have recently attracted particular attention. For example, “Primisulfuron-methyl” possessing two difluoromethyloxy groups acts as herbicides (Figure 1).\(^{2a}\) Difluorocyclopentanone derivatives 1 and 2 which a difluoromethylene moiety have antimalarial effect and anti-bronchitis effect, respectively.\(^{2b,c}\) In spite of their utility, synthetic methods for the preparation of difluoromethylene compounds still remains to be underdeveloped.

![Primisulfuron-methyl (herbicides)](image1)

![1 (antimalarial effect)](image2)

![2 (anti-bronchitis effect)](image3)

Figure 1

The synthetic methods of difluoromethylene compounds reported to date can be classified into two categories: introduction of (i) two fluorine substituents and (ii) a difluoromethylene moiety.

Concerning the introduction of fluorine substituents both electrophilic and nucleophilic fluorinating agents have been used.\(^3\) For example, treatment of diketone 3 with xenon difluoride gives α,α-difluoroketone 4 in 43% yield (eq. 1).\(^4\) Treatment of ketone 6 with N-F-sultam 5 in the presence of potassium bis(trimethylsilyl)amide (KHMDS) affords α,α-difluoroketone 7 in 64%
yield (eq. 2). In these reactions, electrophilic fluorine was attacked by nucleophiles (enols or enolates). On the other hand, by using N,N-diethylaminosulfur trifluoride (DAST), aldehyde 8 is transformed into difluoromethyl compound 9 in 80% yield (eq. 3). Dithioacetal 10 reacts with tetrabutylammonium dihydrogen trifluoride in the presence of N-iodosuccinimide (NIS) to give 11 in 82% yield (eq. 4). These reactions proceed via nucleophilic attack of fluoride ion. Both of these methods for fluorine introduction, (i) and (ii) require expensive reagents and more importantly, construction of the corresponding carbon skeleton is required prior to fluorination.

(i)-1. Electrophilic Introduction of Fluorine Substituents

\[
\begin{align*}
\ce{\text{O=O}} & \xrightarrow{\text{XeF}_2 (2.2 \text{ eq})} \ce{\text{O}} & \xrightarrow{\text{HF (0.25–0.4 eq)}} & \ce{\text{O}} \\
\text{3} & \xrightarrow{\text{CH}_2\text{Cl}_2, 25 \degree \text{C, 1 h}} & \ce{\text{O}} & \xrightarrow{\text{F}} & \ce{\text{O}} \\
& & \text{4 43%} & \text{4} & \text{43%}
\end{align*}
\]

\[
\begin{align*}
\ce{\text{O}} & \xrightarrow{\text{N,S-F}} 5 (3.6 \text{ eq}) \\
\text{6} & \xrightarrow{\text{KN(SiMe}_3)_2, \text{KHMDS, 3.6 eq)}} & \ce{\text{O}} & \xrightarrow{\text{Ph}} & \ce{\text{O}} \\
& \xrightarrow{\text{THF, -78 °C, 40 min then RT}} & \text{7 64%} & \text{7} & \text{64%}
\end{align*}
\]

(i)-2. Nucleophilic Introduction of Fluorine Substituents

\[
\begin{align*}
\ce{\text{O}} & \xrightarrow{\text{N-S-F}} \text{(DAST, 1.0 eq)} \\
\text{8} & \xrightarrow{\text{CCl}_3\text{F, 25 °C, 30 min}} & \ce{\text{O}} & \xrightarrow{\text{F}} & \ce{\text{O}} \\
& & \text{9 80%} & \text{9} & \text{80%}
\end{align*}
\]

\[
\begin{align*}
\ce{\text{O}} & \xrightarrow{\text{N-I}} \text{(NIS)} \\
\text{10} & \xrightarrow{\text{(n-Bu)}_4\text{NH}_2\text{F}_3 (3.0 eq)}} \ce{\text{O}} & \xrightarrow{\text{NIS (2.2 eq)}} & \ce{\text{O}} \\
\text{MeO} & \xrightarrow{\text{CH}_2\text{Cl}_2, -78 °C to RT, 2 h}} & \text{11 82%} & \text{11} & \text{82%}
\end{align*}
\]
Introduction of a difluoromethylene moiety using fluorinated building blocks is convenient, since there are many kinds of difluorinated building blocks of various carbon numbers. The simplest example, difluorocarbene, generated from chlorodifluoromethane and sodium hydride, is a representative one-carbon building block. Difluorocarbene reacts with phenoxide to afford difluoromethoxybenzene in 65% yield (eq. 5).[8] Sulfonium salt 12 serves as difluoromethyl cation equivalent and reacts with sulfonate 13 to afford difluoromethyl ester 14 in 77% yield (eq. 6).[9] Acetylide, prepared by deprotonation of phenylacetylene with butyllithium, reacts with dibromodifluoromethane to give bromodifluoromethylacetylene 15 in 77% yield (eq. 7).[10] Treatment of 1-octene with dibromodifluoromethane in the presence of copper(I) chloride (1 mol%) affords radical addition product 16 in 77% yield (eq. 8).[11] On treatment with peroxide 17 toluene was chlorodifluoromethylated to give 18 in 91% yield via chlorodifluoromethyl radical (eq. 9).[12] Recently, cross coupling reactions have been employed for installing difluoromethylene units. For instance, treatment of iodoarene 19 with trimethyl(difluoromethyl)silane in the presence of a stoichiometric amount of copper(I) iodide affords difluoromethylarene 20 in 90% yield (eq. 10).[13] In a similar manner, difluoromethylation of iodoarene 21 is effected with tributyl(difluoromethyl)tin in the presence of copper(I) iodide (1.3 eq) to afford difluoromethylarene 22 in 61% yield (eq. 11).[14] 2-Phenylbenzaldehyde undergoes a Wittig-type difluoromethylenation reaction with dibromodifluoromethane and tris(dimethylamino)phosphine to give 1,1-difluoroalkene 23 in 87% yield (eq. 12).[15] Difluoroenolate 25, generated from acylsilane 24 and trimethyl(trifluoromethyl)silane via Brook rearrangement, undergoes Michael reaction with methyl vinyl ketone with in the presence of 3 mol% of ytterbium(III) catalyst to afford difluoroketone 26 in 67% yield (eq. 13).[16] In addition to these efforts, versatile reagents have been developed for difluoromethylation. For example, deprotonation of difluoromethylphosphonate 27 with lithium diisopropylamine (LDA) generates cabanion 28, which reacts with aldehyde 29 to give 1,1-difluoroalkene 30 in 67% yield (eq. 14a).[17a] Carbanion 28 also reacts with triflate 31 to give alkylated difluoromethylphosphonate 32 in 56% yield via nucleophilic substitution (eq. 14b).[17b] Organoselen compound 33, prepared from 28 and a selenyl chloride (eq. 14c), reacts with alkene 34 in the presence of 2,2’-azobis(isobutyronitrile) (AIBN) and tributyltin hydride. Difluorophosphonate 35 is obtained through radical process in 82% yield (eq. 14d).[17c]

(ii)-1. Introduction of Difluoromethylene Moiety with One-Carbon Building Blocks

\[
\text{OH} \quad \xrightarrow{\text{HCF}_2\text{Cl (excess)}} \quad \xrightarrow{\text{NaOH (5 eq)}} \quad \xrightarrow{\text{Dioxane, 70 °C, 70 min}} \quad \text{OCHF}_2
\]

(5) 65%
1) n-BuLi (1.05 eq) 
THF, −78 °C, 30 min 
2) CF₂Br₂ (1.50 eq) 
THF, −78 °C, 2 h 

16 77%
Two-carbon building blocks are also adopted for difluoromethylene introduction. For example, Barton ester 36 reacts with dichlorodifluoroethene under irradiation by a 500 W tungsten lamp to afford dichlorodifluoroethane 37 in 40% yield via photo-induced radical process (eq. 15).\[18\] Hydrolysis of 37 reacts with silver(I) nitrate affords difluorocarboxylic acid 38 in 68% yield. On treatment with methyl difluoroiodoacetate in the presence of copper metal, ester 39 gives difluoroiodoester 40 in 88% yield via addition of difluoroacetate radical (eq. 16).\[19\] Nucleophic methods are available for the introduction of difluorinated two-carbon units. Treatment of aldehyde 41 with ethyl bromodifluoroacetate in the presence of zinc metal affords alcohol 42 in 57% yield (eq. 17).\[20\] Cross coupling reaction with ethyl difluoro(trimethylsilyl)acetate 43 allows difluoromethylation. Treatment of iodoarene 44 with 43 in the presence of a stoichiometric amount of copper(I) iodide affords acetate 45 (eq. 18),\[21\] where hydrolysis followed by decarboxylation leads to difluoromethylarene 46 in 84% yield. Our group has already developed a wide variety of difluorinated C2 building blocks with sp$^2$ system. 2,2,2-Trifluoroethyl tosylate 47 is successively treated with LDA and trialkylborane to generate 2,2-difluorovinylborane 48 via alkyl group
migration. Protonolysis of 48 with acetic acid affords 1,1-difluoroalkene 49 in 81% yield (eq. 19a).[22a] On treatment with bromine and sodium methoxide, difluoroborane 48 gives 1,1-difluoroalkene 50 in 65% yield via the second alkyl group migration (eq. 19b).[22b] Furthermore, oxidation of 48 with alkaline hydrogen peroxide affords (difluoromethyl)ketone 51 in 81% yield (eq. 19c).[22c] On treatment with trifluoriodoethene and LDA (2.0 eq) followed by treatment with ketone 52 and then acetic anhydride, affords difluoroalkene 53 in 85% yield (eq. 20).[23] Treatment of 53 with zinc metal affords the difluorovinylidenation product, 1,1-difluoroallene 54 in 96% yield. More recently, we have reported the Negishi cross coupling reaction of (difluorovinyl)zinc(II) 55 (eq. 21).[24]

(ii)-2. Introduction of Difluoromethylene Moiety with Two-Carbon Building Blocks

\[
\begin{align*}
\text{36} & \xrightarrow{\text{hν, CH₃CN, 0 °C, 7 h}} \text{RCF}_2\text{CCl}_2\text{SPy} \rightarrow \text{37} \text{40\%} \\
\text{37} & \xrightarrow{\text{AgNO}_3 (4.0 \text{ eq})} \text{RCF}_2\text{CO}_2\text{H} \rightarrow \text{38} \text{68\%} \\
\text{39} & \xrightarrow{\text{Cu (0.3 \text{ eq})} \text{ICF}_2\text{CO}_2\text{Me (1.3 \text{ eq})}} \text{MeOCOF}_2\text{C} \xrightarrow{\text{DMSO, RT, 4 h}} \text{COOMe} \rightarrow \text{40} \text{88\%} \\
\text{40} & \xrightarrow{\text{BrCF}_2\text{CO}_2\text{Et (1.3 \text{ eq})} \text{Zn (1.1 \text{ eq})}} \text{OH} \rightarrow \text{42} \text{57\%} \\
\text{43} (1.2 \text{ eq}) & \xrightarrow{\text{Me}_3\text{SiCF}_2\text{CO}_2\text{Et, CuI (1.0 \text{ eq})} \text{KF (1.2 \text{ eq})}} \text{DMSO, 60 °C, 15 h} \rightarrow \text{45} \text{71\%} \\
\text{45} & \xrightarrow{1) \text{K}_2\text{CO}_3 (3.0 \text{ eq}) \text{MeOH-H}_2\text{O (1:1)} \text{RT, 2 h}} \text{2) K}_2\text{F (5.0 eq)} \text{DMF, 170 °C, 2 h} \rightarrow \text{46} \text{84\%}
\end{align*}
\]
For difluorinated building blocks with three or more carbons, some representative examples are shown below. Treatment of 3,3,3-trifluoro-1-propene with disilane 57 in the presence of fluoride ion (10 mol%) promotes S$_{N}$2'-type reaction to afford difluoroalkene 58 in 85% yield (eq. 22).\[25\] In our research group, trifluoropropenes have been also employed as building blocks. The S$_{N}$1'-type reaction of trifluoromethylalkene 59 with $p$-xylene is promoted by a stoichiometric amount of ethylaluminium(III) dichloride to afford difluoroalkene 60 in 84% yield (eq. 23).\[26\] Dienol silyl ether 61 undergoes Diels–Alder reaction with fluorinated vinylsulfone 62 to give alcohol 63 in 77% yield (eq. 24).\[27\] Treatment of $\alpha,\alpha$-difluorinated unsaturated ketone 64 (a four-carbon difluorinated building block) with zinc metal generates organozinc reagent 65, which reacts with benzaldehyde.
The resulting alkoxide 65 undergoes 6-endo-trig ring closure to give cyclic ether 66 in 46% yield (eq. 25).[28]

(ii)-3. Introduction of Difluoromethylene Moiety with Three- or More-Carbon Building Blocks

![Chemical structures and reactions](image)

The building block methods presented so far are mostly based on stoichiometric or substoichiometric reactions in terms of promoters. Thus, I envisioned catalytic introduction of a difluoromethylene moiety, which was directed toward synthesis of difluoromethylene compounds. My attention was particularly focused on the simple difluorinated building block, difluorocarbene, containing two categories of free difluorocarbene (: CF$_2$) and transition metal difluorocarbene complexes (L$_n$M=CF$_2$, Figure 2).

![Figure 2](image)
Free difluorocarbene has been widely used as a one-carbone difluorinated building block for synthesis of difluoromethylene compounds.\cite{29} Although many methods for generation of difluorocarbene have been reported, there remains drawbacks in its generation, as well as higher loadings. As mentioned above, treatment of phenol with excess amounts of chlorodifluoromethane in the presence of sodium hydroxide (5 eq) affords difluoromethoxybenzene in 65% yield (eq. 5).\cite{8} Sodium hydroxide deprotonates chlorodifluoromethane to generate chlorodifluoromethyl anion, which undergoes elimination of chloride ion to generate difluorocarbene. Difluorocarbene thus formed causes difluoromethylation of the peroxide. Thus, strongly basic conditions are required for this methods.

Internal alkene 67 reacts with excess amounts of sodium chlorodifluoroacetate (8.0 eq) at 160 °C (boiling point of diglyme) to give difluorocyclopropane 68 in 58% yield (eq. 26).\cite{27} Difluorocyclopropanation of alkene 69 proceeds with smaller amounts (2.0 eq) of sodium bromodifluoroacetate at 165 °C to afford 70 in 99% yield (eq. 27).\cite{31} The reaction of alkene 71 with hexafluoropropylene oxide (HFPO) proceeds at 170–200 °C to afford difluorocyclopropane 72 in 50% yield (eq. 28).\cite{32} High reaction temperature is necessary for these difluorocarbene generation.

Cyclohexene reacts with trimethyl(trifluoromethyl)tin(IV) in the presence of sodium iodide to afford difluorocyclopropane 73 in 89% yield (eq. 29).\cite{33} On treatment with phenyl(trifluoromethyl)mercury(II) in the presence of sodium iodide, cyclohexene also affords difluorocyclopropane 73 in 83% yield (eq. 30).\cite{34} Use of highly toxic reagents, tin or mercury compounds is the drawback to these methods.
We adopted trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate (TFDA) for a catalytic and selective generation of difluorocarbene. This reagent was originally developed by Dolbier,\textsuperscript{[35]} to generate difluorocarbene in the presence of a fluoride ion. It is proposed that the fluoride ion attacks the silicon atom of TFDA to promote its decomposition (eq. 31). Thus generated difluorocarbene is employed in difluorocyclopropanation of alkene 74 under nearly neutral conditions to give difluorocyclopropane 75 in 74% yield with regeneration of a fluoride ion (eq. 32).\textsuperscript{[35a]}

\[
\text{TFDA} \xrightarrow{\text{cat. } F^-} :\text{CF}_2 + \text{F}^- \quad \text{(31)}
\]

\[
\text{n-C}_6\text{H}_{13} \xrightarrow{\text{NaF (1.5 mol%)}} \text{NaI (2.3 eq), } \text{Benzene, reflux, } 19 \text{ h} \quad \begin{array}{c} \text{MeO} \\ \text{PhHgCF}_3 \text{(1.0 eq), } \text{Toluene, reflux, } 7 \text{ h} \end{array} \rightarrow \text{n-C}_6\text{H}_{13} \quad \text{75 74%} \quad \text{(32)}
\]

While being catalytic, the generation of difluorocarbene from TFDA is rapid, which might cause an overreaction. When alkylketone 76 was treated with TFDA and 10 mol% sodium fluoride, the formed enol difluoromethyl ether 77 further undergoes undesigned difluorocyclopropanation with the second molecule of difluorocarbene, affording difluorocyclopropane 78 in 70% yield (eq. 33).\textsuperscript{[36]}

\[
\text{MeO} \xrightarrow{\text{NaF (10 mol%)}} \text{TFDA (4.5 eq), } \text{Toluene, reflux, } 7 \text{ h} \rightarrow \text{MeO} \quad \text{(33)}
\]
To suppress the overreaction, the generation rate of difluorocarbene should be controlled. Thus, we adopted an organocatalyst, N-heterocyclic carbene (NHC), as an activator of TFDA. NHCs are stable and nucleophilic carbenes\[^{[37]}\] that act as nucleophilic catalysts in synthetic reactions.\[^{[38]}\] For instance, benzaldehyde reacts with trimethy(trifluoromethyl)silane in the presence of NHC 79 to afford alcohol 80 in 73\% yield (eq. 34).\[^{[39]}\] Treatment of benzaldehyde with trimethylsilylcyanide in the presence of NHC 81 affords silyl ether 82 in 91\% yield (eq. 35).\[^{[40]}\] In these reactions, NHCs nucleophilically activate the silicon reagents to promote the trifluoromethylation and cyanosilylation. Advantageously, reactivity of NHCs can be tuned by altering the central heterocyclic core and the substituents on the nitrogen. Therefore, NHCs are promising candidates for the catalyst that can regulate the generation rate of difluorocarbene from TFDA.

Our preliminary results have revealed that treatment of cyclic ketone 83 with TFDA in the presence of 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl, NHC precursor) and sodium carbonate affords difluoromethyl ether 85 in 74\% yield without formation of cyclopropane (eq. 36).\[^{[41]}\] This difluoromethylation of ketone 83 can be explained by the proposed mechanism shown in Scheme 1. 1,3-Dimesitylimidazolylidene (IMes), generated in situ from IMes·HCl and sodium carbonate, attacks the silicon atom of TFDA. Decomposition of TFDA generates the key intermediate, difluorocarbene accompanied by formation of CO\(_2\), SO\(_2\), and fluoride ion. Difluorocarbene thus generated electrophilically gives oxycarbenium salt 84, followed by H-shift, to afford the product 85. The formed silylimidazolium salt 86 undergoes desilylation with the released fluoride ion to regenerate free IMes.
In chapter 2, I describe the organocatalyzed syntheses of difluoromethyl imidates and difluoromethoxypyridines. Generation of free difluorocarbene from TFDA under nearly neutral conditions was accomplished by using organocatalysts, NHCs to realize the O-selective difluoromethylation of amides (eq. 37).

\[
\begin{align*}
\text{Mes} &= \text{2,4,6-trymethylphenyl} \\
\text{TFDA} &= \text{1,2,3-trifluoropropanoyl diethyl fluorosulfonate} \\
\text{[CF}_2\text{]} &= \text{difluorocarbene} \\
\end{align*}
\]

Scheme 1

Transition metal carbene complexes are established in organic synthesis as shown below. Treatment of alkene 87 with diazo compound 88 in the presence of 1 mol% rhodium(II) carboxylate affords cyclopropane 89 in 94% yield (cyclopropanation, eq. 38).[42] Diazo compound 91 reacts
with rhodium(II) dimer catalyst 90 to afford lactam 93 in 100% yield via rhodium(II) carbene complex 92 (C–H activation, eq. 39). Diene 95 undergoes ring-closing metathesis in the presence of ruthenium(II) carbene complex 94 to afford oxacyclohexene 96 in 90% yield (eq. 40). On the basis of these achievement, transition metal difluorocarbene complexes are promising intermediates for catalytic synthesis of difloromethylene compounds.

Despite of their potential utility in organic synthesis, two issues are remained unsolved. First, only a limited number of preparations of transition metal difluorocarbene complexes are known. Ruthenium(0) complex 97 reacts with bis(trifluoromethyl)cadmium(II) to afford ruthenium(0) difluorocarbene complex 99 via elimination of trifluoromethylcadmium(II) fluoride from ruthenium–cadmium binuclear complex 98 (eq. 41). Treatment of rhodium(I) fluoride 100 with trimethyl(trifluoromethyl)silane affords rhodium(I) difluorocarbene complex 102 in 85% yield via α-fluorine elimination from rhodium(I) complex 101 (eq. 42). Ruthenium(II) carbene complex 103 undergoes olefin metathesis with difluoroethene to afford ruthenium(II) difluorocarbene complex 104 in 86% yield (eq. 43). In addition to these difluorocarbene complexes, 14 complexes were isolated and 3 complexes were spectroscopically observed (Figure 3,4). However, preparations of difluorocarbene complexes which are suitable especially for catalytic systems are still severely limited.
Figure 3. Isolated Difluorocarbene Complexes

Figure 4. Observed Difluorocarbene Complexes
Second, only two applications of difluorocarbene complexes in organic synthesis are reported. In the presence of 5 mol% of ruthenium(II) difluorocarbene complex 104, cyclooctadiene undergoes ring-opening metathesis polymerization (ROMP) to produce polymer 105 in 92% yield (eq. 44), which the difluorocarbene complex is used as an initiator and not regenerated.\textsuperscript{[45c]} Cross olefin metathesis of tetrafluoroethene with vinyl ether 107 proceeds under catalysis by 10 mol% of ruthenium(II) carbene complex 106, which affords difluorovinyl ether 108 in 64% yield (eq. 45).\textsuperscript{[47]}

\[
\text{Mes}N\bigg(\begin{array}{c} - \text{NMes} \end{array}\bigg)\text{Cl}_2\text{PCy}_3 \quad \text{Cl} \quad \text{Ru} \quad \text{F}_2 \quad \text{Cl} \quad \text{F} \\
\text{104 (5 mol%)}
\]

\[
\text{CD}_2\text{Cl}_2 \text{--Et}_2\text{O}, 50 ^\circ \text{C}, 5 \text{ h} \quad \text{F}_2 \quad \text{C} \quad \begin{array}{c} \cdots \text{C} \end{array} \quad \begin{array}{c} \cdots \text{C} \end{array} \quad \text{F}_2 \quad \text{n} \quad \text{105 92%}
\]

\[
\text{Cl}_2\text{F} \quad \text{Cl} \quad \text{C}_6\text{H}_6, 60 ^\circ \text{C}, 1 \text{ h} \quad \text{F}_2 \quad \text{O} \quad \text{On-C}_{12}\text{H}_{25} \quad \text{107} \quad \text{(2.0 eq)}
\]

\[
\begin{array}{c} \text{F} \quad \text{F} \quad \text{F} \quad \text{F} \end{array} \quad \begin{array}{c} \text{O} \quad \text{On-C}_{12}\text{H}_{25} \end{array} \quad \text{107}
\]

\[
\text{Ar} \quad \text{N} \quad \text{Ar} \quad \text{Cl} \quad \text{Cl} \quad \text{O} \quad \text{Ar} \quad \text{NH} \quad \text{O} \quad \text{On-C}_{12}\text{H}_{25} \\
\text{106 (10 mol%)}
\]

\[
\text{C}_6\text{H}_6, 60 ^\circ \text{C}, 1 \text{ h} \quad \text{F}_2 \quad \text{O} \quad \text{On-C}_{12}\text{H}_{25} \quad \text{108 64%}
\]

In chapter 3, I describe the regioselective syntheses of \(\alpha,\alpha\)- and \(\beta,\beta\)-difluorinated cyclopentanone derivatives, depending on two unprecedented catalytic systems. Namely, a pincer-type Ni(II) catalyst in combination with TFDA afforded 5,5-difluorocyclopent-1-en-1-yl silyl ethers (Scheme 2a). A Cu(I)–phenanthroline catalyst in combination with sodium bromodifluoroacetate afforded 4,4-difluorocyclopent-1-en-1-yl silyl ethers (Scheme 2b). The generation of the key Ni(II)– and Cu(I)–difluorocarbene complexes were supported by the observation of their aminolysis products by HRMS analysis. These achievements will contribute to new chemistry of difluorocarbene complexes as well as synthesis of difluoromethylene compounds.
Scheme 2
References


Chapter 2

O-Selective Difluoromethylation of Amides with Free Difluorocarbene

2.1. Introduction

Difluoromethyl imidates are important structural motifs of agrochemicals (Fig. 5,6).\textsuperscript{[1]} For example, “Primisulfuron-methyl” and 2-difluoromethoxypyridine \textsuperscript{109}, each possessing a difluoromethyl imidate moiety in their substructures, function as herbicides.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{Figure_5_6.png}
\caption{Figure 5: Difluoromethyl imidate. Figure 6: Primisulfuron-methyl (herbicides) and \textsuperscript{109} (herbicides).}
\end{figure}

Difluoromethyl imidates have been synthesized by electrophilic \textit{O}-difluoromethylation of secondary amides \textsuperscript{110} with difluorocarbene (eq. 46).\textsuperscript{[2]} Namely, when secondary amide \textsuperscript{110} was treated with chlorodifluoromethane in the presence of quartenary ammonium salt under alkaline conditions (NaOH), \textit{O}-difluoromethylated product (difluoromethyl imidate, \textsuperscript{112}) was obtained in 19\% yield, accompanied by formation of the undesired \textit{N}-difluoromethylated product \textsuperscript{113} in 26\% yield. Difluoromethoxypyridines are also synthesized by difluoromethylation of pyridones with difluorocarbene. Treatment of 2-pyridone \textsuperscript{114} with sodium chlorodifluoroacetate affords \textit{O}-difluoromethylated product \textsuperscript{115} and \textit{N}-difluoromethylated product \textsuperscript{116} in 72\% and 8\% yields, respectively (eq. 47).\textsuperscript{[3]}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure_46.png}
\caption{Scheme 46: Synthesis of \textsuperscript{112} and \textsuperscript{113}.}
\end{figure}
Concerning synthesis of difluoromethyl imidates and difluoromethoxypyridines, there are two issues to address. The first one is formation of a regioisomeric mixture of O- and N-difluoromethylated products 112 and 113. The strongly basic conditions, required for the generation of difluorocarbene, cause deprotonation of the amides (eq. 46). The resulting, highly nucleophilic amidate ion 111 allows the formation of not only O-difluoromethylation product 112 but also N-difluoromethylation product 113. Second, the yields in difluoromethylation of amides are generally poor, which is presumably due to consumption of difluorocarbene by dimerization (eq. 48).

In order to achieve the high regioselectivity, we adopted the NHC-catalyzed generation of difluorocarbene, which might be conducted under nearly neutral conditions (eq. 36). In general, amide alkylation with alkyl halides under basic conditions proceeds preferentially on the nitrogen atom. Thus, treatment of amide 117 with methyl iodide in the presence of sodium hydride (1.5 eq) affords a mixture of methyl imidate 119 and N-methylamide 120 via amidate ion 118 in 43% and 53% yields, respectively (eq. 49). On the other hand, under neutral conditions amides undergo alkylation with alkyl halide on the oxygen atom, because the more electronegative oxygen center is more nucleophilic than the nitrogen center. For example, amide 121 reacts with methyl iodide in the presence of silver(I) oxide (2.0 eq) to afford methyl imidate 123 exclusively in 72% yield via iminium salt 122 (eq. 50). High selectivity would be also obtained by performing difluoromethylation of amides with difluorocarbene under nonbasic conditions.
Organocatalyzed generation of difluorocarbene would have another beneficial effect on the control of the generation rate of difluorocarbene, leading to the high yields of the difluoromethylated products by suppressing tetrafluoroethene formation. Reactivity of NHC can be tuned by altering the central heterocyclic core and the substituents on the nitrogen.\textsuperscript{[6]} For instance, 1,3-dimesitylimidazolylidene (SIMes) has a large Mayr’s nucleophilicity parameter $N$ (23.35), and 1,3-dimesitylimidazolylidene (IMes) has a medium $N$ value (21.72). Triazolylidene 126 has a smaller $N$ value (14.07, Scheme 3).\textsuperscript{[6b]} Nucleophilic benzylation of these NHCs with benzyl bromide 124 occurs to afford 125 in 86% (SIMes), 75% (IMes), and 60% (126) yields, respectively.\textsuperscript{[6c]} In these reactions, NHC with larger $N$ value affords the product in higher yield.

Choosing suitable the NHC-catalyzed generation of difluorocarbene, I expected that catalytic and $O$-selective difluoromethylation of secondary amides would be facilitated, leading to the selective synthesis of difluoromethyl imidates and difluoromethoxypyridines. Amides 128 reacted with TFDA (2.0 equive) in the presence of 5 mol\% of triazolium salt 127 and 20 mol\% of sodium carbonate to afford difluoromethyl imidates 129 selectively in good to high yield (eq. 51). The details of the synthetic method are described in the following sections.
NHR₂

R²'\text{O}N'R₂

Toluen, 80 °C, 15-30 min

TFDA (2.0 equiv)
Na₂CO₃ (20 mol%)

127 (5 mol%)

R²'OCHF₂

128

62-81%

129

PhN\text{Me}

PhN\text{Br}⁻
2.2. Synthesis of Difluoromethyl Imidates

2.2.1 Optimization of Reaction Conditions

Secondary amide 128a was selected as a model substrate for optimization of the desired O-difluoromethylation. A toluene solution of amide 128a was treated with TFDA (2 equiv) in the presence of a catalyst (5 mol%) for TFDA and heated to 80 °C. The yields of the produced difluoromethyl imidate 129a and the undesired N-difluoromethylated product 130a, if generated, were determined by $^{19}$F NMR spectroscopy. The results of the examination were summarized in Table 1.

Treatment of amide 128a with TFDA in the presence of SIMes·HCl and sodium carbonate (20 mol%) afforded the O-difluoromethylated product (difluoromethyl imidate) 129a in 56% yield (Entry 1). The reaction site (O vs. N) of the difluoromethylation was determined by $^{13}$C NMR and $^{19}$F NMR spectroscopies. The isolated product exhibited a $^{13}$C NMR signal at $\delta$ 157.3 and a $^{19}$F NMR signal at 71.0 (d, $J = 72$ Hz, 2F). Meanwhile, imidate 129b and amide 130b in literatures$^2$ exhibit signals in their $^{13}$C NMR spectra at $\delta$ 157.2 and $\delta$ 171.2 and in their $^{19}$F NMR spectra at $\delta$ 76.2 (d, $J = 72$ Hz, 2F) and $\delta$ 65.4 (d, $J = 61$ Hz, 2F), respectively (Figure 7). On the basis of the comparison of these data, I concluded that O-difluoromethylation, and not N-difluoromethylation, occurred to give imidate 129a. Thus, as expected, N-difluoromethylation was effectively suppressed.

The use of other imidazolium salts (IMes·HCl, IPr·HCl, and thiazolium salt 131) also resulted in formation of 129a in moderate yields (Entries 2–4). Among the salts examined, triazolium salt 127 was found to be most suitable to afford 80% yield of 129a (Entry 5). On the other hand, fluoride ion, the activator originally employed by Dolbier at 105–120 °C,$^7$ gave none of 129a at 80 °C (Entry 6). The use of bromide ion (sodium bromide or tetrabutylammonium bromide) afforded 129a only in low yields (0% and 46%, Entries 7,8, respectively).

Difluoromethyl imidate 129a was obtained as a single diastereomer, which was confirmed by NMR spectroscopy. This imidate 129a was probably thermodynamic stable E-isomer. In general, the E-isomer of imidate is stabler than the Z-isomer (Table 2),$^8$ because dipole moments of E-isomer (MeN=C(OMe)Me, 1.14 D) is lower than that of Z-isomer (2.40 D). Imidates having more bulky groups increase the ratio of Z-isomer for steric reasons. It is become activation barriers to E–Z interconversion of imidates are rather low 15.9–20.8 kcal/mol.
Figure 7

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base</th>
<th>129a / %a</th>
<th>130a / %a</th>
<th>Recovery of TFDA / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SIMes·HCl</td>
<td>Na₂CO₃</td>
<td>56</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>IMes·HCl</td>
<td>Na₂CO₃</td>
<td>53</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>IPr·HCl</td>
<td>Na₂CO₃</td>
<td>42</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>131</td>
<td>Na₂CO₃</td>
<td>5</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>127</td>
<td>Na₂CO₃</td>
<td>80 (80b)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>NaF</td>
<td>none</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>NaBr</td>
<td>none</td>
<td>0</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>(n-Bu)₂NBr</td>
<td>none</td>
<td>46</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

a: ¹⁹F NMR yield based on (CF₃)₂C(C₆H₄p-CH₃)₂. b: isolated yield.

\[ \delta_C = 157.3 \]
\[ \delta_F = 71.0 \text{ (d, } J = 72 \text{ Hz, } 2F) \]

\[ \delta_C = 157.2 \]
\[ \delta_F = 76.2 \text{ (d, } J = 72 \text{ Hz, } 2F) \]

\[ \delta_C = 171.2 \]
\[ \delta_F = 65.4 \text{ (d, } J = 61 \text{ Hz, } 2F) \]
It should be noted that the best catalyst depends on structures of substrates to some extent (Table 3). Namely, among SIMes·HCl, IMes·HCl and triazolium salt 127, SIMes·HCl was the most suitable for difluoromethylation of acetamide (R₁ = Me, Entries 2 and 3). Decomposition of TFDA was initiated by the nucleophilic attack of free NHC generated in situ. As illustrated in Section 2.1, Scheme 3, SIMes has the highest Mayer’s N value, suggesting most nucleophilic among the examined catalysts. It is likely that the nucleophilic SIMes realized the facile generation of difluorocarbene, leading to a high yield of the product. Undesired carbene dimerization did not matter because acetamide 128b is nucleophilic enough to capture difluorocarbene quickly. In contrast, aromatic amide 128a in Table 1 is less nucleophilic than 128b,d and less reactive to difluorocarbene. Triazolyldiene with low N value slowly generates difluorocarbene and prevents undesired loss of carbene by dimerization. Fortunately, triazolyldiene is found to be suitable for difluoromethylation of other aliphatic amides such as 128h. As a result of Table 1 and 3, I adopted triazolium salt 127 as a catalyst.

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>E/Z</th>
<th>ΔG⁺ / kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td>t-Bu</td>
<td>100:0</td>
<td>–</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>100:0</td>
<td>–</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>Me</td>
<td>69:31</td>
<td>19.8</td>
</tr>
<tr>
<td>Me</td>
<td>p-Tol</td>
<td>Me</td>
<td>69:31</td>
<td>20.4</td>
</tr>
<tr>
<td>t-Bu</td>
<td>Me</td>
<td>Me</td>
<td>87:13</td>
<td>15.9</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>Me</td>
<td>89:11</td>
<td>18.9</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>i-Pr</td>
<td>82:18</td>
<td>18.7</td>
</tr>
</tbody>
</table>

a: Activation barriers to E–Z interconversion of imidates.
Catalyst (5 mol%)  
$\text{Na}_2\text{CO}_3$ (20 mol%)  
TFDA (2.0 eq)  
Toluene, 80 °C, 15–30 min

Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 128</th>
<th>129 / %$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SIMes·HCl ($N = 23$)</td>
</tr>
<tr>
<td>1$^b$</td>
<td><img src="128a" alt="Image" /></td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td><img src="128b" alt="Image" /></td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td><img src="128d" alt="Image" /></td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td><img src="128h" alt="Image" /></td>
<td>51</td>
</tr>
</tbody>
</table>

$^a$ $^{19}$F NMR yield based on $(\text{CF}_3)_2\text{C(C}_6\text{H}_4\text{-CH}_3)_2$.  
$^b$ Table 1, Entries 1,2,5.
Effects of solvents were also examined, using 5 mol% of SIMes·HCl as a catalyst (Table 4). Conducting the reaction in toluene afforded 129a in 56% yield (Entry 1). Chlorinated and fluorinated solvents (Entries 2–6 and Entries 7,8, respectively) gave inferior results. Reaction in ethereal solvents (1,4-dioxane or diglyme) did not work well, either (Entries 9 and 10).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>129a / %&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Recovery of TFDA / %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Toluene</td>
<td>56</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>o-Dichlorobenzene</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>CCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>8</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>ClCH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>45</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;CHCH&lt;sub&gt;2&lt;/sub&gt;Cl</td>
<td>52</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;CHCHCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;F&lt;sub&gt;6&lt;/sub&gt;</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>1,4-Dioxane</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>Diglyme</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup>:<sup>19</sup>F NMR yield based on (CF<sub>3</sub>)<sub>2</sub>C(C<sub>6</sub>H<sub>4</sub>p-CH<sub>3</sub>)<sub>2</sub>.<sup>b</sup>: Table 1, Entry 1.

Bases for the in situ-generation of NHC catalyst were also optimized (Table 5). O-Difluoromethylation of amide 128a using sodium carbonate as a base afforded difluoromethyl imidate 129a in 52% yield (Entry 1). The use of potassium carbonate afforded 129a in slightly decreased yield (50%, Entry 2). Potassium phosphate and potassium tert-butoxide also afforded 129a in 48% and 49% yields, respectively (Entries 3 and 4). When the reaction was conducted with sodium hydride, 48% yield of 129a was obtained (Entry 5). Thus, Sodium carbonate was found to be a suitable base.
2.2. Substrate Scope of Difluoromethyl Imidates

Various difluoromethyl imidates were efficiently synthesized by the triazolium salt 127-based catalytic system (Table 6). Namely, not only benzoic acid-derived amides but also aliphatic acid-derived amides afforded the corresponding imidates in high yields as single diastereomers. Amides 128a–h gave imidates 129a–h in 62–84% isolated yields. Electron-donating and -withdrawing groups on the N-aryl groups did not affect the reaction (Entries 3–6). In these cases, partial decomposition of the products during purification by column chromatography was observed and 19F NMR analysis of crude mixtures suggested that 129c–f were formed in 69–83% yields. It must be emphasized that the undesired N-difluoromethylated products were not observed at all by 19F NMR analysis of the crude mixtures.
This difluoromethylation method was successfully applied to the synthesis of 2-difluoromethoxypyridines (eq. 52). When pyridone 132 was subjected to the TFDA/NHC system, the desired 133 was obtained in 60% yield, albeit accompanied by a 9% yield of N-difluoromethylated product 134. The sequential difluoromethylation–dehydrogenation process is also effective for difluoromethoxy heteroarene synthesis: 2-difluoromethoxyquinoline 136 was synthesized from dihydroquinolinone 135 in 92% yield in a one-pot operation (eq. 53).
2.3. Mechanistic Considerations on O-Selective Difluoromethylation of Amides

The O-difluoromethylation of secondary amide 128 can be explained by the proposed mechanism shown in Scheme 4. Triazolylidene 137, generated in situ from triazolium salt 127 and sodium carbonate, attacks the silicon atom of TFDA. Decomposition of TFDA generates the key intermediate, difluorocarbene, accompanied by formation of CO$_2$, SO$_2$, and a fluoride ion. Electrophilic difluorocarbene thus generated is attacked by the amide oxygen to give iminium 139, which in turn undergoes H-shift to afford the product 129 (eq. 54). The formed silyltriazolium salt 138 is desilylated with the released fluoride ion to regenerate free triazolylidene 137.

![Scheme 4](image)
To elucidate the $O$-selectivity observed under the nearly neutral conditions, theoretical calculations were performed (DFT, B3LYP/6-31G*) by using $N$-methylated amide. The neutral amide, in both $Z$ and $E$ forms ($Z$ form is more stable), has its HOMO orbital mainly on its $O$ atom (Figure 8). In addition, the $O$ atom of the neutral amide is more negatively charged (electrostatic, $Z$: $-0.49$; $E$: $-0.52$), compared to the $N$ atom ($Z$: $-0.38$; $E$: $-0.46$). These results can explain the $O$-selectivity under neutral conditions, which were realized by the organocatalytic system. It should be mentioned that HOMO of the corresponding amidate ion, in both $Z$ and $E$ forms, locates both on its $O$ and $N$ atoms. The charge values of the $O$ ($Z$: $-0.71$; $E$: $-0.71$) and the $N$ ($Z$: $-0.72$; $E$: $-0.78$) atoms of the amidate ion are similar. These results rationalize the formation of a mixture of $O$- and $N$-difluoromethylated products under strongly basic conditions as described in eq. 46.

Figure 8. HOMO Orbital and Electrostatic Charge Values (Oxygen and Nitrogen) of Amide

Figure 9. HOMO Orbital and Electrostatic Charge Values (Oxygen and Nitrogen) of Amidate
2.4. Conclusion

In summary, I have developed a synthetic method for difluoromethyl imidates and difluoromethoxypyridines. The NHC-catalyzed generation of difluorocarbene under nearly neutral conditions led to an efficient, regioselective $O$-difluoromethylation of secondary amides. Difluoromethoxypyridines were also synthesized in high yields by applying this method to lactams.
2.5. Experimental Section

2.5.1. General

$^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR spectra were recorded on a Bruker Avance 500. Chemical shift values are given in ppm relative to internal Me$_4$Si (for $^1$H NMR: $\delta = 0.00$ ppm), CDCl$_3$ (for $^{13}$C NMR: $\delta = 77.0$ ppm), and C$_6$F$_6$ (for $^{19}$F NMR: $\delta = 0.00$ ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV. Elemental analyses were carried out at the Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. All reactions were carried out under argon. Column chromatography was performed on silica gel (Kanto Chemical Co. Inc., Silica Gel 60). Toluene was purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. All solvents were distilled before used. Amides 128a–f, 135 were purchased and recrystallized before used. Amides 128g,h were prepared according to the literatures.$^{[9]}$ SIMes·HCl, IMes·HCl, IPr·HCl were prepared according to the literatures.$^{[10]}$ Triazolium salt 127 and thiazolium salt 131 were purchased and were not purification before use. Trimethylsilyl 2,2-difluoro-2-fluorosulfonylecetate (TFDA) was prepared according to the literature.$^{[7b]}$ 1,1,1,3,3,3-hexafluoro-2,2-di(p-tolyl)propane (internal standard for $^{19}$F NMR) was purchased from Tokyo Chemical Industry Co., Ltd.

2.5.2. Synthesis of difluoromethyl imidates and difluoromethoxypyridines

(A) Typical procedure for the synthesis of difluoromethyl imidates 129a–h, difluoromethoxypyridine 133.

To a toluene solution (1.5 mL) of 127 (3.4 mg, 0.0098 mmol), sodium carbonate (4.2 mg, 0.040 mmol), and N-phenylcyclohexanecarboxamide 128h (39 mg, 0.19 mmol) was added TFDA (75 mL, 0.38 mmol) at room temperature. The reaction mixture was stirred and heated at 80 °C for 20 min. After cooling the resulting mixture to room temperature, aquaus NaOH was added to quench the reaction. Extraction with dichloromethane and purification by column chromatography (SiO$_2$, hexane:AcOEt = 50:1, 0 °C) gave 129h (39 mg, 81% yield).

(B) Typical procedure for the synthesis of 2-difluoromethoxyquinoline (136)

To a toluene solution (2.0 mL) of 127 (6.9 mg, 0.0198 mmol), sodium carbonate (8.5 mg, 0.080 mmol), and dihydroquinolinone 135 (58 mg, 0.39 mmol) was added TFDA (154 mL, 0.78 mmol) at room temperature. The reaction mixture was stirred and heated at 80 °C for 20 min. After cooling the resulting mixture, 2,3-dichloro-5,6-dicyano-p-benzoquinon (DDQ, 87 mg, 0.38 mmol) was added and heated at 100 °C for 50 min. After cooling the resulting mixture to room
temperature, aquous NaOH was added to quench the reaction. Extraction with dichloromethane and purification by column chromatography (SiO₂, hexane:AcOEt = 50:1, 0 °C) gave 136 (70 mg, 92% yield).

(C) Spectral data of difluoromethyl imidates and difluoromethoxy pyridines.

Difluoromethyl N-phenyl-1-phenylmethanimidate (129a)

\[
\text{OCHF}_2 \\
\text{N} \\
\text{Ph} \\
\text{Ph}
\]

1H NMR (500 MHz, CDCl₃): δ = 7.48 (t, J = 72.8 Hz, 1H, broad), 7.38 (t, J = 7.5 Hz, 2H), 7.22–7.29 (m, 5H), 7.05 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 2H). 13C NMR (126 MHz, CDCl₃): δ = 153.4 (broad), 146.0, 131.2, 129.5, 129.2, 128.2, 123.9, 120.9, 113.6 (t, J = 255 Hz). 19FNMR (470 MHz, CDCl₃): δ = 70.8 (d, J = 73 Hz, 2F). IR (neat): ν = 2929, 1687, 1267, 1113, 912, 744 cm⁻¹. HRMS (70 eV, EI⁺): m/z calcd. for C₁₄H₁₁F₂NO ([M⁺]: 247.0809; Found: 247.0812.

Difluoromethyl N-phenylethan-1-imidate (129b)

\[
\text{OCHF}_2 \\
\text{N} \\
\text{Ph} \\
\text{Me}
\]

1H NMR (500 MHz, CDCl₃): δ = 7.37 (t, J = 72.1 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 2H), 1.94 (s, 3H). 13C NMR (126 MHz, CDCl₃): δ = 157.3, 146.3, 129.2, 124.1, 120.5, 113.0 (t, J = 255 Hz), 15.6. 19FNMR (470 MHz, CDCl₃): δ = 71.0 (d, J = 72 Hz, 2F). IR (neat): ν = 1701, 1238, 1105, 1086, 912 cm⁻¹. HRMS (70 eV, EI⁺): m/z calcd. for C₉H₉F₂NO ([M⁺]: 185.0652; found: 185.0653.

Difluoromethyl N-(p-tolyl)ethan-1-imidate (129c)

\[
\text{OCHF}_2 \\
\text{N} \\
\text{Me} \\
\text{Me}
\]

1H NMR (500 MHz, CDCl₃): δ = 7.36 (t, J = 72.3 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 6.68 (d, J = 7.8 Hz, 2H), 2.32 (s, 3H), 1.94 (s, 3H). 13C NMR (126 MHz, CDCl₃): δ = 157.2, 143.7, 133.6, 129.7, 120.4, 113.0 (t, J = 255 Hz), 20.8, 15.5. 19FNMR (470 MHz, CDCl₃): δ = 71.1 (d, J = 72 Hz, 2F). IR (neat): ν = 2925, 1699, 1508, 1230, 1065 cm⁻¹. HRMS (70 eV, EI⁺): m/z calcd. for C₁₀H₁₁F₂NO ([M⁺]: 199.0809; Found: 199.0808.
Difluoromethyl \( N-(p\text{-methoxyphenyl})\)ethan-1-imidate (129d)

\[
\begin{align*}
\text{OCHF}_2 & \quad \text{Me} \\
& \quad \text{OMe}
\end{align*}
\]

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta = 7.36 \, (t, \, J = 72.4 \text{ Hz}, \, 1H), \, 6.86 \, (d, \, J = 8.6 \text{ Hz}, \, 2H), \, 6.72 \, (d, \, J = 8.6 \text{ Hz}, \, 2H), \, 3.79 \, (s, \, 3H) \). \( ^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)): \( \delta = 157.4, \, 156.4, \, 139.5, \, 121.6, \, 114.4, \, 113.0 \, (t, \, J = 255 \text{ Hz}), \, 55.4, \, 15.5 \). \( ^{19}\text{FNMR} \) (470 MHz, CDCl\(_3\)): \( \delta = 70.6 \, (d, \, J = 72 \text{ Hz}, \, 2F) \). IR (neat): \( \nu \approx 2956, \, 1699, \, 1506, \, 1230, \, 1103 \text{ cm}^{-1} \). HRMS (70 eV, EI\(^+\)): \( m/z \) calcd. For C\(_{10}\)H\(_{11}\)F\(_2\)NO\(_2\) ([M]\(^+\)): 215.0758; found: 215.0760.

Difluoromethyl \( N-(p\text{-fluorophenyl})\)ethan-1-imidate (129e)

\[
\begin{align*}
\text{OCHF}_2 & \quad \text{Me} \\
& \quad \text{F}
\end{align*}
\]

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta = 7.34 \, (t, \, J = 72.1 \text{ Hz}, \, 1H), \, 7.02 \, (dd, \, J = 8.5 \text{ Hz}, \, 2H), \, 6.74 \, (dd, \, J = 4.0, \, 8.5 \text{ Hz}, \, 2H), \, 1.95 \, (s, \, 3H) \). \( ^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)): \( \delta = 159.7 \, (d, \, J = 242 \text{ Hz}), \, 157.9, \, 142.4 \, (d, \, J = 3 \text{ Hz}), \, 121.9, \, 115.4 \, (d, \, J = 23 \text{ Hz}), \, 112.9 \, (t, \, J = 255 \text{ Hz}), \, 15.6 \). \( ^{19}\text{FNMR} \) (470 MHz, CDCl\(_3\)): \( \delta = 70.5 \, (d, \, J = 72 \text{ Hz}, \, 2F), \, 42.0 \, (tt, \, J = 8.5, \, 4.0 \text{ Hz}, \, 1F) \). IR (neat): \( \nu \approx 1705, \, 1506, \, 1240, \, 1109, \, 914 \text{ cm}^{-1} \). HRMS (70 eV, EI\(^+\)): \( m/z \) calcd. for C\(_9\)H\(_8\)F\(_3\)NO ([M]\(^+\)): 203.0558; found: 203.0553.

Difluoromethyl \( N-(p\text{-chlorophenyl})\)ethanimidate (129f)

\[
\begin{align*}
\text{OCHF}_2 & \quad \text{Me} \\
& \quad \text{Cl}
\end{align*}
\]

\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta = 7.33 \, (t, \, J = 72.0 \text{ Hz}, \, 1H), \, 7.29 \, (d, \, J = 8.5 \text{ Hz}, \, 2H), \, 6.72 \, (d, \, J = 8.5 \text{ Hz}, \, 2H), \, 1.95 \, (s, \, 3H) \). \( ^{13}\text{C NMR} \) (126 MHz, CDCl\(_3\)): \( \delta = 157.8, \, 144.9, \, 129.6, \, 129.3, \, 121.9, \, 112.9 \, (t, \, J = 256 \text{ Hz}), \, 15.6 \). \( ^{19}\text{FNMR} \) (470 MHz, CDCl\(_3\)): \( \delta = 70.4 \, (d, \, J = 72 \text{ Hz}, \, 2F) \). IR (neat): \( \nu \approx 1703, \, 1240, \, 1136, \, 1088, \, 914 \text{ cm}^{-1} \). HRMS (70 eV, EI\(^+\)): \( m/z \) calcd. for C\(_9\)H\(_8\)ClF\(_2\)NO ([M]\(^+\)): 219.0262; found: 219.0260.
Difluoromethyl N-phenyl-2-methylpropan-1-imidate (129g)

\[
\begin{array}{c}
\text{Ph} \\
\text{OCHF}_2 \\
\text{N} \\
\end{array}
\]

\[^1\text{H} \text{NMR (500 MHz, CDCl}_3\): } \delta = 7.33 (t, J = 72.6 \text{ Hz, 1H}), 7.31 (t, J = 8.0 \text{ Hz, 2H}), 7.09 (t, J = 8.0 \text{ Hz, 1H}), 6.75 (d, J = 8.0 \text{ Hz, 2H}), 2.72 (\text{septet, } J = 6.5 \text{ Hz, 1H}), 1.14 (d, J = 6.5 \text{ Hz, 6H}). \]

\[^{13}\text{C NMR (126 MHz, CDCl}_3\): } \delta = 163.0, 146.2, 129.2, 123.8, 120.3, 113.4 (t, J = 254 \text{ Hz}), 28.6, 19.2. \]

\[^{19}\text{FNMR (470 MHz, CDCl}_3\): } \delta = 70.3 \text{ (d, } J = 73 \text{ Hz, 2F). IR (neat): } \nu = 2978, 1695, 1244, 1109, 912 \text{ cm}^{-1}. \]

\[\text{HRMS (70 eV, EI}^+)\): m/z calcd. for C\textsubscript{11}H\textsubscript{13}F\textsubscript{2}NO ([M]\textsuperscript{+}): 213.0965; Found: 213.0968. \]

Difluoromethyl N-phenyl-1-cyclohexylmethanimidate (129h)

\[
\begin{array}{c}
\text{Ph} \\
\text{OCHF}_2 \\
\text{N} \\
\end{array}
\]

\[^1\text{H} \text{NMR (500 MHz, CDCl}_3\): } \delta = 7.31 (t, J = 72.6 \text{ Hz, 1H}), 7.31 (t, J = 8.0 \text{ Hz, 2H}), 7.10 (t, J = 8.0 \text{ Hz, 1H}), 6.74 (d, J = 8.0 \text{ Hz, 2H}), 2.37–2.42 (m, 1H), 1.68–1.74 (m, 4H), 1.57–1.65 (m, 3H), 1.15–1.23 (m, 1H), 1.07–1.13 (m, 2H). \]

\[^{13}\text{C NMR (126 MHz, CDCl}_3\): } \delta = 162.2, 146.1, 129.2, 123.7, 120.4, 113.4 (t, J = 254 \text{ Hz}), 38.4, 29.0, 25.4, 25.2. \]

\[^{19}\text{FNMR (470 MHz, CDCl}_3\): } \delta = 70.5 \text{ (d, } J = 73 \text{ Hz, 2F). IR (neat): } \nu = 2935, 1697, 1238, 1124, 912 \text{ cm}^{-1}. \]

\[\text{HRMS (70 eV, EI}^+)\): m/z calcd. for C\textsubscript{14}H\textsubscript{17}F\textsubscript{2}NO ([M]\textsuperscript{+}): 253.1278; found: 253.1282. \]

2-Difluoromethoxypyridine (133)

\[
\begin{array}{c}
\text{OCHF}_2 \\
\text{N} \\
\end{array}
\]

\[^1\text{H} \text{NMR (500 MHz, CDCl}_3\): } \delta = 8.20 (dd, J = 5.0, 1.5 \text{ Hz, 1H}), 7.73 (t, J = 7.5 \text{ Hz, 1H}), 7.48 (t, J = 73.5 \text{ Hz, 1H}), 7.10 (ddd, J = 7.5, 5.0, 1.5 \text{ Hz, 1H}), 6.90 (d, J = 7.5 \text{ Hz, 1H}). \]

\[^{13}\text{C NMR (126 MHz, CDCl}_3\): } \delta = 159.1, 147.0, 140.0, 120.0, 114.0 (t, J = 255 \text{ Hz}), 111.5. \]

\[^{19}\text{FNMR (470 MHz, CDCl}_3\): } \delta = 72.8 \text{ (d, } J = 74 \text{ Hz, 2F). IR (neat): } \nu = 2925, 1261, 1219, 1099, 773 \text{ cm}^{-1}. \]

\[\text{HRMS (70 eV, EI}^+)\): m/z calcd. for C\textsubscript{6}H\textsubscript{5}F\textsubscript{2}NO ([M]\textsuperscript{+}): 145.0339; found: 145.0341. \]
2-Difluoromethoxyquinoline (136)

![Structure of 2-Difluoromethoxyquinoline](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 8.13$ (d, $J = 8.8$ Hz, 1H), 7.87 (d, $J = 7.7$ Hz, 1H), 7.77 (dd, $J = 7.7$, 3.0 Hz, 1H), 7.74 (t, $J = 72.7$ Hz, 1H), 7.68 (ddd, $J = 7.7$, 7.7, 3.0 Hz, 1H), 7.48 (ddd, $J = 7.7$, 7.7, 3.0 Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 157.3$, 145.5, 140.5, 130.3, 127.8, 127.6, 126.1, 125.7, 113.9 (t, $J = 255$ Hz), 111.8.

$^{19}$FNMR (470 MHz, CDCl$_3$): $\delta = 72.1$ (d, $J = 73$ Hz, 2F).

IR (neat): $\nu = 1604, 1311, 1232, 1065, 912$ cm$^{-1}$.

HRMS (70 eV, EI$^+$): $m/z$ calcd. for C$_{10}$H$_7$F$_2$NO ([M$^+$]): 195.0496; found: 195.0496.
2.6. Reference

(b) Selby, T. P.; Dei, W. US5389600, 1995.


Chapter 3

Regioselective Syntheses of gem-Difluorocyclopentanone Derivatives with Transition Metal Difluorocarbene Complexes

3.1. Introduction

Difluorocyclopentanones are important motifs of pharmaceuticals (Figure 10).\[1\] For example, \(\alpha\)-fluorocyclopentanone derivatives 140 and 141 have antimalarial and antileukemic effects, respectively.\[1a,b\] \(\beta\)-Fluorocyclopentanone derivative 142 has an anti-bronchitis effect.\[1c\] Thus, regioselective synthesis of difluorocyclopentanones is of importance and has been required. These facts prompted me to achieve conduct regioselective synthesis of both \(\alpha,\alpha\)- and \(\beta,\beta\)-difluorocyclopentanone derivatives.

![Figure 10](image)

140 (antimalarial effect)  141 (antileukemic effect)  142 (anti-bronchitis effect)

To date, \(\alpha,\alpha\)-difluorocyclopentanone derivatives have been synthesized via two fluorine introductions: double-electrophilic fluorination of cyclopentanones\[2\] and deoxygenative fluorination of alkoxy cyclopentanones followed by oxidation.\[3\] For instance, treatment of lactone 143 with \(N\)-fluorobenzensulfonimide in the presence of \(N,N\)-bis(trimethylsilyl)amide and manganese(II) bromide at \(-60\) °C affords difluorolactone 144 in 57% yield (eq. 55).\[2a\] Cyclopentanone 145 is treated with DAST (2.2 equiv) to afford difluorocyclopentane 146 in 67% yield. The subsequent hydrolysis and oxidation provide \(\alpha,\alpha\)-difluorocyclopentanone (eq. 56).\[1a\]

These strategies involve considerable effort because they require the construction of the carbon skeleton and the introduction of fluorine. Thus, I envisioned that the concise synthesis of \(\alpha,\alpha\)-difluorinated cyclopentanones would be facilitated by the combination of the metal-catalyzed difluorocyclopropanation of dienol silyl ethers (simultaneous fluorine introduction and C–C bond formation) and vinylcyclopropane–cyclopentene rearrangement (VCP rearrangement, five-membered ring construction).\[4\] When dienol silyl ethers prepared from \(\alpha,\beta\)-unsaturated ketone are subjected to difluorocyclopropanation, the resulting 1,1-difluoro-2-vinylcyclopropanes bearing
a siloxy group would be obtained and then undergo VCP rearrangement to afford silyl 5,5-difluorocyclopent-1-en-1-yl ethers (i.e., the domino synthesis of α,α-difluorocyclopentanone derivatives, eq. 57).

In the first step, the difluorocyclopropanation of silyl enol ethers is an issue to be addressed in this strategy. In general, difluorocyclopropanations of alkenes have been extensively studied for decades using systems such as CHClF₂/KOH (eq. 5),[5] CClF₂CO₂Na (eq. 26),[6] or PhHgCF₃/NaI (eq. 30)[7] to generate free difluorocarbene; these methods are affected by strongly basic conditions, high reaction temperature, and the need for toxic reagents, respectively. Although useful methods for the generation of free difluorocarbene have been reported in the past few years, systems suitable for the difluorocyclopropanation of silyl enol ethers are still limited, probably due to their instabilities to hydrolysis.

On the other hand, metal-catalyzed cyclopropanation of alkenes under mild conditions has been reported.[8] For instance, treatment of alkene 147 with diazoester 148 in the presence 1.0 mol% of rhodium(II) acetate at 25 °C affords cyclopropane 149 in 94% yield (eq. 58).[8b] Alkene 150 reacts with diazomethane in the presence of 0.5 mol% palladium(II) acetate at 0 °C to afford cyclopropane 151 in 73% yield (eq. 59).[8c] Treatment of alkene 152 with a stoichiometric amount of diazomethane in the presence of 10 mol% of tetrakis(triphenylphosphine)nickel(0) affords
cyclopropane 153 in 72% yield (eq. 60).\[^{8d}\] I expected that transition metal difluorocarbene complexes such as those of Rh(II), Pd(II), and Ni(0) would realize the difluorocyclopropanation of the dienol silyl ethers.

Concerning the second ring-opening step, VCP rearrangements of fluorine-free vinylcyclopropanes, including siloxy-substituted ones, are typically conducted at high temperatures (300–550 °C).\[^{4b}\] For example, vinylcyclopropane 154 undergoes to rearrangement at 330 °C to give cyclopentene 155 in 89% yield (eq. 61).\[^{4c}\] As an advantage, fluorine substitution allows the rearrangement conditions to be benign and renders the C–C bond cleavage regioselective. Dolbier reported that 1,1-difluoro-2-vinylcyclopropanes readily underwent VCP rearrangement to selectively afford 3,3-difluorocyclopent-1-enes, albeit at 200–275 °C. When heating to 194–224 °C, vinyldifluorocyclopropane 156 affords difluorocyclopentenes 157 and 158 in 96% and 4% yields, respectively (eq. 62).\[^{4d}\] Recently, Percy conducted the reaction of the difluorinated vinylcyclopropanes with an ester moiety at 100 °C (eq. 63).\[^{4e}\] Namely, difluorovinylcyclopropane 159 reacts at 100 °C to afford difluorocyclopentene 160 in 99% yield. These advantages of fluorine substitution on cyclopropane rings are ascribed to two primary reasons: (i) increased ring strain and (ii) elongation of the C–C bond distal to the geminal fluorine substituents (Figure 11).\[^{9}\] I expected that the VCP rearrangement of 2-siloxy-substituted 1,1-difluoro-2-vinylcyclopropanes would readily proceed, providing the desired domino synthesis of α,α-difluorocyclopentanone derivatives.
For the synthesis of the regioisomeric β,β-difluorocyclopentanone derivatives, I envisaged to adopt [4 + 1] cycloaddition (eq. 64). Dienol silyl ethers would electrophilically attack the CF₂ carbon of difluorocarbene complex to generate the corresponding difluoroalkylmetal, whose Michael-type ring closure would afford 4,4-difluorocyclopent-1-en-1-yl silyl ethers. Although the chemistry of [4 + 1] cycloaddition has been relatively undeveloped compared to other cyclizations in [3 + 2] and [2 + 2 + 1] fashions, I expected that the [4 + 1] cycloaddition of silyl dienol ethers with transition metal difluorocarbene complexes would facilitate the construction of β,β-difluorocyclopentanone skeletons.
In order to conduct the desired [4 + 1] cycloaddition, two issues must be addressed: (i) generation of transition metal difluorocarbene complexes and (ii) promotion of cycloaddition in a [4 + 1] manner. To settle these issues, I adopted copper(I) as a metal species (M) and halodifluoroacetate as a carbene source (XCF₂CO₂⁻). Decarboxylation of copper(I) carboxylate is known to proceed readily as shown in the following example: \[^\text{[10]}\] cross coupling reaction of potassium pentafluorobenzoate 161 and phenyl iodide in the presence 10 mol% of copper(I) iodide proceeds to afford biphenyl 162 in 99% yield (eq. 65).\[^\text{[10a]}\] The resulting (halodifluoromethyl)copper(I) species would undergo elimination of a halide ion (X⁻) to generate the required difluorocarbene complexes.\[^\text{[11]}\] On treatment of trifluoromethylmanganese(II) 163 with trimethylsilyl triflate (2.0 equiv) affords manganese(II) difluorocarbene complex 164 in 87% yield (eq. 66).\[^\text{[11b]}\] Furthermore, there have been several reports on copper-catalyzed [4 + 1] cycloaddition of α,β-unsaturated ketones with diazo compounds, affording the desired five-membered cyclic products. Namely, on treatment with diazo compound 166 in the presence of 1 mol% of copper(I) triflate ketone 165 affords 2,3-dihydrofuran 168 in 79% yield (eq. 67).\[^\text{[12]}\] Copper(I) complex 167 is proposed as intermediate. I expected that the [4 + 1] cycloaddition of dienol silyl ether with copper(I) difluorocarbene complex would readily proceed to provide the desired synthesis of β,β-difluorocyclopentanone derivatives.
\[
\text{O-Ph} \quad \xrightarrow{\text{CuOTf (1.0 mol%)}} \quad \text{ArOCOCH=N} \quad \xrightarrow{\text{ArOCl, RT, 1 h}} \quad \text{O-Ph}
\]

\[
165 \quad \xrightarrow{\text{CuOTf (1.0 mol%) \quad (-)-bpy* (1.3 mol%)}} \quad 166 \quad (1.1 \text{ eq}) \quad \xrightarrow{\text{CH}_2\text{Cl}_2, \text{RT, 1 h}} \quad 167 \quad \xrightarrow{\text{OTf}} \quad 168 \quad 79\%
\]

\[
\text{Ar} = 2,6\text{-diisopropylphenyl}
\]
3.2. Domino Difluorocyclopropanation/Ring Expansion with Nickel Difluorocarbene Complex

3.2.1. Preparation of silyl enol ethers

Silyl enol ethers \(170\) were prepared from the corresponding ketones by using two synthetic methods (Table 7).\(^{[13]}\) Treatment of ketones \(169a, c, d\) with \(\text{tert-}\text{butyl(dimethyl)silyl chloride (TBSCl, 1.0–1.2 equiv)}\) in the presence of \(\text{triethylamine (1.2–1.5 equiv)}\) and \(\text{sodium iodide (1.0–1.2 equiv)}\) afforded silyl enol ethers \(170a, c, d\) in good yields (method A). Silylation of ketone \(169b\) with \(\text{tert-}\text{butyl(dimethyl)silyl trifluoromethanesulfonate (TBSOTf, 1.3 equiv)}\) in place of TBSCI proceeded to give silyl enol ether \(170b\) in 64\% yield (method B).

\[
\begin{align*}
\text{Method A} & \\
\text{TBSCI (1.0–1.2 eq)} & \text{NEt}_3 (1.2–1.5 eq) \\
\text{NaI (1.0–1.2 eq)} & \text{CH}_3\text{CN, 45 °C, 9–15 h} \\
\hline
\text{Method B} & \\
\text{TBSOTf (1.3 eq)} & \text{NEt}_3 (2.0 eq) \\
\text{THF, 0 °C to RT, 13 h} & \\
\end{align*}
\]

Table 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 169</th>
<th>Method</th>
<th>Product 170</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(169a)</td>
<td>A</td>
<td>(170a)</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>(169b)</td>
<td>B</td>
<td>(170b)</td>
<td>64 (E/Z = 4:96)</td>
</tr>
<tr>
<td>3</td>
<td>(169c)</td>
<td>A</td>
<td>(170c)</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>(169d)</td>
<td>A</td>
<td>(170d)</td>
<td>86</td>
</tr>
</tbody>
</table>

\(\text{TBS} = \text{Si(}\text{t-Bu)}\text{Me}_2\)
The silylation of ketones \textbf{169} was successfully applied to the reaction of \(\alpha,\beta\)-unsaturated ketones \textbf{171} (Table 8). Treatment of ketones \textbf{171a–l} with a silylating reagent (TBSCI or TBSOTf) gave the corresponding dienol silyl ethers \textbf{172a–l} in good to moderate yields.

\begin{align*}
\textbf{Method A} & \\
\text{TBSCI (1.0–1.2 eq)} \\
\text{NEt}_3 (1.2–1.5 eq) \\
\text{NaI (1.0–1.2 eq)} \\
\text{CH}_3\text{CN, 45 °C, 6–16 h} \\
\end{align*}

\begin{align*}
\textbf{Method B} & \\
\text{TBSOTf (1.3 eq)} \\
\text{NEt}_3 (2.0 eq) \\
\text{CH}_2\text{Cl}_2 \text{ or THF} \\
\text{–78 °C to RT, 3–20 h} \\
\end{align*}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & Substrate \textbf{171} & Method & Product \textbf{172} & Yield / \% \\
\hline
1 & \begin{align*} & \text{R} = \text{H} \\
\end{align*} & \begin{align*} \text{A} \\
\text{171a} & \end{align*} & \begin{align*} \text{OTBS} \\
\text{172a} & \end{align*} & \begin{align*} & 74 \\
\hline
2 & \begin{align*} & \text{R} = \text{Me} \\
\end{align*} & \begin{align*} \text{B} \\
\text{171b} & \end{align*} & \begin{align*} \text{OTBS} \\
\text{172b} & \end{align*} & \begin{align*} & 76 \\
\hline
3 & \begin{align*} & \text{R} = \text{OMe} \\
\end{align*} & \begin{align*} \text{B} \\
\text{171c} & \end{align*} & \begin{align*} \text{172c} & \\
& & & & 60 \\
\hline
4 & \begin{align*} & \text{R} = \text{Cl} \\
\end{align*} & \begin{align*} \text{A} \\
\text{171d} & \end{align*} & \begin{align*} \text{172d} & \\
& & & & 63 \\
\hline
5 & \begin{align*} & \text{R} = \text{Br} \\
\end{align*} & \begin{align*} \text{B} \\
\text{171e} & \end{align*} & \begin{align*} \text{172e} & \\
& & & & 62 \\
\hline
6 & \begin{align*} & \text{171f} \\
\end{align*} & \begin{align*} \text{B} \\
& & & & 40 \\
\hline
7 & \begin{align*} & \text{n-Pr} \\
\end{align*} & \begin{align*} \text{B} \\
\text{171g} & \end{align*} & \begin{align*} \text{172g} & \\
& & & & 58 \\
\hline
8 & \begin{align*} & \text{Me} \\
\end{align*} & \begin{align*} \text{B} \\
\text{171h} & \end{align*} & \begin{align*} \text{172h} & \\
& & & & 83 \\
\hline
9 & \begin{align*} & \text{Br} \\
\end{align*} & \begin{align*} \text{B} \\
\text{171i} & \end{align*} & \begin{align*} \text{172i} & \\
& & & & 97 \\
\hline
10 & \begin{align*} & \text{Ph} \\
\end{align*} & \begin{align*} \text{A} \\
\text{171j} & \end{align*} & \begin{align*} \text{172j} & \\
& & & & 57 \\
\hline
11 & \begin{align*} & \text{171k} \\
\end{align*} & \begin{align*} \text{B} \\
& & & & 65 \\
\hline
12 & \begin{align*} & \text{171l} \\
\end{align*} & \begin{align*} \text{A} \\
& & & & 73 \ (E/Z = 34:66) \\
\hline
13 & \begin{align*} & \text{171l} \\
\end{align*} & \begin{align*} \text{B} \\
& & & & 65 \ (E/Z = 5:95) \\
\hline
\end{tabular}
\caption{Table 8}
\end{table}
3.2.2. Difluorocyclopropanation of Alkenes with Nickel Difluorocarbene Complex

Silyl enol ether 170a was selected as a model substrate for optimization of the difluorocyclopropanation under metal catalysis. I expected that transmetalation of TFDA would proceed to give the transition metal carboxylate (eq. 68). Its decarboxylation followed by elimination of sulfur dioxide and fluoride ion would generate the desired metal difluorocarbene complex.

\[
\begin{align*}
\text{L}_n\text{MX} + \text{Me}_2\text{Si}O\text{O}O\text{SO}_2\text{F} & \rightarrow \text{L}_n\text{M}O\text{O}O\text{SO}_2\text{F} & \rightarrow \text{L}_n\text{M}^+\text{CF}_2 \\
\text{TFDA} & \Rightarrow & \text{Entry 68}
\end{align*}
\]

Although silyl enol ether 170a was treated with TFDA (2.0 equiv) in the presence of 5 mol% of rhodium(II) acetate at 100 °C, difluorocyclopropane 173a was not obtained and TFDA remained unreacted (97%, Entry 1). The use of tris(triphenylphosphine)rhodium(I) chloride (so-called wilkinson’s catalyst) afforded 173a in 57% yield (Entry 2). Nickel (Entries 3–5), palladium (Entries 6–9), and platinum (Entries 10,11) catalysts having electron-rich ligands such as phosphines and NHCs afforded 173a in 30–72%, 59–64%, and 12–68% yields, respectively. NHC–copper(I) complex also afforded 173a in 40% yield (Entry 12). Especially, a pincer-type NHC–nickel(II) complex 174, which was developed for Heck-type coupling reactions by Inamoto, [14a] afforded 173a in 72% yield (Entry 4).

TFDA was originally designed to generate free difluorocarbene upon treatment with a fluoride ion at 100 °C.[15] Treatment of 170a with TFDA (2.0 equiv) in the presence of sodium fluoride (5 mol%) at 100 °C afforded 173a, albeit only in 31% yield (\(^{19}\text{F}\) NMR). A substantial amount of TFDA (0.62 equiv) remained unreacted, while silyl enol ether 170a was completely consumed (Entry 13). Since our research group previously reported the NHC-catalyzed generation of free difluorocarbene,[16] 170a was treated with TFDA in the presence of SIMes·HCl, IMes·HCl, or triazolium salt 127 (5 mol %) along with sodium carbonate (20 mol%) to afford 173a in 53%, 56%, and 46% yields, respectively (Entries 14–16). To rule out the possibility that the pincer-type NHC ligand served as a catalyst for the decomposition of TFDA, 170a was treated with TFDA in the presence of NHC-salt 180 (5 mol %) and sodium carbonate (20 mol%, entry 17). The product 173a was obtained in 45% yield, suggesting that the difluorocyclopropanation was more efficiently promoted by the nickel catalyst.

The Ni catalyst 174, possessing a rigid and highly electron-rich ligand, showed remarkable effects in this difluorocyclopropanation. This is presumably because the key difluorocarbene complex is stabilized by the ligand. Shriver reported that triphenylphosphine stabilized a difluorocarbene complex.[17] Namely, iron(III) difluorocarbene complex 181 was detected by NMR
spectroscopy only at $-78 \, ^\circ\text{C}$ and decomposed above $-78 \, ^\circ\text{C}$. On the other hand, difluorocarbene complex 182 with a triphenylphosphine ligand was successfully isolated at room temperature and was characterized by single-crystal X-ray analysis (Figure 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>173a / %(^a)</th>
<th>Recovery of TFDA / %(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(_2)(OAc)(_4)</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>RhCl(PPh(_3))(_3)</td>
<td>57</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>Ni(PPh(_3))(_4)</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>Ni complex 174</td>
<td>72 (73(^b))</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>175</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh(_3))(_4)</td>
<td>59</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>176</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>177</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>178</td>
<td>62</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Pt(PPh(_3))(_4)</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>179</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>IPrCuCl</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>13</td>
<td>NaF</td>
<td>31</td>
<td>62</td>
</tr>
<tr>
<td>14</td>
<td>SiMes·HCl + Na(_2)CO(_3) (20 mol%)</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>IMes·HCl + Na(_2)CO(_3) (20 mol%)</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>127 + Na(_2)CO(_3) (20 mol%)</td>
<td>46</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>180 + Na(_2)CO(_3) (20 mol%)</td>
<td>45</td>
<td>0</td>
</tr>
</tbody>
</table>

\(a\): \(^{19}\text{F}\) NMR yield based on (CF\(_3\))\(_2\)C(C\(_6\)H\(_4\)p-CH\(_3\))\(_2\). \(b\): Isolated yield.

![Ni complex 174](image1.png)  ![Ni complex 175](image2.png)  ![Pd complex 176](image3.png)  ![Pd complex 177](image4.png)

![Pd complex 178](image5.png)  ![Pt complex 179](image6.png)  ![IPrCuCl](image7.png)  ![NHC-salt 180](image8.png)

**Figure 12.** List of Catalyst Candidates
This difluorocyclopropanation method was successfully applied to other substrates in a diastereospecific fashion (Table 10). Silyl enol ether 170b \((E/Z = 4:96)\) afforded the corresponding product 173b with 11:89 diastereomer ratio (Entry 2). Sterically hindered 170c afforded the corresponding product 173c in 63% yield (Entry 3). Cyclic silyl enol ether 170d gone also the corresponding product 173d in 78% yield (Entry 4). Furthermore, alkyl vinyl ether 170e underwent difluorocyclopropanation, albeit in 40% yield (Entry 5).

![Figure 13. Stabilization of Iron(III) Difluorocarbene Complexes by Phosphine Ligand](image)

![Chemical structure](image)
It was reported that nickel carbene complex reacted with alkenes to generate metallacyclobutanes, which subsequently underwent reductive elimination providing cyclopropanes diastereospecifically. Treatment of \((E)-184\) with dibromomethane (1.0 equiv) in the presence of nickel(0) complex \(183\) (1.0 eq), zinc metal (1.0 equiv), and sodium iodide (1.0 equiv) affords a trans-isomer \(185\) exclusively in 59% yield. On the other hand, \((Z)-184\) undergoes cyclopropanation to give the mixture of cis- and trans-isomers \(185\) in 71% and 7% yields (Scheme 5). In this reported case, stereospecificity is slightly reduced presumably because of steric effect, which was similarly observed in substrate \(170b\).

3.2.3. Synthesis of 5,5-Difluorocyclopent-1-en-1-yl Silyl Ethers

Having the facile nickel-catalyzed difluorocyclopropanation of silyl enol ethers in hand, the domino difluorocyclopropanation/VCP rearrangement sequence was examined (Table 11). On treatment with TFDA (2.0 equiv) in the presence of 5 mol% of \(174\) at 80 °C, dienol silyl ether \(172a\) afforded difluoro(vinyl)cyclopropane \(186a\) and the desired 5,5-difluorocyclopent-1-en-1-yl silyl ether \(187a\) in 22% and 31%, respectively, accompanied by a 34% yield of the desilylated product \(171a\) (Entry 1). Chemoselective cyclopropanation occurred on the oxygenated electron-rich alkene moiety, and regioselective VCP rearrangement subsequently proceeded to give \(187a\). The
vinylcyclopropane intermediate 186a was completely converted to 187a by conducting the reaction at higher temperatures (Entries 2–5). Conducting of the reaction at 140 °C resulted in the highest 82% yield of 187a (Entry 4).

![Chemical structure]

Various 5,5-difluorocyclopent-1-en-1-yl silyl ethers 187 were efficiently synthesized by the nickel(II) 174-based catalyst system (Table 12). Dienol silyl ether 172a reacted with TFDA (2.0 equiv) in the presence of 5 mol% of 172 at 140 °C to afford 187a in 83% yield (Entry 1). Dienol silyl ethers 172b,d bearing electron-rich and -deficient aryl groups (R1) smoothly underwent the domino process to afford the corresponding products 187b,d in 80% and 79% yields, respectively (Entries 2 and 3). The reaction of the alkylated substrate 172g also worked well to give the product 187g in 71% yield (Entry 4). Substrates 172h–j, which bear substituents at the internal position (R2), similarly afforded the products 187h–j in 73–74% yields (Entries 5–7). Dienol silyl ether 172k, derived from cyclohexenyl methyl ketone, afforded bicyclic silyl enol ether 187k in 49% yield (two-step yield, Entry 8). The lower yield than those of other substrates was probably due to partial decomposition of intermediary vinylcyclopropane 186k. In order to prevent the acid-promoted ring opening of 186k, 172k was treated with TFDA (2.0 equiv) in the presence of 20 mol% of 174 and sodium hydride (2.0 equiv) at 100 °C, which afforded difluorocyclopropane 186k in 60% yield (eq. 69). VCP rearrangement of the obtained 186k with sodium hydride (2.0 equiv) at 100 °C afforded the final product 187k in quantitative yield. When the substrate 172l bearing a methyl group as R3 was employed, the corresponding product 187l was obtained in 54% yield as a single trans diastereomer along with siloxydiene 188 (27%) as a 1,5-hydrogen shift product (Entry 9). It was reported that cis-vinylcyclopropane 189 underwent exclusively 1,5-hydrogen shift to afford diene 190 in 95% yield (eq. 70), while trans-vinylcyclopropane 189 underwent not only 1,5-hydrogen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. / °C</th>
<th>Time / min</th>
<th>186a / %a</th>
<th>187a / %a</th>
<th>171a / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>80</td>
<td>60</td>
<td>22</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>100</td>
<td>60</td>
<td>0</td>
<td>74</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>p-Xylene</td>
<td>120</td>
<td>30</td>
<td>0</td>
<td>72</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>p-Xylene</td>
<td>140</td>
<td>30</td>
<td>0</td>
<td>82 (83c)</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>mesitylene</td>
<td>160</td>
<td>10</td>
<td>0</td>
<td>84</td>
<td>9</td>
</tr>
</tbody>
</table>

a: 19F NMR yield based on (CF3)2C(C6H4p-CH3)2. b: 1H NMR yield based on 187a. c: Isolated yield.
shift but also VCP rearrangement to give a mixture of diene 190 and cyclopentene 191 (1:1.9, eq. 71). Whereas dienol silyl ether 172l mainly consisting of Z form \((E/Z = 5:95)\) was employed, the desired product 187l was obtained in 56% yield along with the undesired product 188 in 20% yields, respectively (Entry 10).

![Chemical Structures]

**Table 12**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 172</th>
<th>Product 187</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R = H</td>
<td>172a</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>R = Me</td>
<td>172b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>R = Cl</td>
<td>172d</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>n-Pr</td>
<td>187g</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>R = Me</td>
<td>172h</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>R = Br</td>
<td>172i</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>R = Ph</td>
<td>172j</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>172k</td>
<td>187k</td>
<td>49</td>
</tr>
<tr>
<td>9</td>
<td>(E/Z = 34:66)</td>
<td>187l(^b)</td>
<td>54(^c)</td>
</tr>
<tr>
<td>10</td>
<td>(E/Z = 5:95)</td>
<td>187l(^b)</td>
<td></td>
</tr>
</tbody>
</table>

* a: Table 11, Entry 4. b: single trans diastereomer. c: 188 was obtained in 27% yield. d: 188 was obtained in 20% yield.
3.2.4. Mechanistic Study on Difluorocyclopropanation

The difluorocyclopropanation of silyl enol ethers can be explained by a generation of nickel(II) difluorocarbene complex and its methylene transfer reaction (Scheme 6). Transmetalation of nickel(II) complex 174 and TFDA proceeds to generate nickel(II) carboxylate A. This complex A eliminates carbon dioxide, sulfer dioxide, and a fluoride ion to generate nickel(II) difluorocarbene complex B. Silyl enol ethers 170 reacts with B to generate nickelacyclobutane C, then reductive elimination of nickel(IV) complex proceeds to give difluorocyclopropanes 173 and the catalyst 174 is regenerated. Cyclopropanation of alkenes with nickel(II) carbene complex was reported by Barefield.[18c] Treatment of cyclooctene with nickel(II) carbene complex 192 to afford cyclopropanation product 193 in 49% yield (eq. 72).
Nickel(II) difluorocarbene complex B was tried to be captured by aminolysis. Roper reported that ruthenium(0) difluorocarbene complex 99 reacted with methylamine to afford ruthenium(0) isonitrile complex 194, liberating two molecules of hydrogen fluoride (eq. 73). On the basis of this fact, nickel(II) complex 175 was treated with TFDA (1.5 equiv) in the presence of 2,6-dimethylphenylamine (10 equiv). As expected, nickel(II) isonitrile complex 195 was observed by ESI mass spectroscopy (eq. 74). In particular the isotope pattern of the observed fragment ion (M$^{2+}$, C$_{38}$H$_{38}$N$_6$Ni) was in complete agreement with its computer simulation (Figure 14). Thus, this operation strongly supports the aforementioned mechanism.
3.2.5. Derivatization of 5,5-Difluorocyclopent-1-en-1-yl Silyl Ethers into α-Fluorocyclopentanone Derivatives

Cyclic silyl enol ethers 187a were transformed to substituted α,α-difluorocyclopentanones to demonstrate their utility in synthesis. Treatment of 187a with tetrabutylammonium fluoride (2.0 equiv) in THF/formic acid/water (6:3:1) at 55 °C afforded a 80% yield (19F NMR) of α,α-difluorocyclopentanone 196, which was not isolated because of its instability toward chromatographic (silica gel and basic alumina) purification. Treatment of 196 with sodium borohydride (2.0 equiv) afforded cyclopentanol 197 in quantitative yield (eq. 74). Cyclopentanone 196 was also treated with tosylhydrazine to afford the corresponding hydrazone 198 in 74% yield (eq. 75). The single-crystal X-ray analysis of 198 confirmed that the difluoromethylene unit was introduced at the position adjacent to the carbonyl group (Figure 15). Furthermore, oxime 199 was obtained from cyclic silyl enol ether 187a by treating the in situ-generated ketone 196 with hydroxylamine hydrochloride (2.0 equiv) in a one-pot operation (87% yield, two-steps, eq. 76).
Oxidative treatment of 187a afforded functionalized fluorine-containing cyclopentenones. Treatment of 187a with N-bromosuccinimide (NBS) under highly diluted conditions \((7 \times 10^{-4}\) mol/L) gave difluorinated cyclopentenone 200 in 86% yield (eq. 77). Oxidation of 187a with \(m\)-chloroperbenzoic acid (\(m\)CPBA, 3.0 equiv) gave the corresponding epoxide 201 in 85% yield as a diastereomeric mixture (78:22). Its desilylation with potassium hydrodifluoride (2.0 equiv) led to the formation of 3-fluorinated 2-hydroxycyclopent-2-en-1-one 202 in 54% yield (eq. 78). The oxygenated cyclopentenone skeleton of 202 is found in cyclotene that is used as a food additive with a caramel-like flavor.[20]
(78) $187a$ reacts with $\text{NBS (1.0 eq)}$ in $\text{CH}_2\text{Cl}_2 (7 \times 10^{-4} \text{ M}, \text{RT}, 96 \text{ h})$ to give $200$ in $86\%$ yield.

(79) $187a$ undergoes reaction with $\text{mCPBA (3.0 eq)}$ in $\text{CH}_2\text{Cl}_2, -20^\circ\text{C}$ to $\text{RT}, 41 \text{ h}$ to afford $201$ in $85\%$ yield (d.r. = 78:22). Further treatment with $\text{KHF}_2 (2.0 \text{ eq})$ in $\text{THF-H}_2\text{O (1:1)}, \text{RT}, 46 \text{ h}$ followed by $\text{aq. NaHCO}_3$ yields $202$ in $54\%$ yield.
3.3. [4 + 1] Cycloaddition with Copper Difluorocarbene Complex

3.3.1. Synthesis of 4,4-Difluorocyclopent-1-en-1-yl Silyl Ethers

Dienol silyl ether 172a was selected as a model substrate to examine the desired cyclopentanone ring construction via (i) the generation of the transition metal difluorocarbene complexes and (ii) promotion of the [4 + 1] cycloaddition. I adopted copper(I) as a metal species (M) and halodifluoroacetate as a carbene source (XCF2CO2–, eq. 80). Decarboxylation of copper(I) carboxylates is known to proceed readily. Elimination of a halide ion (X–) from the resulting (halodifluoromethyl)copper(I) species would generate the required difluorocarbene complexes. The copper(I)-catalyzed [4 + 1] cycloaddition was exemplified by the reaction of α,β-unsaturated ketones with diazo compounds as described in Section 3.1 (eq. 67).

Dienol silyl ether 172a was treated with sodium bromodifluoroacetate in the absence of copper(I) complex in acetonitrile at 50 °C (Table 13, Entry 1). Vinylcyclopropane 186a and α,α-difluorocyclopentanone-based silyl enol ether 187a were obtained in 35% and 5% yields, respectively. Cyclopropane 186a was generated via free difluorocarbene and cyclic silyl enol ether 187a was obtained from 186a via VCP rearrangement. To my delight, treatment of 172a with sodium bromodifluoroacetate (1.1 equiv) in the presence a stoichiometric amount of copper(I) bromide at 50 °C afforded the desired 4,4-difluorocyclopent-1-en-1-yl silyl ether 203a and 186a in 25% and 3% yields, respectively (Entry 2). Copper(I) acetylide and SIMesCuCl also gave the desired 203a in 37% and 10% yields, respectively (Entries 3 and 4).

![Diagram](80)

### Table 13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>203a / %a</th>
<th>186a / %a</th>
<th>187a / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>0</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>25</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CCu≡CPh</td>
<td>37</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>SIMesCuCl</td>
<td>10</td>
<td>19</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

a: 19F NMR yield based on (CF3)2C(C6H4p-CH3)2.
The catalyst system was optimized in detail (Table 14 and Figure 16). The reaction proceeded smoothly with 5 mol % of Cu(Phen)(PPh₃)Cl to afford 203a in 49% yield (Entry 1). Copper(I) catalysts with bromide or iodide ions promoted the reaction to give 203a in 62% and 58% yields, respectively (Entries 2,3). Electron-donating 4,7-dimethylphenanthroline complex 204b afforded 203a in the highest 72% yield (Entry 4), whereas 3,4,7,8-tetramethylphenanthroline complex 204c gave 203a in lower yield (59%, Entry 5), presumably because of the low solubility of this complex in acetonitrile. Sterically hindered complexes, 204d and 204e, led to poor results: 203a was obtained in 16% and 33% yields (Entries 6 and 7), respectively. Complex 204f bearing a bipyridyl ligand afforded 203a only in 39% yield and difluorocyclopropanation proceeded to form 186a and 187a in 40% and 2% yields, respectively (Entry 8). The dimethylphenanthroline ligand in complex 204a probably stabilized the presumed difluorocarbene complex by its electron-donating property and rigid structure.

![Catalyst System Diagram](image)

**Table 14**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>203a / %ᵃ</th>
<th>186a / %ᵃ</th>
<th>187a / %ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(Phen)(PPh₃)Cl</td>
<td>49</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Cu(Phen)(PPh₃)Br 204a</td>
<td>62</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Cu(Phen)(PPh₃)I</td>
<td>58</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>204b</td>
<td>72 (71ᵇ)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>204c</td>
<td>59</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>204d</td>
<td>16</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>204e</td>
<td>33</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>204f</td>
<td>39</td>
<td>40</td>
<td>2</td>
</tr>
</tbody>
</table>

ᵃ: ¹⁹F NMR yield based on (CF₃)₂C(C₆H₄p-CH₃)₂; b: Isolated yield.

![Figure 16](image)
Effects of difluorocarbene sources were also examined, using 5 mol% of 204a as a catalyst (Table 15). Conducting the reaction with potassium bromodifluoroacetate afforded the [4 + 1] cycloaddition product 203a, difluorocyclopropane 186a, and the VCP rearrangement product 187a in 64%, 4%, and 2% yields, respectively (Entry 2). Cesium salt afforded 203a in 32% yield (Entry 3). Sodium salts with leaving groups such as chlorine (Entry 4), fluorine (Entry 5), and a fluorosulfonyl group (Entry 6) did not promote the [4 + 1] cycloaddition.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CF₂ Sources</th>
<th>Temp / °C</th>
<th>Time / h</th>
<th>203a / %a</th>
<th>186a / %a</th>
<th>187a / %a</th>
<th>Recovery of CF₂ Sources / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b</td>
<td>BrCF₂CO₂Na</td>
<td>50</td>
<td>12</td>
<td>62</td>
<td>9</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>BrCF₂CO₂K</td>
<td>50</td>
<td>12</td>
<td>64</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>BrCF₂CO₂Cs</td>
<td>50</td>
<td>12</td>
<td>32</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>ClCF₂CO₂Na</td>
<td>80</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CF₃CO₂Na</td>
<td>80</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>FSO₂CF₂CO₂Na</td>
<td>50</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a: ¹⁹F NMR yield based on (CF₃)₂C(C₆H₄-p-CH₃)₂. b: Table 14, Entry 2.

Effects of phosphine ligands on the yield of 203a were examined (Table 16). Electron-rich and -deficient triarylphosphine complex 204g-j afforded 203a in 39–67% yields (Entries 2–5). Use of tricyclohexylphosphine complex 204k resulted in the formation of 203a in 51% yield (Entry 6). However, the effects of phosphine ligands were not clear.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>203a / %a</th>
<th>186a / %a</th>
<th>187a / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = Ph</td>
<td>204a</td>
<td>62</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>R = C₆H₄-p-CH₃</td>
<td>204g</td>
<td>66</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>R = C₆H₄-p-OCH₃</td>
<td>204h</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>R = C₆H₄-p-Cl</td>
<td>204i</td>
<td>67</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>R = C₆H₄-p-CF₃</td>
<td>204j</td>
<td>39</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>R = Cy</td>
<td>204k</td>
<td>51</td>
<td>4</td>
</tr>
</tbody>
</table>

a: ¹⁹F NMR yield based on (CF₃)₂C(C₆H₄-p-CH₃)₂. b: Table 14, Entry 2.
Various 4,4-difluorocyclopent-1-en-1-yl silyl ethers 203 were efficiently synthesized by the copper(I) 204b-based catalyst system (Table 17). Dienol silyl ether 172a reacted with sodium bromodifluoroacetate (1.1 equiv) in the presence of 5 mol% of 204b at 50 °C to afford 172a in 71% yield (Entry 1). Dienol silyl ethers 172b,c,e, bearing electron-rich and -deficient aryl groups (R1), smoothly underwent the [4 + 1] cycloaddition to afford the corresponding products 203b,c,e in 70%, 61%, and 59% yields, respectively (Entries 2–4). Dienol silyl ethers 172f,g with 2-naphthyl and propyl groups (R1) afforded 203f,g in 59% yields each (Entries 5 and 6). Substrate 172h bearing a substituent at the internal position (R2) similarly afforded the product 203h in 69% yield (Entry 7). Dienol silyl ether 172k, derived from cyclohexenyl methyl ketone, afforded bicyclic silyl enol ether 203k in 63% yield (Entry 8).

### Table 17

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 172</th>
<th>Product 203</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>OTBS R = H 172a</td>
<td>OTBS OTBS</td>
<td>203a 71</td>
</tr>
<tr>
<td>2</td>
<td>OTBS R = Me 172b</td>
<td>OTBS OTBS</td>
<td>203b 70</td>
</tr>
<tr>
<td>3</td>
<td>OTBS R = OMe 172c</td>
<td>OTBS OTBS</td>
<td>203c 61</td>
</tr>
<tr>
<td>4</td>
<td>OTBS R = Br 172e</td>
<td>OTBS OTBS</td>
<td>203e 59</td>
</tr>
<tr>
<td>5</td>
<td>OTBS OTBS 172f</td>
<td>OTBS OTBS</td>
<td>203f 59</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>OTBS n-Pr 172g</td>
<td>OTBS n-Pr OTBS</td>
<td>203g 59</td>
</tr>
<tr>
<td>7</td>
<td>OTBS Me 172h</td>
<td>OTBS OTBS</td>
<td>203h 69</td>
</tr>
<tr>
<td>8</td>
<td>OTBS 172k</td>
<td>OTBS OTBS</td>
<td>203k 63</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Table 14, Entry 4. <sup>b</sup>: Reaction time was 36 h.
The copper(I)-catalyzed difluoromethylene transfer could not be applied to simple silyl enol ether. Treatment of silyl enol ether 170a with sodium bromodifluoroacetate (1.1 equiv) in the presence of 5 mol% of 204a did not afford difluorocyclopropane 173a (eq. 81).

3.3.2. Mechanistic Study on [4 + 1] Cycloaddition with Copper Difluorocarbene Complex

The [4 + 1] cycloaddition of silyl enol ethers can be explained by the generation of copper(I) difluorocarbene complex (Scheme 7). Transmetalation of copper(I) complex D lacking a phosphine ligand with sodium bromodifluoroacetate proceeds to generate copper(I) carboxylate E. The formed complex E eliminates carbon dioxide to generate (bromodifluoromethyl)copper(I) complex F. Then, loss of a bromide ion from F generates the key copper(I) difluorocarbene complex G. Dienol silyl ethers 172 nucleophilically attack the CF₂ carbon of difluorocarbene complex G to generate the corresponding difluoroalkylocopper(I) complex H, whose Michael–type 5-endo-trig ring closure provides 4,4-difluorocyclopent-1-en-1-yl silyl ethers 203. In this final step the catalyst D is regenerated. It should be noted that another migration mechanism for formation of H is also possible. Nucleophilic attack of 172 to the metal center of G, followed by metal carbene migratory insertion, generates H.\textsuperscript{21}
Copper(I) difluorocarbene complex G was captured by aminolysis as mentioned in section 3.2.4 (eq. 73 to support the above mechanism). When copper(I) complex 204b was treated with sodium bromodifluoroacetate (5.5 equiv) in the presence of butylamine (10 equiv), copper(I) isonitrile complex 205, lacking a phosphine ligand was observed by ESI mass spectroscopy (eq. 82). In particular, the isotope pattern of the observed fragment ion (M⁺, C₁₉H₂₁CuN₅) was in complete agreement with its computer simulation (Figure 17).
The reaction was truly affected by the addition of extra triphenylphosphine (eq. 83). Specifically, dienol silyl ether 172a was treated with bromodifluoroacetate (1.1 equiv) in the presence of catalyst 204b (5 mol%) and triphenylphosphine (0.2 equiv). $^{19}$F NMR analysis indicated that the yield of 203a decreased to 32% (v.s. 72% yield in Table 14, Entry 4), accompanied by formation of difluorocyclopropane 186a (25% yield) and isomeric 187a (18% yield).
3.3.3. Derivatization of 4,4-Difluorocyclopent-1-en-1-yl Silyl Ethers into β-Fluorocyclopentanone Derivatives

Hydrolysis of 203a was effected with tetrabutylammonium fluoride (2.0 equiv) in THF/formic acid (5:1), which was accompanied by elimination of hydrogen fluoride to afford β-fluorocyclopentenone 206 in 70% yield (eq. 84).

![Diagram](image)

Treatment of β-fluorocyclopentenone 206 with methyl lithium (2.0 eq) at –78 °C caused 1,2-addition, followed by migration and hydrolysis, to give cyclopentenone 207 in 36% yield (eq. 85).[22] A different synthetic route to 207 was reported by Murakami and Ito,[23a] and the position of the introduced fluorine was confirmed by the comparison of spectral data.

![Diagram](image)
3.4. Conclusion

I have developed the regioselective syntheses of both α,α- and β,β-difluorocyclopentanone derivatives by using unprecedented transition metal difluorocarbene complexes as catalytic species. Dienol silyl ethers underwent the domino difluorocyclopropanation and VCP rearrangement with a nickel(II) difluorocarbene complex to afford 5,5-difluorocyclopent-1-en-1-yl silyl ethers. Copper(I) difluorocarbene complex promoted the [4 + 1] cycloaddition of the same dienol silyl ethers with sodium bromodifluoroacetate to afford 4,4-difluorocyclopent-1-en-1-yl silyl ethers. The two key difluorocarbene complexes of nickel and copper were captured as aminolysis products, which were observed by HRMS analysis.
3.5 Experimental Section

3.5.1. General

$^1$H NMR, $^{13}$C NMR, and $^{19}$F NMR spectra were recorded on a Bruker Avance 500. Chemical shift values are given in ppm relative to internal Me$_4$Si (for $^1$H NMR: $\delta = 0.00$ ppm), CDCl$_3$ (for $^{13}$C NMR: $\delta = 77.0$ ppm), and C$_6$F$_6$ (for $^{19}$F NMR: $\delta = 0.00$ ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV. Elemental analyses were carried out at the Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. All reactions were carried out under argon. Column chromatography was performed on silica gel (Kanto Chemical Co. Inc., Silica Gel 60) and alumina (Aluminium Oxide 90 Active Basic, Merck KGaA for column chromatography). Ethyl bromodifluoracetate supplied by KANTO DENKA KOGYO CO., LTD. and Central Glass Co., Ltd. tert-Butyldimethylsilyl chloride (TBSCI) supplied by Shin-Etsu Chemical Co., Ltd. Toluene, Tetrahydrofuran (THF), dichloromethane were purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. Acetonitrile was distilled from P$_2$O$_5$ and CaH$_2$ before used. $p$-Xylene and mesitylene were distilled from CaCl$_2$. Methanol was distilled from magnesium and iodine. Pincer-type NHC complexes and salt 174–180 were prepared according to the literature.$^{[14]}$ Trimethylsilyl 2,2-difluoro-2-fluorosulfonylacetate (TFDA) was prepared according to the literature.$^{[15]}$ SIMes·HCl and IMes·HCl were prepared according to the literatures.$^{[24]}$ Copper complex Cu(Phen)(PPh$_3$)$_2$Cl, Cu(Phen)(PPh$_3$)$_2$I, 204a–k were prepared according to the literature.$^{[25]}$ Silyl enol ether 170a,c,d were prepared according to the literature.$^{[13]}$ Enol ether 170e was purchased from Aldrich and was distilled before use. 1,1,1,3,3,3-hexafluoro-2,2-di($p$-tolyl)propane (internal standard for $^{19}$F NMR) was purchased from Tokyo Chemical Industry Co., Ltd.

3.5.2. Synthesis of Silyl enol ether and dienol silyl ether.

(A) Typical procedure for the synthesis of silyl enol ether 170a–d and dienol silyl ether 172a–l.

Method A (TBSCI)

To an acetonitrile solution (13 mL) of 4-phenylbut-3-en-2-one 171a (1.47 g, 10.0 mmol), tertbutyl(dimethyl)silyl chloride (1.54 g, 10.2 mmol), and sodium iodide (1.51 g, 10.0 mmol) was added triethylamine (1.67 mL, 12.0 mmol) at room temperature. The reaction mixture was heated to 45 °C, stirred overnight, and then cooled to 0 °C. After being diluted with cold hexane (0 °C, 10 mL), the reaction mixture was poured into a mixture of ice (30 g) and a saturated aqueous solution (15 mL) of sodium hydrogen carbonate to prevent decomposition of the product. Organic materials were extracted with cold hexane (0 °C) three times. The combined extracts were washed with brine...
and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on basic alumina (hexane) to give silyl dienol ether 172a as a colorless liquid (1.94 g, 74% yield).

**Method B (TBSOTf)**

To a dichloromethane solution (10 mL) of hept-3-en-2-one 171g (739 mg, 6.59 mmol) were added triethylamine (1.84 mL, 13.2 mmol) and tert-butyl(dimethyl)silyl trifluoromethanesulfonate (1.96 mL, 8.53 mmol) at 0 °C. The resulting mixture was slowly warmed to room temperature, stirred overnight, and then cooled to 0 °C. After being diluted with cold hexane (0 °C, 10 mL), the reaction mixture was poured into a mixture of ice (30 g) and a saturated aqueous solution (15 mL) of sodium hydrogen carbonate to prevent decomposition of the product. Organic materials were extracted with cold hexane (0 °C, 5 mL) three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by distillation under reduced pressure (bp. 45 °C, 0.38 mmHg) to give silyl dienol ether 172g as a colorless liquid (867 mg, 58% yield).

**(B) Spectral data of silyl enol ether and dienol silyl ether**

1-[**tert**-Butyl(dimethyl)silyloxy]-1-phenylprop-1-ene 170b (**E/Z** = 5:95)

\[
\text{\begin{tikzpicture}
\node [circle, draw, fill=red!30] (A) at (0,0) {\text{OTBS}};
\node [circle, draw, fill=red!30] (B) at (1,0) {\text{Ph}};
\end{tikzpicture}}
\]

\[\begin{array}{c}
\text{\(1^1\) H NMR (500 MHz, CDCl}_3\): (Z-isomer) \(\delta = -0.03\) (s, 6H), 1.00 (s, 9H), 1.74 (d, \(J = 7.0\) Hz, 3H), 5.21 (q, \(J = 7.0\) Hz, 1H), 7.23 (t, \(J = 7.0\) Hz, 1H), 7.28 (t, \(J = 7.0\) Hz, 2H), 7.43 (d, \(J = 7.0\) Hz, 2H).}
\end{array}\]

\[\begin{array}{c}
\text{\(13^1\) C NMR (126 MHz, CDCl}_3\): (Z-isomer) \(\delta = -4.0\), 11.7, 18.3, 25.9, 105.8, 125.7, 127.2, 127.9, 139.8, 150.2. IR (neat): \(\nu = 2929\), 1327 cm\(^{-1}\). HRMS (70 eV, EI\(^{+}\)): \(m/z\) (Z-isomer) calcd. for C\(_{15}\)H\(_{23}\)OSi [M\(^{+}\): 248.1596; Found: 248.1596.
\end{array}\]

3-[**tert**-Butyl(dimethyl)silyloxy]-1-phenylbuta-1,3-diene 172a

\[
\text{\begin{tikzpicture}
\node [circle, draw, fill=red!30] (A) at (0,0) {\text{OTBS}};
\node [circle, draw, fill=red!30] (B) at (1,0) {\text{Ph}};
\end{tikzpicture}}
\]

\[\begin{array}{c}
\text{\(1^1\) H NMR (500 MHz, CDCl}_3\): \(\delta = 0.20\) (s, 6H), 1.01 (s, 9H), 4.40 (s, 1H), 4.43 (s, 1H), 6.56 (d, \(J = 15.6\) Hz, 1H), 6.84 (d, \(J = 15.6\) Hz, 1H), 7.20 (t, \(J = 7.5\) Hz, 1H) 7.29 (t, \(J = 7.5\) Hz, 2H) 7.39 (d, \(J = 7.5\) Hz, 2H). \(13^1\) C NMR (126 MHz, CDCl}_3\): \(\delta = -4.6\), 18.4, 25.9, 96.7, 126.5, 126.7, 127.6, 128.6, 129.2, 136.8, 155.2. IR (neat): \(\nu = 2929\), 2857, 1589, 1327, 1022, 733 cm\(^{-1}\). HRMS (70 eV, EI\(^{+}\)): \(m/z\) calcd. for C\(_{16}\)H\(_{24}\)OSi [M\(^{+}\): 260.1596; Found: 260.1594.
\end{array}\]
3-[tert-Butyl(dimethyl)silyloxy]-1-(p-methylphenyl)buta-1,3-diene 172b

\[
\text{OTBS} \quad \text{Me}
\]

\[
^1H \text{ NMR (500 MHz, CDCl}_3\text{): } \delta = 0.22 (s, 6H), 1.02 (s, 9H), 2.34 (s, 3H), 4.39 (s, 1H), 4.42 (s, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.83 (d, J = 15.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H). ^13C NMR (126 MHz, CDCl\textsubscript{3}): \delta = -4.6, 18.4, 21.2, 25.9, 96.3, 125.6, 126.7, 129.2, 129.3, 134.0, 137.5, 155.4. IR (neat): \nu = 2956, 2929, 1587, 1323, 1003, 837 \text{ cm}^{-1}. \text{HRMS (70 eV, EI+): } m/z \text{ calcd. for C}_{17}H_{26}OSi [M]^+ : 274.1753; \text{Found: 274.1755.}
\]

3-[(tert-Butyldimethylsiloxy)-1-(p-methoxyphenyl)buta-1,3-diene 172c

\[
\text{OTBS} \quad \text{OMe}
\]

\[
^1H \text{ NMR (500 MHz, CDCl}_3\text{): } \delta = 0.22 (s, 6H), 1.02 (s, 9H), 3.81, (s, 3H), 4.37 (s, 1H), 4.40 (s, 1H), 6.46 (d, J = 15.7 Hz, 1H), 6.81 (d, J = 15.7 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H). ^13C NMR (126 MHz, CDCl\textsubscript{3}): \delta = -4.6, 18.4, 25.9, 55.3, 95.8, 114.0, 124.5, 128.0, 128.7, 129.6, 155.4, 159.3. IR (neat): \nu = 2929, 1510, 1250, 1173, 1024, 823 \text{ cm}^{-1}. \text{HRMS (70 eV, EI+): } m/z \text{ calcd. for C}_{17}H_{26}OSi ([M]^+ ): 290.1702; \text{found: 290.1701.}
\]

3-[tert-Butyl(dimethyl)silyloxy]-1-(p-chlorophenyl)buta-1,3-diene 172d

\[
\text{OTBS} \quad \text{Cl}
\]

\[
^1H \text{ NMR (500 MHz, CDCl}_3\text{): } \delta = 0.22 (s, 6H), 1.02 (s, 9H), 4.43 (s, 1H), 4.45 (s, 1H), 6.54 (d, J = 15.6 Hz, 1H), 6.80 (d, J = 15.6 Hz, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H). ^13C NMR (126 MHz, CDCl\textsubscript{3}): \delta = -4.6, 18.4, 25.9, 97.1, 127.2, 127.9, 128.7, 133.2, 135.3, 155.0. IR (neat): \nu = 2929, 1597, 1489, 1323, 1022, 812 \text{ cm}^{-1}. \text{HRMS (70 eV, EI+): } m/z \text{ calcd. for C}_{16}H_{23}ClOSi [M]^+ : 294.1207; \text{Found: 294.1203.}
\]
3-[tert-Butyl(dimethyl)siloxy]-1-(p-bromophenyl)buta-1,3-diene 172e

\[
\begin{align*}
\text{OTBS} & \quad \text{n-Pr} \\
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.22$ (s, 6H), 1.02 (s, 9H), 4.44 (s, 1H), 4.46 (s, 1H), 6.56 (d, $J = 15.6$ Hz, 1H), 6.78 (d, $J = 15.6$ Hz, 1H), 7.27 (d, $J = 8.5$ Hz, 2H), 7.43 (d, $J = 8.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.6, 18.4, 25.9, 97.2, 121.4, 127.3, 127.9, 128.2, 131.7, 135.8, 155.0$. IR (neat); $\tilde{\nu} = 2929, 1487, 1321, 1254, 1024, 1009, 810$ cm$^{-1}$. HRMS (70 eV, EI$^+$/m/z calcd. for C$_{16}$H$_{23}$BrOSi [M$^+$]): 338.0705; found: 338.0705.

3-[tert-Butyl(dimethyl)siloxy]-1-(2-naphthyl)buta-1,3-diene 172f

\[
\begin{align*}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.26$ (s, 6H), 1.07 (s, 9H), 4.46 (s, 1H), 4.51 (s, 1H), 6.73 (d, $J = 16.0$ Hz, 1H), 7.04 (d, $J = 16.0$ Hz, 1H), 7.42–7.49 (m, 2H), 7.63 (dd, $J = 8.5, 1.5$ Hz, 1H), 7.76–7.84 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.6, 18.4, 25.9, 96.9, 123.7, 125.9, 126.3, 126.9, 126.9, 127.6, 128.0, 128.2, 129.3, 133.0, 133.7, 134.3, 155.3$. IR (neat); $\tilde{\nu} = 2954, 1585, 1311, 1254, 1020, 808$ cm$^{-1}$. HRMS (70 eV, EI$^+$/m/z calcd. for C$_{20}$H$_{26}$OSi [M$^+$]): 310.1755; found: 310.1755.

2-[tert-Butyl(dimethyl)silyloxy]hepta-1,3-diene 172g

\[
\begin{align*}
\text{OTBS} & \quad \text{n-Pr} \\
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.18$ (s, 6H), 0.91 (t, $J = 7.5$ Hz, 3H), 0.97 (s, 9H), 1.43 (qt, $J = 7.5, 7.0$ Hz, 2H), 2.07 (dt, $J = 7.0, 7.0$ Hz, 2H), 4.20 (s, 1H), 4.21 (s, 1H), 5.88 (dt, $J = 15.0, 1.2$ Hz, 1H), 6.00 (dt, $J = 15.0, 7.0$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.7, 13.7, 18.3, 22.4, 25.8, 34.2, 93.8, 127.9, 131.7, 155.2$. IR (neat); $\tilde{\nu} = 2958, 2929, 1672, 1593, 1254, 1022, 835$ cm$^{-1}$. HRMS (70 eV, EI$^+$/m/z calcd. for C$_{15}$H$_{26}$OSi [M$^+$]): 226.1753; Found: 226.1755.
3-[tert-Butyl(dimethyl)silyloxy]-2-methyl-1-phenylbuta-1,3-diene 172h

\[
\begin{align*}
&\text{OTBS} \\
&\text{Me} \\
&\text{Ph}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.20 (s, 6H), 0.99 (s, 9H), 1.96 (s, 3H), 4.41 (s, 1H), 4.59 (s, 1H), 7.08 (s, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 7.5$ Hz, 2H), 7.31 (t, $J = 7.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = −4.6, 14.6, 18.4, 25.9, 93.0, 126.5, 127.2, 128.1, 129.3, 133.0, 138.1, 157.5. IR (neat): $\nu$ = 2956, 2858, 1601, 1254, 1018, 827 cm$^{-1}$. HRMS (70 eV, EI+): $m/z$ calcd. for C$_{17}$H$_{26}$O$_3$Si [M]+: 274.1753; Found: 274.1754.

2-Bromo-3-[tert-butyl(dimethyl)silyloxy]-1-phenylbuta-1,3-diene 172i

\[
\begin{align*}
&\text{OTBS} \\
&\text{Ph} \\
&\text{Br}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.24 (s, 6H), 1.01 (s, 9H), 4.64 (s, 1H), 5.22 (s, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.53 (s, 1H), 7.64 (d, $J = 7.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = −4.7, 18.3, 25.8, 97.5, 120.2, 128.1, 129.0, 129.5, 135.9, 153.7. IR (neat): $\nu$ = 2954, 2856, 1603, 1254, 1022, 825 cm$^{-1}$. HRMS (70 eV, EI+): $m/z$ calcd. for C$_{12}$H$_{14}$BrOSi [M−t-Bu]+: 280.9997; Found: 280.9995.

3-[tert-Butyl(dimethyl)silyloxy]-1,2-diphenylbuta-1,3-diene 172j

\[
\begin{align*}
&\text{OTBS} \\
&\text{Ph} \\
&\text{Ph}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.26 (s, 6H), 1.06 (s, 9H), 4.07 (s, 1H), 4.48 (s, 1H), 6.84–6.87 (m, 2H), 7.05–7.12 (m, 3H), 7.14 (s, 1H), 7.19 (dd, $J = 8.0$, 2.0 Hz, 2H), 7.31–7.39 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = −4.6, 18.4, 26.0, 97.6, 126.8, 127.3, 127.9, 128.6, 129.6, 130.1, 136.6, 138.8, 139.0, 157.8. IR (neat): $\nu$ = 2956, 2858, 1589, 1269, 1020, 829 cm$^{-1}$. HRMS (70 eV, EI): $m/z$ calcd. for C$_{22}$H$_{28}$OSi [M]+: 336.1909; Found: 336.1905.

1-{1-[tert-Butyl(dimethyl)silyloxy]ethenyl}cyclohex-1-ene 172k

\[
\begin{align*}
&\text{OTBS} \\
&\text{Ph}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.17 (s, 6H), 0.97 (s, 9H), 1.54–1.60 (m, 2H), 1.63–1.69 (m, 2H), 2.11–2.27 (m, 4H), 4.17 (s, 1H), 4.33 (s, 1H), 6.23–6.27 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ =
−4.6, 18.3, 22.1, 22.7, 25.0, 25.5, 25.9, 89.4, 125.3, 133.2, 156.8. IR (neat): ν = 2929, 2858, 1664, 1255, 831 cm⁻¹. HRMS (70 eV, EI): m/z calcd. for C₁₄H₂₆OSi [M]: 238.1753; Found: 238.1755.

3-[tert-Butyl(dimethyl)silyloxy]-1-phenylpenta-1,3-diene 172I

```
    OTBS
    \Ph
```

¹H NMR (500 MHz, CDCl₃): δ = 0.18 (s, 6H), 1.08 (s, 9H), 1.73 (d, J = 7.0 Hz, 3H), 5.03 (q, J = 7.0 Hz, 1H), 6.58 (d, J = 15.5 Hz, 1H), 6.66 (d, J = 15.5 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃): δ = −3.6, 12.1, 18.5, 26.0, 111.0, 126.3, 126.6, 127.1, 127.5, 128.6, 137.3, 149.5. IR (neat): ν = 2929, 1338, 1254, 1024, 777, 688 cm⁻¹. HRMS (70 eV, EI): m/z calcd. for C₁₇H₂₆OSe [M⁺]: 274.1753; Found: 274.1756.

3.5.3. Synthesis of difluorocyclopropane

(A) Typical procedure for the synthesis of difluorocyclopropane

To a toluene solution (5 mL) of nickel(II) complex 174 (45 mg, 0.097 mmol) and 1,1,1,3,3,3-hexafluoro-2,2-di(p-tolyl)propane (62 mg, 0.19 mmol) was added a toluene solution (5 mL) of silyl enol ether 170a (469 mg, 2.00 mmol) at room temperature. The solution was heated to 100 °C and TFDA (788 mL, 4.00 mmol) was added. The resulting mixture was stirred at 100 °C for 1 h and then cooled to room temperature. ¹⁹F NMR analysis of the mixture revealed that difluorocyclopropane 173a was formed in 72% yield. The solution was diluted with ethyl acetate (10 mL) and a saturated aqueous solution (10 mL) of sodium hydrogen carbonate was added. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to afford difluorocyclopropane 173a as a colorless liquid (415 mg, 73% yield).

(B) Spectral data of difluorocyclopropane.

1-[tert-Butyl(dimethyl)silyloxy]-2,2-difluoro-1-phenylecyclopropane 173a

```
  F  \Ph
   \OTBS
```

¹H NMR (500 MHz, CDCl₃): δ = −0.10 (s, 3H), −0.04 (s, 3H), 0.84 (s, 9H), 1.68 (ddd, J = 16.0, 9.0, 5.0 Hz, 1H), 1.91 (ddd, J = 16.0, 9.0, 6.0 Hz, 1H), 7.31–7.40 (m, 3H), 7.46 (d, J = 7.5 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃): δ = −4.3, −4.1, 17.9, 23.4 (t, J = 9 Hz), 25.5, 62.3 (dd, J = 12, 10 Hz), 26.3 (dd, J = 17.9 Hz, 10 Hz), 137.3, 149.5.
112.1 (t, $J = 296$ Hz), 128.3, 128.5, 136.2. $^{19}$FNMR (470 MHz, CDCl$_3$): $\delta = 21.2$ (ddd, $J = 154, 16, 6$ Hz, 1F), 28.5 (ddd, $J = 154, 16, 5$ Hz, 1F). IR (neat): $\nu = 2931, 1460, 1228, 1173, 827, 698$ cm$^{-1}$. HRMS (70 eV, EI): $m/z$ calcd. for C$_{15}$H$_{22}$F$_2$OSi $[M]$: 284.1408; Found: 284.1404.

1-[*tert*-Butyl(dimethyl)silyloxy]-2,2-difluoro-3-methyl-1-phenylcyclopropane 173b

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = -0.26$ (s, 3H), 0.02 (d, $J = 1.0$ Hz, 3H), 0.81 (s, 9H), 1.26 (ddd, $J = 6.5, 3.0, 1.0$ Hz, 3H), 1.61–1.71 (m, 1H), 7.29–7.38 (m, 3H), 7.46 (d, $J = 8.0$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.6$ (d, $J = 3$ Hz), $-4.3, 18.3, 25.6, 27.7$ (t, $J = 9$ Hz), 62.4 (t, $J = 10$ Hz), 114.0 (dd, $J = 301, 295$ Hz), 128.3, 128.4, 129.5, 138.0. $^{19}$FNMR (470 MHz, CDCl$_3$): $\delta = 12.2$ (d, $J = 155$ Hz, 1F), 34.1 (ddd, $J = 155, 18, 3$ Hz, 1F). IR (neat): $\nu = 2931, 2860, 1473, 1167, 839$ cm$^{-1}$. HRMS (70 eV, EI): $m/z$ calcd. for C$_{16}$H$_{24}$F$_2$OSi $[M]$: 298.1564; Found: 298.1563.

1-[*tert*-Butyl(dimethyl)silyloxy]-2,2-difluoro-3,3-dimethyl-1-phenylcyclopropane 173c

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = -0.43$ (s, 3H), 0.07 (d, $J = 1.8$ Hz, 3H), 0.79 (s, 9H), 0.81 (t, $J = 2.0$ Hz, 3H), 1.30 (dd, $J = 2.0, 1.8$ Hz, 3H), 7.27–7.35 (m, 3H), 7.37 (d, $J = 7.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.9$ (d, $J = 4$ Hz), $-4.5, 12.9$ (dd, $J = 7, 1$ Hz), 16.8 (d, $J = 7$ Hz), 18.2, 25.6, 29.4 (t, $J = 9$ Hz), 64.0 (dd, $J = 10, 9$ Hz), 115.8 (dd, $J = 313, 301$ Hz), 128.1, 128.1, 130.2, 136.0 (d, $J = 2$ Hz). $^{19}$FNMR (470 MHz, CDCl$_3$): $\delta = 17.5$ (d, $J = 154$ Hz, 1F), 22.9 (d, $J = 154$ Hz, 1F). IR (neat): $\nu = 2929, 1471, 1250, 1165, 866, 700$ cm$^{-1}$. HRMS (70 eV, EI): $m/z$ calcd. for C$_{17}$H$_{26}$F$_2$OSi $[M]$: 312.1721; Found: 312.1717.

2-[*tert*-Butyl(dimethyl)silyloxy]-7,7-difluorobicyclo[4.1.0]heptane 173d

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.12$ (s, 3H), 0.13 (s, 3H), 0.88 (s, 9H), 1.20–1.40 (m, 3H), 1.42–1.56 (m, 2H), 1.63 (dd, $J = 13.5, 7.5$ Hz, 1H), 1.76–1.86 (m, 1H), 1.87–1.99 (m, 1H), 2.09–2.21 (m, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.2$ (d, $J = 3$ Hz), $-3.9, 17.1$ (d, $J = 3$ Hz), 17.9, 20.7, 21.0 (d, $J = 3$ Hz), 25.7, 26.4 (dd, $J = 11, 8$ Hz), 27.3, 57.4 (dd, $J = 11, 10$ Hz), 114.6 (dd, $J = 302, 297$
19F NMR (470 MHz, CDCl3): δ = 15.7 (d, J = 157 Hz, 1F), 26.1 (dd, J = 157, 19 Hz, 1F). IR (neat): ν = 2931, 2858, 1473, 1252, 1192, 837 cm\(^{-1}\). EA: calcd. for C\(_{13}\)H\(_{24}\)F\(_2\)OSi: C 59.50%, H 9.22%; Found: C 59.10%, H 9.38%.

1-dodecyloxy-2,2-difluorocyclopropane 173e

\[
\begin{array}{c}
\text{F} \\
\text{F} \\
\text{On-C}_{12}\text{H}_{25}
\end{array}
\]

\(^1\)H NMR (500 MHz, CDCl3): δ = 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.42 (m, 19H), 1.42–1.52 (m, 1H), 1.59 (dt, J = 14.5, 7.0 Hz, 2H), 3.53–3.61 (m, 3H). \(^13\)C NMR (126 MHz, CDCl3): δ = 14.1, 17.9, 18.0 (dt, J = 10 Hz), 22.7, 25.9, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 56.9 (dd, J = 14, 9 Hz), 71.8, 111.5 (dd, J = 290, 289 Hz). \(19\)F NMR (470 MHz, CDCl3): δ = 12.8 (dddd, J = 165, 16, 6, 2 Hz, 1F), 31.4 (ddd, J = 165, 15, 10, 5 Hz, 1F). IR (neat): ν = 2924, 2854, 1468, 1225, 1018, 735 cm\(^{-1}\).

3.5.4. Synthesis of 5,5-difluorocyclopent-1-en-1-yl silyl ethers

(A) Typical procedure for the synthesis of 5,5-difluorocyclopent-1-en-1-yl silyl ethers.

To a p-xylene solution (0.5 mL) of nickel complex 174 (4.8 mg, 0.011 mmol) and 1,1,1,3,3,3-hexafluoro-2,2-di(p-tolyl)propane (6.2 mg, 0.019 mmol) were added silyl dienol ether 172a (53 mg, 0.20 mmol) and p-xylene (0.5 mL). The mixture was heated to 140 °C and TFDA (80 µL, 0.41 mmol) was added. The resulting mixture was stirred at 140 °C for 30 min and then cooled to room temperature. \(19\)F NMR analysis of the mixture revealed that silyl enol ether 187a was formed in 82% yield. The mixture was diluted with dichloromethane (2 mL) and a saturated aqueous solution (10 mL) of sodium hydrogen carbonate was added. Organic materials were extracted with dichloromethane three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane) to afford silyl 5,5-difluorocyclopent-1-en-1-yl ether 187a as a yellow liquid (52 mg, 83% yield).

(B) Spectral data of 5,5-difluorocyclopent-1-en-1-yl silyl ethers.

1-[tert-Butyl(dimethyl)silyloxy]-5,5-difluoro-3-phenylcyclopent-1-ene 187a

\[
\begin{array}{c}
\text{OTBS} \\
\text{F} \\
\text{F} \\
\text{Ph}
\end{array}
\]

\(^1\)H NMR (500 MHz, CDCl3): δ = 0.22 (s, 6H), 0.98 (s, 9H), 2.17 (dddd, J = 17.5, 15.5, 14.0, 4.0 Hz, 1H), 2.82 (ddt, J = 17.5, 15.0, 7.5 Hz, 1H), 3.80–3.88 (m, 1H), 5.19 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 7.0 Hz, 3H)}. IR (neat): ν = 2931, 2858, 1473, 1252, 1192, 837 cm\(^{-1}\). EA: calcd. for C\(_{13}\)H\(_{24}\)F\(_2\)OSi: C 59.50%, H 9.22%; Found: C 59.10%, H 9.38%.
7.5 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ −4.8, 18.2, 25.5, 40.6 (t, J = 3 Hz), 41.9 (dd, J = 25, 25 Hz), 115.4 (t, J = 7 Hz), 126.9, 127.0, 127.2 (t, J = 244 Hz), 128.7, 144.0 (d, J = 5 Hz), 148.5 (t, J = 24 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta =$ 64.4 (ddddd, J = 248, 15, 14, 2 Hz, 1F), 69.1 (ddddd, J = 248, 16, 11, 8 Hz, 1F).

IR (neat): $\nu =$ 2931, 2860, 1655, 1255, 1024, 742 cm$^{-1}$.

HRMS (70 eV, EI$^+$): m/z calcd. for C$_{13}$H$_{15}$F$_2$OSi [M$-$t-Bu]$^+$: 253.0859; Found: 253.0855.

1-[tert-Butyl(dimethyl)silyloxy]-5,5-difluoro-3-(4-methylphenyl)cyclopent-l-ene 187b

![Chemical structure of 187b](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 0.22 (s, 6H), 0.98 (s, 9H), 2.14 (ddddd, J = 18.0, 15.5, 14.0, 4.0 Hz, 1H) 2.33 (s, 3H), 2.80 (ddt, J = 18.0, 15.5, 7.5 Hz, 1H), 3.76–3.83 (m, 1H) 5.17 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ −4.8, 18.2, 21.0, 25.5, 40.2 (t, J = 3 Hz), 42.0 (dd, J = 25, 22 Hz), 115.7 (t, J = 7 Hz), 126.9, 127.3 (t, J = 245 Hz), 129.4, 136.5, 141.0 (d, J = 5 Hz), 148.4 (t, J = 24 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta =$ 64.3 (ddddd, J = 247, 16, 14, 2 Hz, 1F), 69.1 (ddddd, J = 247, 16, 11, 8 Hz, 1F). IR (neat): $\nu =$ 2931, 2860, 1655, 1174, 650 cm$^{-1}$. HRMS (70 eV, EI$^+$): m/z calcd. for C$_{14}$H$_{17}$F$_2$OSi [M$-$t-Bu]$^+$: 267.1015; Found: 267.1015.

1-[tert-Butyl(dimethyl)silyloxy]-3-(4-chlorophenyl)-5,5-difluorocyclopent-l-ene 187d

![Chemical structure of 187d](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 0.22 (s, 6H), 0.98 (s, 9H), 2.06–2.18 (m, 1H), 2.81 (ddt, J = 17.5, 15.5, 7.5 Hz, 1H), 3.77–3.84 (m, 1H) 5.14 (d, J = 2.5 Hz, 1H), 7.12 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ −4.8, 18.2, 25.5, 40.0 (t, J = 3 Hz), 41.8 (dd, J = 25, 22 Hz), 114.8 (t, J = 7 Hz), 126.9 (t, J = 244 Hz), 128.3, 128.9, 132.6, 142.5 (d, J = 5 Hz), 148.9 (t, J = 24 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta =$ 64.1 (dt, J = 248, 15 Hz, 1F), 69.3 (ddddd, J = 248, 18, 10, 8 Hz, 1F). IR (neat): $\nu =$ 2956, 2860, 1655, 1491, 1363, 1255, 841 cm$^{-1}$. HRMS (70 eV, EI$^+$): m/z calcd. for C$_{13}$H$_{14}$ClF$_2$OSi [M$-$t-Bu]$^+$: 287.0470; Found: 287.0468.
1-[\textit{tert}-Butyl(dimethyl)silyloxy]-5,5-difluoro-3-propylcyclopent-1-ene 187g

\[
\begin{align*}
\text{OTBS} & \quad \text{F} \quad \text{F} \\
& \quad \text{n-Pr}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.18$ (s, 3H), 0.19 (s, 3H), 0.91 (t, $J = 7.0$ Hz, 3H), 0.95 (s, 9H), 1.25–1.45 (m, 4H), 1.86 (dddd, $J = 18.5, 14.7, 12.5, 4.0$ Hz, 1H), 2.46 (ddt, $J = 18.0, 14.7, 8.0$ Hz, 1H), 2.53–2.63 (m, 1H), 5.12 (d, $J = 2.5$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.9, 14.1, 18.2, 20.5, 25.5, 34.5$ (t, $J = 3$ Hz), 38.7 (t, $J = 5$ Hz), 38.9 (dd, $J = 27, 22$ Hz), 116.4 (t, $J = 8$ Hz), 127.2 (t, $J = 244$ Hz), 147.4 (t, $J = 25$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta = 65.7$ (dddd, $J = 247, 18, 13, 3$ Hz, 1F), 69.5 (dddd, $J = 247, 19, 11, 8$ Hz, 1F). IR (neat): $\nu^- = 2931, 2859, 1655, 1365, 1242, 1176, 1099, 841$ cm$^{-1}$. HRMS (70 eV, EI$^+$): $m/z$ calcd. for C$_{10}$H$_{17}$F$_2$OSi [M–t-Bu]$^+$: 219.1016; Found: 219.1014.

1-[\textit{tert}-Butyl(dimethyl)silyloxy]-5,5-difluoro-2-methyl-3-phenylcyclopent-1-ene 187h

\[
\begin{align*}
\text{OTBS} & \quad \text{Me} \\
& \quad \text{Ph}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.22$ (s, 6H), 1.00 (s, 9H), 1.46 (t, $J = 3.0$ Hz, 3H), 2.21 (dddd, $J = 18.0, 15.0, 10.0, 4.0$ Hz, 1H), 2.79 (ddt, $J = 18.0, 15.0, 8.5$ Hz, 1H), 3.60 (dd, $J = 10.0, 8.5$ Hz, 1H), 7.14 (t, $J = 7.0$ Hz, 2H), 7.25 (t, $J = 7.0$ Hz, 1H), 7.32 (t, $J = 7.0$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.4, 11.2, 18.3, 25.7, 41.4$ (t, $J = 24$ Hz), 45.3 (t, $J = 2$ Hz), 126.9, 127.2 (t, $J = 11$ Hz), 127.4, 127.5 (t, $J = 242$ Hz), 128.8, 142.5 (t, $J = 25$ Hz), 143.0 (d, $J = 5$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta = 68.3$ (dm, $J = 245$ Hz, 1F), 73.3 (dm, $J = 245$ Hz, 1F). IR (neat): $\nu^- = 2931, 1691, 1346, 1215, 862$ cm$^{-1}$. HRMS (70 eV, EI$^+$): $m/z$ calcd. for C$_{14}$H$_{17}$F$_2$OSi [M–t-Bu]$^+$: 267.1016; Found: 267.1014.

2-Bromo-1-[\textit{tert}-butyl(dimethyl)silyloxy]-5,5-difluoro-3-phenylcyclopent-1-ene 187i

\[
\begin{align*}
\text{OTBS} & \quad \text{Br} \\
& \quad \text{Ph}
\end{align*}
\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.29$ (s, 6H), 1.02 (s, 9H), 2.38 (dddd, $J = 18.0, 15.0, 9.0, 3.5$ Hz, 1H), 2.91 (ddt, $J = 18.0, 15.0, 9.0$ Hz, 1H), 3.90 (ddt, $J = 11.0, 9.0, 3.5$ Hz, 1H), 7.18 (d, $J = 7.5$ Hz, 2H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.2, 18.4, 25.6, 42.0$ (t, $J = 24$ Hz), 46.4, 113.1 (t, $J = 10$ Hz), 125.0 (t, $J = 246$ Hz), 127.5, 128.9, 141.27, 141.31, 145.8 (t, $J = 25$ Hz).
\[^{19}\text{F NMR (470 MHz, CDCl}_3\text{)}\]: \(\delta = 68.2\) (ddd, \(J = 244, 18, 9\) Hz, 1F), 73.2 (dddd, \(J = 244, 18, 11, 9\) Hz, 1F). IR (neat): \(\nu^\text{c} = 2860, 1670, 1340, 1190, 1041, 845\) cm\(^{-1}\).

HRMS (70 eV, EI\(^+\)): \(m/z\) calcd. for \(\text{C}_{13}\text{H}_{14}\text{BrF}_2\text{OSi [M–t-Bu]}^+\): 330.9965; Found: 330.9962.

1-[\textit{tert}-Butyl(dimethyl)silyloxy]-5,5-difluoro-2,3-diphenylcyclopent-1-ene 187j

\[\text{OTBS} \quad \begin{array}{c} F \\ F \\ \text{Ph} \end{array} \quad \begin{array}{c} F \quad \text{Ph} \end{array} \]

\[^{1}\text{H NMR (500 MHz, CDCl}_3\text{)}\]: \(\delta = 0.09\) (s, 3H), 0.17 (s, 3H), 0.94 (s, 9H), 2.27 (dddd, \(J = 17.5, 15.0, 9.0, 3.5\) Hz, 1H), 2.91 (dddd, \(J = 18.5, 15.0, 11.0, 9.0\) Hz, 1H), 4.23 (td, \(J = 9.0, 3.5, 2.5\) Hz, 1H), 7.11–7.25 (m, 8H), 7.37 (d, \(J = 7.0\) Hz, 2H). \(^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}\): \(\delta = -4.3, -4.3, 18.4, 25.7, 41.6\) (t, \(J = 24\) Hz), 43.5, 125.9, 126.6, 127.0 (t, \(J = 8\) Hz), 127.3 (t, \(J = 243\) Hz), 127.3, 127.4, 128.3, 128.6, 133.4, 143.5 (d, \(J = 4\) Hz), 143.5 (t, \(J = 25\) Hz). \(^{19}\text{F NMR (470 MHz, CDCl}_3\text{)}\): \(\delta = 69.3\) (ddd, \(J = 247, 19, 9\) Hz, 1F), 74.2 (ddt, \(J = 247, 18, 11\) Hz, 1F). IR (neat): \(\nu^\text{c} = 2931, 1653, 1367, 1182, 1038, 858\) cm\(^{-1}\). HRMS (70 eV, EI\(^+\)): \(m/z\) calcd. for \(\text{C}_{23}\text{H}_{27}\text{FOSi [M–HF]}^+\): 366.1815; Found: 366.1816.

9-[\textit{tert}-Butyl(dimethyl)silyloxy]-8,8-difluorobicyclo[4.3.0]non-9-ene (187k)

\[\text{OTBS} \quad \begin{array}{c} F \\ F \\ \begin{array}{c} \text{Ph} \\ \text{Ph} \end{array} \end{array} \]

\[^{1}\text{H NMR (500 MHz, CDCl}_3\text{)}\]: \(\delta = 0.15\) (s, 6H), 0.97 (s, 9H), 1.15–1.45 (m, 3H), 1.69–1.88 (m, 4H), 1.95–2.02 (m, 1H), 2.29–2.40 (m, 1H), 2.42–2.53 (m, 1H), 2.61 (dd, \(J = 13.0, 4.5\) Hz, 1H). \(^{13}\text{C NMR (126 MHz, CDCl}_3\text{)}\): \(\delta = -4.7, -4.5, 18.3, 24.3, 25.5, 25.6, 25.7, 35.1\) (d, \(J = 6\) Hz), 35.8 (d, \(J = 5\) Hz), 38.9 (d, \(J = 26, 22\) Hz), 127.8 (t, \(J = 243\) Hz), 130.3 (t, \(J = 8\) Hz), 138.1 (t, \(J = 25\) Hz). \(^{19}\text{F NMR (470 MHz, CDCl}_3\text{)}\): \(\delta = 71.0\) (dm, \(J = 244\) Hz, 1F), 72.3 (dm, \(J = 244\) Hz, 1F). IR (neat): \(\nu^\text{c} = 2929, 2858, 1693, 1371, 1169, 995, 837\) cm\(^{-1}\). HRMS (70 eV, EI\(^+\)): \(m/z\) calcd. for \(\text{C}_{15}\text{H}_{23}\text{FOSi [M–HF]}^+\): 268.1659; Found: 268.1660.

\textit{trans}-1-[\textit{tert}-Butyl(dimethyl)silyloxy]-5,5-difluoro-4-methyl-3-phenylcyclopent-1-ene 187l

and 4-[\textit{tert}-Butyl(dimethyl)silyloxy]-3,3-difluoro-6-phenylhexa-1,4-diene 188

(d.r. = 79:21 isomeric mixture)
$^1$H NMR (500 MHz, CDCl$_3$): (187l) $\delta = 0.23$ (s, 3H), 0.24 (s, 3H), 0.99 (s, 9H), 1.16 (dd, $J = 7.0$, 2.0 Hz, 1H), 2.12–2.24 (m, 1H), 3.24–3.30 (m, 1H), 5.16 (t, $J = 2.0$ Hz, 1H), 7.17–7.36 (m, 5H); (188) $\delta = 0.14$ (s, 6H), 0.91 (s, 9H), 3.55 (dt, $J = 8.5$, 2.5 Hz, 2H), 5.13 (t, $J = 8.5$ Hz, 1H), 5.47 (d, $J = 10.8$ Hz, 1H), 5.72 (dt, $J = 17.5$, 2.5 Hz 1H), 6.07 (ddt, $J = 17.5$, 10.8, 10.8 Hz, 1H), 7.18 (d, $J = 7.0$ Hz, 2H), 7.25 (t, $J = 7.0$ Hz, 1 H), 7.33 (t, $J = 7.0$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): (187l) $\delta = -4.9$, $-4.8$, 10.7 (d, $J = 9$ Hz), 18.2, 25.5, 31.4 (d, $J = 5$ Hz), 48.6 (dd, $J = 24$, 21 Hz), 114.6 (dd, $J = 9$, 7 Hz), 117.3 (t, $J = 241$ Hz), 127.0, 127.2, 128.7 143.0 (d, $J = 4$ Hz), 148.6 (dd, $J = 26$, 23 Hz); (188) $\delta = -4.6$, 18.0, 25.6, 49.6 (d, $J = 7$ Hz), 112.2, 119.5 (t, $J = 9$ Hz), 126.0, 126.5 (t, $J = 247$ Hz), 128.3, 128.4, 132.2 (t, $J = 28$ Hz), 140.9, 144.4 (t, $J = 30$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): (187l) $\delta = 51.7$ (ddd, $J = 247$, 14, 2 Hz, 1F), 63.1 (ddd, $J = 247$, 18, 10 Hz, 1F); (188) $\delta = 66.2$ (d, $J = 11$ Hz). IR (neat): $\nu = 2931, 2860, 1655, 1363, 837, 731 \text{ cm}^{-1}$. HRMS (70 eV, EI$^+$): m/z (187l) calcd. for C$_{18}$H$_{23}$FOSi [M–HF]$^+$: 304.1659; Found: 304.1656; (188) calcd. for C$_{18}$H$_{25}$FOSi [M–HF]$^+$: 304.1659; Found: 304.1655.

3.5.5. Aminolysis of Nickel(II) Difluorocarbene Complex

To a toluene solution (4 mL) of nickel complex 175 (52 mg, 0.083 mmol) were added 2,6-dimethylaniline (100 mL, 0.809 mmol) and TFDA (20 mL, 0.10 mmol) at room temperature. After stirring overnight, the resulting solid was collected by paper filtration, washed with ether, and dissolved in methanol. High-resolution mass-analysis (ESI$^+$) revealed that the ion ($z = 2$) corresponding to the aminolysis product of the nickel(II) difluorocarbene complex, \text{LNi=C=NAr}^{2+} (L = pincer-type NHC ligand, Ar = 2,6-dimethylphenyl) 195, was observed.
3.5.6. Derivatization of 5,5-difluorocyclopent-1-en-1-yl silyl ether

(A) Synthesis of ketone 196

![Ketone 196](image)

To a THF solution (6 mL) of cyclic silyl enol ether 187a (31 mg, 0.10 mmol) and 1,1,1,3,3,3-hexafluoro-2,2-di(p-tolyl)propane (4.0 mg, 0.012 mmol) were added distilled water (1 mL), formic acid (87 wt%, 3 mL), and a THF solution of tetrabutylammonium fluoride (1.0 mol/L, 0.20 mmol) at room temperature. The resulting solution was heated to 55 °C, stirred for 41 h, and then cooled to room temperature. A saturated aqueous solution (20 mL) of sodium hydrogen carbonate was added and organic materials were extracted with dichloromethane three times. The combined extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. $^{19}$F NMR analysis of the resulting oil revealed that 0.080 mmol of ketone 196 was formed (80% yield).

(B) Synthesis of alcohol 197

![Alcohol 197](image)

A methanol solution (3 mL) containing ketone 196 (0.192 mmol) was prepared by the method described in the section 3-5-6 (A). To this solution was added sodium borohydride (15 mg, 0.39 mmol) at room temperature. The resulting mixture was heated to reflux, stirred for 2 h, and then cooled to room temperature. Water (5 mL) was added and organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (pentane/dichloromethane = 5/1 then dichloromethane) to give alcohol 197 as a colorless liquid (39 mg, quant, cis/trans = 64:36).

2,2-Difluoro-4-phenylcyclopentan-1-ol 197 (cis/trans = 67:33 diastereomeric mixture)

$^1$H NMR (500 MHz, CDCl$_3$): (cis isomer) δ = 1.83 (ddddd, J = 14.0, 10.0, 7.0, 3.0 Hz, 1H), 2.20–2.36 (m, 2H), 2.47–2.64 (m, 2H), 3.21 (tt, J = 10.5, 8.0 Hz, 1H), 4.20 (tt, J = 12.0, 6.0 Hz, 1H), 7.21–7.28 (m, 3H), 7.30–7.35 (m, 2H); (trans isomer) δ = 2.01–2.10 (m, 1H), 2.20–2.36 (m, 3H), 2.71 (ddddd, J = 18.0, 15.0, 13.5, 10.5, 1.5 Hz, 1H), 3.68 (tt, J = 10.0, 8.0 Hz, 1H), 4.24–4.30 (m,
1H), 7.21–7.28 (m, 3H), 7.30–7.35 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): (cis isomer) $\delta =$ 37.0 (dd, $J = 7$, 2 Hz), 39.4 (d, $J = 2$ Hz), 40.2 (t, $J = 23$ Hz), 74.2 (dd, $J = 31$, 21 Hz), 126.7, 127.0, 128.2 (dd, $J = 256$, 251 Hz), 128.7, 143.1; (trans isomer) $\delta =$ 39.1 (dd, $J = 6$, 3 Hz), 39.4 (d, $J = 2$ Hz), 40.3 (t, $J = 24$ Hz), 74.7 (dd, $J = 33$, 21 Hz), 126.6, 126.9, 128.7, 129.8 (dd, $J = 256$, 251 Hz), 143.8.

$^{19}$F NMR (470 MHz, CDCl$_3$): (cis isomer) $\delta =$ 50.2 (dmt, $J = 233$ Hz, 1F), 58.1 (ddt, $J = 233$, 24, 12 Hz, 1F); (trans isomer) $\delta =$ 47.1 (dt, $J = 236$, 10 Hz, 1F), 63.8 (ddddd, $J = 236$, 22, 18, 8, 3 Hz, 1F). IR (neat): $\nu$ = 3396, 3030, 1496, 1140, 1061, 698 cm$^{-1}$. HRMS (70 eV, EI): $m/z$: (cis isomer) Calcd. for C$_{11}$H$_{12}$F$_2$O [M$^+$]: 198.0856; Found: 198.0856; (trans isomer) Calcd. for C$_{11}$H$_{12}$F$_2$O [M$^+$]: 198.0856; Found: 198.0856.

(C) Synthesis of hydrazone 198

A methanol solution (5 mL) containing ketone 196 (0.498 mmol) was prepared by the method described in the section 3-5-6 (A). To this solution was added tosylhydrazine (136 mg, 0.730 mmol) at room temperature. The resulting mixture was heated to reflux, stirred for 21 h, and then cooled to room temperature. The formed precipitates were separated by filtration and washed with hexane. Removal of the remained solvents under reduced pressure gave hydrazone 198 as a colorless crystals (93 mg, 51% yield, the first crop). The filtrate was concentrated under reduced pressure and recrystallization from chloroform gave 198 (32 mg, 18% yield, the second crop). The third crop of 198 was also obtained in a similar manner (8 mg, 5% yield).

2,2-Difluoro-4-phenylcyclopentan-1-one 4-methylbenzenesulfonylhydrazone 198

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 2.24 (ddddd, $J = 26.0$, 13.5, 13.5, 10.0 Hz, 1H), 2.36 (dd, $J = 18.2$, 11.0, 4.5 Hz, 1H), 2.44 (s, 3H), 2.69 (td, $J = 13.5$, 6.5 Hz, 1H), 2.87 (dd, $J = 18.2$, 8.0 Hz, 1H), 3.35–3.45 (m, 1H), 7.18 (d, $J = 7.5$ Hz, 2H), 7.28 (d, $J = 7.0$ Hz, 1H), 7.30–7.37 (m, 4H), 7.77 (s,
1H), 7.87 (d, J = 8.0 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 21.7, 33.3, 37.3 (d, J = 7 Hz), 42.2 (dd, J = 25, 20 Hz), 122.4 (dd, J = 257, 246 Hz), 126.6, 127.5, 128.1, 129.0, 129.7, 134.8, 140.4, 144.7, 152.1 (t, J = 22 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ = 55.9 (dd, J = 254, 10 Hz, 1F), 66.8 (dddd, J = 254, 26, 14, 4 Hz, 1F). IR (neat): ν = 3205, 1597, 1496, 1348, 1165, 769 cm$^{-1}$. EA: Calcd. for C$_{18}$H$_{18}$F$_2$N$_2$O$_2$S: C 59.33%, H 4.98%, N 7.69%; Found: C 59.32%, H 5.00%, N 7.58%.

Crystallographic Information for 198

data_at001
_audit_creation_method SHELXL-97
_chemical_name_systematic ;
 ?
 ;
 _chemical_name_common ?
 _chemical_melting_point ?
 _chemical_formula_moiety ?
 _chemical_formula_sum 'C18 H18 F2 N2 O2 S'
 _chemical_formula_weight 364.40
loop_
_atom_type_symbol
_atom_type_description
_atom_type_scat_dispersion_real
_atom_type_scat_dispersion_imag
_atom_type_scat_source
'C'  'C'  0.0033  0.0016
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H'  'H'   0.0000   0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'N'   'N'   0.0061   0.0033
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'O'   'O'   0.0106   0.0060
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'F'   'F'   0.0171   0.0103
International Tables Vol C Tables 4.2.6.8 and 6.1.1.4

'S'  'S'  0.1246  0.1234

International Tables Vol C Tables 4.2.6.8 and 6.1.1.4

_symmetry_cell_setting ?
_symmetry_space_group_name_H-M ?

loop_

_symmetry_equiv_pos_as_xyz 'x, y, z'
 '-x, y+1/2, -z'

_cell_length_a 12.438(10)
_cell_length_b 5.549(4)
_cell_length_c 13.435(11)
_cell_angle_alpha 90.00
_cell_angle_beta 109.323(10)
_cell_angle_gamma 90.00
_cell_volume 875.0(12)
_cell_formula_units_Z 2
_cell_measurement_temperature 120(2)
_cell_measurement_reflns_used ?
_cell_measurement_theta_min ?
_cell_measurement_theta_max ?
_exptl_crystal_description ?
_exptl_crystal_colour ?
_exptl_crystal_size_max 0.11
_exptl_crystal_size_mid 0.03
_exptl_crystal_size_min 0.02
_exptl_crystal_density_meas ?
_exptl_crystal_density_diffrn 1.383
_exptl_crystal_density_method 'not measured'
_exptl_crystal_F_000 380
_exptl_absorpt_coefficient_mu 0.219
_exptl_absorpt_correction_type ?
_exptl_absorpt_correction_T_min 0.9763
_exptl_absorpt_correction_T_max 0.9956
_exptl_absorpt_process_details ?
_exptl_special_details

_diffrn_ambient_temperature  120(2)
_diffrn_radiation_wavelength  0.71073
_diffrn_radiation_type  MoKα
_diffrn_radiation_source  'fine-focus sealed tube'
_diffrn_radiation_monochromator  graphite
_diffrn_measurement_device_type  ?
_diffrn_measurement_method  ?
_diffrn_detector_area_resol_mean  ?
_diffrn_standards_number  ?
_diffrn_standards_interval_count  ?
_diffrn_standards_interval_time  ?
_diffrn_standards_decay_%  ?
_diffrn_reflns_number  5040
_diffrn_reflns_av_R_equivalents  0.0559
_diffrn_reflns_av_sigma/|I|  0.1273
_diffrn_reflns_limit_h_min  -16
_diffrn_reflns_limit_h_max  15
_diffrn_reflns_limit_k_min  -6
_diffrn_reflns_limit_k_max  7
_diffrn_reflns_limit_l_min  -17
_diffrn_reflns_limit_l_max  14
_diffrn_reflns_theta_min  1.61
_diffrn_reflns_theta_max  27.52
_reflns_number_total  3447
_reflns_number_gt  1964
_reflns_threshold_expression  >2sigma(I)
_computing_data_collection  ?
_computing_cell_refinement  ?
_computing_data_reduction  ?
_computing_structure_solution  'SHELXS-97 (Sheldrick, 1990)'
_computing_structure_refinement  'SHELXL-97 (Sheldrick, 1997)'
Refinement of $F^2$ against ALL reflections. The weighted R-factor $wR$ and goodness of fit $S$ are based on $F^2$, conventional R-factors $R$ are based on $F$, with $F$ set to zero for negative $F^2$. The threshold expression of $F^2 > 2\sigma(F^2)$ is used only for calculating R-factors(gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on $F^2$ are statistically about twice as large as those based on $F$, and R-factors based on ALL data will be even larger.

;  
_refine_ls_structure_factor_coef
_Fsqd
_refine_ls_matrix_type
full
_refine_ls_weighting_scheme
calc
_refine_ls_weighting_details
'calc w=1/[\gamma s^2(\text{Fo}^2)+(0.1000\text{P})^2+0.0000\text{P}]$ where $P=(\text{Fo}^2+2\text{Fc}^2)/3$

_atom_sites_solution_primary
direct
_atom_sites_solution_secondary
difmap
_atom_sites_solution_hydrogens
geom
_refine_ls_hydrogen_treatment
mixed
_refine_ls_extinction_method
none
_refine_ls_extinction_coef
?

_refine_ls_abs_structure_details

_refine_ls_abs_structure_Flack
0.38(18)
_refine_ls_number_reflns
3447
_refine_ls_number_parameters
265
_refine_ls_number_restraints
1
_refine_ls_R_factor_all
0.1318
_refine_ls_R_factor_gt
0.0632
_refine_ls_wR_factor_ref
0.1810
_refine_ls_wR_factor_gt
0.1392

_refine_ls_goodness_of_fit_ref
0.895
_refine_ls_restrained_S_all
0.895
<table>
<thead>
<tr>
<th>_refine_ls_shift/su_max</th>
<th>0.428</th>
</tr>
</thead>
<tbody>
<tr>
<td>_refine_ls_shift/su_mean</td>
<td>0.003</td>
</tr>
</tbody>
</table>

```
loop_
  _atom_site_label
  _atom_site_type_symbol
  _atom_site_fract_x
  _atom_site_fract_y
  _atom_site_fract_z
  _atom_site_U_iso_or_equiv
  _atom_site_adp_type
  _atom_site_occupancy
  _atom_site_symmetry_multiplicity
  _atom_site_calc_flag
  _atom_site_refinement_flags
  _atom_site_disorder_assembly
  _atom_site_disorder_group

  S1  S   0.34681(10)  0.7761(3)  0.49203(10)  0.0289(3)  Uani 1 1 d . . .
  O1  O   0.4640(3)  0.7748(9)  0.5566(3)  0.0339(8)  Uani 1 1 d . . .
  O2  O   0.2913(3)  0.9987(7)  0.4513(3)  0.0340(10) Uani 1 1 d . . .
  F1  F   0.0599(3)  0.5454(7)  0.1287(3)  0.0498(10) Uani 1 1 d . . .
  N1  N   0.3444(4)  0.6052(9)  0.3924(4)  0.0295(12) Uani 1 1 d . . .
  H30  H   0.382(5)  0.499(12)  0.403(5)  0.027(19)  Uiso 1 1 d . . .
  N6  N   0.2350(3)  0.5574(9)  0.3230(4)  0.0315(11) Uani 1 1 d . . .
  F4  F   0.0370(2)  0.2581(8)  0.2264(3)  0.0438(9)  Uani 1 1 d . . .
  C8  C   0.2257(4)  0.3885(10) 0.2563(5)  0.0269(13) Uani 1 1 d . A .
  C9  C   0.2676(4)  0.6309(9)  0.5598(4)  0.0263(12) Uani 1 1 d . . .
  C10  C   0.1095(5)  0.3395(11) 0.1782(5)  0.0362(16) Uani 1 1 d . A .
  C11  C   0.0983(5)  0.5900(12) 0.6049(5)  0.0375(15) Uani 1 1 d . . .
  H1  H   0.0241   0.6447   0.5993   0.045   Uiso 1 1 calc R . .
  C12  C   0.3099(5)  0.2269(11) 0.2338(5)  0.0321(15) Uani 1 1 d . . .
  H29  H   0.385(7)  0.312(18)  0.230(6)  0.10(3)  Uiso 1 1 d . . .
  H28  H   0.348(5)  0.118(13)  0.282(5)  0.044(19) Uiso 1 1 d . . .
  C13  C   0.3124(5)  0.4262(10) 0.6188(5)  0.0356(15) Uani 1 1 d . . .
  H2  H   0.3859   0.3693   0.6235   0.043   Uiso 1 1 calc R . .
  C14  C   0.1605(5)  0.7143(10) 0.5529(5)  0.0323(14) Uani 1 1 d . . .
```
<table>
<thead>
<tr>
<th>Atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Uiso</th>
<th>Uani</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3</td>
<td>0.1300</td>
<td>0.8546</td>
<td>0.5130</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>C15</td>
<td>0.2491(5)</td>
<td>0.3061(13)</td>
<td>0.6707(5)</td>
<td>0.0417(15)</td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td>0.2795</td>
<td>0.1659</td>
<td>0.7107</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>C16</td>
<td>0.1422(5)</td>
<td>0.3871(12)</td>
<td>0.6652(5)</td>
<td>0.0392(15)</td>
<td></td>
</tr>
<tr>
<td>C17</td>
<td>0.2795</td>
<td>0.1659</td>
<td>0.7107</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td>0.0968</td>
<td>0.3090</td>
<td>0.7951</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td>H6</td>
<td>0.0891</td>
<td>0.0806</td>
<td>0.7203</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td>H7</td>
<td>-0.0070</td>
<td>0.2850</td>
<td>0.6867</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>0.3901(5)</td>
<td>-0.2039(14)</td>
<td>0.1391(5)</td>
<td>0.0442(16)</td>
<td></td>
</tr>
<tr>
<td>H8</td>
<td>0.4259</td>
<td>-0.1764</td>
<td>0.2124</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td>0.4366(6)</td>
<td>-0.3660(13)</td>
<td>0.0878(6)</td>
<td>0.0507(19)</td>
<td></td>
</tr>
<tr>
<td>H9</td>
<td>0.5038</td>
<td>-0.4513</td>
<td>0.1259</td>
<td>0.061</td>
<td></td>
</tr>
<tr>
<td>C20</td>
<td>0.3857(6)</td>
<td>-0.4057(15)</td>
<td>-0.0195(6)</td>
<td>0.058(2)</td>
<td></td>
</tr>
<tr>
<td>H10</td>
<td>0.4187</td>
<td>-0.5152</td>
<td>-0.0554</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>C21</td>
<td>0.2926(6)</td>
<td>-0.0815(14)</td>
<td>0.0856(6)</td>
<td>0.0517(19)</td>
<td></td>
</tr>
<tr>
<td>C22</td>
<td>0.2418(6)</td>
<td>-0.1289(15)</td>
<td>-0.0208(6)</td>
<td>0.060(2)</td>
<td></td>
</tr>
<tr>
<td>H11</td>
<td>0.1727</td>
<td>-0.0495</td>
<td>-0.0588</td>
<td>0.072</td>
<td></td>
</tr>
<tr>
<td>C24</td>
<td>0.2888(7)</td>
<td>-0.2875(15)</td>
<td>-0.0725(6)</td>
<td>0.064(2)</td>
<td></td>
</tr>
<tr>
<td>H12</td>
<td>0.2531</td>
<td>-0.3146</td>
<td>-0.1459</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>C25</td>
<td>0.1283(6)</td>
<td>0.1576(18)</td>
<td>0.1036(7)</td>
<td>0.078(3)</td>
<td></td>
</tr>
<tr>
<td>H25</td>
<td>0.062(4)</td>
<td>0.099(10)</td>
<td>0.053(4)</td>
<td>0.028(15)</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>0.2266(9)</td>
<td>0.035(3)</td>
<td>0.1561(10)</td>
<td>0.028(4)</td>
<td></td>
</tr>
<tr>
<td>H13</td>
<td>0.184(6)</td>
<td>-0.079(14)</td>
<td>0.202(6)</td>
<td>0.000(19)</td>
<td></td>
</tr>
<tr>
<td>C26</td>
<td>0.2535(13)</td>
<td>0.153(3)</td>
<td>0.1206(12)</td>
<td>0.029(5)</td>
<td></td>
</tr>
<tr>
<td>H26</td>
<td>0.250(8)</td>
<td>0.31(2)</td>
<td>0.087(8)</td>
<td>0.00(2)</td>
<td></td>
</tr>
<tr>
<td>H31</td>
<td>0.163(12)</td>
<td>0.30(3)</td>
<td>0.038(11)</td>
<td>0.20(6)</td>
<td></td>
</tr>
</tbody>
</table>

loop_
_atom_site_aniso_label
_atom_site_aniso_U_11
_atom_site_aniso_U_22
_atom_site_aniso_U_33
_atom_site_aniso_U_23
_atom_site_aniso_U_13
_atom_site_aniso_U_12
S1 0.0278(6) 0.0311(7) 0.0290(7) -0.0028(8) 0.0111(5) -0.0030(7)
<table>
<thead>
<tr>
<th>Atom</th>
<th>U1</th>
<th>U2</th>
<th>U3</th>
<th>U12</th>
<th>U13</th>
<th>U23</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.0185(16)</td>
<td>0.044(2)</td>
<td>0.035(2)</td>
<td>-0.004(2)</td>
<td>0.0034(15)</td>
<td>-0.007(2)</td>
</tr>
<tr>
<td>O2</td>
<td>0.045(2)</td>
<td>0.027(2)</td>
<td>0.034(2)</td>
<td>0.0022(18)</td>
<td>0.017(2)</td>
<td>0.0021(18)</td>
</tr>
<tr>
<td>F1</td>
<td>0.0393(19)</td>
<td>0.059(3)</td>
<td>0.041(2)</td>
<td>0.011(2)</td>
<td>0.0008(17)</td>
<td>-0.0043(19)</td>
</tr>
<tr>
<td>N1</td>
<td>0.026(3)</td>
<td>0.027(3)</td>
<td>0.034(3)</td>
<td>-0.013(2)</td>
<td>0.008(2)</td>
<td>-0.001(2)</td>
</tr>
<tr>
<td>N6</td>
<td>0.022(2)</td>
<td>0.038(3)</td>
<td>0.031(3)</td>
<td>-0.007(2)</td>
<td>0.004(2)</td>
<td>-0.003(2)</td>
</tr>
<tr>
<td>F4</td>
<td>0.0282(15)</td>
<td>0.048(2)</td>
<td>0.058(2)</td>
<td>-0.003(2)</td>
<td>0.0179(15)</td>
<td>-0.0084(19)</td>
</tr>
<tr>
<td>C8</td>
<td>0.0393(19)</td>
<td>0.059(3)</td>
<td>0.041(2)</td>
<td>0.011(2)</td>
<td>0.0008(17)</td>
<td>-0.0043(19)</td>
</tr>
<tr>
<td>C9</td>
<td>0.032(3)</td>
<td>0.020(3)</td>
<td>0.029(3)</td>
<td>-0.003(2)</td>
<td>0.013(2)</td>
<td>-0.007(2)</td>
</tr>
<tr>
<td>C10</td>
<td>0.027(3)</td>
<td>0.039(5)</td>
<td>0.044(4)</td>
<td>-0.010(3)</td>
<td>0.014(3)</td>
<td>-0.002(2)</td>
</tr>
<tr>
<td>C11</td>
<td>0.031(3)</td>
<td>0.042(4)</td>
<td>0.045(4)</td>
<td>-0.004(3)</td>
<td>0.020(3)</td>
<td>-0.007(3)</td>
</tr>
<tr>
<td>C12</td>
<td>0.027(3)</td>
<td>0.035(4)</td>
<td>0.032(3)</td>
<td>0.000(3)</td>
<td>0.007(3)</td>
<td>0.002(3)</td>
</tr>
<tr>
<td>C13</td>
<td>0.035(3)</td>
<td>0.025(3)</td>
<td>0.049(4)</td>
<td>0.000(3)</td>
<td>0.019(3)</td>
<td>-0.006(3)</td>
</tr>
<tr>
<td>C14</td>
<td>0.032(3)</td>
<td>0.029(4)</td>
<td>0.036(3)</td>
<td>0.002(2)</td>
<td>0.012(2)</td>
<td>0.003(2)</td>
</tr>
<tr>
<td>C15</td>
<td>0.052(3)</td>
<td>0.033(4)</td>
<td>0.044(4)</td>
<td>0.005(3)</td>
<td>0.020(3)</td>
<td>-0.007(3)</td>
</tr>
<tr>
<td>C16</td>
<td>0.045(4)</td>
<td>0.038(4)</td>
<td>0.041(4)</td>
<td>-0.006(3)</td>
<td>0.023(3)</td>
<td>-0.008(3)</td>
</tr>
<tr>
<td>C17</td>
<td>0.059(4)</td>
<td>0.046(4)</td>
<td>0.065(4)</td>
<td>0.001(4)</td>
<td>0.036(3)</td>
<td>-0.015(4)</td>
</tr>
<tr>
<td>C18</td>
<td>0.036(3)</td>
<td>0.045(4)</td>
<td>0.055(4)</td>
<td>-0.007(4)</td>
<td>0.019(3)</td>
<td>0.008(3)</td>
</tr>
<tr>
<td>C19</td>
<td>0.044(4)</td>
<td>0.041(4)</td>
<td>0.078(6)</td>
<td>0.003(4)</td>
<td>0.035(4)</td>
<td>0.004(3)</td>
</tr>
<tr>
<td>C20</td>
<td>0.061(5)</td>
<td>0.056(5)</td>
<td>0.072(6)</td>
<td>-0.022(4)</td>
<td>0.043(4)</td>
<td>-0.005(4)</td>
</tr>
<tr>
<td>C21</td>
<td>0.040(4)</td>
<td>0.067(5)</td>
<td>0.042(4)</td>
<td>-0.023(4)</td>
<td>0.005(3)</td>
<td>0.014(3)</td>
</tr>
<tr>
<td>C22</td>
<td>0.056(5)</td>
<td>0.061(5)</td>
<td>0.052(5)</td>
<td>-0.023(4)</td>
<td>0.005(4)</td>
<td>0.014(3)</td>
</tr>
<tr>
<td>C24</td>
<td>0.072(5)</td>
<td>0.071(7)</td>
<td>0.057(5)</td>
<td>-0.020(4)</td>
<td>0.031(4)</td>
<td>0.003(4)</td>
</tr>
<tr>
<td>C25</td>
<td>0.030(4)</td>
<td>0.112(8)</td>
<td>0.088(6)</td>
<td>-0.076(6)</td>
<td>0.015(4)</td>
<td>-0.006(4)</td>
</tr>
<tr>
<td>C1</td>
<td>0.030(6)</td>
<td>0.032(9)</td>
<td>0.023(7)</td>
<td>-0.007(6)</td>
<td>0.011(5)</td>
<td>-0.003(5)</td>
</tr>
<tr>
<td>C26</td>
<td>0.042(8)</td>
<td>0.017(10)</td>
<td>0.030(9)</td>
<td>-0.002(7)</td>
<td>0.015(7)</td>
<td>0.012(7)</td>
</tr>
</tbody>
</table>

_geom_special_details

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.
<table>
<thead>
<tr>
<th>_geom_bond_atom_site_label_1</th>
<th>_geom_bond_atom_site_label_2</th>
<th>_geom_bond_distance</th>
<th>_geom_bond_site_symmetry_2</th>
<th>_geom_bond_publ_flag</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>O1</td>
<td>1.429(3)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>S1</td>
<td>O2</td>
<td>1.433(4)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>S1</td>
<td>N1</td>
<td>1.632(5)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>S1</td>
<td>C9</td>
<td>1.744(5)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>F1</td>
<td>C10</td>
<td>1.362(7)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>N1</td>
<td>N6</td>
<td>1.397(6)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>N1</td>
<td>H30</td>
<td>0.73(6)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>N6</td>
<td>C8</td>
<td>1.275(7)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>F4</td>
<td>C10</td>
<td>1.351(6)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>1.484(8)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C10</td>
<td>1.504(7)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C9</td>
<td>C14</td>
<td>1.384(7)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C9</td>
<td>C13</td>
<td>1.392(8)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C10</td>
<td>C25</td>
<td>1.495(9)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C11</td>
<td>C14</td>
<td>1.386(8)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C11</td>
<td>C16</td>
<td>1.389(9)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C11</td>
<td>H1</td>
<td>0.9500</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C12</td>
<td>C26</td>
<td>1.506(14)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C12</td>
<td>C1</td>
<td>1.606(13)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C12</td>
<td>H29</td>
<td>1.06(9)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C12</td>
<td>H28</td>
<td>0.89(7)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C13</td>
<td>C15</td>
<td>1.383(8)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C13</td>
<td>H2</td>
<td>0.9500</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C14</td>
<td>H3</td>
<td>0.9500</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C15</td>
<td>C16</td>
<td>1.382(9)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C15</td>
<td>H4</td>
<td>0.9500</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C16</td>
<td>C17</td>
<td>1.503(9)</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C17</td>
<td>H5</td>
<td>0.9800</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C17</td>
<td>H6</td>
<td>0.9800</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>C17</td>
<td>H7</td>
<td>0.9800</td>
<td></td>
<td>?</td>
</tr>
<tr>
<td>Atom 1</td>
<td>Atom 2</td>
<td>Atom 3</td>
<td>Distance (Å)</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>C21</td>
<td></td>
<td>1.367(9)</td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>C19</td>
<td></td>
<td>1.386(10)</td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>H8</td>
<td></td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td>C20</td>
<td></td>
<td>1.372(9)</td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td>H9</td>
<td></td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C20</td>
<td>C24</td>
<td></td>
<td>1.367(10)</td>
<td></td>
</tr>
<tr>
<td>C20</td>
<td>H10</td>
<td></td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C21</td>
<td>C22</td>
<td></td>
<td>1.384(10)</td>
<td></td>
</tr>
<tr>
<td>C21</td>
<td>C26</td>
<td></td>
<td>1.518(14)</td>
<td></td>
</tr>
<tr>
<td>C21</td>
<td>C1</td>
<td></td>
<td>1.583(13)</td>
<td></td>
</tr>
<tr>
<td>C22</td>
<td>C24</td>
<td></td>
<td>1.366(10)</td>
<td></td>
</tr>
<tr>
<td>C22</td>
<td>H11</td>
<td></td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C24</td>
<td>H12</td>
<td></td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C25</td>
<td>C1</td>
<td></td>
<td>1.372(14)</td>
<td></td>
</tr>
<tr>
<td>C25</td>
<td>C26</td>
<td></td>
<td>1.497(18)</td>
<td></td>
</tr>
<tr>
<td>C25</td>
<td>H25</td>
<td></td>
<td>0.94(5)</td>
<td></td>
</tr>
<tr>
<td>C25</td>
<td>H31</td>
<td></td>
<td>1.35(15)</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>H13</td>
<td></td>
<td>1.13(8)</td>
<td></td>
</tr>
<tr>
<td>C26</td>
<td>H26</td>
<td></td>
<td>0.95(12)</td>
<td></td>
</tr>
</tbody>
</table>

Loop

<table>
<thead>
<tr>
<th>Atom 1</th>
<th>Atom 2</th>
<th>Atom 3</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>S1</td>
<td>O2</td>
<td>120.2(3)</td>
</tr>
<tr>
<td>O1</td>
<td>S1</td>
<td>N1</td>
<td>103.5(3)</td>
</tr>
<tr>
<td>O2</td>
<td>S1</td>
<td>N1</td>
<td>108.2(3)</td>
</tr>
<tr>
<td>O1</td>
<td>S1</td>
<td>C9</td>
<td>108.6(3)</td>
</tr>
<tr>
<td>O2</td>
<td>S1</td>
<td>C9</td>
<td>108.3(2)</td>
</tr>
<tr>
<td>N1</td>
<td>S1</td>
<td>C9</td>
<td>107.4(3)</td>
</tr>
<tr>
<td>N6</td>
<td>N1</td>
<td>S1</td>
<td>114.0(4)</td>
</tr>
<tr>
<td>N6</td>
<td>N1</td>
<td>H30</td>
<td>113(5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>S1</td>
<td>N1</td>
<td>H30</td>
<td>118(5)</td>
</tr>
<tr>
<td>C8</td>
<td>N6</td>
<td>N1</td>
<td>116.7(4)</td>
</tr>
<tr>
<td>N6</td>
<td>C8</td>
<td>C12</td>
<td>133.0(5)</td>
</tr>
<tr>
<td>N6</td>
<td>C8</td>
<td>C10</td>
<td>117.8(5)</td>
</tr>
<tr>
<td>C12</td>
<td>C8</td>
<td>C10</td>
<td>109.2(5)</td>
</tr>
<tr>
<td>C14</td>
<td>C9</td>
<td>C13</td>
<td>120.4(5)</td>
</tr>
<tr>
<td>C14</td>
<td>C9</td>
<td>S1</td>
<td>120.5(4)</td>
</tr>
<tr>
<td>C13</td>
<td>C9</td>
<td>S1</td>
<td>119.1(4)</td>
</tr>
<tr>
<td>F4</td>
<td>C10</td>
<td>F1</td>
<td>104.4(4)</td>
</tr>
<tr>
<td>F4</td>
<td>C10</td>
<td>C25</td>
<td>111.9(6)</td>
</tr>
<tr>
<td>F1</td>
<td>C10</td>
<td>C25</td>
<td>112.7(6)</td>
</tr>
<tr>
<td>F4</td>
<td>C10</td>
<td>C8</td>
<td>111.5(5)</td>
</tr>
<tr>
<td>F1</td>
<td>C10</td>
<td>C8</td>
<td>111.4(5)</td>
</tr>
<tr>
<td>C25</td>
<td>C10</td>
<td>C8</td>
<td>105.2(5)</td>
</tr>
<tr>
<td>C14</td>
<td>C11</td>
<td>C16</td>
<td>121.3(5)</td>
</tr>
<tr>
<td>C14</td>
<td>C11</td>
<td>H1</td>
<td>119.3</td>
</tr>
<tr>
<td>C16</td>
<td>C11</td>
<td>H1</td>
<td>119.3</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>C26</td>
<td>104.2(6)</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>C1</td>
<td>100.7(5)</td>
</tr>
<tr>
<td>C26</td>
<td>C12</td>
<td>C1</td>
<td>34.8(6)</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>H29</td>
<td>115(5)</td>
</tr>
<tr>
<td>C26</td>
<td>C12</td>
<td>H29</td>
<td>102(4)</td>
</tr>
<tr>
<td>C1</td>
<td>C12</td>
<td>H29</td>
<td>131(5)</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>H28</td>
<td>120(4)</td>
</tr>
<tr>
<td>C26</td>
<td>C12</td>
<td>H28</td>
<td>120(4)</td>
</tr>
<tr>
<td>C1</td>
<td>C12</td>
<td>H28</td>
<td>95(4)</td>
</tr>
<tr>
<td>H29</td>
<td>C12</td>
<td>H28</td>
<td>94(6)</td>
</tr>
<tr>
<td>C15</td>
<td>C13</td>
<td>C9</td>
<td>119.5(6)</td>
</tr>
<tr>
<td>C15</td>
<td>C13</td>
<td>H2</td>
<td>120.2</td>
</tr>
<tr>
<td>C9</td>
<td>C13</td>
<td>H2</td>
<td>120.2</td>
</tr>
<tr>
<td>C11</td>
<td>C14</td>
<td>C9</td>
<td>119.0(5)</td>
</tr>
<tr>
<td>C11</td>
<td>C14</td>
<td>H3</td>
<td>120.5</td>
</tr>
<tr>
<td>C9</td>
<td>C14</td>
<td>H3</td>
<td>120.5</td>
</tr>
<tr>
<td>C13</td>
<td>C15</td>
<td>C16</td>
<td>121.0(6)</td>
</tr>
<tr>
<td>C13</td>
<td>C15</td>
<td>H4</td>
<td>119.5</td>
</tr>
</tbody>
</table>
C26  C25  H25  137(3) . .  ?
C10  C25  H25  115(3) . .  ?
C1   C25  H31  102(6) . .  ?
C26  C25  H31  65(6) . .  ?
C10  C25  H31  101(7) . .  ?
H25  C25  H31  97(7) . .  ?
C25  C1   C21  116.4(10) . . ?
C25  C1   C12  106.2(9) . . ?
C21  C1   C12  108.0(8) . . ?
C25  C1   H13  93(4) . .  ?
C21  C1   H13  122(4) . . ?
C12  C1   H13  110(4) . . ?
C25  C26  C12  105.2(11) . . ?
C25  C26  C21  113.0(12) . . ?
C12  C26  C21  117.1(10) . . ?
C25  C26  H26  92(6) . .  ?
C12  C26  H26  100(6) . . ?
C21  C26  H26  126(6) . . ?
loop_
  _geom_torsion_atom_site_label_1
  _geom_torsion_atom_site_label_2
  _geom_torsion_atom_site_label_3
  _geom_torsion_atom_site_label_4
  _geom_torsion
  _geom_torsion_site_symmetry_1
  _geom_torsion_site_symmetry_2
  _geom_torsion_site_symmetry_3
  _geom_torsion_site_symmetry_4
  _geom_torsion_publ_flag
O1  S1   N1   N6   173.4(4) . .  ?
O2  S1   N1   N6   -58.1(5) . .  ?
C9  S1   N1   N6   58.5(5) . .  ?
S1  N1   N6   C8   -166.4(4) . . ?
N1  N6   C8   C12  -1.4(9) . .  ?
N1  N6   C8   C10  -177.8(5) . . ?
<p>| O1  | S1  | C9   | C14  | 142.3(5) ... | ? |
| O2  | S1  | C9   | C14  | 10.3(5) ... | ? |
| N1  | S1  | C9   | C14  | -106.3(5) ... | ? |
| O1  | S1  | C9   | C13  | -39.3(5) ... | ? |
| O2  | S1  | C9   | C13  | -171.4(4) ... | ? |
| N1  | S1  | C9   | C13  | 72.0(5) ... | ? |
| N6  | C8  | C10  | F4   | -65.4(7) ... | ? |
| C12 | C8  | C10  | F4   | 117.3(5) ... | ? |
| N6  | C8  | C10  | F1   | 50.7(7) ... | ? |
| C12 | C8  | C10  | F1   | -126.5(5) ... | ? |
| N6  | C8  | C10  | C25  | 173.1(6) ... | ? |
| C12 | C8  | C10  | C25  | -4.2(7) ... | ? |
| N6  | C8  | C12  | C26  | -155.5(10) ... | ? |
| C10 | C8  | C12  | C26  | 21.1(11) ... | ? |
| N6  | C8  | C12  | C1   | 169.0(9) ... | ? |
| C10 | C8  | C12  | C1   | -14.4(9) ... | ? |
| C14 | C9  | C13  | C15  | 0.0(9) ... | ? |
| S1  | C9  | C13  | C15  | -178.4(5) ... | ? |
| C16 | C11 | C14  | C9   | 1.2(9) ... | ? |
| C13 | C9  | C14  | C11  | -0.4(8) ... | ? |
| S1  | C9  | C14  | C11  | 77.9(4) ... | ? |
| C9  | C13 | C15  | C16  | -0.3(10) ... | ? |
| C13 | C15 | C16  | C11  | 1.1(10) ... | ? |
| C13 | C15 | C16  | C17  | 179.8(6) ... | ? |
| C14 | C11 | C16  | C15  | -1.5(10) ... | ? |
| C14 | C11 | C16  | C17  | 179.8(6) ... | ? |
| C21 | C18 | C19  | C20  | 0.7(11) ... | ? |
| C18 | C19 | C20  | C24  | -1.4(11) ... | ? |
| C19 | C18 | C21  | C22  | 1.0(11) ... | ? |
| C19 | C18 | C21  | C26  | -158.9(12) ... | ? |
| C19 | C18 | C21  | C1   | 161.7(9) ... | ? |
| C18 | C21 | C22  | C24  | -2.0(12) ... | ? |
| C26 | C21 | C22  | C24  | 160.3(11) ... | ? |
| C1  | C21 | C22  | C24  | -161.2(10) ... | ? |
| C19 | C20 | C24  | C22  | 0.4(12) ... | ? |</p>
<table>
<thead>
<tr>
<th>C21</th>
<th>C22</th>
<th>C24</th>
<th>C20</th>
<th>l.3(12)</th>
<th>. . .</th>
<th>?</th>
</tr>
</thead>
<tbody>
<tr>
<td>F4</td>
<td>C10</td>
<td>C25</td>
<td>C1</td>
<td>-96.4(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>F1</td>
<td>C10</td>
<td>C25</td>
<td>C1</td>
<td>146.4(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C10</td>
<td>C25</td>
<td>C1</td>
<td>24.8(11)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>F4</td>
<td>C10</td>
<td>C25</td>
<td>C26</td>
<td>-136.0(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>F1</td>
<td>C10</td>
<td>C25</td>
<td>C26</td>
<td>106.8(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C10</td>
<td>C25</td>
<td>C26</td>
<td>-14.8(11)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C26</td>
<td>C25</td>
<td>C1</td>
<td>C21</td>
<td>-58.9(13)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C10</td>
<td>C25</td>
<td>C1</td>
<td>C21</td>
<td>-154.6(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C26</td>
<td>C25</td>
<td>C1</td>
<td>C12</td>
<td>61.3(13)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C10</td>
<td>C25</td>
<td>C1</td>
<td>C12</td>
<td>-34.3(12)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C18</td>
<td>C21</td>
<td>C1</td>
<td>C25</td>
<td>-179.7(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C22</td>
<td>C21</td>
<td>C1</td>
<td>C25</td>
<td>-20.0(18)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C26</td>
<td>C21</td>
<td>C1</td>
<td>C25</td>
<td>64.3(15)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C18</td>
<td>C21</td>
<td>C1</td>
<td>C12</td>
<td>61.0(13)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C22</td>
<td>C21</td>
<td>C1</td>
<td>C12</td>
<td>-139.4(8)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C26</td>
<td>C21</td>
<td>C1</td>
<td>C12</td>
<td>-55.1(12)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>C1</td>
<td>C25</td>
<td>30.2(12)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C26</td>
<td>C12</td>
<td>C1</td>
<td>C25</td>
<td>-69.3(15)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>C1</td>
<td>C21</td>
<td>155.8(8)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C26</td>
<td>C12</td>
<td>C1</td>
<td>C21</td>
<td>56.2(11)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C1</td>
<td>C25</td>
<td>C26</td>
<td>C12</td>
<td>-68.6(13)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C10</td>
<td>C25</td>
<td>C26</td>
<td>C12</td>
<td>28.0(14)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C1</td>
<td>C25</td>
<td>C26</td>
<td>C21</td>
<td>60.3(13)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C10</td>
<td>C25</td>
<td>C26</td>
<td>C21</td>
<td>156.9(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>C26</td>
<td>C25</td>
<td>-29.8(13)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C1</td>
<td>C12</td>
<td>C26</td>
<td>C25</td>
<td>58.6(14)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C8</td>
<td>C12</td>
<td>C26</td>
<td>C21</td>
<td>-156.2(12)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C1</td>
<td>C12</td>
<td>C26</td>
<td>C21</td>
<td>-67.9(14)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C18</td>
<td>C21</td>
<td>C26</td>
<td>C25</td>
<td>-138.1(10)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C22</td>
<td>C21</td>
<td>C26</td>
<td>C25</td>
<td>61.2(16)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C1</td>
<td>C21</td>
<td>C26</td>
<td>C25</td>
<td>-53.4(14)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C18</td>
<td>C21</td>
<td>C26</td>
<td>C12</td>
<td>-16(2)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C22</td>
<td>C21</td>
<td>C26</td>
<td>C12</td>
<td>-176.2(11)</td>
<td>. . .</td>
<td>?</td>
</tr>
<tr>
<td>C1</td>
<td>C21</td>
<td>C26</td>
<td>C12</td>
<td>69.1(15)</td>
<td>. . .</td>
<td>?</td>
</tr>
</tbody>
</table>
(D) Synthesis of oxime 199

To a THF solution (6 mL) of cyclic silyl enol ether 187a (311 mg, 1.00 mmol) were added formic acid (87%, 3 mL), distilled water (1 mL), and a THF solution (2.00 mL) of tetrabutylammonium fluoride (1.0 mol/L, 2.0 mmol). The resulting mixture was heated to 55 °C stirred for 3.5 d, and then cooled to room temperature. Hydroxyamine hydrochloride (106 mg, 1.52 mmol) was added and the mixture was heated to 50 °C, stirred for 24 h, and then cooled to room temperature. A saturated aqueous solution (20 mL) of sodium hydrogen carbonate was added and organic materials were extracted with ethyl acetate three times. The combined extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give oxime 199 as yellow crystals (184 mg, 87% yield).

2,2-Difluoro-4-phenylcyclopentan-1-one oxime 199

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 2.31$ (dddd, $J = 26.0, 14.0, 14.0, 10.5$ Hz, 1H), 2.63 (ddd, $J = 19.0,$
11.0, 5.0 Hz, 1H), 2.73 (tdd, J = 14.0, 7.0, 2.0 Hz, 1H), 3.24 (ddt, J = 19.0, 7.0, 2.0 Hz, 1H), 3.42 (tt, J = 11.0, 7.0 Hz, 1H), 7.25 (d, J = 7.0 Hz, 2H), 7.28 (t, J = 7.0 Hz, 1H), 7.36 (t, J = 7.0 Hz, 2H), 8.22 (s, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 32.9, 37.4 (d, J = 7 Hz), 42.8 (dd, J = 25, 20 Hz), 123.2 (dd, J = 256, 246 Hz), 126.7, 127.3, 128.9, 141.0, 156.6 (t, J = 21 Hz).

$^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ = 56.7 (dd, J = 252, 10 Hz, 1F), 67.6 (dddd, J = 252, 26, 14, 2 Hz, 1F). IR (neat): $\nu$ ~ 3269, 1456, 1180, 912, 748 cm$^{-1}$.

HRMS (70 eV, EI): $m/z$ calcd. for C$_{11}$H$_8$F$_2$NO [M]$^+$: 211.0809; Found: 211.0809.

$(E)$ Synthesis of enone 200

![Enone 200](image)

To a dichloromethane solution (300 mL) of cyclic silyl enol ether 187a (64 mg, 0.21 mmol) was added N-bromosuccinimide (38 mg, 0.22 mmol) at room temperature. The resulting mixture was stirred for 96 h. A saturated aqueous solution (30 mL) of sodium hydrogen carbonate was added and most of the organic solvent was removed under reduced pressure. Organic materials were extracted with dichloromethane three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give enone 200 as colorless crystals (34 mg, 86% yield).

5,5-Difluoro-3-phenylcyclopent-2-en-1-one 200

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 3.44 (td, J = 12.0, 2.0 Hz, 2H), 6.70 (tt, J = 2.0, 2.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 39.0 (t, J = 26 Hz), 115.5 (t, J = 255 Hz), 123.3 (t, J = 3 Hz), 127.2, 129.3, 132.3, 133.1, 169.2 (t, J = 6 Hz), 192.9 (t, J = 26 Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): $\delta$ = 50.6 (td, J = 12, 2 Hz). IR (neat): $\nu$ ~ 3101, 2927, 1736, 1593, 1338, 1057, 906 cm$^{-1}$. HRMS (70 eV, EI): $m/z$ calcd. for C$_{11}$H$_8$F$_2$O [M]$^+$: 194.0543; Found: 194.0544.

$(F)$ Synthesis of epoxide 201

![Epoxide 201](image)

To a dichloromethane solution (4 mL) of cyclic silyl enol ether 187a (237 mg, 0.763 mmol) was added a dichloromethane solution (6 mL) of m-chloroperbenzoic acid (mCPBA, 417 mg, 2.42
mmol) at –20 °C. The resulting mixture was slowly warmed to room temperature and stirred for 41 h. A saturated aqueous solution (10 mL) of sodium hydrogen carbonate was added and organic materials were extracted with dichloromethane three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give epoxide 201 as a colorless liquid (212 mg, 85% yield).

2-[\textit{tert}-Butyl(dimethyl)silyloxy]-2,3-epoxy-1,1-difluoro-4-phenylcyclopentane 201 (81:19 diastereomeric mixture)

$^1$H NMR (500 MHz, CDCl$_3$): (major isomer) $\delta = 0.15$ (s, 3H), 0.19 (s, 3H), 0.92 (s, 9H), 2.24 (ddd, $J = 20.0, 15.0, 1.0$ Hz, 1H), 2.46 (ddd, $J = 24.0, 15.0, 10.0$ Hz, 1H), 3.41 (dd, $J = 10.0, 3.0$ Hz, 1H), 3.66 (d, $J = 3.0$ Hz, 1H), 7.24–7.38 (m, 5H); (minor isomer) $\delta = 0.18$ (s, 3H), 0.23 (s, 3H), 0.93 (s, 9H), 2.09 (ddddd, $J = 26.0, 14.0, 12.0, 10.0$ Hz, 1H), 2.37–2.46 (m, 1H), 3.37 (d, $J = 9.0$ Hz, 1H), 3.81 (dd, $J = 2.5, 1.0$ Hz, 1H), 7.24–7.38 (m, 5H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = -4.1, -4.2, 17.8, 25.4, 37.6$ (t, $J = 23$ Hz), 38.3 (t, $J = 23$ Hz), 39.9 (d, $J = 7$ Hz), 40.9 (d, $J = 7$ Hz), 64.5 (d, $J = 6$ Hz), 65.7 (d, $J = 6$ Hz), 83.3 (d, $J = 36, 26$ Hz), 85.0 (dd, $J = 36, 26$ Hz), 124.0 (dd, $J = 262, 245$ Hz), 124.1 (dd, $J = 258, 246$ Hz), 127.4, 127.4 127.6, 127.6, 128.8, 129.0, 138.9, 139.5. $^{19}$F NMR (470 MHz, CDCl$_3$): (major isomer) $\delta = 45.6$ (ddd, $J = 243, 15, 3$ Hz, 1F), 62.5 (ddddd, $J = 243, 24, 20, 3$ Hz, 1F); (minor isomer) $\delta = 43.7$ (dd, $J = 243, 12$ Hz, 1F), 54.8 (ddd, $J = 243, 26, 18$ Hz, 1F). IR (neat): $\nu^{-} =$ 2931, 1437, 1254, 1174, 1059, 837 cm$^{-1}$. HRMS (70 eV, EI): $m/z$ (major isomer) Calcd. for C$_{13}$H$_{15}$F$_2$O$_2$Si [M–t-Bu]$^+$: 269.0809; Found: 269.0809; (minor isomer) calcd. for C$_{13}$H$_{15}$F$_2$O$_2$Si [M–t-Bu]$^+$: 269.0809; Found: 269.0807.

\( (G) \) Synthesis of enone 202

To a THF solution (1 mL) of epoxide 201 (27 mg, 0.083 mmol) was added an aqueous solution (1 mL) of potassium hydrogen difluoride (6.2 mg, 0.079 mmol) at room temperature. The resulting mixture was stirred for 46 h. A saturated aqueous solution (5 mL) of sodium hydrogen carbonate was added and organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. The sulfate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to give enone 202 as
colorless crystals (8.6 mg, 54% yield).

3-Fluoro-2-hydroxy-5-phenylcyclopent-2-en-1-one 202

$^1$H NMR (500 MHz, CDCl$_3$): δ = 2.74 (d, $J = 18.0$ Hz, 1H), 3.18 (dd, $J = 18.0$, 6.5 Hz, 1H), 3.76 (d, $J = 6.5$ Hz, 1H), 6.06 (s, 1H), 7.16 (d, $J = 7.5$ Hz, 2H), 7.28 (t, $J = 7.5$ Hz, 1H), 7.34 (t, $J = 7.5$ Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$): δ = 31.7 (d, $J = 14$ Hz), 48.2, 127.5, 127.7, 129.1, 132.8, 137.2, 164.9 (d, $J = 299$ Hz), 199.7 (d, $J = 11$ Hz). $^{19}$F NMR (470 MHz, CDCl$_3$): δ = 56.0 (s). IR (neat): ν = 3257, 1734, 1660, 1381, 1329, 1219, 1101 cm$^{-1}$. HRMS (ESI, negative): $m/z$ clcd. for C$_{11}$H$_8$FO$_2$ [M–H]$^–$: 191.0508; Found: 191.0508.

3.5.7. Preparation of metal bromodifluoroacetate

(A) Typical procedure for the preparation of sodium bromodifluoroacetate.

To a methanol (30 mL) solution of sodium hydroxide (1.99 g, 49.8 mmol) was added ethyl bromodifluoroacetate (6.5 mL, 50.3 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature, and then heated at 60 °C. After the reaction mixture was stirred for 3 h at 60 °C, the reaction mixture was concentrated in vacuo. The residue was azeotropically removed of water with toluene to give sodium bromodifluoroacetate (9.17 g, 93%) and stored in glove box.

3.5.8. Synthesis of 4,4-difluorocyclopent-1-en-1-yl silyl ether

(A) Typical procedure for the synthesis of 4,4-difluorocyclopent-1-en-1-yl silyl ethers.

To an acetonitrile (1.8 mL) suspension of copper(I) catalyst 204b (10 mg, 0.016 mmol) and sodium bromodifluoroacetate (72 mg, 0.366 mmol), was added a dienol silyl ether 187a (87.6 mg, 0.336 mmol) at room temperature. The reaction mixture was stirred and heated at 50 °C. After the reaction mixture was stirred for 12 h at 50 °C, hexane (5.0 mL) and saturated aqueous NaHCO$_3$ (5.0 mL) were added at 0 °C to quench the reaction at room temperature. Organic materials were extracted with hexane five times, the combined extracts were washed with brine and dried over anhydrous Na$_2$SO$_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$ deactivated by H$_2$O 15 vol%, hexane only) to give five-membered difluoroenol silyl ether 203a (74.0 mg, 71%) as a colorless oil.

(B) Spectral data of 4,4-difluorocyclopent-1-en-1-yl silyl ethers.

1-[tert-Butyl(dimethyl)silyloxy]-4,4-difluoro-3-phenylcyclopent-1-ene 203a

![Diagram](99)
1H NMR (500 MHz, CDCl₃): δ = 0.23 (s, 3H), 0.25 (s, 3H), 0.97 (s, 9H), 2.86 (t, J = 14.0 Hz, 2H), 4.17 (dd, J = 19.5, 7.8 Hz, 1H), 4.68–4.74 (m, 1H), 7.22–7.27 (m, 2H), 7.22–7.31 (m, 1H), 7.31–7.37 (m, 2H). 13C NMR (126 MHz, CDCl₃): δ = −4.6, 18.1, 25.6, 43.5 (t, J = 27 Hz), 56.1 (dd, J = 27, 24 Hz), 103.3 (d, J = 3 Hz), 127.0 (dd, J = 256, 253 Hz), 127.5, 128.3, 128.7, 136.8, 151.0. 19F NMR (470 MHz, CDCl₃): δ = 63.9 (dddt, J = 228, 14, 8, 2 Hz, 1F), 71.6 (dddt, J = 228, 20, 14, 2 Hz, 1F). IR (neat); ν = 2931, 1645, 1255, 906, 731 cm⁻¹. HRMS (70 eV, EI): m/z calcd. for C₁₇H₂₄F₂OSi ([M]⁺): 310.1565; found: 310.1580.

1-[tert-Butyl(dimethyl)silyloxy]-4,4-difluoro-3-(4-methylphenyl)cyclopent-1-ene 203b

OTBS

\[\text{Me} \]

1H NMR (500 MHz, CDCl₃): δ = 0.23 (s, 3H), 0.24 (s, 3H), 0.96 (s, 9H), 2.34 (s, 3H), 2.84 (t, J = 14.0 Hz, 2H), 4.13 (dd, J = 20.0, 8.0 Hz, 1H), 4.69–4.73 (m, 1H), 7.13–7.17 (m, 4H). 13C NMR (126 MHz, CDCl₃): δ = −4.6, 18.1, 21.1, 25.6, 43.4 (t, J = 28 Hz), 55.7 (dd, J = 27, 23 Hz), 103.4 (d, J = 3 Hz), 127.0 (dd, J = 256, 253 Hz), 128.5, 129.0, 133.7 (t, J = 4 Hz), 137.2, 150.8 (t, J = 7 Hz). 19F NMR (470 MHz, CDCl₃): δ = 64.9 (dddt, J = 227, 14, 8, 3 Hz), 72.7 (dddt, J = 227, 20, 14, 2 Hz). IR (neat); ν = 2956, 2931, 2860, 1645, 1340, 835 cm⁻¹. HRMS (70 eV, EI): m/z calcd. for C₁₈H₂₆F₂OSi ([M]⁺): 324.1721; found: 324.1716.

1-[tert-Butyl(dimethyl)silyloxy]-4,4-difluoro-3-(4-methoxyphenyl)cyclopent-1-ene 203c

OTBS

\[\text{OMe} \]

1H NMR (500 MHz, CDCl₃): δ = 0.23 (s, 3H), 0.24 (s, 3H), 0.96 (s, 9H), 2.84 (t, J = 14.0 Hz, 2H), 3.80 (s, 3H), 4.12 (dd, J = 19.0, 7.0 Hz, 1H), 4.70 (s, 1H), 6.88 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H). 13C NMR (126 MHz, CDCl₃): δ = −4.6, 18.1, 25.6, 43.4 (t, J = 27 Hz), 55.3 (dd, J = 27, 23 Hz), 55.2, 103.4 (d, J = 3 Hz), 127.0 (dd, J = 255, 253 Hz), 128.7 (dd, J = 5, 3 Hz), 150.8 (t, J = 7 Hz), 159.0. 19F NMR (470 MHz, CDCl₃): δ = 63.6 (dddt, J = 227, 14, 7, 2 Hz), 71.2 (ddt, J = 227, 19, 14 Hz). IR (neat); ν = 2956, 2931, 2860, 1647, 1514, 1342, 1252, 837 cm⁻¹. HRMS (70 eV, EI): m/z calcd. for C₁₈H₂₆F₂O₂Si ([M]⁺): 340.1670; found: 340.1667.
1-[\textit{tert}-Butyl(dimethyl)silyloxy]-3-(4-bromophenyl)-4,4-difluorocyclopent-1-ene 203e

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) at (0,0) {\text{OTBS}};
\node[draw,shape=circle] (B) at (1,0) {\text{F}};
\node[draw,shape=circle] (C) at (2,0) {\text{F}};
\node[draw,shape=circle] (D) at (1,-1) {\text{Br}};
\end{tikzpicture}
\end{center}

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 0.22 (s, 3H), 0.24 (s, 3H), 0.96 (s, 9H), 2.76–2.92 (m, 2H), 4.12 (dd, $J =$ 19.2, 8.2 Hz, 1H), 4.64–4.69 (m, 1H), 7.11 (d, $J =$ 8.4 Hz, 2H), 7.45 (d, $J =$ 8.4 Hz, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ -4.60, -4.57, 18.1, 25.6, 43.5 (t, $J =$ 27 Hz), 55.6 (dd, $J =$ 27, 24 Hz), 102.7, 121.5, 126.6 (dd, $J =$ 256, 254 Hz), 130.3, 131.4, 135.8, 151.4 (t, $J =$ 7 Hz).

$^{19}$F NMR (470 MHz, CDCl$_3$): $\delta =$ 64.1 (dtdd, $J =$ 228, 14, 8, 3 Hz, 1F), 71.3 (ddtd, $J =$ 228, 19, 14, 3 Hz, 1F).

IR (neat); $\nu_\text{~} =$ 2931, 1645, 1487, 1342, 904, 729 cm$^{-1}$.

HRMS (70 eV, EI): $m/z$ calcd. for C$_{17}$H$_{23}$BrF$_2$OSi ([M]$^+$): 388.0670; found: 388.0667.

1-[\textit{tert}-Butyl(dimethyl)silyloxy]-4,4-difluoro-3-(2-naphthyl)cyclopent-1-ene 203f

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) at (0,0) {\text{OTBS}};
\node[draw,shape=circle] (B) at (1,0) {\text{F}};
\node[draw,shape=circle] (C) at (2,0) {\text{F}};
\node[draw,shape=circle] (D) at (0.5,-1) {\text{n-Pr}};
\node[draw,shape=circle] (E) at (1,-1) {\text{F}};
\end{tikzpicture}
\end{center}

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 0.26 (s, 3H), 0.29 (s, 3H), 0.99 (s, 9H), 2.91 (t, $J =$ 14.0 Hz, 2H), 4.34 (dd, $J =$ 19.0, 8.0 Hz, 1H), 4.80–4.83 (m, 1H), 7.38 (d, $J =$ 8.5 Hz, 1H), 7.43–7.49 (m, 2H), 7.70 (s, 1H), 7.79–7.85 (m, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta =$ -4.6, -4.5, 18.1, 25.6, 43.6 (t, $J =$ 27 Hz), 56.2 (dd, $J =$ 27, 23 Hz), 103.3 (d, $J =$ 3 Hz), 125.8, 126.0, 126.9, 127.1 (dd, $J =$ 256, 253 Hz), 127.3, 127.6, 127.8, 127.9, 132.9, 133.3, 134.3 (dd, $J =$ 5, 3 Hz), 151.1 (t, $J =$ 7 Hz).

$^{19}$F NMR (470 MHz, CDCl$_3$): $\delta =$ 64.2 (dtdd, $J =$ 228, 14, 8, 3 Hz), 72.4 (ddtd, $J =$ 228, 19, 14, 2 Hz).

IR (neat); $\nu_\text{~} =$ 2956, 1645, 1487, 1342, 904, 729 cm$^{-1}$.

HRMS (70 eV, EI): $m/z$ calcd. for C$_{21}$H$_{26}$F$_2$OSi ([M]$^+$): 360.1721; found: 360.1719.

1-[\textit{tert}-Butyl(dimethyl)silyloxy]-4,4-difluoro-3-propylcyclopent-1-ene 203g

\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) at (0,0) {\text{OTBS}};
\node[draw,shape=circle] (B) at (1,0) {\text{F}};
\node[draw,shape=circle] (C) at (2,0) {\text{F}};
\node[draw,shape=circle] (D) at (0.5,-1) {n-Pr};
\node[draw,shape=circle] (E) at (1,-1) {F};
\end{tikzpicture}
\end{center}

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 0.16 (s, 3H), 0.17 (s, 3H), 0.87–0.95 (m, 12H), 1.23–1.32 (m, 1H), 1.31–1.41 (m, 2H), 1.53–1.63 (m, 1H), 2.68–2.78 (m, 2H), 2.79–2.90 (m, 1H), 4.55–4.60 (m, 1H).
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = -4.7, 14.2, 18.1, 20.5, 25.5, 31.4\) (dd, \(J = 8, 2\) Hz), 43.7 (t, \(J = 27\) Hz), 49.6 (dd, \(J = 25, 22\) Hz), 104.2 (d, \(J = 4\) Hz), 128.6 (dd, \(J = 256, 251\) Hz), 149.1 (t, \(J = 7\) Hz).

\(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \(\delta = 56.6\) (ddt, \(J = 229, 15, 8\) Hz, 1F), 71.7 (dddt, \(J = 229, 20, 15, 2\) Hz, 1F). IR (neat); \(\nu = 2931, 1647, 1340, 1254, 1122, 835, 781\) cm\(^{-1}\). HRMS (70 eV, EI): \(m/z\) calcd. for C\(_{14}\)H\(_{26}\)F\(_2\)OSi (\([\text{M}]^+\)): 276.1721; found: 276.1710.

1-[\textit{tert}-Butyl(dimethyl)silyloxy]-4,4-difluoro-2-methyl-3-phenylcyclopent-1-ene 203h

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.21\) (s, 3H), 0.21 (s, 3H), 0.99 (s, 9H), 1.48 (s, 3H), 2.75–2.87 (m, 1H), 2.85–2.96 (m, 1H), 3.91 (dd, \(J = 21.5, 4.5\) Hz, 1H), 7.14–7.18 (m, 2H), 7.27–7.37 (m, 3H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = -4.1, -4.0, 10.3, 18.1, 25.6, 43.3\) (t, \(J = 27\) Hz), 60.1 (dd, \(J = 27, 23\) Hz), 113.5 (d, \(J = 1\) Hz), 126.3 (dd, \(J = 256, 251\) Hz), 127.5, 128.3, 129.1, 135.6 (t, \(J = 4\) Hz), 143.3 (dd, \(J = 8, 4\) Hz). \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \(\delta = 63.0\) (ddt, \(J = 228, 15, 5\) Hz, 1F), 74.2 (dtd, \(J = 228, 22, 15\) Hz, 1F). IR (neat); \(\nu = 2931, 1687, 1254, 1124, 881, 698\) cm\(^{-1}\). HRMS (70 eV, EI): \(m/z\) calcd. for C\(_{18}\)H\(_{26}\)F\(_2\)OSi (\([\text{M}]^+\)): 324.1721; found: 324.1722.

9-[\textit{tert}-Butyl(dimethyl)silyloxy]-7,7-difluorobicyclo[4.3.0]non-9-ene 203k

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.13\) (s, 6H), 0.93 (s, 9H), 1.07–1.17 (m, 1H), 1.18–1.32 (m, 2H), 1.61–1.78 (m, 2H), 1.80–1.93 (d, 2H), 2.52–2.76 (m, 3H), 2.77–2.89 (m, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta = -4.3, -4.2, 18.1, 23.5, 24.7, 25.4, 25.5, 25.7\) (d, \(J = 11\) Hz), 44.1 (t, \(J = 28\) Hz), 50.0 (dd, \(J = 26, 24\) Hz), 116.5 (d, \(J = 4\) Hz), 127.7 (dd, \(J = 254, 250\) Hz), 137.8 (dd, \(J = 6, 5\) Hz). \(^{19}\)F NMR (470 MHz, CDCl\(_3\)): \(\delta = 60.2\) (dddd, \(J = 231, 21, 14, 8\) Hz), 71.4 (dddd, \(J = 231, 20, 18, 8\) Hz). IR (neat); \(\nu = 2933, 2858, 1693, 1119, 856, 837, 779\) cm\(^{-1}\). HRMS (70 eV, EI): \(m/z\) calcd. for C\(_{15}\)H\(_{26}\)F\(_2\)OSi (\([\text{M}]^+\)): 288.1721; found: 288.1722.

3.5.8. Aminolysis of Copper(I) Difluorocarbene Complex

To a acetonitrile solution (3 mL) of copper(I) complex 204b (8 mg, 0.013 mmol) were added butylamine (14 \(\mu\)L, 0.142 mmol) and sodium bromodifluoroacetate (14 mg, 0.071 mmol) at room temperature. After stirring for 24 h, the resulting mixture was dissolved in acetonitrile. High-resolution mass-analysis (ESI\(^{+}\)) revealed that the ion (\(z = 1\)) corresponding to the aminolysis
product of the copper(I) difluorocarbene complex, \( \text{LCu} = \text{C=NBu}^- \) (L = 4,7-dimethyl-1,10-phenanthroline) 205, was observed.

### 3.5.9. Derivatization of 4,4-difluorocyclopent-1-en-1-yl silyl ether

(A) Synthesis of enone 206

![Chemical Structure](image)

To a tetrahydrofuran (THF) solution (5.0 mL) of 203a (63.4 mg, 0.204 mmol), was added aqueous formic acid (87 wt%, 2.0 mL, 19 mmol) at room temperature. The reaction solution was cooled to 0 °C and tetrabutylammonium fluoride solution (1.0 M in THF, 0.40 mL, 0.40 mmol) was added. After the reaction mixture was stirred for 25 min at 0 °C, it was allowed to be warmed up to room temperature. After the reaction mixture was stirred for 10 h at room temperature, pH=7 phosphate buffer (10 mL) was added to quench the reaction at room temperature. Organic materials were extracted with ethyl acetate four times, the combined extracts were washed with brine three times, dried over anhydrous Na2SO4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO2, hexane–ethyl acetate, 10:1) to give fluorocyclopentenone 206 (25.1 mg, 70%) as a pale yellow oil.

3-Fluoro-4-phenylcyclopent-2-en-1-one 206

\(^1\)H NMR (500 MHz, CDCl3): \( \delta = 2.58 \) (dt, \( J = 18.5, 2.5 \) Hz, 1H), 3.10 (ddd, \( J = 18.5, 7.5, 1.5 \) Hz, 1H), 4.18 (d, \( J = 7.5 \) Hz, 1H), 5.83 (d, \( J = 1.5 \) Hz, 1H), 7.22 (d, \( J = 7.0 \) Hz, 2H), 7.32 (t, \( J = 7.0 \) Hz, 1H), 7.38 (dd, \( J = 7.0, 7.0 \) Hz, 2H). \(^{13}\)C NMR (126 MHz, CDCl3): \( \delta = 45.1 \) (d, \( J = 16 \) Hz), 45.6, 112.2 (d, \( J = 5 \) Hz), 127.1, 128.0, 129.2, 137.4, 191.2 (d, \( J = 309 \) Hz), 202.6 (d, \( J = 15 \) Hz). \(^{19}\)F NMR (470 MHz, CDCl3): \( \delta = 81.6 \) (s, 1F). IR (neat): \( \nu = 1714, 1637, 1323, 912, 742 \) cm\(^{-1}\). HRMS (70 eV, EI\(^+\)): \( m/z \) calcd. for C\(_{11}\)H\(_9\)FO ([M]\(^+\)): 176.0637; found: 176.0638.

(B) Synthesis of enone 207

![Chemical Structure](image)

To a tetrahydrofuran (THF) solution (3.0 mL) of 206 (35.2 mg, 0.200 mmol), was added methylolithium (1.2 M in Et\(_2\)O, 0.35 mL, 0.413 mmol) at –78 °C. After the reaction mixture was stirred for 2 h at –78 °C, pH=7 phosphate buffer (5 mL) was added to quench the reaction at –78 °C. It was allowed to be warmed up to room temperature. Organic materials were extracted with ethyl
acetate three times, the combined extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$, hexane–ethyl acetate, 30:1) to give cyclopentenone 207 (12.3 mg, 36%) as a pale yellow oil.
3.6. Reference


Chapter 4

Conclusion

I have achieved catalytic and selective syntheses of difluoromethyl and difluoromethylene compounds (i) free difluorocarbene and (ii) metal difluorocarbene complexes.

In chapter 2, syntheses of difluoromethyl imidates and difluoromethoxypyridines were described. The NHC-catalyzed generation of free difluorocarbene was effected under mild conditions, which enable an efficient and regioselective $O$-difluoromethylation of secondary amides and pyridones.

In chapter 3, regioselective syntheses of both $\alpha,\alpha$- and $\beta,\beta$-difluorocyclopentanone derivatives by unprecedented transition metal difluorocarbene complexes were described. Dienol silyl ethers, readily prepared from $\alpha,\beta$-unsaturated ketones, underwent a sequence of difluorocyclopropanation and VCP rearrangement catalyzed by a nickel(II) difluorocarbene complex to selectively afford 5,5-difluorocyclopent-1-en-1-yl silyl ethers. Copper(I) difluorocarbene complex catalyzed an efficient [4 + 1] cycloaddition of the same dienol silyl ethers with sodium bromodifluoroacetate, which provided 4,4-difluorocyclopent-1-en-1-yl silyl ethers in a selective manner. The key Ni(II)- and Cu(I)-difluorocarbene complexes were captured as aminolysis products, which were detected by mass spectroscopy.

Through these studies, advantages of catalytic introduction of difluorocarbene moiety in synthesis were successfully demonstrated. These results provide a variety of difluoromethylene compounds, which are sufficiently promising in pharmaceutical and agricultural sciences as well as materials sciences.
List of Publications

[1] “NHC-catalyzed generation of difluorocarbene and its application to difluoromethylation of oxygen nucleophiles”

Fuchibe, K.; Koseki, Y.; Aono, T.; Sasagawa, H.; Ichikawa, J.


Aono, T.; Sasagawa, H.; Fuchibe, K.; Ichikawa, J.

Acknowledgement

The studies described in this thesis have been performed under the direction of Professor Junji Ichikawa at the Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, from April 2011 to March 2016.

The author is deeply grateful to Professor Junji Ichikawa for his helpful discussions, experimental guidance, hearty advice, contribution to revising the author’s manuscripts, and encouragement throughout the course of the studies. He would like to express his deep gratitude to Associate Professor Kohei Fuchibe for the helpful discussion, experimental guidance, and contribution to revising the author’s manuscript. He is deeply grateful to Dr. Takeshi Fujita for his practical guidance, helpful discussions, considerate suggestions, and single-crystal X-ray analysis in this dissertation.

The author wishes to thank the member of Ichikawa laboratory. Dr. Tomohiro, Ichitsuka, Mr. Hisashi Sasagawa, and Mr. Yuta Koseki are appreciated for their technical advices and helpful suggestions. Mr. Masaki Bando, Mr. Ryo Takayama, Mr. Ji Hu, Mr. Keisuke Watanabe, and Mr. Tomohiro, Hidano are acknowledged for helpful suggestions and kind assistance. Mr. Naoto Suzuki, Mr. Ikko Takahashi, Mr. Hiroto Matsuno, Mr. Ryu Ueda, Mr. Tsuyoshi Takanohashi, and Mr. Keisuke Miura are acknowledged for their continuous encouragement and kind assistance.

Finally, the author wishes to express his deep gratitude to his parents and brother, Mr. Yuzuru Aono, Ms. Taemi Aono, and Mr. Yoshiaki Aono for their financial support or continuous and heart-warming encouragement through the research.

Tatsuya Aono