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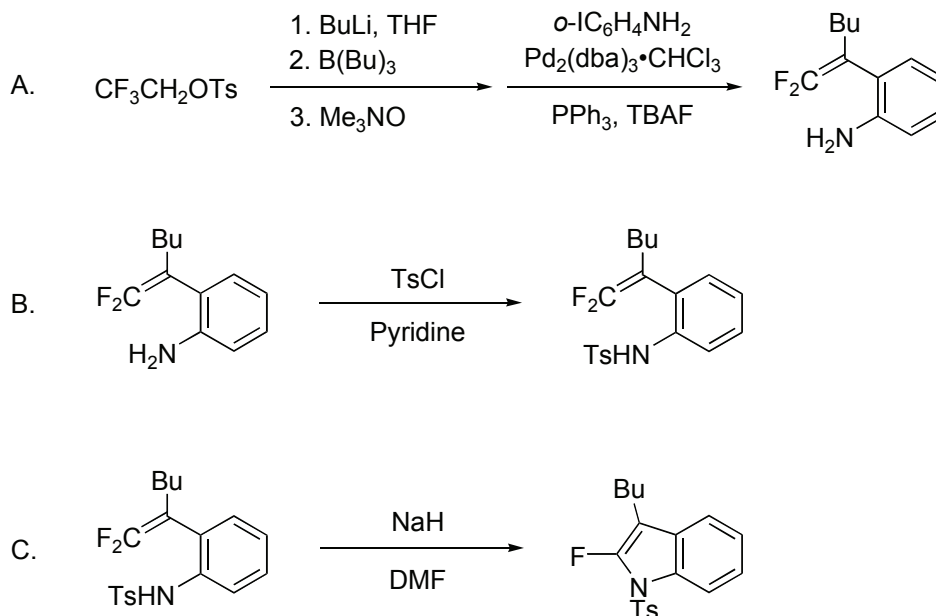
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**5-endo-trig CYCLIZATION OF 1,1-DIFLUORO-1-ALKENES:
SYNTHESIS OF 3-BUTYL-2-FLUORO-1-TOSYLINDOLE
(1*H*-Indole, 3-butyl-2-fluoro-1-[(4-methylphenyl)sulfonyl]-)**



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Discussion Addendum: *Org. Synth.* **2011**, *88*, 162.

1. Procedure

A. *o*-(1,1-Difluorohex-1-en-2-yl)aniline. A 1-L, three-necked, round-bottomed flask is equipped with a Teflon-coated magnetic stirbar, two pressure-equalizing dropping funnels, and a reflux condenser fitted with an argon stopcock inlet. The system is flame-dried and flushed with argon. The flask is charged with anhydrous tetrahydrofuran (200 mL) (Note 1) and 2,2,2-trifluoroethyl *p*-toluenesulfonate (15.3 g, 60 mmol) (Note 2), and the solution is cooled to -78 °C in a dry ice–acetone bath. Butyllithium (76.8 mL, 1.64 M in hexane, 126 mmol) (Note 3) is added via one of the dropping funnels over 10 min (Note 4) and the resulting mixture is stirred for an additional 20 min. Then tributylborane (66.0 mL, 1.0 M in THF, 66 mmol) (Note 5) is added via the other dropping funnel at -78 °C over 3 min. After being stirred for 1 h, the reaction mixture is warmed to room temperature and stirred for an additional 3 h to generate 2,2-difluorovinylborane. This

solution of 2,2-difluorovinylborane is cooled in an ice bath prior to addition of trimethylamine oxide (10.9 g, 145 mmol) (Note 6). The reaction mixture is stirred at 0 °C for 2 h, and then allowed to warm to room temperature. Triphenylphosphine (PPh₃, 2.52 g, 9.60 mmol) (Note 7) and tris(dibenzylideneacetone)dipalladium-chloroform (1/1) (Pd₂(dba)₃·CHCl₃, 2.48 g, 2.40 mmol) (Note 8) are added in this order, and the mixture is stirred for 15 min. To the mixture are added *o*-iodoaniline (9.20 g, 42.0 mmol) (Note 9) and tetrabutylammonium fluoride (168 mL, 1.0 M in tetrahydrofuran, 168 mmol) (Note 10). After being stirred at room temperature for 15 min, the resulting mixture is heated in a 60 °C oil bath for 13 h, at which time TLC analysis indicates the reaction to be complete (Notes 11, 12). Then the reaction mixture is cooled to ambient temperature, and phosphate buffer (200 mL) (Note 13) is added. Organic materials are extracted with ethyl acetate (AcOEt, 3 x 200 mL), the combined extracts are washed successively with water (3 x 200 mL) and brine (200 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through a filter paper and removal of the solvent under reduced pressure (Note 14), the palladium catalyst and ammonium salt are removed by short column chromatography on silica gel (Note 15). The eluent is concentrated under reduced pressure (Note 14) to give the crude product as a brown oil. This oil is distilled twice under reduced pressure (74–77 °C/1.2–1.4 mmHg) to give *o*-(1,1-difluorohex-1-en-2-yl)aniline (5.63 g, 63%) (Note 16) as a pale yellow liquid that was pure enough (90–95%) for use in the next step.

B. o'-(1,1-Difluorohex-1-en-2-yl)-p-toluenesulfonanilide. A 100-mL, two-necked, round-bottomed flask containing *o*-(1,1-difluorohex-1-en-2-yl)aniline (4.94 g, 23.4 mmol) is equipped with a glass stopper, a Teflon-coated magnetic stirbar, and a stopcock inlet connected to the argon line. Pyridine (50 mL) (Note 17) is introduced and the solution is cooled to 0 °C. *p*-Toluenesulfonyl chloride (TsCl, 6.69 g, 35.1 mmol) (Note 18) is added, and the mixture is stirred at room temperature for 15 h. Water (5 mL) is added and the reaction mixture is stirred for 0.5 h. Water (50 mL) and ether (100 mL) are added to the mixture before 2 M aqueous HCl solution (400 mL) is introduced. Organic materials are extracted with ether (4 x 100 mL). The combined organic extracts are washed successively with water (100 mL) and brine (100 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through filter paper and removal of the solvent under reduced pressure (Note 14), a brown liquid (8.77 g) (Note 19) is obtained. This is used in the next step without further purification.

C. *3-Butyl-2-fluoro-1-tosylindole*. A 300-mL, two-necked, round-bottomed flask is equipped with a glass stopper, a Teflon-coated magnetic stirbar, and a reflux condenser connected to the argon line. The system is flame-dried and flushed with argon. The flask is charged with anhydrous *N,N*-dimethylformamide (50 mL) (Note 1) and crude *o'*-(1,1-difluorohex-1-en-2-yl)-*p*-toluenesulfonamide (8.77 g) (Note 19). Sodium hydride (0.65 g, 27 mmol) (Note 20) is added in portions to the solution at 0 °C. After the reaction mixture is stirred at 0 °C for 30 min, the flask is placed in an 80 °C oil bath. The mixture is stirred at this temperature for 7 h, at which time TLC analysis indicates the reaction to be complete (Notes 11, 21). The reaction mixture is cooled to ambient temperature, and phosphate buffer (100 mL) (Note 13) is added. Organic materials are extracted with ethyl acetate (3 x 150 mL), and the combined extracts are washed with water (4 x 100 mL) and brine (100 mL), and then dried over anhydrous magnesium sulfate (30 g). After filtration through a filter paper and removal of the solvent under reduced pressure (Note 14), the resulting brown residue is purified by column chromatography on silica gel (Note 22). The eluent containing the product is concentrated under reduced pressure (Note 14) to provide pure *3-butyl-2-fluoro-1-tosylindole* as a yellow liquid (6.43 g, 80% over two steps) (Note 23).

2. Notes

1. Anhydrous tetrahydrofuran (THF) and *N,N*-dimethylformamide (DMF) (organic synthesis grade) were purchased from Kanto Chemical Co., Inc. and used as supplied. The checkers used anhydrous THF dried by distillation over Mg-anthracene, and DMF (Fluka) that was dried by storing over molecular sieves (3 Å) and subsequent distillation under reduced pressure.

2. Trifluoroethyl *p*-toluenesulfonate (Guaranteed Reagent grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers purchased this compound from Lancaster.

3. Butyllithium (ca. 1.6 M solution in hexane, organic synthesis grade) was purchased from Kanto Chemical Co., Inc. and used as supplied. The checkers purchased BuLi (1.64 M in hexanes) from Fischer Science.

4. The submitters introduced the butyllithium via syringe, adding the solution along the wall of the reaction flask that was cooled by a dry ice–acetone bath.

5. Tributylborane (1.0 M solution in tetrahydrofuran) was purchased from Aldrich Chemical Company, Inc. and used as supplied.

6. Anhydrous trimethylamine oxide was prepared by sublimation of trimethylamine oxide dihydrate under reduced pressure (150 °C, 2.0 mmHg). Trimethylamine oxide dihydrate (Guaranteed Reagent grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. The checkers used anhydrous trimethylamine oxide purchased from Aldrich.

7. Triphenylphosphine (Extra Pure grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and recrystallized from methanol prior to use. The checkers used triphenylphosphine (Aldrich) recrystallized from acetone prior to use.

8. The palladium catalyst was prepared from palladium(II) diacetate and dibenzylideneacetone according to the literature method.²

9. *o*-Iodoaniline (Extra Pure grade) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers used the commercial sample purchased from Acros as received.

10. Tetrabutylammonium fluoride (1.0 M solution in tetrahydrofuran) was purchased from Tokyo Kasei Kogyo Co., Ltd. and used as supplied. The checkers purchased the solution of this reagent from Aldrich.

11. Silica gel TLC plates (60F₂₅₄) were purchased from Merck Ltd. Japan, and visualized with 3% aqueous KMnO₄.

12. The R_f value of iodoaniline was 0.30 (ethyl acetate:hexane (1:5)); the product possessed an R_f = 0.42 in this solvent system. The submitters reported that the reaction was complete after only 6 h.

13. Phosphate buffer (pH 7, 1 L) was prepared by dissolving KH₂PO₄ 9.1 g and Na₂HPO₄·12H₂O (47.7 g) in distilled water.

14. Rotary evaporation was conducted at 100 mmHg in a 40 °C water bath.

15. Short column chromatography was performed by using a 3.5-cm x 40-cm column packed with 250 mL of silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with 500 mL of ethyl acetate:hexane (1:5). The checkers used silica gel purchased from E. Merck, Darmstadt (230–400 mesh).

16. *o*-(1,1-Difluorohex-1-en-2-yl)aniline has the following physical properties: R_f = 0.42 (ethyl acetate:hexane (1:5)); ¹H NMR (300 MHz, CDCl₃) δ: 0.84–0.89 (m, 3 H), 1.30–1.35 (m, 4 H), 2.24–2.32 (m, 2 H), 3.59 (br. s, 2 H), 6.70–6.77 (m, 2 H), 6.99 (dd, 1 H, *J* = 1.6, 7.6 Hz), 7.11 (ddd, 1 H, *J* = 1.6, 7.5, 7.8 Hz); ¹³C NMR (75 MHz, CDCl₃) δ: 13.8, 22.3, 27.7, 29.8

(dd, $J = 2, 3$ Hz), 89.0 (dd, $J = 17, 22$ Hz), 115.6, 118.4, 119.1 (dd, $J = 1, 4$ Hz), 128.9, 130.4 (dd, $J = 2, 3$ Hz), 144.2 (dd, $J = 1, 3$ Hz), 152.8 (dd, $J = 287, 288$ Hz); ^{19}F NMR (282 MHz, $\text{CDCl}_3/\text{CFCl}_3$) δ : -89.2 (d, 1 F, $J = 43$ Hz), -93.2 (d, 1 F, $J = 43$ Hz); IR (KAP) 3475, 3385, 2958, 2930, 2862, 1737, 1617, 1496, 1232 cm^{-1} ; MS (70 eV) m/z (rel intensity) 211 (M^+ ; 80), 168 (98), 148 (100); Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NF}_2$: C, 68.23; H, 7.16; N, 6.63. Found: C, 66.95; H, 7.86; N, 5.78.

17. Pyridine (JIS special grade) was purchased from Kokusan Chemical Works, Ltd. and used as supplied. The checkers used pyridine (E. Merck, Darmstadt) distilled over KOH prior to use.

18. *p*-Toluenesulfonyl chloride (Extra Pure grade) was purchased from Kanto Chemical Co., Inc. and recrystallized from toluene prior to use. The checkers used tosyl chloride as received from Aldrich.

19. An analytically pure sample of the toluenesulfonanilide can be isolated by column chromatography on silica gel (Fuji Silysia Chemical Ltd., PSQ100B, >100 μm). The product was eluted with ethyl acetate:hexane (1:5) and the eluent was concentrated with a rotary evaporator (Note 14) to give *o'*-(1,1-difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide as a white powder. The product exhibits the following physical properties: $R_f = 0.31$ (ethyl acetate:hexane (1:5)) (Note 11); ^1H NMR (400 MHz, CDCl_3) δ : 0.79 (t, 3 H, $J = 7.1$ Hz), 1.05–1.23 (m, 4 H), 1.98 (br. s, 2 H), 2.35 (s, 3 H), 6.52 (s, 1 H), 6.98–7.06 (m, 2 H), 7.19–7.27 (m, 3 H), 7.60 (d, 1 H, $J = 7.9$ Hz), 7.68 (d, 2 H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.6, 21.5, 22.2, 28.0, 29.4, 88.0 (dd, $J = 16, 23$ Hz), 119.7, 124.1 (d, $J = 4$ Hz), 124.3, 127.2, 129.1, 129.7, 130.6, 135.0, 136.4, 144.1, 153.0 (dd, $J = 288, 291$ Hz); ^{19}F NMR (282 MHz, $\text{CDCl}_3/\text{CFCl}_3$) δ : -86.9 (d, 1 F, $J = 39$ Hz), -90.3 (d, 1 F, $J = 41$ Hz); IR (KAP) 3274, 2958, 1742, 1494, 1401, 1339, 1247, 1167, 1092, 920, 666 cm^{-1} ; MS (70 eV) m/z (rel intensity) 365 (M^+ ; 0.5), 210 (100), 148 (62); HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2\text{F}_2\text{SNa}$ 388.11533 ($\text{M}^+ + \text{Na}$); found 388.11525.

20. The checkers used pure NaH by removing the mineral oil from the commercial sample (Aldrich) with pentane (three washings). The submitters used sodium hydride (NaH) in mineral oil (1.06 g, 60% dispersion in mineral oil, 27 mmol, organic synthesis grade) purchased from Kanto Chemical Co., Inc. without further purification.

21. The product possessed an $R_f = 0.39$ (ethyl acetate:hexane (1:5)).

22. Column chromatography was performed by using a 3-cm x 50-cm column packed with 300 mL of silica gel (Fuji Silysia Chemical Ltd.,

PSQ100B, >100 μm). The product was eluted with ethyl acetate:hexane (1:10). After collection of 200 mL of eluent, 50 mL-fractions were collected. The KMnO_4 -active product was eluted in the fractions 6–11 (Note 11). The checkers used silica purchased from E. Merck, Darmstadt (230–400 mesh).

23. 3-Butyl-2-fluoro-1-tosylindole exhibits the following physical properties: ^1H NMR (400 MHz, CDCl_3) δ : 0.84 (t, 3 H, $J = 7.3$ Hz), 1.16–1.25 (m, 2 H), 1.48–1.56 (m, 2 H), 2.33 (s, 3 H), 2.51 (dt, 2 H, $J = 0.8, 7.4$ Hz), 7.19 (d, 2 H, $J = 8.0$ Hz), 7.23 (ddd, 1 H, $J = 1.1, 7.6, 7.6$ Hz), 7.25–7.29 (m, 1 H), 7.33 (d, 1 H, $J = 7.1$ Hz), 7.71 (d, 2 H, $J = 8.3$ Hz), 8.07 (d, 1 H, $J = 8.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.7, 21.3 (d, $J = 2$ Hz), 21.6, 22.1, 30.5 (d, $J = 2$ Hz), 99.7 (d, $J = 11$ Hz), 114.4, 118.9 (d, $J = 7$ Hz), 123.9, 124.0 (d, $J = 4$ Hz), 126.8, 128.1 (d, $J = 6$ Hz), 129.8, 130.6, 134.7, 145.2, 147.4 (d, $J = 277$ Hz); ^{19}F NMR (282 MHz, $\text{CDCl}_3/\text{CFCl}_3$) δ : -132.8; IR (KAP) 2957, 2931, 2861, 1659, 1453, 1393, 1190, 1179, 746, 689, 663 cm^{-1} ; MS (70 eV) m/z (rel intensity) 345 (M^+ ; 91), 190 (100), 148 (71); HRMS calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2\text{FSNa}$ 368.10910 ($\text{M}^+ + \text{Na}$); found 368.10906; Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_2\text{FS}$: C, 66.06; H, 5.84; N, 4.05. Found: C, 65.97; H, 5.90; N, 4.10.

Waste Disposal Information

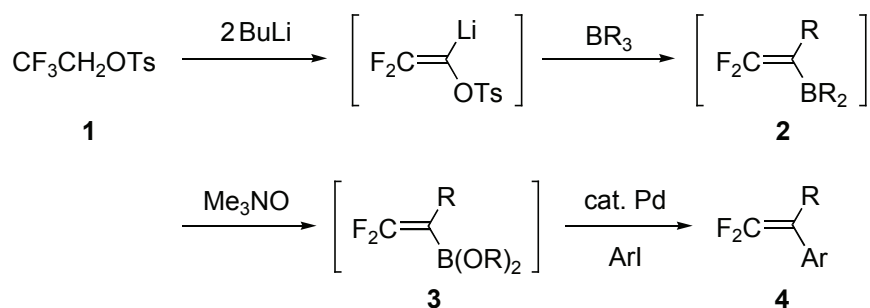
All hazardous materials should be handled and disposed of in accordance with “Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

Synthetic methods for the preparation of 2-fluoroindoles have been limited to difluorination of indole derivatives followed by elimination^{3a,b} and electrophilic fluorination of stannylindoles.^{3c} The procedures described herein illustrate an efficient construction of 2-fluoroindoles via intramolecular substitution of the vinylic fluorine in β,β -difluorostyrenes bearing an *ortho*-amido substituent.⁴ This reaction can be classified as a 5-*endo-trig* ring closure, a disfavored process according to Baldwin’s rules.⁵⁻⁸ While having only rarely been observed in synthetic chemistry,⁶ the nucleophilic 5-*endo-trig* cyclization was successfully achieved by taking advantage of the unique properties of fluorine: (i) the highly polarized difluorovinylidene double bond (^{13}C NMR: ca. 150 ppm and 90 ppm for

CF₂=C) aids initial ring formation by electrostatic attraction between the CF₂ carbon and the internal nucleophile, and (ii) the successive elimination of the fluoride ion suppresses the reverse ring opening, thus functioning as a “lock”.⁴

Difluorostyrene derivatives **4** including *o*-(2,2-difluorovinyl)anilines are easily prepared by using a one-pot sequence as outlined below.^{9a,c} The sequence comprises the following two processes starting from 2,2,2-trifluoroethyl *p*-toluenesulfonate (**1**): (i) a boron-mediated alkylation via 1,2-migration, leading to 2,2-difluorovinylboranes **2** and (ii) subsequent palladium-catalyzed coupling reaction with aryl iodides via 2,2-difluorovinylboronates **3**, which affords difluorostyrenes **4** in good yield. The substituent R at the vinylic position of **4** is derived from a trialkylborane (BR₃), which is readily generated by hydroboration of the corresponding alkene. The selective oxidation of boron–alkyl bonds with trimethylamine oxide prevents the coupling reaction of B-alkyl groups in **2**.



Another vinyl-selective coupling reaction of **2** with aryl iodides is accomplished via the transmetalation to 2,2-difluorovinylcopper species by adding cuprous iodide.^{4a,9b,c} β,β-Difluorostyrenes **4** (R = H) without a vinylic substituent can also be prepared via 2,2-difluorovinylzirconocene from **1**.¹⁰

After tosylation of *o*-(2,2-difluorovinyl)anilines, treatment of the obtained sulfonanilides with 1.1 equiv of NaH in DMF promotes the normally “disfavored” 5-*endo-trig* cyclization to afford the corresponding 2-fluoroindoles in high yield. High-dilution conditions are not required in this ring closure.

This methodology for constructing five-membered rings is widely applicable to the cyclization of (i) β,β-difluorostyrene derivatives and (ii) 1,1-difluoro-1-butene derivatives bearing a nucleophilic nitrogen, oxygen, or sulfur atom at the *ortho* or the homoallylic position, respectively. Under

similar conditions, these substrates undergo cyclization to afford ring-fluorinated heterocycles such as pyrrolines, furans, and thiophenes in high yield as shown in the Table. Five-membered carbocycles bearing a fluorine on the ring can also be obtained by this method.^{4a,11} Moreover, six-membered ring-fluorinated heterocyclic and carbocyclic compounds can be provided in line with the “intramolecular substitution” concept.^{11b,12}

Table. Nucleophilic 5-*endo-trig*-Cyclization of 1,1-Difluoro-1-alkenes

Substrate	Product	Conditions ^a	Yield
		80 °C, 5 h	81%
		70 °C, 23 h	73%
		60 °C, 2 h	80%
		reflux, 3 h ^b	82%
		90 °C, 4 d	80%
		90 °C, 7 h	67%
		90 °C, 4 h	76%

a. NaH (1.1–1.2 equiv), DMF. b. (i) (CF₃CO)₂O (3 equiv), NEt₃ (3 equiv), CH₂Cl₂, 0 °C, 0.5 h. (ii) K₂CO₃ (6 equiv), MeOH, 0 °C–rt, 1 h then reflux.

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Appendix

Chemical Abstracts Nomenclature; (Registry Number)

- o*-(1,1-Difluorohex-1-en-2-yl)aniline: Benzenamine, 2-[1-(difluoromethylene)pentyl]-; (134810-59-6)
- o'*-(1,1-Difluorohex-1-en-2-yl)-*p*-toluenesulfonanilide: Benzenesulfonamide, *N*-[2-[1-(difluoromethylene)pentyl]phenyl]-4-methyl-; (195734-33-9)
- 3-Butyl-2-fluoro-1-tosylindole: 1*H*-Indole, 3-butyl-2-fluoro-1-[4-methylphenyl)sulfonyl]-; (195734-36-2)
- 2,2,2-Trifluoroethyl *p*-toluenesulfonate: Ethanol, 2,2,2-trifluoro-, 4-methylbenzenesulfonate; (433-06-7)
- Trimethylamine oxide: Methanamine, *N,N*-dimethyl-, *N*-oxide; (1184-78-7)
- Tetrabutylammonium fluoride: 1-Butanaminium, *N,N,N*-tributyl-, fluoride; (429-41-4)
- o*-Iodoaniline: Benzenamine, 2-iodo-; (615-43-0)
- Triphenylphosphine: Phosphine, triphenyl-; (603-35-0)
- Tris(dibenzylideneacetone)dipalladium(0)-chloroform (1/1): Palladium, tris[-[(μ 1,2- η :4,5- η)-(1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one]]di-, compound with trichloromethane (1:1); (52522-40-4)

