Studies on the Synthesis of Selectively Ring-Fluorinated Heterocycles Based on Intramolecular Substitution of *gem*-Difluoroolefins

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gem-ジフルオロオレフィンの分子内置換を基盤とする含フッ素ヘテロ環化合物の合成研究

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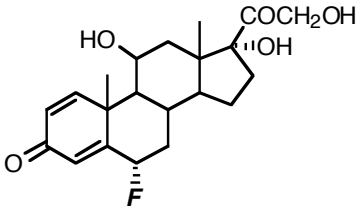
Chapter 1

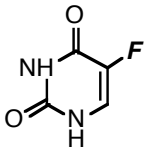
Introduction

Fluorine-containing compounds have received considerable attention in various fields such as medicinal and agricultural chemistry and material sciences, due to their biological activities and physical properties.[1] These unique properties are caused by the following factors of fluorine: (i) the steric demand of fluorine as the second smallest substituent, (ii) the highest electronegativity of fluorine, (iii) the great strength of C–F bond, (iv) the hydrophobicity increased by fluorine, and (v) the leaving group ability of fluoride ion.

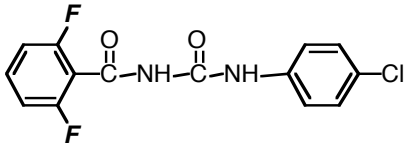
In the fields of medicinal and agricultural chemistry, introduction of fluorine into molecules has been employed as one of the most important approaches for modification of the lead compounds. In fact, many successful examples have already been reported. For instance, the biological activities of **1**, **2**, and **3** are dramatically enhanced or modified by introducing a fluorine atom onto their original molecules. Among dyestuffs, **4** has high sticking tendency compared to its chlorinated counterpart (Fig. 1). Thus, fluorine-containing compounds have been synthesized so far mainly for the purpose of utilizing their physical properties including bioactivities.



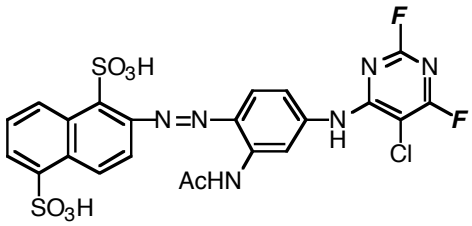
1 fluprednisolone
(local anti-inflammatory agent)



2 5-fluorouracil
(anti-cancer agent)



3 diflubenzuron
(insecticide)



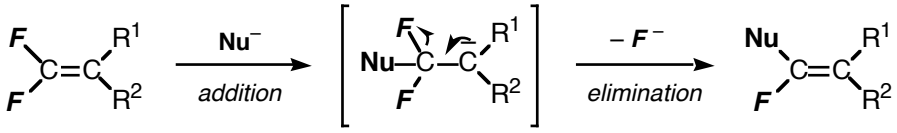
4 verofix dye
(reactive dye)

Fig. 1

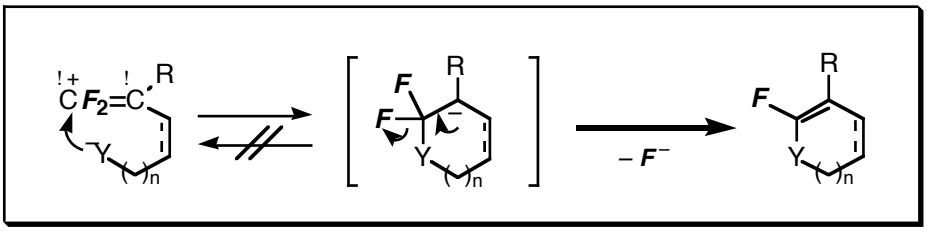
In contrast to such application-based approach, fluorine has not been fully utilized as a tool in organic synthesis in spite of its unique properties. This fact led us to study on "fluorine as a tool in organic synthesis". In our laboratory massive efforts have been directed toward developing new synthetic reactions by the use of the unique properties of fluorine. As part of our studies, I picked up the theme, studies on the synthesis of selectively ring-fluorinated heterocycles based on intramolecular substitution of *gem*-difluoroolefins.

Fluorine-containing heterocycles are widely used as important components in the pharmaceutical, agrochemical, and dyestuffs industries.[2] Although introduction of fluorine into heterocyclic compounds has been effected by employing Balts–Schiemann-type fluorination, electrochemical fluorination, and fluorinating reagents, there still remain problems in the regioselectivity of fluorination, the requirement of multistep procedures, and the difficulty in handling the fluorinating reagents. Especially, concerning ring-fluorinated heterocyclic compounds, only a limited number of methods have been reported for their synthesis. Furthermore, it is known to be difficult that introducing a fluorine atom on heterocyclic ring carbons, compared to fused benzene ring carbons. These circumstances prompted me to investigate the synthesis of selectively ring-fluorinated heterocycles by making use of the unique properties of fluorine.

gem-Difluoroolefins possess the remarkable reactivity toward nucleophilic substitution for their vinylic fluorines *via* addition–elimination processes.[3] This reactivity is due to (i) the electrophilic activation of the C–C double bond by the two fluorine atoms, (ii) the stabilization of the intermediary carbanion by the β-anion stabilizing effect of fluorine, and (iii) the leaving-group ability of fluoride ion (Scheme 1). These unique properties attracted my attention and led me to explore an intramolecular version of this substitution, which could give a solution to construct ring-fluorinated heterocycles as shown in Scheme 2. For the purpose of conducting this type of cyclization, I adopted β,β-difluorostyrene derivatives bearing a nucleophilic functional group at the *ortho* position as substrates.

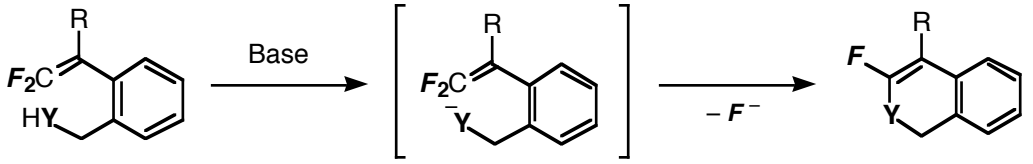


Scheme 1



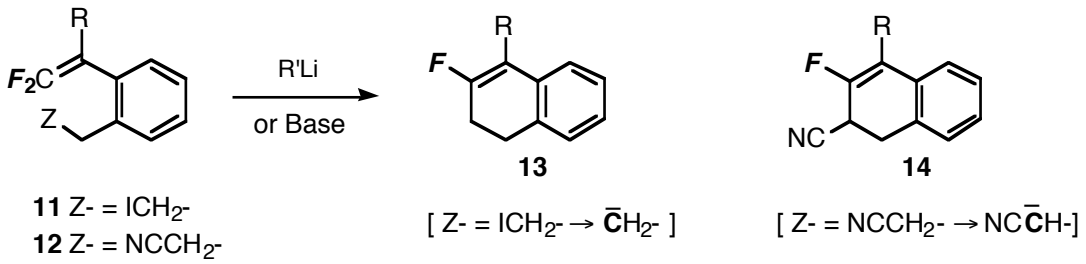
Scheme 2

Based on the above mentioned considerations, I initially examined the construction of 6-membered heterocycles *via* intramolecular ring-formation of *o*-substituted β,β-difluorostyrenes. The intramolecular substitution of oxygen, sulfur, and nitrogen for the vinylic fluorine was investigated under basic conditions. The attempted ring closure smoothly proceeded to provide 3-fluoroisochromenes **8**, isothiochromenes **9**, and isoquinoline derivatives **10** (Scheme 3, Section 2.2).



Scheme 3

Furthermore, I exploited similar cyclizations by intramolecular carbon nucleophiles instead of heteroatom nucleophiles mentioned above. These reactions provide facile methods for the construction of fluorinated naphthalene and quinoline frameworks (Schemes 4 and 5, Section 2.3).

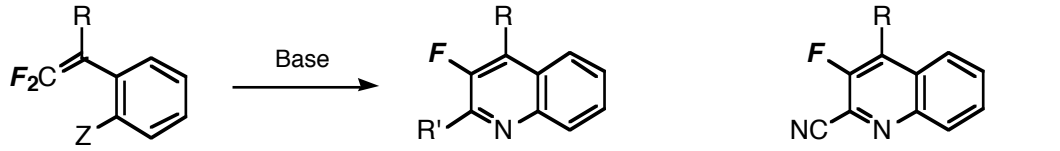


11 Z- = ICH_2-
12 Z- = $NCCH_2$-

[Z- = ICH_2- → $\bar{C}H_2$-]

[Z- = $NCCH_2$- → $NC\bar{C}H$-]

Scheme 4



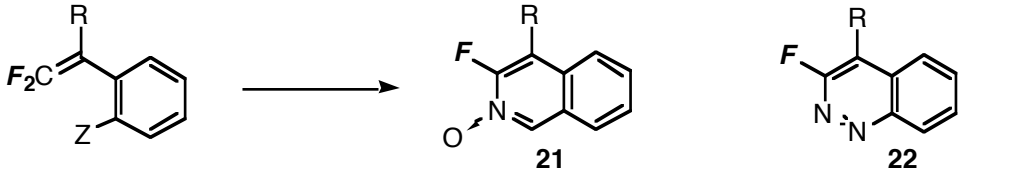
15 Z- = NCCH(R')NH-
16 Z- = $NCCH_2N$(Ts)-

[Z- = NCCH(R')NH- → $NC\bar{C}$(R')NH-]

[Z- = NCH_2CN(Ts)- → $NC\bar{C}HN$(Ts)-]

Scheme 5

For the construction of aromatized isoquinoline framework, I next tried similar replacement of the vinylic fluorine by an oxime imino nitrogen. This sequence provides an easy access to 3-fluoroisoquinoline *N*-oxides **21** (Scheme 6, Section 2.4). In addition, the reactions of the remaining fluorine in **21** with various nucleophiles were examined. Introduction of heteroatoms at the 3-position of **21** was successfully achieved *via* similar addition–elimination processes. As an expansion of this strategy for aromatic heterocycles, I also effected the intramolecular substitution of a diazenyl nitrogen, which nicely afforded 3-fluorocinnolines **22** (Scheme 6, Section 2.4).



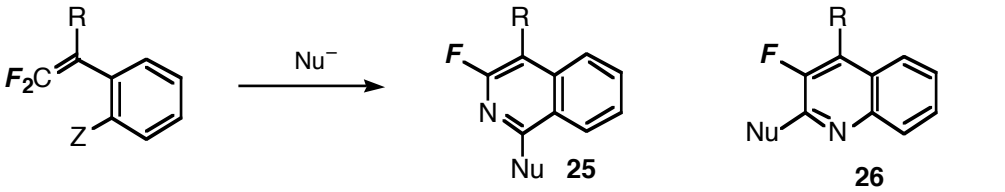
19 Z- = OHC-
20 Z- = H_2N-

[Z- = OHC- → HO**N**=H_2C-]

[Z = H_2N → H**N**=N-]

Scheme 6

Concerning the generation of intramolecular nucleophiles, I investigated another method, that is, addition of external nucleophiles to unsaturated functional groups such as cyano and isocyano groups, which generates nitrogen and carbon nucleophiles, respectively. Their cyclizations proceeded well, and the synthesis of 3-fluoroisoquinolines **25** and 3-fluoroquinolines **26** was accomplished, being accompanied by introduction of a substituent on the heterocyclic rings (Scheme 7, Section 2.5).

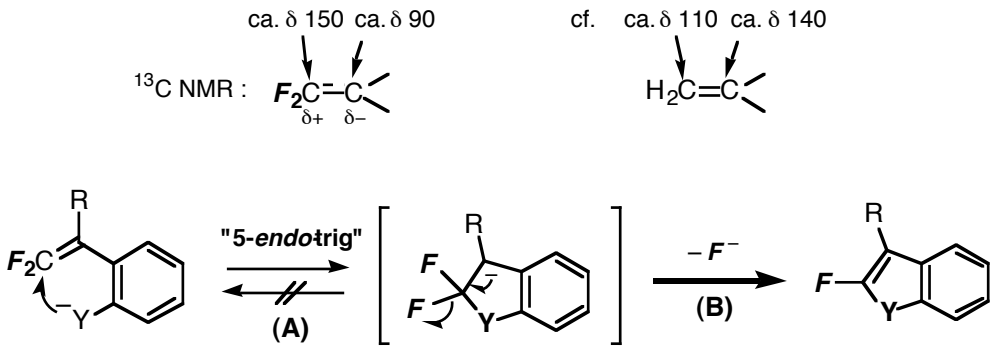


23 Z- = NC-
24 Z- = CN-

[Z = NC- → $\bar{\mathbf{N}}$=C(Nu)-] [Z = CN- → Nu$\bar{\mathbf{C}}$=N-]

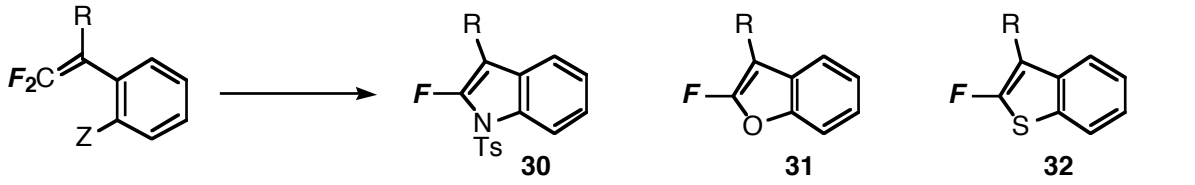
Scheme 7

After achieving the construction of ring-fluorinated 6-membered heterocycles *via* intramolecular cyclization of *o*-substituted β,β-difluorostyrenes, I turned my attention to the construction of ring-fluorinated 5-membered heterocycles by means of similar strategy. According to Baldwin's rules,[4] the general rules of intramolecular cyclization, this type of cyclization is classified as 5-*endo*-trig ring closure. Although this process is disfavored in the rules, I expected that the unique properties of fluorine could make this nucleophilic approach feasible. For one thing, I thought about (A) a partial single bond character of difluoroolefins, which is suggested by ^{13}C NMR. This highly polarized double bond would allow initial ring formation. And after the cyclization, (B) successive elimination of a fluoride ion could suppress the reverse ring opening (Scheme 8).



Scheme 8

On the basis of these considerations, I tried this type of nucleophilic 5-*endo*-trig cyclization and found that the expected reaction smoothly proceeded to afford 2-fluoroindoles **30**, 2-fluorobenzofurans **31**, and 2-fluorobensothiophenes **32** under basic conditions (Scheme 9, Section 3.2).



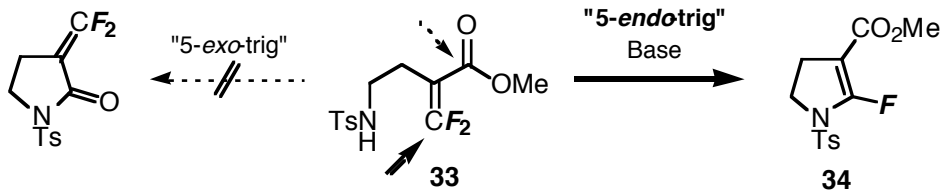
27 Z- = TsHN-
28 Z- = HO-
29 Z- = MeS(O)-

[Z- = TsNH- → Ts$\bar{\mathbf{N}}$-] [Z- = HO- → $\bar{\mathbf{O}}$-] [Z- = MeS(O)- → $\bar{\mathbf{S}}$-]

Scheme 9

In order to confirm the effect of fluorine on the 5-*endo*-trig cyclization, I tried the competitive reaction between 5-*endo*-trig and 5-*exo*-trig processes. When the substrate **33** was subjected to basic conditions, 5-*endo*-trig cyclization exclusively occurred leading to 2-fluorinated pyrroline **34** (Scheme 10). This result shows a remarkable contrast by comparison with the reaction of the corresponding fluorine free substrate, clearly indicating the effect of fluorines on the cyclization pathways. Moreover, I attempted the reaction of β-monofluoro, β,β-dichloro, and β,β-dibromostyrenes under the same conditions for comparison with β,β-difluorostyrenes in terms of the reactivity in the 5-*endo*-trig cyclization.

The 5-*endo*-trig ring closures of these substrates were highly retarded, which results clearly show that two vinylic fluorines are essential in this cyclization (Section 3.3).



Scheme 10

Detailed results and discussions are described in the following two chapters, eight sections.

References and notes

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(2) (a) Elguero, J. In *Comprehensive Organic Chemistry*; Potts, K. T., Ed.; pergamon Press: Oxford, 1984; Vol. 5, pp 167–303. (b) Grimmett, M. R. In *Comprehensive Organic Chemistry*; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1979; Vol. 4, pp 357–410.

(3) Sprague, L. G.; Baucom, K. B.; Sellers S. F.; DuBoisson, R. A. In *Chemistry of Organic Fluorine Compounds II*; ed. M. Hudlicky and A. E. Pavlath, ACS Monograph 187, American Chemical Society, Washington, DC, 1995, p. 729.

(4) (a) Baldwin, J. E.; *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman L.; Thomas, R. C.; *J. Chem. Soc., Chem. Commun.* **1976**, 736. (c) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.

Chapter 2

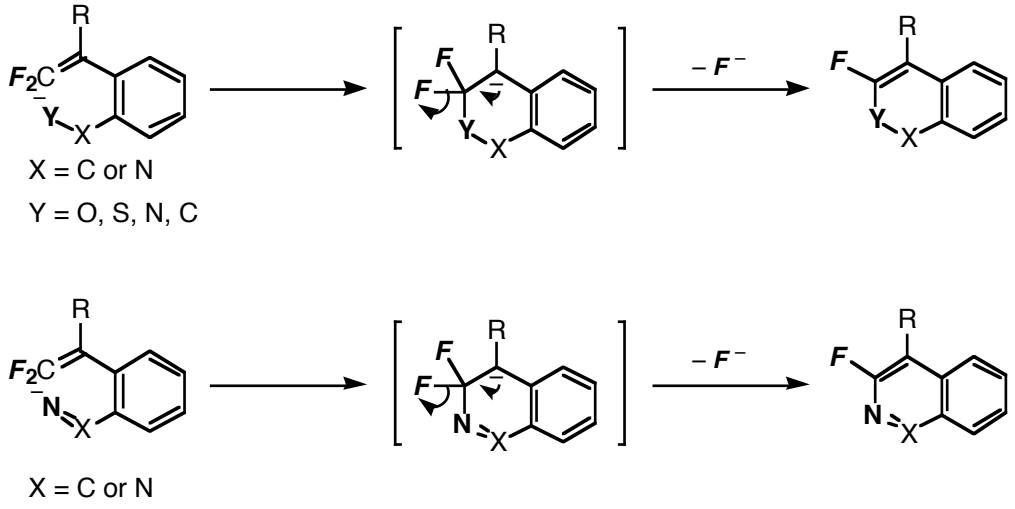
Construction of Ring-Fluorinated 6-Membered Heterocycles *via* Intramolecular Cyclizations of *o*-Substituted β,β-Difluorostyrenes

2.1 Introduction

Initially, my attention was focused on selectively ring-fluorinated 6-membered heterocycles. Among them, fluorine-containing isochromenes, isoquinolines, quinolines, and cinnolines were selected as synthetic targets suitable for the tactics of intramolecular substitution mentioned in Chapter 1. Furthermore, they could be employed as intermediates in the synthesis of medicinal and agrochemical agents; in spite of their potential their synthetic methods still remaine to be developed.

For the purpose of constructing these skeletons, β,β-difluorostyrene derivatives with an oxygen, a sulfur, a nitrogen, or a carbon nucleophile linked by a carbon or a heteroatom to the *ortho* position were designed and subjected to the intramolecular ring-forming reaction (Scheme 1). Here the following four methods were adopted for the generation of intramolecular nucleophiles: (i) deprotonation of active hydrogens (HY- → $^{-}$**Y**- ; Y = O, S, NTs, CH(CN)) (Sections 2.2 and 2.3), (ii) metal–halogen exchange (ICH_2- → $^{-}$**C**H_2-) (Section 2.3), (iii) conversion of functional groups into N=C or N=N groups (OHC- → HO**N**=H_2C-, N≡N^{+}- → H**N**=N-) (Section 2.4), and (iv) addition of external nucleophiles to unsaturated functional groups (NC- → $^{-}$**N**=C(Nu)-, CN- → $^{-}$**C**Nu=N-) (Section 2.5). The methods (i) and (ii) generate sp^3 heteroatom and carbon nucleophiles, whereas (iii) and (iv) generate sp^2 nitrogen and carbon nucleophiles, leading to the direct construction of 6-membered aromatic rings.

In this chapter, I describe the synthesis of 3-fluoroisochromenes (1*H*-2-benzopyran derivatives),[1] 3-fluoroisothiochromenes (1*H*-2-benzothiopyran derivatives),[2] 3-fluoroisoquinolines, 3-fluoroquinolines,[3] fluoronaphthalenes, 3-fluoroisoquinoline *N*-oxides, and 3-fluorocinnolines in due order.

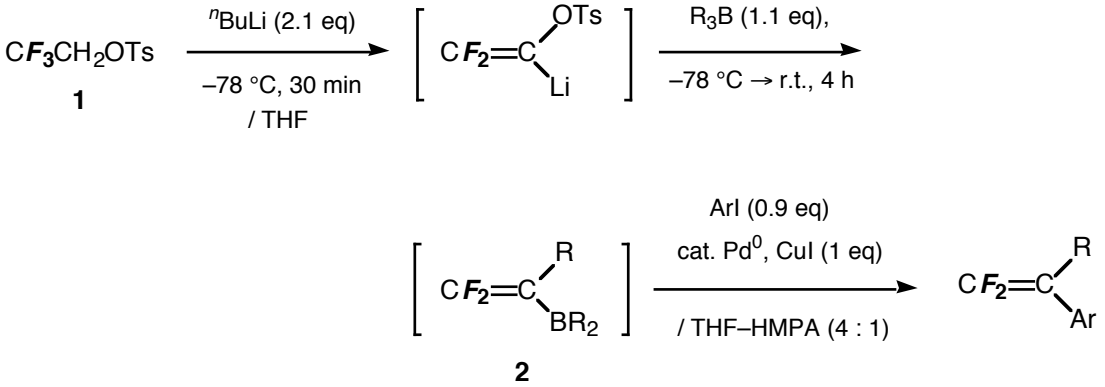


Scheme 1

2.2 Cyclization of β,β-Difluorostyrenes Bearing an sp^3 Heteroatom Nucleophile Linked by a Methylene Unit to the *Ortho* Carbon

2.2.1 Preparation of β,β-Difluorostyrenes Bearing a Heteroatom Nucleophile Linked by a Methylene Unit to the *Ortho* Carbon

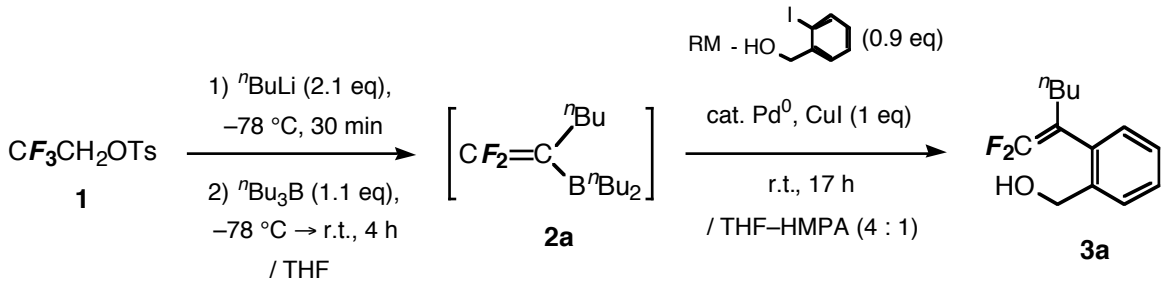
The starting materials, *o*-substituted β,β-difluorostyrenes were easily prepared from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) using the one-pot method which has been previously established in our laboratory: (i) the *in-situ* generation of 2,2-difluorovinylboranes **2** and (ii) their palladium-catalyzed cross-coupling reaction with aryl iodides (Scheme 2).[4]



Scheme 2

Difluorostyrenes **3** bearing a hydroxymethyl group at the *ortho* position, precursors of 3-fluoroisochromenes, were successfully obtained by the direct coupling of **2** with the corresponding aryl iodides without their OH protection. *o*-Iodobenzyl alcohol was pretreated with equimolecular amounts of several alkylmetals such as methylmagnesium iodide and dibutylmagnesium to generate the metal alkoxides, which in turn coupled with **2** in the presence of a palladium catalyst to afford the desired styrene **3a** as summarized in Table 1. The butylmagnesium alkoxide improved the yield of **3a** up to 69%, which was slightly better than that of the iodomagnesium alkoxide, probably due to their solubility (Table 1, Entries 2 and 5). Under thus obtained reaction conditions, **3a–c** were prepared in good yields from **1** (Table 2).

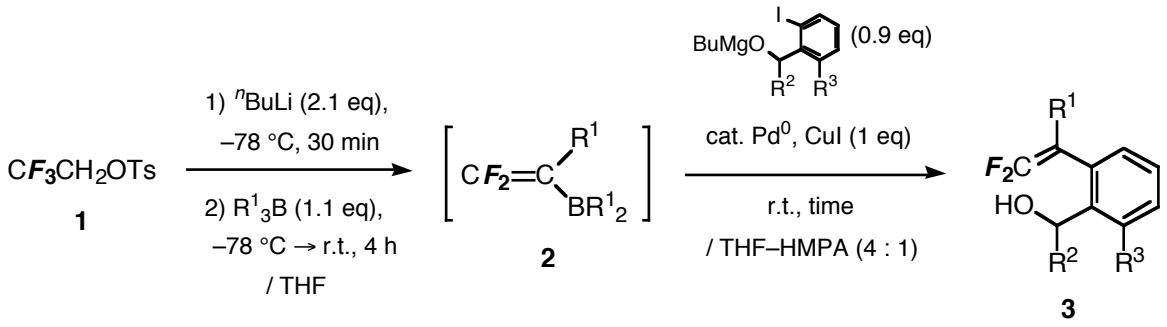
Table 1. Effect of Metal Alkoxide



Entry	RM[a)]	Yield / %	Entry	RM[a)]	Yield / %
1	^{n}BuLi	34	**5**	**^{n}Bu$_2$Mg**	**69**
2	MeMgI	64	6	Ph_2Mg	50
3	^{n}BuMgBr	49	7	Et_2Zn	25
4	Me_2Mg	31	8	KH	27

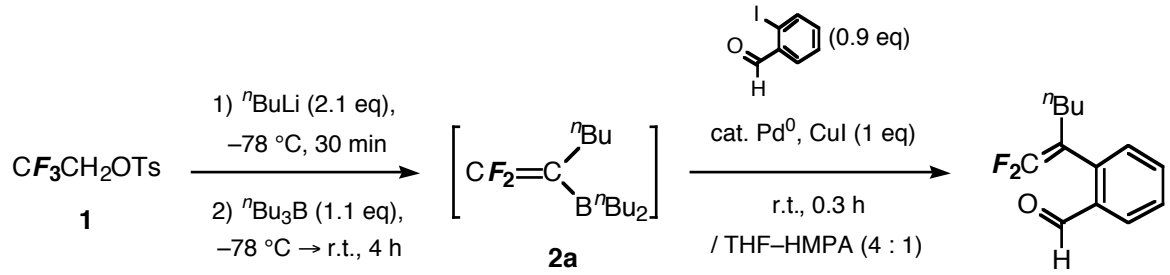
a) Equimolecular amounts of RM were used.

Table 2. Preparation of β,β-Difluorostyrenes Bearing a Hydroxymethyl Group **3**



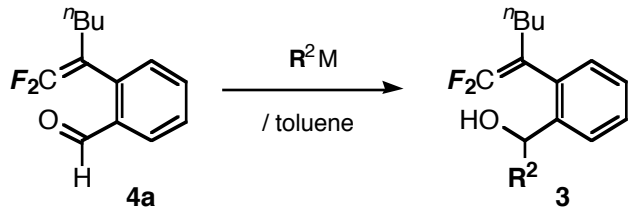
Entry	R^1	R^2	R^3	Time / h	Yield / %
1	^{n}Bu	H	H	17	69 (**3a**)
2	^{s}Bu	H	H	5	61 (**3b**)
3	^{n}Bu	-$(CH_3)_2$-		4	55 (**3c**)

Alcohols **3** were also obtained *via* another route, which allows the introduction of a substituent (R^2) on the benzylic carbon. The coupling of **2a** with *o*-iodobenzaldehyde afforded β,β-difluoro-*o*-formylstyrene **4a** in a 84% yield determined by ^{19}F NMR, while the isolated yield was 62% because of its instability (Scheme 3). The addition of nucleophiles such as Grignard reagents and diisobutylalminum hydride to **4a** regioselectively occurred at the formyl carbon in a less polar solvent, toluene to give **3a**,**d**–**f** in good yields. The results are summarized in Table 3.



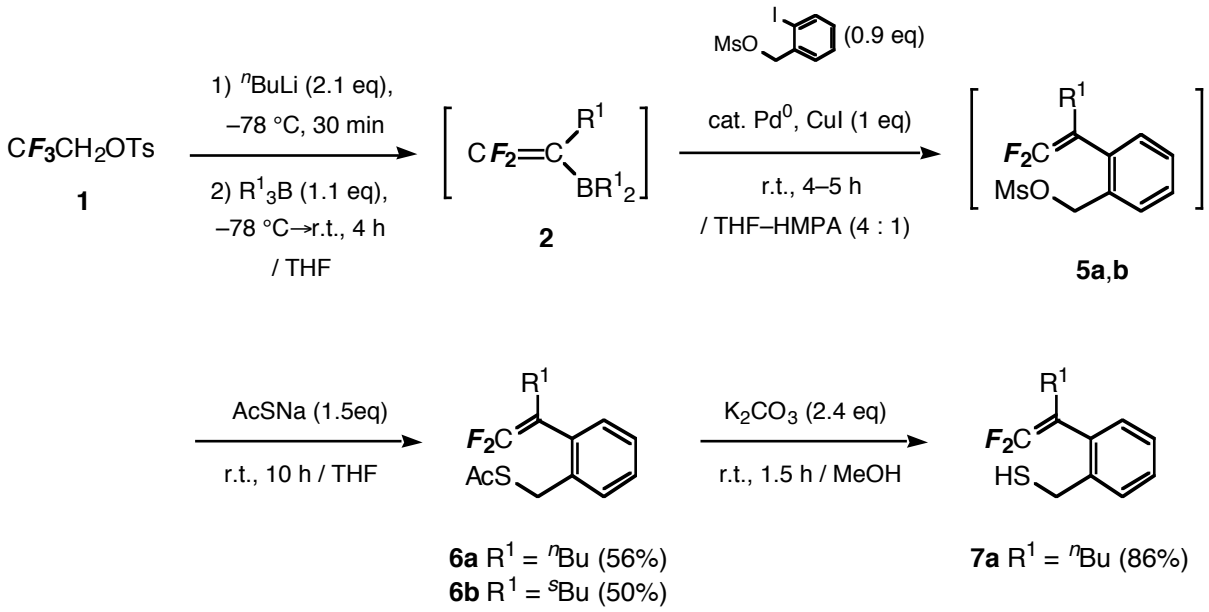
Scheme 3

Table 3. Preparation of β,β-Difluorostyrenes Bearing a Hydroxymethyl Group **3**



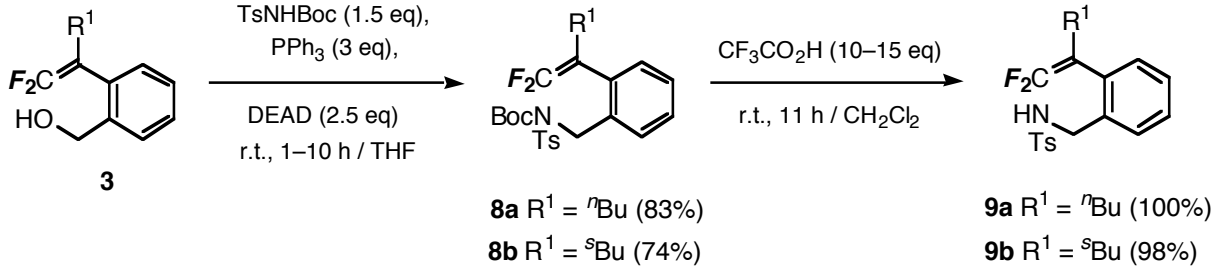
Entry	$\mathbf{R^2}$M (eq)	Conditions	Yield / %
1	^{n}**Bu**MgBr (1.2)	0 °C, 15 min	77 (**3d**)
2	**Me**MgI (1.5)	0 °C, 15 min	55 (**3e**)
3	**Ph**MgBr (1.5)	–78 °C, 30 min	54 (**3f**)
4	**H**Al^{i}Bu$_2$ (1.5)	0 °C, 30 min	44 (**3a**)

As sulfur-containing substrates for the synthesis of 3-fluoroisothiochromenes, thioacetates **6** were readily prepared from **1** *via* mesylates **5** in a one-pot operation: (i) the coupling reaction of **2** with *o*-iodobenzyl methanesulfonate leading to **5** and (ii) the successive introduction of an acetylthio group at the benzylic position on treatment with sodium thioacetate. Thioacetate **6a** was transformed into thiol **7a** *via* solvolysis with K_2CO_3 in methanol (Scheme 4).



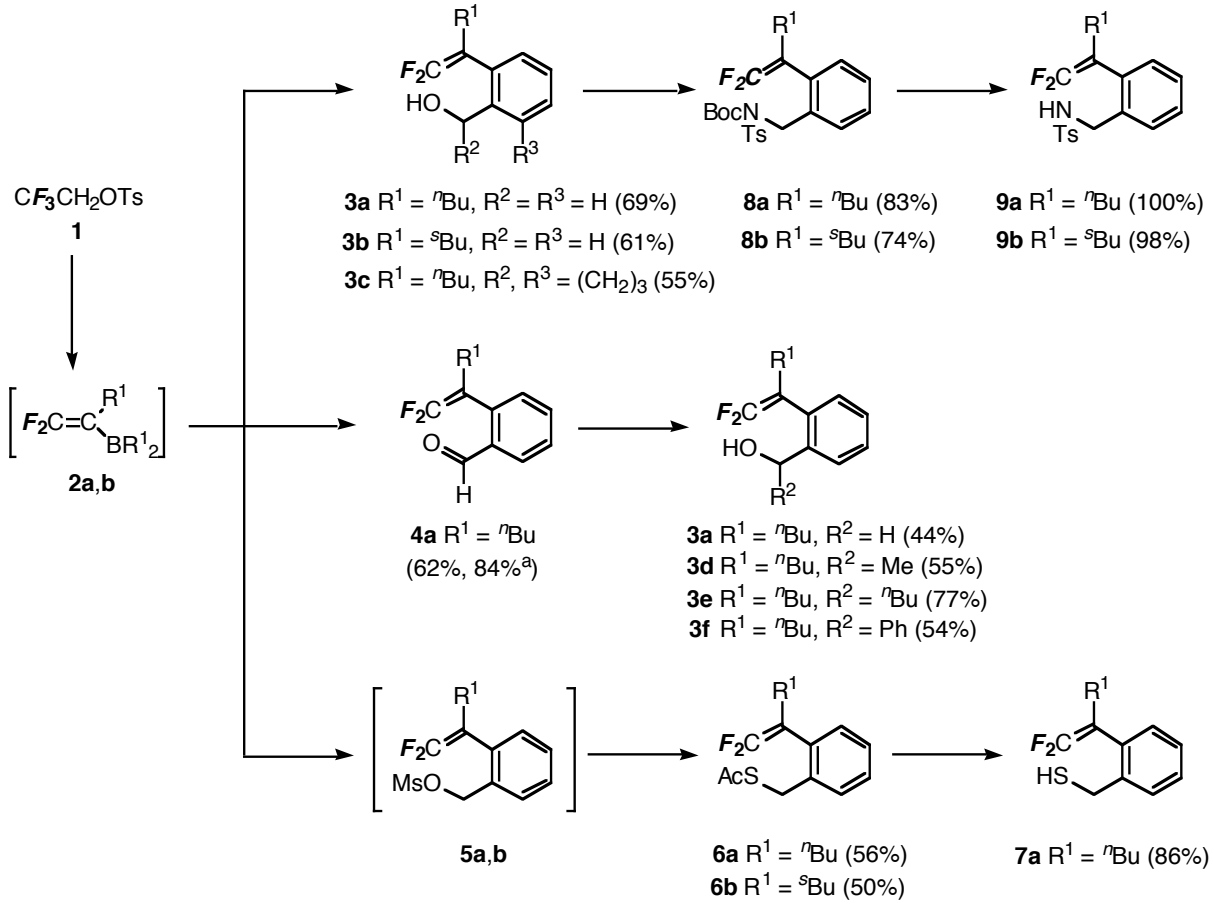
Scheme 4

The corresponding nitrogen-containing substrates **9**, precursors of 3-floroisoquinoline derivatives, were easily obtained from alcohol **3**. The Mitsunobu reaction[5] of alcohol **3** with BocNHTs allowed the introduction of a nitrogen atom to give compounds **8**, whose deprotection of the Boc group led to sulfonamides **9** (Scheme 5).



Scheme 5

Thus, the starting materials with a *O*-nucleophile **3**, *S*-nucleophile **6**,**7**, and *N*-nucleophile **9** were prepared as depicted in Scheme 6.



[a] Determined by ^{19}F NMR.

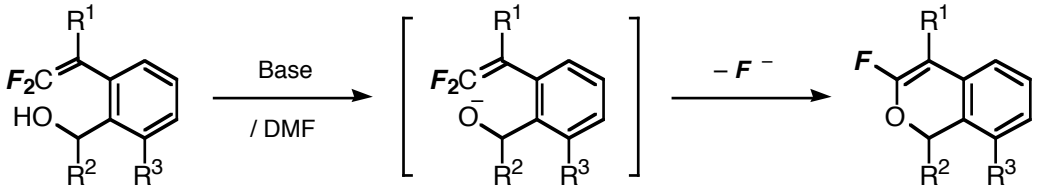
Scheme 6

2.2.2 Synthesis of 3-Fluorinated Isochromenes, Isothiochromenes, and Isoquinoline Derivatives

The cyclization of the difluorostyrenes obtained above was attempted under basic conditions. Although treatment of **3a** with 1.0 equiv of butyllithium in tetrahydrofuran (THF) resulted in a complex mixture of products, the expected intramolecular substitution was effected by the use of NaH (1.1 equiv) or KH (1.2 equiv) in dimethylformamide (DMF) at room temperature, where the cyclized product, 3-fluoroisochromene **11a** was obtained in 78% or 72% yields, respectively (Table 4, Entries 1 and 2). Furthermore, adding 2 equiv of NaH improved the yield of **11a** up to 84% (Entry 3). In a similar manner, several other 3-fluoroisochromenes **11** were synthesized from hydroxystyrenes **3**. The ring closure of **3b**

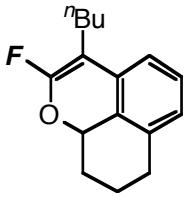
bearing a secondary alkyl group (R^1) at the vinylic position successfully proceeded to afford **11b** in a 84% yield (Entry 4). Even in the case of secondary alcohols **3c–f**, the cyclization of the corresponding alkoxides occurred under similar conditions, leading to **11c–f** including fused tricyclic compound **11c** in good yields (Entries 5–8).

Table 4. Synthesis of 3-Fluoroisochromenes **11**



3 **11**

Entry	R^1	R^2	R^3	Substrate	Base (equiv)	Conditions	Yield / %
1	^{n}Bu	H	H	**3a**	NaH (1.1)	r.t., 1.5 h	78 (**11a**)
2	^{n}Bu	H	H	**3a**	KH (1.2)	r.t., 2.0 h	72 (**11a**)
3	^{n}Bu	H	H	**3a**	NaH (2.0)	r.t., 1.2 h	84 (**11a**)
4	^{s}Bu	H	H	**3b**	NaH (2.0)	r.t., 1.7 h	84 (**11b**)
5	^{n}Bu	-$(CH_2)_3$-		**3c**	NaH (1.9)	r.t., 2.2 h	66 (**11c**)
6	^{n}Bu	Me	H	**3d**	NaH (2.0)	r.t., 2.0 h	60 (**11d**)
7	^{n}Bu	^{n}Bu	H	**3e**	NaH (2.0)	r.t., 2.0 h	71 (**11e**)
8	^{n}Bu	Ph	H	**3f**	NaH (2.0)	r.t., 2.0 h	50 (**11f**)



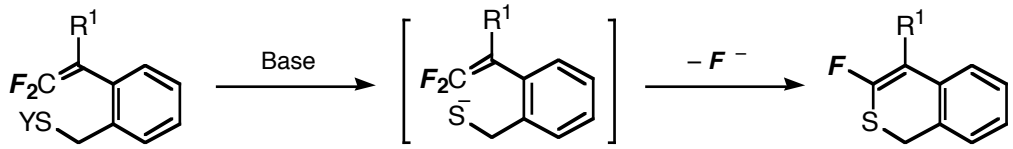
11c

In addition, a similar intramolecular substitution was investigated by employing the difluorostyrenes with sulfur nucleophiles. On treatment of thiol **7a** with KH (1.2 equiv) in DMF, the corresponding 3-fluoroisothiochromene **12a** was obtained in a 90% yield (Table 5, Entry 1). Having found the cyclization of the potassium thiolate, I examined the

combination of the two processes of deacetylation (**6→7**) and cyclization (**7→12**) into a one-pot operatation, so as to refine the synthesis of **12** to be more efficient. After the deacetylation of **6a** with K_2CO_3 (2.4 equiv; 1.2-fold molar amount) in MeOH, the reaction mixture was heated at 60 °C to drive the *in-situ* generated thiolate to undergo the cyclization, and **12a** was obtained in a 61% yield (Entry 2). Screening of the reaction conditions such as base and solvent revealed that treatment of **6a**,**b** with sodium methoxide (2.0 equiv) in DMF successively promoted the two processes to proceed without heating, leading to **12a**,**b** in excellent yields (Entries 3 and 4).

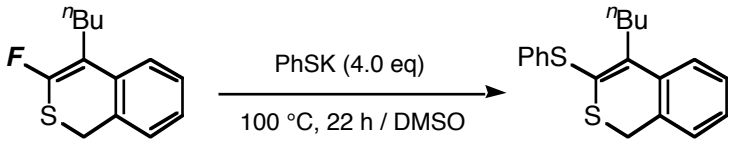
The remaining fluorine in the cyclized products **12a** was expected to be replaced by nucleophiles *via* similar addition–elimination processes. On treatment of **12a** with potassium benzenethiolate as a nucleophile, the desired **13a** was obtained as shown in Scheme 7. The reaction allows to introduce substituents at the 3-position and provides a method for the synthesis of 3,4-disubstituted isothiochromenes in combination with the cyclization described above.

Table 5. Synthesis of 3-Fluoroisothiochromenes **12**



6,**7** **12**

Entry	Y	R^1	Substrate	Base (equiv)	Solvent	Conditions	Yield / %
1	H	^{n}Bu	**7a**	KH (1.2)	THF	r.t., 2.5 h	90 (**12a**)
2	Ac	^{n}Bu	**6a**	K_2CO_3 (2.4)	MeOH	60 °C, 8.5 h	61 (**12a**)
3	**Ac**	**^{n}Bu**	**6a**	**NaOMe (2.0)**	**DMF**	**r.t., 0.3 h**	**94 (12a)**
4	**Ac**	**^{s}Bu**	**6b**	**NaOMe (2.0)**	**DMF**	**r.t., 0.3 h**	**90 (12b)**

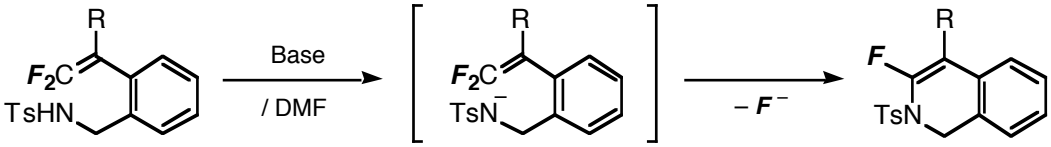


12a **13a** (71%)

Scheme 7

As a further example of the cyclization, I also examined the reaction of the substrates bearing an *N*-nucleophile generated by deprotonation on the nitrogen under similar conditions. When β,β-difluorostyrene **9a** was treated with 1.0 equiv of NaH in DMF at 0 °C and then at room temperature, intramolecular cyclization readily proceeded as expected to afford 3-fluoro-1,2-dihydroisoquinoline **14a** in a 77% yield (Table 6, Entry 1). Conducting the reaction by using 1.1 equiv of NaH raised the yield of **14a** up to 89% (Entry 3). Successful ring closure procceded smoothly even in the case of styrene **5b** with a secondary alkyl group at the α-position (Entry 5).

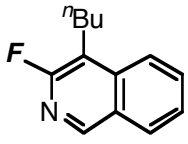
Table 6. Synthesis of 3-Fluorodihydroisoquinolines **14**



9 **14**

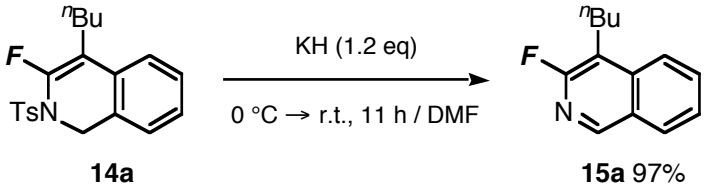
Entry	R	Substrate	Base (equiv)	Conditions	Yield / % [a]	
1	*n*Bu	**9a**	NaH (1.0)	0 °C → r.t., 4 h	77 (91)	(**14a**)
2	***n*Bu**	**9a**	**NaH (1.1)**	**0 °C → r.t., 5 h**	**89 (94)**	**(14a)**
3	*n*Bu	**9a**	NaH (1.2)	0 °C → r.t., 4 h	80[b] (89)	(**14a**)
4	*n*Bu	**9a**	KH (1.2)	0 °C → r.t., 4 h	33[c]	(**14a**)
5	***s*Bu**	**9b**	**NaH (1.1)**	**0 °C → r.t., 9 h**	**89 (94)**	**(14b)**

a) Isolated yield. ^{19}F NMR yield relative to internal $C_6H_5CF_3$ standard is given in parentheses. b) 3-Fluoroquinoline **15a** was obtained in a10% yield. c) **15a** was obtained in a 49% yield.



15a

When an excess amount of base was used, 3-fluoroisoquinoline **15a** was also formed as a by-product *via* aromatization of **14a** (Entries 3 and 4). Moreover, KH was more suitable for the formation of **15a**. It seemed that styrene **9a** underwent the cyclization followed by elimination of sulfinic acid to give isoquinoline **15a**. In order to confirm this route from **9a** to **15a** *via* **14a**, dihydroisoquinoline **14a** was treated with 1.2 equiv of KH in DMF. The reaction readily proceeded with a loss of sulfinic acid to afford 3-fluoroisoquinoline **15a** in an almost quantitative yield (Scheme 8).

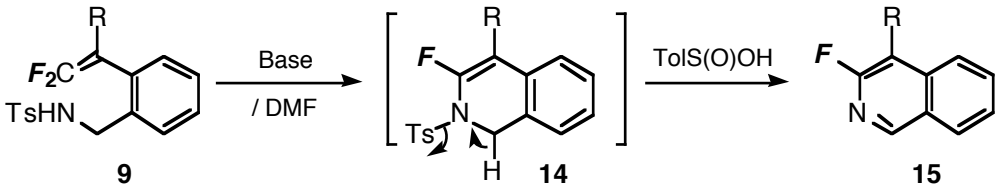


14a **15a** 97%

Scheme 8

These results suggested that employing 2 equiv of base should promote not only the cyclization but also the successive elimination of sulfinic acid, leading to a one-pot synthesis of **15** from **9**. On treatment of difluorostyrene **9a** with 2.1 equiv of KH, the corresponding 3-fluoroisoquinoline **15a** was obtained in a 81% yield without being accompanied by **14a** as expected (Table 7, Entry 1). By the use of 2.5–2.6 equiv of KH, the reaction was completed in several hours, and the yields of **15a**,**b** turned out to be excellent (Table 7, Entries 2 and 3).

Table 7. Synthesis of 3-Fluoroisoquinoline **15**



9 **14** **15**

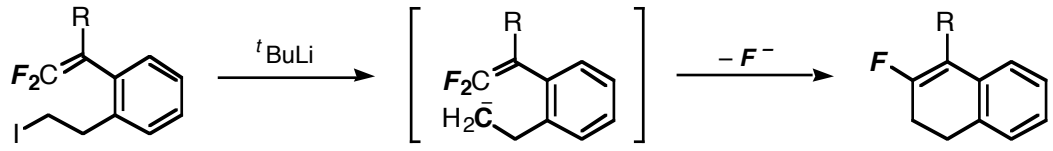
Entry	R	Substrate	Base (eq)	Conditions	Yield / %
1	^{n}Bu	**9a**	KH (2.1)	0 °C → r.t., 26 h	81 (**15a**)
2	^{n}Bu	**9a**	KH (2.5)	0 °C → r.t., 4 h	**95** (**15a**)
3	^{s}Bu	**9b**	KH (2.6)	0 °C → r.t., 9 h	**90** (**15b**)

2.3 Cyclization of β,β-Difluorostyrenes Bearing an sp^3 Carbon Nucleophile Linked by a Carbon or a Nitrogen Spacer to the *Ortho* Position

In Section 2.2 it was demonstrated that intramolecular substitutions for vinylic fluorines are successfully achieved by heteroatom nucleophiles such as oxygen, sulfur, and nitrogen nucleophiles, providing an easy access to 6-membered heterocyclic compounds with a fluorine on the ring carbon. Next, I attempted similar cyclizations by employing carbon nucleophiles to broaden the scope of this methodology. As the methods for generations of carbon nucleophiles, I adopted two ways: (i) metal–halogen exchange and (ii) deprotonation of active methylene groups. For the methods (i) and (ii), β,β-difluorostyrenes bearing an 2-iodoethyl and a 2-cyanoethyl group at the *ortho* position were designed, respectively. Their cyclizations *via in-situ* generation of carbon nucleophiles would produce β-fluorinated naphthalene derivatives as shown in Schemes 9 and 10.

— Methods for the Generation of ***C-Nucleophiles*** —

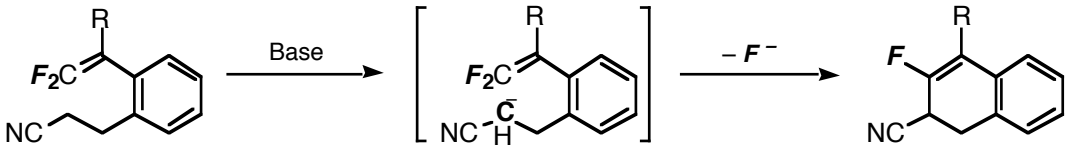
(i) ***Metal–Halogen Exchange***



16 **18**

Scheme 9

(ii) ***Deprotonation***

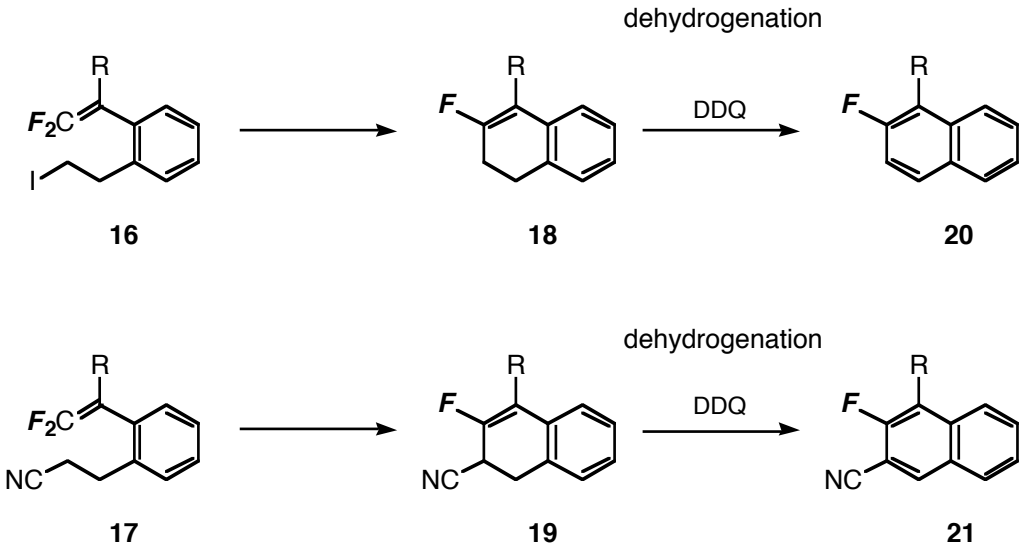


17 **19**

Scheme 10

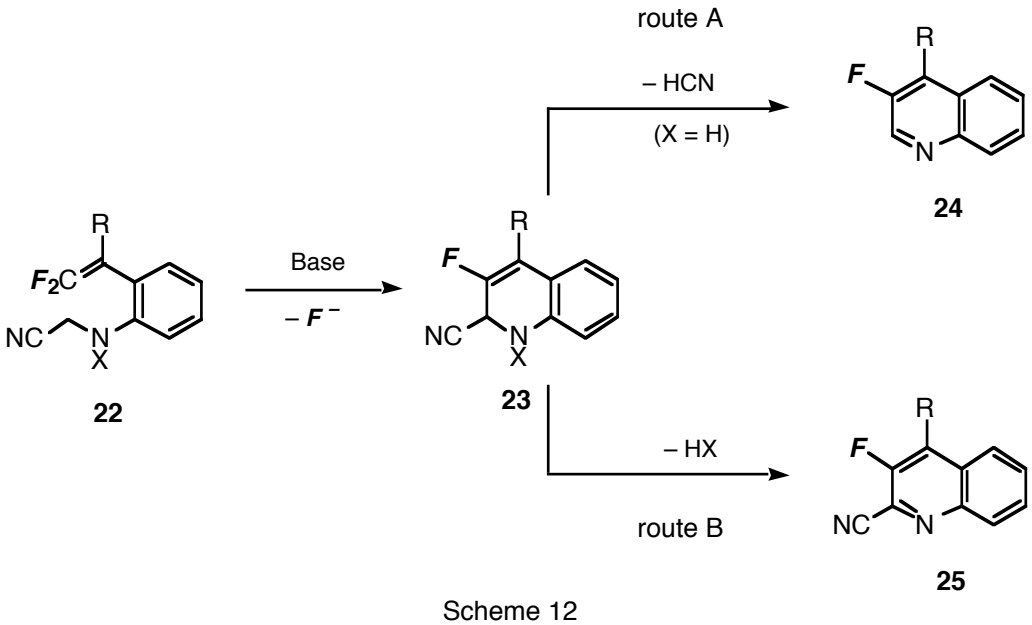
By means of a similar strategy, 3-fluoroquinolines would be also produced as well as the naphthalene derivatives by changing the *ortho* benzylic carbon of **17** to a nitrogen atom. Thus, precursors of 3-fluoroquinolines should be β,β-difluorostyrenes **22** bearing a cyanomethylamino group at the *ortho* position (Scheme 12). As shown in Scheme 11, both of the reactions include dehydrogenation step for the purpose of aromatization. In the synthesis of 3-fluoroquinolines, I examined two methods for the aromatization of cyclized product **23** : (i) elimination of HCN leading to 3-fluoroquinoline **24** (route A, X = H) and (ii) elimination of HX leading to 2-cyano-3-fluoroquinoline **25** (route B, X = leaving group).

— Synthesis of *Fluorinated* Naphthalene Derivatives —



Scheme 11

— Synthesis of 3-*Fluorinated* Quinolines —

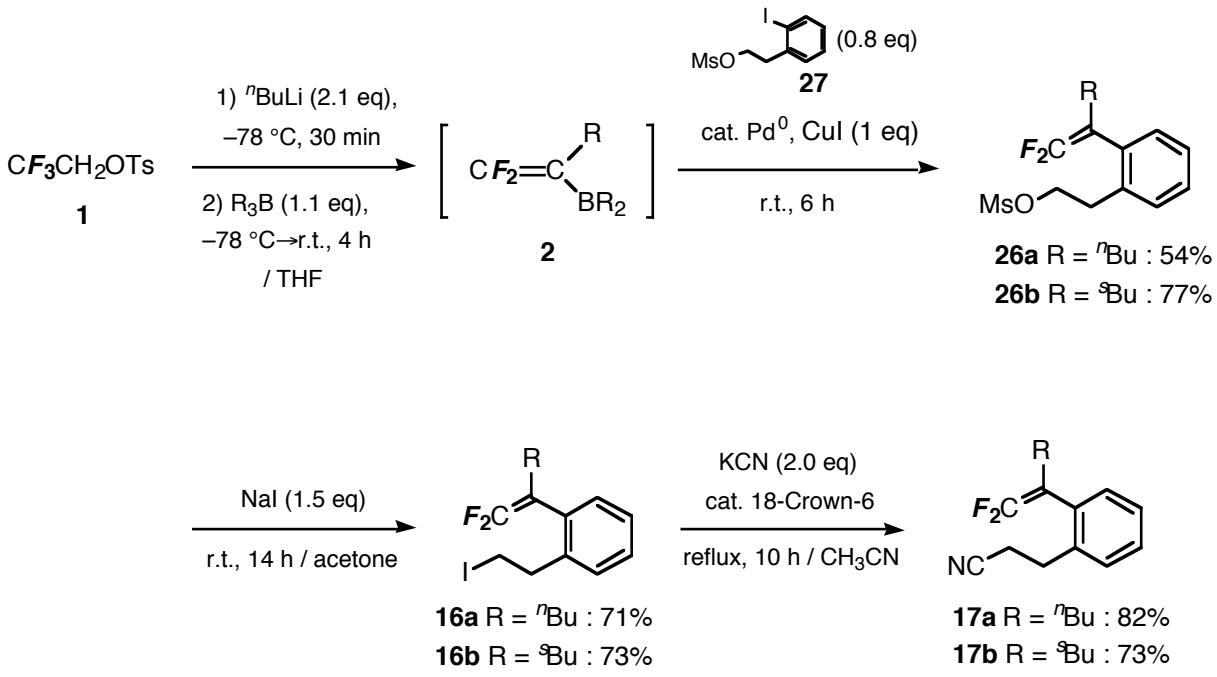


Scheme 12

2.3.1 Preparation of β,β-Difluorostyrenes Bearing an Iodoethyl or a Cyanoethyl Group at the *Ortho* Position

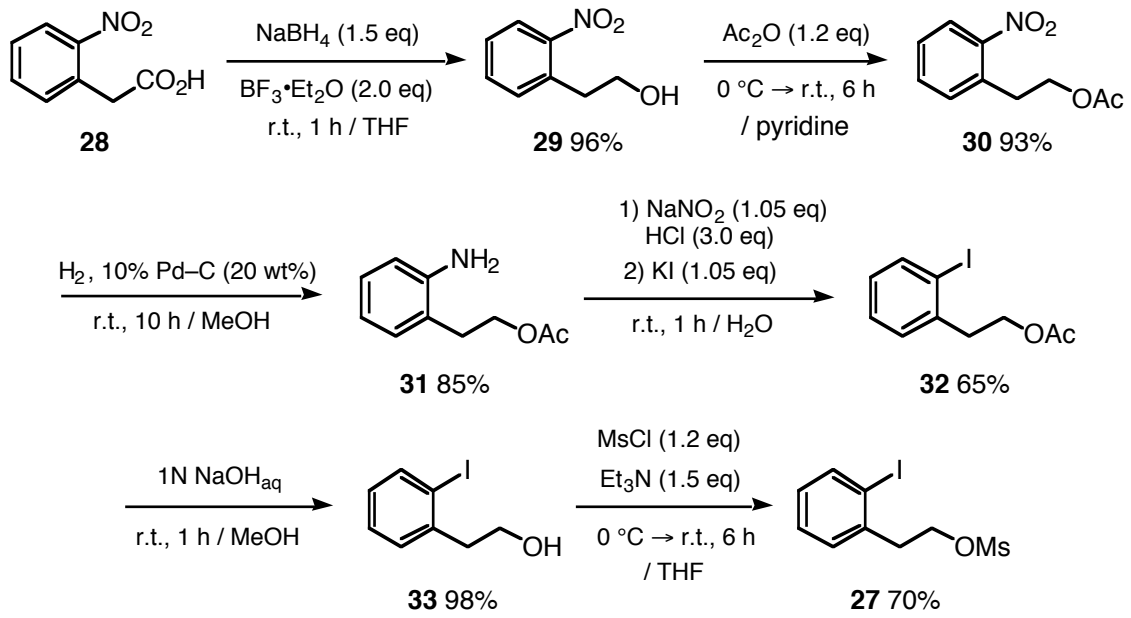
The starting materials, *ortho* substituted β,β-difluorostyrenes **16a**,**b**, **17a**,**b** were derived from the intermediary mesylates **26a**,**b**, which were readily prepared by the coupling

reaction of 2,2-difluorovinylborane **2a**,**b** generated from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) with *o*-iodophenethyl methanesulfonate as described in the previous section. β,β-Difluorostyrenes **16a**,**b** bearing a 2-iodoethyl group at the *ortho* position were prepared by iodination of **26a**,**b** with sodium iodide in 71% and 73% yields. Thus obtained **16a**,**b** were further transformed into β,β-difluorostyrenes **17a**,**b** bearing a 2-cyanoethly group *via* substitution with potassium cyanide and a catalytic amount of 18-crown-6 in 82% and 77% yields (Scheme 13).



Scheme 13

The aryl iodide used in the coupling reaction yielding **26a**,**b**, *o*-iodophenethyl methanesulfonate **27**[6] was prepared from *o*-nitrophenylacetic acid **28**. Compound **28** was reduced with *in-situ* generated BH_3 to give alcohol **29**, whose acetylation afforded **30**. Acetate **30** was reduced again and the successive iodination *via* the corresponding diazonium salt yielded acetate **32**. Hydrolysis of **32** gave alcohol **33**, which was mesylated to afford *o*-iodophenethyl methanesulfonate **27** (Scheme 14).

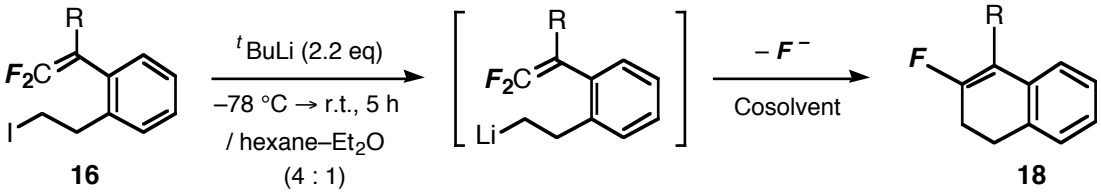


Scheme14

2.3.2 Synthesis of Fluorinated Naphthalene Derivatives

Treatment of β,β-difluorostyrenes **16a**,**b** bearing an iodoethyl group at the *ortho* position with *tert*-butyllithium (^{t}BuLi) generated the corresponding alkyllithium *via* lithium–iodine exchange,[7] which in turn underwent intramolecular substitution of the vinylic fluorine, leading to 3-fluoro-1,2-dihydronaphthalenes **18a**,**b** in excellent yields (Table 8, Entries 1, 4). Whereas polar solvents such as THF and HMPA were added as a cosolvent to promote the substitution of the generated carbanion, these attempts resulted in drastic decreases in yield of **18a** (Entries 2, 3).

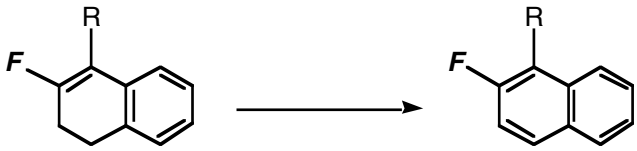
Table 8. Synthesis of 3-Fluoro-1,2-dihydronaphthalenes **18**



Entry	R	Cosolvent	Conditions	Yield / %
1	**^{n}Bu**	———	**–78 °C → r.t., 5 h**	**96 (18a)**
2	^{n}Bu	THF (5)	–78 °C → r.t., 4.5 h	39 (**18a**)
3	^{n}Bu	HMPA (1)	–78 °C → r.t., 2.5 h	32 (**18a**)
4	**^{s}Bu**	———	**–78 °C → r.t., 5 h**	**91 (18b)**

Furthermore, I attempted to convert thus obtained dihydronaphthalenes **18a**,**b** into 2-fluoronaphthalenes **20a**,**b** by dehydrogenation. Compound **18a** was oxidized with tetrachloro-1,4-benzoquinone (chloranil) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). On treatment of **18a**,**b** with 3 equiv of DDQ in refluxing benzene, the reaction proceeded to afford aromatized 2-fluoronaphthalenes **20a**,**b** in a good yields (Table 9, Entries 5, 6).

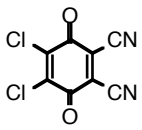
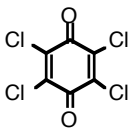
Table 9. Synthesis of 2-Fluoronaphthalenes **20**



18 **20**

Entry	R	Reagent (eq)	Solvent	Conditions	Yield / %	
1	^{n}Bu	10% Pd–C (20 wt%)	diglyme	r.t. → reflux 48 h	trace	**(20a)**
2	^{n}Bu	Chloranil (1.2)	xylene	reflux 6 h	26	**(20a)**
3	^{n}Bu	DDQ (1.2)	benzene	reflux 12 h	35	**(20a)**
4	^{n}Bu	DDQ (2.0)	diglyme	reflux 2 h	43	**(20a)**
5	**^{n}Bu**	**DDQ (3.0)**	**benzene**	**reflux 3 h**	**71 (73)**[a)]	**(20a)**
6	**^{s}Bu**	**DDQ (3.0)**	**benzene**	**reflux 3 h**	**70**	**(20b)**

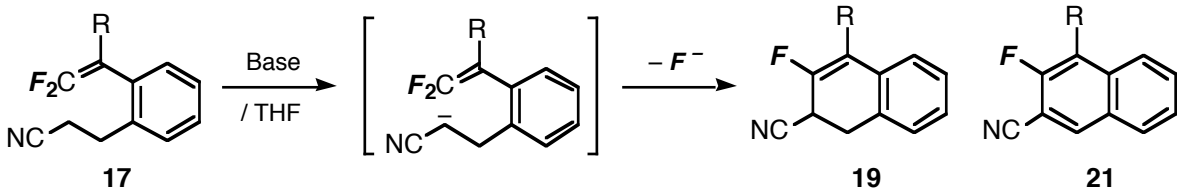
a) ^{19}F NMR yield relative to internal $C_6H_5CF_3$ standard.

DDQ:  Chloranil : 

In the above mentioned reaction, the carbon nucleophile was generated by lithium–iodide exchange. Next, I examined the generation of carbanion *via* abstraction of an α-hydrogen to the cyano group by base.[8] Treatment of difluorostyrene **17a** bearing a cyanoethyl group with 2 equiv of *tert*-butyllithium gave 3-fluoro-1,2-dihydro-2-naphthonitrile **19a** in a 39% yield, while its aromatized product, 3-fluoro-2-naphthonitrile **21a** was obtained in a 47% yield on treatment with 2 equiv of butyllithium (Table 10, Entries 1 and 2). Preventing alkyllithium from attacking at the terminal difluoromethylene carbon or the cyano group, I tried to use 2 equiv of a bulky base such as lithium diisopropylamide (LDA) and lithium hexamethyldisilazide (LHMDS). The latter raised the total yield of **19a** (23%) and **21a** (55%) up to 78% (Table 10, Entry 4). In order to improve the yield of **21a**, oxidative treatment was examined after the cyclization. The crude products including **19a**,**21a**,

19b,**21b** were treated with DDQ under reflux in benzene for 3 h to afford 3-fluoro-2-naphthonitriles **21a**,**b** as a single cyclized products in 68% and 58% yields from **17a**,**b**.

Table 10. Synthesis of Fluoronaphthonitrile Derivatives **19** and **20**



17 **19** **21**

Entry	R	Base (eq)	Conditions	**19** / %	**21** / %
1	^{n}Bu	^{t}BuLi (2.0)	–78 °C → r.t., 5 h	39	3
2	^{n}Bu	^{n}BuLi (2.0)	–78 °C → r.t., 7 h	47	7
3	^{n}Bu	LDA (1.2)	–78 °C → r.t., 11 h	30	41
4	^{n}Bu	LiHMDS (2.0)	–78 °C → r.t., 1 h	23	52
5[a)]	^{n}Bu	**LiHMDS (2.0)**	**–78 °C → r.t., 6 h**	**0**	**68**
6[a)]	^{s}Bu	**LiHMDS (3.0)**	**–78 °C → r.t., 6 h**	**0**	**58**

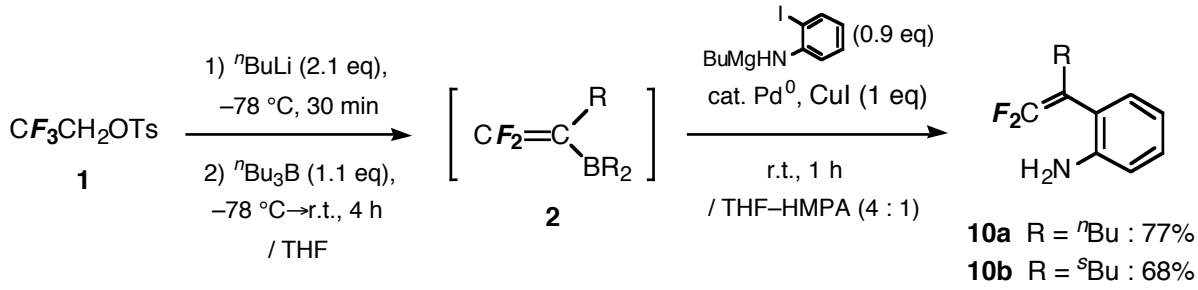
a) The crude products were treated with DDQ (3 eq) in refluxing benzene for 3 h.

2.3.3 Preparation of β,β-Difluorostyrenes Bearing a Cyanomethylamino Group at the *Ortho* Position

After having accomplished the construction of naphthalene framework *via* intramolecular substitution of carbon nucleophiles, I applied this type of cyclization to the synthesis of 3-fluoroquinoline derivatives.

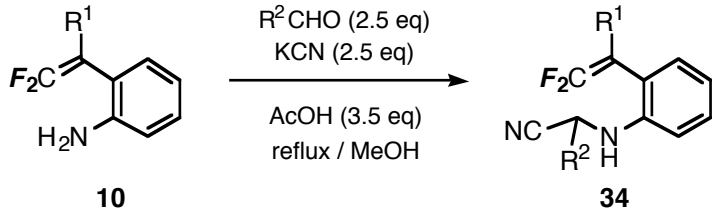
The starting materials for route A, β,β-difluorostyrenes bearing a cyanomethylamino group (X = H) at the *ortho* position, were prepared in one step from aminostyrenes **10**, which were successfully obtained by the direct coupling of 2,2-difluorovinylborane **2** with *N*-butylmagnesio-*o*-iodoaniline generated form *o*-iodoaniline and dibutylmagnesium (Scheme

15). The Strecker reaction of **10** with several aldehydes gave difluorostyrenes **34a–e**, as summarized in Table 11.



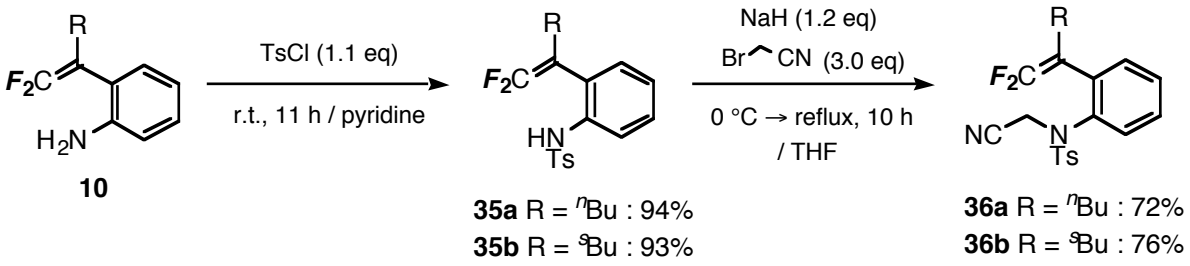
Scheme 15

Table 11. Synthesis of β,β-Difluorostyrenes **34** Bearing a Cyanomethylamino Group



Entry	R^1	R^2	Substrate	Time / h	Yield / %
1	*n*Bu	H	**10a**	8	87 (**34a**)
2	*s*Bu	H	**10b**	7	70 (**34b**)
3	*n*Bu	Ph	**10a**	6	40 (**34c**)
4	*n*Bu	2-furyl	**10a**	7	45 (**34d**)
5	*n*Bu	1-cyclohexenyl	**10a**	4	53 (**34e**)

For the substrate of route B, a tosyl group was selected as a leaving group (X) on the nitrogen atom. Compound **36a** was easily prepared *via* cyanomethylation of sulfonamidestyrene **35a** with bromoacetonitrile and NaH (Scheme 16).

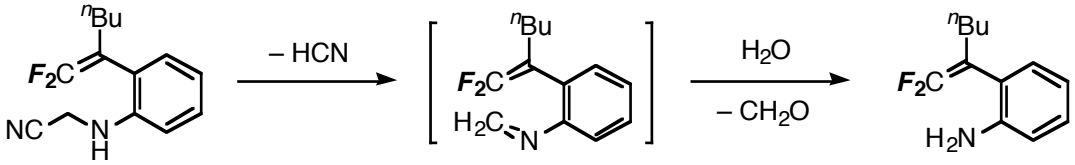


Scheme 16

2.3.4 Synthesis of 3-Fluorinated Quinoline

On treatment of **34a** with 6 equiv of NaH, 3 equiv of LDA, or 6 equiv lithium hexamethyldisilazide (LiHMDS), the attempted synthesis of 3-fluoroquinoline **24a** was unsuccessful, and **10a** was obtained instead (Table 12, Entries 1, 2, 5). It seemed that **34a** underwent the abstraction of the hydrogen on the nitrogen atom and that the loss of HCN followed by hydrolysis of the resulting imine **38** gave **10a** (Scheme 17). Moreover, treatment of 6 equiv of LDA or 2.5 equiv of sodium hexamethyldisilazide (NaHMDS) afforded biquinoline **37a** (Table 12, Entries 3, 4). After many trials of this reaction, I found that treatment with 6 equiv of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) peculiarly promoted the expected intramolecular substitution even at –78 °C to afford **24a** in a 64% yield (Table 12, Entry 8).

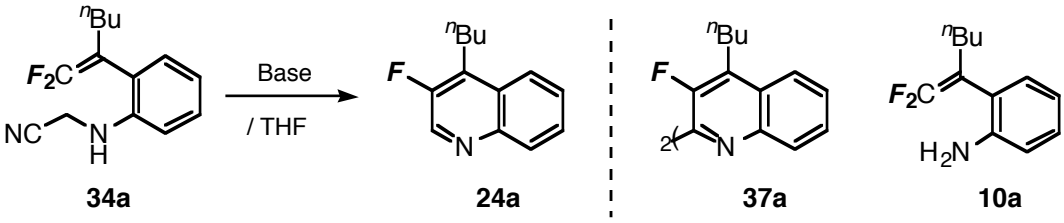
In order to improve the yield of **24a**, I examined the reaction of **34a** in several other solvents under similar conditions. Solvents such as toluene, hexane, and Et_2O, however, gave poor results (Table 13, Entries 1–3). Conducting the reaction at a higher temperature was found to be less effective (Table 13, Entry 4).



34a **38** **10a**

Scheme 17

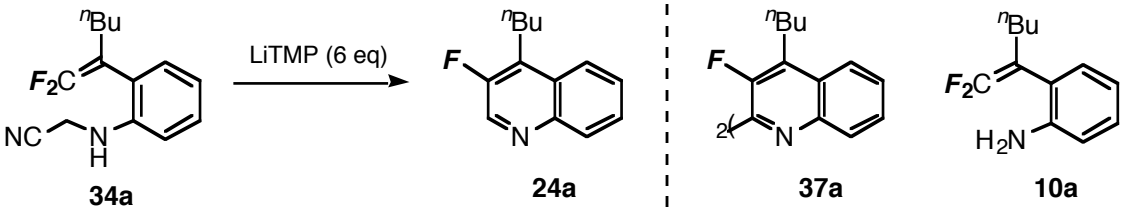
Table 12. Effect of Bases and Its Amount



34a **24a** **37a** **10a**

Entry	Base (equiv)	Conditions	**24a** / %	**37a** / %	**10a** / %
1	NaH (6)	–78 °C → r.t., 24 h	0	0	53
2	LDA (3)	–78 °C, 1 h	0	0	23
3	LDA (6)	–78 °C, 1 h	0	22	0
4	NaHMDS (2.5)	–78 °C, 7 h	0	10	0
5	LiHMDS (6)	–78 °C, 1 h	0	0	45
6	LiTMP (3)	–78 °C, 1 h	0	12	0
7	LiTMP (5)	–78 °C, 1 h	45	0	0
8	**LiTMP (6)**	**–78 °C, 1 h**	**64**	**0**	**0**
9	LiTMP (7)	–78 °C, 1 h	61	0	0

Table 13. Effect of Solvents and Rection Temperature

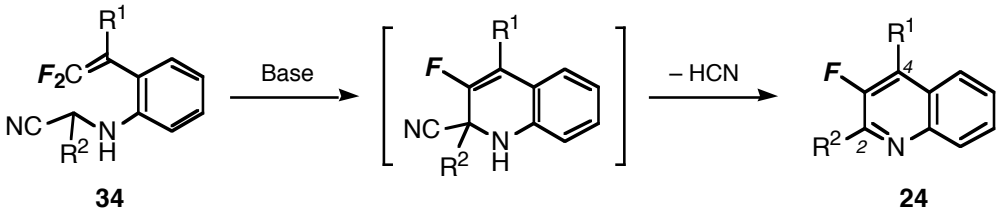


34a **24a** **37a** **10a**

Entry	Solvent	Conditions	**24a** / %	**37a** / %	**10a** / %
1	toluene	–78 °C, 1 h	0	0	29
2	hexane	–78 °C, 1 h	0	16	23
3	Et_2O	–78 °C, 1 h	0	0	18
4	THF	–45 °C, 1 h	41	10	18
5	THF	–78 °C, 1 h	64	0	0

As further examples of the reaction, I also examined the cyclization of difluorostyrene **34b**,**c** under similar conditions. On their treatmnt with 6 equiv of LiTMP, **34b** afforded the expected product **24b**, whereas **34c** gave a complex mixture of products (Table 14, Entries 2, 3). Screening of bases and reaction conditions was conducted again for **34c** to reveal the following fact. When **34c** was treated with 2.1 equiv of NaH in DMF, the intramolecular substitution of the *in-situ* generated carbon nucleophile successfully proceeded to give **43c** in a 81% yield (Table 14, Entry 5). Substrates **34d**,**e** bearing a heteroaryl and an alkenyl groups as R^2 also underwent the cyclization under similar conditions (Table 14, Entries 7, 8).

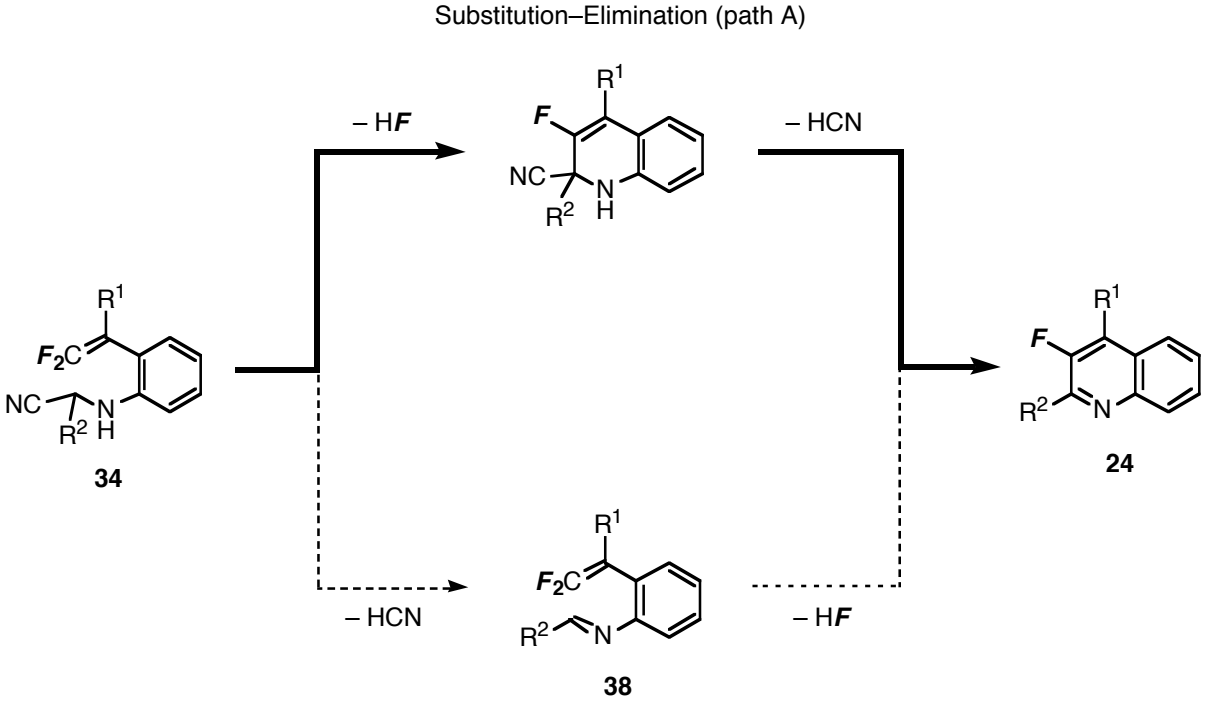
Table 14. Synthesis of 2,4-Disubstituted 3-Fluoroquinolines **24**



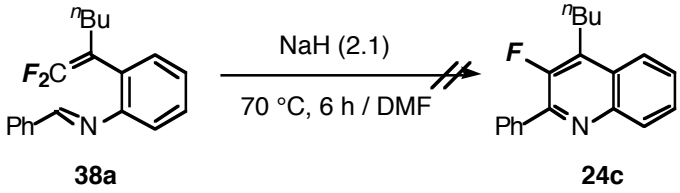
34 **24**

Entry	R^1	R^2	Substrate	Base (eq)	Solvent	Conditions	Yield / %
1	^{n}Bu	H	**34a**	LiTMP (6.0)	THF	–78 °C, 1 h	64 (**24a**)
2	^{s}Bu	H	**34b**	LiTMP (6.0)	THF	–78 °C, 1 h	56 (**24b**)
3	^{n}Bu	Ph	**34c**	LiTMP (6.0)	THF	–78 °C, 1 h	Complex mix.
4	^{n}Bu	Ph	**34c**	NaH (6.0)	DMF	0 °C, 0.5 h	76 (**24c**)
5	^{n}Bu	Ph	**34c**	NaH (2.1)	DMF	0 °C, 1.5 h	81 (**24c**)
6	^{n}Bu	Ph	**34c**	NaH (1.1)	DMF	0 °C → r.t., 24 h	76 (**24c**)
7	^{n}Bu	2-furyl	**34d**	NaH (2.1)	DMF	r.t., 1.5 h	81 (**24d**)
8	^{n}Bu	1-cyclohexenyl	**34e**	NaH (2.1)	DMF	70 °C, 0.5 h	27 (**24e**)

Next I tried to elucidate the reaction pathway of this cyclization. There is one more plausible reaction pathway of elimination–cycloaddition (path B) process other than substitution–elimination process (path A) as depicted in Scheme 18. In order to disprove the existence of path B, I prepared imine **38** from aminostyrene **10a** and benzaldehyde, and subjected it to the reaction conditions (Scheme 19). In this case 3-fluoroquinoline **24c** was not obtained, which result cleanly ruled out the possibility of path B, a 6π–electrocyclization process. Consequently, the cyclization proceeded through substitution for the fluorine and elimination of HCN (path A).



Scheme 18

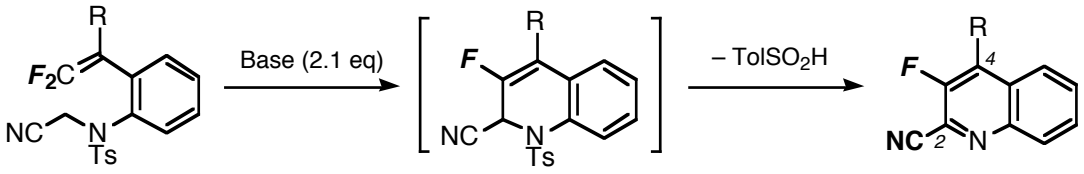


Scheme 19

In order to synthesize 3-fluoroquinolines functinalized at the 2-position, I next tried to suppress elimination of the cyano group, which is easily converted into other functional groups such as carboxy and aminomethyl groups. I introduced a tosyl group on the nitrogen atom of difluorostyrene **36a** as a leaving group instead of the cyano group. Treatment of **36a** with 2.1 equiv of NaH in DMF at room temperature promoted intramolecular substitution of the carbon nucleophile for the fluorine and successive elimination of toluenesulfinic acid, leading to the desired 2-cyano-3-fluoroquinoline **25a** (Table 15, Entry 1). After screening of the reaction conditions such as bases and solvents, I found that **36a** smoothly underwent the two processes to afford **25a** in a 85% yield on treatment with 2.1 equiv of K_2CO_3 in DMF

(Table 15, Entry 4).

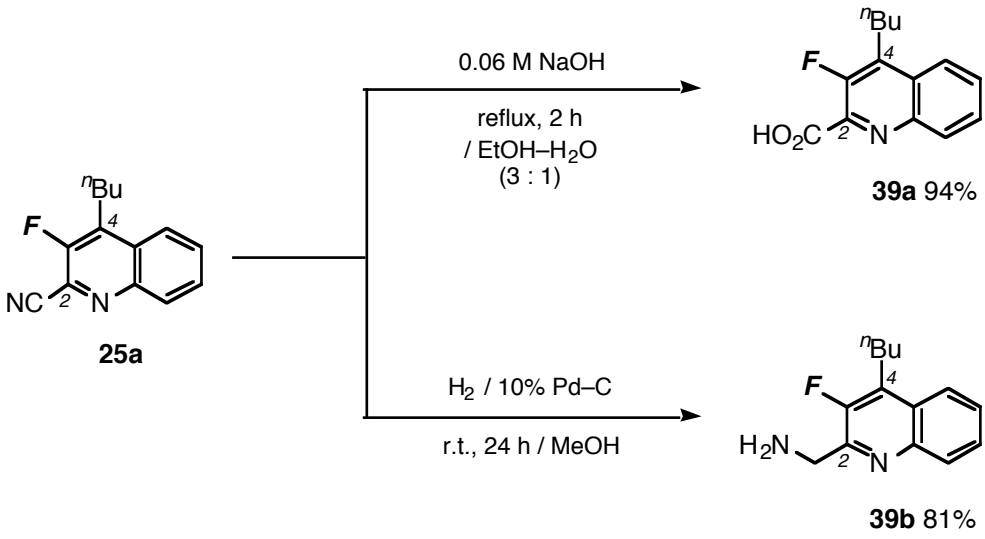
Table 15. Synthesis of 2-Cyano-3-fluoroquinolines **25**



36 **25**

Entry	R	Base	Solvent	Conditions	Yield / %
1	^{n}Bu	NaH	DMF	r.t., 7 h	57 (**25a**)
2	^{n}Bu	NaH	DMF	50 °C, 3 h	75 (**25a**)
3	^{n}Bu	NaH	DMF	70 °C, 2 h	64 (**25a**)
4	**^{n}Bu**	**K_2CO_3**	**DMF**	**50 °C, 7 h**	**85** (**25a**)
5	^{n}Bu	K_2CO_3	DMSO	50 °C, 7 h	70 (**25a**)
6	^{n}Bu	K_2CO_3	DMPU	50 °C, 5 h	70 (**25a**)
7	**^{s}Bu**	**K_2CO_3**	**DMF**	**50 °C, 7 h**	**79** (**25b**)

After having obtained 2-cyano-3-fluoroquinolines **25**, I attempted the transformation of the cyano group into carboxy and aminomethyl groups. On treatment of **25a** with aqueous NaOH, hydrolysis of the cyano group selectively occurred without the loss of fluorine to afford **39a** in an excellent yield (Scheme 20). Moreover, hydrogenation of **25a** in methanol in the presence of palladium on activated carbon successfully reduced the cyano group to give the **39b** bearing an aminomethyl group at the 2-position in a high yield (Scheme 20). Thus obtained functionalized 3-fluoroquinolines **39a**,**b** are attractive compounds as synthetic intermediates, because of the carboxy and the amino groups, which allow to introduce the fluoroquinoline moiety into molecules.

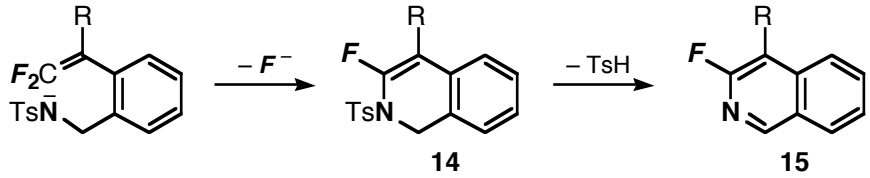

0.06 M NaOH
reflux, 2 h
/ EtOH–H2O
(3 : 1)
nBu
F
4
NC
2
N
25a
HO2C
39a 94%
H2 / 10% Pd–C
r.t., 24 h / MeOH
H2N
39b 81%

Scheme 20

2.4 Cyclization of β,β-Difluorostyrenes Bearing an sp^2 Nitrogen Nucleophile Linked by a Carbon or a Nitrogen Spacer to the *Ortho* Position

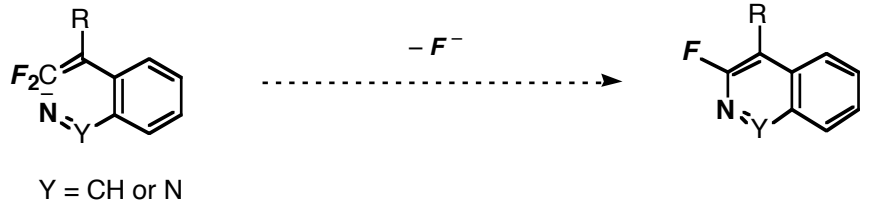
As described in Section 2.2, β,β-difluorostyrenes bearing a nucleophilic sp^3 nitrogen linked by a methylene unit to the *ortho* carbon readily undergo intramolecular cyclization and aromatization, leading to 3-fluoroisoquinolines **15** in excellent yields (Scheme 21). In this reaction, aromatization was effected by a loss of sulfinic acid after the substitution of the nitrogen. For the direct construction of aromatic rings, I next investigated a similar replacement of the vinylic fluorine by sp^2 nitrogens such as imino and diazenyl nitrogens, which would provide an access to 3-fluorinated isoquinoline and cinnoline frameworks, respectively (Scheme 22).

— Intramolecular Substitution of **sp^3** Nitrogen —



Scheme 21

— Intramolecular Substitution of **sp^2** Nitrogen —



Y = CH or N

Scheme 22

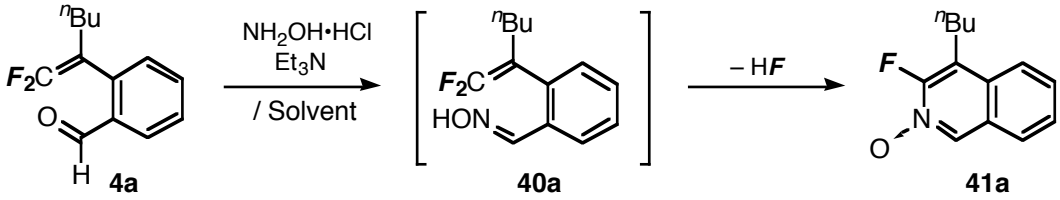
2.4.1 Synthesis of 3-Fluorinated Isoquinoline *N*-Oxides

At first oxime was adopted as an imino group of the intramolecular nitrogen nucleophile in β,β-difluorostyrenes. For the purpose of preparing the starting β,β-difluorostyrenes with an oxime moiety at the *ortho* position, β,β-difluoro-*o*-formylstyrene

4a was treated with 1.0 equiv of hydroxylamine hydrochloride (NH_2OH•HCl) in the presence of 1.0 equiv of triethylamine (Et_3N). Unexpectedly, the reaction directly afforded 3-fluoroisoquinoline *N*-oxide **41a** rather than the expected oxime **40a** (Table 16, Entry 1). This result suggests that β,β-difluoro-*o*-formylstyrene **4a** was initially converted into oxime **40a**, which in turn readily underwent cyclization *via* substitution of the oxime nitrogen for the fluorine, followed by deprotonation on the oxygen to provide isoquinoline *N*-oxide **41a**.

In order to raise the yield of **41a**, screening of the amount of NH_2OH•HCl and Et_3N was then conducted in THF and DMF. Treatment of **4a** with 1.2 equiv of NH_2OH•HCl and 2.4 equiv of Et_3N in THF gave a 50% yield of **41a**. Conducting the reaction by using 1.2 equiv of NH_2OH•HCl and 2.2 equiv of Et_3N in DMF was found to raise the yield of **41a** up to 64% (Table 16, Entry 5).

Table 16. Effect of the Amount of NH_2OH•HCl and Et_3N

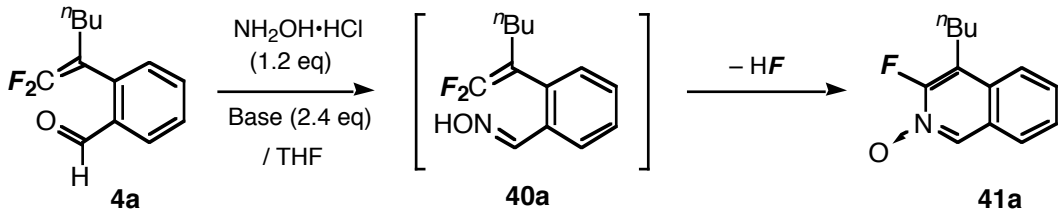


Entry	NH_2OH•HCl (eq)	Et_3N (eq)	Solvent	Conditions	Yield / %
1	1.0	1.0	THF	r.t., 17 h	29
2	1.2	2.4	THF	r.t., 10 h	50
3	3.0	4.4	THF	r.t., 12 h	37
4	1.0	2.0	DMF	r.t., 15 h	54
5	**1.2**	**2.2**	**DMF**	**r.t., 11 h**	**64**
6	1.2	2.4	DMF	r.t., 12 h	52
7	1.2	4.4	DMF	r.t., 12 h	52

To prevent the nucleophilic attack of the Et_3N to the terminal vinylic carbon, I conducted the reaction by using bases with a lower nucleophilicity than that of Et_3N.

Pyridine and $^{i}Pr_2NEt$ were, however, found to be less effective (Table 17, Entries 2–4).

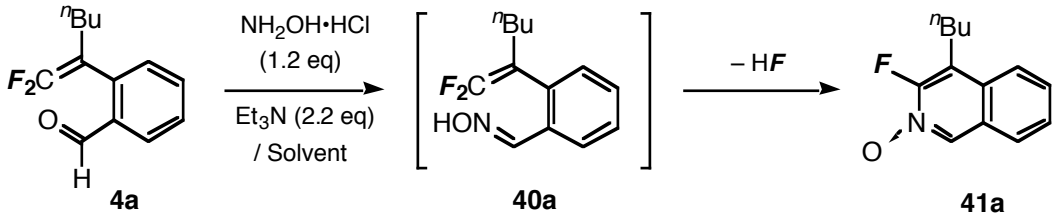
Table 17. Effect of Bases



Entry	Base	Conditions	Yield / %
1	Et_3N	r.t., 10 h	50
2	pyridine	r.t., 13 h	47
3	$^{i}Pr_2NEt$	r.t., 13 h	43
4	HMPA	r.t., 10 h	N.R.

Moreover, I examined the reaction of **4a** in several other solvents under similar conditions. Whereas solvents such as benzene and EtOH gave poor results (Table 18, Entries 2 and 3), DMF–H_2O (10:1) mixed solvent improved the yield of 3-fluoroisoquinoline *N*-oxide **41a** up to 67% (Entry 8).

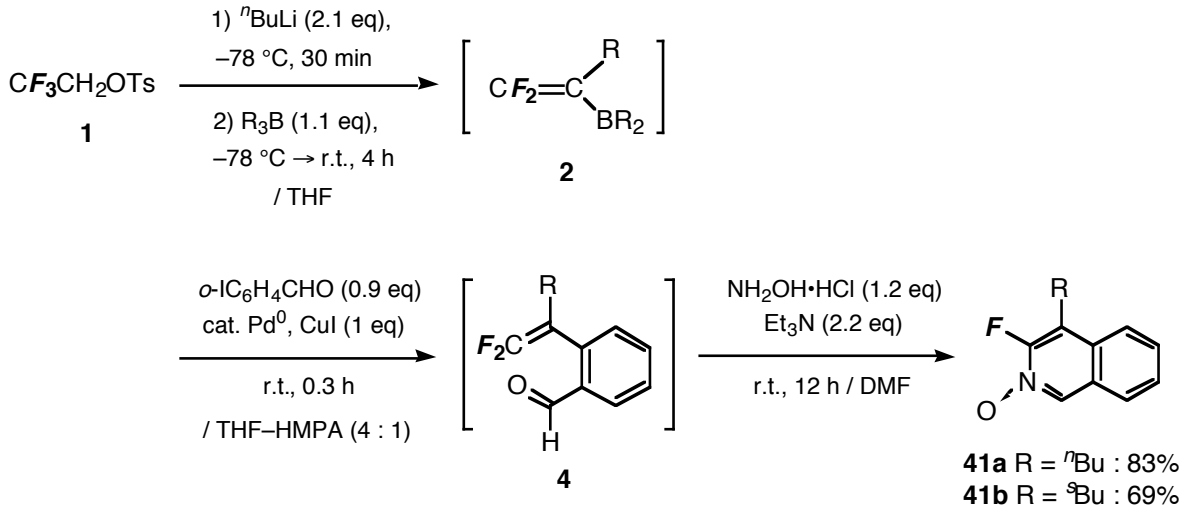
Table 18. Effect of Solvents



Entry	Solvent	Conditions	Yield / %
1	THF	r.t., 16 h	17
2	benzene	r.t., 11 h	20
3	EtOH	r.t., 12 h	27
4	CH_3CN	r.t., 10 h	49
5	DMSO	r.t., 9 h	53
6	CH_2Cl_2	r.t., 15 h	62
7	DMF	r.t., 11 h	64
8	**DMF–H_2O (10:1)**	**r.t., 9 h**	**67**

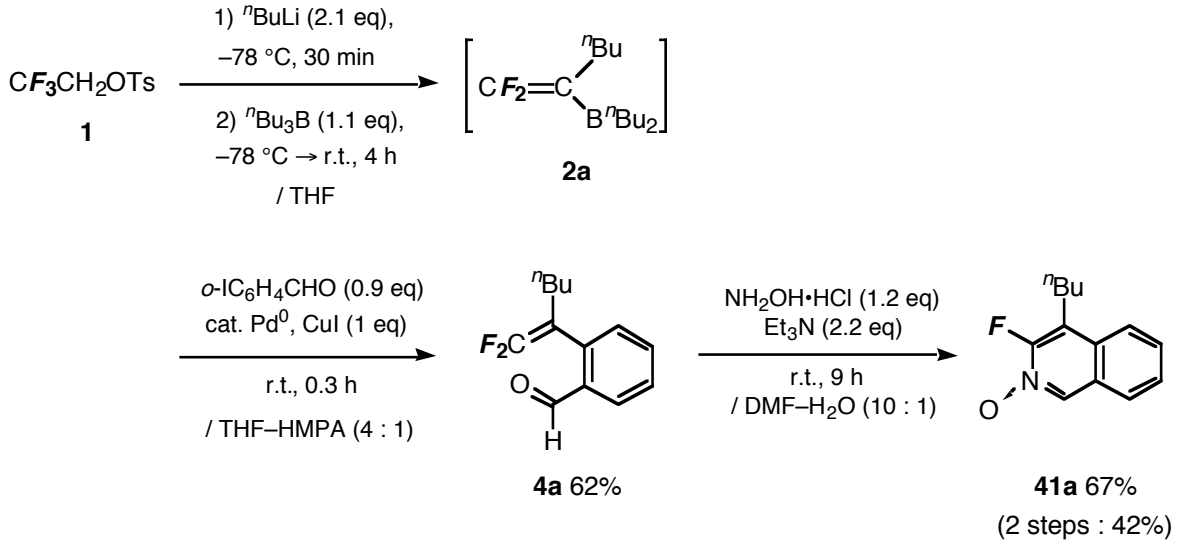
Although this cyclization afforded **41a** in a good yield, there was a drawback in the thermal stability of the starting material, *o*-formylstyrene **4a** as described in Subsection 2.2.1: the coupling reaction of 2,2-difluorovinylborane **2a** (generated from **1**) with *o*-iodobenzaldehyde afforded **4a** in a 84% yield determined by ^{19}F NMR, while the isolated yield was reduced to 62%. Then, I tried to combine the coupling reaction (**1**→**4**) and the cyclization (**4**→**41**) into one-pot operation without isolation of unstable **4**, which process could refine the synthesis of **41**. After the coupling reaction of borane **2a**,**b** with *o*-iodobenzaldehyde in THF and successive removal of the solvent, the residues were treated with 1.2 equiv of NH_2OH•HCl and 2.2 equiv of Et_3N in DMF, leading to **41a**,**b** in 83% and 69% yields from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**), respectively (Scheme 23). This sequence provides a more efficient route to 3-fluoroisoquinoline *N*-oxide **41**, compared to the above mentioned two-pot process (total yield of **41a** from **1**: 42%) as shown in Scheme 24.

— *One*-pot Process —



Scheme 23

— *Two*-pot Process —

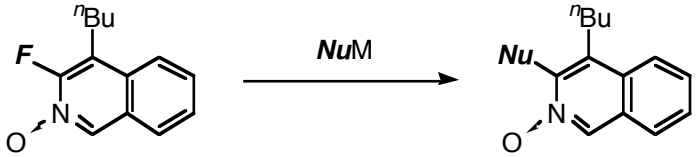


Scheme 24

The remaining fluorine in **41** was expected to be quite reactive toward replacement by heteroatom nucleophiles *via* similar addition–elimination processes,[9] which allows the introduction of another substituent into isoquinoline framework. Initially I attempted the reaction of **41a** with oxygen and sulfur nucleophiles. On treatment of **41a** with *tert*-butoxide

(^{t}BuOK) or lithium benzenethiolate (PhSLi) as a nucleophile in THF, the expected substitution of the fluorine proceeded smoothly to give the corresponding isoquinoline *N*-oxide **42a** or **42b** bearing an oxygen or a sulfur functional group at the 3-position (Table 19, Entries 1 and 2). A nitrogen nucleophile also brought about a similar substitution even under less basic conditions as shown in Entry 3. Thus, this reaction provides a versatile method for the synthesis of 3,4-disubstituted isoquinoline *N*-oxides **42** in combination with the ring-formation starting from **1**.

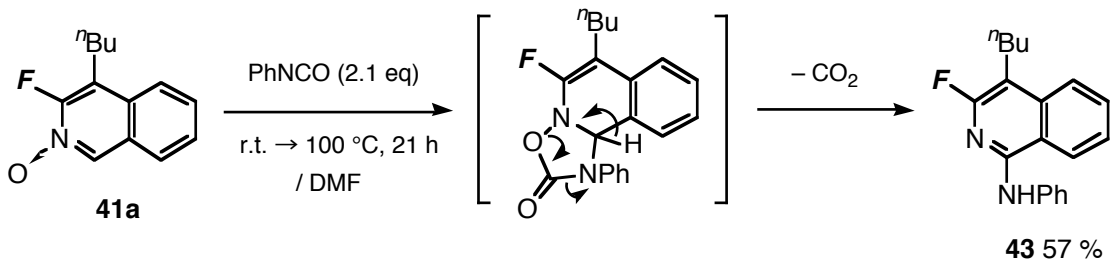
Table 19. Introduction of a Substituent at the 3-Position of **41a**



41a **42**

Entry	NuM (eq)	Solvent	Conditions	Yield / %
1	^{t}Bu**O**K (1.5)	THF	–78 °C, 0.5 h	**72** (**42a**)
2	Ph**S**Li (1.2)	THF	–78 → 0 °C, 5 h	**85** (**42b**)
3	 (4.1)	toluene	reflux, 23 h	**74** (**42c**)

In addition, the cycloaddition of **41a** was attempted by using phenylisocyanate (PhNCO) as a dipolarophile, because it is well known that isoquinoline *N*-oxides act as 1,3-dipoles. On treatment of **41a** with PhNCO in DMF, the expected reaction proceeded along with decarboxylation to give 3-fluoroquinoline **43** bearing a phenylamino group at the 1-position (Scheme 25).

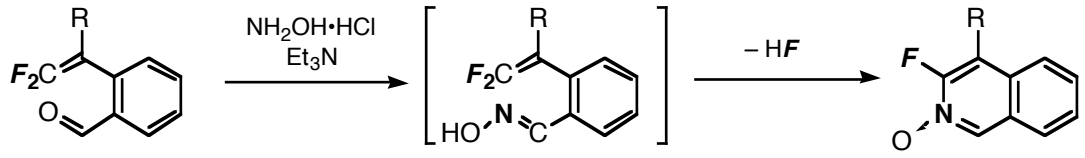


Scheme 25

2.4.2 Synthesis of 3-Fluorinated Cinnolines

In Subsection 2.4.1 it was demonstrated that the direct construction of isoquinoline framework is successfully achieved by intramolecular substitution of the imino nitrogen (-**N**=CH-) for the vinylic fluorine in **40** (Scheme 26). By means of this strategy for heteroaromatic ring formation, I next investigated the intramolecular substitution of a diazenyl nitrogen (-**N**=N-), where the imino carbon (-N=**CH**-) was replaced by a nitrogen atom. A similar reaction of β,β-difluorostyrenes **45** bearing an diazenyl group at the *ortho* position would provide 3-fluorinated cinnolines **46** (Scheme 27). Furthermore, the intermediary diazene **45** was expected to be easily derived from the corresponding arenediazonium salt **44** *via* its site-selective and partial reduction. On the basis of these considerations, I chose the β,β-difluorostyrenes **10** bearing an amino group at the *ortho* position as precursors of 3-fluorocinnolines **46**. (Scheme 15).

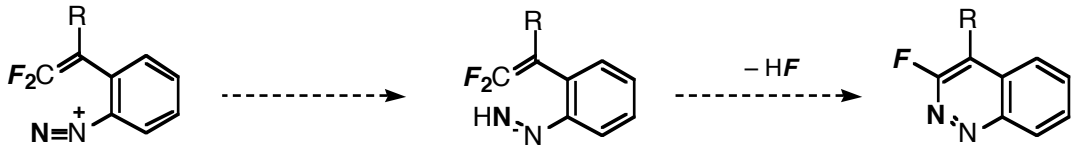
— Intramolecular Substitution of ***Imino*** Nitrogen —



4 **40** **41**

Scheme 26

— Intramolecular Substitution of ***Diazenyl*** Nitrogen —

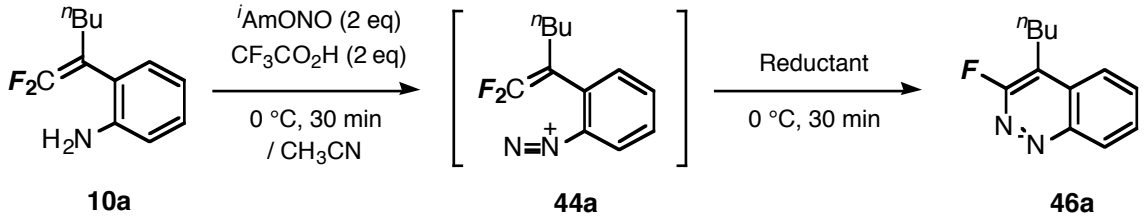


44 **45** **46**

Scheme 27

Aminostyrene **10a** was treated with isoamyl nitrite (^{i}AmONO) and trifluoroacetic acid (CF_3CO_2H) for diazotization of the amino group, and then successively treated with sodium sulfite (Na_2SO_3) for reduction of the generated diazonium cation.[10] The expected intramolecular substitution of the terminal diazenyl nitrogen smoothly proceeded to give 3-fluorocinnoline **46a** in 37% yield (Table 20, Entry 1). Then, I tried several other reducing agents, and found that CH_3COSH raised the yield of 3-fluorocinnoline **46a** up to 77% (Table 9, Entry 4).

Table 20. Syntesis of 3-Fluorocinnoline **46a**



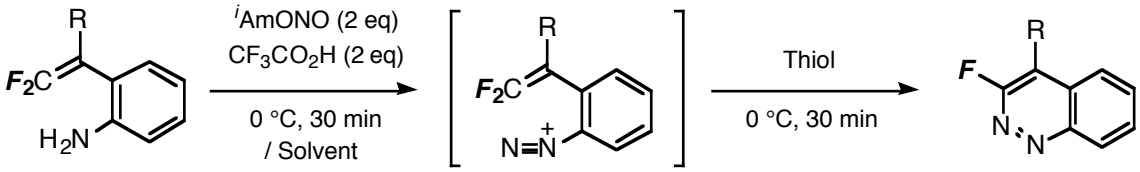
10a **44a** **46a**

Entry	Reductant (Reductant/**10a**)		Yield / %
1	Na_2SO_3	(5)	37
2	Et_3SiH	(3)	Complex mixture
3	$^nBu_3SnH$	(3)	58
4	$CH_3C(O)SH$	(3)	77

Based on the results obtained above, further screening of thiols as reducing agents was performed.[11] The results are summarized in Table 21. Treatment of *in-situ* generated diazonium salt **44a**,**b** with benzenethiol (PhSH) successfully promoted the cyclization to afford 3-fluorocinnolines **46a**,**b** in 88% and 87% yields, respectively (Table 21, Entries 3 and 12). In the case of Entry 3, diphenyl disulfide (PhSSPh) was obtained in 90% yield based on benzenthiol, which evidence implied that benzenthiol acted as a reducing agent.

On the other hand, alkanethiols and sodium methanethiolate (MeSNa) acted as nucleophiles toward **44a** to give the corresponding sulfide **47a–c** *via* replacement as shown in Entries 9–11. This sulfur-containing compound **47a** turns out to be a starting material for the synthesis of 2-fluorobenzo[*b*]thiophene, which is described in Chapter 3.

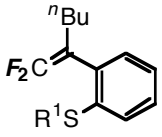
Table 21. Effect of Thiol and Solvents



10 **44** **46**

Entry	R	Substrate	Thiol (thiol/**10a**)	Solvent	Yield / %
1	^{n}Bu	**10a**	CH_3COSH (3)	CH_3CN	77 (**46a**)
2	^{n}Bu	**10a**	PhSH (2)	CH_3CN	50 (**46a**)
3	**^{n}Bu**	**10a**	**PhSH (3)**	**CH_3CN**	**88 (46a)**
4	^{n}Bu	**10a**	PhSH (4)	CH_3CN	87 (**46a**)
5	^{n}Bu	**10a**	*p*-Cl-PhSH (3)	CH_3CN	84 (**46a**)
6	^{n}Bu	**10a**	*p*-^{t}BuPhSH (3)	CH_3CN	69 (**46a**)
7	^{n}Bu	**10a**	PhSH (3)	$CHCl_3$	62 (**46a**)
8	^{n}Bu	**10a**	PhSH (3)	AcOEt	87 (**46a**)
9	^{n}Bu	**10a**	MeSNa (3)	CH_3CN	0[a)]
10	^{n}Bu	**10a**	EtSH (3)	CH_3CN	0[a)]
11	^{n}Bu	**10a**	^{t}BuSH (3)	CH_3CN	0[a)]
12	**^{s}Bu**	**10b**	**PhSH (3)**	**CH_3CN**	**87 (46b)**

a) Sulfide **47** was obtained.



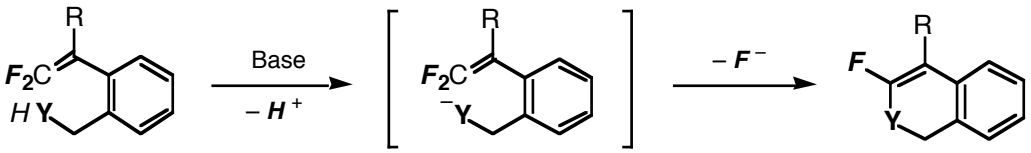
47

47a R^1 = Me : 67%
47b R^1 = Et : 53%
47c R^1 = ^{t}Bu : 50%

2.5 Cyclization of β,β-Difluorostyrenes Bearing an sp^2 Nitrogen or Carbon Nucleophle generated from an Unsaturated Functional Group at the *Ortho* Position

In Sections 2.2 and 2.3 was demonstrated intramolecular substitution of the nucleophiles generated by deprotonation of active hydrogen with one exception of lithium–iodine exchange (Scheme 28). Next, I investigated another method for the generation of intramolecular nucleophiles, that is, addition of external anionic nucleophiles to unsaturated functional groups such as cyano and isocyano groups. The *in-situ* generated nucleophiles would undergo similar cyclizations as mentioned above, which sequence allows the construction of ring-fluorinated isoquinolines and quinolines accompanied by introduction of a substituent on the ring (Scheme 29). In this scheme the external nucleophile should exclusively add to the unsaturated functional group (Y≡X-) without attacking at the terminal difluoromethylene carbon despite being also reactive toward nucleophiles.

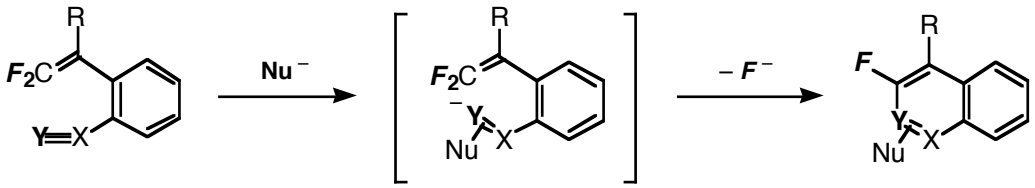
— Deprotonation —



Y = O, S, N, C

Scheme 28

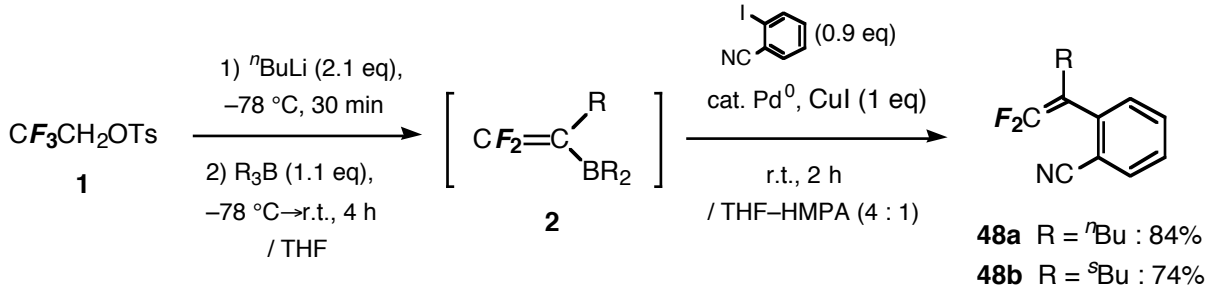
— Nucleophilic Attack to Unsaturated Functional Group —



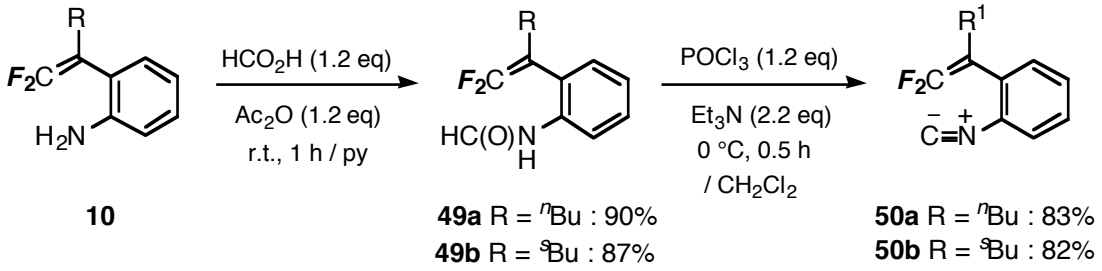
Scheme 29

2.5.1 Preparation of β,β-Difluorostyrenes Bearing a Cyano or an Isocyano Group at the *Ortho* Position

The substrates, β,β-difluorostyrenes bearing a cyano or an isocyano group at the *ortho* position were prepared as follows. *o*-Cyanostyrenes **48** were directly obtained from tosylate **1** *via* the cross–coupling reaction of 2,2-difluorovinylborane **2** with *o*-iodobenzonitrile in good yields (Scheme 30). *o*-Isocyanostyrenes **50** were prepared as depicted in Scheme 31. Aminostyrenes **10** obtained above were subjected to formylation of the nitrogen followed by dehydration of its product, formamides **49** to give the desired *o*-isocyanostyrenes **50** in high yields.



Scheme 30



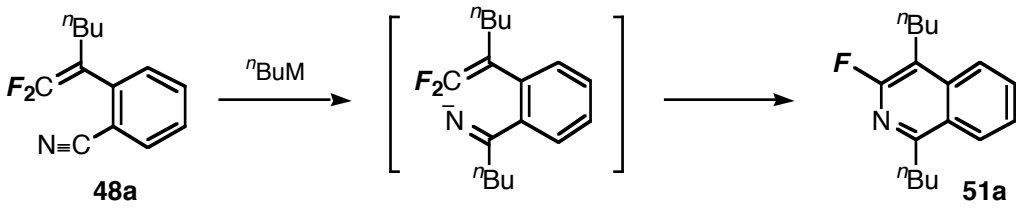
Scheme 31

2.5.2 Synthesis of 3-Fluorinated Isoquinolines

I firstly attempted the cyclization of *o*-cyanostyrene **48a** along with introduction of a substituent. When **48a** was treated with ^{n}BuMgBr, its attack to the cyano carbon generated

the corresponding imino nitrogen nucleophile, which in turn underwent intramolecular substitution to give the expected 3-fluoroisoquinoline **51a** in a 43% yield (Table 22, Entry 1). Treatment of **48a** with ^{n}BuLi/$CeCl_3$, effective reagents for 1,2-addition to α,β-unsaturated ketones, afforded **51a** in a 62% yield (Table 22, Entry 2). Moreover, the reaction of **48a** with ^{n}BuLi was examined in several solvents under similar conditions. It was found that the addition of ^{n}BuLi to **48a** regioselectively occurred at the cyano carbon in Et_2O. The generated nitrogen anion promoted the intramolecular substitution to afford **51a** in a high yield (Table 22, Entry 4).

Table 22. Effect of Carbon Nucleophiles and Solvents

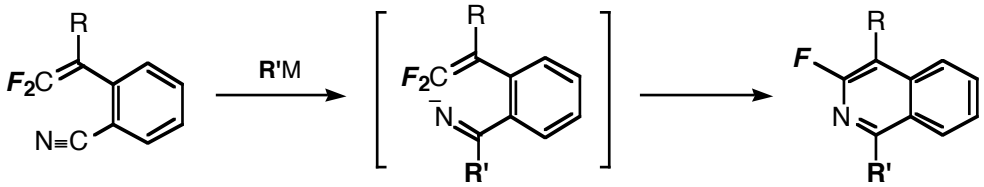


Entry	^{n}BuM (eq)	Solvent	Conditions	Yield / %
1	^{n}BuMgBr (11.2)	THF	–78 °C → reflux, 26 h	43
2	^{n}BuLi / $CeCl_3$ (3.0)	THF	–78 °C, 3 h	62
3	^{n}BuLi (1.2)	THF	–78 °C, 4 h	74
4	**^{n}BuLi (1.2)**	**Et_2O**	**–78 °C, 0.5 h**	**86**
5	^{n}BuLi (1.2)	hexane	–78 °C, 1 h	72
6	^{n}BuLi (1.2)	toluene	–78 °C, 1 h	82

Under the reaction conditions obtained above, I also examined the reaction of other nucleophiles such as methyllithium, phenyllithium, and diisobutylaluminum hydride. As summarized in Table 23, treatment of **48a** with these nucleophiles successfully gave rise to the cyclization to afford 3-fluoroisoquinolines **51a–e** bearing a methyl, a phenyl, and a hydrogen at the 2-position in high yields. Thus, this sequence provides a facile access to

1,4-disubstituted 3-fluoroisoquinolines.

Table 23. Synthesis of 1,4-Disubstituted 3-Fluoroisoquiolines **51**



48a **51**

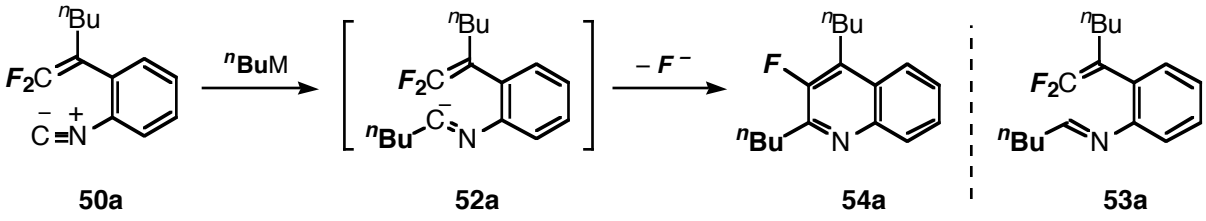
Entry	R	R'M (eq)	Solvent	Conditions	Yield / %
1	^{n}Bu	**^{n}Bu**Li (1.2)	Et_2O	–78 °C, 0.5 h	86 (**51a**)
2	^{n}Bu	**^{n}Bu**Li (1.2)	toluene	–78 → –45 °C, 0.8 h	84 (**51a**)
3	^{s}Bu	**^{n}Bu**Li (1.2)	Et_2O	–78 °C, 7 h	81 (**51b**)
4	^{n}Bu	**Me**Li (1.2)	Et_2O	0 °C, 0.2 h	80 (**51c**)
5	^{n}Bu	**Me**Li (1.2)	toluene	0 °C, 0.5 h	81 (**51c**)
6	^{n}Bu	**Ph**Li (1.2)	Et_2O	–78 °C, 0.3 h	81 (**51d**)
7	^{n}Bu	**Ph**Li (1.2)	toluene	–78 °C, 1 h	85 (**51d**)
8	^{n}Bu	**H**Al^{i}Bu$_2$ (1.05)	toluene	–45 °C, 10 min → 90 °C,7 h	84 (**51e**)

2.5.3 Synthesis of 3-Fluorinated Quinolines

After having accomplished the construction of isoquinoline framework as described in Subsection 2.5.2, I tried to construct the framework of quinoline,[12] a regioisomer of isoquinoline by means of a similar strategy. For that purpose an isocyano group instead of a cyano group should be introduced at the *ortho* position of β,β-difluorostyrenes. The reaction of *o*-isocyanostyrenes would proceed in a similar manner *via* the corresponding carbanion to provide 3-fluoroquinoline bearing a substituent at the 2-position. On the basis of these considerations, I treated isocyanostyrene **50a** with 1.2 equiv of ^{n}BuLi, which resulted in a failure probably due to its high nucleophilicity. Then I examined the cyclization of **50a** by employing nucleophiles with a lower nucleophilicity such as cuprates and Grignard reagents.

While the desired initial attack was not observed in the case of ^{n}BuCu(CN)Li (Table 24, Entry 2), ^{n}BuMgBr afforded imine **53a**, the protonated product of the expected carbanion **52a**. After screening of solvents in the reaction of **50a** with ^{n}BuMgBr, I found that the yield of imine **53a** was raised up to 73% by conducting the reaction in toluene (Table 24, Entry 5). This result indicated that the addition of Grignard reagent to the isocyano carbon selectively proceeded in a good yield. In order to promote the cyclization of intermediate **52a**, HMPA was added to the reaction mixture after its generation was complete, leading to the desired 3-fluoroquinoline **54a** in a 69% isolated yield (Table 24, Entry 6).

Table 24. Effect of Counter Cation and Solvents



50a **52a** **54a** **53a**

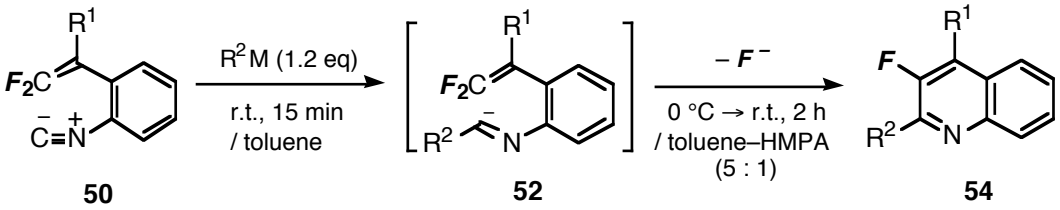
Entry	^{n}BuM (equiv)	Solvent	Conditions	**54a** / %	**53a** / %
1	^{n}BuLi (1.2)	THF	–78 °C → r.t., 2 h	complex mixture	
2	$^{n}Bu_2Cu(CN)Li_2$ (1.5)	THF	–78 °C → r.t., 5 h	no reaction	
3	^{n}BuMgBr (1.2)	THF	–78 °C → r.t., 7 h	0	10
4	^{n}BuMgBr (1.2)	Et_2O	–78 °C → r.t., 4 h	0	16
5	^{n}BuMgBr (1.2)	toluene	–78 °C → r.t., 0.8 h	0	73
6	**^{n}BuMgBr** (1.2)	**toluene–HMPA**[b] **(5 : 1)**	**0 °C → r.t., 2.3 h**	**69 (72)**[a]	0

a) Determined by ^{19}F-NMR

b) HMPA was added at 0 °C after the generation of **52a**.

Several other 2,4-disubstituted 3-fluoroquinolines **54b–e** were successfully synthesized on treatment of isocyanostyrenes **50a**,**b** with primary, secondary, and tertiary alkyl metals such as EtMgBr, ^{i}PrMgCl, and ^{t}BuLi. The results are summarized in Table 25.

Table 25. Synthesis of 2,4-Disubstituted 3-Fluoroquinolines **54**

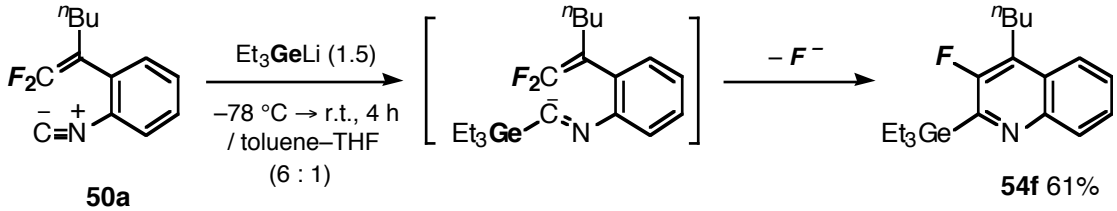


50 **52** **54**

Entry	R^1	Substarate	R^2M	Yield / %[a]	
1	^{n}Bu	**50a**	^{n}**Bu**MgBr	69 (72)	(**54a**)
2	^{s}Bu	**50b**	^{n}**Bu**MgBr	62 (65)	(**54b**)
3	^{n}Bu	**50a**	**Et**MgBr	59 (62)	(**54c**)
4	^{n}Bu	**50a**	^{i}**Pr**MgCl	64	(**54d**)
5	^{n}Bu	**50a**	^{t}**Bu**Li	71	(**54e**)

a) ^{19}F NMR yield is given in parentheses.

I also examined similar cyclizations of **50** with germanium, silicon, and tin nucleophiles as homologous series of carbon nucleophiles. On treatment of **50a** with triethylgermyllithium[13] (prepared *in-situ* from triethylgermanium hydride, *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA), and *tert*-butyllithium), the corresponding carbanion was generated to cause replacement of the vinylic fluorine, leading to 3-fluoroquinoline **54f** bearing a germyl group at the 2-position (Scheme 32).

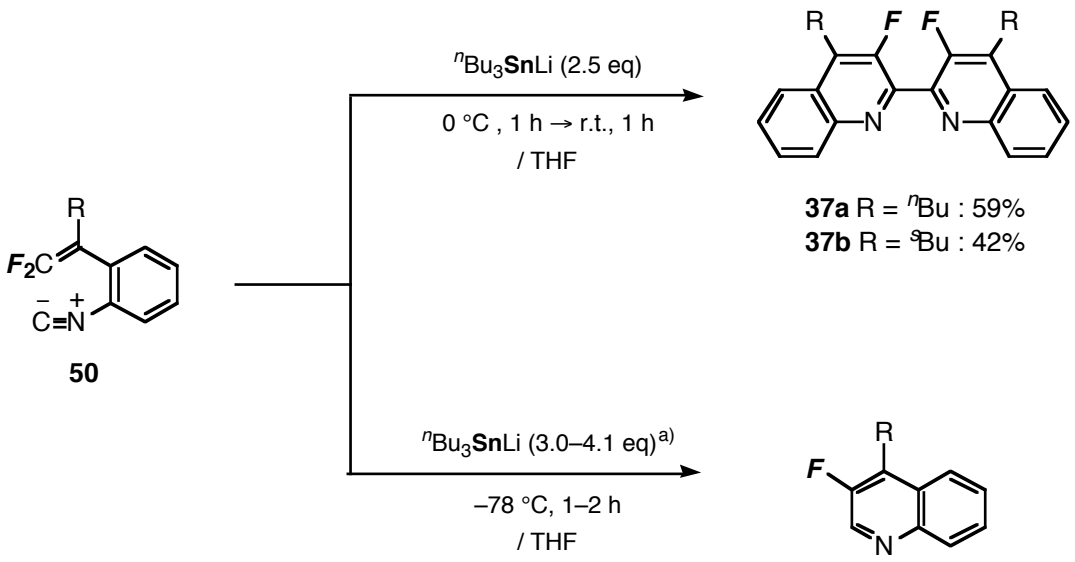


50a **54f** 61%

Scheme 32

In the case of triphenylsilyllithium and dimethylphenylsiliyllithium, the attempted synthesis of 3-fluoroquinolines bearing a silyl group at the 2-position was unsuccessful, and **24a** was obtained instead, probably due to their instability.

Moreover, the reaction was attempted by using tributylstannyllithium[14] which was prepared *in-situ* from the combination of hexabutylditin and butyllithium or tributyltin hydride and lithium diisopropylamide (LDA). Unexpectedly, dimeric products **37a**,**b** were obtained rather than the expected 3-fluoroquinoline bearing a stannyl group at the 2-position. When **50** was added to tributylstannyllithium in reverse order, 3-fluoroquinolines **24a**,**b** unsubstituted at the 2-position were obtained in 80% and 65% yields (Scheme 33). These reactions probably proceeded *via* one-electron reduction of **50** with tributylstannyllithium to generate 3-fluoro-2-quinolyl radical,[15] which led to 3-fluoroquinoline derivatives **37** and **24** *via* radical coupling and further one-electoron reduction, respectively.



a) *o*-Isocyanodifluorostyrene was added to $^{n}Bu_3SnLi$.

Scheme 33

It should be noted that the above mentioned cyclizations of *o*-cyano and *o*-isocyano-β,β-difluorostyrenes provide versatile methods for the synthesis of both

regioisomers, isoquinolines and quinolines bearing a fluorine at the 3-position.

References and notes

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Capter 2 Experimental Section

General. IR spectra were recorded on a Shimadzu IR-408 spectrometer or a JEOL JIR-WINSPEC50 spectrometer. NMR spectra were obtained on a JEOL JNM-A-500, or a Bruker DRX 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 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. Methanol was distilled from magnesium methoxide and stored over molecular sieves 3A. DMF was dried over P_2O_5, then distilled under reduced pressure from CaH_2 and stored over molecular sieves 4A. Commercial NaH and KH were used without further purification. Sodium methoxide was prepared from sodium and excess methanol, and then dried under vacuum at 100 °C.

***o*-(1-Butyl-2,2-difluorovinyl)benzyl alcohol (3a)**

Butyllithium (1.9 ml, 1.6 M in hexane, 3.1 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (368 mg, 1.5 mmol) in THF (7.5 ml) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (1.7 ml, 1.0 M in THF, 1.7 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 1.5 ml), triphenylphosphine (30 mg, 0.12 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (30 mg, 0.029 mmol) and stirred for 15 min. To the solution was added the magnesium salt (generated from *o*-iodobenzyl alcohol (307 mg, 1.3 mmol) and dibutylmagnesium (1.3 ml, 1.0 M in Et_2O, 1.3 mmol) in THF (3 ml) at 0 °C for 30 min) and copper(I) iodide (304 mg, 1.6 mmol). After the mixture had been stirred for 17 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and 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 5:1) to give **3a** (205 mg, 69%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.0 Hz), 1.25–1.35 (4H, m), 1.97 (1H, br s), 2.25–2.31 (2H, m), 4.62 (2H, s), 7.14 (1H, dd, J = 7.6, 1.4 Hz), 7.28 (1H, ddd, J = 7.6, 7.6, 1.4 Hz), 7.34 (1H, ddd, J = 7.6, 7.6, 1.4 Hz), 7.53 (1H, d, J = 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 29.1, 29.6 (d, J_{CF} = 2 Hz), 62.6 (d, J_{CF} = 2 Hz), 90.5 (dd, J_{CF} = 22, 17 Hz), 127.6, 127.9, 128.3, 129.9 (d, J_{CF} = 5 Hz), 132.2 (d, J_{CF} = 5 Hz), 139.5, 152.6 (dd, J_{CF} = 289, 284 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 67.8 (1F, dt, J_{FF} = 47 Hz, J_{FH} = 3 Hz), 72.2 (1F, d, J_{FF} = 47 Hz) ppm.

IR (neat) 3300, 2960, 2880, 1740, 1240, 1135, 1045, 790, 765, 735 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 226 (M^+; 38), 159 (87), 117 (100).

HRMS calcd for $C_{13}H_{16}OF_2$ 226.1170 (M^+); found 226.1176.

_o_-(1-_sec_-Butyl-2,2-difluorovinyl)benzyl alcohol (3b)

Compound **3b** was prepared by the method described for **3a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (254 mg, 1.0 mmol), butyllithium (1.4 ml, 1.5 M in hexane, 2.1 mmol), tri-*sec*-butylborane (1.1 ml, 1.0 M in THF, 1.1 mmol), hexamethylphosphoric triamide (1.4 ml), triphenylphosphine (21 mg, 0.080 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (21 mg, 0.020 mmol), *o*-iodobenzyl alcohol (213 mg, 0.90 mmol) and methylmagnesium iodide (1.0 ml, 0.89 M in THF, 0.90 mmol), and copper(I) iodide (209 mg, 1.1 mmol) in THF (8 ml). Purification by thin layer chromatography on silica gel (chloroform–AcOEt 20:1) gave **3b** (123 mg, 61%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 °C) δ 0.92 (3H, t, J = 7.0 Hz), 1.02 (3H, d, J = 7.0 Hz), 1.26–1.40 (1H, m), 1.55 (1H, dqd, J = 14.0, 7.0, 7.0 Hz), 2.41 (1H, tq, J = 7.0, 7.0 Hz), 3.00 (1H, br s), 4.47 (2H, s), 7.08 (1H, d, J = 7.5 Hz), 7.23 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.32 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.56 (1H, d, J = 7.5 Hz).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 11.1, 17.3, 27.0, 35.1, 60.1, 94.0 (dd, J_{CF} = 24, 16

Hz), 125.8, 127.0, 127.2, 129.0 (d, J_{CF} = 2 Hz), 130.3 (d, J_{CF} = 4 Hz), 140.7, 151.4 (dd, J_{CF} = 290, 284 Hz).

^{19}F NMR (470 MHz, $(CD_3)_2SO$, 100 °C) 70.2 (1F, br s), 74.9 (1F, d, J_{FF} = 47 Hz) ppm.

IR (neat) 3330, 2990, 1735, 1460, 1290, 1235, 1200, 1065, 1020, 935, 760, 670 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 226 (M^+; 60), 159 (99), 129 (100).

HRMS calcd for $C_{13}H_{16}OF_2$ 226.1170 (M^+); found 226.1171.

8-(1-Butyl-2,2-difluorovinyl)-1,2,3,4-tetrahydro-1-naphthol (3c)

Compound **3c** was prepared by the method described for **3a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (165 mg, 0.65 mmol), butyllithium (0.82 ml, 1.7 M in hexane, 1.4 mmol), tributylborane (0.71 ml, 1.0 M in THF, 0.71 mmol), hexamethylphosphoric triamide (1 ml), triphenylphosphine (14 mg, 0.053 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (13 mg, 0.013 mmol), 8-iodo-1,2,3,4-tetrahydro-1-naphthol (156 mg, 0.57 mmol) and dibutylmagnesium (1.1 ml, 0.51 M in Et_2O, 0.57 mmol) and copper(I) iodide (136 mg, 0.71 mmol) in THF (4 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 4:1) gave **3c** (84 mg, 55%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 120 °C) δ 0.85 (3H, t, *J* = 7.0 Hz), 1.24–1.37 (4H, m), 1.58–1.70 (2H, m), 1.90–2.07 (2H, m), 2.21–2.30 (1H, m), 2.37–2.45 (1H, m), 2.62–2.70 (1H, m), 2.80 (1H, t, *J* = 4.6 Hz), 4.18 (1H, br s), 4.66 (1H, br s), 6.91 (1H, d, *J* = 7.6 Hz), 7.04 (1H, d, *J* = 7.6 Hz), 7.14 (1H, dd, *J* = 7.6, 7.6 Hz).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 120 °C) δ 13.4, 16.8, 21.7, 28.8, 29.0, 29.1 (dd, J_{CF} = 3, 3 Hz), 32.0, 63.3, 91.9 (dd, J_{CF} = 21, 17 Hz), 126.8, 127.6 (d, J_{CF} = 2 Hz), 128.7, 134.1 (d, J_{CF} = 5 Hz), 137.8 (d, J_{CF} = 3 Hz), 138.0, 152.2 (dd, J_{CF} = 284, 281 Hz).

^{19}F NMR (470 MHz, $(CD_3)_2SO$, 120 °C) 67.2 (1F, br d, J_{FF} = 49 Hz), 73.0 (1F, br s) ppm.

IR (neat) 3350, 2950, 1745, 1470, 1240, 1135, 1075, 1035, 1005, 785 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 266 (M^+; 6), 246 (43), 175 (54), 155 (100).

HRMS calcd for $C_{16}H_{20}OF_2$ 266.1483 (M^+); found 266.1461.

***o*-(1-Butyl-2,2-difluorovinyl)benzaldehyde (4a)**

Butyllithium (5.0 ml, 1.7 M in hexane, 8.4 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (1.0 g, 4.0 mmol) in THF (20 ml) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (4.4 ml, 1.0 M in THF, 4.4 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (5 ml), triphenylphosphine (30 mg, 0.11 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (29 mg, 0.028 mmol) and stirred for 15 min. To the solution was added *o*-iodobezaldehyde (738 mg, 3.2 mmol) and copper(I) iodide (757 mg, 4.0 mmol). After the mixture was stirred for 0.3 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (Et_2O–hexane 1:20) to give **4a** (441 mg, 62%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2 Hz), 1.29–1.35 (4H, m), 2.37–2.43 (2H, m), 7.31 (1H, dd, J = 7.6, 0.6 Hz), 7.47 (1H, dd, J = 7.6, 7.6 Hz), 7.61 (1H, ddd, J = 7.6, 7.6, 1.5 Hz), 7.96 (1H, dd, J = 7.6, 1.5 Hz), 10.16 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 22.2, 29.5 (d, J_{CF} = 3 Hz), 29.5, 89.1 (dd, J_{CF} = 24, 17 Hz), 128.3, 128.6, 130.6 (d, J_{CF} = 2 Hz), 133.9, 134.1, 137.3 (d, J_{CF} = 4 Hz), 152.7 (dd, J_{CF} = 290, 287 Hz), 191.1.

^{19}F NMR (470 MHz, $CDCl_3$) 70.0 (1F, dt, J_{FF} = 43 Hz, J_{FH} = 3 Hz), 72.8 (1F, dd, J_{FF} = 43 Hz, J_{FH} = 2 Hz) ppm.

IR (neat) 2970, 2950, 2890, 1840, 1745, 1705, 1600, 1470, 1465, 1245 cm^{-1}.

MS (70 eV) *m*/*z* (rel intensity) 224 (M^+; 20), 205 (44), 131 (100), 91 (44).

HRMS calcd for $C_{13}H_{14}OF_2$ 224.1012 (M^+); found 224.1000.

***o*-(1-Butyl-2,2-difluorovinyl)benzyl alcohol (3a)**

To a solution of **6a** (204 mg, 0.91 mmol) in toluene (6 ml) was added DIBAL (1.4 ml, 0.95 M in hexane, 1.4 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred for 30 min, 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 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 5:1) to give **3a** (90 mg, 44%) as a colorless liquid.

1-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]ethanol (3d)

Compound **3d** was prepared by the method described for **3a** using **6a** (210 mg, 0.93 mmol) and methylmagnesium iodide (1.4 ml, 1.0 M in Et_2O, 1.4 mmol) in toluene (6 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **3d** (124 mg, 55%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz), 1.30–1.32 (4H, m), 1.44 (3H, d, J = 6.3 Hz), 1.89 (1H, br s), 2.16–2.36 (2H, m), 5.00 (1H, q, J = 6.3 Hz), 7.09 (1H, d, J = 7.7 Hz), 7.26 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.37 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.61 (1H, dd, J = 7.7, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 24.8, 29.4, 29.6, 66.8, 90.6 (dd, J_{CF} = 22, 17 Hz), 125.8, 127.5, 128.6, 129.9, 131.3, 144.5, 152.7 (dd, J_{CF} = 285, 285 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 72.2 (1F, br s), 67.7 (1F, br s) ppm.

IR (neat) 3369, 2960, 2861, 1741, 1456, 1232, 1132, 1076, 966, 762 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 240 (M^+; 41), 220 (93).

HRMS calcd for $C_{14}H_{18}OF_2$ 240.1326 (M^+); found 249.1333.

1-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]pentan-1-ol (3e)

Compound **3e** was prepared by the method described for **3a** using **6a** (141 mg, 0.63 mmol) and butylmagnesium bromide (0.69 ml, 1.1 M in THF, 0.76 mmol) in toluene (4 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **3e** (137 mg, 77%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 120 °C) δ 0.84 (3H, t, J = 7.2 Hz), 0.84 (3H, t, J = 7.0 Hz), 1.22–1.42 (8H, m), 1.46–1.55 (1H, m), 1.58–1.68 (1H, m), 2.21–2.32 (2H, m), 4.50 (1H, br d, J = 4.6 Hz), 4.54–4.60 (1H, m), 7.05 (1H, d, J = 7.6 Hz), 7.20 (1H, dd, J = 7.6, 7.6 Hz), 7.31 (1H, dd, J = 7.6, 7.6 Hz), 7.53 (1H, d, J = 7.6 Hz).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 120 °C) δ 12.5, 12.8, 21.0, 21.2, 27.1, 28.0, 28.3 (dd, J_{CF} = 5, 3 Hz), 37.8, 68.6, 91.0 (d, J_{CF} = 22, 17 Hz), 125.8, 125.8, 127.3, 128.9, 130.3 (d, J_{CF} = 5 Hz), 144.4, 151.6 (dd, J_{CF} =287, 283 Hz).

^{19}F NMR (470 MHz, $(CD_3)_2SO$, 120 °C) 67.9 (1F, d, J_{FF} = 50 Hz), 73.1 (1F, d, J_{FF} = 50 Hz) ppm.

IR (neat) 3379, 2958, 2862, 1741, 1468, 1234, 1132, 1045, 972, 760 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 282 (M^+; 38), 145 (23), 88 (100).

HRMS calcd for $C_{17}H_{24}OF_2$ 282.1795 (M^+); found 282.1802.

1-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]-1-phenylmethanol (3f)

Compound **3f** was prepared by the method described for **3a** using **6a** (114 mg, 0.51 mmol) and phenylmagnesium bromide (0.81 ml, 0.94 M in THF, 0.76 mmol) in toluene (3 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **3f** (83 mg, 54%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, br s), 1.28 (4H, br), 2.17–2.24 (2H, m), 2.30 (1H, br s), 5.92 (1H, s), 7.12 (1H, d, J = 7.3 Hz), 7.22–7.35 (7H, m), 7.49 (1H, dd, J = 7.9, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.3, 29.0, 29.5, 72.6, 90.7 (dd, J_{CF} = 23, 15 Hz), 126.6, 127.4, 127.5, 127.6, 128.3, 128.4, 130.2, 132.5 (d, J_{CF} = 4 Hz), 142.3, 143.3, 152.7 (dd, J_{CF} = 287, 287 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 73.1 (1F, br s), 67.9 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 3381, 2958, 1741, 1452, 1236, 1132, 1018, 764, 700 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 302 (M^+; 21), 235 (94), 179 (100).

HRMS calcd for $C_{19}H_{20}OF_2$ 302.1482 (M^+); found 302.1469.

***S*-*o*-(1-Butyl-2,2-difluorovinyl)benzyl thioacetate (6a)**

Compound **6a** was prepared by the method described for **4a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (766 mg, 3.0 mmol), butyllithium (3.8 ml, 1.7 M in hexane, 6.3 mmol), tributylborane (3.3 ml, 1.0 M in THF, 3.3 mmol), hexamethylphosphoric triamide (3.5 ml), triphenylphosphine (189 mg, 0.72 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (62 mg, 0.060 mmol), *o*-iodobenzyl methanesulfonate (846 mg, 2.7 mmol) and copper(I) iodide (573 mg, 3.0 mmol) in THF (15 ml). To the resulting solution of **7a** was added a sodium thioacetate generated from thioacetic *S*-acid (0.32 ml, 4.5 mmol) and sodium hydride (175 mg, 62% dispersion in mineral oil, 4.5 mmol). After the mixture had been stirred for 10 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and 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 50:1) to give **6a** (428 mg, 56%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $C_6D_5CD_3$, 90 °C) δ 0.81 (3H, t, J = 7.3 Hz), 1.22 (2H, tq, J = 7.3, 7.3 Hz), 1.31 (2H, tt, J = 7.3, 7.3 Hz), 1.93 (3H, s), 2.23 (2H, tdd, J = 7.3 Hz, J_{HF} = 2.3, 2.3 Hz), 4.12 (2H, s), 6.97–7.02 (3H, m), 7.23 (1H, d, J = 7.0 Hz).

^{13}C NMR (126 MHz, $C_6D_5CD_3$, 90 °C) δ 13.7, 22.7, 29.4, 29.6, 30.1 (dd, J_{CF} = 3, 3 Hz), 31.3, 91.5 (dd, J_{CF} = 39, 18 Hz), 127.6, 128.6, 130.6, 134.1 (d, J_{CF} = 4 Hz), 137.2, 137.6, 153.7 (dd, J_{CF} = 289, 286 Hz), 193.1.

^{19}F NMR (471 MHz, $C_6D_5CD_3$, 90 °C) 69.1 (1F, d, J_{FF} = 45 Hz), 74.7 (1F, d, J_{FF} = 45 Hz) ppm.

IR (neat) 2950, 2925, 2850, 1740, 1690, 1240, 1130, 970, 760 cm^{-1}.

Found: C, 63.21; H, 6.44%. Calcd for $C_{15}H_{18}OF_2S$: C, 63.36; H, 6.38%.

_S_-_o_-[1-_sec_-Butyl-2,2-difluorovinyl]benzyl thioacetate (6b)

Compound **6b** was prepared by the method described for **6a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (255 mg, 1.0 mmol), butyllithium (1.3 ml, 1.7 M in hexane, 2.1 mmol), tri-*sec*-butylborane (1.1 ml, 1.0 M in THF, 1.1 mmol), hexamethylphosphoric triamide (1.5

ml), triphenylphosphine (21 mg, 0.080 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (21 mg, 0.020 mmol), 2-iodobenzyl methanesulfonate (282 mg, 0.90 mmol), copper(I) iodide (191 mg, 1.0 mmol), and thioacetic *S*-acid (0.11 ml, 1.5 mmol) and sodium hydride (58 mg, 62% dispersion in mineral oil, 1.5 mmol) in THF (5 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 50:1) gave **6b** (128 mg, 50%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 0.90–1.64 (8H, m), 2.33 (3H, s), 2.32–2.38 (1H, m), 4.16 (2H, s), 7.08 (1H, br s), 7.20 (1H, ddd, J = 7.4, 7.4, 1.2 Hz), 7.26 (1H, dd, J = 7.4, 7.4 Hz), 7.37 (1H, d, J = 7.4 Hz).

IR (neat) 2970, 2940, 1735, 1695, 1235, 1135, 1105, 760, 670, 630 cm^{-1}.

Found: C, 63.35; H, 6.44%. Calcd for $C_{15}H_{18}OF_2S$: C, 63.36; H, 6.38%.

_o_-(1-Butyl-2,2-difluorovinyl)phenylmethanethiol (7a)

K_2CO_3 (168 mg, 1.2 mmol) was added to a solution of **6a** (299 mg, 1.0 mmol) in methanol (3.5 ml) at 0 °C. After the reaction mixture was stirred for 2 h, 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 thin layer chromatography on silica gel (hexane–AcOEt 20:1) to give **7a** (207 mg, 86%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 6.9 Hz), 1.28–1.37 (4H, m), 1.73 (1H, t, J = 7.5 Hz), 2.26–2.36 (2H, m), 3.70 (2H, d, J = 7.5 Hz), 7.11 (1H, d, J = 7.3 Hz), 7.22 (1H, ddd, J = 7.3, 7.3, 1.2 Hz), 7.30 (1H, ddd, J = 7.3, 7.3, 1.2 Hz), 7.45 (1H, d, J = 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 26.0, 29.0, 29.7, 90.7 (dd, J_{CF} = 22, 17 Hz), 127.1, 128.5, 129.5, 130.3 (dd, J_{CF} = 3, 3 Hz), 132.5 (d, J_{CF} = 5 Hz), 139.9, 152.8 (dd, J_{CF} = 289, 286 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 67.9 (1F, d, J_{FF} = 45 Hz), 73.1 (1F, d, J_{FF} = 45 Hz) ppm.

IR (neat) 2960, 2940, 1750, 1315, 1290, 1240, 1135, 970, 765, 670 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 242 (M^+; 51), 166 (100), 179 (44).

HRMS calcd for $C_{13}H_{16}F_2S$ 242.0941 (M^+); found 242.0912.

***o*-(1-Butyl-2,2-difluorovinyl)-*N*-*tert*-butoxycarbonyl-*p*-toluenesulfonylbenzylamide (8a)**

To a solution of *N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonamide (314 mg, 1.16 mmol) in THF (5 ml) was added triphenylphosphine (624 mg, 2.32 mmol), **3a** (175 mg, 0.772 mmol) in THF (2 ml) and diethyl azodicarboxylate (0.3 ml, 1.93 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 1 h, concentrated under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–ethyl acetate 3:1) to give **8a** (306 mg, 0.638 mmol, 83%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H,t, J = 7.0 Hz), 1.36–1.40 (13H, m), 2.30 (2H, br s), 2.43 (3H, s), 5.04 (2H, s), 7.15 (1H, d, J = 7.0 Hz), 7.24–7.35 (5H, m), 7.70 (2H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 21.6, 22.4, 27.8, 28.7, 29.6 (dd, J_{CF} = 3, 3 Hz), 47.9 (d, J_{CF} = 2 Hz), 84.5, 90.3 (dd, J_{CF} = 22, 17 Hz), 126.2, 127.0, 128.1, 128.3, 129.2, 130.0 (d, J_{CF} = 2 Hz), 131.8 (d, J_{CF} = 5 Hz), 136.0, 137.0, 144.3, 151.1, 152.6 (dd, J_{CF} = 287, 287 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.5 (1F, d, J_{FF} = 44 Hz), 73.0 (1F, d, J_{FF}= 44 Hz) ppm.

IR (neat) 2958, 1739, 1367, 1286, 1236, 1155, 1089, 790, 765, 676, 592, 545 cm^{-1}.

HRFABMS calcd for $C_{25}H_{32}O_4NSF_2$ 480.2020 (M+1^{+}); found 480.2050.

***o*-(1-*sec*-Butyl-2,2-difluorovinyl)-*N*-*tert*-butoxycarbonyl-*p*-toluenesulfonylbenzylamide (8b)**

Compound **8b** was prepared by the method described for **8a** using *N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonamide (173 mg, 0.639 mmol), THF (3 ml) triphenylphosphine (343 mg, 1.28 mmol), **3b** (96 mg, 0.426 mmol) in THF (2 ml), and diethyl azodicarboxylate (0.17 ml, 1.07 mmol). Purification by thin layer chromatography on silica gel (chloroform–AcOEt 20:1) gave **8b** (151 mg, 0.315 mmol, 74%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 90 °C) δ 0.89–1.68 (8H, m), 1.25 (9H, s), 2.42–2.48 (1H, m), 5.00 (2H, s), 7.18 (1H, br s), 7.25 (1H, d, J = 7.4 Hz), 7.30 (1H, dd, J = 7.4, 7.4 Hz), 7.77 (2H, dd, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) (major): δ 12.3, 14.0, 18.1, 21.9, 27.6, 48.4, 84.7, 91.9 (dd, J_{CF}

= 20, 14 Hz), 124.6, 126.6, 128.2, 129.0 (d, J_{CF} = 5 Hz), 129.2, 129.3, 130.1, 130.6 (d, J_{CF} = 5 Hz), 135.6, 136.1, 144.7, 150.8, 151.8 (dd, J_{CF} = 290, 290 Hz). (minor): δ 12.4, 14.2, 18.1, 21.9, 28.0, 48.2, 84.7, 93.9 (dd, J_{CF} = 20, 13 Hz), 124.6, 126.6, 128.2, 129.0 (d, J_{CF} = 5 Hz), 129.2, 129.3, 130.4, 130.6 (d, J_{CF} = 5 Hz), 135.7, 136.1, 144.7, 150.8, 151.7 (dd, J_{CF} = 292, 287 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) (major): 70.1 (1F, d, J_{FF} = 44 Hz), 74.2 (1F, d, J_{FF}= 44 Hz) ppm. (mior): 71.3 (1F, d, J_{FF} = 44 Hz), 75.5 (1F, d, J_{FF}= 44 Hz) ppm.

IR (neat) 2969, 1727, 1367, 1286, 1249, 1232, 1187, 1170, 1089, 676 cm^{-1}.

HRFABMS calcd for $C_{25}H_{32}O_4NSF_2$ 480.2020 (M+1$^+$); found 480.1983.

_o_-(1-Butyl-2,2-difluorovinyl)-_p_-toluenesulfonylbenzylamide (9a)

To a solution of **8a** (69 mg, 0.15 mmol) in CH_2Cl_2 (1.5 ml) was added trifluoroacetic acid (0.17 ml, 2.2 mmol) at room temperature. The reaction mixture was stirred for 11 h at room temperature, and then aqueous $NaHCO_3$ was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 3:1) to give **9a** (55 mg, 100%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.2 Hz), 1.14–1.28 (4H, m), 2.13 (2H, br s), 2.43 (3H, s), 4.05 (2H, d, J = 5.9 Hz), 4.79 (1H, t, J = 5.9 Hz), 7.07–7.15 (1H, m), 7.23–7.27 (2H, m), 7.31 (2H, d, J = 8.1, 8.1 Hz), 7.33–7.37 (1H, m), 7.76 (2H, d, J = 8.1, 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.5, 22.3, 28.9, 29.4 (dd, J_{CF} = 3, 3 Hz), 44.5, 90.3 (dd, J_{CF} = 22, 17 Hz), 127.2, 128.0, 128.4, 129.1, 129.8, 130.1 (d, J_{CF} = 2 Hz), 133.0 (d, J_{CF} = 5 Hz), 134.8 (d, J_{CF} = 2 Hz), 136.6, 143.6, 152.5 (dd, J_{CF} = 287, 287 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.3 (1F, d, J_{FF} = 46 Hz), 72.7 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 3280, 2958, 2929, 1739, 1328, 1236, 1162, 1093, 813, 765 cm^{-1}.

HRFABMS calcd for $C_{20}H_{24}O_2NSF_2$ 380.1496 (M+1$^+$); found 380.1491.

_o_-(1-Butyl-2,2-difluorovinyl)-_p_-toluenesulfonylbenzylamide (9b)

Compound **9b** was prepared by the method described for **9a** using **8b** (103 mg, 0.215 mmol), CH_2Cl_2 (2 ml), and trifluoroacetic acid (0.17 ml, 2.2 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 3:1) gave **9b** (76 mg, 0.210 mmol, 98%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78 (2.1H, d, J = 7.2 Hz), 0.82 (1.9H, t, J = 7.1 Hz), 0.93 (2.1H, t, J = 7.1 Hz), 1.40–1.47 (2H, m), 2.27 (0.3H, tq, J = 7.1 Hz), 2.28–2.46 (0.7H, m), 2.44 (3H, s), 3.97–4.18 (2H, m), 4.70 (1H, br s), 7.04 (0.7H, d, J = 7.0 Hz), 7.09 (0.3 H, d, J = 7.0 Hz), 7.20–7.30 (2H, m), 7.32 (2H, d, J = 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) (major): δ 12.0, 17.9, 21.5, 28.0, 35.2, 44.5, 93.1 (dd, J_{CF} = 20, 14 Hz), 127.1, 127.7, 128.4, 129.0, 129.7, 130.6, 131.3, 135.4, 136.4, 143.6, 152.4 (dd, J_{CF} = 291, 280 Hz). (minor): δ 11.9, 13.9, 21.5, 27.4, 36.0, 44.6, 94.4 (dd, J_{CF} = 20, 14 Hz), 127.1, 127.7, 128.3, 129.0, 129.7, 130.6, 131.3, 135.0, 136.4, 143.6, 152.3 (dd, J_{CF} = 291, 280 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) (major): 69.6 (1F, d, J_{FF} = 47 Hz), 74.6 (1F, d, J_{FF}= 44 Hz) ppm. (mior): 70.6 (1F, d, J_{FF} = 44 Hz), 75.1 (1F, d, J_{FF}= 44 Hz) ppm.

IR (neat) 3282, 2966, 1729, 1450, 1328, 1288, 1232, 1160, 1093, 1060 cm^{-1}.

HRFABMS calcd for $C_{20}H_{24}O_2NSF_2$ 380.1496 (M+1$^+$); found 380.1499.

4-Butyl-3-fluoro-1*H*-2-benzopyran (11a)

To a DMF suspension (0.5 ml) of sodium hydride (28 mg, 60% dispersion in mineral oil, 0.69 mmol) was added **3a** (78 mg, 0.35 mmol) in DMF (1 ml) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred at room temperature for 1.2 h, 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 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 5:1) to give **11a** (60 mg, 84%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.4 Hz), 1.40 (2H, tq, J = 7.4, 7.4 Hz), 1.46–1.56 (2H, m), 2.42 (2H, td, J = 7.4, J_{HF} = 1.4 Hz), 5.22 (2H, s), 7.00 (1H, d, J = 7.5 Hz), 7.08–7.14 (2H, m), 7.25 (1H, dd, J = 7.5, 0.9 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.4, 22.5, 30.7, 71.4, 89.0 (d, J_{CF} = 23 Hz), 120.9 (d, J_{CF}

= 7 Hz), 123.7, 125.2, 126.6, 128.4, 133.3 (d, J_{CF} = 6 Hz), 158.0 (d, J_{CF} = 264 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.0 (1F, s) ppm.

IR (neat) 2960, 2870, 1680, 1490, 1460, 1390, 1245, 1195, 760, 670 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 206 (M^+; 100), 164 (79), 135 (88), 115 (96).

Found: C, 75.43; H, 7.45%. Calcd for $C_{13}H_{15}OF$: C, 75.70; H, 7.33%.

4-*sec*-Butyl-3-fluoro-1*H*-2-benzopyran (11b)

Compound **11b** was prepared by the method described for **11a** using sodium hydride (16 mg, 60% dispersion in mineral oil, 0.40 mmol) and **3b** (45 mg, 0.20 mmol) in DMF (1 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **11b** (35 mg, 84%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.4 Hz), 1.28 (3H, dd, *J* = 7.4, J_{HF} = 1.2 Hz), 1.62 (1H, dqdd, *J* = 21.6, 7.4, 7.4, J_{HF} = 1.2 Hz), 1.73 (1H, dqdd, *J* = 21.6, 7.4, 7.4, J_{HF} = 1.5 Hz), 2.67 (1H, tq, *J* = 7.4, 7.4 Hz), 5.17 (2H, s), 7.02 (1H, d, *J* = 7.3 Hz), 7.07–7.13 (1H, m), 7.21–7.27 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 19.3 (d, J_{CF} = 3 Hz), 28.3 (d, J_{CF} = 3 Hz), 32.0 (d, J_{CF} = 2 Hz), 71.4, 93.8 (d, J_{CF} = 28 Hz), 121.4 (d, J_{CF} = 6 Hz), 123.9, 125.1, 126.9, 128.3, 133.9 (d, J_{CF} = 7 Hz), 158.2 (d, J_{CF} = 268 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 72.2 (1F, s) ppm.

IR (neat) 2860, 1660, 1605, 1450, 1385, 1240, 1190, 1060, 930, 760 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 206 (M^+; 9), 167 (37), 149 (100).

Found: C, 75.63; H, 7.36%. Calcd for $C_{13}H_{15}OF$: C, 75.70; H, 7.33%.

3-Butyl-2-fluoro-7,8,9,9a-tetrahydro-1-oxaphenalene (11c)

Compound **11c** was prepared by the method described for **11a** using sodium hydride (11 mg, 60% dispersion in mineral oil, 0.27 mmol) and **3c** (36 mg, 0.14 mmol) in DMF (1.7 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **11c** (22 mg, 66%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, *J* = 7.3 Hz), 1.33–1.57 (4H, m), 1.67–1.78 (1H, m),

1.93–2.10 (2H, m), 2.36–2.45 (3H, m), 2.69–2.84 (2H, m), 5.26 (1H, dd, J = 10.1, 6.1 Hz), 6.91 (1H, d, J = 7.6 Hz), 6.95 (1H, d, J = 7.6 Hz), 7.16 (1H, dd, J = 7.6, 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 20.8, 22.4, 22.5, 28.3, 28.6, 30.8, 78.1, 89.6 (d, J_{CF} = 23 Hz), 118.5 (d, J_{CF} = 7 Hz), 125.8 (d, J_{CF} = 2 Hz), 126.0, 128.0, 133.6 (d, J_{CF} = 6 Hz), 135.4, 158.0 (d, J_{CF} = 266 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 67.9 (1F, s) ppm.

IR (neat) 2950, 2880, 1685, 1595, 1465, 1245, 1180, 1020, 810, 780, 755 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 246 (M^+; 78), 203 (58), 155 (100).

HRMS calcd for $C_{16}H_{19}OF$ 246.1421 (M^+); found 246.1418.

4-Butyl-3-fluoro-1-methyl-1*H*-2-benzopyran (11d)

Compound **11d** was prepared by the method described for **11a** using sodium hydride (35 mg, 60% dispersion in mineral oil, 0.86 mmol) and **3d** (104 mg, 0.43 mmol) in DMF (3 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **11d** (57 mg, 60%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.39 (2H, tq, J = 7.3, 7.3 Hz), 1.50 (2H, tt, J = 7.3, 7.3 Hz), 1.63 (3H, d, J = 6.4 Hz), 2.42 (2H, td, J = 7.3 Hz, J_{HF} = 1.7 Hz), 5.42 (1H, q, J = 6.4 Hz), 7.00 (1H, dd, J = 7.6, 0.6 Hz), 7.12 (1H, ddd, J = 7.6, 7.6, 0.6 Hz), 7.13 (1H, d, J = 7.6 Hz), 7.25 (1H, ddd, J = 7.6, 7.6, 0.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 19.4, 22.3, 22.4, 30.7, 77.8, 88.0 (d, J_{CF} = 23 Hz), 121.1 (d, J_{CF} = 7 Hz), 123.2, 125.2 (d, J_{CF} = 2 Hz), 128.0, 131.2, 132.5 (d, J_{CF} = 7 Hz), 156.5 (d, J_{CF} = 264 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.2 (1F, s) ppm.

IR (neat) 2960, 2930, 2860, 1685, 1560, 1490, 1460, 1375, 1360, 1240, 760 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 220 (M^+; 100), 163 (24), 149 (48), 129 (60).

HRMS calcd for $C_{14}H_{17}OF$ 220.1263 (M^+); found 220.1287.

1,4-Dibutyl-3-fluoro-1*H*-2-benzopyran (11e)

Compound **11e** was prepared by the method described for **11a** using sodium hydride (48 mg,

60% dispersion in mineral oil, 1.2 mmol) and **3e** (171 mg, 0.61 mmol) in DMF (6 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **11e** (113 mg, 71%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 0.93 (3H, t, J = 7.3 Hz), 1.32–1.58 (8H, m), 1.69–1.77 (1H, m), 2.02–2.10 (1H, m), 2.36–2.46 (2H, m), 5.24 (1H, ddd, J = 8.2, 4.8 Hz, J_{HF} = 2.3 Hz), 6.96 (1H, d, J = 7.6 Hz), 7.09 (1H, ddd, J = 7.5, 7.5, 1.2 Hz), 7.12 (1H, dd, J = 7.5, 0.9 Hz), 7.23 (1H, dd, J = 7.5, 7.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 22.3, 22.5, 27.2, 30.7, 30.7, 33.5, 81.8, 87.7 (d, J_{CF} = 23 Hz), 121.2 (d, J_{CF} = 7 Hz), 123.8, 125.0, 128.0, 130.5, 132.4 (d, J_{CF} = 6 Hz), 156.2 (d, J_{CF} = 264 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.2 (1F, s) ppm.

IR (neat) 2955, 2930, 2860, 1685, 1490, 1455, 1375, 1235, 1155, 965, 760 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 262 (M^+; 89), 205 (89), 88 (100).

HRMS calcd for $C_{17}H_{23}OF$ 262.1733 (M^+); found 262.1740.

4-Butyl-3-fluoro-1-phenyl-1*H*-2-benzopyran (11f)

Compound **11f** was prepared by the method described for **11a** using sodium hydride (36 mg, 60% dispersion in mineral oil, 0.91 mmol) and **3f** (137 mg, 0.45 mmol) in DMF (4 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **11f** (64 mg, 50%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.3 Hz), 1.23–1.52 (4H, m), 2.38–2.45 (2H, m), 6.28 (1H, s), 6.77 (1H, d, J = 7.3 Hz), 7.08 (1H, ddd, J = 8.5, 8.5, 1.2 Hz), 7.28–7.39 (7H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.3, 22.3, 30.5, 83.0, 89.2 (d, J_{CF} = 23 Hz), 121.2 (d, J_{CF} = 6 Hz), 125.2 (d, J_{CF} = 2 Hz), 125.5, 128.0, 128.4, 128.6 (d, J_{CF} = 3 Hz), 128.8, 129.3, 133.1 (d, J_{CF} = 6 Hz), 138.1, 156.5 (d, J_{CF} = 266 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.3 (1F, s) ppm.

IR (neat) 2929, 2872, 1726, 1680, 1493, 1454, 1387, 1232, 1151, 1093 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 282 (M^+; 41), 225 (100).

HRMS calcd for $C_{19}H_{19}OF$ 282.1420 (M^+); found 282.1429.

4-Butyl-3-fluoro-1*H*-2-benzothiopyran (12a)

To a THF suspension (6.5 ml) of potassium hydride (KH, 41 mg, 35% dispersion in mineral oil, 0.36 mmol) was added **7a** (72 mg, 0.30 mmol) in THF (1.5 ml) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred at room temperature for 2.5 h, 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 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 20:1) to give **12a** (61 mg, 90%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, J = 7.3 Hz), 1.38 (2H, tq, J = 7.3, 7.3 Hz), 1.45–1.53 (2H, m), 2.66 (2H, td, J = 7.6 Hz, J_{HF} = 3.4 Hz), 3.92 (2H, d, J_{HF} = 4.9 Hz), 7.13 (1H, d, J = 7.6 Hz), 7.17 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.25 (1H, dd, J = 7.5, 7.5 Hz), 7.28 (1H, d, J = 7.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.5, 24.8 (d, J_{CF} = 4 Hz), 30.8 (d, J_{CF} = 2 Hz), 33.6, 116.8 (d, J_{CF} = 14 Hz), 124.1 (d, J_{CF} = 6 Hz), 126.6, 126.9, 127.6, 128.6, 134.6 (d, J_{CF} = 4 Hz), 153.9 (d, J_{CF} = 282 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 64.7 (1F, tt, J_{FH} = 4, 4 Hz) ppm.

IR (neat) 2960, 2890, 1620, 1570, 1490, 1450, 1155, 1100, 765 cm^{-1}.

MS (70 eV) *m*/*z* (rel intensity) 222 (M^+; 82), 179 (100), 146 (73), 135 (45).

Found: C, 70.37; H, 6.85%. Calcd for $C_{13}H_{15}FS$: C, 70.23; H, 6.80.

4-Butyl-3-fluoro-1*H*-2-benzothiopyran (12a)

To a DMF suspension (4 ml) of sodium methoxide (33 mg, 0.61 mmol) was added **6a** (87 mg, 0.31 mmol) in DMF (1 ml). After the mixture was stirred at room temperature for 15 min, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 30:1) to give **12a** (64 mg, 94%) as a

colorless liquid.

4-*sec*-Butyl-3-fluoro-1*H*-2-benzothiopyran (12b)

Compound **12b** was prepared by the method described for **12a** using sodium methoxide (28 mg, 0.52 mmol) and **6b** (70 mg, 0.25 mmol) in DMF (6 ml). Purification by column chromatography on silica gel (hexane–AcOEt 30:1) gave **12b** (49 mg, 90%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.34 (3H, dd, J = 7.3 Hz, J_{HF} = 1.2 Hz), 1.69 (1H, dqdd, J = 14.6, 7.3, 7.3 Hz, J_{HF} = 1.4 Hz), 1.83 (1H, dqdd, J = 14.6, 7.3, 7.3 Hz, J_{HF} = 1.4 Hz), 2.84 (1H, tq, J= 7.3, 7.3 Hz), 3.84 (1H, dd, J = 13.7, Hz, J_{HF} = 5.2 Hz), 3.93 (1H, dd, J = 13.7 Hz, J_{HF} = 4.6 Hz), 7.14 (1H, dd, J = 7.3, 1.3 Hz), 7.17 (1H, tq, J = 7.3, 1.3 Hz), 7.24 (1H, tq, J = 7.3, 1.3 Hz), 7.37 (1H, d, J = 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9, 19.6 (d, J_{CF} = 3 Hz), 28.5 (d, J_{CF} = 4 Hz), 34.1, 36.4, 121.3 (d, J_{CF} = 12 Hz), 124.4 (d, J_{CF} = 5 Hz), 126.4, 126.7, 127.4, 129.2, 136.0 (d, J_{CF} = 7 Hz), 155.3 (d, J_{CF} = 287 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 68.3 (1F, br s) ppm.

IR (neat) 2960, 2890, 1615, 1490, 1455, 1175, 1145, 1100, 890, 760 cm^{-1}.

MS (70 eV) *m*/*z* (rel intensity) 222 (M^+; 70), 193 (100), 160 (59).

HRMS calcd for $C_{13}H_{15}FS$ 222.0878 (M^+); found 222.0861.

4-Butyl-3-phenylthio-1*H*-2-benzothiopyran (13a)

To a dimethylsulfoxide (DMSO) suspension (3 ml) of potassium hydride (156 mg, 35% dispersion in mineral oil, 0.85 mmol) was added benzenethiol (0.14 ml, 1.4 mmol) at room temperature under a nitrogen atmosphere, and the mixture was stirred for 0.5 h. To the resulting solution was added **12a** (76 mg, 0.34 mmol) in DMSO (1 ml), and the mixture was stirred at 100 °C for 22 h. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and 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

30:1) to give **13a** (76 mg, 71%) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.5 Hz), 1.40 (2H, tq, J = 7.5, 7.5 Hz), 1.55 (2H, tt, J = 7.5, 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.70 (2H, s), 7.11–7.15 (1H, m), 7.19–7.32 (5H, m), 7.33–7.37 (2H, m), 7.40 (1H, d, J = 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.6, 30.9, 32.2, 33.9, 124.8, 126.2, 126.4, 126.5, 127.2, 128.1, 128.9, 128.9, 130.9, 134.8, 136.6, 141.0.

IR (neat) 3050, 2950, 2930, 2860, 1580, 1470, 1440, 760, 740, 685 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 312 (M^+; 45), 269 (32), 123 (100).

Found: C, 72.92; H, 6.44%. Calcd for $C_{19}H_{20}S_2$: C, 73.03; H, 6.45%.

4-Butyl-3-fluoro-2-*p*-toluensulfonyldihydroisoquinoline (14a)

To a solution of NaH (9 mg, 60.0% dispersion in mineral oil, 0.22 mmol) in DMF (0.5 ml) was added **9a** (75 mg, 0.20 mmol) in DMF (1.5 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 4.5 h at room temperature, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with diethyl ether three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (pentane–diethyl ether 5 : 1 containing of 1% of Et_3N) to give **14a** (63 mg, 89%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91(3H, t, J = 7.5 Hz), 1.29–1.43(4H, m), 2.23 (3H, s), 2.45 (2H, td, J = 7.5 Hz, J_{HF} = 2.5 Hz), 4.79 (2H, d, J_{HF} = 3.7 Hz), 6.88 (1H, dd, J = 7.3, 1.5 Hz), 6.91–6.95 (1H, m), 6.92 (2H, dd, J = 7.9, 0.6 Hz), 7.00–7.07 (2H, m), 7.42–7.46 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 21.4, 22.5, 23.9, 30.6 (d, J_{CF} = 2 Hz), 51.6, 109.8 (d, J_{CF} = 23 Hz), 122.5 (d, J_{CF} = 6 Hz), 125.1, 126.7 (d, J_{CF} = 2 Hz), 127.4, 127.6, 128.7, 128.9, 131.6 (d, J_{CF} = 4 Hz), 133.9, 144.1, 147.7 (d, J_{CF} = 267 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 65.0 (1F, t, J_{FH} = 3 Hz) ppm.

IR (neat) 2964, 1670, 1359, 1243, 1168, 1085, 1054, 817, 759, 680, 566, 545 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 359 (M^+; 12), 204 (100), 148 (57).

HRMS calcd for $C_{20}H_{22}O_2NFS$ 359.1355 (M^+); found 359.1367.

4-*sec*-Butyl-3-fluoro-2-*p*-toluenesulfonyldihydroisoquinoline (14b)

To a solution of NaH (10 mg, 60.0% dispersion in mineral oil, 0.24 mmol) in DMF (1 ml) was added **9b** (82 mg, 0.22 mmol) in DMF (1.5 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 9h at room temperature and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with diethyl ether three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (pentane–diethylether 10 : 1 containing of 1% of Et_3N) to give **14b** (69 mg, 89%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, t, J = 7.3 Hz), 1.23 (3H, dd, J = 7.3 Hz, J_{HF} = 1.1 Hz) 1.56–1.74 (2H, m), 2.22 (3H, s), 2.61 (1H, td, J = 7.3, 7.3 Hz), 4.77 (2H, ddd, J_{HF} = 25.6 Hz, J = 16.3, 3.6 Hz), 6.90 (2H, d, J = 8.2 Hz) 6.93–6.98 (2H, m), 6.99–7.05 (2H, m), 7.40 (2H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.6, 18.9 (d, J_{CF} = 3 Hz), 21.3, 27.9 (d, J_{CF} = 4 Hz), 34.0 (d, J_{CF} = 3 Hz), 51.7, 114.2 (d, J_{CF} = 20 Hz), 122.8 (d, J_{CF} = 7 Hz), 125.2, 126.5 (d, J_{CF} = 2 Hz), 127.2, 127.5, 128.6, 129.0, 132.2 (d, J_{CF} = 5 Hz), 133.7, 144.0, 147.9 (d, J_{CF} = 271 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 69.3 (1F, s) ppm.

IR (neat) 2969, 1654, 1452, 1357, 1234, 1164, 927, 765, 678, 578 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 359 (M^+; 24), 204 (78), 174 (76), 148 (100).

HRMS calcd for $C_{20}H_{22}O_2NFS$ 359.1355 (M^+); found 359.1347.

4-Butyl-3-fluoroisoquinoline (15a)

To a solution of KH (85 mg, 33.0% dispersion in mineral oil, 0.70 mmol) in DMF (1 ml) was added **9a** (104 mg, 0.27 mmol) in DMF (2 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 4 h at room temperature and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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-ethyl acetate 3 : 1) to give **15a** (53 mg, 95%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 1.46 (2H, tq, J = 7.5, 7.5 Hz), 1.63–1.71 (2H, m), 3.03 (2H, td, J = 7.5 Hz, J_{HF}= 0.9 Hz), 7.52 (1H, ddd, J = 7.9, 7.9 Hz, J_{HF} = 0.8 Hz), 7.71 (1H, dd, J = 7.6, 7.6 Hz), 7.97 (1H, d, J = 8.2 Hz), 7.99 (1H, d, J = 8.9 Hz), 8.80 (1H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.8, 24.1, 32.1, 115.0 (d, J_{CF} = 30 Hz), 122.9 (d, J_{CF} = 7 Hz), 125.6 (d, J_{CF} = 2 Hz), 127.6 (d, J_{CF} = 2 Hz), 128.4, 130.7, 138.4 (d, J_{CF} = 6 Hz), 148.6 (d, J_{CF} = 16 Hz), 159.1 (d, J_{CF} = 232 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 79.3 (1F, s) ppm.

IR (neat) 2960, 2930, 2870, 1620, 1590, 1440, 1425, 1250, 1220, 750 cm^{-1}.

MS (20 eV) *m/z* 203 (M^+; 67), 160 (100).

Anal. Calcd for $C_{13}H_{14}NF$: C, 76.82; H, 6.94; N, 6.89. Found: C, 76.54; H, 6.95; N, 6.76.

4-*sec*-Butyl-3-fluoroisoquinoline (15b)

To a solution of KH (70 mg, 33.0% dispersion in mineral oil, 0.57 mmol) in DMF (1 ml) was added **9b** (83 mg, 0.22 mmol) in DMF (2.5 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 9 h at room temperature and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 5:1) to give **15b** (40 mg, 90%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 1.48 (3H, d, J = 7.2 Hz), 1.84–2.04 (2H, m), 3.55 (1H, tq, J = 7.2, 7.2 Hz), 7.58 (1H, dd, J = 7.6, 7.6 Hz), 7.66 (1H, dd, J = 7.6, 7.6 Hz), 8.07–8.20 (2H, m), 8.71 (1H, dd, J_{HF} = 3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 19.2, 28.5 (d, J_{CF} = 3 Hz), 33.7, 123.6, 127.1, 127.8, 128.0 (d, J_{CF} = 5 Hz), 130.5, 135.4, (d, J_{CF} = 10 Hz), 141.8 (d, J_{CF} = 40 Hz), 145.7, 154.9 (d, J_{CF} = 254 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 33.0 (1F, s) ppm.

IR (neat) 2966, 2875, 1599, 1512, 1460, 1371, 1252, 1209, 1144, 760 cm^{-1}.

HRMS calcd for $C_{13}H_{14}NF$ 203.1110 (M^+); found 203.1083.

2-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]ethyl methansulfonate (26a)

Butyllithium (3.0 ml, 1.4 M in hexane, 4.2 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (509 mg, 2.00 mmol) in THF (10 ml) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (2.2 ml, 1.0 M in THF, 2.2 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 2 ml), triphenylphosphine (42 mg, 0.16 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (41 mg, 0.040 mmol) and stirred for 15 min. To the solution was added **27** (522 mg, 1.60 mmol) and copper(I) iodide (381 mg, 2.00 mmol). After the mixture was stirred for 6 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and 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 5:1) to give **26a** (275 mg, 54%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.0 Hz), 1.27–1.36 (4H, m), 2.27 (2H, br s), 2.87 (3H, s), 3.04 (2H, t, J = 7.2 Hz), 4.38 (2H, t, J = 7.2 Hz), 7.15 (1H, d, J = 7.3 Hz), 7.24–7.32 (3H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.3, 29.0, 29.5 (d, J_{CF} = 2 Hz), 32.5, 37.2, 69.5, 90.8 (dd, J_{CF} = 22, 18 Hz), 127.1, 128.2, 129.6, 130.5 (d, J_{CF} = 4 Hz), 133.7 (d, J_{CF} = 4 Hz), 134.9, 152.8 (dd, J_{CF} = 290, 285 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 68.0 (1F, dt, J_{FF} = 46, J_{FH} = 3 Hz), 72.7 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 2958, 2861, 1741, 1359, 1236, 1176, 958, 906, 804, 765 cm^{-1}.

MS (20 eV) *m/z* 318 (M^+; 21), 180 (100), 129 (50).

HRMS calcd for $C_{15}H_{20}O_3SF_2$ 318.1102 (M^+); found 318.1102.

2-[*o*-(1-*sec*-Butyl-2,2-difluorovinyl)phenyl]ethyl methansulfonate (26b)

Compound **26b** was prepared by the method described for **26a** using Butyllithium (32.4 ml, 1.5 M in hexane, 49.6 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (6.0 g, 23.6 mmol), tri-*sec*-butylborane (26.0 ml, 1.0 M in THF, 26.0 mmol), HMPA (24 ml), triphenylphosphine (496 mg, 1.89 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1), **27** (6.16 g, 18.9 mmol), and copper(I) iodide (4.50 g, 23.6 mmol). Purification by column chromatography on silica gel (hexane–AcOEt 5:1) to give **26b** (4.7 g, 14.6 mmol, 77%) as a pale yellow liquid..

^{1}H NMR (270 MHz, $(CD_3)_2SO$, 90 °C) δ 1.20–2.18 (8H, m), 2.72–2.94 (1H, m), 3.43 (2H, t, *J* = 6.7 Hz), 3.48 (3H, s), 4.82 (2H, t, *J* = 6.7 Hz), 7.49–7.90 (4H, m).

^{13}C NMR (68 MHz, $(CD_3)_2SO$, 90 °C) δ 11.2, 17.3, 27.0, 31.5, 35.2, 36.5, 68.9, 94.5 (d, J_{CF} = 25, 16 Hz), 126.1, 126.1, 127.6, 128.8, 129.8, 135.3, 151.7 (dd, J_{CF} = 287, 283 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 110 °C) 70.7 (1F, br s), 75.8 (1F, br s) ppm.

IR (neat) 2966, 2937, 1732, 1358, 1230, 1174, 1059, 958, 804, 761 cm^{-1}.

MS (20 eV) *m/z* 318 (M^+; 18), 193 (100), 173 (76).

HRMS calcd for $C_{15}H_{20}O_3SF_2$ 318.1102 (M^+); found 318.1070.

2-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]ethyl iodide (16a)

To a solution of **26a** (208 mg, 0.65 mmol) in acetone (3 ml) was added sodium iodide (147 mg, 0.65 mmol) at room temperature under a nitrogen atomosphere. After the mixture had been stirred for 6 h, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and 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) to give **16a** (163 mg, 0.46 mmol, 71%) as a collorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 6.9 Hz), 1.26–1.36 (4H, m), 2.18–2.36 (2H, m), 3.15 (2H, t, *J* = 8.2 Hz), 3.29 (2H, t, *J* = 8.2 Hz), 7.12 (1H, d, *J* = 7.0 Hz), 7.23–7.21 (3H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.3, 29.1, 29.6 (d, J_{CF} = 11 Hz), 37.6, 45.0, 90.8 (dd, J_{CF}

= 22, 22 Hz), 126.9, 128.2, 128.9, 130.5 (d, J_{CF} = 2 Hz), 133.0 (d, J_{CF} = 4 Hz), 139.8, 152.8 (dd, J_{CF} = 290, 290 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 72.6 (1F, d, J_{FF} = 47 Hz), 67.9 (1F, d, J_{FF} = 47 Hz) ppm.

IR (neat) 2956, 2860, 1740, 1466, 1234, 1173, 1126, 1012, 968, 754 cm^{-1}.

MS (20 eV) *m/z* 350 (M^+; 93), 223 (100), 231 (99).

HRMS calcd for $C_{14}H_{17}F_2I$ 350.0345 (M^+); found 350.0341.

2-[*o*-(1-*sec*-Butyl-2,2-difluorovinyl)phenyl]ethyl iodide (16b)

Compound **16b** was prepared by the method described for **16a** using **26b** (4.66 g, 14.6 mmol), acetone (20 ml) sodium iodide (3.29 g, 21.9 mmol). Purification by column chromatography on silica gel (hexane) gave **16b** (3.7 g, 10.7 mmol, 73%) as a collorless liquid.

1H NMR (500 MHz, $(CD_3)_2SO$, 100 °C) δ 0.97–1.60 (8H, m), 2.40 (1H, br s), 3.14 (2H, t, *J* = 7.9 Hz), 3.14 (2H, t, *J* = 7.9 Hz), 7.12 (1H, d, *J* = 7.5 Hz), 7.27 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.32 (1H, ddd, *J* = 7.5, 7.5, 1.3 Hz), 7.39 (1H, d, *J* = 7.5 Hz).

^{13}C NMR (125 MHz, $(CD_3)_2SO$, 100 °C) δ 3.73, 11.1, 17.3, 26.9, 35.3, 36.3, 94.5 (d, J_{CF} = 24, 19 Hz), 126.0, 127.6, 128.1, 129.3, 130.0, 138.9, 151.6 (dd, J_{CF} = 290, 284 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 100 °C) 70.8 (1F, br s), 75.8 (1F, br s) ppm.

IR (neat) 2966, 2933, 1731, 1459, 1284, 1230, 1170, 1058, 944, 757 cm^{-1}.

MS (20 eV) *m/z* 350 (M^+; 77), 223 (100), 167 (44).

HRMS calcd for $C_{14}H_{17}F_2I$ 350.0345 (M^+); found 350.0331.

2-[*o*-(1-Butyl-2,2-difluorovinyl)phenyl]ethyl cyanide (17a)

To a solution of **16a** (107 mg, 0.31 mmol) in acetonitrile (3 ml) was added potassium cyanide (40 mg, 0.67 mmol) and catalytic amount of 18-crown-6 under a nitrogen atmosphere. The reaction mixture was refluxed for 10 h. 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 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 5:1) to give **17a** (63 mg, 0.25 mmol, 83%) as a collorless liquid.

^{1}H NMR (500 MHz, CDCl3) δ 0.88 (3H, t, J = 6.9 Hz), 1.29–1.35 (4H, m), 2.27 (2H, br s), 2.58 (2H, t, J = 7.8 Hz), 2.94 (2H, t, J = 7.6 Hz), 7.15 (1H, d, J = 7.0 Hz), 7.25–7.35 (3H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 18.4, 22.4, 28.6, 29.2, 29.6 (dd, J_{CF} = 3, 3 Hz), 90.7 (dd, J_{CF} = 22, 22 Hz), 119.2, 127.3, 128.5, 128.8, 130.6 (d, J_{CF} = 2 Hz), 133.1 (d, J_{CF} = 4 Hz), 136.8 (d, J_{CF} = 2 Hz), 152.7 (dd, J_{CF} = 290, 290 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 72.9 (1F, d, J_{FF} = 46 Hz), 68.2 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 2958, 2931, 2861, 2249, 1740, 1450, 1236, 1132, 968, 764 cm^{-1}.

MS (20 eV) *m/z* 249 (M^+; 16), 207 (100).

HRMS calcd for $C_{15}H_{17}NF_2$ 249.1329 (M^+); found 249.1311.

2-[*o*-(1-*sec*-Butyl-2,2-difluorovinyl)phenyl]ethyl cyanide (17b)

Compound **17b** was prepared by the method described for **17a** using **16b** (1.50 g, 4.28 mmol) acetonitrile (8 ml), potassium cyanide (558 mg, 8.57 mmol), and catalytic amount of 18-crown-6. Purification by column chromatography on silica gel (hexane–AcOEt 10:1) gave **17b** (781 mg, 3.13 mmol, 73%) as a collorless liquid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 °C) δ 0.95 (3H, t, J = 6.8 Hz), 1.04 (3H, br s), 1.37 (1H, br s), 1.48–1.62 (1H, m), 2.43 (1H, br s), 2.77 (2H, t, J = 7.3 Hz), 2.92 (2H, t, J = 7.3 Hz), 7.16 (1H, d, J = 7.5 Hz), 7.28 (1H, dd, J = 7.5, 7.5 Hz), 7.35 (1H, dd, J = 7.5, 7.5 Hz), 7.43 (1H, d, J = 7.5 Hz).

^{13}C NMR (125 MHz, $(CD_3)_2SO$, 100 °C) δ 11.0, 16.4, 17.2, 27.0, 27.3, 35.2, 94.4 (d, J_{CF} = 22, 17 Hz), 118.9, 126.0, 127.6, 127.9, 130.0, 131.5, 137.1, 151.6 (dd, J_{CF} = 291, 284 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 100 °C) 70.8 (1F, br s), 75.9 (1F, br s) ppm.

IR (neat) 2968, 2935, 2877, 2249, 1734, 1458, 1232, 1059, 935, 760 cm^{-1}.

MS (20 eV) *m/z* 249 (M^+; 16), 200 (100), 159 (68).

HRMS calcd for $C_{15}H_{17}NF_2$ 249.1329 (M^+); found 249.1315.

4-Butyl-3-fluoro-1,2-dihydronaphthalene (18a)

To a solution of **16a** (1010 mg, 2.88 mmol) in Et_2O–hexane (1:4, 20 ml) was added *tert*-butyllithium (3.87 ml, 1.64 M in pentane, 6.35 mmol) at –78 °C under a nitrogen

atmosphere. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. The reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane) to give **18a** (567 mg, 2.77 mmol, 96%) as a collorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.39 (2H, tq, J = 7.2, 7.2 Hz), 1.44–1.57 (2H, m), 2.48–2.56 (4H, m), 2.94 (2H, dt, J = 8.4, 2.7 Hz), 7.06–7.12 (2H, m), 7.17–7.22 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.6, 23.0 (d, J_{CF} = 4 Hz), 24.7, 24.9, 28.9 (d, J_{CF} = 7 Hz), 30.5 (d, J_{CF} = 2 Hz), 114.3 (d, J_{CF} = 15 Hz), 122.8 (d, J_{CF} = 6 Hz), 125.7 (d, J_{CF} = 2 Hz), 126.5, 127.3, 133.2, 134.5 (d, J_{CF} = 7 Hz), 158.4 (d, J_{CF} = 265 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 57.3 (1F, s) ppm.

IR (neat) 2956, 2872, 1680, 1487, 1452, 1365, 1227, 1180, 1151, 760 cm^{-1}.

MS (20 eV) *m/z* 204 (M^+; 96), 162 (100).

HRMS calcd for $C_{14}H_{17}F$ 204.1314 (M^+); found 204.1316.

4-*sec*-Butyl-3-fluoro-1,2-dihydronaphthalene (18b)

Compound **18b** was prepared by the method described for **18a** using **16b** (312 mg, 0.892 mmol), Et_2O–hexane (1:4, 18 ml), *tert*-butyllithium (1.2 ml, 1.6 M in pentane, 2.0 mmol). Purification by thin layer chromatography on silica gel (hexane) gave **18b** (167 mg, 0.816 mmol, 91%) as a collorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.29 (3H, dd, J = 7.3, J_{HF} = 1.2 Hz), 1.60–1.71 (1H, m), 1.74–1.84 (1H, m), 2.44–2.50 (2H, m), 2.76 (1H, ddq, J = 14.7, 7.3, 7.3 Hz), 2.83–2.94 (2H, m), 7.05–7.12 (2H, m), 7.17 (1H, ddd, J = 7.4, 7.4, 0.9 Hz), 7.31 (1H, d, J = 7.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.8, 19.1 (d, J_{CF} = 26 Hz), 28.2 (d, J_{CF} = 4 Hz), 29.3 (d, J_{CF} = 7 Hz), 33.5, 118.5 (d, J_{CF} = 11 Hz), 123.2 (d, J_{CF} = 7 Hz), 125.6, 126.4, 127.4, 133.6, 135.4 (d, J_{CF} = 8 Hz), 159.4 (d, J_{CF} = 267 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 61.3 (1F, s) ppm.

IR (neat) 2962, 2836, 1666, 1484, 1452, 1224, 1180, 1149, 921, 759 cm^{-1}.

MS (20 eV) *m/z* 204 (M^+; 88), 175 (100), 147 (40).

HRMS calcd for $C_{14}H_{17}F$ 204.1314 (M^+); found 204.1335.

1-Butyl-2-fluoronaphthalene (20a)

To a solution of **18a** (61 mg, 0.30 mmol) in benzene (6 ml) was added DDQ (202 mg, 0.89 mmol) under a nitrogen atmosphere. After the reaction mixture was refluxed for 3 h, and then the mixture was filtered. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane) to give **20a** (43 mg, 0.21 mmol, 71%) as a collorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.7 Hz), 1.46 (3H, tq, J = 7.4, 7.4 Hz), 1.63–1.69 (2H, m), 3.07 (2H, td, J = 7.9, 2.2 Hz), 7.22 (1H, dd, J = 9.2, 9.2 Hz), 7.42 (1H, dd, J = 7.0, 7.0 Hz), 7.52 (1H, dd, J = 7.6, 7.6 Hz), 7.67 (1H, dd, J = 9.2, 5.5 Hz), 7.82 (1H, d, J = 7.6 Hz), 7.99 (1H, d, J = 8.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 22.8, 24.1 (d, J_{CF} = 4 Hz), 32.3, 116.0 (d, J_{CF} = 27 Hz), 123.6 (d, J_{CF} = 7 Hz), 124.5 (d, J_{CF} = 3 Hz), 126.5, 127.9 (d, J_{CF} = 10 Hz), 128.7, 130.8, 133.0 (d, J_{CF} = 6 Hz), 158.2 (d, J_{CF} = 243 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 43.7 (1F, m) ppm.

IR (neat) 2958, 2873, 1628, 1516, 1468, 1392, 1227, 806, 744, 665 cm^{-1}.

MS (20 eV) *m/z* 202 (M^+; 53), 159 (100), 133 (32).

HRMS calcd for $C_{14}H_{15}F$ 202.1158 (M^+); found 202.1135.

1-*sec*-Butyl-2-fluoronaphthalene (20b)

Compound **20b** was prepared by the method described for **20a** using **18b** (90 mg, 0.44 mmol), benzene (6 ml), DDQ (300 mg, 1.32 mmol). Purification by thin layer chromatography on silica gel (hexane) gave **20b** (63 mg, 0.310 mmol, 70%) as a collorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2 Hz), 1.46 (3H, dd, J = 7.2, J_{HF} = 1.2 Hz), 1.81–2.03 (2H, m), 3.50–3.62 (1H, m), 7.19 (1H, dd, J_{HF} = 11.3, J = 9 Hz), 7.40 (1H, dd, J = 7.0, 7.0 Hz), 7.50 (1H, dd, J = 7.8, 7.8 Hz), 7.66 (1H, dd, J = 9.0, J_{HF} = 5.4 Hz), 7.80 (1H, d, J

= 7.8 Hz), 8.14 (1H, d, J = 7.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.9, 19.6 (d, J_{CF} = 4 Hz), 28.8 (d, J_{CF} = 4 Hz), 33.8, 116.8 (d, J_{CF} = 29 Hz), 123.7, 124.4 (d, J_{CF} = 3 Hz), 126.4, 126.6 (d, J_{CF} = 11 Hz), 128.3 (d, J_{CF} = 10 Hz), 128.9, 131.0, 133.1 (d, J_{CF} = 8 Hz), 159.1 (d, J_{CF} = 246 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 48.9 (1F, br s) ppm.

IR (neat) 2946, 2873, 1598, 1515, 1463, 1394, 1222, 929, 808, 744 cm^{-1}.

MS (20 eV) *m/z* 202 (M^+; 31), 173 (100), 171 (13).

HRMS calcd for $C_{14}H_{15}F$ 202.1158 (M^+); found 202.1127.

4-Butyl-3-fluoro-1,2-dihydro-2-naphthonitrile (19a)

To a solution of *tert*-butyllithium (0.59 ml, 1.64 M in pentane, 0.98 mmol) in THF (4 ml) was added **17a** (122 mg, 0.49 mmol) in THF (2 ml) at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. The reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and 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 **19a** (34 mg, 0.15 mmol, 31%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, J = 7.3 Hz), 1.39 (2H, tq, J = 7.3, 7.3 Hz), 1.44–1.59 (2H, m), 2.51–2.62 (2H, m), 3.18–3.33 (2H, m), 3.72 (1H, dt, J = 6.0, 6.0 Hz), 7.17–7.30 (4H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.6, 23.4 (d, J_{CF} = 4 Hz), 28.2 (d, J_{CF} = 27 Hz), 30.2 (d, J_{CF} = 2 Hz), 33.1 (d, J_{CF} = 3 Hz), 117.6, 118.6 (d, J_{CF} = 12 Hz), 123.9 (d, J_{CF} = 7 Hz), 127.3 (d, J_{CF} = 2 Hz), 127.8, 128.0, 129.0, 132.1 (d, J_{CF} = 6 Hz), 149.4 (d, J_{CF} = 266 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 50.9 (1F, s) ppm.

IR (neat) 2958, 2241, 1680, 1489, 1454, 1236, 1190, 1157, 1111, 764 cm^{-1}.

MS (20 eV) *m/z* 229 (M^+; 44), 187 (100).

HRMS calcd for $C_{15}H_{16}NF$ 229.1267 (M^+); found 229.1261.

4-Butyl-3-fluoro-2-naphthonitrile (21a)

Butyllithium (0.42 ml, 1.5 M in hexane, 0.65 mmol) was added to a THF (1 ml) solution of HMDS (0.14 ml, 0.65 mmol) at –78 °C under a nitrogen atmosphere. The reaction was stirred for 30 min, and then **17a** (81 mg, 0.33 mmol) in THF (2 ml) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. 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 dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude products were treated with DDQ (111 mg, 0.448 mmol) in refluxing benzene (4 ml) for 3 h. 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 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 **21a** (50 mg, 0.513 mmol, 68%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 1.45 (2H, tq, J = 7.4, 7.4 Hz), 1.61–1.69 (2H, m), 3.08 (2H, dt, J = 7.8, 2.3 Hz), 7.55 (1H, d, J = 7.3 Hz), 7.68 (1H, d, J = 7.6 Hz), 7.86 (1H, d, J = 7.9 Hz), 8.01 (1H, d, J = 8.2 Hz), 8.06 (1H, d, J = 6.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.7, 24.2 (d, J_{CF} = 4 Hz), 32.0, 101.1 (d, J_{CF} = 22 Hz), 114.8, 123.9 (d, J_{CF} = 6 Hz), 124.8 (d, J_{CF} = 15 Hz), 126.3 (d, J_{CF} = 2 Hz), 129.3, 129.7, 133.8 (d, J_{CF} = 2 Hz), 134.8 (d, J_{CF} = 6 Hz), 155.5 (d, J_{CF} = 249 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 45.2–45.3 (1F, m) ppm.

IR (neat) 2958, 2931, 2235, 1741, 1628, 1448, 1254, 777, 750, 665 cm^{-1}.

MS (20 eV) *m/z* 227 (M^+; 58), 184 (100).

HRMS calcd for $C_{15}H_{14}NF$ 227.1110 (M^+); found 227.1125.

4-*sec*-Butyl-3-fluoro-2-naphthonitrile (21b)

Compound **21b** was prepared by the method described for **21a** using butyllithium (0.40 ml, 1.6 M in hexane, 0.66 mmol), THF (2 ml), HMDS (106 mg, 0.66 mmol), **17b** (55 mg, 0.22 mmol) in THF (2 ml), DDQ (149 mg, 0.657 mmol), and benzene (4 ml). Purification by thin

layer chromatography on silica gel (hexane–AcOEt 5:1) gave **21b** (29 mg, 0.128 mmol, 58%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, t, J = 7.2 Hz), 1.47 (3H, dd, J = 7.2, J_{HF} = 1.4 Hz), 1.82–2.03 (2H, m), 3.58 (1H, tq, J = 7.2, 7.2 Hz), 7.54 (1H, dd, J = 7.9, 7.9 Hz), 7.67 (1H, dd, J = 7.9, 7.9 Hz), 7.87 (1H, d, J = 7.2 Hz), 8.09 (1H, d, J_{HF} = 6.1 Hz), 8.18 (1H, d, J = 7.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.8, 19.3, 28.6 (d, J_{CF} = 4 Hz), 34.0, 101.9 (d, J_{CF} = 22 Hz), 114.7, 123.5, 124.0, 126.1, 128.8 (d, J_{CF} = 11 Hz), 129.6, 129.8, 134.2, 135.0 (d, J_{CF} = 8 Hz), 156.4 (d, J_{CF} = 251 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 49.6 (1F, br s) ppm.

IR (neat) 2966, 2933, 2875, 2233, 1626, 1506, 1442, 1207, 748, 607 cm^{-1}.

MS (20 eV) *m/z* 227 (M^+; 75), 198 (100), 184 (35).

HRMS calcd for $C_{15}H_{14}NF$ 227.1110 (M^+); found 227.1096.

_o_-(1-Butyl-2,2-difluorovinyl)aniline (10a)

Butyllithium (1.56 ml, 1.63 M in hexane, 2.54 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (766 mg, 3.01 mmol) in THF (10 ml) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (1.33 ml, 1.0 M in THF, 1.33 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 3 ml), triphenylphosphine (25 mg, 0.10 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (25 mg, 0.02 mmol) and stirred for 15 min. To the solution was added the magnesium salt (generated from *o*-iodoaniline (238 mg, 1.09 mmol) and dibutylmagnesium (2.47 ml, 0.44 M in Et_2O, 1.09 mmol) in THF (3 ml) at 0 °C for 30 min) and copper(I) iodide (230 mg, 1.21 mmol). After the mixture had been stirred for 1 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column

chromatography on silica gel (hexane–AcOEt 10:1) to give **10a** (176 mg, 0.831 mmol, 77%) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.1 Hz), 1.30–1.35 (4H, m), 2.29 (1H, tt, J = 7.0 Hz, J_{HF} = 2.3 Hz), 3.66 (2H, br s), 6.70–6.77 (2H, m), 7.00 (1H, dd, J = 7.6, 1.5 Hz), 7.12 (1H, ddd, J = 7.6, 7.6, 1.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 27.7, 29.8 (dd, J_{CF} = 3, 3 Hz), 89.1 (dd, J_{CF} = 22, 17 Hz), 115.6, 118.4, 119.0 (d, J_{CF} = 3 Hz), 128.9, 130.6, (d, J_{CF} = 2 Hz), 144.3, 152.8 (dd, J_{CF} = 290, 288 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 72.7 (1F, d, J_{FF} = 43 Hz), 68.7 (1F, d, J_{FF} = 43 Hz) ppm.

IR (neat) 3475, 3375, 2960, 2930, 2860, 1740, 1620, 1495, 1230 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 211 (M^+; 100), 168 (59), 148 (43).

Anal. Found: C, 68.14; H, 7.07, N; 6.52. Calcd for $C_{12}H_{15}NF_2$: C, 68.23; H, 7.16; N, 6.63%.

***o*-(1-*sec*-Butyl-2,2-difluorovinyl)aniline (10b)**

Compound **6b** was prepared by the method described for **6a** using butyllithium (1.56 ml, 1.63 M in hexane, 2.54 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (766 mg, 3.01 mmol), THF (10 ml), tributylborane (1.33 ml, 1.0 M in THF, 1.33 mmol), hexamethylphosphoric triamide (3 ml), triphenylphosphine (25 mg, 0.10 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (25 mg, 0.02 mmol), *o*-iodoaniline (238 mg, 1.09 mmol), dibutylmagnesium (2.47 ml, 0.44 M in Et_2O, 1.09 mmol), THF (3 ml), and copper(I) iodide (230 mg, 1.21 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **10b** (157 mg, 0.741 mmol, 68%) as a pale yellow liquid.

^{1}H NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 0.99 (3H, t, J = 7.3 Hz), 1.03–1.15 (3H, m), 1.31–1.45 (1H, m), 1.54–1.66 (1H, m), 2.44–2.58 (1H, m), 4.58 (2H, br s), 6.62 (1H, ddd, J = 7.4, 7.4, 1.4 Hz), 6.79 (1H, d, J = 7.4 Hz), 6.92 (1H, d, J = 7.4 Hz), 7.07 (1H, ddd, J = 7.4, 7.4, 1.4 Hz).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 10.1, 17.2, 26.9, 34.5, 92.4 (dd, J_{CF} = 16, 16 Hz), 114.5, 115.4, 116.1, 127.8, 129.6, 145.8, 151.7 (dd, J_{CF} = 290, 288 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 100 °C) 71.2 (1F, d, J_{FF} = 49 Hz), 74.1 (1F, d, J_{FF} = 49 Hz)

ppm.

IR (neat) 3390, 2960, 1730, 1615, 1495, 1455, 1300, 1215, 935, 750 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 211 (M^+; 100), 182 (57), 162 (82).

HRMS calcd for $C_{12}H_{15}NF_2$ 211.1173 (M^+); found 211.1184.

***o*-(1-Butyl-2,2-difluorovinyl)-*N*-cyanomethylaniline (34a)**

AcOH (0.75 ml, 13 mmol) was added to a solution of paraformaldehyde (286 mg, 9.5 mmol), KCN (620 mg, 9.5 mmol), and **10a** (804 mg, 3.8 mmol) in MeOH (15 ml) at room temperature under a nitrogen atmosphere. After the mixture was heated at reflux 8 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 10:1) to give **34a** (826 mg, 3.3 mmol, 87%) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.24–1.34 (4H, m), 2.20–2.28 (2H, m), 4.10 (3H, br s), 6.74 (1H, d, J = 7.5 Hz), 6.87 (1H, ddd, J = 7.5, 7.5, 1.1 Hz), 7.06 (1H, dd, J = 7.5, 1.1 Hz), 7.29 (1H, ddd, J = 7.5, 7.5, 1.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 22.2, 27.7, 29.6, 32.4, 88.2 (dd, J_{CF} = 23, 17 Hz), 111.0, 116.8, 119.4, 120.3, (d, J_{CF} = 5 Hz), 129.3, 130.6 (d, J_{CF} = 2 Hz), 142.7 (d, J_{CF} = 2 Hz), 152.9 (dd, J_{CF} = 291, 288 Hz).

^{19}F NMR (470 MHz, $CDCl_3$ / C_6F_6) 70.3 (1F, d, J_{FF} = 41 Hz), 74.0 (1F, d, J_{FF} = 41 Hz) ppm.

IR (neat) 3386, 2958, 2861, 1735, 1604, 1583, 1511, 1457, 1313, 1228, 750 cm^{-1}.

MS (70 eV) *m/z* 250 (M^+; 59), 210 (99), 148 (100).

HRMS calcd for $C_{14}H_{16}N_2F_2$ 250.1283 (M^+); found 250.1266.

***o*-(1-*sec*-Butyl-2,2-difluorovinyl)-*N*-cyanomethylaniline (34b)**

Compound **34b** was prepared by the method described for **34a** using AcOH (0.52 ml, 8.3 mmol), paraformaldehyde (178 mg, 5.9 mmol), KCN (87 mg, 1.3 mmol), **10b** (501 mg, 2.4 mmol), and MeOH (8 ml). Purification by thin layer chromatography on silica gel

(hexane–AcOEt 5:1) gave **34b** (415 mg, 1.66 mmol, 70%) as a yellow liquid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 100 °C) δ 0.80–1.20 (6H, m), 1.36 (1H, br s), 1.53–1.63 (1H, m), 2.48–2.59 (1H, m), 4.29 (2H, d, J = 4 Hz), 5.46 (1H, br s), 6.81 (1H, ddd, J = 7.7, 7.7, 1.6 Hz).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 100 °C) δ 11.0, 17.0, 26.9, 31.3, 34.3, 91.4 (dd, J_{CF} = 23, 18 Hz), 110.6, 117.0, 117.4, 117.9, 128.4, 129.7, 144.0, 151.8 (dd, J_{CF} = 290, 285 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 110 °C) 72.4 (1F, d, J_{FF} = 37 Hz), 75.0 (1F, br s) ppm.

IR (neat) 3381, 2960, 2877, 2250, 1728, 1514, 1456, 1248, 931, 756 cm^{-1}.

Anal. Found: C, 67.39; H, 6.58; N; 11.21. Calcd for $C_{12}H_{15}NF_2$: C, 67.18; H, 6.44; N, 11.19%.

_o_-(1-Butyl-2,2-difluorovinyl)-_N_-cyanophenylmethylaniline (34c)

Compound **34c** was prepared by the method described for **34a** using MeOH (5.0 ml), AcOH (0.11 ml, 1.9 mmol), benzaldehyde (142 mg, 1.3 mmol), KCN (87 mg, 1.3 mmol), **10a** (113 mg, 0.54 mmol). The reaction was carried out at reflux for 23 h. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **34c** (70 mg, 0.21 mmol, 40%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.0 Hz), 1.22–1.37 (4H, m), 2.16–2.30 (2H, m), 4.09 (1H, d, J = 8.2 Hz), 5.48 (1H, d, J = 8.2 Hz), 6.85–6.92 (2H, m), 7.08 (1H, d, J = 7.3 Hz), 7.29 (1H, dd, J = 7.3, 7.3 Hz), 7.41–7.50 (3H, m), 7.55–7.60 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.3, 27.9, 29.7, 50.1, 88.2 (d, J_{CF} = 22, 16 Hz), 112.2, 118.0, 119.8, 120.6 (d, J_{CF} = 4 Hz), 127.0, 129.3, 129.5, 130.7, 133.9, 142.4, 153.0 (dd, J_{CF} = 290, 290 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 70.6 (1F, d, J_{FF} = 40 Hz), 74.2 (1F, d, J_{FF} = 40 Hz) ppm.

IR (neat) 2958, 2929, 1736, 1581, 1508, 1454, 1311, 1246, 1228, 750 cm^{-1}.

MS (70 eV) *m/z* 326 (M^+; 13), 210 (100), 148 (87).

HRMS calcd for $C_{20}H_{20}N_2F_2$ 326.1595 (M^+); found 326.1609.

_o_-(1-Butyl-2,2-difluorovinyl)-_N_-cyano-(2-furyl)-methylaniline (34d)

Compound **34d** was prepared by the method described for **34a** using MeOH (10 ml), AcOH

(0.19 ml, 3.4 mmol), 2-furaldehyde (462 mg, 4.8 mmol), KCN (157 mg, 2.4 mmol), **10a** (203 mg, 0.96 mmol). The reaction was carried out at reflux for 7 h. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **34d** (136 mg, 0.43 mmol, 45%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.0 Hz), 1.24-1.41 (4H, m), 2.21–2.32 (2H, m), 4.23 (1H, d, J = 8.7 Hz), 5.52 (1H, d, J = 8.7 Hz), 6.42 (1H, dd, J = 2.7, 2.7 Hz), 6.56 (1H, d, J = 2.7 Hz), 6.87 (1H, d, J = 7.7 Hz), 6.90 (1H, ddd, J = 7.7, 7.7, 0.9 Hz), 7.07 (1H, dd, J = 7.7, 1.3 Hz), 7.29 (1H, ddd, J = 7.7, 7.7, 1.3 Hz), 7.47 (1H, d, J = 2.7 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 22.3, 27.8, 29.6, 44.3, 88.2 (dd, J_{CF} = 22, 16 Hz), 109.6, 110.9, 112.5, 116.3, 120.2, 121.0, 129.3, 130.8, 142.0, 144.0, 146.0, 153.1 (dd, J_{CF} = 290, 290 Hz).

^{19}F NMR (471 MHz, $CDCl_3$ / C_6F_6) 70.7 (1F, d, J_{FF} = 40 Hz), 74.3 (1F, d, J_{FF} = 40 Hz) ppm.

IR (neat) 3379, 2958, 2929, 1736, 1583, 1508, 1456, 1248, 1230, 748 cm^{-1}.

MS (70 eV) *m/z* 316 (M^+; 13), 155 (87), 91 (100).

HRMS calcd for $C_{18}H_{18}ON_2F_2$ 316.1387 (M^+); found 316.1416.

***o*-(1-Butyl-2,2-difluorovinyl)-*N*-cyano(1-cyclohexenyl)methylaniline (34e)**

Compound **34e** was prepared by the method described above using MeOH (5 ml), AcOH (0.08 ml, 1.4 mmol), 1-cyclohexene-1-carboxaldehyde (219 mg, 2.0 mmol), KCN (65 mg, 1.0 mmol), **10a** (84 mg, 0.40 mmol). The reaction was carried out at reflux for 4 h. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **34e** (69 mg, 0.21 mmol, 53%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 6.9 Hz), 1.23–1.40 (4H, m), 1.58–1.77 (4H, m), 1.87–2.07 (1H, m), 2.17–2.32 (5H, m), 3.82 (1H, d, J = 8.7 Hz), 4.70 (1H, d, J = 8.7 Hz), 6.15–6.23 (1H, m), 6.78 (1H, d, J = 7.5 Hz), 6.85 (1H, dd, J = 7.5, 7.5 Hz), 7.05 (1H, dd, J = 7.5, 1.1 Hz), 7.26 (1H, ddd, J = 7.5, 7.5, 1,1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.7, 22.3, 22.4, 25.1, 27.9, 29.7, 51.7, 88.3 (d, J_{CF} = 22, 16 Hz), 111.9, 117.8, 119.4, 120.4 (d, J_{CF} = 4Hz), 128.2, 129.2, 130.7, 131.0, 142.8, 153.0 (dd, J_{CF} = 289, 289 Hz).

^{19}F NMR (471 MHz, $CDCl_3$ / C_6F_6) 70.4 (1F, d, J_{FF} = 40 Hz), 74.1 (1F, d, J_{FF} = 40 Hz) ppm.

IR (neat) 2931, 2862, 1738, 1581, 1510, 1456, 1311, 1246, 1228, 748 cm^{-1}.

MS (20 eV) *m/z* 316 (M^+; 13), 155 (87), 91 (100).

HRMS calcd for $C_{18}H_{18}ON_2F_2$ 316.1387 (M^+); found 316.1416.

o-(1-Butyl-2,2-difluorovinyl)-*N*-cyanomethyl-*p*-toluenesulfonanilide (36a)

To a suspension of sodium hydride (NaH, 15 mg, 60% dispersion in mineral oil, 0.38 mmol) in THF (4 ml) was added **35a** (115 mg, 0.32 mmol), bromoacetonitrile (113 mg, 0.945 mmol) at room temperature. After the mixture was heated at reflux 10 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 10:1) to give **36a** (92 mg, 0.227 mmol, 72%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.0 Hz), 1.29–1.43 (4H, m), 2.35–2.45 (2H, m), 2.47 (3H, s), 3.94–4.92 (2H, br s), 7.00 (1H, d, *J* = 7.8 Hz), 7.25–7.32 (2H, m), 7.37 (2H, d, *J* = 8.2 Hz), 7.40 (1H, ddd, *J* = 7.8, 7.8, 1.1 Hz), 7.71 (2H, d, *J* = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 21.6, 22.2, 27.8, 29.8, 39.5, 90.7 (d, J_{CF} = 24. 15 Hz), 114.1, 128.4, 128.4, 129.1, 129.6, 129.9, 132.7, 135.0, 135.3 (d, J_{CF} = 5 Hz), 137.5, 145.0, 153.2 (dd, J_{CF} =289, 286 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 69.4 (1F, d, J_{FF} = 46 Hz), 73.2 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 2952, 2925, 1743, 1360, 1238, 1163, 1099, 850, 665, 555 cm^{-1}.

Anal. Found: C, 62.17; H, 5.56; N; 6.76. Calcd for $C_{12}H_{15}NF_2$: C, 62.36; H; 5.48; N, 6.93%.

o-(1-*sec*-Butyl-2,2-difluorovinyl)-*N*-cyanomethyl-*p*-toluenesulfonanilide (36b)

Compound **36b** was prepared by the method described for **36a** using sodium hydride (NaH, 19 mg, 60% dispersion in mineral oil, 0.46 mmol), THF (4 ml), **35b** (141 mg, 0.385 mmol), and bromoacetonitrile (139 mg, 1.16 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **36b** (119 mg, 0.294 mmol, 76%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.28 (3H, br s), 1.50–1.62 (1H, m), 1.79 (1H, br s), 2.34 (1H, br s), 2.47 (3H, s), 4.18 (1H, br s), 4.80 (1H, br s), 6.94 (1H, d, J = 7.7 Hz), 7.24 (1H, ddd, J = 7.7, 7.7, 1.3 Hz), 7.31 (1H, dd, J = 7.7, 1.3 Hz), 7.33–7.41 (3H, m), 7.70 (2H, d, J = 6.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.2, 17.9, 20.9, 28.2, 37.1, 39.6, 95.7 (d, J_{CF} = 20, 13 Hz), 114.3, 128.2, 128.5, 128.8, 129.6, 129.8, 132.4, 134.9, 136.9, 137.4, 145.0, 153.3 (dd, J_{CF} = 293, 285 Hz).

^{19}F NMR (254 MHz, $CDCl_3$) 74.4 (1F, br s), 77.1 (1F, br s) ppm.

IR (neat) 2970, 2935, 2877, 1732, 1491, 1360, 1236, 1167, 1093, 665 cm^{-1}.

Anal. Found: C, 62.36; H, 5.76; N; 6.67. Calcd for $C_{12}H_{15}NF_2$: C, 62.36; H; 5.48; N, 6.93%.

4-Butyl-3-fluoroquinoline (24a)

Butyllithium (0.93 ml, 1.5 M in hexane, 1.4 mmol) was added to a tetrahydrofuran (THF, 3.5 ml) solution of 2,2,6,6-tetramethylpiperidine (221 mg, 1.6 mmol) at –78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1h at the same temperature, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and 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 5:1) gave **24a** (31 mg, 0.15 mmol, 64%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.46 (2H, tq, J = 7.4, 7.4 Hz), 1.65–1.72 (2H, m), 3.08 (2H, dt, J = 7.8, J_{HF} = 1.8 Hz), 7.59 (1H, dd, J = 7.6, 7.6 Hz), 7.66 (1H, ddd, J = 7.6, 7.6, 0.8 Hz), 7.98 (1H, dd, J = 8.4, 0.8 Hz), 8.11 (1H, dd, J = 8.4, 0.8 Hz), 8.74 (1H, d, J_{HF} = 1.2 Hz).

^{13}C NMR (126 MHz, CDCl3) δ 13.8, 22.8, 23.9(d, J_{CF} = 3 Hz), 31.8, 123.5(d, J_{CF} = 6 Hz), 127.2, 127.9(d, J_{CF} = 3 Hz), 128.0(d, J_{CF} = 4 Hz), 130.3, 131.6 (d, J_{CF} = 12 Hz), 141.0(d, J_{CF} = 29 Hz), 145.5(d, J_{CF} = 2 Hz), 154.3(d, J_{CF} = 251 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 28.6 (1F, s) ppm.

IR (neat) 2960, 2931, 1512, 1464, 1379, 1323, 1225, 1142, 760, 665 cm^{-1}.

MS (20 eV) *m/z* 203 (M^+; 100), 161 (98).

HRMS calcd for $C_{13}H_{14}NF$ 203.1110 (M^+); found 203.1128.

4-*sec*-Butyl-3-fluoroquinoline (24b)

Compound **24b** was prepared by the method described for **24a** using THF (3.5 ml), Butyllithium (0.79 ml, 1.6 M in hexane, 1.3 mmol), 2,2,6,6-tetramethylpiperidine (201 mg, 1.4 mmol), **34b** (54 mg, 0.22 mmol) in THF (1.5 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **24b** (25 mg, 0.12 mmol, 56%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.2 Hz), 1.48 (3H, d, J = 7.2 Hz), 1.84–2.04 (2H, m), 3.55 (1H, tq J = 7.2, 7.2 Hz), 7.58 (1H, dd, *J* = 7.6, 7.6 Hz), 7.66 (1H, dd, *J* = 7.6, 7.6 Hz), 8.07–8.20 (2H, m), 8.71 (1H, dd, J_{HF} = 3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 19.2, 28.5 (d, J_{CF} = 3 Hz), 33.7, 123.6, 127.1, 127.8, 128.0 (d, J_{CF} = 5 Hz), 130.5, 135.4, (d, J_{CF} = 10 Hz), 141.8 (d, J_{CF} = 40 Hz), 145.7, 154.9 (d, J_{CF} = 254 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 33.0 (1F, s) ppm.

IR (neat) 2966, 2875, 1599, 1512, 1460, 1371, 1252, 1209, 1144, 760 cm^{-1}.

HRMS calcd for $C_{13}H_{14}NF$ 203.1110 (M^+); found 203.1083.

4-Butyl-3-fluoro-2-phenylquinoline (24c)

To a suspension of sodium hydride (NaH, 15 mg, 60% dispersion in mineral oil, 0.37 mmol) in N,N-dimethyl formamide (DMF, 2.5 ml) was added **34c** (58 mg, 0.18 mmol) in DMF (1.5 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1.5 h at room temperature, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 5:1) to give **24c** (40 mg, 0.14 mmol, 81%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, *J* = 7.6 Hz), 1.49 (2H, tq, *J* = 7.6, 7.6 Hz),

1.67–1.76 (2H, m), 3.14 (2H, td J = 7.6 Hz, J_{HF} = 1.9 Hz), 7.49–7.57 (4H, m), 7.63–7.67 (1H, m), 7.96 (1H, d, J = 8.2 Hz), 8.02–8.06 (2H, m), 8.16 (1H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.8, 24.7 (d, J_{CF} = 4 Hz), 31.9, 123.3 (d, J_{CF} = 5 Hz), 126.8, 127.8 (d, J_{CF} = 3 Hz), 128.1, 128.4, 129.3, 129.4, 130.8, 132.6 (d, J_{CF} = 15 Hz), 136.2 (d, J_{CF} = 5 Hz), 145.2 (d, J_{CF} = 3 Hz), 148.6 (d, J_{CF} = 17 Hz), 152.9 (d, J_{CF} = 256 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 32.4 (1F, s) ppm.

IR (neat) 2958, 2929, 2871, 1603, 1458, 1406, 1381, 1362, 1192, 760 cm^{-1}.

MS (20 eV) *m/z* 279 (M^+; 100), 237 (93), 236 (92).

HRMS calcd for $C_{19}H_{18}NF$ 279.1423 (M^+); found 279.1385.

4-Butyl-3-fluoro-2-(2-furyl)-quinoline (24d)

Compound **24d** was prepared by the method described for **24c** using DMF (3 ml), NaH (18 mg, 60% dispersion in mineral oil, 0.45 mmol), **34d** (68 mg, 0.22 mmol) in DMF (2 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **24d** (47 mg, 0.17 mmol, 81%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.5 Hz), 1.48 (2H, tq, J = 7.5, 7.5 Hz), 1.71 (2H, tt, J = 7.5, 7.5 Hz), 3.12 (2H, td, J = 7.5 Hz, J_{HF} = 2.0 Hz), 6.61 (1H, dd, J = 3.7 Hz), 7.27 (1H, dd, J = 3.7, 3.7 Hz), 7.53 (1H, dd, J = 7.9, 7.9 Hz), 7.65 (1H, dd, J = 7.9, 7.9 Hz), 7.72 (1H, s), 7.92 (1H, dd, J = 7.9 Hz), 8.21 (1H, d, J = 7.9 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.8, 24.0 (d, J_{CF} = 4 Hz), 31.8, 112.0, 114.6 (d, J_{CF} = 14 Hz), 123.2 (d, J_{CF} = 5 Hz), 126.7, 127.2, 128.3, 130.2, 132.4 (d, J_{CF} = 14 Hz), 139.1 (d, J_{CF} = 16 Hz), 144.5, 145.0, 148.8, 151.4 (d, J_{CF} = 258 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 32.9(1F, s) ppm.

IR (neat) 2958, 2873, 1606, 1504, 1427, 1356, 1026, 758, 594 cm^{-1}.

MS (20 eV) *m/z* 269 (M^+; 100), 227 (17), 198 (21).

HRMS calcd for $C_{17}H_{16}ONF$ 269.1216 (M^+); found 269.1187.

4-Butyl-2-(1-cyclohexenyl)-3-fluoroquinoline (24e)

Compound **24e** was prepared by the method described for **24c** using DMF (1 ml), NaH (8.9

mg, 60% dispersion in mineral oil, 0.22 mmol), **34e** (35 mg, 0.11 mmol) in DMF (2 ml). The reaction was carried out at 70 °C for 1.5 h. Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **24e** (8.9 mg, 0.028 mmol, 27%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.6 Hz), 1.47 (2H, tq, J = 7.6, 7.6 Hz), 1.64–1.86 (6H, m), 2.28–2.35 (2H, m), 2.59–2.66 (2H, m), 3.07 (2H, td, J = 7.6 Hz, J_{HF} = 2.0 Hz), 6.49–6.54 (1H, m), 7.51 (1H, dd, J = 7.8, 7.8 Hz), 6.61 (1H, ddd, J = 7.8, 7.8, 1.2 Hz), 7.90 (1H, d, J = 7.8 Hz), 8.06 (1H, d, J = 7.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.0, 22.8, 22.8, 24.1 (d, J_{CF} = 4 Hz), 26.0, 27.1 (d, J_{CF} = 3 Hz), 31.9, 123.2 (d, J_{CF} = 5 Hz), 126.3, 127.4, 127.7, 130.1, 131.8 (d, J_{CF} = 15 Hz), 132.4 (d, J_{CF} = 7 Hz), 134.9 (d J_{CF} = 5 Hz), 144.7, 151.1 (d, J_{CF} = 17 Hz), 152.8 (d, J_{CF} = 256 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 35.2 (1F, s) ppm.

IR (neat) 2956, 1603, 1502, 1412, 1385, 1338, 11236, 1184, 1143, 758 cm^{-1}.

MS (20 eV) *m/z* 283 (M^+; 100), 203 (29), 193 (47).

HRMS calcd for $C_{19}H_{22}NF$ 283.1736 (M^+); found 283.1713.

4-Butyl-2-cyano-3-fluoroquinoline (25a)

To a suspension of potassium carbonate (K_2CO_3, 43 mg, 0.31 mmol) in DMF (4 ml) was added **36a** (60 mg, 0.15 mmol) in DMF (1.5 ml) at 50 °C under a nitrogen atmosphere. The reaction mixture was stirred for 7 h at same temperature, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and 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 5:1) to give **25a** (29 mg, 0.13 mmol, 85%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.6 Hz), 1.47 (2H, tq, J = 7.6, 7.6 Hz), 1.66–1.74 (2H, m), 3.14 (2H, td, J = 7.6 Hz, J_{HF} = 1.8 Hz), 7.71–7.76 (1H, m), 7.78 (1H, ddd, J = 6.9, 6.9, 1.5 Hz), 8.01–8.04 (1H, m), 8.13–8.17 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 24.5, 32.0, 114.0, 123.6 (d, J_{CF} = 5 Hz), 124.6 (d, J_{CF} = 1

Hz), 129.6 (d, J_{CF} = 3 Hz), 129.9 130.3, 131.2, 134.7 (d, J_{CF} = 12 Hz), 145.6, 154.4 (d, J_{CF} = 260 Hz).

^{19}F NMR (471 MHz $CDCl_3$ / C_6D_6) 34.7 (1F,s) ppm.

IR (neat) 2960, 2931, 2873, 2239, 1599, 1504, 1456, 1363, 1184, 764 cm^{-1}.

Anal. Found: C, 73.58; H, 5.80; N; 12.14. Calcd for $C_{14}H_{13}N_2F$: C, 73.66; H; 5.74; N, 12.27%.

4-*sec*-Butyl-2-cyano-3-fluoroquinoline (25b)

Compound **25b** was prepared by the method described for **25a** using potassium carbonate (K_2CO_3, 119 mg, 0.861 mmol), DMF (8 ml), and **36b** (166 mg, 0.410 mmol) in DMF (1.5 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **25b** (74 mg, 0.322 mmol, 79%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, J = 7.2 Hz), 1.51 (3H, dd, J = 7.2, J_{HF} = 1.5 Hz), 1.88–2.04 (2H, m), 3.61 (1H, tq, J = 7.2 7.2 Hz), 7.20–7.83 (2H, m), 8.14–8.17 (1H, m), 8.20 (1H, d, J = 8.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.6, 18.9 (d, J_{CF} = 3 Hz), 28.3 (d, J_{CF} = 3 Hz), 34.1, 113.7 (d, J_{CF} = 3 Hz), 123.6 (d, J_{CF} = 4 Hz), 125.0 (d, J_{CF} = 22 Hz), 129.3 (d, J_{CF} = 5 Hz), 129.5, 129.9, 131.0, 138.3 (d, J_{CF} = 9 Hz), 145.4, 154.7 (d, J_{CF} = 262 Hz).

^{19}F NMR (254 MHz, $CDCl_3$) 38.5 (1F, s) ppm.

IR (neat) 2968, 2937, 2239, 1589, 1504, 1454, 1354, 1198, 1149, 762 cm^{-1}.

Anal. Found: C, 73.44; H, 5.83; N; 11.99. Calcd for $C_{14}H_{13}N_2F$: C, 73.66; H; 5.74; N, 12.27%.

4-Butyl-3-fluoro-2-quinolinecarboxylic acid (39a)

To a solution of **25a** in EtOH–H_2O (3:1, 4 ml) was added sodium hydroxide (NaOH, 45 mg, 1.2 mmol) at room temperature. The reaction mixture was heated under reflux for 2 h, and then 2 N HCl (10 ml) was added. Organic materials were extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, to give **39a** (49 mg, 0.21 mmol, 94%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.6 Hz), 1.48 (2H, tq, J = 7.6, 7.6 Hz), 1.70 (2H, tt, J = 7.6, 7.6 Hz), 3.17 (2H, td, J = 7.6, 7.6Hz), 7.74 (1H, ddd, J = 7.7, 7.7, 1.1 Hz),

7.78 (1H, ddd, J = 7.7, 7.7, 1.3 Hz), 8.05 (1H, d, J = 7.7 Hz), 8.15 (1H, dd, J = 7.7 1.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.7, 24.3 (d, J_{CF} = 3 Hz), 31.8, 123.7 (d, J_{CF} = 5 Hz), 129.6, 129.7, 130.2, 130.8 (d, J_{CF} = 3 Hz), 153.7 (d, J_{CF} = 266 Hz), 161.5 (d, J_{CF} = 6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 34.1 (1F, s) ppm.

IR (neat) 2958, 2931, 2873, 1732, 1460, 1381, 1329, 1221, 1173, 762 cm^{-1}.

MS (20 eV) *m/z* 247 (M^+; 11), 203 (100), 174 (72).

HRMS calcd for $C_{14}H_{14}NO_2F$ 247.1009 (M^+); found 247.0990.

4-Butyl-2-aminomethyl-3-fluoro quinoline (39b)

10% Palladium on carbon (12 mg) and **25a** (60 mg, 0.26 mmol) was added to a MeOH (5 ml) solution at room temperature under a hydrogen atmosphere. The reaction mixture was stirred for 24 h at room temperature. The solution was filtered and then removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20 containing of 1% of Et_3N) to give **39b** (49 mg, 0.213 mmol, 81%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.5 Hz), 1.46 (2H, tq, J = 7.5, 7.5 Hz), 1.62–1.71 (2H, m), 2.01 (2H, s), 3.06 (2H, td, J = 7.5, J_{HF} = 1.9 Hz), 4.02 (2H, d, J_{HF} = 1.6 Hz), 7.54 (1H, dd, J = 8.0, 8.0 Hz), 7.64 (1H, ddd, J = 8.0, 8.0, 1.1 Hz), 7.93 (1H, d, J = 8.0 Hz), 8.06 (1H, d, J = 8.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.7, 23.9 (d, J_{CF} = 3 Hz), 31.8, 442.9, 123.4 (d, J_{CF} = 5 Hz), 126.4, 127.7 (d, J_{CF} = 3 Hz), 127.8, 129.7, 131.1 (d, J_{CF} = 13 Hz), 144.7 (d, J_{CF} = 3 Hz), 152.6 (d, J_{CF} = 253 Hz).

^{19}F NMR (254 MHz, $CDCl_3$) 27.0 (1F, s) ppm.

IR (neat) 3371, 3068, 2958, 2929, 2862, 1508, 1389, 1344, 1141, 760 cm^{-1}.

MS (20 eV) *m/z* 232 (M^+; 53), 216 (100), 204 (55).

HRMS calcd for $C_{14}H_{17}N_2F$ 232.1376 (M^+); found 232.1362.

4-Butyl-3-fluoroisoquinoline *N*-oxide (41a)

Butyllithium (1.1 ml, 1.49 M in hexane, 1.7 mmol) was added to a THF (4.5 ml) solution of

2,2,2-trifluoroethyl *p*-toluenesulfonate (203 mg, 0.80 mmol) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (0.88 ml, 1.0 M in THF, 0.88 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with HMPA (1.5 ml), triphenylphosphine (17 mg, 0.06 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (25 mg, 0.02 mmol) and stirred for 15 min To the resulting solution was added *o*-iodobenzaldehyde (167 mg, 0.72 mmol) and copper(I) iodide (153 mg, 0.80 mmol). After the mixture had been stirred for 15 min at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then organic materials were extracted with Et_2O three times. After removal of the solvent under reduced pressure, the residue was dissolved in DMF 3 ml. The resulting mixture was treated with $NH_2OH \cdot HCl$ (160 mg, 0.96 mmol) and Et_3N (0.22 ml, 1.76 mmol) stirred for 12 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with $CHCl_3$ three times. After removal of the solvent under reduced pressure by thin layer chromatography on silica gel (methanol–ethyl acetate 1: 20) to give **41a** (112 mg, 0.512 mmol, 83%) as a pale yellow liquid.

^{1}H NMR ((500 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.5 Hz), 1.47 (2H, tq, J = 7.5, 7.5 Hz), 1.69 (2H, tt, J = 7.5, 7.5 Hz), 3.06 (2H, dt, J_{HF} = 2.0 Hz, J = 7.5 Hz), 7.59 (1H, t, J = 7.8 Hz), 7.66 (1H, t, J = 7.8 Hz), 7.74 (1H, d, J = 7.8 Hz), 7.90 (1H, d, J = 7.8 Hz), 8.75 (1H, d, J_{HF} = 6.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.6, 24.3, 31.5, 119.0 (d, J_{CF} = 17 Hz), 123.2 (d, J_{CF} = 6 Hz), 125.6 (d, J_{CF} = 2 Hz), 126.1 (d, J_{CF} = 3 Hz), 128.2, 128.23, 129.5, 135.6 (d, J_{CF} = 7 Hz), 153.5 (d, J_{CF} = 252 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 46.7 (d, J_{FH} = 6 Hz) ppm.

IR (KBr disk) 1630, 1605, 1500, 1485, 1440, 1390, 1325, 1240, 1190, 1120 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 219 (M^+; 100), 160 (72), 149 (47), 101 (17).

Anal. Calcd for $C_{13}H_{14}NOF$: C, 71.21; H, 6.44; N, 6.39. Found: C, 71.15; H, 6.43; N, 6.24.

4-*sec*-Butyl-3-fluoroisoqunoline *N*-oxide (41b)

Compound **41b** was prepared by the method described for **41a** using Butyllithium (1.1 ml, 1.49 M in hexane, 1.7 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (203 mg, 0.80 mmol), tri-*sec*-butylborane (0.88 ml, 1.0 M in THF, 0.88 mmol), HMPA (1.5 ml), triphenylphosphine (17 mg, 0.06 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1), *o*-iodobenzaldehyde (167 mg, 0.72 mmol), copper(I) iodide (153 mg, 0.80 mmol) in THF (4.5 ml). $NH_2OH \cdot HCl$ (160 mg, 0.96 mmol), and Et_3N (0.22 ml, 1.76 mmol) in DMF (3 ml). Purification by thin layer chromatography on silica gel (methanol–ethyl acetate 1:20) to give **41b** (109 mg, 0.497 mmol, 69%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, J = 7.2 Hz), 1.48 (3H, dd, J = 7.2, 1.4 Hz), 1.84-2.04 (2H, m), 3.50 (1H, tq, J = 7.2, 7.2 Hz), 7.58 (1H, t, J = 7.8 Hz), 7.65 (1H, t, J = 7.8 Hz), 7.74 (1H, d, J = 7.8 Hz), 8.05 (1H, d, J = 7.8 Hz), 8.77 (1H, d, J_{HF} = 6.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 28.2 (d, J_{CF} = 3 Hz), 33.6, 123.2 (d, J_{CF} = 15 Hz), 123.2 (d, J_{CF} = 4 Hz), 125.8 (d, J_{CF} = 2 Hz), 126.2 (d, J_{CF} = 3 Hz), 128.0 (d, J_{CF} = 3 Hz), 129.5, 129.6 (d, J_{CF} = 8 Hz), 135.7 (d, J_{CF} = 8 Hz), 153.9 (d, J_{CF} = 256 Hz).

^{19}F NMR (471 MHz $CDCl_3$) 50.9 (1F, bs) ppm.

IR (KBr disk) 2960, 2940, 2870, 1480, 1435, 1315, 1230, 1215, 1190, 1120, 920 cm^{-1}.

MS (70 eV) *m*/*z* (rel intensity) 219 (M^+; 100), 174 (50), 115 (47).

HRMS Calcd for $C_{13}H_{14}NOF$ 219.1060 (M^+); found 219.1082.

3-*tert*-Butoxy-4-butylisoquinoline *N*-oxide (42a)

To a solution of potassium *tert*-butoxide (62.8 mg, 0.560 mmol) in THF (2.5 ml) was treated with **41a** (82.0 mg, 0.374 mmol) at –78 °C. After the mixture had been stirred for 30 min at –78 °C, the reaction was quenched with H_2O–THF. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under redused pressure, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **42a** (74.1 mg, 0.271 mmol, 72%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.5 Hz), 1.49 (2H, tq, J = 7.5, 7.5 Hz), 1.62 (9H, s), 1.61–1.68 (2H, m), 3.07 (2H, t, J = 7.5 Hz), 7.47 (1H, t, J = 7.8 Hz), 7.54 (1H, dt, J =

7.8, 1.2 Hz), 7.64 (1H, d, J = 7.8 Hz), 7.82 (1H, d, J = 7.8 Hz), 8.67 (1H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 23.0, 26.6, 29.1, 31.9, 87.2, 123.5, 125.1, 126.1, 127.2, 127.4, 128.2, 129.6, 135.0, 152.1.

IR (KBr disk) 2960, 2920, 1590, 1465, 1360, 1320, 1230, 1180, 1150, 750 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 273 (M^+; 2), 217 (100), 201 (15), 158 (12).

HRMS calcd for $C_{17}H_{23}NO_2$ 273.1728 (M^+), found 273.1752.

4-Butyl-3-phenylthioisoquinoline *N*-oxide (42b)

To a solution of thiophenol (54 ml, 0.53 mmol) in THF (1 ml) was added butyllthium (0.35 ml, 1.51 M in hexane, 0.53 mmol) at –78 °C under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at –78 °C and then treated with **41a** (96 mg, 0.44 mmol) at –78 °C. After being stirred for 3 h, the reaction mixture warm and stirred for an additional 2 h. to 0 °C for 5 h. The reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with (MeOH–AcOEt 1:20) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under redused pressure, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **42b** (115 mg, 0.372 mmol, 85%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.6 Hz), 1.51 (2H, tq, J = 7.6, 7.6 Hz), 1.63 (2H, tt, J = 7.6, 7.6 Hz), 3.43 (2H, t, J = 7.6 Hz), 7.14–7.19 (1H, m), 7.21–7.24 (4H, m), 7.58–7.63 (2H, m), 7.67–7.70 (1H, m), 7.93–7.96 (1H, m), 8.81 (1H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 23.0, 31.4, 32.8, 124.5, 125.3, 126.5, 127.8, 127.9, 128.8, 129.1, 129.4, 129.6, 134.5, 135.0, 141.8, 144.1.

IR (KBr disk) 3050, 2950, 2920, 1580, 1565, 1480, 1320, 1185, 1135, 740 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 309 (M^+; 9), 292 (100), 250 (75), 174 (75), 115 (22), 77 (12).

HRMS calcd for $C_{19}H_{19}NOS$ 309.1166 (M^+); found 309.1216.

4-Butyl-3-pyroridinylisoquinoline *N*-oxide (42c)

To a solution of **41a** (77.0 mg, 0.35 mmol) in toluene (2 ml) was treated with pyrolodine (0.12 ml, 1.44 mmol) at room temperature. After the mixture is refluxed for 23 h, the

volatile components were removal by evapolation, the residue was purified by thin layer chromatography on silica gel (MeOH–AcOEt 1:20) to give **42c** (69 mg, 0.253 mmol, 74%) as pale brown solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (3H, t, J = 7.4 Hz), 1.50 (2H, tq, J = 7.4, 7.4 Hz), 1.59–1.67 (2H, m), 2.06–2.10 (4H, m), 3.11–3.14 (2H, m), 7.48–7.53 (2H, m), 7.64 (1H, dd, J = 7.3, 1.2 Hz), 7.86 (1H, d, J = 8.5 Hz), 8.67 (1H, s).

^{13}CNMR (126 MHz, $CDCl_3$) δ 13.9, 23.2, 26.7, 27.9, 33.0, 49.5, 124.2, 125.1, 127.7, 127.8, 128.0, 129.5, 135.3, 135.9, 148.6.

IR (KBr disk) 3289, 2954, 2925, 1473, 1430, 1321, 1226, 1168, 1122, 759 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 270 (M^+; 12), 254 (100).

HRMS calcd for $C_{17}H_{22}N_2O$ 270.1746 (M^+), found 270.1764.

4-Butyl-3-fluoro-1-phenylaminoisoquinoline (**43**)

To a solution of **41a** (72.5 mg, 0.323 mmol) in DMF (4 ml) was added phenyl isocyanate (0.074 ml, 0.678 mmol) under a nitrogen atmosphere, and the mixture was warmed to 100 °C. After the reaction mixture had been stirred at 100 °C for 21 h, phosphate buffer (pH 7) was added. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:3) to give **43** (55 mg, 0.185 mmol, 57%) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.5 Hz), 1.43 (2H, tq, J = 7.5, 7.5 Hz), 1.61 (2H, tt, J = 7.5, 7.5 Hz), 2.89 (2H, t, J = 7.5 Hz), 7.05 (1H, tt, J = 7.3, 1.1 Hz), 7.15 (1H, s), 7.34 (2H, dd, J = 8.6, 7.3 Hz), 7.42 (1H, t, J = 7.8 Hz), 7.64 (1H, t, J = 7.8 Hz), 7.68 (2H, dd, J = 8.6, 1.1 Hz), 7.88 (1H, d, J = 7.8 Hz), 7.89 (1H, d, J = 7.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 14.0, 22.6, 23.6, 32.2, 104.4 (d, J_{CF} = 31 Hz), 117.0 (d, J_{CF} = 2 Hz), 120.0, 122.0, 123.9 (d, J_{CF} = 7 Hz), 124.5 (d, J_{CF} = 2 Hz), 129.0, 130.3, 139.7 (d, J_{CF} = 7 Hz), 139.7, 149.8 (d, J_{CF} = 20 Hz), 157.2 (d, J_{CF} = 20 Hz).

^{19}F NMR (471 MHz $CDCl_3$) 79.4 (1F, s) ppm.

IR (neat) 3450, 2950, 2870, 1620, 1540, 1440, 1415, 1340, 1120, 755 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 294 (M^+; 45), 251 (100), 204 (7), 128 (7), 77 (19).

Anal. Calcd for $C_{19}H_{19}N_2F$: C, 77.52; H, 6.51; N, 9.52. Found: C, 77.22; H, 6.64; N, 9.31.

4-Butyl-3-fluorocinnoline (46a)

CF_3CO_2H (0.05 ml, 0.612 mmol) and ^{i}AmONO (0.08 ml, 0.612 mmol) were added to a CH_3CN (3 ml) solution of **10a** (64.7 mg, 0.306 mmol) at 0 °C. The reaction mixture was stirred for 30 min. The solution was treated with PhSH (0.10 ml, 0.92 mmol) and stirred for 0.5 h at 0 °C. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and 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 5:1) to give **46a** (54.9 mg, 0.269 mmol, 88%) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.6 Hz), 1.47 (2H, tq, J = 7.6, 7.6 Hz), 1.71 (2H, tt, J = 7.6, 7.6 Hz), 3.09 (2H, t, J = 7.6 Hz), 7.70–7.78 (2H, m), 8.00–8.05 (1H, m), 8.48–8.52 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.8, 23.7, 31.7, 122.0 (d, J_{CF} = 25 Hz), 122.8 (d, J_{CF} = 7 Hz), 129.2 (d, J_{CF} = 2 Hz), 129.4 (d, J_{CF} = 5 Hz), 130.6, 131.5, 150.5 (d, J_{CF} = 2 Hz), 162.4 (d, J_{CF} = 236 Hz).

^{19}F NMR (471 MHz $CDCl_3$) 67.6 (1F, s) ppm.

IR (neat) 2960, 2870, 1620, 1580, 1535, 1440, 1320, 1135, 1080, 965, 760 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 204 (M^+; 100), 162 (43), 133 (47).

Anal. Calcd for $C_{12}H_{13}N_2F$: C, 70.57; H, 6.42; N, 13.72. Found: C, 70.32; H, 6.28; N, 13.34.

4-*sec*-Butyl-3-fluorocinnoline (46b)

Compound **46b** was prepared by the method described for **46a** using CH_3CN (3 ml), CF_3CO_2H (0.06 ml, 0.72 mmol), ^{i}AmONO (0.10 ml, 0.72 mmol), **5b** (75.7 mg, 0.358 mmol), and PhSH (0.11 ml, 1.07 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) to give **46b** (63.5 mg, 0.311 mmol, 87%) as a yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.49 (3H, dd, J = 7.2 Hz, J_{HF} = 1.5 Hz), 1.87–2.03 (2H, m), 3.57 (1H, tq, J = 7.2 Hz), 7.75–7.80 (2H, m), 8.14–8.20 (2H, m), 8.48–8.52 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 18.9 (d, J_{CF} = 3 Hz), 28.2 (d, J_{CF} = 4 Hz), 33.0 (d, J_{CF} = 3 Hz), 122.9 (d, J_{CF} = 6 Hz), 125.8 (d, J_{CF} = 22 Hz), 129.1 (d, J_{CF} = 2 Hz), 129.4 (d, J_{CF} = 7 Hz), 130.7, 131.5, 160.6, 162.4 (d, J_{CF} = 238 Hz).

^{19}F NMR (471 MHz $CDCl_3$) 74.1 (1F, s) ppm.

IR (neat) 2960, 2940, 2860, 1565, 1525, 1435, 1315, 1235, 1130, 760 cm^{-1}.

MS (20 eV) *m*/*z* (rel intensity) 204 (M^+; 100), 146 (34).

Anal. Calcd for $C_{12}H_{13}N_2F$: C, 70.57; H, 6.42; N, 13.72. Found: C, 70.57; H, 6.54; N, 13.72.

_o_-(1-Butyl-2,2-difluorovinyl)benzonitrile (48a)

Butyllithium (6.63 ml, 1.60 M, in hexane, 10.6 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (1.28 mg, 5.05 mmol) in THF (20 ml) at –78 °C over 10 min under a nitrogen atomosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tri-butylborane (5.56 ml, 1.00 M in THF, 5.56 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with HMPA (6 ml), triphenylphosphine (106 mg, 0.404 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (105 mg, 0.101 mmol) and stirred for 15 min. To the resulting solution was added *o*-iodobenzonitrile (1.12 g, 4.88 mmol) and copper(I) iodide (1.06 g, 5.57 mmol). After the mixture had been stirred for 1 h at room temperature , the reaction was quenched with phosphate buffer (pH 7). The mixture was filttered, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (AcOEt–hexane 1:5) to give **48a** (906 mg, 4.19 mmol, 84%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 1.26–1.38 (4H, m), 2.44 (2H, tt, J = 7.3 Hz, J_{CF} = 2.2 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.42 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.60 (1H, ddd, J = 7.7, 7.7, 1.2 Hz) 7.70 (1H, dd, J = 7.7, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.1, 28.2, 29.6 (d, J_{CF} = 2 Hz), 90.6 (dd, J_{CF} = 24, 15 Hz), 113.4, 117.6, 128.2, 130.4 (d, J_{CF} = 2 Hz), 132.7, 133.2, 138.2 (dd, J_{CF} = 5, 2 Hz), 153.4 (dd, J_{CF} = 290, 290 Hz).

^{19}F NMR (471 MHz $CDCl_3$) 71.7 (1F, dt, J_{FF} = 39 Hz, JFH = 2 Hz), 74.1 (1F, dt, J_{FF} = 39 Hz, J_{FH} = 3 Hz) ppm.

IR (neat) 2970, 2940, 2870, 2240, 1740, 1280, 1240, 1140, 975, 765 cm^{-1}.

MS (70 eV) *m/z* 221 (M^+; 36), 179 (100), 131 (45).

HRMS calcd for $C_{13}H_{13}NF_2$ 221.1016 (M^+), found 221.1000.

Anal. Calcd for C, 70.57; H, 5.92; N, 6.33. Found: C, 70.93; H, 5.95; N, 6.17.

_o_-(1-_sec_-Butyl-2,2-difluorovinyl)benzonitrile (48b)

Compound **48b** was prepared by the method described for **48a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (749 mg, 2.95 mmol), butyllithium (4.15 ml, 1.49 M in hexane, 6.19 mmol), tri-*sec*-butylborane (3.24 ml, 1.0 M in THF, 3.24 mmol), hexamethylphosphoric triamide (3 ml), triphenylphosphine (62 mg, 0.24 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (61 mg, 0.059 mmol), *o*-iodobenzonitrile (606 mg, 2.64 mmol) and copper(I) iodide (561 mg, 2.95 mmol) in THF (15 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 50:1) gave **48b** (433 mg, 1.96 mmol, 74%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, *J* = 7.1 Hz), 1.09 (3H, d, *J* = 7.1 Hz), 1.38 (1H, ddq, *J* = 14.3, 7.1, 7.1 Hz), 1.53 (1H, ddq, *J* = 14.3, 7.1, 7.1 Hz), 2.61 (1H, ddq, *J* = 7.1, 7.1, 7.1 Hz), 7.30 (1H, d, *J* = 6.7 Hz), 7.43 (1H, td, *J* = 6.7, 1.2 Hz), 7.59 (1H, td, *J* = 6.7, 1.2 Hz), 7.71 (1H, dd, *J* = 6.7, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.2, 18.6 (dd, J_{CF} = 3, 3 Hz), 28.0 (dd, J_{CF} = 3, 3 Hz), 35.7, 94.0 (dd, J_{CF} = 23, 13 Hz), 114.5, 117.9, 128.3, 130.9 (dd, J_{CF} = 2, 2 Hz), 132.4, 133.2, 137.0 (d, J_{CF} = 6 Hz), 153.4 (dd, J_{CF} = 292, 292 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 71.9 (1F, d, J_{FF} = 41 Hz), 75.6 (1F, d, J_{FF} = 41 Hz) ppm.

IR (neat) 2970, 2930, 2880, 2230, 1735, 1720, 1460, 1235, 1060, 760, 670 cm^{-1}.

MS (70 eV) m/z 221 (M^+; 30), 192 (100), 172 (40), 165 (76), 152 (35).

Anal. Calcd for $C_{13}H_{13}NF_2$: C, 70.57; H, 5.92; N, 6.33. Found: C, 70.51; H, 5.98; N, 6.39.

2-(1-Butyl-2,2-difluorovinyl)phenyl isocyanide (50a)

To a solution of **49a** (223 mg, 0.93 mmol) in CH_2Cl_2 (8 ml) was added triethylamine (0.29 ml, 2.05 mmol) and phosphorus oxychloride (0.10 ml, 1.12 mmol) at 0 °C under a nitrogen atmosphere. After being stirred for 0.5 h, the reaction mixture was poured into 10% aqueous sodium carbonate. Organic materials were extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and 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 **50a** (171 mg, 0.77 mmol, 83%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.0 Hz), 1.25–1.37 (4H, m), 2.38–2.43 (2H, m), 7.28 (1H, dd, J = 7.7, 1.4 Hz), 7.35 (1H, ddd, J = 7.7, 7.7, 1.6 Hz), 7.38–7.44 (2H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.1, 27.8, 29.6 (dd, J_{CF} = 3, 3 Hz), 88.9 (dd, J_{CF} = 26, 16 Hz), 127.4, 128.7, 129.4, 130.6, 131.7, 131.8, 153.2 (dd, J_{CF} = 290, 290 Hz), 166.7.

^{19}F NMR (470 MHz, $CDCl_3$) 74.5 (1F, d, J_{FF} = 39 Hz), 70.5 (1F, d, J_{FF} = 39 Hz) ppm.

IR (neat) 2960, 2930, 2860, 2130, 1740, 1705, 1275, 1240, 1135, 760 cm^{-1}.

MS (20 eV) *m/z* 221 (M^+; 14), 167 (45), 149 (100).

HRMS calcd for $C_{13}H_{13}NF_2$ 221.1016 (M^+); found 221.1022.

2-(1-*sec*-Butyl-2,2-difluorovinyl)phenyl isocyanide (50b)

To a solution of **49b** (526 mg, 2.20 mmol) in CH_2Cl_2 (15 ml) was added triethylamine (0.77 ml, 5.50 mmol) and phosphorus oxychloride (0.30 ml, 3.29 mmol) at 0 °C under a nitrogen atmosphere. After being stirred for 0.5 h, the reaction mixture was poured into 10% aqueous sodium carbonate. Organic materials were extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 10:1) to give **50b** (398 mg, 1.80 mmol, 82%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $C_6D_5CD_3$) δ 0.86 (3H, t, J = 7.3 Hz), 0.99 (3H, dd, J = 7.0, 0.9 Hz),1.22

(1H, tq, J = 7.0, 7.0 Hz), 2.44 (1H, dtq, J = 7.1, 7.1, 1.1 Hz), 6.78 (1H, ddd, J = 7.6, 7.6, 1.6 Hz), 6.85–7.00 (3H, m).

^{19}F NMR (470 MHz, $C_6D_5CD_3$) 76.8 (1F, d, J_{FF} = 41 Hz), 72.6 (1F, d, J_{FF} = 41 Hz) ppm.

IR (neat) 2966, 2877, 2121, 1736, 1460, 1238, 1061, 993, 937, 762 cm^{-1}.

MS (20 eV) *m/z* 221 (M^+; 46), 206 (69), 192 (100).

HRMS calcd for $C_{13}H_{13}NF_2$ 221.1016 (M^+); found 221.1000.

1,4-Dibutyl-3-fluoroisoquinoline (51a)

To a solution of **48a** (93 mg, 0.42 mmol) in Et_2O (3 ml) was added butyllithium (0.34 ml, 1.49 M in hexane, 0.50 mmol) at –78 °C under a nitrogen atmosphere. After the mixture had been stirred for 0.5 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The conbined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:5) to give **51a** (94 mg, 0.36 mmol, 86%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.6 Hz), 0.98 (3H, t, J = 7.6 Hz), 1.45 (2H, tq, J = 7.6, 7.6 Hz), 1.49 (2H, tq, J = 7.6, 7.6 Hz), 1.61–1.69 (2H, m), 1.80–1.87 (2H, m), 2.99 (2H, t, J = 7.6 Hz), 3.22 (2H, t, J = 7.9 Hz), 7.49 (1H, ddd, J = 8.2, 7.0, 0.9 Hz), 7.67 (1H, dd, J = 7.6, 7.6 Hz), 7.98 (1H, d, J = 8.6 Hz), 8.15 (1H, d, J = 8.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 22.8, 22.9, 24.0, 31.8, 32.1, 34.5, 112.3 (d, J_{CF} = 30 Hz), 123.6 (d, J_{CF} = 7 Hz), 125.1 (d, J_{CF} = 2 Hz), 125.7 (d, J_{CF} = 2 Hz), 126.2, 130.1, 138.9 (d, J_{CF} = 6 Hz), 157.9 (d, J_{CF} = 230 Hz), 159.9 (d, J_{CF} = 16 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 78.9 (1F, s) ppm.

IR (neat) 2960, 2930, 2875, 1620, 1595, 1560, 1505, 1460, 1350, 1115, 760 cm^{-1}.

MS (20 eV) *m/z* 259 (M^+; 17), 217 (100), 174 (43).

Anal. Calcd for $C_{17}H_{22}NF$: C, 78.73; H, 8.55; N, 5.40. Found: C, 79.01; H, 8.66; N, 5.08.

1-Butyl-4-*sec*-butyl-3-fluoroisoquinoline (51b)

To a solution of **48b** (122 mg, 0.55 mmol) in Et_2O (5 ml) was added butyllithium (0.40 ml,

1.64 M in hexane, 0.66 mmol) at –78 °C over 10 min under a nitrogen atmosphere. After the mixture had been stirred for 7 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The conbined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:5) to give **51b** (117 mg, 0.45 mmol, 81%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.3 Hz), 0.98 (3H, t, J = 7.3 Hz), 1.44 (3H, dd, J = 7.0 Hz, J_{HF} = 1.2 Hz), 1.49 (2H, tq, J = 7.3, 7.3 Hz), 1.80–1.89 (3H, m), 1.94 (1H, ddq, J = 14.7, 7.3, 7.3 Hz), 3.23 (2H, t, J = 7.6 Hz), 3.45 (1H, ddq, J = 7.0, 7.0, 7.0 Hz), 7.49 (1H, dd, J = 7.6, 7.6 Hz), 7.66 (1H, dd, J = 7.6, 7.6 Hz), 8.14 (1H, d, J = 8.9 Hz), 8.17 (1H, d, J = 8.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.8, 13.9, 19.3 (d, J_{CF} = 3 Hz), 22.9, 28.5 (d, J_{CF} = 4 Hz), 31.6, 32.8 (d, J_{CF} = 4 Hz), 34.5, 116.4 (d, J_{CF} = 26 Hz), 123.6 (d, J_{CF} = 6 Hz), 124.9 (d, J_{CF} = 2 Hz), 125.7, 126.2, 129.9, 139.0 (d, J_{CF} = 7 Hz), 158.1 (d, J_{CF} = 233 Hz), 159.8 (d, J_{CF} = 16 Hz).

^{19}F NMR (471 MHz, $C_6D_5CD_3$) 88.1 (1F, s) ppm.

IR (neat) 2960, 2930, 2870, 1615, 1585, 1560, 1505, 1460, 1340, 1120, 790, 760 cm^{-1}.

MS (70 eV) *m/z* 259 (M^+; 26), 217 (100), 188 (41).

Anal. Calcd for $C_{17}H_{22}NF$: C, 78.73; H, 8.55; N, 5.40. Found: C, 78.57; H, 8.62; N, 5.26.

4-Butyl-3-fluoro-1-methylisoquinoline (51c)

To a solution of **48a** (95 mg, 0.43 mmol) in toluene (3 ml) was added methyllithium (0.58 ml, 0.89 M in Et_2O, 0.52 mmol) at 0 °C under a nitrogen atmosphere. After the mixture had been stirred for 0.5 h at 0 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (benzene–hexane 1:1) to give **51c** (76 mg, 0.35 mmol, 81%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.5 Hz), 1.45 (2H, tq, J = 7.5, 7.5 Hz), 1.61–1.69 (2H, m), 2.91 (3H, s), 3.00 (2H, t, J = 7.5 Hz), 7.51 (1H, ddd, J = 8.1, 6.7, 1.1 Hz),

7.69 (1H, dd, J = 7.6, 7.6 Hz), 7.98 (1H, d, J = 8.5 Hz), 8.11 (1H, d, J = 8.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 21.8, 22.7, 23.9, 32.1, 112.5 (d, J_{CF} = 30 Hz), 123.5 (d, J_{CF} = 7 Hz), 125.2 (d, J_{CF} = 2 Hz), 126.3 (d, J_{CF} = 3 Hz), 126.5, 130.3, 138.6 (d, J_{CF} = 6 Hz), 155.9 (d, J_{CF} = 17 Hz), 157.7 (d, J_{CF} = 231 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 78.5 (1F, s) ppm.

IR (neat) 2960, 2930, 2870, 1620, 1595, 1560, 1435, 1340, 1115, 760 cm^{-1}.

MS (20 eV) *m/z* 217 (M+; 24), 174 (100), 147 (22).

Anal. Calcd for $C_{14}H_{16}NF$: C, 77.39; H, 7.42; N, 6.45. Found: C, 77.41; H, 7.49; N, 6.44.

4-Butyl-3-fluoro-1-phenylisoquinoline (51d)

To a solution of **48a** (92 mg, 0.42 mmol) in toluene (3 ml) was added phenyllithium (0.49 ml, 1.01 M in chexane-Et_2O, 0.50 mmol) at –78 °C under a nitrogen atmosphere. After the mixture had been stirred for 1 h at –78 °C, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:5) to give **51d** (99 mg, 0.35 mmol, 85%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.5 Hz), 1.50 (2H, tq, J = 7.5, 7.5 Hz), 1.72 (2H, tt, J = 7.5, 7.5 Hz), 3.07 (2H, t, J = 7.5 Hz), 7.43 (1H, t, J = 7.6 Hz), 7.45–7.54 (3H, m), 7.64–7.72 (3H, m), 8.04 (1H, d, J = 8.6 Hz), 8.13 (1H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.8, 24.2, 32.1, 113.9 (d, J_{CF} = 30 Hz), 123.3 (d, J_{CF} = 7 Hz), 125.4 (d, J_{CF} = 2 Hz), 125.4 (d, J_{CF} = 3 Hz), 128.4, 128.5, 128.8, 130.1, 130.3, 138.4, 139.5 (d, J_{CF} = 6 Hz), 157.7 (d, J_{CF} = 14 Hz), 157.9 (d, J_{CF} = 231 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 79.6 (1F, s) ppm.

IR (neat) 2950, 2930, 2870, 1615, 1590, 1545, 1440, 1390, 1335, 1145, 700 cm^{-1}.

MS (70 eV) *m/z* 279 (M^+; 39), 236 (100), 179 (24), 84(97).

Anal. Calcd for $C_{19}H_{18}NF$: C, 81.69; H, 6.49; N, 5.01. Found: C, 81.71; H, 6.78; N, 4.77.

4-Butyl-3-fluoroisoquinoline (51e)

To a solution of **48a** (102 mg, 0.46 mmol) in toluene (3 ml) was added DIBAL (0.32 ml, 1.50 M in toluene, 0.49 mmol) at –45 °C over 10 min under a nitrogen atmosphere. After the mixture was warmed to 90 °C and stirred for 7 h, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:5) to give **51e** (78 mg, 0.39 mmol, 84%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 1.46 (2H, tq, J = 7.5, 7.5 Hz), 1.63–1.71 (2H, m), 3.03 (2H, td, J = 7.5 Hz, J_{HF} = 0.9 Hz), 7.52 (1H, ddd, J = 7.9, 7.9 Hz, J_{HF} = 0.8 Hz), 7.71 (1H, dd, J = 7.6, 7.6 Hz), 7.97 (1H, d, J = 8.2 Hz), 7.99 (1H, d, J = 8.9 Hz), 8.80 (1H, s).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.8, 24.1, 32.1, 115.0 (d, J_{CF} = 30 Hz), 122.9 (d, J_{CF} = 7 Hz), 125.6 (d, J_{CF} = 2 Hz), 127.6 (d, J_{CF} = 2 Hz), 128.4, 130.7, 138.4 (d, J_{CF} = 6 Hz), 148.6 (d, J_{CF} = 16 Hz), 159.1 (d, J_{CF} = 232 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 79.3 (1F, s) ppm.

IR (neat) 2960, 2930, 2870, 1620, 1590, 1440, 1425, 1250, 1220, 750 cm^{-1}.

MS (20 eV) *m/z* 203 (M^+; 67), 160 (100).

Anal. Calcd for $C_{13}H_{14}NF$: C, 76.82; H, 6.94; N, 6.89. Found: C, 76.54; H, 6.95; N, 6.76.

2,4-Dibutyl-3-fluoroquinoline (54a)

To a solution of **50a** (63 mg, 0.29 mmol) in toluene (2 ml) was added butylmagnesium bromide (0.31 ml, 1.12 M in THF, 0.34 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 15 min, the reaction mixture was cooled to 0 °C and added toluene (3 ml) and HMPA (1 ml). After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. 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 dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 10:1) to give **54a** (51 mg, 0.20 mmol, 69%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz), 0.97 (3H, t, J = 7.5 Hz), 1.41–1.51 (4H, m), 1.63–1.71 (2H, m), 1.75–1.81 (2H, m), 3.01 (2H, td, J = 7.6, 2.4 Hz), 3.06 (2H, td, J = 7.6, 1.7 Hz), 7.51 (1H, dd, J = 7.9, 7.9 Hz), 7.61 (1H, ddd, J = 7.9, 7.9, 0.9 Hz), 7.91 (1H, dd, J = 7.9, 0.9 Hz), 8.04 (1H, dd, J = 7.9, 0.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 14.0, 22.8, 22.8, 24.0 (d, J_{CF} = 4 Hz), 30.9, 31.9, 33.1, 123.4 (d, J_{CF} = 5 Hz), 126.1, 127.4 (d, J_{CF} = 3 Hz), 127.7 (d, J_{CF} = 2 Hz), 129.5, 130.9 (d, J_{CF} = 15 Hz), 144.8 (d, J_{CF} = 3 Hz), 153.3 (d, J_{CF} = 253 Hz), 153.4 (d, J_{CF} = 21 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 29.8 (1F, s) ppm.

IR (neat) 2958, 2931, 2873, 1506, 1460, 1417, 1387, 1228, 1142, 760 cm^{-1}.

MS (20 eV) *m/z* 259 (M^+; 8), 217 (25), 129 (60).

HRMS calcd for $C_{17}H_{22}NF$ 259.1736 (M^+); found 259.1718.

2-Butyl-4-*sec*-butyl-3-fluoroquinoline (54b)

To a solution of **50b** (115 mg, 0.52 mmol) in toluene (4 ml) was added butylmagnesium bromide (0.55 ml, 1.12 M in THF, 0.89 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 15 min, the reaction mixture was cooled to 0 °C and added toluene (6 ml) and HMPA (2 ml). After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. 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 dried over Na_2SO_4. After removal of the

ica gel (hexane–AcOEt 50:1) to give **54b** (81 mg, 0.31 mmol, 62%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.3 Hz), 0.97 (3H, t, J = 7.3 Hz), 1.46 (3H, t, J = 7.0 Hz), 1.47 (2H, tq, J = 7.4, 7.4 Hz), 1.76–2.04 (4H, m), 3.01 (2H, dt, J = 7.9, 2.6 Hz), 3.53 (1H, tq, J = 7.2, 7.2 Hz), 7.49 (1H, dd, J = 7.8, 7.8 Hz), 7.61 (1H, dd, J = 8.2, 8.2 Hz), 8.06 (2H, dd, J = 9.6, 9.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.8, 14.0, 19.2 (d, J_{CF} = 4 Hz), 22.8, 28.5 (d, J_{CF} = 4 Hz), 30.9, 33.0, 33.7, 123.4, 126., 127.5 (d, J_{CF} = 5 Hz), 127.6 (d, J_{CF} = 2 Hz), 129.7, 134.7 (d, J_{CF} = 10 Hz), 145.0 (d, J_{CF} = 4 Hz), 154.0 (d, J_{CF} = 254 Hz), 154.1 (d, J_{CF} = 22 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 34.2 (1F, br s) ppm.

IR (neat) 2962, 2873, 1605, 1504, 1460, 1412, 1383, 1144, 1111, 758 cm^{-1}.

MS (20 eV) *m/z* 259 (M^+; 26), 244 (49), 217 (100).

HRMS calcd for $C_{17}H_{22}NF$ 259.1736 (M^+); found 259.1735.

4-Butyl-2-ethyl-3-fluoroquinoline (54c)

To a solution of **50a** (96 mg, 0.43 mmol) in toluene (6 ml) was added ethylmagnesium bromide (0.48 ml, 1.08 M in THF, 0.52 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 15 min, the reaction mixture was cooled to 0 °C and added HMPA (1.2 ml). After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. 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 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 5:1) to give **54c** (59 mg, 0.26 mmol, 59%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.38 (3H, t, J = 7.6 Hz), 1.46 (2H, tq, J = 7.4, 7.4 Hz), 1.64–1.71 (2H, m), 3.02–3.08 (4H, m), 7.51 (1H, dd, J = 7.6, 7.6 Hz), 7.61 (1H, ddd, J = 8.2, 7.0, 1.2 Hz), 7.91 (1H, d, J = 7.6 Hz), 8.04 (1H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.6, 13.8, 22.8, 23.9 (d, J_{CF} = 3 Hz), 26.6, 31.8, 123.3 (d, J_{CF} = 5 Hz), 126.1, 127.4 (d, J_{CF} = 3 Hz), 127.7 (d, J_{CF} = 2 Hz), 129.5, 130.9 (d, J_{CF} = 13 Hz), 144.8 (d, J_{CF} = 3 Hz), 153.2 (d, J_{CF} = 253 Hz), 154.2 (d, J_{CF} = 27 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 29.3 (1F, s) ppm.

IR (neat) 2960, 2933, 1506, 1458, 1410, 1389, 1315, 1228, 1142, 760 cm^{-1}.

MS (20 eV) *m/z* 231 (M+; 100), 230 (77).

HRMS calcd for $C_{15}H_{18}NF$ 231.1423 (M^+); found 231.1415.

4-Butyl-3-fluoro-2-isopropylquinoline (54d)

To a solution of **50a** (90 mg, 0.41 mmol) in toluene (6 ml) was added isopropylmagnesium chloride(0.25 ml, 1.92 M in THF, 0.49 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 15 min, the reaction mixture was cooled to 0 °C and added toluene (6 ml) and HMPA (1.2 ml). After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. 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 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 50:1) to give **54d** (64 mg, 0.26 mmol, 64%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.41 (6H, d, J = 6.7 Hz), 1.43–1.50 (2H, m), 1.62–1.70 (2H, m), 3.05 (2H, td, J = 7.8, 1.8 Hz), 3.52 (1H, qqd, J = 6.9, 6.9, 1.5 Hz), 7.50 (1H, dd, J = 7.6, 7.6 Hz), 7.60 (1H, dd, J = 7.5, 7.5 Hz),7.90 (1H, d, J = 8.6 Hz), 8.05 (1H, d, J = 8.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 20.9 (d, J_{CF} = 2 Hz), 22.8, 24.0 (d, J_{CF} = 4 Hz), 31.1, 31.9, 123.3 (d, J_{CF} = 6 Hz), 126.1, 127.3 (d, J_{CF} = 3 Hz), 127.5 (d, J_{CF} = 2 Hz), 129.8, 130.8 (d, J_{CF} = 13 Hz), 144.8 (d, J_{CF} = 3 Hz), 153.0 (d, J_{CF} = 253 Hz), 157.3 (d, J_{CF} = 19 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 28.8 (1F, s) ppm.

IR (neat) 3068, 2962, 2873, 1736, 1612, 1506, 1458, 1313, 1142, 760 cm^{-1}.

MS (20 eV) *m/z* 245 (M^+; 35), 230 (100), 187 (49).

HRMS calcd for $C_{16}H_{20}NF$ 245.1580 (M^+); found 245.1576.

4-Butyl-2-*tert*-butyl-3-fluoroquinoline (54e)

To a solution of **50a** (96 mg, 0.43 mmol) in toluene (6 ml) was added *tert*-butyllithium (0.32

ml, 1.64 M in pentane, 0.52 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 15 min, the reaction mixture was cooled to 0 °C and added toluene (6 ml) and HMPA (1.2 ml). After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. 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 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 50:1) to give **54e** (80 mg, 0.31 mmol, 71%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.8 Hz), 1.43–1.52 (11H, m), 1.62–1.71 (2H, m), 3.05 (2H, dt, J = 7.8, 2.1 Hz), 7.49 (1H, dd, J = 8.0, 8.0 Hz), 7.59 (1H, ddd, J = 8.2, 8.0, 1.2 Hz),7.88 (1H, d, J = 8.2 Hz), 8.04 (1H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.8, 23.9 (d, J_{CF} = 5 Hz), 28.7 (d, J_{CF} = 4 Hz), 31.9, 38.0 (d, J_{CF} = 5 Hz), 123.0 (d, J_{CF} = 5 Hz), 126.2, 127.4 (d, J_{CF} = 2 Hz), 127.5 (d, J_{CF} = 3 Hz), 130.2, 131.5 (d, J_{CF} = 16 Hz), 144.0 (d, J_{CF} = 3 Hz), 154.1 (d, J_{CF} = 258 Hz), 158.2 (d, J_{CF} = 17 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 36.9 (1F, s) ppm.

IR (neat) 2958, 2873, 1608, 1402, 1383, 1365, 1275, 1211, 1142, 758 cm^{-1}.

MS (20 eV) *m/z* 259 (M^+; 12), 201 (100).

HRMS calcd for $C_{17}H_{22}NF$ 259.1736 (M^+); found 259.1712.

4-Butyl-3-fluoro-2-triethylgermylquinoline (54f)

To a solution of triethylgermane (0.10 ml, 0.62 mmol) and TMEDA (0.12 ml, 0.62 mmol) in THF (1 ml) was added *tert*-butyllithium (0.47 ml, 1.64 M in pentane, 0.62 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture had been stirred for 15 min, **50a** (114 mg, 0.51 mmol) in toluene (2 ml) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. 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 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 **54f** (114 mg, 0.32 mmol,

61%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.5 Hz), 1.10–1.24 (15H, m), 1.41–1.51 (2H, m), 1.63–1.71 (2H, m), 3.04 (2H, td, J = 7.9, 1.6 Hz), 7.52 (1H, dd, J = 7.5, 7.5 Hz), 7.60 (1H, ddd, J = 8.3, 8.3, 1.4 Hz), 7.94 (1H, dd, J = 8.6, 0.9 Hz), 8.13 (1H, dd, J = 8.4, 0.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 4.7 (d, J_{CF} = 2 Hz), 9.1, 13.9, 22.8, 23.8 (d, J_{CF} = 3 Hz), 31.9, 123.4 (d, J_{CF} = 6 Hz), 126.5, 127.1 (d, J_{CF} = 2 Hz), 127.6 (d, J_{CF} = 4 Hz), 127.9 (d, J_{CF} = 17 Hz), 130.7, 146.6, 158.8 (d, J_{CF} = 244 Hz), 161.2 (d, J_{CF} = 43 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 39.1 (1F, s) ppm.

IR (neat) 2956, 2872, 1600, 1460, 1317, 1138, 1020, 960, 758, 607 cm^{-1}.

MS (20 eV) *m/z* 362 (M^+; 9), 335 (100), 333 (97), 278 (90), 276 (88), 231 (68), 184 (50).

HRMS calcd for $C_{19}H_{28}NFGe$ 363.1416 (M^+); found 363.1411.

4,4'-Dibutyl-3,3'-difluoro-2,2'-biquinoline (37a)

To a solution of hexabutylditin (0.44 ml, 0.86 mmol) in THF (1.5 ml) was added butyllithium (0.54 ml, 1.6 M in hexane, 0.86 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture had been stirred for 15 min, **50a** (76 mg, 0.35 mmol) in THF (4 ml) was added at 0 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 1 h. Phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 5:1) to give **37a** (41 mg, 0.102 mmol, 59%) as a pale yellow liquid.

1H NMR (500 MHz, $CDCl_3$) δ 1.00 (3H, t, J = 7.3 Hz), 1.51 (2H, tq, J = 7.5, 7.5 Hz), 1.72–1.80 (2H, m), 3.20 (2H, t, J = 7.8 Hz), 7.66 (1H, ddd, J = 8.2, 7.0, 1.2 Hz), 7.72 (1H, ddd, J = 8.4, 6.9, 1.5 Hz), 8.06 (1H, dd, J = 8.4, 8.4 Hz), 8.31 (1H, dd, J = 8.4, 8.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.7, 24.1, 31.8, 123.3, 127.6, 128.2, 128.5, 130.9, 132.8 (dd, J_{CF} = 10, 3 Hz), 145.2, 145.3, 152.9 (dd, J_{CF} = 256, 2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 31.0 (1F, s) ppm.

IR (neat) 2958, 2929, 2872, 1504, 1456, 1377, 1338, 1221, 1188, 1144, 762 cm^{-1}.

MS (20 eV) *m/z* 405 (M^+; 24), 375 (94), 317 (100).

HRMS calcd for $C_{26}H_{26}N_2F_2$ 404.2064 (M^+); found 404.2057.

4-Butyl-3-fluoroquinoline (24a)

Butyllithium (1.0 ml, 1.6 M in hexane, 0.64 mmol) was added to a solution of hexabutylditin (102 mg, 1.0 mmol) in THF (1.5 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture stirred for 15 min. The solution was cooled to –78 °C and then **50a** (75 mg, 0.36 mmol) in THF (5 ml) was added at –78 °C. After being stirred for 1 h, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 5:1) to give **24a** (55 mg, 0.271 mmol, 80%) as a pale yellow liquid.

4-*sec*-Butyl-3-fluoroquinoline (24b)

Compound **24b** was prepared by the method described for **24a** using butyllithium (0.88 ml, 1.6 M in hexane, 1.4 mmol), hexabutylditin (0.71 ml, 1.4 mmol) in THF (2 ml), and **50b** (75 mg, 0.34 mmol) in THF (4 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **24b** (45 mg, 0.222 mmol, 65%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, J = 7.2 Hz), 1.48 (3H, d, J = 7.2 Hz), 1.84–2.04 (2H, m), 3.55 (1H, tq J = 7.2, 7.2 Hz), 7.58 (1H, dd, J = 7.6, 7.6 Hz), 7.66 (1H, dd, J = 7.6, 7.6 Hz), 8.07–8.20 (2H, m), 8.71 (1H, dd, J_{HF} = 3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 12.7, 19.2, 28.5 (d, J_{CF} = 3 Hz), 33.7, 123.6, 127.1, 127.8, 128.0 (d, J_{CF} = 5 Hz), 130.5, 135.4, (d, J_{CF} = 10 Hz), 141.8 (d, J_{CF} = 40 Hz), 145.7, 154.9 (d, J_{CF} = 254 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 33.0 (1F, s) ppm.

IR (neat) 2966, 2875, 1599, 1512, 1460, 1371, 1252, 1209, 1144, 760 cm^{-1}.

HRMS calcd for $C_{13}H_{14}NF$ 203.1110 (M^+); found 203.1083.

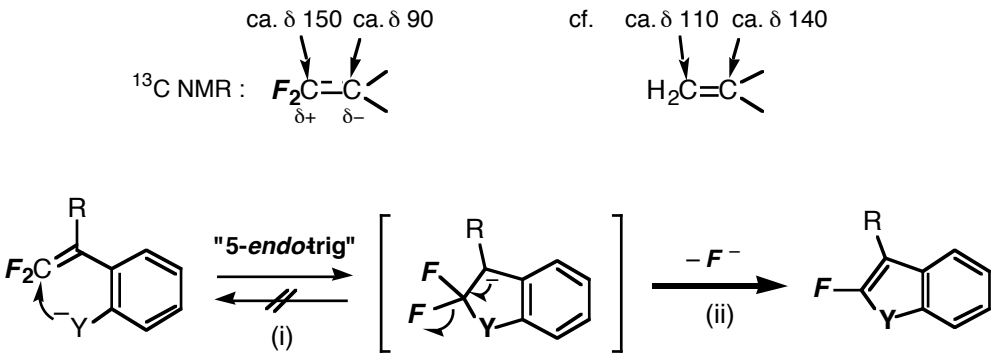
Chapter 3

Construction of Ring-Fluorinated 5-Membered Heterocycles *via* Intramolecular Cyclizations of *o*-Substituted β,β-Difluorostyrenes

3.1 Introduction

In the previous chapter it was demonstrated that the 6-menbered ring-fluorinated heterocycles and carbocycles such as isochromene, isothiochromene, isoquinoline, quinoline, and naphthalene derivatives are readily obtained from β,β-difluorostyrenes *via* intramolecular substitution of heteroatom (O, S, N) and carbon for the vinylic fluorine. According to Baldwin's rules,[1] this type of cyclization is classified as 6-*endo*-trig ring closure, and this process is favored in the rules. On the other hand, for the construction of 5-membered rings based on the same concept, I have to effect the 5-*endo*-trig ring closure. Since this cyclization is disfavored in the Baldwin's rules, it is a quite challenging problem.

There are three types of 5-*endo*-trig cyclizations reported so far, such as nucleophile-driven,[2] electrophile-driven,[3] and radical-initiated ring closures.[4] Among them, such nucleophilic 5-*endo*-trig cyclizations as I intended have only rarely been observed in synthetic chemistry. However, I expected that the unique properties of fluorine could make this nucleophilic approach feasible. Specifically, I thought that (i) the highly polarized difluorovinyliden olefinic bond diplays significant single bond character (suggested by ^{13}C NMR: ca. δ 150 and 90 for CF_2=C) and would allow initial ring formation, and (ii) the successive elimination of fluoride ion could suppress the reverse ring opening. On the basis of these considerations, I investigated the cyclization of β,β-difluorostyrenes bearing heteroatom directly at the *ortho* position (Scheme 1).

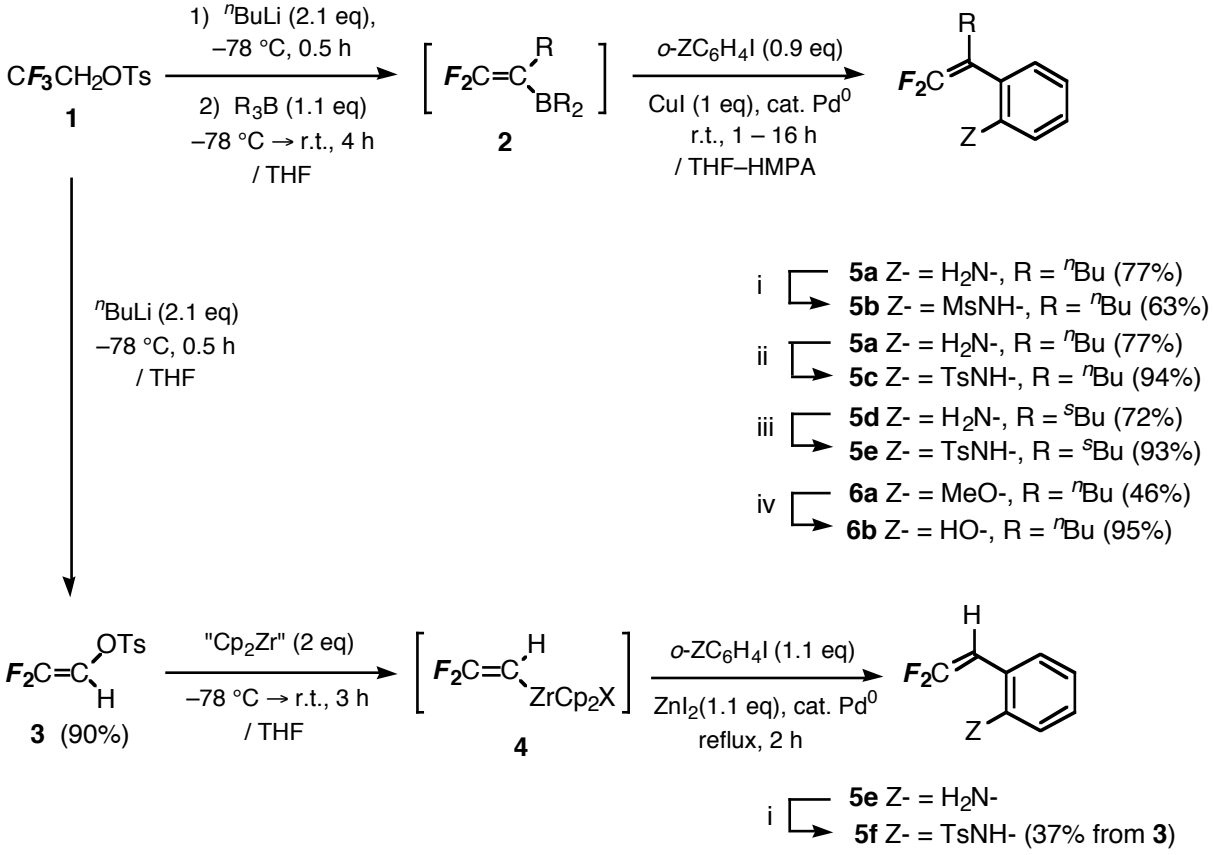


Scheme 1

3.2 5-*endo*-Trig Cyclization of β,β-Difluorostyrenes Bearing a Heteroatom Nucleophile at the *Ortho* Position

3.2.1 Preparation of β,β-Difluorostyrenes Bearing a Heteroatom Nucleophile at the *Ortho* Position

I designed the *gem*-difluorostyrenes[5] bearing a nucleophilic *ortho* nitrogen, oxygen or sulfur heteroatom as substrates for the 5-*endo*-trig cyclizations. The starting materials were easily prepared as outlined in Scheme 2 by using the one-pot sequences which we have previously developed for the preparation of *gem*-difluorostyrenes. The coupling reactions of 2,2-difluorovinylboranes **2** (generated *in situ* from 2,2,2-trifluoroethyl *p*-toluenesulfonate) or 2,2-difluorovinylzirconocene **4** (generated *in situ* from 2,2-difluorovinyl *p*-toluenesulfornate) with *N*-butylmagnesio-*o*-iodoaniline or *o*-iodoaniline were effected in the presence of CuI or ZnI_2 and a palladium catalyst, respectively. The corresponding *o*-amino-β,β-difluorostyrenes **5**, which would act as precursors of 2-fluoroindoles were obtained in good yields. *o*-Hydroxy-β,β-difluorostyrene **6b**, a precursor of 2-fluorobenzo[*b*]furan, was similarly prepared by the coupling of **2** with *o*-iodoanisole, followed by demethylation with BBr_3.

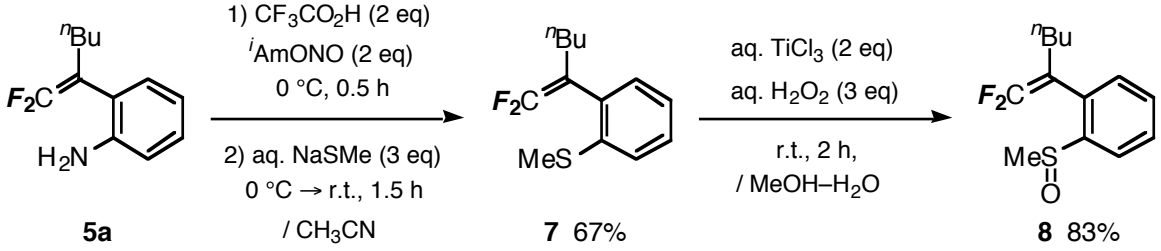


1 3 (90%) 2 4

i, MsCl (1.2 eq), pyridine, 0 °C → r.t., 11 h; ii, TsCl (1.1 eq), pyridine, 0 °C → r.t., 11 h; iii, BBr_3 (1.1 eq), CH_2Cl_2, –15 °C → r.t., 2 h

Scheme 2

For the purpose of generating a thiolate moiety, the methyl sulfinyl group was selected as an *ortho* substituent of β,β-difluorostyrene. Compound **8**, a precursor of 2-fluorobenzo[*b*]thiophene, was easily prepared from **5a** *via* diazotization and introduction of a methylthio group followed by oxidation of **7** as shown in Scheme 3.



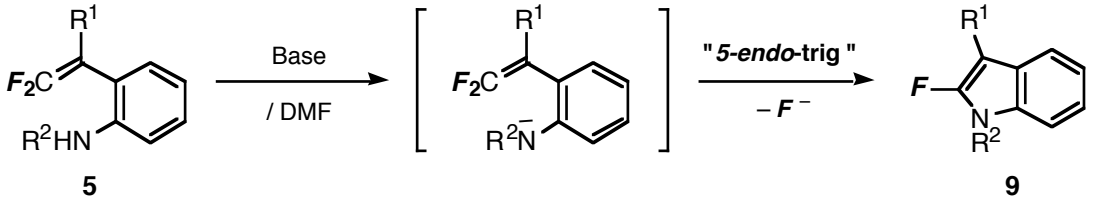
5a **7** 67% **8** 83%

Scheme 3

3.2.2 Syntheses of 2-Fluorinated Indoles, Benzo[*b*]furans, and Benzo[*b*]thiophenes

On treatment with 1.2 equiv of ^{n}BuLi, the attempted 5-*endo*-trig cyclization of **5a** was unsuccessful (Table 1, Entry 1). Then, I examined the cyclization of β,β-difluorostyrenes bearing acyl groups such as an acetyl and a trifluoroacetyl group on the nitrogen, while the desired 2-fluoroindole was not obtained. In contrast, treatment of methansulfonamide **5b** and *p*-toluenesulfonamide **5c** with 1.2 equiv of NaH in DMF successfully promoted the "disfavoured" 5-*endo*-trig cyclization to afford 2-fluoroindole **9b**,**c** in 72% and 84% yields, respectively (Table 1, Entries 4 and 6). Successful ring closure did not necessitate the use of high-dilution conditions, and proceeded smoothly even in the case of the starting styrenes **5e** and **5f** with a secondary alkyl group or a hydrogen atom at the α-position (Table 1, Entries 7, 8).

Table 1. Synthesis of 2-Fluoroindoles **9**

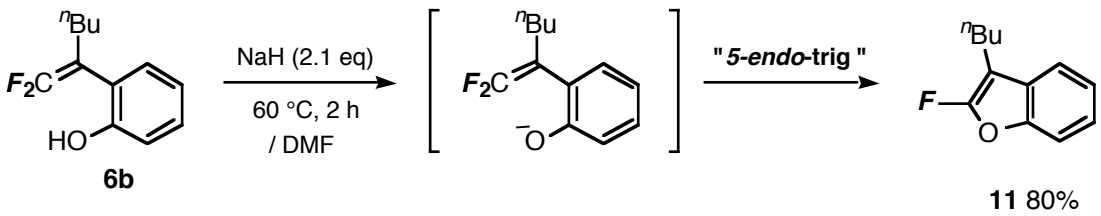


5 **9**

Entry	R^1	R^2		Base (equiv)	Conditions	Yield / %
1[a)]	^{n}Bu	H	(**5a**)	^{n}BuLi (1.2)	–78 °C → reflux, 19 h	Recovery 20
2	^{n}Bu	CH_3CO	(**5g**)	NaH (1.2)	r.t., 30 h	Complex mix.
3	^{n}Bu	CF_3SO_2	(**5h**)	NaH (1.5)	r.t. → 80 °C, 4.5 h	No reaction
4	^{n}Bu	Ms	(**5b**)	NaH (1.0)	0 → 80 °C, 6 h	72 (**9b**)
5[b)]	^{n}Bu	Ms	(**5b**)	^{n}BuLi (1.0)	–78 °C → reflux, 2.5 h	64 (**9b**)
6	**^{n}Bu**	**Ts**	**(5c)**	**NaH (1.2)**	**80 °C, 7 h**	**84** (**9c**)
7	**^{s}Bu**	**Ts**	**(5e)**	**NaH (1.2)**	**80 °C, 5 h**	**81** (**9e**)
8	**H**	**Ts**	**(5f)**	**NaH (1.2)**	**70 °C, 23 h**	**73** (**9f**)

a) toluene–HMPA (40 : 1) b) THF–HMPA (2 : 1)

Moreover, this type of cyclization was satisfactorily applied to intramolecular oxygen nucleophile. When hydroxystyrene **6b** was treated under similar conditions, the 5-*endo*-trig cyclization of the corresponding alkoxide occurred leading to 2-fluorobenzo[*b*]furan **11** in a 80% yield (Scheme 4).[8]



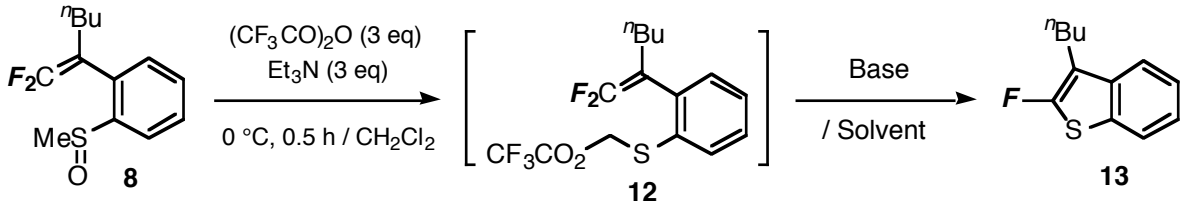
6b

11 80%

Scheme 4

As a further example of the cyclization, I also tried the intramolecular substitution utilizing a sulfur nucleophile, which Baldwin's rules allow for normally disfavored 5-*endo*-trig process. The Pummerer rearrangement of *o*-methysulfinyl-β,β-diflurostyrene **8** followed by solvolysis would bring about the cyclization *via* the unisolated intermediate, hemiacetal trifluoroacetate **12**. Successive treatment of **8** with (i) trifluoroacetatic anhydride and Et_3N in CH_2Cl_2 and (ii) Et_3N in MeOH provided 2-fluorobenzo[*b*]thiophene **13** in a 56% yield as expected (Table 2, Entry 1).[9] After screening of bases and solvents in the cyclization step (**12→13**), I found that 6 equiv of K_2CO_3 in MeOH effectively promoted the cyclization, leading to **13** in a 82% yield (Table 2, Entry 7).

Table 2. Syntesis of 2-Fluorobenzo[*b*]thiophene **13**

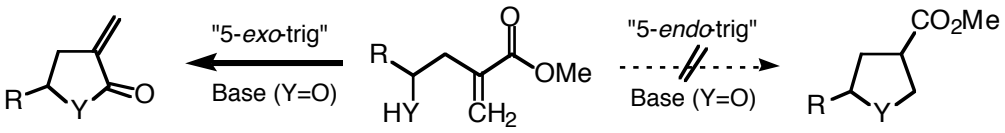


Entry	Base (equiv)	Solvent	Conditions	Yield / %
1	Et_3N (6)	MeOH	0 °C → reflux, 2.5 h	56
2	NaOMe(6)	DMF	0 → 70 °C, 2 h	57
3	NaOMe(6)	MeOH	0 °C → reflux, 5.5 h	67
4	K_2CO_3 (2)	MeOH	0 °C → reflux, 3 h	55
5	K_2CO_3 (3)	MeOH	0 °C → reflux, 2 h	61
6	K_2CO_3 (5)	MeOH	0 °C → reflux, 2 h	71
7	**K_2CO_3 (6)**	**MeOH**	**0 °C → reflux, 2 h**	**82**
8	K_2CO_3 (7)	MeOH	0 °C → reflux, 2 h	81
9	$CsCO_3$ (6)	MeOH	0 °C → reflux, 2 h	81

3.3 Effect of Fluorine Substituents on 5-*endo*-Trig Cyclization

3.3.1 Competitive Cyclization Between 5-*endo*-Trig and 5-*exo*-Trig Processes

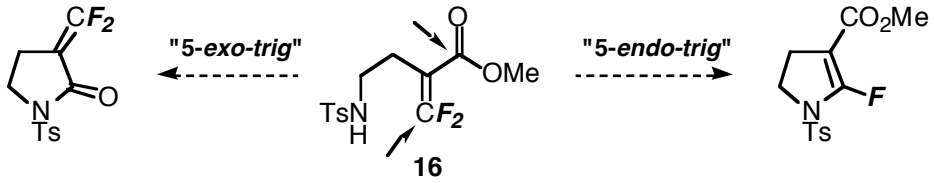
The favored nature of 5-*endo*-trig cyclization in *gem*-difluoroolefins could be demonstrated by the competitive reaction between 5-*endo*-trig and 5-*exo*-trig processes. Baldwin reported the cyclization of unsaturated esters **14a**,**b**, showing how difficult 5-*endo*-trig cyclizations are.[1a] In these fluorine-free substrates, there are two competitive reaction sites to be attacked by the intramolecular nitrogen in a 5-*endo*-trig fashion and a 5-*exo*-trig fashion. In these cases only 5-*exo*-trig products **15a**,**b** were obtained (Scheme 5). For comparison I selected the difluorinated analog, β,β-difluoro-α,β-unsaturated ester **16** bearing a 2-(*p*-toluenesulfonamido)ethyl group as a substrate, which could undergo the Michael reaction and the transacylation *via* 5-*endo*-trig and 5-*exo*-trig processes, respectively (Scheme 6).



15a
15b

14a Y=O, R=H
14b Y=NH, R=CO_2Me

Scheme 5

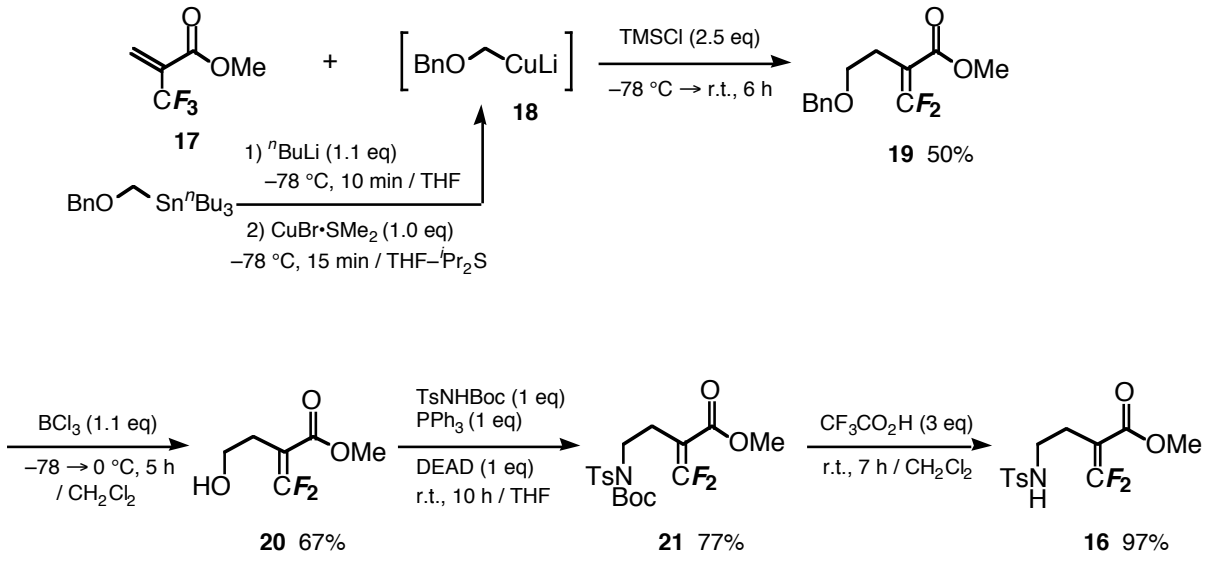


16

Scheme 6

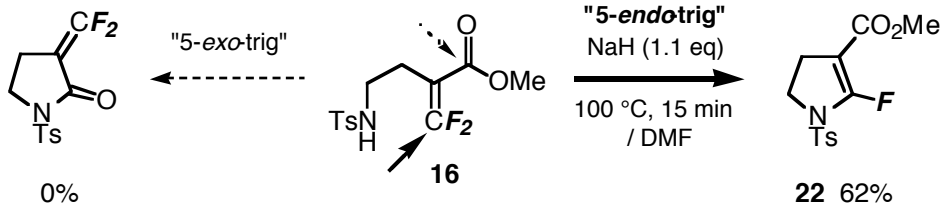
Compound **16** was prepared as depicted in Scheme 7. The S_N2' reaction of methyl 2-(trifluoromethyl)propenoate[10] with benzyloxymethylcopper[11] proceeded with the loss of a fluoride ion to afford β,β-difluoro-α,β-unsaturated ester **19**. Successive deprotection of the benzyl group, followed by the introduction of NHTs group *via* the Mitsunobu reaction[12] with

BocNHTs yielded **21**, whose deprotection finally gave the desired substrate **16**.[13]



Scheme 7

On treatment of **16** with NaH in DMF, the 5-*endo*-trig cyclization exclusively occurred to give 2-fluorinated pyrroline **22** in a 62% yield as shown in Scheme 8.[13] The 5-*exo*-trig product was not detected in the reaction mixture by ^{19}F NMR measurement. This result shows a remarkable contrast by comparison with the reaction of **14b**, clearly indicating the effect of fluorines on the cyclization pathways.

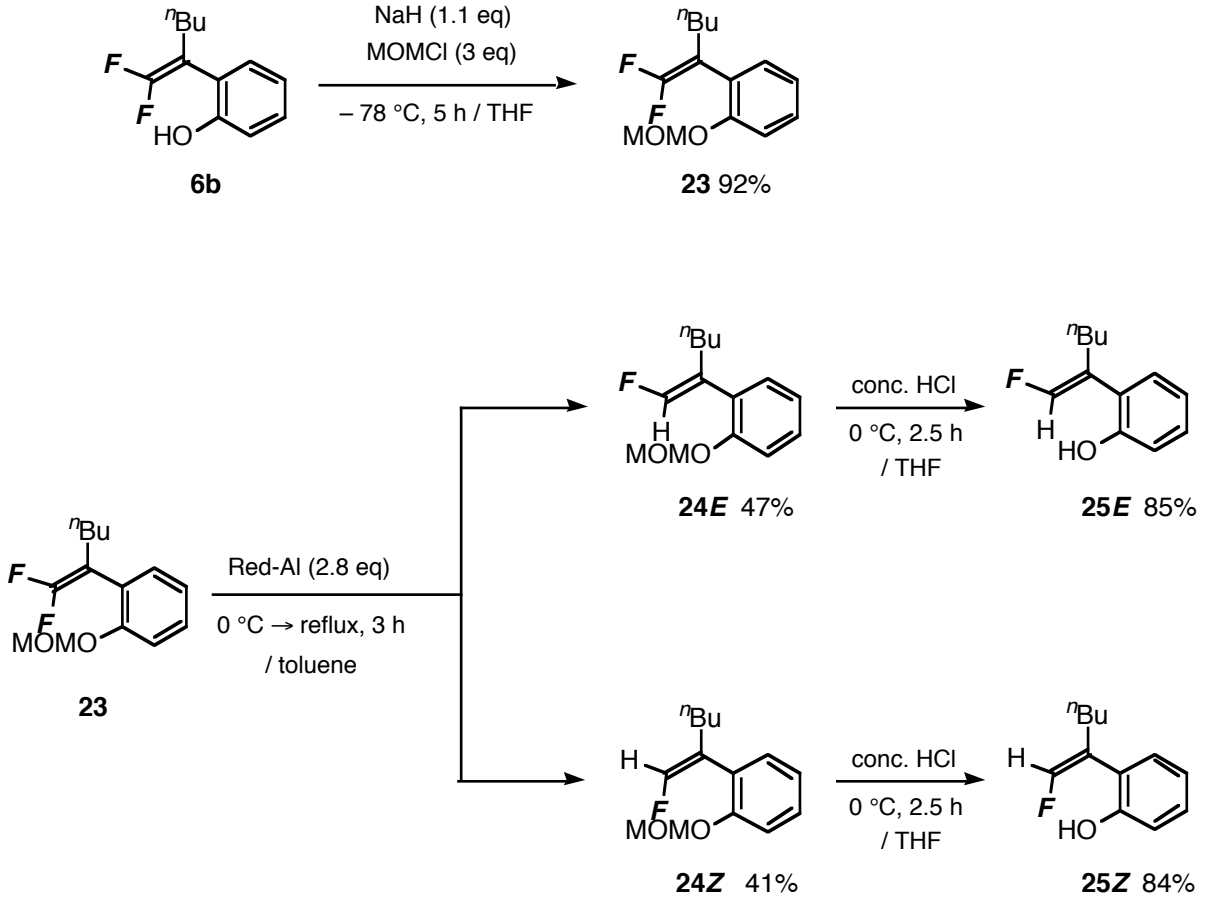


Scheme 8

3.3.2 5-*endo*-Trig Cyclization of β-Monofluoro, β,β-Dichloro, and β,β-Dibromostyrenes

In order to confirm the effect of fluorine on the reactivity in the 5-*endo*-trig

cyclization, I conducted similar reactions of β-monofluoro-*o*-hydroxystyrenes **25** and β,β-dichloro and β,β-dibromo-*o*-hydroxystyrenes, **26**,**27**. *E*- and *Z*-isomers of **25** were readily obtained by the reduction of OH-protected hydroxystyrene **23** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), and then separated by chromatography in the ratio of 58 : 42 (**24*E*** : **24*Z***). They were deprotected to give ***25E***,***25Z***. Dichloro and dibromostyrenes **26**,**27** were prepared *via* dihalomethylenation of the corresponding OH-protected ketone according to the reported methods.[14]

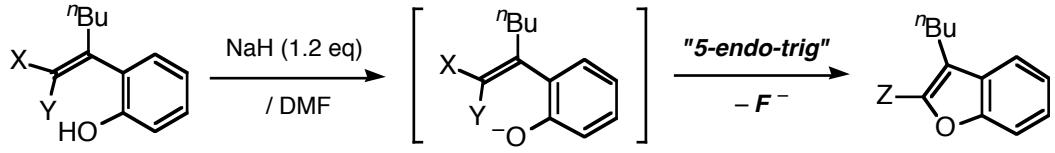


Scheme 9

The reactions of the both isomers ***25E***,***25Z*** with NaH required harsher conditions (80 °C, 43 h) compared to difluorostyrene **6b**, leading to no more than 20% yields of the cyclized product (Table 3, Entries 2 and 3). These observations revealed that two vinylic

fluorines are inevitable to activate the substrate sufficiently for the nucleophilic 5-*endo*-trig cyclization.

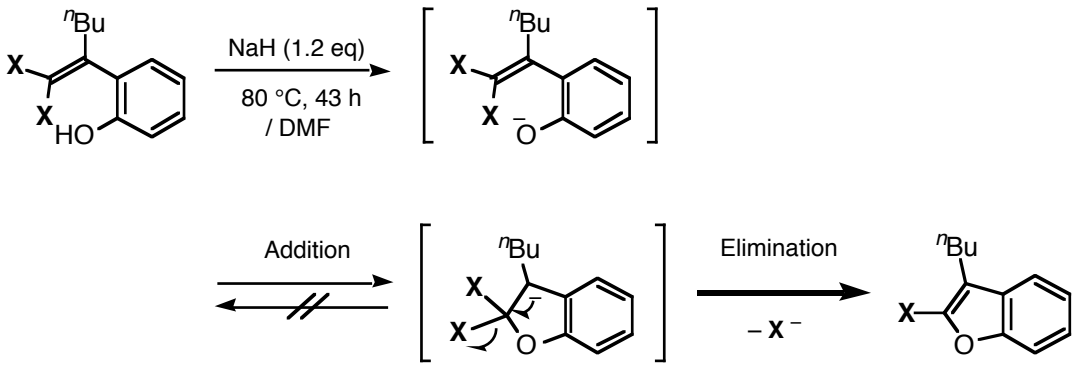
Table 3. Effect of Fluorine Substituents on the 5-*endo*-trig Cyclization



Entry	X	Y	Substrate	Conditions	Yield / %
1	***F***	***F***	**6b**	0 → 60 °C, 2 h	**80** (Z = ***F***) (**6b**)
2	*F*	H	**25*E***	80 °C, 43 h	17 (Z = H) (**26**)
3	H	*F*	**25*Z***	80 °C, 43 h	19 (Z = H) (**26**)

The reactions of dichloro and dibromohydroxystyrenes **27**,**28** were also attempted, and the results are summarized in Table 4. Chlorine and bromine substituents gave poor results, even though they have better leaving-group ability compared to fluorine (Entries 2 and 3). These facts suggest that the cyclization step is more crucial than the elimination step. Thus, the point may be a partial single bond character of the *gem*-difluoroolefins, which is caused by the repulsive interaction between the lone pairs of fluorine and π-electrons, and it is stronger than that of the other halogens. Consequently, the two vinylic fluorine substituents are essential and play a critical role in promoting the 5-*endo*-trig cyclization of β,β-difluoroolefins such as **5b**, **5c**, **5e**, **5f**, **6b**, and **16**.

Table 4. Effect of Fluorine Substituents on the 5-*endo*-Trig Cyclization



Entry	X	Substrate	Conditions	Yield / %
1	***F***	**6b**	60 °C, 2 h	**80** (**11**)
2	Cl	**27**	60 °C, 8 h	Recovery 80
3	Br	**28**	60 °C, 5 h	15 (**29**)

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Capter 3 Experimental Section

General. IR spectra were recorded on a Shimadzu IR-408 spectrometer or a JEOL JIR-WINSPEC50 spectrometer. NMR spectra were obtained on a JEOL JNM-A-500, or a Bruker DRX 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 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. DMF was dried over P_2O_5, then distilled under reduced pressure from CaH_2 and stored over molecular sieves 4A.

***o*-(1-Butyl-2,2-difluorovinyl)-*p*-toluenesulfonanilide (5c)**

p-Toluenesulfonyl chloride (TsCl, 518 mg, 2.71 mmol) was added to a pyridine (6 ml) solution of **5a** (382 mg, 1.81 mmol) at 0 °C. The reaction mixture was stirred for 11 h at room temperature . The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with aq. HCl and 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 5:1) to give **5c** (620 mg, 1.70 mmol, 94%) as an orange solid.

^1H NMR (500 MHz, $CDCl_3$) δ 0.79 (3H, t, J = 7.3 Hz), 1.06–1.22 (4H, m), 1.99 (2H, br s), 2.35 (3H, s), 6.85 (1H, s), 7.02 (1H, dd, J = 7.4, 1.7 Hz), 7.05 (1H, ddd, J = 7.4, 7.4, 1.0 Hz), 7.19–7.27 (3H, m), 7.63 (1H, d, J = 7.9 Hz), 7.73 (2H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.5, 21.4, 22.2, 28.0, 29.3, 87.9 (dd, J_{CF} = 23, 17 Hz), 119.6, 124.2, 127.1, 129.0, 129.6, 130.7, 135.0, 136.4, 144.0, 152.9 (dd, J_{CF} = 292, 288 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 71.8 (1F, d, J_{FF} = 39 Hz), 74.9 (1F, d, J_{FF} = 39 Hz) ppm.

IR (neat) 3274, 2958, 1741, 1494, 1402, 1340, 1245, 1168, 1093, 916, 665, 566 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 365 (M^+; 3), 210 (100), 148 (86).

HRMS calcd for $C_{19}H_{21}O_2NF_2S$ 356.1261 (M^+); found 365.1221.

***o*-(1-*sec*-Butyl-2,2-difluorovinyl)-*p*-toluenesulfonanilide (5e)**

Compound **5e** was prepared by the method described for **5c** using TsCl (265 mg, 1.39 mmol), pyridine (5 ml), and **5d** (196 mg, 0.928 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **5e** (315 mg, 0.863 mmol, 93%) as a pale yellow solid.

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 80 °C) δ 0.93 (3H, t, J = 7.1 Hz), 1.06 (3H, d, J = 7.1 Hz), 1.24–1.37 (1H, m), 1.57 (1H, dqd, J = 13.8, 7.1, 7.1 Hz), 2.30–2.43 (1H, m), 2.41 (3H, s), 7.11–7.16 (2H, m), 7.22–7.27 (2H, m), 7.41 (2H, d, J = 8.1 Hz), 7.80 (2H, d, J = 8.1 Hz), 8.28 (1H, br s).

^{13}C NMR (126 MHz, $(CD_3)_2SO$, 80 °C) δ 11.2, 17.1, 20.4, 27.0, 34.8, 92.7 (dd, J_{CF} = 19, 15 Hz), 121.6, 124.9, 152.2 (dd, J_{CF} = 290, 284 Hz).

^{19}F NMR (254 MHz, $(CD_3)_2SO$, 80 °C) 73.6 (1F, d, J_{FF} = 46 Hz), 76.9 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 3280, 2966, 2933, 1732, 1495, 1400, 1338, 1244, 1163, 665 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 365 (M^+; 16), 210 (100), 136 (100).

Anal. Calcd for $C_{19}H_{21}O_2SNF_2$: C, 62.45; H, 5.79; N, 3.83. Found : C, 62.38; H, 5.89; N, 3.90.

***o*-(2,2-difluorovinyl)-*p*-toluenesulfonanilide (5f)**

Butyllithium (13.9 ml, 1.60 M in hexane, 22.2 mmol) was added to a tetrahydrofuran (THF, 40 ml) solution of zirconocene dichloride (3.25 g, 11.1 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 **3** (1.3 g, 5.55 mmol) in THF (2 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 (233 mg, 0.89 mmol) and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (115 mg, 0.11 mmol) were added at 0 °C, and the mixture was stirred for 10 min. To the resulting solution were successively added *o*-iodoaniline (1.34 g, 6.12 mmol) and zinc iodide (4.3 g, 19.6 mmol). The mixture was filtered and organic materials wre extracted with Et_2O three times. After removal of the solvent under reduced pressure, the residue was treated with *p*-toluenesulfonyl

chloride (534 mg, 2.80 mmol) in pyridine (3 ml) at 0 °C. The reaction mixture was stirred for 11 h at room temperature. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with ethyl acetate (AcOEt) three times. The combined extracts were washed with aq. HCl and 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 5:1) to give **5f** (630 mg, 2.04 mmol, 37%) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (3H, s), 5.21 (1H, dd, J = 3.2 Hz, J_{HF} = 25.2 Hz), 6.67 (1H, s), 7.33–7.37 (1H, m), 7.61 (2H, d, J = 8.2 Hz), 7.73 (2H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 21.5, 108.9 (d, J_{CF} = 16 Hz), 126.2, 127.0, 127.3, 128.2, 129.2, 129.2, 130.0, 133.4 (d, J_{CF} = 3), 136.2, 144.1, 156.5 (dd, J_{CF} = 298, 290 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 79.0 (1F, ddd, J_{FF} = 25 Hz, J_{FH} = 25, 2 Hz), 80.6 (1F, dd, J_{FF} = 25 Hz, J_{FH} = 4 Hz) ppm.

IR (neat) 3266, 1727, 1490, 1400, 1334, 1222, 1160, 1091, 815, 673, 566, 549 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 309 (M^+; 47), 155 (100), 154 (100), 127 (100).

HRMS calcd for $C_{15}H_{13}O_2NSF_2$ 309.1635 (M^+); found 309.0643.

_o_-(1-Butyl-2,2-difluorovinyl)anisole (6a)

Butyllithium (0.79 ml, 1.62 M in hexane, 1.28 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (155 g, 0.61 mmol) in THF (3 ml) at –78 °C over 10 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C, and then tributylborane (0.67 ml, 1.0 M in THF, 0.67 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (1 ml), triphenylphosphine (25 mg, 0.098 mmol), and tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (12.7 mg, 0.012 mmol) and stirred for 15 min. To the solution was added *o*-iodoanisole (0.071 mg, 0.548 mmol) and cuprous iodide (116 mg, 0.609 mmol). After the mixture was stirred for 16 h at room temperature, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered, and then

organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (AcOEt–hexane 1:50) to give **6a** (57.6 mg, 0.255 mmol, 46%) as coloress liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.21–1.34 (4H, m), 2.30–2.35 (2H, m), 3.80 (3H, s), 6.89 (1H, d, J = 7.6 Hz), 6.93 (1H, ddd, J = 7.6, 7.6, 0.9 Hz), 7.12 (1H, dd, J = 7.6, 1.6 Hz), 7.27 (1H, ddd, J = 7.6, 7.6, 1.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.2, 27.5, 29.7 (d, J_{CF} = 2 Hz), 55.4, 89.4 (dd, J_{CF} = 23, 16 Hz), 111.0, 120.4, 123.0 (dd, J_{CF} = 3, 3 Hz) 129.0, 131.1 (d, J_{CF} = 2 Hz), 153.0 (dd, J_{CF} = 286, 286 Hz), 157.4 (d, J_{CF} = 2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 67.1 (1F, dd, J_{FF} = 46 Hz, J_{FH} = 3 Hz), 70.9 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 2960, 2930, 1740, 1490, 1460, 1270, 1245, 1230, 1025, 750 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 226 (M^+; 73), 215 (58), 149 (100).

HRMS calcd for $C_{13}H_{16}OF_2$ 226.1169 (M^+); found 226.1171.

***o*-(1-Butyl-2,2-difluorovinyl)phenol (6c)**

BBr_3 (0.85 ml, 1.0 M in CH_2Cl_2, 0.85 mmol) was added to a CH_2Cl_2 solution (5 ml) of **6a** (175 mg, 0.773 mmol) at –15 °C. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and 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 **6c** (156 mg, 0.735 mmol, 95%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.25–1.36 (4H, m), 2.33 (2H, tt, J = 7.2 Hz, J_{HF} = 2.2 Hz), 4.88 (1H, s), 6.88–6.96 (2H, m), 7.03–7.12 (1H, m), 7.19–7.26 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.2, 28.0, 29.7 (dd, J_{CF} = 3, 3 Hz), 87.7 (dd, J_{CF} = 23, 16 Hz), 115.6, 115.9 (d, J_{CF} = 6 Hz) 120.8 (d, J_{CF} = 11 Hz), 129.4, 129.7, 130.7 (d, J_{CF} = 6 Hz),

153.2 (dd, J_{CF} = 307, 280 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 70.3(1F, dt, J_{FF} = 41 Hz, J_{FH} = 3 Hz), 73.8 (1F, d, J_{FF} = 41 Hz) ppm.

IR (neat) 3430, 2950, 2930, 2860, 1740, 1450, 1130, 965, 755 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 212 (M^+; 34), 192 (33), 107 (74).

HRMS calcd for $C_{12}H_{14}OF_2$ 212.1013 (M^+); found 212.1008.

o-(1-Butyl-2,2-difluorovinyl)phenylmethyl sulfide (7)

CF_3CO_2H (0.049 ml, 0.640 mmol) and ^{i}AmONO (0.085 ml, 0.64 mmol) were added to a CH_3CN (3 ml) solution of **5a** (67.4 mg, 0.320 mmol) at 0 °C. The reaction mixture was stirred for 30 min. The solution was treated with sodium methanethiolate (449 mg, 15% water solution, 0.96 mmol) and stirred for 1.5 h at 0 °C. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and 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 **7** (45.2 mg, 0.215 mmol, 67%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.9 Hz), 1.27–1.36 (4H, m), 2.28–2.36 (2H, m),2.43 (3H, s), 7.09 (1H, dd, *J* = 7.2, 1.4 Hz), 7.12 (1H, ddd, *J* = 7.2, 7.2, 1.4 Hz), 7.21 (1H, d, *J* = 7.2 Hz), 7.29 (1H, ddd, *J* = 7.2, 7.2, 1.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 15.5, 22.4, 27.9, 29.6 (dd, J_{CF} = 3, 3 Hz), 91.0 (dd, J_{CF} = 23, 16 Hz), 124.5, 125.1, 128.5, 130.3 (d, J_{CF} = 3 Hz) 132.4 (d, J_{CF} = 5 Hz), 138.8, 153.0 (dd, J_{CF} = 288, 287 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 68.0 (1F, ddd, J_{FF} = 43 Hz, J_{FH} = 3, 3 Hz), 72.8 (1F, ddd, J_{FF} = 43, J_{FH} = 2, 2 Hz) ppm.

IR (neat) 2958, 2927, 1741, 1467, 1436, 1259, 1232, 1122, 971, 746 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 242 (M^+; 68), 165 (100), 134 (74).

HRMS calcd for $C_{13}H_{16}SF_2$ 242.0941 (M^+); found 242.0916.

o-(1-Butyl-2,2-difluorovinyl)phenylmethyl sulfoxide (8)

$TiCl_3$ (602 mg, 20% water solution, 0.780 mmol) was added to a MeOH–H_20 (6 : 1, 7.6 ml) solution **7** at 0 °C. The solution was treated with H_2O_2 (133 mg, 1.17 mmol, 30% H_20 solution, 1.17 mmol) and stirred for 2 h at room temperature. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and 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 1:2) to give **8** (83.3 mg, 0.322 mmol, 83%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85–0.90 (3H, m), 1.27–1.39 (4H, m), 2.28–2.40 (2H, m), 2.67 (3H, s), 7.21 (1H, dd, J = 7.6, 1.3 Hz), 7.51 (1H, ddd, J = 7.6, 7.6, 1.3 Hz), 7.60 (1H, ddd, J = 7.6, 7.6, 1.3 Hz), 8.10 (1H, dd, J = 7.6, 1.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.7, 22.3, 28.7, 29.5 (dd, J_{CF} = 3, 3 Hz), 43.5 (d, J_{CF} = 2 Hz), 89.9 (dd, J_{CF} = 24, 16 Hz), 123.9, 129.7, 130.5 (d, J_{CF} = 3 Hz), 131.0 (d, J_{CF} = 4 Hz), 131.2, 145.0 (d, J_{CF} = 2 Hz), 152.0 (dd, J_{CF} = 291, 286 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 70.4 (1F, d, J_{FF} = 42 Hz), 74.1 (1F, br s) ppm.

IR (neat) 2958, 2931, 1739, 1467, 1234, 1122, 1072, 1243, 968, 769 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 258 (M^+; 46), 241 (23), 215 (100).

HRMS calcd for $C_{13}H_{16}OSF_2$ 258.0890 (M^+); found 258.0876.

3-Butyl-2-fluoro-1-tosylindole (9c)

To a suspension of sodium hydride (NaH, 31 mg, 61.8% dispersion in mineral oil, 0.79 mmol) in DMF (0.5 ml) was added **5c** (232 mg, 0.63 mmol) in DMF (2.5 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 7 h at 80 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 5:1) to give **9c** (184 mg, 84%) as an orange liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.4 Hz), 1.21 (2H, tq, J = 7.4, 7.4 Hz), 1.53 (2H, tt, J = 7.4, 7.4 Hz), 2.34 (3H, s), 2.52 (2H, td, J = 7.4 Hz, J_{HF} = 0.8 Hz), 7.20 (2H, d, J = 8.4 Hz), 7.23 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.28 (1H, ddd, J = 7.7 , 7.7, 1.4 Hz), 7.33 (1H, dd, J = 7.7, 1.2 Hz), 7.73 (2H, d, J = 8.4 Hz), 8.08 (1H, d, J = 7.7 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.6, 21.3 (d, J_{CF} = 3 Hz), 21.5, 22.1, 30.5, 99.7 (d, J_{CF} = 11 Hz), 114.4, 118.9 (d, J_{CF} = 7 Hz), 124.0, 124.0 (d, J_{CF} = 4 Hz), 126.8, 128.1 (d, J_{CF} = 6 Hz), 129.8, 130.6, 134.7, 145.2, 147.4 (d, J_{CF} = 276 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 29.1 (1F, s) ppm.

IR (neat) 2960, 2930, 2860, 1660, 1455, 1395, 1190, 1180, 745, 690, 665 cm^{-1}.

MS (20 eV) *m/z* 345 (M^+; 100), 190 (68), 148 (92).

HRMS calcd for $C_{19}H_{20}O_2SNF$ 345.1199 (M^+); found 345.1188.

3-*sec*-Butyl-2-fluoro-1-tosylindole (9e)

To a suspension of sodium hydride (NaH, 17 mg, 60.0% dispersion in mineral oil, 0.43 mmol) in DMF (1.0 ml) was added **5e** (131 mg, 0.36 mmol) in DMF (1.0 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 5 h at 80 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 5:1) to give **9e** (100 mg, 81%) as an orange liquid.

^{1}H NMR (396 MHz, $CDCl_3$) δ 0.70 (3H, t, J = 7.1 Hz), 1.26 (3H, dd, J = 7.1, J_{HF} = 0.7 Hz), 1.64 (2H, ddq, J = 13.5, 7.1, 7.1 Hz), 2.33 (3H, s), 2.77 (1H, ddq, J = 7.1, 7.1, 7.1 Hz), 7.17–7.30 (4H, m), 7.30 (1H, dd, J = 7.7, 1.0 Hz), 7.72 (2H, d, J = 8.2 Hz), 8.06-8.11 (1H, m).

^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 19.4 (d, J_{CF} = 2 Hz), 21.6, 28.6 (d, J_{CF} = 2 Hz), 30.8 (d, J_{CF} = 3 Hz), 103.9 (d, J_{CF} = 9 Hz), 114.6, 119.5 (d, J_{CF} = 7 Hz), 123.9, 123.9, 126.8, 127.6 (d, J_{CF} = 5 Hz), 129.8, 130.7 (d, J_{CF} = 1 Hz), 134.6, 145.3, 147.1 (d, J_{CF} = 276 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) 31.2 (1F, s) ppm.

IR (neat) 2970, 2930, 1740, 1650, 1600, 1450, 1395, 1245, 1180, 1090, 745 cm^{-1}.

Anal. Calcd for $C_{19}H_{20}O_2SNF$: C, 66.07; H, 5.84; N, 4.05. Found : C, 66.22; H, 5.94; N, 4.03.

2-Fluoro-1-tosylindole (9f)

To a suspension of NaH (16 mg, 60.0% dispersion in mineral oil, 0.41 mmol) in DMF (0.5 ml) was added **5f** (105 mg, 0.34 mmol) in DMF (1.5 ml) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 23 h at 70 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 3:1) to give **9f** (72 mg, 73%) as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (3H, s), 5.91 (1H, d, J_{HF} = 3.4 Hz), 7.20–7.24 (3H, m), 7.29 (1H, ddd, J = 8.4, 7.3, 1.2 Hz), 7.36 (1H, d, J = 7.9 Hz), 7.78 (2H, d, J = 8.2 Hz), 8.09 (1H, d, J = 8.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 86.7 (d, JCF = 12 Hz), 114.1, 120.7 (d, J_{CF} = 6 Hz), 124.1 (d, J_{CF} = 4 Hz), 124.2, 126.6 (d, J_{CF} = 5 Hz), 126.9, 130.0, 130.8, 134.9, 145.6, 150.8 (d, J_{CF} = 279 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 35.7 (1F, d, J_{FH} = 3 Hz) .

IR (neat) 2950, 2930, 1625, 1450, 1385, 1245, 1175, 1090, 745, 690 cm^{-1}.

MS (70 eV) *m/z* 289 (M^+; 23), 155(50), 134 (80), 91 (100).

HRMS calcd for $C_{15}H_{13}O_2SNF$ 309.0635 (M^+); found 309.0643.

3-Butyl-2-fluorobenzo[*b*]furan (11)

To a solution of **6b** (94 mg, 0.44 mmol) in DMF (4 ml) was added sodium hydride (NaH, 21 mg, 61.8 % dispersion in mineral oil, 0.53 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 2 h at 60 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The

combined extracts were washed with brine and 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–ethyl acetate 30:1) to give **11** (68 mg, 80%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.4 Hz), 1.39 (2H, tq, J = 7.4, 7.4 Hz), 1.66 (2H, tt, J = 7.4, 7.4 Hz), 2.57 (2H, td, J = 7.4 Hz, J_{HF} = 1.0 Hz), 7.19–7.25 (2H, m), 7.32–7.36 (1H, m), 7.40–7.45 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 21.0 (d, J_{CF} = 3 Hz), 22.4, 30.7 (d, J_{CF} = 2 Hz), 90.6 (d, J_{CF} = 12 Hz), 110.8, 119.2 (d, J_{CF} = 6 Hz), 123.1 (d, J_{CF} = 4 Hz), 123.2, 129.3 (d, J_{CF} = 3 Hz), 147.1, 157.1 (d, J_{CF} = 278 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 42.0 (1F, s) ppm.

IR (neat) 2960, 2940, 2860, 1675, 1455, 1380, 1295, 1260, 1185, 1140, 740 cm^{-1}.

MS (20 eV) *m/z* 192 (M^+; 43), 149 (100).

HRMS calcd for $C_{12}H_{13}OF$ 192.0950 (M^+); found 192.0918.

3-Butyl-2-fluorobenzo[*b*]thiophene (13)

To a solution of **8** (93 mg, 0.36 mmol) in dichloromethane (CH_2Cl_2, 3 ml) was added trifluoroacetic anhydride (0.15 ml, 1.09 mmol) and triethylamine (0.15 ml, 1.09 mmol) at 0 °C under a nitrogen atmosphere. After the reaction mixture was stirred for 0.5 h, the volatile components were removed by evaporation, and the residue was dissolved in methanol (3 ml). The resulting mixture was treated with K_2CO_3 (300 mg, 2.17 mmol) at 0 °C and stirred for 1 h at room temperature, and then heated under reflux for an additional 2 h. Phosphate buffer (pH 7) was added to quench the reaction, and organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 50:1) to give **13** (62 mg, 82%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.5 Hz), 1.39 (2H, tq, J = 7.5, 7.5 Hz), 1.64 (2H, tt, J = 7.5, 7.5 Hz), 2.75 (2H, td, J = 7.5 Hz, J_{HF} = 1.3 Hz), 7.28 (1H, ddd, J = 7.6, 7.6,

1.4 Hz), 7.35 (1H, ddd, J = 7.6, 7.6, 0.9 Hz), 7.58 (1H, d, J = 7.9 Hz), 7.64 (1H, d, J = 7.9 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.5, 23.6, 31.0 (d, J_{CF} = 2 Hz), 115.5 (d, J_{CF} = 10 Hz), 121.5 (d, J_{CF} = 6 Hz), 122.6, 124.0 (d, J_{CF} = 4 Hz), 124.6, 131.3 (d, J_{CF} = 2 Hz), 136.8 (d, J_{CF} = 6 Hz), 159.2 (d, J_{CF} = 289 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 29.1 (1F, s) .

IR (neat) 2960, 2930, 2860, 1610, 1460, 1435, 1265, 1190, 1065, 755, 730 cm^{-1}.

MS (20 eV) m/z 208 (M^+; 50), 165 (100).

HRMS calcd for $C_{12}H_{13}SF$ 208.0722 (M^+); found 208.0694.

Anal. Calcd for $C_{12}H_{13}SF$: C, 69.20; H, 6.29. Found: C, 68.94; H, 6.33.

Benzyl-(4,4-difluoro-3-methoxycarbonyl-3-buten-1-yl) ether (19)

The solution of benzyl(tributylstannylmethyl) ether (3.5 g, 8.6 mmol) in THF (34 ml) was treated with butyllithium (5.9 ml, 1.5 M in hexane, 9.1 mmol) at –78 °C under a nitrogen atmosphere. The reaction mixture was transferred *via* a cooled cannula to a solution of copper(I) bromide–dimethyl sulfide complex (1.9 g, 9.1 mmol) in diisopropyl sulfide (7.5 ml) and THF (8.6 ml) at –78 °C, which had been treated with two drops of 2.0M isopropyl magnesium chloride in THF followed by stirring at –78 °C for 15 min. To the solution was added the chlorotrimethylsilane (2.7 ml, 22 mmol) and **17** (1.5 g, 9.5 mmol). After the mixture had been stirred for 5 min at –78 °C, the reaction mixture was warmed to room temperature and stirred for an additional 6 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 5:1) to give **19** (1.2 g, 4.65 mmol, 54%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (2H, tt, J= 6.6, J_{HF} = 2.2, 2.2 Hz), 3.56 (2H, t, J = 6.6 Hz), 3.76 (3H, s), 4.50 (2H, s), 7.26–7.60 (5H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 25.2, 52.1, 68.0 (dd, J_{CF} = 3 Hz), 72.8, 85.8 (dd, J_{CF} = 24, 7

Hz), 127.5, 127.6, 128.4, 138.2, 160.4 (dd, J_{CF} = 310, 296 Hz), 165.2 (dd, J_{CF} = 13, 7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 89.1 (1F, dt, J_{FF} = 6 Hz, J_{FH} = 3 Hz), 94.2 (1F, d, J_{FF} = 6 Hz) ppm.

IR (neat) 2954, 2863, 1749, 1718, 1438, 1349, 1270, 1157, 1112, 1027 cm^{-1}.

HRMS calcd for $C_{13}H_{14}O_3F_2$ 256.0911 (M^+); found 256.0863.

4,4-difluoro-3-methoxycarbonyl-3-buten-1-ol (20)

BCl_3 (2.0 ml, 1.0 M in CH_2Cl_2, 2.0 mmol) was added to a CH_2Cl_2 solution (12 ml) of **19** (493 mg, 1.92 mmol) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 5 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine and 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 5:1) to give **20** (213 mg, 1.28 mmol, 67%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (2H, tt, *J*= 6.3, J_{HF} = 2.2, 2.2 Hz), 2.55 (1H, br s), 3.71 (2H, t, J = 6.3 Hz), 3.80 (3H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 27.9, 52.2, 60.8 (dd, J_{CF} = 3 Hz), 85.7 (dd, J_{CF} = 24, 7 Hz), 160.4 (dd, J_{CF} = 310, 296 Hz), 165.7 (dd, J_{CF} = 13, 7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 89.4 (1F, dt, J_{FF} = 6, J_{FH} = 3 Hz), 94.9 (1F, d, J_{FF} = 6 Hz) ppm.

IR (neat) 3511, 2958, 1774, 1720, 1440, 1351, 1272, 1178, 1095, 1024 cm^{-1}.

MS (70 eV) *m/z* 167 (M^++1; 32), 136 (100), 105 (100).

4,4-difluoro-3-methoxycarbonyl-3-buten-1-yl-*N*-*tert*-butoxycarbonyl *p*-toluene sulfonamide (21)

To a solution of *N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonamide (348 mg, 1.28 mmol) in THF (15 ml) was added triphenylphosphine (336 mg, 1.28 mmol), **20** (213 mg, 1.28 mmol) in THF (2 ml) and diethyl azodicarboxylate (223 mg, 1.28 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 10 h, concentrated under reduced

pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 5:1) to give **21** (415 mg, 0.986 mmol, 77%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (9H, s), 2.43 (3H, s), 2.68 (2H, tt, J = 6.4 Hz, J_{HF} = 2.1 Hz), 3.82 (3H ,s), 4.00 (2H, t, J = 6.4 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.77 (2H, d, J = 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 25.2, 25.8, 45.4 (dd, J_{CF} = 2, 2 Hz), 52.2, 84.3, 85.8 (dd, J_{CF} = 23, 7 Hz), 127.9, 129.2, 137.2, 144.2, 150.7, 160.7 (dd, J_{CF} = 311, 297 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 89.8 (1F, dt, J_{FF} = 8 Hz, J_{FH} = 3 Hz), 95.6 (1F, d, J_{FF} = 8 Hz) ppm.

IR (neat) 2981, 1720, 1438, 1355, 1286, 1155, 1087, 1051, 673, 595 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 421 (M^+; 1), 184 (96), 155 (98).

HRMS calcd for $C_{18}H_{25}O_6NSF_2$ 421.1370 (M^+); found 421.1342.

4,4-difluoro-3-methoxycarbonyl-3-buten-1-yl-*p*-toluenesulfonamide (16)

To a solution of **21** (421 mg, 0.998 mmol) in CH_2Cl_2 (8 ml) was added trifluoroacetic acid (0.23 ml, 2.99 mmol) at room temperature. The reaction mixture was stirred for 4 h at room temperature, and then 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 brine and 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–ethyl acetate 3:1) to give **16** (310 mg, 0.971 mmol, 97%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (2H, tt, J = 6.5 Hz, J_{HF} = 2.1 Hz), 2.42 (3H, s), 3.09 (2 H, td, J = 6.5, 6.5 Hz), 3.75 (3H, s), 5.09 (1H, t, J = 6.5 Hz), 7.30 (2H, d, J = 8.1 Hz), 7.73 (2H, d, J = 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4, 25.2, 41.1, 52.3, 85.6 (dd, J_{CF} = 23, 7 Hz), 127.0, 129.6, 137.0, 143.4, 160.4 (dd, J_{CF} = 312, 297 Hz), 165.1 (dd, J_{CF} = 13, 8 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 90.5 (1F, dt, J_{FF} = 9 Hz, J_{FH} = 3 Hz), 96.2 (1F, d, J_{FF} = 9 Hz) ppm.

IR (neat) 3293, 2956, 1718, 1438, 1328, 1218, 1159, 1093, 815, 663, 551 cm^{-1}.

HRFABMS calcd for $C_{13}H_{16}O_4NSF_2$ 320.0768 ($M+1^+$); found 320.0775.

2-Fluoro-3-methoxycarbonyl-1-tosyl-2-pyloline (22)

To a suspension of sodium hydride (NaH, 6.1 mg, 60.0 % dispersion in mineral oil, 0.152 mmol) in DMF (1.0 ml) was added **16** (44 mg, 0.138 mmol) in DMF (1.0 ml) at 100 °C under a nitrogen atmosphere. The reaction mixture was stirred for 15 min at 100 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 1:1) to give **22** (25 mg, 0.085 mmol, 62%) as colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (3H, s), 2.62 (2H, td, J = 9.0 Hz, J_{HF} = 4.8 Hz), 3.70 (3H, s), 3.78 (2H, td, J = 9.0 Hz, J_{HF} = 0.8 Hz), 7.38 (2H, d, J = 8.2 Hz), 7.78 (2H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 21.6, 22.9, 46.4, 51.4, 88.7 (d, J_{CF} = 5 Hz), 127.6, 130.2, 133.6, 145.4, 156.2 (d, J_{CF} = 296 Hz), 163.5(d, J_{CF} = 6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$) 61.8 (1F, dd, J_{FH} = 4.7, 4.7 Hz) ppm.

IR (neat) 1703, 1674, 1441, 1394, 1367, 1277, 1171, 1144, 1099, 577 cm^{-1}.

MS (70 eV) *m/z* (rel intensity) 299 (M^+; 48), 155 (77), 91 (100).

HRMS calcd for $C_{13}H_{14}O_4NFS$ 299.0627 (M^+); found 299.0627.

***o*-(1-Butyl-2,2-difluorovinyl)phenoxymethoxymethane (23)**

To a THF suspension (12 ml) of NaH (134 mg, 60% dispersion in mineral oil, 3.36 mmol) was added **6b** (648 mg, 3.05 mmol) at –78 °C for 10 min under a nitrogen atmosphere. To the solution was added chloromethyl methyl ether (0.69 ml, 9.2 mmol) at –78 °C and stirred for 5 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 20:1) to give **23** (716 mg, 2.76

mmol, 92%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.22–1.36 (4H, m), 2.30–2.38 (2H, m), 3.46 (3H, s), 5.18 (2H, s), 7.00 (1H, ddd, J = 7.4, 7.4, 1.1 Hz), 7.10–7.16 (2H, m), 7.25 (1H, ddd, J = 7.4, 7.4, 1.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.1, 27.7, 29.6 (dd, J_{CF} = 3, 3 Hz), 56.0, 89.1 (dd, J_{CF} = 24, 16 Hz), 94.3, 114.4, 121.5, 123.5, 129.0, 131.0 (d, J_{CF} = 2 Hz), 153.0 (dd, J_{CF} = 286, 286 Hz), 155.0.

^{19}F NMR (470 MHz, $CDCl_3$) 67.2 (1F, dt, J_{FF} = 46 Hz, J_{FH} = 3 Hz), 71.3 (1F, d, J_{FF} = 46 Hz) ppm.

IR (neat) 2958, 1745, 1492, 1454, 1228, 1197, 1155, 1079, 1004, 754 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 256 (M^+; 11), 193 (100), 150 (100).

HRMS calcd for $C_{14}H_{18}O_2F_2$ 256.1275 (M^+); found 256.1275.

_o_-(1-Butyl-2,2-difluorovinyl)phenoxymethoxymethane (24)

Red-Al (0.34 ml, 3.4 M in toluene, 1.2 mmol) was added to a solution of **23** (107 mg, 0.417 mmol) in toluene (1.5 ml) at 0 °C under a nitrogen atmosphere. The reaction mixture was heated under reflux for 3 h, phosphate buffer (pH 7) was added to quench the reaction. The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–AcOEt 20:1) to give **24*E*** (47 mg, 0.198 mmol, 47%) and **24*Z*** (41 mg, 0.173 mmol, 41%) as colorless liquids.

24*E*

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 6.9 Hz), 1.24–1.34 (4H, m), 2.50–2.57 (2H, m), 3.45 (3H, s), 5.18 (2H, s), 6.60 (1H, d, J_{HF} = 86.7 Hz), 6.96 (1H, dd, J = 7.4, 7.4 Hz), 7.10 (2H, d, J = 7.4 Hz), 7.22–7.27 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.4, 26.7 (d, J_{CF} = 3 Hz), 29.6 (d, J_{CF} = 2 Hz), 56.1, 94.4, 114.5, 121.6, 123.3 (d, J_{CF} = 10 Hz), 126.4 (d, J_{CF} = 10 Hz), 128.8, 130.9 (d, J_{CF} = 2 Hz), 146.1 (d, J_{CF} = 260 Hz), 155.4 (d, J_{CF} = 3 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 31.4 (1F, dt, J_{FH} = 86, 3 Hz) ppm.

IR (neat) 2956, 1488, 1228, 1195, 1155, 1114, 1101, 1079, 1004, 754 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 238 (M^+; 27), 174 (90), 132 (100).

HRMS calcd for $C_{14}H_{19}O_2F$ 238.1370 (M^+); found 238.1377.

24*Z*

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.2 Hz), 1.32–1.35 (4H, m), 2.22–2.30 (2H, m), 3.47 (3H, s), 5.17 (2H, s), 6.60 (1H, dt, J_{HF} = 86.7, J = 1.2 Hz), 7.00 (1H, dd, J = 7.3, 7.3 Hz), 7.11–7.16 (2H, m), 7.22–7.27 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.2, 29.9 (d, J_{CF} = 3 Hz), 30.4 (d, J_{CF} = 5 Hz), 56.0, 94.5, 114.7, 121.0 (d, J_{CF} = 4 Hz), 121.6, 125.2 (d, J_{CF} = 2 Hz), 128.7, 130.7 (d, J_{CF} = 2 Hz), 143.7 (d, J_{CF} = 257 Hz), 155.5.

^{19}F NMR (470 MHz, $CDCl_3$) 31.1 (1F, dt, J_{FH} = 86, 3 Hz) ppm.

IR (neat) 2931, 1675, 1490, 1450, 1240, 1197, 1155, 1081, 1004, 754 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 238 (M^+; 25), 174 (74), 132 (100).

HRMS calcd for $C_{14}H_{19}O_2F$ 238.1370 (M^+); found 238.1370.

***o*-(1-Butyl-2-fluorovinyl)phenol (25*E*)**

conc. HCl (3.5 ml) was added to a solution of **24*E*** (168 mg, 0.703 mmol) in THF (7 ml) at 0 °C. The reaction mixture was stirred for 2.5 h at 0 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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 1:1) to give **25*E*** (117 mg, 0.603 mmol, 86%) as colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, t, J = 7.2 Hz), 1.28–1.36 (4H, m), 2.43–2.50 (2H, m), 5.14 (1H, s), 6.65 (1H, d, J_{HF} = 85.1 Hz), 6.80–6.93 (2H, m), 6.90–7.10 (1H, m), 7.18–7.23 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.5, 27.7 (d, J_{CF} = 2 Hz), 30.3 (d, J_{CF} = 2 Hz), 115.5,

120.5, 120.9 (d, J_{CF} = 8 Hz), 122.5 (d, J_{CF} = 9 Hz), 129.2, 130.4 (d, J_{CF} = 3 Hz), 146.9 (d, J_{CF} = 264 Hz), 153.4 (d, J_{CF} = 2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$) 35.6 (1F, dt, J_{FH} = 85, 3 Hz) ppm.

IR (neat) 3529, 2958, 2931, 2861, 1488, 1450, 1284, 1211, 1178, 1110, 754 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 194 (M^+; 51), 145 (40), 131 (100).

HRMS calcd for $C_{12}H_{15}OF$ 194.1108 (M^+); found 194.1108.

_o_-(1-Butyl-2-fluorovinyl)phenol (25*Z*)

Compound **25*Z*** was prepared by the method described for **25*E*** using conc. HCl (3.3 ml), THF (6.5 ml), and **24*Z*** (155mg, 0.652 mmol). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) gave **25*Z*** (106 mg, 0.548 mmol, 84%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.0 Hz), 1.25–1.34 (4H, m), 2.23–2.29 (2H, m), 5.01 (1H, d, J_{HF} = 3.1 Hz), 6.73 (1H, dt, J_{HF} = 85.5, J = 1.2 Hz), 6.92–6.96 (2H, m), 7.70–7.11 (1H, m), 7.19–7.24 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.2, 30.0 (d, J_{CF} = 2 Hz), 30.9 (d, J_{CF} = 5 Hz), 115.9, 119.4 (d, J_{CF} = 3 Hz), 120.6, 121.5, 128.8, 129.3, 144.3 (d, J_{CF} = 259 Hz), 152.7.

^{19}F NMR (470 MHz, $CDCl_3$) 35.0 (1F, dtd, J_{FH} = 85, 6, 3 Hz) ppm.

IR (neat) 3554, 3450, 2931, 1488, 1450, 1234, 1180, 1114, 1085, 752 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 194 (M^+; 58), 152 (29), 131 (100).

HRMS calcd for $C_{12}H_{15}OF$ 194.1108 (M^+); found 194.1108.

3-butylbenzo[*b*]furan (26)

To a solution of **25*E*** (117 mg, 0.603 mmol) in DMF (6 ml) was added NaH (29 mg, dispersion in mineral oil, 0.72 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was heated to 80 °C and stirred for 43 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and 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

5:1) to give **26** (18 mg, 0.104 mmol, 17%) as a colorless liquid.

To a solution of ***25Z*** (90 mg, 0.46 mmol) in DMF (5 ml) was added NaH (22 mg, dispersion in mineral oil, 0.55 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was heated to 80 °C and stirred for 43 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with AcOEt three times. The combined extracts were washed with brine and 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 5:1) to give **26** (15 mg, 0.086 mmol, 19%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (3H, t, *J* = 7.5 Hz), 1.42 (2H, tq, *J* = 7.5, 7.5 Hz), 1.69 (2H, tt, *J* = 7.5, 7.5 Hz), 2.67 (2H, td, *J* = 7.5, 0.9 Hz), 7.22 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz), 7.28 (1H, ddd, *J* = 7.6, 7.6, 1.3 Hz), 7.39 (1H, s), 7.45 (1H, d, *J* = 8.2 Hz), 7.55 (1H, d, *J* = 7.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.5, 23.2, 31.2, 111.4, 119.6, 120.7, 122.1, 124.0, 128.4, 141.0, 155.4.

IR (neat) 2958, 2929, 2858, 1452, 1278, 1186, 1089, 1008, 856, 744, 422 cm^{-1}.

MS (70 eV) *m/z* 174 (M^+; 32), 132 (75), 131 (100), 102 (67).

HRMS calcd for $C_{12}H_{14}O$ 174.1045 (M^+); found 174.1059.

_o_-(1-Butyl-2,2-dibromovinyl)phenol (28)

28 was prepared according to literature procedure.[14]

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, *J* = 7.0 Hz), 1.28–1.41 (4H, m), 2.46–2.64 (2H, m), 4.94 (1H, s), 6.91 (1H, dd, *J* = 7.5, 0.9 Hz), 6.95 (1H, ddd, *J* = 7.5, 7.5, 1.2 Hz), 7.00 (1H, dd, *J* = 7.5, 1.5 Hz), 7.24 (1H, ddd, *J* = 7.5, 7.5, 1.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.5, 28.9, 38.5, 90.3, 116.1, 120.8, 127.5, 128.6, 129.6, 144.0, 151.4.

IR (neat) 3448, 2958, 2927, 2859, 1484, 1448, 1286, 1267, 1176, 827, 752 cm^{-1}.

MS (20 eV) *m/z* (rel intensity) 334 (M^+; 80), 174 (87), 131 (100).

2-Bromo-3-butylbenzo[*b*]furan (29)

To a suspension of sodium hydride (NaH, 18 mg, 61.8% dispersion in mineral oil, 0.45 mmol) in DMF (3.5 ml) was added **27** (94 mg, 0.44 mmol) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 5 h at 60 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with ethyl acetate three times. The combined extracts were washed with brine and 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–ethyl acetate 30:1) to give **29** (14 mg, 15%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (3H, t, *J* = 7.5Hz), 1.39 (2H, tq, *J* = 7.5, 7.5 Hz), 1.65 (2H, tt, *J* = 7.5, 7.5 Hz), 2.64 (2H, t, *J* = 7.5 Hz), 7.20–7.26 (2H, m), 7.41 (1H, dd *J* = 7.2, 2.0 Hz), 7.46–7.50 (1H, m).

^{13}C NMR (126 MHz, $CDCl_3$) δ 13.9, 22.4, 23.8, 30.9, 110.9, 118.9, 119.6, 122.8, 124.0, 126.2, 128.8, 155.2.

IR (neat) 2956, 2929, 2858, 1581, 1448, 1265, 1224, 1130, 1103, 1083, 875, 744. cm^{-1}.

MS (70 eV) *m/z* 252 (M^+; 82), 209 (98), 131 (100), 102 (67).

HRMS calcd for $C_{12}H_{13}OBr$ 252.0150 (M^+); found 252.0125.

Conclusion

This dissertation demonstrates that versatile methods for the synthesis of ring-fluorinated heterocycles have been established by using the unique properties of fluorine.

In Chapter 2 is described the construction of ring-fluorinated 6-memberd hetero and carbocycles *via* intramolecular cyclizations of β,β-difluorostyrenes bearing heteroatom and carbon nucleophiles at the *ortho* position. The intramolecular nucleophiles are generated by (i) deprotonation of active hydrogens (HY- → $^{-}$**Y**- ; Y = O, S, NTs, CH(CN)), (ii) conversion into N=C or N=N groups (OHC- → HO**N**=H_2C-, N≡N^{+}- → H**N**=N-), (iii) metal–halogen exchange (ICH_2- → $^{-}$**C**H_2-), and (iv) addition of external nucleophiles to unsaturated functional groups (NC- → $^{-}$**N**=C(Nu)-, CN- → $^{-}$**C**Nu=N-). Their substitutions afford 3-fluoroisochromenes, 3-fluoroisothiochromenes, 3-fluoroisoquinolines, 3-fluoroquinolines, 3-fluorocinnolines, and fluoronaphthalenes. In addition, the remaining fluorine in the 3-fluoroisothiochoromenes and 3-fluoroisoquinoline *N*-oxides are replaced by heteroatom nucleophiles, providing a facile method for the synthesis of 3,4-disubstituted isothiochoromenes and isoquinoline *N*-oxides.

In Chapter 3 is described the construction of ring-fluorinated 5-membered heterocycles such as 2-fluoroindoles, 2-fluorobenzofurans, and 2-fluorobenzothiophenes *via* intramolecular substitution for the vinylic fluorine of *o*-substituted β,β-difluorostyrenes. Although this type of reaction is classified as 5-*endo*-trig ring closure, disfavored process in Baldwin's rules and has only rarely been observed in synthetic chemistry, the nucleophilic 5-*endo*-trig cyclizations have been achieved by making use of the properties of fluorine. In addition, the effect of fluorine substituents on the 5-*endo*-trig cyclization is elucidated by conducting the competitive reaction of β,β-difluoro-α,β-unsaturated ester between 5-*endo*-trig and 5-*exo*-trig processes and the cyclization of β-monofluoro, β,β-dichloro, and β,β-dibromostyrenes. Consequently, it has been revealed that the two vinylic fluorine substituents are essential and play a critical role in promoting the 5-*endo*-trig cyclization.

The intramolecular cyclizations of β,β-difluoroolefins selectively afford ring-fluorinated heterocycles, for which only a limited number of synthetic methods have been reported. Thus, the present methodology is one of the solutions to the synthetic

problem of fluorinated heterocycles. The synthesized compounds would be widely used as important components in the pharmaceutical, agrochemical, and dyestuffs industries. Furthermore, the "anti-Baldwin" results indicate that some of the unique reactivity of *gem*-difluoroolefins may be derived from a partial single bond character of the olefin, which sheds light on a new function of fluorine.

List of Publication

Junji Ichikawa, Yukinori Wada, Tatsuo Okauchi, Toru Minami
;5-*endo*-Trigonal Cyclization of *o*-Substituted *gem*-Difluorostyrenes:
Syntheses of 2-Fluorinated Indoles, Benzo[*b*]furans and Benzo[*b*]thiophenes
;*Chemical Communications*, **1997**, 1537-1538.

Junji Ichikawa, Masaki Fujiwara, Yukinori Wada, Tatsuo Okauchi, Toru Minami
;The Nucleophilic 5-*endo*-Trig Cyclization of *gem*-Difluoroolefins with Homoallylic Functional Groups: Syntheses of Ring-Fluorinated Dihydroheteroaromatics
;*Chemical Communications*, **2000**, 1887-1888.

Yukinori Wada, Junji Ichikawa, Tadayuki Katsume, Hiroko Nohiro, Tatsuo Okauchi, and Toru Minami
;Intramolecular Cyclizations of *o*-Substituted β,β-Difluorostyrenes:
Synthesis of 3-Fluorinated Isochromenes and Isothiochromenes
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