Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.16, 14.18, 17.01, 35.88, 37.74, 60.60, 77.22, 171.80, 175.23; IR (neat) 1737 cm^{-1} (ν(C=O)); MS *m/e* 143 (97), 115 (100), 87 (47), 73 (36), 45 (31), 29 (93).

3: ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 6 H), 1.95 (tt, *J* = 7.4 and 7.4 Hz, 2 H), 2.36 (t, *J* = 7.4 Hz, 4 H), 4.13 (q, *J* = 7.1 Hz, 4 H); IR (neat) 1740 cm^{-1} (ν(C=O)); MS *m/e* 143 (100), 115 (73), 114 (59), 87 (53), 55 (31), 45 (23), 42 (31), 29 (75).

5: MS *m/e* 131 (25), 116 (33), 115 (23), 73 (100), 45 (100), 29 (84).

Co-Catalyzed Carbonylation. A stirred mixture of $Co_2(CO)_8$ (34.0 mg, 0.10 mmol), 1-iodooctane (181 μL, 1.0 mmol), EtOH (0.6 mL, 10 mmol), and TMU (1.4 mL) in a 10-mL stainless steel autoclave was heated at 100 °C for 24 h under 50 atm of CO. The mixture was made slightly acidic and was extracted with Et_2O. The extract was washed with water and dried ($MgSO_4$). The extract was concentrated, and the residue was purified by flash chromatography to provide a mixture (161.0 mg) of ethyl nonanoate and ethyl octyl ether. ^1H NMR analysis showed that ethyl nonanoate was formed in 86% yield and ethyl octyl ether in 1% yield.

Ethyl nonanoate: ^1H NMR ($CDCl_3$) δ 0.88 (bt, 3 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 1.10–1.80 (br, 12 H), 2.32 (t, *J* = 7.0 Hz, 2 H), 4.16 (q, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.08, 14.27, 22.64, 25.00, 29.12, 29.16, 29.23, 31.81, 34.41, 60.13, 173.86; IR (neat) 1744 cm^{-1} (ν(C=O)); MS *m/e* 186 (M^+, 1), 141 (12), 101 (34), 88 (100), 73 (25), 71 (13), 70 (18), 69 (12), 61 (30), 60 (34), 57 (30), 55 (30), 45 (20), 43 (37), 41 (65), 39 (19), 29 (93).

Ethyl octyl ether: ^1H NMR ($CDCl_3$) δ 0.89 (bt, 3 H), 1.1–1.8 (m, 15 H), 3.42 (t, *J* = 7.0 Hz, 2 H), 3.48 (t, *J* = 7.0 Hz, 2 H); MS *m/e* 112 (7), 84 (23), 83 (13), 59 (100), 57 (19), 56 (31), 47 (30), 42 (18), 41 (38), 31 (81), 29 (42).

For products other than those listed above, all the spectroscopic (^1H and ^{13}C NMR, and IR) data were identical with those of authentic samples.

Difluoromethylation of Alkenes via Borohydride Reduction of 1,3-Dibromo-1,1-difluoroalkanes

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The synthesis of difluoromethyl-substituted compounds has been an area of active interest, as many of these compounds have been found to be biologically active.[1] The difluoromethyl group has been classically prepared by geminal difluorination of a corresponding aldehyde.[2,3] More recently the use of fluorinated building blocks in synthesis has gained increasing popularity, and methods involving these are being reported for the synthesis of functionalized, difluoromethyl-substituted compounds.[4-6]

Scheme I

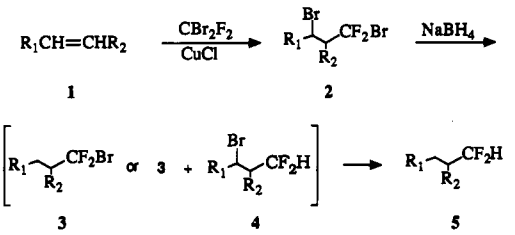
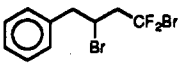
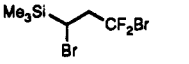
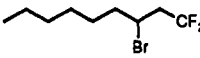
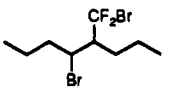
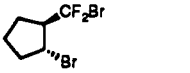
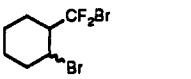
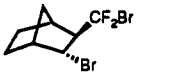


Table I. Yields of Dibromides 2, Bromides 3, and *gem*-Difluoroalkanes 5

	starting alkene, 1	CBr_2F_2 adduct, 2	% yield[a] 2	3	5
1a	allylbenzene		32	74	(30)
1b	vinyltrimethylsilane		58	61	29
1c	1-octene		77	34	57
1d	*trans*-4-octene		50	12	38
1e	cyclopentene		31		(21)
1f	cyclohexene		51		27
1g	norbornene		76		(48)

[a] Isolated yields based on starting material charged. Parentheses denote GC or crude yields.

In the course of investigating the reactions of 1,3-dibromo-1,1-difluoroalkanes **2** with various nucleophiles,[7,8] we have found that these compounds undergo selective reduction of one or both carbon–bromine bonds upon treatment with sodium borohydride in DMSO.[9-12] In the

(1) (a) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha, Elsevier Biomedical: Tokyo, 1983. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Walsh, C. *Tetrahedron* **1982**, *38*, 871.

(2) A wide range of fluorinating agents has been used for this transformation. Some of these include: (a) DAST (diethylamino)sulfur trifluoride): Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. For a review, see: Hudlicky, M. *Org. React.* **1988**, *35*, 513–637. (b) SF_4: Boswell, G. A.; Ripka, W. C.; Scribner, R. M.; Tullock, C. W. *Org. React.* **1974**, *21*, 1. Also, see: Dmowski, W. *J. Fluorine Chem.* **1986**, *32*, 255. (c) SeF_4: Olah, G. A.; Nojima, M.; Kerekes, I. *J. Am. Chem. Soc.* **1974**, *96*, 925. (d) MoF_6: Mathey, F.; Bensoam, J. *Tetrahedron* **1971**, *27*, 3965. (e) Phenylsulfur trifluoride: Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3058.

(3) This conversion has also been effected in two steps via the intermediate 1,3-dithiolanes (Sondej, S. C.; Katzenellenbogen, J. A. *J. Org. Chem.* **1986**, *51*, 3508) or hydrazones (Rozen, S.; Brand, M.; Zamir, D.; Hebel, D. *J. Am. Chem. Soc.* **1987**, *109*, 896).

(4) For example, some enolate carbanions can be alkylated with $CHClF_2$ (via insertion of difluorocarbene): (a) Bey, P.; Gerhart, F.; Dorsselaer, V. V.; Danzin, C. *J. Med. Chem.* **1983**, *26*, 1551. (b) Tsushima, T.; Kawada, K.; Ishihara, S.; Uchida, N.; Shiratori, O.; Higaki, J.; Hirata, M. *Tetrahedron* **1988**, *44*, 5375. (c) Bey, P.; Vevert, J. P.; Dorsselaer, V. V.; Kolb, M. *J. Org. Chem.* **1979**, *44*, 2732.

(5) For examples involving the hydrogenation of difluoromethylene derivatives, see: (a) α-Difluoromethyl carboxylic acids: Kitazume, T.; Ohnogi, T.; Miyauchi, H.; Yamazaki, T.; Watanabe, S. *J. Org. Chem.* **1989**, *54*, 5630. (b) Motherwell, W. B.; Tozer, M. J.; Ross, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, *19*, 1437.

(6) Other examples include: (a) Allylic difluoromethyl compounds: Hartgraves, G. A.; Burton, D. J. *J. Fluorine Chem.* **1988**, *39*, 425. (b) α-Difluoromethyl alcohols: Stahly, G. P. *J. Fluorine Chem.* **1989**, *43*, 53. (c) α-Difluoromethyl ketones: Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 5437.

(7) For a review on the free-radical addition of dibromodifluoromethane to alkenes, see: Sosnovsky, G. *Free Radical Reactions in Preparative Organic Chemistry*; Macmillian: New York, 1964; Chapter 2, pp 42–44.

(8) The CF_2Br_2-alkene adducts react with some nucleophiles via elimination–addition chemistry, often resulting in facile dehalogenations to give α,β-unsaturated carbonyl compounds: (a) Elsheimer, S.; Michael, M.; Landavazo, A.; Slattery, D. K.; Weeks, J. *J. Org. Chem.* **1988**, *53*, 6151. (b) Elsheimer, S.; Slattery, D. K.; Michael, M.; Weeks, J.; Topoleski, K. *Ibid.* **1989**, *54*, 3992.

(9) For a review on the dehalogenation of halofluoroalkanes, see: Mettille, F. J.; Burton, D. J. *Fluorine Chem. Rev.* **1967**, *1(2)*, 315. For a review on the reduction of alkyl halides in general, see: Pinder, A. R. *Synthesis* **1980**, 425.

(10) Sodium borohydride in polar, aprotic solvents has been proposed as a reagent for the reduction of alkyl halides: (a) Hutchins, R. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259. (b) Bell, H. M.; Vanderslice, C. W.; Spehar, A. *Ibid.* **1969**, *34*, 3923.

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case of adducts **2a–d**, derived from *acyclic* alkenes, loss of the first bromine occurs regioselectively and yields the terminal trihalomethyl compounds **3a–d**, uncontaminated with any of the secondary bromides **4**.[13,14] The relatively inaccessible bromodifluoromethyl-substituted compounds **3** could be used as potential precursors to other *gem*-difluoro compounds.[15] Cyclic adducts **2e–g** underwent simultaneous reduction of *both* carbon–bromine bonds, however, resulting in mixtures of **3** and **4**. After longer reaction times, all dibromides are subsequently reduced to the *gem*-difluoroalkanes **5**. The reductions were clean for all adducts except the allylbenzene-derived compound **2a**, which yielded 1,1-difluoro-4-phenyl-1-butene (**6**) as the major product.[16]

Radical addition of dibromodifluoromethane to an olefin[7,17] followed by reduction with sodium borohydride amounts to a two-step method for adding difluoromethane across an alkene.

Experimental Section

General Methods. NMR spectra were obtained in $CDCl_3$ solutions at ambient temperature on a Varian Gemini 200 spectrometer. IR spectra were obtained from neat liquids as capillary films between KBr plates. Preparative and analytical gas–liquid chromatography were performed on either 20% Carbowax 20M (column A) or 20% DC 200 (column B) on Chromosorb P (80–100 mesh) in 4 ft × 0.25 in. tubing. All reagents were obtained from commercial sources and used without further purification. The DMSO was Aldrich anhydrous grade.

Addition of CBr_2F_2 to Alkenes. General Procedure. The procedure reported by Burton and Kehoe[17] was used with some modifications. The alkenes were reacted with 100% excess CBr_2F_2 in the presence of CuCl, ethanolamine, and *tert*-butyl alcohol in a 1:50:100 mol ratio under pressure at 80–85 °C for at least 24 h. *As some additions may be exothermic, this procedure should be done using a safety shield!* The products were isolated by fractional distillation. The addition to 1-octene is representative.

1,3-Dibromo-1,1-difluorononane (2c). A 150-mL screw-cap culture tube (Pyrex no. 9825) was Teflon taped and charged with a stirring bar, 1-octene (22.4 g, 0.2 mol), ethanolamine (6.1 g, 0.1 mol), *tert*-butyl alcohol (20 mL), CBr_2F_2 (83.9 g, 0.4 mol), and CuCl (0.198 g, 0.002 mol). The tube was placed in an oil bath and stirred at 80–85 °C for 24 h. The mixture changed color from deep blue to green to brown during this time. After cooling, the tube was diluted with 20 mL of hexane. (Optional: The unreacted halomethane can be recovered at this time by distillation into a cold trap.) The mixture separated into a cloudy supernatant and a brown resin. The hexane layer was separated and the resin was extracted with two 20-mL portions of hexane. The combined extracts were filtered through 50 cm^3 of silica gel, yielding a colorless solution. After rotary evaporation, the resulting oil was vacuum distilled through a 15-cm Vigreux column. A forerun (4.4 g) of product contaminated with olefinic impurities was collected, followed by a fraction, 49.8 g (77%), bp 118–122 °C (20 Torr), that was 98% pure product by GC on column B. The ^1H NMR spectrum is consistent with that previously reported:[17] ^{13}C NMR δ 121.1 (t, J = 308 Hz, CF_2Br), 52.9 (t, J = 21.5 Hz, C-2), 47.2 (t, J = 2.6 Hz, C-3), 38.9, 31.8, 28.6, 27.3, 22.8, 14.2.

(1,3-Dibromo-3,3-difluoropropyl)trimethylsilane (2b). The procedure described for **2c** was followed: bp 78–79 °C (12 Torr); lit.[18] bp 95 °C (25 Torr); ^1H NMR δ 3.38–3.29 (m, 1 H, CHBr), 3.02–2.65 (m, 2 H, CH_2), 0.16 (s, 9 H, Me_3Si); ^{13}C NMR δ 123.1 (t, J = 310 Hz, CF_2Br), 48.0 (t, J = 22.2 Hz, C-2), 31.9 (s, C-1); IR 1255, 1202, 1114, 1079, 991, 926, 850 cm^{-1}.

***threo*- and *erythro*-4-(Bromodifluoromethyl)-5-bromooctanes (2d).** This compound was formed as a 60:40 mixture of diastereomers (arbitrarily referred to as A and B, respectively): bp 109–113 °C (20 Torr); ^1H NMR (A) δ 4.53 (m, 1 H, CHBr), 2.89–2.67 (m, 1 H, H2); (B) δ 4.40–4.31 (m, 1 H, CHBr), 2.46–2.25 (m, 1 H, H-2); (both isomers) δ 2.01–2.25 (m, CH_2), 1.06–0.85 (m, CH_3); ^{13}C NMR (A) δ 125.0 (t, J = 312 Hz, CF_2Br), 58.2 (t, J = 18.2 Hz, C-2) 54.3 (t, J = 2.8 Hz, C-3); (B) δ 125.9 (t, J = 311 Hz CF_2Br), 56.2 (t, J = 18.5 Hz, C-2), 54.1 (t, J = 3.1 Hz, C-3); (both isomers) 40.1, 35.9, 30.5, 28.4, 22.3, 22.2, 21.8, 21.3, 14.3, 14.2, 13.39, 13.36; IR 1185, 1102, 932, 885 cm^{-1}. Anal. Calcd for $C_9H_{16}Br_2F_2$: C, 33.57; H, 5.01. Found: C, 34.33; H, 5.21.

***exo*-2-(Bromodifluoromethyl)-*endo*-3-bromobicyclo[2.2.1]heptane (2g).** Addition of CBr_2F_2 to norborene was exothermic and resulted in an explosion under the usual reaction conditions. Decreasing the catalyst to 0.1 mol % (based on the alkene) gave a 5:95 mixture of CF_2Br endo to exo that was obtained in 85–87% yield. Essentially pure exo was obtained in 76% yield by fractionating the mixture, bp 115–116 °C (20 Torr).

Reaction of Adducts 2 with Sodium Borohydride. The dibromides were treated with 4 equiv (1 mol per equiv) of sodium borohydride in DMSO under anhydrous conditions. The reductions were monitored by GC. The more reactive adducts, **2a** and **2b**, could also be reduced with 1 equiv of hydride by increasing the reaction time. For the cyclic compounds **2e–g**, the reactions were worked up after 50% conversion and the products isolated by preparative GC on column A (the trihalomethyl compounds **3** elute first). Other polar aprotic solvents such as DMPU and HMPA were used in some cases. The products were isolated by distillation. The reduction of compound **2a** is representative.

1-Bromo-1,1-difluoro-4-phenylbutane (3a). A 25-mL, round-bottomed, three-necked flask was fitted with a septum, a N_2 inlet tube, a thermometer and adapter, a stirring bar, and a condenser. The apparatus was purged with N_2 and charged with $NaBH_4$ (1.51 g, 0.04 mol) and **2a** (3.28 g, 0.01 mol). Anhydrous DMSO (15 mL) was added by syringe. The mixture was stirred and heated at a bath temperature of 65–70 °C for 22 h to give an opaque white semisolid. This gel was quenched with approximately 100 cm^3 of ice and 50 mL of ether and then slowly acidified (caution!) with concentrated HCl until the vigorous gas evolution ceased. The ether layer was separated, the aqueous layer was extracted twice with 25-mL portions of ether, and the combined extracts were washed twice with 50-mL portions of dilute brine. After drying over $CaCl_2$ and concentration, a clear oil was obtained (2.34 g), consisting of essentially pure (>95% by GC) **3a**. Short-path distillation yielded 1.84 g (74%): bp 98–102 °C (10 Torr); ^1H NMR δ 7.52–7.14 (m, 5 H, AR-H), 2.75 (t, J = 7.5 Hz, 2 H, H-4), 2.53–2.29 (m, 2 H, H-3), 2.11–1.93 (m, 2 H, H-2); ^{13}C NMR δ 141.3, 129.2, 129.0, 126.9, 123.6 (t, J = 306 Hz, CF_2Br), 43.9 (t, J = 21.7 Hz, C-2), 34.7 (C-4), 25.9 (t, J = 2.8 Hz, C-3); IR 1602, 1196, 1102, 920, 744, 697 cm^{-1}. Anal. Calcd for

(11) Other solvents used in this study included HMPA, DMPU, DMF, and sulfolane. With the exception of DMPU, use of these solvents in sodium borohydride reductions has been reported.[12a] In general, DMSO reductions appeared to be cleaner. Use of the nitrogenous solvents (DMF in particular) led to olefinic impurities. Borohydride reductions of alkyl halides have been effected in polyethylene glycols, which react with borohydride to form reactive crown ether-like complexes (Santaniello, E.; Fiecchi, A.; Manzocchi, A.; Ferraboschi, P. *J. Org. Chem.* **1983**, *48*, 3074); however, use of this reagent system led to foaming due to the high viscosity. The use of phase-transfer catalysis in borohydride reductions of alkyl halides has also been reported (Rolla, F. *J. Org. Chem.* **1981**, *46*, 3909), but this work was difficult to reproduce due to the instability of sodium borohydride in hot aqueous solutions.

(12) Lithium triethylborohydride has been proposed as a reagent of choice for hydrodehalogenation reactions (Krishnamurthy, C.; Brown, H. C. *J. Org. Chem.* **1983**, *48*, 3085); however, its use in this study led to competitive elimination side reactions.

(13) An attempt to effect this transformation with the use of zinc led, instead, to the formation of *gem*-difluorocyclopropanes: Tarrant, P.; Lovelace, A. M.; Lilyquist, M. R.; *J. Am. Chem. Soc.* **1955**, *77*, 2783.

(14) This result only holds true if the reaction medium is anhydrous. Although sodium borohydride reacts with water, small quantities (0.1–0.5 equiv) of water have a rate-enhancing effect on the reduction of the trihalomethyl group. This unusual result has been observed in the reduction of CCl_4 under these conditions.[12a]

(15) For example, compound **3b** underwent facile dehydrobromination upon treatment with DBU to yield the corresponding *gem*-difluoroallyltrimethylsilane. (This compound has been synthesized via a phosphorous ylide: Seyferth, D.; Wursthorn, K. R.; Lim, T. F. O.; Sepelak, D. J. *J. Organometallic Chem.* **1981**, *205*, 301.)

(16) This compound, which may be formed from competitive elimination of HBr from the **3a**, apparently does not undergo further reduction under these conditions.

(17) Burton, D. J.; Kehoe, L. J. *J. Org. Chem.* **1970**, *35*, 1339.

(18) Geyer, A. M.; Haszeldine, R. N.; Leedham, K.; Marklow, R. J. *J. Chem. Soc.* **1957**, 4472.

$C_{10}H_{11}BrF_2$: C, 48.22; H, 4.45. Found: C, 48.57; H, 4.58.

(3-Bromo-3,3-difluoropropyl)trimethylsilane (3b). The procedure for the preparation of **3a** was followed using 3.03 g (0.08 mol) of $NaBH_4$, 6.2 g (0.02 mol) of **2b**, and 40 mL of DMSO. The mixture was slowly warmed, and as the temperature reached 80 °C the reaction became moderately exothermic and cooling was necessary to maintain a temperature of about 85 °C. After about 10 min the exotherm subsided and analysis by GC indicated the conversion was quantitative, and that some overreduction to **5b** had occurred. Workup as described for **3a** yielded 3.85 g of crude (about 93% by GC) material containing some ether and difluoroalkane. Distillation yielded 1.4 g (30%) of pure **3b**, bp 139–140 °C.

In an alternate procedure $NaBH_4$ (0.83 g, 0.022 mol), **2b** (6.2 g, 0.02 mol), and HMPA (10 mL) were used. The reaction mixture became exothermic upon addition of HMPA, and the reaction was complete after stirring for 1 h at 80–85 °C. After the usual workup, removal of the ether on the rotary evaporator yielded 2.84 g (61%) of pure **3b** (>98% by GC): ^1H NMR δ 2.38–2.14 (m, 2 H, H-2), 0.83–0.72 (m, 2 H, H-1), 0.016 (s, 9 H, Me_3Si); ^{13}C NMR δ 125.4 (t, J = 307 Hz, CF_2Br), 40.0 (t, J = 22.6 Hz, C-2), 10.8 (s, C-1), −1.94 (Me_3Si); IR 1249, 1196, 1085, 867 cm^{-1}. Anal. Calcd for $C_6H_{13}SiBrF_2$: C, 31.18; H, 5.67. Found: C, 31.59; H, 5.89.

1-Bromo-1,1-difluorononane (3c). The procedure described above for **3a** was followed. After 3 h at 80–85 °C using 4 equiv of $NaBH_4$, the conversion and selectivity were both about 90% by GC (some overreduction to **5c** occurred). Four fractional distillations of the crude material through a 15-cm vigreux column yielded pure **3c**: bp 80–81 °C (12 Torr); ^1H NMR δ 2.44–2.19 (m, 2 H, H-2), 1.69–1.48 (m, 2 H, H-3), 1.42–1.17 (m, 10 H), 0.94–0.81 (t, 3 H, CH_3); ^{13}C NMR δ 123.8 (t, J = 306 Hz, CF_2Br), 44.6 (t, J = 21.4 Hz, C-2), 24.15 (t, J = 2.9 Hz, C-3), 32.0, 29.4, 29.2, 28.7, 22.8, 14.3 (CH_3); IR 1202, 1132, 1091, 914 cm^{-1}. Anal. Calcd for $C_9H_{17}BrF_2$: C, 44.46; H, 7.05. Found: C, 44.54; H, 7.19.

4-(Bromodifluoromethyl)octane (3d). The procedure described for **3a** was followed (4 equiv of $NaBH_4$, 75 °C, 12 h). The conversion was 90%, and **3d** was formed with **5d** in a 7:2 ratio. The product was isolated by preparative GC on column B: bp 190–192 °C; ^1H NMR δ 2.06–1.82 (m, 1 H, H-2), 1.71–1.51 (m, 2 H, H-3), 1.50–1.16 (m, 8 H, CH_2), 0.96–0.82 (m, 6 H, CH_3); ^{13}C NMR δ 129.1 (t, J = 310 Hz, CF_2Br), 50.9 (t, J = 18 Hz, C-2), 32.7 (t, J = 2.7 Hz), 30.3 (t, J = 2.7 Hz), 29.6, 23.0, 20.7, 14.4, 14.1 (CH_3). Anal. Calcd for $C_9H_{17}BrF_2$: C, 44.46; H, 7.05. Found: C, 44.46; H, 6.90.

(Bromodifluoromethyl)cyclopentane (3e): ^1H NMR δ 2.89–2.57 (m, 1 H, H-1), 1.98–1.45 (m, 8 H, CH_2); ^{13}C NMR δ 127.3 (t, J = 308 Hz, CF_2Br), 52.4 (t, J = 20 Hz, C-1), 28.35 (t, J = 2.5 Hz, C-2, C-5), 26.05 (C-3, C-4). Anal. Calcd for $C_6H_9BrF_2$: C, 36.21; H, 4.56; H, 4.56. Found: C, 36.50; H, 4.66.

(Bromodifluoromethyl)cyclohexane (3f): ^1H NMR δ 2.19–1.51 (m, 6 H), 1.46–1.00 (m, 5 H); ^{13}C NMR δ 127.9 (t, J = 307 Hz, CF_2Br), 50.8 (t, J = 19.5 Hz, C-2), 27.3 (t, J = 2.6 Hz, C-2, C-6), 25.85 (C-3, C-5), 25.3 (C-4). Anal. Calcd for $C_7H_{11}BrF_2$: C, 39.46; H, 5.20. Found: C, 40.19; H, 5.45.

***exo*-2-(Bromodifluoromethyl)bicyclo[2.2.1]heptane (3g):** ^1H NMR δ 2.51 (br s, 1 H, H-1), 2.44–2.22 (m, 2 H, H-2, H-4), 1.63–1.40 (m, 5 H), 1.23–1.08 (m, 3 H); ^{13}C NMR δ 126.2 (t, J = 307 Hz, CF_2Br), 55.7 (t, J = 20.2 Hz, C-2), 39.2, 36.6, 36.2, 34.4, 30.3, 28.1.

***trans*-1-(Difluoromethyl)-2-bromocyclopentane (4e):** ^1H NMR δ 5.85 (td, J_{HF} = 57 Hz, J_{HH} = 3.3 Hz, 1 H, CF_2H), 4.4 (q, J = 6.6, 1 H, CH-Br), 2.83–2.52 (m, 1 H, H1), 2.32–1.56 (m, 6 H, CH_2); ^{13}C NMR δ 116.7 (t, J = 243 Hz, CF_2H), 53.5 (t, J = 20.7 Hz, C-1), 47.7 (dd, J = 7.3 Hz, J' = 3.9 Hz, C-2), 38.2 (C-3), 23.6 (unresolved m, fortuitous overlap of 3-Hz triplet on singlet, C-4, C-5). Anal. Calcd for $C_6H_9BrF_2$: C, 36.21; H, 4.56. Found: C, 36.70; H, 4.52.

1-(Difluoromethyl)-2-bromocyclohexane (4f). This compound was obtained as a mixture of isomers. **Cis:** ^1H NMR δ 5.61 (td, J_{HF} = 56.4 Hz, J_{HH} = 7.0 Hz, 1 H, CF_2H), 4.59 (br s, 1 H, CHBr), 2.41 (br s, 1 H, H1), 2.21–1.13 (m, 8 H, CH_2); ^{13}C NMR δ 119.6 (dd, J = 240 Hz, CF_2H), 52.7 (dd, J = 8.0 Hz, J' = 3.3 Hz, C-Br), 49.5 (t, J = 21.5 Hz, C-1), 34.4 (C-3), 24.5, 20.9 (dd, J = 7.0 Hz, J' = 1.7 Hz, C-6), 20.3. **Trans:** ^1H NMR δ 6.18 (t, J_{HF} = 56.6 Hz, CF_2H), 3.89 (td, J = 11.4 Hz, J' = 4.4 Hz, CH-Br), 2.35 (br s, H-1), 2.21–1.13 (m, 8 H, CH_2); ^{13}C NMR δ 117.7 (dd, J = 241 Hz, CF_2H), 51.2 (dd, J = 8.2 Hz, J' = 1.2 Hz, C-Br), 46.3 (dd, J = 19.3 Hz, C-1), 38.6, 27.3, 24.3, 23.4 (t, J = 4.5 Hz, C-6). Anal. Calcd for $C_7H_{11}BrF_2$: C, 39.46; H, 5.20. Found: C, 39.50; H, 5.26.

***exo*-2-(Difluoromethyl)-*endo*-3-bromobicyclo[2.2.1]heptane (4g):** ^1H NMR δ 5.69 (td, J_{HF} = 56.3 Hz, J_{HH} = 4.5, 1 H, CF_2H), 4.11 (t, 1 H, CHBr), 2.45 (m, 1 H, H-4), 2.29 (m, 1 H, H-1), 2.02–1.85 (m, 2 H, H-2), 1.66–1.45 (m, 3 H), 1.40–1.27 (m, 2 H); ^{13}C NMR δ 117.0 (t, J = 243 Hz, CF_2H), 56.6 (t, J = 20.2 Hz, C-2), 51.0 (t, J = 4.68 Hz C-Br), 44.0, 37.7 (t, J = 3.6 Hz, C-1), 36.0, 29.9, 23.8; IR 1149, 1108, 1067, 1002, 944, 879 cm^{-1}. Anal. Calcd for $C_8H_{11}BrF_2$: C, 42.69; H, 4.93. Found: C, 42.63; H, 4.98.

Synthesis of 1,1-Difluoroalkanes (5a–g). These compounds were prepared by reduction of the corresponding dibromides with 4–8 equiv of $NaBH_4$ in DMSO. A small amount of water had a rate-enhancing effect and was used in some cases. The synthesis of **5c** is representative.

1,1-Difluorononane (5c). A 100-mL three-necked, round-bottomed flask was charged with 3.02 g (0.08 mol) of $NaBH_4$, 6.44 g (0.02 mol) of **2c**, 0.05 g (0.0028 mol) of water, and 35 mL of DMSO. The mixture was warmed to 80 °C, stirred for 18 h, and worked up as described for **3a**. Most of the ether was removed on the rotary evaporator, leaving 3.52 g of crude material. GC analysis showed 90% conversion of total alkyl bromides. The crude was fractionated through a 15-cm Vigreux column yielding 1.86 g (57%): bp 80–82 °C (40 Torr); ^1H NMR δ 5.8 (tt, J_{HF} = 57.1 Hz, J_{HH} = 4.8 Hz, 1 H, CF_2H), 1.94–1.64 (m, 2 H, H-2), 1.48–1.16 (m, 12 H, CH_2), 0.86 (t, J = 6 Hz, 3 H, CH_3); ^{13}C NMR δ 118.0 (t, J = 239 Hz, CF_2H), 34.3 (t, J = 20.7 Hz, C-2), 29.6, 29.34, 29.29, 22.8, 22.3 (t J = 5 Hz, C-3), 14.2 (CH_3); IR 1120, 1055 cm^{-1}. Anal. Calcd for $C_9H_{18}F_2$: C, 65.82; H, 11.05. Found: C, 65.60; H, 11.12.

1,1-Difluoro-4-phenylbutane (5a). This compound was formed as a minor product in combination with **6**. An increase in the amount of hydride or reaction time did not affect the yield of **5a**. The procedure described for **5c** was followed, under anhydrous conditions, using 8 equiv of $NaBH_4$ and *p*-xylene as an internal GC standard. After 18 h at 80 °C the reaction mixture consisted of a 1:3:6 mixture of **3a**, **5a**, and **6**, respectively. An analytical sample of **5a** was isolated by preparative GC on column A: ^1H NMR δ 7.37–7.14 (m, 5 H, ArH), 5.80 (tt, J_{HF} = 56.8 Hz, J_{HH} = 4.1 Hz, 1 H, CF_2H), 2.67 (t, J = 7.1 Hz, 2 H, H-4), 1.99–1.69 (m, 4 H, H-2, H-3); ^{13}C NMR δ 141.8, 129.0, 128.9, 126.6 (ArC), 117.8 (t, J = 239 Hz, CF_2H), 35.4 (C-4), 33.7 (t, J = 21.0 Hz, C-2), 24.0 (t, J = 5.5 Hz, C-3). Anal. Calcd for $C_{10}H_{12}F_2$: C, 70.57; H, 7.11. Found: C, 70.70; H, 7.12.

1,1-Difluoro-4-phenyl-1-butene (6): bp 64–68 °C (14 Torr); ^1H NMR δ 7.51–7.27 (m, 5 H, ArH), 4.41–4.18 (dtd, J_{HF} = 25.5 Hz, J_{HH} = 7.8 Hz, J'_{HF} = 2.8 Hz, 1 H, H-2), 2.88–2.77 (m, 2 H, H-4), 2.52–2.37 (m, 2 H, H-3); ^{13}C NMR δ 157.1 (dd, J = 286 Hz, CF_2), 141.6, 129.1, 126.8, 77.8 (t, J = 21.6 Hz, C-2), 36.1 (t, J = 2.2 Hz, C-3), 24.46, 24.37; IR 1741 (C=CF_2 stretch), 1599, 1309, 1217, 1158, 1093, 739 cm^{-1}. Anal. Calcd for $C_{10}H_{10}F_2$: C, 71.42; H, 5.99. Found: C, 71.24; H, 6.05.

(3,3-Difluoropropyl)trimethylsilane (5b): bp 108–110 °C; ^1H NMR δ 5.71 (tt, J_{HF} = 57.5 Hz, J_{HH} = 4.5 Hz, 1 H, CF_2H), 1.89–1.61 (m, 2 H, H-2), 0.61–0.51 (m, 2 H, H-1), 0.0, (s, 9 H, Me_3Si); ^{13}C NMR δ 118.9 (t, J = 240 Hz, CF_2H), 29.0 (t, J = 21.5 Hz, C-2), 8.37 (t, J = 3.7 Hz, C-1), −1.90 (Me_3Si); IR 1249, 1179, 1126, 1049, 867 cm^1. Anal. Calcd for $C_6H_{14}SiF_2$: C, 47.33; H, 9.27. Found: C, 47.98; H, 9.55.

4-(Difluoromethyl)octane (5d): bp 146–149 °C; ^1H NMR δ 5.69 (td, J_{HF} = 57.0 Hz, J_{HH} = 3.7 Hz, 1 H, CF_2H), 1.85–1.59 (m, 1 H, H-2), 1.56–1.45 (m, 10 H, CH_2), 0.99–0.78 (m, 6 H, CH_3); ^{13}C NMR δ 119.5 (t, J = 241 Hz, CF_2H), 42.0 (t, J = 18.3 Hz, C-2), 30.1 (t, J = 4.5 Hz, C-3′), 29.2, 27.5 (t, J = 4.5, C-3), 23.1, 20.2, 14.5, 12.4 (CH_3); IR 1100, 1027 cm^{-1}. Anal. Calcd for $C_9H_{18}F_2$: C, 65.82; H, 11.05. Found: C, 65.97; H, 11.14.

(Difluoromethyl)cyclopentane (5e). The usual procedure was followed (8 equiv of $NaBH_4$, 80 °C, 23 h). After quenching with ice and hydrochloric acid, the product was extracted with seven 4-mL portions of *p*-cymene. Fractional distillation of the extract, followed by spinning band distillation and preparative GC, yielded an analytical sample: bp 82–85 °C; ^1H NMR δ 5.62 (td, J_{HF} = 58 Hz, J_{HH} = 6 Hz, 1 H, CF_2H), 2.45–2.15 (m, 1 H, H-1),

1.9–1.4 (m, 8 H, CH_2); ^{13}C NMR δ 120 (t, J = 243 Hz, CF_2H), 43 (t, J = 20 Hz), 26.0, 25.9.

(Difluoromethyl)cyclohexane (5f). Dibromide **2f** was treated with 8 equiv of $NaBH_4$ at 70 °C for 13 h. The volatile material was vaccum transferred at 20–30 Torr to a −80 °C cold trap. The trap contents, which consisted of **5f**, dimethyl sulfide, and a few minor components, were distilled, yielding pure **5f**: bp 117–120 °C (lit.[2c] bp 125 °C): ^1H NMR δ 5.50 (td, J_{HF} = 56 Hz, J_{HH} = 4 Hz, 1 H, CF_2H), 1.85–1.6 (m), 1.4–0.95 (m).

***exo*-2-(Difluoromethyl)bicyclo[2.2.1]heptane (5g).** This compound was particularly difficult to prepare, due to the low reactivity of adduct **2g**. Regardless of the solvent (i.e. DMSO, sulfolane, DMPU) this reaction required at least 10 days at 80–85 °C for the conversion to exceed 70% (the choice of solvent had no effect on the product distribution). The following run illustrates the use of DMPU: A 150-mL tube was charged with $NaBH_4$ (6.05 g, 0.16 mol, 8 equiv), **2g** (6.08 g, 0.02 mol), and DMPU (50 mL). The mixture was stirred at 80–85 °C for 12 days. The usual workup yielded 1.66 g of crude containing about 15% unreacted monobromide **4g**. The pure compound had the following physical properties: bp 64–65 °C (50 Torr); ^1H NMR δ 5.48 (td, J_{HF} = 57.6 Hz, J_{HH} = 6.0 Hz, CF_2H), 2.42–2.18 (m, 2 H, H-1, H-4), 1.96–1.70 (m, 1 H, H-2), 1.64–1.06 (m, 8 H, CH_2); ^{13}C NMR δ 119.2 (t, J = 241 Hz, CF_2H), 46.0 (t, J = 19.5 Hz, C-2), 37.3 (dd, J = 6.6 Hz, J' = 2.9 Hz, C-1), 36.32, 36.25, 31.3 (dd, J = 5.3 Hz, J' = 2.5 Hz, C-3), 29.9, 28.6; IR 1179, 1126, 1067, 1014 cm^{-1}. Anal. Calcd for $C_8H_{12}F_2$: C, 65.73; H, 8.27. Found: C, 65.19; H, 8.41.

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Improved Metalation of 2,4,6-Tribromoanisole: Synthesis of 2-Methoxyresorcinol

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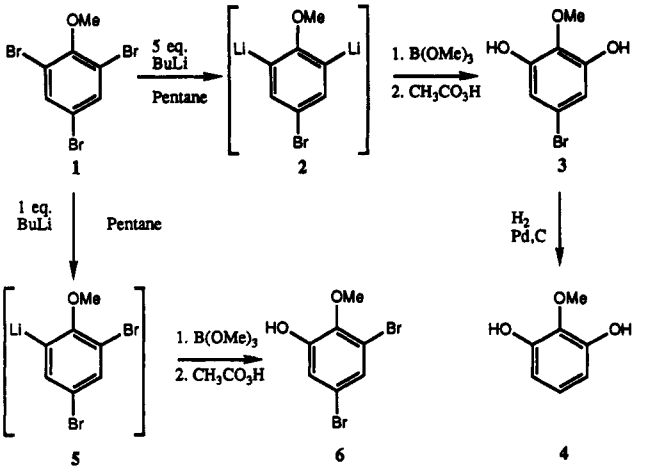
The only reported syntheses of 2-methoxyresorcinol (4) involve methylation of pyrogallol and separation of all possible methylated products, which produces the compound in about 1% yield.[1] We required large quantities of this material and envisioned a process based on bis-ortho metalation of anisole. Direct metalation of anisole requires addition of a chelating agent (e.g. TMEDA) to achieve a reasonable conversion to the anion.[2] For toxicological reasons this approach was not considered feasible. Of the readily available halogenated anisole derivatives, the chloro compounds do not lend themselves to metalation nearly as well as the corresponding bromo analogues; and in addition, in terms of cost and availability, the 2,4,6-tribromo derivative was considered to be the more practical substrate.

The metalation of 2,4,6-tribromoanisole (1) has been reported to occur in pentane at room temperature with *n*-butyllithium. The resultant dianion reacted with carbon dioxide to give 2-methoxy-5-bromo 1,3-dicarboxylic acid in 75% yield.[3] Adaption of this protocol using trimethyl borate[4] in place of carbon dioxide provided only very complex product mixtures. Use of tetrahydrofuran as solvent to solubilize the tribromide at lower temperatures led to no improvement in the complexity of the resultant product mixture. Only after unsuccessfully examining various approaches to effect metalation on *solutions* of the tribromide at low temperature was the metalation attempted on a pentane *suspension* of this compound at −10 to −20 °C.[5] As indicated in Scheme I, this proved successful. Cooling a *room temperature pentane solution* of 1 to −20 °C produces a *suspension*, which, upon addition of *n*-butyllithium, gave an even thicker suspension. Depending on the stoichiometry of the metalation step, the dianion (2) or the monoanion (5) could be quenched with trimethyl borate and the dimethyl borate derivative(s) subsequently oxidized to give 3 or 6 in 91% and 87% yields, respectively. Additionally, 3 was subjected to a standard catalytic hydrogenation to produce 2-methoxyresorcinol 4 quantitatively.

Scheme I



Presumably, during this heterogeneous lithiation procedure, insoluble, unreacted 1 is protected from reactions with the metalated species being generated, thereby reducing side reactions. Reaction of the lithiated intermediates with other electrophiles, especially in a stepwise manner, presents a possible route to highly functionalized anisole derivatives. Moreover, this approach provides ready access to 2-methoxyresorcinol a compound which heretofore was essentially inaccessible.

Experimental Section

5-Bromo-2-methoxybenzene-1,3-diol (3). To a suspension of 1 (10 g, 30 mmol) in 200 mL of dry pentane at −20 °C under Ar was added a solution of *n*-butyllithium in hexanes (93.8 mL of a 1.6 M solution, 150 mmol) over 10 min with vigorous mechanical stirring. This suspension was allowed to warm to −10 °C over 15 min. Upon cooling to −30 °C, neat trimethyl borate (15.6 g, 150 mmol) was added all at once. The solution was warmed to 0 °C over 30 min and then cooled to −10 °C. A solution

(1) Geissman, T. A.; Moje, W. *J. Am. Chem. Soc.* **1951**, *73*, 5765. Spath, E.; Schmidt, H. *Ber.* **1941**, *74*, 193.
(2) Crowther, G. P.; Sundberg, A. M.; Sarpeshkar, A. M. *J. Org. Chem.* **1984**, *49*, 4657.
(3) Gilman, H.; Langham, W.; Moore, F. W. *J. Am. Chem. Soc.* **1940**, *62*, 2327.
(4) For leading references describing the use of this approach to synthesize phenolic compounds, see: Kidwell, R. L.; Murphy, M.; Darling, S. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 918. Alabaster, R. J.; Cottrell, I. F.; Marley, H.; Wright, S. H. B. *Synthesis* **1988**, 950.
(5) In addition to using Gilman's exact conditions for this reaction, other room temperature experiments were performed in which the trimethyl borate stoichiometry was varied from 1:1 to 10:1 with respect to both the lithiated anisole and *n*-BuLi. During these experiments, the reaction components were all soluble and in all cases only complex reaction mixtures were obtained.

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