Available online at www.sciencedirect.com
SCIENCE DIRECT
Journal of Fluorine Chemistry 125 (2004) 585–593
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Ring-fluorinated naphthalene and indene synthesis via 6- and 5-*endo-trig* cyclizations of *gem*-difluoroalkenes by carbon nucleophiles

Junji Ichikawa[a,*], Hiroyuki Miyazaki[b], Kotaro Sakoda[a], Yukinori Wada[a]

[a]*Department of Chemistry, Graduate School of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Department of Applied Chemistry, Kyushu Institute of Technology, Sensui-cho, Tobata, Kitakyushu 804-8550, Japan*

Received 17 October 2003; received in revised form 28 December 2003; accepted 6 January 2004

Abstract

The intramolecular vinylic substitution of *gem*-difluoroalkenes is accomplished with sp^3 and sp^2 carbon nucleophiles (2-arylethyllithium and aryllithium) in a 6-*endo-trig* and a normally disfavored 5-*endo-trig* fashion, leading to the synthesis of 3-fluoro-1,2-dihydronaphthalenes and 3-fluoroindenes, respectively. The dihydronaphthalenes are readily aromatized on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford 2-fluoronaphthalenes.

Keywords: Fluoronaphthalene; Fluoroindene; Baldwin's rules; 5-*Endo-trig* cyclization; 6-*Endo-trig* cyclization; *Gem*-difluoroalkene; Nucleophilic substitution; Addition–elimination; Organolithium

1. Introduction

Fluorinated carbocyclic π-systems are units of increasing significance in pharmaceuticals, agrochemicals, and materials due to their biological activities and physical properties [1,2]. Introduction of fluorine into aromatic and alicyclic π-systems is usually achieved by the Balz–Schiemann reaction or by use of various fluorinating reagents [3–5]. However, lack of regioselectivity, the necessity of multistep procedures, and difficulties in handling these fluorinating reagents continue to be problems with these conventional methods. Therefore, the development of efficient methods for the selective construction of those fluorinated carbocycles remains a highly desirable goal.Recently, we have introduced a new concept for the synthesis of five- and six-membered ring-fluorinated heterocyclic compounds, such as indoles, benzo[*b*]furans, benzo[*b*]thiophenes, 2-pyrrolines, 2,3-dihydrofurans, 2,3-dihydrothiophenes, isochromenes, isothiochromenes, quinolines, and isoquinolines [6–11]. This flexible methodology is based on vinylic nucleophilic substitution (SNV) of the fluorines in *gem*-difluoroalkenes via intramolecular addition–elimination processes [12–14]. Their remarkable reactivity toward substitution is due to (i) the electrophilic activation of the carbon–carbon double bond by the two fluorines and (ii) the leaving group ability of the fluoride ions.

We expected that our ''intramolecular substitution'' concept could easily be adapted to the construction of carbocyclic π-systems, such as naphthalene and indene nuclei. For these ring constructions, intramolecular carbon nucleophiles must be employed, and particularly for the construction of the indene nucleus, 5-*endo-trig* cyclizations that are disfavored by Baldwin's rules must proceed [15–17]. Herein we wish to report the results of our studies on the intramolecular cyclization of *gem*-difluoroalkenes with sp^3 and sp^2 carbon nucleophiles leading to the synthesis of ring-fluorinated naphthalene and indene derivatives.

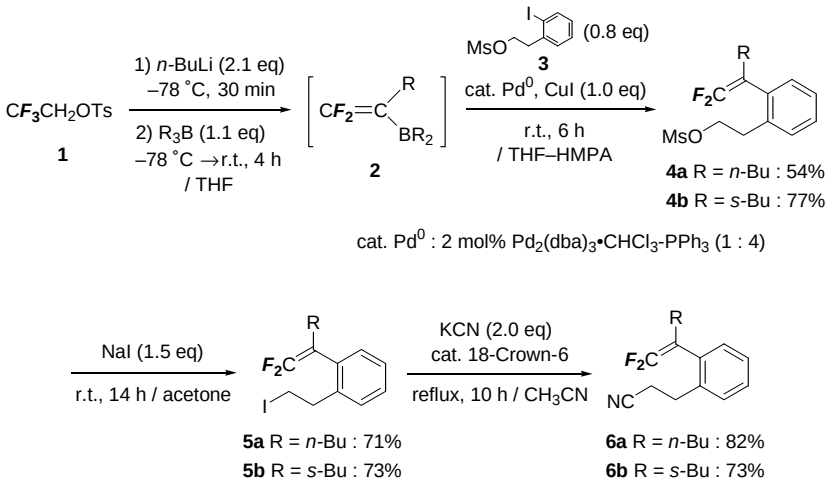
2. Results and discussions

2.1. Synthesis of 2-fluorinated naphthalene derivatives

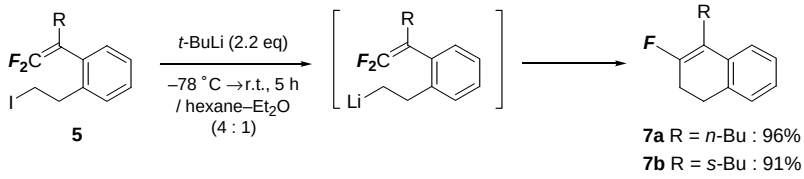
For the synthesis of 2-fluoronaphthalenes, we adopted the following two methods in order to generate the intramolecular carbon nucleophiles: (i) metal–halogen exchange of iodomethyl groups ($ICH_2- \rightarrow {}^-CH_2-$), (ii) deprotonation

* Corresponding author. Tel.: +81-3-5841-4345; fax: +81-3-5841-4345.
E-mail address: junji@chem.s.u-tokyo.ac.jp

0022-1139/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2004.01.004



Scheme 1. Preparation of the substrates **5** and **6**.



Scheme 2. Synthesis of 3-fluoro-1,2-dihydronaphthalenes **7**.

of active methylenes next to a cyano group ($CH_2(CN)-$ → $^-CH(CN)-$). Thus, we designed *β*,*β*-difluorostyrenes **5** and **6** bearing 2-iodoethyl and 2-cyanoethyl groups at the *o*-position as precursors of 2-fluoronaphthalenes. These substrates **5** and **6** were prepared as outlined in Scheme 1 via the one-pot sequence that we have previously established for a wide range of *gem*-difluoroalkenes [18]. 2,2-Difluorovinylboranes **2** were prepared in situ from 2,2,2-trifluoroethyl *p*-toluenesulfonate **1** and trialkylboranes. The coupling reactions of **2** with aryl iodide **3** were conducted in the presence of palladium catalyst and CuI, followed by replacement of the OMs group by I and CN groups, leading to **5** and **6**.

According to the reported procedure for lithium–halogen exchange for primary alkyl iodides [19,20], *o*-(2-iodoethyl)-styrenes **5a,b** were treated with 2.2 eq. of *tert*-butyllithium to generate carbon nucleophiles. The desired intramolecular substitution of the carbanions for the vinylic fluorines occurred to afford 3-fluoro-1,2-dihydronaphthalenes **7a,b** in excellent yield (Scheme 2). The synthesis of such 1-monofluorinated cycloalkenes is limited to the method via difluorination of cyclic ketones and dehydrofluorination [21]. Addition of a polar solvent, such as THF or HMPA as a cosolvent resulted in a drastic decrease in the yield of **7**.

Furthermore, we attempted conversion of thus obtained dihydronaphthalenes **7** into 2-fluoronaphthalenes **8** by oxidation. Dehydrogenation of **7** was examined with palladium on charcoal, tetrachloro-1,4-benzoquinone (chloranil), or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). On treatment of **7** with 3 eq. of DDQ in refluxing benzene, the desired aromatization proceeded to afford 2-fluoronaphthalenes **8a,b** in good yield (Table 1, Entries 5, 6).

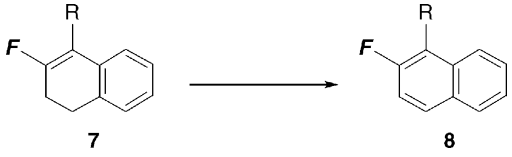


Table 1
Synthesis of 2-fluoronaphthalenes **8**

Entry	*R*	Reagent (eq.)	Solvent	Conditions	Yield (%)
1	*n*-Bu (**7a**)	10% Pd–C (0.038)	Diglyme	Reflux 48 h	Trace (**8a**)
2	*n*-Bu (**7a**)	Chloranil (1.2)	Xylene	Reflux 6 h	26 (**8a**)
3	*n*-Bu (**7a**)	DDQ (1.2)	Benzene	Reflux 12 h	35 (**8a**)
4	*n*-Bu (**7a**)	DDQ (2.0)	Diglyme	Reflux 2 h	43 (**8a**)
5	*n*-Bu (**7a**)	DDQ (3.0)	Benzene	Reflux 3 h	**71** (**8a**)
6	*s*-Bu (**7b**)	DDQ (3.0)	Benzene	Reflux 3 h	**70** (**8b**)

Next, we examined the generation of carbanions via abstraction of an α-hydrogen of a cyano group by a base instead of the above-mentioned lithium–halogen exchange. This would allow construction of naphthalene derivatives bearing a cyano group, a versatile substituent that can be readily converted into other functional groups, such as carboxy, aminomethyl, and amino groups. When difluorostyrene **6a** bearing a cyanoethyl group was treated with 1 eq. of butyllithium [22], the expected cyclization proceeded to give 3-fluoro-1,2-dihydro-2-naphthonitrile **9a** along with recovered starting material **6a**. Using 2 eq. of butyllithium or *tert*-butyllithium raised the yield of **9a** to 47% or 39%, respectively (Table 2, Entries 1 and 2). To prevent the attack of butyllithium at the terminal difluoromethylene and the cyano carbons, we tried a bulky amide base, such as lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LiHMDS). The reaction with LiHMDS (2 eq.) afforded **9a** in 23% yield along with the oxidized product **10a** in 52% yield, giving rise to an increase in the total yield of the cyclized products **9a** and **10a** up to 75% (Table 2, Entry 4). In order to obtain **10** as a single cyclized product, oxidative post-treatment was conducted. The crude products including **9** and **10** were treated with DDQ (3 eq.) under reflux in benzene for 3 h to afford 3-fluoro-2-naphthonitriles **10a,b** in 68 and 58% yield from **6a,b**, respectively (Entries 5 and 6).

Thus, the ''cyclization–dehydrogenation'' sequence provides a synthetic method for 2-fluorinated naphthalenes **8** and **10** with or without a cyano group at the 3-position. Such compounds are less accessible by conventional electrophilic methods. Electrophilic fluorination of naphthalenes affords 1-fluoronaphthalenes as major products and is severely deactivated by electron-withdrawing groups [3–5] (for the synthesis of fluoronaphthalenes, see [23,24]; for the synthesis of naphthalenes, see [25]).

2.2. Synthesis of 3-fluorinated indene

In order to construct the five-membered ring of the indene nucleus, the normally disfavored 5-*endo-trig* cyclization must proceed in the intramolecular substitution of *gem*-difluoroalkenes by phenyl or benzyl anions. Since we have already accomplished this type of 5-*endo-trig* cyclization by sp^3 carbanions [26] (see also [27] for 5-*endo* carbocyclization of *gem*-difluoroalkenes in the presence of $SnCl_4$), a phenyl anion of an sp^2 carbon nucleophile was adopted to broaden the scope of the nucleophilic 5-*endo-trig* ring closures (for the nucleophilic 5-*endo-trig* cyclization, see [9] and references therein). We expected the nucleophilic 5-*endo-trig* cyclization to proceed due to the unique properties of *gem*-difluoroalkenes: (i) the electrostatic attraction between the cationic CF_2 carbon and nucleophilic center (anion) would allow initial ring formation and (ii) the successive elimination of fluoride ion could suppress the reverse ring opening, thus functioning as a ''lock''. On the basis of these considerations, we designed difluoroallylbenzenes **13** bearing bromine or iodine at the *ortho* position as precursors for 3-fluoroindenes, which were prepared as depicted in Schemes 3 and 4.

The acid chloride generated in situ from carboxylic acid **11** and thionyl chloride was treated with benzene in the presence of aluminum chloride to undergo Friedel–Crafts acylation, leading to 2′-bromodeoxybenzoin **12**. Thus obtained **12** was difluoromethylated with dibromodifluoromethane and tris(dimethylamino)phosphine in THF via Wittig-type reaction [28] to give α-(*o*-bromophenylmethyl)-β,β-difluorostyrene **13a** (Scheme 3).

The corresponding iodide **13b** was prepared as follows (Scheme 4): dilithiated pivalanilide **14′** was generated in situ from **14** [29] to undergo the SN2' reaction of α-trifluoromethylstyrene [30] leading to *o*-(3,3-difluoro-2-phenylallyl)-pivalanilide **16**. Thus obtained **16** was hydrolyzed with hydrochloric acid to give *o*-(3,3-difluoroallyl)aniline **17**.

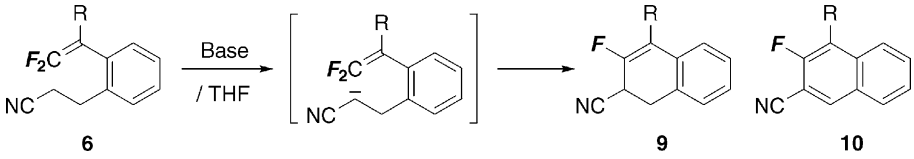
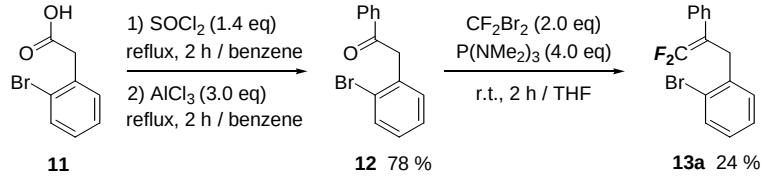


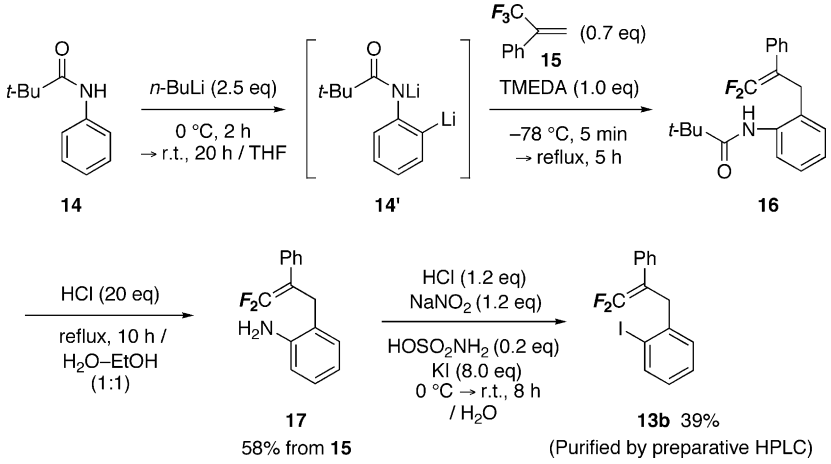
Table 2
Synthesis of fluoronaphthonitrile derivatives **9** and **10**

Entry	*R*	Base (eq.)	Conditions	**9** (%)	**10** (%)
1	*n*-Bu (**6a**)	*n*-BuLi (2.0)	−78 °C → RT, 7 h	47 (**9a**)	7 (**10a**)
2	*n*-Bu (**6a**)	*t*-BuLi (2.0)	−78 °C → RT, 5 h	39 (**9a**)	3 (**10a**)
3	*n*-Bu (**6a**)	LDA (1.2)	−78 °C → RT, 11 h	30 (**9a**)	41 (**10a**)
4	*n*-Bu (**6a**)	LiHMDS (2.0)	−78 °C → RT, 1 h	23 (**9a**)	52 (**10a**)
5[a]	*n*-Bu (**6a**)	LiHMDS (2.0)	−78 °C → RT, 6 h	0 (**9a**)	**68** (**10a**)
6[a]	s-Bu (**6b**)	LiHMDS (3.0)	−78 °C → RT, 6 h	0 (**9b**)	**58** (**10b**)

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



Scheme 3. Preparation of the substrate **13a**.



Scheme 4. Preparation of the substrate **13b**.

Transformation of the amino group in **17** via diazotization afforded β,β-difluoro-α-(*o*-iodophenylmethyl)styrene **13b**.

We examined the cyclization of **13a,b** via their lithium–halogen exchange reaction. The results are summarized in Table 4. On treatment of **13a** with *tert*-butyllithium in diethyl ether, monofluoroalkene **20** was obtained as a major product by the direct substitution of *tert*-butyllithium for the vinylic fluorine (Table 3, Entry 1). Screening of alkyllithiums for metal–halogen exchange and reaction conditions revealed the following: After iodide **13b** was treated with 1 eq. of butyllithium in Et_2O–hexane (1:4) at −110 °C, conducting the cyclization at room temperature raised the yield of indene **18** up to 52% (Entry 5). Since the formation of alkylated indenes **21** and benzyldifluorostyrene **19** suggested that deprotonation of indene **18** by aryllithium **13′** decreased the yield (Entries 5 and 6, Scheme 5), NaH or LDA was added for deprotonation of **18** in order to prevent quenching **13′** with **18**, but the expected results were not obtained.

Thus, we have accomplished the 5-*endo-trig* cyclization with an sp^2 carbon nucleophile as well as sp^3 carbon nucleophiles [26], providing a regioselective entry to less accessible 3-fluoroindenes (for the synthesis of indenes bearing a fluorine on the five-membered ring, see: 3-fluoroindene: [31], 1-fluoroindene: [32]).

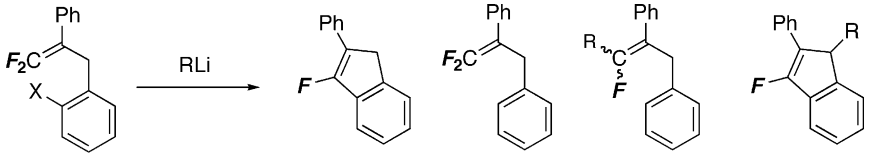
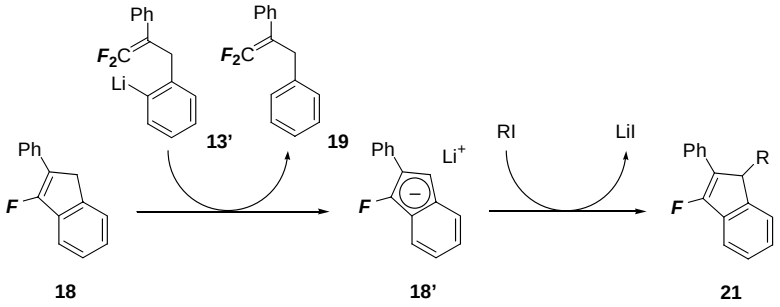


Table 3
Synthesis of 3-fluoroindene **18**

Entry	X	RLi (eq.)	Solvent	Conditions	Yield (%)			
					18	**19**	**20**	**21**
1	Br (**13a**)	*t*-BuLi (2.2)	Et_2O	−78 °C, 0.5 h → RT, 1 h	26	10	34 (**20a**)	0
2	Br (**13a**)	*t*-BuLi (2.2)	Et_2O–hexane (1:4)	−100 °C, 0.5 h → RT, 1 h	31	38	21 (**20a**)	0
3	I (**13b**)	*t*-BuLi (2.2)	Et_2O–hexane (1:4)	−110 °C, 1 h → −78 °C, 1 h → RT, 2 h	41	26	17 (**20a**)	0
4	I (**13b**)	*s*-BuLi (1.1)	Et_2O–hexane (1:4)	−110 °C, 1 h → −78 °C, 1 h → RT, 2 h	51	24	0	0
5	I (**13b**)	*n*-BuLi(1.0)	Et_2O–hexane (1:4)	−110 °C, 1 h → −78 °C, 1 h → RT, 2 h	**52**	19	0	5 (**21b**)
6	I (**13b**)	MeLi (1.0)	Et_2O–hexane (1:4)	−110 °C, 1 h → −78 °C, 1 h → RT, 2 h	47	17	14 (**20c**)	12 (**21c**)



Scheme 5. Generation and alkylation of indenyl anion **18′**.

2.3. Conclusion

In carbocyclization of *gem*-difluoroalkenes, 6-*endo-trig* and 5-*endo-trig* ring closures are successfully achieved to construct naphthalene and indene frameworks, showing that not only heteroatom nucleophiles but also sp^3 and sp^2 carbon nucleophiles can be adapted to this intramolecular substitution. Thus, the scope of this methodology has been expanded in terms of six- and five-membered ring formation.

3. Experimental

3.1. General experimental procedure

NMR spectra were obtained on a JEOL JNM-A-500, a JEOL-EX-270, or a Bruker DRX-500 spectrometer. Chemical shift values were given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR: δ-value) or internal C_6F_6 (for ^{19}F NMR: δ_F-value). IR spectra were recorded on a Horiba FT-300S or a JEOL JIR-WINSPEC50 spectrometer. 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.

3.2. Synthesis of 2-fluorinated naphthalene derivatives

3.2.1. 2-[o-(1-Butyl-2,2-difluorovinyl)phenyl]ethyl methansulfonate (*4a*)

Butyllithium (3.0 ml, 1.40 M in hexane, 4.2 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**, 509 mg, 2.0 mmol) in THF (10 ml) at −78 °C over 10 min under nitrogen. 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 2-(*o*-iodophenyl)ethyl methansulfonate (**3**, 522 mg, 1.6 mmol) and copper(I) iodide (381 mg, 2.0 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 through Celite, 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 **4a** (275 mg, 54%) as a pale yellow liquid.

^1H 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 (471 MHz, $CDCl_3$) δ_F 68.0 (1F, dt, $J_{FF} = 46$ Hz, $J_{FH} = 3$ Hz), 72.7 (1F, d, $J_{FF} = 46$ Hz). 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.

3.2.2. 2-[o-(1-sec-Butyl-2,2-difluorovinyl)phenyl]ethyl methansulfonate (*4b*)

Compound **4b** was prepared by the method described for **4a** using butyllithium (32 ml, 1.57 M in hexane, 50 mmol), 2,2,2-trifluoroethyl *p*-toluenesulfonate (6.0 g, 24 mmol), tri-*sec*-butylborane (26 ml, 1.0 M in THF, 26 mmol), HMPA (24 ml), triphenylphosphine (496 mg, 1.89 mmol), tris(dibenzylideneacetonyl)bispalladium-chloroform (1/1) (489 mg, 0.47 mmol), **3** (6.2 g, 19 mmol), and copper(I) iodide (4.5 g, 24 mmol). Purification by column chromatography on silica gel (hexane–AcOEt 5:1) to give **4b** (4.7 g, 77%) as a pale yellow liquid.

^1H 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) δ_F 70.7 (1F, br s), 75.8 (1F, br s). 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.

*3.2.3. α-Butyl-β,β-difluoro-o-(2-iodoethyl)styrene (**5a**)*

To a solution of **4a** (208 mg, 0.65 mmol) in acetone (3 ml) was added sodium iodide (147 mg, 0.65 mmol) at room temperature under nitrogen. After the mixture was 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 **5a** (163 mg, 71%) as a colorless 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 3.7, 13.8, 22.3, 29.1, 29.6 (d, $J_{CF} = 11$ Hz), 37.6, 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 (471 MHz, $CDCl_3$) δ_F 72.6 (1F, d, $J_{FF} = 47$ Hz), 67.9 (1F, d, $J_{FF} = 47$ Hz). 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.

*3.2.4. α-sec-Butyl-β,β-difluoro-o-(2-iodoethyl)styrene (**5b**)*

Compound **5b** was prepared by the method described for **5a** using **4b** (4.7 g, 14.6 mmol), acetone (20 ml) sodium iodide (3.3 g, 22 mmol). Purification by column chromatography on silica gel (hexane) gave **5b** (3.7 g, 73%) as a colorless liquid.

^{1}H 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 (126 MHz, $(CD_3)_2SO$, 100 °C) δ 3.7, 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) δ_F 70.8 (1F, br s), 75.8 (1F, br s). 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.

*3.2.5. 3-[o-(1-Butyl-2,2-difluorovinyl)phenyl]propanitrile (**6a**)*

To a solution of **5a** (107 mg, 0.306 mmol) in acetonitrile (3 ml) was added potassium cyanide (40 mg, 0.67 mmol) and catalytic amount of 18-crown-6 under nitrogen. After 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 **6a** (63 mg, 82%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.29–1.35 (4H, m), 2.27 (2H, br s), 2.58 (2H, t, $J = 7.7$ Hz), 2.94 (2H, t, $J = 7.7$ 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 (471 MHz, $CDCl_3$) δ_F 72.9 (1F, d, $J_{FF} = 46$ Hz), 68.2 (1F, d, $J_{FF} = 46$ Hz). 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.

*3.2.6. 3-[o-(1-sec-Butyl-2,2-difluorovinyl)phenyl]propanitrile (**6b**)*

Compound **6b** was prepared by the method described for **6a** using **5b** (1.50 g, 4.3 mmol) acetonitrile (8 ml), potassium cyanide (558 mg, 8.6 mmol), and catalytic amount of 18-crown-6. Purification by column chromatography on silica gel (hexane–AcOEt 10:1) gave **6b** (781 mg, 73%) as a colorless 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 (126 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) δ_F 70.8 (1F, br s), 75.9 (1F, br s). 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.

*3.2.7. 4-Butyl-3-fluoro-1,2-dihydronaphthalene (**7a**)*

To a solution of **5a** (1.01 g, 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 nitrogen. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. After 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 **7a** (567 mg, 96%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, t, $J = 7.2$ 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, td, J=8.4 Hz, J_{HF} = 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), 24.8 (d, J_{CF} = 25 Hz), 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, $CDCl_3$) δ_F 57.3 (t, J_{FH} = 3 Hz). 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.

3.2.8. 4-sec-Butyl-3-fluoro-1,2-dihydronaphthalene (7b)

Compound **7b** was prepared by the method described for **7a** using **5b** (312 mg, 0.892 mmol), Et_2O–hexane (1:4, 18 ml), *tert*-butyllithium (1.20 ml, 1.64 M in pentane, 1.96 mmol). Purification by thin layer chromatography on silica gel (hexane) gave **7b** (167 mg, 91%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.3 Hz), 1.29 (3H, dd, J = 7.3 Hz, 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} = 3 Hz), 25.6 (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, $CDCl_3$) δ_F 61.3 (br s). 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.

3.2.9. 1-Butyl-2-fluoronaphthalene (8a)

To a solution of **7a** (61 mg, 0.30 mmol) in benzene (6 ml) was added DDQ (202 mg, 0.89 mmol) under nitrogen. The reaction mixture was refluxed for 3 h, and then filtered through Celite. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane) to give **8a** (43 mg, 71%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.6 Hz), 1.46 (2H, tq, J = 7.6, 7.4 Hz), 1.66 (2H, tt, J = 7.9, 7.4 Hz), 3.07 (2H, td, J = 7.9 Hz, J_{HF} = 2.2 Hz), 7.22 (1H, dd, J = 9.2 Hz, J_{HF} = 9.2 Hz), 7.42 (1H, dd, J = 7.6, 7.6 Hz), 7.52 (1H, dd, J = 8.1, 7.6 Hz), 7.67 (1H, dd, J = 9.2 Hz, J_{HF} = 5.5 Hz), 7.82 (1H, d, J = 7.6 Hz), 7.99 (1H, d, J = 8.1 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), 122.6 (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, $CDCl_3$) δ_F 43.7 (m). 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.

3.2.10. 1-sec-Butyl-2-fluoronaphthalene (8b)

Compound **8b** was prepared by the method described for **8a** using **7b** (90 mg, 0.44 mmol), benzene (6 ml), DDQ (300 mg, 1.32 mmol). Purification by thin layer chromatography on silica gel (hexane) gave **8b** (63 mg, 70%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, J = 7.2 Hz), 1.46 (3H, dd, J = 7.2 Hz, 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 Hz, J = 9.0 Hz), 7.40 (1H, dd, J = 7.6, 7.3 Hz), 7.50 (1H, dd, J = 8.2, 7.3 Hz), 7.66 (1H, dd, J = 9.0 Hz, J_{HF} = 5.4 Hz), 7.80 (1H, d, J = 7.6 Hz), 8.14 (1H, d, J = 8.2 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, $CDCl_3$) δ_F 48.9 (br s). 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.

3.2.11. 4-Butyl-3-fluoro-1,2-dihydro-2-naphthonitrile (9a)

To a solution of butyllithium (0.24 ml, 1.41 M in hexane, 0.34 mmol) in THF (1.5 ml) was added **6a** (41 mg, 0.17 mmol) in THF (1.5 ml) at −78 °C. After being stirred for 1 h, the reaction mixture was warmed to room temperature and stirred for an additional 6 h. The reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with AcOEt three times, and 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 **9a** (18 mg, 47%) 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, td, J = 6.0 Hz, J_{HF} = 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 (471 MHz, $CDCl_3$) δ_F 50.9 (s). 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.

3.2.12. 4-Butyl-3-fluoro-2-naphthonitrile (10a)

Butyllithium (0.42 ml, 1.53 M in hexane, 0.65 mmol) was added to a THF (1 ml) solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 0.14 ml, 0.65 mmol) at −78 °C under nitrogen. The reaction mixture was stirred for 30 min, and then **6a** (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. After 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 crude products were treated with DDQ (111 mg, 0.45 mmol) in refluxing benzene (4 ml) for 3 h, and then filtered through Celite. 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 **10a** (50 mg, 68%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, $J = 7.5$ Hz), 1.45 (2H, qt, $J = 7.5$, 7.5 Hz), 1.61–1.69 (2H, m), 3.08 (2H, dt, $J = 7.8$ Hz, $J_{HF} = 2.3$ Hz), 7.55 (1H, dd, $J = 7.6$, 7.5 Hz), 7.68 (1H, dd, $J = 7.9$, 7.5 Hz), 7.86 (1H, d, $J = 7.6$ Hz), 8.01 (1H, d, $J = 7.9$ Hz), 8.06 (1H, d, $J_{HF} = 6.4$ 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, 129.6, 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, $CDCl_3$) δ_F 45.2–45.3 (m). 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.

3.2.13. 4-sec-Butyl-3-fluoro-2-naphthonitrile (*10b*)

Compound **10b** was prepared by the method described for **10a** using butyllithium (0.40 ml, 1.64 M in hexane, 0.66 mmol), THF (2 ml), HMDS (106 mg, 0.66 mmol), **6b** (55 mg, 0.22 mmol) in THF (2 ml), DDQ (149 mg, 0.66 mmol), and benzene (4 ml). Purification by thin layer chromatography on silica gel (hexane–AcOEt 5:1) give **10b** (29 mg, 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, $J = 7.2$ Hz, $J_{HF} = 1.4$ Hz), 1.82–2.03 (2H, m), 3.58 (1H, tq, $J = 7.2$, 7.2 Hz), 7.54 (1H, dd, $J = 7.9$, 7.7 Hz), 7.67 (1H, dd, $J = 8.2$, 7.7 Hz), 7.87 (1H, d, $J = 7.9$ Hz), 8.09 (1H, d, $J_{HF} = 6.1$ Hz), 8.18 (1H, d, $J = 8.2$ 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 (471 MHz, $CDCl_3$) δ_F 49.6 (br s). 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.

3.3. Synthesis of 3-fluorinated indene

3.3.1. α-(o-Bromophenylmethyl)-β,β-difluorostyrene (*13a*)

To a solution of dibromodifluoromethane (126 mg, 0.60 mmol) in THF (2 ml), tris(dimethylamino)phosphine (196 mg, 1.2 mmol) was added at −78 °C under argon. The mixture was stirred for 30 min at that temperature, and then warmed to room temperature. 2′-Bromodeoxybenzoin (**12**, 83 mg, 0.30 mmol) was added, and then the mixture was stirred for 2 h. After 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 column chromatography on silica gel (AcOEt–hexane 1:10) to give **13a** (22.4 mg, 24%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (2H, dd, $J_{HF} = 2.1$, 2.1 Hz), 7.02 (1H, td, $J = 7.0$, 3.0 Hz), 7.13–7.16 (2H, m), 7.21 (1H, tt, $J = 7.0$, 3.0 Hz), 7.25–7.29 (4H, m), 7.51 (1H, d, $J = 7.9$ Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.0, 90.4 (dd, $J_{CF} = 21$, 15 Hz), 124.6, 127.4, 127.4, 128.0, 128.2 (dd, $J_{CF} = 3$, 3 Hz), 128.4, 129.6, 132.8, 133.0 (dd, $J_{CF} = 4$, 4 Hz), 137.4, 154.5 (dd, $J_{CF} = 292$, 289 Hz). ^{19}F NMR (254 MHz, $CDCl_3$) δ_F 72.4 (1F, d, $J_{FF} = 37$ Hz), 73.1 (1F, d, $J_{FF} = 37$ Hz). IR (neat) 3059, 2918, 1728, 1444, 1242, 1099, 974, 748, 731, 694 cm^{-1}.

3.3.2. o-(3,3-Difluoro-2-phenylallyl)aniline (*17*)

To a solution of pivalanilide (**14**) (165 mg, 1.00 mmol) in THF (2.5 ml) was added butyllithium (1.6 ml, 1.56 M in hexane, 2.5 mmol) dropwise at 0 °C under argon. After the mixture was stirred at 0 °C for 2 h and at room temperature for 20 h, α-trifluoromethylstyrene (**15**, 121 mg, 0.70 mmol) and *N,N,N′,N′*-tetramethylethylenediamine (116 mg, 1.0 mmol) were added at −78 °C. After the solution was heated to reflux for 5 h, the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through Celite, and then organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_2. After removal of the solvent under reduced pressure, the residue was treated with aqueous hydrochloric acid (2.5 ml, 12 M, 30 mmol) in EtOH (2.5 ml). The reaction mixture was heated to reflux for 16 h, and 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 column chromatography on silica gel (AcOEt–hexane 1:3) to give **17** (100 mg, 58%) as a pale yellow liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.46 (2H, br s), 3.51 (2H, dd, $J_{HF} = 2.0$, 2.0 Hz), 6.57 (1H, dd, $J = 7.6$, 1.0 Hz), 6.62 (1H, td, $J = 7.6$, 1.0 Hz), 6.93 (1H, br d, $J = 7.6$ Hz), 6.98 (1H, td, $J = 7.6$, 1.0 Hz), 7.16–7.20 (1H, m), 7.22–7.25 (4H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.6, 90.4 (dd, $J_{CF} = 21$, 14 Hz), 115.6, 118.6, 122.2 (dd, $J_{CF} = 3$, 3 Hz), 127.4, 127.4, 128.1 (dd, $J_{CF} = 3$, 3 Hz), 128.3, 129.3, 133.3 (dd, $J_{CF} = 3$, 3 Hz), 144.2, 154.0 (dd, $J_{CF} = 292$, 287 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F 71.4 (1F, d, $J_{FF} = 41$ Hz), 72.2 (1F, d, $J_{FF} = 41$ Hz). IR (neat) 1716, 1622, 1495, 1456, 1234, 1101, 985, 744, 694, 603, 576 cm^{-1}. Anal. calcd. for $C_{15}H_{13}NF_2$: C, 73.45; H, 5.34; N, 5.71%. Found: C, 73.64; H, 5.50; N, 5.67%.

*3.3.3. β,β-Difluoro-α-(o-iodophenylmethyl)styrene (**13b**)*

o-(3,3-Difluoro-2-phenylallyl)aniline (**17**, 4.04 g, 16 mmol) was dissolved in aqueous hydrochloric acid (20 ml, 4.5 M, 90 mmol), and then treated with a solution of sodium nitrite (1.37 g, 20 mmol) in water (3 ml) at below 5 °C. After 30 min, excess reagent was decomposed by the addition with amidosulfuric acid (320 mg, 3.3 mmol), and a cold solution of potassium iodide (27.3 g, 165 mmol) in water (82 ml) was added dropwise. The reaction mixture was stirred at room temperature in the dark for 8 h. Organic materials were extracted with CH_2Cl_2 three times, and 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–Et_3N 100:1). Further purification was conducted by gel permeation chromatography (GPC, $CHCl_3$) to give **13b** (2.29 g, 39%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (2H, s), 6.84 (1H, t, $J = 7.4$ Hz), 7.12 (1H, d, $J = 7.4$ Hz), 7.17 (1H, d, $J = 7.4$ Hz), 7.19–7.22 (1H, m), 7.25–7.28 (4H, m), 7.79 (1H, d, $J = 7.9$ Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.1, 90.6 (dd, $J_{CF} = 21$, 14 Hz), 100.8, 127.4, 128.1 (dd, $J_{CF} = 4$, 4 Hz), 128.2, 128.3, 128.4, 128.8, 132.9 (dd, $J_{CF} = 4$, 4 Hz), 139.5, 140.4 (dd, $J_{CF} = 2$, 2 Hz), 154.5 (dd, $J_{CF} = 293$, 289 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F 72.6 (1F, d, $J_{FF} = 36$ Hz), 73.5 (1F, d, $J_{FF} = 36$ Hz, $J_{FH} = 2$ Hz). IR (neat) 1716, 1437, 1238, 1012, 991, 744, 729, 692 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}F_2I$ (M^+) 355.9874, found 355.9889.

*3.3.4. 3-Fluoro-2-phenylindene (**18**)*

Butyllithium (0.35 ml, 1.57 M in hexane, 0.55 mmol) was added to a solution of **13b** (195 mg, 0.55 mmol) in Et_2O–hexane (1:4, 14 ml) at −110 °C over 10 min under argon. The reaction mixture was stirred for 1 h at that temperature, and then stirred at −78 °C for 1 h. After the mixture was stirred at room temperature for an additional 2 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 (pentane) and then by GPC ($CHCl_3$) to give **18** (59 mg, 52%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (2H, d, $J_{HF} = 6.0$ Hz), 7.26 (2H, tdd, $J = 8.0$, 1.2 Hz, $J_{HF} = 2.4$ Hz), 7.33 (1H, t, $J = 7.6$ Hz), 7.37–7.44 (4H, m), 7.70 (2H, dd, $J = 8.0$, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.6 (d, $J_{CF} = 4$ Hz), 117.7 (d, $J_{CF} = 3$ Hz), 118.1 (d, $J_{CF} = 2$ Hz), 124.0 (d, $J_{CF} = 3$ Hz), 126.2, 126.7 (d, $J_{CF} = 7$ Hz), 126.9, 127.1 (d, $J_{CF} = 2$ Hz), 128.7, 133.4 (d, $J_{CF} = 5$ Hz), 137.6 (d, $J_{CF} = 25$ Hz), 139.3 (d, $J_{CF} = 8$ Hz), 156.0 (d, $J_{CF} = 277$ Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ_F 30.8 (td, $J_{FH} = 6$, 2 Hz). IR (neat) 3045, 1626, 1493, 1371, 1070, 912, 752, 717, 688 cm^{-1}. HRMS: calcd. for $C_{15}H_{11}F$ (M^+) 210.0845, found 210.0849.

Acknowledgements

We gratefully acknowledge the financial support for this research by Central Glass Co. Ltd.

References

[1] R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry: Principles and Commercial Applications, Plenum Press, New York, 1994.
[2] J.T. Welch, Ed. Selective Fluorination in Organic and Bioorganic Chemistry, American Chemical Society, Washington, DC, 1991.
[3] J.H. Clark, D. Wails, T.W. Bastock, Aromatic Fluorination, CRC Press, Boca Raton, 1996.
[4] M. Hudlicky, A.E. Pavlath (Eds.), Chemistry of Organic Fluorine Compounds II, American Chemical Society, Washington, DC, 1995.
[5] J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, 1991 (Chapters 1 and 12).
[6] J. Ichikawa, Y. Wada, T. Okauchi, T. Minami, Chem. Commun. (1997) 1537–1538.
[7] J. Ichikawa, M. Fujiwara, Y. Wada, T. Okauchi, T. Minami, Chem. Commun. (2000) 1887–1888.
[8] Y. Wada, J. Ichikawa, T. Katsume, T. Nohiro, T. Okauchi, T. Minami, Bull. Chem. Soc. Jpn. 74 (2001) 971–977.
[9] J. Ichikawa, Y. Wada, M. Fujiwara, K. Sakoda, Synthesis (2002) 1917–1936.
[10] J. Ichikawa, Y. Wada, H. Miyazaki, T. Mori, H. Kuroki, Org. Lett. 5 (2003) 1455–1458.
[11] Y. Wada, T. Mori, J. Ichikawa, Chem. Lett. (2003) 1000–1001.
[12] R.D. Chambers, Fluorine in Organic Chemistry, Antony Rowe, Chippenham, 1973 (Chapter 1).
[13] B.E. Smart, Characteristics of C–F systems, in: R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organofluorine Chemistry: Principles and Commercial Applications, Plenum Press, New York, 1994 (Chapter 3).
[14] M. Hudlicky, Chemistry of Organic Fluorine Compounds, second ed., Ellis Horwood, Chichester, 1976 (Chapter 5).
[15] J.E. Baldwin, J. Chem. Soc., Chem. Commun. (1976) 734–736.
[16] J.E. Baldwin, J. Cutting, W. Dupont, L.I. Kruse, L. Silberman, R.C. Thomas, Chem. Commun. (1976) 736–731.
[17] J.E. Baldwin, R.C. Thomas, L.I. Kruse, L. Silberman, J. Org. Chem. 42 (1977) 3846–3852.
[18] J. Ichikawa, J. Fluorine Chem. 105 (2000) 257–263, references therein.
[19] W.F. Bailey, E.R. Punzalan, J. Org. Chem. 55 (1990) 5404–5406.
[20] E. Negishi, D.R. Swanson, C.J. Rousset, J. Org. Chem. 55 (1990) 5406–5409.
[21] D.R. Strobach, G.A. Boswell Jr, J. Org. Chem. 36 (1971) 818–820.
[22] E.M. Kaiser, C.R. Hauser, J. Org. Chem. 33 (1968) 3402–3404.
[23] K.K. Laali, G.I. Borodkin, J. Chem. Soc. Perkin 2 (2002) 953–957, references therein.
[24] T. Shamma, H. Buchholz, G.K.H. Prakash, G.A. Olah, Isr. J. Chem. 39 (1999) 207–210, references therein.
[25] T.V.V. Ramakrishna, P.R. Sharp, Org. Lett. 5 (2002) 877–879, references therein.
[26] J. Ichikawa, K. Sakoda, Y. Wada, Chem. Lett. (2002) 282–283.
[27] A. Saito, M. Okada, Y. Nakamura, O. Kitagawa, H. Horikawa, T. Taguchi, J. Fluorine Chem. 123 (2003) 75–80.
[28] W.A. Vinson, K.S. Prickett, B. Spahic, P.R.O. de Montellano, J. Org. Chem. 48 (1983) 4661–4668.
[29] W. Fuhrer, H.W. Gschwend, J. Org. Chem. 44 (1979) 1133–1136.
[30] J.-P. Bégué, D. Bonnet-Delpon, M.H. Rock, J. Chem. Soc. Perkin Trans. 1 (1996) 1409–1413.
[31] R.A. Moss, S. Xue, R.R. Sauers, J. Am. Chem. Soc. 118 (1996) 10307–10308.
[32] W.E. Barnette, J. Am. Chem. Soc. 106 (1984) 452–454.