Selective Syntheses of Difluoromethylene Compounds via Difluorocarbene Catalyses

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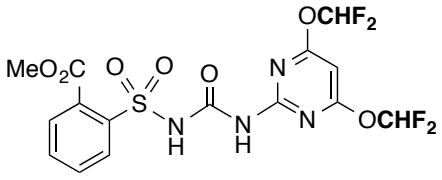
Contents

Chapter 1

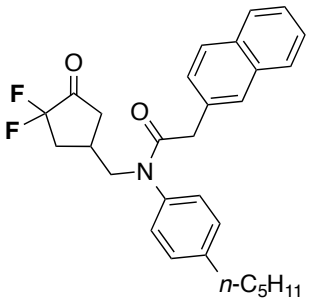
1. General Introduction

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. Fortheremore, being the smallest substituents next to hydrogen, fluorine has been recognized as a mimic of hydrogen.

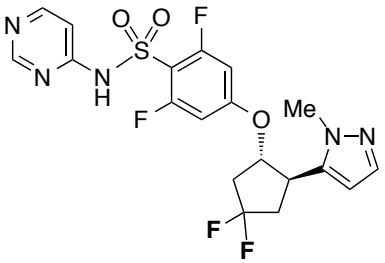
Among organofluorine compounds, difluoromethylene compounds containing a -CHF_2 group or a -CF_2- group have recently attracted particular attention. For example, "Primisulfuron-methyl" possessing two difluoromethyloxy groups acts as herbicides (Figure 1).[2a] Difluorocyclopentanone derivatives **1** 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)



1 (antimalarial effect)



2 (anti-bronchitis effect)

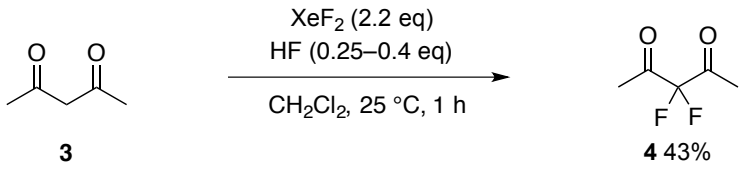
Figure 1

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.

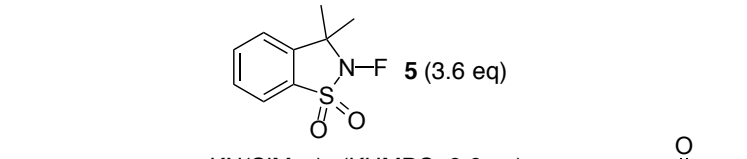
Concerning the introduction of fluorine substituents both electrophilic and nucleophilic fluorinating agents have been used.[3] For example, treatment of diketone **3** with xenon difluoride gives α,α-difluoroketone **4** in 43% yield (eq. 1).[4] Treatment of ketone **6** with *N*-F-sultam **5** in the presence of potassium bis(trimethylsilyl)amide (KHMDS) affords α,α-difluoroketone **7** in 64%

yield (eq. 2).[5] 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).[6] Dithioacetal **10** reacts with tetrabutylammonium dihydrogen trifluoride in the presence of *N*-iodosuccinimide (NIS) to give **11** in 82% yield (eq. 4).[7] 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 prier to fluorination.

(i)-1. Electrophilic Introduction of Fluorine Substituents



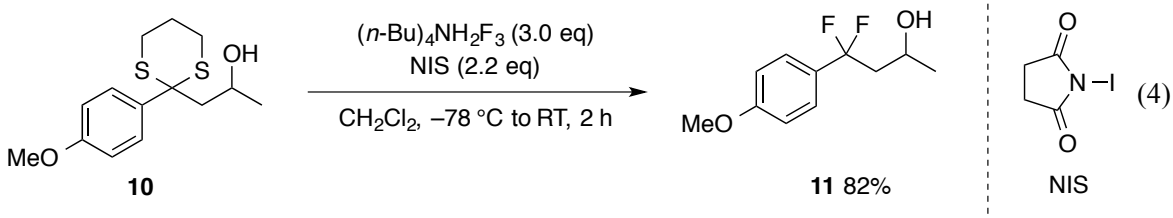
3 **4** 43% (1)



6 **7** 64% (2)

(i)-2. Nucleophilic Introduction of Fluorine Substituents

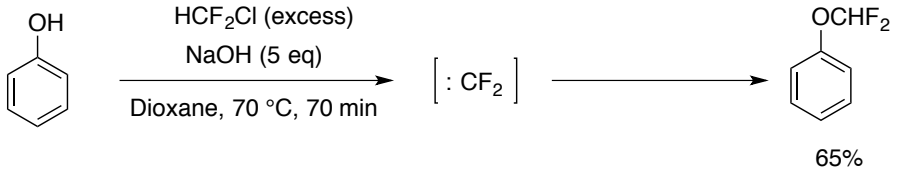
8 **9** 80% (3)



10 **11** 82% (4)

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 hydroxide, 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 difluoromethylenation. 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



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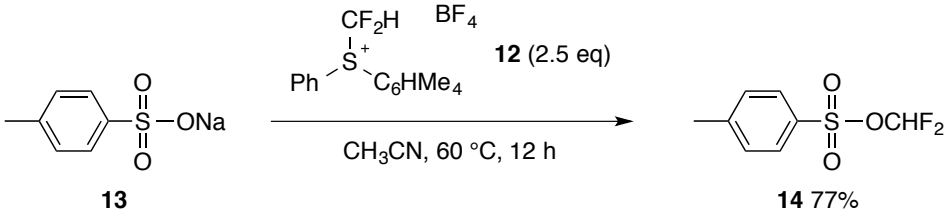
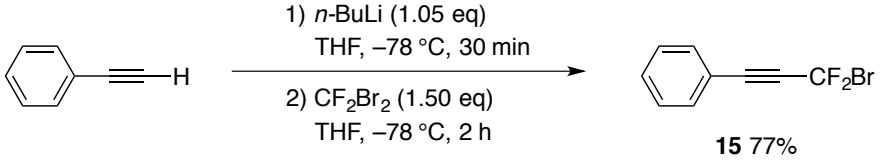
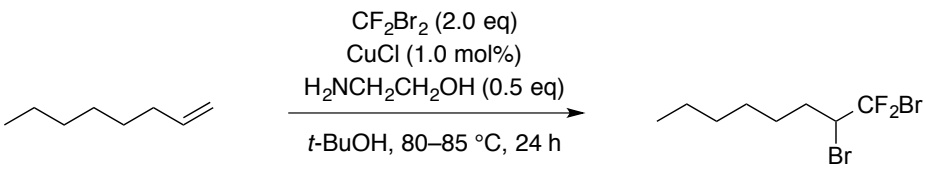


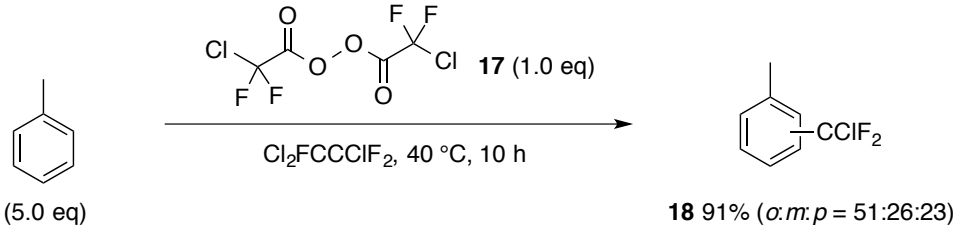
13 **14** 77% (6)



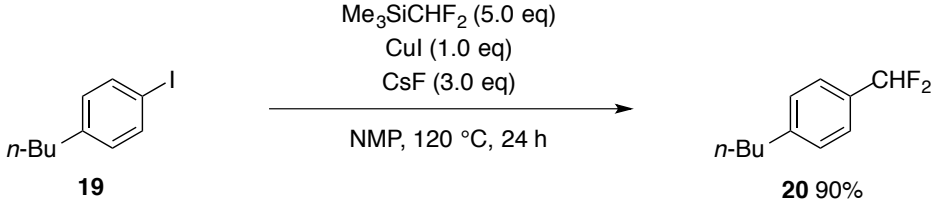
15 77% (7)



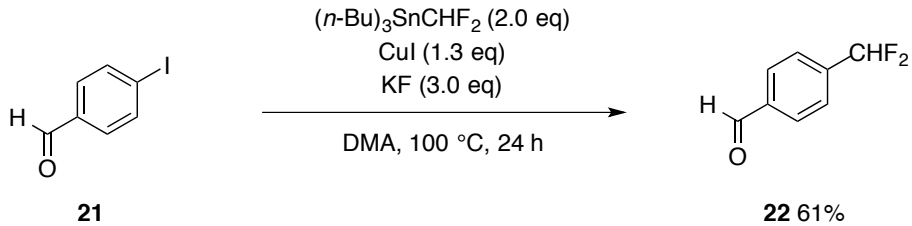
16 77% (8)



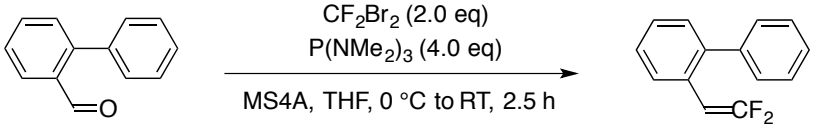
(5.0 eq) **18** 91% (*o*:*m*:*p* = 51:26:23) (9)



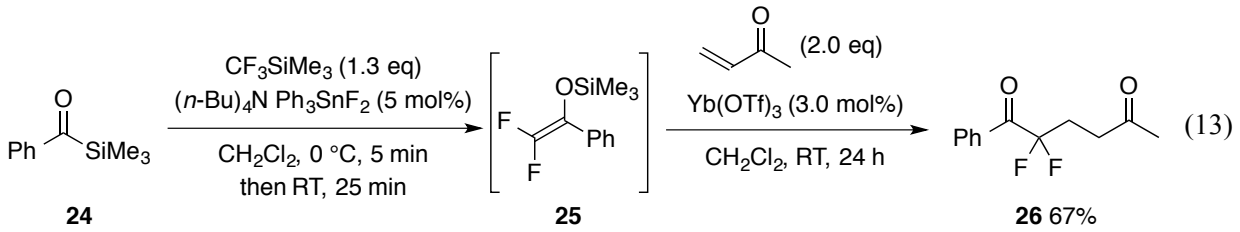
19 **20** 90% (10)



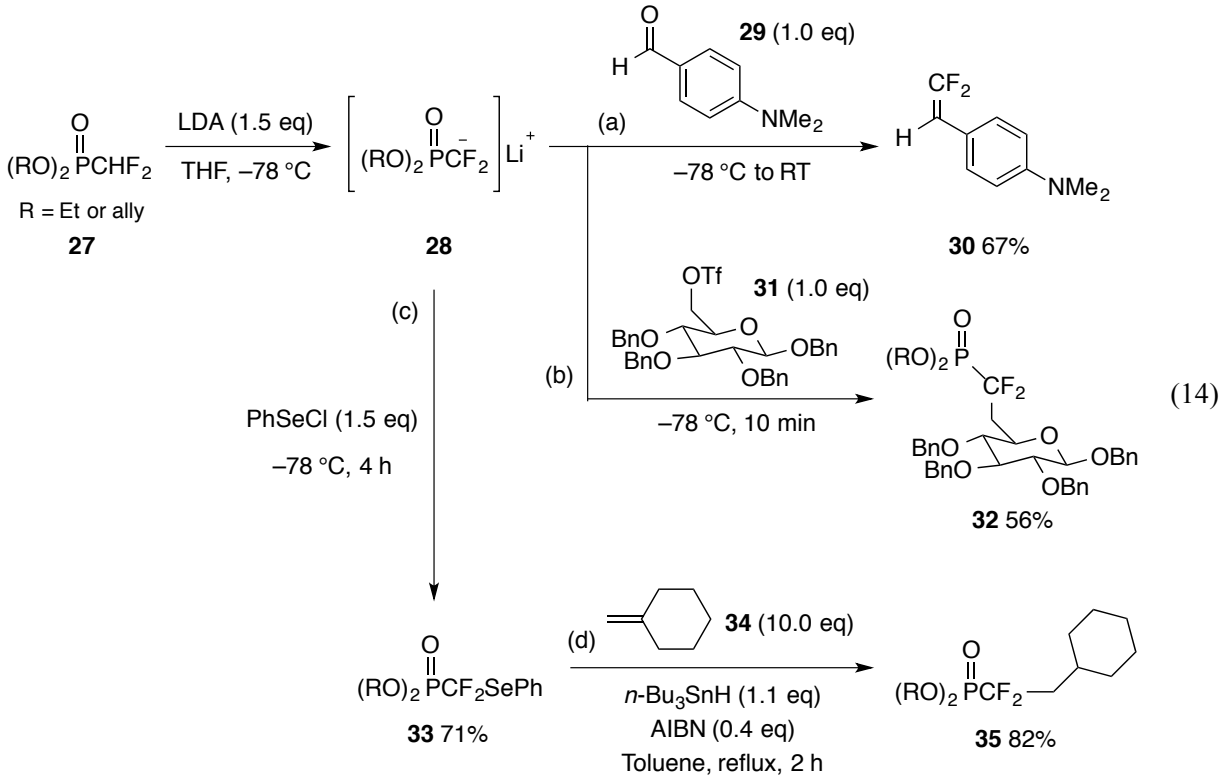
21 **22** 61% (11)



23 87% (12)



(13)

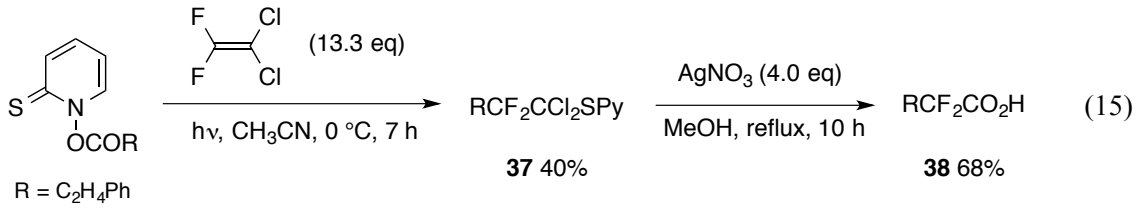


(14)

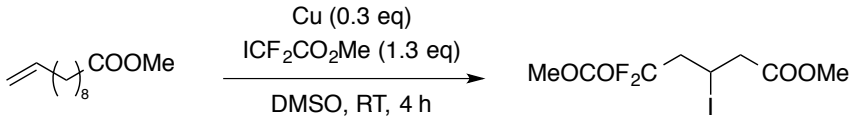
Two-carbon building blocks are also adopted for difluoromethylene introduction. For example, Barton ester **36** reacts with dichlorodifluoroethene under irradiation by a 500 W tungsten lamp to afford dichlorodifluoroethane **37** in 40% yield via photo–induced radical process (eq. 15).[18] Hydrolysis 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 trifluoroiodoethene 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] Treatment of difluoroethylene with *sec*-butyllithium in the presence of *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) generates (difluorovinyl)zinc(II) **55** in 95% yield. Zinc(II) reagent **55** reacts with 2-naphthyl triflate in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium to give 1,1-difluoroalkene **56** in 90% yield.

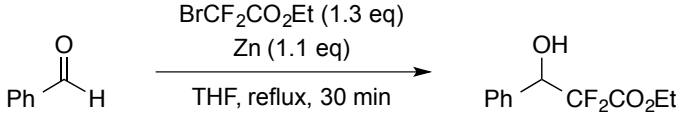
(ii)-2. Introduction of Difluoromethylene Moiety with Two-Carbon Building Blocks



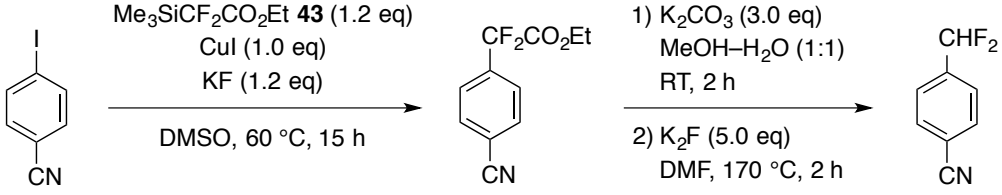
36 **37** 40% **38** 68% (15)



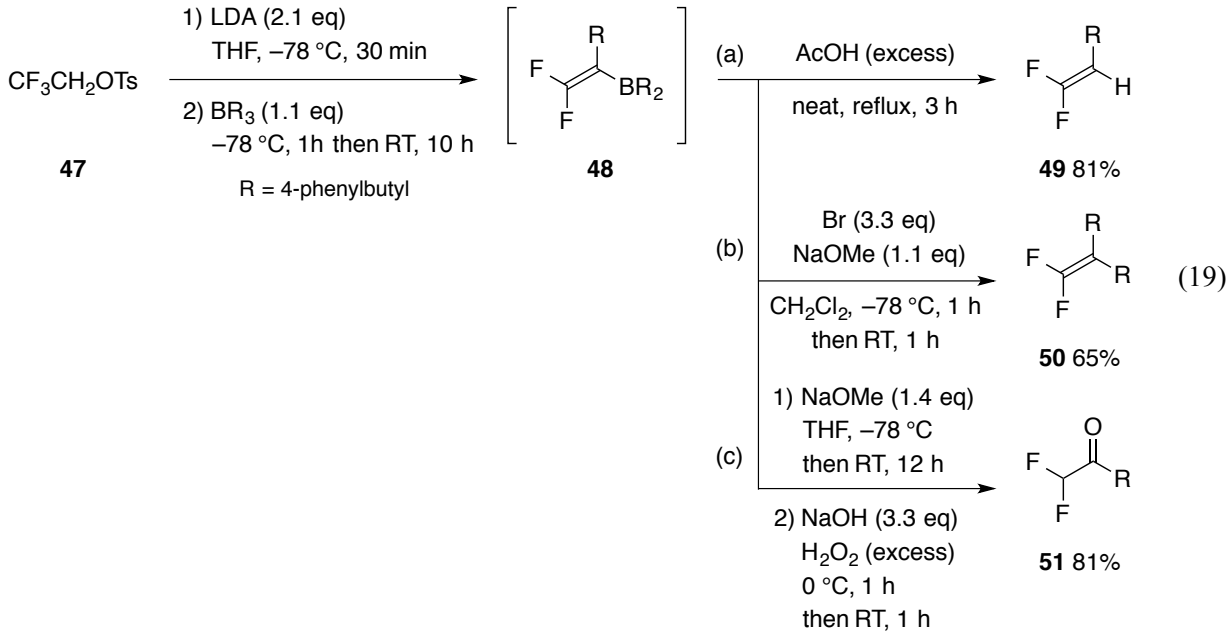
39 **40** 88% (16)



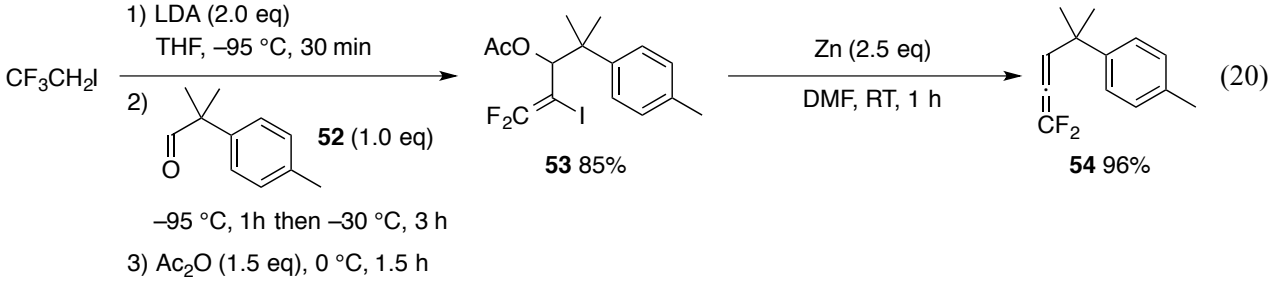
41 **42** 57% (17)



44 **45** 71% **46** 84% (18)



(19)



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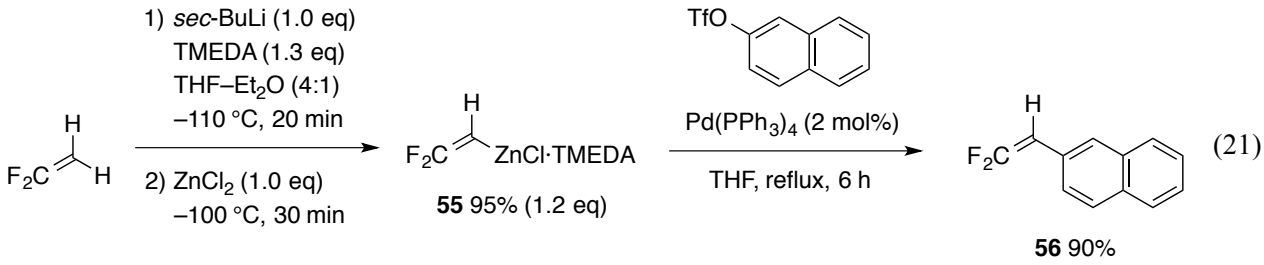
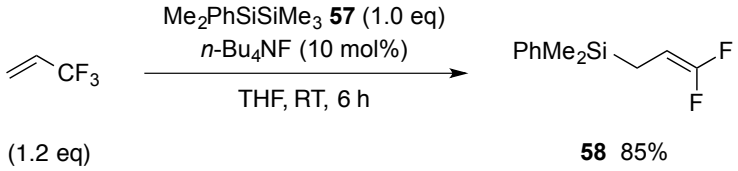


(21)

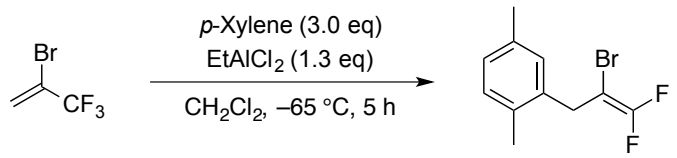
For difluorinated building blocks with three or more carbons, some representative examples are shown below. Treatment of 3,3,3-trifluoro-1-propene with disilane **57** in the presence of fluoride ion (10 mol%) promotes S_N2'-type reaction to afford difluoroalkene **58** in 85% yield (eq. 22).[25] In our research group, trifluoropropenes have been also employed as building blocks. The S_N1'-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 α,α-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]

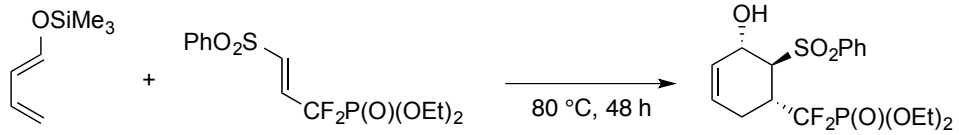
(ii)-3. Introduction of Difluoromethylene Moiety with Three- or More-Carbon Building Blocks



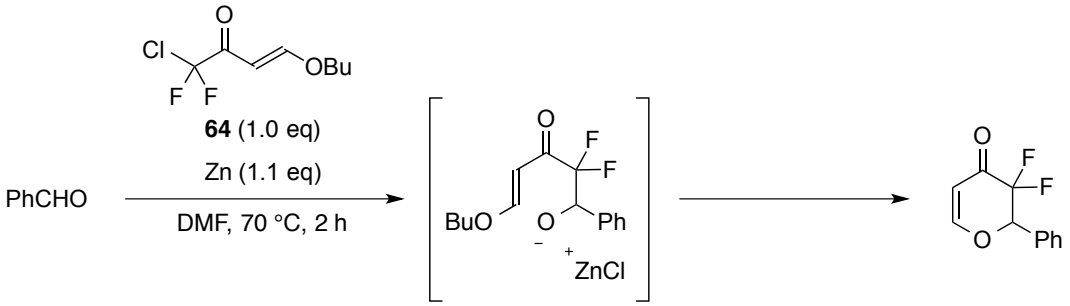
(1.2 eq) **58** 85% (22)



59 **60** 84% (23)



61 **62** **63** 77% (24)



65 **66** 46% (25)

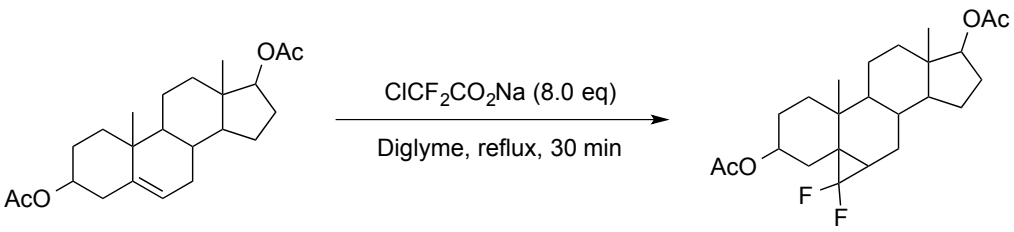
The building block methods presented so far are mostly based on stoichiometric or substoichiometric reactions in terms of promoters. Thus, I envisioned *catalytic* introduction of a difluoromethylene moiety, which was directed toward synthesis of difluoromethylene compounds. My attention was particularly focused on the simple difluorinated building block, difluorocarbene, containing two categories of free difluorocarbene (: CF_2) and transition metal difluorocarbene complexes ($L_nM{=}CF_2$, Figure 2).

: CF_2	$L_nM{=}CF_2$
Free difluorocarbene	Transition metal difluorocarbene complex

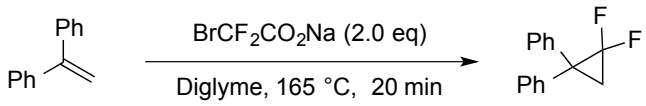
Figure 2

Free difluorocarbene has been widely used as a one-carbone difluorinated building block for synthesis of difluoromethylene compounds.[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).[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.

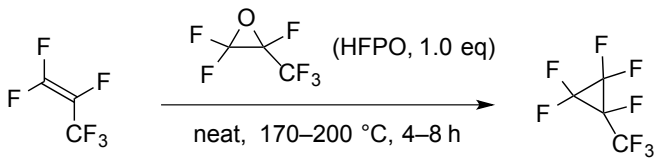
Internal alkene **67** reacts with excess amounts of sodium chlorodifluoroacetate (8.0 eq) at 160 °C (boiling point of diglyme) to give difluorocyclopropane **68** in 58% yield (eq. 26).[30] Difluorocyclopropanation of alkene **69** proceeds with smaller amounts (2.0 eq) of sodium bromodifluoroacetate at 165 °C to afford **70** in 99% yield (eq. 27).[31] The reaction of alkene **71** with hexafluoropropylene oxide (HFPO) proceeds at 170–200 °C to afford difluorocyclopropane **72** in 50% yield (eq. 28).[32] High reaction temperature is necessary for these difluorocarbene generation.



67 **68** 58% (26)

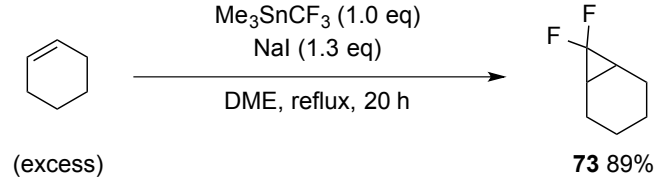


69 **70** 99% (27)



71 **72** 50% (28)

Cyclohexene reacts with trimethyl(trifluoromethyl)tin(IV) in the presence of sodium iodide to afford difluorocyclopropane **73** in 89% yield (eq. 29).[33] On treatment with phenyl(trifluoromethyl)mercury(II) in the presence of sodium iodide, cyclohexene also affords difluorocyclopropane **73** in 83% yield (eq. 30).[34] Use of highly toxic reagents, tin or mercury compounds is the drawback to these methods.



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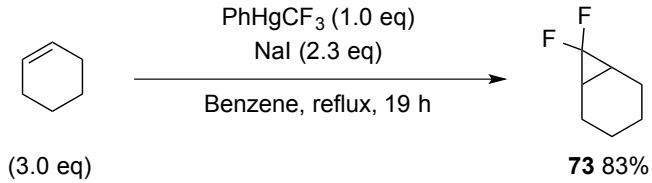
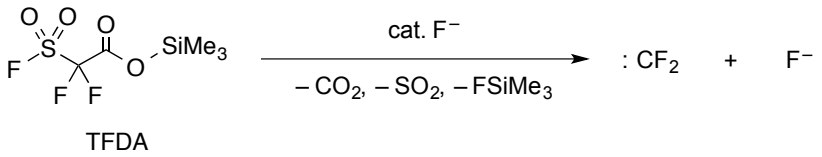
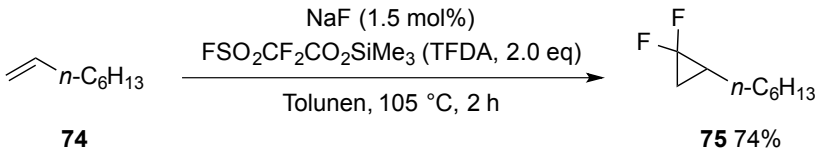


(30)

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, [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).[35a]

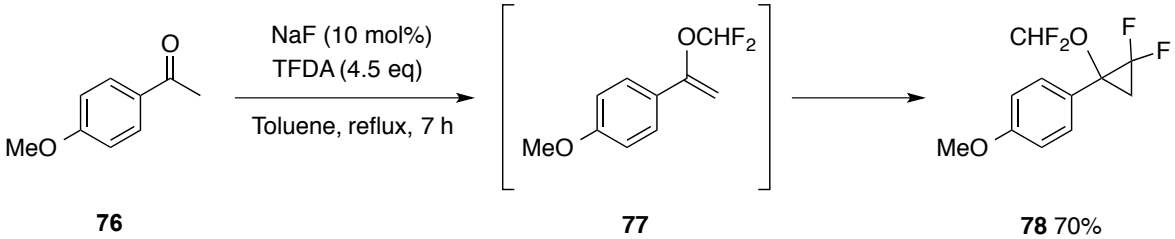


(31)



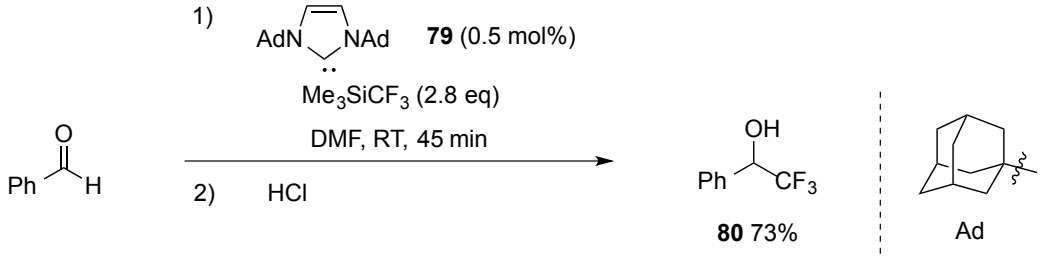
(32)

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).[36]

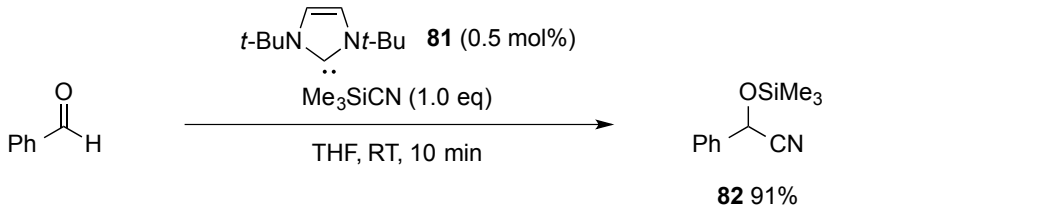


(33)

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.

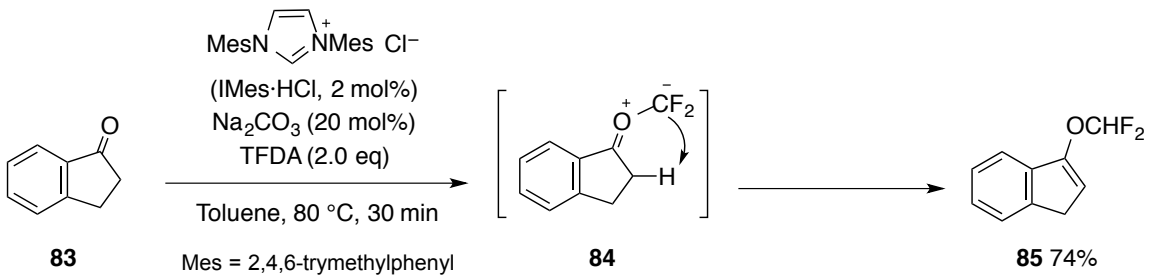


(34)

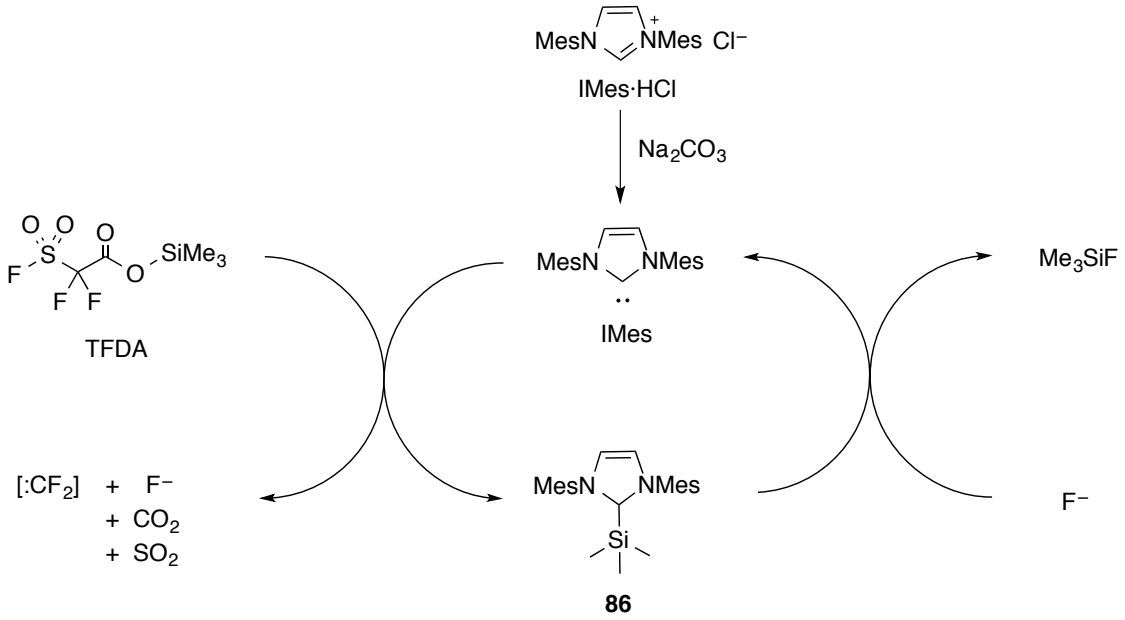


(35)

Our preliminary results have revealed that treatment of cyclic ketone **83** with TFDA in the presence of 1,3-bis(2,4,6-trimethylphenyl)imidazolinium 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.

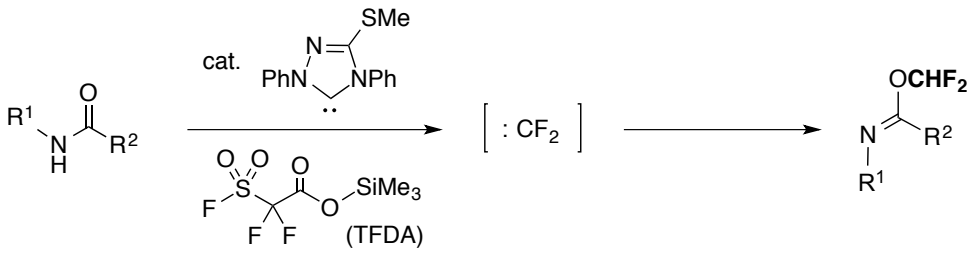


(36)



Scheme 1

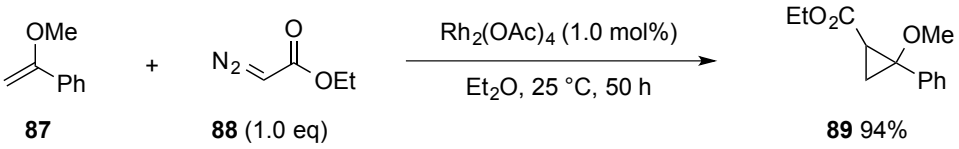
In chapter 2, I describe the organocatalyzed syntheses of difluoromethyl imidates and difluoromethoxypyridines. Generation of free difluorocarbene from TFDA under nearly neutral conditions was accomplished by using organocatalysts, NHCs to realize the *O*-selective difluoromethylation of amides (eq. 37).



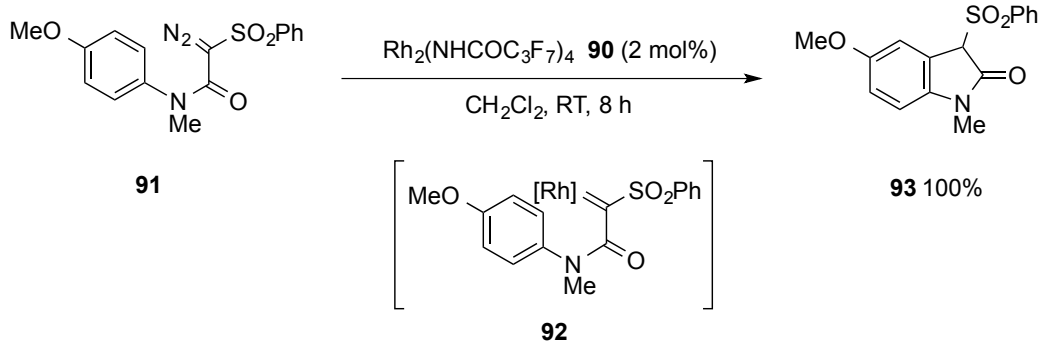
(37)

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).[43] Diene **95** undergoes ring-closing metathesis in the presence of ruthenium(II) carbene complex **94** to afford oxacyclohexene **96** in 90% yield (eq. 40).[44] On the basis of these achievement, transition metal difluorocarbene complexes are promising intermediates for catalytic synthesis of difloromethylene compounds.

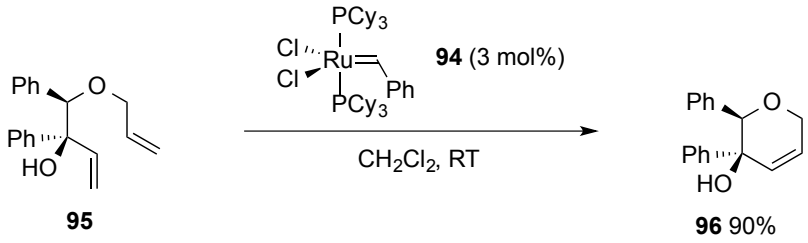


87 **88** (1.0 eq) **89** 94% (38)



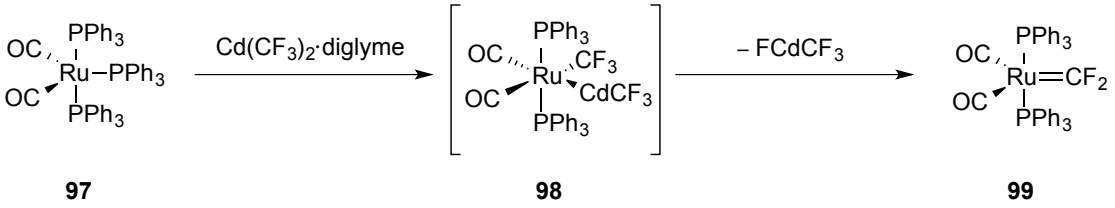
91 **93** 100% (39)

92

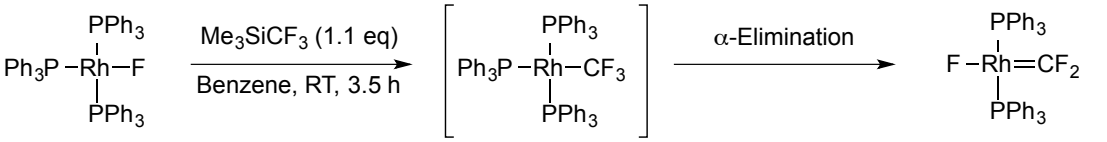


95 **96** 90% (40)

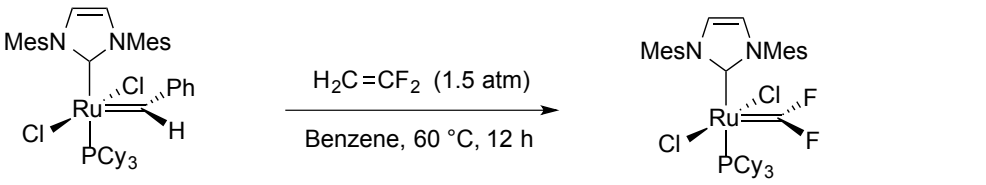
Despite of their potential utility in organic synthesis, two issues are remained unsolved. First, only a limited number of preparations of transition metal difluorocarbene complexes are known. Ruthenium(0) complex **97** reacts with bis(trifluoromethyl)cadmium(II) to afford ruthenium(0) difluorocarbene complex **99** via elimination of trifluoromethylcadmium(II) fluoride from ruthenium–cadmium binuclear complex **98** (eq. 41).[45a] 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).[45b] Ruthenium(II) carbene complex **103** undergoes olefin metathesis with difluoroethene to afford ruthenium(II) difluorocarbene complex **104** in 86% yield (eq. 43).[45c] In addition to these difluorocarbene complexes, 13 complexes were isolated and 3 complexes were spectroscopically observed (Figure 3,4).[45,46] However, preparations of difluorocarbene complexes which are suitable especially for catalytic systems are still severely limited.



97 **98** **99**



100 **101** **102** 85%



103 **104** 86%

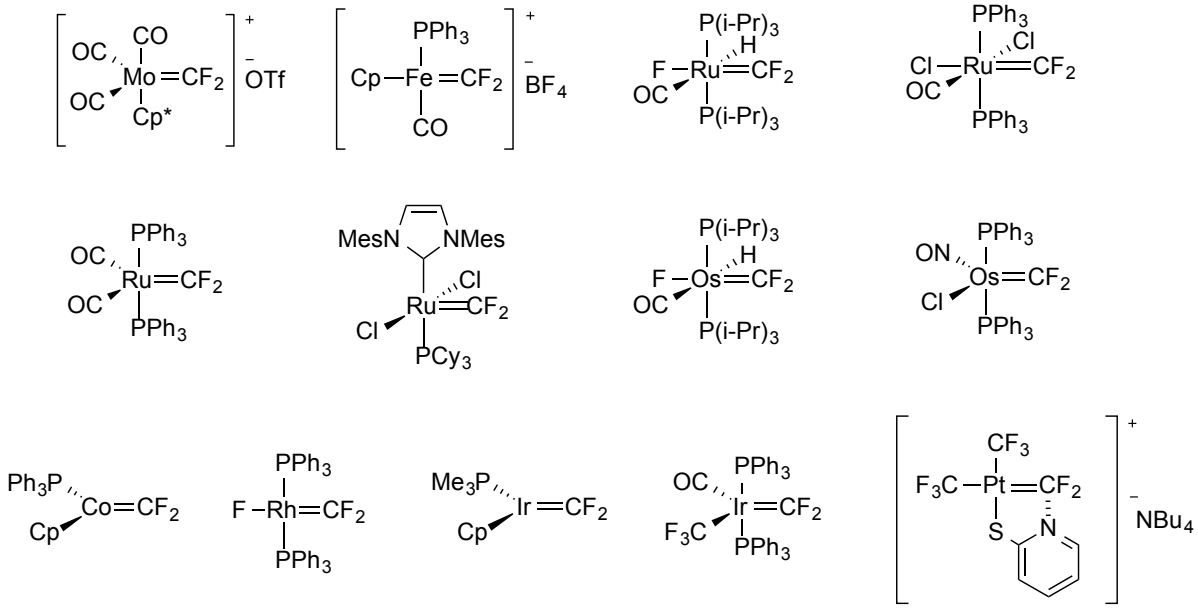


Figure 3. Isolated Difluorocarbene Complexes

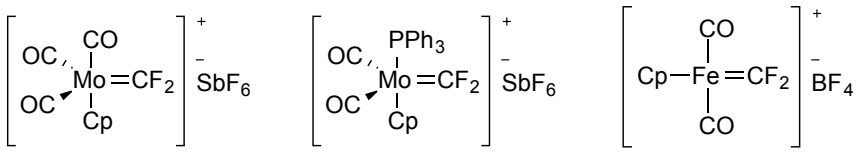
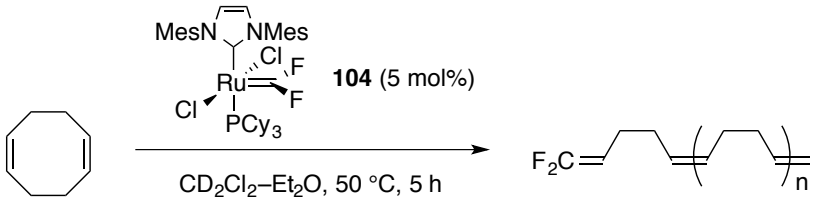
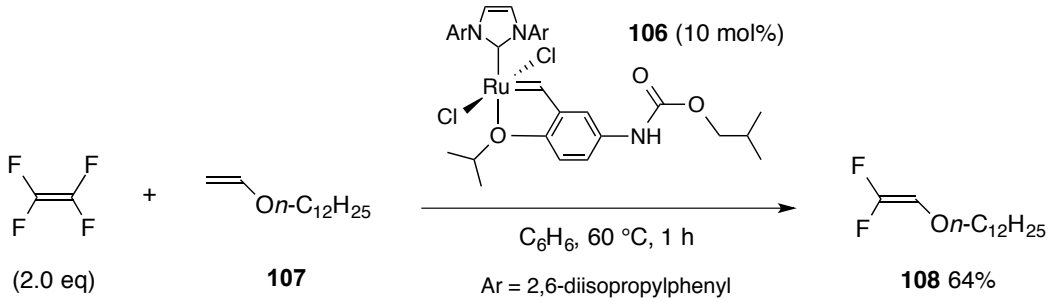


Figure 4. Observed Difluorocarbene Complexes

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.[45c] Cross olefin metathesis of tetrafluoroethene with vinyl ether **107** proceeds under catalytsis by 10 mol% of ruthenium(II) carbene complex **106**, which affords difluorovinyl ether **108** in 64% yield (eq. 45).[47]

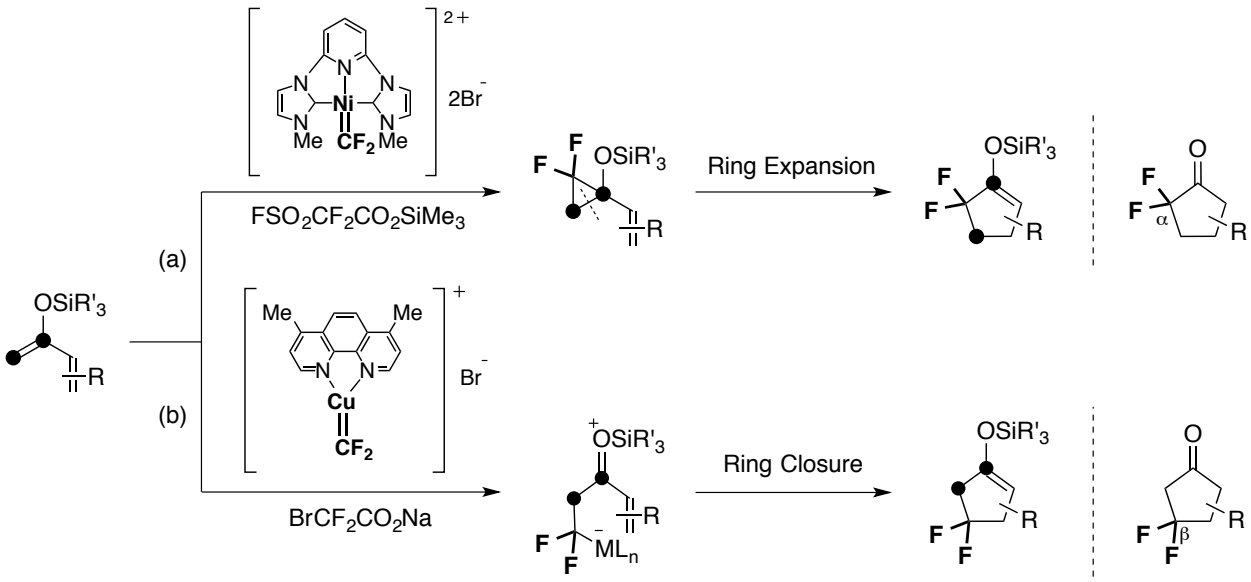


(44)



(45)

In chapter 3, I describe the regioselective syntheses of α,α- and β,β-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 achivements will contribute to new chemistry of difluorocarbene complexes as well as synthesis of difluoromethylene compounds.


2+
2Br-
Ni
Me
CF2
Me
FSO2CF2CO2SiMe3
(a)
OSiR'3
R
(b)
Me
Me
Cu
CF2
Br-
BrCF2CO2Na
F
F
OSiR'3
R
Ring Expansion
OSiR'3
F
F
R
O
F
F
α
R
+
OSiR'3
R
F
F
ML n
Ring Closure
OSiR'3
R
F
F
O
F
F
β
R

Scheme 2

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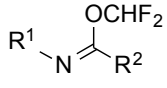
Chapter 2

O-Selective Difluoromethylation of Amides with Free Difluorocarbene

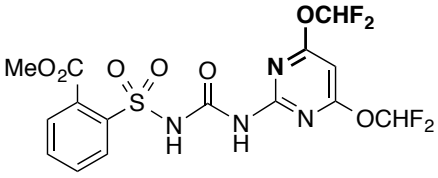
2.1. Introduction

Difuoromethyl imidates are important structural motifs of agrochemicals (Fig. 5,6).[1] For example, "Primisulfuron-methyl" and 2-difluoromethoxypyridine **109**, each possessing a difluoromethyl imidate moiety in their substructures, function as herbicides.

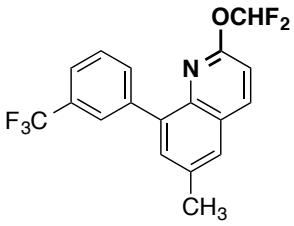


Difluoromethyl imidate

Figure 5



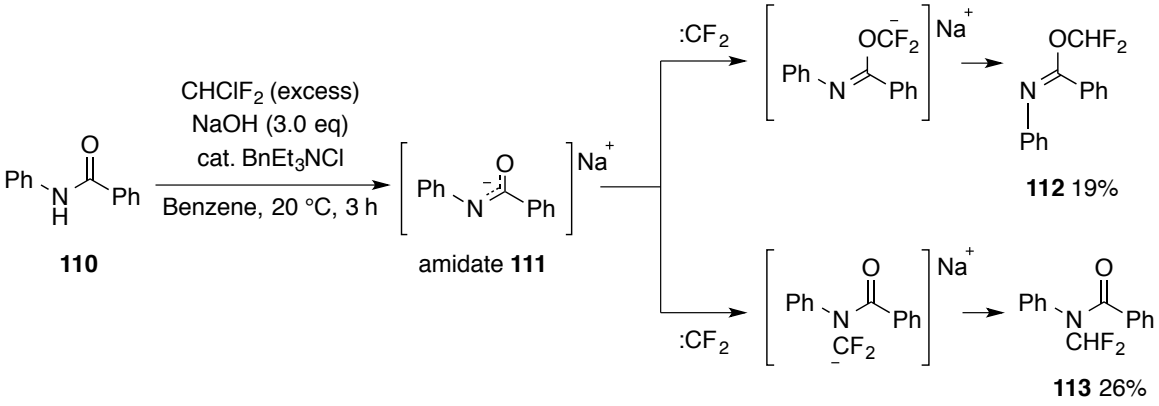
Primisulfuron-methyl (herbicides)



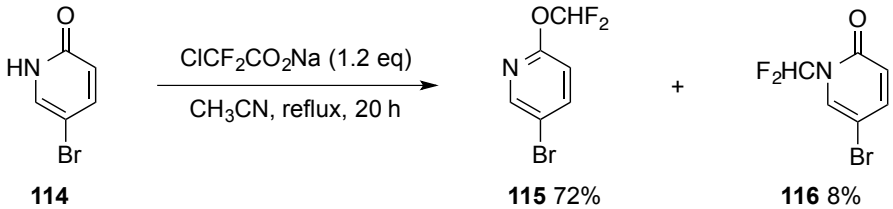
109 (herbicides)

Figure 6

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



(46)

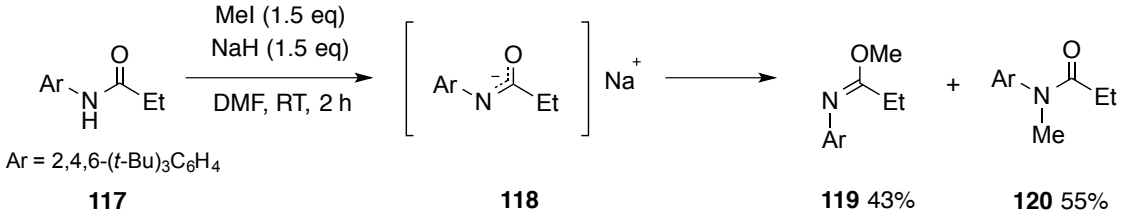


(47)

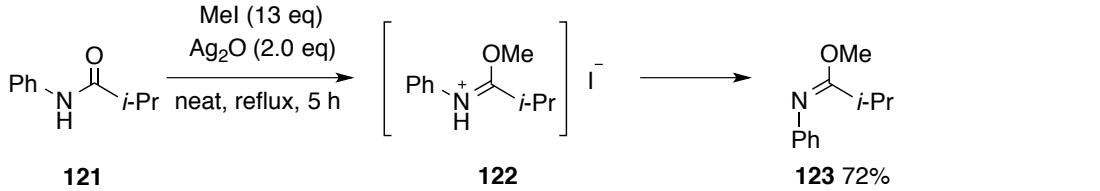
Concerning synthesis of difluoromethyl imidates and difluoromethoxypyridines, there are two issues to address. The first one is formation of a regioisomeric mixture of *O*- and *N*-difluoromethylated products **112** and **113**. The strongly basic conditions, required for the generation of difluorocarbene, 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).

(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).[4] 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).[5] High selectivity would be also obtained by performing difluoromethylation of amides with difluorocarbene under nonbasic conditions.

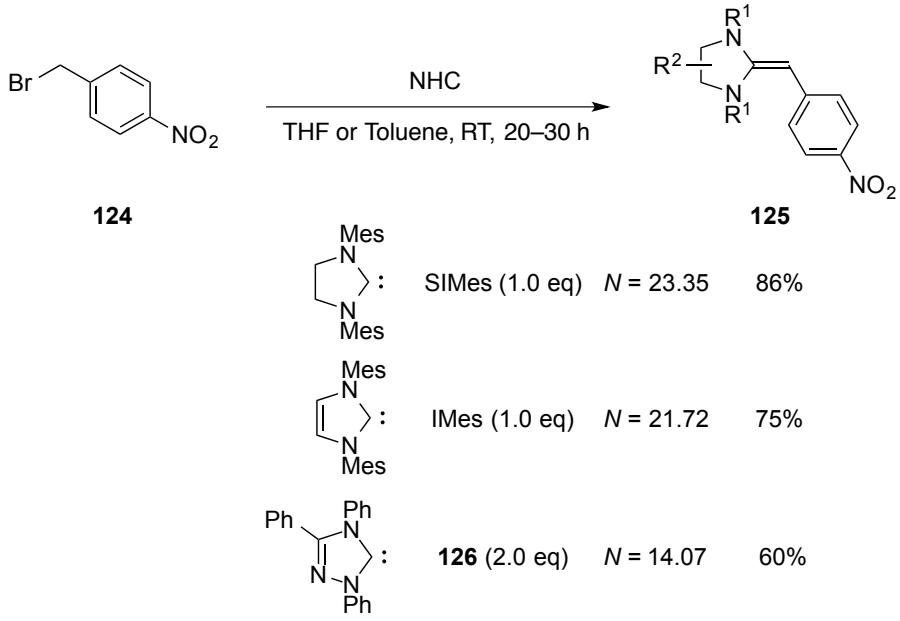


(49)



(50)

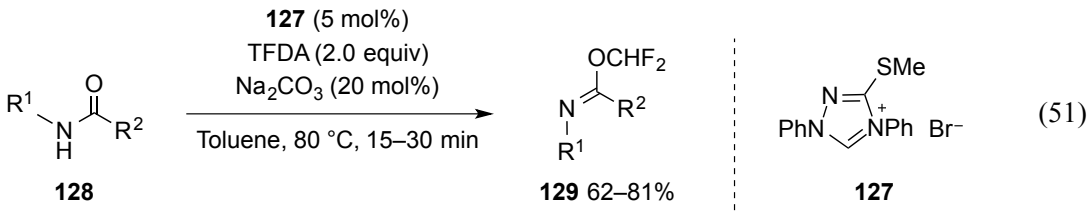
Organocatalyzed generation of difluorocarbene would have another beneficial effect on the control of the generation rate of difluorocarbene, leading to the high yields of the difluoromethylated products by suppressing tetrafluoroethene formation. Reactivity of NHC can be tuned by altering the central heterocyclic core and the substituents on the nitrogen.[6] For instance, 1,3-dimesitylimidazolinylidene (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).[6b] Nucleophilic benzylation of these NHCs with benzyl bromide **124** occurs to afford **125** in 86% (SIMes), 75% (IMes), and 60% (**126**) yields, respectively.[6c] In these reactions, NHC with larger *N* value affords the product in higher yield.



Mes = 2,4,6-trimethylphenyl.

Scheme 3

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.



(51)

2.2. Synthesis of Difluoromethyl Imidates

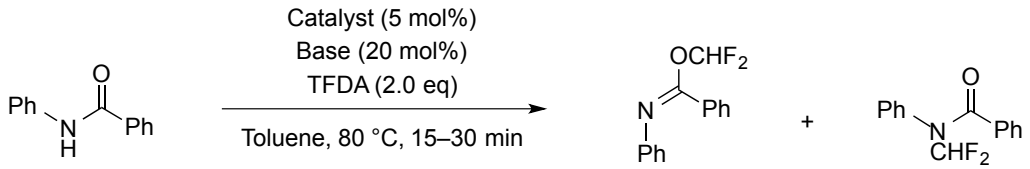
2.2.1 Optimization of Reaction Conditions

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 δ 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 δ 157.2 and δ 171.2 and in their ^{19}F NMR spectra at δ 76.2 (d, J = 72 Hz, 2F) and δ 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.

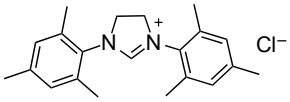
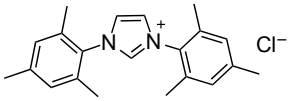
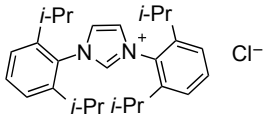
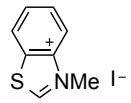
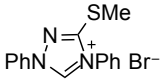
The use of other imidazolium salts (IMes·HCl, IPr·HCl, and thiazolium salt **131**) also resulted in formation of **129a** in moderate yields (Entries 2–4). Amang the salts examined, triazolium salt **127** was found to be most suitable to afford 80% yield of **129a** (Entry 5). On the other hand, fluoride 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.

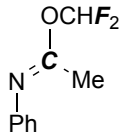


128a **129a** **130a**

Table 1

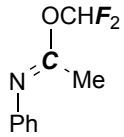
Entry	Catalyst	Base	**129a** / %[a]	**130a** / %[a]	Recovery of TFDA / %[a]
1	 SIMes·HCl	Na_2CO_3	56	0	1
2	 IMes·HCl	Na_2CO_3	53	0	1
3	 IPr·HCl	Na_2CO_3	42	0	7
4	 **131**	Na_2CO_3	5	0	71
5	 **127**	Na_2CO_3	80 (80[b])	0	2
6	NaF	none	0	0	100
7	NaBr	none	0	0	91
8	$(n\text{-Bu})_4NBr$	none	46	0	1

a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: Isolated yield.



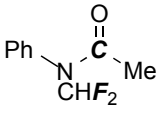
129b (Observed)

δ_C = 157.3
δ_F = 71.0 (d, *J* = 72 Hz, 2F)



129b (Reported)[2]

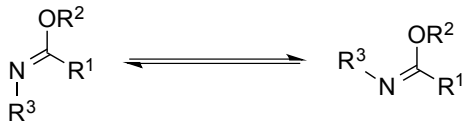
δ_C = 157.2
δ_F = 76.2 (d, *J* = 72 Hz, 2F)



130b (Reported)[2]

δ_C = 171.2
δ_F = 65.4 (d, *J* = 61 Hz, 2F)

Figure 7



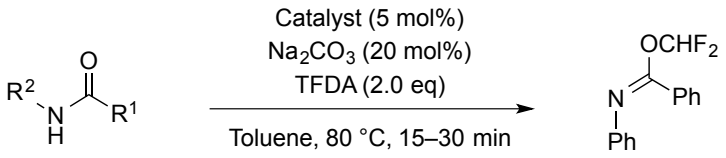
E-isomer　　*Z*-isomer

Table 2

R^1	R^2	R^3	*E*/*Z*	$\Delta G^{\ddagger}$ / kcal/mol[a]
H	Me	*t*-Bu	100:0	–
Me	Me	Me	100:0	–
Me	Ph	Me	69:31	19.8
Me	*p*-Tol	Me	69:31	20.4
t-Bu	Me	Me	87:13	15.9
Ph	Me	Me	89:11	18.9
Ph	Me	*i*-Pr	82:18	18.7

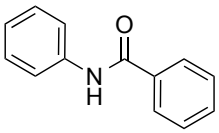
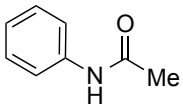
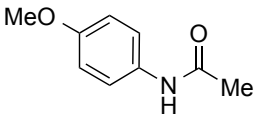
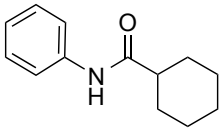
a: Activation barriers to *E*–*Z* interconversion of imidates.

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 (R^1 = 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 guickly. In contrast, aromatic amide **128a** in Table 1 is less nucleophilic than **128b**,**d** and less reactive to difluorocarbene. Triazolylidene with low *N* value slowly generates difluorocarbene and prevents undesired loss of carbene by dimerization. Fortunately, triazolylidene 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.



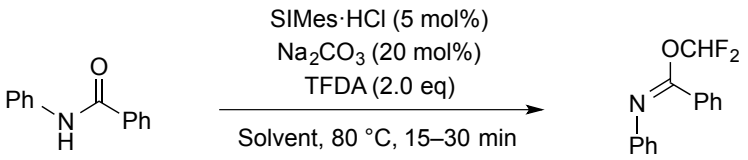
128 **129**

Table 3

Entry	Substrate **128**		**129** / %[a]		
			SIMes·HCl (*N* = 23)	IMes·HCl (*N* = 22)	**127** (*N* = 14)
1[b]		**128a**	56	53	80
2		**128b**	92	71	80
3		**128d**	80	85	69
4		**128h**	51	21	85

a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *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).



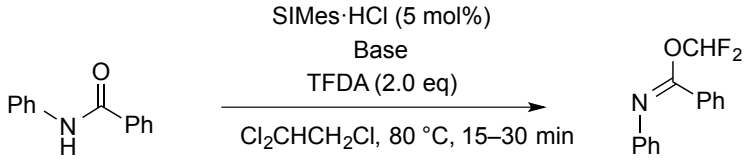
128a **129a**

Table 4

Entry	Solvent	**129a** / %[a]	Recovery of TFDA / %[a]
1[b]	Toluene	56	1
2	*o*-Dichlorobenzene	44	1
3	CCl_4	8	56
4	$ClCH_2CH_2Cl$	45	<1
5	Cl_2CHCH_2Cl	52	1
6	$Cl_2CHCHCl_2$	44	1
7	C_6F_6	0	45
8	$C_6H_5CF_3$	32	1
9	1,4-Dioxane	21	15
10	Diglyme	3	2

a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: 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 sutable base.



128a **129a**

Table 5

Entry	Base (mol%)	**129a** / %[a]	Recovery of TFDA / %[a]
1[b]	Na_2CO_3 (20)	52	1
2	K_2CO_3 (20)	50	1
3	K_3PO_4 (13)	48	<1
4	*t*-BuOK (40)	49	2
5	NaH (40)	48	<1

a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: Table 4, Entry 5.

2.2.2. 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 ^{19}F 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 ^{19}F NMR analysis of the crude mixtures.

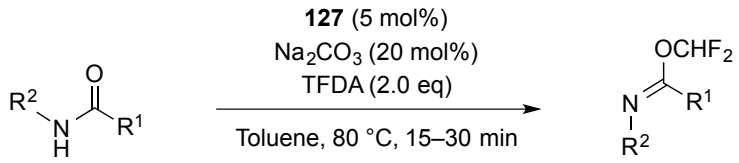
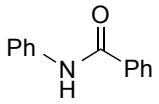
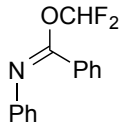
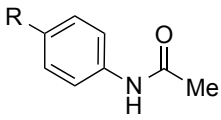
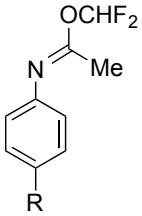
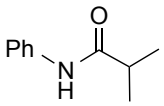
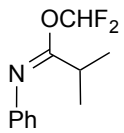
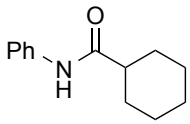
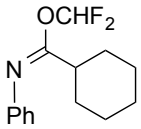
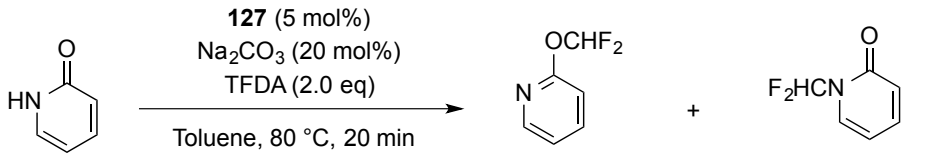


Table 6

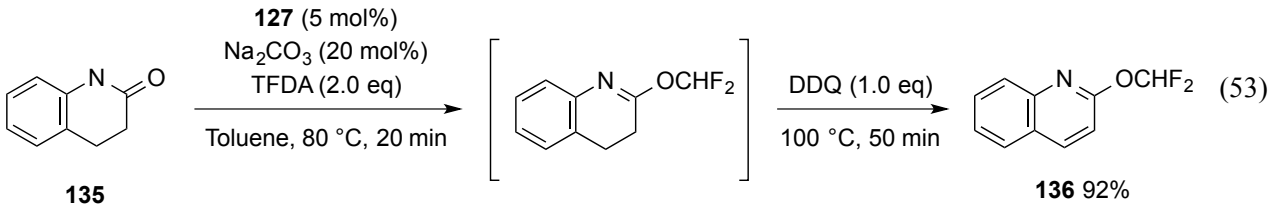
Entry	Substrate **128**		Product **129**[a]		Yield / %
1[b]		**128a**		**129a**	80
2[c]		R = H **128b**		R = H **129b**	77
3		R = Me **128c**		R = Me **129c**	62 (83[f])
4[d]		R = OMe **128d**		R = OMe **129d**	62 (69[f])
5		R = F **128e**		R = F **129e**	67 (77[f])
6		R = Cl **128f**		R = Cl **129f**	72 (83[f])
7		**128g**		**129g**	84
8[e]		**128h**		**129h**	81

a: Single diastereomer. *b*: Table 1, Entry 5. *c*: Table 3, Entry 2. *d*: Table 3, Entry 3. *e*: Table 3, Entry 4. *f*: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$.

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).



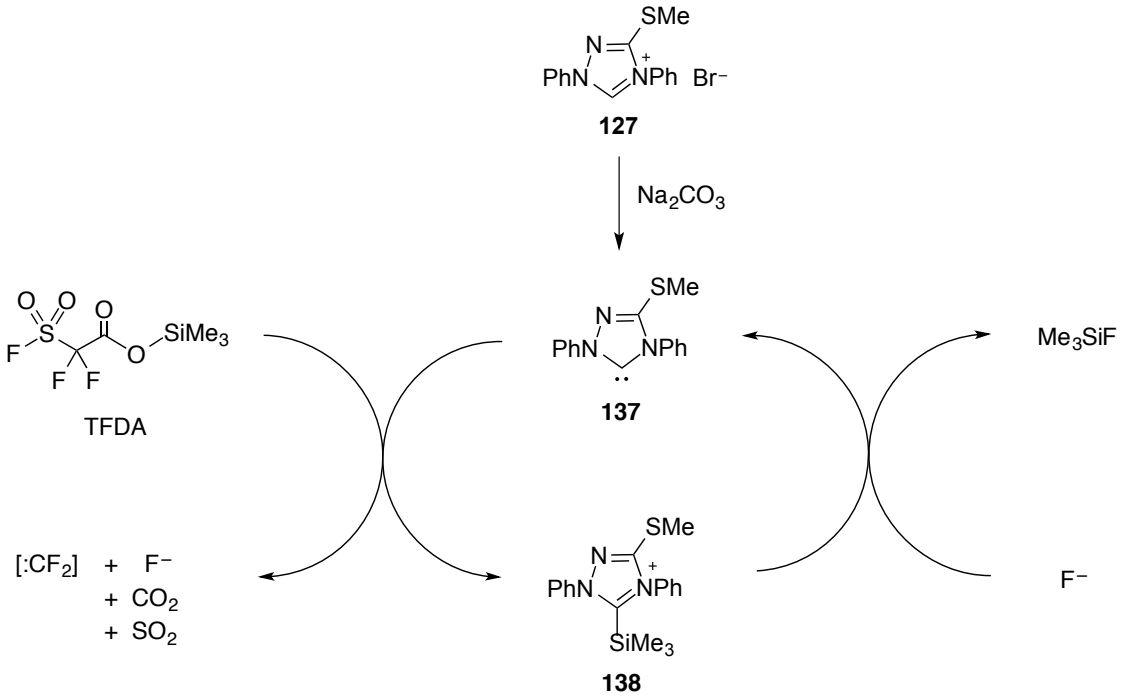
132 **133** 60% (^{19}F NMR) **134** 9% (^{19}F NMR) (52)



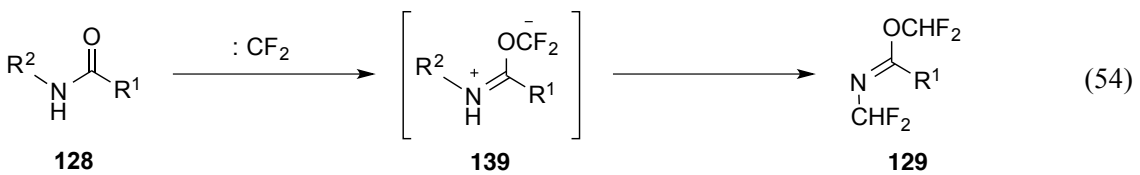
(53)

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 generats 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



(54)

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.

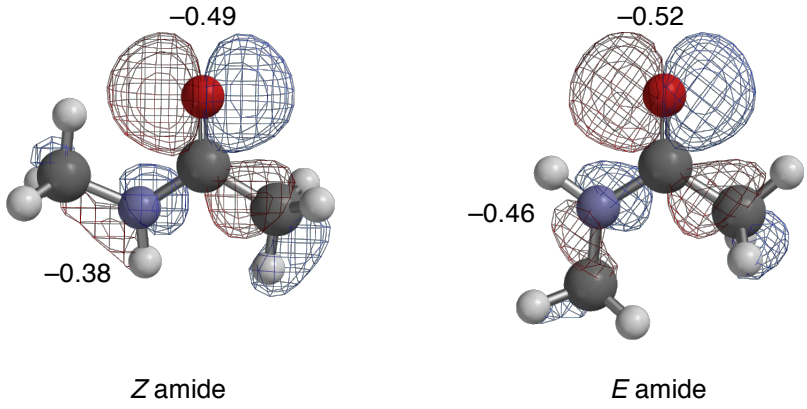


Figure 8. HOMO Orbital and Electrostatic Charge Values (Oxygen and Nitrogen) of Amide

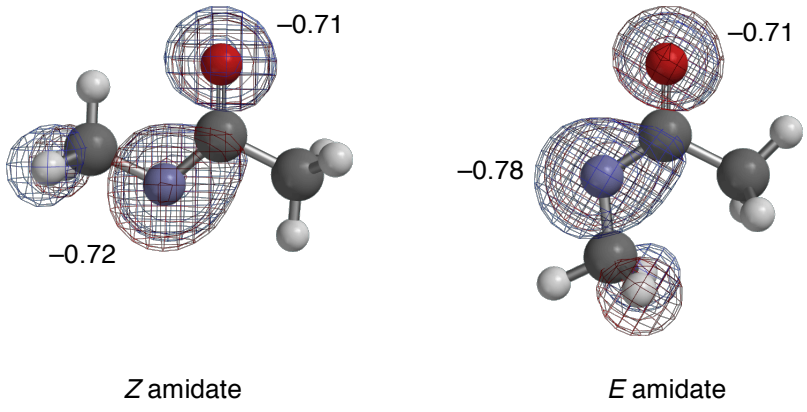


Figure 9. HOMO Orbital and Electrostatic Charge Values (Oxygen and Nitrogen) of Amidate

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_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_6 (for ^{19}F NMR: δ = 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-fluorosulfonylacetate (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 dfluoromethyl 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, 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 **136** (70 mg, 92% yield).

(*C*) Spectral data of difluoromethyl imidates and difluoromethoxypyridines.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (t, *J* = 72.8 Hz, ^{1}H, 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.4 (broad), 146.0, 131.2, 129.5, 129.2, 128.2, 123.9, 120.9, 113.6 (t, *J* = 255 Hz). ^{19}FNMR (470 MHz, $CDCl_3$): δ = 70.8 (d, *J* = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2929, 1687, 1267, 1113, 912, 744 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{14}H_{11}F_2NO$ ($[M]^+$): 247.0809; Found: 247.0812.

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

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.3, 146.3, 129.2, 124.1, 120.5, 113.0 (t, *J* = 255 Hz), 15.6. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 71.0 (d, *J* = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1701, 1238, 1105, 1086, 912 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_9H_9F_2NO$ ($[M]^+$): 185.0652; found: 185.0653.

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

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 143.7, 133.6, 129.7, 120.4, 113.0 (t, *J* = 255 Hz), 20.8, 15.5. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 71.1 (d, *J* = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2925, 1699, 1508, 1230, 1065 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{10}H_{11}F_2NO$ ($[M]^+$): 199.0809; Found: 199.0808.

Difluoromethyl *N*-(*p*-methoxyphenyl)ethan-1-imidate (**129d**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 72.4 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.4, 156.4, 139.5, 121.6, 114.4, 113.0 (t, *J* = 255 Hz), 55.4, 15.5. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 70.6 (d, *J* = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2956, 1699, 1506, 1230, 1103 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. For $C_{10}H_{11}F_2NO_2$ ($[M]^+$): 215.0758; Found: 215.0760.

Difluoromethyl *N*-(*p*-fluorophenyl)ethan-1-imidate (**129e**)

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.34 (t, *J* = 72.1 Hz, 1H), 7.02 (dd, *J* = 8.5 Hz, 2H), 6.74 (dd, *J* = 4.0, 8.5 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.7 (d, *J* = 242 Hz), 157.9, 142.4 (d, *J* = 3 Hz), 121.9, 115.4 (d, *J* = 23 Hz), 112.9 (t, *J* = 255 Hz), 15.6. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 70.5 (d, *J* = 72 Hz, 2F), 42.0 (tt, *J* = 8.5, 4.0 Hz, 1F). IR (neat): $\tilde{\nu}$ = 1705, 1506, 1240, 1109, 914 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_9H_8F_3NO$ ($[M]^+$): 203.0558; found: 203.0553.

Difluoromethyl *N*-(*p*-chlorophenyl)ethanimidate (**129f**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 72.0 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.8, 144.9, 129.6, 129.3, 121.9, 112.9 (t, *J* = 256 Hz), 15.6. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 70.4 (d, *J* = 72 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1703, 1240, 1136, 1088, 914 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_9H_8ClF_2NO$ ($[M]^+$): 219.0262; found: 219.0260.

Difluoromethyl *N*-phenyl-2-methylpropan-1-imidate (**129g**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 72.6 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 2.72 (septet, *J* = 6.5 Hz, 1H), 1.14 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.0, 146.2, 129.2, 123.8, 120.3, 113.4 (t, *J* = 254 Hz), 28.6, 19.2. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 70.3 (d, *J* = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2978, 1695, 1244, 1109, 912 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{11}H_{13}F_2NO$ ($[M]^+$): 213.0965; Found: 213.0968.

Difluoromethyl *N*-pheny-1-cyclohexylmethanimidate (**129h**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 72.6 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 8.0 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}C NMR (126 MHz, $CDCl_3$): δ = 162.2, 146.1, 129.2, 123.7, 120.4, 113.4 (t, *J* = 254 Hz), 38.4, 29.0, 25.4, 25.2. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 70.5 (d, *J* = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2935, 1697, 1238, 1124, 912 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{14}H_{17}F_2NO$ ($[M]^+$): 253.1278; found: 253.1282.

2-Difluoromethoxypyridine (**133**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 73.5 Hz, 1H), 7.10 (ddd, *J* = 7.5, 5.0, 1.5 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.1, 147.0, 140.0, 120.0, 114.0 (t, *J* = 255 Hz), 111.5. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 72.8 (d, *J* = 74 Hz, 2F). IR (neat): $\tilde{\nu}$ = 2925, 1261, 1219, 1099, 773 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_6H_5F_2NO$ ($[M]^+$): 145.0339; found: 145.0341.

2-Difluoromethoxyquinoline (**136**)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 72.1 (d, *J* = 73 Hz, 2F). IR (neat): $\tilde{\nu}$ = 1604, 1311, 1232, 1065, 912 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{10}H_7F_2NO$ ($[M]^+$): 195.0496; found: 195.0496.

2.6. Reference

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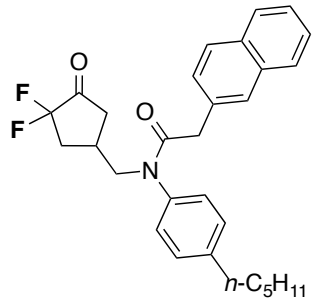
Chapter 3

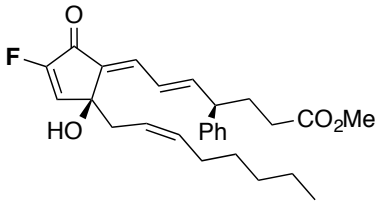
Regioselective Syntheses of *gem*-Difluorocyclopentanone Derivatives with Transition Metal Difluorocarbene Complexes

3.1. Introduction

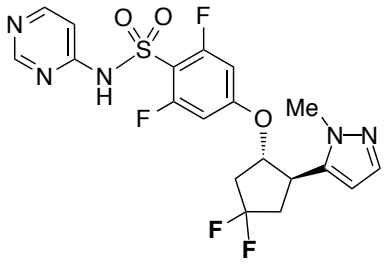
Difluorocyclopentanones are important motifs of pharmaceuticals (Figure 10).[1] For example, α-fluorocyclopentanone derivatives **140** and **141** have antimalarial and antileukemic effects, respectively.[1a,b] β-Fluorocyclopentanone derivative **142** has an anti-bronchitis effect.[1c] Thus, regioselective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



140 (antimalarial effect)



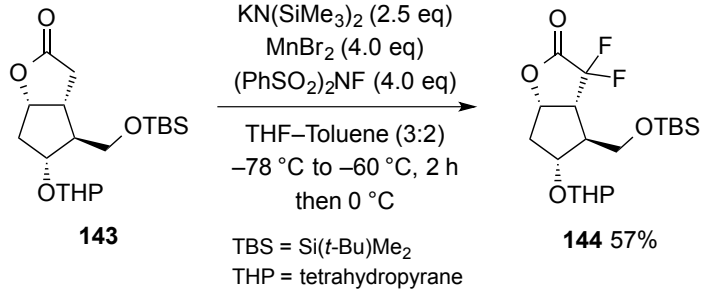
141 (antileukemic effect)



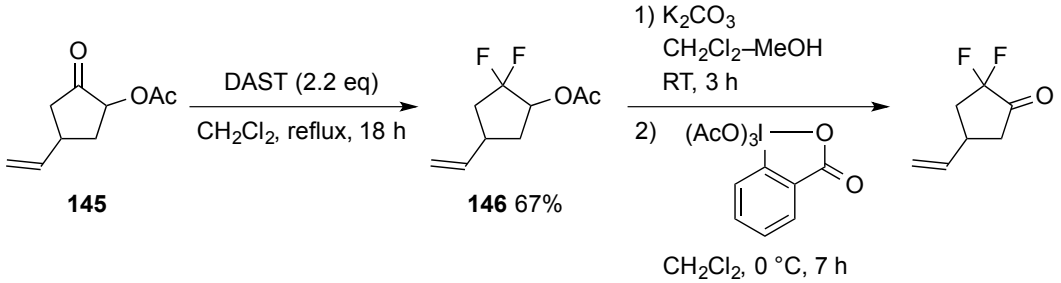
142 (anti-bronchitis effect)

Figure 10

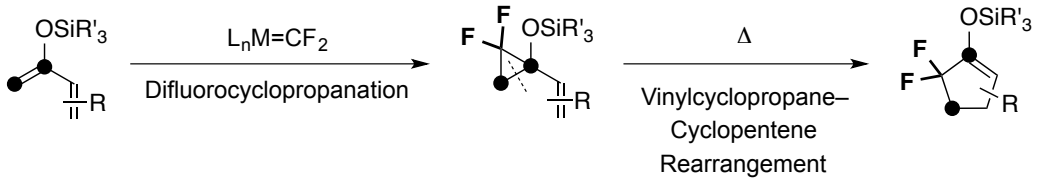
To date, α,α-difluorocyclopentanone derivatives have been synthesized via two fluorine introductions: double-electrophilic fluorination of cyclopentanones[2] and deoxygenative fluorination of alkoxy cyclopentanones followed by oxidation.[3] For instance, treatment of lactone **143** with *N*-fluorobenzensulfonimide 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 α,α-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 α,α-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 α,β-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).



(55)



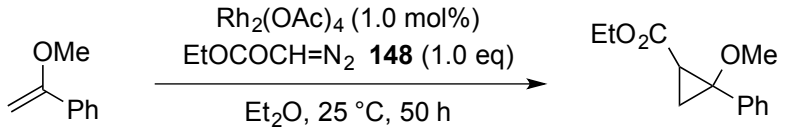
(56)



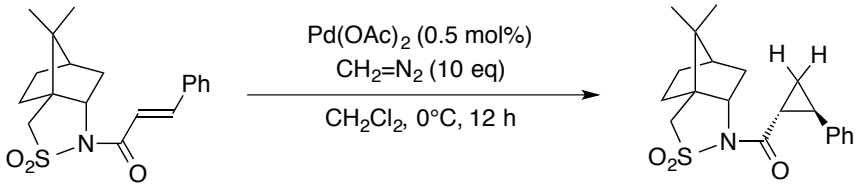
(57)

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 $CHClF_2$/KOH (eq. 5),[5] $CClF_2CO_2Na$ (eq. 26),[6] or $PhHgCF_3$/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.

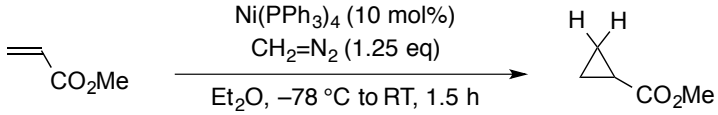
On the other hand, metal-catalyzed cyclopropanation of alkenes under mild conditions has been reported.[8] For instance, treatment of alkene **147** with diazoester **148** in the presence 1.0 mol% of rhodium(II) acetate at 25 °C affords cyclopropane **149** in 94% yield (eq. 58).[8b] Alkene **150** 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.



147 **149** 94% (58)

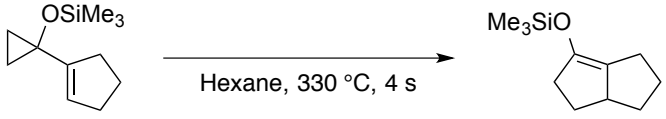


150 **151** 73% (59)

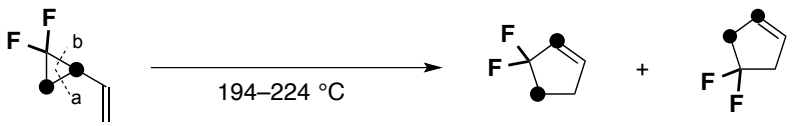


152 **153** 72% (60)

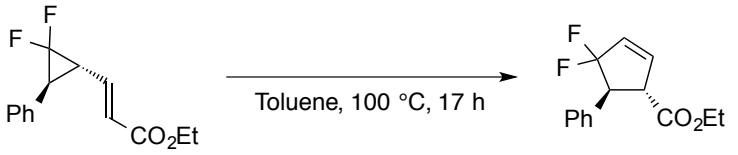
Concerning the second ring-opening step, VCP rearrangements of fluorine-free vinylcyclopropanes, including siloxy-substituted ones, are typically conducted at high temperatures (300−550 °C).[4b] For example, vinylcyclopropane **154** undergoes to rearrangement at 330 °C to give cyclopentene **155** in 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.



154 **155** 89% (61)



156 **157** 96% (cleavage a) **158** 4% (cleavage b) (62)



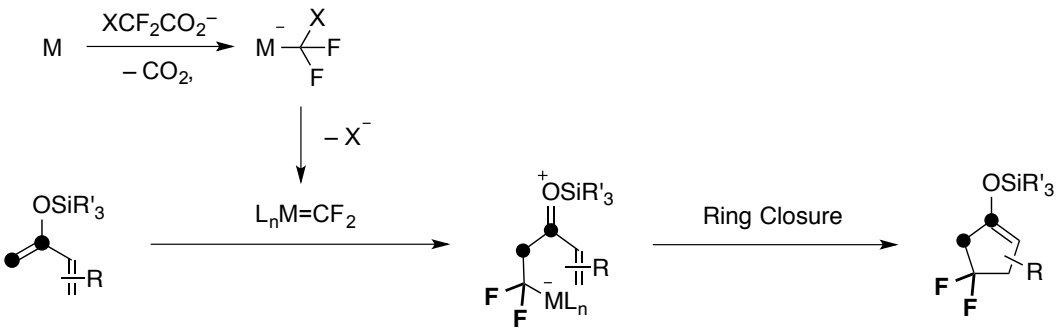
(63)

159 **160** 99%

Ring Strain Energy	26.5–28.7 kcal / mol	35.7–42.4 kcal / mol

Figure 11

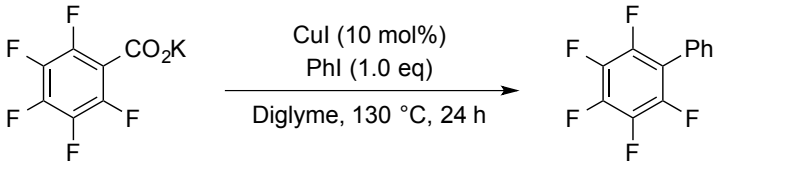
For the synthesis of the regioisomeric β,β-difluorocyclopentanone derivatives, I envisaged to adopt [4 + 1] cycloaddition (eq. 64). Dienol silyl ethers would electrophilically attack the CF_2 carbon of difluorocarbene complex to generate the corresponding difluoroalkylmetal, whose Michael-type ring closure 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.



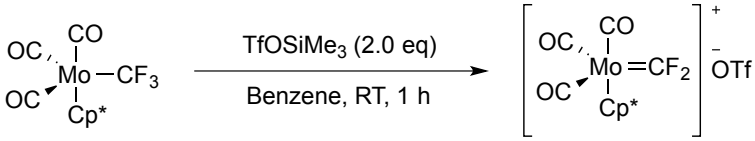
(64)

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 ($XCF_2CO_2^-$). Decarboxylation of copper(I) carboxylate is known to proceed readily as shown in the following example:[10] cross coupling reaction of

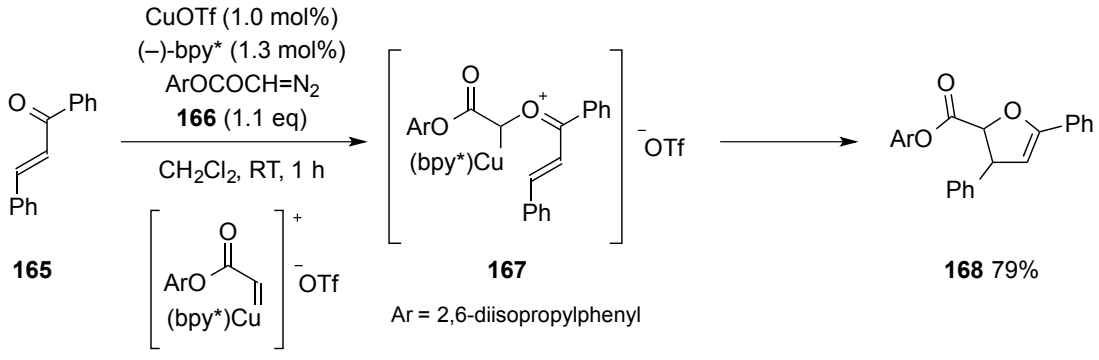
potassium pentafluorobenzoate **161** and phenyl iodide in the presence 10 mol% of copper(I) iodide proceeds to afford biphenyl **162** in 99% yield (eq. 65).[10a] The resulting (halodifluoromethyl)copper(I) species would undergo elimination of a halide ion (X^-) to generate the required difluorocarbene complexes.[11] On treatment of trifluoromethylmanganese(II) **163** with trimethylsilyl trifllate (2.0 equiv) affords manganese(II) difluorocarbene complex **164** in 87% yield (eq. 66).[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).[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.



161 **162** 99% (65)

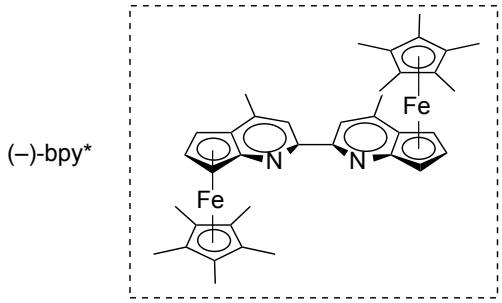


163 **164** 87% (66)



165 **167** **168** 79% (67)

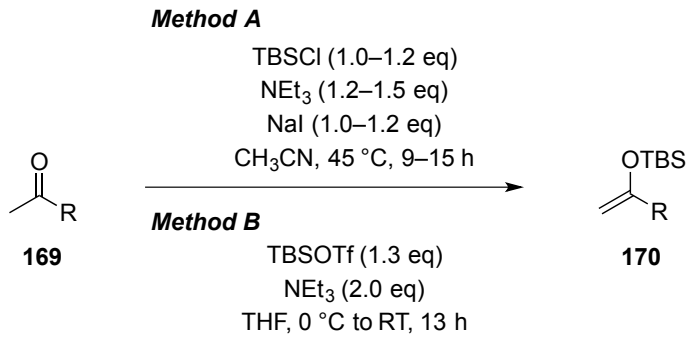
Ar = 2,6-diisopropylphenyl



3.2. Domino Difluorocyclopropanation/Ring Expansion with Nickel Difluorocarbene Complex

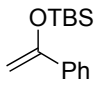
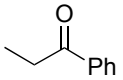
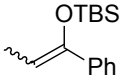
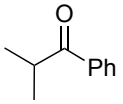
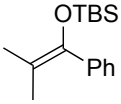
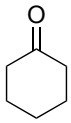
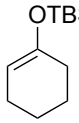
3.2.1. Preparation of silyl enol ethers

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 *tert*-butyl(dimethyl)silyl chloride (TBSCl, 1.0–1.2 equiv) in the presence of triethylamine (1.2–1.5 equiv) and sodium iodide (1.0–1.2 equiv) afforded silyl enol ethers **170a**,**c**,**d** in good yields (method A). Silylation of ketone **169b** with *tert*-butyl(dimethyl)silyl trifluoromethanesulfonate (TBSOTf, 1.3 equiv) in place of TBSCl proceeded to give silyl enol ether **170b** in 64% yield (method B).



169 **170**

Table 7

Entry	Substrate **169**		Method	Product **170**		Yield / %
1		**169a**	A		**170a**	69
2		**169b**	B		**170b**	64 (*E*/*Z* = 4:96)
3		**169c**	A		**170c**	71
4		**169d**	A		**170d**	86

TBS = Si(*t*-Bu)Me_2

The silylation of ketones **169** was successfully applied to the reaction of α,β-unsaturated ketones **171** (Table 8). Treatment of ketones **171a**–**l** with a silylating reagent (TBSCl or TBSOTf) gave the corresponding dienol silyl ethers **172a**–**l** in good to moderate yields.

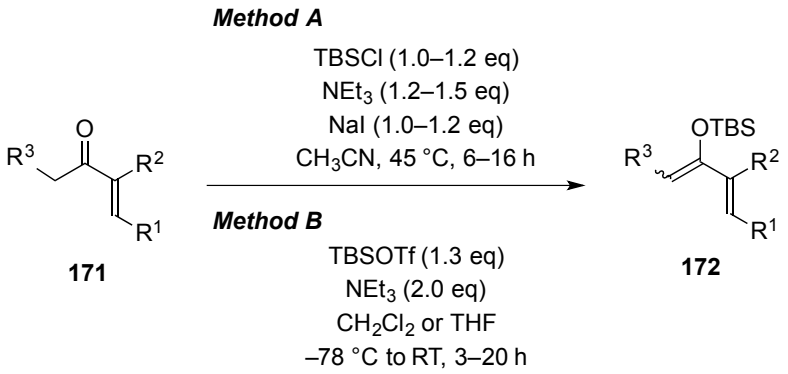
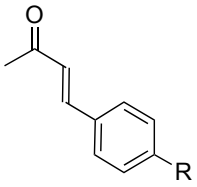
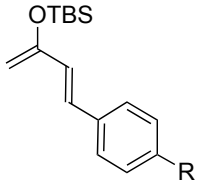
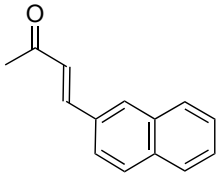
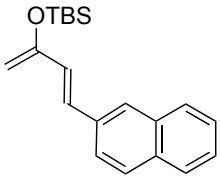
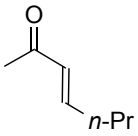
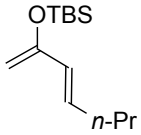
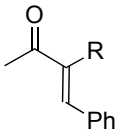
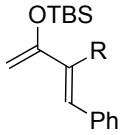
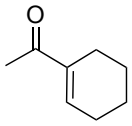
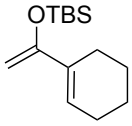
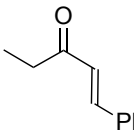
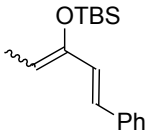
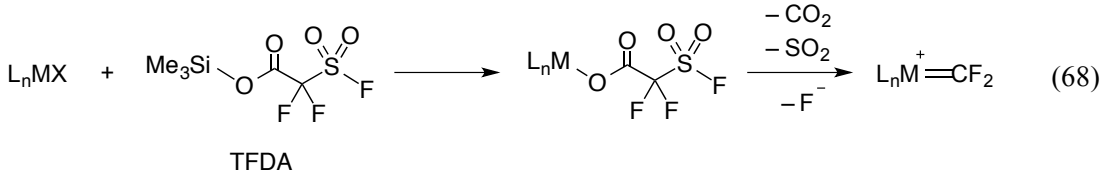


Table 8

Entry	Substrate **171**		Method	Product **172**	Yield / %
1		R = H **171a**	A	 **172a**	74
2		R = Me **171b**	B	**172b**	76
3		R = OMe **171c**	B	**172c**	60
4		R = Cl **171d**	A	**172d**	63
5		R = Br **171e**	B	**172e**	62
6		**171f**	B	 **172f**	40
7		**171g**	B	 **172g**	58
8		R = Me **171h**	B	 **172h**	83
9		R = Br **171i**	B	**172i**	97
10		R = Ph **171j**	A	**172j**	57
11		**171k**	B	 **172k**	65
12		**171l**	A	 **172l**	73 (*E*/*Z* = 34:66)
13			B		65 (*E*/*Z* = 5:95)

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.



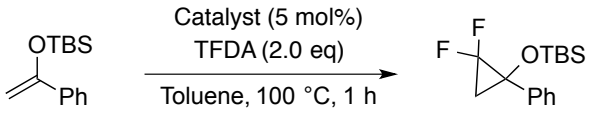
(68)

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}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 °C and decomposed above −78 °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).

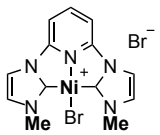


170a **173a**

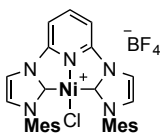
Table 9

Entry	Catalyst	**173a** / %[a]	Recovery of TFDA / %[a]
1	$Rh_2(OAc)_4$	0	97
2	$RhCl(PPh_3)_3$	57	<1
3	$Ni(PPh_3)_4$	30	19
4	Ni complex **174**	72 (73[b])	0
5	**175**	37	0
6	$Pd(PPh_3)_4$	59	7
7	**176**	64	0
8	**177**	62	0
9	**178**	62	0
10	$Pt(PPh_3)_4$	12	0
11	**179**	68	0
12	IPrCuCl	40	33
13	NaF	31	62
14	SIMes·HCl + Na_2CO_3 (20 mol%)	56	0
15	IMes·HCl + Na_2CO_3 (20 mol%)	53	0
16	**127** + Na_2CO_3 (20 mol%)	46	0
17	**180** + Na_2CO_3 (20 mol%)	45	0

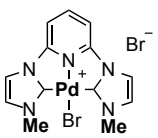
a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: Isolated yield.



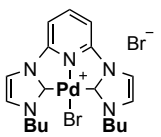
Ni complex **174**



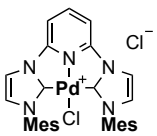
Ni complex **175**



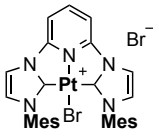
Pd complex **176**



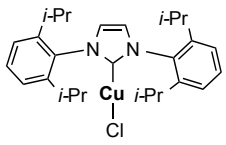
Pd complex **177**



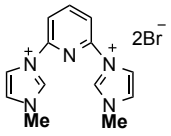
Pd complex **178**



Pt complex **179**

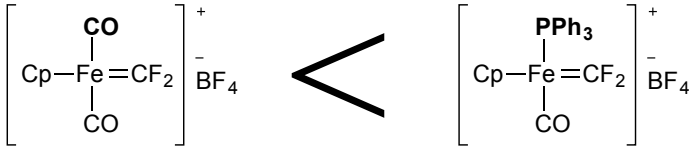


IPrCuCl



NHC-salt **180**

Figure 12. List of Catalyst Candidates

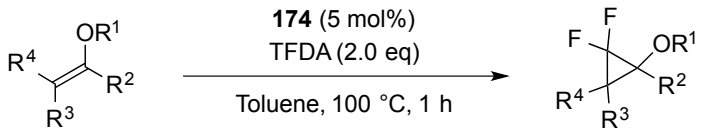


181 **182**

Decomposed above –78 °C Isolated at RT

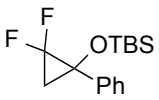
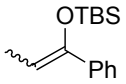
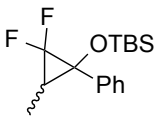
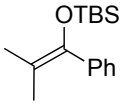
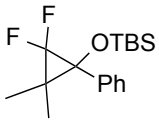
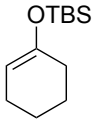
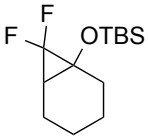
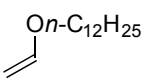
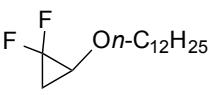
Figure 13. Stablization of Iron(III) Difluorocarbene Complexes by Phosphine Ligand

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).



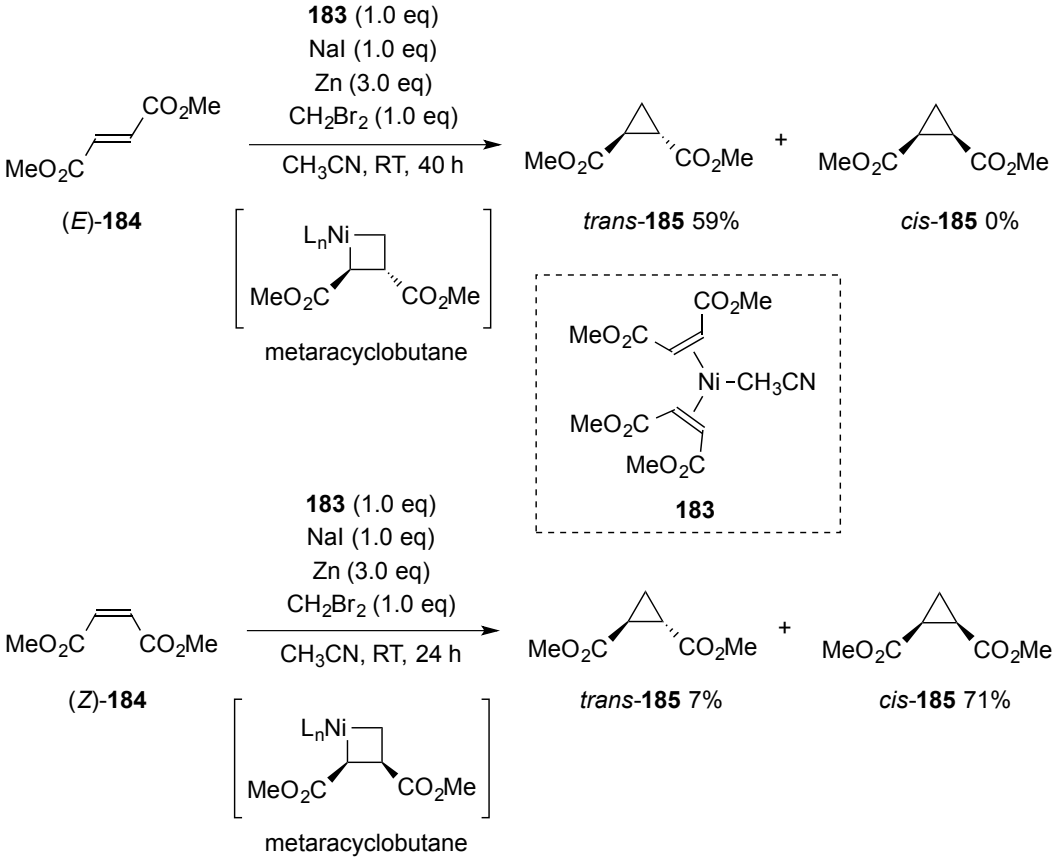
170 **173**

Table 10

Entry	Substrate **170**		Product **173**		Yield / %
1[a]		**170a**		**173a**	73
2		**170b** (*E*/*Z* = 4:96)		**173b**	68 (d.r. = 11:89)
3		**170c**		**173c**	63
4		**170d**		**173d**	78
5		**170e**		**173e**	40

a: Table 9, Entry 4.

It was reported that nickel carbene complex reacted with alkenes to generate metallacyclobutanes, which subsequently underwent reductive elimination providing cyclopropanes diastereospecificially.[18] 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).[18b] In this reported case, stereospecificity is slightly reduced presumably because of steric effect, which was similarly observed in substrate **170b**.

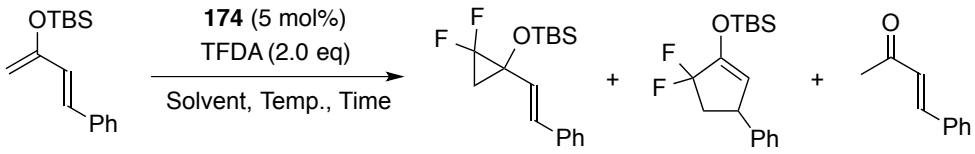


Scheme 5

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 occuerred 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).



172a **186a** **187a** **171a**

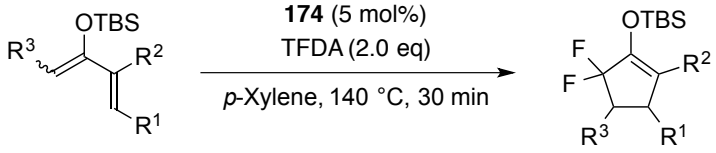
Table 11

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

a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: ^{1}H NMR yield based on **187a**. *c*: Isolated yield.

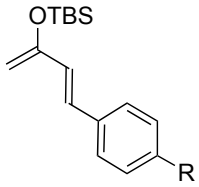
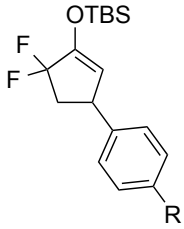
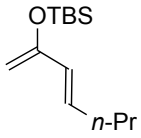
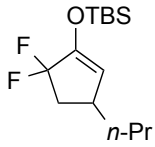
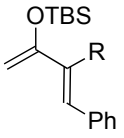
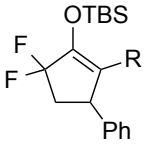
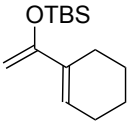
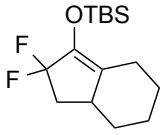
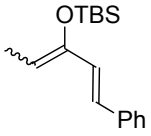
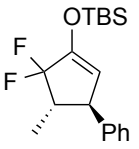
Various 5,5-difluorocyclopent-1-en-1-yl silyl ethers **187** were efficiently synthesized by the nickel(II) **174**-based catalyst system (Table 12). Dienol silyl ether **172a** reacted with TFDA (2.0 equiv) in the presence of 5 mol% of **172** at 140 °C to afford **187a** in 83% yield (Entry 1). Dienol silyl ethers **172b**,**d** bearing electron-rich and -deficient aryl groups (R^1) 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 (R^2), 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 R^3 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*-vinylcylopropane **189** underwent exclusively 1,5-hydrogen shift to afford diene **190** in 95% yield (eq. 70),[4d] while *trans*-vinylcylopropane **189** underwent not only 1,5-hydrogen

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).

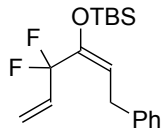


172 **187**

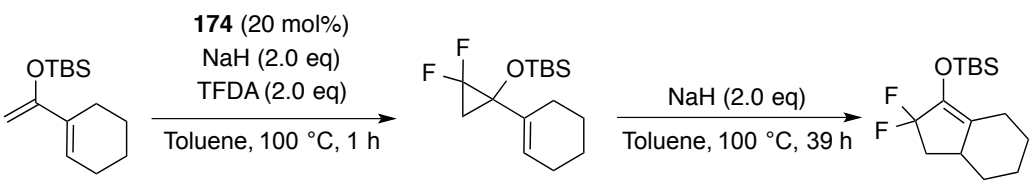
Table 12

Entry	Substrate **172**			Product **187**		Yield / %
1[a]		R = H	**172a**		**187a**	83
2		R = Me	**172b**		**187b**	80
3		R = Cl	**172d**		**187d**	79
4		**187g**			**187g**	71
5		R = Me	**172h**		**187h**	73
6		R = Br	**172i**		**187i**	74
7		R = Ph	**172j**		**187j**	74
8		**172k**			**187k**	49
9		**172l**	(*E*/*Z* = 34:66)		**187l**[b]	54[c]
10			(*E*/*Z* = 5:95)			56[d]

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

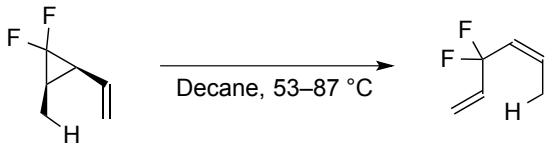


188

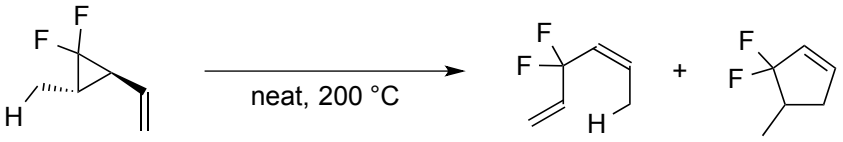


(69)

172k **186k** 60% **187k** quant (60%: 2 steps)



cis-**189** **190** 95% (70)

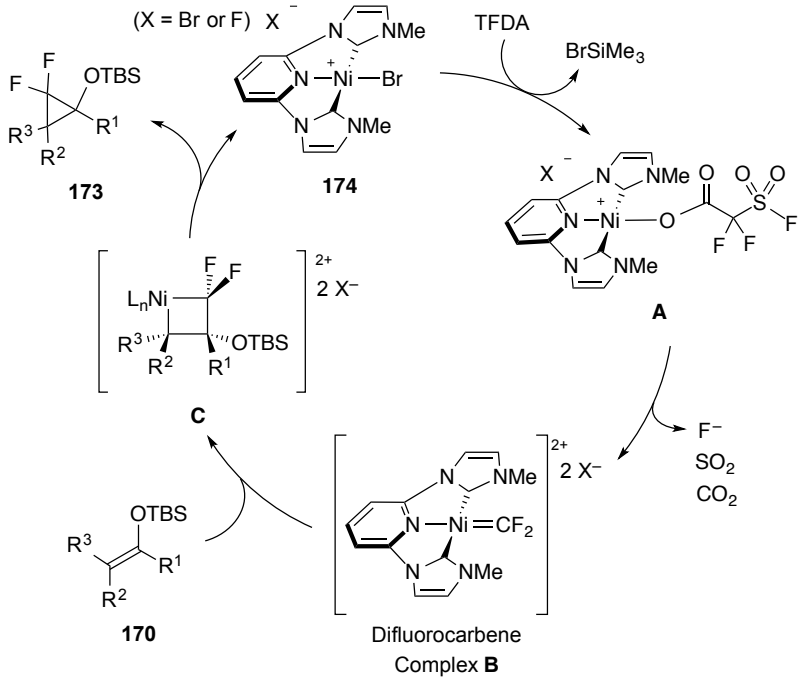


trans-**189** **190** **191** (71)

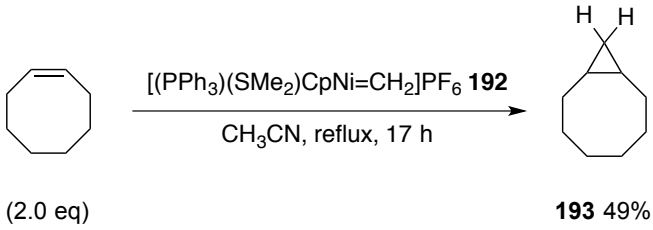
(**190**:**191** = 1:1.9)

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).

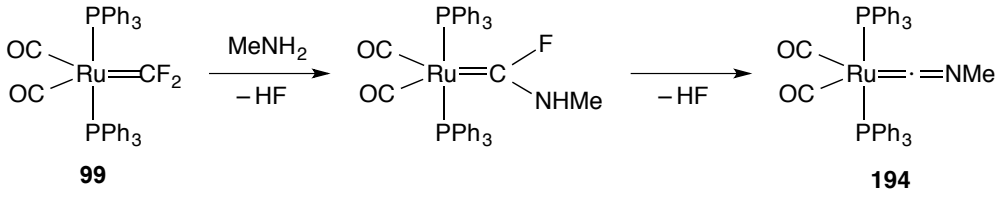


Scheme 6

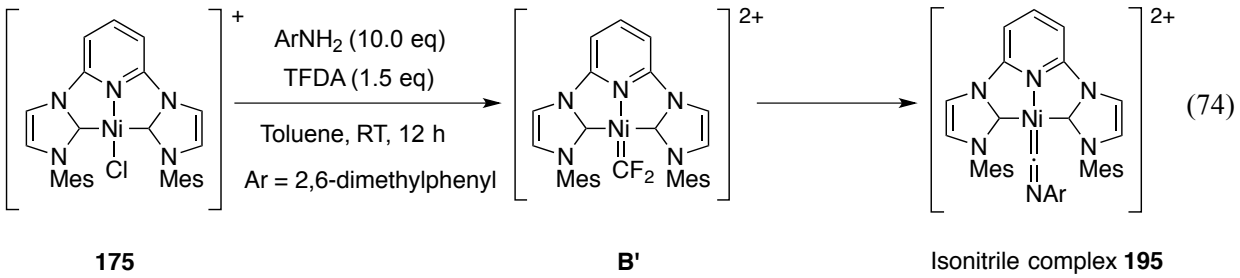


(72)

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).[19] 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+}, $C_{38}H_{38}N_6Ni$) was in complete agreement with its computer simulation (Figure 14). Thus, this operation stlongly supports the aforementioned mechanism.



(73)



(74)

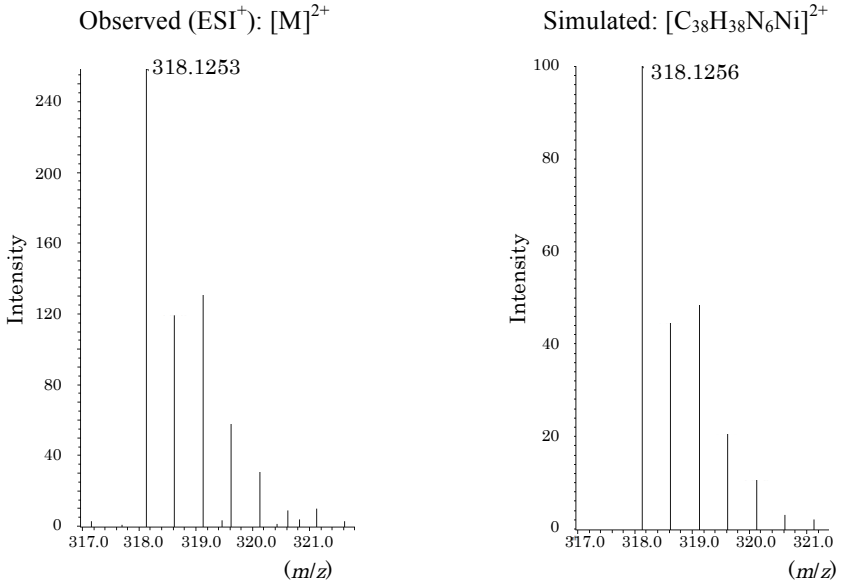
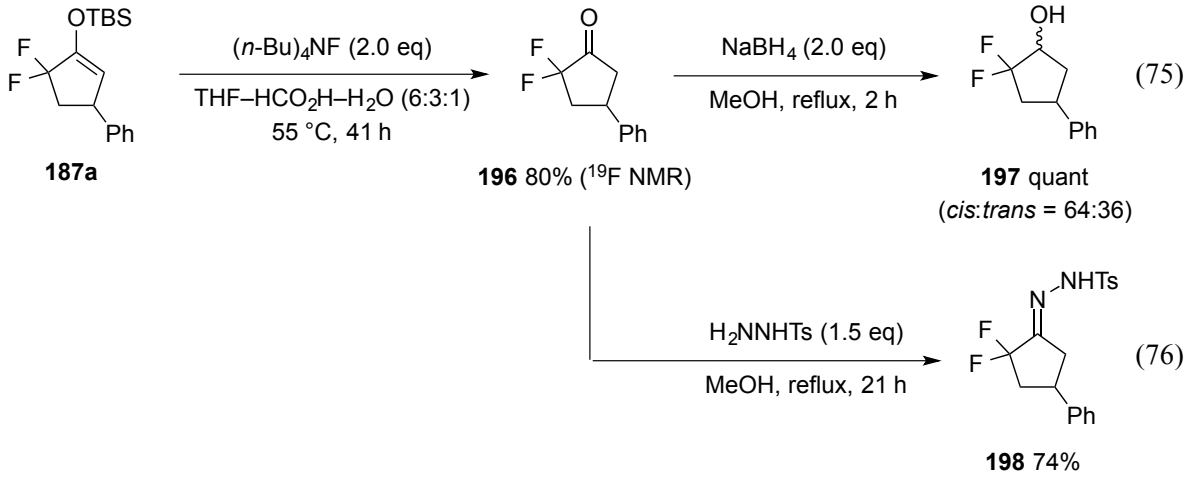


Figure 14

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 tetrabutylmmonium fluoride (2.0 equiv) in THF/formic acid/water (6:3:1) at 55 °C afforded a 80% yield (^{19}F 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).



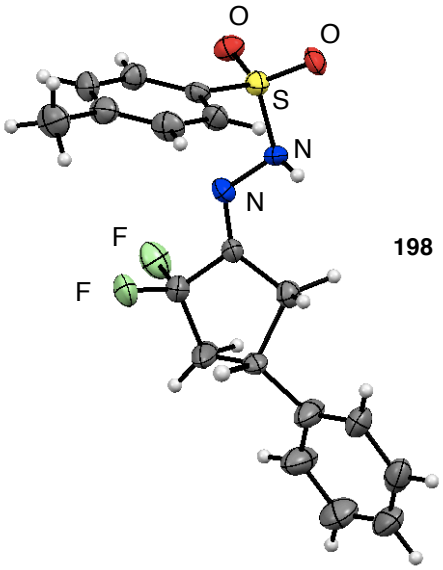
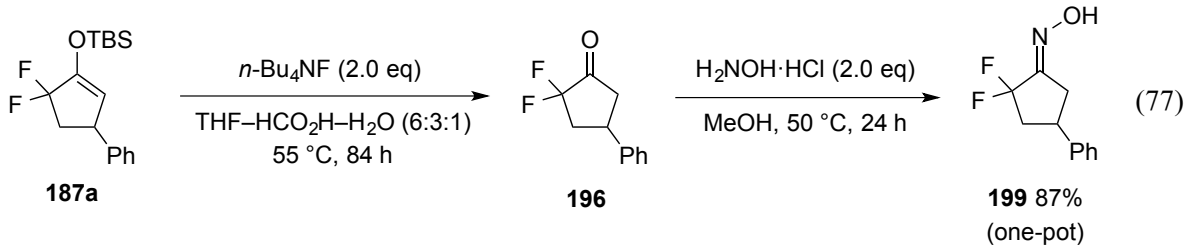
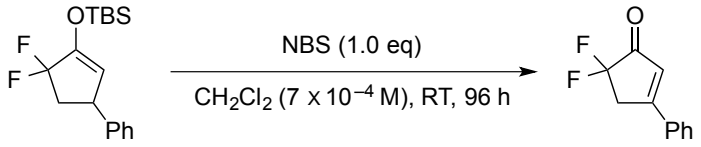


Figure 15

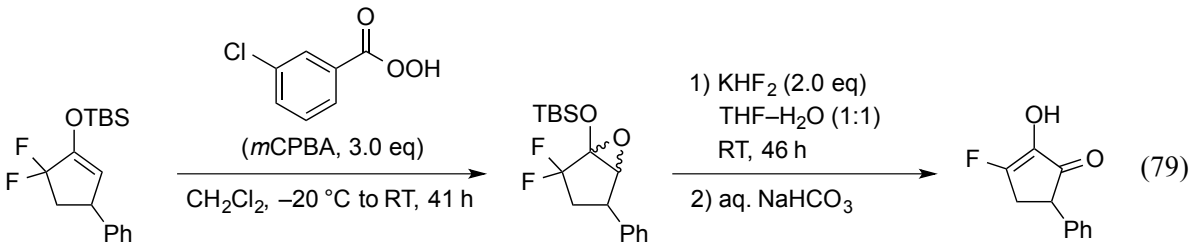


Oxidative treatment of **187a** afforded functionalized fluorine-containing cyclopentenones. Treatment of **187a** with *N*-bromosuccinimide (NBS) under highly diluted conditions (7×10^{-4} mol/L) gave difluorinated cyclopentenone **200** in 86% yield (eq. 77). Oxidation of **187a** with *m*-chloroperbenzoic 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]



187a **200** 86%

(78)



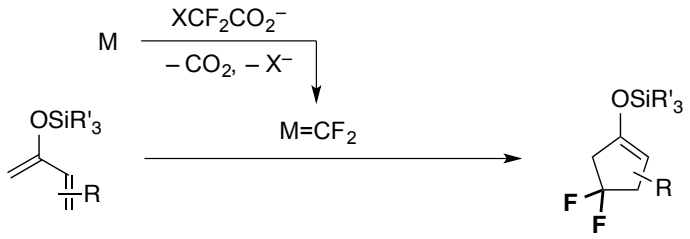
187a **201** 85% (d.r. = 78:22) **202** 54%

(79)

3.3. [4 + 1] Cycloaddition with Copper Difluorocarbene Complex

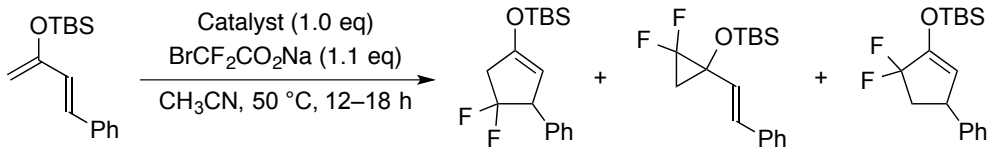
3.3.1. Synthesis of 4,4-Difluorocyclopent-1-en-1-yl Silyl Ethers

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 ($XCF_2CO_2^-$, 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).



(80)

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).



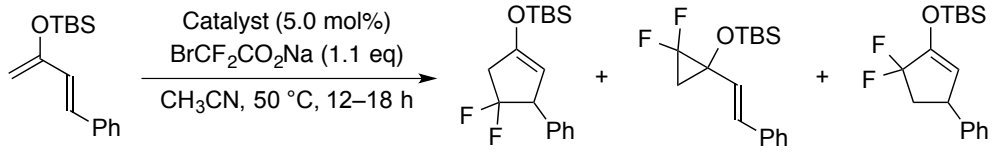
172a **203a** **186a** **187a**

Table 13

Entry	Catalyst	**203a** / %[a]	**186a** / %[a]	**187a** / %[a]
1	None	0	35	5
2	CuBr	25	3	0
3	CCu≡CPh	37	10	0
4	SIMesCuCl	10	19	<1

a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$.

The catalyst system was optimized in detail (Table 14 and Figure 16). The reaction proceeded smoothly with 5 mol % of Cu(Phen)(PPh_3)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.

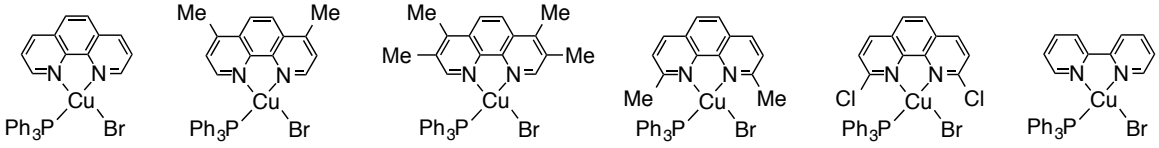


172a **203a** **186a** **187a**

Table 14

Entry	Catalyst	**203a** / %[a]	**186a** / %[a]	**187a** / %[a]
1	Cu(Phen)(PPh_3)Cl	49	6	2
2	Cu(Phen)(PPh_3)Br **204a**	62	7	3
3	Cu(Phen)(PPh_3)I	58	5	2
4	**204b**	72 (71[b])	7	2
5	**204c**	59	17	0
6	**204d**	16	7	9
7	**204e**	33	18	0
8	**204f**	39	40	2

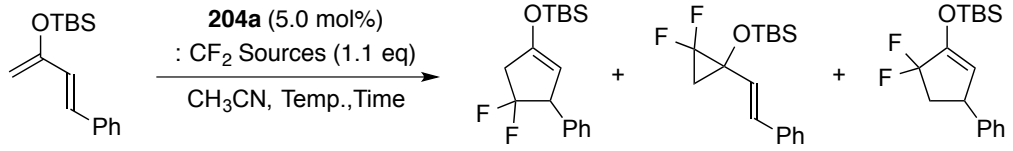
a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: Isolated yield.



204a **204b** **204c** **204d** **204e** **204f**

Figure 16

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.



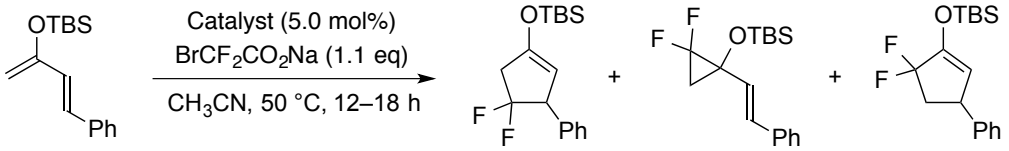
172a **203a** **186a** **187a**

Table 15

Entry	: CF_2 Sources	Temp / °C	Time / h	**203a** / %[a]	**186a** / %[a]	**187a** / %[a]	Recovery of : CF_2 Sources / %[a]
1[b]	$BrCF_2CO_2Na$	50	12	62	9	2	0
2	$BrCF_2CO_2K$	50	12	64	4	2	0
3	$BrCF_2CO_2Cs$	50	12	32	4	3	0
4	$ClCF_2CO_2Na$	80	11	0	0	0	0
5	CF_3CO_2Na	80	3	0	0	0	94
6	$FSO_2CF_2CO_2Na$	50	16	0	0	0	0

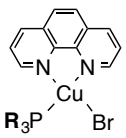
a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b*: Table 14, Entry 2.

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 compex **204k** resulted in the formation of **203a** in 51% yield (Entry 6). However, the effects of phosphine ligands were not clear.



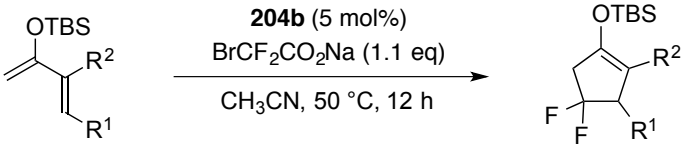
172a **203a** **186a** **187a**

Table 16

Entry	Catalyst			**203a** / %[a]	**186a** / %[a]	**187a** / %[a]
1		R = Ph	**204a**	62	7	3
2		R = $C_6H_4p\text{-}CH_3$	**204g**	66	7	0
3		R = $C_6H_4p\text{-}OCH_3$	**204h**	47	7	0
4		R = $C_6H_4p\text{-}Cl$	**204i**	67	10	0
5		R = $C_6H_4p\text{-}CF_3$	**204j**	39	12	0
6		R = Cy	**204k**	51	4	0

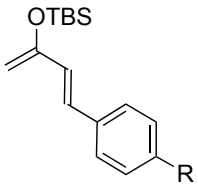
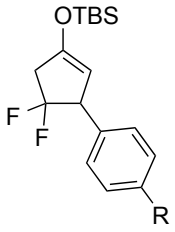
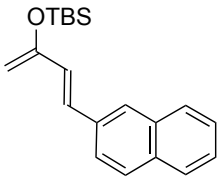
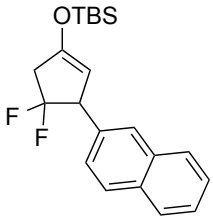
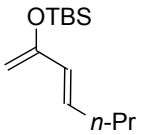
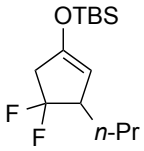
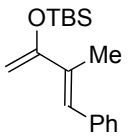
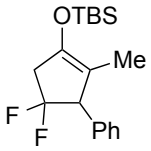
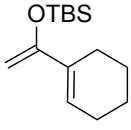
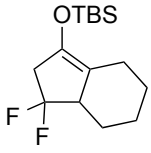
a: ^{19}F NMR yield based on $(CF_3)_2C(C_6H_4p\text{-}CH_3)_2$. *b* :Table 14, Entry 2.

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 (R^1), 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 (R^1) afforded **203f**,**g** in 59% yields each (Entries 5 and 6). Substrate **172h** bearing a substituent at the internal position (R^2) 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).



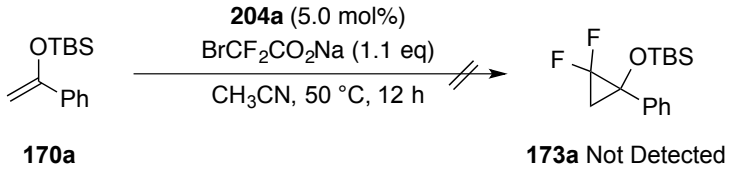
172 **203**

Table 17

Entry	Substrate **172**			Product **203**		Yield / %
1[a]		R = H	**172a**		**203a**	71
2		R = Me	**172b**		**203b**	70
3		R = OMe	**172c**		**203c**	61
4		R = Br	**172e**		**203e**	59
5			**172f**		**203f**	59
6[b]			**172g**		**203g**	59
7			**172h**		**203h**	69
8			**172k**		**203k**	63

a: Table 14, Entry 4. *b*: Reaction time was 36 h.

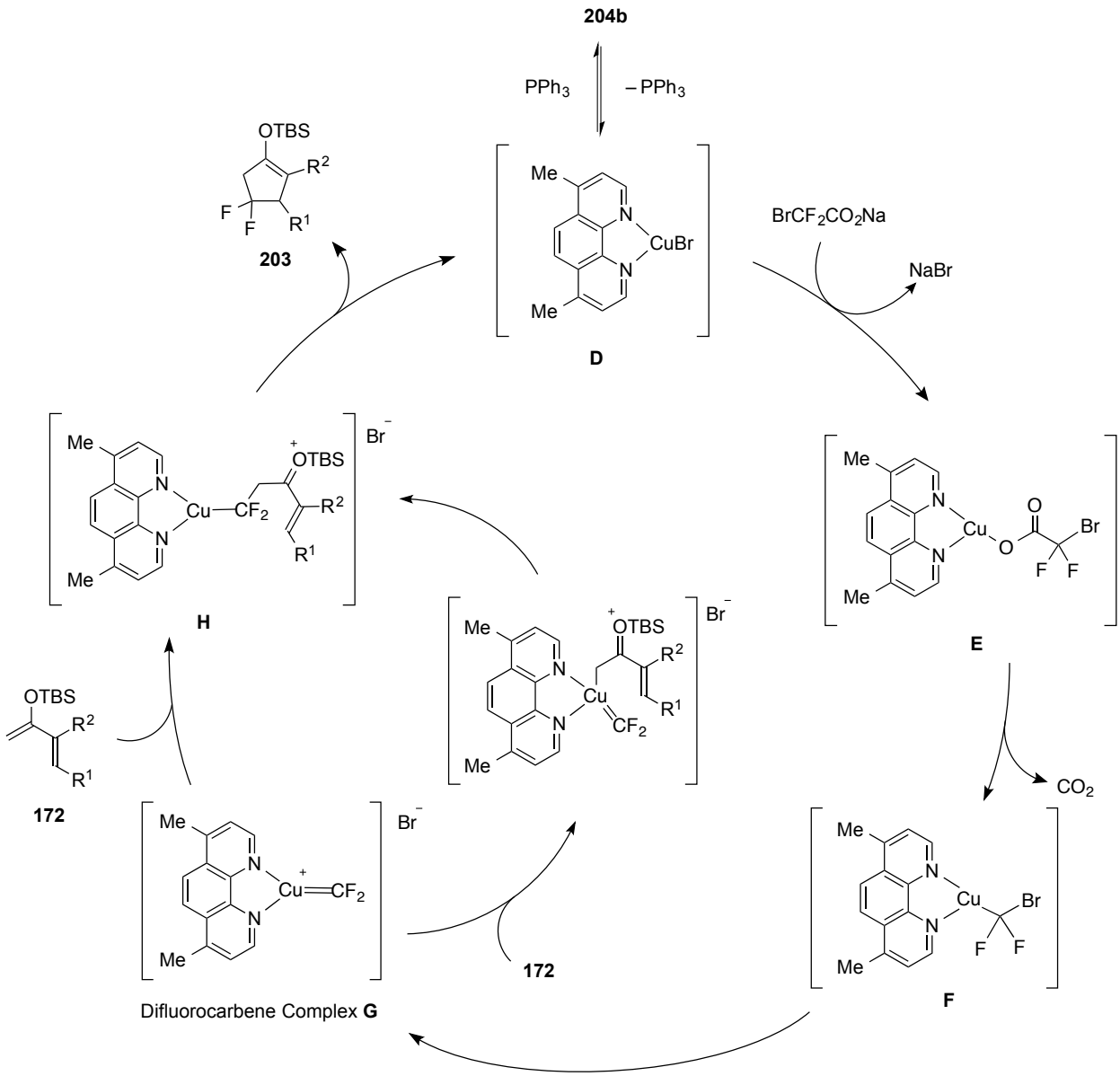
The copper(I)-catalyzed difluoromethylene transfer could not be applied to simple silyl enol ether. Treatment of silyl enol ether **170a** with sodium bromodifluoroacetate (1.1 equiv) in the presence of 5 mol% of **204a** did not afford difluorocyclopropane **173a** (eq. 81).



170a **173a** Not Detected (81)

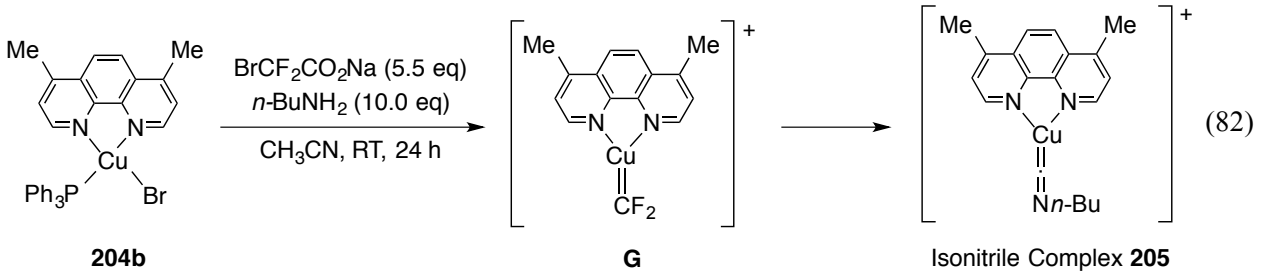
3.3.2. Mechanistic Study on [4 + 1] Cycloaddition with Copper Difluorocarbene Complex

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 CF_2 carbon of difluorocarbene complex **G** to generate the corresponding difluoroalkylcopper(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**.[21]



Scheme 7

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^+, $C_{19}H_{21}CuN_3$) was in complete agreement with its computer simulation (Figure 17).



(82)

204b **G** Isonitrile Complex **205**

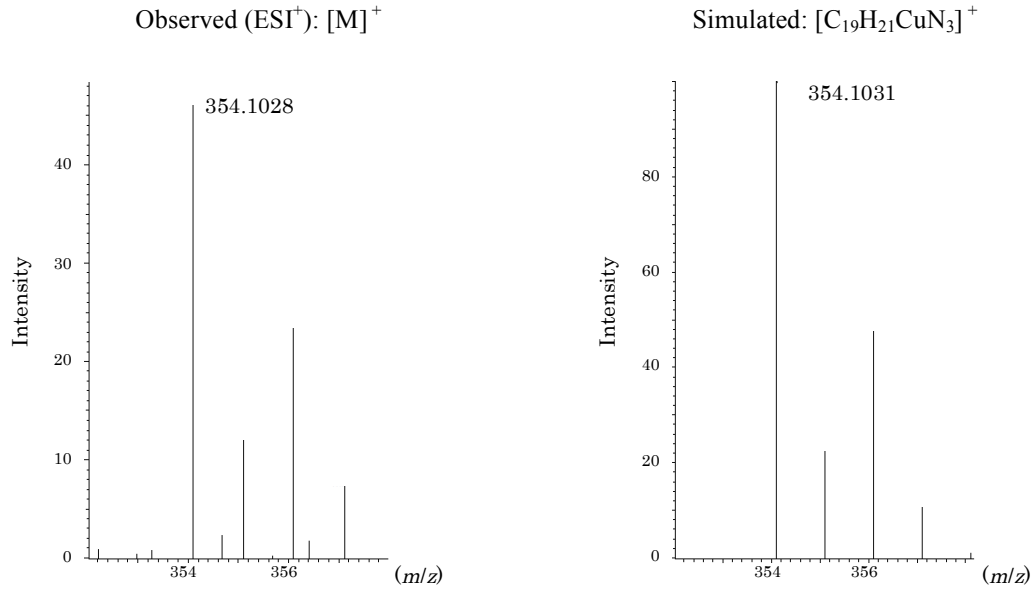
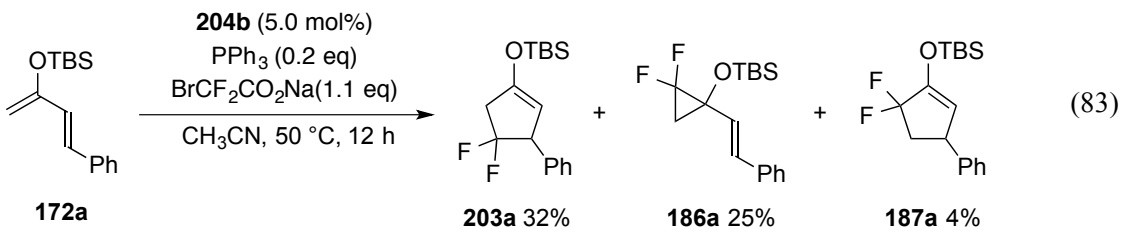


Figure 17

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).

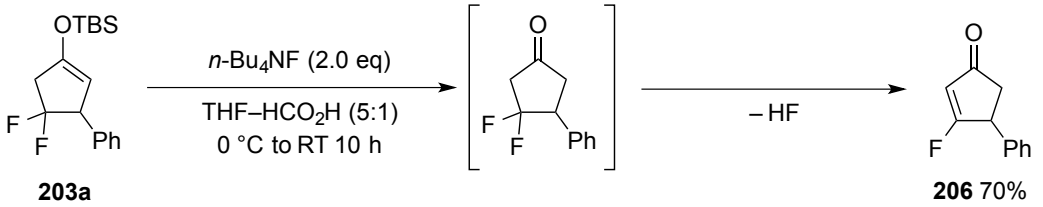


172a **203a** 32% **186a** 25% **187a** 4%

(83)

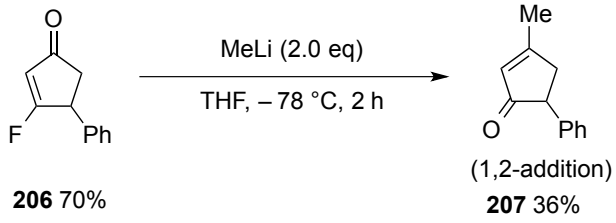
3.3.3. Derivatization of 4,4-Difluorocyclopent-1-en-1-yl Silyl Ethers into β-Fluorocyclopentanone Derivatives

Hydroysis of **203a** was effected with tetrabutylmmonium 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).



(84)

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 introducted fluorine was confirmed by the comparison of spectral data.



(85)

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_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_6 (for ^{19}F NMR: δ = 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 (TBSCl) 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_2O_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)Cl, Cu(Phen)(PPh_3)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 (TBSCl)

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)

^{1}H NMR (500 MHz, $CDCl_3$): (*Z*-isomer) δ = –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). ^{13}C NMR (126 MHz, $CDCl_3$): (*Z*-isomer) δ = –4.0, 11.7, 18.3, 25.9, 105.8, 125.7, 127.2, 127.9, 139.8, 150.2. IR (neat): $\tilde{\nu}$ = 2929, 1321, 1254, 1059, 866, 837, 779, 735. HRMS (70 eV, EI+): *m*/*z* (*Z*-isomer) calcd. for $C_{15}H_{24}OSi$ $[M]^+$: 248.1596; Found: 248.1596.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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}C NMR (126 MHz, $CDCl_3$): δ = −4.6, 18.4, 25.9, 96.7, 126.5, 126.7, 127.6, 128.6, 129.2, 136.8, 155.2. IR (neat): $\tilde{\nu}$ = 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.

3-[*tert*-Butyl(dimethyl)silyloxy]-1-(*p*-methylphenyl)buta-1,3-dien **172b**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = −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): $\tilde{\nu}$ = 2956, 2929, 1587, 1323, 1003, 837 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{17}H_{26}OSi$ $[M]^+$: 274.1753; Found: 274.1755.

3-(*tert*-Butyldimethylsiloxy)-4-(*p*-methoxyphenyl)-1,3-butadiene **172c**

^1H NMR (500 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = –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); $\tilde{\nu}$ = 2929, 1510, 1250, 1173, 1024, 823 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{17}H_{26}OSi$ ($[M]^+$): 290.1702; found: 290.1701.

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

^1H NMR (500 MHz, $CDCl_3$): δ= 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = −4.6, 18.4, 25.9, 97.1, 127.2, 127.9, 128.7, 133.2, 135.3, 155.0. IR (neat); $\tilde{\nu}$ = 2929, 1597, 1489, 1323, 1022, 812 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{16}H_{23}ClOSi$ $[M]^+$: 294.1207; Found: 294.1203.

3-(*tert*-Butyldimethylsiloxy)-1-(*p*-bromophenyl)-1,3-butadiene **172e**

^1H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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 $C_{16}H_{23}BrOSi$ ($[M]^+$): 338.0702; found: 338.0705.

3-(*tert*-Butyldimethylsiloxy)-4-(2-naphtyl)-1,3-butadiene **172f**

^1H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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 $C_{20}H_{26}OSi$ ($[M]^+$): 310.1753; found: 310.1755.

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

^1H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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 $C_{13}H_{26}OSi$ $[M]^+$: 226.1753; Found: 226.1755.

3-[*tert*-Butyl(dimethyl)silyloxy]-2-methyl-1-phenylbuta-1,3-diene **172h**

^1H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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): $\tilde{\nu}$ = 2956, 2858, 1601, 1254, 1018, 827 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{17}H_{26}OSi$ $[M]^+$: 274.1753; Found: 274.1754.

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

H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −4.7, 18.3, 25.8, 97.5, 120.2, 128.1, 128.1, 129.0, 129.5, 135.9, 153.7. IR (neat): $\tilde{\nu}$ = 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**

^1H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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): $\tilde{\nu}$ = 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**

^1H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −4.6, 18.3, 22.1, 22.7, 25.0, 25.5, 25.9, 89.4, 125.3, 133.2, 156.8. IR (neat): $\tilde{\nu}$ = 2929, 2858, 1664, 1255, 831 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{14}H_{26}OSi$ $[M]^+$: 238.1753; Found: 238.1755.

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

^1H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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): $\tilde{\nu}$ = 2929, 1338, 1254, 1024, 777, 688 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{17}H_{26}OSi$ $[M]^+$: 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. ^{19}F 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-phenylcyclopropane **173a**

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): δ = −4.3, –4.1, 17.9, 23.4 (t, *J* = 9 Hz), 25.5, 62.3 (dd, *J* = 12, 10 Hz), 112.1 (t, *J* = 296 Hz), 128.3, 128.5, 136.2. ^{19}FNMR (470 MHz, $CDCl_3$): δ = 21.2 (ddd, *J* = 154, 16, 6 Hz, 1F), 28.5 (ddd, *J* = 154, 16, 5 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 1460, 1228, 1173, 827, 698 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{15}H_{22}F_2OSi$ $[M]^+$: 284.1408; Found: 284.1404.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = –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, $CDCl_3$): δ = −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, $CDCl_3$): δ = 12.2 (d, *J* = 155 Hz, 1F), 34.1 (ddd, *J* = 155, 18, 3 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 2860, 1473, 1167, 839 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{16}H_{24}F_2OSi$ $[M]^+$: 298.1564; Found: 298.1563.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = –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, $CDCl_3$): δ = −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, $CDCl_3$): δ = 17.5 (d, *J* = 154 Hz, 1F), 22.9 (d, *J* = 154 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2929, 1471, 1250, 1165, 866, 700 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{17}H_{26}F_2OSi$ $[M]^+$: 312.1721; Found: 312.1717.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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 Hz). ^{19}FNMR (470 MHz, $CDCl_3$): δ = 15.7 (d, *J* = 157 Hz, 1F), 26.1 (dd, *J* = 157, 19 Hz, 1F).
IR (neat): $\tilde{\nu}$ = 2931, 2858, 1473, 1252, 1192, 837 cm^{-1}. EA: calcd. for $C_{13}H_{24}F_2OSi$: C 59.50%, H 9.22%; Found: C 59.10%, H 9.38%.

1-dodecyloxy-2,2-difluorocyclopropane **173e**

^{1}H NMR (500 MHz, $CDCl_3$): 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, $CDCl_3$): δ =14.1, 17.9, 18.0 (t, *J* = 10 Hz), 22.7, 25.9, 29.3, 29.4, 29.5, 29.6, 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, $CDCl_3$): δ = 12.8 (dddd, *J* = 165, 16, 6, 2 Hz, 1F), 31.4 (dddd, *J* = 165, 15, 10, 5 Hz, 1F). IR (neat): $\tilde{\nu}$ = 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**

^{1}H NMR (500 MHz, $CDCl_3$): 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* = 7.5 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = −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, $CDCl_3$): δ = 64.4 (dddd, *J* = 248, 15, 14, 2 Hz, 1F), 69.1 (dddd, *J* = 248, 16, 11, 8 Hz, 1F).

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

HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{13}H_{15}F_2OSi$ [M–*t*-Bu]$^+$: 253.0859; Found: 253.0855.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.22 (s, 6H), 0.98 (s, 9H), 2.14 (dddd, *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, $CDCl_3$): δ = −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, $CDCl_3$): δ = 64.3 (dddd, *J* = 247, 16, 14, 2 Hz, 1F), 69.1 (dddd, *J* = 247, 16, 11, 8 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 2860, 1655, 1174, 650 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{14}H_{17}F_2OSi$ [M–*t*-Bu]$^+$: 267.1016; Found: 267.1015.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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, $CDCl_3$): δ= 64.1 (dt, *J* = 248, 15 Hz, 1F), 69.3 (dddd, *J* = 248, 18, 10, 8 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2956, 2860, 1655, 1491, 1363, 1255, 841 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{13}H_{14}ClF_2OSi$ $[M–t\text{-}Bu]^+$: 287.0470; Found: 287.0468.

1-[*tert*-Butyl(dimethyl)silyloxy]-5,5-difluoro-3-propylcyclopent-1-ene **187g**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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, $CDCl_3$): δ = 65.7 (dddd, *J* = 247, 18, 13, 3 Hz, 1F), 69.5 (dddd, *J* = 247, 19, 11, 8 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 2859, 1655, 1365, 1242, 1176, 1099, 841 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{10}H_{17}F_2OSi$ $[M–t\text{-}Bu]^+$: 219.1016; Found: 219.1014.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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 (d, *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, $CDCl_3$): δ = −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, $CDCl_3$): δ = 68.3 (dm, *J* = 245 Hz, 1F), 73.3 (dm, *J* = 245 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 1691, 1346, 1215, 862 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{14}H_{17}F_2OSi$ $[M–t\text{-}Bu]^+$: 267.1016; Found: 267.1014.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = −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}F NMR (470 MHz, $CDCl_3$): δ = 68.2 (ddd, *J* = 244, 18, 9 Hz, 1F), 73.2 (dddd, *J* = 244, 18, 11, 9 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2860, 1670, 1340, 1190, 1041, 845 cm^{-1}.

HRMS (70 eV, EI+): *m*/*z* calcd. for $C_{13}H_{14}BrF_2OSi$ $[M–t\text{-}Bu]^+$: 330.9965; Found: 330.9962.

1-[*tert*-Butyl(dimethyl)silyloxy]-5,5-difluoro-2,3-diphenylcyclopent-1-ene **187j**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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 (tdd, *J* = 9.0, 3.5, 2.5 Hz, 1H), 7.11–7.25 (m, 8H), 7.37 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = –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}F NMR (470 MHz, $CDCl_3$): δ = 69.3 (ddd, *J* = 247, 19, 9 Hz, 1F), 74.2 (ddt, *J* = 247, 18, 11 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 1653, 1367, 1182, 1038, 858 cm^{-1}. HRMS (70 eV, EI+): *m*/*z*: calcd. for $C_{23}H_{27}FOSi$ $[M–HF]^+$: 366.1815; Found: 366.1816.

9-[*tert*-Butyl(dimethyl)silyloxy]-8,8-difluorobicyclo[4.3.0]non-9-ene (**187k**)

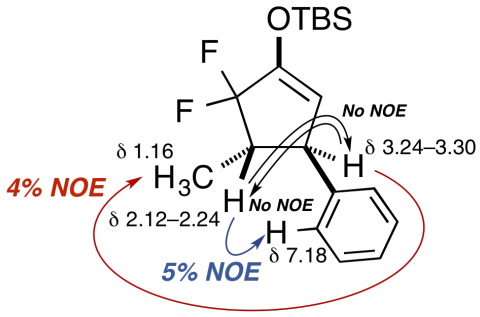
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.15 (s, 6H), 0.97 (s, 9H), 1.15−1.45 (m, 3H), 1.69–1.88 (m, 4H), 1.95–2.02 (m, 1H), 2.29–2.40 (m, 1H), 2.42–2.53 (m, 1H), 2.61 (dd, *J* = 13.0, 4.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = −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}F NMR (470 MHz, $CDCl_3$): δ = 71.0 (dm, *J* = 244 Hz, 1F), 72.3 (dm, *J* = 244 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2929, 2858, 1693, 1371, 1169, 995, 837 cm^{-1}. HRMS (70 eV, EI+): *m*/*z*: calcd. for $C_{15}H_{25}FOSi$ $[M–HF]^+$: 268.1659; Found: 268.1660.

trans-1-[*tert*-Butyl(dimethyl)silyloxy]-5,5-difluoro-4-methyl-3-phenylcyclopent-1-ene **187l** and 4-[*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**) δ = 0.23 (s, 3H), 0.24 (s, 3H), 0.99 (s, 9H), 1.16 (dd, *J* = 7.0, 2.0 Hz, 3H), 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**) δ = 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**) δ = –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**) δ = –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**) δ = 51.7 (ddd, *J* = 247, 14, 2 Hz, 1F), 63.1 (ddd, *J* = 247, 18, 10 Hz, 1F); (**188**) δ = 66.2 (d, *J* = 11 Hz). IR (neat): $\tilde{\nu}$ = 2931, 2860, 1655, 1363, 837, 731 cm^{-1}. HRMS (70 eV, EI+): *m*/*z* (**187l**) calcd. for $C_{18}H_{25}FOSi$ $[M–HF]^+$: 304.1659; Found: 304.1656; (**188**) calcd. for $C_{18}H_{25}FOSi$ $[M–HF]^+$: 304.1659; Found: 304.1655.



187l

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, $LNi{=}C{=}NAr^{2+}$ (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

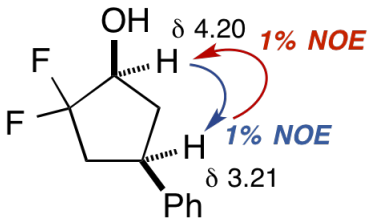
(*A*) Synthesis of ketone **196**

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).

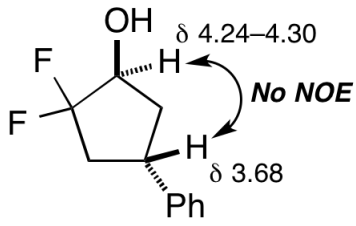
(*B*) Synthesis of alcohol **197**

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 (dddd, *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) δ = 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) δ = 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) δ = 50.2 (dm, *J* = 233 Hz, 1F), 58.1 (ddt, *J* = 233, 24, 12 Hz, 1F); (*trans* isomer) δ = 47.1 (dt, *J* = 236, 10 Hz, 1F), 63.8 (ddddd, *J* = 236, 22, 18, 8, 3 Hz, 1F). IR (neat): $\tilde{\nu}$ = 3396, 3030, 1496, 1140, 1061, 698 cm^{-1}. HRMS (70 eV, EI): *m*/*z*: (*cis* isomer) Calcd. for $C_{11}H_{12}F_2O$ $[M]^+$: 198.0856; Found: 198.0856; (*trans* isomer) Calcd. for $C_{11}H_{12}F_2O$ $[M]^+$: 198.0856; Found: 198.0856.



***cis*-197**



***trans*-197**

(*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 temerature. The resulting mixture was heated to reflux, stirred for 21 h, and then cooled to room temperature. The formed precipitates were seperated 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 recystalization 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, $CDCl_3$): δ = 2.24 (dddd, *J* = 26.0, 13.5, 13.5, 10.0 Hz, 1H), 2.36 (ddd, *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): $\tilde{\nu}$ = 3205, 1597, 1496, 1348, 1165, 769 cm^{-1}. EA: Calcd. for $C_{18}H_{18}F_2N_2O_2S$: C 59.33%, H 4.98%, N 7.69%; Found: C 59.32%, H 5.00%, N 7.58%.

Crystallographic Information for **198**

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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 . . .
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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 . . .
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C14  C   0.1605(5)   0.7143(10)  0.5529(5)   0.0323(14) Uani 1 1 d . . .
H3   H   0.1300      0.8546      0.5130      0.039      Uiso 1 1 calc R . .
C15  C   0.2491(5)   0.3061(13)  0.6707(5)   0.0417(15) Uani 1 1 d . . .
H4   H   0.2795      0.1659      0.7107      0.050      Uiso 1 1 calc R . .
C16  C   0.1422(5)   0.3871(12)  0.6652(5)   0.0392(15) Uani 1 1 d . . .
C17  C   0.0744(5)   0.2538(15)  0.7217(5)   0.0529(18) Uani 1 1 d . . .
H5   H   0.0968      0.3090      0.7951      0.079      Uiso 1 1 calc R . .
H6   H   0.0891      0.0806      0.7203      0.079      Uiso 1 1 calc R . .
H7   H   -0.0070     0.2850      0.6867      0.079      Uiso 1 1 calc R . .
C18  C   0.3901(5)   -0.2039(14) 0.1391(5)   0.0442(16) Uani 1 1 d . A .
H8   H   0.4259      -0.1764     0.2124      0.053      Uiso 1 1 calc R . .
C19  C   0.4366(6)   -0.3660(13) 0.0878(6)   0.0507(19) Uani 1 1 d . . .
H9   H   0.5038      -0.4513     0.1259      0.061      Uiso 1 1 calc R . .
C20  C   0.3857(6)   -0.4057(15) -0.0195(6)  0.058(2)   Uani 1 1 d . A .
H10  H   0.4187      -0.5152     -0.0554     0.069      Uiso 1 1 calc R . .
C21  C   0.2926(6)   -0.0815(14) 0.0856(6)   0.0517(19) Uani 1 1 d . . .
C22  C   0.2418(6)   -0.1289(15) -0.0208(6)  0.060(2)   Uani 1 1 d . A .
H11  H   0.1727      -0.0495     -0.0588     0.072      Uiso 1 1 calc R . .
C24  C   0.2888(7)   -0.2875(15) -0.0725(6)  0.064(2)   Uani 1 1 d . . .
H12  H   0.2531      -0.3146     -0.1459     0.077      Uiso 1 1 calc R A .
C25  C   0.1283(6)   0.1576(18)  0.1036(7)   0.078(3)   Uani 1 1 d . . .
H25  H   0.062(4)    0.099(10)   0.053(4)    0.028(15)  Uiso 1 1 d . . .
C1   C   0.2266(9)   0.035(3)    0.1561(10)  0.028(4)   Uani 0.55(3) 1 d P A 1
H13  H   0.184(6)    -0.079(14)  0.202(6)    0.000(19)  Uiso 0.55(3) 1 d P A 1
C26  C   0.2535(13)  0.153(3)    0.1206(12)  0.029(5)   Uani 0.45(3) 1 d P A 2
H26  H   0.250(8)    0.31(2)     0.087(8)    0.00(2)    Uiso 0.45(3) 1 d P A 2
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N6	0.022(2)	0.038(3)	0.031(3)	-0.007(2)	0.004(2)	-0.003(2)
F4	0.0282(15)	0.048(2)	0.058(2)	-0.003(2)	0.0179(15)	-0.0084(19)
C8	0.021(3)	0.026(3)	0.033(3)	-0.003(3)	0.009(2)	-0.002(2)
C9	0.032(3)	0.020(3)	0.029(3)	-0.003(2)	0.013(2)	-0.007(2)
C10	0.027(3)	0.039(5)	0.044(4)	-0.010(3)	0.014(3)	-0.002(2)
C11	0.031(3)	0.042(4)	0.045(4)	-0.004(3)	0.020(3)	-0.007(3)
C12	0.027(3)	0.035(4)	0.032(3)	0.000(3)	0.007(3)	0.002(3)
C13	0.035(3)	0.025(3)	0.049(4)	0.000(3)	0.019(3)	-0.006(3)
C14	0.032(3)	0.029(4)	0.036(3)	0.002(2)	0.012(2)	0.003(2)
C15	0.052(3)	0.033(4)	0.044(4)	0.005(3)	0.020(3)	-0.007(3)
C16	0.045(4)	0.038(4)	0.041(4)	-0.006(3)	0.023(3)	-0.008(3)
C17	0.059(4)	0.046(4)	0.065(4)	0.001(4)	0.036(3)	-0.015(4)
C18	0.036(3)	0.045(4)	0.055(4)	-0.007(4)	0.019(3)	0.008(3)
C19	0.044(4)	0.041(4)	0.078(6)	0.003(4)	0.035(4)	0.004(3)
C20	0.061(5)	0.056(5)	0.072(6)	-0.022(4)	0.043(4)	-0.005(4)
C21	0.040(4)	0.067(5)	0.042(4)	-0.023(4)	0.005(3)	0.014(3)
C22	0.056(5)	0.061(5)	0.052(5)	-0.023(4)	0.005(4)	0.014(3)
C24	0.072(5)	0.071(7)	0.057(5)	-0.020(4)	0.031(4)	0.003(4)
C25	0.030(4)	0.112(8)	0.088(6)	-0.076(6)	0.015(4)	-0.006(4)
C1	0.030(6)	0.032(9)	0.023(7)	-0.007(6)	0.011(5)	-0.003(5)
C26	0.042(8)	0.017(10)	0.030(9)	-0.002(7)	0.015(7)	0.012(7)

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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.

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C21 C22 1.384(10) . ?
C21 C26 1.518(14) . ?
C21 C1 1.583(13) . ?
C22 C24 1.366(10) . ?
C22 H11 0.9500 . ?
C24 H12 0.9500 . ?
C25 C1 1.372(14) . ?
C25 C26 1.497(18) . ?
C25 H25 0.94(5) . ?
C25 H31 1.35(15) . ?
C1 H13 1.13(8) . ?
C26 H26 0.95(12) . ?
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O1 S1 O2 120.2(3) . . ?
O1 S1 N1 103.5(3) . . ?
O2 S1 N1 108.2(3) . . ?
O1 S1 C9 108.6(3) . . ?

O2	S1	C9	108.3(2) . .	?
N1	S1	C9	107.4(3) . .	?
N6	N1	S1	114.0(4) . .	?
N6	N1	H30	113(5) . .	?
S1	N1	H30	118(5) . .	?
C8	N6	N1	116.7(4) . .	?
N6	C8	C12	133.0(5) . .	?
N6	C8	C10	117.8(5) . .	?
C12	C8	C10	109.2(5) . .	?
C14	C9	C13	120.4(5) . .	?
C14	C9	S1	120.5(4) . .	?
C13	C9	S1	119.1(4) . .	?
F4	C10	F1	104.4(4) . .	?
F4	C10	C25	111.9(6) . .	?
F1	C10	C25	112.7(6) . .	?
F4	C10	C8	111.5(5) . .	?
F1	C10	C8	111.4(5) . .	?
C25	C10	C8	105.2(5) . .	?
C14	C11	C16	121.3(5) . .	?
C14	C11	H1	119.3 . .	?
C16	C11	H1	119.3 . .	?
C8	C12	C26	104.2(6) . .	?
C8	C12	C1	100.7(5) . .	?
C26	C12	C1	34.8(6) . .	?
C8	C12	H29	115(5) . .	?
C26	C12	H29	102(4) . .	?
C1	C12	H29	131(5) . .	?
C8	C12	H28	120(4) . .	?
C26	C12	H28	120(4) . .	?
C1	C12	H28	95(4) . .	?
H29	C12	H28	94(6) . .	?
C15	C13	C9	119.5(6) . .	?
C15	C13	H2	120.2 . .	?
C9	C13	H2	120.2 . .	?
C11	C14	C9	119.0(5) . .	?

C11	C14	H3	120.5 . .	?
C9	C14	H3	120.5 . .	?
C13	C15	C16	121.0(6) . .	?
C13	C15	H4	119.5 . .	?
C16	C15	H4	119.5 . .	?
C15	C16	C11	118.7(6) . .	?
C15	C16	C17	120.3(6) . .	?
C11	C16	C17	121.0(6) . .	?
C16	C17	H5	109.5 . .	?
C16	C17	H6	109.5 . .	?
H5	C17	H6	109.5 . .	?
C16	C17	H7	109.5 . .	?
H5	C17	H7	109.5 . .	?
H6	C17	H7	109.5 . .	?
C21	C18	C19	120.6(6) . .	?
C21	C18	H8	119.7 . .	?
C19	C18	H8	119.7 . .	?
C18	C19	C20	120.2(7) . .	?
C18	C19	H9	119.9 . .	?
C20	C19	H9	119.9 . .	?
C24	C20	C19	119.5(7) . .	?
C24	C20	H10	120.3 . .	?
C19	C20	H10	120.3 . .	?
C18	C21	C22	118.1(6) . .	?
C18	C21	C26	125.6(8) . .	?
C22	C21	C26	113.6(8) . .	?
C18	C21	C1	115.7(7) . .	?
C22	C21	C1	123.1(7) . .	?
C26	C21	C1	35.0(6) . .	?
C24	C22	C21	121.5(7) . .	?
C24	C22	H11	119.3 . .	?
C21	C22	H11	119.3 . .	?
C20	C24	C22	120.1(7) . .	?
C20	C24	H12	119.9 . .	?
C22	C24	H12	119.9 . .	?

```
C1    C25   C26   37.7(6) . .    ?
C1    C25   C10   107.5(7) . .    ?
C26   C25   C10   107.1(7) . .   ?
C1    C25   H25   129(4) . .     ?
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) . .     ?
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O2    S1    N1    N6    -58.1(5) . . . .    ?
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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)	?
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 1	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)	?
C21	C22	C24	C20 1	.3(12)	?
F4	C10	C25	C1	-96.4(10)	?
F1	C10	C25	C1	146.4(10)	?
C8	C10	C25	C1	24.8(11)	?
F4	C10	C25	C26	-136.0(10)	?
F1	C10	C25	C26	106.8(10)	?
C8	C10	C25	C26	-14.8(11)	?
C26	C25	C1	C21	-58.9(13)	?
C10	C25	C1	C21	-154.6(10)	?
C26	C25	C1	C12	61.3(13)	?
C10	C25	C1	C12	-34.3(12)	?
C18	C21	C1	C25	-179.7(10)	?
C22	C21	C1	C25	-20.0(18)	?
C26	C21	C1	C25	64.3(15)	?
C18	C21	C1	C12	61.0(13)	?
C22	C21	C1	C12	-139.4(8)	?
C26	C21	C1	C12	-55.1(12)	?
C8	C12	C1	C25	30.2(12)	?
C26	C12	C1	C25	-69.3(15)	?
C8	C12	C1	C21	155.8(8)	?
C26	C12	C1	C21	56.2(11)	?
C1	C25	C26	C12	-68.6(13)	?
C10	C25	C26	C12	28.0(14)	?
C1	C25	C26	C21	60.3(13)	?
C10	C25	C26	C21	156.9(10)	?
C8	C12	C26	C25	-29.8(13)	?
C1	C12	C26	C25	58.6(14)	?
C8	C12	C26	C21	-156.2(12)	?
C1	C12	C26	C21	-67.9(14)	?
C18	C21	C26	C25	-138.1(10)	?
C22	C21	C26	C25	61.2(16)	?

```
C1    C21   C26   C25   -53.4(14) . . . .   ?
C18   C21   C26   C12   -16(2) . . . .      ?
C22   C21   C26   C12   -176.2(11) . . . .  ?
C1    C21   C26   C12   69.1(15) . . . .    ?
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N1   H30   O1   0.73(6)   2.20(6)   2.903(7)   161(6)   2_646
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```

(*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), distiled 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 columnchromatography 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 56.7 (dd, *J* = 252, 10 Hz, 1F), 67.6 (dddd, *J* = 252, 26, 14, 2 Hz, 1F). IR (neat): $\tilde{\nu}$ = 3269, 1456, 1180, 912, 748 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{11}H_{11}F_2NO$ $[M]^+$: 211.0809; Found: 211.0809.

(*E*) Synthesis of enone **200**

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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 50.6 (td, *J* = 12, 2 Hz). IR (neat): $\tilde{\nu}$ = 3101, 2927, 1736, 1593, 1338, 1057, 906 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{11}H_8F_2O$ $[M]^+$: 194.0543; Found: 194.0544.

(*F*) Synthesis of epoxide **201**

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 (*m*CPBA, 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-[*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) δ = 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 (dtd, *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) δ = 0.18 (s, 3H), 0.23 (s, 3H), 0.93 (s, 9H), 2.09 (dddd, *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, $CDCl_3$): δ = –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 (dd, *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) δ = 45.6 (ddd, *J* = 243, 15, 3 Hz, 1F), 62.5 (dddd, *J* = 243, 24, 20, 3 Hz, 1F); (minor isomer) δ = 43.7 (dd, *J* = 243, 12 Hz, 1F), 54.8 (ddd, *J* = 243, 26, 18 Hz, 1F). IR (neat): $\tilde{\nu}$ = 2931, 1437, 1254, 1174, 1059, 837 cm^{-1}. HRMS (70 eV, EI): *m*/*z* (major isomer) Calcd. for $C_{13}H_{15}F_2O_2Si$ $[M–t\text{-}Bu]^+$: 269.0809; Found: 269.0809; (minor isomer) calcd. for $C_{13}H_{15}F_2O_2Si$ $[M–t\text{-}Bu]^+$: 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): $\tilde{\nu}$ = 3257, 1734, 1660, 1381, 1329, 1219, 1101 cm^{-1}. HRMS (ESI, negative): *m*/*z* clcd. for $C_{11}H_8FO_2$ $[M–H]^-$: 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 azeotropic removal 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 (1.00 mL) suspension of copper(I) catalyst **204b** (10 mg, 0.016 mmol) and sodium bromodifluoroacetae (72 mg, 0.366 mmol), was added an acetonitrile (1.8 mL) solution of 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_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2 deactivated by H_2O 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**

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 63.9 (dtdd, *J* = 228, 14, 8, 2 Hz, 1F), 71.6 (ddtd, *J* = 228, 20, 14, 2 Hz, 1F). IR (neat); $\tilde{\nu}$ = 2931, 1645, 1255, 906, 731 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{17}H_{24}F_2OSi$ ($[M]^+$): 310.1565; found: 310.1580.

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

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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). ^{19}F NMR (470 MHz, $CDCl_3$): δ = 64.9 (dtdd, *J* = 227, 14, 8, 3 Hz), 72.7 (ddtd, *J* = 227, 20, 14, 2 Hz). IR (neat); $\tilde{\nu}$ = 2956, 2931, 2860, 1645, 1340, 835 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{18}H_{26}F_2OSi$ ($[M]^+$): 324.1721; found: 324.1716.

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

^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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. ^{19}F NMR (470 MHz, $CDCl_3$): δ = 60.2 (dtdd, *J* = 227, 14, 7, 2 Hz), 71.2 (ddt, *J* = 227, 19, 14 Hz). IR (neat); $\tilde{\nu}$ = 2956, 2931, 2860, 1647, 1514, 1342, 1252, 837 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{18}H_{26}F_2O_2Si$ ($[M]^+$): 340.1670; found: 340.1667.

1-[*tert*-Butyl(dimethyl)silyloxy]-3-(4-bromophenyl)-4,4-difluorocyclopent-1-ene **203e**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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, $CDCl_3$): δ = 64.1 (dtdd, *J* = 228, 14, 8, 3 Hz, 1F), 71.3 (ddtd, *J* = 228, 19, 14, 3 Hz, 1F). IR (neat); $\tilde{\nu}$ = 2931, 1645, 1487, 1342, 904, 729 cm^{-1}. HRMS (70 eV, EI): *m*/*z* calcd. for $C_{17}H_{23}BrF_2OSi$ ($[M]^+$): 388.0670; found: 388.0667.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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, $CDCl_3$): δ = 64.2 (dtdd, J = 228, 14, 8, 3 Hz), 72.4 (ddtd, J = 228, 20, 14, 2 Hz). IR (neat); $\tilde{\nu}$ = 2956, 2931, 1647, 1342, 836, 734 cm^{-1}. HRMS (70 eV, EI): m/z calcd. for $C_{21}H_{26}F_2OSi$ ($[M]^+$): 360.1721; found: 360.1719.

1-[*tert*-Butyl(dimethyl)silyloxy]-4,4-difluoro-3-propylcyclopent-1-ene **203g**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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, $CDCl_3$): δ = 56.6 (dtd, J = 229, 15, 8 Hz, 1F), 71.7 (ddtd, J = 229, 20, 15, 2 Hz, 1F). IR (neat); $\tilde{\nu}$ = 2931, 1647, 1340, 1254, 1122, 835, 781 cm^{-1}. HRMS (70 eV, EI): m/z calcd. for $C_{14}H_{26}F_2OSi$ ($[M]^+$): 276.1721; found: 276.1710.

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

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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, $CDCl_3$): δ = 63.0 (ddt, J = 228, 15, 5 Hz, 1F), 74.2 (dtd, J = 228, 22, 15 Hz, 1F). IR (neat); $\tilde{\nu}$ = 2931, 1687, 1254, 1124, 881, 698 cm^{-1}. HRMS (70 eV, EI): m/z calcd. for $C_{18}H_{26}F_2OSi$ ($[M]^+$): 324.1721; found: 324.1722.

9-[*tert*-Butyl(dimethyl)silyloxy]-7,7-difluorobicyclo[4.3.0]non-9-ene **203k**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = –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, $CDCl_3$): δ = 60.2 (dddd, J = 231, 21, 14, 8 Hz), 71.4 (dddd, J = 231, 20, 18, 8 Hz). IR (neat); $\tilde{\nu}$ = 2933, 2858, 1693, 1119, 856, 837, 779 cm^{-1}. HRMS (70 eV, EI): m/z calcd. for $C_{15}H_{26}F_2OSi$ ($[M]^+$): 288.1721; found: 288.1758.

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 mL, 0.142 mmol) and sodium bromodifluoroacetae (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, $LCu{=}C{=}NBu^+$ (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**

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 Na_2SO_4, filtered, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 81.6 (s, 1F). IR (neat); $\tilde{\nu}$ = 1714, 1637, 1323, 912, 742 cm^{-1}. HRMS (70 eV, EI+): m/z calcd. for $C_{11}H_9FO$ ($[M]^+$): 176.0637; found: 176.0638.

(*B*) Synthesis of enone **207**

To a tetrahydrofuran (THF) solution (3.0 mL) of **206** (35.2 mg, 0.200 mmol), was added methyllithium (1.2 M in Et_2O, 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_2SO_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

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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 pyridons.

In chapter 3, regioselective syntheses of both α,α- and β,β-difluorocyclopentanone derivatives by unprecedented transition metal difluorocarbene complexes were described. Dienol silyl ethers, readly prepared from α,β-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.

Journal of Fluorine Chemistry. **2012**, *133*, 52–60.

[2] "Regioselective Synthesis of α,α-Difluorocyclopentanone Derivatives: Domino Nickel-Catalyzed Difluorocyclopropanation/Ring-Expansion Sequence of Silyl Dienol Ethers"

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

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