The Nucleophilic 5-*endo-trig* Cyclization of 1,1-Difluoro-1-alkenes: Ring-Fluorinated Hetero- and Carbocycle Synthesis and Remarkable Effect of the Vinylic Fluorines on the Disfavored Process

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Received 21 May 2002; revised 12 June 2002

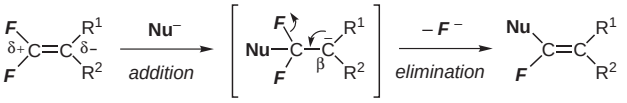
Abstract: The disfavored 5-*endo-trig* cyclizations have been accomplished for 1,1-difluoro-1-alkenes with nitrogen, oxygen, sulfur, and carbon nucleophiles by taking advantage of the properties of fluorine. β,β-Difluorostyrenes bearing tosylamido, hydroxy, or methylsulfinyl group at the *o*-position undergo intramolecular nucleophilic substitution with a loss of the vinylic fluorine, leading to 2-fluorinated indole, benzo[*b*]furan, and benzo[*b*]thiophene in high yields. 1,1-Difluoro-1-butenes bearing homoallylic tosylamido, hydroxy, mercapto, or iodomethyl group also successfully cyclize via a 5-*endo-trig* process with the in situ generated intramolecular nucleophiles to afford 2-fluoro-2-pyrroline, 5-fluoro-2,3-dihydrofuran, 5-fluoro-2,3-dihydrothiophene, and 1-fluorocyclopentene. The two vinylic fluorines proved to be essential and play a critical role in these 'anti-Baldwin' cyclizations.

Key words: cyclizations, fluorine, alkenes, heterocycles, carbocycles

Introduction

The 5-*endo-trig* cyclization has long been considered, according to Baldwin's rules, to be a disfavored process for the construction of five-membered rings, due to severe distortions in the reaction geometry.[1] As examples of this disfavored cyclization, nucleophile-driven, electrophile-driven, and radical-initiated ring closures have been reported. The electrophile-driven cyclizations are initiated by the coordination of a double bond in the substrate to an external electrophile such as I_2, PhSeCl, or metal salts,[2] although this type of cyclization does not seem likely to be an exception to Baldwin's rules.[1c] Examples of efficient radical-initiated cyclizations have been recently devised to synthesize heterocyclic compounds including γ-lactams.[3] In contrast to the above-mentioned two types of 5-*endo-trig* cyclization, the corresponding nucleophile-driven ring closure has been rarely observed in synthetic chemistry (vide infra).[4–6]

1,1-Difluoro-1-alkenes are susceptible to nucleophilic substitution of the vinylic fluorines via an addition–elimination process,[7] in which the fluorine can affect reactivity by: (i) the electrophilic activation of the carbon-carbon double bond by the two fluorine atoms, (ii) the stabilization of the intermediary carbanion by the β-anion stabilizing effect of fluorine, and (iii) the leaving-group ability of the fluoride ion (Scheme 1). Thus, the attack of nucleophiles is strictly regulated to occur at the difluoromethylene carbon, so that the fluorines are placed at the position β to the electron-rich carbon in the transition state to avoid electron-pair repulsion.



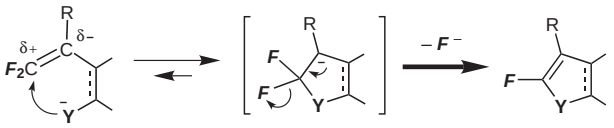
Scheme 1 Nucleophilic substitution of vinylic fluorines.

Taking advantage of this reactivity, we have already reported regioselective syntheses of 3- and 5-fluoropyrazoles by the reactions of 2,2-difluorovinyl ketones with hydrazines as external nucleophiles through a two-site reaction, the substitution–cyclodehydration sequence.[8,9] Our interest in further applications of difluoroalkene chemistry to ring constructions led us to explore an intramolecular version of the substitution. This method provides an efficient access to ring-fluorinated hetero- and carbocyclic compounds, whose synthetic methods are quite limited in spite of their potential uses as components of agrochemicals, pharmaceuticals, and dyestuffs.[10]

Moreover, we expected that the unique properties of 1,1-difluoro-1-alkenes could make a nucleophilic approach to 5-*endo-trig* cyclization feasible. Specifically, we thought that (i) the highly polarized difluorovinylidene double bond (^{13}C NMR: ca. 150 ppm and 90 ppm for CF_2=C) would allow initial ring formation by electrostatic attraction between the CF_2 carbon and the internal nucleophile and (ii) the successive elimination of fluoride ion could suppress the reverse ring opening, thus functioning as a 'lock' (Scheme 2). On the basis of these considerations, we have investigated the nucleophilic 5-*endo-trig* cyclizations of 1,1-difluoro-1-alkenes as a solution to conducting ring closures disfavored according to Baldwin's rules, and the preliminary results have been briefly reported.[5] In this paper, full accounts of these five-membered ring closures are reported with the study to elucidate the effect of fluorine on the 'anti-Baldwin' cyclization.[11]

Synthesis 2002, No. 13, Print: 20 09 2002.
Art Id.1437-210X,E;2002,0,13,1917,1936,ftx,en;F04302SS.pdf.

ISSN 0039-7881



Scheme 2 Nucleophilic 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes.

Results and Discussion

Preparation of Functionalized 1,1-Difluoro-1-alkenes

As substrates for the 5-*endo-trig* cyclizations, (i) β,β-difluorostyrene and (ii) 1,1-difluoro-1-butene derivatives were designed with a nucleophilic nitrogen, oxygen, sulfur, or carbon atom at the *ortho* or homoallylic position suitable for substitution in a 5-*endo-trig* fashion.

Biographical Sketches

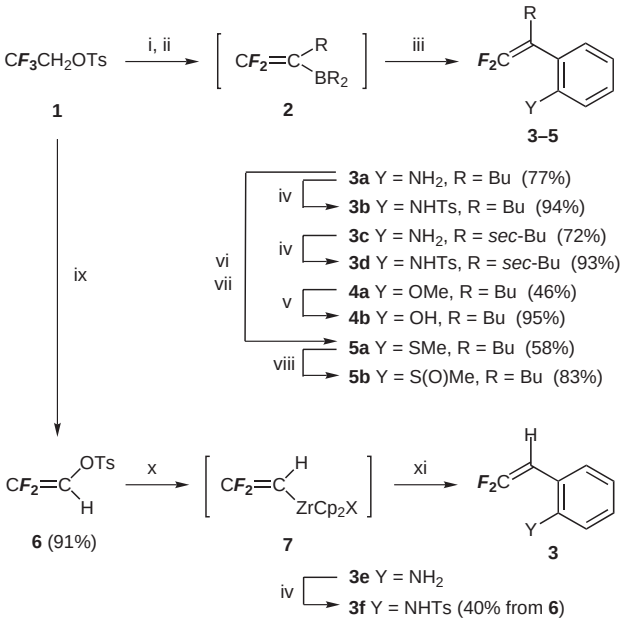
Junji Ichikawa was born in Tokyo, Japan in 1958. He received his BSc in 1981 and PhD in 1986 from the University of Tokyo under the supervision of Professor Teruaki Mukaiyama. He joined the Institute of Advanced Material Study, Kyushu University as Assistant Professor in 1985. From 1989 to 1990, he worked as a postdoctoral research associate at Harvard University with Professor E. J. Corey. After returning to Japan, he moved to the Department of Applied Chemistry, Kyushu Institute of Technology as Lecturer in 1991 and was promoted to Associate Professor in 1993. In 1999, he was appointed Associate Professor in the Graduate School of Science at the University of Tokyo. He received a Nippon Kasei Chemical Award in Synthetic Organic Chemistry, Japan in 1991, Progress Award in Synthetic Organic Chemistry, Japan in 1994, and the Daiichi Pharmaceutical Award in Synthetic Organic Chemistry, Japan in 1996 from the Society of Synthetic Organic Chemistry, Japan. His research interests lie in the area of synthetic methodology, specifically the development of novel reactions based on the properties of metals and fluorine. Special attention is given to a new function of fluorine as *a versatile synthetic tool*.

Yukinori Wada was born in Kurume, Japan in 1972. He studied chemistry at the Department of Applied Chemistry, Kyushu Institute of Technology, where he received his BEng in 1996 and PhD in 2001 under the guidance of Dr. Junji Ichikawa. After studying as a research student at the University of Tokyo from 1999 to 2001, he joined Ube Laboratory of Ube Industries, Ltd. He currently works at the Pharmaceutical Research Department, Ube Industries, Ltd.

Masaki Fujiwara was born in Hiroshima, Japan in 1972. He studied chemistry at the Department of Applied Chemistry, Kyushu Institute of Technology, where he received his BEng in 1995 and PhD in 2000 under the guidance of Dr. Junji Ichikawa. After studying as a research student at the University of Tokyo from 1999 to 2000, he joined the Chemical Research Center of Central Glass Co., Ltd. He currently works as a visiting postdoctoral research associate at the State University of New York at Stony Brook with Professor Iwao Ojima.

Kotaro Sakoda was born in Urawa, Japan in 1977. He was trained as a chemist at the University of Tokyo and received his BSc in 2001. He is currently working as a PhD student at the same University under the guidance of Dr. Junji Ichikawa.

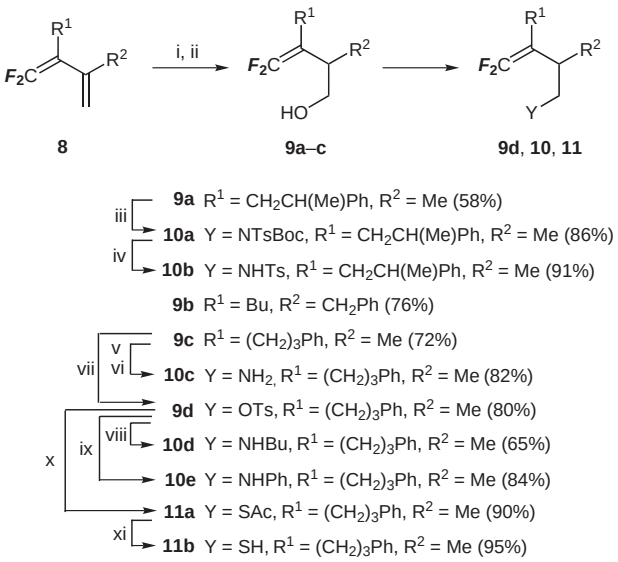
The difluorostyrenes were easily prepared as outlined in Scheme 3 by using two kinds of one-pot sequences that we have previously established for a wide range of 1,1-difluoro-1-alkenes.[12–14] The coupling reactions of 2,2-difluorovinylboranes **2** [generated in situ from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**)] or 2,2-difluorovinylzirconocene **7** [generated in situ from 2,2-difluorovinyl *p*-toluenesulfonate (**6**)] with *N*-butylmagnesio-*o*-iodoaniline or *o*-iodoaniline, respectively, were effected in the presence of copper(I) iodide or zinc(II) iodide and a palladium catalyst. The *o*-amino-β,β-difluorostyrene derivatives **3a**–**f**, which would act as precursors of 2-fluoroindoles, were obtained in good yields. *o*-Hydroxy-β,β-difluorostyrene **4b**, a precursor of 2-fluorobenzo[*b*]furan, was similarly prepared by the coupling of **2** with *o*-iodoanisole, followed by demethylation with tribromoborane. For generation of the thiolate moiety, methyl sulfinyl group was selected as an *ortho* substituent of difluorostyrene. Sulfoxide **5b**, a precursor of 2-fluorobenzo[*b*]thiophene, was prepared from **3a** via diazotization and introduction of a methylthio group, which was oxidized to give the target molecule.



Scheme 3 Preparation of β,β-difluorostyrenes **3**–**5**
Reagents and conditions: i, BuLi (2.1 equiv), THF, –78 °C, 0.5 h; ii, BR_3 (1.1 equiv), THF, –78 °C, 1 h then r.t., 3 h; iii, ArI (0.9 equiv), CuI (1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.02 equiv), PPh_3 (**3a**: 0.08 equiv; **3c**,**4a**: 0.16 equiv), THF–HMPA (4:1), r.t., 1 h; iv, TsCl (1.1 equiv), Pyridine, 0 °C to r.t., 11 h; v, BBr_3 (1.1 equiv), CH_2Cl_2, –15 °C to r.t., 2 h; vi, CF_3CO_2H (2 equiv), *i*-AmONO (2 equiv), CH_3CN, 0 °C, 0.5 h; vii, aq NaSMe (3 equiv), CH_3CN, 0 °C to r.t., 1.5 h; viii, aq $TiCl_3$ (2 equiv), aq H_2O_2 (3 equiv), MeOH–H_2O, r.t., 2 h; ix, BuLi (2.1 equiv), THF, –78 °C, 0.5 h; x, 'Cp_2Zr' (2 equiv), THF, –78 °C to r.t., 3 h; xi, ArI (1.1 equiv), ZnI_2 (1.1 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.02 equiv), PPh_3 (0.16 equiv), THF, reflux, 2 h.

To introduce a functional group at the homoallylic position of difluorobutene, we tried the regioselective hydroboration of the non-fluorinated double bond in 1,1-difluoro-1,3-butadienes **8** (Scheme 4), which were readily prepared from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**) and vinyl halides according to our method.[12,15] The electron-rich, non-fluorinated double bond in **8** was expected to be more reactive toward borane reagents. Treatment of difluorodienes **8** with 9-borabicyclo[3.3.1]nonane (9-BBN) under reflux in THF promoted hydroboration selectively at the fluorine-free double bond to generate difluorohomoallylboranes. Subsequent treatment with alkaline aqueous hydrogen peroxide gave difluorohomoallyl alcohols **9a**–**c**, precursors of 5-fluorinated 2,3-dihydrofurans, in good yields.

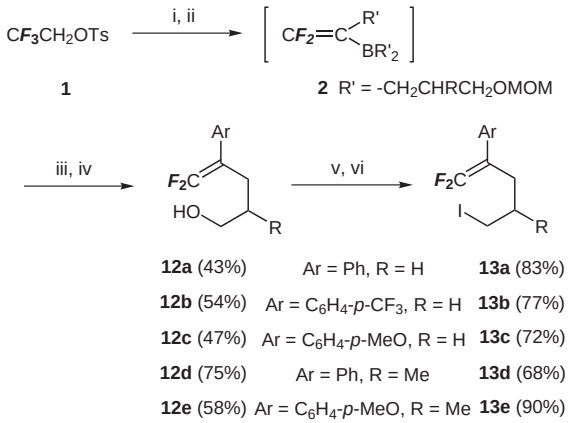
The corresponding nitrogen-containing substrates as precursors of 2-fluorinated 2-pyrrolines were prepared from **9** as shown in Scheme 4. *N*-Difluorohomoallyl-*p*-toluenesulfonamide **10b** was derived from **9a** by Mitsunobu reaction with BocNHTs followed by deprotection of the Boc group.[16] The Gabriel synthesis starting from **9c** gave amine **10c**.[17] *N*-Butyl and *N*-phenyldifluorohomoallylamines **10d**,**e** were prepared from **9c** via its tosylate **9d** by substitution with excess butylamine and aniline, respectively. Difluorohomoallyl hydrosulfide **11b**, a precursor of 5-fluorinated 2,3-dihydrothiophene, was similarly obtained from **9d** by the introduction of the acetylthio group, followed by transesterification by treatment with potassium carbonate in methanol (Scheme 4).



Scheme 4 Preparation of 1,1-difluoro-1-butenes **9**–**11**
Reagents and conditions: i, 9-BBN (**9a**,**c**: 1.1 equiv; **9b**: 1.4 equiv), THF, reflux, 6–7 h; ii, aq H_2O_2, aq NaOH, 0 °C, 2 h; iii, BocNHTs (1 equiv), PPh_3 (1 equiv), $EtO_2CN{=}NCO_2Et$ (1 equiv), THF, r.t., 2 h; iv, CF_3CO_2H (15 equiv), CH_2Cl_2, r.t., 2 h; v, phthalimide (1 equiv), PPh_3 (1 equiv), $EtO_2CN{=}NCO_2Et$ (1 equiv), THF, r.t., 2 h; vi, $NH_2NH_2{\cdot}H_2O$ (2 equiv), EtOH, reflux, 2 h; vii, TsCl (1 equiv), Pyridine, r.t., 8 h; viii, $BuNH_2$ (26 equiv), reflux, 6 h; ix, $PhNH_2$ (26 equiv), reflux, 6 h; x, AcSNa (1 equiv), DMF, 70 °C, 3 h; xi, K_2CO_3 (1 equiv), MeOH, 0 °C, 1 h.

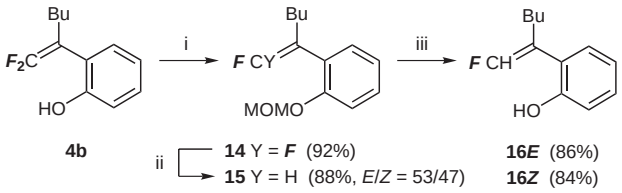
Difluoroalkene substrates bearing a carbon nucleophile, 1,1-difluoro-5-iodo-1-pentenes **13**, were easily prepared as outlined in Scheme 5 by using our one-pot sequence.[12,13] 2,2-Difluorovinylboranes **2** were prepared in

situ from **1** and trialkylboranes (generated by hydroboration of MOM ethers of allyl and methallyl alcohols). The palladium-catalyzed coupling reactions of **2** with aryl iodides were successively conducted in the presence of copper(I) iodide, followed by deprotection of the MOM group to afford **12a**–**e**. Thus alcohols **12a**–**e** were transformed into the desired iodides **13a**–**e** via their mesylates.



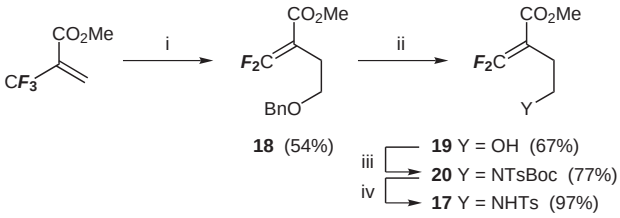
Scheme 5 Preparation of 1,1-difluoro-5-iodo-1-pentenes **13**
Reagents and conditions: i, BuLi (2.1 equiv), THF, –78 °C, 0.5 h; ii, BR'_3 (**12a**,**b**,**d**: 1.0 equiv; **12c**,**e**: 1.1 equiv), THF, –78 °C, 1 h then reflux, 1 h; iii, ArI (0.8 equiv), CuI (1.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (0.02 equiv), PPh_3 (**12a**,**b**,**d**: 0.08 equiv; **12c**,**e**: 0.16 equiv), THF–HMPA (4:1), r.t., 1 h; iv, aq HCl, THF, r.t., 1 h; v, MsCl (1.5 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C to r.t., 4 h; vi, NaI (10 equiv), acetone, reflux, 5 h.

β-Monofluorinated *o*-hydroxystyrenes **16** were prepared as shown in Scheme 6. Both *E*- and *Z*-isomers of **15** were obtained in a ratio of 53:47 by the reduction of OH-protected hydroxystyrene **14** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al).[18] After separation by chromatography, they were deprotected to give **16*E*** and **16*Z*** (Scheme 6).



Scheme 6 Preparation of β-fluorostyrenes **16**
Reagents and conditions: i, NaH (1.1 equiv), MOMCl (3 equiv), THF, –78 °C, 5 h; ii, Red-Al (2.8 equiv), toluene, 0 °C to reflux, 3 h; iii, concd HCl, THF, 0 °C, 2.5 h.

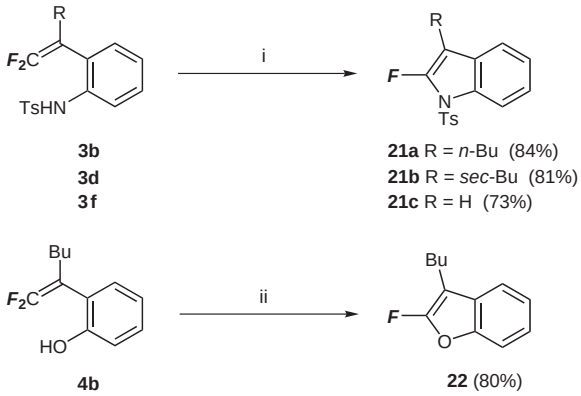
3,3-Difluoroacrylate **17** was prepared as depicted in Scheme 7. The S_N2' reaction of methyl 2-(trifluoromethyl)acrylate[19] with (benzyloxymethyl)copper[20] [generated in situ from (benzyloxymethyl)tributyltin] proceeded with a loss of a fluoride ion to afford β,β-difluoro-α,β-unsaturated ester **18**. Subsequent deprotection of the benzyl group followed by the introduction of *N*-functional group via Mitsunobu reaction with BocNHTs yielded **20**, which after deprotection gave the desired substrate **17**.[16]



Scheme 7 Preparation of 3,3-difluoroacrylate **17**
Reagents and conditions: i, $BnOCH_2Cu$ (1 equiv), TMSCl (2.5 equiv), THF, –78 °C to r.t., 6 h; ii, BCl_3 (1.1 equiv), CH_2Cl_2, –78 °C to 0 °C, 5 h; iii, BocNHTs (1 equiv), PPh_3 (1 equiv), $EtO_2CN{=}NCO_2Et$ (1 equiv), THF, r.t., 10 h; iv, CF_3CO_2H (3 equiv), CH_2Cl_2, r.t., 7 h.

5-*endo-trig* Cyclization of Functionalized 1,1-Difluoro-1-alkenes

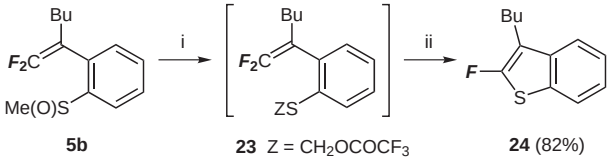
Cyclization of *o*-amino-β,β-difluorostyrene **3a** by treatment with 1.2 equivalents of BuLi did not proceed. To alter the reactivity of the *N*-nucleophile, **3a** was transformed to the corresponding acetamide and *p*-toluenesulfonamide **3b**.[2a,21] Although treatment of the acetamide with 1.2 equivalents of sodium hydride in DMF resulted in a complex mixture of products, the same conditions successfully promoted the 'disfavored' 5-*endo-trig*-cyclization of sulfonamide **3b** to afford 2-fluoroindole **21a** in 84% yield (Scheme 8).[22] Successful ring closure did not require the use of high-dilution conditions, and proceeded smoothly even in the case of difluorostyrenes **3d** and **3f** bearing a secondary alkyl group or a hydrogen atom at the α-position. Similarly, this type of cyclization was satisfactorily achieved with an intramolecular oxygen nucleophile. When hydroxystyrene **4b** was treated under similar conditions, the 5-*endo-trig* cyclization of the corresponding alkoxide occurred leading to 2-fluorobenzo[*b*]furan **22** in 80% yield (Scheme 8).[23]



Scheme 8 Synthesis of 2-fluoroindoles **21** and 2-fluorobenzo[*b*]furan **22**
Reagents and conditions: i, NaH (1.2 equiv), DMF, **3b**: 80 °C, 7 h; **3d**: 80 °C, 5 h; **3f**: 70 °C, 23 h, [**3**] = 0.2 M; ii, NaH (1.2 equiv), DMF, 60 °C, 2 h, [**4b**] = 0.1 M.

As a further example of this cyclization, we next tried the intramolecular substitution utilizing a sulfur nucleophile, which is favored by Baldwin's rules since second-row el-

ements are allowed to obtain the appropriate conformation in the 5-*endo-trig* process.[1b] The Pummerer rearrangement of β,β-difluoro-*o*-methysulfinylstyrene **5b** followed by transesterification brought about the cyclization via intermediary hemiacetal trifluoroacetate **23** (not isolated) by loss of formaldehyde. Namely, successive treatment of **5b** with (i) trifluoroacetic anhydride and triethylamine in dichloromethane and (ii) potassium carbonate in methanol provided 2-fluorobenzo[*b*]thiophene **24** in 82% yield (Scheme 9).[24]



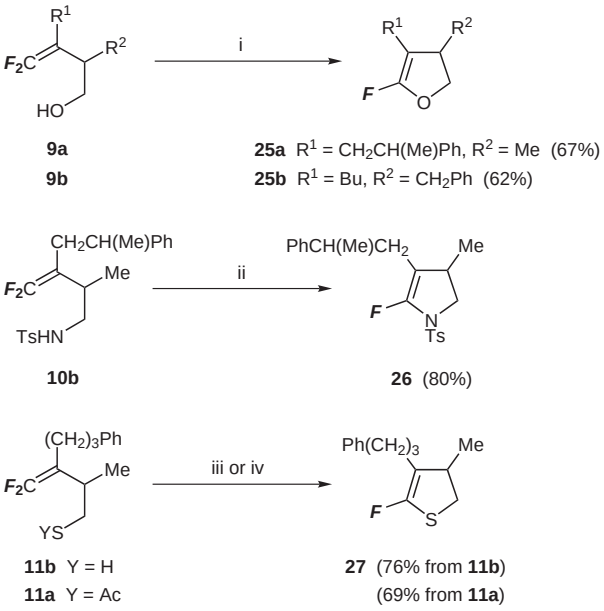
5b **23** Z = CH_2OCOCF_3 **24** (82%)

Scheme 9 Synthesis of 2-fluorobenzo[*b*]thiophene **24**
Reagents and conditions: i, $(CF_3CO)_2O$ (3 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C, 0.5 h; ii, K_2CO_3 (6 equiv), MeOH, 0 °C to reflux, 3 h.

In the above-mentioned ring-forming reaction, the substrates contain a benzene ring as an sp^2-carbon linker between the nucleophilic functional group and the difluoroalkene part, which could allow a 6π-electrocyclization process to work. In order to rule out the possibility of the electrocyclization mechanism[25] and to broaden the scope of this nucleophilic 5-*endo-trig* cyclization, we investigated the reaction of 1,1-difluoro-1-butenes **9**–**11** bearing an N-, O-, or S-functional group linked by two sp^3 carbons to the vinylic carbon. Thus, the reaction would afford ring-fluorinated five-membered heterocycles, such as pyrroline, dihydrofuran, and dihydrothiophene.

The cyclization of homoallyl alcohols **9a**,**b** was attempted by treatment with 1.2 equivalents of sodium hydride in several solvents. While the use of *N*,*N*′-dimethylpropyleneurea (DMPU) or 1-methyl-2-pyrrolidinone (NMP) gave no cyclized products, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylacetamide (DMA), or DMF successfully promoted the 5-*endo-trig* cyclization to afford 5-fluoro-2,3-dihydrofurans **25a**,**b** in good yields (Scheme 10).[26] Potassium hydride was less effective than sodium hydride, and high-dilution conditions ([**9a**] = 0.03 M) raised the yield by 10% compared to the case of [**9a**] = 0.2 M.

Furthermore, we examined the 5-*endo-trig* cyclization of the substrates with a N-nucleophile under similar conditions, and found that the course of reaction depended on the substituents on the nitrogen.[21] Whereas N-unsubstituted and *N*-butylhomoallylamines **10c**,**d** did not cyclize, *N*-phenylated substrate **10e** afforded 4-methyl-1-phenyl-3-(3-phenylpropyl)-2-pyrrolidone in 62% yield via hydrolysis of the C–F bond in the expected 2-fluoropyrroline. *p*-Toluenesulfonamide **10b** underwent the desired ring closure to give 2-fluorinated pyrroline **26** in 80% yield (Scheme 10).[27] A similar preference for the tosylamido group was observed in the cyclization of *o*-substituted β,β-difluorostyrenes **3**, which leads to 2-fluoroindoles **21** as mentioned above. As a further example of the cyclization, the intramolecular substitution of sulfur nucleophiles (which is allowed for normally disfavored 5-*endo-trig* process by Baldwin's rules) was also examined.[1b] The reaction of **11b** under the above mentioned conditions provided 5-fluorinated dihydrothiophene **27** in 76% yield.[28] In addition, treatment of thioacetic *S*-acid ester **11a** with sodium methoxide directly gave the cyclization product **27** via in situ generated thiolate.



9a **25a** R^1 = $CH_2CH(Me)Ph$, R^2 = Me (67%)
9b **25b** R^1 = Bu, R^2 = CH_2Ph (62%)

10b **26** (80%)

11b Y = H **27** (76% from **11b**)
11a Y = Ac (69% from **11a**)

Scheme 10 Synthesis of 5-fluoro-2,3-dihydrofurans **25**, 2-fluoropyrroline **26**, and 5-fluoro-2,3-dihydrothiophene **27**
Reagents and conditions: i, NaH (1.2 equiv), DMF, 90 °C, **25a**: 7 h; **25b**: 11 h; ii, NaH (1.1 equiv), DMF, 90 °C, 4 d; iii, **11b**: NaH (1.1 equiv), DMF, 90 °C, 4 h; iv, **11a**: NaOMe (1 equiv), DMF, 90 °C, 8 h.

These results demonstrate that the cyclization proceeds not via the 6π-electrocyclization process[25] but via the intramolecular addition–elimination process and that normally 'disfavored' 5-*endo-trig* ring closures are successfully achieved in the reaction of 1,1-difluoro-1-alkenes bearing a nucleophilic heteroatom linked by two sp^3-carbons to the vinylic carbon as well as two sp^2-carbons. Thus, 4,4-difluorohomoallylic amine, alcohol, and thiol derivatives open a new route for the synthesis of selectively ring-fluorinated heterocyclic compounds.

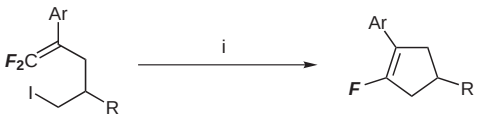
Including our examples mentioned above,[5a-b] most nucleophilic 5-*endo-trig* ring closures that have been reported are effected by heteronucleophiles.[4a–c,6] Although carbocyclizations have great potential as effective carbon-carbon bond-forming reactions,[29] they are mostly limited to a few examples of 5-*endo trig* addition of stabilized carbanions (anions α to carbonyl or cyano groups) to electrophilic double bonds such as (1) alkenes activated by sulfonyl, cyano, nitro, or carbonyl groups,[4c–e] (2) imines,[4f,g] and also to (3) π-allylpalladium system.[4h] One exception, to our knowledge, is the cyclization of 2-(3-bromopropyl)-2-cyclohexenone via alkyl anion generated by electrochemical reduction. This cyclization is remarkably facilitated in microemulsions.[4i]

We therefore turned our attention to the 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes with a non-stabilized sp^3-carbon nucleophile to broaden the application of this cyclization. For the generation of sp^3-carbanions, metal-halogen exchange was adopted. Thus, the ring-forming reaction of 1,1-difluoro-1-alkenes bearing an iodine substituent was examined as a new synthetic method for 1-fluorocyclopentenes,[5c] which is currently limited to a difluorination–dehydrofluorination sequence starting from cyclic ketones.[30]

Following the reported procedure for lithium-halogen exchange of primary alkyl iodides,[31] 1,1-difluoro-5-iodo-4-methyl-2-phenyl-1-pentene **13d** was treated with 2.2 equivalents of *tert*-butyllithium in diethyl ether–hexane at –78 °C. The reaction was quenched at –78 °C to give the cyclized product, 1-fluorocyclopentene **28d** in 28% yield along with 28% yield of the reduced product, 1,1-difluoro-4-methyl-2-phenyl-1-pentene, whose formation confirmed the generation of the carbanion. The cyclization was effectively promoted by allowing the reaction mixture to stand at room temperature for 1 h, improving the yield of **28d** up to 69%. When 1,1-difluoro-2-phenyl-1-hexene was treated with 1.1 equivalents of butyllithium as an external nucleophile under the same reaction conditions, the intermolecular substitution of the butyl group for the vinylic fluorine occurred to give the *E*/*Z* mixture (*E*/*Z* = 70:30) of products in 69% yield. In the case of the reaction of **13d** in diethyl ether, direct replacement of the fluorine by *tert*-butyllithium took place as a side reaction in 10% yield.

Cyclizations of several other 1,1-difluoro-5-iodo-1-pentenes **13** were examined under the conditions optimized above, and their results are shown in Scheme 11. Concerning *para*-substituents on the 2-phenyl group, electron-withdrawing and electron-donating groups had little effect on the cyclization. 1,1-Difluoro-2-(3-iodopropyl)-4-phenyl-1-pentene, a substrate without an aryl group on the vinylic carbon, underwent no cyclization on treatment with 2.2 equivalents of *tert*-butyllithium under the same reaction conditions as those for **13**, which shows a sharp contrast to the cyclizations of 4,4-difluorohomoallylic amine, alcohol, and thiol derivatives (Scheme 10).

5-*endo-trig* Cyclizations of 1,1-difluoro-1-alkenes are successfully achieved not only by intramolecular heteronucleophiles but also by sp^3-carbon nucleophiles, to which much less contribution has been made in spite of their potential utility. By addition of this carbocyclization, the scope of the intramolecular substitution of 1,1-difluoro-1-alkenes has been expanded in terms of five-membered ring formation.



13a–e

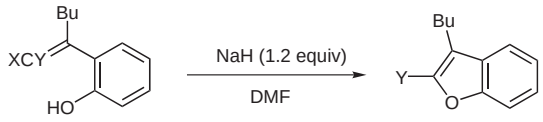
28a Ar = Ph, R = H (76%)
28b Ar = C_6H_4-*p*-CF_3, R = H (65%)
28c Ar = C_6H_4-*p*-MeO, R = H (74%)
28d Ar = Ph, R = Me (69%)
28e Ar = C_6H_4-*p*-MeO, R = Me (69%)

Scheme 11 Synthesis of 1-fluorocyclopentenes **28**
Reagents and conditions: i, *t*-BuLi (2.2 equiv), Et_2O–hexane (1:4), –78 °C, 0.5 h then r.t., 1 h, [**13**] = 0.04 M.

Effect of Fluorine Substituents on 5-*endo-trig* Cyclization

In order to confirm the effect of fluorine on the reactivity in the 5-*endo-trig* cyclization, we conducted similar reactions of β-monofluoro-, β,β-dichloro-, and β,β-dibromo-*o*-hydroxystyrenes **16**, **29**, and **30**. The results are summarized in Table 1.

Table 1 Effect of Vinylic Fluorine on 5-*endo-trig* Cyclization

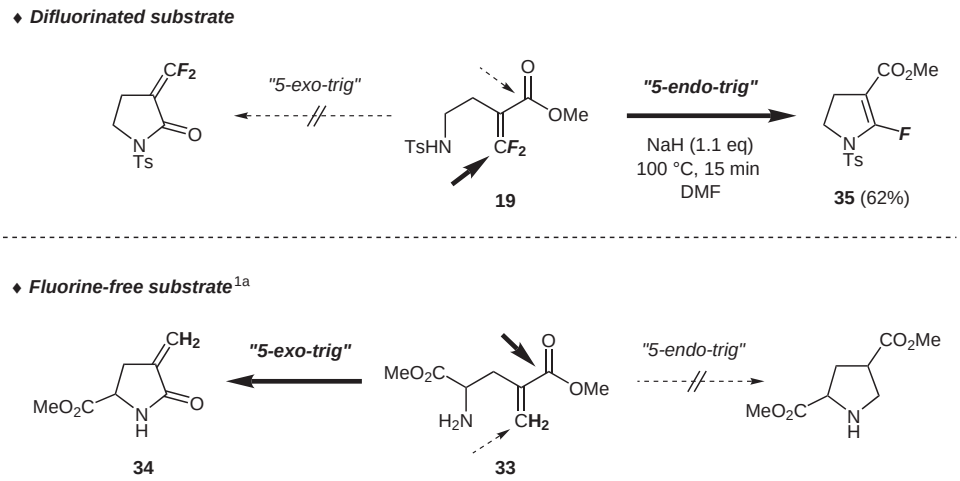


4b, **16**, **29**, **30** **22**, **31**, **32**

Entry	X	Y	Substrate	Conditions	Product	Yield (%)
1	***F***	***F***	**4b**	60 °C, 2 h	**22**	80
2	***F***	H	**16*E***	80 °C, 43 h	**31**	17
3	***F***	H	**16*Z***	80 °C, 43 h	**31**	19
4	Cl	Cl	**29**	60 °C, 8 h	–	–[a]
5	Br	Br	**30**	60 °C, 5 h	**32**	15

[a] Starting material **29** (80%) was recovered.

The reactions of the both *E* and *Z* isomers, **16*E*** and ***Z***, with sodium hydride required harsher conditions (Table 1, Entries 2 and 3) than that of **4b** (Entry 1), leading to low yields of the cyclized product (no more than 20 %). These observations revealed that two vinylic fluorines are essential to activate the substrate sufficiently for the nucleophilic 5-*endo-trig* cyclization. Dichloro and dibromo counterparts **29** and **30** (prepared via dihalomethylenation of the corresponding OH-protected ketone according to reported methods[32]) gave poor results, even though chlorine and bromine have better leaving-group ability compared to fluorine (Entries 4 and 5). These results suggest that the crucial step is the cyclization (addition), not the elimination. Thus, the major distinction of the 1,1-difluoro-1-alkenes appears to be the remarkable polarization of the double bond, which is caused by the repulsive interaction between the lone pairs of fluorine and the π-electrons. Such repulsion is much stronger for fluorine than for other halogens, due to the 2p-orbital occupancy of both the lone pairs and π-electrons. Consequently, the two vinylic fluorine substituents have proven to be essential and play a critical role in promoting the 5-*endo-trig* cyclization of 1,1-difluoro-1-alkenes.



Scheme 12 Competitive cyclization: 5-*endo-trig* vs 5-*exo-trig*.

The favored nature of 5-*endo-trig* cyclization in 1,1-difluoro-1-alkenes could be demonstrated by the competitive reaction between 5-*endo-trig* and 5-*exo-trig* processes. Baldwin reported the cyclization of dimethyl 4-methyleneglutamate **33**, showing how difficult 5-*endo-trig* cyclizations are.[1a] In this substrate, although there are two competitive reaction sites to be attacked by the intramolecular nitrogen in a 5-*endo-trig* fashion (Michael addition) and a 5-*exo-trig* fashion (transacylation), the reaction afforded only the 5-*exo-trig* product **34** (Scheme 12). For comparison, we selected the difluorinated analog, β,β-difluoro-α,β-unsaturated ester **19** bearing a 2-(*p*-toluenesulfonamido)ethyl group, as a substrate.

On treatment of **19** with sodium hydride in DMF, the 5-*endo-trig* cyclization occurred exclusively to give the 2-fluorinated pyrroline derivative **35** in 62% yield as shown in Scheme 12. The 5-*exo-trig* product was not detected in the reaction mixture by ^{19}F NMR measurement. This result shows a striking contrast to the reaction of **33**, clearly indicating the effect of fluorines on the course of cyclization.

Conclusion

The ring-fluorinated 5-membered hetero- and carbocycles such as indole, benzo[*b*]furan, benzo[*b*]thiophene, 2-pyrroline, 2,3-dihydrofuran, 2,3-dihydrothiophene, and cyclopentene have been successfully constructed via intramolecular substitution of the vinylic fluorine in 1,1-difluoro-1-alkenes bearing a nucleophilic moiety. This type of reaction is classified as a 5-*endo-trig* ring closure, a disfavored process in Baldwin's rules, and has only rarely been observed in synthetic chemistry. The nucleophilic 5-*endo-trig* cyclizations have been achieved by taking advantage of the exceptional properties of fluorine. In addition, by conducting the cyclization of β-monofluoro-, β,β-dichloro-, and β,β-dibromostyrenes and the competitive reaction between 5-*endo-trig* and 5-*exo-trig* processes, it has been revealed that the two vinylic fluorine substituents are essential and play a critical role in such 5-*endo-trig*-cyclization.

The intramolecular cyclizations of 1,1-difluoro-1-alkenes selectively afforded ring-fluorinated cyclic compounds, for which only a limited number of synthetic methods have been reported. Thus, the present methodology provides a solution to the synthetic problem of fluorinated hetero- and carbocycles. The synthesized compounds may be widely used as important components in the pharmaceutical, agrochemical, and dyestuffs industries. Furthermore, the 'anti-Baldwin' results indicate that some of the unique reactivities of 1,1-difluoro-1-alkenes are derived from the properties of fluorine, which sheds light on a new function of fluorine in synthetic chemistry.

NMR spectra were obtained on a JEOL JNM-A-500, JNM-AL-270, or a Bruker DRX-500 spectrometer. Chemical shift values were given in ppm relative to internal $SiMe_4$ (for ^1H and ^{13}C NMR: δ-value) or C_6F_6 (for ^{19}F NMR: δ_F-value). IR spectra were recorded on a Horiba FT-300S or a JEOL JIR-WINSPEC50 spectrometer. Mass spectra were taken with a JEOL JMS-DX-300 or a JEOL JMS-SX-102A spectrometer under electron impact (EI) unless otherwise noted. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus. THF was distilled from sodium diphenylketyl prior to use. Methanol was distilled from magnesium methoxide and stored over molecular sieves 3Å. DMF was dried over P_2O_5, then distilled under reduced pressure from CaH_2 and stored over molecular sieves 4Å. Commercial NaH was used without further purification. NaOMe was prepared from sodium and excess MeOH, and then dried under vacuum at 100 °C. 2,2,2-Trifluoroethyl *p*-toluenesulfonate (**1**) was purchased from Aldrich and recrystallized from hexane–Et_2O. 1,1-Difluoro-1,3-butadienes **8** were prepared according to the literature.[15]

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

BuLi (1.6 mL, 1.6 M in hexane, 2.5 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**, 307 mg, 1.2 mmol) in THF (10 mL) at –78 °C over 10 min under nitrogen. The reaction mixture was stirred for 20 min at –78 °C, and then Bu_3B (1.3 mL, 1.0 M in THF, 1.3 mmol) was added at –78 °C. After stirring for 1 h, the reaction mixture was warmed to r.t. and stirred for an addi-

tional 3 h. The solution was treated with HMPA (3 mL), PPh_3 (25 mg, 0.10 mmol), and $Pd_2(dba)_3{\cdot}CHCl_3$, (25 mg, 0.024 mmol) and stirred for 15 min. To the solution was added the magnesium salt [generated from *o*-iodoaniline (238 mg, 1.1 mmol) and dibutylmagnesium (2.5 mL, 0.44 M in Et_2O, 1.1 mmol) in THF (3 mL) at 0 °C for 30 min] and CuI (230 mg, 1.2 mmol). After the mixture had been stirred for 1 h at r.t., the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through Celite, and then organic materials were extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give **3a** (176 mg, 77%) as a yellow liquid.

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

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

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

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

MS (70 eV): *m*/*z* (%) = 211 (M^+, 100), 168 (59), 148 (43).

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

o′-(1-Butyl-2,2-difluorovinyl)-*p*-toluenesulfonanilide (3b)

TsCl (518 mg, 2.7 mmol) was added to a solution of **3a** (382 mg, 1.8 mmol) in pyridine (6 mL) at 0 °C. The reaction mixture was stirred for 11 h at r.t., and the reaction was quenched with phosphate buffer (pH 7). Organic materials was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with aq HCl (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative thin layer chromatography (PTLC) on silica gel (hexane–EtOAc, 5:1) to give **3b** (620 mg, 94%) as an orange solid.

IR (neat): 3274, 2958, 1741, 1494, 1402, 1340, 1245, 1168, 1093, 916, 665, 566 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.79 (3 H, t, *J* = 7.3 Hz), 1.06–1.22 (4 H, m), 1.99 (2 H, br s), 2.35 (3 H, s), 6.85 (1 H, s), 7.02 (1 H, dd, *J* = 7.4, 1.7 Hz), 7.05 (1 H, ddd, *J* = 7.4, 7.4, 1.0 Hz), 7.19–7.27 (3 H, m), 7.63 (1 H, d, *J* = 7.9 Hz), 7.73 (2 H, d, *J* = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.5, 21.4, 22.2, 28.0, 29.3, 87.9 (dd, J_{CF} = 23, 17 Hz), 119.6, 124.2, 127.1, 129.0, 129.6, 130.7, 135.0, 136.4, 144.0, 152.9 (dd, J_{CF} = 292, 288 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 71.8 (1 F, d, J_{FF} = 39 Hz), 74.9 (1 F, d, J_{FF} = 39 Hz).

MS (70 eV): *m*/*z* (%) = 365 (M^+, 3), 210 (100), 148 (86).

HRMS: *m*/*z* calcd for $C_{19}H_{21}NO_2F_2S$ (M^+): 365.1261; found: 365.1221.

***o*-(1-*sec*-Butyl-2,2-difluorovinyl)aniline (3c)**

Compound **3c** was prepared by the method described for **3a** using BuLi (3.7 mL, 1.6 M in hexane, 6.0 mmol), **1** (719 mg, 2.8 mmol), THF (14 mL), *s*-Bu_3B (3.1 mL, 1.0 M in THF, 3.1 mmol), HMPA (4 mL), PPh_3 (119 mg, 0.45 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (59 mg, 0.057 mmol), *o*-iodoaniline (558 mg, 2.6 mmol), dibutylmagnesium (2.6 mL, 1.0 M in Et_2O, 2.6 mmol), THF (2 mL), and CuI (593 mg, 2.8 mmol). Purification by column chromatography on silica gel (hexane–EtOAc, 30:1) gave **3c** (395 mg, 72%) as a pale yellow liquid.

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

^1H NMR [500 MHz, $(CD_3)_2SO$, 100 °C]: δ = 0.99 (3 H, t, *J* = 7.3 Hz), 1.03–1.15 (3 H, m), 1.31–1.45 (1 H, m), 1.54–1.66 (1 H, m), 2.44–2.58 (1 H, m), 4.58 (2 H, br s), 6.62 (1 H, ddd, *J* = 7.4, 7.4, 1.4 Hz), 6.79 (1 H, d, *J* = 7.4 Hz), 6.92 (1 H, d, *J* = 7.4 Hz), 7.07 (1 H, ddd, *J* = 7.4, 7.4, 1.4 Hz).

^{13}C NMR [126 MHz, $(CD_3)_2SO$, 100 °C]: δ = 10.1, 17.2, 26.9, 34.5, 92.4 (dd, J_{CF} = 16, 16 Hz), 114.5, 115.4, 116.1, 127.8, 129.6, 145.8, 151.7 (dd, J_{CF} = 291, 285 Hz).

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

MS (70 eV): *m*/*z* (%) = 211 (M^+, 100), 182 (57), 162 (82).

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

o′-(1-*sec*-Butyl-2,2-difluorovinyl)-*p*-toluenesulfonanilide (3d)

Compound **3d** was prepared by the method described for **3b** using TsCl (265 mg, 1.4 mmol), pyridine (5 mL), and **3c** (196 mg, 0.93 mmol). Purification by PTLC on silica gel (hexane–EtOAc 5:1) gave **3d** (315 mg, 93%) as a pale yellow solid.

IR (neat): 3280, 2966, 2933, 1732, 1495, 1400, 1338, 1244, 1163, 665 cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$, 80 °C]: δ = 0.93 (3 H, t, *J* = 7.1 Hz), 1.06 (3 H, d, *J* = 7.1 Hz), 1.24–1.37 (1 H, m), 1.57 (1 H, dqd, *J* = 13.8, 7.1, 7.1 Hz), 2.30–2.43 (1 H, m), 2.41 (3 H, s), 7.11–7.16 (2 H, m), 7.22–7.27 (2 H, m), 7.41 (2 H, d, *J* = 8.1 Hz), 7.80 (2 H, d, *J* = 8.1 Hz), 9.28 (1 H, br s).

^{13}C NMR [126 MHz, $(CD_3)_2SO$, 80 °C]: δ = 11.2, 17.1, 20.4, 27.0, 34.8, 92.7 (dd, J_{CF} = 19, 15 Hz), 121.6, 124.0, 126.3, 126.5, 128.0, 129.1, 130.9, 135.9, 137.9, 142.7, 152.2 (dd, J_{CF} = 290, 284 Hz).

^{19}F NMR [254 MHz, $(CD_3)_2SO$, 80 °C]: δ = 73.6 (1 F, d, J_{FF} = 46 Hz), 76.9 (1 F, d, J_{FF} = 46 Hz).

MS (70 eV): *m*/*z* = 365 (M^+), 210, 136.

Anal. Calcd for $C_{19}H_{21}NO_2SF_2$: C, 62.45; H, 5.79; N, 3.83. Found: C, 62.38; H, 5.89; N, 3.90.

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

BuLi (0.79 mL, 1.6 M in hexane, 1.3 mmol) was added to a solution of **1** (155 mg, 0.61 mmol) in THF (3 mL) at –78 °C over 10 min under nitrogen. The reaction mixture was stirred for 20 min at –78 °C, and then Bu_3B (0.67 mL, 1.0 M in THF, 0.67 mmol) was added at –78 °C. After being stirred for 1 h, the reaction mixture was warmed to r.t. and stirred for an additional 3 h. The solution was treated with HMPA (1 mL), PPh_3 (25 mg, 0.098 mmol), and $Pd_2(dba)_3{\cdot}CHCl_3$ (13 mg, 0.012 mmol) and stirred for 15 min. To the solution was added *o*-iodoanisole (129 mg, 0.55 mmol) and CuI (116 mg, 0.61 mmol). After the mixture was stirred for 16 h at r.t., the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through Celite, and then organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 50:1) to give **4a** (58 mg, 46%) as a colorless liquid.

IR (neat): 2960, 2930, 1740, 1490, 1460, 1270, 1245, 1230, 1025, 750 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, *J* = 7.2 Hz), 1.21–1.34 (4 H, m), 2.30–2.35 (2 H, m), 3.80 (3 H, s), 6.89 (1 H, d, *J* = 7.6 Hz), 6.93 (1 H, ddd, *J* = 7.6, 7.6, 0.9 Hz), 7.12 (1 H, dd, *J* = 7.6, 1.6 Hz), 7.27 (1 H, ddd, *J* = 7.6, 7.6, 1.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.2, 27.5, 29.7 (d, J_{CF} = 2 Hz), 55.4, 89.4 (dd, J_{CF} = 23, 16 Hz), 111.0, 120.4, 123.0 (dd, J_{CF} = 3, 3 Hz) 129.0, 131.1 (d, J_{CF} = 2 Hz), 153.0 (dd, J_{CF} = 286, 286 Hz), 157.4 (d, J_{CF} = 2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 67.1 (1 F, dd, J_{FF} = 46 Hz, J_{FH} = 3 Hz), 70.9 (1 F, d, J_{FF} = 46 Hz).

MS (20 eV): *m*/*z* (%) = 226 (M^+, 73), 215 (58), 149 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{16}OF_2$ (M^+): 226.1169; found: 226.1171.

_o_-(1-Butyl-2,2-difluorovinyl)phenol (4b)

BBr_3 (0.85 mL, 1.0 M in CH_2Cl_2, 0.85 mmol) was added to a solution of **4a** (175 mg, 0.77 mmol) in CH_2Cl_2 (5 mL) at –15 °C. The reaction mixture was stirred for 2 h at r.t. The reaction was quenched with phosphate buffer (pH 7), and then organic materials were extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc 10:1) to give **4b** (156 mg, 95%) as a colorless liquid.

IR (neat): 3430, 2950, 2930, 2860, 1740, 1450, 1130, 965, 755 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3 H, t, *J* = 7.2 Hz), 1.25–1.36 (4 H, m), 2.33 (2 H, tt, *J* = 7.2 Hz, J_{HF} = 2.2 Hz), 4.88 (1 H, s), 6.88–6.96 (2 H, m), 7.03–7.12 (1 H, m), 7.19–7.26 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.7, 22.2, 28.0, 29.7 (dd, J_{CF} = 3, 3 Hz), 87.7 (dd, J_{CF} = 23, 16 Hz), 115.6, 115.9 (d, J_{CF} = 6 Hz) 120.7, 129.4, 129.7, 130.5, 153.2 (dd, J_{CF} = 307, 280 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.3 (1 F, dt, J_{FF} = 41 Hz, J_{FH} = 3 Hz), 73.8 (1 F, d, J_{FF} = 41 Hz).

MS (70 eV): *m*/*z* (%) = 212 (M^+, 34), 192 (33), 107 (74).

HRMS: *m*/*z* calcd for $C_{12}H_{14}OF_2$ (M^+): 212.1013; found: 212.1008.

_o_-(1-Butyl-2,2-difluorovinyl)phenyl Methyl Sulfide (5a)

CF_3CO_2H (0.049 mL, 0.64 mmol) and isopentyl nitrite (0.085 mL, 0.64 mmol) were added to a solution of **3a** (67 mg, 0.32 mmol) in CH_3CN (3 mL) at 0 °C. The reaction mixture was stirred for 30 min. The solution was treated with NaSMe (449 mg, 15% in H_2O, 0.96 mmol) and stirred for 1.5 h at 0 °C. The reaction was quenched with phosphate buffer (pH 7), and then organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 10:1) to give **5a** (45 mg, 58%) as a colorless liquid.

IR (neat): 2958, 2927, 1741, 1467, 1436, 1259, 1232, 1122, 971, 746 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3 H, t, *J* = 6.9 Hz), 1.27–1.36 (4 H, m), 2.28–2.36 (2 H, m),2.43 (3 H, s), 7.09 (1 H, dd, *J* = 7.2, 1.8 Hz), 7.12 (1 H, ddd, *J* = 7.2, 7.2, 1.1 Hz), 7.21 (1 H, d, *J* = 7.2 Hz), 7.29 (1 H, ddd, *J* = 7.2, 7.2, 1.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 15.5, 22.4, 27.9, 29.6 (dd, J_{CF} = 3, 3 Hz), 91.0 (dd, J_{CF} = 23, 16 Hz), 124.5, 125.1, 128.5, 130.3 (d, J_{CF} = 3 Hz) 132.4 (d, J_{CF} = 5 Hz), 138.8, 153.0 (dd, J_{CF} = 288, 287 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 68.0 (1 F, ddd, J_{FF} = 43 Hz, J_{FH} = 3, 3 Hz), 72.8 (1 F, ddd, J_{FF} = 43, J_{FH} = 2, 2 Hz).

MS (70 eV): *m*/*z* (%) = 242 (M^+, 68), 165 (100), 134 (74).

HRMS: *m*/*z* calcd for $C_{13}H_{16}F_2S$ (M^+): 242.0941; found: 242.0916.

_o_-(1-Butyl-2,2-difluorovinyl)phenyl Methyl Sulfoxide (5b)

$TiCl_3$ (602 mg, 20% in H_2O, 0.78 mmol) was added to a solution of **5a** (94 mg, 0.39 mmol) in MeOH–H_2O (6:1, 8 mL) at 0 °C. The solution was treated with H_2O_2 (133 mg, 30% in H_2O, 1.2 mmol) and stirred for 2 h at r.t. The reaction was quenched with phosphate buffer (pH 7), and then organic materials were extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 1:2) to give **5b** (83 mg, 83%) as a colorless liquid.

IR (neat): 2958, 2931, 1739, 1467, 1234, 1122, 1072, 1043, 968, 769 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85–0.90 (3 H, m), 1.27–1.39 (4 H, m), 2.28–2.40 (2 H, m), 2.67 (3 H, s), 7.21 (1 H, dd, *J* = 7.6, 1.3 Hz), 7.51 (1 H, ddd, *J* = 7.6, 7.6, 1.3 Hz), 7.60 (1 H, ddd, *J* = 7.6, 7.6, 1.3 Hz), 8.10 (1 H, dd, *J* = 7.6, 1.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.7, 22.3, 28.7, 29.5 (dd, J_{CF} = 3, 3 Hz), 43.5 (d, J_{CF} = 2 Hz), 89.9 (dd, J_{CF} = 24, 16 Hz), 123.9, 129.7, 130.5 (d, J_{CF} = 3 Hz), 131.0 (d, J_{CF} = 4 Hz), 131.2, 145.0 (d, J_{CF} = 2 Hz), 152.0 (dd, J_{CF} = 291, 286 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.4 (1 F, d, J_{FF} = 42 Hz), 74.1 (1 F, br d).

MS (70 eV): *m*/*z* (%) = 258 (M^+, 46), 241 (23), 215 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{16}OF_2S$ (M^+): 258.0890; found: 258.0876.

2,2-Difluorovinyl _p_-Toluenesulfonate (6)

BuLi (39 mL, 1.6 M in hexane, 63 mmol) was added to a solution of **1** (7.62 g, 30 mmol) in THF (150 mL) at –78 °C over 10 min under nitrogen. The reaction mixture was stirred for 20 min at –78 °C, and then the reaction was quenched with H_2O–THF (1:1, 100 mL). Organic materials were extracted with EtOAc (3 × 80 mL), the combined extracts were washed with brine (80 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 10:1) to give **6** (6.40 g, 91%) as a colorless liquid.

IR (neat): 1759, 1383, 1344, 1248, 1178, 1119, 1090, 928, 748, 665 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (3 H, s), 6.08 (1 H, dd, J_{HF} = 14.5, 3.8 Hz), 7.39 (2 H, br d, *J* = 8.3 Hz), 7.82 (2 H, br d, *J* = 8.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.6, 100.8 (dd, J_{CF} = 60, 15 Hz), 128.3, 130.0, 131.1, 1401, 156.9 (dd, J_{CF} = 293, 283 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ_F = 52.9 (1 F, dd, J_{FF} = 51 Hz, J_{FH} = 4 Hz), 71.5 (1 F, dd, J_{FF} = 51 Hz, J_{FH} = 14 Hz).

Anal. Calcd for $C_9H_8O_3F_2S$: C, 46.15; H, 3.44. Found: C, 46.17; H, 3.58.

_o′_-(2,2-Difluorovinyl)-_p_-toluenesulfonanilide (3f)

BuLi (23 mL, 1.6 M in hexane, 36 mmol) was added to a solution of zirconocene dichloride (5.25 g, 18 mmol) in THF (100 mL) at –78 °C under nitrogen, and the resulting mixture was stirred at the same temperature for 1 h. To the reaction mixture was added a solution of **6** (2.10 g, 9.0 mmol) in THF (5 mL) at –78 °C. After stirring for 5 min, the mixture was warmed to r.t. and stirred for an additional 3 h. PPh_3 (376 mg, 1.4 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (186 mg, 0.18 mmol) were added at 0 °C, and the mixture was stirred for 10 min. To the resulting solution were successively added *o*-iodoaniline (2.16 g, 9.9 mmol) and ZnI_2 (6.87 g, 22 mmol). The mixture was filtered through Celite and organic materials were extracted with Et_2O (3 × 50 mL). After removal of the solvent under reduced pressure, the residue was treated with TsCl (1.88 g, 9.9 mmol) in pyridine (3 mL) at 0 °C. The reaction mixture was stirred for 12 h at r.t. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with EtOAc (3 × 50 mL). The combined extracts were washed with aq HCl (50 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc 2:1) to give **3f** (1.11 g, 40%) as an orange solid.

IR (neat): 3266, 1727, 1490, 1400, 1334, 1222, 1160, 1091, 815, 673, 566, 549 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (3 H, s), 5.21 (1 H, dd, J_{HF} = 25.2, 3.2 Hz), 6.67 (1 H, s), 7.17–7.26 (5 H, m), 7.33–7.37 (1 H, m), 7.61 (2 H, d, J = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.5, 108.9 (d, J_{CF} = 16 Hz), 126.2, 127.0, 127.3, 128.2, 129.2, 129.2, 130.0, 133.4 (d, J_{CF} = 3 Hz), 136.2, 144.1, 156.5 (dd, J_{CF} = 298, 290 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 79.0 (1 F, ddd, J_{FF} = 25 Hz, J_{FH} = 25, 2 Hz), 80.6 (1 F, dd, J_{FF} = 25 Hz, J_{FH} = 4 Hz).

MS (70 eV): *m*/*z* (%) = 309 (M^+), 155, 154, 127.

HRMS: *m*/*z* calcd for $C_{15}H_{13}NO_2F_2S$ (M^+): 309.0635; found: 309.0643.

4,4-Difluoro-3-(2-phenylpropyl)-2-methyl-but-3-ene-1-ol (9a)

9-BBN (0.8 mL, 0.5 M in THF, 0.40 mmol) was added to a solution of 1,1-difluoro-3-methyl-2-(2-phenylpropyl)-1,3-butadiene (**8a**, 80 mg, 0.36 mmol) in THF (2 mL) under nitrogen. The reaction mixture was heated under reflux for 5 h and then cooled to 0 °C. To the resulting solution were added successively, NaOH (0.10 mL, 3 M in H_2O, 0.30 mmol) and H_2O_2 (0.10 mL, 30% in H_2O, 1.0 mmol). The mixture was stirred for 2 h, then quenched with phosphate buffer (pH 7). Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc 2:1) to give **9a** (1:1 diastereomeric mixture, 50 mg, 58%) as a colorless liquid.

IR (neat): 3340, 2966, 1735, 1602, 1494, 1452, 1376, 1224, 1033, 979, 763, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (1.5 H, d, J = 7.3 Hz), 1.00 (1.5 H, d, J = 6.7 Hz), 1.00–1.80 (1 H, br m), 1.27 (1.5 H, d, J = 7.3 Hz), 1.28 (1.5 H, d, J = 7.3 Hz), 2.10–2.30 (2 H, m), 2.39 (0.5 H, dd, J = 13.0, 6.7 Hz), 2.41 (0.5 H, dd, J = 13.0, 7.3 Hz), 2.91 (1 H, tq, J = 7.3, 7.3 Hz), 3.37 (0.5 H, d, J = 7.9 Hz), 3.39 (0.5 H, d, J = 7.9 Hz), 3.51 (0.5 H, d, J = 7.3 Hz), 3.52 (0.5 H, d, J = 7.9 Hz), 7.20–7.24 (3 H, m), 7.30 (1 H, t, J = 7.3 Hz), 7.31 (1 H, t, J = 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.0, 15.0, 21.4, 21.6, 34.8, 34.9, 35.8, 35.8, 38.3 (dd, J_{CF} = 3, 2 Hz), 38.6 (dd, J_{CF} = 3, 2 Hz), 65.4 (dd, J_{CF} = 3, 3 Hz), 65.5 (dd, J_{CF} = 3, 3 Hz), 89.3 (dd, J_{CF} = 14, 14 Hz), 89.3 (dd, J_{CF} = 14, 14 Hz), 126.3, 126.4, 126.9, 126.9, 128.4, 128.4, 146.3, 146.4, 154.4 (dd, J_{CF} = 288, 287 Hz), 154.4 (dd, J_{CF} = 288, 286 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ_F = 70.7 (0.5 F, d, J_{FF} = 53 Hz), 70.8 (0.5 F, d, J_{FF} = 53 Hz), 71.8 (0.5 F, d, J_{FF} = 53 Hz), 72.5 (0.5 F, d, J_{FF} = 53 Hz).

MS (70 eV): *m*/*z* (%) = 240 (M^+, 3), 220 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{18}OF_2$ (M^+): 240.1326; found: 240.1328.

2-Benzyl-3-butyl-4,4-difluorobut-3-en-1-ol (9b)

Compound **9b** was prepared by the method described for **9a** using THF (3 mL), 9-BBN (2.5 mL, 0.5 M in THF, 1.3 mmol), 3-benzyl-2-butyl-1,1-difluoro-1,3-butadiene (**8b**, 200 mg, 0.90 mmol), NaOH (1.8 mL, 3 M in H_2O, 5.4 mmol), and H_2O_2 (1.8 mL, 30% in H_2O, 18 mmol). Hydroboration was carried out under reflux for 7 h. Purification by PTLC on silica gel (hexane–EtOAc 3:1) gave **9b** (172 mg, 76%) as a colorless liquid.

IR (neat): 3336, 2956, 1740, 1605, 1497, 1456, 1250, 1219, 1032, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, J = 7.0 Hz), 1.18–1.25 (4 H, m), 1.53 (1 H, s), 1.79–1.85 (2 H, m), 2.70–2.74 (2 H, m), 2.83 (1 H, dd, J = 17.1, 10.4 Hz), 3.63 (2 H, d, J = 6.1 Hz), 7.15 (2 H, d, J = 7.3 Hz), 7.19 (1 H, t, J = 7.3 Hz), 7.27 (2 H, dd, J = 7.6, 7.0 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.7, 22.5, 25.7 (d, J_{CF} = 3 Hz), 30.5, 35.9, 43.5, 64.0, 89.3 (dd, J_{CF} = 17, 13 Hz), 126.2, 128.3, 128.8, 139.6, 154.3 (dd, J_{CF} = 287, 287 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.4 (1 F, d, J_{FF} = 54 Hz), 70.8 (1 F, d, J_{FF} = 54 Hz).

MS (70 eV): *m*/*z* (%) = 254 (M^+, 10), 234 (32), 203, (66), 91 (100).

HRMS: *m*/*z* calcd for $C_{15}H_{20}OF_2$ (M^+): 254.1482; found: 254.1495.

4,4-Difluoro-2-methyl-3-(3-phenylpropyl)but-3-ene-1-ol (9c)

Compound **9c** was prepared by the method described for **9a** using THF (20 mL), 9-BBN (16.0 mL, 0.5 M in THF, 7.9 mmol) and 1,1-difluoro-3-methyl-2-(3-phenylpropyl)-1,3-butadiene (**8c**, 1.60 g, 7.2 mmol), NaOH (9.6 mL, 3 M in H_2O, 29 mmol), and H_2O_2 (9.6 mL, 30% in H_2O, 96 mmol). Hydroboration was carried out under reflux for 6 h. Purification by column chromatography on silica gel (hexane–EtOAc 4:1) gave **9c** (1.25 g, 72%) as a colorless liquid.

IR (neat): 3350, 2939, 1739, 1605, 1497, 1454, 1214, 1032, 748, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (3 H, d, J = 7.3 Hz), 1.69–1.79 (3 H, m), 1.93–2.00 (2 H, m), 2.49 (1 H, tq, J = 7.6, 7.3 Hz), 2.61 (2 H, d, J = 7.6 Hz), 3.48 (2 H, d, J = 7.6 Hz), 7.16 (2H, d, J = 7.6 Hz), 7.17 (1 H, t, J = 7.3 Hz), 7.27 (2 H, dd, J = 7.6, 7.3 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.0 (dd, J_{CF} = 3, 2 Hz), 24.8 (d, J_{CF} = 3 Hz), 30.4 (dd J_{CF} = 3, 2 Hz), 35.3 (d, J_{CF} = 2 Hz), 35.7, 65.4 (dd, J_{CF} = 3, 3 Hz), 90.5 (dd, J_{CF} = 16, 15 Hz), 125.8, 128.3, 128.3, 141.8, 154.0 (dd, J_{CF} = 287, 286 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 69.2 (1 F, d, J_{FF} = 55 Hz), 70.1 (1 F, d, J_{FF} = 55 Hz) ppm.

MS (70 eV): *m*/*z* (%) = 240 (M^+, 7), 220 (77), 189 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{18}OF_2$ (M^+): 240.1325; found: 240.1363.

***N*-*tert*-Butoxycarbonyl-*N*-[4,4-difluoro-2-methyl-3-(2-phenylpropyl)but-3-enyl]-*p*-toluenesulfonamide (10a)**

To a solution of **9a** (132 mg, 0.55 mmol) in THF (5 mL) was added PPh_3 (144 mg, 0.55 mmol), *N*-*tert*-butoxycarbonyl-*p*-toluenesulfonamide (149 mg, 0.55 mmol), and DEAD (239 mg, 40% in toluene, 0.55 mmol) at r.t. under nitrogen. After the reaction mixture was stirred for 2 h at r.t., phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc 7:1) to give **10a** (1:1 diastereomeric mixture, 233 mg, 86%) as a pale yellow liquid.

IR (neat): 2974, 1732, 1599, 1495, 1358, 1255, 1157, 1090, 849, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (1.5 H, d, J = 7.1 Hz), 1.09 (1.5H, d, J = 7.3 Hz), 1.28 (1.5 H, d, J = 7.0 Hz), 1.31 (4.5 H, s), 1.32 (1.5 H, d, J = 7.0 Hz), 1.33 (4.5 H, s), 2.22–2.32 (2 H, m), 2.43 (1.5 H, s), 2.43 (1.5 H, s), 2.69 (0.5 H, qtd, J = 7.3, 7.3 Hz, J_{HF} = 2.4 Hz), 2.80 (0.5 H, tq, J = 7.0, 7.0 Hz), 2.94 (1 H, tq, J = 7.3, 7.3 Hz), 3.73 (0.5 H, d, J = 7.0 Hz), 3.74 (0.5 H, d, J = 8.5 Hz), 3.80 (1 H, d, J = 7.6 Hz), 7.17–7.33 (7 H, m), 7.73 (1 H, d, J = 8.5 Hz), 7.75 (1 H, d, J = 8.5 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15 5, 15.7, 21.5, 21.6, 27.7, 27.7, 33.3, 33.7, 35.0, 35.0, 35.8, 35.8, 38.4, 38.4, 50.2, 50.4, 84.2, 84.2, 89.4 (dd, J_{CF} = 15, 15 Hz), 89.8 (dd, J_{CF} = 15, 15 Hz), 126.2, 126.2, 126.9, 127.1, 127.8, 127.8, 128.3, 128.3, 129.2, 129.2, 137.3, 137.3, 144.1, 144.1, 146.3, 146.6, 151.0, 151.0, 154.6 (dd, J_{CF} = 289, 289 Hz), 154.6 (dd, J_{CF} = 286, 286 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 72.1 (0.5 F, d, J_{FF} = 52 Hz), 72.2 (0.5 F, d, J_{FF} = 52 Hz), 72.3 (0.5 F, d, J_{FF} = 52 Hz), 72.8 (0.5 F, d, J_{FF} = 52 Hz).

MS (70 eV): *m*/*z* = 493 (M^+).

N-[4,4-Difluoro-2-methyl-3-(2-phenylpropyl)but-3-enyl]-*p*-toluenesulfonamide (10b)

Trifluoroacetic acid (0.47 mL, 6.0 mmol) was added to a solution of **10a** (200 mg, 0.40 mmol) in CH_2Cl_2 (2.5 mL) at r.t. After the reaction mixture was stirred for 1.5 h at r.t., aq $NaHCO_3$ (10 mL) was added to quench the reaction. Organic materials were extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with H_2O, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 4:1) to give **10b** (a 1:1 diastereomeric mixture, 143 mg, 91%) as a colorless liquid.

IR (neat): 3282, 2966, 1735, 1600, 1494, 1452, 1326, 1160, 1093, 815, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (1.5 H, d, *J* = 6.7 Hz), 0.96 (1.5 H, d, *J* = 7.0 Hz), 1.21 (1.5 H, d, *J* = 6.7 Hz), 1.22 (1.5 H, d, *J* = 7.0 Hz), 2.01–2.19 (2 H, m), 2.26–2.34 (1 H, m), 2.41 (1.5 H, s), 2.42 (1.5 H, s), 2.67–2.93 (3 H, m), 4.44 (0.5 H, br d, *J* = 5.6 Hz), 4.62 (0.5 H, br d, *J* = 6.1 Hz), 7.11–7.32 (7 H, m), 7.68 (1 H, d, *J* = 8.2 Hz), 7.32 (1 H, d, *J* = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 16.1, 16.3, 21.5, 21.5, 21.7, 21.7, 33.6, 33.7, 34.7 (d, J_{CF} = 3 Hz), 34.9, 38.2, 38.5, 46.5, 46.7, 89.3 (dd, J_{CF} = 14, 4 Hz), 89.4 (dd, J_{CF} = 13, 5 Hz), 126.3, 126.4, 126.9, 126.9, 127.0, 127.0, 128.4, 128.5, 129.6, 129.7, 136.9, 137.0, 143.3, 143.4, 146.0, 146.1, 154.3 (dd, J_{CF} = 288, 288 Hz), 154.3 (dd, J_{CF} = 288, 288 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 71.8 (0.5 F, d, J_{FF} = 52 Hz), 72.0 (0.5 F, d, J_{FF} = 52 Hz), 72.5 (0.5 F, d, J_{FF} = 52 Hz), 73.1 (0.5 F, d, J_{FF} = 52 Hz).

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

HRMS: *m*/*z* calcd for $C_{21}H_{25}NO_2F_2S$ (M^+): 393.1574; found: 393.1581.

4,4-Difluoro-2-methyl-3-(3-phenylpropyl)but-3-enyl *p*-Toluenesulfonate (9d)

TsCl (286 mg, 1.5 mmol) was added to a solution of **9c** (300 mg, 1.3 mmol) in pyridine (3 mL) at r.t. After the reaction mixture was stirred for 8 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc 10:1) to give **9d** (422 mg, 80%) as a colorless liquid.

IR (neat): 2935, 1741, 1599, 1497, 1362, 1176, 970, 835, 700, 667 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (3 H, d, *J* = 7.0 Hz), 1.61–1.69 (2 H, m), 1.85–1.91 (2 H, m), 2.44 (3 H, s), 2.56 (2 H, t, *J* = 7.6 Hz), 2.61 (1 H, tq, *J* = 7.3, 7.0 Hz), 3.90 (2 H, d, *J* = 7.3 Hz), 7.14 (2 H, d, *J* = 7.3 Hz), 7.19 (1 H, t, *J* = 7.3 Hz), 7.28 (2 H, dd, *J* = 7.3, 7.3 Hz), 7.32 (2 H, d, *J* = 8.4 Hz), 7.75 (2 H, d, *J* = 8.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.0, 21.6, 25.1, 30.0, 32.4 (d, J_{CF} = 2 Hz), 35.5, 71.8 (dd, J_{CF} = 3, 3 Hz), 89.5 (dd J_{CF} = 17,4 Hz), 125.9, 127.8, 128.2, 128.3, 129.8, 132.9, 141.6, 144.8, 153.9 (dd, J_{CF} = 288, 287 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 70.9 (1 F, d, J_{FF} = 53 Hz), 71.0 (1 F, d, J_{FF} = 53 Hz).

MS (70 eV): *m*/*z* = 394 (M^+).

HRMS: *m*/*z* calcd for $C_{21}H_{24}O_3F_2S$ (M^+): 394.1414; found: 394.1401.

S-4,4-Difluoro-2-methyl-3-(3-phenylpropyl)but-3-enyl Thioacetate (11a)

To a solution of thioacetic *S*-acid (90 mg, 1.2 mmol) in DMF (5 mL) was added NaH (47 mg, 60% dispersion in mineral oil, 1.2 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 min, a solution of **9d** (358 mg, 0.91 mmol) in THF (2 mL) was added and heated at 70 °C for 3 h, then quenched with phosphate buffer (pH 7). Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with H_2O, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to give **11a** (243 mg, 90%) as a colorless liquid.

IR (neat): 2935, 1740, 1695, 1605, 1497, 1454, 1354, 1213, 1136, 957 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.11 (3 H, d, *J* = 7.0 Hz), 1.74 (2 H, tt, *J* = 7.8, 7.8 Hz), 1.90–2.02 (2 H, m), 2.31 (3 H, s), 2.48 (1 H, ddq, *J* = 7.5, 7.5, 7.5 Hz), 2.62 (2 H, dd, *J* = 8.5, 7.0 Hz), 2.86 (1 H, dd, *J* = 13.4, 8.2 Hz), 2.96 (1 H, dd, *J* = 13.4, 7.3 Hz), 7.15–7.20 (3 H, m), 7.28 (2 H, dd, *J* = 7.6, 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 18.4, 24.9 (d, J_{CF} = 4 Hz), 30.3, 30.6, 32.9, 33.8, 35.7, 91.8 (dd, J_{CF} = 17, 14 Hz), 125.8, 128.3, 128.3, 141.8, 153.9 (dd, J_{CF} = 288, 286 Hz), 195.5.

^{19}F NMR (470 MHz, $CDCl_3$): δ_F = 69.7 (1 F, d, J_{FF} = 54 Hz), 70.4 (1 F, d, J_{FF} = 54 Hz).

4,4-Difluoro-2-methyl-3-(3-phenylpropyl)but-3-ene-1-thiol (11b)

K_2CO_3 (46 mg, 0.34 mmol) was added to a solution of **11a** (91 mg, 0.31 mmol) in MeOH (2 mL) at 0 °C. After the reaction mixture was stirred for 1 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 50:1) to give **11b** (75 mg, 95%) as a colorless liquid.

IR (neat): 2935, 2573, 1740, 1605, 1495, 1454, 1252, 1213, 1092, 980 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (3 H, d, *J* = 7.0 Hz), 1.33 (1 H, t, *J* = 8.1 Hz), 1.68–1.82 (2 H, m), 1.89–2.02 (2 H, m), 2.38–2.59 (3 H, m), 2.62 (2 H, t, *J* = 7.8 Hz), 7.18 (2 H, d, *J* = 7.6 Hz), 7.18 (1 H, t, *J* = 7.6 Hz), 7.28 (2 H, dd, *J* = 7.6, 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 18.1 (dd, J_{CF} = 3, 2 Hz), 24.8 (d, J_{CF} = 3 Hz), 29.3 (dd J_{CF} = 3, 2 Hz), 30.5 (d, J_{CF} = 3 Hz), 35.7, 36.7 (d, J_{CF} = 3 Hz), 91.6 (dd, J_{CF} = 16, 14 Hz), 125.9, 128.3, 128.3, 141.8, 153.9 (dd, J_{CF} = 287, 287 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 69.7 (1 F, d, J_{FF} = 54 Hz), 70.0 (1 F, d, J_{FF} = 54 Hz).

MS (70 eV): *m*/*z* (%) = 256 (M^+, 12), 189 (51), 165 (44), 91 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{18}OF_2S$ (M^+): 256.1097; found 256.1094.

5,5-Difluoro-4-phenylpent-4-en-1-ol (12a)

BuLi (67 mL, 1.6 M in hexane, 109 mmol) was added to a solution of **1** (13 g, 52 mmol) in THF (270 mL) at –78 °C over 10 min under argon, and the reaction mixture was stirred for 20 min at –78 °C. Tris[3-(methoxymethoxy)propyl]borane [Borane–THF complex (57 mL, 1.0 M in THF, 57 mmol) was added to a solution of allyl methoxymethyl ether (16 g, 156 mmol) in THF (69 ml) at 0 °C, and the mixture was stirred for 3 h at r.t.] was then added at –78 °C. After being stirred for 1 h, the reaction mixture was heated to reflux for an additional 1 h. After being cooled to r.t., the solution was

treated with HMPA (108 mL), PPh_3 (1.1 g, 4.2 mmol), and $Pd_2(dba)_3{\cdot}CHCl_3$ (1.2 g, 1.0 mmol) and was stirred for 15 min. To the resulting solution was added iodobenzene (8.5 g, 42 mmol) and CuI (9.9 g, 52 mmol). After the mixture was stirred for 1 h at r.t., the reaction was quenched with phosphate buffer (pH 7). The mixture was filtered through Celite, and the organic materials were extracted with EtOAc (3 × 100 mL). The combined extracts were washed with brine (100 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) to give a crude product (9.0 g) as a yellow liquid. HCl (98 mL, 12 M in H_2O, 1.2 mol) was added to a solution of the crude product (9.0 g) in THF (74 mL) at r.t. under air. The reaction mixture was stirred for 1 h at r.t., the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 3:1) to give **12a** (3.6 g, 43%) as a colorless liquid.

IR (neat): 3352, 2935, 2873, 1732, 1446, 1232, 1124, 1061, 947, 762, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (1 H, br s), 1.63 (2 H, tt, *J* = 6.9, 6.9 Hz), 2.51 (2 H, tt, *J* = 6.9 Hz, J_{HF} = 2.4 Hz), 3.62 (2 H, t, *J* = 6.9 Hz), 7.27 (1 H, t, *J* = 7.3 Hz), 7.31 (2 H, d, *J* = 7.3 Hz), 7.35 (2 H, dd, *J* = 7.3, 7.3 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.0, 30.7, 62.0, 91.9 (dd, J_{CF} = 35, 14 Hz), 127.3, 128.2 (dd, J_{CF} = 3, 3 Hz), 128.5, 133.5 (dd, J_{CF} = 3, 3 Hz), 153.6 (dd, J_{CF} = 290, 287 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 70.3 (1 F, dt, J_{FF} = 43 Hz, J_{FH} = 2 Hz), 70.4 (1 F, dt, J_{FF} = 43 Hz, J_{FH} = 2 Hz).

Anal. Calcd for $C_{11}H_{12}OF_2$: C, 66.66; H, 6.10. Found: C, 66.48; H, 6.11.

5,5-Difluoro-4-(*p*-trifluoromethylphenyl)pent-4-en-1-ol (12b)

Compound **12b** was prepared by the method described for **12a** using BuLi (6.9 mL, 1.6 M in hexane, 11 mmol), **1** (1.3 g, 5.3 mmol), THF (27 mL), borane–THF complex (5.8 mL, 1.0 M in THF, 5.8 mmol), allyl methoxymethyl ether (609 mg, 16 mmol), THF (7 ml), HMPA (11 mL), PPh_3 (110 mg, 0.42 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (121 mg, 0.21 mmol), *p*-iodotrifluoromethylbenzene (1.0 g, 3.7 mmol), and CuI (1.0 g, 5.3 mmol). Purification by column chromatography on silica gel (hexane–EtOAc 5:1) gave a crude product (1.2 g) as a yellow liquid. Treatment of the product with HCl (10 mL, 12 M in H_2O, 0.12 mol) and THF (8 mL) and purification by PTLC on silica gel (hexane–EtOAc, 2:1) gave **12b** (534 mg, 54%) as a colorless liquid.

IR (neat): 3446, 2955, 1728, 1618, 1358, 1329, 1244, 1174, 1128, 1068, 947, 847, 528 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.57 (1 H, br s), 1.59–1.66 (2 H, m), 2.51-2.57 (2 H, m), 3.64 (2 H, dt, *J* = 5.3, 5.3 Hz), 7.45 (2 H, d, *J* = 7.8 Hz), 7.61 (2 H, d, *J* = 7.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8, 30.6, 61.8, 91.4 (dd, J_{CF} = 23, 13 Hz), 124.0 (q, J_{CF} = 272 Hz), 125.5 (q, J_{CF} = 4 Hz), 128.5 (dd, J_{CF} = 3, 3 Hz), 129.5 (q, J_{CF} = 33 Hz), 137.4, 153.9 (dd, J_{CF} = 292, 289 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 72.3 (1 F, d, J_{FF} = 39 Hz), 72.6 (1 F, dt, J_{FF} = 39 Hz, J_{FH} = 3 Hz), 99.0 (3 F, s).

HRMS: *m*/*z* calcd for $C_{12}H_{11}OF_5$ (M^+): 266.0730; found: 266.0706.

5,5-Difluoro-4-(*p*-methoxyphenyl)pent-4-en-1-ol (12c)

Compound **12c** was prepared by the method described for **12a** using BuLi (1.5 mL, 1.6 M in hexane, 2.3 mmol), **1** (277 mg, 1.1 mmol), THF (5 mL), borane–THF complex (1.2 mL, 1.0 M in THF, 1.2 mmol), allyl methoxymethyl ether (367 mg, 3.6 mmol), THF (1.5 mL), HMPA (3 mL), PPh_3 (46 mg, 0.17 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (23 mg, 0.022 mmol), *p*-iodoanisole (204 mg, 0.87 mmol)), and CuI (207 mg, 1.1 mmol). Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave a crude product (170 mg) as a yellow liquid. Treatment of the product with HCl (1.0 mL, 12 M in H_2O, 12 mmol) and THF (1 mL) and purification by PTLC on silica gel (hexane–EtOAc, 1:1) gave **12c** (86 mg, 47%) as a colorless liquid.

IR (neat): 3359, 2945, 1732, 1610, 1514, 1444, 1253, 1180, 1034, 873 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.61 (2 H, tt, *J* = 7.0, 7.0 Hz), 1.64 (1 H, br s), 2.45 (2 H, tdd, *J* = 7.0 Hz, J_{HF} = 2.4, 2.4 Hz), 3.59 (2 H, t, *J* = 7.0 Hz), 3.79 (3 H, s), 6.88 (2 H, d, *J* = 8.7 Hz), 7.23 (2H, d, *J* = 8.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.0, 30.7, 55.2, 61.9, 91.3 (dd, J_{CF} = 22, 14 Hz), 114.0, 125.7, 129.3 (dd, J_{CF} = 3, 3 Hz), 153.5 (dd, J_{CF} = 289, 286 Hz), 158.8.

^{19}F NMR (254 MHz, $CDCl_3$): δ = 69.3 (1 F, dt, J_{FF} = 53 Hz, J_{FH} = 2 Hz), 69.6 (1 F, d, J_{FF} = 53 Hz).

HRMS: *m*/*z* calcd for $C_{12}H_{14}O_2F_2$ (M^+): 228.0962, found: 228.0954.

5,5-Difluoro-2-methyl-4-phenyl-4-pent-4-en-1-ol (12d)

Compound **12d** was prepared by the method described for **12a** using BuLi (1.2 mL, 1.6 M in hexane, 2.1 mmol), **1** (254 mg, 1.0 mmol), THF (5 mL), borane–THF complex (1.0 mL, 1.0 M in THF, 1.0 mmol), methoxymethyl 2-methyl-2-propenyl ether (348 mg, 3.0 mmol), THF (1.5 ml), HMPA (2.5 mL), PPh_3 (21 mg, 0.080 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (21 mg, 0.020 mmol), iodobenzene(163 mg, 0.80 mmol), and CuI (190 mg, 1.0 mmol). Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave a crude product (131 mg) as a yellow liquid. Treatment of the product with HCl (1.3 mL, 12 M in H_2O, 16 mmol) and THF (1 mL) and purification by PTLC on silica gel (hexane–EtOAc, 2:1) gave **12d** (127 mg, 75%) as a colorless liquid.

IR (neat): 3348, 2958, 2873, 1732, 1446, 1234, 1038, 771, 725, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, d, *J* = 6.8 Hz), 1.51 (1 H, br s), 1.58–1.69 (1 H, m), 2.24 (1 H, dddd, *J* = 14.3, 8.5 Hz, J_{HF} = 2.8, 2.8 Hz), 2.54 (1 H, dddd, *J* = 14.3, 6.0 Hz, J_{HF} = 2.9, 2.9 Hz), 3.41 (1 H, dd, *J* = 10.6, 5.9 Hz), 3.45 (1 H, dd, *J* = 10.6, 5.9 Hz), 7.26 (1 H, tt, *J* = 7.1, 1.9 Hz), 7.31 (2 H, d, *J* = 7.1 Hz), 7.34 (2 H, t, *J* = 7.1 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 31.1, 34.1, 67.4, 91.0 (dd, J_{CF} = 20, 16 Hz), 127.3, 128.3 (dd, J_{CF} = 3, 3 Hz), 128.5, 133.7, 154.0 (dd, J_{CF} = 288, 288 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 70.5 (s).

HRMS: *m*/*z* calcd for $C_{12}H_{14}OF_2$ (M^+): 212.1013; found: 212.1010.

5,5-Difluoro-4-(*p*-methoxyphenyl)-2-methylpent-4-en-1-ol (12e)

Compound **12e** was prepared by the method described for **12a** using BuLi (1.4 mL, 1.6 M in hexane, 2.1 mmol), **1** (254 mg, 1.0 mmol), THF (5 mL), borane–THF complex (1.1 mL, 1.0 M in THF, 1.1 mmol), methoxymethyl 2-methyl-2-propenyl ether (383 mg, 3.3 mmol), THF (1.5 ml), HMPA (2.5 mL), PPh_3 (42 mg, 0.16 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (21 mg, 0.020 mmol), *p*-iodoanisole (187 mg, 0.80 mmol), and CuI (190 mg, 1.0 mmol). Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave a crude product (190 mg) as a yellow liquid. Treatment of the product with HCl (1.2 mL, 12 M in H_2O, 14 mmol) and THF (1 mL) and purification by PTLC on silica gel (hexane–EtOAc, 1:1) gave **12e** (113 mg, 58%) as a colorless liquid.

IR (neat): 3346, 2958, 1732, 1610, 1514, 1462, 1292, 1248, 1180, 1105, 1036, 964, 833 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (3 H, d, *J* = 6.8 Hz), 1.48 (1 H, br s), 1.59–1.70 (1 H, m), 2.21 (1 H, dddd, *J* = 14.3, 8.9 Hz, J_{HF} = 2.2, 1.2 Hz), 2.50 (1 H, dddd, *J* = 14.3, 6.1 Hz, J_{HF} = 3.0, 3.0 Hz), 3.43 (1 H, dd, *J* = 10.6, 5.9 Hz), 3.45 (1 H, dd, *J* = 10.6, 6.0 Hz), 3.80 (3 H, s), 6.88 (2 H, ddd, *J* = 8.5 Hz, J_{HF} = 2.6, 2.6 Hz), 7.24 (2H, d, *J* = 8.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.1, 31.2, 34.1, 55.2, 67.4, 90.4 (dd, J_{CF} = 20, 15 Hz), 114.0, 125.8, 129.3 (dd, J_{CF} = 3, 3 Hz), 153.9 (dd, J_{CF} = 288, 287 Hz), 158.7.

^{19}F NMR (254 MHz, $CDCl_3$): δ = 69.6 (1 F, d, J_{FF} = 47 Hz), 69.6 (1 F, d, J_{FF} = 47 Hz).

HRMS: *m*/*z* calcd for $C_{13}H_{16}O_2F_2$ (M^+): 242.1118; found: 242.1117.

1,1-Difluoro-5-iodo-2-phenylpent-1-ene (13a)

Et_3N (2.6 g, 26 mmol) and MsCl (2.7 g, 26 mmol) were added to a solution of **12a** (3.4 g, 17 mmol) in CH_2Cl_2 (130 mL) at 0 °C under argon. The reaction mixture was stirred for 6 h at r.t., and the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with Et_2O (3 × 40 mL). The combined extracts were washed with brine (30 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 2:1) to give a crude product (4.9 g) as a colorless liquid. NaI (26 g, 176 mmol) was added to a solution of the product (4.9 g) in acetone (192 mL) at r.t. under air. The reaction mixture was heated under reflux for 5 h, and the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with Et_2O (3 × 50 mL). The combined extracts were washed with saturated aq $Na_2S_2O_3$ (30 mL), brine (30 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) followed by bulb-to-bulb distillation (bp 85–95 °C/0.44 mmHg) in the dark to give **13a** (4.4 g, 83%) as a colorless liquid.

IR (neat): 3059, 2958, 1734, 1498, 1446, 1306, 1236, 1141, 1007, 912, 768, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (2 H, tt, *J* = 7.1, 7.1 Hz), 2.49–2.54 (2 H, m), 3.12 (2 H, t, *J* = 7.1 Hz), 7.27 (1 H, t, *J* = 7.5 Hz), 7.29 (2 H, d, *J* = 7.5 Hz), 7.35 (2H, dd, *J* = 7.5, 7.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 5.0, 28.5, 31.5, 91.0 (dd, J_{CF} = 21, 15 Hz), 127.5, 128.2 (dd, J_{CF} = 3, 3 Hz), 128.5, 133.1, 153.8 (dd. J_{CF} = 291, 288 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 71.2 (1 F, d, J_{FF} = 43 Hz), 71.3 (1 F, d, J_{FF} = 43 Hz).

Anal. Calcd for $C_{11}H_{11}F_2I$: C, 42.88; H, 3.60. Found: C, 42.61; H, 3.54.

1,1-Difluoro-5-iodo-2-(*p*-trifluoromethylphenyl)pent-1-ene (13b)

Compound **13b** was prepared by the method described for **13a** using Et_3N (187 mg, 1.8 mmol), MsCl (194 mg, 1.8 mmol), **12b** (330 mg, 1.2 mmol), and CH_2Cl_2 (9 mL). Purification by PTLC on silica gel (hexane–EtOAc, 2:1) gave a crude product (387 mg) as a colorless liquid. Treatment of the product with NaI (1.67 g, 11 mmol) in acetone (17 mL) and purification by PTLC on silica gel (hexane) gave **13b** (360 mg, 77%) as a colorless liquid.

IR (neat): 2960, 1923, 1726, 1618, 1410, 1327, 1246, 1169, 1128, 1070, 845 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (2 H, tt, *J* = 7.2, 7.2 Hz), 2.56 (2 H, tt, *J* = 7.2 Hz, J_{HF} = 2.3 Hz), 3.14 (2 H, t, *J* = 7.2 Hz), 7.44 (2 H, d, *J* = 8.2 Hz), 7.63 (2 H, d, *J* = 8.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 4.7, 28.3, 31.4, 90.5 (dd, J_{CF} = 22, 13 Hz), 124.0 (q, J_{CF} = 270 Hz), 125.5 (q, J_{CF} = 4 Hz), 128.5 (dd, J_{CF} = 3, 3 Hz), 129.6 (q, J_{CF} = 32 Hz), 136.9, 154.1 (dd. J_{CF} = 291, 288 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 73.1 (1 F, d, J_{FF} = 32 Hz), 73.7 (1 F, dt, J_{FF} = 32 Hz, J_{FH} = 2 Hz), 99.1 (3 F, s).

HRMS: *m*/*z* calcd for $C_{12}H_{10}F_5I$ (M^+): 375.9747; found: 375.9773.

1,1-Difluoro-5-iodo-2-(*p*-methoxyphenyl)pent-1-ene (13c)

Compound **13c** was prepared by the method described for **13a** using Et_3N (115mg, 1.1 mmol), MsCl (118 mg, 1.1 mmol), **12c** (173 mg, 0.76 mmol), and CH_2Cl_2 (6 mL). Purification by PTLC on silica gel (hexane–EtOAc, 1:1) gave a crude product (197 mg) as a colorless liquid. Treatment of the product with NaI (1.2 g, 7.8 mmol) in acetone (12 mL) and purification by PTLC on silica gel (hexane–EtOAc, 3:1) gave **13c** (185 mg, 72%) as a colorless liquid.

IR (neat): 2958, 2837, 1732, 1610, 1516, 1290, 1250, 1180, 1103, 1036, 831 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (2 H, tt, *J* = 7.2, 7.2 Hz), 2.49 (2 H, tt, *J* = 7.2 Hz, J_{HF} = 2.1 Hz), 3.13 (2 H, t, *J* = 7.2 Hz), 3.81 (3 H, s), 6.90 (2 H, d, *J* = 8.4 Hz), 7.22 (2 H, d, *J* = 8.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 5.1, 28.6, 31.5, 55.3, 90.5 (dd, J_{CF} = 20, 15 Hz), 114.1, 125.2, 129.3 (dd, J_{CF} = 3, 3 Hz), 153.7 (dd. J_{CF} = 289, 286 Hz), 158.9.

^{19}F NMR (254 MHz, $CDCl_3$): δ = 70.2 (1 F, br d, J_{FF} = 44 Hz), 70.3 (1 F, dt, J_{FF} = 44 Hz, J_{FH} = 3 Hz).

Anal. Calcd for $C_{12}H_{13}OF_2I$: C, 42.63; H, 3.88. Found: C, 42.53; H, 3.90.

1,1-Difluoro-5-iodo-4-methyl-2-phenylpent-1-ene (13d)

Compound **13d** was prepared by the method described for **13a** using Et_3N (1.9 g, 19 mmol), MsCl (2.0 g, 19 mmol), **12d** (2.7 g, 13 mmol), and CH_2Cl_2 (95 mL). Purification by column chromatography on silica gel (hexane–EtOAc, 4:1) gave a crude product (3.3 g) as a colorless liquid. Treatment of the product with NaI (17 g, 110 mmol) in acetone (125 mL) and purification by column chromatography on silica gel (hexane–EtOAc, 20:1) followed by distillation (bp 115-120 °C/9.0 mmHg) gave **13d** (2.9 g, 68%) as a colorless liquid.

IR (neat): 2964, 1730, 1498, 1446, 1379, 1244, 962, 769, 725, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (3 H, d, *J* = 6.6 Hz), 1.45–1.56 (1 H, m), 2.31 (1 H, dddd, *J* = 14.4, 8.0 Hz, J_{HF} = 2.4, 1.1 Hz), 2.54 (1 H, dddd, *J* = 14.4, 6.3 Hz, J_{HF} = 3.1, 3.1 Hz), 3.11 (1 H, dd, *J* = 9.8, 5.8 Hz), 3.16 (1 H, dd, *J* = 9.8, 5.2 Hz), 7.28 (1 H, t, *J* = 7.7 Hz), 7.30 (2 H, d, *J* = 7.7 Hz), 7.36 (2 H, dd, *J* = 7.7, 7.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.7, 20.1, 33.1, 34.4, 90.7 (dd, J_{CF} = 21, 14 Hz), 127.5, 128.3 (dd, J_{CF} = 3, 3 Hz), 128.6, 133.2 (dd, J_{CF} = 4, 4 Hz), 154.0 (dd, J_{CF} = 291, 288 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 71.1 (1 F, d, J_{FF} = 40 Hz), 71.6 (1 F, d, J_{FF} = 40 Hz).

HRMS: *m*/*z* calcd for $C_{12}H_{13}F_2I$ (M^+): 322.0030; found: 322.0059.

1,1-Difluoro-5-iodo-2-(*p*-methoxyphenyl)-4-methylpent-1-ene (13e)

Compound **13e** was prepared by the method described for **13a** using Et_3N (58 mg, 0.57 mmol), MsCl (60 mg, 0.57 mmol), **12e** (93 mg, 0.38 mmol), and CH_2Cl_2 (3 mL). Purification by PTLC on silica gel (hexane–EtOAc, 1:1) gave a crude product (131 mg) as a colorless liquid. Treatment of the product with NaI (572 mg, 3.8 mmol) in acetone (3 mL) and purification by PTLC on silica gel (hexane–EtOAc, 3:1) gave **13e** (120 mg, 90%) as a colorless liquid.

IR (neat): 2954, 2833, 1425, 1284, 1234, 951, 744, 723, 579 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (3 H, d, *J* = 6.5 Hz), 1.47–1.55 (1H, m), 2.28 (1 H, br dd, *J* = 14.3, 8.0 Hz), 2.50 (1 H, dddd, *J* = 14.3, 5.9 Hz, J_{HF} = 2.9, 2.9 Hz), 3.11 (1 H, dd, *J* = 9.8, 5.8 Hz), 3.15 (1 H, dd, *J* = 9.8, 5.2 Hz), 3.81 (3 H, s), 6.89 (2 H, d, *J* = 8.7 Hz), 7.23 (2 H, d, *J* = 8.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.8, 20.1, 33.1, 34.5, 55.3, 90.1 (dd, J_{CF} = 22, 14 Hz), 114.1, 125.2, 129.4, 154.0 (dd, J_{CF} = 287, 287 Hz), 158.9.

^{19}F NMR (254 MHz, $CDCl_3$): δ = 70.3 (1 F, d, J_{FF} = 44 Hz), 70.7 (1 F, d, J_{FF} = 44 Hz).

Anal. Calcd for $C_{13}H_{15}F_2I$: C, 44.34; H, 4.29. Found: C, 44.37; H, 4.32.

o-(1-Butyl-2,2-difluorovinyl)phenoxymethyl Methyl Ether (14)

To a suspension of NaH (134 mg, 60% dispersion in mineral oil, 3.4 mmol) in THF (12 mL) was added **4b** (648 mg, 3.1 mmol) at –78 °C under nitrogen. After stirring for 10 min, chloromethyl methyl ether (0.69 mL, 9.2 mmol) was added to the solution at –78 °C, and the mixture was stirred for 5 h. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) to give **14** (716 mg, 92%) as a colorless liquid.

IR (neat): 2958, 1745, 1492, 1454, 1228, 1197, 1155, 1079, 1004, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, *J* = 7.2 Hz), 1.22–1.36 (4 H, m), 2.30–2.38 (2 H, m), 3.46 (3 H, s), 5.18 (2 H, s), 7.00 (1 H, ddd, *J* = 7.4, 7.4, 1.1 Hz), 7.10–7.16 (2 H, m), 7.25 (1 H, ddd, *J* = 7.4, 7.4, 1.8 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.1, 27.7, 29.6 (dd, J_{CF} = 3, 3 Hz), 56.0, 89.1 (dd, J_{CF} = 24, 16 Hz), 94.3, 114.4, 121.5, 123.5, 129.0, 131.0 (d, J_{CF} = 2 Hz), 153.0 (dd, J_{CF} = 286, 286 Hz), 155.0.

^{19}F NMR (470 MHz, $CDCl_3$): δ = 67.2 (1 F, dt, J_{FF} = 46 Hz, J_{FH} = 3 Hz), 71.3 (1 F, d, J_{FF} = 46 Hz).

MS (20 eV): *m*/*z* = 256 (M^+), 193, 150.

HRMS: *m*/*z* calcd for $C_{14}H_{18}O_2F_2$ (M^+): 256.1275; found: 256.1275.

o-(1-Butyl-2-fluorovinyl)phenoxymethyl Methyl Ether (15)

Red-Al (0.34 mL, 3.4 M in toluene, 1.2 mmol) was added to a solution of **14** (107 mg, 0.42 mmol) in toluene (1.5 mL) at 0 °C under nitrogen. After the reaction mixture was heated to reflux for 3 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 20:1) to give **15*E*** (47 mg, 47%) and **15*Z*** (41 mg, 41%) as colorless liquids.

15*E*

IR (neat): 2956, 1488, 1228, 1195, 1155, 1114, 1101, 1079, 1004, 754 cm^{-1}.

MS (20 eV): *m*/*z* (%) = 238 (M^+, 27), 174 (90), 132 (100).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, *J* = 6.9 Hz), 1.24–1.34 (4 H, m), 2.50–2.57 (2 H, m), 3.45 (3 H, s), 5.18 (2 H, s), 6.60 (1 H, d, J_{HF} = 86.7 Hz), 6.96 (1 H, dd, *J* = 7.4, 7.4 Hz), 7.10 (2 H, d, *J* = 7.4 Hz), 7.22–7.27 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.4, 26.7 (d, J_{CF} = 3 Hz), 29.6 (d, J_{CF} = 2 Hz), 56.1, 94.4, 114.5, 121.6, 123.3 (d, J_{CF} = 10 Hz), 126.4 (d, J_{CF} = 10 Hz), 128.8, 130.9 (d, J_{CF} = 2 Hz), 146.1 (d, J_{CF} = 260 Hz), 155.4 (d, J_{CF} = 3 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 31.4 (1 F, dt, J_{FH} = 86, 3 Hz).

HRMS: *m*/*z* calcd for $C_{14}H_{19}O_2F$ (M^+): 238.1370; found: 238.1377.

15*Z*

IR (neat): 2931, 1675, 1490, 1450, 1240, 1197, 1155, 1081, 1004, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (3 H, t, *J* = 7.2 Hz), 1.32–1.35 (4 H, m), 2.22–2.30 (2 H, m), 3.47 (3 H, s), 5.17 (2 H, s), 6.60 (1 H, dt, J_{HF} = 86.7, *J* = 1.2 Hz), 7.00 (1 H, dd, *J* = 7.3, 7.3 Hz), 7.11–7.16 (2H, m), 7.22–7.27 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.2, 29.9 (d, J_{CF} = 3 Hz), 30.4 (d, J_{CF} = 5 Hz), 56.0, 94.5, 114.7, 121.0 (d, J_{CF} = 4 Hz), 121.6, 125.2 (d, J_{CF} = 2 Hz), 128.7, 130.7 (d, J_{CF} = 2 Hz), 143.7 (d, J_{CF} = 257 Hz), 154.5.

^{19}F NMR (470 MHz, $CDCl_3$): δ = 31.1 (1 F, dt, J_{FH} = 86, 3 Hz).

MS (20 eV): *m*/*z* (%) = 238 (M^+, 25), 174 (74), 132 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{19}O_2F$ (M^+): 238.1370; found: 238.1370.

o-(1-Butyl-2-fluorovinyl)phenol (16*E*)

To a solution of **15*E*** (168 mg, 0.70 mmol) in THF (7 mL) was added concd HCl (3.5 mL) at 0 °C. The reaction mixture was stirred for 2.5 h at 0 °C, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 1:1) to give **16*E*** (117 mg, 86%) as a colorless liquid.

IR (neat): 3529, 2958, 2931, 2861, 1488, 1450, 1284, 1211, 1178, 1110, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (3 H, t, *J* = 7.2 Hz), 1.28–1.36 (4 H, m), 2.43–2.50 (2 H, m), 5.14 (1 H, s), 6.65 (1 H, d, J_{HF} = 85.1 Hz), 6.80–6.93 (2 H, m), 6.90–7.10 (1 H, m), 7.18–7.23 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.5, 27.7 (d, J_{CF} = 2 Hz), 30.0 (d, J_{CF} = 2 Hz), 115.5, 120.5, 120.9 (d, J_{CF} = 8 Hz), 122.5 (d, J_{CF} = 9 Hz), 129.2, 130.4 (d, J_{CF} = 3 Hz), 146.9 (d, J_{CF} = 264 Hz), 153.4 (d, J_{CF} = 2 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 35.6 (1 F, dt, J_{FH} = 85, 3 Hz).

MS (20 eV): *m*/*z* (%) = 194 (M^+; 51), 145 (40), 131 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{15}OF$ (M^+): 194.1108; found: 194.1108.

o-(1-Butyl-2-fluorovinyl)phenol (16*Z*)

Compound **16*Z*** was prepared by the method described for **16*E*** using concd HCl (3.3 mL), THF (6.5 mL), and **15*Z*** (155mg, 0.652 mmol). Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave **16*Z*** (106 mg, 84%) as a colorless liquid.

IR (neat): 3554, 3450, 2931, 1488, 1450, 1234, 1180, 1114, 1085, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3 H, t, *J* = 7.0 Hz), 1.25–1.34 (4 H, m), 2.23–2.29 (2 H, m), 5.01 (1 H, d, J_{HF} = 3.1 Hz), 6.73 (1 H, dt, J_{HF} = 85.5, *J* = 1.2 Hz), 6.92–6.96 (2 H, m), 7.70–7.11 (1 H, m), 7.19–7.24 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.2, 30.0 (d, J_{CF} = 2 Hz), 30.9 (d, J_{CF} = 5 Hz), 115.9, 119.4 (d, J_{CF} = 3 Hz), 120.6, 121.5, 128.8, 129.3, 144.3 (d, J_{CF} = 259 Hz), 152.7.

^{19}F NMR (470 MHz, $CDCl_3$): δ = 35.0 (1 F, dtd, J_{FH} = 85, 6, 3 Hz).

MS (20 eV): *m*/*z* (%) = 194 (M^+, 58), 152 (29), 131 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{15}OF$ (M^+): 194.1108; found: 194.1108.

Methyl 2-(2-benzyloxyethyl)-3,3-difluoroacrylate (18)

A solution of (benzyloxymethyl)tributylstannane (3.5 g, 8.6 mmol) in THF (34 mL) was treated with BuLi (5.9 mL, 1.5 M in hexane, 9.1 mmol) at –78 °C under nitrogen. The reaction mixture was transferred via a cooled cannula to a solution of $CuBr·(CH_3)_2S$ complex (1.9 g, 9.1 mmol) in *i*-Pr_2S (7.5 mL) and THF (9 mL) [which had been treated with isopropyl magnesium chloride (two drops, 2.0 M in THF) followed by stirring at –78 °C for 15 min] at –78 °C. To the solution was added $(CH_3)_3SiCl$ (2.7 mL, 22 mmol) and methyl 2-(trifluoromethyl)acrylate (1.5 g, 9.5 mmol). The reaction mixture was stirred for 5 min at –78 °C and then at r.t. for an additional 6 h. The reaction was quenched with phosphate buffer (pH 7), and organic materials were extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (30 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 5:1) to give **18** (1.2 g, 54%) as a colorless liquid.

IR (neat): 2954, 2863, 1749, 1718, 1438, 1349, 1270, 1157, 1112, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.56 (2 H, tdd, *J* = 6.6, J_{HF} = 2.2, 2.2 Hz), 3.56 (2 H, t, *J* = 6.6 Hz), 3.76 (3 H, s), 4.50 (2 H, s), 7.26–7.60 (5 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.2, 52.1, 68.0 (dd, J_{CF} = 3 Hz), 72.8, 85.8 (dd, J_{CF} = 24, 7 Hz), 127.5, 127.6, 128.4, 138.2, 160.4 (dd, J_{CF} = 310, 296 Hz), 165.2 (dd, J_{CF} = 13, 7 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 89.1 (1 F, dt, J_{FF} = 6 Hz, J_{FH} = 3 Hz), 94.2 (1 F, d, J_{FF} = 6 Hz).

MS (20 eV): *m*/*z* (%) = 256 (M^+, 21), 107 (89), 91 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{14}O_3F_2$ (M^+): 256.0911; found: 256.0863.

Methyl 2-(2-hydroxyethyl)-3,3-difluoroacrylate (19)

BCl_3 (2.0 mL, 1.0 M in CH_2Cl_2, 2.0 mmol) was added to a solution of **18** (493 mg, 1.9 mmol) in CH_2Cl_2 (12 mL) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 5 h. The reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 5:1) to give **19** (213 mg, 67%) as a colorless liquid.

IR (neat): 3511, 2958, 1774, 1720, 1440, 1351, 1272, 1178, 1095, 1024 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.50 (2 H, tdd, *J* = 6.3, J_{HF} = 2.2, 2.2 Hz), 2.55 (1 H, br s), 3.71 (2 H, t, J = 6.3 Hz), 3.80 (3 H, s).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 27.9, 52.2, 60.8 (dd, J_{CF} = 3 Hz), 85.7 (dd, J_{CF} = 24, 7 Hz), 160.4 (dd, J_{CF} = 310, 296 Hz), 165.7 (dd, J_{CF} = 13, 7 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 89.4 (1 F, dt, J_{FF} = 6, J_{FH} = 3 Hz), 94.9 (1 F, d, J_{FF} = 6 Hz).

MS (70 eV): *m*/*z* = 167 ($[M+H]^+$), 149 ($[M–OH]^+$), 136, 105.

Methyl 2-(*N*-*tert*-Butoxycarbonyl-*p*-toluenesulfonamidoethyl)-3,3-difluoroacrylate (20)

To a solution of *N*-*tert*-butoxycarbonyl-*N*-*p*-toluenesulfonamide (348 mg, 1.3 mmol) in THF (15 mL) was added PPh_3 (336 mg, 1.3 mmol), **19** (213 mg, 1.3 mmol), and DEAD (223 mg, 1.3 mmol) in THF (2 mL) at r.t. under nitrogen. The reaction mixture was stirred for 10 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc, 5:1) to give **20** (415 mg, 77%) as a colorless liquid.

IR (neat): 2981, 1720, 1438, 1355, 1286, 1155, 1087, 1051, 673, 595 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (9 H, s), 2.43 (3 H, s), 2.68 (2 H, tdd, *J* = 6.4 Hz, J_{HF} = 2.1, 2.1 Hz), 3.82 (3 H,s), 4.00 (2 H, t, *J* = 6.4 Hz), 7.30 (2 H, d, *J* = 8.1 Hz), 7.77 (2 H, d, *J* = 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.6, 25.2, 25.8, 45.4 (dd, J_{CF} = 2, 2 Hz), 52.2, 84.3, 85.8 (dd, J_{CF} = 23, 7 Hz), 127.9, 129.2, 137.2, 144.2, 150.7, 160.7 (dd, J_{CF} = 311, 297 Hz), 164.8 (dd, J_{CF} = 13, 7 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 89.8 (1 F, dt, J_{FF} = 8 Hz, J_{FH} = 3 Hz), 95.6 (1 F, d, J_{FF} = 8 Hz).

MS (70 eV) = *m*/*z* (%) 421 ($[M + 2 H]^+$, 1), 363 (61), 184 (96), 155 (98), 57 (100).

HRMS: *m*/*z* calcd for $C_{18}H_{25}NO_6F_2S$ ($[M + 2 H]^+$): 421.1370; found: 421.1342.

Methyl 3,3-Difluoro-2-(2-*p*-toluenesulfonamidoethyl)acrylate (17)

To a solution of **20** (421 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) was added trifluoroacetic acid (0.23 mL, 3.0 mmol) at r.t. The reaction mixture was stirred for 7 h at r.t., and then aq $NaHCO_3$ was added to quench the reaction. Organic materials were extracted with CH_2Cl_2 (3 × 15 mL), and the combined extracts were washed with brine (15 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 3:1) to give **17** (310 mg, 97%) as a pale yellow liquid.

IR (neat): 3293, 2956, 1718, 1438, 1328, 1218, 1159, 1093, 815, 663, 551 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.40 (2 H, tdd, *J* = 6.5 Hz, J_{HF} = 2.1, 2.1 Hz), 2.42 (3 H, s), 3.09 (2 H, td, *J* = 6.5, 6.5 Hz), 3.75 (3 H, s), 5.09 (1 H, t, *J* = 6.5 Hz), 7.30 (2 H, d, *J* = 8.1 Hz), 7.73 (2 H, d, *J* = 8.1 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.4, 25.2, 41.1, 52.3, 85.6 (dd, J_{CF} = 23, 7 Hz), 127.0, 129.6, 137.0, 143.4, 160.4 (dd, J_{CF} = 312, 297 Hz), 165.1 (dd, J_{CF} = 13, 8 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 90.5 (1 F, dt, J_{FF} = 9 Hz, J_{FH} = 3 Hz), 96.2 (1 F, d, J_{FF} = 9 Hz).

HRMS–FAB: *m*/*z* calcd for $C_{13}H_{16}O_4NF_2S$ ($[M+H]^+$): 320.0768; found: 320.0775.

3-Butyl-2-fluoro-1-tosylindole (21a)

To a suspension of NaH (31 mg, 62% dispersion in mineral oil, 0.79 mmol) in DMF (0.5 mL) was added **3b** (232 mg, 0.63 mmol) in DMF (2.5 mL) at r.t. under nitrogen. The reaction mixture was stirred at 80 °C for 7 h, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL), and the combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 5:1) to give **21a** (184 mg, 84%) as an orange liquid.

IR (neat): 2960, 2930, 2860, 1660, 1455, 1395, 1190, 1180, 745, 690, 665 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3 H, t, *J* = 7.4 Hz), 1.21 (2 H, tq, *J* = 7.4, 7.4 Hz), 1.53 (2 H, tt, *J* = 7.4, 7.4 Hz), 2.34 (3 H, s), 2.52 (2 H, td, *J* = 7.4 Hz, J_{HF} = 0.8 Hz), 7.20 (2 H, d, *J* = 8.4 Hz), 7.23 (1 H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.28 (1 H, ddd, *J* = 7.7, 7.7, 1.2 Hz), 7.33 (1 H, dd, *J* = 7.7, 1.2 Hz), 7.73 (2 H, d, *J* = 8.4 Hz), 8.08 (1 H, d, *J* = 7.7 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.6, 21.3 (d, J_{CF} = 3 Hz), 21.5, 22.1, 30.5, 99.7 (d, J_{CF} = 11 Hz), 114.4, 118.9 (d, J_{CF} = 7 Hz), 124.0, 124.0 (d, J_{CF} = 4 Hz), 126.8, 128.1 (d, J_{CF} = 6 Hz), 129.8, 130.6, 134.7, 145.2, 147.4 (d, J_{CF} = 276 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 29.1 (s).

MS (20 eV): *m*/*z* (%) = 345 (M^+; 100), 190 (68), 148 (92).

HRMS calcd for $C_{19}H_{20}NO_2FS$ (M^+): 345.1199; found: 345.1188.

Anal. Calcd for $C_{19}H_{20}NO_2FS$: C, 66.07; H, 5.84; N, 4.05. Found: C, 65.97; H, 5.90; N, 4.10.

3-*sec*-Butyl-2-fluoro-1-tosylindole (21b)

Compound **21b** was prepared by the method described for **21a** using NaH (17 mg, 60% dispersion in mineral oil, 0.43 mmol) in DMF (1 mL), and **3d** (131 mg, 0.36 mmol) in DMF (1 mL). The reaction was carried out at 80 °C for 5 h. Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave **21b** (100 mg, 81%) as an orange liquid.

IR (neat): 2970, 2930, 1740, 1650, 1600, 1450, 1395, 1245, 1180, 1090, 745 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.70 (3 H, t, *J* = 7.1 Hz), 1.26 (3 H, dd, *J* = 7.1, J_{HF} = 0.7 Hz), 1.55–1.73 (2 H, m), 2.33 (3 H, s), 2.77 (1 H, ddq, *J* = 7.1, 7.1, 7.1 Hz), 7.17–7.30 (4 H, m), 7.39 (1 H, dd, *J* = 7.7, 1.0 Hz), 7.72 (2 H, d, *J* = 8.2 Hz), 8.06–8.11 (1 H, m).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.1, 19.4 (d, J_{CF} = 2 Hz), 21.6, 28.6 (d, J_{CF} = 2 Hz), 30.8 (d, J_{CF} = 3 Hz), 103.9 (d, J_{CF} = 9 Hz), 114.6, 119.5 (d, J_{CF} = 7 Hz), 123.9, 123.9, 126.8, 127.6 (d, J_{CF} = 5 Hz), 129.8, 130.7 (d, J_{CF} = 1 Hz), 134.6, 145.3, 147.1 (d, J_{CF} = 277z Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = 31.2 (s).

Anal. Calcd for $C_{19}H_{20}O_2SNF$: C, 66.07; H, 5.84; N, 4.05. Found: C, 66.22; H, 5.94; N, 4.03.

2-Fluoro-1-tosylindole (21c)

Compound **21c** was prepared by the method described for **21a** using NaH (16 mg, 60% dispersion in mineral oil, 0.41 mmol) in DMF (0.5 mL), and **3f** (105 mg, 0.34 mmol) in DMF (1.5 mL). The reaction was carried out at 70 °C for 23 h. Purification by PTLC on silica gel (hexane–EtOAc, 3:1) gave **21c** (72 mg, 73%) as a colorless liquid.

IR (neat): 2950, 2930, 1625, 1450, 1385, 1245, 1175, 1090, 745, 690 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.34 (3 H, s), 5.91 (1 H, d, J_{HF} = 3.4 Hz), 7.20–7.24 (3 H, m), 7.29 (1 H, ddd, *J* = 8.4, 7.3, 1.2 Hz), 7.36 (1 H, d, *J* = 7.9 Hz), 7.78 (2 H, d, *J* = 8.2 Hz), 8.09 (1 H, d, *J* = 8.4 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.6, 86.7 (d, J_{CF} = 12 Hz), 114.1, 120.7 (d, J_{CF} = 6 Hz), 124.1 (d, J_{CF} = 4 Hz), 124.2, 126.6 (d, J_{CF} = 5 Hz), 126.9, 130.0, 130.8, 134.9, 145.6, 150.8 (d, J_{CF} = 279 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 35.7 (d, J_{FH} = 3 Hz).

MS (70 eV): *m*/*z* (%) = 289 (M^+, 23), 155 (50), 134 (80), 91 (100).

HRMS *m*/*z* calcd for $C_{15}H_{12}NO_2FS$ (M^+): 289.0574; found: 289.0565.

3-Butyl-2-fluorobenzo[*b*]furan (22)

To a solution of **4b** (94 mg, 0.44 mmol) in DMF (4 mL) was added NaH (21 mg, 62% dispersion in mineral oil, 0.53 mmol) at 0 °C under nitrogen. The reaction mixture was stirred at 60 °C for 2 h, and then phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 30:1) to give **22** (68 mg, 80%) as a colorless liquid.

IR (neat): 2960, 2940, 2860, 1675, 1455, 1380, 1295, 1260, 1185, 1140, 740 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (3 H, t, *J* = 7.4 Hz), 1.39 (2 H, tq, *J* = 7.4, 7.4 Hz), 1.66 (2 H, tt, *J* = 7.4, 7.4 Hz), 2.57 (2 H, td, *J* = 7.4 Hz, J_{HF} = 1.0 Hz), 7.19–7.25 (2 H, m), 7.32–7.36 (1 H, m), 7.40–7.45 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 21.0 (d, J_{CF} = 3 Hz), 22.4, 30.7 (d, J_{CF} = 2 Hz), 90.6 (d, J_{CF} = 12 Hz), 110.8, 119.2 (d, J_{CF} = 6 Hz), 123.1 (d, J_{CF} = 4 Hz), 123.2, 129.3 (d, J_{CF} = 3 Hz), 147.1, 157.1 (d, J_{CF} = 278 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 42.0 (s).

MS (20 eV): *m*/*z* (%) = 192 (M^+, 43), 149 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{13}OF$ (M^+): 192.0950; found: 192.0918.

3-Butyl-2-fluorobenzo[*b*]thiophene (24)

To a solution of **5b** (93 mg, 0.36 mmol) in CH_2Cl_2 (3 mL) was added trifluoroacetic anhydride (0.15 mL, 1.1 mmol) and Et_3N (0.15 mL, 1.1 mmol) at 0 °C under nitrogen. After the reaction mixture was stirred for 0.5 h, the volatile components were removed by evaporation, and the remaining residue was dissolved in MeOH (3 mL). The resulting solution was treated with K_2CO_3 (300 mg, 2.2 mmol) at 0 °C and stirred at r.t. for 1 h, and then heated under reflux for an additional 2 h. Phosphate buffer (pH 7) was added to quench the reaction, and organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 50:1) to give **24** (62 mg, 82%) as a colorless liquid.

IR (neat): 2960, 2930, 2860, 1610, 1460, 1435, 1265, 1190, 1065, 755, 730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (3 H, t, *J* = 7.5 Hz), 1.39 (2 H, tq, *J* = 7.5, 7.5 Hz), 1.64 (2 H, tt, *J* = 7.5, 7.5 Hz), 2.75 (2 H, td, *J* = 7.5 Hz, J_{HF} = 1.3 Hz), 7.28 (1 H, ddd, *J* = 7.7, 7.7, 1.4 Hz), 7.35 (1 H, ddd, *J* = 7.7, 7.7, 0.9 Hz), 7.58 (1 H, d, *J* = 7.7 Hz), 7.64 (1 H, d, *J* = 7.7 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 22.5, 23.6, 31.0 (d, J_{CF} = 2 Hz), 115.5 (d, J_{CF} = 10 Hz), 121.5 (d, J_{CF} = 6 Hz), 122.6, 124.0 (d, J_{CF} = 4 Hz), 124.6, 131.3 (d, J_{CF} = 2 Hz), 136.8 (d, J_{CF} = 6 Hz), 159.2 (d, J_{CF} = 289 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 29.1 (s).

MS (20 eV): *m*/*z* (%) = 208 (M^+, 50), 165 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{13}FS$ (M^+): 208.0722; found: 208.0694.

Anal. Calcd for $C_{12}H_{13}FS$: C, 69.20; H, 6.29. Found: C, 68.94; H, 6.33.

5-Fluoro-3-methyl-4-(2-phenylpropyl)-2,3-dihydrofuran (25a)

NaH (12 mg, 60% dispersion in mineral oil, 0.30 mmol) was added to a solution of **9a** (60 mg, 0.25 mmol) in DMF (8 mL) under nitrogen. After the reaction mixture was stirred at 90 °C for 7 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with EtOAc (3 × 10 mL). The combined extracts were washed with H_2O and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 10:1) to give **25a** (a 1:1 diastereomeric mixture, 37 mg, 67%) as a colorless liquid.

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

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

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

^{19}F NMR (470 MHz, $CDCl_3$): δ = 42.1 (0.5 F, s), 42.5 (0.5 F, s).

MS (70 eV): *m*/*z* (%) = 220 (M^+; 80), 115 (100).

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

3-Benzyl-4-butyl-5-fluoro-2,3-dihydrofuran (25b)

Compound **9b** was prepared by the method described for **25a** using NaH (9.6 mg, 60% dispersion in mineral oil, 0.24 mmol) and **9b** (51 mg, 0.20 mmol) in DMF (10 mL). The reaction was carried out at 90 °C for 11 h. Purification by PTLC on silica gel (hexane–EtOAc, 10:1) gave **25b** (29 mg, 62%) as a colorless liquid.

IR (neat): 2929, 1736, 1454, 1377, 1246, 1165, 1126, 1030, 731, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 (3 H, t, *J* = 7.2 Hz), 1.22–1.50 (4 H, m), 1.85–2.00 (1 H, m), 2.14 (1 H, dt, *J* = 15.3, 7.6 Hz), 2.51 (1 H, dd, *J* = 13.7, 10.1 Hz), 2.99 (1 H, dd, *J* = 13.7, 4.6 Hz), 3.21 (1 H, dddd, *J* = 10.1, 9.2, 5.6, 4.6 Hz), 4.05 (1 H, dd, *J* = 9.2, 5.6 Hz), 4.22 (1 H, dd, *J* = 9.2, 9.2 Hz), 7.15 (2 H, d, *J* = 7.6 Hz), 7.21 (1 H, t, *J* = 7.6 Hz), 7.29 (2 H, dd, *J* = 7.6, 7.6 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.8, 21.8 (d, J_{CF} = 2 Hz), 22.3, 29.9, 39.4, 43.5 (d, J_{CF} = 2 Hz), 72.1 (d, J_{CF} = 3 Hz), 82.5 (d, J_{CF} = 14 Hz), 126.3, 128.5, 128.8, 139.2, 156.4 (d, J_{CF} = 271 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 42.4 (s).

MS (70 eV): *m*/*z* (%) = 234 (M^+), 143 (100).

HRMS: *m*/*z* calcd for $C_{15}H_{19}OF$ (M^+): 234.1420; found: 234.1429.

2-Fluoro-4-methyl-3-(2-phenylpropyl)-1-tosyl-2-pyrroline (26)

Compound **26** was prepared by the method described for **25a** using NaH (5.6 mg, 60% dispersion in mineral oil, 0.14 mmol) and **10b** (50 mg, 0.13 mmol) in DMF (6.5 mL). The reaction was carried out at 90 °C for 4 d. Purification by PTLC on silica gel (hexane–EtOAc, 7:1) gave **26** (1:1 diastereomeric mixture, 38 mg, 80%) as a colorless liquid.

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

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

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

^{19}F NMR (470 MHz, $CDCl_3$): δ = 36.2 (0.5 F, s), 36.6 (0.5 F, s).

MS (70 eV): *m*/*z* (%) = 373 (M^+, 7), 268 (56), 117 (100).

HRMS: *m*/*z* calcd for $C_{21}H_{24}NO_2FS$ (M^+): 373.1512; found: 373.1506.

5-Fluoro-3-methyl-4-(3-phenylpropyl)-2,3-dihydrothiophene (27)

From **11b**: Compound **27** was prepared by the method described for **25a** using NaH (6.9 mg, 60% dispersion in mineral oil, 0.17 mmol) and **11b** (40 mg, 0.16 mmol) in DMF (4.5 mL). The reaction was carried out at 90 °C for 4 h. Purification by PTLC on silica gel (hexane–EtOAc, 50:1) gave **27** (28 mg, 76%) as a colorless liquid.

From **11a**: Compound **27** was prepared by the method described for **25a** using NaOMe (7.5 mg, 0.14 mmol) instead of NaH and **11a** (40 mg, 0.13 mmol) in DMF (4 mL). The reaction was carried out at 90 °C for 8 h. Purification by PTLC on silica gel (hexane–EtOAc, 50:1) gave **27** (22 mg, 69%) as a colorless liquid.

IR (neat): 2929, 1672, 1603, 1497, 1452, 1188, 1153, 1030, 746, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.10 (3 H, dd, *J* = 6.7 Hz, J_{HF} = 1.2 Hz), 1.61–1.80 (2 H, m), 1.91–1.99 (1 H, m), 2.29 (1 H, ddd, *J* = 15.2, 8.2, 7.0 Hz), 2.56–2.67 (2 H, m), 2.85 (1 H, ddd, *J* = 10.7, 6.4 Hz, J_{HF} = 1.8 Hz), 2.89–2.98 (1 H, m), 3.42 (1 H, ddd, *J* = 10.7, 7.9, J_{HF} = 1.2 Hz), 7.17 (2 H, d, *J* = 7.9 Hz), 7.18 (1 H, t, *J* = 7.2 Hz), 7.28 (2 H, dd, *J* = 7.9, 7.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 17.7, 24.4, 29.2, 35.5, 37.9, 39.4 (d, J_{CF} = 4 Hz), 113.4 (d, J_{CF} = 8 Hz), 125.7, 128.3, 128.4, 142.1, 151.1 (d, J_{CF} = 290 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 35.7 (br s).

MS (70 eV): *m*/*z* (%) = 236 (M^+, 100), 161 (38), 84 (71).

HRMS: *m*/*z* calcd for $C_{14}H_{17}FS$ (M^+): 236.1035; found: 236.1039.

1-Fluoro-2-phenyl-1-cyclopentene (28a)

t-BuLi (0.79 mL, 1.4 M in pentane, 1.1 mmol) was added to a solution of **13a** (153 mg, 0.52 mmol) in Et_2O–hexane (1:4, 14 mL) at –78 °C over 10 min under argon. The reaction mixture was stirred for 30 min at –78 °C, then warmed to r.t. After stirred for 1 h, the reaction was quenched with phosphate buffer (pH 7). Organic materials were extracted with Et_2O (3 × 10 mL), and the combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (pentane) to give **28a** (64 mg, 76%) as a white solid.

IR (KBr): 2960, 2854, 1678, 1496, 1354, 1198, 1063, 945, 762, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98 (2 H, tt, *J* = 7.5, 7.5 Hz), 2.63–2.72 (4 H, m), 7.20 (1 H, t, *J* = 7.7 Hz), 7.33 (2 H, dd, *J* = 7.7, 7.7 Hz), 7.49 (2 H, d, *J* = 7.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ =18.1 (d, J_{CF} = 10 Hz), 29.7 (d, J_{CF} = 8 Hz), 30.8 (d, J_{CF} = 21 Hz), 113.1 (d, J_{CF} = 4 Hz), 126.6, 126.6, 128.2, 133.8 (d, J_{CF} = 5 Hz), 157.8 (d, J_{CF} = 284 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 45.0 (s).

Anal. Calcd for $C_{11}H_{11}F$: C, 81.45; H, 6.84. Found: C, 81.15; H, 6.85.

1-Fluoro-2-(*p*-trifluoromethylphenyl)cyclo-1-pentene (28b)

Compound **28b** was prepared by the method described for **28a** using *t*-BuLi (0.77 mL, 1.5 M in pentane, 1.1 mmol), **13b** (193 mg, 0.51 mmol), and Et_2O–hexane (1:4, 14 mL). Purification by PTLC on silica gel (pentane) gave **28b** (79 mg, 65%) as a white solid.

IR (KBr): 2927, 2862, 1676, 1618, 1329, 1167, 1120, 1066, 841, 607 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.03 (2H, tt, *J* = 7.3, 7.3 Hz), 2.67–2.74 (4H, m), 7.58 (4H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (d, J_{CF} = 10 Hz), 29.6 (d, J_{CF} = 7 Hz), 30.9 (d, J_{CF} = 21 Hz), 112.4 (d, J_{CF} = 3 Hz), 124.3 (q,

J_{CF} = 204 Hz), 125.2 (q, J_{CF} = 4 Hz), 126.7 (d, J_{CF} = 7 Hz), 128.3 (q, J_{CF} = 32 Hz), 137.3 (d, J_{CF} = 270 Hz), 159.7 (d, J_{CF} = 287 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 48.5 (1 F, s), 99.3 (3 F, s).

Anal. Calcd for $C_{12}H_{10}F_4$: C, 62.61; H, 4.38. Found: C, 62.75; H, 4.56.

1-Fluoro-2-(*p*-methoxyphenyl)cyclo-1-pentene (28c)
Compound **28c** was prepared by the method described for **28a** using *t*-BuLi (0.75 mL, 1.4 M in pentane, 1.1 mmol), **13c** (165 mg, 0.49 mmol), and Et_2O–hexane (1:4, 14 mL). Purification by PTLC on silica gel (hexane–Et_2O, 3:1) gave **28c** (70 mg, 0.36 mmol 74%) as a white solid.

IR (KBr): 2954, 2854, 1685, 1608, 1512, 1254, 1182, 1029, 835 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97 (2 H, tt, *J* = 7.5, 7.5 Hz), 2.63–2.67 (4 H, m), 3.80 (3 H, s), 6.88 (2 H, br d, *J* = 9.4 Hz), 7.44 (2 H, br d, *J* = 9.4 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.1 (d, J_{CF} = 10 Hz), 29.8 (d, J_{CF} = 8 Hz), 30.7 (d, J_{CF} = 21 Hz), 55.2, 112.5 (d, J_{CF} = 4 Hz), 113.7, 126.6 (d, J_{CF} = 5 Hz), 127.8 (d, J_{CF} = 7 Hz), 156.2 (d, J_{CF} = 281 Hz), 158.1.

^{19}F NMR (254 MHz, $CDCl_3$): δ = 42.2 (s).

Anal. Calcd for $C_{12}H_{13}OF$: C, 74.98; H, 6.82. Found: C, 75.03; H, 6.94.

1-Fluoro-4-methyl-2-phenylcyclo-1-pentene (28d)
Compound **28d** was prepared by the method described for **28a** using *t*-BuLi (1.5 mL, 1.4 M in pentane, 2.2 mmol), **13d** (325 mg, 1.0 mmol), and Et_2O–hexane (1:4, 28 mL). Purification by PTLC on silica gel (pentane) gave **28d** (123 mg, 69%) as a colorless liquid.

IR (neat): 2956, 2848, 1678, 1496, 1446, 1352, 1200, 762, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (3 H, dd, *J* = 7.0 Hz, J_{HF} = 1.1 Hz), 2.24–2.32 (2 H, m), 2.45 (1 H, ddddqd, *J* = 7.0, 7.0, 7.0, 7.0, 7.0 Hz, J_{HF} = 1.1 Hz), 2.78–2.89 (2 H, m), 7.19 (1 H, t, *J* = 7.8 Hz), 7.32 (2 H, dd, *J* = 7.8, 7.8 Hz), 7.48 (2 H, dt, *J* = 7.8, 1.0 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 27.0 (d, J_{CF} = 9 Hz), 38.1 (d, J_{CF} = 7 Hz), 39.0 (d, J_{CF} = 9 Hz), 112.4 (d, J_{CF} = 3 Hz), 126.5, 126.6 (d, J_{CF} = 7 Hz), 128.2, 133.9 (d, J_{CF} = 5 Hz), 156.3 (d, J_{CF} = 284 Hz).

^{19}F NMR (254 MHz, $CDCl_3$): δ = 46.1 (s).

Anal. Calcd for $C_{12}H_{13}F$: C, 81.78; H, 7.44. Found: C, 81.77; H, 7.66.

1-Fluoro-4-methyl-2-(*p*-methoxyphenyl)-cyclo-1-pentene (28e)
Compound **28e** was prepared by the method described for **28a** using *t*-BuLi (0.60 mL, 1.4 M in pentane, 0.86 mmol), **13e** (138 mg, 0.39 mmol), and Et_2O–hexane (1:4, 11 mL). Purification by PTLC on silica gel (hexane–EtOAc, 3:1) gave **28e** (56 mg, 69%) as a colorless liquid.

IR (neat): 2956, 2837, 1682, 1610, 1514, 1292, 1252, 1180, 1038, 831 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (3 H, d, *J* = 6.9 Hz), 2.21–2.31 (2 H, m), 2.44 (1 H, ddddq, *J* = 6.9, 6.9, 6.9, 6.9, 6.9 Hz), 2.78–2.87 (2 H, m), 3.80 (3 H, s), 6.87 (2 H, d, *J* = 8.8 Hz), 7.42 (2 H, d, *J* = 8.8 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 27.0 (d, J_{CF} = 9 Hz), 38.3 (d, J_{CF} = 7 Hz), 38.9 (d, J_{CF} = 19 Hz), 55.2, 111.8 (d, J_{CF} = 3 Hz), 113.7, 126.7 (d, J_{CF} = 5 Hz), 127.8 (d, J_{CF} = 7 Hz), 154.8 (d, J_{CF} = 282 Hz), 158.2.

^{19}F NMR (254 MHz, $CDCl_3$): δ = 43.3 (s).

HRMS: *m*/*z* calcd for $C_{13}H_{15}OF$ (M^+): 206.1107; found: 206.1117.

3-Butylbenzo[*b*]furan (31)
From **16*E***: Compound **31** was prepared by the method described for **22** using NaH (29 mg, 60% dispersion in mineral oil, 0.72 mmol) and **16*E*** (117 mg, 0.60 mmol) in DMF (6 mL). The reaction mixture was stirred at 80 °C for 43 h. Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave **31** (18 mg, 17%) as a colorless liquid.

From **16*Z***: Compound **31** was prepared by the method described for **22** using NaH (22 mg, 60% dispersion in mineral oil, 0.55 mmol) and **16*Z*** (90 mg, 0.46 mmol) in DMF (5 mL). The reaction mixture was stirred at 80 °C for 43 h. Purification by PTLC on silica gel (hexane–EtOAc, 5:1) gave **31** (15 mg, 19%) as a colorless liquid.

IR (neat): 2958, 2929, 2858, 1452, 1278, 1186, 1089, 1008, 856, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (3 H, t, *J* = 7.5 Hz), 1.42 (2 H, tq, *J* = 7.5, 7.5 Hz), 1.69 (2 H, tt, *J* = 7.5, 7.5 Hz), 2.67 (2 H, td, *J* = 7.5, 0.9 Hz), 7.22 (1 H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.28 (1 H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.39 (1 H, s), 7.45 (1 H, d, *J* = 7.6 Hz), 7.55 (1 H, dd, *J* = 7.6, 1.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.2, 31.2, 111.4, 119.6, 120.7, 122.1, 124.0, 128.4, 141.0, 155.4.

MS (70 eV): *m*/*z* (%) = 174 (M^+, 32), 131 (100), 103 (12).

HRMS: *m*/*z* calcd for $C_{12}H_{14}O$ (M^+): 174.1045; found: 174.1059.

2-Bromo-3-butylbenzo[*b*]furan (32)
Compound **32** was prepared by the method described for **21a** using NaH (18 mg, 62% dispersion in mineral oil, 0.45 mmol) in DMF (3.5 mL) and **30** (126 mg, 0.38 mmol). The reaction was carried out at 60 °C for 5 h. Purification by PTLC on silica gel (hexane–EtOAc, 30:1) gave **32** (14 mg, 15%) as a colorless liquid.

IR (neat): 2956, 2929, 2858, 1581, 1448, 1265, 1224, 1130, 1103, 1083, 875, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (3 H, t, *J* = 7.5Hz), 1.39 (2 H, tq, *J* = 7.5, 7.5 Hz), 1.65 (2 H, tt, *J* = 7.5, 7.5 Hz), 2.64 (2 H, t, *J* = 7.5 Hz), 7.20–7.26 (2 H, m), 7.41 (1 H, dd *J* = 7.2, 2.0 Hz), 7.46–7.50 (1 H, m).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 13.9, 22.4, 23.8, 30.9, 110.9, 118.9, 119.6, 122.8, 124.0, 126.2, 128.8, 155.2.

MS (70 eV): *m*/*z* (%) = 252 (M^+, 82), 209 (98), 131 (100), 102 (67).

HRMS: *m*/*z* calcd for $C_{12}H_{13}OBr$ (M^+): 252.0150; found: 252.0125.

2-Fluoro-3-methoxycarbonyl-1-tosyl-2-pyrroline (35)
Compound **35** was prepared by the method described for **21a** using NaH (6.1 mg, 60% dispersion in mineral oil, 0.15 mmol) in DMF (1 mL) and **19** (44 mg, 0.14 mmol) in DMF (1 mL). The reaction was carried out at 100 °C for 15 min. Purification by PTLC on silica gel (hexane–EtOAc, 1:1) gave **35** (25 mg, 62%) as a colorless liquid.

IR (neat): 1703, 1674, 1441, 1394, 1367, 1277, 1171, 1144, 1099, 577 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.46 (3 H, s), 2.62 (2 H, ddd, *J* = 9.0, 9.0 Hz, J_{HF} = 4.8 Hz), 3.70 (3 H, s), 3.78 (2 H, ddd, *J* = 9.0, 9.0 Hz, J_{HF} = 0.8 Hz), 7.38 (2 H, d, *J* = 8.2 Hz), 7.78 (2 H, d, *J* = 8.2 Hz).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 21.6, 22.9, 46.4, 51.4, 88.7 (d, J_{CF} = 5 Hz), 127.6, 130.2, 133.6, 145.4, 156.2 (d, J_{CF} = 296 Hz), 163.5 (d, J_{CF} = 6 Hz).

^{19}F NMR (470 MHz, $CDCl_3$): δ = 61.8 (dd, J_{FH} = 4.7, 4.7 Hz).

MS (70 eV): *m*/*z* (%) = 299 (M^+, 48), 155 (77), 91 (100).

HRMS: *m*/*z* calcd for $C_{13}H_{14}NO_4FS$ (M^+): 299.0627; found: 299.0627.

Acknowledgement

We gratefully acknowledge the financial support for this research by Central Glass Co., Ltd. We also thank F-Tech, Inc. for a generous gift of methyl 2-(trifluoromethyl)acrylate.

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