Methods for Syntheses of Five-Membered Hetero- and Carbocyclic Compounds via C–F Bond Activation

Ryutaro Morioka

February 2022

Methods for Syntheses of Five-Membered Hetero- and Carbocyclic Compounds via C–F Bond Activation

Ryutaro Morioka

Doctoral Program in Chemistry

Submitted to the Graduate School of

Pure and Applied Sciences

in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy in Science

at the

University of Tsukuba

TABLE OF CONTENTS

Abbreviations

Ac = acetyl

Bu = butyl

cod = 1,5-cyclooctadiene

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DMF = *N*,*N*-dimethylformamide

DCE = 1,2-dichloroethane

Et = ethyl

DAST = *N*,*N*-diethylaminosulfur trifluoride

HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol

KHMDS = potassium hexamethyldisilazide

NaHMDS = sodium hexamethyldisilazide

nep = neopentyl

NFSI = *N*-fluorobenzenesulfonimide

NMP = *N*-methylpyrrolidone

pin = pinacolato

PDFA = (triphenylphosphino)difluoroacetate

TBS = *tert*-butyldimethylsilyl

TfOH = trifluoromethanesulfonic acid

THF = tetrahydrofuran

TsOH = *p*-toluenesulfonic acid

CHAPTER 1

General Introduction

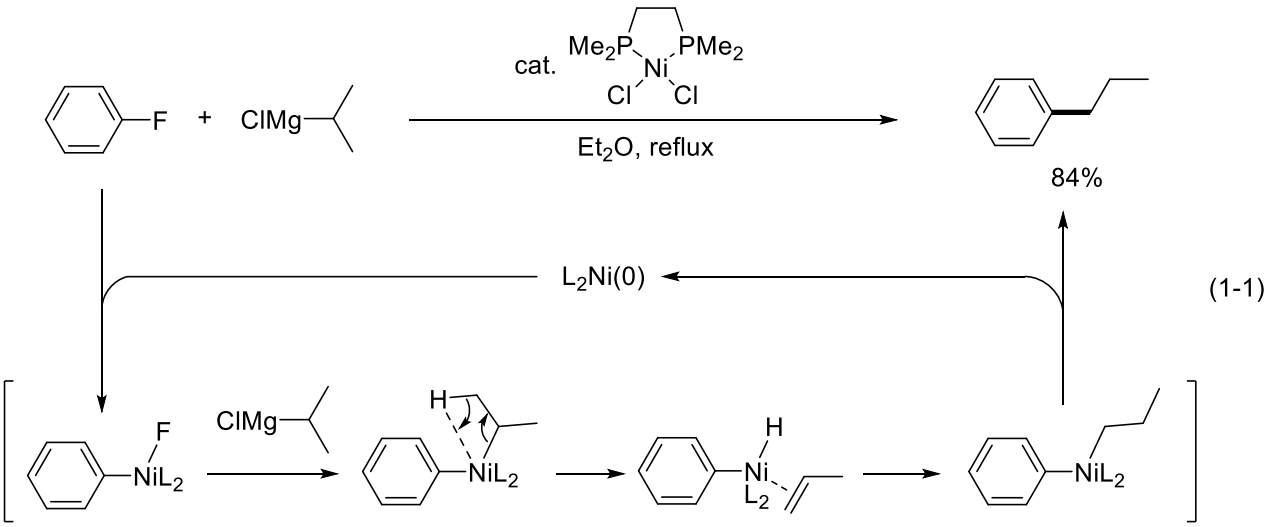
1-1. C–F Bond Activation

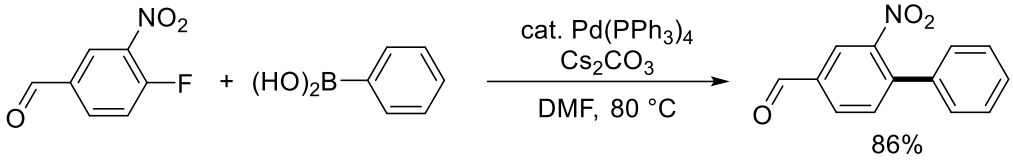
Halogens, group 17 elements such as iodine, bromine, chlorine, and fluorine, are indispensable elements in chemistry. They have served as well-convertible moieties in chemicals, except for fluorine. The activation of carbon–halogen bonds is one of the most typical conversion methods in the whole history of chemistry. Particularly, transition-metal-catalyzed coupling reactions using organic halides have been developed as reliable methods for carbon–carbon (C–C) bond formation,[1] which proceeds through oxidative addition of carbon–halogen (C–X) bonds to metals. However, coupling via carbon–fluorine (C–F) bond cleavage is still far from common. The difficulty in activating C–F bonds is mainly due to its high bond dissociation energy (Table 1-1).[2,3] Furthermore, properties peculiar to fluorine such as low Lewis basicity and weak leaving group ability also render C–F bond activation difficult.

Table 1-1. Properties of atoms (X) and their single bonds with carbon (C–X) [2,3]

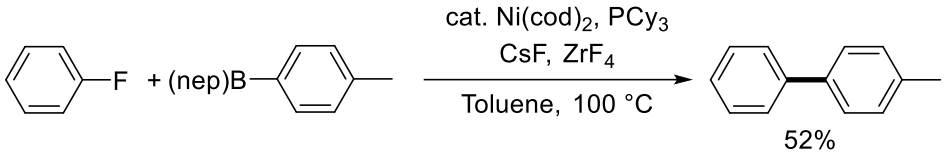
Atom (X)	Electronegativity	van der Waals radii (Bondi)/ Å	Average C–X bond lengths/ Å	Bond dissociation energy (C–X)/ kcal mol^{-1}
H	2.1	1.20	1.09	98.8
C	2.5	1.70	1.54	83.1
N	3.0	1.55	1.47	69.7
O	3.5	1.52	1.43	84.0
F	**4.0**	**1.47**	**1.35**	**105.4**
Cl	3.0	1.74	1.77	78.5
Br	2.8	1.85	1.93	65.9
I	2.5	1.98	2.13	57.4

Notwithstanding its difficulty, C–F bond activation has been eagerly studied because of its potential for the synthesis of chemicals used in various fields, such as pharmaceutical, agrochemical, and material sciences.[4,5] To solve the challenging problem, transition metals have been employed. Although oxidative addition of C–F bonds to transition metals is hard to occur, in some cases it has been accomplished and typically utilized for coupling reactions with organometallic reagents. The first example via the metal-catalyzed aromatic C–F bond activation is the Kumada coupling of fluorobenzene with an isopropylmagnesium reagent, which was reported in 1973 (eq 1-1).[6] In this reaction, oxidative addition of the C–F bond of fluorobenzene to an in situ-generated nickel(0) species first proceeds to generate an arylnickel fluoride intermediate. Subsequent transmetalation, hydride migration, and reductive elimination afford propylbenzene. The ligand, bis(dimethylphosphino)ethane, has an important role in the migration process. Thirty years later, the Suzuki–Miyaura coupling of fluoroarenes bearing electron-withdrawing groups was achieved with arylboronic acids by Yu (eq 1-2).[7] In 2011, Chatani and coworkers reported the nickel-catalyzed Suzuki–Miyaura coupling of fluoroarenes without electron-withdrawing groups (eq 1-3).[8]



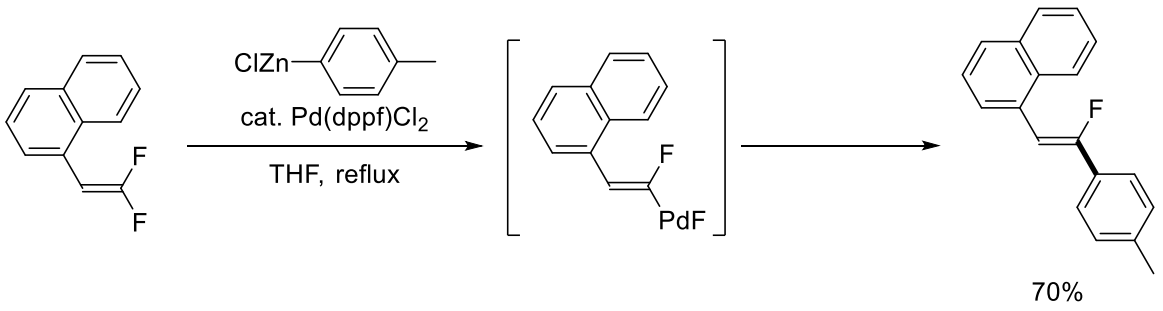


(1-2)

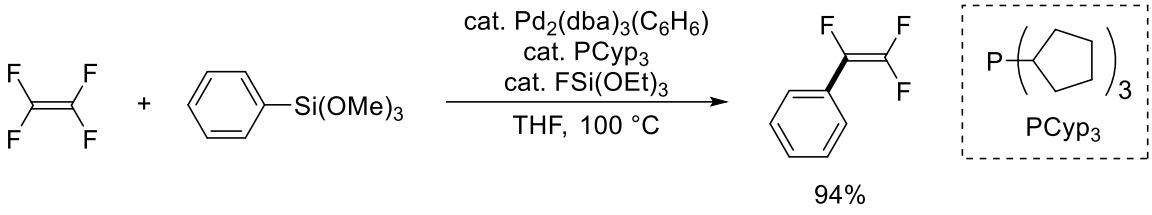


(1-3)

Vinylic C–F bond activation has been also achieved with transition metals. In 2005, Tamao achieved the Negishi coupling of difluorostyrene derivatives with arylzinc reagents (eq 1-4).[9] Ogoshi and coworkers reported the Hiyama coupling of tetrafluoroethylene with arylsilanes (eq 1-5).[10]

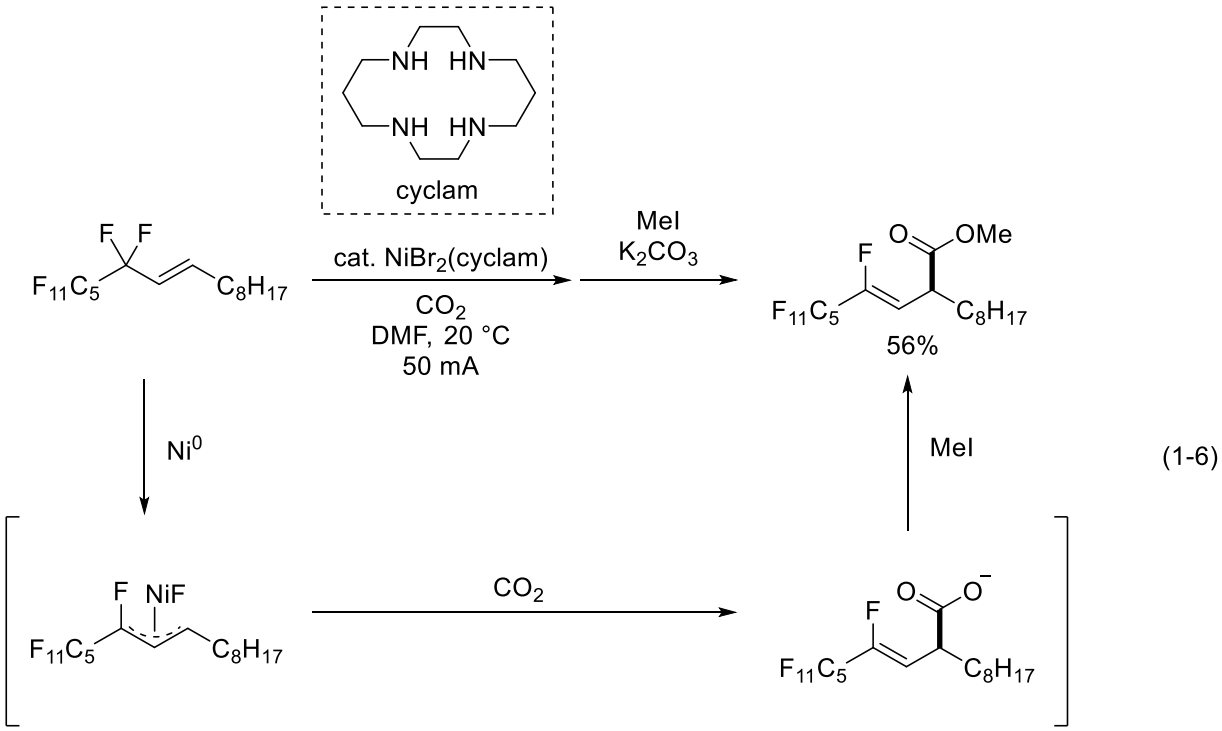


(1-4)

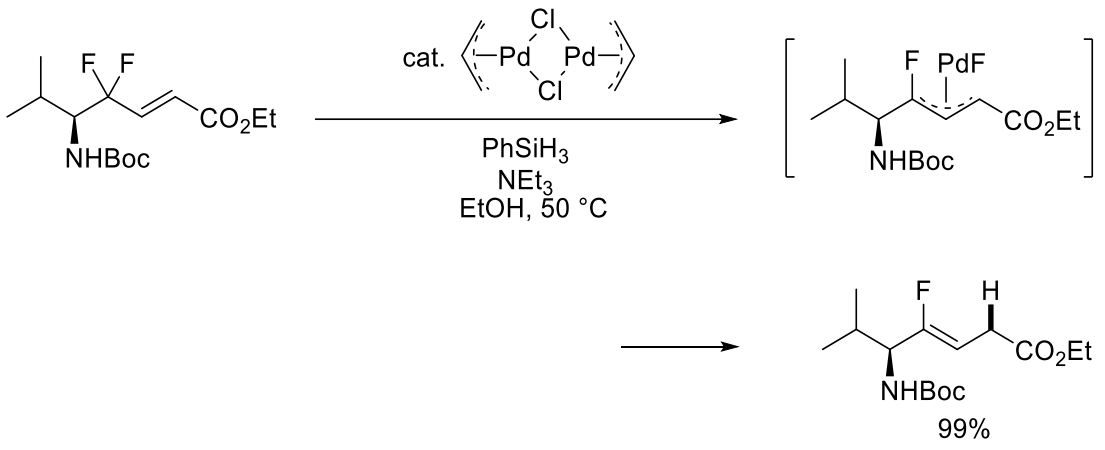


(1-5)

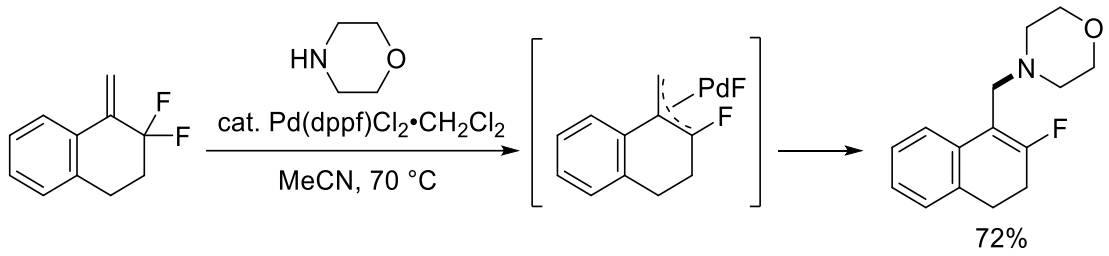
Recently, metal-catalyzed C–F bond activation on sp^3 carbon atoms via oxidative addition has been developed. The first C–C bond formation via allylic C–F bond activation was accomplished by a nickel catalyst with the electrochemical method. The electrochemically reduced nickel catalyst induced oxidative addition to afford allylnickel intermediates. Subsequent carboxylation with bubbled CO_2 followed by methylation with iodomethane gave the ester with a fluoroalkene moiety (eq 1-6).[11] Fujii reported a palladium-catalyzed reduction of difluoroallylic compounds without electrochemistry. In this reaction, difluoroallylic compounds underwent oxidative addition to palladium to generate π-allylpalladium intermediates. The Tsuji–Trost-type reactions with phenylsilane afforded the reduced products, monofluoroalkenes (eq 1-7).[12] Cyclic difluoroallylic compounds also underwent palladium-catalyzed oxidative addition, in which subsequent C–N bond formation with morpholine afforded the corresponding products (eq 1-8).[13] As described above, aromatic, vinylic, and allylic C–F bond activation via oxidative addition has been examined mainly during the last two decades. However, the necessity of expensive transition metals and limitations in the substrates remain major problems. Thus, efficient methods for C–F bond activation, which resolves these problems, are eagerly required.



(1-6)



(1-7)



(1-8)

1-2. Construction of Fluorinated Five-Membered Rings

1-2-1. Fluorinated Heteroles

In recent years, fluorinated heterocycles have important roles in various fields. Even if limited to five-membered heterocycles, tremendous compounds are known and used on earth, as natural products, pharmaceuticals, agrochemicals, and materials. Among them, fluorine-containing ones have attracted much attention in this half a century. Living bodies can not distinguish and absorb chemical compounds in which a C–H bond is converted to a C–F bond (mimic effect). In addition, fluorine-containing compounds exhibit improved stability to oxidative metabolism due to their strong C–F bonds and electron-withdrawing fluorine substituents (block effect). For example, as represented by Gemcitabine and Sofosbuvir, a lot of ring-fluorinated furan derivatives are on the market (Figure 1-1). [14,15] Therefore, efficient methods for the syntheses of ring-fluorinated five-membered heterocycles have been developed and still required.

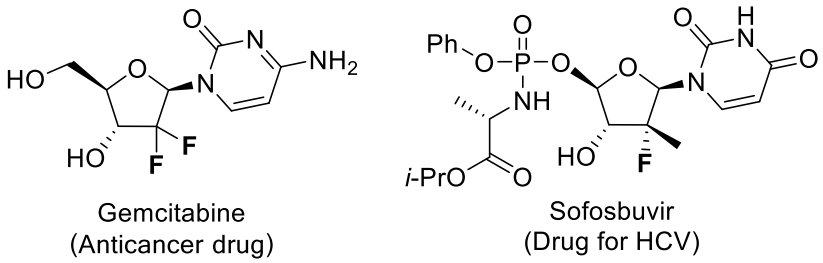
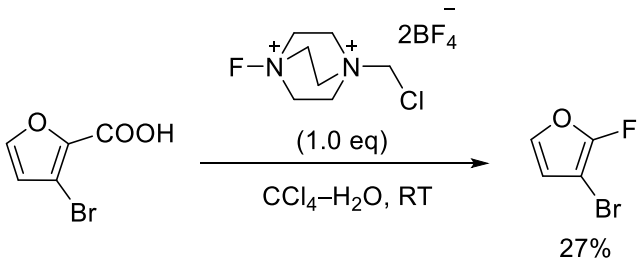
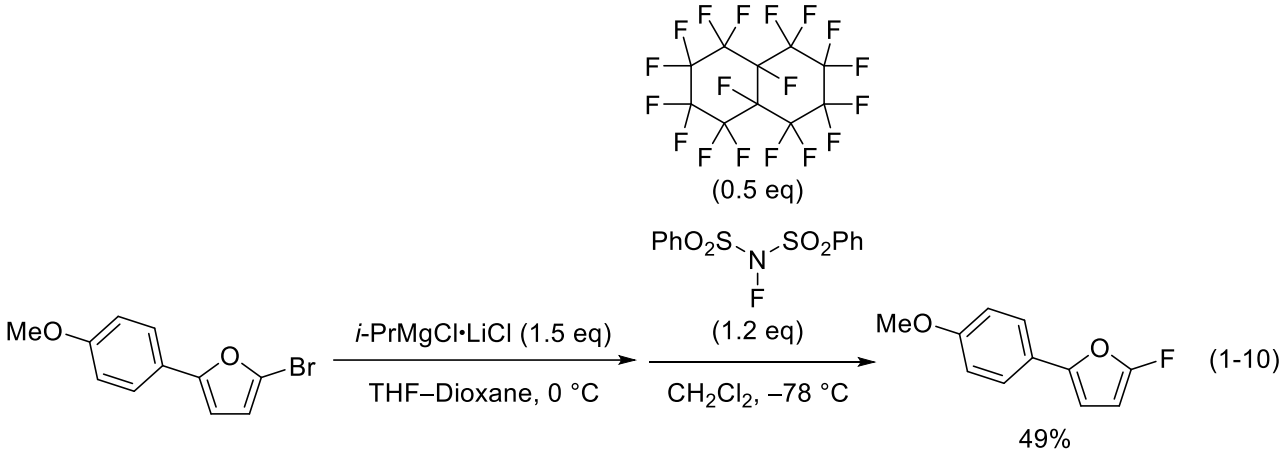


Figure 1-1. Gemcitabine and Sofosbuvir

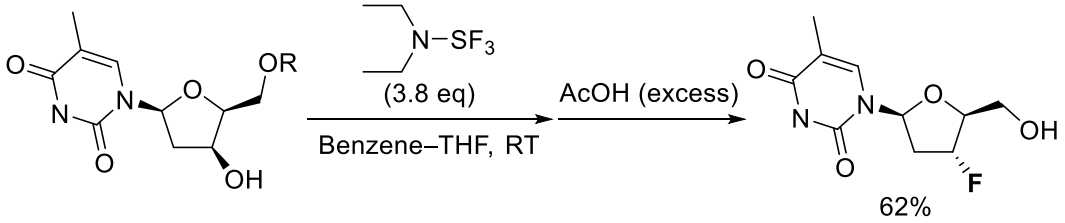
The syntheses of fluorofurans have been achieved by two major methods: (i) direct fluorination methods and (ii) building block methods. The direct fluorination methods have emerged along with the development of fluorinating agents.[16] Ring-fluorinated furans and their derivatives have been synthesized using electrophilic and nucleophilic fluorinating agents. In 1995, Forrest reported the decarboxylative electrophilic fluorination at the 2-position of furans by using (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA, Selectfluor) (eq 1-9).[17] Later, Knochel reported electrophilic fluorination of (furan-2-yl)magnesium species with *N*-fluorobenzenesulfonimide (NFSI) (eq 1-10).[18] In particular, fluorination at the 3-position has been established via nucleophilic deoxofluorination with diethylaminosulfur trifluoride (DAST) (eq 1-11, 12).[19,20] However, direct fluorination methods require toxic and/or expensive fluorine reagents and prefunctionalization of furan rings.



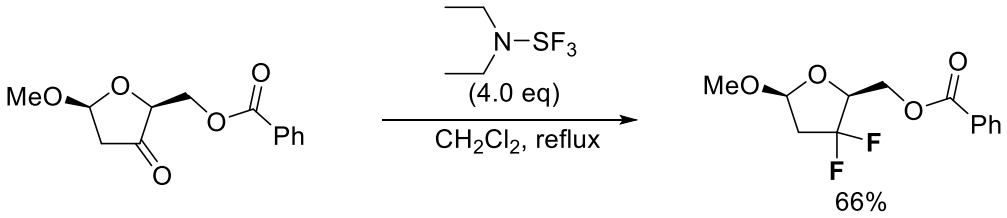
(1-9)



(1-10)

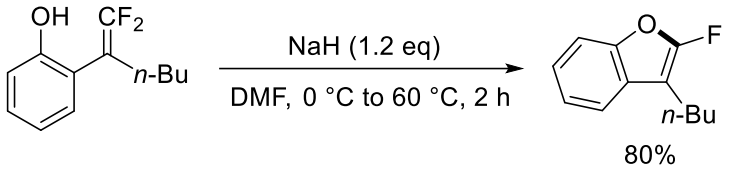


(1-11)

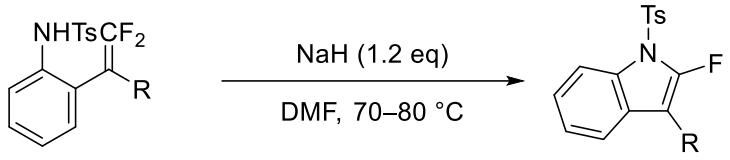


(1-12)

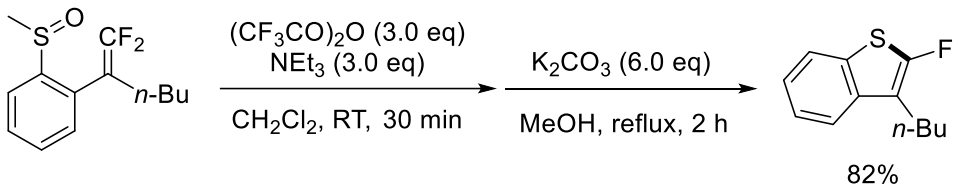
In contrast to direct fluorination methods, simultaneous ring construction and fluorine installation are possible by building block methods. For example, *o*-hydroxy-β,β-difluorostyrenes underwent 5-*endo-trig* cyclization, which is considered to be a disfavored process according to Baldwin's rules, to afford 2-fluorinated benzofurans (eq 1-13).[21] The negative inductive effects of fluorine substituents and the increased polarization of the difluoroalkene moieties enable disfavored cyclization. Although this is a useful method without using fluorinating agents, limited substrate scope remains a problem. Apart from fluorofurans, the methods for fluorinated *N*- and *S*-heterocycle syntheses have been also investigated, albeit as a rare example (eq 1-14, 1-15).[22,23] The demand for efficient building block methods for the synthesis of ring-fluorinated heterocycles is so high that the supply cannot meet.



80% (1-13)



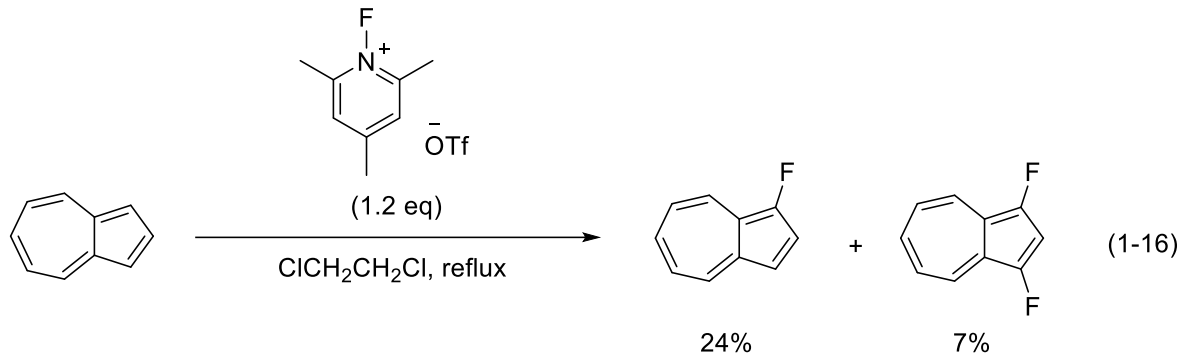
R = *n*-Bu 84% (7 h)
R = *sec*-Bu 81% (5 h)
R = H 73% (23 h) (1-14)



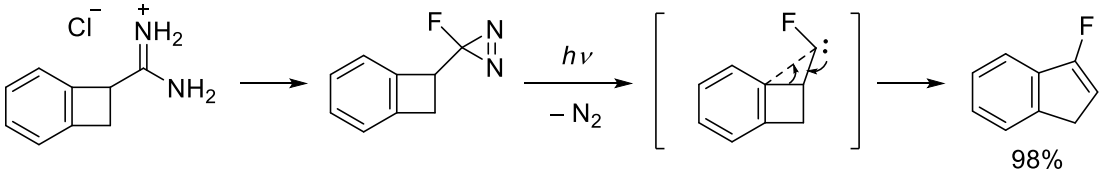
82% (1-15)

1-2-2. Fluorinated Carbocycles

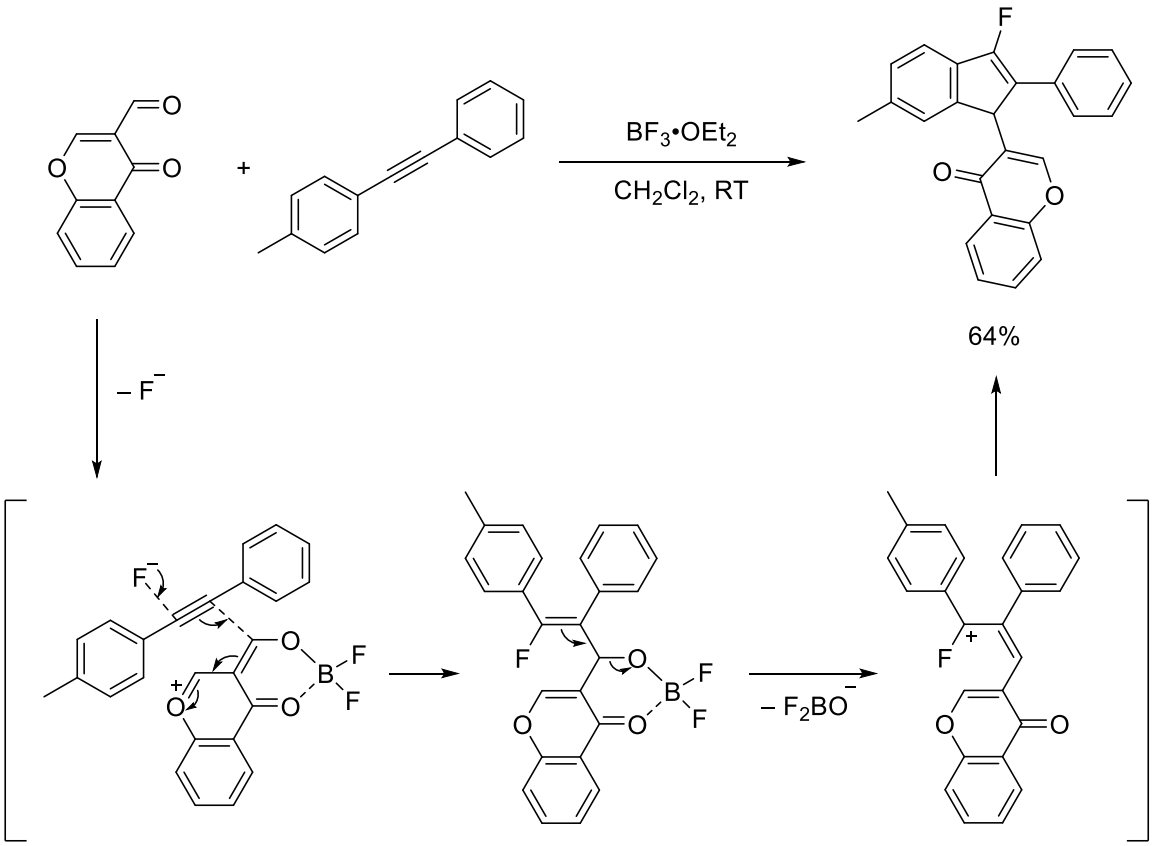
Compared to the syntheses of fluorinated five-membered heterocycles, there are even fewer methods for constructing fluorinated five-membered carbocycles. Both direct fluorination and building block methods have been used for the construction of fluorinated carbocycles. For example, the direct C–H fluorination of azulene derivatives was achieved by using electrophilic fluorinating agents such as *N*-fluoropyridinium, NFSI, and Selectfluor (eq 1-16).[24] In contrast, 3-fluoroindene was synthesized by the building block method. A fluorocarbene intermediate, generated via photolysis of a diazirine substrate bearing a benzocyclobutane moiety, undergoes ring expansion to afford 3-fluoroindene (eq 1-17).[25] Recently, another synthesis of fluoroindene has been presented. In this reaction, the reaction of 3-formylchlomone and BF_3 generates an oxonium intermediate and a fluoride ion. Subsequent C–C bond formation with alkyne along with fluorine installation results in ring construction to afford a 3-fluoroindene derivative (eq 1-18).[26]


F
N+
OTf
(1.2 eq)
ClCH2CH2Cl, reflux
F
F
F
+
24%
7%

(1-16)

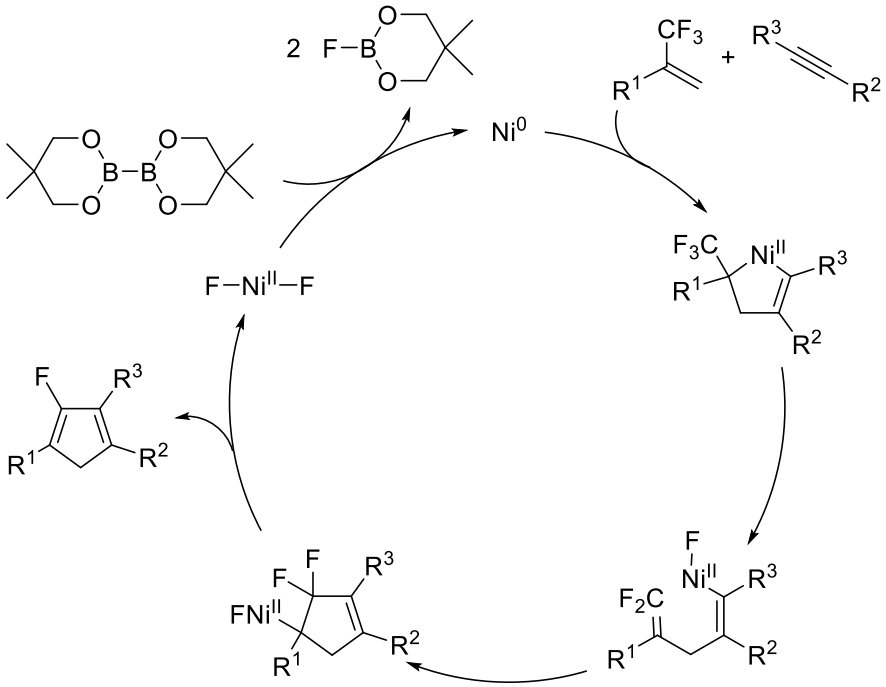

Cl−
+NH2
NH2
F
N
N
hν
– N2
F
F
98%

(1-17)


O
O
O
+
BF3•OEt2
CH2Cl2, RT
F
O
O
64%
– F−
F−
O
B
F
F
O
O
F
O
B
F
F
O
O
– F2BO−
F
+
O
O

(1-18)

Our group has reported nickel-catalyzed [3 + 2] annulation of (trifluoromethyl)alkenes with alkynes via double allylic C–F bond activation (Scheme 1-2).[27] Oxidative cyclization of (trifluoromethyl)alkenes and alkynes mediated by a nickel catalyst generates nickelacyclopentene intermediates. Successive β-fluorine elimination, insertion, and the second β-fluorine elimination proceed to afford 2-fluorocyclopentadienes. Nickel difluoride is reduced to nickel(0) by $B_2(nep)_2$. Although this method effectively enables the construction of fluorinated five-membered carbocycles, an expensive transition metal catalyst ($Ni(cod)_2$) is essential. To address an economical issue and to avoid metal contamination, transition metal-free methods for the synthesis of fluorinated five-membered carbocycles is desirable.



Scheme 1-2. Nickel-catalyzed [3+2] annulation

1-3. Survey of This Thesis

In this thesis, I developed facile and practical methods for constructing five-membered carbo- and heterocycles, mostly containing fluorine substituents, via C–F bond activation. Throughout all the activation process, toxic fluorinating agents and expensive transition metals were excluded by taking full advantage of the chemical properties of fluorine, such as (a) the β-carbanion stabilizing effect and (b) the α-carbanion stabilization effect. Fluorine stabilizes β-carbanions by the negative inductive effect, while it stabilizes α-carbocations by its lone pairs (Figure 1-2). In addition, fluorine exhibits (c) substantial leaving group ability as a fluoride ion from β-carbanions despite high bond dissociation energy of C–F bonds.

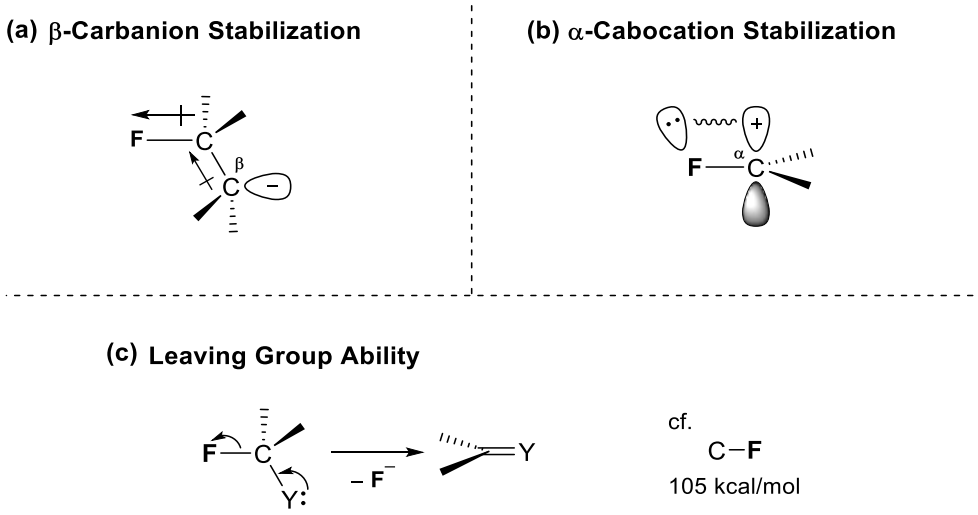


Figure 1-2. Properties of fluorine

By using the above-mentioned properties of fluorine, transition metal-free C–F bond activation is possible. As for allylic C–F bond activation, S_N2'-type reactions with nucleophiles are achieved by a combination of the β-carbanion stabilizing effect (a) and the leaving group ability (c). Nucleophilic attack to allylic fluorides first generates β-carbanion intermediates. Subsequent β-fluorine elimination from the intermediates proceeds to afford fluorovinylic products (Figure 1-3, A). In addition, allylic C–F bond activation is also affected by Lewis acids. Lewis acids cause fluoride abstraction from allylic fluorides bearing more than one fluorine,

leading to the formation of stabilized α-carbocations (b) (Figure 1-3, B). Similar to allylic fluorides, vinylic fluorides undergo nucleophilic addition–elimination processes (S_NV reactions) via β-carbanion intermediates (a, c) (Figure 1-3, C). Aromatic C–F bonds can be activated with Brønsted acids. Fluoroarenes undergo protonation at carbons β to the fluorine substituent gives fluorine-stabilized arenium ion intermediates (c). Subsequent Friedel–Crafts-type C–C bond formation followed by HF elimination completes aromatic defluorinative substitution.

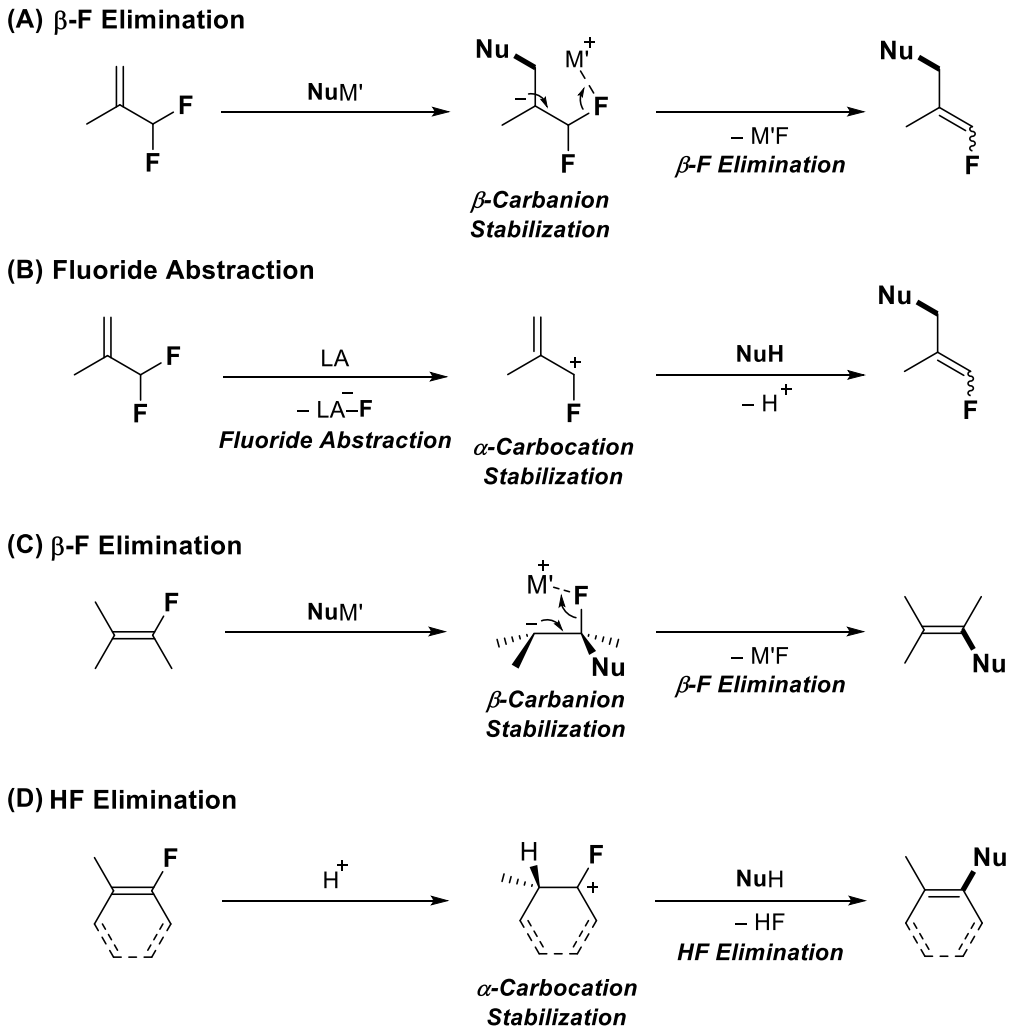
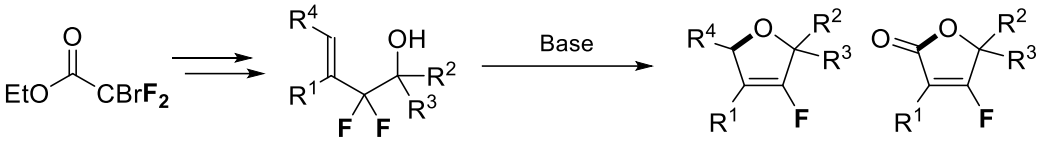


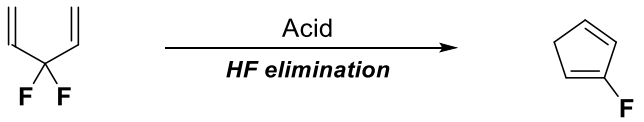
Figure 1-3. C–F bond activation

In Chapter 2, I successfully synthesized 3-fluorodihydrofurans from difluorohomoallylic alcohols (Scheme 1-3). In this synthesis, 5-*endo-trig* cyclization was achieved by defluorinative S_N2'-type reactions, which proceed in a stepwise manner. Generation of carbanions at the β-positions of the fluorine substituents after the nucleophilic attack of alkoxide moieties enables the cyclization that is difficult to proceed through a concerted mechanism. Furthermore, oxidation of the products afforded 4-fluorofuranones, which are expected to serve as pharmaceuticals or agrochemicals.



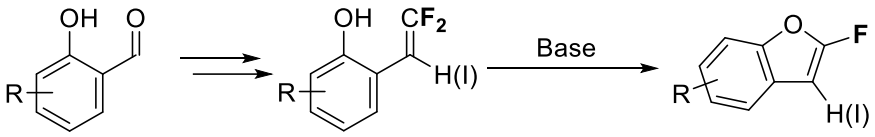
Scheme 1-3. 5-*endo-trig* Cyclization of Difluorohomoallylic alcohols

Chapter 3 demonstrates the Nazoarov-type cyclization via direct defluorination of 3,3-difluoro-1,4-pentadienes. Lewis acid caused fluoride abstraction from 3,3-difluoro-1,4-pentadienes to generate fluorine-stabilized pentadienyl cations by the aid of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP). Pentadienyl cations thus obtained underwent electrocyclization to afford 2-fluoro-cyclopenta-1,3-dienes (Scheme 1-4).



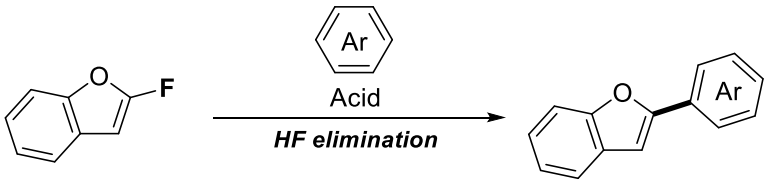
Scheme 1-4. Nazarov-type cyclization via fluoride abstraction

Chapter 4 describes the development of a facile method for the synthesis of 2-flurobenzofurans. Conventional 2-fluorobenzofuran synthesis has problems such as the requirement of expensive fluorinating agents and limited substrate scope. In contrast, the reaction I developed is applicable to the synthesis of variously substituted 2-fluorobenzofurans starting from readily available precursors. In addition, 2-fluoro-3-iodobenzofuran, containing a convertible iodine substituent, is also synthesized in this method (Scheme 1-5).



Scheme 1-5. 5-*endo*-*trig* Cyclization of *o*-Hydroxydifluorostyrenes

In Chapter 5, I developed acid-mediated aromatic C–F/C–H coupling of 2-fluorobenzofurans with arenes (Scheme 1-6). 2-Fluorobenzofuran substrates were readily prepared from salicylaldehyde derivatives. A facile synthesis of bioactive compounds including a natural product was also achieved by this method. Furthermore, I revealed that the reaction is initiated by the protonation of benzofuran and that α-fluorocarbocations serve as the key intermediates.



Scheme 1-6. C–F/C–H coupling via Aromatic C–F bond activation

1-4. References

[1] (a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron. Lett.* **1965**, 4387-4388. (b) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. (c) Corriu, R. J. P.; Massse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (d) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (e) Heck, R. F.; Nolley, Jr., J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322. (f) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467-4470. (g) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683-684. (h) Negishi, E; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821-1823. (i) Kosugi, M. Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301-302. (j) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638. (j) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867. (k) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440. (l) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918-920.

[2] (a) Pauling, L. *The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry*, Cornell University Press, Ithaca, NY, 1939. (b) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451. (c) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11. (d) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

[3] (a) Kiolinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373–431. (b) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119–2183. (c) Clot, E.; Eisenstein, O.; Jasim, N.; Macgregor, S. A.; McGrady, J. E.; Perutz, R. N. *Acc. Chem. Res.* **2011**, *44*, 333–348. (d) Klahn, M; Rosenthal, U. *Organometallics* **2012**, *31*, 1235–1244. (e) Kuehnel, M. F.; Lentz, D.; Brayn, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 3328–3348. (f) Stahl, T.; Klare, H. F. T.; Oestreich, M. *ACS Catal.* **2013**, *3*, 1578–1587. (g) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev.* **2015**, *115*, 931–972. (h) Unzner, T. A.; Magauer, T. *Tetrahedron Lett.* **2015**, *56*, 877–883. (i) Zhang, X.; Cao, S. *Tetrahedron Lett.* **2017**, *58*, 375–392.

[4] (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320–330. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369. (d) O'Hagan *J. Fluorine Chem.* **2010**, *131*, 1071–1081.

[5] (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003–1022. (b) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496–3508. (c) Kirsch, P. *J. Fluorine Chem.* **2015**, *177*, 29–36.

[6] Kiso, Y.; Tamao, K.; Kumada, M. *J. Organomet. Chem.* **1973**, C12-C14.

[7] Kim, Y. M. and Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696-1697.

[8] Tobisu, M.; Xu, T.; Shimasaki, N.; Chatani, N. *J. Am. Chem. Soc.* **2011**,*133*, 19505-19511.

[9] Saeki, M.; Takashima, M.; Tamao, K. *Synlett* **2005**, 1771-1774.

[10] Saijo, H.; Sakaguchi, H.; Ohashi, M.; Ogoshi, S. *Organomet.* **2014**, *33*, 3669-3672.

[11] Chiozza, E.; Desigaud, M.; Greiner, J.; Duñach, E. *Tetrahedron Lett.* **1998**, *39*, 4831-4834.

[12] Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Org. Lett.* **2007**, *9*, 3465-3468.

[13] Pigeon, X.; Bergeron, M.; Barabé, F.; Dubé, P.; Frost, H. N.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1123-1127.

[14] Hertel, L. W.; Kroin, J. S.; Misner, J. W.; Tustin, J. M. *J. Org. Chem.* **1988**, *53*, 2406-2409.

[15] Murakami, E.; Tolstykh, T.; Bao, H.; Niu, C.; Steuer Holly, M. M.; Bao, D.; Chang, W.; Espiritu, C.; Bansal, S.; Lam, A. M.; *J. Biol. Chem.* **2010**, *285*, 34337-34347.

[16] (a) Martín-Santamaría, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, D. A. *Chem. Commun.* **2000**, 649– 650. (b) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431– 12477. (c) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31– 44. (d) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192– 212. (e) Kiselvov, A. S. *Chem. Soc. Rev.* **2005**, *34*, 1031– 1037.

[17] Forrest, A. K. and O'Hanlon, P. J. *Tetrahedron Lett.* **1995**, *36*, 2117-2118.

[18] Yamada, S. and Knochel, P. *Synthesis* **2010**, 2490-2494.

[19] Herdewjin, P.; Balzarini, J.; Clercq, E. D.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. *J. Med. Chem.* **1987**, *30*, 1270-1278.

[20] Chong, Y.; Gumina, G.; Mathew, J. S.; Schinazi, R.; Chu, C. K. *J. Med. Chem.* **2003**, *46*, 3245-3256.

[21] Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, *16*, 1537-1538

[22] (a) Ichikawa, J. *Chim. Oggi*, **2007**, *25*, 54-57. (b) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun*. **1997**, 1537-1538. (c) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis*, **2002**, 1917-1936. (d) Ichikawa, J; Nadano, R.; Mori, T.; Wada, Y. *Org. Synth*. **2006**, 83, 111-120. (e) Ichikawa, J. *Org. Synth.* **2011**, *88*, 162-167.

[23] (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, *16*, 1537-1538. (b) Ichikawa, J.; Wada, Y.; Okauchi, T.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, *13*, 1917-1936. (c) Ichikawa, J.; Nadano, R.; Mori, T.; Wada, Y. *Org. Synth.* **2006**, *83*, 111-120.

[24] Ueno, T.; Toda, H.; Yasunami, M.; Yoshifuji, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1645-1656.

[25] Moss, R. A.; Xue, S.; Sauer, R. R. *J. Am. Chem. Soc.* **1996**, *118*, 10307-10308.

[26] Sultana, S. and Lee, Y. R. *Adv. Synth. Catal.* **2020**, *362*, 927-941.

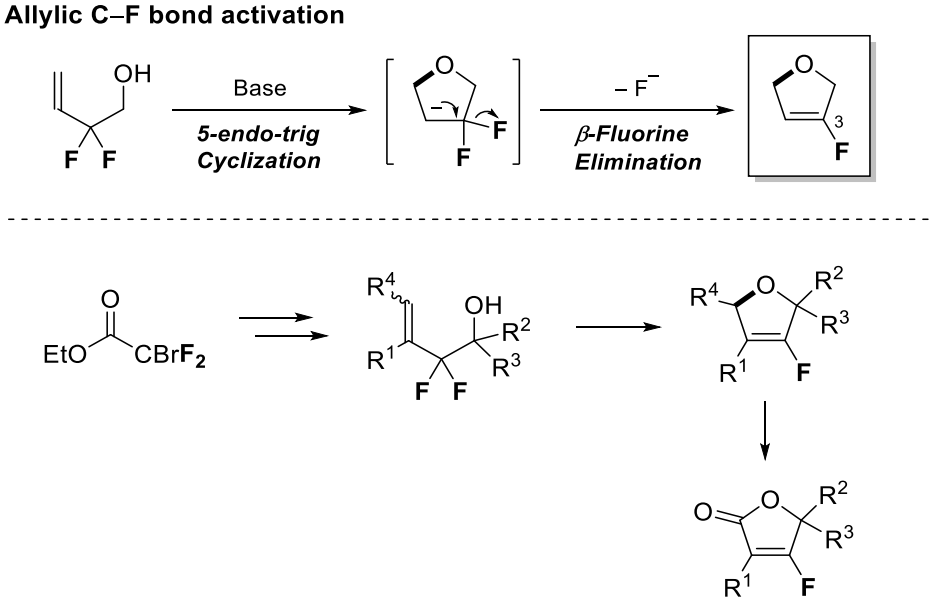
[27] (a) Ichistuka, T.; Fujita, T.; Arita, T.; Ichikawa, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 7564-7568. (b) Ichitsukuka, T.; Fujita, T.; Ichikawa, J. *ACS Catal.* **2015**, *5*, 5947-5950. (c) Fujita, T.; Arita, T.; Ichitsuka, T.; Ichikawa, J. *Dalton Trans.* **2015**, *44*, 19460-19463.

CHAPTER 2

Allylic C–F Bond Activation:
5-*endo-trig* Cyclization of Difluorohomoallylic Alcohols

Abstract

Nucleophilic 5-*endo-trig* cyclization was achieved in 2,2-difluorohomoallylic alcohols. Upon treatment with potassium hydride, 2,2-difluorohomoallylic alcohols underwent an intramolecular S_N2'-type reaction to afford 3-fluoro-2,5-dihydrofurans in high yields. In addition, the oxidation of these dihydrofurans formed 4-fluorofuran-2(5*H*)-ones. Thus, ring-fluorinated furan derivatives were efficiently obtained via allylic sp^3 carbon–fluorine bond activation.



2-1. Introduction

2-1-1. 3-Fluorinated Furan Derivatives

Fluorine-substituted heterocycles have gained increased attention as bioactive compounds, mainly as promising candidates for pharmaceuticals and agrochemicals.[1] In particular, 3-fluorinated furan derivatives exhibit a wide variety of bioactivities (Figure 2-1) such as anti-HCV activity (sofosbuvir),[2] anticancer activity (gemcitabine),[3] and platelet aggregation inhibitory activity (AFP-07).[4]

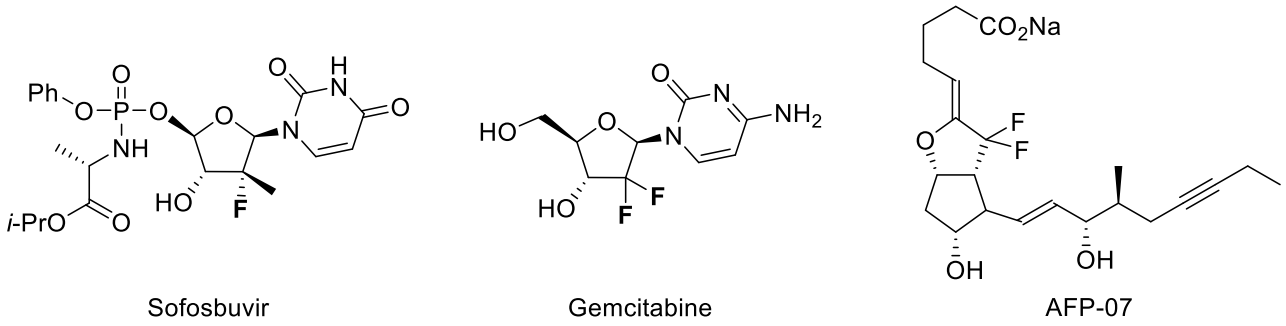


Figure 2-1. 3-Fluorinated furan derivatives

2-1-2. Strategy for the Synthesis of 3-Fluorodihydrofurans

Direct fluorination using either electrophilic[5] or nucleophilic fluorinating agents[6] is a straightforward method to synthesize ring-fluorinated heterocycles; however, regioselectivity is not always retained, depending on ring substituents. The building block approach involving the intramolecular cyclization of fluoroalkenes serves as an alternative method, which enables the simultaneous construction of a heterocyclic framework and regioselective installation of a fluorine substituent. Since fluorine substituents are regioselectively installed on constructed rings, a rational design of cyclization precursors allows the synthesis of heterocycles bearing fluorine substituents at desired positions.

The synthesis of 2-fluorofurans via 5-*endo*-*trig* cyclization, which is considered to be a disfavored process according to Baldwin's rules (Figure 2-2),[7,8] has already been achieved by our group (Scheme 2-1). Vinylic C–F bond activation is successfully affected in 1,1-difluoro-1-alkenes bearing a hydroxy group under basic conditions (S_NV reaction, Scheme 2-1a).[9] Our group has also developed 5-*endo*-*trig* cyclization of 2-trifluoromethyl-1-alkenes via the single activation of allylic sp^3 C–F bonds by a "S_N2'-type reaction," which means a stepwise formal S_N2' reaction through the intermediary carbanions stabilized by β-fluorines. This S_N2'-type reaction allows the synthesis of tetrahydrofurans bearing an *exo*-difluoromethylene moiety at the 3-position (Scheme 2-1b).[10,11] Thus, I assumed that ring-fluorinated cyclic compounds might be formed by changing the position of fluorine substituents from the outside of the constructed rings to the inside. These considerations prompted me to investigate the cyclization of 2,2-difluorohomoallylic alcohols for the synthesis of 3-fluorinated furan derivatives (Scheme 2-1c), which is complementary to our previously reported protocol for 2-fluorinated ones (Scheme 2-1a).

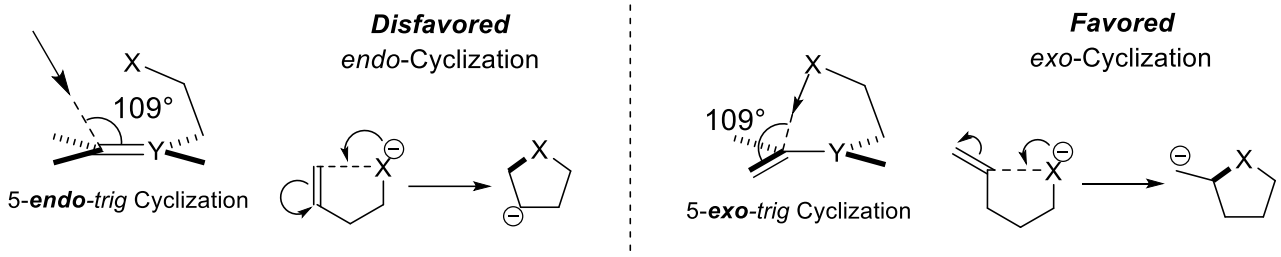
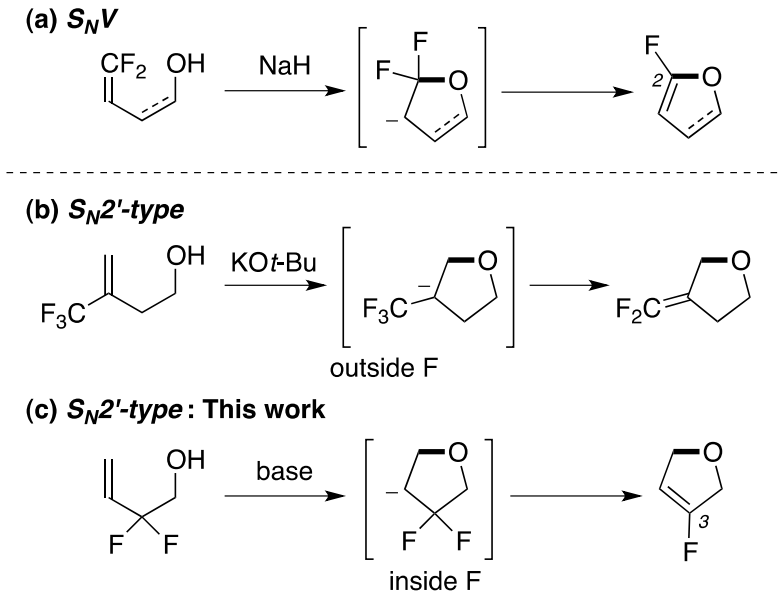


Figure 2-2. 5-*endo*-*trig* Cyclization



Scheme 2-1. Syntheses of fluorinated furan derivatives via nucleophilic 5-*endo-trig* cyclizations of fluoroalkenes

Generally in *concerted* S_N2' reactions, the approach of nucleophiles and elimination of leaving groups are confined to an antiperiplanar or synperiplanar alignment.[12] Thus, intramolecular S_N2' reactions via elimination of leaving groups from the inside of the constructed rings seem to be more difficult, due to the high rigidity in their transition states than those via elimination from the outside, where rotation about the C–C bond proximal to the leaving groups is readily allowed (Figure 2-3, upper). In fact, no successful examples of 5-*endo-trig* cyclization in such an inside manner have been reported to date. To overcome the difficulty, the use of fluorine as a leaving group should be reasonable, because the strong β-anion-stabilizing effect of fluorine would induce a *stepwise* "S_N2'-type reaction"[10b] in the 5-*endo-trig* cyclization of 2,2-difluorohomoallylic alcohols (Figure 2-3, lower).

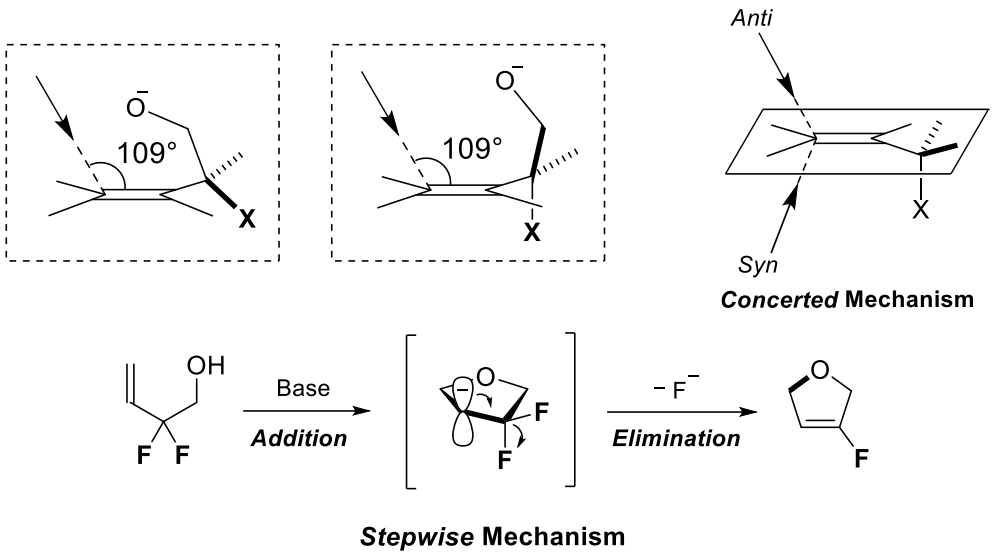
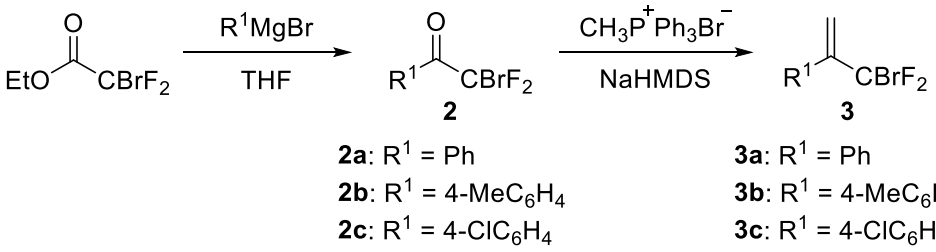


Figure 2-3. 5-*endo-trig* Cyclization of difluorohomoallylic alcohols

2-2. Synthesis of 3-Fluorodihydrofurans

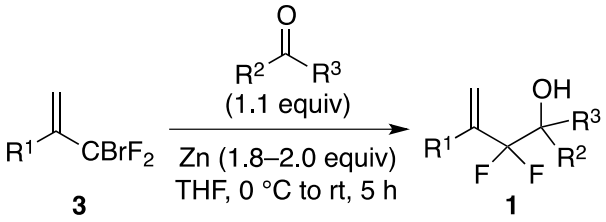
2-2-1. Preparation of Precursors

Ethyl bromodifluoroacetate was used as the starting material for synthesizing the cyclization precursors, 2,2-difluorohomoallylic alcohols **1** (Scheme 2-2, Table 2-1). First, the treatment of ethyl bromodifluoroacetate with organomagnesium reagents afforded bromodifluoromethyl ketones **2** (Scheme 2-2).[13] Subsequent Wittig reaction of ketones **2** with an ylide generated from methyltriphenylphosphonium bromide and sodium hexamethyldisilazide (NaHMDS) afforded 2-substituted 3-bromo-3,3-difluoropropenes **3** (Scheme 2-2).[14] Finally, precursor alcohols **1** were obtained via the difluoroallylation of ketones or aldehydes with **3** and zinc powder (Table 2-1).

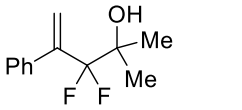


Scheme 2-2. Preparation of 3-bromo-3,3-difluoropropenes **3**.

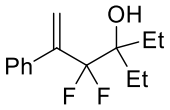
Table 2-1. Preparation of 2,2-difluorohomoallylic alcohols **1**



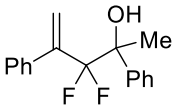
3 **1**



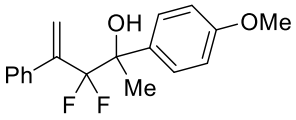
1a 90%[b]



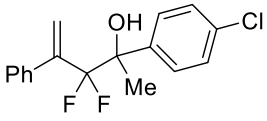
1b 78%[b]



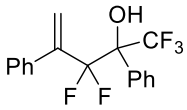
1c 53%[b]



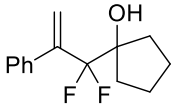
1d 45%



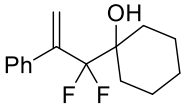
1e 47%



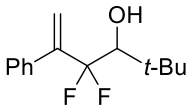
1f 65%



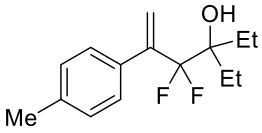
1g 51%



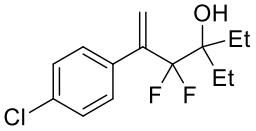
1h 83%[c]



1i 45%



1j 78%



1k 34%

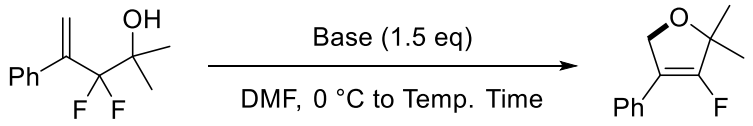
a: Isolated yield. b: Ketone (2.0 eq). c: Ketone (3.0 eq)

2-2-2. Screening of Reaction Conditions

I sought suitable bases for 5-*endo-trig* cyclization using 3,3-difluoro-2-methyl-4-phenylpent-4-en-2-ol (**1a**) as a model substrate (Table 2-2). Upon treatment with *t*-BuOK, which was used as the base suitable for the cyclization of 2-trifluoromethyl-1-alkenes,[10] **1a** underwent the desired cyclization followed by β-fluorine elimination in DMF to afford the corresponding 3-fluoro-2,5-dihydrofuran **4a**, albeit in moderate yield (Table 2-2, entry 1). Although 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and sodium hydride hardly and barely gave cyclized products, respectively (Table 2-2, entries 2 and 3), potassium hexamethyldisilazide (KHMDS) afforded **4a** in 66% yield (Table 2-2, entry 4). Potassium

hydride remarkably improved the yield of **4a** to 85% (isolated yield, entry 5). Using THF as a solvent instead of DMF severely retarded cyclization (Table 2-2, entry 6).

Table 2-2. Screening of bases for 5-*endo-trig* cyclization of **1a**



1a **4a**

Entry	Base	Teperature	**4a** / %[a]
1	*t*-BuOK	RT	36
2	DBU	100 °C	N.D.[b]
3	NaH	40 °C	11
4	KHMDS	RT	66
5	KH	RT	86(85)[c]
6[d]	KH	RT	N.D.[b]

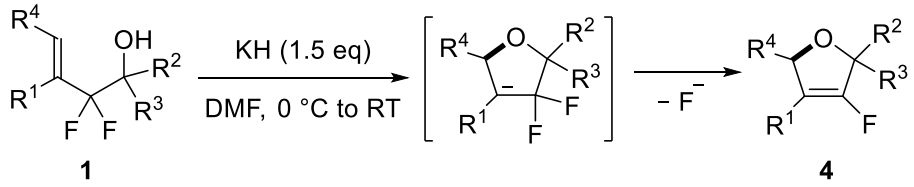
a: Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard. b: N.D. = Not detected. c: Isolated yield. d: THF was used as a solvent.

2-2-3. Substrate Scope

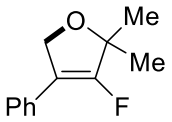
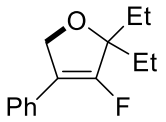
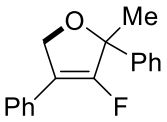
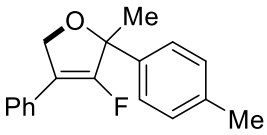
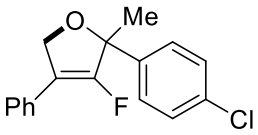
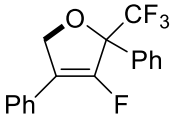
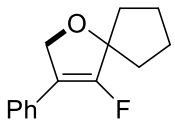
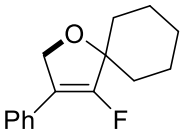
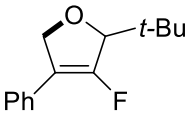
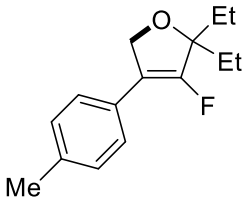
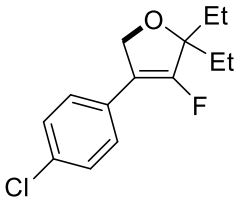
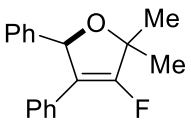
With optimal conditions in hand, the substrate scope was investigated using several other 2,2-difluorohomoallylic alcohols **1** (Table 2-3).[15] Alcohol **1b**, in which two methyl groups of **1a** were replaced by two ethyl groups, successfully underwent 5-*endo-trig* cyclization to afford the corresponding 3-fluoro-2,5-dihydrofuran **4b** in 86% yield. 2,2-Difluorohomoallylic alcohols **1c**–**1f** bearing both an alkyl group and an aryl group at the 1-position in the homoallylic system also participated in the reaction. Dihydrofuran **4f** has two fluorine functions, a fluorine substituent and a trifluoromethyl group, on the ring. Cyclization of alcohols **1g** and **1h**, which possess cyclopentane and cyclohexane rings, afforded spirocyclic products **4g** and **4h** in moderate yields, probably because the carbocyclic moiety kept the hydroxy group farther away from the electrophilic carbon from than in **1a**. Secondary alcohol **1g** bearing a *tert*-butyl group was also applied to the reaction to afford the

corresponding dihydrofuran **4i** in a 77% yield. The reactions of alcohols **1j** and **1k** bearing an electron-rich *p*-tolyl group and an electron-deficient 4-chlorophenyl group at the 3-position afforded the corresponding dihydrofurans **4j** and **4k** in 72% and 71% yields, respectively. When the cyclization was applied to internal alkenes, 2,2,4,5-tetrasubstituted 3-fluoro-2,5-dihydrofuran **4l** was obtained in 52% yield from 4-phenylated 2,2-difluorohomoallylic alcohol **1l**.[16]

Table 2-3. Synthesis of 3-fluoro-2,5-dihydrofurans **4**



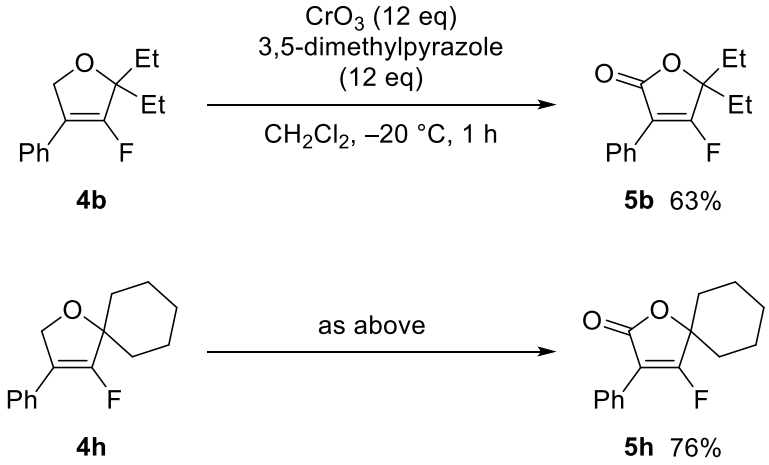
1 **4**

 **4a** 85%	 **4b** 86%	 **4c** 74%
 **4d** 93%	 **4e** 69%	 **4f** 60%
 **4g** 52%	 **4h** 70(50)[b]%	 **4i** 77%
 **4j** 72%	 **4k** 71%	 **4l** 52%

a: Isolated yield. b: 1 mmol scale.

2-2-4. Synthesis of 4-Fluorofuranones

3-Fluoro-2,5-dihydrofurans **4** obtained in this protocol were successfully transformed into 4-fluorofuran-2(5*H*)-ones **5** via the oxidation of the methylene moiety without loss of the fluorine substituent (Scheme 2-3). Treatment of **4b** and **4h** with CrO_3 and 3,5-dimethylpyrazole afforded the corresponding 4-fluorofuranones **5b** and **5h** in 63% and 76% yields, respectively.[17] The oxidation efficiency of fluorinated dihydrofurans **4** was comparable to that of fluorine-free dihydrofurans as reported in the literature.[18] Since furanones often exhibit antifungal effects, the obtained fluorofuranones **5** might also possess such bioactivities.[19]



Scheme 2-3. Synthesis of 4-fluorofuranones **5**

2-3. Summary

In summary, I demonstrated the synthesis of ring-fluorinated furan derivatives based on single sp^3 C–F bond activation of difluorinated alkenes. 2,2-Difluorohomoallylic alcohols underwent a normally disfavored 5-*endo-trig* cyclization at room temperature with the aid of potassium hydride to afford 3-fluoro-2,5-dihydrofurans. Furthermore, the resulting 3-fluoro-2,5-dihydrofurans underwent oxidation by CrO_3 to afford 4-fluorofuranones. Since 3-fluorofurans have so far been synthesized by multistep routes,[15,17] my protocol is of significance as a method for providing a series of 3-fluorinated furan derivatives, which would serve as pharmaceuticals and agrochemicals.

2-4. References

[1] *Fluorine in Heterocyclic Chemistry vol. 1 and 2*, ed. Nenajdenko, V. Springer, Heidelberg, **2014**.

[2] Sofia, M. J.; Bao, D.; Chang, W.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Reddy, P. G.; Ross, B. S.; Wang, P.; Zhang, H.-R.; Bansal, S.; Espiritu, C.; Keilman, M.; Lam, A. M.; Steuer, H. M. M.; Niu, C.; Otto, M. J.; Furman, P. A. *J. Med. Chem.* **2010**, *53*, 7202–7218.

[3] Gandhi, V. and Plunkett, W. *Cancer Res.* **1990**, *50*, 3675–3680.

[4] Chang, C.-S.; Negishi, M.; Nakano, T.; Morizawa, Y.; Matsumura, Y.; Ichikawa, A. *Prostaglandins* **1997**, *53*, 83–90.

[5] For selected reviews on electrophilic fluorination, see: (a) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477. (b) Singh, R. P. and Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31–44. (c) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192–212. (d) Kiselyov, A. S. *Chem. Soc. Rev.* **2005**, *34*, 1031–1037.

[6] For selected reviews on nucleophilic fluorination, see: (a) Singh, R. P. and Shreeve, J. M. *Synthesis* **2002**, 2561–2578. (b) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289–4294.

[7] For recent reports on nucleophilic 5-*endo*-*trig* cyclization, see: (a) Tong, K.; Tu, J.; Qi, X.; Wang, M.; Wang, Y.; Fu, H.; Pittman, Jr. C. U.; Zhou, A. *Tetrahedron* **2013**, *69*, 2369–2375. (b) En, D.; Zou, G.-F.; Guo, Y.; Liao, W.-W. *J. Org. Chem.* **2014**, *79*, 4456–4462. (c) Johnston, C. P.; Kothari, A. Sergeieva, T.; Okovytyy, S. I.; Jackson, K. E.; Paton R. S.; Smith, M. D. *Nat. Chem.* **2015**, *7*, 171–177. (d) Kapoorr, R.; Singh, S. N.; Tripathi, S.; Yadav, L. D. S. *Synlett* **2015**, *26*, 1201–1206. (e) Sharma, K.; Wolstenhulme, J. R.; Painter, P. P.; Yeo, D.; Grande-Carmona, F.; Johnston, C. P.; Tantillo, D. J.; Smith, M. D. *J. Am. Chem. Soc.* **2015**, *137*, 13414–13424. (f) Williams, B. M. and Trauner, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 2191–2194. (g) Markwell-Heys A. W. and George, J. H. *Org. Biomol. Chem.* **2016**, *14*, 5546–5549. (h) Xiao, T.; Li, L.; Zhou, L. *J. Org. Chem.* **2016**, *81*, 7908–

7916. (i) Zhang, B.; Zhang, X.; Hao, J.; Yang, C. *Org. Lett.* **2017**, *19*, 1780–1783. (j) Hao, J.; Milcent, T.; Retailleau, P.; Soloshonok, V. A.; Ongeri, S.; Crousse, B. *Eur. J. Org. Chem.* **2018**, 3688–3692.

[8] For Baldwin's rules, see: (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734–736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Commun.* **1976**, 736–738.

[9] (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, 1537–1538. (b) Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **2000**, 1887–1888. (c) Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917–1936. (d) Fujita, T.; Sakoda, K.; Ikeda, M.; Hattori, M.; Ichikawa, J. *Synlett* **2013**, *24*, 57–60. (e) Fujita, T.; Ikeda, M.; Hattori, M.; Sakoda, K.; Ichikawa, J. *Synthesis* **2014**, *46*, 1493–1505.

[10] (a) Ichikawa, J.; Iwai, Y.; Nadano, R.; Mori, T.; Ikeda, M. *Chem. Asian J.* **2008**, *3*, 393–406. (b) Ichikawa, J. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1175–1184.

[11] For similar S_N2'-type reactions, see: (a) Fuchibe, K.; Takahashi, M.; Ichikawa, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 12059–12062. (b) Bergeron, M.; Guyader, D.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5888–5891. (c) Yang, J.; Mao, A.; Zhu, W.; Luo, X.; Zhu, C.; Xiao, Y.; Zhang, J. *Chem. Commun.* **2015**, *51*, 8326–8329. (d) Fujita, T.; Sugiyama, K.; Sanada, S.; Ichitsuka, T.; Ichikawa, J. *Org. Lett.* **2016**, *18*, 248–251. (e) Fujita, T.; Takazawa, M.; Sugiyama, K.; Suzuki, N.; Ichikawa, J. *Org. Lett.* **2017**, *19*, 588–591.

[12] (a) Bach, R. D. and Wolber, G. J. *J. Am. Chem. Soc.* **1985**, *107*, 1352–1357. (b) Borrmann, T. and Stohrer, W.-D. *Liebigs Ann*. **1996**, 1593–1597. (c) La Cruz, T. E. and Rychnovsky, S. D. *Chem. Commun.* **2004**, 168–169.

[13] Nihei, T.; Iwai, N.; Matsuda, T.; Kitazume, T. *J. Org. Chem.* **2005**, *70*, 5912–5915.

[14] Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233.

[15] For the synthesis of 3-fluoro-2,5-dihydrobenzofurans, see: (a) Mackman, R. L.; Lin, K.-Y.; Boojamra, C. G.; Hui, H.; Douglas, J.; Grant, D.; Petrakovsky, O.; Prasad, V.; Ray A. S.; Cihlar, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1116–1119. (b) Boojamra, C. G.; Mackman, R. L.; Markevitch, D. Y.; Prasad, V.; Ray, A. S.; Douglas, J.; Grant, D.; Kim, C. U.; Cihlar, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1120–1123. (c) Mackman, R. L.; Ray, A. S.; Hui, H. C.; Zhang, L.; Birkus, G.; Boojamra, C. G.; Desai, M. C.; Douglas, J. L.; Gao, Y.; Grant, D.; Laflamme, G.; Lin, K.-Y.; Markevitch, D. Y.; Mishra, R.; McDermott, M.; Pakdaman, R.; Petrakovsky, O. V.; Vela, J. E.; Cihlar, T. *Bioorg. Med. Chem.* **2010**, *18*, 3606–3617. (d) Srivastav, N. C.; Shakya, N.; Mak, M.; Agrawal, B.; Tyrrell, D. L.; Kumar, R. *J. Med. Chem.* **2010**, *53*, 7156–7166. (e) Rayala, R.; Giuglio-Tonolo, A.; Broggi, J.; Terme, T.; Vanelle, P.; Theard, P.; Médebielle, M.; Wnuk, S. *Tetrahedron* **2016**, *72*, 1969–1977.

[16] 4-Phenylated 2,2-difluorohomoallylic alcohols **1l** was prepared via (i) coupling of bromodifluoromethyl ketones **2a** with acetone in the presence of zinc powder, (ii) THP protection of the hydroxy group, (iii) Wittig reaction with benzyltriphenylphosphonium bromide and (iv) deprotection. For details, see Electronic Supplementary Information.

[17] For the synthesis of 4-fluorofuran-2(5*H*)-ones, see: (a) Zhou, C.; Ma, Z.; Gu, Z.; Fu, C.; Ma, S. *J. Org. Chem.* **2008**, *73*, 772–774. (b) Lü, B.; Fu, C.; Ma, S. *Org. Biomol. Chem.* **2010**, *8*, 274–281. (c) Liu, Y.; Zhu, J.; Qian, J.; Xu, Z. *J. Org. Chem.* **2012**, *77*, 5411–5417. (d) Liao, F.-M.; Cao, Z.-Y.; Yu, J.-S.; Zhou, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 2459–2463.

[18] (a) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057–2059. (b) Alberto, J. M.; Miguel, C.; Santiago, R.; Encarnación, C.; María, K. N. *Tetrahedron* **2003**, *59*, 4085-4101.

[19] Senel, P.; Tichotová, L.; Votruba, I.; Buchta, V.; Spulák, M.; Kunes, J.; Nobilis, M.; Krenk, O.; Pour, M. *Bioorg. Med. Chem.* **2010**, *18*, 1988–2000.

2-5. Experimental Section

General

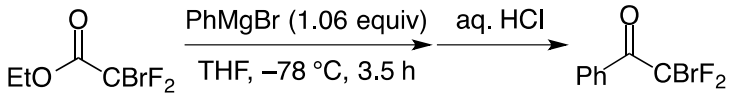
^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shift values are given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm) and C_6F_6 (for ^{19}F NMR: δ = 0.00 ppm; –164.9). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV or a JEOL JMS-T100CS spectrometer. Elemental analyses were carried out at Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. Melting points were measured on a Yanaco micro melting point apparatus and were uncorrected.

Column chromatography was conducted on Florisil (Wako Pure Chemical Industries, Ltd., 75–150 μm) or silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc., 63–210 μm). All the reactions were conducted under argon or nitrogen.

Tetrahydrofuran (THF) was purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 and stored over activated molecular sieves 4A. Potassium hydride was washed with dry hexane three times, dried under vacuum and stored in a glove box. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purifications.

2. Preparation of Bromodifluoromethyl Ketones 2

2-Bromo-2,2-difluoro-1-phenylethan-1-one (2a)

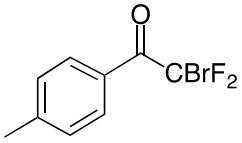


2a

To a THF (30 mL) solution of ethyl bromodifluoroacetate (6.1 g, 30 mmol) was added phenylmagnesium bromide, prepared from bromobenzene (5.0 g, 32 mmol), magnesium turnings (0.80 g, 33 mmol) and THF (30 mL), at –78 °C over 0.5 h. After stirring for 3 h at –78 °C, the reaction was quenched with an aqueous HCl solution (2 M, 30 mL). Organic materials were extracted with ether three times. The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by passing through a short column of silica gel (hexane/ethyl acetate = 50/1) to give **2a** (6.3 g, 90%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.[1]

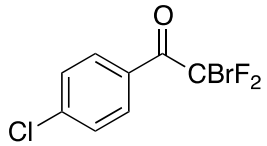
2-Bromo-2,2-difluoro-1-(4-methylphenyl)ethan-1-one (2b)



Bromodifluoromethyl ketone **2b** was prepared by the method described for **2a** using ethyl bromodifluoroacetate (6.1 g, 30 mmol), 4-bromotoluene (5.38 g, 31.5 mmol) and magnesium turnings (802 mg, 33.0 mmol). Passing through a short column of silica gel (hexane/ethyl acetate = 10/1) gave **2b** (6.90 g, 93%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.[2]

2-Bromo-1-(4-chlorophenyl)-2,2-difluoroethan-1-one (2c)

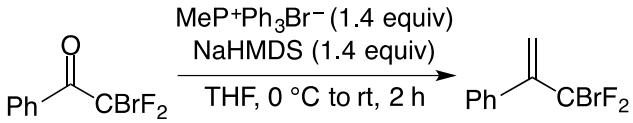


Bromodifluoromethyl ketone **2c** was prepared by the method described for **2a** using ethyl bromodifluoroacetate (3.05 g, 15.0 mmol), 1-bromo-4-chlorobenzene (3.03 g, 15.8 mmol) and magnesium turnings (401 mg, 16.5 mmol). Passing through a short column of silica gel (hexane/ethyl acetate = 10/1) gave **2c** (1.84 g, 45%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.[3]

3. Preparation of 3-Bromo-3,3-difluoropropenes 3

(3-Bromo-3,3-difluoroprop-1-en-2-yl)benzene (3a)

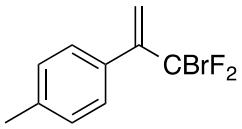


2a **3a**

To a THF (60 mL) solution of methyltriphenylphosphonium bromide (5.0 g, 14 mmol) was added NaHMDS (1.9 M in THF, 7.5 mL, 14 mmol) at –78 °C over 0.5 h. After stirring at –78 °C for 1 h, the mixture was warmed to 0 °C. After stirring at 0 °C for 1 h, bromodifluoromethyl ketone **2a** (2.4 g, 10 mmol) was added to the reaction mixture. After stirring at room temperature for 2 h, the reaction was quenched with an aqueous HCl solution (2 M, 30 mL). Organic materials were extracted with ether three times. The combined extracts were washed with brine and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (hexane) to give **3a** (1.5 g, 65%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.[4]

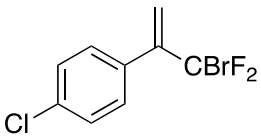
1-(3-Bromo-3,3-difluoroprop-1-en-2-yl)-4-methylbenzene (3b)



3-Bromo-3,3-difluoropropene **3b** was prepared by the method described for **3a** using methyl triphenylphosphonium bromide (5.1 g, 14 mmol), NaHMDS (1.9 M in THF, 7.5 mL, 14 mmol) and bromodifluoromethyl ketone **2b** (2.5 g, 10 mmol). Purification by silica gel column chromatography (hexane) gave **3b** (1.6 g, 65%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 5.51 (s, 1H), 5.84 (s, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 117.7 (t, J_{CF} = 7 Hz), 118.3 (t, J_{CF} = 303 Hz), 128.1, 129.1, 131.2, 139.0, 145.5 (t, J_{CF} = 22 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 115.7 (s). IR (neat): ν 2923, 1504, 1151, 1070, 914, 821, 742, 571 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{10}H_9{}^{79}BrF_2$ $[M]^+$: 245.9856; Found: 245.9856.

1-(3-Bromo-3,3-difluoroprop-1-en-2-yl)-4-chlorobenzene (3c)

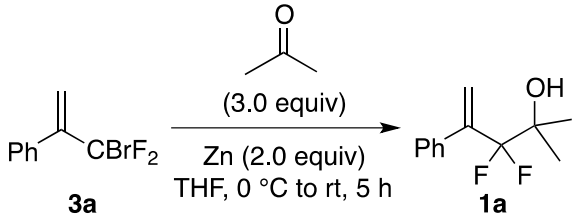


3-Bromo-3,3-difluoropropene **3c** was prepared by the method described for **3a** using methyl triphenylphosphonium bromide (3.38 g, 9.46 mmol), NaHMDS (1.9 M in THF, 5.0 mL, 9.5 mmol) and bromodifluoromethyl ketone **2c** (1.84 g, 6.83 mmol). Purification by silica gel column chromatography (hexane) gave **3c** (578 mg, 32%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51 (t, J_{HF} = 1.8 Hz, 1H), 5.87 (s, 1H), 7.33–7.40 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 117.7 (t, J_{CF} = 306 Hz), 118.7 (t, J_{CF} = 7 Hz), 128.6, 129.6, 133.0, 135.1, 144.6 (t, J_{CF} = 21 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 116.4 (s). IR (neat): ν 1491, 1155, 1093, 1072, 922, 833, 555 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_9H_6{}^{79}BrClF_2$ $[M]^+$: 265.9309; Found: 265.9315.

4. Preparation of 2,2-Difluorohomoallylic Alcohols 1

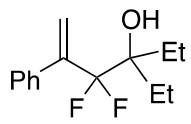
3,3-Difluoro-2-methyl-4-phenylpent-4-en-2-ol (1a)



To the mixture of acetone (517 mg, 8.90 mmol) and zinc powder (activated with an aqueous HCl solution, 390 mg, 5.96 mmol) in THF (4.0 mL) was added a THF (4.0 mL) solution of 3-bromo-3,3-difluoropropene **3a** (699 mg, 3.00 mmol) at 0 °C over 30 min. Then, the reaction mixture was warmed to room temperature, and stirred at room temperature for 5 h. The reaction was quenched with an aqueous HCl solution (2 M, 5 mL). Organic materials were extracted with dichloromethane 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 silica gel column chromatography (hexane/ethyl acetate = 10/1) to give **1a** (575 mg, 90%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 6H), 5.53 (d, J = 2.3 Hz, 1H), 5.78 (d, J = 2.3 Hz, 1H), 7.30–7.34 (m, 3H), 7.40–7.43 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.1, 74.1 (t, J_{CF} = 28 Hz), 122.0 (t, J_{CF} = 9 Hz), 122.3 (t, J_{CF} = 252 Hz), 128.0, 128.2, 128.6, 138.4, 142.9 (t, J_{CF} = 22 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 52.7 (s). IR (neat): ν 3442, 2989, 1494, 1147, 1070, 775, 698, 590 cm^{-1}. HRMS (ESI+): m/z Calcd for $C_{12}H_{14}F_2NaO$ $[M + Na]^+$: 235.0910; Found: 235.0914.

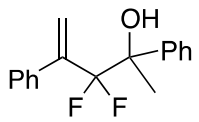
3-Ethyl-4,4-difluoro-5-phenylhex-5-en-3-ol (1b)



2,2-Difluorohomoallylic alcohol **1b** was prepared by the method described for **1a** using diethyl ketone (258 mg, 3.00 mmol), zinc powder (131 mg, 2.0 mmol) and 3-bromo-3,3-difluoropropene **3a** (231 mg, 0.996 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1b** (186 mg, 78%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (t, J = 7.5 Hz, 6H), 1.28 (s, 1H), 1.55–1.66 (m, 4H), 5.49 (s, 1H), 5.77 (s, 1H), 7.30–7.32 (m, 3H), 7.40–7.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.4, 25.6, 77.7 (t, J_{CF} = 27 Hz), 121.5 (t, J_{CF} = 9 Hz), 123.2 (t, J_{CF} = 253 Hz), 127.8, 128.0, 128.5, 138.4, 143.4 (t, J_{CF} = 21 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 58.0 (s). IR (neat): ν 3585, 3482, 2972, 2949, 2887, 1496, 1463, 1078, 1027, 935, 775, 700 cm^{-1}. HRMS (ESI+): m/z Calcd for $C_{14}H_{18}F_2NaO$ $[M + Na]^+$: 262.1223; Found: 262.1224.

3,3-Difluoro-2,4-diphenylpent-4-en-2-ol (1c)

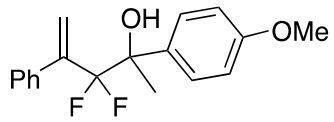


2,2-Difluorohomoallylic alcohol **1c** was prepared by the method described for **1a** using acetophenone (132 mg, 1.1 mmol), zinc powder (126 mg, 1.9 mmol) and 3-bromo-3,3-difluoropropene **3a** (235 mg, 1.01 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1c** (148 mg, 53%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67 (s, 3H), 2.05 (s, 1H), 5.31 (d, J = 0.8 Hz, 1H), 5.37 (d, J = 0.8 Hz, 1H), 7.21–7.28 (m, 8H), 7.43–7.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.6 (dd, J_{CF} = 2, 2 Hz), 77.6 (dd, J_{CF} = 27, 27 Hz), 121.6 (dd, J_{CF} = 254, 254 Hz), 122.5 (dd, J_{CF} = 9, 9 Hz), 126.4, 127.6, 127.7, 127.7, 127.9, 128.6, 138.2, 140.6, 142.6 (dd, J_{CF} = 24, 24 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 56.3 (d, J_{FF} = 248 Hz, 1F), 58.6 (d, J_{FF} = 248 Hz, 1F). IR (neat): ν 3566, 3483, 3059, 2993, 2941, 1495, 1448,

1070, 1028, 933, 760, 698 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{17}H_{17}F_2O$ $[M + H]^+$: 275.1247; Found: 275.1239.

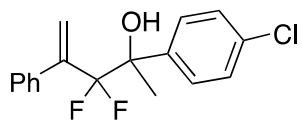
3,3-Difluoro-2-(4-methoxyphenyl)-4-phenylpent-4-en-2-ol (1d)



2,2-Difluorohomoallylic alcohol **1d** was prepared by the method described for **1a** using 4'-methoxyacetophenone (331 mg, 2.20 mmol), zinc powder (261 mg, 3.99 mmol) and 3-bromo-3,3-difluoropropene **3a** (466 mg, 2.00 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1d** (275 mg, 45%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65 (s, 3H), 2.08 (s, 1H), 3.80 (s, 3H), 5.33 (s, 1H), 5.38 (s, 1H), 6.79–6.80 (m, 2H), 7.25–7.27 (m, 5H), 7.34 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.5, 55.2, 77.3 (dd, J_{CF} = 29, 29 Hz), 113.0, 121.8 (t, J_{CF} = 254 Hz), 122.5 (t, J_{CF} = 9 Hz), 127.67, 127.70, 127.9, 128.6, 132.8, 138.3, 142.7 (t, J_{CF} = 24 Hz), 159.0. ^{19}F NMR (470 MHz, $CDCl_3$): δ 56.4 (d, J_{FF} = 242 Hz, 1F), 58.7 (d, J_{FF} = 242 Hz, 1F). IR (neat): ν 3494, 2999, 2941, 2839, 1612, 1514, 1252, 1028, 775, 700 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{18}H_{18}F_2NaO$ $[M + Na]^+$: 327.1173; Found: 327.1166.

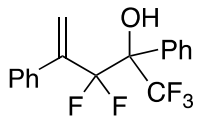
2-(4-Chlorophenyl)-3,3-difluoro-4-phenylpent-4-en-2-ol (1e)



2,2-Difluorohomoallylic alcohol **1e** was prepared by the method described for **1a** using 4'-chloroacetophenone (340 mg, 2.20 mmol), zinc powder (261 mg, 3.99 mmol) and 3-bromo-3,3-difluoropropene **3a** (467 mg, 2.00 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1e** (293 mg, 47%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.66 (s, 3H), 2.09 (s, 1H), 5.35 (s, 1H), 5.42 (s, 1H), 7.20–7.37 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.5 (t, J_{CF} = 2 Hz), 77.2 (dd, J_{CF} = 29, 29 Hz), 121.4 (t, J_{CF} = 255 Hz), 122.6 (t, J_{CF} = 9 Hz), 125.3, 127.7, 127.8, 127.9, 128.5, 133.6, 139.09, 139.11, 142.3 (t, J_{CF} = 24 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 55.0 (d, J_{FF} = 243 Hz, 1F), 57.4 (d, J_{FF} = 243 Hz, 1F). IR (neat): ν 3581, 1495, 1095, 1012, 941, 798, 700, 548 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{17}H_{15}ClF_2NaO$ $[M + Na]^+$: 331.0677; Found: 331.0678.

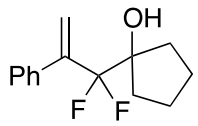
1,1,1,3,3-Pentafluoro-2,4-diphenylpent-4-en-2-ol (1f)



2,2-Difluorohomoallylic alcohol **1f** was prepared by the method described for **1a** using 2,2,2-trifluoroacetophenone (96 mg, 0.55 mmol), zinc powder (65 mg, 0.99 mmol) and 3-bromo-3,3-difluoropropene **3a** (116 mg, 0.50 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1f** (106 mg, 65%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (s, 1H), 5.51 (d, J = 2.0 Hz, 1H), 5.52 (d, J = 2.0 Hz, 1H), 7.06–7.07 (m, 2H), 7.21–7.35 (m, 6H), 7.54–7.56 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 79.0 (dd, J_{CF} = 26, 26 Hz), 119.7 (dd, J_{CF} = 260, 256 Hz), 123.69 (dd, J_{CF} = 9, 9 Hz), 123.72 (q, J_{CF} = 291 Hz), 127.0, 127.8, 127.9, 128.0, 128.6, 129.2, 131.3, 136.9, 141.4 (dd, J_{CF} = 23, 23 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 57.9 (dq, J_{FF} = 249 Hz, J_{FF} = 12 Hz, 2F), 58.9 (dq, J_{FF} = 249 Hz, J_{FF} = 12 Hz, 2F), 89.5 (dd, J_{FF} = 12, 12 Hz). IR (neat): ν 3589, 3548, 1259, 1205, 1173, 1074, 916, 901, 729, 698 cm^{-1}. Elem. Anal. Calcd for $C_{17}H_{13}F_5O$: C, 62.20; H, 3.99. Found: C, 62.22; H, 4.20.

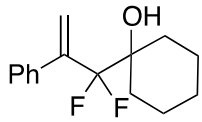
1-(1,1-Difluoro-2-phenylallyl)cyclopentan-1-ol (1g)



2,2-Difluorohomoallylic alcohol **1g** was prepared by the method described for **1a** using cyclopentanone (190 mg, 2.3 mmol), zinc powder (266 mg, 4.07 mmol) and 3-bromo-3,3-difluoropropene **3a** (468 mg, 2.01 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1g** (245 mg, 51%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42–1.48 (m, 2H), 1.57–1.63 (m, 2H), 1.70–1.79 (m, 2H), 1.84–1.89 (s, 2H), 5.51 (s, 1H), 5.81 (s, 1H), 7.32–7.33 (m, 3H), 7.33–7.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.0, 35.6, 85.1 (t, J_{CF} = 29 Hz), 121.5 (t, J_{CF} = 9 Hz), 121.9 (t, J_{CF} = 287 Hz), 128.0, 128.1, 128.7, 138.3, 143.5 (t, J_{CF} = 22 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 55.9 (s). IR (neat): ν 3593, 3464, 2958, 2875, 1153, 1030, 1016, 937, 775, 698 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{14}H_{16}F_2NaO$ $[M + Na]^+$: 261.1067; Found: 261.1073.

1-(1,1-Difluoro-2-phenylallyl)cyclohexan-1-ol (1h)

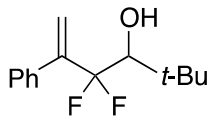


2,2-Difluorohomoallylic alcohol **1h** was prepared by the method described for **1a** using cyclohexanone (389 mg, 3.96 mmol), zinc powder (240 mg, 3.67 mmol) and 3-bromo-3,3-difluoropropene **3a** (471 mg, 2.02 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1h** (424 mg, 83%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (s, 1H), 1.36–1.56 (m, 10H), 5.45 (s, 1H), 5.66 (s, 1H), 7.24–7.25 (m, 3H), 7.34–7.35 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.6, 25.2, 30.6, 74.8 (t, J_{CF} = 27 Hz), 121.8 (t, J_{CF} = 10 Hz), 122.3 (t, J_{CF} = 254 Hz), 127.8, 128.1, 128.5, 138.5, 142.8 (t, J_{CF} = 24 Hz). ^{19}F

NMR (470 MHz, $CDCl_3$): δ 52.4 (s). IR (neat): ν 3575, 3482, 2937, 2862, 1446, 1263, 1139, 1041, 987, 775, 698, 590 cm^{-1}. Elem. Anal. Calcd for $C_{15}H_{18}F_2O$: C, 71.41; H, 7.19. Found: C, 71.46; H, 7.28.

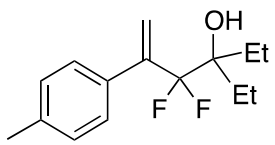
4,4-Difluoro-2,2-dimethyl-5-phenylhex-5-en-3-ol (1i)



2,2-Difluorohomoallylic alcohol **1i** was prepared by the method described for **1a** using 2,2-dimethylpropanal (95 mg, 1.1 mmol), zinc powder (133 mg, 2.0 mmol) and 3-bromo-3,3-difluoropropene **3a** (230 mg, 0.987 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1i** (106 mg, 45%) as a colorless liquid.

^1H NMR (500 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.74 (s, 1H), 3.43 (dd, J_{HF} = 22.0, 5.3 Hz, 1H), 5.53 (d, J = 3.3 Hz, 1H), 5.81 (d, J = 3.3 Hz, 1H), 7.34–7.35 (m, 3H), 7.43–7.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.9 (dd, J_{CF} = 3, 3 Hz), 34.9, 77.2 (dd, J_{CF} = 26, 26 Hz), 119.2 (dd, J_{CF} = 11, 8 Hz), 122.6 (dd, J_{CF} = 254, 249 Hz), 128.1, 128.2, 128.4, 137.0 (d, J_{CF} = 4 Hz), 144.6 (dd, J_{CF} = 21, 21 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 50.4 (dd, J_{FF} = 248 Hz, J_{FH} = 22 Hz, 1F), 66.4 (d, J_{FF} = 248 Hz, 1F). IR (neat): ν 3600, 3496, 2960, 2912, 2877, 1496, 1369, 1180, 1049, 1016, 935, 779, 698 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{14}H_{18}F_2NaO$ $[M + Na]^+$: 263.1223; Found: 263.1222.

3-Ethyl-4,4-difluoro-5-(4-methylphenyl)hex-5-en-3-ol (1j)

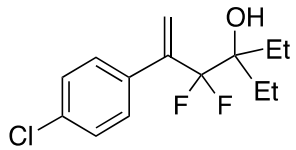


2,2-Difluorohomoallylic alcohol **1j** was prepared by the method described for **1a** using diethyl ketone (277 mg, 3.22 mmol), zinc powder (388 mg, 5.93 mmol) and 3-bromo-3,3-difluoropropene **3b**

(744 mg, 3.01 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1j** (598 mg, 78%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.6 Hz, 6H), 1.53–1.68 (m, 4H), 2.34 (s, 3H), 5.48 (d, J = 2.4 Hz 1H), 5.74 (d, J = 2.4 Hz 1H), 7.13 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.5, 21.1, 25.8, 77.8 (t, J_{CF} = 2 Hz), 121.0 (t, J_{CF} = 9 Hz), 123.3 (t, J_{CF} = 252 Hz), 128.5, 128.9, 135.6, 137.8, 143.3 (t, J_{CF} = 23 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 56.9 (s). IR (neat): ν 3597, 2974, 2887, 1084, 912, 742 cm^{-1}. HRMS (ESI+): m/z Calcd for $C_{15}H_{20}F_2NaO$ $[M + Na]^+$: 277.1380; Found: 277.1382.

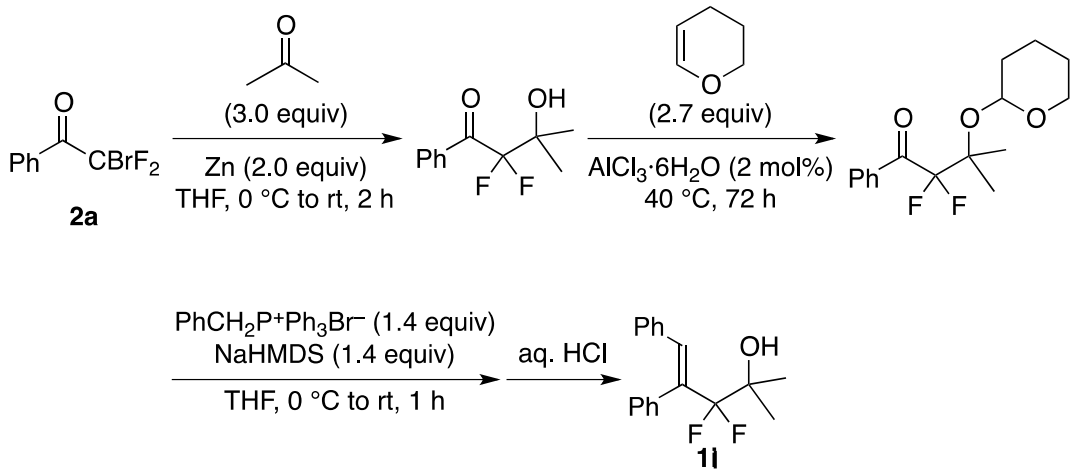
5-(4-Chlorophenyl)-3-ethyl-4,4-difluorohex-5-en-3-ol (1k)



2,2-Difluorohomoallylic alcohol **1k** was prepared by the method described for **1a** using diethyl ketone (261 mg, 3.03 mmol), zinc powder (131 mg, 2.0 mmol) and 3-bromo-3,3-difluoropropene **3c** (267 mg, 0.998 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **1k** (93 mg, 34%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, J = 7.6 Hz, 6H), 1.57–1.65 (m, 4H), 5.50 (s, 1H), 5.78 (s, 1H), 7.28–7.32 (m, 2H), 7.36 (d, J = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.4, 25.6, 77.7 (t, J_{CF} = 26 Hz), 122.0 (t, J_{CF} = 9 Hz), 122.0 (t, J_{CF} = 254 Hz), 128.2, 130.0, 133.9, 137.0, 142.6 (t, J_{CF} = 24 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 58.1 (s). IR (neat): ν 3587, 3469, 2974, 2887, 1493, 1092, 835 cm^{-1}. HRMS (ESI+): m/z Calcd for $C_{14}H_{17}ClF_2NaO$ $[M + H]^+$: 275.1014; Found: 275.1009.

3,3-Difluoro-2-methyl-4,5-diphenylpent-4-en-2-ol (1l)



2a **1l**

To the mixture of acetone (870 mg, 15.0 mmol) and zinc powder (activated with an aqueous HCl solution, 645 mg, 9.87 mmol) in THF (5.0 mL) was added a THF (5.0 mL) solution of bromodifluorodifluoromethyl ketone **2a** (1.17 g, 4.98 mmol) at 0 °C over 30 min. Then, the reaction mixture was warmed to room temperature and stirred at room temperature for 2 h. The reaction was quenched with aqueous HCl solution (2 M, 5 mL). Organic materials were extracted with dichloromethane 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 silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 2,2-difluoro-3-hydroxy-3-methyl-phenylbutan-1-one (423 mg, 40%) as a colorless liquid.

Spectral data for this compound showed good agreement with the literature data.[5]

To the mixture of 2,2-difluoro-3-hydroxy-3-methyl-phenylbutan-1-one (513 mg, 2.39 mmol) and 3,4-dihydro-2*H*-pyran (546 mg, 6.49 mmol) was added $AlCl_3 \cdot 6H_2O$ (12 mg, 0.050 mmol) at room temperature. After stirring at 40 °C for 72 h, the reaction was quenched with water. Organic materials were extracted with dichloromethane 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

silica gel column chromatography (hexane/ethyl acetate = 10/1) to give 2,2-difluoro-3-methyl-1-phenyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]butan-1-one (687 mg, 96%) as a colorless liquid.

2,2-Difluoro-3-methyl-1-phenyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]butan-1-one: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26–1.57 (m, 12H), 3.39–3.43 (m, 1H), 3.68–3.73 (m, 1H), 4.91 (dd, *J* = 3.4, 3.4 Hz, 1H), 7.44 (dd, *J* = 8.1, 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.82, 18.85, 21.9 (dd, J_{CF} = 3, 3 Hz), 25.0, 30.9, 61.7, 78.8 (dd, J_{CF} = 26, 26 Hz), 93.2, 118.5 (dd, J_{CF} = 260, 260 Hz), 127.9, 130.5, 133.5, 134.6, 191.8 (dd, J_{CF} = 28, 28 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 50.9 (d, J_{FF} = 253 Hz, 1F), 51.5 (d, J_{FF} = 253 Hz, 1F). IR (neat): ν 2947, 1695, 1138, 1108, 1024, 897, 715 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{16}H_{20}F_2NaO_3$ $[M + Na]^+$: 321.1278; Found: 321.1268.

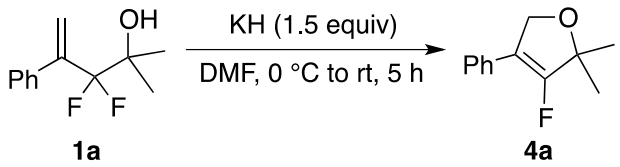
To a THF (5.0 mL) solution of benzyltriphenylphosphonium bromide (603 mg, 1.39 mmol) was added NaHMDS (1.9 M in THF, 0.750 mL, 1.4 mmol) at –78 °C over 0.5 h. After stirring at –78 °C for 1 h, the reaction mixture was warmed to 0 °C. After stirring at 0 °C for 1 h, a THF (1.0 mL) solution of 2,2-difluoro-3-methyl-1-phenyl-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]butan-1-one (305 mg, 1.02 mmol) was added to the reaction mixture at 0 °C over 0.5 h. After stirring at room temperature for 1 h, the reaction was quenched with an aqueous HCl solution (2 M, 5 mL). Organic materials were extracted with ether and were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column gel chromatography (hexane/ethyl acetate = 1/1) to give **1l** (230 mg, 78%, *E*/*Z* = 99/1) as white solid.

(*E*)-**1i**: mp 76.5–77.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 6H), 2.17 (s, 1H), 6.89 (m, 2H), 7.06–7.13 (m, 4H), 7.30–7.33 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.2, 74.8 (t, J_{CF} = 29 Hz), 122.2 (t, J_{CF} = 253 Hz), 127.5 (t, J_{CF} = 64 Hz), 127.8, 127.9, 128.5, 129.8, 130.5, 133.3 (t, J_{CF} = 10 Hz), 134.6 (t, J_{CF} = 23 Hz), 134.9, 135.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ 55.2 (s). IR (neat): ν 3560,

3477, 3059, 2987, 1448, 1225, 1151, 1066, 943, 719, 696 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd for $C_{18}H_{19}F_2O$ $[M + H]^+$: 289.1404; Found: 289.1399.

5. Synthesis of 3-Fluoro-2,5-dihydrofurans 4

3-Fluoro-2,2-dimethyl-4-phenyl-2,5-dihydrofuran (4a)

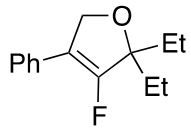


1a **4a**

To the suspension of potassium hydride (9.1 mg, 0.23 mmol) in DMF (2 mL) was slowly added 2,2-difluorohomoallylic alcohol **1a** (32 mg, 0.15 mmol) at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred at 0 °C for 5 h. Organic materials were extracted with 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 silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) to give **4a** (24 mg, 85%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 6H), 4.92 (d, J_{HF} = 4.9 Hz, 2H), 7.26–7.29 (m, 1H), 7.35–7.39 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.6, 69.9 (d, J_{CF} = 10 Hz), 82.0 (d, J_{CF} = 25 Hz), 107.9 (d, J_{CF} = 4 Hz), 126.3 (d, J_{CF} = 6 Hz), 127.6 (d, J_{CF} = 1 Hz), 128.6, 130.2 (d, J_{CF} = 5 Hz), 157.7 (d, J_{CF} = 286 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 24.1 (t, J_{FH} = 5 Hz). IR (neat): ν 2966, 914, 744, 669, 656 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{12}H_{13}FO$ $[M]^+$: 192.0950; Found: 192.0960.

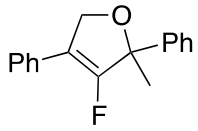
2,2-Diethyl-3-fluoro-4-phenyl-2,5-dihydrofuran (4b)



3-Fluoro-2,5-dihydrofurans **4b** was synthesized by the method described for **4a** using potassium hydride (18 mg, 0.45 mmol) and 2,2-difluorohomoallylic alcohol **1b** (72 mg, 0.30 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4b** (56 mg, 86%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (t, J = 7.4 Hz, 6H), 1.65–1.77 (m, 4H), 4.94 (d, J_{HF} = 4.8 Hz, 2H), 7.25–7.30 (m, 1H), 7.35–7.41 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.8, 30.7 (d, J_{CF} = 3 Hz), 72.0 (d, J_{CF} = 10 Hz), 88.4 (d, J_{CF} = 23 Hz), 110.5 (d, J_{CF} = 4 Hz), 126.3 (d, J_{CF} = 6 Hz), 127.5 (d, J_{CF} = 2 Hz), 128.6, 130.2 (d, J_{CF} = 6 Hz), 154.4 (d, J_{CF} = 285 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 25.6 (t, J_{FH} = 5 Hz). IR (neat): ν 2970, 2854, 1704, 912, 733, 650 cm^{-1}. HRMS (EI): m/z Calcd for $C_{14}H_{13}FO$ $[M]^+$: 220.1263; Found: 220.1268.

3-Fluoro-2-methyl-2,4-diphenyl-2,5-dihydrofuran (4c)

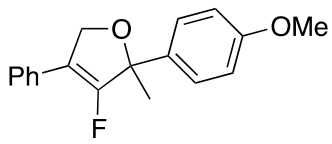


3-Fluoro-2,5-dihydrofurans **4c** was synthesized by the method described for **4a** using potassium hydride (9.1 mg, 0.23 mmol) and 2,2-difluorohomoallylic alcohol **1c** (41 mg, 0.15 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4c** (28 mg, 74%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81 (s, 3H), 5.05 (d, J = 10.8 Hz, J_{HF} = 4.9 Hz, 1H), 5.08 (d, J = 10.8 Hz, J_{HF} = 5.0 Hz, 1H), 7.24–7.31 (m, 2H), 7.33–7.40 (m, 6H), 7.51–7.53 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.4 (d, J_{CF} = 3 Hz), 70.6 (d, J_{CF} = 10 Hz), 84.8 (d, J_{CF} = 24 Hz), 108.8 (d, J_{CF} = 4 Hz), 124.9, 126.4 (d, J_{CF} = 6 Hz), 127.6, 127.7 (d, J_{CF} = 1 Hz), 128.4, 128.6, 129.9 (d, J_{CF} = 5 Hz), 143.2 (d, J_{CF} = 4 Hz), 156.1 (d, J_{CF} = 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 27.5 (dd, J_{FH} = 5, 5 Hz). IR

(neat): ν 3089, 3060, 3030, 2935, 2979, 2852, 1699, 1498, 1446, 1072, 1022, 762, 692 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{17}H_{15}FO$ $[M]^+$: 254.1107; Found: 254.1112.

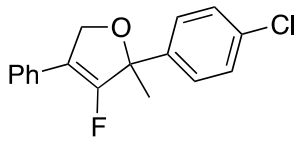
3-Fluoro-2-(4-methoxyphenyl)-2-methyl-4-phenyl-2,5-dihydrofuran (4d)



3-Fluoro-2,5-dihydrofurans **4d** was synthesized by the method described for **4a** using potassium hydride (9.1 mg, 0.23 mmol) and 2,2-difluorohomoallylic alcohol **1d** (46 mg, 0.15 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4d** (40 mg, 93%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.78 (s, 3H), 3.79 (s, 3H), 5.03 (dd, J = 10.6 Hz, J_{HF} = 4.9 Hz, 1H), 5.06 (dd, J = 10.6 Hz, J_{HF} = 4.9 Hz, 1H), 6.89–6.90 (m, 2H), 7.24–7.27 (m, 1H), 7.33–7.42 (m, 4H), 7.42–7.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.2 (d, J_{CF} = 3 Hz), 55.2, 70.5 (d, J_{CF} = 10 Hz), 84.6 (d, J_{CF} = 24 Hz), 108.6 (d, J_{CF} = 4 Hz), 113.7, 126.36 (d, J_{CF} = 3 Hz), 126.42, 127.7, 128.6, 130.0 (d, J_{CF} = 5 Hz), 135.4 (d, J_{CF} = 4 Hz), 156.4 (d, J_{CF} = 289 Hz), 159.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ 27.7 (dd, J_{FH} = 5, 5 Hz). IR (neat): ν 2979, 2836, 1699, 1610, 1508, 1250, 1024, 829, 762, 692 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{18}H_{17}FO$ $[M]^+$: 284.1213; Found: 284.1204.

2-(4-Chlorophenyl)-3-fluoro-2-methyl-4-phenyl-2,5-dihydrofuran (4e)

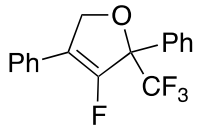


3-Fluoro-2,5-dihydrofurans **4e** was synthesized by the method described for **4a** using potassium hydride (9.2 mg, 0.23 mmol) and 2,2-difluorohomoallylic alcohol **1e** (46 mg, 0.15 mmol). Purification

by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4e** (30 mg, 69%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.76 (s, 3H), 5.02 (dd, J = 10.8 Hz, J_{HF} = 4.9 Hz, 1H), 5.06 (dd, J = 10.8 Hz, J_{HF} = 4.9 Hz, 1H), 7.24–7.35 (m, 7H), 7.43–7.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.5 (d, J_{CF} = 3 Hz), 70.7 (d, J_{CF} = 10 Hz), 84.5 (d, J_{CF} = 24 Hz), 109.1 (d, J_{CF} = 4 Hz), 126.4, 126.5, 127.9 (d, J_{CF} = 1 Hz), 128.6, 128.7, 129.7 (d, J_{CF} = 5 Hz), 133.5, 141.9 (d, J_{CF} = 3 Hz), 155.6 (d, J_{CF} = 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 27.0 (br s). IR (neat): ν 2981, 2854, 1701, 1489, 1092, 1012, 829, 762, 692 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{17}H_{14}ClFO$ $[M]^+$: 288.0717; Found: 288.0722.

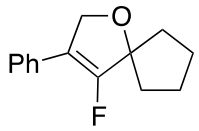
3-Fluoro-2,4-diphenyl-2-(trifluoromethyl)-2,5-dihydrofuran (4f)



3-Fluoro-2,5-dihydrofurans **4f** was synthesized by the method described for **4a** using potassium hydride (17 mg, 0.42 mmol) and 2,2-difluorohomoallylic alcohol **1f** (90 mg, 0.27 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4f** (51 mg, 60%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.11 (dd, J = 11.0 Hz, J_{HF} = 5.4 Hz, 1H), 5.24 (dd, J = 11.0 Hz, J_{HF} = 5.2 Hz, 1H), 7.32–7.46 (m, 8H), 7.72 (d, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 72.3 (d, J_{CF} = 9 Hz), 114.9, 124.0 (qd, J_{CF} = 288, 4 Hz), 125.9, 126.8 (d, J_{CF} = 6 Hz), 127.9 (q, J_{CF} = 12 Hz), 128.5, 128.6 (q, J_{CF} = 15 Hz), 128.77, 128.81 (d, J_{CF} = 2 Hz), 129.2, 134.1 (d, J_{CF} = 4 Hz), 148.2 (d, J_{CF} = 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 27.7 (s, 1F), 85.4 (s, 3F). IR (neat): ν 3066, 2877, 2852, 1701, 1263, 1172, 912, 733, 690 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{17}H_{12}F_4O$ $[M]^+$: 308.0824; Found: 308.0827.

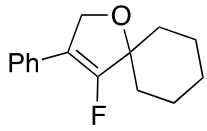
4-Fluoro-3-phenyl-1-oxaspiro[4.4]non-3-ene (4g)



3-Fluoro-2,5-dihydrofurans **4g** was synthesized by the method described for **4a** using potassium hydride (12 mg, 0.30 mmol) and 2,2-difluorohomoallylic alcohol **1g** (48 mg, 0.20 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4g** (23 mg, 52%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65–1.75 (m, 2H), 1.78–1.96 (m, 6H), 4.87 (d, J_{HF} = 5.0 Hz, 2H), 7.23–7.27 (m, 1H), 7.33–7.38 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 24.7, 36.6 (d, J_{CF} = 3 Hz), 70.1 (d, J_{CF} = 1 Hz), 92.1 (d, J_{CF} = 25 Hz), 108.7 (d, J_{CF} = 4 Hz), 126.2 (d, J_{CF} = 6 Hz), 127.4 (d, J_{CF} = 1 Hz), 128.5, 130.2 (d, J_{CF} = 6 Hz), 155.4 (d, J_{CF} = 285 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 25.2 (s). IR (neat): ν 2960, 2871, 2850, 1700, 1362, 1078, 993, 761, 692 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{14}H_{15}FO$ $[M]^+$: 218.1107; Found: 218.1111.

4-Fluoro-3-phenyl-1-oxaspiro[4.5]dec-3-ene (4h)



3-Fluoro-2,5-dihydrofurans **4h** was synthesized by the method described for **4a** using potassium hydride (15 mg, 0.37 mmol) and 2,2-difluorohomoallylic alcohol **1h** (63 mg, 0.25 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 25/1/1) gave **4h** (40 mg, 70%) as a white solid.

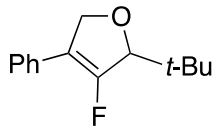
mp 58.6–59.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21–1.31 (m, 1H), 1.63–1.77 (m, 9H), 4.90 (d, J_{HF} = 4.9 Hz, 2H), 7.24–7.28 (m, 1H), 7.33–7.39 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.9, 24.9, 34.0 (d, J_{CF} = 3 Hz), 69.8 (d, J_{CF} = 10 Hz), 83.1 (d, J_{CF} = 23 Hz), 108.1 (d, J_{CF} = 4 Hz), 126.3 (d, J_{CF} = 6

Hz), 127.4 (d, J_{CF} = 1 Hz), 128.6, 130.4 (d, J_{CF} = 5 Hz), 158.3 (d, J_{CF} = 286 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 25.4 (s). IR (neat): ν 3060, 2933, 2852, 1703, 1078, 906, 731, 692 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{15}H_{17}FO$ [M]$^+$: 232.1263; Found: 232.1261.

<1 mmol scale>

3-Fluoro-2,5-dihydrofurans **4h** was synthesized by the method described for **4a** using potassium hydride (61 mg, 1.5 mmol) and 2,2-difluorohomoallylic alcohol **1h** (252 mg, 0.999 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4h** (117 mg, 50%) as a white solid.

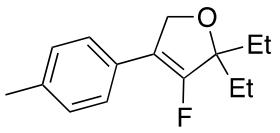
2-(*tert*-Butyl)-3-fluoro-4-phenyl-2,5-dihydrofuran (4i)



3-Fluoro-2,5-dihydrofurans **4i** was synthesized by the method described for **4a** using potassium hydride (9.1 mg, 0.23 mmol) and 2,2-difluorohomoallylic alcohol **1i** (37 mg, 0.15 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4i** (26 mg, 77%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (s, 9H), 4.47 (ddd, J_{HF} = 4.6 Hz, J = 4.6, 4.6 Hz 1H), 4.92 (dd, J = 10.8 Hz, J_{HF} = 4.2 Hz, 1H), 4.95 (dd, J = 10.8 Hz, J_{HF} = 4.6 Hz, 1H), 7.25–7.30 (m, 1H), 7.35–7.40 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.2 (d, J_{CF} = 2 Hz), 35.8 (d, J_{CF} = 4 Hz), 72.3 (d, J_{CF} = 10 Hz), 87.8 (d, J_{CF} = 22 Hz), 111.5 (d, J_{CF} = 4 Hz), 126.3 (d, J_{CF} = 6 Hz), 127.6 (d, J_{CF} = 2 Hz), 128.6, 130.0 (d, J_{CF} = 5 Hz), 154.2 (d, J_{CF} = 287 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 33.9 (s). IR (neat): ν 2956, 2850, 1697, 1498, 1363, 1078, 760, 692 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{14}H_{17}FO$ [M]$^+$: 220.1263; Found: 220.1258.

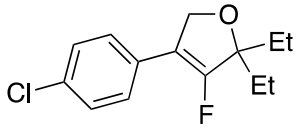
2,2-Diethyl-3-fluoro-4-(4-methylphenyl)-2,5-dihydrofuran (4j)



3-Fluoro-2,5-dihydrofurans **4j** was synthesized by the method described for **4a** using potassium hydride (46 mg, 1.1 mmol) and 2,2-difluorohomoallylic alcohol **1j** (190 mg, 0.75 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4j** (126 mg, 72%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.4 Hz, 6H), 1.64–1.76 (m, 4H), 2.35 (s, 3H), 4.94 (d, J_{HF} = 4.8 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 8.0, 21.2, 30.8 (d, J_{CF} = 3 Hz), 72.1 (d, J_{CF} = 11 Hz), 88.4 (d, J_{CF} = 24 Hz), 110.4 (d, J_{CF} = 4 Hz), 126.18, 126.23, 129.3, 137.4, 153.8 (d, J_{CF} = 284 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 24.4 (t, J_{FH} = 5 Hz). IR (neat): ν 2970, 2854, 1704, 912, 733, 650 cm^{-1}. HRMS (EI): m/z Calcd for $C_{15}H_{19}FO$ $[M]^+$: 234.1420; Found: 234.1428.

4-(4-Chlorophenyl)-2,2-diethyl-3-fluoro-2,5-dihydrofuran (4k)

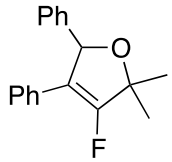


3-Fluoro-2,5-dihydrofurans **4k** was synthesized by the method described for **4a** using potassium hydride (9.2 mg, 0.23 mmol) and 2,2-difluorohomoallylic alcohol **1k** (42 mg, 0.15 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4k** (28 mg, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, J = 7.4 Hz, 6H), 1.66–1.71 (m, 4H), 4.88 (d, J_{HF} = 4.9 Hz, 2H), 7.28–7.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.9, 30.7 (d, J_{CF} = 4 Hz), 71.8 (d, J_{CF} = 10 Hz),

88.5 (d, J_{CF} = 23 Hz), 109.7, 127.5 (d, J_{CF} = 6 Hz), 128.6 (d, J_{CF} = 5 Hz), 128.8, 133.2, 155.0 (d, J_{CF} = 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 27.9 (t, J_{FH} = 5 Hz). IR (neat): ν 2968, 2924, 2879, 2850, 1701, 1496, 1088, 1030, 827 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{14}H_{16}ClFO$ $[M]^+$: 254.0874; Found: 254.0870.

3-Fluoro-2,2-dimethyl-4,5-diphenyl-2,5-dihydrofuran (4l)

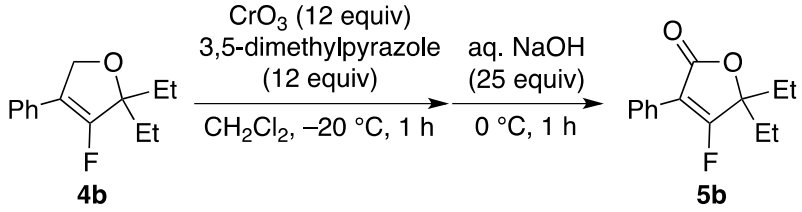


3-Fluoro-2,5-dihydrofurans **4l** was synthesized by the method described for **4a** using potassium hydride (18 mg, 0.45 mmol) and 2,2-difluorohomoallylic alcohol **1l** (*E*/*Z* = 99/1, 86 mg, 0.30 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **4l** (42 mg, 52%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 3H), 1.53 (s, 3H), 6.03 (d, J_{HF} = 4.5 Hz), 7.14–7.18 (m, 1H), 7.21–7.25 (m, 2H), 7.27–7.34 (m, 5H), 7.38–7.41 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 26.1 (d, J_{CF} = 3 Hz), 26.9 (d, J_{CF} = 3 Hz), 81.1 (d, J_{CF} = 24 Hz), 83.2 (d, J_{CF} = 10 Hz), 110.5, 127.27 (d, J_{CF} = 6 Hz), 127.30, 128.1, 128.4, 128.5, 128.7, 130.2 (d, J_{CF} = 5 Hz), 140.6, 159.7 (d, J_{CF} = 290 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 27.0 (d, J_{FH} = 5 Hz). IR (neat): ν 3064, 3030, 2978, 2927, 2886, 1695, 1496, 1448, 1142, 1016, 760, 692, 611 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{18}H_{17}FO$ $[M]^+$: 268.1263; Found: 268.1269.

6. Synthesis of 4-Fluorofuranones 5

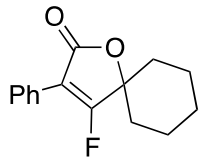
5,5-Diethyl-4-fluoro-3-phenylfuran-2(5*H*)-one (5b)



To the suspension of CrO_3 (60 mg, 0.60 mmol) in dichloromethane (0.5 mL) was added 3,5-dimethylpyrazole (59 mg, 0.61 mmol) at –20 °C. After stirring at –20 °C for 15 min, 3-fluoro-2,5-dihydrofurans **4b** (11 mg, 0.050 mmol) was added. After stirring at –20 °C for 1 h, an aqueous NaOH solution (5.0 M, 0.25 mL, 1.3 mmol) was added to the reaction mixture. Stirring at 0 °C for 1 h, the reaction was quenched with an aqueous HCl solution (2 M, 0.5 mL). Organic materials were extracted with dichloromethane 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 silica gel column chromatography (hexane/ethyl acetate/Et_3N = 20/2/1) to give **5b** (7.4 mg, 63%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.4 Hz, 6H), 1.88–2.05 (m, 4H), 7.38 (t, J = 7.4 Hz, 1H), 7.44 (dd, J = 7.4, 7.2 Hz, 2H), 7.90 (d, J = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.3, 28.4 (d, J_{CF} = 3 Hz), 84.8 (d, J_{CF} = 21 Hz), 108.1, 126.4 (d, J_{CF} = 4 Hz), 127.7 (d, J_{CF} = 5 Hz), 128.6, 129.0, 169.1 (d, J_{CF} = 23 Hz), 176.2 (d, J_{CF} = 304 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 55.0 (s). IR (neat): ν 2978, 1755, 1689, 1703, 1198, 904, 727, 650 cm^{-1}. HRMS (EI): m/z Calcd for $C_{14}H_{15}FO_2$ $[M]^+$: 234.1056; Found: 234.1045.

4-Fluoro-3-phenyl-1-oxaspiro[4.5]dec-3-ene-2-one (5h)



4-Fluorofuranone **5h** was synthesized by the method described for **5b** using CrO_3 (60 mg, 0.60 mmol), 3,5-dimethylpyrazole (59 mg, 0.62 mmol), 3-fluoro-2,5-dihydrofurans **4h** (13 mg, 0.056 mmol) and an aqueous NaOH solution (5.0 M, 0.25 mL, 1.3 mmol). Purification by silica gel column chromatography (hexane/ethyl acetate/triethylamine = 20/2/1) gave **5h** (10 mg, 76%) as a colorless oil. mp 112.4–113.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.23–1.30 (m, 2H), 1.77–1.79 (m, 6H), 1.87–1.91 (m, 2H), 7.35–7.37 (m, 1H), 7.40–7.43 (m, 2H), 7.86–7.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.5, 24.2, 32.6 (d, J_{CF} = 2 Hz), 80.7 (d, J_{CF} = 21 Hz), 105.7, 126.6 (d, J_{CF} = 5 Hz), 127.7 (d, J_{CF} = 5 Hz), 128.5, 128.9, 168.7 (d, J_{CF} = 21 Hz), 179.1, (d, J_{CF} = 305 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 55.4 (s). IR (neat): ν 2941, 2858, 1757, 1699, 1362, 1192, 1126, 958, 787, 694 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{15}H_{15}FO_2$ $[M]^+$: 246.1056; Found: 246.1061.

References

[1] Nihei, T.; Iwai, N.; Matsuda, T.; Kitazume, T. *J. Org. Chem.* **2005**, *70*, 5912–5915.

[2] Prakash, G. K. S.; Hu, J.; Alauddin, M. M.; Conti, P. S.; Olar, G. A. *J. Fluorine Chem.* **2003**, *121*, 239–243.

[3] John, J. P. and Colby, D. A. *J. Org. Chem.* **2011**, *76*, 9163–9168.

[4] Min, Q.-Q.; Yin, Z.; Feng, Z.; Guo, W.-H.; Zhang, X. *J. Am. Chem. Soc.* **2014**, *136*, 1230–1233.

[5] Sasaki, S.; Suzuki, T.; Uchiya, T.; Toyota, S.; Hirano, A.; Tanemura, M.; Teramoto, H.; Yamauchi, T.; Higashiyama, K. *J. Fluorine Chem.* **2016**, *192*, 78–85.

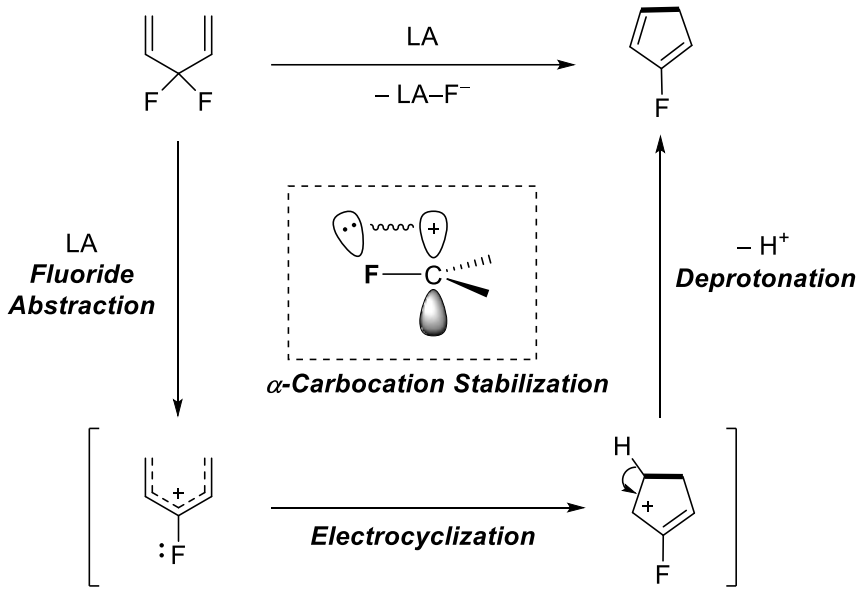
CHAPTER 3

Allylic C–F Bond Activation:

Nazarov-type Cyclization via Fluoride Abstraction

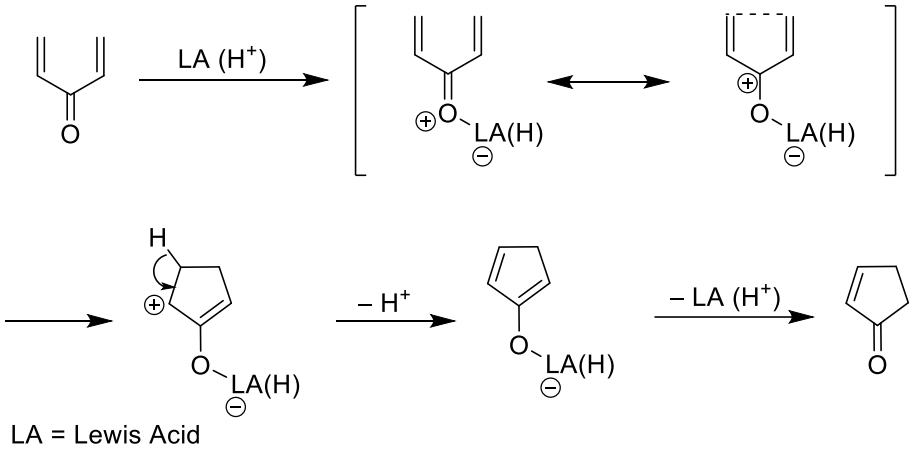
Abstract

A Nazarov-type cyclization of 3,3-difluoropenta-1,4-dienes was achieved via acid-mediated single allylic C–F bond activation. Fluoride abstraction of 3,3-difluoropenta-1,4-dienes with $BF_3 \cdot OEt_2$ or $TiCl_4$ generates fluorine-stabilized pentadienyl cation intermediates, which undergo electrocyclization followed by deprotonation to afford 2-fluorocyclopenta-1,3-dienes.

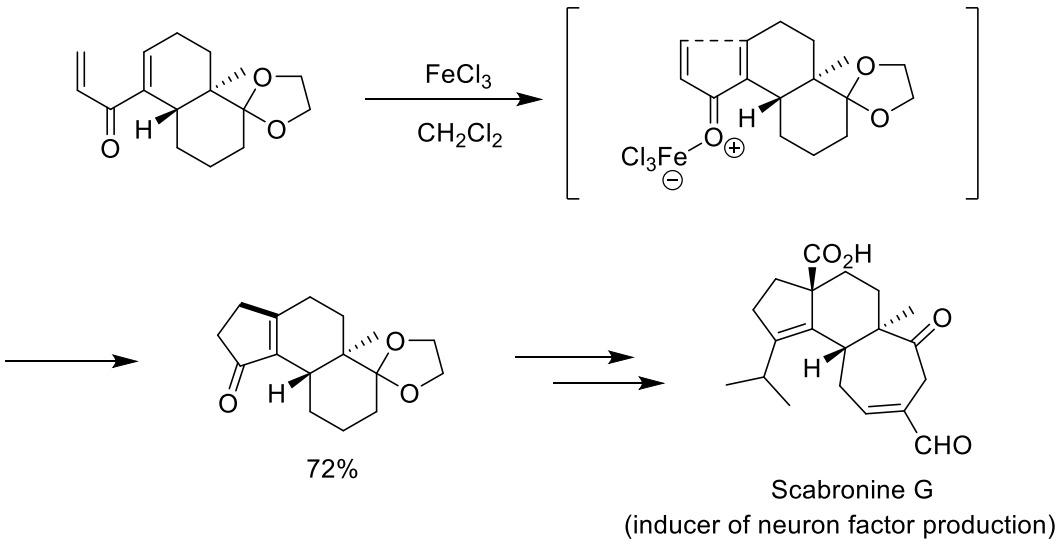


3-1. Introduction

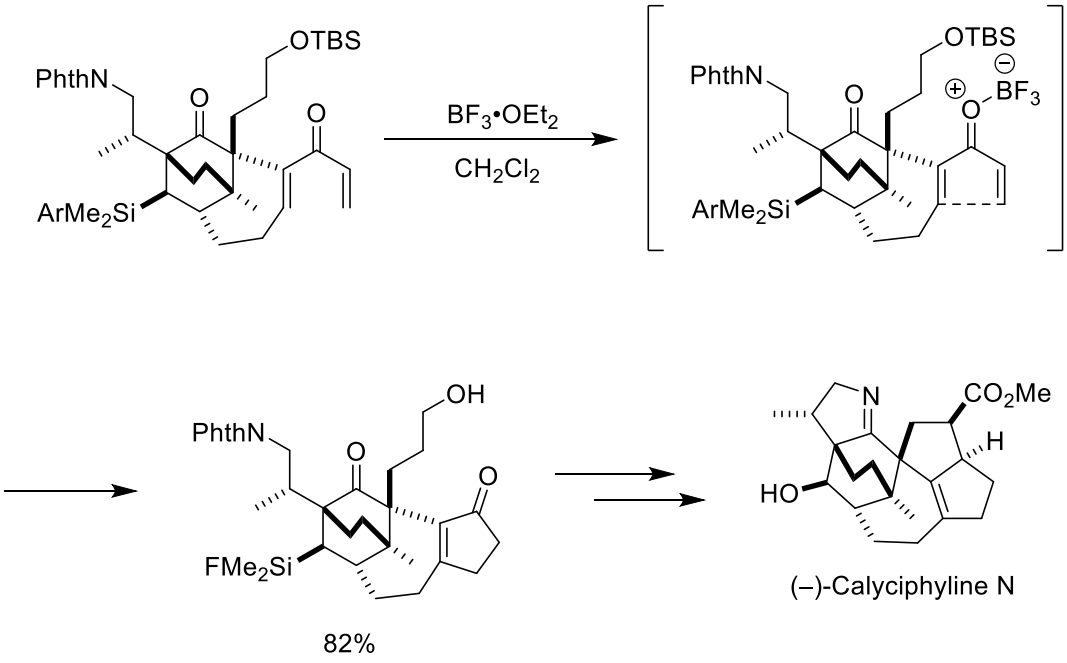
Nazarov cyclization, a representative of electrocyclic reactions, is widely used as an important method for constructing cyclopentenone frameworks. In this reaction, pentadienyl cation intermediates bearing four π-electrons, generated from divinyl ketones and Lewis or Brønsted acids, undergo electrocyclization followed by deprotonation to afford cyclopentenones (Scheme 3-1).[1,2] Due to its reliability, Nazarov cyclization is often utilized in the syntheses of natural products including five-membered carbocyclic rings. For example, in the total synthesis of scabronine G, which is an inducer of neurotrophic factor production, the construction of the cyclopentene ring was conducted via Nazarov cyclization. (eq 3-1).[3] Similarly, Nazarov cyclization is also adopted in the synthesis of (−)-calyciphylline N (eq 3-2).[4]



Scheme 3-1. Nazarov cyclization

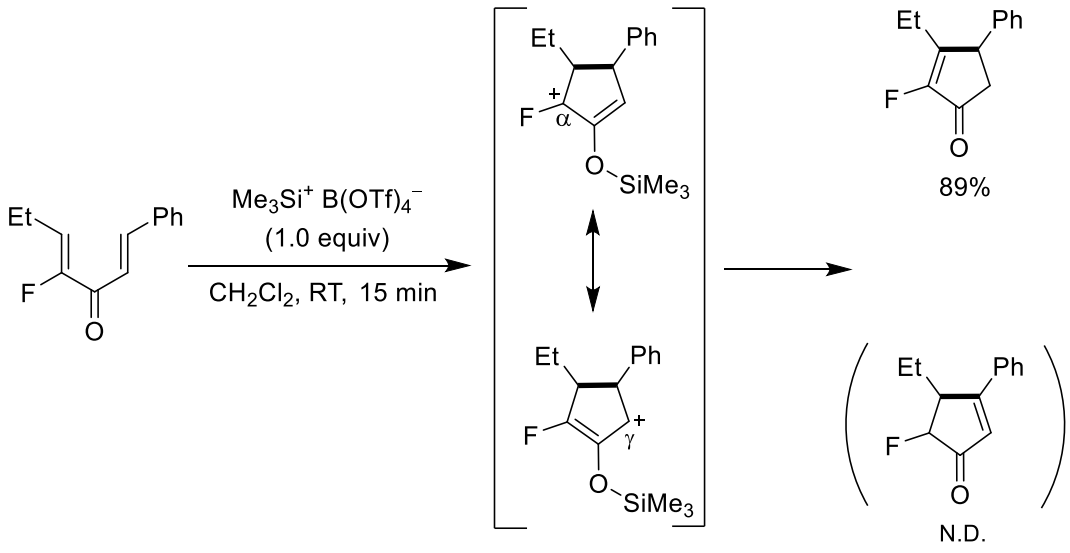


(3-1)



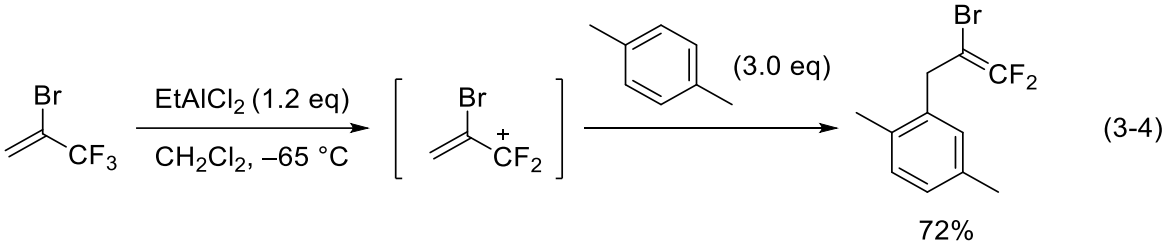
(3-2)

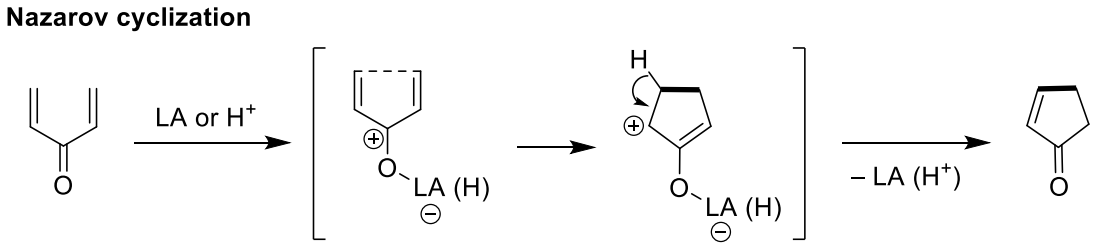
Despite the utility of Nazarov cyclization, it has a problem in controlling the regioselectivity of the double bonds in the products. To solve this problem, our group has used the properties of fluorine substituents. For example, the Nazarov cyclization of α-fluorovinyl vinyl ketones affords 2-fluorocyclopentenones with perfect regioselectivity, where a double bond is placed in the ring by deprotonation from the cyclopentenyl cation intermediates bearing a delocalized cationic carbon α to the fluorine, due to its α-carbocation stabilizing effect (eq 3-3).[5]

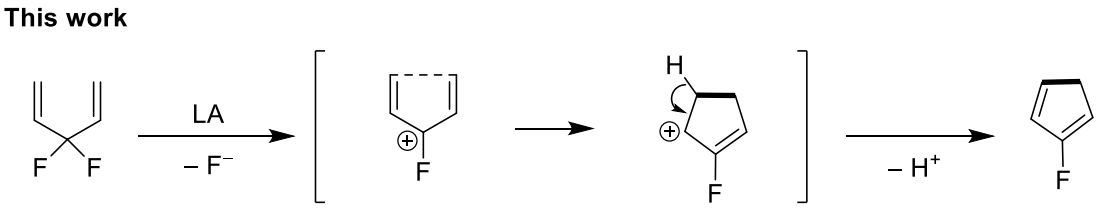


(3-3)

Meanwhile, our group has achieved single allylic C–F bond activation via acid-mediated fluoride abstraction. In this reaction, fluoride abstraction from (trifluoromethyl)alkenes is promoted with $EtAlCl_2$ to generate fluorine-stabilized cation intermediates, which undergo Friedel–Crafts-type C–C bond formation with arenes to afford (difluoroallyl)arenes (eq 3-4).[6] Inspired by the reactions described above, I assumed that a Nazarov-type electrocyclization of fluorine-stabilized pentadienyl cation intermediates would be possible by starting from 3,3-difluoropenta-1,4-dienes as substrates. Similar to the above reaction, treatment of 3,3-difluoropenta-1,4-dienes with appropriate Lewis acids actually generated the corresponding fluorine-stabilized pentadienyl cations, which underwent electrocyclization followed by deprotonation to afford 2-fluorocyclopenta-1,3-dienes (Scheme 3-2).





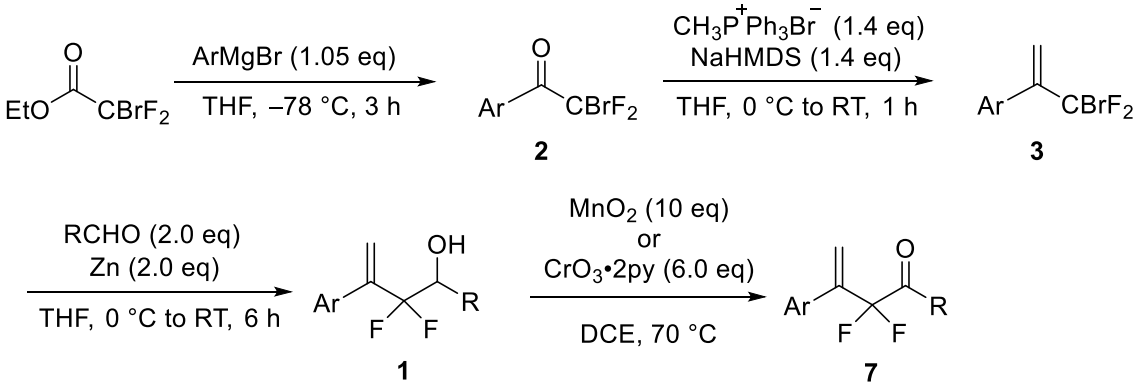


Scheme 3-2. Nazarov and Nazarov-type cyclizations via stabilized pentadienyl cations

3-2. Synthesis of 2-Fluorocyclopentadienes

3-2-1. Preparation of Precursors

Cyclization precursors, 3,3-difluoro-1,4-dienes **6** were prepared from ethyl bromodifluoroacetate as a starting material via difluorohomoallylic alcohols **1**, that is, the precursors for 3-fluorodihydrofurans (Chapter 2). According to the method described in Chapter 2, alcohols **1** were prepared by reactions of ketones or aldehydes with difluoroallylzinc reagents generated from (bromodifluoromethyl)styrenes **3**, which was obtained via addition–elimination of ethyl bromodifluoroacetate with organomagnesium reagents and subsequent Wittig methylenation (Scheme 3-3). Next, oxidation of **1** with MnO_2 or $CrO_3 \cdot 2Py$ afforded the corresponding (1,1-difluoroallyl)ketones **7**. Wittig reaction or Horner–Wadsworth–Emmons (HWE) reaction of **7** finally afforded 3,3-difluoro-1,4-dienes **6** (Table 3-1). As an alternative method, Suzuki–Miyaura coupling of (bromodifluoromethyl)styrenes **3** with vinylboronic acids or boronates also gave 1-substituted 3,3-difluoro-1,4-dienes **6af**–**6ai** (Table 3-2).

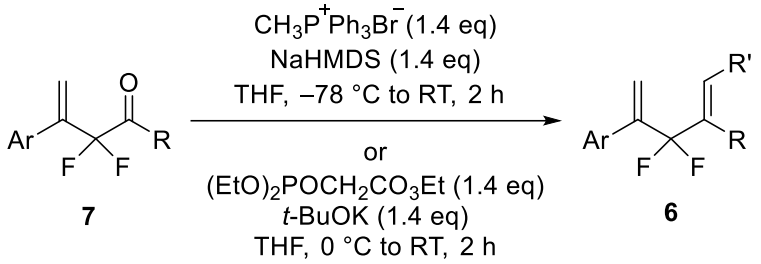


2 **3** **1** **7**

Entry	**7**	Ar	R	Yield / %
1	**7aa**	Ph	Ph	99
2	**7ab**	Ph	*p*-Tol	91
3	**7ac**	Ph	*n*-Hex	90
4	**7ad**	Ph	*i*-Pr	84
5	**7ae**	Ph	*t*-Bu	80
6	**7ba**	*p*-Tol	Ph	80
7	**7cb**	4-MeO(C_6H_4)	*p*-Tol	49

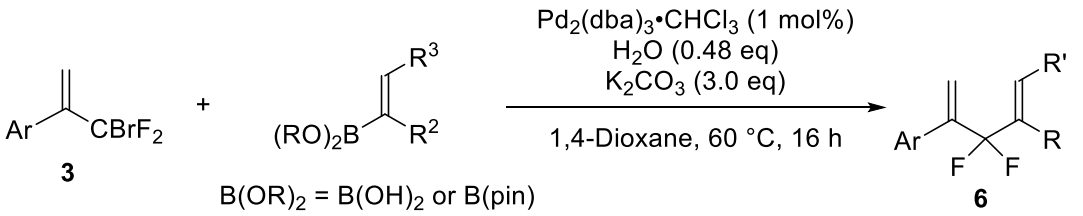
Scheme 3-3. Preparation of 2,2-difluorobut-3-en-1-ones **7**

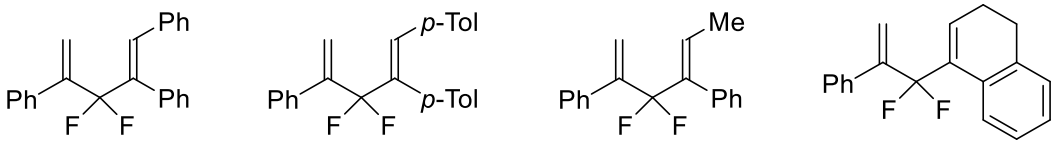
Table 3-1. Preparation of 3,3-difluoro-1,4-dienes **6aa-6cb**



Entry	6	Ar	R	R'	Yield / %
1	**6aa**	Ph	Ph	H	66
2	**6ab**	Ph	*p*-Tol	H	68
3	**6ac**	Ph	*n*-Hex	H	28
4	**6ad**	Ph	*i*-Pr	H	37
5	**6ae**	Ph	*t*-Bu	H	60
6	**6ba**	*p*-Tol	Ph	CO_2Et	80
7	**6cb**	4-MeO(C_6H_4)	*p*-Tol	CO_2Et	49

Table 3-2. Preparation of 3,3-difluoro-1,4-dienes **6af-6ai**



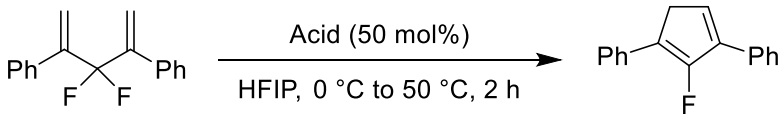


6af 95% **6ag** 82% **6ah** 61% **6ai** 31%

3-2-2. Screening of Reaction Conditions

I sought suitable conditions for the Nazarov-type reaction using 3,3-difluoro-2,4-diphenylpenta-1,4-diene (**6aa**) as a model substrate (Table 3-3). Upon treatment with trifluoromethanesulfonic acid (TfOH, Table 3-3, entry 1) or magic acid ($SbF_5 \cdot FSO_3H$, Table 3-3, entry 2) in 1,1,1-3,3,3-hexafluoropropan-2-ol (HFIP), **6aa** gave 2-fluorocyclopenta-1,3-diene **8aa** albeit in low yields. Other Brønsted acids such as hydrochloric acid (Table 3-3, entry 3) and trifluoroacetic acid (Table 3-3, entry 4) afforded no product. To improve the yield of **8aa**, various Lewis acids were screened. Among Lewis acids examined, boron trifluoride–diethyl ether complex slightly improved the yield of **8aa** up to 19% (Table 3-3, entry 5).

Table 3-3. Screening of acids



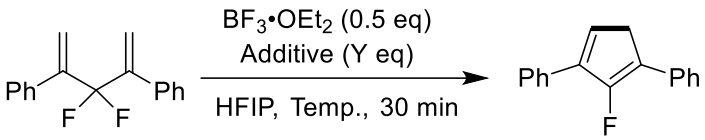
6aa **8aa**

Entry	Acid	**8aa** (%)
1	TfOH	7
2	SbF_5•FSO_3H	13
3	HCl aq. (6 M)	N.D.
4	CF_3CO_2H	N.D.
5	TiF_4	N.D.
6	ZrF_4	N.D.
7	BF_3•OEt_2	19
8	$EtAlCl_2$	N.D.
9	SbF_5	N.D.

Yield was determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

In this reaction, the concentration of proton would be increased, accompanied by the generation of the product, which might decrease the product yield. To avoid the decrease, various metal oxides were screened as proton scavengers (Table 3-4). Stoichiometric amounts of metal oxides retarded full consumption of the precursor **6aa** (Table 3-4, entries 1–5). When 0.5 equiv. of Al_2O_3 was used as a HF captor along with $BF_3 \cdot OEt_2$, **6aa** was fully converted at room temperature to afford **8aa** in a 56% yield (Table 3-4, entry 6; Method A).

Table 3-4. Screening of metal oxides



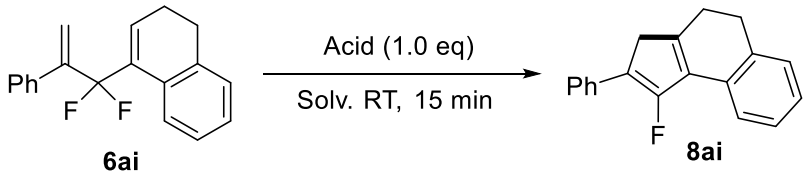
6aa **8aa**

Entry	Additive	Y	Temp.	**8aa** (%)	**6aa** (%)	
1	MgO	1.0	50 °C	45	17	
2	CuO	1.0	50 °C	25	36	
3	TiO_2	1.0	50 °C	31	18	
4	ZrO_2	1.0	50 °C	42	24	
5	Al_2O_3	1.0	50 °C	29	46	
6	Al_2O_3	0.5	RT	56	0	**Method A**

Yield was determined by ^{19}F NMR using $PhCF_3$ as an internal standard.

Further optimization using **6ai** bearing a dihydronaphthalene moiety was conducted (Table 3-5). $BF_3 \cdot OEt_2$ and TfOH gave the corresponding product **8ai** albeit in low yields (Table 3-5, entry 1, 2). While aluminum(III) chloride and titanium(IV) fluoride were ineffective for the reaction (Table 3-5, entry 3, 4), titanium(IV) chloride improved the yield of **8ai** up to 60% (Table 3-5, entry 5). Furthermore, the use of a two-phase solvent system consisting of HFIP and cyclohexane (3/2) improved the yield of **8ai** to 79% (Table 3-5, entry 6; Method B).

Table 3-5. Further optimization[a]



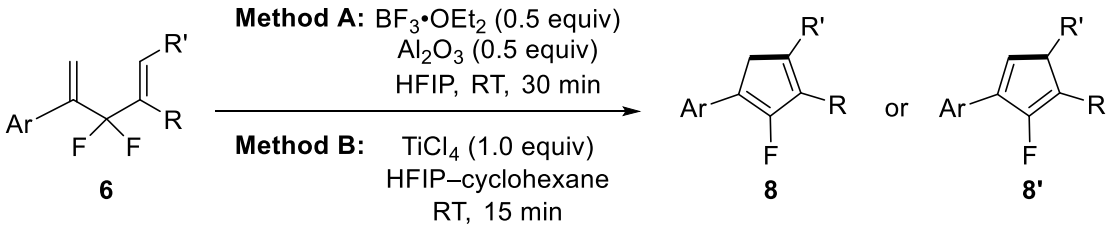
Entry	Acid	Solv.	**8ai** / %	
1	BF_3•OEt_2	$(CF_3)_2CHOH$	40[b]	**Method A**
2	TfOH	$(CF_3)_2CHOH$	23	
3	$AlCl_3$	$(CF_3)_2CHOH$	0	
4	TiF_4	$(CF_3)_2CHOH$	0	
5	$TiCl_4$	$(CF_3)_2CHOH$	60	
6	$TiCl_4$	$(CF_3)_2CHOH$–Cyclohexane (3:2)	79	**Method B**

a: Yield was determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
b: Al_2O_3 (0.5 eq) was added.

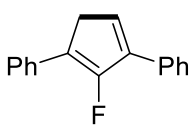
3-2-3. Substrate Scope

With optimal conditions in hand, the substrate scope was investigated using various 3,3-difluoropentadienes **6** (Table 3-6). Difluoropentadiene **6ab**, in which one phenyl group of **6aa** was replaced with a tolyl group, underwent the Nazarov-type cyclization to afford the corresponding 2-fluorocyclopentadiene **8ab** in a 30% yield as a 51:49 mixture of regioisomers. 3,3-Difluoropentadienes **6ac**–**6ae** bearing an alkyl group at the 2-position also participated in the reaction to afford **8ac**–**8ae** in 25%, 78%, and 89% yields, respectively. It is noted that *i*-propyl- and *t*-butyl-substituted **8ad** and **8ae** were obtained as a single isomer. Ethoxycarbonyl-substituted dienes **6ba** and **6cb** underwent cyclization to afford **8ba** and **8cb** in 49% and 66% yields, respectively. Although tetrasubstituted cylopentadienes **8af**–**8ah** were obtained in low yields, tricyclic compound **8ai** was successfully synthesized in a 60% isolated yield.

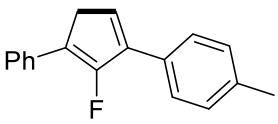
Table 3-6. Substrate scope



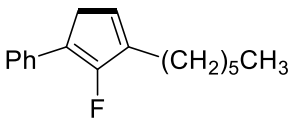
6 **8** **8'**



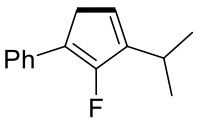
8aa 56%[a] (**A**)



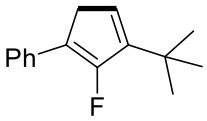
8ab 30% (51:49, **A**)



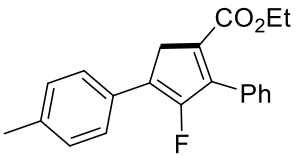
8ac 25% (80:20, **A**)



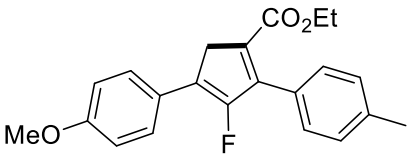
8ad 78%[a] (**A**)



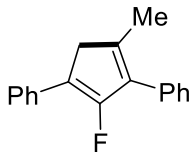
8ae 89%[a] (**A**)



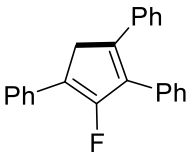
8ba 49%[a] (**B**)



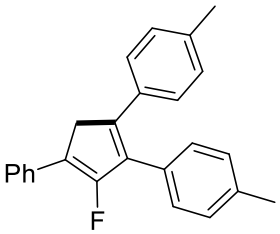
8cb 66%[a] (**B**)



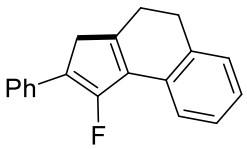
8af 21%[a] (**B**)



8ag 32%[a] (**B**)



8ah 32%[a] (**B**)



8ai 79% (60%,**B**)[a]

Yield was determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
a: Single isomer.

3-3. Summary

In summary, I demonstrated the synthesis of 2-fluorocyclopenta-1,3-dienes via the Nazarov-type cyclization of 3,3-difluoropenta-1,4-dienes, which allows single C–F bond activation. Fluoride abstraction at the allylic position was promoted by $BF_3 \cdot OEt_2$ or $TiCl_4$ to generate fluorine-stabilized pentadienyl cation intermediates. Subsequent electrocyclization followed by deprotonation gave fluorocyclopentadienes. Since methods for the construction of ring-fluorinated five-membered carbocycles have been scarcely reported, this method would be a powerful tool to create new bioactive agents and functional materials.

3-4. References

[1] (a) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429–442. (b) Ramaiah, M. *Synthesis* **1984**, 529–570. (c) Denmark, S. E. in Comprehensive Organic Synthesis, Vol. 5 (Eds.: Trost, B. M.; Fleming, I.), **1991**, 751–784. (d) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React*. **1994**, *45*, 1–158.

[2] For recent reviews on the Nazarov cyclization and its variations, see: a) West, F. G.; Scadeng, O.; Wu, Y.-K.; Fradette, R. J.; Joy, S. in Comprehensive Organic Synthesis, 2nd Ed. Vol. 5 (Eds.: Knochel, P. and Molander, G. A.), Elsevier, Amsterdam, **2014**, 827–866. b) Harmata, M.; *Chemtracts* **2004**, *17*, 416–435. c) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. d) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. e) Tius, M. A. *Chem. Soc. Rev.* **2014**, *43*, 2979–3002. f) Wenz, D. R.; Read de Alaniz, J. *Eur. J. Org. Chem.* **2015**, 23- 37. g) Simeonov, S. P.; Nunes, J. P. M.; Guerra, K.; Kurteva, V. B.; Afonso, C. A. M.; *Chem. Rev.* **2016**, *116*, 5744–5893. h) Ichikawa, J. *J. Synth. Org. Chem. Jpn.* **2010**, *68*, 1175–1184.

[3] Waters, S. P.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 13514-13515.

[4] Smith III, A. B. and Shvartsbart, A. *J. Am. Chem. Soc.* **2015**, *137*, 3510-3519.

[5] Fuchibe, K; Takayama, R.; Yokoyama, T.; Ichikawa, J. *Chem. Eur. J.* **2017**, *23*, 2831-2838.

[6] Fuchibe, K.; Hatta, H.; Ph, K.; Oki, R.; Ichikawa, J. *Angew. Chem. Int. Ed.* **2017**, *129*, 5984-5987.

3-5. Experimental Section

General

^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shift values are given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm) and C_6F_6 (for ^{19}F NMR: δ = 0.00 ppm; –164.9). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV or a JEOL JMS-T100CS spectrometer. Elemental analyses were carried out at Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. Melting points were measured on a Yanaco micro melting point apparatus and were uncorrected.

Column chromatography was conducted on Florisil (Wako Pure Chemical Industries, Ltd., 75–150 μm) or silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc., 63–210 μm). All the reactions were conducted under argon or nitrogen.

Tetrahydrofuran (THF) was purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. *N*,*N*-Dimethylformamide (DMF) was distilled from CaH_2 and stored over activated molecular sieves 4A. Potassium hydride was washed with dry hexane three times, dried under vacuum and stored in a glove box. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purifications.

Synthesis of 2,2-difluorohomoallylic alcohols **1**

To the mixture of aldehyde (1.1 mmol) and zinc powder activated with aq. HCl (2.0 mmol) in THF (1 mL) was added a THF (1 mL) solution of 3-bromo-3,3-difluoropropene **3** (1.0 mmol) at 0 °C over 30 min. Then the reaction mixture was warmed to room temperature and stirred at the same temperature for 5 h. The reaction was quenched with 2 M aq. HCl. 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 silica gel column chromatography (hexane/EtOAc = 10/1) to give 2,2-difluorohomoallilic alcohol **1**.

Synthesis of 2,2-difluoro-3-ene-1-ones **7**

To the mixture of 2,2-difluorohomoalilic alcohol **1** (1.0 mmol) in 1,2-dichloroethane (6 mL) was added manganese dioxide (10 mmol) or pyridine–chromic anhydride complex (6.0 mmol) at room temperature. Then the reaction mixture was warmed to 70 °C and stirred at the same temperature for 12 h. The reaction mixture was filtrated through a pad of celite. After removal of the solvent under reduced pressure, the residue was purified by silica gel column gel chromatography (hexane/EtOAc = 10:1) to give 2,2-difluoro-3-ene-1-one **7**.

Synthesis of 3,3-difluoro-1,4-dienes **6**

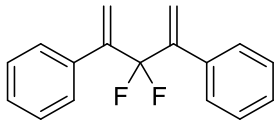
To a THF (60 mL) solution of methyltriphenylphosphonium bromide (14 mmol) was slowly added NaHMDS (1.9 M in THF, 14 mmol) at –78 °C over 0.5 h. After stirring at the same temperature for 1 h, the reaction mixture was warmed to 0 °C. After stirring at the same temperature another 1 h, a THF (10 mL) solution of 2,2-difluoro-3-ene-1-one **7** (10 mmol) was then added slowly to the reaction

mixture at 0 °C over 0.5 h. After stirring at room temperature for 1 h, the reaction was quenched 2 M aq. HCl. Organic materials were extracted with Et_2O 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 silica gel column chromatography (hexane) to give 3,3-difluoro-1,4-diene **6**.

Synthesis of 2-fluorocyclopentadienes **8**

To the mixture of 3,3-difluoro-1,4-diene **7** (0.05 mmol) and aluminum oxide (0.025 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (0.5 mL) was added $BF_3 \cdot OEt_2$ (0.025 mmol) or $TiCl_4$ (0.025 mmol) at room temperature. After stirring at the same temperature for 30 min, the reaction was quenched with triethylamine.

3,3-Difluoro-2,4-diphenylpent-1,4-diene (6aa)



IR (neat): $\tilde{\nu}$ = 3056, 1495, 1144, 1024, 933, 773, 694, 617, 536 cm^{-1}.

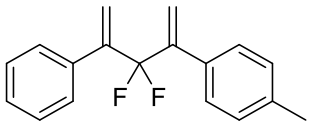
^1H NMR: δ 5.54 (d, J = 0.7 Hz, 2H), 5.75 (td, J = 1.7 Hz, J_{HF} = 0.7 Hz, 2H), 7.25–7.32 (m, 10H).

^{13}C NMR: δ 119.9 (t, J_{CF} = 246 Hz), 119.9 (t, J_{CF} = 8 Hz), 128.05, 128.09, 128.13, 136.4, 144.2 (J_{CF} = 24 Hz).

^{19}F NMR: δ 71.4 (s).

HRMS (EI+): Calcd for $C_{17}H_{14}F_2$ $[M]^+$ 256.1064, Found: 256.1072

3,3-Difluoro-2-(4'-methylphenyl)-4-phenyl-1,4-diene (6ab)



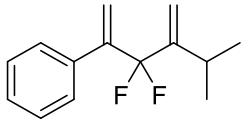
IR (neat): $\tilde{\nu}$ = 3055, 3030, 2920, 2866, 2360, 1495, 1444, 1396, 1300 cm^{-1}.

^{1}H NMR: δ 2.33 (s, 3H), 5.52 (d, J = 0.8 Hz, 1H), 5.54 (d, J = 0.8 Hz, 1H), 5.71 (td, J_{CF} = 1.3 Hz, J = 0.6 Hz, 2H), 7.08–7.31 (m, 9H).

^{13}C NMR: δ 21.1, 119.2 (t, J_{CF} = 8 Hz), 119.8 (t, J_{CF} = 8 Hz), 119.9 (t, J_{CF} = 119.9 Hz), 127.95, 128.00, 128.02, 128.11, 128.75, 133.5, 136.4, 137.9, 144.0 (t, J_{CF} = 25 Hz), 144.2 (t, J_{CF} = 25 Hz).

^{19}F NMR: δ 71.4 (s).

3,3-Difluoro-5-methyl-4-methylidene-2-phenylhex-1-ene (7ad)



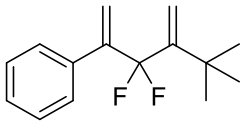
IR (neat): $\tilde{\nu}$ = 2966, 2875, 1496, 1464, 1400, 1251, 1136, 1099 cm^{-1}.

^{1}H NMR: δ 1.05 (d, J = 6.9 Hz, 6 H), 2.45 (d, J = Hz, 1H), 5.24 (d, J = 0.7 Hz, 1H), 5.45 (td, J_{HF} = 2.1 Hz, J = 0.7 Hz, 1H), 5.61 (td, J_{HF} = 1.2 Hz, J = 0.7 Hz, 1H), 5.77 (td, J_{HF} = 1.2 Hz, J = 0.7 Hz), 7.29-7.40 (m, 5H).

^{13}C NMR: δ 23.3, 28.2 (t, J_{CF} = 2 Hz), 114.6 (t, J_{CF} = 8 Hz), 119.0 (t, J_{CF} = 8 Hz), 121.2 (t, J_{CF} = 244 Hz), 128.07, 128.09, 128.10, 136.7, 144.4 (t, J_{CF} = 24 Hz), 150.5 (t, J_{CF} = 24 Hz) .

^{19}F NMR: δ 67.8 (s).

3,3-Difluoro-5,5-dimethyl-4-methylidene-2-phenylhex-1-ene (7ae)

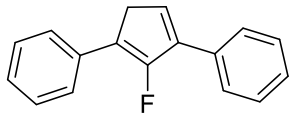


IR (neat): $\tilde{\nu}$ = 2962, 2910, 2873, 1495, 1389, 1363, 1134, 1105 cm^{-1}.

^{1}H NMR: δ 1.19 (s, 9H), 5.39 (dt, J = 5.5 Hz, J_{HF} = 2.1 Hz, 2H), 5.60 (td, J_{HF} = 1.2 Hz, J = 0.7 Hz, 1H), 5.74 (td, J_{HF} = 1.2 Hz, J = 0.7 Hz, 1H), 7.30–7.55 (m, 5H).

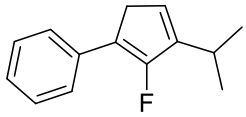
^{19}F NMR: δ 75.5 (s).

2-Fluoro-1,3-diphenylcyclopent-1,3-diene (8aa)



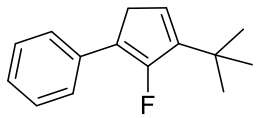
^{19}F NMR: δ 37.6 (td, J = 6 Hz, J = 6 Hz).

2-Fluoro-1-(1-methylethyl) -3-phenylcyclopent-1,3-diene (8ad)



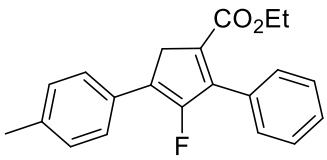
^{19}F NMR: δ 34.4 (td, J = 6 Hz, J = 6 Hz).

2-Fluoro-1-(1,1-dimethylethyl)-3-phenylcyclopent-1,3-diene (8ae)



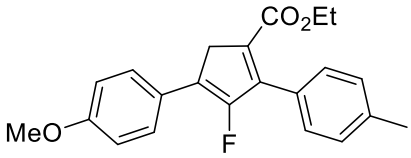
^{19}F NMR: δ 40.9 (dt, J = 7 Hz, J = 6 Hz).

Ethyl 3-fluoro-2-phenyl-4-(*p*-tolyl)cyclopenta-1,3-diene-1-carboxylate (8ba)



^{19}F NMR: δ 37.2 (t, J = 6 Hz).

Ethyl 3-fluoro-4-(4-methoxyphenyl)-2-(*p*-tolyl)cyclopenta-1,3-diene-1-carboxylate (8cb)



^{19}F NMR: δ 36.7 (t, *J* = 6 Hz).

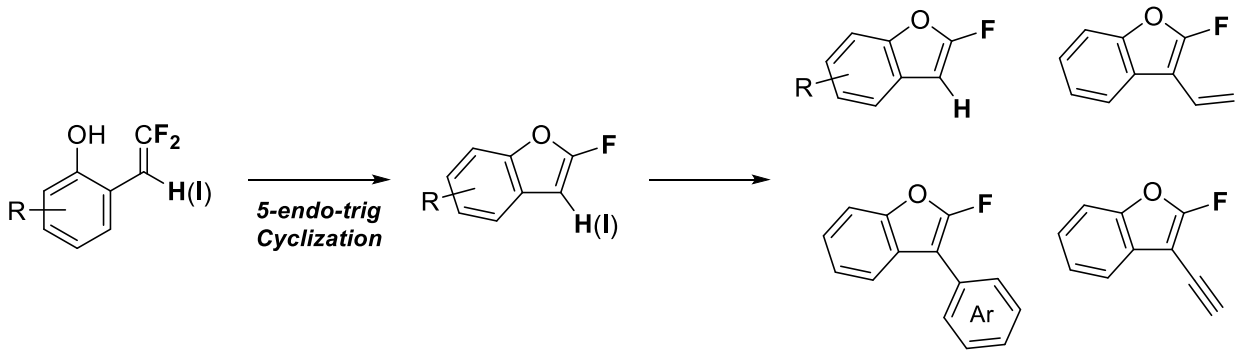
CHAPTER 4

Vinylic C–F Bond Activation:

5-*endo-trig* Cyclization of β,β-Difluoro-*o*-hydroxystyrenes

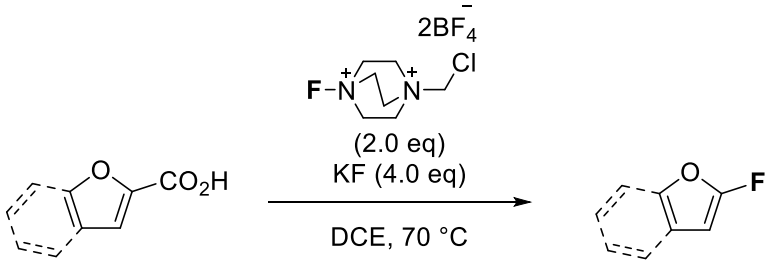
Abstract

Efficient synthetic methods were established for obtaining 2-fluorobenzofurans involving various substituents. Upon being treated with 1,8-diazabicyclo[5.4.0]undec-7-ene under microwave irradiation, the α-unsubstituted β,β-difluoro-*o*-hydroxystyrenes underwent nucleophilic 5-*endo-trig* cyclization to afford the corresponding 2-fluorobenzofurans in high yields. Furthermore, 2-fluoro-3-iodobenzofuran was successfully synthesized, and its transformation to various 3-substituted 2-fluorobenzofurans was demonstrated.

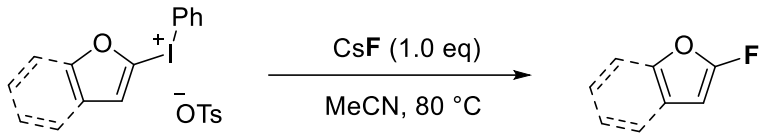


4-1. Introduction

The ring-fluorinated heterocycles have attracted considerable attention as synthetic intermediates, functional materials, and promising candidates for pharmaceuticals and agrochemicals owing to their unique characteristics, which are based on the properties of the fluorine substituent.[1] Therefore, facile and efficient methods are required to obtain ring-fluorinated heterocycles. To satisfy this requirement, direct fluorination methods have been developed till date. However, there are very few efficient methods to synthesize 2-fluorobenzofuran derivatives.[2-10] The representative examples include decarboxylative fluorination[4] using electrophilic fluorinating agents[11-14] and nucleophilic fluorination using hypervalent iodonium intermediates (eqs 4-1, 4-2).[3] Although these fluorination methods are simple approaches to obtain heterocyclic ring-fluorinated benzofurans, expensive reagents for fluorination have to be used at appropriate positions. In addition, the product yields are generally low during the fluorination processes.



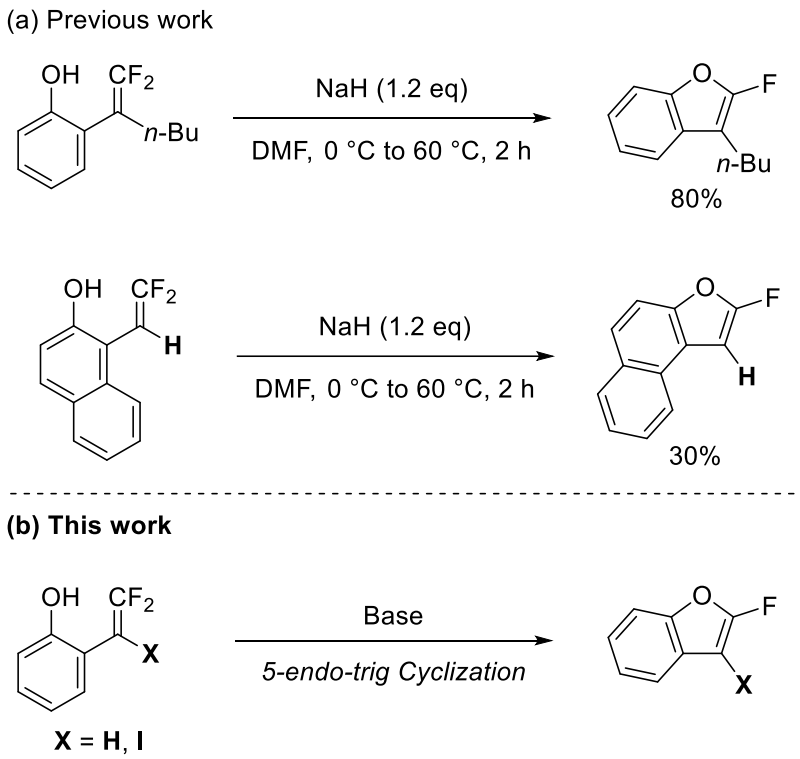
(4-1)



(4-2)

Previously, our group has developed an alternative approach to obtain ring-fluorinated heterocycles via the intramolecular cyclization of fluoroalkenes, which simultaneously induced the construction of heterocycle skeletons and regioselective installation of the fluorine substituents.[1,15-24] 5-*Endo-trig* cyclization of the β,β-difluorostyrene bearing a hydroxy group at the *ortho*-position was achieved, which leads to the synthesis of 3-alkylated 2-fluorobenzofuran (Scheme 4-1a)[20,21]. Although 5-*endo-trig* cyclization is considered to be

difficult according to Baldwin's rules[25-35], this type of cyclization is enabled by the abnormally polarized double bonds in difluoroalkenes. However, the application of this method has limitations. Specifically, moisture-sensitive NaH is required, and the method is observed to be less effective in the cyclization of substrates without substituents at the α-position such as 1-(2,2-difluorovinyl)-2-hydroxynaphthalene (Scheme 4-1a; 30% yield). Thus, we searched for a method that can be applied to various substrates by screening the reaction conditions. Finally, I established a facile method to synthesize 2-fluorobenzofurans without a substituent at the 3-position and 3-iodinated 2-fluorobenzofuran (Scheme 4-1b). In addition, 2-fluoro-3-iodobenzofuran was readily transformed to 2-fluorobenzofurans bearing unsaturated groups at the 3-position via metal-catalyzed coupling.

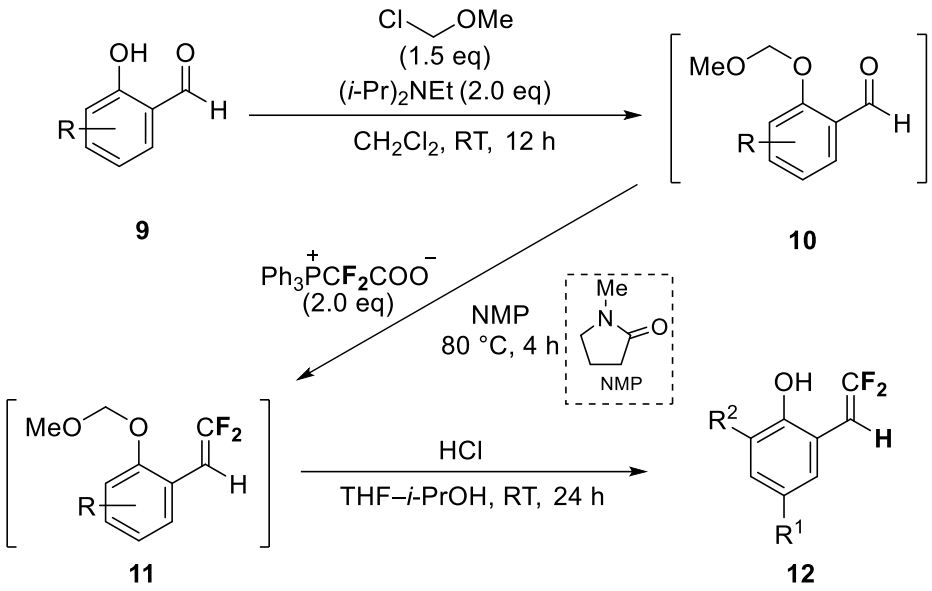


Scheme 4-1. Synthesis of 2-fluorobenzofurans via nucleophilic 5-*endo-trig* cyclization.

4-2. Synthesis of 2-Fluorobenzofurans

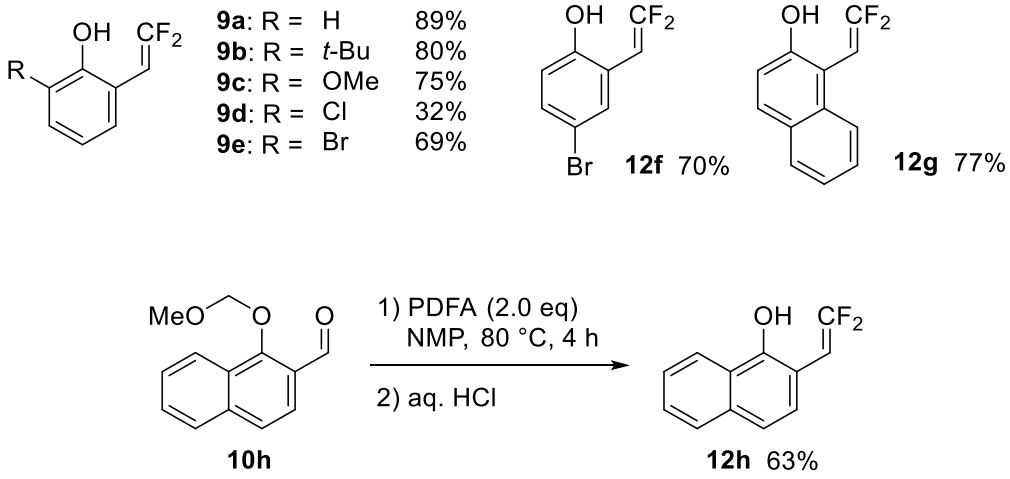
4-2-1. Preparation of Precursors and Screening

The commercially available salicylaldehydes **9** were used as the starting materials to prepare the cyclization precursors, i.e., β,β-difluoro-*o*-hydroxystyrenes **12** (Scheme 4-2, Table 4-1). After the protection of the hydroxy group by the methoxymethyl (MOM) group, the resulting aldehydes **10** were subjected to difluoromethylidenation with $Ph_3P^+CF_2CO_2^-$ (PDFA)[36] and then deprotected with aqueous hydrochloric acid. In this sequence, the intermediary aldehydes **10** and difluorostyrenes **11** were used further without purification. Thus, unsubstituted β,β-difluoro-*o*-hydroxystyrene (**12a**) and ring-substituted and naphthalene-based difluorostyrenes **12b**–**12g** were readily prepared from **9a**–**9g**. The naphthalene-based difluorostyrene **12h** was obtained from **10h**, which was prepared via the MOM-protection of 1-naphthol and subsequent formylation (Scheme 4-3).[37] The aryl substituents of β,β-difluoro-*o*-hydroxystyrenes **12i**–**12k** were installed via the Suzuki–Miyaura coupling[38] of the bromine-bearing MOM-protected salicylaldehyde **10e** and difluorostyrenes **11f** with arylboronic acids (Scheme 4-4). In addition, β,β-difluoro-*o*-hydroxy-α-iodostyrene (**12l**) was prepared from 1,1,1-trifluoro-2-iodoethane (**13**, Scheme 4-5).[39] The Negishi coupling of 1-iodo-2-methoxybenzene with a 2,2-difluoro-1-iodovinylzinc reagent, which was generated by the treatment of **13** with lithium diisopropylamide (LDA) and $ZnCl_2$, gave β,β-difluoro-α-iodo-*o*-methoxystyrene (**14**). The subsequent demethylation of **14** with BBr_3 afforded **12l**.

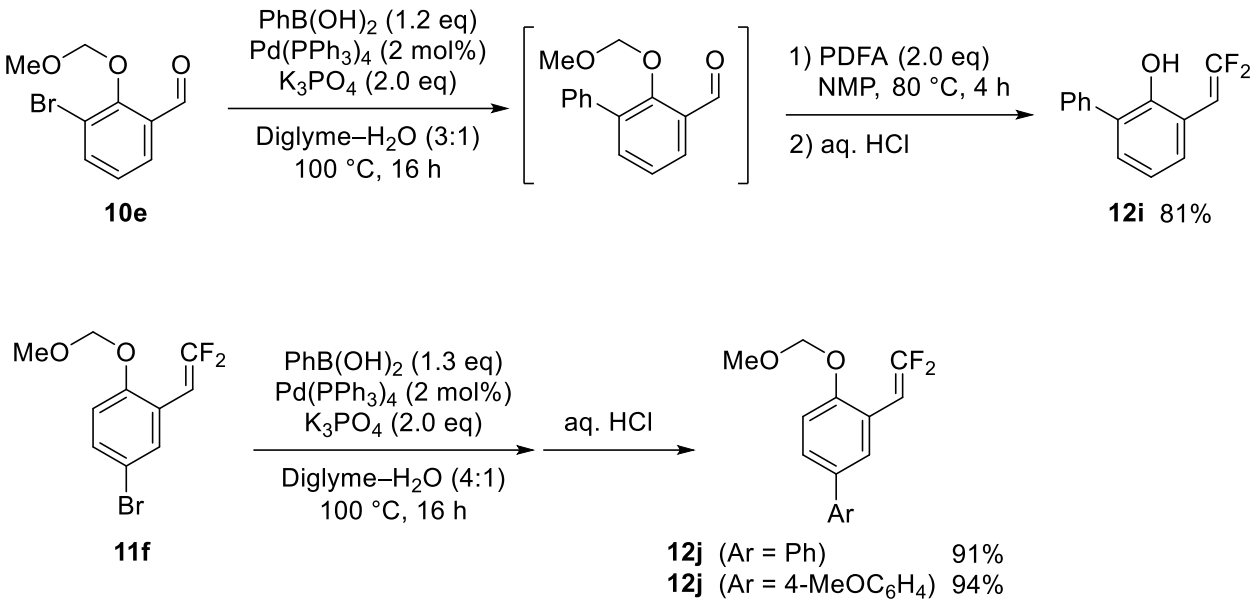


Scheme 4-2. One-pot procedure for the preparation of β,β-difluoro-*o*-hydroxystyrenes **12** from salicylaldehydes **13**.

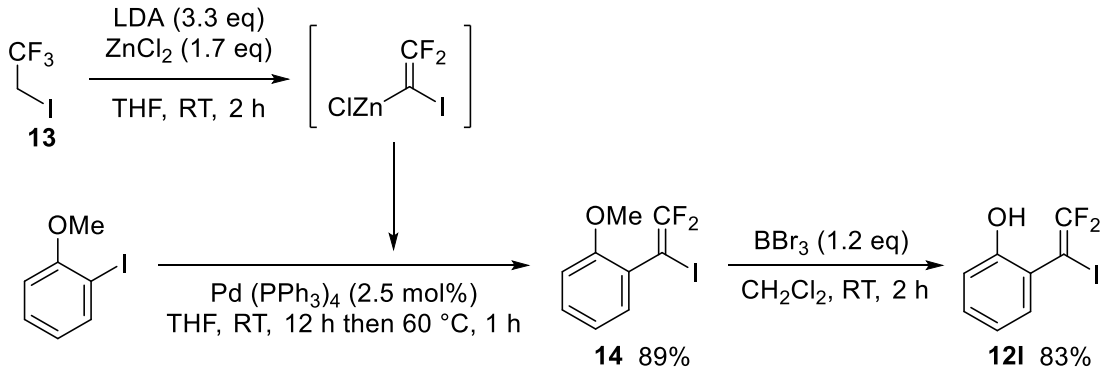
Table 4-1. Synthesis of precursors



Scheme 4-3. Preparation of naphthalene-based β,β-difluoro-*o*-hydroxystyrene **12h**.



Scheme 4-4. Preparation of arylated β,β-difluoro-*o*-hydroxystyrenes **12i**–**12k**.

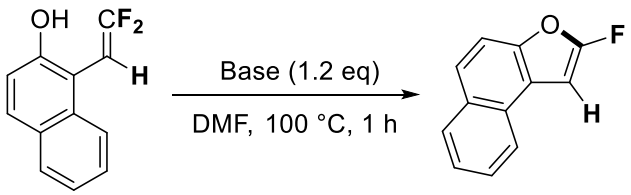


Scheme 4-5. Preparation of β,β-difluoro-*o*-hydroxy-α-iodostyrene (**12l**).

4-2-2. Screening of Reaction Conditions

First, I sought suitable conditions for 5-*endo-trig* cyclization of α-unsubstituted β,β-difluoro-*o*-hydroxystyrenes using **12g** as a model substrate (Table 4-2). Upon the treatment with NaH, which was the best base in the nucleophilic 5-*endo-trig* cyclization of α-alkylated β,β-difluoro-*o*-hydroxystyrene, **12g** underwent cyclization at 100 °C to afford fluoronaphthofuran **15g** in a 47% yield (Entry 1). When other sodium and potassium salts were examined (Entries 2–4), KO*t*-Bu gave a better yield (Entry 4). Among organic bases examined (Entries 5–7), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) specifically promoted the cyclization to improve the yield of **15g** up to 72% (Entry 7).[40] Consequently, the use of DBU under microwave irradiation afforded **15g** in a 83% yield (Entry 8).

Table 4-2. Screening of bases for nucleophilic 5-*endo-trig* cyclization of **12g**.



12g **15g**

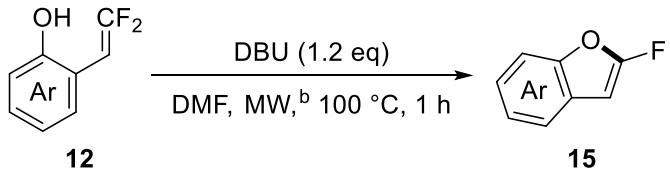
Entry	Base	**15g** / %[a]
1	NaH	47
2	NaOEt	9
3	K_3PO_4	42
4	KO*t*-Bu	62
5	*i*-Pr_2NEt	N.D.[b]
6	Pyridine	N.D.[b]
7	DBU	72
8[c]	DBU (Microwave)	83

a: Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard.
b: N.D. = Not detected
c: The reaction was conducted under microwave irradiation

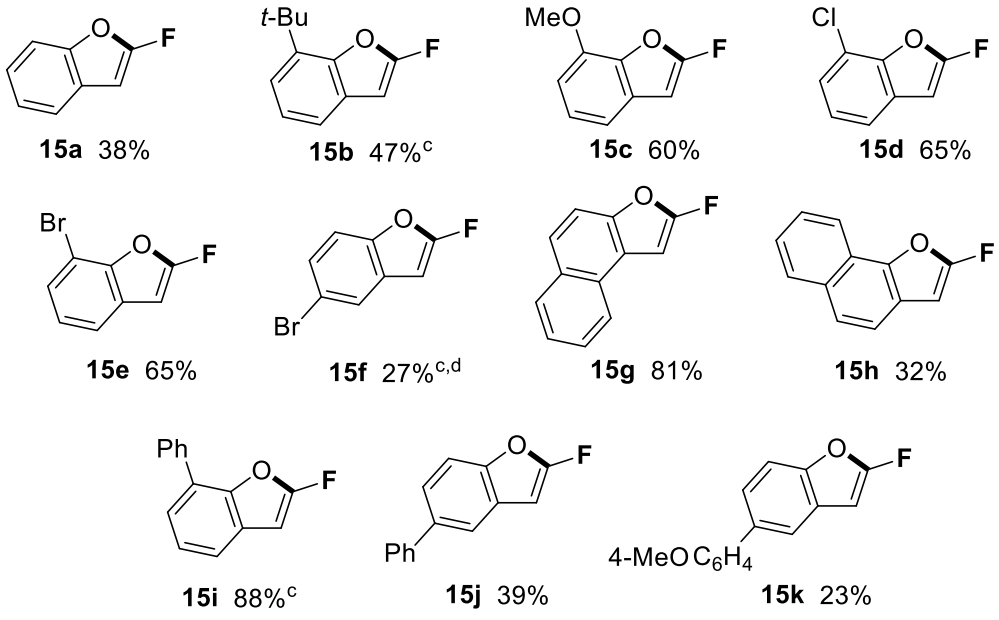
4-2-3. Substrate Scope

The optimal conditions for the 5-*endo*-*trig* cyclization obtained above were successfully applied to other α-unsubstituted β,β-difluoro-*o*-hydroxystyrenes (Table 4-3). Simple β,β-difluoro-*o*-hydroxystyrene (**12a**) underwent cyclization to afford 2-fluorobenzofuran (**15a**) in a 38% yield. Electron-donating 3-(*t*-butyl)- and 3-methoxy-substituted difluorostyrenes **12b** and **12c** were applicable in cyclization to afford the corresponding 2-fluorobenzofurans **15b** and **15c** in 47% and 60% yields, respectively. The cyclization of difluorostyrenes **12d**–**12f** bearing a chlorine or bromine substituent proceeded without the cleavage of the C–Cl or C–Br bond. Naphthalene-based difluorostyrenes **12g** and **12h** underwent cyclization to afford fluorinated naphthofurans **15g** and **15h** in 81% and 32% yields, respectively. 7-Phenylated, 5-phenylated, and 5-*p*-anisylated 2-fluorobenzofurans **15i**–**15k** were obtained in 88, 39, and 23% yields from arylated β,β-difluoro-*o*-hydroxystyrenes **12i**–**12k**, respectively.

Table 4-3. Synthesis of 2-fluorobenzofurans **15** bearing no substituent at the 3-position[a]



12 **15**



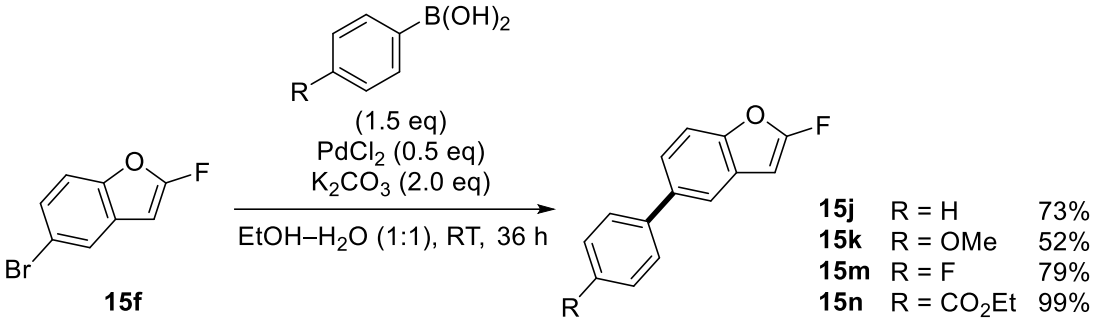
15a 38% **15b** 47%[c] **15c** 60% **15d** 65%

15e 65% **15f** 27%[c,d] **15g** 81% **15h** 32%

15i 88%[c] **15j** 39% **15k** 23%

a: Isolated yield. b: Under microwave irradiation.
c: 20 min d: Nitromethane was used as a solvent. MS 3A was added.

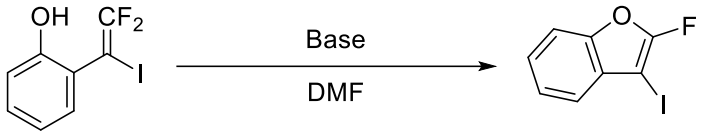
5-Arylated 2-fluorobenzofurans were also synthesized via the Suzuki–Miyaura coupling of 5-bromo-2-fluorobenzofuran (**15f**) with arylboronic acids (Scheme 4-6). In the presence of a palladium catalyst, the treatment of **15f** with phenyl- and *p*-anisylboronic acids afforded the corresponding 2-fluorobenzofurans **15j** and **15k**, respectively. Furthermore, fluorine-, and ethoxycarbonyl-bearing benzene rings were successfully installed, which led to the synthesis of 5-arylated 2-fluorobenzofurans **15m** and **15n**. Thus, this protocol can be used as a substitute for the former one (Table 4-3), which requires pre-arylation of cyclization precursors **12**.



Scheme 4-6. Synthesis of 5-aryl-2-fluorobenzofurans **15j**, **15k**, **15m**, **15n**.

To broaden the scope, the 5-*endo-trig* cyclization of β,β-difluoro-*o*-hydroxy-α-iodostyrene (**12l**) was examined for the synthesis of 2-fluoro-3-iodobenzofuran (**15l**), which would serve as a precursor of 3-substituted 2-fluorobenzofurans (Table 4-4). While the abovementioned optimal conditions for the synthesis of 3-unsubstituted 2-fluorobenzofurans afforded **15l**, albeit in a 24% yield (Entry 1), a comparable yield of **15l** was observed at 0 °C even without microwave irradiation (Entry 2). Thus, several lithium, sodium, and potassium bases (Entries 3–8) were examined at 0 °C without microwave irradiation. It was determined that $LiOH·H_2O$ was the best base for the cyclization of **12l** to afford **15l** in a 63% isolated yield (Entry 5).

Table 4-4. Screening of conditions for nucleophilic 5-*endo-trig* cyclization of **12l**.

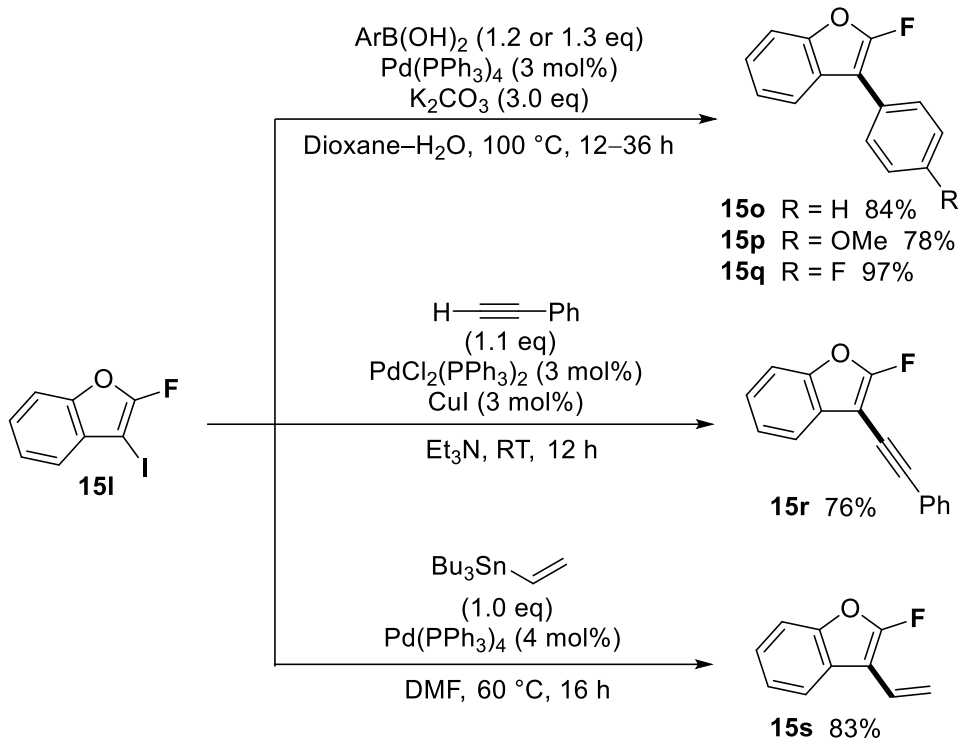


12l **15l**

Entry	Base	Conditions	Yield / %[a]
1	DBU (1.2 eq)	MW, 100 °C, 1 h	24
2	DBU (1.2 eq)	0 °C, 4 h	22
3	NaH (1.2 eq)	0 °C, 4 h	37
4	KH (1.2 eq)	0 °C, 4 h	7
5	$LiOH•H_2O$ (1.05)	0 °C, 4 h	67(63)[b]
6	LiOH (1.05)	0 °C, 4 h	48
7	NaOH (1.05)	0 °C, 4 h	36
8	KOH (1.05)	0 °C, 4 h	34

a: Yield was determined by ^{19}F NMR measurement using $PhCF_3$ as an internal standard.
b: Isolated yield.

Thus, the further transformation of **15l** was achieved via metal-catalyzed coupling. The Suzuki–Miyaura coupling of **15l** with arylboronic acids effectively proceeded to afford 3-arylated 2-fluorobenzofurans **15o**–**15q** in high yields (Scheme 4-7). This protocol compensates cyclization of pre-arylated precursors as a method for the synthesis of 3-aryl-2-fluorobenzofurans, because cyclization of β,β-difluoro-*o*-hydroxy-α-phenylstyrene with NaH, DBU, or $LiOH·H_2O$ afforded 2-fluoro-3-phenylbenzofuran **15o** only in a 33, 15, or 24% yield, respectively. In addition, **15l** underwent Sonogashira coupling and Stille coupling with phenylacetylene and tributyl(vinyl)stannane, which readily afforded the corresponding 3-alkynylated and 3-alkenylated 2-fluorobenzofurans **15r** and **15s** in 76% and 83% yields, respectively.



Scheme 4-7. Synthesis of 3-substituted 2-fluorobenzofurans **15o**–**15s**.

4-3. Summary

In summary, I demonstrated an efficient synthesis of various 2-fluorinated benzofurans via 5-*endo-trig* cyclization of β,β-difluoro-*o*-hydroxystyrenes, which were readily prepared (i) via difluoromethylidenation of salicylaldehydes with PDFA or (ii) via difluoroiodovinylation of iodoanisoles with 1,1,1-trifluoro-2-iodoethane. In addition, the obtained ring-halogenated 2-fluorobenzofurans were subjected to metal-catalyzed coupling with organometallic reagents to expand the availability of substituted 2-fluorobenzofurans.[2-5] The method shown here allows to systematically synthesize 2-fluorobenzofurans with various substituents; these compounds are expected to be bioactive agents and organic semiconductors.[1-10]

4-4. References

[1] Nenajdenko, V. ed. 'Fluorine in Heterocyclic Chemistry vol. 1 and 2', Springer, Heidelberg, **2014**.

[2] Nash, S. A.; Gammill, R. B. *Tetrahedron Lett*. **1987**, *28*, 4003-4006.

[3] Martín-Santamaría, S.; Carroll, M. A.; Carroll, C. M.; Carter, C. D.; Pike, V. W.; Rzepa, H. S.; Widdowson, H. A. *Chem. Commun*. **2000**, 649-650.

[4] Yuan, X.; Yao, J.-F.; Tang, Z.-Y. *Org. Lett*. **2017**, *19*, 1410-1413.

[5] Lu, B.; Shen, X.; Zhang, L.; Liu, D.; Zhang, C.; Cao, J.; Shen, R.; Zhang, J.; Wang, D.; Wan, H.; Xu, Z.; Ho, M.-H.; Zhang, M.; Zhang, L.; He, F.; Tao, W. *ACS Med. Chem. Lett*. **2018**, *9*, 98-102.

[6] Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Pechet, M. M. *J. Chem. Soc. Perkin Trans*. *1* **1977**, 2604-2608.

[7] Wang, M.; Liu, X.; Zhou, L.; Zhu, J.; Sun, X. *Org. Biomol. Chem.* **2015**, *13*, 3190-3193.

[8] Milner, P. J.; Yang, Y.; Buchwald, S. L. *Organometallics* **2015**, *34*, 4775-4780.

[9] Hariss, L.; Bouhadir, K. H.; Roisnel, T.; Grée, R.; Hachem, A. *Synlett* **2017**, *28*, 195-200.

[10] Narayanam, M. K.; Ma, G.; Champagne, P. A.; Houk, K. N.; Murphy, J. M. *Synlett* **2018**, *29*, 1131-1135.

[11] Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431-12477.

[12] Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res*. **2004**, *37*, 31-44.

[13] Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192-212.

[14] Kiselyov, A. S. *Chem. Soc. Rev*. **2005**, *34*, 1031-1037.

[15] Ichikawa, J. *Pure Appl. Chem.* **2000**, *72*, 1685-1689.

[16] Ichikawa, J.; Wada, Y.; Fujiwara, M.; Sakoda, K. *Synthesis* **2002**, 1917-1936.

[17] Ichikawa, J. *Chim. Oggi*. **2007**, *25*, 54-57.

[18] Ichikawa, J. *J. Synth. Org. Chem. Jpn*. **2010**, *68*, 1175-1184

[19] Fujita, T.; Ichikawa, J. *Heterocycles* **2017**, *95*, 694-714.

[20] Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.* **1997**, 1537-1538.

[21] Ichikawa, J.; Fujiwara, M.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun*. **2000**, 1887-1888.

[22] Fujita, T.; Morioka, R.; Arita, T.; Ichikawa, J. *Chem. Commun*. **2018**, *54*, 12938-12941.

[23] Fujita, T.; Hattori, M.; Matsuda, M.; Morioka, R.; Jankins, T. C.; Ikeda, M.; Ichikawa, J. *Tetrahedron* **2019**, *75*, 36-46.

[24] Fuchibe, K.; Fushihara, K.; Ichikawa, J. *Org. Lett*. **2020**, *22*, 2201-2205.

[25] Baldwin, J. E. *J. Chem. Soc. Chem. Commun*. **1976**, 734-736.

[26] Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Commun*. **1976**, 736-738.

[27] Johnston, C. P.; Kothari, A.; Sergeieva, T.; Okovytyy, S. L.; Jackson, K. E.; Paton, R. S.; Smith, M. D. *Nat. Chem.* **2015**, *7*, 171-177.

[28] Kapoorr, R.; Singh, S. N.; Tripathi, S.; Yadav, L. D. S. *Synlett* **2015**, *26*, 1201-1206.

[29] Sharma, K.; Wolstenhulme, J. R.; Painter, P. P.; Yeo, D.; Grande-Carmona, F.; Johnston, C. P.; Tantillo, D. J.; Smith, M. D. *J. Am. Chem. Soc.* **2015**, *137*, 13414-13424.

[30] Williams, B. M.; Trauner, D. *Angew. Chem. Int. Ed*. **2016**, *55*, 2191-2194.

[31] Markwell-Heys, A. W. and George, J. H. *Org. Biomol. Chem.* **2016**, *14*, 5546-5549.

[32] Xiao, T.; Li, L.; Zhou, L. *J. Org. Chem*. **2016**, *81*, 7908-7916.

[33] Zhang, B.; Zhang, X.; Hao, J.; Yang, C. *Org. Lett*. **2017**, *19*, 1780-1783.

[34] Hao, J.; Milcent, T.; Retailleau, P.; Soloshonok, V. A.; Ongeri, S.; Crousse, B. *Eur. J. Org. Chem.* **2018**, 3688-3692.

[35] Zhang, X.; He, J.; Cao, S. *Asian J. Org. Chem.* **2019**, *8*, 279-282.

[36] Zheng, J.; Cai, J.; Lin, J.-H.; Guo, Y.; Xiao, J.-C. *Chem. Commun.* **2013**, *49*, 7513-7515.

[37] Guo, Z.-Q.; Chen, W.-Q.; Duan, X.-M. *Org. Lett.* **2010**, *12*, 2202-2205.

[38] Takeuchi, D.; Chiba, Y.; Takano, S.; Osakada, K. *Angew. Chem. Int. Ed*. **2013**, *52*, 12536-12540.

[39] Anilkumar, R. and Burton, D. J. *J. Fluorine Chem.* **2005**, *126*, 457-463.

[40] When 4-(2,2-difluorovinyl)-1,1'-biphenyl, a β,β-difluorostyrene bearing no nucleophilic hydroxy group, was treated with DBU in DMF at 100 °C for 1 h, the difluorostyrene was completely consumed. Thus, initial defluorinative substitution of β,β-difluoro-o-hydroxystyrenes with DBU might proceed prior to the cyclization, which could promote subsequent 5-endo-trig cyclization. In addition, the possibility that further isomerization into the iminium intermediate allows 5-exo-trig cyclization (formal 5-endo-trig cyclization) cannot be ruled out.

[41] Aitken, H. R. M.; Furkert, D. P.; Hubert, J. G.; Wood, J. M.; Brimble, M. A. *Org. Biomol. Chem.* **2013**, *11*, 5147-5155.

[42] Harvey, R. G.; Cortez, C.; Ananthanarayan, T. P.; Schmolka, S. *J. Org. Chem.* **1988**, *53*, 3936-3943.

[43] Landelle, G.; Turcotte-Savard, M.-O.; Marterer, J.; Champagne, P. A.; Paquin, J.-F. *Org. Lett*. **2009**, *11*, 5406-5409.

4-5. Experimental Section

General

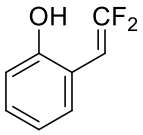
^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance 500. Chemical shift values are given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_6 (for ^{19}F NMR: δ = 0.00 ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV spectrometer. Elemental analyses were carried out at the Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. Microwave experiments were conducted in a CEM Discover or a PreeKem APEX.

Column chromatography was conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc.). N,N-

Dimethylformamide (DMF), dichloromethane, and tetrahydrofuran (THF) was purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. 1,4-Dioxane and ethanol were distilled from sodium and stored over activated molecular sieves 4A or 3A. Dimethoxyethane, diglyme, and triethylamine were distilled from CaH_2 and stored over activated molecular sieves 4A. (Triphenylphosphonio)difluoroacetate (PDFA) was prepared according to the literature procedure.[36] Methoxymethyl-protected salicylaldehyde **10e**[41] and hydroxynaphthaldehyde **10h**[42] and β,β-difluoro-α-iodo-o-methoxystyrenes (**14I**)[43] were prepared according to the literature procedures. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purifications.

Preparation of β,β-Difluoro-o-hydroxystyrenes **12**

Typical Procedure 1: Preparation of 2-(2,2-Difluorovinyl)phenol (**12a**)



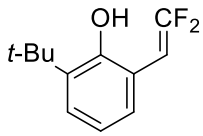
To a dichloromethane (30 mL) solution of salicylaldehyde (1a, 1.57 mL, 15.0 mmol) and chloromethyl methyl ether (1.71 mL, 22.5 mmol) was added diisopropylethylamine (5.25 mL, 30.1 mmol). After stirring at room temperature for 12 h, water (30 mL) was added to the reaction mixture. Organic materials were extracted with dichloromethane (20 mL) three times. The combined extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a crude mixture including **10a**.

To a N-methylpyrrolidone (30 mL) solution of the obtained crude mixture was added PDFA (10.7 g, 30.0 mmol). After stirring at 80 °C for 4 h, water (150 mL) was added to the reaction mixture. Organic materials were extracted with diethyl ether (20 mL) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, aqueous HCl (6.0 M, 15 mL), isopropyl alcohol (15 mL), and THF (15 mL) were added to the residue including **11a**. After stirring at room

temperature for 24 h, organic materials were extracted with dichloromethane (20 mL) 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 silica gel column chromatography (hexane/diethyl ether = 10/1) to give **12a** (2.08 g, 89%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 (s, 1H), 5.54 (dd, J_{HF} = 26.4, 4.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.91 (dd, J = 8.0, 7.8 Hz, 1H), 7.09 (ddd, J = 7.8, 7.8, 1.5 Hz, 1H), 7.39 (ddd, J = 7.8, 1.5, 1.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 75.8 (dd, J_{CF} = 31, 14 Hz), 115.4, 117.4 (dd, J_{CF} = 6, 6 Hz), 121.2, 128.3, 128.9 (dd, J_{CF} = 2, 2 Hz), 152.2 (d, J_{CF} = 5 Hz), 156.4 (dd, J_{CF} = 298, 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.6 (dd, J_{FF} = 30 Hz, J_{FH} = 26 Hz, 1F), 79.8 (dd, J_{FF} = 30 Hz, J_{FH} = 4 Hz, 1F). IR (neat): ν 3381, 1728, 1456, 1350, 1167, 939, 750 cm^{-1}. HRMS (EI): Calcd for $C_8H_6F_2O$ $[M]^+$ 156.0387, Found 156.0387.

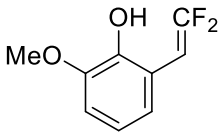
2-*tert*-Butyl-6-(2,2-difluorovinyl)phenol (**12b**)



Compound **12b** was prepared according to Typical Procedure 1 using salicylaldehyde **9b** (0.510 mL, 2.98 mmol), chloromethyl methyl ether (0.340 mL, 4.48 mmol), diisopropylethylamine (1.05 mL, 6.03 mmol), and PDFA (2.14 g, 6.01 mmol). Purification of silica gel column chromatography (hexane/diethyl ether = 10/1) gave **12b** (503 mg, 80%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 9H), 5.00 (s, 1H), 5.36 (dd, J_{HF} = 25.5, 2.8 Hz, 1H), 6.86 (dd, J = 7.9, 7.7 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.7, 34.4, 75.6 (dd, J_{CF} = 29, 16 Hz), 117.4 (dd, J_{CF} = 5, 4 Hz), 120.5, 126.4, 127.3 (dd, J_{CF} = 5, 1 Hz), 136.2, 151.7 (d, J_{CF} = 4 Hz), 156.7 (dd, J_{CF} = 297, 291 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.3 (dd, J_{FF} = 27 Hz, J_{FH} = 26 Hz, 1F), 80.5 (d, J_{FF} = 27 Hz, 1F). IR (neat): ν 3554, 2958, 1728, 1435, 1227, 1167, 964, 744 cm^{-1}. HRMS (EI): Calcd for $C_{12}H_{14}F_2O$ $[M]^+$ 212.1013, Found 212.1009.

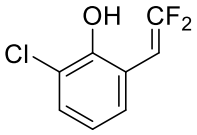
2-(2,2-Difluorovinyl)-6-methoxyphenol (**12c**)



Compound **12c** was prepared according to Typical Procedure 1 using salicylaldehyde **9c** (457 mg, 3.00 mmol), chloromethyl methyl ether (0.340 mL, 4.48 mmol), diisopropylethylamine (1.05 mL, 6.03 mmol), and PDFA (2.12 g, 5.95 mmol). Purification of silica gel column chromatography (hexane/diethyl ether = 10/1) gave **12c** (419 mg, 75%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 5.65 (dd, J_{HF} = 26.7, 4.6 Hz, 1H), 5.88 (s, 1H), 6.72 (dd, J = 8.1, 1.2 Hz, 1H), 6.81 (dd, J = 8.1, 8.1 Hz, 1H), 7.06 (dd, J = 8.1, 1.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.9, 75.9 (dd, J_{CF} = 32, 14 Hz), 109.1, 116.6 (dd, J_{CF} = 6, 6 Hz), 119.7, 120.2 (d, J_{CF} = 10 Hz), 142.7 (d, J_{CF} = 5 Hz), 146.4, 156.3 (dd, J_{CF} = 298, 287 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.3 (dd, J_{FF} = 31 Hz, J_{FH} = 5 Hz, 1F), 79.6 (dd, J_{FF} = 31 Hz, J_{FH} = 27 Hz, 1F). IR (neat): ν 3543, 1728, 1473, 1442, 1346, 1070, 966, 725 cm^{-1}. HRMS (EI): Calcd for $C_9H_8F_2O_2$ $[M]^+$ 186.0492, Found 186.0497.

2-Chloro-6-(2,2-difluorovinyl)phenol (**12d**)

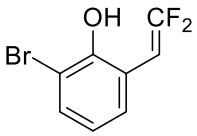


Compound **12d** was prepared according to Typical Procedure 1 using salicylaldehyde **9d** (1.20 g, 7.69 mmol), chloromethyl methyl ether (0.870 mL, 1.15 mmol), diisopropylethylamine (2.69 mL, 15.4 mmol), and PDFA (5.45 g, 15.3 mmol). Purification of silica gel column chromatography (hexane/diethyl ether = 10/1) gave **12d** (475 mg, 32%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.62 (dd, J_{HF} = 24.3, 6.1 Hz, 1H), 5.69 (s, 1H), 6.83 (dd, J = 8.0, 8.0 Hz, 1H), 7.17 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.34 (ddd, J = 8.0, 1.5, 1.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 76.0 (dd, J_{CF} = 31, 15 Hz), 118.7 (dd, J_{CF} = 5, 5 Hz), 120.1, 121.0, 127.1 (dd, J_{CF} = 9, 2 Hz), 127.3, 148.1 (d,

J_{CF} = 3 Hz), 156.5 (dd, J_{CF} = 298, 290 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.6 (dd, J_{FF} = 28 Hz, J_{FH} = 24 Hz, 1F), 80.7 (dd, J_{FF} = 28 Hz, J_{FH} = 6 Hz, 1F). IR (neat): ν 3537, 1730, 1450, 1248, 1180, 1165, 960, 856, 829, 771, 727, 712, 528 cm^{-1}. HRMS (EI): Calcd for $C_8H_5ClF_2O$ $[M]^+$ 189.9997, Found 189.9990.

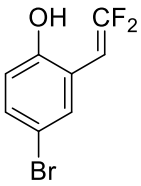
2-Bromo-6-(2,2-difluorovinyl)phenol (**12e**)



Compound **12e** was prepared according to Typical Procedure 1 using salicylaldehyde **9e** (605 mg, 3.01 mmol), chloromethyl methyl ether (0.340 mL, 4.48 mmol), diisopropylethylamine (1.05 mL, 6.03 mmol), and PDFA (2.14 g, 6.01 mmol). Purification of silica gel column chromatography (hexane/diethyl ether = 10/1) gave **12e** (486 mg, 69%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.64 (dd, J_{HF} = 25.4, 4.8 Hz, 1H), 6.79 (dd, J = 8.0, 7.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 76.3 (dd, J_{CF} = 31, 14 Hz), 110.6, 118.7 (dd, J_{CF} = 6, 6 Hz), 121.6, 127.9 (d, J_{CF} = 10 Hz), 130.4, 149.0, 156.5 (dd, J_{CF} = 298, 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.6 (dd, J_{FF} = 28 Hz, J_{FH} = 25 Hz, 1F), 80.7 (dd, J_{FF} = 28 Hz, J_{FH} = 5 Hz, 1F). IR (neat): ν 3508, 1723, 1446, 1246, 1180, 1165, 953, 768, 725, 690 cm^{-1}. HRMS (EI): Calcd for $C_8H_5{}^{79}BrF_2O$ $[M]^+$ 233.9492, Found 233.9493.

4-Bromo-2-(2,2-difluorovinyl)phenol (**12f**)

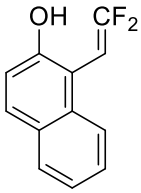


Compound **12f** was prepared according to Typical Procedure 1 using salicylaldehyde **9f** (4.02 g, 20.0 mmol), chloromethyl methyl ether (3.04 mL, 40.0 mmol), diisopropylethylamine (5.27 mL, 30.3 mmol), and PDFA (14.2 g, 40.0 mmol). Purification of silica gel column chromatography (hexane/diethyl ether = 10/1) gave **12f**

(3.30 g, 70%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.86 (s, 1H), 5.51 (dd, J_{HF} = 19.8, 10.5 Hz, 1H), 6.64 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 8.6 Hz, J = 2.4 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 75.3 (dd, J_{CF} = 26, 20 Hz), 113.2, 117.0, 119.6, 131.0, 131.3 (dd, J_{CF} = 7, 5 Hz), 151.3 (dd, J_{CF} = 3, 3 Hz), 156.5 (dd, J_{CF} = 296, 293 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 81.2–81.4 (m, 2F). IR (neat): ν 3456, 1728, 1491, 1412, 1242, 1178, 1103, 951, 806 cm^{-1}. HRMS (EI): Calcd for $C_8H_5{}^{79}BrF_2O$ $[M]^+$ 233.9492, Found 233.9492.

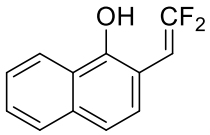
1-(2,2-Difluorovinyl)naphthalen-2-ol (**12g**)



Compound **12g** was prepared according to Typical Procedure 1 using hydroxynaphthaldehyde **9g** (1.03 g, 5.98 mmol), chloromethyl methyl ether (0.680 mL, 8.95 mmol), diisopropylethylamine (2.10 mL, 12.1 mmol), and PDFA (4.28 g, 12.0 mmol). Purification of silica gel column chromatography (hexane/diethyl ether = 10/1) gave **12g** (947 mg, 77%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.23 (s, 1H), 5.46 (d, J_{HF} = 26.8 Hz, 1H), 7.15 (d, J = 8.9, 1H), 7.35 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.48 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.73–7.77 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 72.7 (dd, J_{CF} = 29, 20 Hz), 117.4, 123.6 (d, J_{CF} = 18 Hz), 126.9, 128.3, 128.9, 130.2, 132.1, 132.8, 133.7 (d, J_{CF} = 20 Hz), 151.2, 156.2 (dd, J_{CF} = 296, 293 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.6 (d, J_{FF} = 24 Hz, 1F), 83.5 (dd, J_{FH} = 27 Hz, J_{FF} = 24 Hz, 1F). IR (neat): ν 3423, 1738, 1593, 1327, 1217, 1184, 1144, 924, 816, 752 cm^{-1}. HRMS (EI): Calcd for $C_{12}H_8F_2O$ $[M]^+$ 206.0543, Found 206.0541.

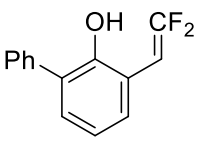
2-(2,2-Difluorovinyl)naphthalen-1-ol (**12h**)



To a *N*-methylpyrrolidone (3 mL) solution of methoxymethyl-protected hydroxynaphthaldehyde **10h** (362 mg, 1.67 mmol) was added PDFA (871 mg, 2.44 mmol). After stirring at 80 °C for 4 h, water (15 mL) was added to the reaction mixture. Organic materials were extracted with diethyl ether (6 mL) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, aqueous HCl (6.0 M, 2.0 mL), isopropyl alcohol (2 mL), and THF (2 mL) were added to the residue including **11h**. After stirring at room temperature for 24 h, organic materials were extracted with dichloromethane (6 mL) 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 silica gel column chromatography (hexane/diethyl ether = 10/1) to give **12h** (216 mg, 63%) as pale yellow crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.30 (s, 1H), 5.67 (dd, J_{HF} =26.1, 3.6 Hz, 1H), 7.45–7.56 (m, 2H), 7.48–7.53 (m, 2H), 7.79–7.81 (m, 1H), 8.03–8.05 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 76.1 (dd, J_{CF} = 30, 16 Hz), 111.0 (d, J_{CF} = 6 Hz), 120.6, 121.0, 124.2, 125.9, 126.0, 126.4, 128.0, 133.7, 147.9 (dd, J_{CF} = 5, 2 Hz), 156.5 (dd, J_{CF} = 298, 294 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.2 (dd, J_{FF} = 28 Hz, J_{FH} = 26 Hz, 1F), 80.4 (dd, J_{FF} = 28 Hz, J_{FH} = 4 Hz, 1F). IR (neat): ν 3575, 1728, 1396, 1338, 1271, 1215, 1174, 976, 806, 742 cm^{-1}. HRMS (EI): Calcd for $C_{12}H_8F_2O$ $[M]^+$ 206.0543, Found 206.0545.

3-(2,2-Difluorovinyl)-[1,1'-biphenyl]-2-ol (**12i**)

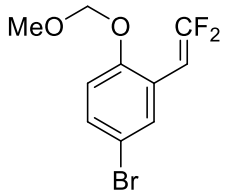


A diglyme (3 mL) and water (1 mL) solution of methoxymethyl-protected salicylaldehyde **10e** (246 mg, 1.00 mmol), phenylboronic acid (194 mg, 1.2 mmol), $Pd(PPh_3)_4$ (24 mg, 0.021 mmol), and K_3PO_4 (430 mg, 2.03

mmol) were degassed by using the freeze-pump-thaw method three times. After stirring at 100 °C for 16 h, the reaction mixture was filtered through a pad of silica gel (hexane/ethyl acetate = 3/1). Removal of the solvent under reduced pressure gave a crude mixture including 2-(methoxymethoxy)-[1,1'-biphenyl]-3-carbaldehyde. To a *N*-methylpyrrolidone (1 mL) solution of the obtained crude mixture was added PDFA (712 mg, 2.00 mmol). After stirring at 80 °C for 4 h, water (5 mL) was added to the reaction mixture. Organic materials were extracted with diethyl ether (3 mL) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, aqueous HCl (6.0 M, 1.0 mL), isopropyl alcohol (1 mL), and THF (1 mL) were added to the residue including **11i**. After stirring at room temperature for 24 h, organic materials were extracted with dichloromethane (6 mL) 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 silica gel column chromatography (hexane/diethyl ether = 10/1) to give **12i** (188 mg, 81%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.38 (s, 1H), 5.66 (dd, J_{HF} =26.8, 4.1 Hz, 1H), 6.95 (dd, J = 7.7, 7.7 Hz, 1H), 7.08 (dd, J = 7.6 ,1.6 Hz, 1H), 7.37–7.48 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 76.3 (dd, J_{CF} = 31, 13 Hz), 117.6 (dd, J_{CF} = 6, 6 Hz), 120.6, 128.0 (d, J_{CF} = 9 Hz), 128.17, 128.22, 128.8, 129.0, 129.5, 136.6, 149.2 (d, J_{CF} = 5 Hz), 156.4 (dd, J_{CF} = 298, 288 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.2 (dd, J_{FF} = 31 Hz, J_{FH} = 27 Hz, 1F), 79.7 (d, J_{FF} = 31 Hz, 1F). IR (neat): ν 3546, 1728, 1454, 1433, 1240, 1161, 951, 837, 758, 742, 702 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_{10}F_2O$ $[M]^+$ 232.0700, Found 232.0702.

4-Bromo-2-(2,2-difluorovinyl)-1-(methoxymethoxy)benzene (**11f**)

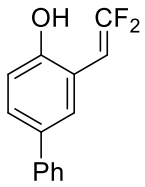


To a dichloromethane (80 mL) solution of salicylaldehyde **9f** (8.04 g, 40.0 mmol) and chloromethyl methyl ether (4.56 mL, 60.0 mmol) was added diisopropylethylamine (14.1 mL, 80.9 mmol). After stirring at room temperature for 12 h, water (80 mL) was added to the reaction mixture. Organic materials were extracted with dichloromethane (40 mL) three times. The combined extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave a crude mixture including **10f**.

To a *N*-methylpyrrolidone (40 mL) solution of the obtained crude mixture was added PDFA (28.5 g, 80.0 mmol). After stirring at 80 °C for 4 h, water (200 mL) was added to the reaction mixture. Organic materials were extracted with diethyl ether (40 mL) 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 silica gel column chromatography (hexane/diethyl ether = 40/1) to give **11f** (9.63 g, 86%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.46 (s, 3H), 5.16 (s, 2H), 5.61 (dd, J_{HF} =22.4, 8.1 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 7.27 (d, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.1, 75.6 (dd, J_{CF} = 29, 16 Hz), 94.7, 114.3, 115.9, 122.0, 130.79 (dd, J_{CF} = 9, 3 Hz), 130.80, 152.9 (d, J_{CF} = 2 Hz), 156.4 (dd, J_{CF} = 297, 291 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.9–81.0 (m, 2F). IR (neat): ν 2956, 2904, 2827, 1724, 1483, 1221, 1151, 1076, 943, 876, 808 cm^{-1}. HRMS (EI): Calcd for $C_{10}H_9{}^{79}BrF_2O_2$ $[M]^+$ 277.9754, Found 277.9753.

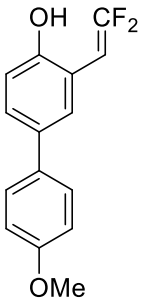
3-(2,2-Difluorovinyl)-[1,1'-biphenyl]-4-ol (**12j**)



A dimethoxyethane (12 mL) and water (3 mL) solution of methoxymethyl-protected difluorostyrene **11f** (837 mg, 3.00 mmol), phenylboronic acid (475 mg, 3.90 mmol), $Pd(PPh_3)_4$ (69 mg, 0.060 mmol), and K_3PO_4 (1.28 g, 6.01 mmol) were degassed by using the freeze-pump-thaw method three times. After stirring at 80 °C for 12 h, aqueous HCl (6.0 M, 5.0 mL) was added to the reaction mixture. After stirring at room temperature for 24 h, organic materials were extracted with dichloromethane (10 mL) 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 silica gel column chromatography (hexane/diethyl ether = 10/1) to give **12j** (635 mg, 91%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (s, 1H), 5.58 (dd, J_{HF} =25.8, 4.5 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.28–7.33 (m, 2H), 7.40 (dd, J = 7.8, 7.5 Hz, 2H), 7.51 (d, J = 7.8 Hz, 2H) 7.63 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 75.9 (dd, J_{CF} = 30, 14 Hz), 115.8, 117.6 (dd, J_{CF} = 6, 6 Hz), 126.8, 126.9, 127.1, 127.6 (dd, J_{CF} = 9, 2 Hz), 128.7, 134.4, 140.5, 151.8 (d, J_{CF} = 3 Hz), 156.4 (dd, J_{CF} = 297, 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 80.1 (dd, J_{FF} = 29 Hz, J_{FH} = 26 Hz, 1F), 80.2 (d, J_{FF} = 29 Hz, 1F). IR (neat): ν 3357, 1726, 1363, 1252, 1207, 953, 889, 760, 692, 573 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_{10}F_2O$ $[M]^+$ 232.0700, Found 232.0703.

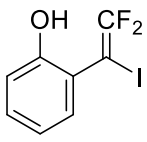
3-(2,2-Difluorovinyl)-4’-methoxy-[1,1’-biphenyl]-4-ol (**12k**)



A dimethoxyethane (12 mL) and water (3 mL) solution of methoxymethyl-protected difluorostyrene **11f** (836 mg, 2.99 mmol), 4-methoxyphenylboronic acid (592 mg, 3.90 mmol), $Pd(PPh_3)_4$ (70 mg, 0.060 mmol), and K_3PO_4 (1.27 g, 5.96 mmol) was degassed by using the freeze-pump-thaw method three times. After stirring at 80 °C for 12 h, aqueous HCl (6.0 M, 5.0 mL) was added to the reaction mixture. After stirring at room temperature for 24 h, organic materials were extracted with dichloromethane (10 mL) 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 silica gel column chromatography (hexane/diethyl ether = 10/1) to give **12k** (734 mg, 94%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H), 5.60 (dd, J_{HF} = 25.8, 4.6 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 7.26 (dd, J = 8.3, 2.3 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.58 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.4, 76.0 (dd, J_{CF} = 30, 14 Hz), 114.2, 115.7, 117.6 (dd, J_{CF} = 6, 5 Hz), 126.6, 127.1 (dd, J_{CF} = 8, 1 Hz), 127.8, 133.3, 133.9, 151.6 (d, J_{CF} = 5 Hz), 156.4 (dd, J_{CF} = 297, 289 Hz), 158.6. ^{19}F NMR (470 MHz, $CDCl_3$): δ 79.8 (dd, J_{FF} = 30 Hz, J_{FH} = 26 Hz, 1F), 80.0 (d, J_{FF} = 30 Hz, 1F). IR (neat): ν 3340, 1728, 1608, 1495, 1238, 1176, 951, 808 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{12}F_2O_2$ $[M]^+$ 262.0805, Found 262.0815.

2-(2,2-Difluoro-1-iodovinyl)phenol (**12l**)



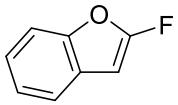
To a dichloromethane (8 mL) solution of β,β-difluoro-α-iodo-*o*-methoxystyrenes (**14**, 2.44 g, 8.24 mmol) was

slowly added BBr_3 (0.94 mL, 9.9 mmol) at –20 °C. After stirring at room temperature for 2 h, the reaction was quenched with ice. Organic materials were extracted with dichloromethane (15 mL) 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 silica gel column chromatography (hexane/diethyl ether = 5/1) to give **12l** (1.92 g, 83%) as a pale brown liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.18 (s, 1H), 6.85-6.87 (d, J = 8.1 Hz, 1H), 6.93 (dd, J = 8.1, 7.1 Hz, 1H), 7.20–7.25 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 39.6 (dd, J_{CF} = 32, 32 Hz), 116.4, 120.1, 121.1, 131.2, 131.3, 152.9 (dd, J_{CF} = 298, 298 Hz), 153.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ 89.1 (d, J_{FF} = 19 Hz, 1F), 91.3 (d, J_{FF} = 19 Hz, 1F). IR (neat): ν 3442,1716, 1452, 1257, 978, 899, 750, 652 cm^{-1}. HRMS (EI): Calcd for $C_8H_5F_2IO$ $[M]^+$ 281.9353, Found 281.9358.

5-endo-trig Cyclization of β,β-Difluoro-o-hydroxystyrenes **12**

Typical Procedure 2: Synthesis of 2-Fluorobenzofuran (**15a**)



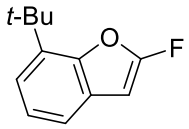
To a DMF (100 mL) solution of difluorostyrene **12a** (390 mg, 2.50 mmol) was added DBU (0.450 mL, 3.02 mmol). After stirring at 100 °C for 1 h under microwave irradiation, water (250 mL) was added to the reaction mixture. Organic materials were extracted with diethyl ether (50 mL) three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (pentane/diethyl ether = 10/1) to give **15a** (129 mg, 38%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (d, J_{HF} = 6.5 Hz, 1H), 7.18–7.22 (m, 2H), 7.33–7.35 (m, 1H), 7.41–7.43 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 78.3 (d, J_{CF} = 14 Hz), 110.9, 120.6 (d, J_{CF} = 6 Hz), 123.3 (d, J_{CF} = 4 Hz), 123.6, 128.0 (d, J_{CF} = 3 Hz), 147.8, 160.5 (d, J_{CF} = 280 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 50.2 (d, J_{FH}

= 6 Hz, 1F). IR (neat): ν 1631, 1454, 1333, 1180, 980, 771, 742, 665 cm^{-1}.

Spectral data for this compound showed good agreement with literature data.[4]

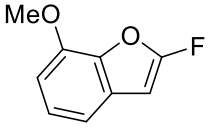
7-tert-Butyl-2-fluorobenzofuran (**15b**)



Compound **15b** was synthesized according to Typical Procedure 2 using difluorostyrene **12b** (43 mg, 0.20 mmol), DBU (36 μL, 0.24 mmol), and DMF (6 mL) for 20 min. Purification of silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **15b** (18 mg, 47%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 5.81 (d, J_{HF} = 6.6 Hz, 1H), 7.14–7.18 (m, 2H), 7.31 (dd, J = 6.5 Hz, J = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.8, 34.2, 77.9 (d, J_{CF} = 13 Hz), 118.6 (d, J_{CF} = 5 Hz), 120.3 (d, J_{CF} = 4 Hz), 123.5, 128.5 (d, J_{CF} = 3 Hz), 134.5, 145.9, 159.8 (d, J_{CF} = 278 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 49.7 (d, J_{FH} = 7 Hz). IR (neat): ν 2962, 2914, 2873, 1645, 1415, 1342, 1335, 1161, 985, 795, 742 cm^{-1}. HRMS (EI): Calcd for $C_{12}H_{13}FO$ $[M]^+$ 192.0950, Found 192.0955.

2-Fluoro-7-methoxybenzofuran (**15c**)

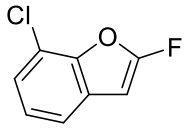


Compound **15c** was synthesized according to Typical Procedure 2 using difluorostyrene **12c** (373 mg, 2.00 mmol), DBU (0.360 mL, 2.41 mmol), and DMF (100 mL). Purification of silica gel column chromatography (pentane/diethyl ether = 10/1) gave **15c** (201 mg, 60%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.97 (s, 3H), 5.82 (d, J_{HF} = 6.7 Hz, 1H), 6.77 (dd, J = 8.1, 0.9 Hz, 1H), 7.05 (dd, J = 8.0 Hz, J = 0.9 Hz, 1H), 7.15 (dd, J = 8.1, 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 56.0, 78.7 (d,

J_{CF} = 13 Hz), 106.2 (d, J_{CF} = 19 Hz), 113.0 (d, J_{CF} = 5 Hz), 124.2, 129.5 (d, J_{CF} = 3 Hz), 136.7, 144.8, 160.2 (d, J_{CF} = 284 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 50.6 (d, J_{FH} = 7 Hz). IR (neat): ν 1637, 1496, 1437, 1294, 1200, 1092, 982, 785, 725 cm^{-1}. HRMS (EI): Calcd for $C_9H_7FO_2$ $[M]^+$ 166.0430, Found 166.0422.

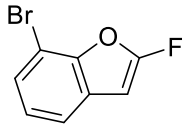
7-Chloro-2-fluorobenzofuran (**15d**)



Compound **15d** was synthesized according to Typical Procedure 2 using difluorostyrene **12d** (420 mg, 2.20 mmol), DBU (0.390 mL, 2.61 mmol), and DMF (66 mL). Purification of silica gel column chromatography (hexane) gave **15d** (243 mg, 65%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (d, J_{HF} = 6.6 Hz, 1H), 7.12 (dd, J = 8.0, 7.8 Hz, 1H), 7.20 (dd, J = 8.0, 1.1 Hz, 1H), 7.32 (dd, J = 7.8, 1.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 79.2 (d, J_{CF} = 13 Hz), 116.3, 119.1 (d, J_{CF} = 6 Hz), 123.7 (d, J_{CF} = 4 Hz), 124.5, 129.3 (d, J_{CF} = 3 Hz), 143.6, 160.5 (d, J_{CF} = 282 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 51.8 (br s). IR (neat): ν 1641, 1429, 1327, 1174, 951, 787, 729 cm^{-1}. HRMS (EI): Calcd for C_8H_4ClFO $[M]^+$ 169.9935, Found 169.9927.

7-Bromo-2-fluorobenzofuran (**15e**)

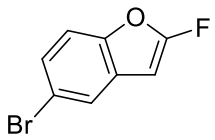


Compound **15e** was synthesized according to Typical Procedure 2 using difluorostyrene **12e** (44 mg, 0.19 mmol), DBU (34 μL, 0.23 mmol), and DMF (6 mL) for 20 min. Purification of silica gel column chromatography (hexane) gave **15e** (26 mg, 65%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94 (d, J_{HF} = 6.6 Hz, 1H), 7.10–7.14 (m, 1H), 7.39–7.42 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 79.4 (d, J_{CF} = 13 Hz), 103.5, 119.8 (d, J_{CF} = 6 Hz), 124.9, 126.6 (d, J_{CF} = 4 Hz), 129.1

(d, J_{CF} = 3 Hz), 145.1, 160.4 (d, J_{CF} = 282 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 52.3 (d, J_{FH} = 7 Hz). IR (neat): ν 1641, 1423, 1333, 1173, 976, 924, 785, 729 cm^{-1}. HRMS (EI): Calcd for $C_8H_4{}^{79}BrFO$ [M]$^+$ 213.9430, Found 213.9427.

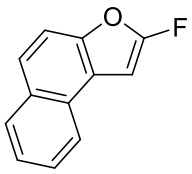
5-Bromo-2-fluorobenzofuran (**15f**)



Compound **15f** was synthesized according to Typical Procedure 2 using difluorostyrene **12f** (822 mg, 3.50 mmol), DBU (0.630 mL, 4.22 mmol), activated molecular sieves 3A (3.5 g), and nitromethane (105 mL) for 20 min. Purification of silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **15f** (200 mg, 27%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (d, J_{HF} = 6.5 Hz, 1H), 7.25–7.27 (m, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.60 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 78.3 (d, J_{CF} = 14 Hz), 112.5, 116.8, 123.4, 126.4, 129.8, 146.4, 160.8 (d, J_{CF} = 282 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 53.1 (d, J_{FH} = 7 Hz). IR (neat): ν 1633, 1442, 1333, 1267, 1184, 1049, 980, 800, 658 cm^{-1}. HRMS (EI): Calcd for $C_8H_4{}^{79}BrFO$ [M]$^+$ 213.9430, Found 213.9432.

2-Fluoronaphtho[2,1-b]furan (**7g**)

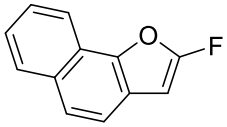


Compound **15g** was synthesized according to Typical Procedure 2 using difluorostyrene **12g** (41 mg, 0.20 mmol), DBU (36 μL, 0.24 mmol), and DMF (6 mL). Purification of silica gel column chromatography (hexane) gave **15g** (30 mg, 81%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 (d, J_{HF} = 6.6 Hz, 1H), 7.42–7.52 (m, 3H), 7.61 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 77.9 (d,

J_{CF} = 13 Hz), 111.6, 123.2, 124.0 (d, J_{CF} = 4 Hz), 124.8, 126.2, 127.3 (d, J_{CF} = 4 Hz), 128.8, 130.5, 144.2, 159.7 (d, J_{CF} = 280 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 50.1 (d, J_{FH} = 7 Hz). IR (neat): ν 1637, 1585, 1387, 1327, 1244, 1215, 989, 802, 766 cm^{-1}. HRMS (EI): Calcd for $C_{12}H_7FO$ $[M]^+$ 186.0481, Found 186.0485.

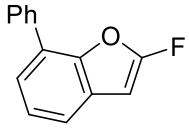
2-Fluoronaphtho[1,2-b]furan (**15h**)



Compound **15h** was synthesized according to Typical Procedure 2 using difluorostyrene **12h** (414 mg, 2.01 mmol), DBU (0.360 mL, 2.41 mmol), and DMF (60 mL). Purification of silica gel column chromatography (hexane) gave **15h** (121 mg, 32%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (d, J_{HF} = 6.8 Hz, 1H), 7.45–7.48 (m, 1H), 7.55–7.60 (m, 2H), 7.69 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 79.6 (d, J_{CF} = 13 Hz), 119.1, 119.2 (d, J_{CF} = 4 Hz), 120.8, 123.6, 124.2, 124.7, 126.7, 128.5, 130.8, 142.2, 159.7 (d, J_{CF} = 280 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 49.9 (d, J_{FH} = 7 Hz). IR (neat): ν 1628, 1329, 1259, 1171, 1076, 980, 810, 742, 683 cm^{-1}. HRMS (EI): Calcd for $C_{12}H_7FO$ $[M]^+$ 186.0481, Found 186.0483.

2-Fluoro-7-phenylbenzofuran (**15i**)

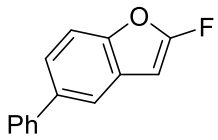


Compound **15i** was synthesized according to Typical Procedure 2 using difluorostyrene **12i** (53 mg, 0.23 mmol), DBU (41 μL, 0.27 mmol), and DMF (7 mL) for 20 min. Purification of silica gel column chromatography (hexane) gave **15i** (43 mg, 88%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (d, J_{HF} = 6.6 Hz, 1H), 7.31 (dd, J = 7.7, 7.7 Hz, 1H), 7.38–7.44 (m, 3H), 7.47–7.50 (m, 2H), 7.77–7.79 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 78.5 (d, J_{CF} = 13 Hz), 119.7 (d, J_{CF} =

6 Hz), 123.2 (d, J_{CF} = 4 Hz), 124.2, 125.3, 127.9, 128.5, 128.65, 128.72 (d, J_{CF} = 3 Hz), 135.7, 144.9, 160.5 (d, J_{CF} = 280 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 50.8 (d, J_{FH} = 7 Hz, 1F). IR (neat): ν 1637, 1479, 1412, 1338, 1284, 1201, 1167, 980, 798, 694 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_9FO$ $[M]^+$ 212.0637, Found 212.0643.

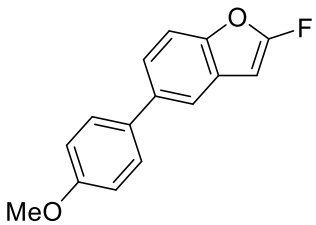
2-Fluoro-5-phenylbenzofuran (**15j**)



Compound **15j** was synthesized according to Typical Procedure 2 using difluorostyrene **12j** (12 mg, 0.050 mmol), DBU (9.0 μL, 0.060 mmol), and DMF (1.5 mL). Purification of silica gel column chromatography (hexane) gave **15j** (4.1 mg, 39%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (d, J_{HF} = 6.5 Hz, J = 0.5 Hz, 1H), 7.32–7.35 (m, 1H), 7.41–7.45 (m, 4H), 7.56–7.58 (m, 2H), 7.63–7.64 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 78.6 (d, J_{CF} = 13 Hz), 111.0, 119.3 (d, J_{CF} = 6 Hz), 122.9 (d, J_{CF} = 4 Hz), 127.0, 127.4, 128.4 (d, J_{CF} = 3 Hz), 128.7, 137.4, 141.4, 147.3, 160.7 (d, J_{CF} = 285 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 51.7 (d, J_{FH} = 7 Hz). IR (neat): ν 1635, 1466, 1331, 1178, 978, 758, 698 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_9FO$ $[M]^+$ 212.0637, Found 212.0633.

2-Fluoro-5-(4-methoxyphenyl)benzofuran (**15k**)

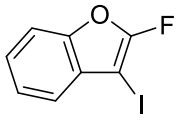


Compound **15k** was synthesized according to Typical Procedure 2 using difluorostyrene **12k** (13 mg, 0.050 mmol), DBU (9.0 μL, 0.060 mmol), and DMF (1.5 mL). Purification of silica gel column chromatography (hexane) gave **15k** (2.8 mg, 23%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.82 (s, 3H), 5.85 (d, J_{HF} = 6.6 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.38 (s, 2H),

7.49 (d, J = 8.8 Hz, 2H), 7.57 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.3, 78.5 (d, J_{CF} = 13 Hz), 111.0, 114.2, 118.8 (d, J_{CF} = 5 Hz), 122.6 (d, J_{CF} = 4 Hz), 127.7, 128.3, 133.9, 137.0, 147.0, 159.0, 160.7 (d, J_{CF} = 280 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 51.4 (d, J_{FH} = 7 Hz). IR (neat): ν 3136, 2958, 2839, 1639, 1468, 1180, 1038, 976, 800, 739 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{11}FO_2$ $[M]^+$ 242.0743, Found 242.0740.

2-Fluoro-3-iodobenzofuran (**15l**)



To a DMF (140 mL) solution of difluorostyrene **12l** (2.00 g, 7.07 mmol) was added $LiOH \cdot H_2O$ (312 mg, 7.44 mmol). After stirring at 0 °C for 4 h, the reaction was quenched with phosphate buffer (pH 7, 10 mL), and water (300 mL) was then added to the mixture. Organic materials were extracted with diethyl ether (75 mL) 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 silica gel column chromatography (hexane/ethyl acetate = 10/1) to give **15l** (1.16 g, 63%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.33 (m, 3H), 7.36–7.38 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 33.8 (d, J_{CF} = 19 Hz), 111.2, 120.9 (d, J_{CF} = 5 Hz), 124.3, (d, J_{CF} = 4 Hz), 129.9, 147.7, 160.0 (d, J_{CF} = 277 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 52.1 (s). IR (neat): ν 2924, 1641, 1448, 1327, 1178, 1041, 741 cm^{-1}. HRMS (EI): Calcd for C_8H_4FIO $[M]^+$ 261.9291, Found 261.9289.

Chemical Transformation of 5-Bromo-2-fluorobenzofuran (**15f**)

Typical Procedure 3: Synthesis of 2-Fluoro-5-phenylbenzofuran (**15j**)

To an ethanol (0.4 mL) and water (0.4 mL) solution of 5-bromo-2-fluorobenzofuran (**15f**, 21 mg, 0.10 mmol), phenylboronic acid (19 mg, 0.15 mmol), and K_2CO_3 (28.0 mg, 0.20 mmol) was added $PdCl_2$ (0.1 mg, 0.5 μmol). After stirring at room temperature for 36 h, organic materials were extracted with dichloromethane (1

mL) 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 silica gel column chromatography (hexane) to give **15j** (15 mg, 73%) as a colorless oil.

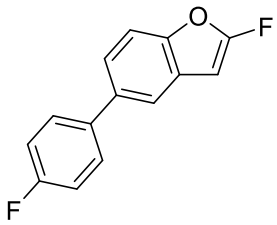
Spectral data for this compound showed good agreement with **15j** synthesized according to Typical procedure 2 (vide supra).

2-Fluoro-5-(4-methoxyphenyl)benzofuran (**15k**)

Compound **15k** was synthesized according to Typical Procedure 3 using 5-bromo-2-fluorobenzofuran (**15f**, 107 mg, 0.50 mmol), (4-methoxyphenyl)boronic acid (117 mg, 0.77 mmol), $PdCl_2$ (0.4 mg, 2 μmol), K_2CO_3 (141 mg, 1.0 mmol), ethanol (2 mL), and water (2 mL). Purification of silica gel column chromatography (hexane) gave **15k** (63 mg, 52%) as a colorless oil.

Spectral data for this compound showed good agreement with **15k** synthesized according to Typical procedure 2 (vide supra).

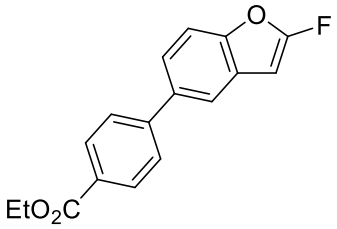
2-Fluoro-5-(4-fluorophenyl)benzofuran (**15m**)



Compound **15m** was synthesized according to Typical Procedure 3 using 5-bromo-2-fluorobenzofuran (**15f**, 107 mg, 0.50 mmol), (4-fluorophenyl)boronic acid (105 mg, 0.75 mmol), $PdCl_2$ (0.4 mg, 2 μmol), K_2CO_3 (140 mg, 1.0 mmol), ethanol (2 mL), and water (2 mL). Purification of silica gel column chromatography (hexane) gave **15m** (90 mg, 79%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (d, J_{HF} = 6.6 Hz, 1H), 7.11–7.16 (m, 2H), 7.39–7.44 (m, 2H), 7.52–7.56 (m, 2H), 7.60 (d, J = 1.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 78.6 (d, J_{CF} = 13 Hz), 111.1, 115.6 (d, J_{CF} = 21 Hz), 119.2 (d, J_{CF} = 6 Hz), 122.8 (d, J_{CF} = 4 Hz), 128.5 (d, J_{CF} = 8 Hz), 128.9 (d, J_{CF} = 8 Hz), 136.5, 137.5 (d, J_{CF} = 3 Hz), 147.3, 160.8 (d, J_{CF} = 281 Hz), 162.3 (d, J_{CF} = 247 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 46.8 (1F), 52.0 (d, J_{FH} = 7 Hz, 1F). IR (neat): ν 1637, 1466, 1335, 1228, 1184, 980, 834, 806 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_8F_2O$ $[M]^+$ 230.0543, Found 230.0533.

Ethyl 4-(2-fluorobenzofuran-5-yl)benzoate (**15n**)

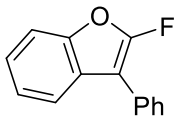


Compound **15n** was synthesized according to Typical Procedure 3 using 5-bromo-2-fluorobenzofuran (**15f**, 108 mg, 0.50 mmol), [4-(ethoxycarbonyl)phenyl]boronic acid (146 mg, 0.75 mmol), $PdCl_2$ (0.4 mg, 2 μmol), K_2CO_3 (140 mg, 1.0 mmol), ethanol (2 mL), and water (2 mL). Purification of silica gel column chromatography (hexane/ethyl acetate = 10/1) gave **15n** (141 mg, 99%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 5.92 (d, J_{HF} = 6.6 Hz, 1H), 7.45–7.50 (m, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 1.8 Hz, 1H), 8.11 (d, J = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 60.9, 78.6 (d, J_{CF} = 14 Hz), 111.2, 119.4 (d, J_{CF} = 6 Hz), 122.9 (d, J_{CF} = 4 Hz), 127.2, 128.5 (d, J_{CF} = 3 Hz), 129.0, 130.0, 136.2, 145.6, 147.7, 160.8 (d, J_{CF} = 281 Hz), 166.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ 52.0 (d, J_{FH} = 7 Hz,). IR (neat): ν 3140, 2982, 1712, 1637, 1468, 972, 768 cm^{-1}. HRMS (EI): Calcd for $C_{17}H_{13}FO_3$ $[M]^+$ 284.0849, Found 284.0857.

Chemical Transformation of 2-Fluoro-3-iodobenzofuran (**15l**)

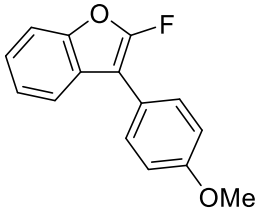
Typical Procedure 4: Synthesis of 2-Fluoro-3-phenylbenzofuran (**15o**)



A 1,4-dioxane (2.0 mL) and water (0.2 mL) solution of 2-fluoro-3-iodo-benzofuran (**15l**, 262 mg, 1.00 mmol), phenylboronic acid (145 mg, 1.2 mmol), $Pd(PPh_3)_4$ (34 mg, 0.029 mmol), and K_2CO_3 (417 mg, 3.01 mmol) was degassed by using the freeze-pump-thaw method three times. After stirring at 100 °C for 36 h, water (5 mL) was added to the reaction mixture. Organic materials were extracted with dichloromethane (5 mL) 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 silica gel column chromatography (hexane) to give **15o** (178 mg, 84%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.31 (m, 2H), 7.32–7.35 (m, 1H), 7.40–7.43 (m, 1H), 7.46 (dd, J = 8.0, 7.7 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.72–7.75 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 93.2 (d, J_{CF} = 8 Hz), 111.1, 120.0 (d, J_{CF} = 6 Hz), 123.8 (d, J_{CF} = 4 Hz), 123.9, 127.2, 127.7 (d, J_{CF} = 3 Hz), 128.7, 128.9, 129.5 (d, J_{CF} = 5 Hz), 147.1, 156.5 (d, J_{CF} = 283 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 47.3 (s). IR (neat): ν 1653, 1452, 1385, 1296, 1211, 1003, 766, 741, 694 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_9FO$ $[M]^+$ 212.0637, Found 212.0635.

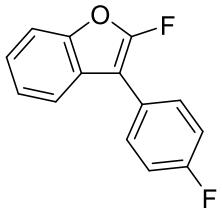
2-Fluoro-3-(4-methoxyphenyl)benzofuran (**15p**)



Compound **15p** was synthesized according to Typical Procedure 4 using 2-fluoro-3-iodobenzofuran (**15l**, 209 mg, 0.796 mmol), (4-methoxyphenyl)boronic acid (158 mg, 1.0 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), K_2CO_3 (332 mg, 2.40 mmol), 1,4-dioxane (2.0 mL), and water (0.2 mL) at 100 °C for 12 h. Purification of silica gel column chromatography (hexane) gave **15p** (151 mg, 78%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (s, 3H), 7.00 (d, J = 8.9 Hz, 2H), 7.26–7.28 (m, 2H), 7.40–7.42 (m, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.68–7.70 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.3, 92.8 (d, J_{CF} = 9 Hz), 111.1, 114.4, 119.9 (d, J_{CF} = 6 Hz), 121.8 (d, J_{CF} = 5 Hz), 123.66 (d, J_{CF} = 4 Hz), 123.74, 127.6, 128.9 (d, J_{CF} = 3 Hz), 147.0, 156.2 (d, J_{CF} = 282 Hz), 158.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ 45.9 (s, 1F). IR (neat): ν 2837, 1658, 1610, 1514, 11452, 1211, 1176, 1020, 995, 827, 741 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{11}FO_2$ $[M]^+$ 242.0743, Found 242.0751.

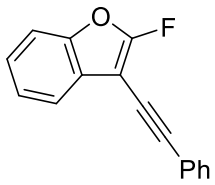
2-Fluoro-3-(4-fluorophenyl)benzofuran (**15q**)



Compound **15q** was synthesized according to Typical Procedure 4 using 2-fluoro-3-iodobenzofuran (**15l**, 209 mg, 0.799 mmol), (4-fluorophenyl)boronic acid (146 mg, 1.0 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol), K_2CO_3 (331 mg, 2.40 mmol), 1,4-dioxane (2.0 mL), and water (0.2 mL) at 100 °C for 12 h. Purification of silica gel column chromatography (hexane) gave **15q** (179 mg, 97%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (dd, J_{HF} = 8.7 Hz, J = 8.7 Hz, 2H), 7.27–7.32 (m, 2H), 7.40–7.44 (m, 1H), 7.57–7.60 (m, 2H), 7.65–7.69 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 92.4 (d, J_{CF} = 9 Hz), 111.2, 115.9 (d, J_{CF} = 22 Hz), 119.7 (d, J_{CF} = 6 Hz), 123.92, 123.95, 129.3 (d, J_{CF} = 3 Hz), 129.4 (d, J_{CF} = 3 Hz), 133.7 (d, J_{CF} = 19 Hz), 147.1, 156.4 (d, J_{CF} = 283 Hz), 161.9 (d, J_{CF} = 248 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 46.7 (s, 1F), 48.50-48.54 (m, 1F). IR (neat): ν 1655, 1512, 1454, 1213, 999, 833, 742 cm^{-1}. HRMS (EI): Calcd for $C_{14}H_8F_2O$ $[M]^+$ 230.0543, Found 230.0552.

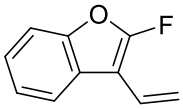
2-Fluoro-3-(phenylethynyl)benzofuran (**15r**)



A triethylamine (5 mL) solution of 2-fluoro-3-iodo-benzofuran (**15l**, 261 mg, 0.994 mmol), ethynylbenzene (0.12 mL, 1.1 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.030 mmol), and CuI (5.7 mg, 0.030 mmol) was degassed by using the freeze-pump-thaw method three times. After stirring at room temperature for 12 h, water (10 mL) was added to the reaction mixture. Organic materials were extracted with dichloromethane (5 mL) 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 silica gel column chromatography (hexane) to give **15r** (179 mg, 76%) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.41 (m, 6H), 7.56–7.58 (m, 2H), 7.62–7.64 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 75.6 (d, J_{CF} = 2 Hz), 78.2 (d, J_{CF} = 11 Hz), 94.4, 111.1, 120.2 (d, J_{CF} = 5 Hz), 122.8, 124.3, 124.5 (d, J_{CF} = 4 Hz), 127.9, 128.4, 128.5, 131.6, 146.7, 160.6 (d, J_{CF} = 289 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 57.1 (s). IR (neat): ν 1655, 1454, 1396, 1304, 1120, 957, 742, 688 cm^{-1}. HRMS (EI): Calcd for $C_{16}H_9FO$ $[M]^+$ 236.0637, Found 236.0642.

2-Fluoro-3-vinylbenzofuran (**15s**)



A DMF (2 mL) solution of 2-fluoro-3-iodo-benzofuran (**15l**, 135 mg, 0.51 mmol), tributyl(vinyl)stannane (145 mg, 0.50 mmol), and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol) was degassed by using the freeze-pump-thaw method three times. After stirring at 60 °C for 16 h, water (10 mL) was added to the reaction mixture. Organic materials

were extracted with diethyl ether (5 mL) 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 silica gel column chromatography (hexane) to give **15s** (67 mg, 83%) as a colorless liquid.

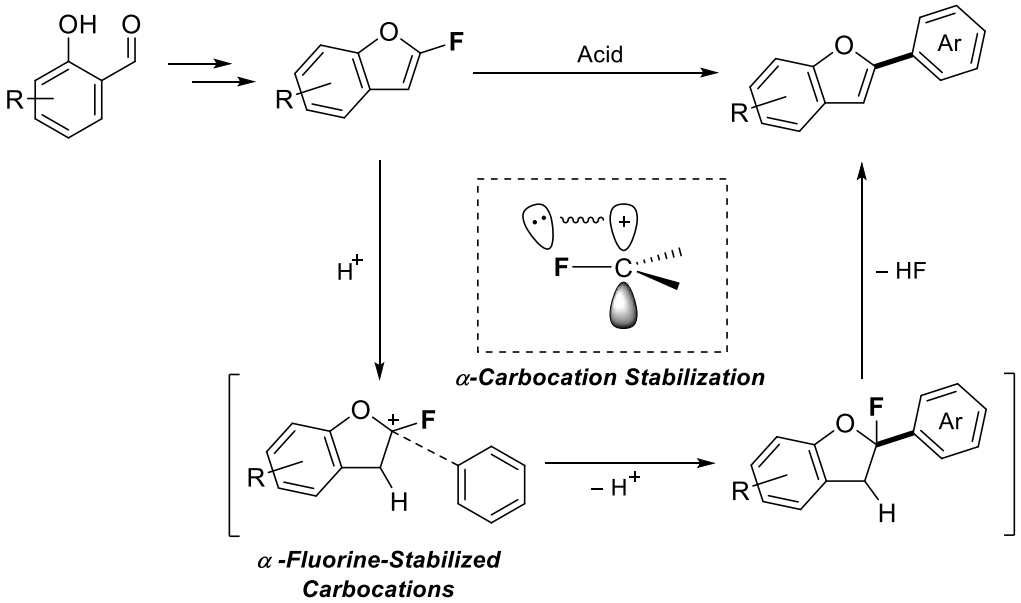
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.35 (d, *J* = 11.5 Hz, 1H), 5.73 (dd, *J* = 17.9, 1.0 Hz, 1H), 6.62 (dd, *J* = 17.9, 11.5 Hz, 1H), 7.23–7.29 (m, 2H), 7.35–7.37 (m, 1H), 7.66–7.68 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 91.7 (d, J_{CF} = 9 Hz), 111.1, 114.9 (d, J_{CF} = 4 Hz), 120.3 (d, J_{CF} = 5 Hz), 123.2 (d, J_{CF} = 4 Hz), 123.8 (d, J_{CF} = 4 Hz), 123.9, 126.7, 147.2, 157.5 (d, J_{CF} = 286 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 49.6 (s). IR (neat): ν 1662, 1456, 1381, 1196, 742 cm^{-1}. HRMS (EI): Calcd for $C_{10}H_7FO$ $[M]^+$ 162.0481, Found 162.0485.

CHAPTER 5

Aromatic C–F Bond Activation:
C–F/C–H Coupling of 2-Fluorobenzofurans with Arenes

Abstract

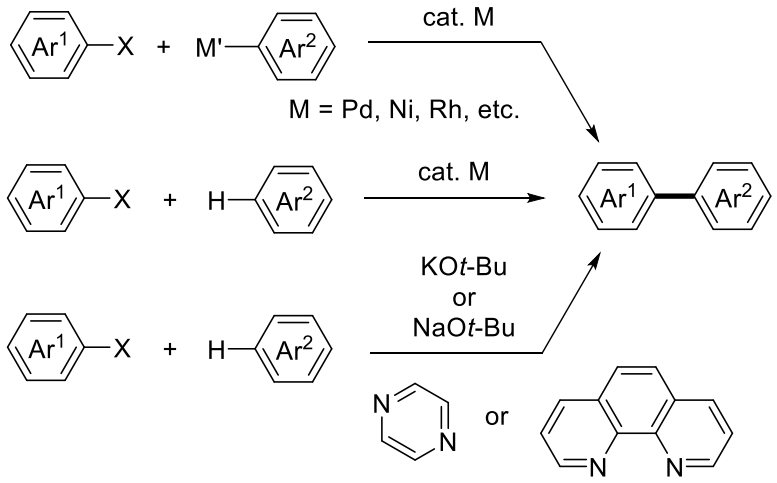
Transition-metal-free acid-promoted biaryl construction was achieved via intermolecular C–F/C–H cross-coupling. By treating 2-fluorobenzofurans with arenes in the presence of $AlCl_3$, 2-arylbenzofurans were obtained. This protocol was successfully applied to the short-step orthogonal synthesis of a bioactive 2-arylbenzofuran natural product, which allows independent transformations of C–F and C–Br bonds. Mechanistic studies indicated that α-fluorine-stabilized carbocations, generated via the protonation of 2-fluorobenzofurans, served as key intermediates. The Friedel–Crafts-type C–C bond formation between the α-fluorocarbocations and arenes, followed by hydrogen fluoride elimination, afforded 2-arylbenzofurans.



5-1. Introduction

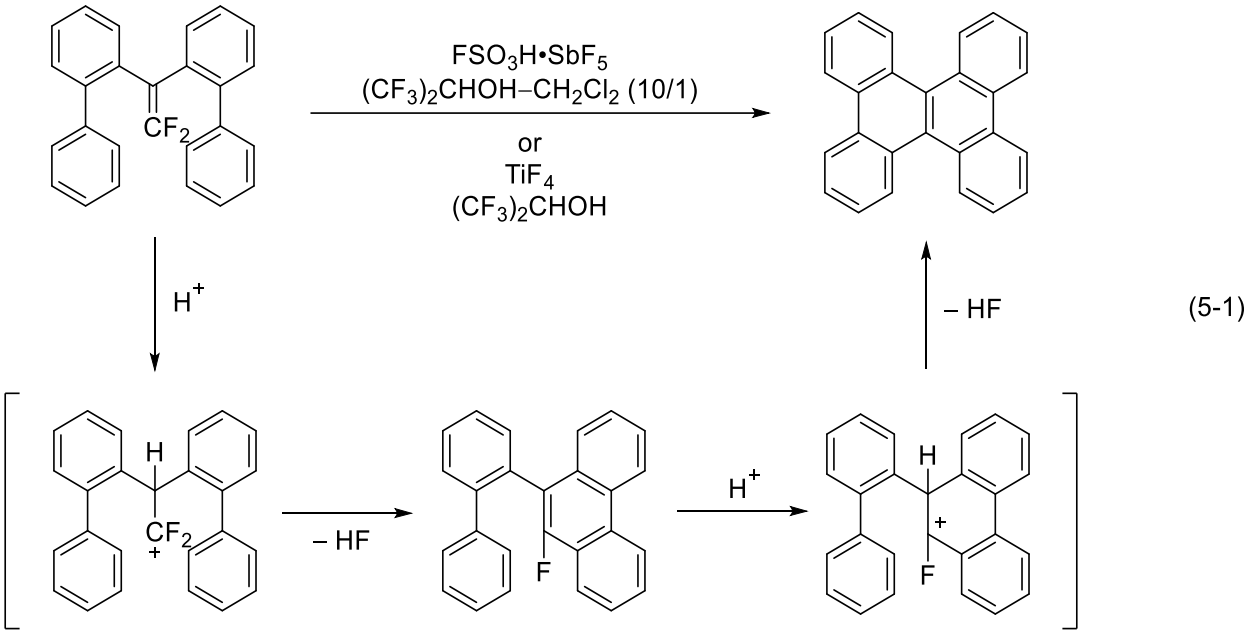
5-1-1. Acid-Mediated Biaryl Construction via C–F Bond Activation

For a long time, biaryl construction through intermolecular cross-coupling via C(sp^2)–C(sp^2) bond formation has been one of the most important studies in synthetic organic chemistry. For the past half-century, a wide variety of transition-metal-catalyzed cross-coupling reactions typically between aryl halides (Ar^1X) and arylmetal species (Ar^2M') have been developed to provide tremendous support for pharmaceutical and material sciences (Scheme 5-1, top).[1] Among the transition-metal-catalyzed cross-coupling reactions, the intermolecular direct arylation of aryl halides (Ar^1X) with arenes (Ar^2H) via C–H bond cleavage has been exponentially studied (Scheme 5-1, middle).[2] This protocol allows an improved atom-economical alternative for biaryl construction because Ar^2H instead of Ar^2M' can be used. More recently, the transition-metal-free cross-coupling of Ar^1X with Ar^2H in an intermolecular fashion has also been reported (Scheme 5-1, bottom).[3] In these reactions, nitrogen-containing substrates or additives were often combined with metal *tert*-butoxide to generate aryl radical species from Ar^1X, which undergo C–C bond formation with Ar^2H. Although this approach is an improved alternative to the aforementioned methods for intermolecular cross-coupling, the aryl (pseudo)halide substrates have been limited to aryl iodides, bromides, chlorides, or sulfonates. Aryl fluorides have never been applicable to this type of reaction, presumably because aryl radical species are difficult to generate via the homolytic cleavage of C–F bonds, which exhibit higher dissociation energy.

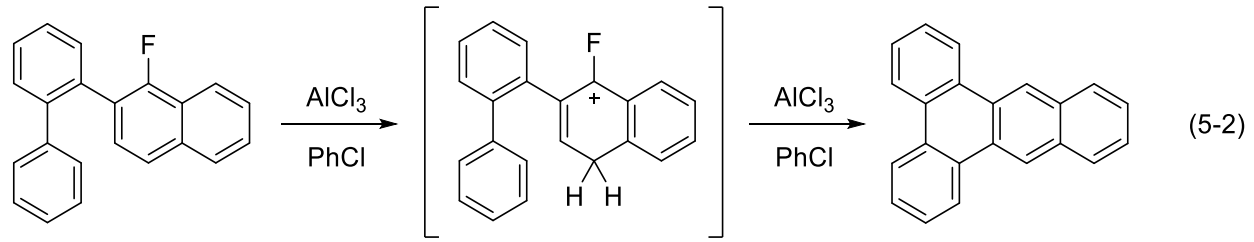


Scheme 5-1. Biaryl construction via coupling reaction

In contrast, our group has already developed a strategy for acid-mediated intramolecular cross-coupling via vinylic or aromatic C–F bond activation involving C(sp^2)–C(sp^2) bond formation.[4] In this strategy, the initial protonation generated intermediary arenium ions, which were stabilized by the fluorine substituent.[5] The ions reacted with nucleophilic Ar^2H units via the intramolecular Friedel–Crafts-type C–C bond formation. Subsequent hydrogen fluoride elimination afforded a benzene-fused aromatic system. For example, 1,1-difluoroethylenes bearing two biaryl moieties undergo domino vinylic/aromatic C–F bond activation mediated by $FSO_3H{\cdot}SbF_5$ or TiF_4 to afford dibenzo[*g*,*p*]chrysenes (eq 5-1).[4a] Furthermore, aromatic C–F bond activation of 1-fluoronaphthalenes bearing a biaryl moiety proceeds in the presence of $AlCl_3$, leading to the synthesis of benzo[*f*]tetraphenes (eq 5-2).[4b]



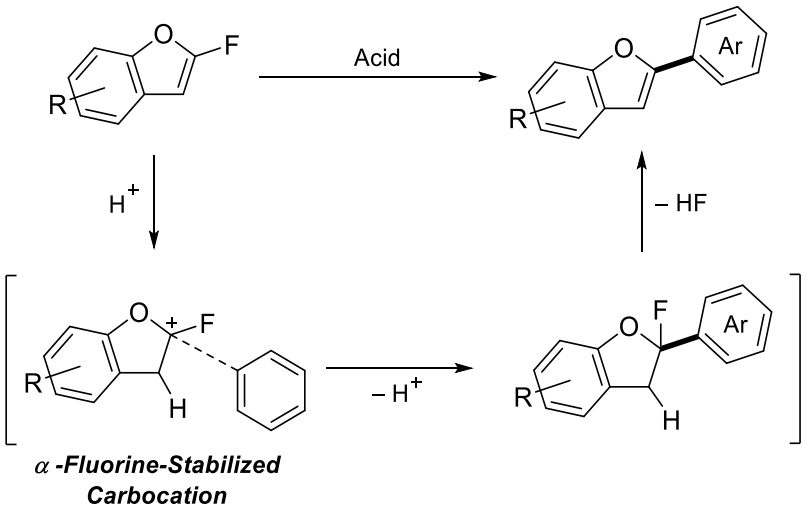
(5-1)



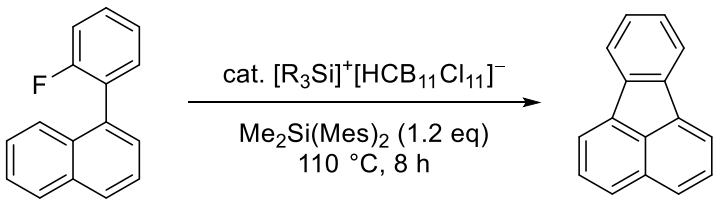
(5-2)

5-1-2. Strategy for the Synthesis of 2-Arylbenzofurnas

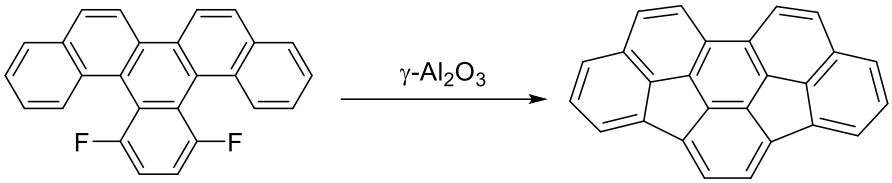
As the next challenge of formal cross-coupling reactions, I explored acid-mediated C–F/C–H coupling of aryl fluorides with arenes in an intermolecular fashion, which is considered more difficult entropically. In this study, I chose 2-fluorobenzofurans[6] as substrates because intermediary arenium ions would be readily generated through double stabilization by the fluorine and oxygen substituents. I discovered that $AlCl_3$ was effective in promoting the intermolecular coupling of 2-fluorobenzofurans with Ar^2H, resulting in the synthesis of 2-arylbenzofurans (Scheme 5-2). Although defluorinative $C(sp^2)$–$C(sp^2)$ coupling by silylium[7] or γ-Al_2O_3[8] have recently been reported, these are limited to intramolecular reactions or require silyl groups on the fluorine-containing substrates because they proceed via extremely unstable aryl cation(-like) species (eqs 5-3, 5-4).



Scheme 5-2. Strategy for the synthesis of 2-arylbenzofurans



(5-3)



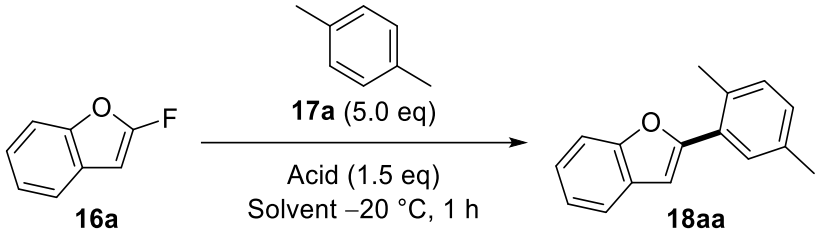
(5-4)

5-2. Synthesis of 2-Arylbenzofurans

5-2-1. Screening of Reaction Conditions

First, I investigated this intermolecular C–F/C–H coupling reaction using 2-fluorobenzofuran (**16a**) and 5 equiv of *p*-xylene (**17a**) as model compounds (Table 5-1). Although no coupling product was obtained in the presence of acetic acid or *p*-toluenesulfonic acid (Table 5-1, Entries 1 and 2), the use of trifluoromethanesulfonic acid in CH_2Cl_2 at −20 °C afforded the expected defluorinated coupling product, 2-xylylbenzofuran (**18aa**), in an 8% yield (Table 5-1, Entry 3). Among the Lewis acids screened (Table 5-1, Entries 4–6), $AlCl_3$ was found to be the best, affording **18aa** in a 63% isolated yield (Table 5-1, Entry 6). The cross-coupling was sluggish in the presence of molecular sieves, to afford **18aa** in a 34% yield (Table 5-1, Entry 7).[9] To improve the yield of **18aa**, we screened the solvents. Out of the several solvents that were examined (Table 5-1, Entries 6 and 8–11), CH_2Cl_2 was found to be an exceptionally effective solvent. Oxygen- or nitrogen-containing solvents probably coordinate to $AlCl_3$ to retard the reaction. When the reaction was conducted with 20 equiv of **17a** without any solvent, **18aa** was obtained in a 91% isolated yield (Table 5-1, Entry 12). Based on these results, I concluded that two types of conditions are suitable: one can suppress the amount of Ar^2H used (Table 5-1, Entry 6; Method A) and the other does not use any solvent (Table 5-1, Entry 12; Method B).

Table 5-1. Screening of acids and solvents



Entry	Acid	Solvent	**18aa** / %[a]
1	AcOH	CH_2Cl_2	N.D.[b]
2	TsOH	CH_2Cl_2	N.D.[b]
3	TfOH	CH_2Cl_2	8
4	$FeCl_3$	CH_2Cl_2	N.D.[b]
5	BF_3•OEt_2	CH_2Cl_2	N.D.[b]
6	$AlCl_3$	CH_2Cl_2	68(63)[c]
7[d]	$AlCl_3$	CH_2Cl_2	34
8	$AlCl_3$	THF	N.D.[b]
9	$AlCl_3$	MeCN	N.D.[b]
10	$AlCl_3$	$MeNO_2$	N.D.[b]
11[e]	$AlCl_3$	$(CF_3)CHOH$	Trace
12[f]	$AlCl_3$	None	96(91)[c]

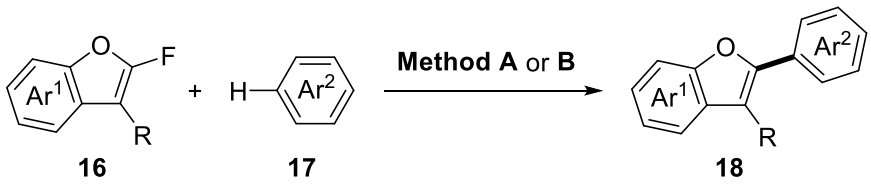
a: Yield was determined by ^{1}H NMR using CH_2Br_2 as an internal standard. b: N.D. = Not detected. c: Isolated yield.
d: Molecular sieves 4 A (250 wt%) was added. e: 0 °C.
f: Reaction was conducted at room temperature using **17a** (20 eq).

5-2-2. Substrate Scope

The coupling reactions of a variety of substituted **16** with several arenes **17** were investigated using Method A and/or Method B mentioned above (Table 5-2).[10,11] Relatively electron-rich Ar^{2}H, such as **17a**, *m*-xylene (**17b**), thiophene (**17c**), phenol (**17d**), 1,3-dimethoxybenzene (**17e**), and 1,4-dimethoxybenzene (**17f**), were successfully coupled with unsubstituted and substituted **16**. Notably, C–C bond formation, rather than C–O bond formation, occurred exclusively in the case of the reaction with **17d** to produce **18ad**, despite substantial nucleophilicity of the hydroxyl group. To afford **18ba**–**18bc**, **18bf**, **18ca**, and **18da**, 2-fluorobenzofurans **16b**–**16d** bearing an alkyl or an aryl group at the 3-position underwent defluorinative coupling. Using Method B,

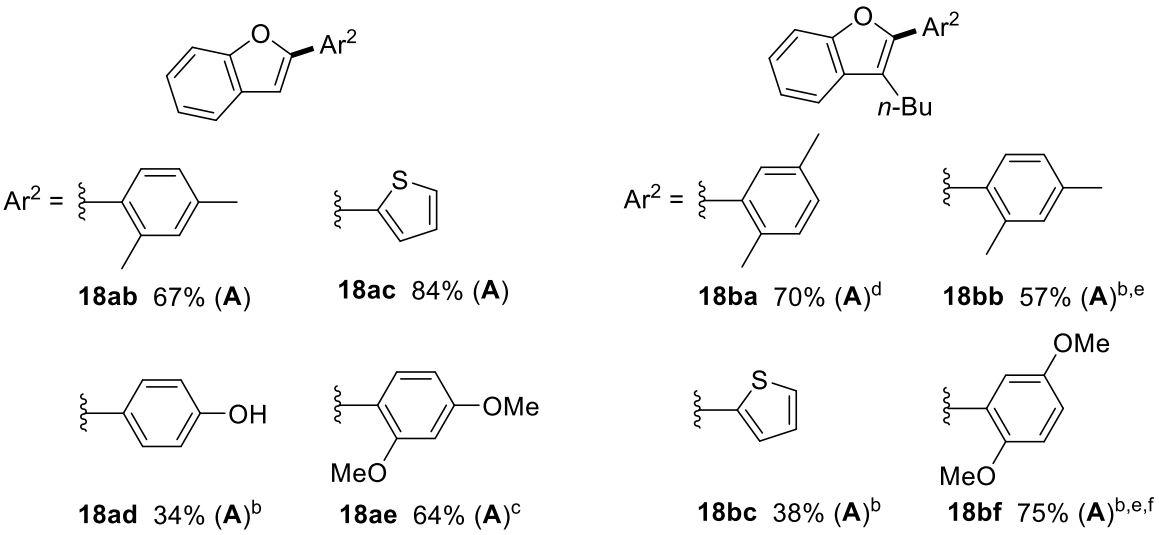
the yields of 2-arylated 5-phenylbenzofurans **18ea** and **18eb** were drastically improved up to 96% and 99% yields, respectively. The coupling of 2-fluorobenzofurans **16i**–**16k** bearing a methoxy group at the 5-, 6-, or 7-position proceeded regardless of the position of the substituent. Not only 2-fluorobenzofurans but also 2-fluoronaphtho[2,1-*b*]furan (**16l**) and 2-fluorobenzothiophene (**16m**) participated in the reaction to afford the corresponding 2-arylated naphthofuran **18la** in a 43% yield (Method B) and benzothiophene **18mb** in a 33% yield (Method A), respectively. The one-step synthesis of 2-(2,4-dihydroxyphenyl)benzofuran (**18ag**, DHBF),[12] which possesses a bacterial biofilm formation inhibitory activity, was achieved through the $AlCl_3$-mediated coupling of **16a** with resorcinol (**17g**) in a CH_2Cl_2–$(CF_3)_2CHOH$ (10/1) mixed solvent system at room temperature. In addition, the coupling of 7-chloro-2-fluorobenzofuran (**16n**) with **17d** proceeded at room temperature to afford the corresponding benzofuran **18nd** in a 54% yield, which served as a cholinesterase inhibitor (ChEI).[13] It is noteworthy that bromine- and chlorine-bearing fluorobenzofurans **16h** and **16n** exclusively underwent defluorinative coupling without C–Br and C–Cl bond cleavage (**18ha**–**18hc** and **18nd**). Furthermore, even electron-withdrawing groups (CO_2Et **18ga**, Br, and Cl) on 2-fluorobenzofuran nucleophiles are not only tolerated in the reaction but also do not reduce the efficiency.

Table 5-2. Substrate Scope

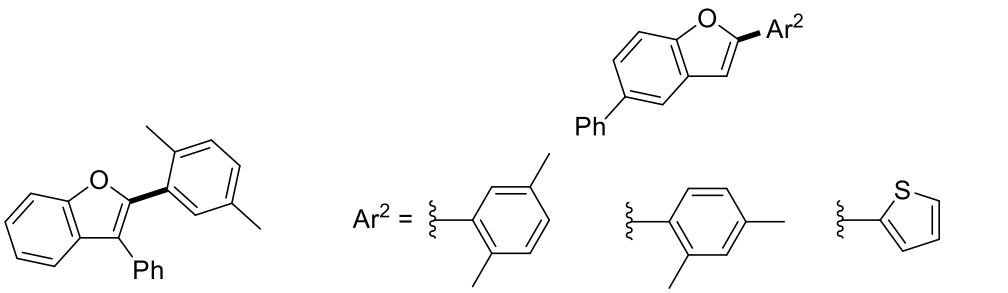


16 **17** **18**

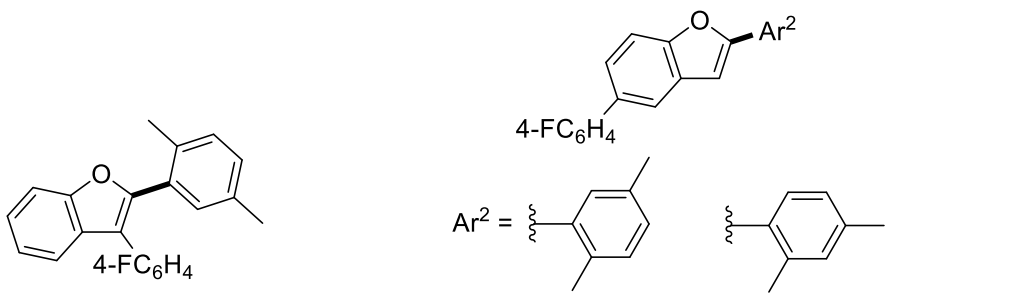
Method A: **2** (4.8–5.1 eq), $AlCl_3$ (1.4–1.6 eq), CH_2Cl_2, –20 °C, 1 h
Method B: **2** (18–20 eq), $AlCl_3$ (1.4–1.6 eq), RT, 1 h



18ab 67% (**A**)
18ac 84% (**A**)
18ba 70% (**A**)[d]
18bb 57% (**A**)[b,e]
18ad 34% (**A**)[b]
18ae 64% (**A**)[c]
18bc 38% (**A**)[b]
18bf 75% (**A**)[b,e,f]



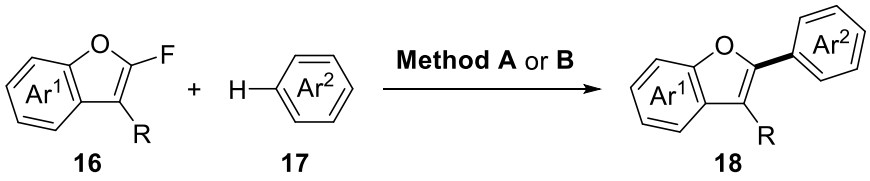
18ca 21% (**A**)
26% (**B**)[g]
18ea 70% (**A**)
96% (**B**)
18eb 51% (**A**)
99% (**B**)
18ec 30% (**A**)



18da 25% (**A**)
33% (**B**)[h]
18fa 74% (**A**)
18fb 56% (**A**)
65% (**B**)

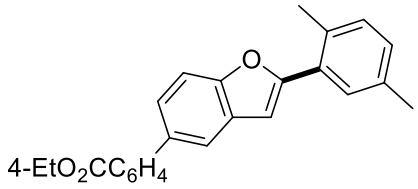
---

a; Isolated yield. b; RT c: 40 °C, 24 h. d: 3 h. e: 2 h. f: **17f** (2.0 equiv). g: $AlCl_3$ (2.0 equiv), **17a** (26 equiv). h: **17a** (23 equiv). i: CH_2Cl_2–$(CF_3)_2CHOH$ (10/1).

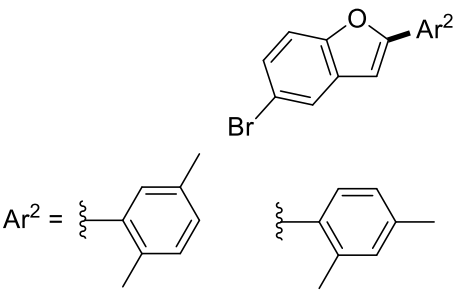


16 **17** **18**

Method A: **2** (4.8–5.1 eq), $AlCl_3$ (1.4–1.6 eq), CH_2Cl_2, –20 °C, 1 h
Method B: **2** (18–20 eq), $AlCl_3$ (1.4–1.6 eq), RT, 1 h



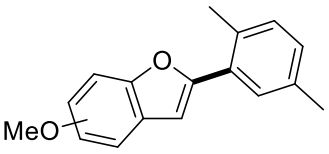
18ga 52% (**A**)



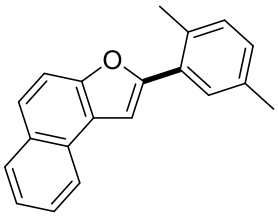
18ha 74% (**A**)
86% (**B**)

18hb 79% (**A**)
86% (**B**)

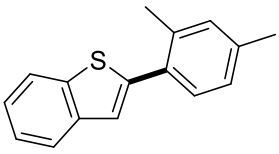
18hc 40% (**A**)



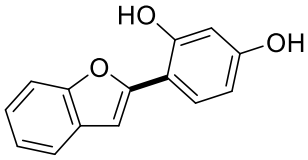
5-MeO: **18ia** 43% (**A**)[b]
6-MeO: **18ja** 43% (**A**)[b]
7-MeO: **18ka** 46% (**A**)[b]



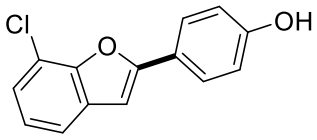
18la 37% (**A**)[b]
43% (**B**)



18mb 33% (**A**)



18ag 49% (**A**)[b,e,j]

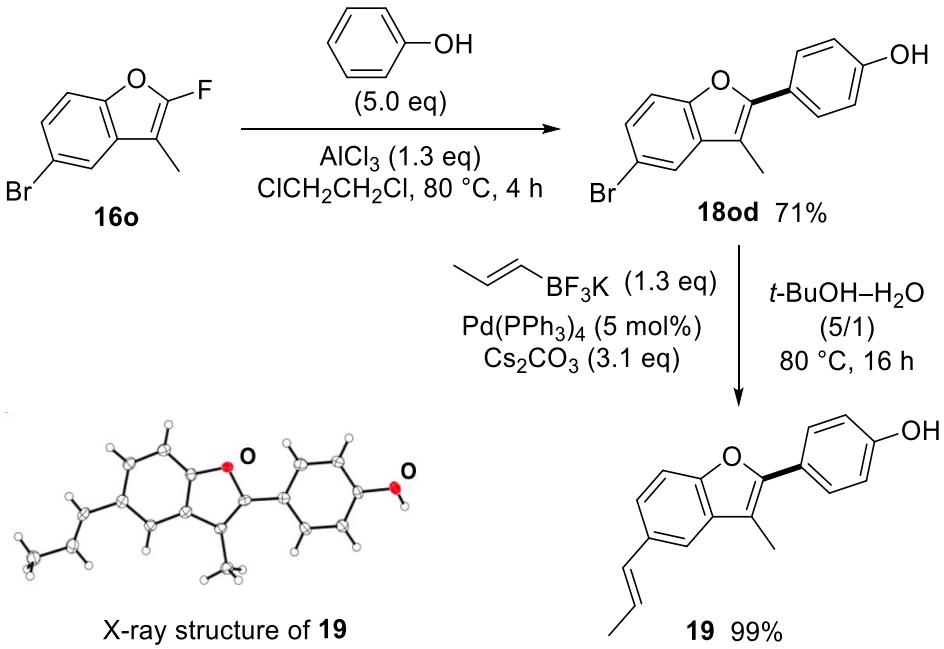


18nd 54% (**A**)[b]

---

a; Isolated yield. b; RT c: 40 °C, 24 h. d: 3 h. e: 2 h. f: **17f** (2.0 equiv). g: $AlCl_3$ (2.0 equiv), **17a** (26 equiv). h: **17a** (23 equiv). i: CH_2Cl_2–$(CF_3)_2CHOH$ (10/1).

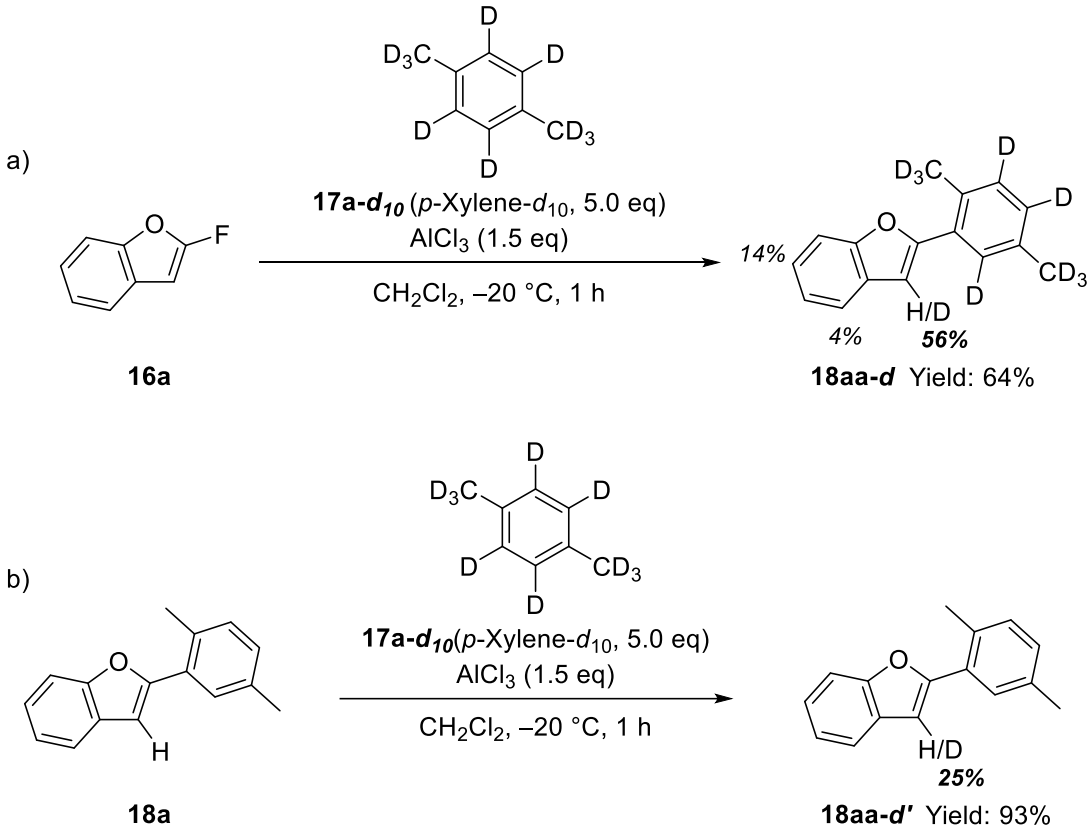
This protocol was successfully applied to the short-step synthesis of bioactive eupomatenoid 6 (**19**), which is a member of a family of naturally occurring 2-aryl-3-methyl-5-[(*E*)-prop-1-en-1-yl]benzofurans with antifungal, insecticidal, and antioxidant properties.[14] The strategy is based on the orthogonal coupling reaction using fluorine and bromine substituents on the benzofuran nucleus. In the presence of $AlCl_3$, the treatment of readily available 5-bromo-2-fluoro-3-methylbenzofuran (**16o**) with **17d** in 1,2-dichloroethane (DCE) at 80 °C afforded the corresponding coupling product **18od** in a 71% yield via the exclusive C–F bond cleavage and C–C bond formation (Scheme 5-2). Subsequent Suzuki–Miyaura coupling of **18od** with potassium (*E*)-(prop-1-en-1-yl)trifluoroborate afforded **19** quantitatively. The unambiguous structural determination of **19** was achieved by X-ray crystallographic analysis (Scheme 5-2).



Scheme 5-2. Synthesis of Eupomatenoid-6 (**19**)

5-2-3. Mechanistic Studies

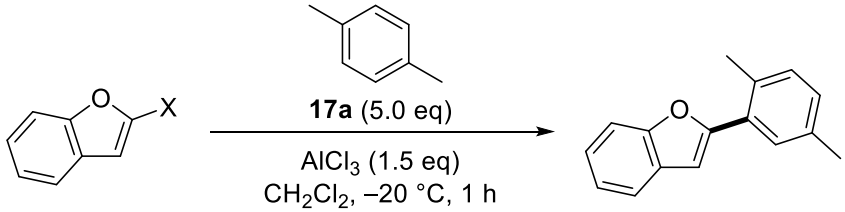
To gain mechanistic insight, I conducted control experiments using a deuterated substrate. In the presence of $AlCl_3$, the treatment of **16a** with fully deuterated **17a** (**17a-*d*$_{10}$**) afforded benzofuran ring-deuterated **18aa** (**18aa-*d***), which exhibited significant deuterium incorporation at the 3-position (56% D) and a low level of deuterium incorporation at the 4- and 6-positions (Scheme 5-3a). The source of the deuterium incorporated on the benzofuran ring should be the deuteron (D^+) generated not only via the elimination of the deuteron during the C–C bond formation but also via the H–D exchange of **17a-*d*$_{10}$** by residual protons. Thus, when nondeuterated product **18aa** was subjected to the same conditions, only a relatively small amount of deuterium incorporation was observed at the 3-position (25% D, Scheme 5-3b). The results of these experiments strongly suggest that substrates **16** are susceptible to protonation at the 3-position, which results in the generation of fluorine-stabilized carbocation intermediates[4,5] during the coupling process.



Scheme 5-3. Deuterium-labeling experiments

Furthermore, the effect of halogens on the 2-positions in benzofurans was investigated by reacting 2-halogenated benzofurans (**16a-Cl**: X = Cl; **16a-Br:** X = Br; **16a-I**: X = I) with **17a** in the presence of $AlCl_3$ (Table 5-3). Compared to the fluorine substituent (**16a**: X = F, Table 5-3, Entry 1), chlorine (**16a-Cl**), bromine (**16a-Br**), and iodine (**16a-I**) substituents hardly promoted the reaction (Table 5-3, Entries 2–4). These results, along with those of the aforementioned control experiments (Scheme 5-3), clearly indicate that the fluorine substituent plays a crucial role in the stabilization of the intermediary carbocations,[4,5] resulting in an acceleration of the cation generation, that is, the rate-determining step in the Friedel–Crafts-type coupling reaction.

Table 5-3. Effect of fluorine



16a: X = F
16a-Cl: X = Cl
16a-Br: X = Br
16a-I: X = I

18aa

Entry	X	**18aa** / %
1	**F**	68
2	Cl	10
3	Br	3
4	I	N.D.

Yield is determined by ^{1}H NMR using CH_2Br_2 as internal standard.

5-3. Summary

In summary, I developed an intermolecular cross-coupling reaction of 2-fluorobenzofurans with arenes via acid-mediated C–F bond activation. In this reaction, α-fluorocarbocations, which are generated from the treatment of 2-fluorobenzofurans with an acid, served as key intermediates. This renders my method significantly different from other methods for C–F bond arylation using transition metals.[15] This protocol allows coupling under mild conditions and enables the direct and efficient synthesis of 2-arylbenzofurans, which includes bioactive agents and a natural product. Furthermore, because of the difficulty in the cleavage (stability) of the C–F bonds, I expect this method to be useful for the orthogonal synthesis of complex molecules via late-stage C–F bond activation.

5-4. References

[1] For selected reviews on transition-metal-catalyzed cross-coupling reactions of aryl halides with arylmetals, see: (a) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669-679. (b) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340-348. (c) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524. (d) Miyaura N. and Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (e) Hiyama, T. and Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471-1478.

[2] For selected reviews on transition-metal-catalyzed direct arylation of aryl halides with arenes, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev*. **2007**, *107*, 174-238. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826.

[3] For selected reviews on transition-metal-free direct arylation of aryl halides with arenes, see: (a) Sun, C.-L. and Shi, A.-J. *Chem. Rev.* **2014**, *114*, 9219-9280. (b) Rossi, R.; Lessi, M.; Manzini, C.; Marianetti G.; Bellina, F. *Adv. Synth. Catal*. **2015**, *357*, 3777-3814.

[4] (a) Suzuki, N.; Fujita, T.; Ichikawa, J. *Org. Lett.* **2015**, *17*, 4984-4987. (b) Suzuki, N.; Fujita, T.; Amsharov, K. Y.; Ichikawa, J. *Chem. Commun.* **2016**, *52*, 12948-12951.

[5] (a) Ichikawa, J.; Yokota, M.; Kudo T.; Umezaki, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 4870-4873. (b) Fuchibe, K.; Takao, G.; Takahashi, H.; Ijima, S.; Ichikawa, J. *Bull. Chem. Soc. Jpn.* **2019**, *92*, 2019-2029.

[6] 2-Fluorobenzofurans are now more readily available than other positional isomers such as 3-fluorobenzofurans. See: (a) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun*. **1997**, 1537-1538. (b) Morioka, R.; Fujita, T.; Ichikawa, J. *Helv. Chim. Acta* **2020**, *103*, e2000159. (c) Yuan, X.; Yao, J.-F.; Tang, Z.-Y. *Org. Lett.* **2017**, *19*, 1410-1413.

[7] (a) Allemann, O.; Duttwyler, S.; Romanato, P.; Baldridge, K. K.; Siegel, J. S. *Science* **2011**, *332*, 574-577. (b) Allemann, O.; Baldridge, K. K.; Siegel, J. S. *Org. Chem. Front.* **2015**, *2*, 1018-1021. (c) Shao, B.; Bagdasarian, A. L.; Popov, S.; Nelson, H. M. *Science*, **2017**, *355*, 1403-1407.

[8] (a) Amsharov, K. Y.; Kabdulov, M. A.; Jansen, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 4594-4597. (b) Steiner, A.-K. and Amsharov, K. Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 14732-14736. (c) Steiner, A.-K.; Sharapa, D. I.; Troyanov, S. I.; Nuss, J.; Amsharov, K. Y. *Chem. Eur. J.* **2021**, *27*, 6223-6229.

[9] The protons might be initially present in the reaction system as the superacid [$HAlCl_4$-n(OH)n] formed from $AlCl_3$ and a tiny amount of contaminated water. This is supported by the decrease in the reaction rate by the addition of molecular sieves.

[10] Even when the yields of 3 were low, 2-fluorobenzofurans 1 were completely consumed, and the dimers or trimers of 1 were obtained by their self-coupling.

[11] When the reactions were initiated at room temperature in Method A with smaller amounts of arenes 2, the formation of the dimers and/or trimers of 2-benzofurans 1 increased. Thus, Method A was applied mainly at –20 °C.

[12] Artini, M.; Papa, R.; Barbato, G.; Scoarughi, G. L.; Cellini, A.; Morazzoni, P.; Bombardelli, E.; Selan, L. *Bioorg. Med. Chem.* **2012**, *20*, 920-923.

[13] Delogu, G. L.; Matos, M. J.; Fanti, M.; Era, B.; Medda, R.; Pieroni, E.; Fais, A.; Kumar, A.; Pintus, F. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2308-2313.

[14] (a) Morelli, L.; Bernardi, A.; Sattin, S. *Carbohydr. Res*. **2014**, *390*, 33-41. (b) Heravi, M. M.; Zadsirjan, V.; Hamidi, H.; Amiri, P. H. T. *RSC Adv.* **2017**, *7*, 24470-24521.

[15] (a) Sun, A. D. and Love, J. A. *Dalton Trans*. **2010**, *39*, 10362-10374. (b) Weaver, J. and Senaweera, S. *Tetrahedron* **2014**, *70*, 7413-7428. (c) Yu, D.; Lu, L.; Shen, Q. *Org. Lett*. **2013**, *15*, 940-943. (d) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. *Chem. Rev*. **2015**, *115*, 931-972. (e) Dewanji, A.; Bülow, R. F.; Rueping, M. *Org. Lett.* **2020**, *22*, 1611-1617. (f) Nohira, I. and Chatani, N. *ACS Catal.* **2021**, *11*, 4644-4649.

5-5. Experimental Section

1. General Statement

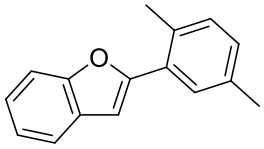
^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Avance 500. Chemical shift values are given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ = 0.00 ppm), $CDCl_3$ (for ^{13}C NMR: δ = 77.0 ppm), and C_6F_6 (for ^{19}F NMR: δ = 0.00 ppm). IR spectra were recorded on a Horiba FT-300S spectrometer by the attenuated total reflectance (ATR) method. Mass spectra were measured on a JEOL JMS-T100GCV and a JEOL JMS-T100CS spectrometer. Gel permeation chromatography (GPC) was performed on a Japan Analytical Industry LC-908 apparatus equipped with a JAIGEL-1H and -2H assembly. Elemental analyses were carried out at the Elemental Analysis Laboratory, Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba. X-ray diffraction studies were performed on a Bruker APEXII ULTRA instrument equipped with a CCD diffractometer using MoKα (graphite monochromated, λ = 0.71069 Å)

radiation. The structure refinement was performed using the Yadokari-XG software.[1] The structure was solved by direct methods (SIR97).[2] The positional and thermal parameters of non-hydrogen atoms were refined anisotropically on F2 by the full-matrix least-squares method using SHELX-97.[3] Hydrogen atoms were placed at calculated positions and refined with the riding mode on their corresponding carbon atoms. The CCDC deposition number of compound **19** is 2075144.

Column chromatography and preparative thin-layer chromatography were conducted on silica gel (Silica Gel 60 N, Kanto Chemical Co., Inc. for column chromatography and Wakogel B-5F, Wako Pure Chemical Industries for preparative thin-layer chromatography). Dichloromethane was purified by a solvent-purification system (GlassContour) equipped with columns of activated alumina and supported-copper catalyst (Q-5) before use. 1,1,1,3,3,3-Hexafluoropropan-2-ol (HFIP) was distilled from molecular sieves 4A and stored over activated molecular sieves 4A. 1,2-Dichloroethane (DCE) was distilled from P_2O_5 and stored over activated molecular sieves 4A. *p*-Xylene (**17a**) and *m*-xylene (**17b**) were distilled from CaH_2 and stored over activated molecular sieves 4A. 2-Fluorobenzofurans **16a**–**16l** and **16n**,[4,5] 2-fluorobenzothiophene (**16m**),[6] 5-bromo-3-methylbenzofuran-2-carboxylic acid,[7,8] 2-chlorobenzofuran (**16a-Cl**),[9,10] 2-bromobenzofuran (**16a-Br**),[11,12] and 2-iodobenzofuran (**16a-I**)[13,14] were prepared according to the literature procedures, and their spectral data showed good agreement with the literature data. Unless otherwise noted, materials were obtained from commercial sources and used directly without further purifications.

2. Synthesis of 2-Arylbenzofurans 18

2-(2,5-Dimethylphenyl)benzofuran (18aa)



Method A:

To a dichloromethane (2.0 mL) suspension of $AlCl_3$ (41 mg, 0.31 mmol) and *p*-xylene (**17a**, 0.12 mL, 1.0 mmol) was added 2-fluorobenzofuran (**16a**, 27 mg, 0.20 mmol) at –20 °C. After stirring at the same temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added and allowed to warm to room temperature. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) to give **18aa** (28 mg, 63%) as colorless crystals.

Method B:

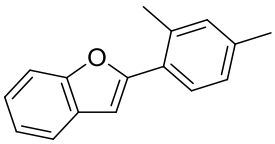
To a mixture of $AlCl_3$ (41 mg, 0.31 mmol) and *p*-xylene (**17a**, 0.50 mL, 4.1 mmol) was added 2-fluorobenzofuran (**16a**, 28 mg, 0.20 mmol) at room temperature. After stirring at room temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) to give **18aa** (41 mg, 91%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.53 (s, 3H), 6.88 (d, *J* = 0.9 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.22–7.30 (m, 2H), 7.52 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.68 (s,

1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.9, 21.4, 104.9, 111.0, 120.8, 122.7, 124.1, 128.5, 129.16, 129.23, 129.6, 131.2, 132.7, 135.5, 154.3, 155.7.

Spectral data for this compound showed good agreement with literature data.[14]

2-(2,4-Dimethylphenyl)benzofuran (18ab)

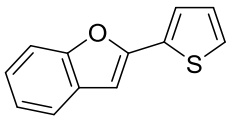


2-Arylbenzofuran **18ab** was synthesized by Method A using 2-fluorobenzofuran (**16a**, 27 mg, 0.20 mmol), *m*-xylene (**17b**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ab** (29 mg, 67%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.56 (s, 3H), 6.86 (s, 1H), 7.13–7.14 (m, 2H), 7.23–7.31 (m, 2H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.61 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 21.9, 104.5, 111.1, 120.8, 122.7, 124.0, 126.9, 127.2, 128.1, 129.3, 132.1, 135.7, 138.5, 154.3, 155.9.

Spectral data for this compound showed good agreement with literature data.[15]

2-(Thiophen-2-yl)benzofuran (18ac)



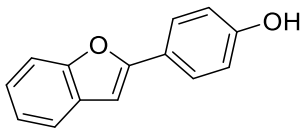
2-Arylbenzofuran **18ac** was synthesized by Method A using 2-fluorobenzofuran (**16a**, 27 mg, 0.20 mmol), thiophene (**17c**, 80 μL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **3**

18ac (33 mg, 84%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (d, *J* = 0.9 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.20–7.29 (m, 2H), 7.34 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.48–7.50 (m, 2H), 7.54 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 101.1, 111.1, 120.7, 123.1, 124.3, 124.6, 125.8, 127.9, 129.1, 133.3, 151.3, 154.5.

Spectral data for this compound showed good agreement with literature data.[16]

4-(Benzofuran-2-yl)phenol (18ad)

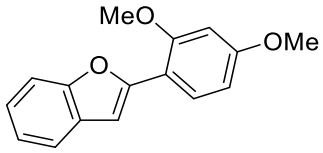


2-Arylbenzofuran **18ad** was synthesized by Method A using 2-fluorobenzofuran (**16a**, 27 mg, 0.20 mmol), phenol (**17d**, 94 mg, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 3/1) gave **18ad** (14 mg, 34%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.99 (s, 1H), 6.88 (d, *J* = 0.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.19–7.27 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.55 (d, *J* = 6.5 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 99.7, 111.0, 115.7, 120.6, 122.8, 123.6, 123.8, 126.7, 129.4, 154.7, 155.9, 156.0.

Spectral data for this compound showed good agreement with literature data.[17]

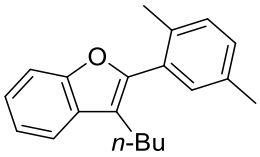
2-(2,4-Dimethoxyphenyl)benzofuran (18ae)



2-Arylbenzofuran **18ae** was synthesized by Method A using 2-fluorobenzofuran (**16a**, 56 mg, 0.41 mmol), 1,3-dimethoxybenzene (**17e**, 0.26 mL, 2.0 mmol), $AlCl_3$ (82 mg, 0.61 mmol), and dichloromethane (4.0 mL) at 40 °C for 24 h. Purification by GPC (chloroform) gave **18ae** (67 mg, 64%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.96 (s, 3H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.61 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.17–7.24 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 55.45, 55.48, 98.8, 104.2, 104.8, 110.6, 112.8, 120.7, 122.5, 123.5, 128.0, 130.0, 152.4, 153.7, 157.8, 160.9. IR (neat): ν 2960, 2939, 2837, 1612, 1504, 1452, 1290, 1254, 1211, 1159, 1049, 1032, 798, 750 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{16}H_{14}O_3$ $[M]^+$: 254.0943; Found: 254.0947.

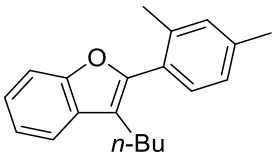
3-Butyl-2-(2,5-dimethylphenyl)benzofuran (18ba)



2-Arylbenzofuran **18ba** was synthesized by Method A using 3-butyl-2-fluorobenzofuran (**16b**, 39 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (1.0 mL) at –20 °C for 3 h. Purification by silica gel column chromatography (hexane/ethyl acetate = 25/1) gave **18ba** (40 mg, 70%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.3 Hz, 3H), 1.29–1.36 (m, 2H), 1.62–1.68 (m, 2H), 2.27 (s, 3H), 2.36 (s, 3H), 2.65 (t, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.19–7.21 (m, 2H), 7.23–7.30 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.8, 19.7, 20.9, 22.5, 23.7, 31.7, 111.1, 116.8, 119.7, 122.1, 123.7, 129.6, 129.8, 130.2, 130.4, 131.1, 134.9, 135.2, 152.3, 154.3. IR (neat): ν 2954, 2927, 2858, 1452, 1257, 1101, 872, 812, 743 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{20}H_{22}O$ $[M]^+$: 278.1671; Found: 278.1670.

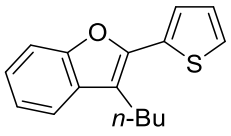
3-Butyl-2-(2,4-dimethylphenyl)benzofuran (18bb)



2-Arylbenzofuran **18bb** was synthesized by Method A using 3-butyl-2-fluorobenzofuran (**16b**, 48 mg, 0.25 mmol), *m*-xylene (**17b**, 133 mg, 1.3 mmol), $AlCl_3$ (52 mg, 0.39 mmol), and dichloromethane (2.5 mL) at room temperature for 2 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18bb** (39 mg, 57%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.33 (qt, *J* = 7.5, 7.5 Hz, 2H), 1.65 (tt, *J* = 7.5, 7.5 Hz, 2H), 2.30 (s, 3H), 2.40 (s, 3H), 2.66 (t, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.15 (s, 1H), 7.24–7.30 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.8, 20.1, 21.3, 22.6, 23.7, 31.8, 111.1, 116.8, 119.7, 122.0, 123.6, 126.2, 127.5, 129.7, 130.5, 131.3, 138.2, 138.9, 152.3, 154.3. IR (neat): ν 2956, 2927, 2858, 1614, 1454, 1259, 744, 592 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{20}H_{22}O$ $[M]^+$: 278.1671; Found: 278.1680.

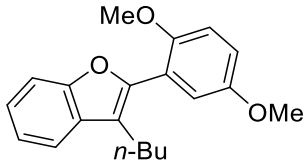
3-Butyl-2-(thiophen-2-yl)benzofuran (18bc)



2-Arylbenzofuran **18bc** was synthesized by Method A using 3-butyl-2-fluorobenzofuran (**16b**, 39 mg, 0.20 mmol), thiophene (**17c**, 84 mg, 1.0 mmol), $AlCl_3$ (42 mg, 0.31 mmol), and dichloromethane (2.0 mL) at room temperature for 1 h. Purification by silica gel column chromatography (hexane) gave **18bb** (20 mg, 38%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.46–1.54 (m, 2H), 1.69–1.74 (m, 2H), 2.92 (t, *J* = 8.0 Hz, 2H), 7.14–7.15 (m, 1H), 7.21–7.29 (m, 2H), 7.37 (ddd, *J* = 5.1, 1.2, 1.2 Hz, 1H), 7.45–7.48 (m, 2H), 7.53 (dd, *J* = 7.7, 0.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.0, 22.9, 24.0, 31.5, 110.9, 116.0, 119.4, 122.5, 124.3, 124.8, 125.5, 127.5, 130.4, 133.2, 146.5, 153.8. IR (neat): *ν* 2954, 2927, 2858, 1454, 1259, 1214, 1103, 1013, 851, 743, 694 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{16}H_{16}OS$ $[M]^+$: 256.0922; Found: 256.0925.

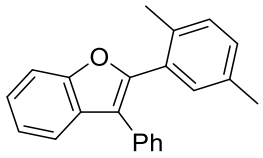
3-Butyl-2-(2,4-dimethoxyphenyl)benzofuran (18bf)



2-Arylbenzofuran **18bf** was synthesized by Method A using 3-butyl-2-fluorobenzofuran (**16b**, 39 mg, 0.20 mmol), 1,4-dimethoxybenzene (**17f**, 57 mg, 0.41 mmol), $AlCl_3$ (41 mg, 0.31 mmol), and dichloromethane (2.0 mL) at room temperature for 2 h. Purification by silica gel column chromatography (toluene/dichloromethane = 10/1) gave **18bf** (47 mg, 75%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.35 (qt, *J* = 7.5, 7.4 Hz, 2H), 1.63–1.69 (m, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.93–6.97 (m, 2H), 7.05 (dd, *J* = 1.1, 1.1 Hz, 1H), 7.22–7.29 (m, 2H), 7.48 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.59 (dd, *J* = 7.6, 0.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.9, 22.8, 24.1, 31.6, 55.8, 56.3, 111.1, 112.8, 115.6, 116.6, 118.1, 119.8, 121.0, 122.0, 123.8, 129.9, 148.6, 151.8, 153.4, 154.5. IR (neat): *ν* 2954, 2858, 2832, 2360, 1498, 1454, 1473, 1223, 1174, 1039, 804, 733 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{20}H_{22}O_3$ $[M]^+$: 310.1569; Found: 310.1564.

2-(2,5-Dimethylphenyl)-3-phenylbenzofuran (18ca)

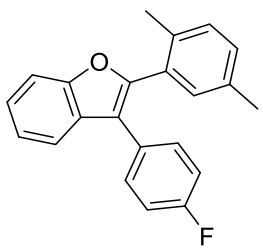


2-Arylbenzofuran **18ca** was synthesized by Method A using 2-fluoro-3-phenylbenzofuran (**16c**, 42 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1) gave **18ca** (12 mg, 21%) as a white solid.

2-Arylbenzofuran **18ca** was also synthesized by Method B using 2-fluoro-3-phenylbenzofuran (**16c**, 25 mg, 0.12 mmol), *p*-xylene (**17a**, 0.38 mL, 3.1 mmol), and $AlCl_3$ (31 mg, 0.23 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ca** (9.0 mg, 26%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.29 (s, 3H), 7.10 (d, *J* = 1.7 Hz, 1H), 7.24–7.39 (m, 9H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.74–7.76 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.6, 20.8, 111.2, 118.3, 120.0, 122.8, 124.3, 126.9, 127.1, 128.6, 128.67, 128.72, 130.0, 130.5, 131.2, 132.8, 134.5, 135.1, 152.1, 154.5. IR (neat): ν 3033, 2924, 1653, 1606, 1452, 814, 742, 698 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{22}H_{18}O$ $[M]^+$: 298.1358; Found: 298.1350.

2-(2,5-Dimethylphenyl)-3-(4-fluorophenyl)benzofuran (18da)

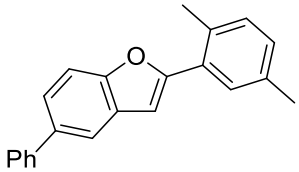


2-Arylbenzofuran **18da** was synthesized by Method A using 2-fluoro-3-(4-fluorophenyl)benzofuran (**16d**, 46 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1) gave **18da** (16 mg, 25%) as a white solid.

2-Arylbenzofuran **18da** was also synthesized by Method B using 2-fluoro-3-(4-fluorophenyl)benzofuran (**16d**, 31 mg, 0.14 mmol), *p*-xylene (**17a**, 0.38 mL, 3.1 mmol), and $AlCl_3$ (30 mg, 0.22 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18da** (14 mg, 33%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.03 (s, 3H), 2.28 (s, 3H), 7.03 (dd, J_{HF} = 8.6 Hz, J = 8.6 Hz, 2H), 7.10 (s, 1H), 7.21 (br s, 1H), 7.27–7.35 (m, 4H), 7.53 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.6, 20.8, 111.4, 115.7 (d, J_{CF} = 21 Hz, 1H), 117.4, 119.8, 122.9, 124.4, 128.4, 128.9 (d, J_{CF} = 3 Hz, 1H), 129.9 (d, J_{CF} = 5 Hz, 1H), 130.1, 130.4 (d, J_{CF} = 8 Hz, 1H), 130.6, 131.2, 134.5, 135.2, 152.2, 154.5, 161.9 (d, J_{CF} = 247 Hz, 1H). ^{19}F NMR (500 MHz, $CDCl_3$): δ 47.8 (tt, J_{FH} = 9, 5 Hz). IR (neat): ν 2962, 2922, 1512, 1450, 1221, 837, 812, 744, 525 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{22}H_{17}FO$ $[M]^+$: 316.1263; Found: 316.1265.

2-(2,5-Dimethylphenyl)-5-phenylbenzofuran (18ea)



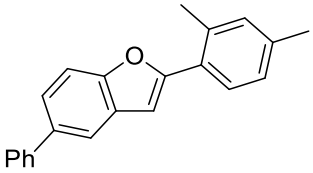
2-Arylbenzofuran **18ea** was synthesized by Method A using 2-fluoro-5-phenylbenzofuran (**16e**, 42 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –

20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ea** (42 mg, 70%) as a white solid.

2-Arylbenzofuran **18ea** was also synthesized by Method B using 2-fluoro-5-phenylbenzofuran (**16e**, 43 mg, 0.20 mmol), *p*-xylene (**17a**, 0.50 mL, 4.1 mmol), and $AlCl_3$ (39 mg, 0.29 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ea** (59 mg, 96%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H), 2.55 (s, 3H), 6.91 (s, 1H), 7.10–7.19 (m, 2H), 7.33–7.36 (m, 1H), 7.43–7.78 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 21.4, 105.1, 111.1, 119.3, 123.9, 126.8, 127.4, 128.6, 128.7, 129.3, 129.5, 129.7, 131.2, 132.7, 135.5, 136.4, 141.7, 153.9, 156.5. IR (neat): ν 3030, 2922, 2862, 1458, 1036, 804, 760, 698 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{22}H_{18}O$ $[M]^+$: 298.1358; Found: 298.1361. Elem. Anal. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.52; H, 6.12.

2-(2,4-Dimethylphenyl)-5-phenylbenzofuran (18eb)

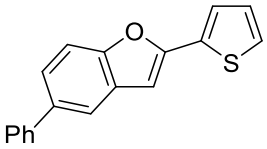


2-Arylbenzofuran **18eb** was synthesized by Method A using 2-fluoro-5-phenylbenzofuran (**16e**, 44 mg, 0.21 mmol), *m*-xylene (**17b**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane) gave **18eb** (31 mg, 51%) as colorless crystals.

2-Arylbenzofuran **18eb** was also synthesized by Method B using 2-fluoro-5-phenylbenzofuran (**16e**, 43 mg, 0.20 mmol), *m*-xylene (**17b**, 0.50 mL, 4.1 mmol), and $AlCl_3$ (40 mg, 0.30 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane) gave **18eb** (61 mg, 99%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.54 (s, 3H), 6.86 (s, 1H), 7.10–7.11 (m, 2H), 7.31–7.34 (m, 1H), 7.43 (dd, *J* = 8.0, 7.9 Hz, 2H), 7.49 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.61 (dd, *J* = 8.0, 0.9 Hz, 2H), 7.74–7.76 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 21.8, 104.6, 111.1, 119.2, 123.7, 126.79, 126.84, 127.0, 127.4, 128.1, 128.7, 129.8, 132.0, 135.6, 136.4, 138.5, 141.7, 153.9, 156.6. IR (neat): ν 3030, 2922, 1462, 1036, 800, 760, 696 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{22}H_{18}O$ $[M]^+$: 298.1358, Found: 298.1359.

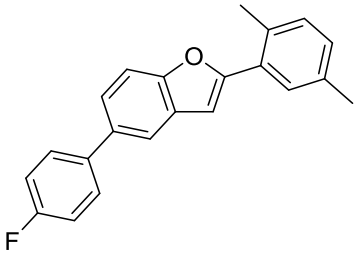
5-Phenyl-2-(thiophen-2-yl)benzofuran (18ec)



2-Arylbenzofuran **18ec** was synthesized by Method A using 2-fluoro-5-phenylbenzofuran (**16e**, 42 mg, 0.20 mmol), thiophene (**17c**, 80 μL, 1.0 mmol), $AlCl_3$ (41 mg, 0.31 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ec** (17 mg, 30%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H), 7.11–7.13 (m, 1H), 7.34–7.37 (m, 2H), 7.44–7.56 (m, 5H), 7.62–7.64 (m, 2H), 7.73 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 101.2, 111.1, 119.2, 124.0, 124.7, 125.9, 126.9, 127.4, 127.9, 128.7, 129.6, 133.2, 136.8, 141.6, 151.9, 154.2. IR (neat): ν 1464, 1265, 1201, 1147, 999, 879, 827, 800, 762, 696 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{18}H_{12}OS$ $[M]^+$: 276.0609; Found: 276.0617.

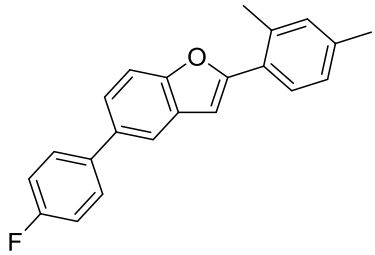
2-(2,5-Dimethylphenyl)-5-(4-fluorophenyl)benzofuran (18fa)



2-Arylbenzofuran **18fa** was synthesized by Method A using 2-fluoro-5-(4-fluorophenyl)benzofuran (**16f**, 46 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 20/1) gave **18fa** (47 mg, 74%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.53 (s, 3H), 6.88 (s, 1H), 7.09–7.13 (m, 3H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.53–7.56 (m, 3H), 7.68 (br s, 1H), 7.70 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 21.5, 105.0, 111.2, 115.5 (d, J_{CF} = 21 Hz), 119.2, 123.7, 128.6, 128.9 (d, J_{CF} = 8 Hz), 129.4, 129.5, 129.8, 131.3, 132.7, 135.5, 135.6, 137.8 (d, J_{CF} = 3 Hz), 153.9, 156.6, 162.2 (d, J_{CF} = 260 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 46.3 (tt, J_{FH} = 9, 5 Hz). IR (neat): □ 3039, 2927, 2864, 1514, 1460, 1219, 1157, 837, 802, 526 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{22}H_{17}FO$ $[M]^+$: 316.1263; Found: 316.1262.

2-(2,4-Dimethylphenyl)-5-(4-fluorophenyl)benzofuran (18fb)



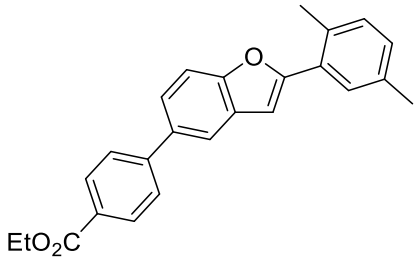
2-Arylbenzofuran **18fb** was synthesized by Method A using 2-fluoro-5-(4-fluorophenyl)benzofuran (**16f**, 47 mg, 0.21 mmol), *m*-xylene (**17b**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0

mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18fb** (37 mg, 56%) as colorless crystals.

2-Arylbenzofuran **18fb** was also synthesized by Method B using 2-fluoro-5-(4-fluorophenyl)benzofuran (**16f**, 51 mg, 0.22 mmol), *m*-xylene (**17b**, 0.50 mL, 4.1 mmol), and $AlCl_3$ (41 mg, 0.31 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18fb** (46 mg, 65%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.55 (s, 3H), 6.85 (s, 1H), 7.10–7.14 (m, 4H), 7.42 (dd, J = 8.5, 1.9 Hz, 1H), 7.53–7.57 (m, 3H), 7.70 (d, J = 1.9 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 21.8, 104.5, 111.1, 115.5 (d, J_{CF} = 21 Hz), 119.1, 123.6, 126.9, 127.0, 128.1, 128.9 (d, J_{CF} = 8 Hz), 129.9, 132.1, 135.5, 135.7, 137.9 (d, J_{CF} = 3 Hz), 138.6, 153.8, 156.7, 162.2 (d, J_{CF} = 246 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ 46.2 (tt, J_{FH} = 9, 5 Hz). IR (neat): ν 2983, 2918, 1514, 1464, 1225, 1161, 1018, 798 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{22}H_{17}FO$ $[M]^+$: 316.1263; Found: 316.1260.

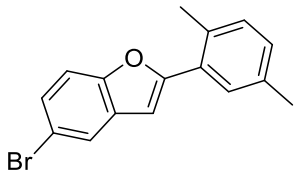
Ethyl 4-[2-(2,5-Dimethylphenyl)benzofuran-5-yl]benzoate (18ga)



2-Arylbenzofuran **18ga** was synthesized by Method A using ethyl 4-(2-fluorobenzofuran-5-yl)benzoate (**16g**, 57 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 10/1) gave **18ga** (38 mg, 52%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.2 Hz, 3H), 2.41 (s, 3H), 2.56 (s, 3H), 4.41 (q, *J* = 7.2 Hz, 2H), 6.94 (d, *J* = 0.8 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 1H), 7.70–7.71 (m, 3H), 7.83–7.84 (m, 1H), 8.13 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.4, 21.0, 21.5, 60.9, 105.1, 111.3, 119.6, 123.9, 127.2, 128.6, 128.8, 129.4, 129.5, 129.9, 130.1, 131.3, 132.8, 135.3, 135.6, 146.1, 154.3, 156.8, 166.6. IR (neat): ν 2976, 2927, 1714, 1608, 1275, 1103, 810, 771 cm^{-1}. HRMS (ESI+): *m*/*z* Calcd. for $C_{25}H_{23}O_3$ $[M + H]^+$: 371.1647; Found: 371.1644.

5-Bromo-2-(2,5-dimethylphenyl)benzofuran (18ha)



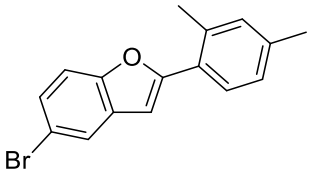
2-Arylbenzofuran **18ha** was synthesized by Method A using 5-bromo-2-fluorobenzofuran (**16h**, 43 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (41 mg, 0.31 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ha** (45 mg, 74%) as colorless crystals.

2-Arylbenzofuran **18ha** was also synthesized by Method B using 5-bromo-2-fluorobenzofuran (**16h**, 46 mg, 0.21 mmol), *p*-xylene (**17a**, 0.50 mL, 4.1 mmol), and $AlCl_3$ (41 mg, 0.30 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ha** (55 mg, 86%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.51 (s, 3H), 6.80 (s, 1H), 7.10–7.19 (m, 2H), 7.37–7.38 (m, 2H), 7.67 (s, 1H), 7.71 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.9, 21.4, 104.2, 112.4, 115.7, 123.4, 126.9, 128.6,

129.0, 129.6, 131.2, 131.3, 132.8, 135.6, 153.0, 157.1. IR (neat): ν 2922, 2862, 1504, 1442, 1263, 1178, 904, 795, 771, 669 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{16}H_{13}{}^{79}BrO$ [M]$^{+}$: 300.0150; Found: 300.0155.

5-Bromo-2-(2,4-dimethylphenyl)benzofuran (18hb)

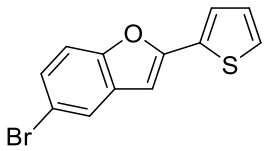


2-Arylbenzofuran **18hb** was synthesized by Method A using 5-bromo-2-fluorobenzofuran (**16h**, 43 mg, 0.20 mmol), *m*-xylene (**17b**, 0.12 mL, 1.0 mmol), $AlCl_3$ (41 mg, 0.31 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18hb** (47 mg, 79%) as colorless crystals.

2-Arylbenzofuran **18hb** was also synthesized by Method B using 5-bromo-2-fluorobenzofuran (**16h**, 44 mg, 0.20 mmol), *m*-xylene (**17b**, 0.50 mL, 4.1 mmol), and $AlCl_3$ (41 mg, 0.31 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18hb** (53 mg, 86%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.51 (s, 3H), 6.75 (s, 1H), 7.09–7.10 (m, 2H), 7.33–7.37 (m, 2H), 7.68–7.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.2, 21.8, 103.7, 112.4, 115.7, 123.3, 126.5, 126.8, 126.9, 128.1, 131.3, 132.1, 135.7, 138.9, 153.0, 157.2. IR (neat): ν 3016, 2922, 2862, 1610, 1454, 1441, 1259, 1049, 1020, 793, 671 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{16}H_{13}{}^{79}BrO$ [M]$^{+}$: 300.0150; Found: 300.0155.

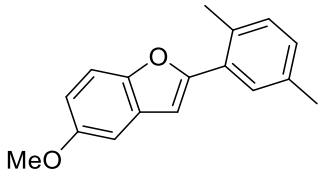
5-Bromo-2-(thiophen-2-yl)benzofuran (18hc)



2-Arylbenzofuran **18hc** was synthesized by Method A using 5-bromo-2-fluorobenzofuran (**16h**, 43 mg, 0.20 mmol), thiophene (**17c**, 80 μL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18hc** (23 mg, 40%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 1H), 7.11 (dd, *J* = 5.0, 3.6 Hz, 1H), 7.35–7.37 (m, 3H), 7.49 (d, *J* = 3.6, 1.0 Hz, 1H), 7.66 (dd, *J* = 1.2, 1.2 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 100.3, 112.4, 116.1, 123.2, 125.1, 126.3, 127.0, 127.9, 131.1, 132.6, 152.5, 153.2. IR (neat): *ν* 1442, 1263, 1200, 1051, 997, 876, 850, 795, 706 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{12}H_7{}^{79}BrOS$ $[M]^+$: 277.9401; Found: 277.9394.

2-(2,5-Dimethylphenyl)-5-methoxybenzofuran (18ia)

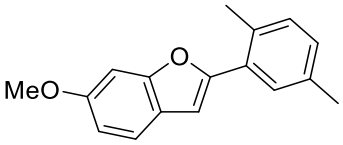


2-Arylbenzofuran **18ia** was synthesized by Method A using 2-fluoro-5-methoxybenzofuran (**16i**, 28 mg, 0.17 mmol), *p*-xylene (**17a**, 0.10 mL, 0.84 mmol), $AlCl_3$ (33 mg, 0.25 mmol), and dichloromethane (2.0 mL) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ia** (18 mg, 43%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.51 (s, 3H), 3.84 (s, 3H), 6.80 (d, *J* = 0.8 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.05 (d, *J* = 2.6 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.64 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.9, 21.4, 55.9, 103.2, 105.1, 111.4, 112.8, 128.5,

129.2, 129.65, 129.68, 131.2, 132.6, 135.5, 149.3, 155.9, 156.5. IR (neat): ν 2954, 2831, 1616, 1477, 1205, 1032, 808 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{17}H_{16}O_2$ $[M]^+$: 252.1150; Found: 252.1145.

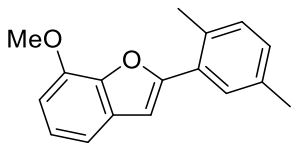
2-(2,5-Dimethylphenyl)-6-methoxybenzofuran (18ja)



2-Arylbenzofuran **18ja** was synthesized by Method A using 2-fluoro-6-methoxybenzofuran (**16j**, 28 mg, 0.17 mmol), *p*-xylene (**17a**, 0.10 mL, 0.84 mmol), $AlCl_3$ (33 mg, 0.25 mmol), and dichloromethane (2.0 mL) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ja** (18 mg, 43%) as a colorless oil.

^1H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H), 2.53 (s, 3H), 3.88 (s, 3H), 6.82 (s, 1H), 6.89 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.08–7.09 (m, 2H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.67 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 21.5, 55.7, 95.7, 104.8, 111.8, 120.9, 122.6, 128.2, 128.8, 129.8, 131.2, 132.2, 135.5, 154.9, 155.3, 158.0. IR (neat): ν 2952, 2833, 1620, 1491, 1306, 1275, 1151, 1111, 812 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{17}H_{16}O_2$ $[M]^+$: 252.1150; Found: 252.1157. Elem. Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.80; H, 6.66.

2-(2,5-Dimethylphenyl)-7-methoxybenzofuran (18ka)

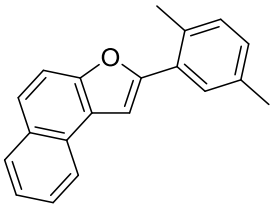


2-Arylbenzofuran **18ka** was synthesized by Method A using 2-fluoro-7-methoxybenzofuran (**16k**, 33 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at room

temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18ka** (23 mg, 46%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.53 (s, 3H), 4.05 (s, 3H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.87 (s, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.14–7.21 (m, 3H), 7.71 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.9, 21.4, 56.2, 105.3, 106.6, 113.3, 123.4, 128.7, 129.3, 129.5, 130.9, 131.1, 132.6, 135.5, 143.6, 145.3, 155.8. IR (neat): ν 2966, 2839, 1493, 1321, 1271, 1198, 1101, 983, 808, 731 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{17}H_{16}O_2$ [M]$^+$: 252.1150; Found: 252.1159.

2-(2,5-Dimethylphenyl)naphtho[2,1-*b*]furan (18la)

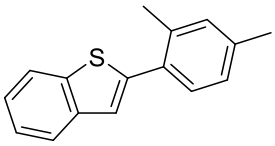


2-Arylnaphthofuran **18la** was synthesized by Method A using fluoronaptho[2,1-*b*]furan (**16l**, 37 mg, 0.20 mmol), *p*-xylene (**17a**, 0.12 mL, 1.0 mmol), $AlCl_3$ (40 mg, 0.30 mmol), and dichloromethane (2.0 mL) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18la** (20 mg, 37%) as a yellow solid.

2-Arylnaphthofuran **18la** was also synthesized by Method B using fluoronaptho[2,1-*b*]furan (**16l**, 37 mg, 0.20 mmol), *p*-xylene (**17a**, 0.50 mL, 4.1 mmol), and $AlCl_3$ (41.2 mg, 0.30 mmol) at room temperature for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) gave **18la** (23 mg, 43%) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.59 (s, 3H), 7.08 (d, *J* = 6.9 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.34 (s, 1H), 7.46 (dd, *J* = 7.0, 6.9 Hz, 1H), 7.57 (dd, *J* = 7.0, 7.0 Hz, 1H), 7.67–7.73 (m, 3H), 7.93 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 21.6, 104.0, 112.2, 123.4, 124.38, 124.44, 125.0, 126.2, 127.6, 128.4, 128.8, 129.1, 129.7, 130.3, 131.3, 132.4, 135.6, 151.8, 155.2. IR (neat): *ν* 3051, 2922, 2862, 1504, 1385, 1169, 993, 798, 771, 774 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_{20}H_{16}O$ $[M]^+$: 272.1201, Found 272.1191.

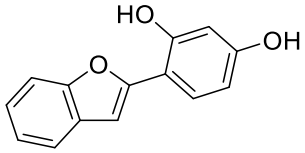
2-(2,4-Dimethylphenyl)benzo[*b*]thiophene (18mb)



2-Arylbenzothiophene **18mb** was synthesized by Method A using 2-fluorobenzo[*b*]thiophene (**16m**, 30 mg, 0.20 mmol), *m*-xylene (**17b**, 0.12 mL, 1.0 mmol), $AlCl_3$ (41 mg, 0.31 mmol), and dichloromethane (2.0 mL) at –20 °C for 1 h. Purification by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) and GPC (chloroform) gave **18mb** (16 mg, 33%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.43 (s, 3H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.11 (s, 1H), 7.21 (s, 1H), 7.29–7.37 (m, 3H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 21.1, 122.0, 122.7, 123.3, 123.9, 124.3, 126.7, 130.5, 131.2, 131.6, 136.2, 138.2, 140.0, 140.2, 143.6. IR (neat): *ν* 3060, 3012, 2952, 2918, 1493, 1456, 1435, 814, 744, 725 cm^{-1}. HRMS (EI): *m*/*z* Calcd for $C_{16}H_{14}S$ $[M]^+$: 238.0816; Found: 238.0812.

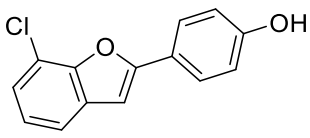
4-(Benzofuran-2-yl)benzene-1,2-diol (18ag, DHBF)



To a HFIP (12.0 mL) and dichloromethane (1.2 mL) solution of $AlCl_3$ (40 mg, 0.30 mmol) and resorcinol (**17g**, 110 mg, 1.0 mmol) was added 2-fluorobenzofuran (**16a**, 27 mg, 0.20 mmol) at room temperature. After stirring at room temperature for 2 h, aqueous NaOH (2 M, 3 mL) was added. To the mixture was added aqueous HCl (2 M, 3 mL), and organic materials were extracted with dichloromethane (3 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) to give **18ag** (22 mg, 49%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.97 (br s, 1H), 6.48–6.50 (m, 2H), 6.90 (d, *J* = 0.9 Hz, 1H), 7.22–7.28 (m, 2H), 7.35 (br s, 1H), 7.48–7.50 (m, 1H), 7.53–7.57 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 101.4, 104.0, 107.9, 108.7, 109.4, 110.9, 120.7, 123.4, 124.0, 128.6, 153.7, 154.6, 154.9, 157.5. IR (neat): ν 3494, 3379, 1624, 1599, 1506, 1446, 1304, 1242, 1151, 976, 916, 796, 735 cm^{-1}. HRMS (ESI–): *m*/*z* Calcd for $C_{14}H_9O_3$ $[M - H]^-$: 225.0552; Found: 225.0550.

4-(7-Chlorobenzofuran-2-yl)phenol (18nd)



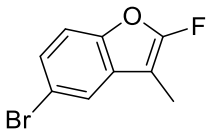
To a dichloromethane (2.0 mL) suspension of $AlCl_3$ (39 mg, 0.29 mmol) and phenol (**17d**, 96 mg, 1.0 mmol) was added 7-chloro-2-fluorobenzofuran (**16n**, 34 mg, 0.20 mmol) at room temperature. After stirring at room temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were extracted with dichloromethane (1 mL) three times. The combined extracts

were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 4/1) to give **18nd** (27 mg, 54%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (s, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.12 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.22 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 100.1, 115.8, 116.4, 119.1, 122.9, 123.7, 123.9, 126.9, 131.1, 150.4, 156.4, 156.8. IR (neat): ν 3336, 1502, 1473, 1423, 1290, 1244, 1236, 906, 835, 808, 735 cm^{-1}. HRMS (ESI–): *m*/*z* Calcd for $C_{14}H_8ClO_2$ [M – H]$^-$: 243.0213; Found: 243.0210.

3. Orthogonal Synthesis of Eupomatenoid 6 (19)

5-Bromo-2-fluoro-3-methylbenzofuran (16o)[18]

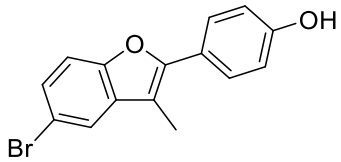


To a 1,2-dichloroethane (20 mL) and H_2O (10 mL) suspension of Selectfluor (4.25 g, 12.0 mmol) and KF (1.39 g, 23.9 mmol) was added 5-bromo-3-methylbenzofuran-2-carboxylic acid (1.47 g, 5.76 mmol) at room temperature. After stirring at 70 °C for 12 h, H_2O (20 mL) was added, and organic materials were extracted with dichloromethane (20 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane) to give **16o** (1.07 g, 81%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06 (d, J_{HF} = 1.7 Hz, 3H) 7.20 (d, *J* = 8.6 Hz, 1H), 7.32 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.51 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 5.4, 86.1 (d, J_{CF} = 13 Hz), 112.2, 116.4, 121.8 (d, J_{CF} = 6 Hz), 126.1 (d, J_{CF} = 4 Hz), 131.6, 145.6, 157.4 (d, J_{CF} = 280 Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ

44.7 (s). IR (neat): ν 2931, 1676, 1454, 1442, 1354, 1194, 796, 744, 623, 519 cm^{-1}. HRMS (EI): *m*/*z* Calcd. for $C_9H_6{}^{79}BrFO$ $[M]^+$: 227.9586; Found: 227.9581.

4-(5-Bromo-3-methylbenzofuran-2-yl)phenol (18od)

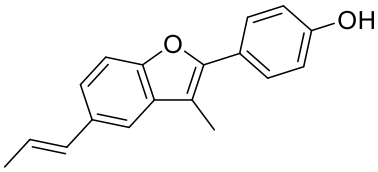


To a 1,2-dichloroethane (4.0 mL) suspension of $AlCl_3$ (70 mg, 0.52 mmol) and phenol (**17d**, 189 mg, 2.0 mmol) was added 5-bromo-3-methyl-2-fluorobenzofuran (**16o**, 93 mg, 0.40 mmol) at room temperature. After stirring at 80 °C for 4 h, aqueous NaOH (2 M, 3 mL) was added. To the mixture was added aqueous HCl (2 M, 3 mL), and organic materials were extracted with dichloromethane (3 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica gel column chromatography (hexane/diethyl ether = 5/1) to give **18od** (87 mg, 71%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.00 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H) 7.30 (d, *J* = 8.6 Hz, 1H), 7.33 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 9.3, 109.2, 112.2, 115.4, 115.7, 121.8, 123.8, 126.6, 128.5, 133.3, 152.0, 152.3, 155.6.

Spectral data for this compound showed good agreement with literature data.[17]

Eupomatenoid 6 (19)



A *t*-BuOH (0.5 mL) and H_2O (0.1 mL) suspension of 4-(5-bromo-3-methylbenzofuran-2-yl)phenol (**18od**, 16 mg, 0.051 mmol), potassium (*E*)-propenyltetrafluoroborate (9.9 mg, 0.067 mmol), $Pd(PPh_3)_4$ (2.9 mg, 2.5

□mol), and Cs_2CO_3 (52 mg, 0.16 mmol) was degassed by using freeze-pump-thaw method three times. After stirring at 80 °C for 16 h, H_2O (2 mL) was added, and organic materials were extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (hexane/ether = 5/1) to give **19** (13 mg, 99%) as colorless crystals.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.91 (dd, *J* = 6.6, 1.7 Hz, 3H), 2.42 (s, 3H), 4.92 (s, 1H), 6.23 (dq, *J* = 15.5, 6.6 Hz, 1H), 6.51 (dd, *J* = 15.5, 1.7 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.27 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 1.7 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 9.4, 18.5, 109.8, 110.6, 115.6, 116.1, 122.2, 124.2, 124.4, 128.3, 131.3, 131.5, 132.6, 151.1, 152.9, 155.3.

Spectral data for this compound showed good agreement with literature data.[19] The structure of **19** was also confirmed by X-ray diffraction analysis (Figure S1 and Table S1).

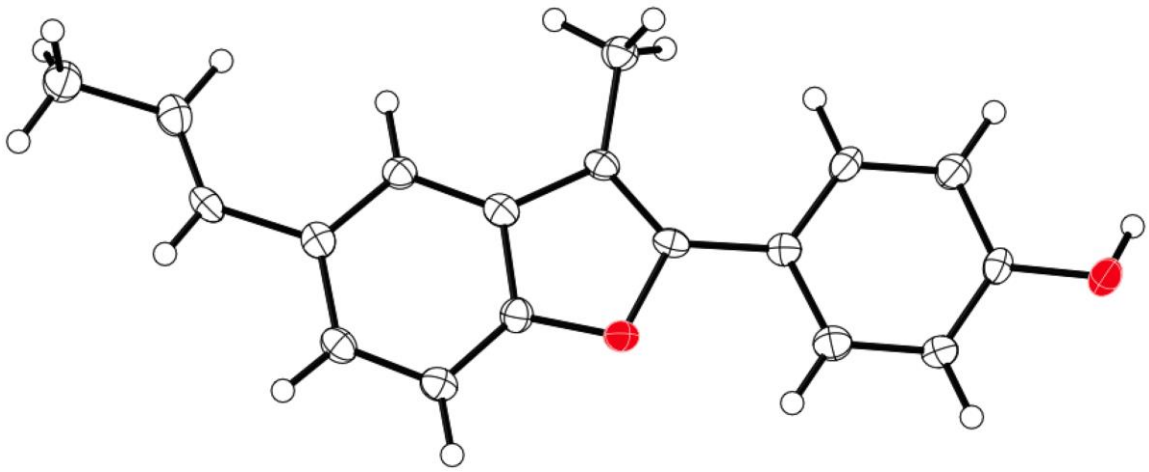


Figure S1. ORTEP Drawing of **19** with 50% Ellipsoid Probability

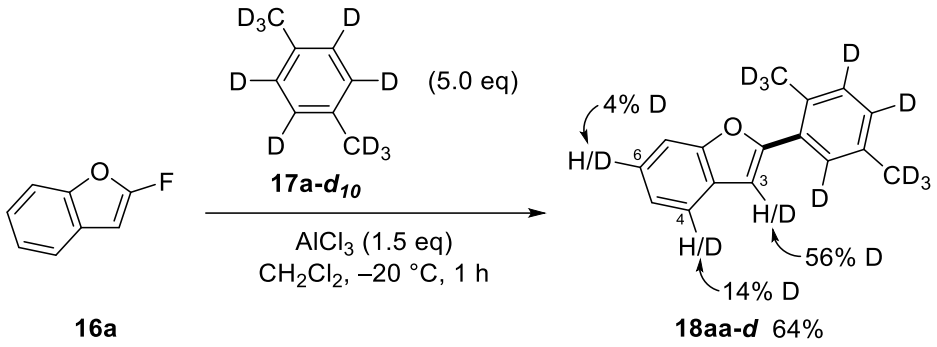
Table S1. Crystal Data Collection Parameters for **19**

Table S1. Crystal Data Collection Parameters for **19**

compound	**19**
formula	$C_{18}H_{16}O_2$
crystal system	Orthorhombic
space group	*Pbca*
R, R_w ($I > 2\sigma(I)$)	0.0884, 0.1791
$R1$, $wR2$ (all data)	0.1546, 0.2040
GOF on F^2	1.079
a (Å)	4.768(2)
b (Å)	18.775(9)
c (Å)	31.234(15)
α (deg)	90
β (deg)	90
γ (deg)	90
V (Å^3)	2796(2)
Z	8
T (K)	120(2)
crystal size (mm)	0.47, 0.35, 0.01
D_{calcd} (g/cm^3)	1.256
$2\theta_{min}$, $2\theta_{max}$ (deg)	2.60, 50.00

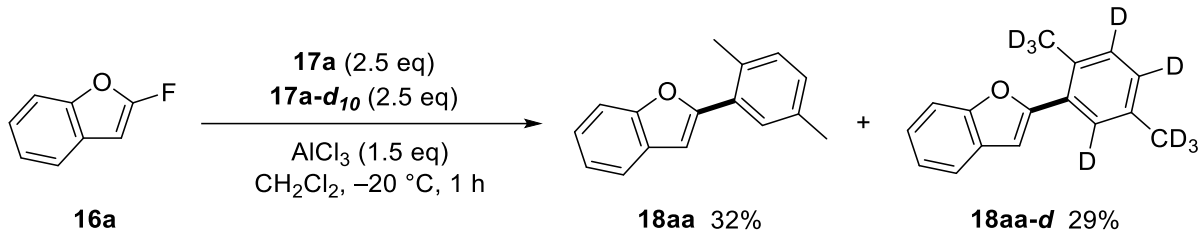
4. Mechanistic Studies

Control Experiments Using 16a and 17a-d_{10}



To a dichloromethane (2.0 mL) suspension of $AlCl_3$ (41 mg, 0.31 mmol) and *p*-xylene-d_{10} (**17a-*d*$_{10}$**, 0.12 mL, 1.0 mmol) was added 2-fluorobenzofuran (**16a**, 28 mg, 0.20 mmol) at –20 °C. After stirring at the same temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added and allowed to warm to room temperature. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 30/1) to give **18aa** (30 mg, 64%) as a colorless oil. The ratio of deuterium incorporation of each position was determined by ^{1}H NMR spectroscopy.

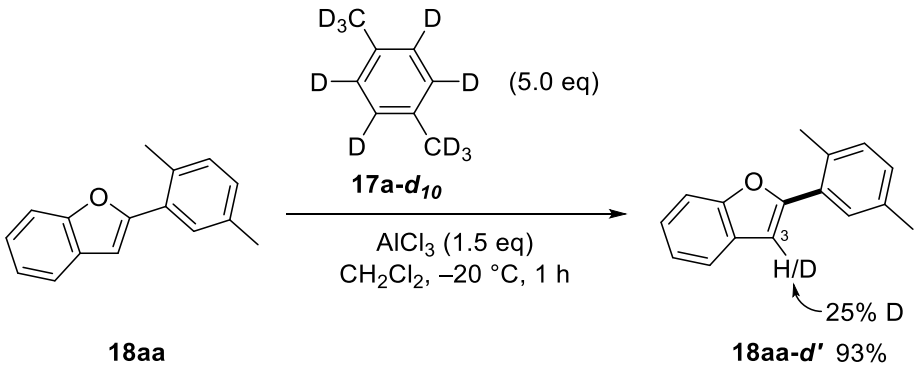
Control Experiments Using 16a, 17a, and 17a-d_{10}



To a dichloromethane (2.0 mL) suspension of $AlCl_3$ (40 mg, 0.30 mmol), *p*-xylene (**17a**, 62 μL, 0.50 mmol), and *p*-xylene-d_{10} (**17a-*d*$_{10}$**, 61 μL, 0.50 mmol) was added 2-fluorobenzofuran (**16a**, 27 mg, 0.20 mmol) at –20 °C. After stirring at the same temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added and allowed to warm to room temperature. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were

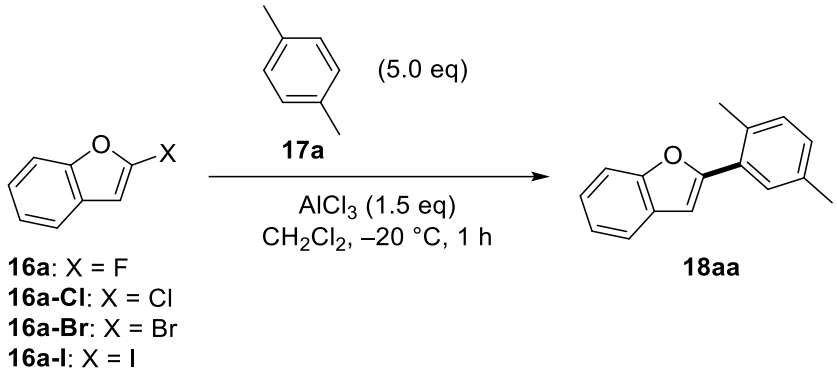
extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the yields of **18aa** and **18aa-*d*** were determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

Control Experiments Using 18aa and 17a-d_{10}



To a dichloromethane (1.0 mL) suspension of $AlCl_3$ (20 mg, 0.15 mmol) and *p*-xylene-d_{10} (**17a-d_{10}**, 61 μL, 0.50 mmol) was added 2-arylbenzofuran **18aa** (22 mg, 0.10 mmol) at –20 °C. After stirring at the same temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added and allowed to warm to room temperature. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the yield of **18aa-*d*** **'** and the ratio of deuterium incorporation of each position was determined by ^{1}H NMR spectroscopy.

Effect of Halogens on the 2-Positions in Benzofurans



To a dichloromethane (2.0 mL) suspension of $AlCl_3$ (1.5 equiv) and *p*-xylene (**17a**, 5.0 equiv) was added 2-halobenzofuran (**16a**: X = F; **16a-Cl**: X = Cl; **16a-Br**: X = Br; **16a-I**: X = I) at –20 °C. After stirring at the same temperature for 1 h, aqueous NaOH (2 M, 1 mL) was added and allowed to warm to room temperature. To the mixture was added aqueous HCl (2 M, 1 mL), and organic materials were extracted with dichloromethane (2 mL) three times. The combined extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the yield of **18aa** was determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard.

5. Reaction Mechanisms

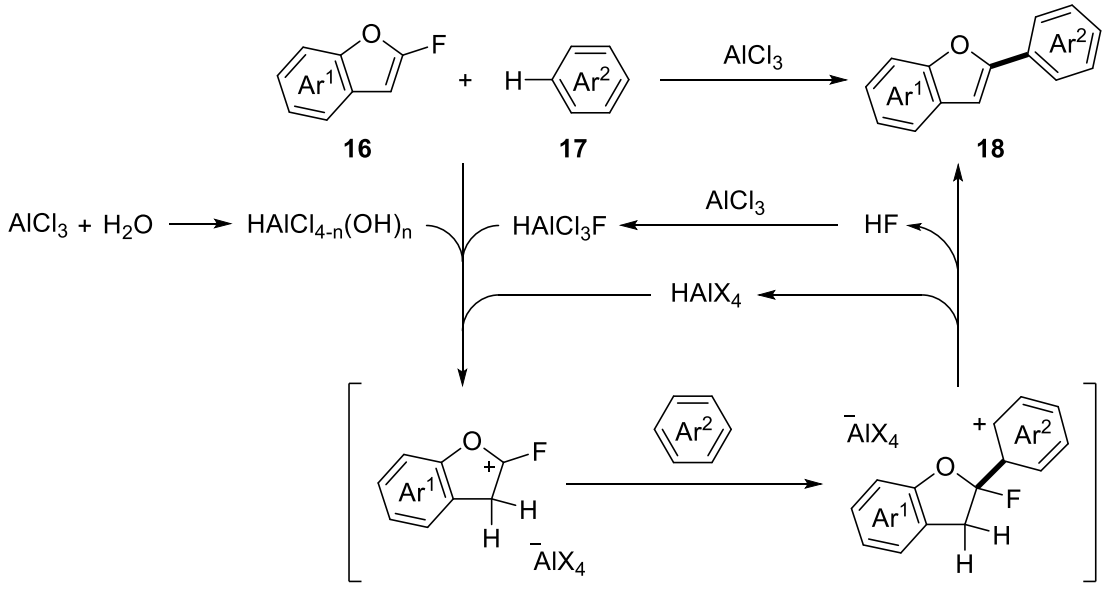


Figure S2. Plausible Mechanism

References

[1] Kabuto, C.; Akine, S.; Nemoto, S.; Kwon, E. *J. Cryst. Soc. Jpn.* **2009**, *51*, 218–224.

[2] Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, C.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[3] Sheldrick, G. M. *Programs for Crystal Structure Analysis (Release 972)*; Institut für Anorganische Chemie der Universität: Göttingen, Germany, **1998**.

[4] Morioka, R.; Fujita, T.; Ichikawa, J. *Helv. Chim. Acta* **2020**, *103*, e2000159.

[5] Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *Chem. Commun.*, **1997**, 1537–1538.

[6] Hofsäß, R.; Rombach, D.; Wagenknecht, H.-A. *Synlett* **2017**, *28*, 1422–1426.

[7] Li, J.; Rush III, T. S.; Li, W.; DeVincentis, D.; Du, X.; Hu, Y.; Thomason, J. R.; Xiang, J. S.; Skotnicki, J. S.; Tam, S.; Cunningham, K. M.; Chockalingam, P. S.; Morris, E. A.; Levin, J. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4961–4966.

[8] Adams, N. D.; Aquino, C. J.; Ghergurovich, J. M.; Musso, D. L.; Parrish, C. A.; Reif, A. J. WO2012037299, **2012**.

[9] Yang, J.; Liu, S.; Zheng J.-F.; Zhou, J. S. *Eur. J. Org. Chem.* **2012**, 6248–6249.

[10] Lu, L.; Yan, H.; Sun, P.; Zhu, Y.; Yang, H.; Liu, D.; Rong, G.; Mao, J. *Eur. J. Org. Chem.* **2013**, 1644–1648.

[11] Yao, M.-L.; Reddy, M.S.; Yong, L.; Walfish, I.; Blevins, D. W.; Kabalka, G. W. *Org. Lett.* **2010**, *12*, 700–703.

[12] Nguyen, T. T. B.; Lomberget, T.; Tran, N. C.; Colomb, E.; Nachtegaele, L.; Thoret, S.; Dubois, J.; Guillaume, J.; Abdayem, R.; Haftek, M. Barret, R. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7227–7231.

[13] Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007**, *129*, 1921–1930.

[14] Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137–3139.

[15] Li, Y.; Cheng, L.; Liu, X.; Li, B.; Sun, N. *Beilstein J. Org. Chem.* **2014**, ***10***, 2886–2891.

[16] Duan, X.-F.; Zeng, J.; Zhang, Z. -B.; Zi, G.-F. *J. Org. Chem.* **2007**, *72*, 10283–10286.

[17] Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, 1491–1509.

[18] Yuan, X.; Yao, J.-F.; Tang, Z.-Y. *Org. Lett.* **2017**, *19*, 1410–1413.

[19] Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761–1763.

CHAPTER 6

Conclusions

I developed facile and practical methods for constructing five-membered carbo- and heterocycles, which mostly contain fluorine substituents, via C–F bond activation. These methods exclude toxic fluorinating agents and expensive transition metals by taking full advantage of the chemical properties of fluorine. Fluorine-containing (benzo)furans, cyclopentadienes, and 2-arylbenzofurans thus obtained are expected to serve as pharmaceuticals, agrochemicals, and materials.

In Chapter 2, an efficient synthesis of 3-fluorodihydrofurans was achieved via 5-*endo-trig* cyclization of difluorohomoallylic alcohols. In this reaction, 5-*endo-trig* cyclization proceeded via the stepwise defluorinative S_N2'-type reaction. Generation of carbanions at the β-positions to the fluorine substituents after the nucleophilic attack of alkoxide moieties enables the cyclization that is difficult through a concerted mechanism. Furthermore, oxidation of the 3-fluorodihydrofuran products afforded 4-fluorofuranones, which are expected to serve as pharmaceuticals or agrochemicals.

Chapter 3 demonstrates the Nazoarov-type cyclization via direct defluorination of 3,3-difluoro-1,4-pentadienes. Lewis acids caused fluoride abstraction from 3,3-difluoro-1,4-pentadienes to generate fluorine-stabilized pentadienyl cations by the aid of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) as solvent. Pentadienyl cations thus generated underwent electrocyclization to afford 2-fluoro-cyclopenta-1,3-dienes.

Chapter 4 describes a facile method for the synthesis of 2-flurobenzofurans via 5-*endo-trig* cyclization by appropriate choice of bases. I successfully synthesized variously substituted 2-fluorobenzofurans from readily available precursors. In addition, since 2-fluoro-3-iodobenzofuran, containing a convertible iodine substituent, is also synthesized by this method, 3-arylated, -alkenylated, and -alkynylated 2-fluorobenzofurans were also obtained via coupling reaction.

In Chapter 5, I developed acid-mediated aromatic C–F/C–H coupling of 2-fluorobenzofurans with arenes. A short-step synthesis of bioactive compounds including a natural product was also achieved by this method. Furthermore, I revealed that the reaction is initiated by protonation of 2-fluorobenzofurans and that the resulting α-fluorocarbocations serve as the key intermediates.

Throughout these studies, I developed state-of-the-art methods for allylic, vinylic, and aromatic C–F bond activation without using transition metals by utilizing the leaving group ability and the α-carbocation and β-carbanion stabilizing effects of fluorine. These protocols enable rapid access for ring-fluorinated dihydrofurans, furanones, cyclopentadienes, and benzofurans as well as 2-arylbenzofurans, which had been synthesized by only limited methodologies.

LIST OF PUBLICATIONS

(1) Fujita, T.; Morioka, R.; Arita, T.; Ichikawa, J.

Sp3 carbon-fluorine bond activation in 2,2-difluorohomoallylic alcohols via nucleophilic 5-*endo-trig* cyclization: synthesis of 3-fluorinated furan derivatives

Chem. Commun. **2018**, *54*, 12938.

(2) Morioka, R.; Fujita, T.; Ichikawa, J.

Facile Synthesis of 2-Fluorobenzofurans: 5-*endo-trig* Cyclization of β,β-Difluoro-o-hydroxystyrenes

Helv. Chim. Acta **2020**, *103*, e2000159.

(3) Fujita, T.; Morioka, R.; Fukuda, T.; Suzuki, N.; Ichikawa, J.

Acid-mediated intermolecular C–F/C–H cross-coupling of 2-fluorobenzofurans with arenes: synthesis of 2-arylbenzofurans

Chem. Commun. **2021**, *57*, 8500.

SUPPLEMENTARY PUBLICATIONS

(1) Fujita, T.; Hattori, M.; Matsuda, M.; Morioka, R.; Jankins, T. C.; Ikeda, M.; Ichikawa, J.

Nucleophilic 5-*endo-trig* cyclization of 2-(trifluoromethyl)allylic metal enolates and enamides: Synthesis of tetrahydrofurans and pyrrolidines bearing exo-difluoromethylene units

Tetrahedron **2019**, *75*, 36.

(2) Guèrin, T.; Pikun, N. V.; Morioka, R.; Panossian, A.; Hanquet, G.; Leroux, F. R.

Synthesis and Use of Trifluoromethylthiolated Ketenimines

Chem. Eur. J. **2020**, *26*, 14852.

(3) Fujita, T.; Kobayasi, M.; Takahashi, I.; Morioka, R.; Ichikawa, J.

Nickel-catalyzed reductive allyl-aryl cross-electrophile coupling via allylic C–F bond activation

Chem. Eur. J. **2021**, *in press.* DOI: 10.1002/chem.202103643.

ACKNOWLEDGEMENT

The studies described in this thesis have been carried out under the direction of Professor Junji Ichikawa at the Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba, from April 2016 to March 2022.

I express my deepest appreciation to Professor Junji Ichikawa for the tremendous support, hearty encouragement, and guidance on how to proceed research and experiment for 6 years. I learned the attitude of a scientist from his education. Research Associate Takeshi Fujita has been encouraging and advising me with a gentle heart. I was helped by Associate Professor Kohei Fuchibe's unexpected and valuable ideas many times.

J'apprécie beaucoup les membres du Chimie Organique & Hétérochimie Appliquées groupe à Strasbourg. Professor Frédéric Leroux, Research Director Gilles Hanquet, Research Associate Morgan Donnard, and Research Associate Armen Panossian gave me nice guidance and helpful discussions while I was in Strasbourg.

Especially, I appreciate Gilles and his family for meilleur apartment, life support in France, also great guidance for mariage de foie gras et du Vin de Porto.

I make special mention of Dr. Yota Watabe for his helpful guidance and support. I owe much inspiration to him. It was my pleasure to be a comrade of Ms. Haruna Yabuki, Mr. Kota Ichikawa, Mr. Masaki Kitajima, and Mr. Gentaro Hida. I am deeply indebted to my senior alumni of Ichikawa group, Dr. Naoto Suzuki, Dr. Ikko Takahashi, Dr. Ryo Takayama, Dr. Go Takao, Mr. Tomohiro Arita, Mr. Yutaro Kobayashi, Mr. Fumiya Tomura, Mr. Hisanori Imaoka, Ms. Rie Oki, Mr. Keisuke Watanabe, Mr. Takuya Fukuda, Mr. Rikuo Akisaka, Mr. Kyosuke Suto, Mr. Tomohiro Hidano, Mr. Atsushi Yamada, Mr. Masaki Hyashi, Ms. Yuki Inarimori for their kind advice. I would like to express my thanks to the other colleagues in the Ichikawa group, Mr. Nobushige Tsuda, Mr. Hiroto Watanabe, Ms. Kyoko Kanematsu, Mr. Keisuke Ide, Mr. Ryo Kinoshita, Ms. Fen Huang, Mr. Kazuki Sakon, Mr. Noriaki Shoji, Mr. Kosei Hachinohe, Mr. Tatsuya Higuma, Ms. Mizore Sasaki, Mr. Tao Min, Mr. Tatsuki Hushihara, Mr. Masahumi Takeishi, Mr. Kosuke Sano, Mr. Ibuki Mukohara, Mr. Hiroto Idate, Mr. Sho Nakazono, Mr. Hinato Arimoto, Mr. Daisuke Miyazaki, Mr. Yuki Morota, Mr. Nozomi Uzuhashi, Mr. Taro Matsuo, Ms. Runa Kasahara, Mr. Yusuke Urushibara, Mr. Takaya Miura, Ms. Konami Kudo for their helpful assistance and dedication. I also express thanks to my mentor in Strasbourg, Dr. Thomas Guèrin, coffee friends, Alberto and Matus, kind colleagues, Jordan, Augustin, Laura, and all the members of the COHA group.

This work was supported by JST SPRING

Finally, I express my deepest gratitude to my parents, Sekihiro Morioka and Kahoru Morioka for their kindly continuous encouragement and for providing a very comfortable environment, which allows me to concentrate on research.

February 2022

Ryutaro Morioka