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Catalytic Epoxidation of Alkenes with Oxone. 2. Fluoroketones

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SUPPORTING INFORMATION

General Experimental

NMR data were collected on a Varian Unity-400 (400 MHz ^1H , 376.3 MHz ^{19}F , 100.6 MHz ^{13}C), or a Varian Unity-500 (500 MHz ^1H , 125.8 MHz ^{13}C) in the University of Illinois School of Chemical Sciences Varian/Oxford Instrument Center for Excellence in NMR laboratory. ^1H NMR spectra were obtained in deuteriochloroform (CDCl_3) with either tetramethylsilane (TMS, $\delta = 0.00$ for ^1H) or chloroform ($\delta = 7.26$ for ^1H) as an internal reference unless otherwise stated. ^{13}C NMR spectra were proton decoupled and in CDCl_3 with either TMS ($\delta = 0.00$ for ^{13}C) or chloroform ($\delta = 77.0$ for ^{13}C) as an internal reference unless otherwise stated. All ^1H and ^{13}C NMR spectra were, if not in deuterated chloroform, obtained in one of the following deuterated solvents: acetone- d_6 with acetone as an internal reference ($\delta = 2.04$ ppm ^1H , 205.7 ppm, 29.8 ppm ^{13}C), acetonitrile- d_3 ($\delta = 1.94$ ppm ^1H , 1.39 ppm ^{13}C), or dimethyl- d_6 sulfoxide (DMSO; $\delta = 2.49$ ppm ^1H , 40.6 ppm ^{13}C). ^{19}F NMR spectra were referenced to CFCl_3 (0 ppm, internal), $\text{C}_6\text{H}_5\text{CF}_3$ (-63.73 ppm, external) or C_6F_6 (-163.0 ppm external) unless otherwise noted. Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), app. (apparent) and exch (D_2O exchangeable); coupling constants, J , are reported in Hertz (Hz); integration is provided; and assignments of individual resonances are supported in most cases by the following NMR experiments: APT/DEPT, COSY, or HETCOR. Data are presented in the form: chemical shift (multiplicity, coupling constants, integration and assignments where relevant). Infrared spectra (IR) were

recorded as thin films (neat), KBr pellets, or in solution with either carbon tetrachloride (CCl₄) or chloroform (CHCl₃) on a Mattson Galaxy 5020 spectrometer. Peaks are reported in units of cm⁻¹ with the following relative intensities: s (strong, 67 - 100 %), m (medium, 34 - 66 %), w (weak, 0 - 33 %) and br (broad). Mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Low-resolution electron impact (EI) mass spectra were obtained on a Finnigan-MAT CH-5 spectrometer with a typical ionization voltage of 70 eV; high-resolution EI spectra were obtained on a Finnigan-MAT 731 spectrometer. Low-resolution fast atom bombardment (FAB) spectra were obtained on a VG ZAB-SE spectrometer in magic bullet (3/1, dithiothreitol/dithioerythritol) or 3-nitrobenzyl alcohol. Data are reported in the form *m/z* (intensity relative to base = 100). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical capillary gas chromatography (GC) was performed using the following gas chromatographs fitted with a flame ionization detector (H₂ carrier gas, 1 mL/min): Hewlett Packard 5890, and Hewlett Packard 5890 Series II. The following columns were used: OV-1 50-m cross-linked methyl silicone gum phase, HP-5 50-m cross-linked 5 % phenyl methyl silicone gum phase, and G-TA (Chiraldex™) 30-m trifluoroacetyl γ -cyclodextrin. The injector temperature was 225 °C, the detector temperature was 300 °C. Temperature programs are reported in the form: initial temperature [time (min)], temperature ramp rate (deg/min), final temperature [time (min)]. Retention times (*t_R*) and integrated ratios were obtained from Hewlett Packard 3393A integrators. Analytical thin-layer chromatography (TLC) was performed on E. Merck (Darmstadt) pre-coated (0.25 mm) silica gel 60 plastic sheets or glass plates with QF-254 indicator unless otherwise indicated. Visualization was accomplished with UV light, iodine, *p*-anisaldehyde solution, phosphomolybdic acid solution, KMnO₄ solution, 2,4-DNP (aqueous solution of HCl instead of the recommended H₃PO₄).

Kugelrohr distillations were performed with a Büchi GKR-50 Kugelrohr Glass Tube Oven; boiling points (bp) refer to air-bath temperatures and are not necessarily an accurate measure

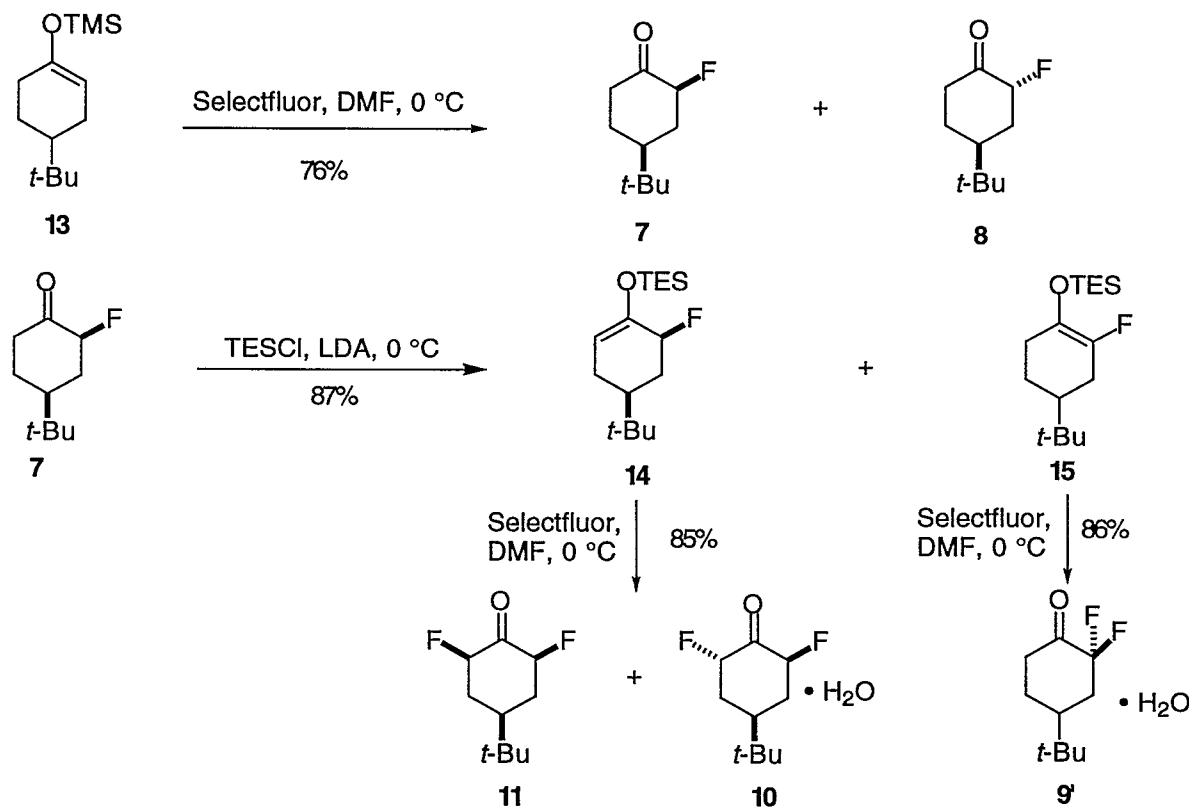
of boiling points. Melting points (mp) were determined in vacuum-sealed capillaries on a Thomas-Hoover capillary melting point apparatus and are corrected.

The solvents used in reactions were reagent grade and distilled from the indicated drying agents under a nitrogen atmosphere: tetrahydrofuran (THF), diethyl ether (Et₂O): sodium metal/benzophenone ketyl; acetonitrile, dichloromethane (CH₂Cl₂), P₂O₅; dimethylformamide (DMF) was used as reagent grade solvent after drying over a bed of 4 Å molecular sieves for a period of not less than 4 days. The solvents used for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane, pentane, dichloromethane (CH₂Cl₂): CaCl₂; ethyl acetate (EtOAc): K₂CO₃; diethyl ether (Et₂O), *tert*-butyl methyl ether (TBME): CaSO₄/FeSO₄. All solvents used for recrystallization were distilled. Brine refers to a saturated aqueous solution of NaCl. Unless otherwise noted, all nonaqueous reactions were performed in oven- and/or flame-dried glassware under an atmosphere of dry nitrogen or argon, except for the Oxone reactions.

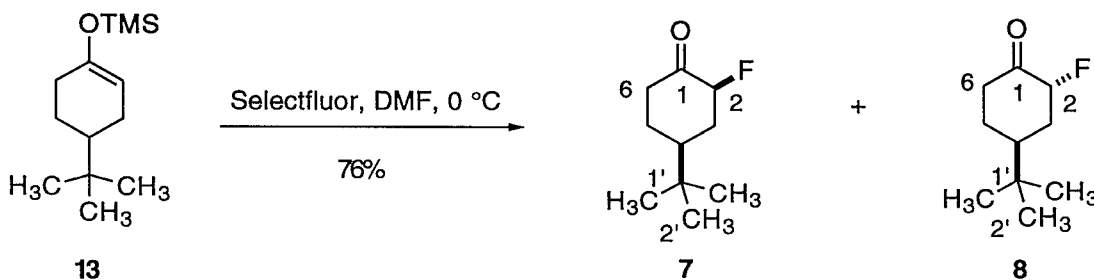
Literature Preparations

The following compounds were prepared by literature methods: 1,1,1-trifluoro-2-octanone (**3b**),^{1a,1b} 1,1,1-trifluoro-2-dodecanone (**4b**),^{1a,1c} (*E*)-6-phenylmethoxy-2-hexene (**5**),² 4-*tert*-butyl-1-trimethylsilyloxycyclohexene(**13**),³ 8-methyl-8-azabicyclo[3.2.1]octan-2-one.⁴

Preparation Scheme of Cyclic Fluoroketones



cis-4-*tert*-Butyl-2-fluorocyclohexanone (7)^{5,6} and *trans*-4-*tert*-Butyl-2-fluorocyclohexanone (8)^{5,6}



A three-necked, round-bottomed flask equipped with a thermometer, N₂ inlet, septum and magnetic stir bar was charged with a solution of enolsilane **13** (22.40 g, 98.90 mmol) in 200 mL DMF at 0 °C. A solution of Selectfluor (52.56 g, 148.39 mmol, 1.4 equiv) in 80 mL of DMF was

added dropwise via syringe. The reaction mixture was stirred at 0 °C for 6 h and then was warmed to rt and allowed to stir for 16 h. The reaction was quenched with 160 mL water and extracted with diethyl ether (4 x 400 mL). The combined organic layers were washed with brine (200 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The resulting oily mixture of products was purified and separated by repeated silica gel chromatography (hexane/*t*-BuOMe, 13/1) to afford 6.783 g (39%) of **7** and 6.405 g (37%) of **8** as colorless oils. The NMR data matched those reported in this literature.^{5,6}

Analytical data for 7

¹H NMR: (400 MHz)
5.03-4.86 (m, 1H, HC(2)), 2.54-2.48 (m, 2H), 2.36-2.27 (m, 1H), 2.11-2.05 (m, 1H), 1.65-1.55 (m, 2H), 1.49-1.38 (m, 1H), 0.94 (s, 9H, 3CH₃)

¹³C NMR: (125 MHz)
205.86 (d, *J* = 13.8, C(1)), 92.44 (d, *J* = 191.5, C(2)), 45.29 (d, *J* = 8.3, C(6)), 39.05, 35.38 (d, *J* = 7.5), 32.41, 27.78, 27.55

¹⁹F NMR: (376.3 MHz)
-189.20 (dd, *J* = 48.8, 6.1)

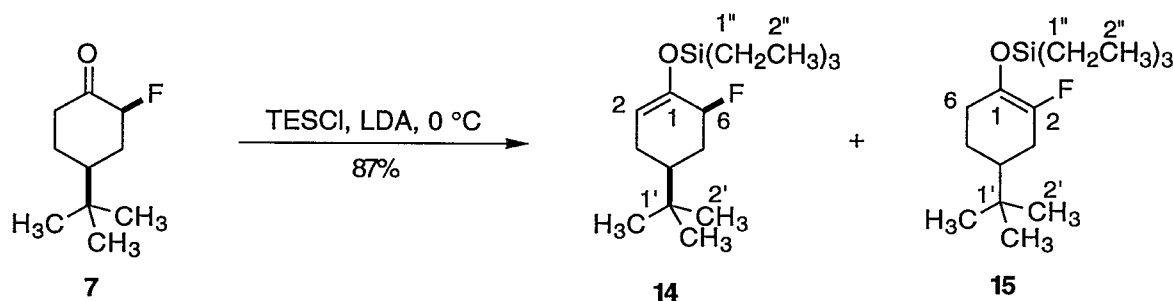
Analytical data for 8

¹H NMR: (400 MHz)
4.63 (ddd, *J* = 50.8, 3.4, 1.8, 1H, HC(2)), 2.80-2.71 (m, 1H), 2.40-2.30 (m, 2H), 2.11-2.06 (m, 1H), 1.87-1.81 (m, 1H), 1.66-1.40 (m, 2H), 0.88 (s, 9H)

¹³C NMR: (125 MHz)
207.92 (d, *J* = 20.2, C(1)), 92.59 (d, *J* = 176.7, C(2)), 40.44, 37.67 (d, *J* = 2.8), 34.36 (d, *J* = 22.1), 32.00, 27.89, 27.37

¹⁹F NMR: (376.3 MHz)
-186.68 (tdd, *J* = 44.3, 12.2, 4.6)

cis-4-*tert*-Butyl-6-fluoro-1-triethylsiloxycyclohexene (**14**) and 4-*tert*-Butyl-2-fluoro-1-triethylsiloxycyclohexene (**15**)



A three-necked, round-bottomed flask equipped with a thermometer, N₂ inlet, septum and a magnetic stir bar was charged with a solution of diisopropylamine (1.5 mL, 11.27 mmol, 1 equiv) in THF (8 mL) at 0 °C. *n*-BuLi (9.4 mL, 1.2 M solution in hexane, 11.27 mmol, 1 equiv) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 15 min and then was added to a solution of fluoroketone **7** (1.94 g, 11.27 mmol) and triethylsilyl chloride (2.08 mL, 12.40 mmol, 1.1 equiv) in THF (25 mL) at 0 °C in another flame-dried, 3-necked round bottom flask. Upon complete addition, the reaction mixture was allowed to warm to room temperature and was stirred for another hour. The solvent was then removed in vacuo and pentane (80 mL) was added to the slurry. The pentane solution was filtered through Celite, dried (Na₂SO₄), and concentrated in vacuo. The resulting oily mixture of products was separated and purified by silica gel column chromatography (pentane) followed by distillation to afford 0.80 g (25%) of **14** and 2.01 g (62%) of **15** as colorless oils.

Analytical data for **14**

bp: 160 °C (0.5 mmHg)

¹H NMR: (400 MHz)

5.02 (dd, *J* = 6.2, 2.2, 1H, HC(2)), 5.00-4.87 (m, 1H, HC(6)), 2.26-2.22 (m, 1H, H_aC(5)), 2.03-1.85 (m, 2H, HC(3)), 1.54-1.33 (m, 2H, H_bC(5), HC(4)),

0.98 (t, $J = 7.8$, 9H, HC(2'')), 0.88 (s, 9H, HC(2')), 0.68 (q, $J = 7.8$, 6H, HC(1''))

^{13}C NMR: (125 MHz)
148.00 (d, $J = 5.2$, C(1)), 108.14 (d, $J = 4.5$, C(2)), 89.06 (d, $J = 169.4$, C(6)),
42.75 (d, $J = 6.8$, C(4)), 31.96 (C(1')), 31.68 (d, $J = 17.5$, C(5)), 26.95 (C(2')),
25.24 (d, $J = 3.1$, C(3)), 6.48 (C(2'')), 4.83 (C(1''))

^{19}F NMR: (376.3 MHz)
-181.40 (ddd, $J = 51.9, 16.7, 5.4$)

IR: (neat)
3025 (m), 2968 (s), 2960 (s), 2947 (s), 2936 (s), 2912 (s), 2890 (s), 2878 (s),
2809 (s), 1667 (s), 1475 (s), 1466 (s), 1460 (s), 1413 (s), 1383 (s), 1367 (s),
1329 (s), 1304 (s), 1274 (s), 1253 (s), 1222(s), 1182 (s), 1166 (s), 1089 (s),
1073 (s), 1029 (s), 1004 (s), 991 (s), 947 (s), 877 (s)

MS: (70 ev)
286 (8), 267 (12), 257 (33), 201 (82), 187 (21), 105 (21), 87 (13), 77 (29), 57
(100)

TLC: R_f 0.17 (pentane)

Analysis: $\text{C}_{16}\text{H}_{31}\text{FOSi}$ (MW 286.51)

Calcd: C, 67.08; H, 10.91; F, 6.63.

Found: C, 67.16; H, 10.69; F, 6.54.

Analytical data for 15

bp: 150 °C (0.2 mmHg)

^1H NMR: (400 MHz)
2.18-2.00 (m, 4H, $\text{H}_a\text{C}(3)$, HC(4), $\text{H}_2\text{C}(6)$), 1.77-1.73 (m, 1H, $\text{H}_a\text{C}(5)$), 1.40-
1.33 (m, 1H, $\text{H}_b\text{C}(3)$), 1.25-1.17 (m, 1H, $\text{H}_b\text{C}(5)$), 0.98 (t, $J = 8.0$, 9H,
 $\text{H}_3\text{C}(2'')$), 0.88 (s, 9H, $\text{H}_3\text{C}(2')$), 0.66 (q, $J = 8.0$, 6H, $\text{H}_2\text{C}(1'')$).

¹³C NMR: (100 MHz)
144.61 (d, $J = 243.4$, C(2)), 130.05 (d, $J = 9.2$, C(1)), 44.64 (d, $J = 7.7$, C(4)),
31.95 (d, $J = 1.6$, C(1')), 29.06 (d, $J = 1.5$, C(6)), 27.02 (C(2')), 26.70 (d, $J =$
19.9, C(3)), 23.90 (d, $J = 1.5$, C(5)), 6.46 (C(2'')), 4.96 (C(1')).

¹⁹F NMR: (376.3 MHz)
-132.64 (d, $J = 6.1$)

IR: (neat)
2965 (s), 2960 (s), 2953 (s), 2948 (s), 2945 (s), 2939 (s), 2935 (s), 2932 (s),
2927 (s), 2920 (s), 2916 (s), 2911 (s), 2906 (s), 2901 (s), 2893 (s), 2888 (s),
2879 (s), 2874 (s), 2852 (s), 2812 (s), 2807 (s), 1731 (s), 1468 (s), 1459 (s),
1413 (m), 1395 (m), 1366 (s), 1353 (s), 1309 (s), 1256 (s), 1237 (s), 1198 (s),
1175 (s), 1112 (s), 1063 (s), 1006 (s), 986 (s), 975 (s), 961 (s), 916 (s), 885 (s),
850 (s), 820 (s).

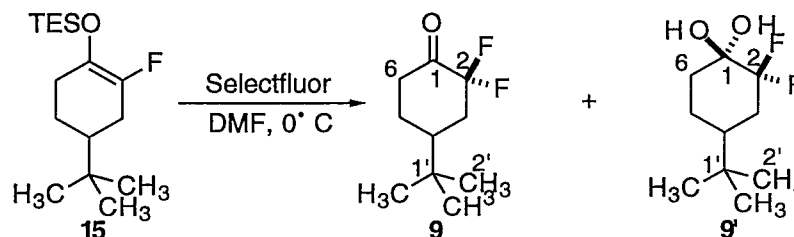
MS: (70 ev)
286 (84), 257 (33), 201 (100), 173 (14), 145 (14), 135 (13), 123 (41), 115 (14),
109 (18), 105 (50), 93 (36), 77 (56), 57 (65).

TLC: R_f 0.23 (pentane)

Analysis: C₁₆H₃₁FOSi (MW 286.51)

Calcd: C, 67.08; H, 10.91; F, 6.63.

Found: C, 67.08; H, 10.94; F, 6.39.

4-tert-Butyl-2,2-difluorocyclohexanone (9)

In a three-necked, round-bottomed flask equipped with a thermometer, N₂ inlet, septum and a magnetic stir bar was placed a solution of enolsilane **15** (0.32 g, 1.12 mmol) in dry DMF (12 mL). The flask was immersed in an ice bath and cooled to 0 °C and then Selectfluor (0.675 g, 1.76 mmoles, 1.5 equiv) was added in one portion. The reaction was monitored by GC analysis of aliquots (OV-1, 75° C (2 min), 20° C/min, 200° C (15 min)). After 3 h the solution was warmed to room temperature and then quenched after 1 h by the addition of 15 mL of water. Extraction of the resulting mixture with diethyl ether (3 x 200 mL) was followed by drying with brine, MgSO₄, filtration and evaporation to afford a crude oil. Purification of the oil by silica gel chromatography (diethyl ether/pentane, 1/1) followed by distillation afforded 150 mg (68%) of the difluoroketone **9** and its hydrate **9'**.⁷

Analytical Data for **9/9'**mp: 74-75 °Cbp: 100 °C (25 mmHg)¹H NMR: (400 MHz, CDCl₃/D₂O)

2.72-2.46 (m, 2H H₂C(3, **9'**) and 4H H₂C(3 and 6, **9**)); 2.18-2.10 (m, 1H H₂C(6, **9'**) and 1H (**9**)); 1.86-1.60 (m, 3H (**9'**)); 1.52-1.38 (m, 1H (**9'**) and 2H (**9**)); 0.94 (s, 9H, H₃C(2', **9'**)); 0.88 (s, 9H, H₃C(2', **9**)).

¹³C NMR: (100.5 MHz, CDCl₃/D₂O)

199.0 (dd, $J = 28.2, 22.9$, C(1, **9**)), 117.3 (d, $J = 243.4$, C(2, **9**)), 114.7 (t, $J = 244.1$, C(2, **9'**)), 113.0 (s, C(1, **9'**)), 44.0 (d, $J = 8.4$, C(6, **9**)), 43.5 (d, $J = 7.63$, C(6, **9'**)), 38.2 (C(5, **9'**)), 37.5 (dd, $J = 24.0, 19.1$, C(9, **9'**)), 35.1 (C(5, **9**)), 32.4 (dd, $J = 2.32, 19.8$, C(3, **9**)), 32.1 (C(4, **9**)), 31.9 (C(4, **9'**)), 27.3 (C(2, **9'**)), 27.2 (C(2', **9**)), 22.6 (C(1', **9'**)).

¹⁹F NMR: (376 MHz, CDCl₃/D₂O)
 -104.4 (ddd, $J = 253.3, 36.6, 15.36$, **9**, axF), -112.3 (ddd, $J = 241.1, 36.6, 9.2$, **9'**, axF), -114.2 (d, $J = 253.3$, **9**, eqF), -120.4 (d, $J = 238$, **9'**, eqF)

IR: (KBr)
 3410 (br, m.); 2965 (s); 1757 (s); 1384 (s); 1370 (s); 1185 (s); 1152 (s); 1104 (s); 1079 (s); 1034 (m).

MS: (EI, 70 eV)
 208 (M⁺, 5), 190 (M⁺-H₂O, 6), 175 (M⁺-CH₃, 7), 155 (4), 134 (6), 133 (5), 127 (4), 113 (4), 98 (5), 83 (16), 73 (23), 57 (100), 55 (30)

MS: (CI)
 208 (M⁺, 1), 192 (12), 191 (M⁺+1-H₂O, 100), 171 (29), 153 (32), 151 (25), 125 (12), 123 (16), 107 (11), 83 (14), 57 (94).

TLC: *R_f* 0.19 (pentane/Et₂O, 1/1)

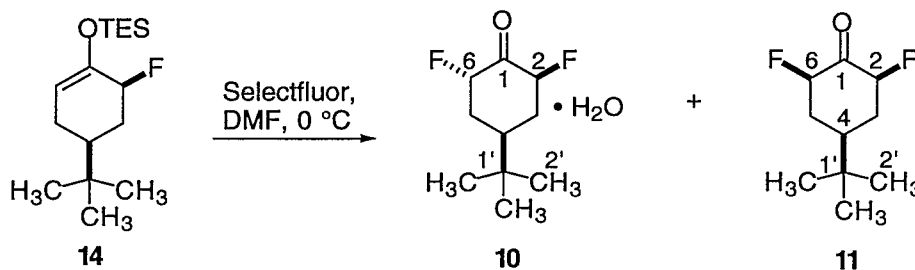
GC: *t_R* 7.81 min (OV-1, 75° C (2 min), 20° C/min, 200° C (15 min))

Analysis: C₁₀H₁₈F₂O₂ (hydrate, **9'**) (MW 208.25)

Calcd: C, 57.68; H, 8.71; F, 18.25

Found: C, 57.77; H, 8.73; F, 18.06

rel-(2*S*,6*S*)-4-*tert*-Butyl-2,6-difluorocyclohexanone Hydrate (10) and rel-(2*S*,4*S*,6*R*)-4-*tert*-Butyl-2,6-difluorocyclohexanone (11)



In a three-necked, round-bottomed flask equipped with a thermometer, N₂ inlet, septum and a magnetic stir bar was placed a solution of enolsilane **14** (0.463 g, 1.62 mmol) in DMF (7 mL) at 0 °C. A solution of Selectfluor (0.687 g, 1.94 mmol, 1.2 equiv) in DMF (8 mL) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 10 h and then was quenched with water (10 mL). The mixture was extracted with diethyl ether (4 x 20 mL) and the combined organic layers were back-washed with brine (200 mL), then were dried (Na₂SO₄), filtered and concentrated in vacuo. The resulting solid mixture of products was separated and purified by silica gel chromatography (hexane/EtOAc, 4/1) and recrystallization (hexane) to afford 0.101 g (33%) of **10** and 0.159 g (52%) of **11** as white solids.

Analytical data for **10**

mp: 102-103 °C (hexane)

¹H NMR: (400 MHz)
 4.80-4.55 (m, 2H, HC(2), HC(6)), 2.99-2.96 (m, 2H, 2OH), 2.10-2.00 (m, 2H, H_aC(3), H_aC(5)), 1.65-1.46 (m, 3H, H_bC(3), H_bC(5), HC(4)), 0.90 (s, 9H, HC(2'))

¹³C NMR: (125 MHz)
 93.20 (d, *J* = 179.3, C(6)), 93.02 (dd, *J* = 174.7, 3.7, C(7)), 38.62 (d, *J* = 9.9, C(4)), 31.69, 29.21 (d, *J* = 16.8), 28.60 (d, *J* = 21.3), 27.21

¹⁹F NMR: (376.3 MHz)
-194.88 (td, $J = 49.5, 10.6$, FC(6)), -204.52 (d, $J = 45.8$, FC(2))

IR: (neat)
3550 (s), 3366-3257 (br), 2967 (s), 1397 (m), 1367 (s), 1193 (m), 1162 (s), 1152 (s), 1138 (s), 1118 (s), 1100 (s), 1076 (s), 1048 (s), 1031 (s), 1006 (s), 866 (m)

MS: (70 ev)
210 (0.7), 190 (2.5), 175 (3), 155 (4), 135 (4), 127 (3), 111 (2), 101 (4), 92 (7), 70 (12), 57 (100), 56 (12)

TLC: R_f 0.10 (pentane/Et₂O, 1/1)

Analysis: C₁₀H₁₈O₂F₂ (MW 208.24)

Calcd:	C, 57.68;	H, 8.71;	F, 18.25.
Found:	C, 57.39;	H, 8.76;	F, 17.96.

Analytical data for 11

mp: 64-65 °C

¹H NMR: (400 MHz)
4.95 (ddd, $J = 47.8, 11.5, 6.2$, 2H, HC(2)), 2.54-2.51 (m, 2H, H_aC(3)), 1.67-1.58 (m, 3H, H_bC(3), HC(4)), 0.97 (s, 9H, HC(2'))

¹³C NMR: (125 MHz)
200.10 (t, $J = 14.7$, C(1)), 90.70 (dd, $J = 195.2, 2.8$, C(2)), 38.88 (t, $J = 9.2$, C(4)), 34.88 (d, $J = 17.5$, C(3)), 32.29 (C(1')), 27.48 (C(2'))

¹⁹F NMR: (376.3 MHz)
-195.16 (d, $J = 48.8$)

IR: (KBr)
2974 (s), 2910 (m), 1748 (s), 1475 (m), 1465 (s), 1456 (w), 1399 (m), 1371 (m), 1268 (m), 1116 (s), 1076 (s), 1056 (m), 1010 (m), 964 (s), 959 (s), 883 (m)

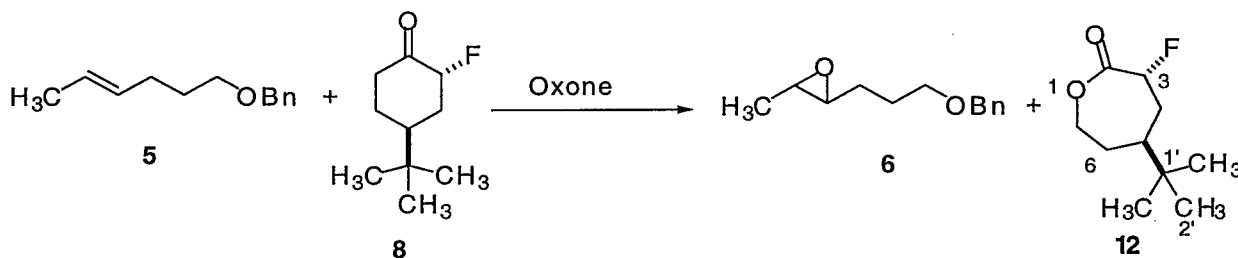
MS: (70 ev)
190 (7), 175 (4), 155 (3), 135 (8), 101 (6), 73 (7), 57 (100), 56 (7), 55 (8)

TLC: 0.25 (pentane/Et₂O, 1/1)

Analysis: C₁₀H₁₆OF₂ (MW 190.23)

Calcd:	C, 63.14;	H, 8.48;	F, 19.97.
Found:	C, 63.04;	H, 8.57;	F, 19.62.

rel-(3*R*,5*S*)-5-*tert*-Butyl-3-fluorooxepan-2-one (12)



Following the general procedure for biphasic OxoneTM epoxidation,² the phosphate buffer (22 mL, pH 7.8), methylene chloride (20 mL), olefin **5** (0.382 g, 2.01 mmol), the promoter **8** (0.350 g, 2.0 mmol, 1 equiv) and OxoneTM (0.53 M, 38 mL, 20 mmol, 10 equiv) (8 h addition) were allowed to stir at 0 °C for 24 h at a pH of 7.8. The reaction was periodically monitored by GC (HP-5, 180° C, isothermal) and the percent conversion of substrate **5** and decomposition of **8** as a function of time were obtained. The product mixture was purified by silica gel column chromatography (hexane/EtOAc, 12/1) to recover 0.200 g (52%) of substrate **5** as a clear oil and afford 0.473 g of a mixture of the epoxide **6** and lactone **12** which was separated by MPLC (hexane/EtOAc, 30/1; flow rate, 8 mL/min) to provide 149 mg (36%) of **6** as a colorless oil and 0.202 g (58%) of **12** as a white solid. Lactone **12** was further purified by sublimation (38 °C, 0.1 Torr).

Analytical data for 12:¹H NMR: (400 MHz)

5.38 (ddd, $J = 49.2, 6.8, 2.9$, 1H, HC(3)), 4.61-4.56 (ddd, $J = 12.6, 8.4, 2.2$, 1H, H_aC(7)), 4.27-4.22 (m, 1H, H_bC(7)), 2.38-2.32 (m, 1H, H_aC(4)), 2.16-2.11 (m, 1H, H_bC(6)), 1.74-1.60 (m, 1H, HC(5)), 1.64-1.54 (m, 1H, H_bC(4)), 1.51-1.44 (m, 1H, H_bC(6)), 0.912 (s, 9H, H₃C(2')).

¹³C NMR: (100 MHz)

170.14 (d, $J = 22.1$, C(2)), 91.34 (d, $J = 186.2$, C(3)), 67.71 (d, $J = 6.2$, C(7)), 42.77 (d, $J = 2.3$, C(5)), 32.52 (C(1')), 29.39 (d, $J = 22.1$, C(4)), 29.38 (C(6)), 27.21 (C(2'))

¹⁹F NMR: (376.3 MHz)

-189.11 (t, $J = 36.6$)

IR: (KBr)

2968 (m), 2959 (w), 1746 (s), 1346 (w), 1279 (w), 1266 (w), 1204 (m), 1191 (w), 1105 (s), 1053 (m), 1036 (m).

MS: (70 ev)

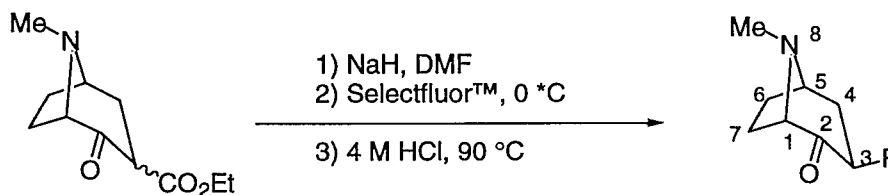
189 (48), 173 (10), 132 (22), 98 (16), 86 (52), 69 (12), 57 (100).

TLC: R_f 0.40 (hexane/EtOAc, 4/1)GC: t_R 6.14 min (HP-5, 180° C isothermal)Analysis: C₁₀H₁₇O₂F (MW 188.24)

Calcd: C, 63.81; H, 9.10, F, 10.09.

Found: C, 63.94, H, 9.11, F, 9.83.

Preparation of 3-Fluoro-8-methyl-8-azabicyclo[3.2.1]octan-2-one



In a 250-mL, 3-necked round-bottom flask, equipped with a septum, thermometer, stir bar, and nitrogen inlet was placed NaH (60% oil dispersion, 323 mg, 8.06 mmol) which was washed with hexane (3 X 2 mL) and dried in vacuo. To this was added DMF (80 mL), and the suspension was cooled to 0 °C in an ice bath. A solution of the β -ketoester⁴ (1.42 g, 6.72 mmol) in DMF (10 mL) was added to the suspension at 0 °C, and the resulting clear pale orange solution was stirred at room temperature for 1 h. Then the reaction mixture was cooled back to 0 °C, and Selectfluor™ (2.64 g, 7.39 mmol) was added in one portion. The pale yellow reaction mixture was stirred at 0 °C for 4 h and then was poured into H₂O (150 mL), and extracted with CH₂Cl₂ (5 X 30 mL). The combined organic extracts were dried (K₂CO₃), filtered, concentrated, and the residue was left in vacuo at rt overnight. The crude yellow oil was purified by silica gel chromatography (CH₂Cl₂/MeOH, 15/1, ϕ = 2 x 40 cm) to give 977 mg of a yellow oil which was further purified by bulb-to-bulb distillation (120 - 130 °C/0.5 torr) to afford 599 mg (39%) of 3-fluoro β -ketoester as a mixture of diastereomers.

The fluoro β -ketoester (524 mg, 2.29 mmol) was dissolved in 4 M HCl (14 mL), and the colorless solution was heated at 90 °C for 5 h. The solution was cooled in an ice bath, and then was neutralized with sat. aq. K₂CO₃ solution to adjust the solution to pH 10. The basic solution was extracted with CH₂Cl₂ (5 x 20 mL), and the combined organic extracts were dried (K₂CO₃), filtered, and concentrated in vacuo. The crude oil was purified by bulb-to-bulb distillation (100 °C/1.5 mmHg) to afford 312 mg (87%) of the fluoroketone as a colorless oil.

Analytical data for 3-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-2-one

bp: 120 °C (1.5 mmHg)

¹H NMR: (500 MHz, CD₃CN)

5.02 (ddd, $J = 48.8, 10.4, 9.2$, 1H, HC(3)), 3.40 (m, 2H, HC(1 and 5)), 2.47 (ddd, $J = 11.2, 8.4, 2.0$, 1H, HC(4)), 2.42 (s, 3H, CH₃-N), 2.35 (m, 1H, HC(4)), 2.21 (m, 2H, HC(6 and 7)), 1.74 (m, 2H, HC(6 and 7)).

¹³C NMR: (100.6 MHz, CD₃CN)

204.22 (d, $J = 11.5$, C(2)), 87.68 (d, $J = 194.0$, C(3)), 69.90 (C(5)), 58.28 (d, $J = 9.2$, C(1)), 39.02 (d, $J = 16.0$, C(4)), 35.84 (CH₃-N), 27.49 (C(6 or 7)), 25.88 (C(7 or 6)).

¹⁹F NMR: (376.3 MHz, CDCl₃)

-196.73 (dd, $J_{F-H} = 47.4, 21.4$, FC(3)).

IR: (neat)

2951 (s), 1736 (s), 1732 (s), 1452 (m), 1082 (m), 913 (s), 733 (s).

MS: (EI)

158 (MH⁺, 6.9), 157 (M⁺, 1.1), 129 (33), 83 (100), 82 (86), 67 (10).

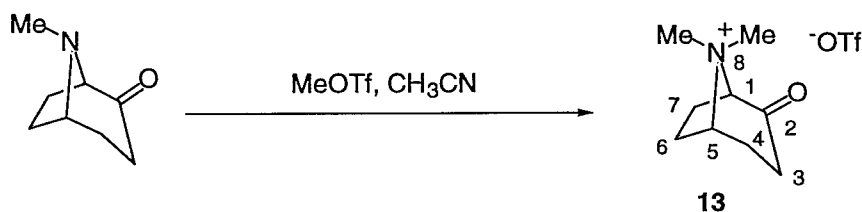
Rotation: $[\alpha]_D^{28} = 223.6^\circ$ ($c = 1.000$, CHCl₃).

Analysis: (C₈H₁₂NO₃F)

Calcd: C, 61.13; H, 7.69; N, 8.91 F, 12.09.

Found: C, 61.01; H, 7.67; N, 8.84 F, 11.85.

**Preparation of 8,8-Dimethyl-8-azonia-bicyclo[3.2.1]octan-2-one
Trifluoromethanesulfonate (13)**



To a solution of (±)-8-methyl-8-azabicyclo[3.2.1]octan-2-one⁴ (123 mg, 0.880 mmol) in CH₃CN (1 mL) was added MeOTf (0.100 mL, 0.880 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 14 h. The solvent was removed in vacuo, and the residual white solid was purified by crystallization from EtOAc/CH₃CN to yield 165 mg (62%) of ammonium triflate (±)-**13** as colorless plates.

Analytical data for (±)-**13**

mp: 267 °C (dec, CH₃CN - EtOAc)

¹H NMR: (500.1 MHz, (CD₃)₂CO)
4.49 (brs, 1H, HC(1)), 4.26 (d, *J* = 7.5, 1H, HC(5)), 3.41 (s, 3H, CH₃-N), 3.38 (s, 3H, CH₃-N), 3.04 (dt, *J* = 17.5, 9.5, 1H, HC(3)), 2.85 (m, 1H, HC(3)), 2.76 (m, 1H, HC(4)), 2.62 (m, 1H, HC(7)), 2.55 (dd, *J* = 18.0, 7.5, 1H, HC(4)), 2.50 (brt, *J* = 12.0, 1H), 2.37 (m, 1H), 2.27 (m, 1H)

¹³C NMR: (100.6 MHz, DMSO-*d*₆)
202.60 (C(2)), 76.71 (C(1)), 68.50 (C(5)), 49.50 (CH₃-N), 15.12 (CH₃-N), 29.72 (C(3)), 24.99 (C(4)), 24.18 (C(6 or 7)), 24.12 (C(7 or 6)).

IR: (KBr)
3117 (m), 3062 (m), 3040 (m), 2986 (m), 1745 (s), 1736 (s), 1494 (m), 1468 (s), 1271 (s), 1265 (s), 1230 (s), 1177 (s), 1171 (s), 1035 (s), 951 (m), 930 (m), 915

(s), 844 (w), 839 (w), 641 (s).

MS: (FAB)

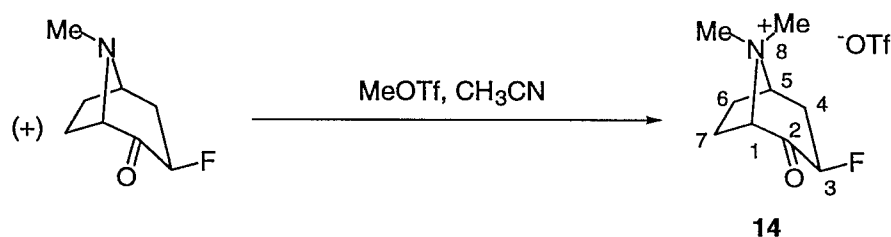
155 (MH⁺, 10), 154 (M⁺, 100)

Analysis: (C₁₀H₁₆NO₄SF₃)

Calcd: C, 39.60; H, 5.32; N, 4.62.

Found: C, 39.56; H, 5.24; N, 4.56.

Preparation of (1*S*, 3*R*, 5*R*)-3-Fluoro-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octan-2-one Trifluoromethanesulfonate (14**)**



Chiral nonracemic (+)-3-fluoro-8-methyl-8-azabicyclo[3.2.1]octan-2-one was prepared by optical resolution of the racemate using (-) 3-bromocamphor-8-sulfonic acid. The absolute configuration was confirmed by X-ray single crystal structure determination of the salt. Decomposition of the salt gave rise to the (+)-ketone.

To a solution of (+)-3-fluoro-2-tropanone (59 mg, 0.375 mmol) in CH₃CN (2 mL) was added MeOTf (0.0420 mL, 0.375 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo, and the residual white solid was purified by crystallization from EtOAc/CH₃CN to afford 88 mg (73%) of the ammonium triflate **14** as colorless needles.

Analytical data for **14**

mp: 200.5 - 202.0 °C (CH₃CN/EtOAc)

- ¹H NMR: (400 MHz, CD₃CN)
5.55 (ddd, $J = 45.2, 10.0, 10.0$, 1H, HC(3)), 4.22 (brs, 1H, HC(1)), 4.16 (m, 1H, HC(5)), 3.11 (s, 3H, CH₃-N), 3.08 (s, 3H, CH₃-N), 2.79 (m, 1H, HC(4)), 2.10 - 2.70 (m, 7H, HC(6, 7, and 4))
- ¹³C NMR: (100.6 MHz, CD₃CN)
86.72 (d, $J_{F-C} = 192$, C(3)), 77.86 (C(1)), 70.78 (C(5)), 51.08 (C(6 or 7)), 47.07 (C(7 or 6)), 33.46 (d, $J_{F-C} = 2.0$, C(4)), 26.25 (CH₃-N), 24.03 (CH₃-N).
- ¹⁹F NMR: (376.3 MHz, CD₃CN)
-78.16 (s, CF₃SO₃), -202.67 (dd, $J_{F-H} = 45.5, 18.1$, FC(3)).
- IR: (KBr)
1760 (s), 1468 (m), 1270 (s), 1263 (s), 1156 (s), 1098 (m), 1030 (s), 941 (s), 931 (w), 639 (s).
- MS: (FAB)
173 (MH⁺, 11), 172 (M⁺, 40), 119 (60).
- Rotation: $[\alpha]_D^{26} = -73.8^\circ$ (c = 1.000, CH₃CN).
- Analysis: (C₁₀H₁₅NO₄SF₄)
Calcd: C, 37.38; H, 4.71; N, 4.36.
Found: C, 37.23; H, 4.71; N, 4.29.

Monophasic Epoxidation General Procedure

A 50-mL, round-bottom flask equipped with stir bar was charged with a solution of EDTA (10 mg), olefin **5** (1.0 mmol) and promoter (0.1 mmol, 0.1 equiv) in CH₃CN (15 mL) and H₂O (10 mL). The mixture was cooled to 0 °C in an ice bath. Eight portions of Oxone (0.307 g, 0.5 mmol, 0.5 equiv each) were added with NaHCO₃ (0.109 g, 1.3 mmol, 1.3 equiv (2.6 equiv per Oxone) each) at the beginning of each hour over 8 hours. The progress of the reaction was monitored at ca. 2-4 h intervals by removing approximately 0.1 mL of the reaction mixture and analyzing the aliquots by GC (HP-5, 180 °C, isothermal). After the reaction was complete, or after 24 h (whichever came first), the reaction mixture was diluted with H₂O (40 mL) and extracted with CH₂Cl₂ (4 x 60 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography and/or distillation.

NMR Studies of Hemiketalization General Procedure

An NMR tube was charged with a solution of ketone (0.1 mmol) in neat CD₃OD (1 mL) at rt. The equilibration was monitored by obtaining ¹H NMR and ¹⁹F NMR spectra at ca. 1-4 h intervals.

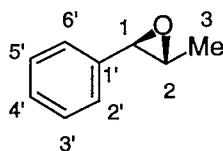
Asymmetric epoxidation: General Procedure.

Epoxidation of β-methyl styrene.

In a 25-mL, round-bottom flask equipped with stir bar were added β-methyl styrene (59.1 mg, 0.50 mmol), **14** (16.1 mg, 0.050 mmol), CH₃CN (7.5 mL), and 0.09% Na₂EDTA aqueous solution (5.0 mL). The solution was cooled to 0 °C with an ice bath. Five portions of Oxone (154 mg, 0.25 mmol) and NaHCO₃ (51 mg, 0.60 mmol) were each added hour over 4 hours. The reaction was monitored with GC (HP-5, 130 °C). After the reaction was complete (5 h), the mixture was diluted with H₂O (100 mL) and extracted with CH₂Cl₂ (6 x 10 mL). The combined organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified

by bulb-to-bulb distillation (105 °C), 2.5 torr) to give 56.8 mg of colorless liquid in 85% yield (35%ee). The enantiomeric excess was determined with chiral GC (GTA, column temp 80 °C, 15 psi). The first enantiomer appeared at 7.40 min (32.6 %) whereas second one appeared at 8.84 min (67.4%). Absolute configuration of the product was determined as (*1R*, *2R*) based on the comparison of the rotation with its previously reported value.⁸

Analytical data for β -methyl styrene oxide



¹H NMR: (400 MHz, CDCl₃)

7.36-7.24 (m, 5H, Ar-H), 3.58 (d, *J* = 2.0, 1H, HC(1)), 3.04 (qd, *J* = 5.1, 2.2, 1H, HC(2)), 1.46 (d, *J* = 5.2, 3H, HC(3)).

¹³C NMR: (100.6 MHz, CDCl₃)

137.72 (C(1')), 128.41 (C(3' and 5')), 128.01 (C(4')), 125.52 (C(2' and 6')), 59.51 (C(1)), 59.04 (C(2)), 17.91 (C(3)).

Rotation: [α]_D²² = 18.6 ° (c = 0.89, CHCl₃)

References

- (1) (a) Ramachandran, P. V.; Teodorovic', A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry*. **1994**, 1075. (b) Dishart, K. T.; Levine, R. *J. Am. Chem. Soc.* **1955**, 78, 2268. (c) Friour, G.; Cahiez, G.; Normant, J. F. *Syn. Commun.* **1984**, 37.
- (2) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; Depue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, 60, 1391.
- (3) (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, 2324.
- (4) Davis, W.A.M.; Pinder, A.R.; Morris, I.G. *Tetrahedron* **1962**, 18, 405.
- (5) Lal, G. S. *J. Org. Chem.* **1993**, 58, 2791.
- (6) (a) Basso, E. A.; Kaiser, C.; Rittner, R.; Lambert, J. B. *J. Org. Chem.* **1993**, 58, 7865. (b) Cantacuzene, J.; Jantzen, R. *Tetrahedron*, **1970**, 26, 2429. (c) Moreau, P.; Casadevall, A.; Casadevall, E. *Bull. Soc. Chim. Fr.* **1969**, 2013.
- (7) It should be noted that once dissolved in neat CDCl₃ the equilibrium between the ketone and the hydrate was re-established. Thus the solution characterizations (i.e. NMR spectra) contain both the ketone and hydrate. The solid state characterizations (specifically elemental analysis) give results consistent with one water of hydration.
- (8) Kolb, H.C.; Sharpless, K.B. *Tetrahedron* **1992**, 48, 10515.