学位論文

Studies on the Development of Cationic Cyclizations Utilizing the Properties of Fluorine and the Generation of Novel Fluorinated Vinylzirconocenes

フッ素の特性を活用するカチオン環化反応の開発と新規含フッ素ビニル金属の創製に関する研究

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Chapter 1

Introduction

Fluorine-containing compounds have been attracting much interest in various fields such as medicinal and agricultural chemistry and material sciences, because of their biological activities and physical properties.[1] These potent available characters of organofluorine compounds are derived from fundamental physical and chemical properties of fluorine: (1) the van der Waals' radius of fluorine (1.35 Å) close to that of hydrogen (1.20 Å), (2) the high electronegativity (4.0), and (3) the high carbon-fluorine bond energy (485.7 kJ/mol) (cf. carbon-hydrogen (410.6 kJ/mol, carbon-chloride (329.6 kJ/mol), and carbon-bromine (284.4 kJ/mol)). For example in the field of medicine, many fluorinated compounds act as antimetabolites with respect to their corresponding halogen-free natural products by the use of similarity of steric bulk and the dissimilarity of chemical behavior. Since fluorine most closely mimics hydrogen in terms of steric requirement at the active site of receptors, enzyme receptors incorporate a fluorinated analogue. Once the molecule is incorporated, its metabolism is inhibited by high electronegativity and carbon-fluorine bond energy to result in its bioactivities.[2]

Thus, today's diverse commercial application of organofluorine materials clearly manifest the beneficial effects of fluorination of organic molecules. Consequently, from the viewpoint of synthetic organic chemistry, a number of fluorinated compounds have been synthesized only for the use of their versatility. On the other hand, heteroatoms such as sulfur, silicon, and phosphorus have well been studied in synthetic organic chemistry (for example, Wittig reaction) as well as biological and material sciences. Unlike other heteroatoms, fluorine is not fully utilized as a tool in organic synthesis in spite of its unique properties.

On the basis of these considerations, it has been conducted in the author's laboratory that the study on "fluorine as a tool in organic synthesis"; developing new synthetic reactions by positively utilizing the unique properties of fluorine: electronic effect and leaving-group ability

It is well known that fluorine has high electronegativity, which causes good leaving-group ability of a fluoride ion (F^-) (A) and inductive effects such as β-cation-destabilizing effect (B) and β-carbanion-stabilizing effect, which can be also rationalized by negative hyperconjugation

(C). By contrast, fluorine also stabilizes α-carbocations by back donation of an unshared electron pair of fluorine to the vacant orbital of the α-carbon (D) and destabilizes α-carbanions by Iπ electron-pair repulsion (E) (Fig 1).

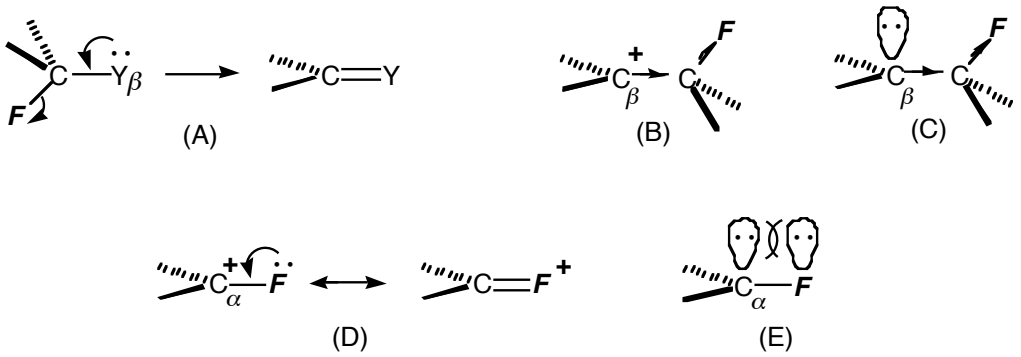
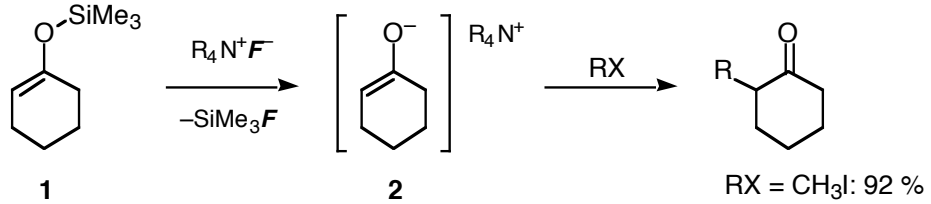


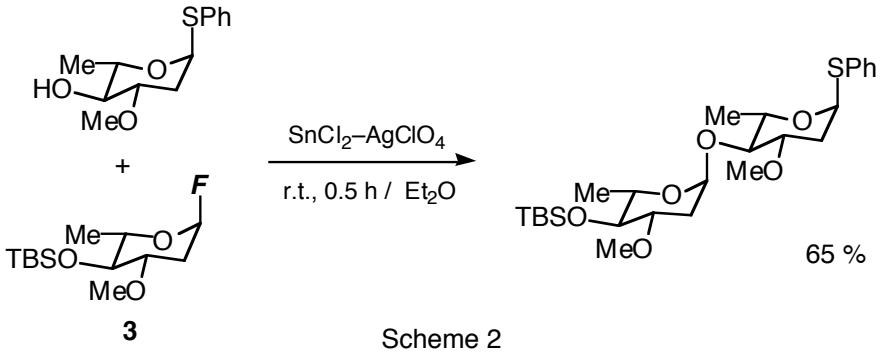
Fig. 1 Electronic effects and leaving group ability of fluorine

As the examples showing the potential applicability of fluorine in organic synthesis, there are two well established methodologies for the utilization of the nucleophilicity (Scheme 1) and the leaving group ability of fluorine (Scheme 2): (i) The activation of silicon compounds **1** is effectively carried out by fluoride ion as shown in Scheme 1, where fluorine is a reagent to cleave the silicon-oxgen bond to afford enolate **2** because of the high value of silicon-fluorine bond energy,[4] and (ii) highly stereoselective glycosylations have been developed starting from fluorosugars.[3] The use of glycosyl fluoride **3** as glycosyl donors with a number of fluorophilic activators (for example $SnCl_2$-$AgClO_4$) were studied (Scheme 2).



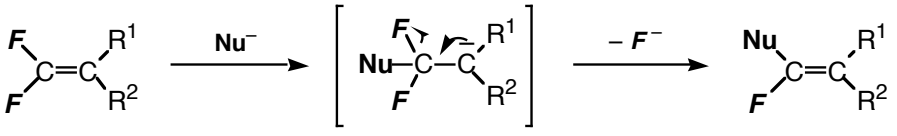
1 **2**

Scheme 1

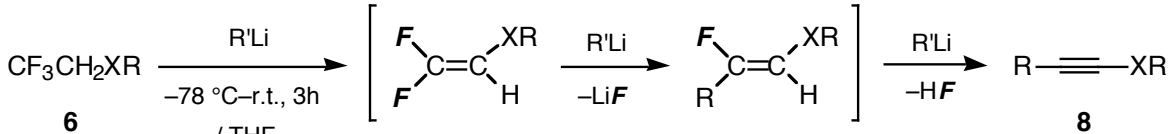


Scheme 2

With regard to the use of fluorine in anionic reactions, a few methods in which its β-anion-stabilizing and α-anion destabilizing effects (Fig. 1, C, E and/or A) are exerted have been studied as a building block methodology for constructing the versatile fluorinated (or non-fluorinated) molecules **5**.[5] Olefins with a terminal difluoromethylene group **4** are considered a particularly versatile and useful class of compounds because their C–C double bonds exhibit remarkable reactivity toward nucleophilic substitution for their fluorine atoms *via* addition-elimination process (Scheme 3).[6] For example of pioneering work on potential applicability of fluorine-containing carbanions in organic synthesis, the convenient synthesis of acethylenic ether derivatives **8** was achieved by the reaction of readily available trifluoroethanol derivatives **6** with organolithiums (Scheme 4).[7] The formation of these acethylenic products **8** are rationalized by addition of R'Li to the first formed difluoroolefins **7** and successive elimination of LiF and HF.



Scheme 3

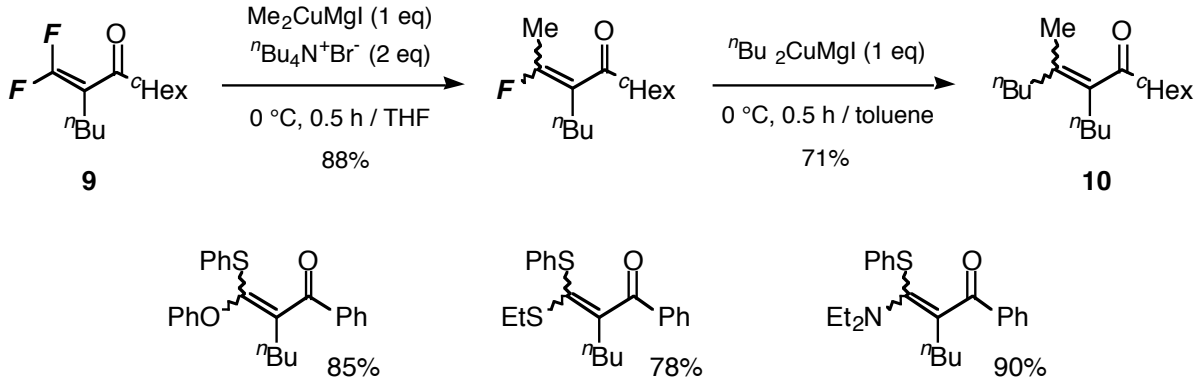


R' = ^{n}Bu XR = OTs 63%
OEt 52%
STs 63%

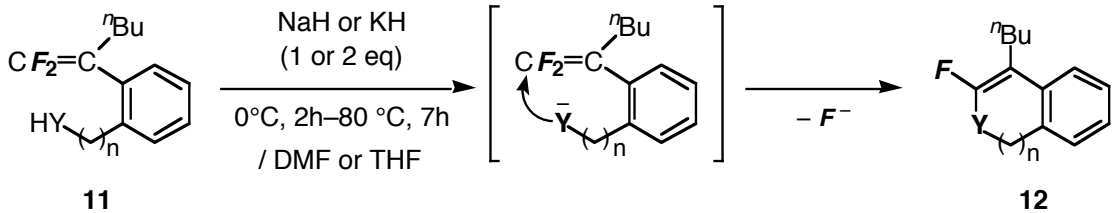
Scheme 4

Recently, it has been accomplished in the author's laboratory that the synthesis of a wide

variety of inaccessible compounds from *gem*-difluoroolefins by utilizing the addition-elimination process. The reactions of *gem*-difluorovinyl carbonyl compounds **9** with various carbon and heteroatom nucleophiles have been studied (Scheme 5). Due to a highly electrophilic C-C double bond activated by two fluorine atoms (Fig. 1, E) and carbonyl group, the substitution for the fluorine atoms was readily induced by various carbon as well as heteroatom nucleophiles, which permitted the stepwise introduction of two different units onto the β-vinylic carbon, to provide a general method for fully substituted α,β-unsaturated ketones **10** by selecting nucleophiles.[8] A similar replacement of the fluorine in difluoroolefins without a carbonyl group **11** was also readily induced by intramolecular nucleophiles to afford selectively fluorinated heterocycles **12** which had been hitherto inaccessible compounds (Scheme 6).[9] In addition, the difluorostyrenes with a nucleophilic part at *ortho* position **11** (n = 0) underwent the 5-*endo*-trigonal ring closure despite this cyclization being disfavored in Baldwin's rules.[10]



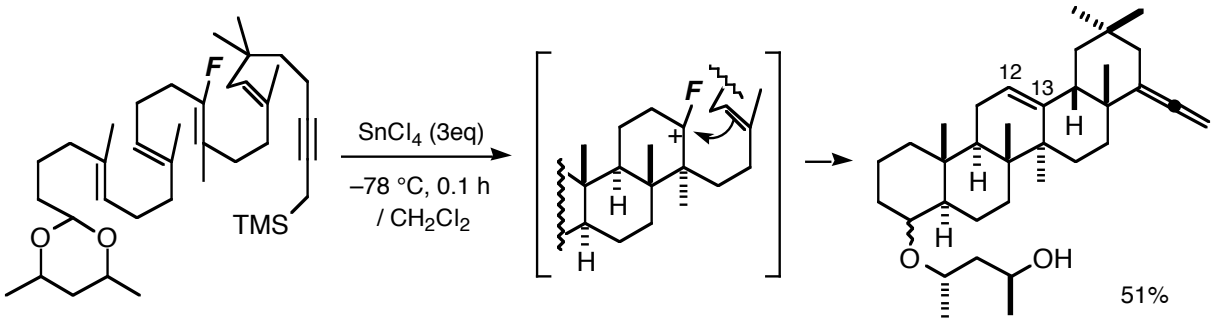
Scheme 5



Scheme 6 (n = 1) Y = NTs : 89% O : 84% S : 94%
(n = 0) Y = NTs : 84% O : 80%

In contrast to the utilization of the effects of fluorine (Fig. 1, A, C, E) mentioned above (Scheme 1-6), few examples has been reported on potential applicability of fluorine-containing

carbocations in organic synthesis.[11] One successful methodology by using the α-cation-stabilizing effect (Fig. 1, D) was reported so far. Johnson demonstrated the effect of a strategically placed fluorine atom on cationic polyene cyclizations (Scheme 7).[11a-c] Acetal **13** incorporates a fluorine atom as a cation-stabilizing auxiliary which promotes and controls the cyclization so as to exclusively give the six membered C-ring (not five-membered ring) of **14**, followed by dehydrofluorination to create the $C_{12\text{-}13}$ olefinic bond.[11c] In particular, there is no example of the reactions involving the β-cation-destabilizing of fluorine (Fig. 1, B).



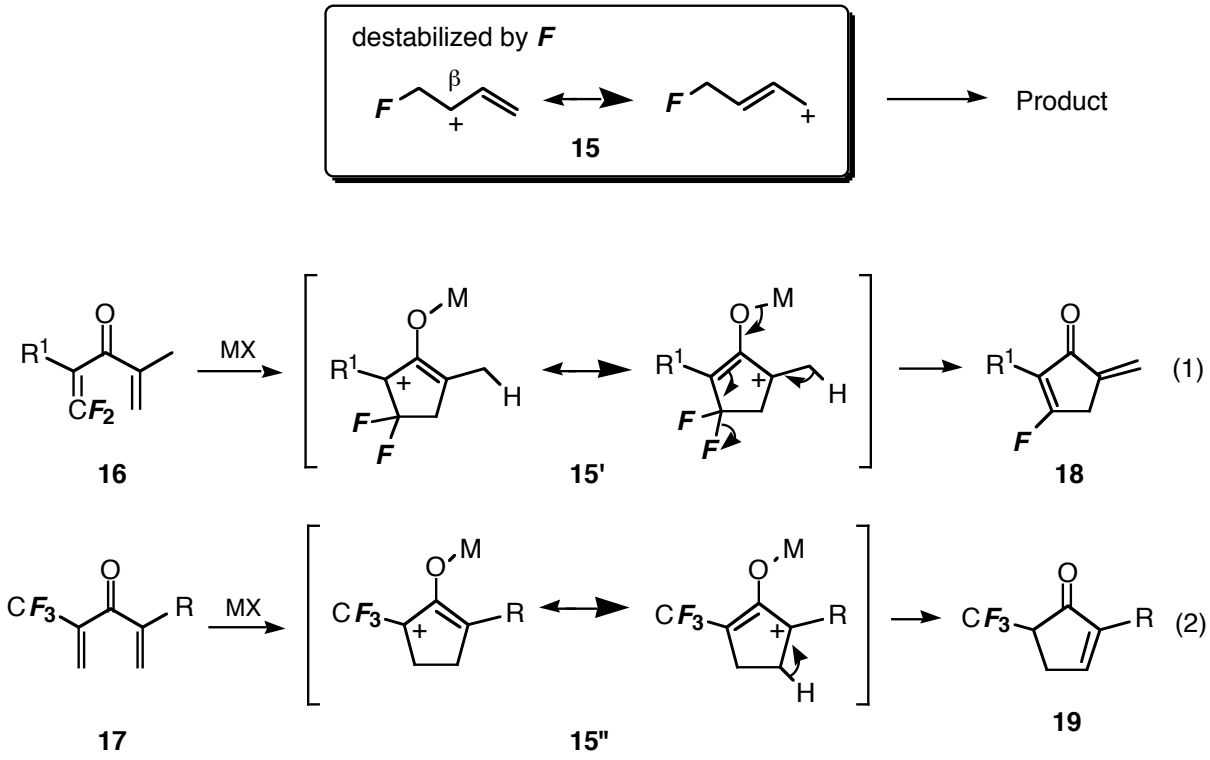
13 **14**

Scheme 7

Based on the above mentioned background, the author focused on a positive use of the interesting effects on cations (Fig. 1, B or D) and attempted to develop a new reactions *via* fluorine-containing carbocations (Chapter 2, 3).

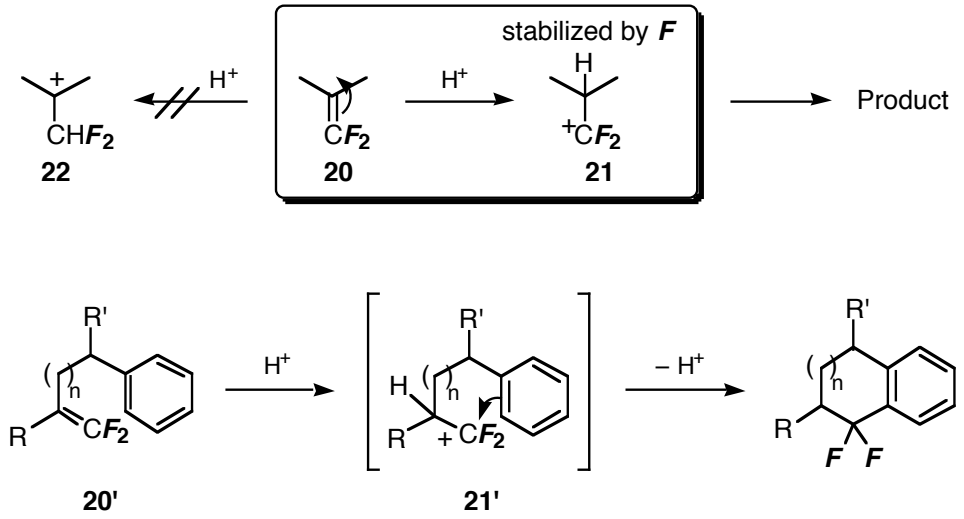
The author speculated that intermediary allylic cation **15** could be controlled by using the β-cation-destabilizing effect (Fig. 1, B) as illustrated in Scheme 8. In Chapter 2 was described the fluorine-directed Nazarov cyclizations of 2,2-difluorovinyl vinyl ketones **16** or 1-trifluoromethylvinyl vinyl ketones **17** by utilizing the fluorine as a controller, which provide a method for the controlled synthesis of cross-conjugated 3-fluoro-2-cyclopentenons **18**[12] (eq. 1, Section 1) and 5-trifluoromethyl-2-cyclopentenones **19**[13] (eq. 2, Section 2) *via* **15'** and **15"** with defined place of double bonds in **18**, **19**, respectively. In addition, the reactions of highly functionalized cyclopentenones **18** with various nucleophiles were examined and regioselective 1,2-, *exo*-1,4-, and *endo*-1,4-additions were successfully achieved by selecting reagents (Section

3).



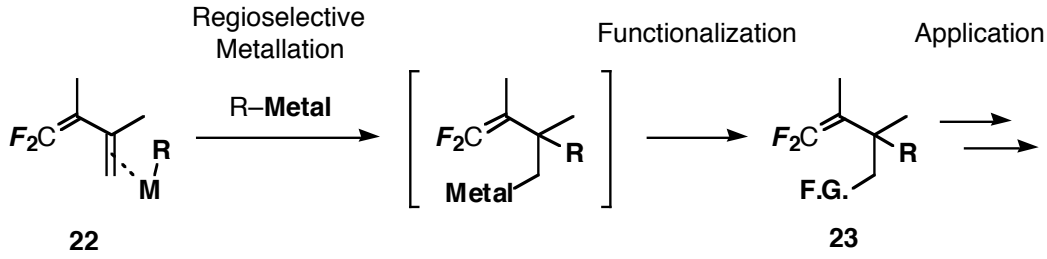
Scheme 8

The author also investigated the generation of α-fluorocarbocations **21'** from *gem*-difluoroolefins **20'** and tried various ring constructions by intramolecular trapping of these cations with unsaturated groups as shown in Scheme 9. The α-cation-stabilizing effect (Fig. 1, D) directed the reaction of *gem*-difluoroolefin **20** with acid, so that protonations occurred on the inner carbon of olefins, since this process leads to a carbocation in preference for **21** stabilized by two α-fluorine over **22** without stabilization. Furthermore, to expand the scope of α-fluorocarbocation chemistry, the author tried the generation of fluoroallylic cations from conjugated 1,1-difluorodienes by regioselective protonation of the non-fluorinated double bond. Chapter 3 deals with intramolecular Friedel-Crafts cyclizations of 1,1-difluoroolefins (Chapter 3, Section 1) and 1,1-difluoro-1,3-dienes (Chapter 3, Section 2) bearing aryl groups. These reactions efficiently provide a variety of fused polycyclic compounds.



Scheme 9

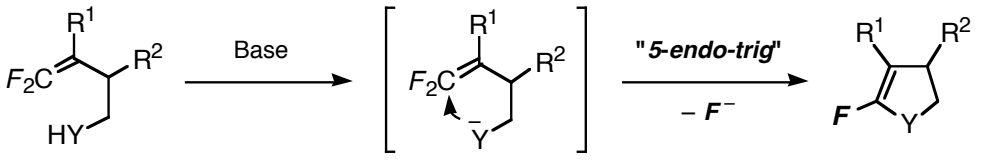
After development of the Friedel-Crafts cyclization of 1,1-difluoro-1,3-dienes **22** (Chapter 3, Section 2), the author attempted to further develop synthetic potentialities of **22**. Functionalization of **22** was examined by applying the regioselective addition reaction of electron-rich non-fluorinated double bond as outlined in Scheme 10, which would provide *gem*-difluoroolefins bearing a homoallylic functional group **23**.



Scheme 10

gem-Difluoroolefins possess remarkable reactivity toward nucleophilic substitution for their fluorine atoms *via* addition–elimination processes as mentioned in Scheme 3. This electrophilicity was utilized intramolecularly to allow the 5-*endo*-trigonal cyclization of β,β-difluorostyrenes bearing *ortho* heteroatom nucleophiles, leading to ring-fluorinated heteroaromatics despite this cyclization being disfavored in Baldwin's rules (Scheme 6). These selectively fluorinated heterocycles are important components in the pharmaceutical,

agrochemical, and dyestuffs industries.[1,14] Only a limited number of methods, however, have been reported for the synthesis of ring-fluorinated heterocyclic compounds. To further extend the unique reaction of *gem*-difluoroolefins which lead to inaccessible fluoroheterocycles, the author explored the 5-*endo*-trigonal ring closure of *gem*-difluoroolefins **24**, whose nucleophilic oxygen-, nitrogen-, or sulfur functional groups are linked by two sp^3 carbon to the olefin (Scheme 11). The ring closure smoothly proceeded to provide fluorinated dihydroheteroaromatics **25**, which is described in Chapter 4.



24 **25**

Y = O, NR, S

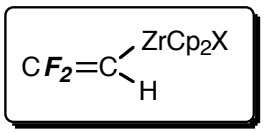
Scheme 11

In above-mentioned reactions the unique properties of fluorinated alkene substrates were positively utilized. Due to their reactive carbon-carbon double bonds, these compounds have recently received much attention not only as building blocks for selectively fluorinated compounds[5,6] but also as a new type of enzyme inhibitors designed upon a mechanism-based concept.[15] Consequently, a general method for the synthesis of *gem*-difluoroolefins has become a highly desirable goal.

Fluorinated vinyl metals provide a straightforward route to synthesize various fluoroolefins.[16] Among those organometallics, most reported 2,2-difluorovinyl- and 1-fluorovinylmetals incorporate (i) an α-position electron-withdrawing group[17] or (ii) β-position bulky or chelating substituents[18], respectively, in order to enhance their thermal stability against β- or α-elimination of metal fluoride and/or 1,2-rearrangement. On the other hand, few fluorinated vinyl metals without stabilizing substituent have been described. In the author's laboratory, it was developed two non-stabilized examples; *α-alkylated gem*-difluorovinylboranes[19] and coppers[20], which were thermally quite stable due to the covalent

character of C–B or C–Cu bond.

In order to develop thermostable fluorinated vinyl metals which are powerful synthetic intermediates for preparing fluoroolefins, the author tried to develop facile generation of 2,2-difluorovinyl- and 1-fluorovinylzirconocenes by making use of a rather stable C–Zr bond instead of introducing a stabilizing group. Chapter 5 describes that the generation of **26** and **27** with excellent thermal stability, which couple *in situ* with various halide in the presence of a palladium catalyst and zinc halide to afford the corresponding difluoro-[21] and monofluoroolefins[22] in high yields. Detailed results and discussions are described in the following chapters.



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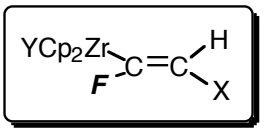

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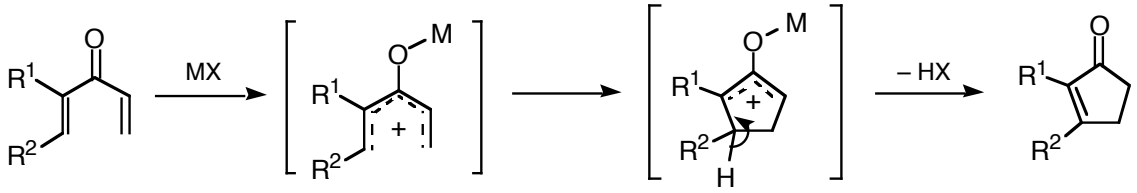
Chapter 2

Fluorine-Directed Nazarov Cyclization :

Utilizing the *β-Cation-destabilizing* Effect of Fluorine

2.1 Introduction

The Nazarov cyclization is a cationic electrocyclic reaction to provide a versatile protocol for the construction of the cyclopentenone framework, a structural motif found in a number of natural products.[1] The classical reactions, however, have a major limitation: the lack of control over the position of the double bond in the five-membered ring. The double bond normally occupies the most substituted position because of its thermodynamic stability, which has restricted their use as a general tool for organic synthesis (Scheme 1). Their improved versions, silicon- (tin-) directed Nazarov cyclization[1a,1b,2] have successfully addressed the problem of double-bond positional selectivity by making use of two properties of silicon: (i) its *β-cation-stabilizing* effect, and (ii) its function as an *electrofuge*, that is, leaving-group ability as a silyl cation (Si^+) (Scheme 2).[3] In terms of these properties, interestingly, fluorine is a kind of negative image of silicon. Fluorine possesses a *β-cation-destabilizing* effect and also functions as a *nucleofuge*, the leaving group of a fluoride ion (F^-) as described in Chapter 1.[4] These facts suggest that not only silicon but fluorine might also be a controller of the electrocyclic reaction. Based on these considerations, the author investigated Nazarov cyclizations of 2,2-difluorovinyl vinyl ketones **1** and 1-trifluoromethylvinyl vinyl ketones **4** as the fluorinated substrates which would generate cyclopentenylic cations destabilized by β-fluorines. The controlled syntheses of cross-conjugated 2-cyclopenten-1-ones **3** and trifluoromethylated 2-cyclopentenones **6** were



Scheme 1

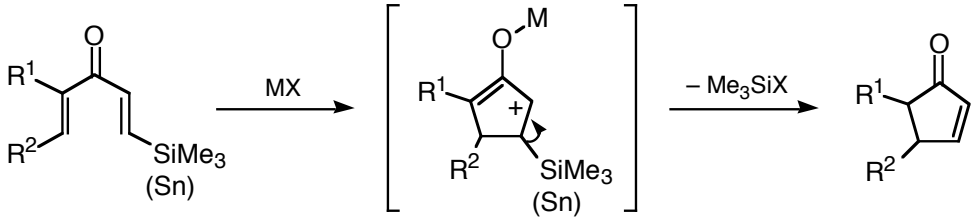
thermodynamically stable C = C

achieved with defined placement of the double bonds (Scheme 3, eq 1,2, Section 1,2).[5,6] In

Section 2.2 and 2.3 are desclibed in detail these results on the fluorine-directed cyclizations.

Silicon-directed Nazarov cyclization

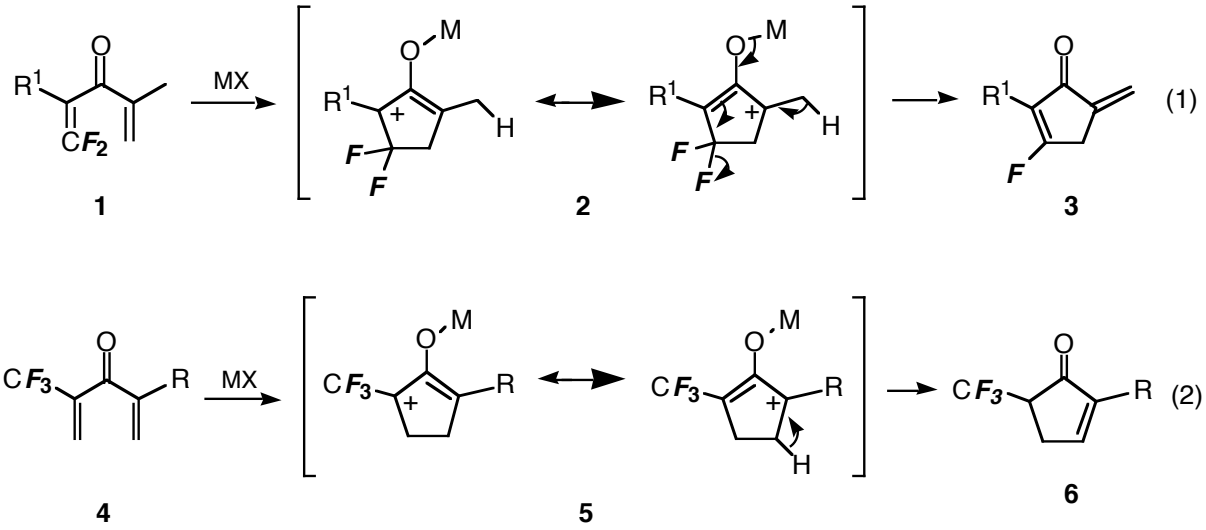
Properties of silicon
i) *β-Cation-**Stabilizing*** Effect
ii) ***Electrofuge*** (Leaving-Group Ability as **Si** $^{+}$)



Scheme 2

Fluorine-directed Nazarov cyclization

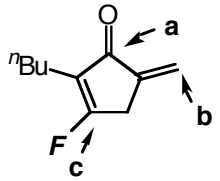
Properties of fluorine
i) *β-Cation-**Destabilizing*** Effect
ii) ***Nucleofuge*** (Leaving-Group Ability as **F** $^{-}$)



Scheme 3

The preparation of functionalized five-membered cyclic ketones is an area of considerable interest, since many biologically active compounds such as steroids and prostaglandines contain related substructures.[1,7] The above obtained cyclopentenones **3** are attractive compounds as synthetic intermediates, because of there highly functionalized structure: two olefin moieties

conjugated to the carbonyl group and a vinylic fluorine, which would allow their transformation into various substituted 2-cyclopentenones. For example, there are three reaction sites to be attacked by nucleophiles in **3**: 1,2-addition, and *exo*-cyclic and *endo*-cyclic 1,4-additions. Therefore, the author was interested in developing the synthetic utilities of **3** as building blocks, and investigated the regioselective addition of carbon or heteroatom nucleophiles to **3**. In Section 2.4 is described a new approach to several types of substituted 2-cyclopentenones including an entry to antibiotic methylenomycin B analogs.[5i,8]

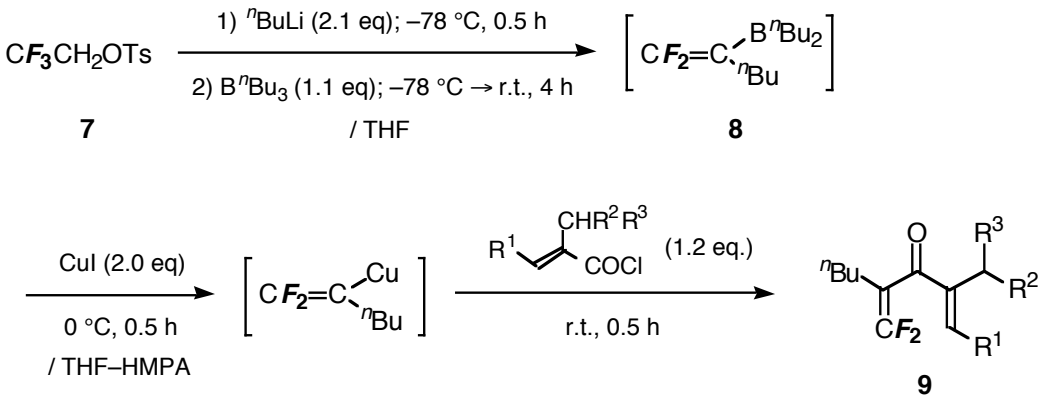


3

2.2 Fluorine-Directed Nazarov Cyclizations of 2,2-Difluorovinyl Vinyl Ketones: Controlled Synthesis of Cross-Conjugated 2-Cyclopentenones[9]

2.2.1 Preparation of 2,2-Difluorovinyl Vinyl Ketones

We initially intended to prepare the divinyl ketones which bear two fluorine substituents on the terminal vinylic carbon. Recently, in the author's laboratory has been developed the one-pot method for the synthesis of 2,2-difluorovinyl ketones from commercially available 2,2,2-trifluoroethyl *p*-toluenesulfonate **7**, wherein the two processes are included: (i) a boron-mediated alkylation leading to 2,2-difluorovinylborans **8**, and (ii) a copper-mediated acylation of **8** with acyl chlorides.[10] The vinylcarbonylation of *in-situ* generated **8** was attempted with α,β-unsaturated acyl chlorides under similar conditions to afford the fluorine-containing Nazarov substrates **9a**–**g** in good yields from **7** (Scheme 4, Table 1).



Scheme 4

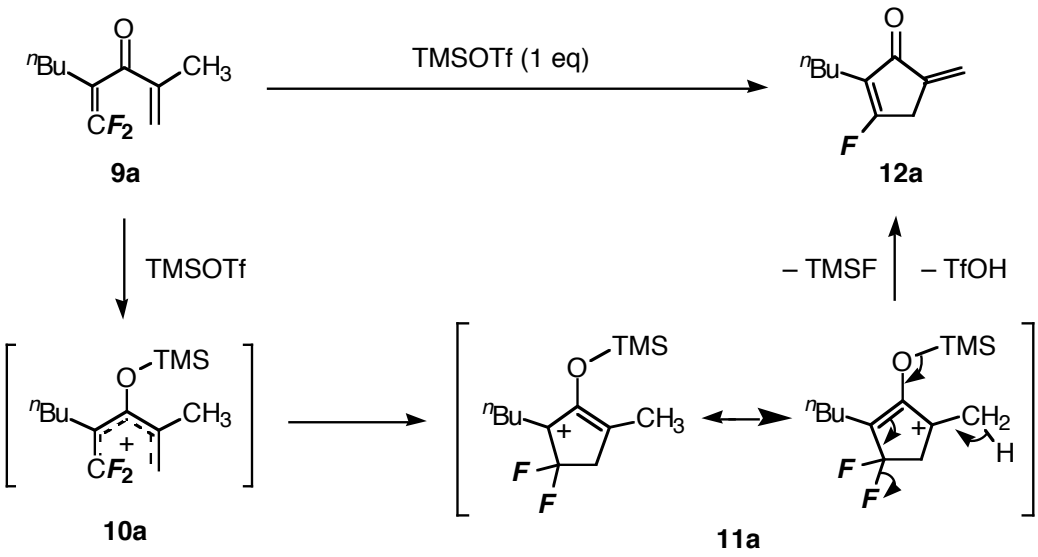
Table 1. Preparation of 2,2-Difluorovinyl Vinyl Ketones **9** from **7**

R^1	R^2	R^3	Product **9**	Yield / %
H	H	H	**9a**	54
H	Ph	H	**9b**	62
H	^{n}Pr	H	**9c**	60
H	Me	Me	**9d**	59
Me	H	H	**9e**	57
– $(CH_2)_3$ –		H	**9f**	63
– $(CH_2)_4$ –		H	**9g**	65

2.2.2 Nazarov Cyclizations of 2,2-Difluorovinyl Vinyl Ketones

After treatment of **9a** (R = ^{n}Bu, $R^1 = R^2 = R^3 = H$) with several Lewis and Brønsted acids, we found that 1 equiv of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane (CH_2Cl_2) readily induced the cyclization at room temperature,[11] leading to 3-fluoro-5-methylene-2-cyclopentenone **12a** in 44% yield without any other cyclized products as shown in Table 2, entry 7. This result indicated that the reaction proceeded as expected according to Scheme 5. The Nazarov-type ring closure occurred *via* silylation of the carbonyl oxygen in **9a** to generate the cyclopentenylic cation **11a**, followed by its collapse in a *fluorine-directed* manner with the loss of a fluoride ion and a proton.[12,13] These losses resulted in the regioselective formation of the *endo*-cyclic and *exo*-cyclic double bonds in **12a**. Screening of solvents in the

above reaction of **9a** revealed that the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a cosolvent dramatically promoted and accelerated the cyclization, probably due to its high ionizing power and low nucleophilicity (entry 8).[14,15] That is, its high ionizing power assisted the generation of intermediary cations and low nucleophilicity prevented HFIP itself from attacking the cations. Conducting the

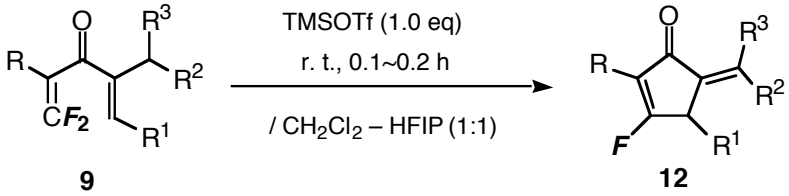


Scheme 5

Table 2. Effect of acid and solvents on the Nazarov cyclization of **9a**

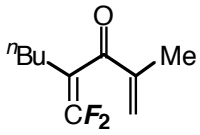
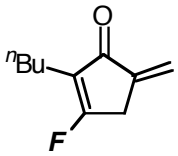
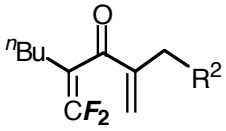
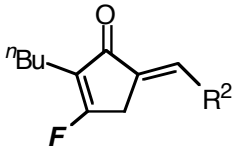
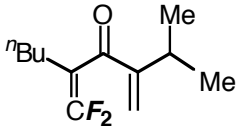
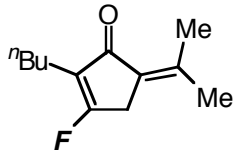
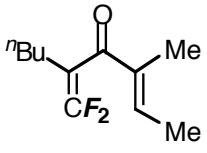
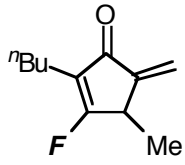
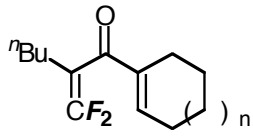
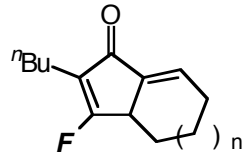
Entry	Additive (eq)	Solvents	Conditions	**12a** / %
1	TsOH (10)	THF	reflux, 1.5 h	0
2	PPA (10)		60°C, 0.5 h	0
3	$FeCl_3$ (1)	CH_2Cl_2	r.t., 1.3 h	6
4	BF_3•OEt_2 (1)		reflux, 10 h	trace
5	Et_2AlCl (1)		r.t., 3 h	0
6	TMSI (1)		2 h	0
7	TMSOTf (1)		4 h	44
8	**(1)**	**CH_2Cl_2–HFIP (1:1)**	**0.1 h**	**73**
9	TfOH (1) $(CF_3)_2CHOTMS$ (1)		0.1 h	44

reaction in CH_2Cl_2–HFIP (1:1) at room temperature improved the yield of the desired product **12a** up to 73%. Additionally, we confirmed that TMSOTf was a real promotor in this mixed-solvent system without decomposition to TfOH and trimethylsilyl hexafluoro-2-propyl ether $(CF_3)_2CHOTMS$, whose combination gave a poor result (entries 8 and 9).



9 **12**

Table 3. *Fluorine-Directed* Nazarov Cyclization of 2,2-Difluorovinyl Vinyl Ketones **9**

Entry	Substrate (**9**)		Product (**12**)	Yield, % (*E*/*Z*)[a]
1		**9a**		**12a** 73
2		**9b** (R^2 = Ph)		**12b** 71[b] (99/1)[c]
3		**9c** (R^2 = ^{n}Pr)		**12c** 82 (99/1)[d]
4		**9d**		**12d** 78
5		**9e**		**12e** 86
6		**9f** (n = 1)		**12f** 92
7		**9g** (n = 2)		**12g** 97

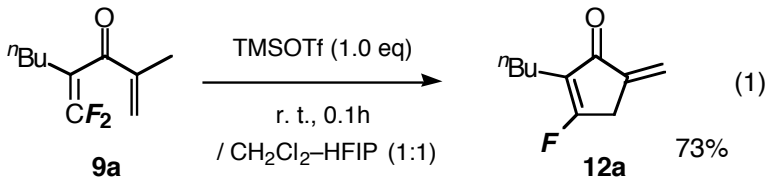
a) *E*/*Z* ratio on the exocyclic double bond. b) The reaction was conducted at 0 °C in HFIP for 0.7 h. c) Determined by ^{19}F NMR. d) Determined by GLC.

Under the conditions thus obtained, other fluorinated divinyl ketones **9b–g**, including cyclic systems as well as acyclic ones, underwent the reaction very rapidly to afford the corresponding cyclopentenones **12b–g** in good to excellent yields (Table 3). The double bonds are selectively placed under the strict control of fluorine regardless of the substrates. In addition, concerning the configuration of the *exo*-cyclic double bond, *E* isomers were almost exclusively obtained (entries 2 and 3).[16]

2.2.3 The Effect of Fluorine on the Regiochemistry

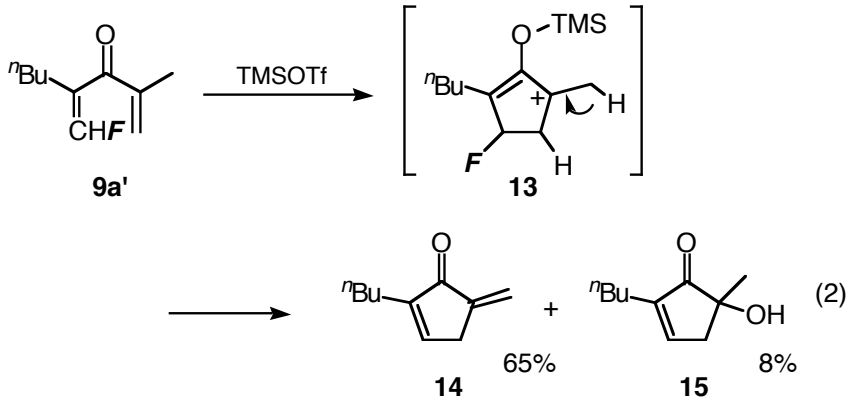
In order to confirm the effect of fluorine on the regiochemistry, we conducted the reaction employing a mono-fluorinated substrate **9a'** and a fluorine-free substrate **9a"**. **9a** gave a single product as shown in Scheme 6, eq 1 (and Table 3, entry 1), and even in the case of mono-fluorinated substrate **9a'** the position of *endo*-cyclic double bond was perfectly controlled in the defluorination step on **13** to afford **14** and **15** (eq 2). In contrast, its non-fluorinated counterpart **9a"** afforded a mixture of three products **17–19** without control (eq 3). Furthermore, in the case of the pseudo-symmetrical divinylketone **9c** leading the same substrates on both vinyl groupsexcept for fluorine, the reaction proceeded through a defined pathway to give **12c**, not yielding a product **20** with an *exo*-cyclic double bond on the other side of the carbonyl group (Scheme 7; Table 3, entry 3). These results cleanly show that fluorine plays a critical role in promoting the regioselective cyclization.

♦ ***Di-****Fluorinated* Substrate



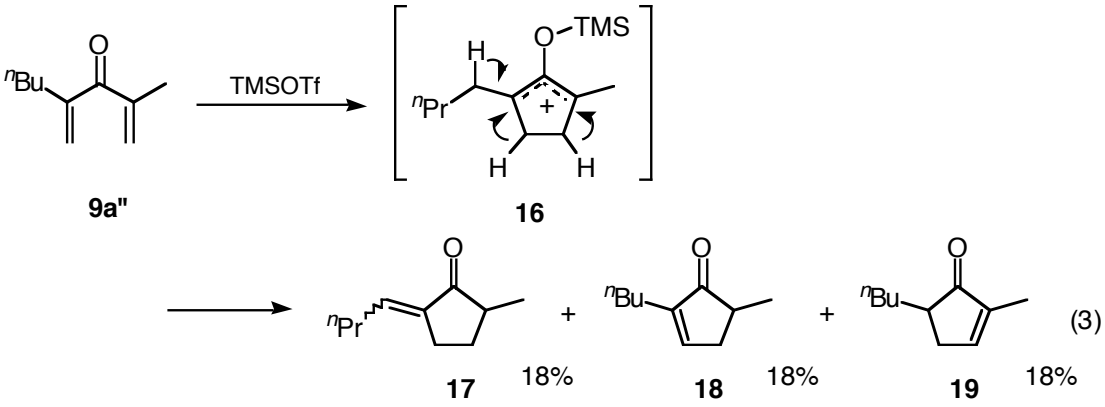
(1)

♦ ***Mono**-Fluorinated* Substrate



9a' **13** **14** **15**

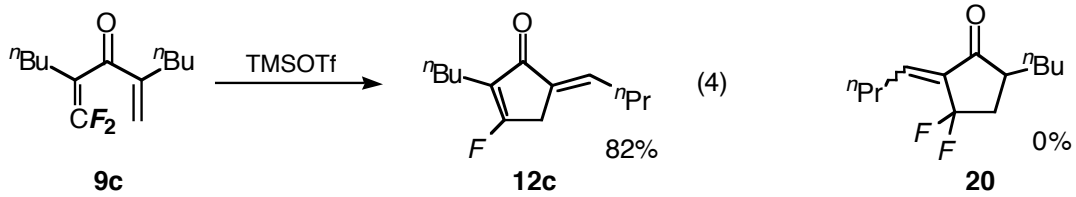
♦ ***Non**-Fluorinated* Substrate



9a" **16** **17** **18** **19**

Scheme 6

• ***Symmetrical*** Substrate Except for Fluorine



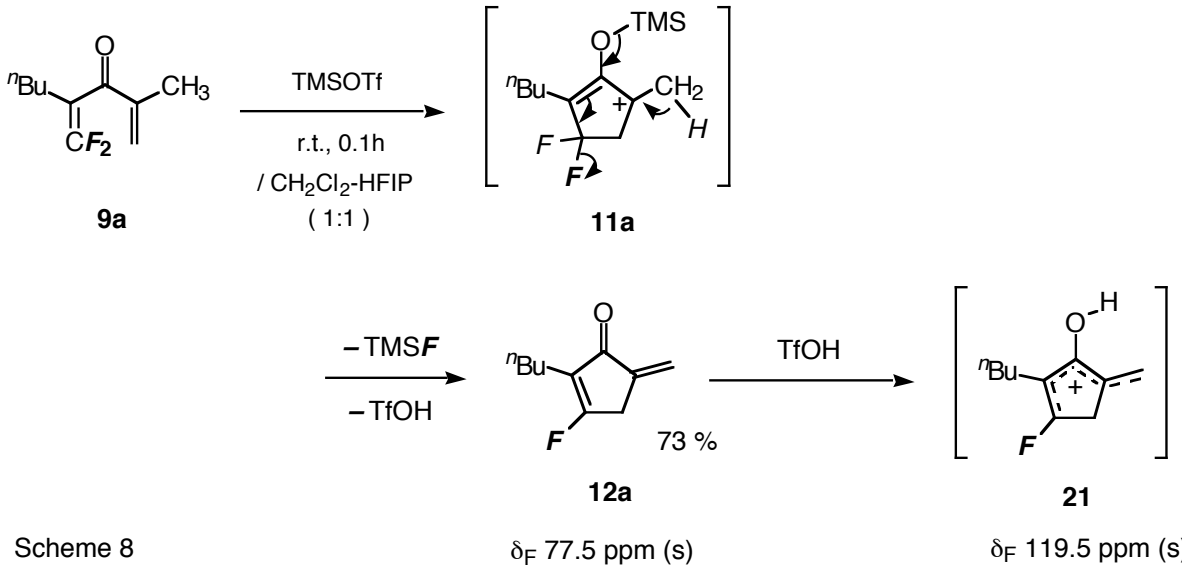
9c **12c** **20**

Scheme 7

2.2.4 Mechanistic Study by ^{19}F-NMR Measurement

In elucidation of the reaction mechanism the reaction was monitored by ^{19}F-NMR (Scheme 8). The ^{19}F-NMR spectrum of the reaction mixture of **9a** and 1 equiv of TMSOTf was measured after stirring for 0.1 h in CH_2Cl_2–HFIP (1:1), which indicated the appearance of two sets of peaks. The signals obserbed at (δ_F 4.6 (10, J_{FF} = 6 Hz) correspond to TMSF, (72%

determined by the integration relative to internal $C_6H_5CF_3$ standard). The signal appeared at (δ_F 119.5 (s)), which was in accordance with that of **21** (68%) prepared by tratment of the cyclization product **12a** with TfOH. These result reveal that elimination of fluoride ion (TMSF) and proton (TfOH) rapidly occurred from cation **11a**, which caused the protonation of **12a** to generate the stable cationic species **21** in the reaction mixture before quenching.



9a **11a** **12a** **21**

Scheme 8 δ_F 77.5 ppm (s) δ_F 119.5 ppm (s)

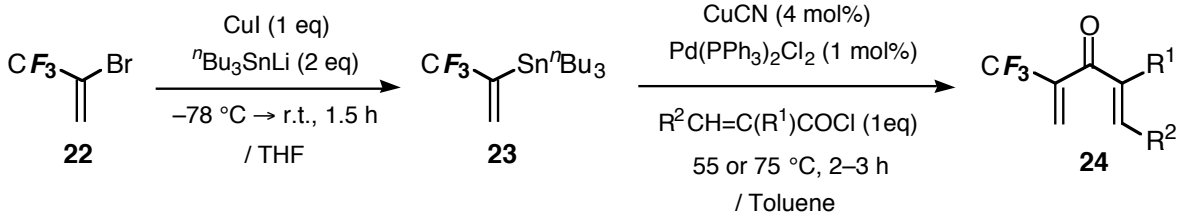
2.3 Fluorine-Directed Nazarov Cyclization of 1-Trifluoromethylvinyl Vinyl Ketones: Regioselective Synthesis of 5-Trifluoromethyl-2-cyclopentenones[17]

2.3.1 Preparation of 1-Trifluoromethylvinyl Vinyl Ketones

In order to expand the synthetic potential of the fluorine-directed Nazarov cyclizations, the author next examined the introduction of fluorine at an alternative position on the substrates, so that the β-cation-destabilizing effect could be exerted on the intermediary cyclopentenylic cation to control the reaction. Thus, fluorine should be introduced at the allylic position on divinylketones. The author investigate the second-generation fluorine-directed Nazarov cyclization of 1-trifluoromethylvinyl vinyl ketones **24**, and found a method for the regioselective preparation of trifluoromethylated 2-cyclopentenones **27** (Scheme 10).[6]

A series of 1-trifluoromethylvinyl vinyl ketones **24** were prepared by Stille-type cross-

coupling of tributyl(1-trifluoromethylvinyl)tin **23**,[18] prepared *via* stannylation of 2-bromo-3,3,3-trifluoropropene **22**, with α,β-unsaturated acyl chlorides. The reaction was conducted under modified conditions in the presence of catalytic amount of $PdCl_2(PPh_3)_2$ and CuCN[19], leading to the desired Nazarov substrates in good yields (Scheme 9, Table 4).



Scheme 9

Table 4. Preparation of 1-Trifluoromethylvinyl Vinyl Ketones **24**

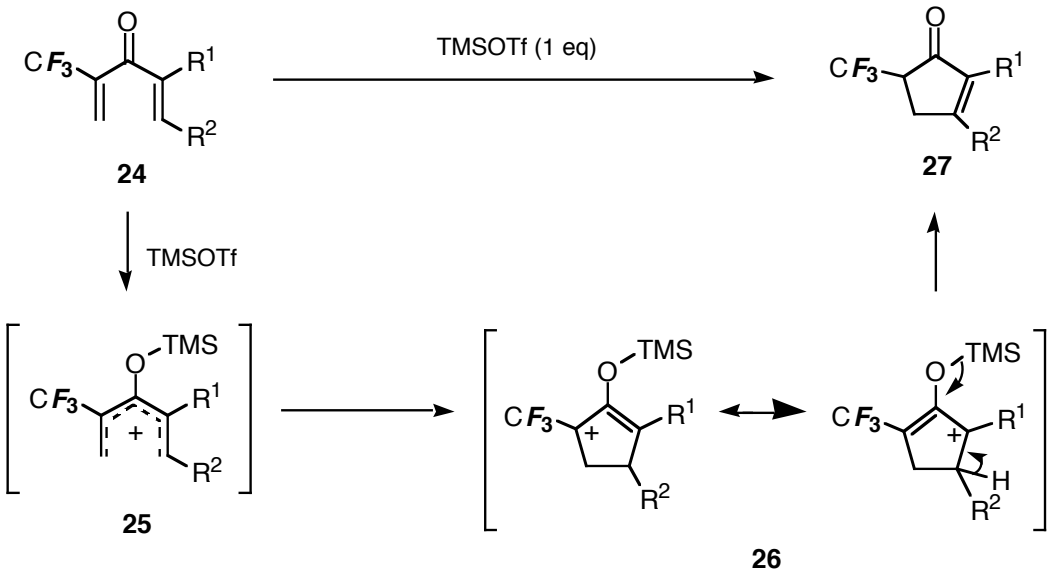
Entry	R^1	R^2	Substrate	Conditions	Yield / %[a)]
1	Et	^{n}Pr	**24a**	75 °C, 2 h	75
2	Me	Me	**24b**	75 °C, 3 h	59[b)]
3	–$(CH_2)_3$–		**24c**	75 °C, 2 h	72
4	–$(CH_2)_4$–		**24d**	75 °C, 4 h	75
5	^{n}Bu	H	**24e**	55 °C, 3 h	50
6	Me	H	**24f**	55 °C, 3 h	37[b)]

a) Isolated yield from **23**. b) A volatile compound.

2.3.2 Nazarov Cyclizations of 1-Trifluoromethylvinyl Vinyl Ketones

As described in the Section 2.2, we have found that the use of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in a mixed-solvent system, dichloromethane (CH_2Cl_2) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), is an optimal set of conditions for the fluorine-directed Nazarov cyclizations of **9**. When these conditions (1 equiv of TMSOTf in CH_2Cl_2–HFIP (1:1) at room temperature) were applied to **24a** (R^1 = Et, R^2 = ^{n}Pr), 5-trifluoromethyl-2-cyclopentenone **27a** was obtained in 79% yield as the sole cyclized product. Other acids such as TMSOTf, $FeCl_3$, $EtAlCl_2$, $SnCl_4$, and trifluoromethanesulfonic acid (TfOH)

also promoted these cyclizations even in CH_2Cl_2 at room temperature in moderate yields (Table 5). This result indicates that the *O*-silylated pentadienylic cation **25a** undergoes electrocyclic ring closure to generate the cyclopentenylic cation **26a**, with a subsequent positionally selective loss of a proton under the strict electronic control of the trifluoromethyl group (Scheme 10).[12,20] In contrast with the cyclization of 2,2-diflurovinyl vinyl ketones as described in the former section (Scheme 5), the elimination of fluoride ion from cyclopentenylic cation **26** was not observed.[21]



Scheme 10

Table 5. Effect of acid and solvents on the Nazarov cyclization of **24a**

Entry	R^1	R^2	Acid (eq)	Conditions	Solvents	**27a** / %
1	Me	^{n}Pr	PPA (10)	140 °C, 3 h	CH_2Cl_2	14
2			TfOH (1)	r.t. , 0.1 h		71
3			$FeCl_3$ (1)	r.t. , 11 h		71
4			$SnCl_4$ (1)	r.t. , 12 h		45
5			$EtAlCl_2$ (1)	r.t. , 12 h		65
6			TMSOTf (1)	r.t. , 7 h		60
7			(1)	**r.t. , 0.1 h**	**CH_2Cl_2–HFIP (1:1)**	**79**

Under similar reaction conditions several other trifluoromethylated substrates **24b-f**,

including both acyclic and cyclic examples, were examined. The cyclization of these substrates affords the corresponding cyclopentenones **27b-f** in good to excellent yields (Table 6).

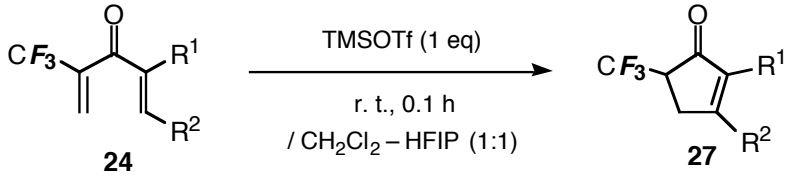
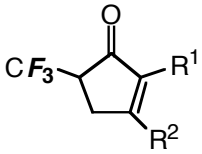
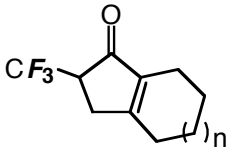
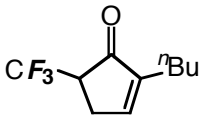
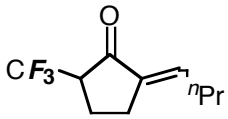
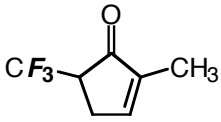


Table 6. Synthesis of 5-Trifluoromethyl-2-cyclopentenones **27** *via* Fluorine-directed Nazarov Cyclizations of **24**.

Entry	R^1	R^2	Substrate **1**	Product **4**	Yield / %
1	Et	^{n}Pr	**24a**		**27a** 79
2	CH_3	CH_3	**24b**		**27b** 61[a] (93)[b]
3	–$(CH_2)_3$–		**24c**		**27c** (n=0) 58[c]
4	–$(CH_2)_4$–		**24d**		**27d** (n=1) 95
5	^{n}Bu	H	**24e**	 **27e**	 **27e'** 83 (**27e**/**27e'** = 53/47)[d]
6	CH_3	H	**24f**		**27f** 55[a] (87)[b]

a) The product is volatile. b) ^{19}F NMR yield relative to internal $C_6H_5CF_3$ standard. c) The reaction was conducted for 5 h. d) The ratio was determined by ^{19}F NMR.

2.3.3 The Effect of Fluorine on the Regiochemistry

In the cyclization of 2-butyl-4-trifluoromethyl-1,4-pentadien-3-one (**24e**), a mixture of two

Chapter 2 Experimental Section

General. IR spectra were recorded on a Shimazu IR-408 spectrometer. NMR spectra were obtained on a JEOL JNM-FX-60, a JEOL JNM-FX-100, a JEOL JNM-EX-270, or a JEOL JNM-A-500 spectrometer. Chemical shift value were given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR: ! -value) or internal C_6F_6 (for ^{19}F NMR). Mass spectra were taken with a JEOL JMS-DX-300 spectrometer. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus. THF was distilled from sodium benzophenone ketyl prior to use. HFIP from Central Glass Co., Ltd (purity 99.9%) was distilled from and stored over 3A molecular sieves.

Synthesis of 2,2-Difluorovinyl Vinyl Ketones 9.

2-Butyl-1,1-difluoro-4-metyl-1,4-pentadien-3-one 9a.

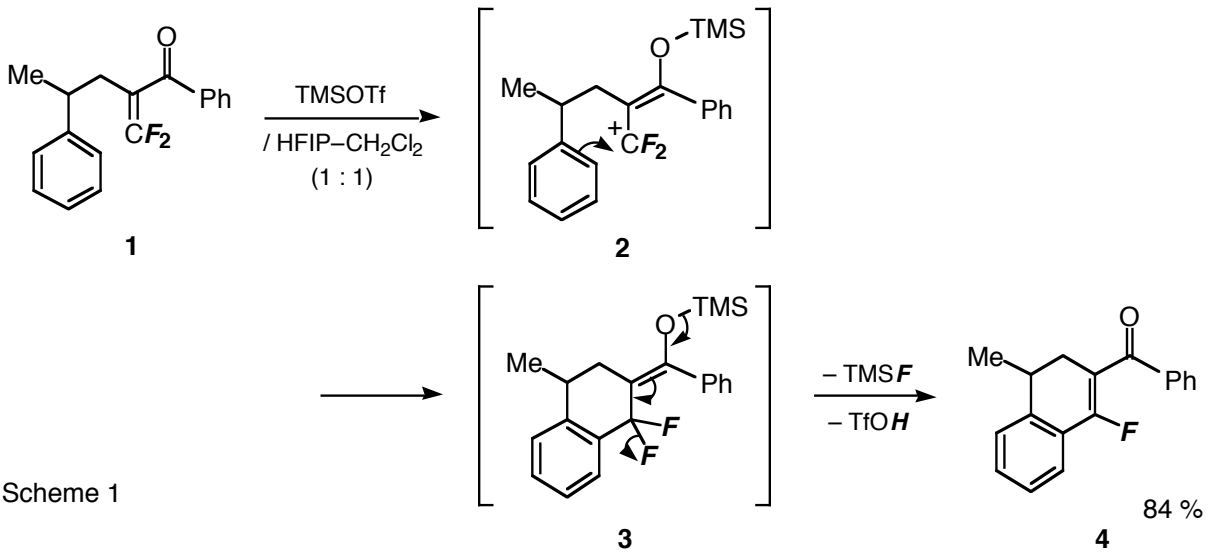
Butyllithium (20 ml, 1.63 M in hexane, 33 mmol) was added to a tetrahydrofuran (THF, 80ml) solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (4.0 g, 15.7 mmol) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 30 min and then tributylborane (17.3 ml, 1.0M in THF, 17.3 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed up to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 18 ml) and cuprous iodide (6.0 g, 31 mmol) at 0 °C and stirred for 30 min at the same temperature. To the resulting solution was added methacryloyl chloride (1.84 ml, 18.8 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with phosphate buffer (pH 7), followed by addition of a large quantity of ice-cold water (about 100 ml). To the resulting mixture was added aqueous hydrogen peroxide (7 ml, 30%) dropwise at 0 °C. After being stirred for 15 min at room temperature, the mixture was filtered. Organic materials were extracted with CH_2Cl_2 three times. The combined extracts were washed with aqueous $Na_2S_2O_3$ and water, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–Et_2O 30:1), followed by bulb-to-bulb

Chapter 3

Friedel–Crafts Cyclizations *via* α-Fluorocarbocations: Utilizing the *α-Cation-stabilizing* Effect of Fluorine

3.1 Introduction

In the previous chapter it was demonstrated that the fluorine substituent strongly directed the regiochemistry of Nazarov cyclizations, where the β-cation-destabilizing effect of fluorine plays an important role. By contrast to this destabilization of cations, interestingly, fluorine stabilizes α-carbocations by back-donation. That is, fluorine stabilizes α-carbocations by sharing its lone-pair electrons with the adjacent vacant p-orbital as described in Chapter 1. There are few examples on cationic cyclizations where fluorine acts as an α-cation-stabilizing substituent.[1,2] Recently, the author's laboratory have developed the Friedel–Crafts cyclization of 2,2-difluorovinyl ketones such as **1**, where α-fluorocarbocation **2** is generated by silylation of the carbonyl oxygen with TMSOTf then trapped with an intramolecular aryl group to give **4** *via* the elimination of fluoride (Scheme 1).[3] To expand the scope of the cyclizations of fluorine-containing carbocations, the author sought their generation from simple 1,1-difluoroolefins **5** without a carbonyl group. We expected to generate α-fluorocarbocations, not tertiary cations, by the regioselective protonation of the double bond,



Scheme 1

Chapter 3 Experimental Section

General. IR spectra were recorded on a Shimazu IR-408 or a Horiba FT-300S spectrometer. NMR spectra were obtained on a JEOL JNM-FX-60, a JEOL JNM-FX-100, a JEOL JNM-EX-270, JEOL JNM-A-500, or a Bruker DRX 500 spectrometer. Chemical shift values were given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR: δ-value) or internal C_6F_6 (for ^{19}F NMR). Mass spectra were taken with a JEOL JMS-DX-300 or a JEOL JMS-SX-102A spectrometer. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus. THF was distilled from sodium benzophenone ketyl prior to use. HFIP from Central Glass Co., Ltd (purity 99.9%) was distilled from and stored over 3A molecular sieves.

Synthesis of 1,1-Difluoroolefins.

2-benzyl-1,1-difluoro-1-hexene **13a**[3], 1,1-difluoro-4-phenyl-1-pentene **13c**[6], 2-butyl-1,1-difluoro-3-phenyl-1,3-diene **21a**[11], 1,1-difluoro-2-(2-phenylpropyl)-4-phenyl-1-pentene **21d**[10], and 2-butyl-1,1-difluoro-3-phenyl-1,3-diene **32a**[14] were prepared according to literature procedures.

1,1-difluoro-4-phenyl-1-butene 13b.

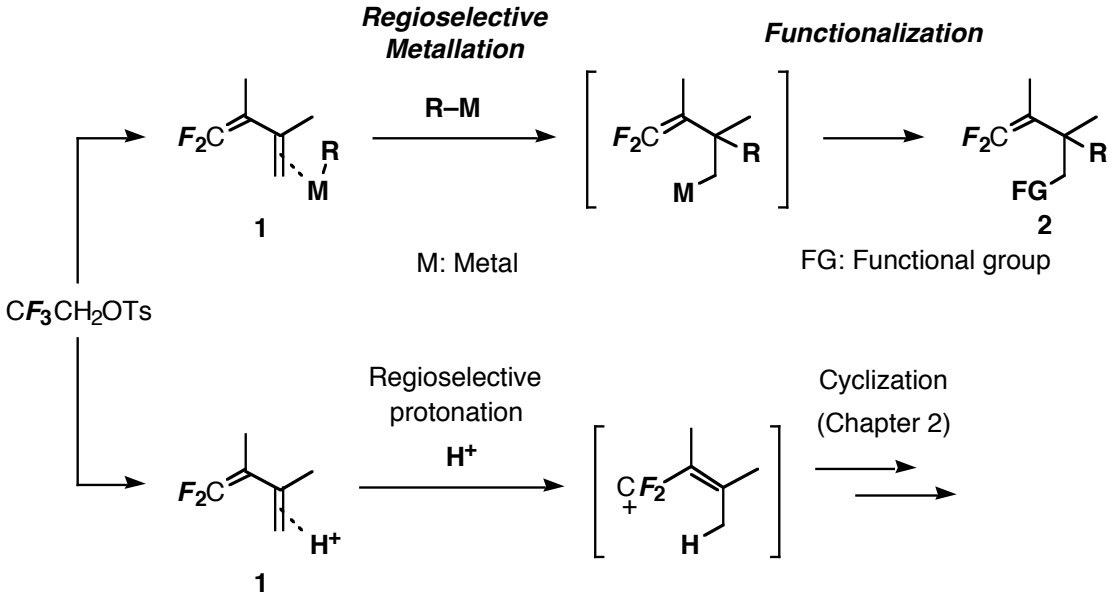
Butyllithium (7.00 ml, 1.50 M in hexane, 10.5 mmol) was added to a tetrahydrofuran (THF, 25.0 ml) solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (127 g, 5.00 mmol) in at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at –78 °C, and then tris(2-phenethyl)borane (*vide infra*) was added at –78 °C over 30 min. After being stirred for 1 h, the reaction mixture was warmed up to room temperature and stirred for an additional 3 h. The resulting solution was cooled to 0 °C and treated with hexamethylphosphoric triamide (HMPA, 8.5 ml) and cuprous iodide (1.90 g, 10.0 mmol). After the mixture was stirred for 0.5 h at room temperature, phosphate buffer (pH 7) was added to quench the reaction. The mixture was filtered, and organic materials were extracted with diethyl ether (Et_2O) three times. The combined extracts were washed with water and dried over

Chapter 4

5-*endo*-Trigonal Cyclizations of *gem*-Difluoroolefins Bearing a Homoallylic Heteroatom Nucleophiles

4.1 Introduction

In Chapter 3, Section 2 was described the Friedel-Crafts cyclization *via* α-fluorocarbocations generated by regioselective protonation of 1,1-difluoro-1,3-dienes **1**. To expand a synthetic utility of the unique reactivity of the difluorodiene system, the author turned his attention to conducting regioselective metallations at the electron-rich, non-fluorinated double bond of **1**.[1] Generation of difluorohomoallylmetals and their functionalization were planned as outlined in Scheme 1, which would provide difluoroolefins **2** bearing a homoallylic functional group, difficult to be synthesized by previously reported methods.[2]



Scheme 1

gem-Difluoroolefins possess remarkable reactivity toward nucleophilic substitution for their fluorine atoms *via* addition–elimination processes. This reactivity is due to (i) the electrophilic activation of the carbon–carbon double bond by the two fluorines and (ii) the leaving group ability of the fluoride ion.[3] Recently, it was found in the Ichikawa group that β,β-difluorostyrenes bearing *ortho* nitrogen, oxygen, or sulfur heteroatoms readily undergo

Chapter 4 Experimental Section

General. IR spectra were recorded on a Shimazu IR-408 or a Horiba FT-300S spectrometer. NMR spectra were obtained on a JEOL JNM-FX-60, a JEOL JNM-FX-100, a JEOL JNM-EX-270, JEOL JNM-A-500, or a Bruker DRX 500 spectrometer. Chemical shift values were given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR: δ-value) or internal C_6F_6 (for ^{19}F NMR). Mass spectra were taken with a JEOL JMS-DX-300 or a JEOL JMS-SX-102A spectrometer. THF was distilled from sodium benzophenone ketyl prior to use. DMF was pre-dried with P_2O_5 and distilled from CaH_2 and stored over 4A molecular sieves.

Synthesis of 1,1-Difluoroolefins bearing a homoallylic heteroatom.

4,4-difluoro-3-(2-phenylpropyl)-2-methyl-3-butene-1-ol 6a.

9-Borabicyclo[3,3,1]nonane (0.8 ml, 0.5 M in THF, 0.40 mmol) was added to a solution of 1,1-difluoro-2-(2-phenylpropyl)-3-methyl-1,3-diene (**1a**, 80 mg, 0.36 mmol) in THF (2.0 ml) under a nitrogen atmosphere. The resulting mixture was heated at reflux for 5 h and then cooled to 0 °C. To the resulting solution were added aqueous sodium hydroxide (0.10 ml, 3N, 0.30 mmol) and aqueous hydrogenperoxide (0.10 ml, 10N, 1.00 mmol) successively. The mixture was stirred for 2 h, then quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 2:1) to give **6a** (50 mg, 0.21 mmol, 58%) as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (1.5H, d, J = 7.3 Hz), 1.00 (1.5H, d, J = 6.7 Hz), 1.00–1.80 (1H, br. m), 1.27 (1.5H, d, J = 7.3 Hz), 1.28 (1.5H, d, J = 7.3 Hz), 2.10–2.30 (2H, m), 2.39 (0.5H, dd, J = 13.0, 6.7 Hz), 2.41 (0.5H, dd, J = 13.0, 7.3 Hz), 3.37 (0.5H, d, J = 7.9 Hz), 3.39 (0.5H, d, J = 7.9 Hz), 3.51 (0.5H, d, J = 7.3 Hz), 3.52 (0.5H, d, J = 7.9 Hz), 7.20–7.24 (3H, m), 7.30 (1H, d, J = 7.3 Hz), 7.31 (1H, d, J = 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 15.0, 15.0, 21.4, 21.6, 34.9 (d, J_{CF} = 3 Hz), 35.8 (d, J_{CF} = 3

Chapter 5

Generation of Novel 2,2-Difluoro- and 1-Fluorovinylzirconocene and Their Cross-coupling Reactions

5.1 Introduction

As mentioned in Chapter 3-4, we demonstrated that fluoroolefins are particularly versatile and useful class of compounds which exhibit unique reactivities in cationic (Chapters 2 and 3) and anionic (Chapter 4) reactions. However, there are hitherto few general methods for syntheses of fluoroolefins. Thus, the author tried to develop a novel method to provide these valuable fluoroolefins.

Fluorinated vinylmetals provide a straightforward route to synthesize fluoroolefins,[1,2b] which are valuable both as building blocks for fluorinated compounds and polymers[2] and as enzyme inhibitors.[3] Among those organomatallics, most reported 2,2-difluorovinyl- and 1-fluorovinylmetals incorporate (i) an α-position electron-withdrawing group such as oxygen-containing groups[4], halogens[5], trifluoromethyl[6], or aryl groups[7] and (ii) β-position bulky substituents or chalating functional groups, respectively. These groups enhance their thermal stability against β- or α-elimination of metal fluoride and/or 1,2-rearrangement (Fig. 1).[8]

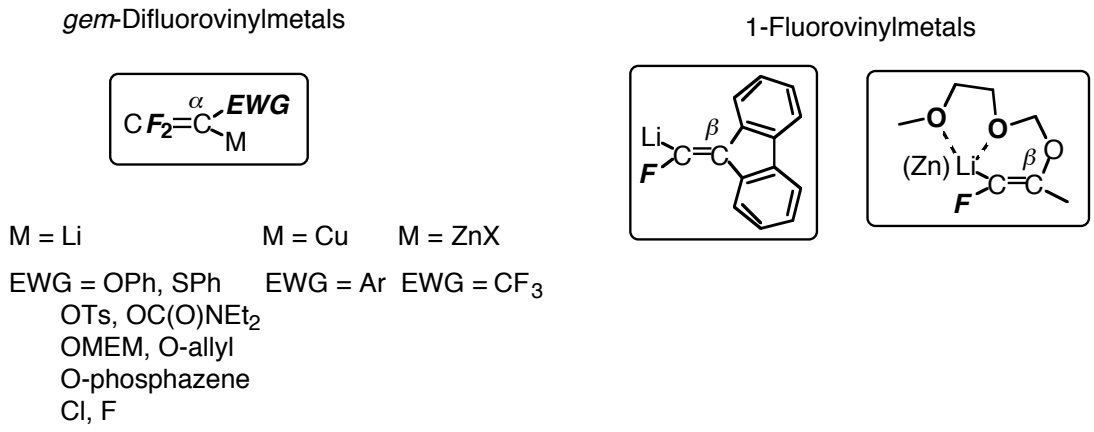


Fig. 1 *gem*-Difluorovinylmetals and 1-fluorovinylmetals with an stabilizing group

On the other hand, few fluorinated vinylmetals without any stabilizing substituents have

Chapter 5 Experimental Section

General. IR spectra were recorded on a Shimazu IR-408 spectrometer. NMR spectra were obtained on a JEOL JNM-FX-60, a JEOL JNM-FX-100, a JEOL JNM-EX-270, or a JEOL JNM-A-500 spectrometer. Chemical shift value were given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR: δ-value) or internal C_6F_6 (for ^{19}F NMR). Mass spectra were taken with a JEOL JMS-DX-300 spectrometer. THF was distilled from sodium benzophenone ketyl prior to use.

Synthesis of β,β-Difluoroolefins

β,β-Difluoro-4-nitrostyrene 5a.

Butyllithium (0.65 ml, 1.58 M in hexane, 1.02 mmol) was added to a tetrahydrofuran (THF, 2.0 ml) solution of zirconocene dichloride (150 mg, 0.51 mmol) at –78 °C under a nitrogen atmosphere, and the resulting mixture was stirred at the same temperature for 1 h. To the reaction mixture was added a solution of 2,2-difluorovinyl *p*-toluenesulfonate (**1a**, 60 mg, 0.26 mmol) in THF (0.5 ml) at –78 °C. After being stirred for 5 min, the mixture was warmed to room temperature and stirred for an additional 3 h. Triphenylphosphine (11 mg, 0.041 mmol) and tris(dibenzylideneacetonyl)bispalladium–chloroform (1/1) (5mg, 0.005 mmol) were added at 0 °C, and the mixture was stirred for 10 min. To the resulting solution were successively added *p*-iodonitorobenzene (70 mg, 0.28 mmol) and zinc iodide (196 mg, 0.61 mmol). After the mixture was heated under reflux for 2 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was filtered and organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 10:1) to give β,β-difluoro-4-nitrostyrene (**5a**, 36 mg, 0.198 mmol, 76%) as a light yellow liquid.

^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (1H, dd, J_{HF} = 25.3, 3.4 Hz), 7.49 (2H, br d, J = 8.9 Hz), 8.19 (2H, br d, J = 8.9 Hz).

***N*-4,4-Difluoro-3-(2-phenylpropyl)-2-methyl-3-buten-1-yl-*p*-toluenesulfonamide**

To a solution of 4,4-difluoro-3-(3-phenylpropyl)-2-methyl-3-butene-1-ol (734 mg, 3.06 mmol) in THF (30 ml) was added triphenylphosphine (802 mg, 3.06 mmol), *N*-tert-butoxycarbonyl-*p*-toluenesulfonamide (830 mg, 3.06 mmol), and diethyl azodicarboxylate (1.309 g, 40% in toluene, 3.06 mmol) at room temperature under a nitrogen atmosphere. After the reaction mixture was stirred for 2 h at room temperature, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short chromatography on silica gel (hexane–AcOEt 7:1) to give crude pale yellow liquid (*N-tert*-Butoxycarbonyl-*N*-4,4-difluoro-3-(3-phenylpropyl)-2-methyl-3-buten-1-yl-*p*-toluenesulfonamide). Trifruoroacetic acid (0.47 mL, 6.0 mmol) was added to a solution of above obtained crude products (*N-tert*-butoxycarbonyl-*N*-4,4-difluoro-3-(2-phenylpropyl)-3-buten-1-yl-*p*-toluenesulfonamide (1.501 g, c.a. 3.045 mmol) in CH_2Cl_2 (15 ml) at room temperature. After the reaction mixture was stirred for 2 h at room temperature, aqueous $NaHCO_3$ was added to quench the reaction. Organic materials were extracted with CH_2Cl_2 three times. The combined extracts were washed with water, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane–AcOEt 4:1), followed by HPLC to give ***N*-4,4-Difluoro-3-(2-phenylpropyl)-2-methyl-3-buten-1-yl-*p*-toluenesulfonamide** (881 mg, 2.24 mmol, 73% from 4,4-difluoro-3-(3-phenylpropyl)-2-methyl-3-butene-1-ol) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.9 Hz), 1.60–1.70 (2H, m), 1.79–2.90 (2H, m), 2.41 (3H, s), 2.38–2.47 (1H, m), 2.55 (2H, t, J = 7.6 Hz), 2.79–2.94 (2H, m), 4.65 (1H, br s), 7.13 (2H, d, J = 7.5 Hz), 7.18 (1H, dd, J = 8.0, 7.1 Hz), 7.24–7.30 (4H, m), 7.72 (2H, dd, J = 8.0, 1.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 16.4, 21.4, 24.7, 30.2, 33.0 (d, J_{CF} = 2 Hz), 35.6, 46.6, 90.4 (dd, J_{CF} = 6, 4 Hz), 125.9, 127.0, 128.3, 128.3, 129.7, 137.0, 141.6, 143.4, 153.9 (dd, J_{CF} = 288, 287 Hz).

^{19}F NMR (270 MHz, $CDCl_3/C_6F_6$): 70.3 (1F, d, J_{FF} = 53 Hz), 71.0 (1F, d, J_{FF} = 53 Hz ppm.

IR (neat) 3280, 2935, 1739, 1599, 1496, 1454, 1423, 1306, 1161, 1066 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 393 (M^+; 2), 105 (98), 155 (99), 184 (100).

HRMS calcd for $C_{21}H_{25}ONF_2S$ 393.1574 (M^+); found 393.1581.

Synthesis of Fluorinated Dihydroheteroaromatics.

5-Fluoro-3-methyl-4-(2-phenylpropyl)-2,3-dihydrofuran 9a.

NaH (12 mg, 60.0% dispersion in mineral oil, 0.30 mmol) was added to a solution of 4,4-difluoro-3-(2-phenylpropyl)-2-methyl-3-butene-1-ol (**6a**, 60 mg, 0.25 mmol) in DMF (8.3 ml) under a nitrogen atmosphere. After the reaction mixture was stirred for 7 h at 90 °C, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with water, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 10:1) to give **9a** (37 mg, 0.168 mmol, 67%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (1.5H, dd, *J* = 7.6 Hz, J_{HF} = 1.2 Hz), 1.06 (1.5H, dd, *J* = 7.6 Hz, J_{HF} = 1.2 Hz), 1.27 (1.5H, d, *J* = 7.0 Hz), 1.31 (1.5H, d, *J* = 7.0 Hz), 2.18 (0.5H, dd, *J* = 15.2, 7.6 Hz), 2.19 (0.5H, dd, *J* = 15.2, 7.6 Hz), 2.35 (0.5H, dd, *J* = 15.2, 8.2 Hz), 2.39 (0.5H, dd, *J* = 15.2, 9.1 Hz), 2.77–2.85 (1H, m), 2.85–2.94 (1H, m), 3.82 (0.5H, dd, *J* = 8.6, 7.0 Hz), 3.87 (0.5H, dd, *J* = 8.6, 7.0 Hz), 4.35 (0.5H, dd, *J* = 8.9, 8.6 Hz), 4.43 (0.5H, dd, *J* = 9.1, 8.6 Hz), 7.20–7.28 (3H, m), 7.31 (1H, t, *J* = 7.6 Hz), 7.33 (1H, t, *J* = 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 18.5 (d, J_{CF} = 2 Hz), 18.6, 21.2, 22.0, 30.7 (d, J_{CF} = 3 Hz), 30.8 (d, J_{CF} = 2 Hz), 36.2 (d, J_{CF} = 3 Hz), 36.9 (d, J_{CF} = 4 Hz), 38.3 (d, J_{CF} = 2 Hz), 38.4 (d, J_{CF} = 2 Hz), 74.5 (d, J_{CF} = 3 Hz), 74.6 (d, J_{CF} = 3 Hz), 82.0 (d, J_{CF} = 13 Hz), 82.4 (d, J_{CF} = 15 Hz), 126.0, 126.1, 126.8, 126.8, 128.2, 128.3, 146.5, 147.3, 156.7 (d, J_{CF} = 271 Hz), 156.8 (d, J_{CF} = 270 Hz).

^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$): 42.1 (0.5F, s), 42.5 (0.5F, s) ppm.

IR (neat) 2962, 1740, 1603, 1495, 1452, 1383, 1252, 1120, 957, 762 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 220 (M^+; 80), 115 (100).

HRMS calcd for $C_{14}H_{17}OF$ 220.1263 (M^+); found 220.1257.

2-Fluoro-4-methyl-3-(2-phenylpropyl)-1-(*p*-tolylsulfonyl)-2-pyrroline 10.

Compound **7** was prepared by the method described above using NaH (5.6 mg, 60.0% dispersion in mineral oil, 0.14 mmol) and *N*-4,4-difluoro-3-(2-phenylpropyl)-2-methyl-3-butenyl-*p*-toluenesulfonamide (**7b**, 50 mg, 0.127 mmol) in DMF (6.4 ml). The reaction was carried out at 90 °C for 4 d. Purification by thin layer chromatography on silica gel (hexane–AcOEt 7:1) gave **10** (38 mg, 0.102 mmol, 80%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66 (1.5H, d, J = 7.3 Hz), 0.68 (1.5H, d, J = 7.3 Hz), 1.07 (1.5H, d, J = 6.7 Hz), 1.15 (1.5H, d, J = 6.7 Hz), 2.01 (0.5H, ddd, J = 14.3, 6.4, 1.8 Hz), 2.09 (0.5H, ddd, J = 14.3, 6.4, 1.8 Hz), 2.14–2.23 (0.5H, m), 2.23–2.40 (1.5H, m), 2.45 (1.5H, s), 2.46 (1.5H, s), 2.62 (0.5H, tq, J = 7.3, 7.3 Hz), 2.79 (0.5H, tq, J = 6.7, 6.7 Hz), 3.21 (0.5H, ddd, J = 11.3, 5.8, 1.5 Hz), 3.17 (0.5H, ddd, J = 11.3, 6.1, 1.2 Hz), 3.67 (0.5H, dd, J = 11.0, 9.8 Hz), 3.77 (0.5H, dd, J = 11.0, 9.8 Hz), 7.00–7.07, (2H, m), 7.12–7.30, (4H, m), 7.34 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 8.2 Hz), 7.71 (1H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 18.7, 18.7, 21.2, 21.6, 21.6, 21.9, 31.4, 31.7, 32.4 (d, J_{CF} = 3 Hz), 33.1, 38.0, 38.1, 54.4, 54.5, 101.6, 102.4, 126.2, 126.3, 126.6, 126.6, 127.9, 128.0, 128.3, 128.4, 129.7, 129.8, 132.5, 132.6, 144.2, 144.4, 145.7, 146.5, 147.1 (d, J_{CF} = 318 Hz), 147.2, (d, J_{CF} = 318 Hz).

^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$): 36.2, (0.5F, s), 36.6, (0.5F, s) ppm.

IR (neat) 2962, 1738, 1603, 1495, 1377, 1174, 1092, 908, 814, 733 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 373 (M^+; 7), 268 (56), 117 (100).

HRMS calcd for $C_{21}H_{24}O_2NFS$ 373.1512 (M^+); found 373.1506.

Conclusion

This dissertation demonstrates that the remarkable properties of fluorine, which include (i) electronic effect on cations and anions and (ii) leaving-group ability as a fluoride ion, *activate* the substrates and *control* the reaction pathways to provide new methodologies for synthesizing a wide variety of inaccessible compounds.

In Chapter 2, by utilizing the β-cation-destabilizing effect of fluorine, the author developed fluorine-directed Nazarov cyclizations, which provide a facile approach to highly functionalized fluorinated cyclopentenones: 5-alkylidene-3-fluoro-2-cyclopentenones, and 5-trifluoromethyl-2-cyclopentenones with defined placement of double bonds. In classical Nazarov cyclizations, normally, the formed double bond occupies the most substituted position because of its thermodynamic stability. So the position of the double bond varies depending on the substitution pattern of substrates. These results demonstrate that fluorine substituent strongly directs the double-bond regiochemistry of Nazarov cyclizations. Furthermore, the author showed that cyclized products, cross-conjugated 3-fluoro-2-cyclopentenones are versatile intermediates in the syntheses of cyclopentanoid natural products, including methylenomycin B antibiotic analogues, by regioselective substitution of various carbon and heteroatom nucleophiles.

In Chapter 3, by using the α-cation-stabilizing effect of fluorine, the author developed fluorine-directed Friedel-Crafts cyclizations of 1,1-difluoroolefins and 1,1-difluoro-1,3-dienes *via* α-fluorocarbocations which generated by the regioselective protonation of the double bonds to construct fused cyclic systems. Moreover, the sequence of reactions: cross-coupling, tandem cyclizations, and dehydrogenation, afforded fused polycyclic compounds, such as helicenes in only three steps from readily available trifluoroethyl tosylate. Since most examples of helicenes were prepared by photo cyclization of stilbene moieties, other methods for supplying large amount of them have became desirable goal. These results could be an approach to solve this question.

In Chapter 4 was described that the preparation of *gem*-difluoroolefins bearing homoallylic oxygen, nitrogen, and sulfur functional groups, difficult to be synthesized by previously reported

List of Publication

Junji Ichikawa, Shinji Miyazaki, Masaki Fujiwara, Toru Minami
; Fluorine-Directed Nazarov Cyclizations :
A Controlled Synthesis of Cross-Conjugated 2-Cyclopenten-1-ones.
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the Generation and Cross-Coupling Reaction of 1-Fluorovinylzirconcene.
; *Tetrahedron Letters*, **1999**, *40*, 7261-7265.

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