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for the Preparation
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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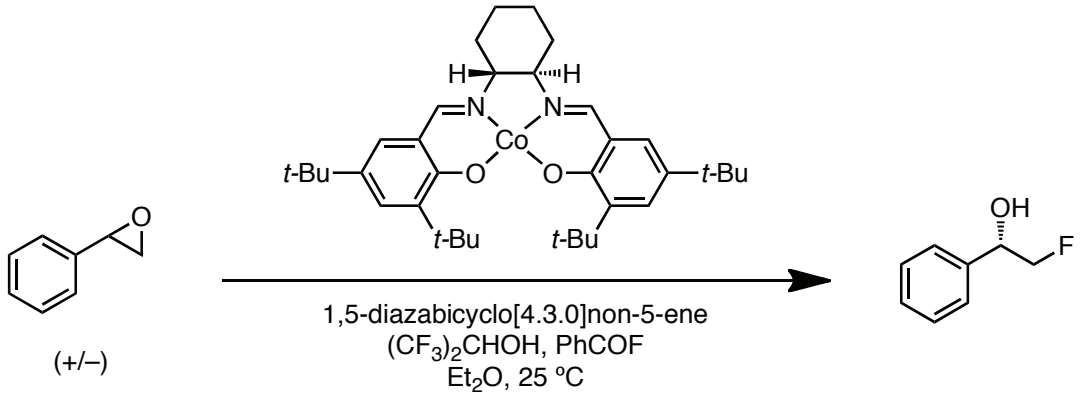
Fluoride Ring-Opening Kinetic Resolution of Terminal Epoxides: Preparation of (*S*)-2-Fluoro-1-Phenylethanol



Submitted by Travis W. Shaw, Julia A. Kalow, and Abigail G. Doyle.[1]
Checked by Florian Vogt and Brian M. Stoltz.

1. Procedure

Caution! This procedure should be carried out in an efficient fume hood. Appropriate precautions should be taken to avoid inhalation or direct contact with styrene oxide, which is a known carcinogen, and benzoyl fluoride, which is toxic and a potent lachrymator.

(S)-2-Fluoro-1-phenylethanol. A 500-mL, single-necked, round-bottomed flask equipped with a magnetic stir bar (24 x 8 mm), (Note 1) is charged with (*R,R*)-(−)-*N,N*′-bis(3,5-di-*tert*butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (1.51 g, 2.5 mmol, 0.025 equiv (Note 2). 1,5-Diazabicyclo[4.3.0]non-5-ene (247 μL, 2 mmol, 0.02 equiv(Note 3) and 1,1,1,3,3,3-hexafluoroisopropanol (8.66 mL, 82.5 mmol, 0.825 equiv) are added to the flask via syringe. The mixture is diluted with diethyl ether (250 mL (Note 4) to afford a dark brown solution and stirring is initiated at 500 rpm. Styrene oxide (11.4 mL, 100 mmol, 1.0 equiv (Note 5) and benzoyl fluoride (5.99 mL, 55 mmol, 0.55 equiv) are both added via syringe. The reaction is allowed to stir open to air for 15 min (Note 6) at room temperature (Note 7). The flask is then capped with a polyethylene cap and secured with Parafilm wrap (Note 8). The reaction is stirred at 500 rpm for 13–14 h at room temperature (Note 9), and then quenched by the addition of methanolic ammonia (7 N, 150 mL) via syringe (Note 10). The solution is

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allowed to stir for 2–3 h or until the disappearance of 1,1,1,3,3,3-hexafluoropropan-2-yl benzoate, as monitored by TLC (Notes 11 and 12). The reaction is then transferred to a 1-L separatory funnel (Note 13) and washed with aqueous 1M NaOH (3 x 200 mL). The combined aqueous portions are then extracted with diethyl ether (3 x 100 mL). The combined organic portions are dried over 10 g of anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporator (25 °C, 100 mmHg, then 60 mmHg) to afford a dark brown oil. The crude product is charged onto a column (75 mm x 300 mm) packed with 200 g SiO_2 (Note 14) as a slurry with hexanes. The loaded column is topped with a 1 cm layer of sand and 75 mL fractions are collected, eluting with 500 mL hexanes, 625 mL of 5% diethyl ether-hexanes, 625 mL of 10% diethyl ether-hexanes, 375 mL of 15% diethyl ether-hexanes, and then 1625 mL of 20% diethyl ether-hexanes. TLC is used to monitor the course of the column (Note 15). Fractions 39–56 are concentrated by rotary evaporation under vacuum (25 °C, 100 mmHg, then 60 mmHg) to provide (*S*)-2-fluoro-1-phenylethanol (5.8–5.9 g, 41–42% yield) as a brown oil (Note 16) in 98–98% enantiomeric excess (Note 17).

2. Notes

1. No special precautions were taken to exclude air or moisture from the reaction.

2. The (salen)Co(II) precatalyst was purchased from Strem Chemicals, Inc. and stored in a dessicator. 1,5-Diazabicyclo[4.3.0]non-5-ene (98%) (DBN), styrene oxide (97%) and methanolic ammonia (7 N) were purchased from Aldrich Chemical Company, Inc. Benzoyl fluoride (98%) was purchased from Alfa Aesar. 1,1,1,3,3,3-Hexafluoro-2-propanol (>99%) (HFIP) was purchased from TCI America. All chemicals, except for DBN (see Note 3) and styrene oxide (see Note 5), were used as received. All chemicals were stored at room temperature on the benchtop except for the methanolic ammonia, which was stored in a refrigerator at 0 °C. However, we have found that open bottles of benzoyl fluoride slowly hydrolyze under air, generating benzoic acid (7.4 wt% over 4 months), the presence of which leads to depressed rates in the fluorination reactions.

3. DBN was distilled under reduced pressure (12 mmHg, bp = 101-102 ºC) from calcium hydride into a Schlenk flask containing 3Å molecular sieves and stored under a nitrogen atmosphere on the benchtop. Use of DBN that had been aged under air led to slower rates of reaction (see Note 9).

Molecular sieves 3Å 8-12 mesh were purchased from Acros Organics and were flame dried under reduced pressure (0.1 mmHg) and the flask was backfilled with argon (three cycles) prior to use.

4. Diethyl ether (99.9%) was obtained from Fisher Scientific and purified by a solvent delivery system, with passage through a packed dry neutral alumina column.[2]

5. Commercial styrene oxide is contaminated with approximately 1% carbonyl-containing impurities that lead to depressed rates in the kinetic resolutions. On a 0.3 mmol scale, after 5 h, the reaction reaches 50% conversion with pure styrene oxide and only 35% conversion using unpurified material. Therefore, styrene oxide is purified prior to use as follows: A 1-L, 1-necked, round-bottomed flask is equipped with a magnetic stir bar (50 x 8.5 mm) and charged with styrene oxide (16.0 mL, 140 mmol). HPLC-grade methanol (700 mL, 99.8%, EMD Chemicals Inc.) is added and the flask is held in an ice-water bath with stirring (600 rpm) for the remaining duration of the procedure. After the solution has cooled for 45 min, $NaBH_4$ (529.6 mg, 14 mmol, 98%, J.T. Baker Chemical Co.) is added in a single portion. The reaction is allowed to stir for 1 h or until disappearance of acetophenone by TLC (see Note 11). The R_f of the acetophenone is 0.48 (1:1 hexanes:diethyl ether) visualizing with a UV light source (254 nm). The methanol is then removed under reduced pressure on the rotary evaporator (25 °C, 100 mmHg) and the remaining material is purified by column chromatography using 130 g silica gel (see Note 14) on a 70 mm x 350 mm glass column, eluting with 9:1 hexanes:diethyl ether (250 mL) and then 4:1 hexanes:diethyl ether (750 mL). The eluent containing the product is concentrated under reduced pressure (25 °C, 100 mmHg) to yield pure styrene oxide (12.3 g, 102 mmol, 73%).

In addition to the purification described above, the checkers alternatively purified styrene oxide as follows: A 500-mL, 1-necked, round-bottomed flask is equipped with a magnetic stir bar (24 x 8 mm) and charged with styrene oxide (28.6 mL, 250 mmol, 1.0 equiv) and diethyl ether (250 mL) (Note 4). The flask is sealed with a rubber septum, connected to a nitrogen/vacuum manifold and brought to 0 °C in an ice-water bath with stirring (600 rpm) for the remaining duration of the procedure. After the solution has been cooled for 15 min, $LiBH_4$ (10 mL, 10 mmol, 0.025 equiv, 1 M in THF, Aldrich Chemical Company, Inc.) is added with a syringe over a period of 10 min. The water-ice bath is removed after the addition is completed and the reaction is allowed to stir for 1 h at ambient temperature.

Ethanol (1 mL) is added and the reaction mixture further allowed to stir until the evolution of hydrogen gas stops. Sodium sulfate (2 g) is added and the solids are then removed by filtration through a short column (2 cm) of Celite® (washed with 50 mL of diethyl ether) and the remaining solution is concentrated by rotary evaporation under reduced pressure (25 °C, 100 mmHg). The remaining oil is transferred into a 50-mL round-bottomed flask and short path distillation (a forerun of about 2 mL is collected) yields pure styrene oxide as a clear, colorless oil (22.7 g, 76%).

6. The color of the solution changes to a dark brown upon addition of the liquid reagents, indicative of aerobic oxidation of the Co(II) precatalyst (red) to the active Co(III) species. Rapid stirring of the reaction open to air facilitates this oxidation.

7. The ambient temperature was recorded as 25 °C by the submitters. The checkers recorded it as 23 °C.

8. A polyethylene cap is preferred to a rubber septum, as polyethylene does not absorb solvent.

9. Reactions with opened bottles of DBN that had been stored under air were observed to take up to 20 h to reach completion. However, the selectivity of the fluoride ring-opening reactions remained the same in all cases. Thus, to obtain optimal results, the course of the reaction should be monitored and the reaction quenched at the specified end-point: the reaction was found to be complete when the enantiomeric excess of the styrene oxide was approximately 90% by chiral GC analysis on an Agilent 6850 using a Supelco BetaDex 120 column (30.0 m x 0.25 mm), and a flame ionization detector. The assay conditions are 76 °C for 35 min, a gradient of 15 °C/min until 150 °C is reached, followed by a 2 min hold at 150 °C. The retention times for the two enantiomers of styrene oxide are t_R(major) = 28.3 min, t_R(minor) = 31.0 min). The submitters reported using an Agilent 7890 with a J&W Scientific Cyclodex–β column (30.0 m x 0.25 mm), and a flame ionization detector. The assay conditions then are 100 °C for 15 min, a gradient of 15 °C/min until 150 °C is reached, followed by a 4 min hold at 150 °C. The retention times for the two enantiomers of styrene oxide are t_R(major) = 13.4 min, t_R(minor) = 13.9 min. GC samples were obtained by passing a small aliquot (~0.1 mL) of the reaction through a Pasteur pipette containing a cotton plug and 350 mg silica gel and eluting with diethyl ether.

10. Ammonia converts the 1,1,1,3,3,3-hexafluoropropan–2–yl benzoate, derived from the solvolysis of benzoyl fluoride by HFIP, to benzamide, which may be removed by alkaline aqueous workup. Ammonia also

converts the (salen)Co catalyst to a species that does not elute on silica gel. This procedure simplifies purification of the product by column chromatography. The rate at which the methanolic ammonia is added does not affect yield or selectivity.

11. All TLC measurements were performed using plates pre-coated with silica Gel 60 F_{254} purchased from EMD Chemicals Inc.

12. 1,1,1,3,3,3-Hexafluoropropan–2–yl benzoate has an R_f of 0.76 (4:1 hexanes:diethyl ether) and can be visualized with a UV light source (254 nm)

13. The reaction flask is rinsed with three 20 mL portions of diethyl ether.

14. SiliCycle SiliaFlash F60 (40–53 μm, 60 Å) silica gel was used.

15. The R_f value of the title compound is 0.46 (1:1 hexanes:diethyl ether) and the starting material has an R_f of 0.55 (1:1 hexanes:diethyl ether). Both compounds can be visualized with a UV light source (254 nm).

16. The brown oil was found to be clean judged by ^{1}H NMR spectroscopy (purity >95%). A colorless oil is obtained by short path distillation of the title compound at 110 °C under 16 mmHg of pressure with 91.4% (5.3 g from 5.8 g) of the compound recovered. This material was submitted to elemental analysis (Note 17).

17. Enantiomeric excess was determined by chiral GC analysis on a Agilent 6850 using a Supelco Beta DEX^{TM} 120 column (30.0 m x 0.25 mm), and a flame ionization detector. The assay conditions are 102 °C for 40 min, a gradient of 80 °C/min until 180 °C is reached, followed by a 1-minute hold at 180 °C. The retention times for the two enantiomers of the title compound are t_R(major) = 32.4 min, t_R(minor) = 35.6 min. (*S*)-2-Fluoro-1-phenylethanol has the following spectroscopic data: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.44 (br s, 1 H), 4.48 (dddd, *J* = 3.2, 5.8, 9.6, 48.5 Hz, 2 H), 5.03 (ddd, *J* = 3.2, 8.3, 13.9 Hz, 1 H), 7.32–7.41 (m, 5 H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 72.9 (d, *J* = 19.7 Hz), 87.1 (d, *J* = 174.4 Hz), 126.3 (s), 128.4 (s), 128.6 (s), 138.1 (d, *J* = 8.2 Hz); FTIR (neat, cm^{-1}) 3391 (br), 3064 (m), 3033 (m), 2979 (m), 2950 (m), 2891 (m), 1494 (s), 1455 (s), 1311 (m), 1199 (s), 1098 (s), 1072 (s), 1010 (s), 916 (m), 897 (s), 835 (m), 759 (s), 701 (s); $[\alpha]^{20}_D$ = +55.6 ($CHCl_3$, c = 1.01); HRMS (*m/z*) (GC-EI$^+$) calc. for C_8H_9FO (M^+ 140.0637, found 140.0639; TLC (Hex/Et_2O = 1:1) R*f* = 0.46; Anal calcd for C_8H_9FO: C 68.56, H 6.47, found C 68.60, H 6.49.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academies Press; Washington, DC, 2011.

3. Discussion

The selective incorporation of fluorine atoms into organic molecules profoundly affects their physical properties and is a common strategy for the optimization of pharmaceuticals, agrochemicals, materials, and catalysts. Accordingly, approximately 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom.[3] While catalytic asymmetric methods for C–F bond formation using electrophilic "F^+" equivalents have been identified, complementary strategies using abundant, inexpensive nucleophilic fluoride sources are scarce.[4] This procedure describes an application of the first highly enantioselective catalytic method for nucleophilic fluorination to the kinetic resolution of racemic styrene oxide, providing (*S*)-2-fluoro-1-phenylethanol in >98% ee.[5] Previous methods to access such fluorohydrins from the enantiopure epoxide proceed with variable regioselectivity and require elevated temperatures, prolonged reaction times, and rigorous exclusion of water.[6]

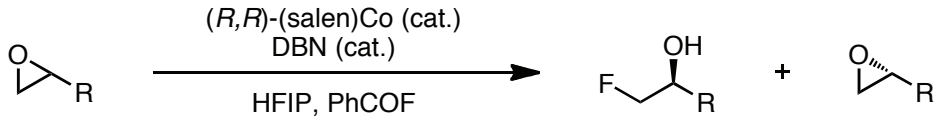
The protocol is operationally simple, and may be performed in standard glassware without the exclusion of air or moisture. The chiral (salen)Co precatalyst, amine cocatalyst, and fluoride source are commercially available. Notably, unlike many metal fluorides and HF-containing reagents, benzoyl fluoride is a bench-stable, non-hydroscopic liquid that can be handled using standard techniques. The combination of benzoyl fluoride and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) serves as a latent source of HF, allowing mild conditions and efficient catalysis.

Under these conditions, aliphatic and aromatic epoxides undergo kinetic resolution by fluoride ring-opening exclusively at the terminal position (Table 1).[7] A silyl glycidyl ether is tolerated, highlighting the chemoselectivity of the nucleophilic fluorine species generated in the co-catalytic reaction (Table 1, entry 3). In the above procedure, purification of the styrene oxide prior to the kinetic resolution allows the catalyst loadings to be lowered to 2.5 and 2.0 mol%, and the stoichiometries of benzoyl

fluoride and HFIP to be reduced. The kinetic resolution offers complementary scope to well-developed strategies for the organocatalytic electrophilic fluorination of aldehydes, which can provide the alternative regioisomer in high enantiomeric excess ((*R*)-2-fluoro-2-phenyl-1-ethanol, 54% yield, 99% ee).[8]

Using the commercially available chiral isothiourea (–)-tetramisole in place of DBN, meso epoxides undergo efficient desymmetrization, yielding trans fluorohydrins in 55–88% yield and 58–95% ee (Table 2). Intriguingly, a significant mismatched effect on rate and enantioselectivity is observed when the opposite enantiomer of (salen)Co is used with (–)-tetramisole. Based on this and other preliminary mechanistic evidence, the reactivity and selectivity are ascribed to a cooperative effect between the chiral Lewis acid and amine co-catalysts.

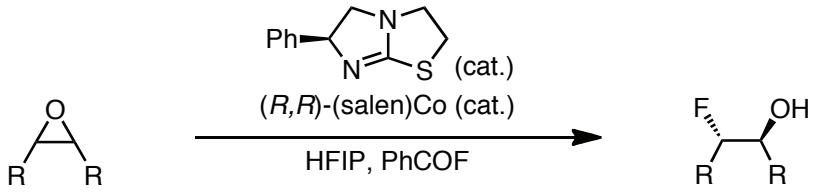
Table 1. Kinetic resolution of terminal epoxides by fluoride opening.[7]

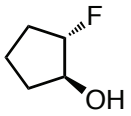
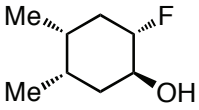
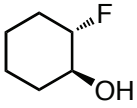
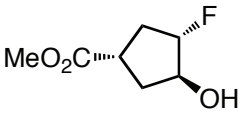
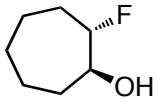
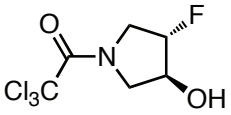
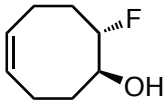
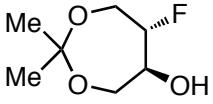


entry	R	Co (mol %)	yield (%)	ee (%)	k_{rel}
1	*n*-Bu	2	36	99	>300
2[a]	Ph	2.5	42	98.2	>200
3	$TBSOCH_2$	5	44	88	32

[a] This work.

Table 2. Desymmetrization of meso epoxides by fluoride opening.[7]



product	yield (%)	ee (%)	product	yield (%)	ee (%)
	77	85		75	90
	65	93		88	86
	82	90		84	80
	87	95		55	58

1. Department of Chemistry, Frick Laboratory, Princeton University, Princeton, NJ 08544; agdoyle@princeton.edu; Financial support was provided by Princeton University and the donors of the American Chemical Society Petroleum Research Fund.

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Appendix
Chemical Abstract Nomenclature; (Registry Number)

(*R*,*R*)-(–)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II): Cobalt, [[2,2'-[(1*R*,2*R*)-1,2-cyclohexanediylbis[(nitrilo-κ*N*)methylidyne]]bis[4,6-bis(1,1 dimethylethyl)phenolato-κ*O*]](2-)]-, (SP-4-2)-; (176763-62-5)

Styrene oxide: 2-Phenyloxirane; (96-09-3)

1,5-Diazabicyclo[4.3.0]non-5-ene: Pyrrolo[1,2-a]pyrimidine, 2,3,4,6,7,8-hexahydro-; (3001-72-7)

Benzoyl fluoride: Benzoyl fluoride; (455-32-3)

1,1,1,3,3,3-Hexafluoro-2-propanol: 2-Propanol, 1,1,1,3,3,3-hexafluoro-; (920-66-1)

Sodium borohydride: Borate(1-), tetrahydro-, sodium (1:1); (16971-29-2)

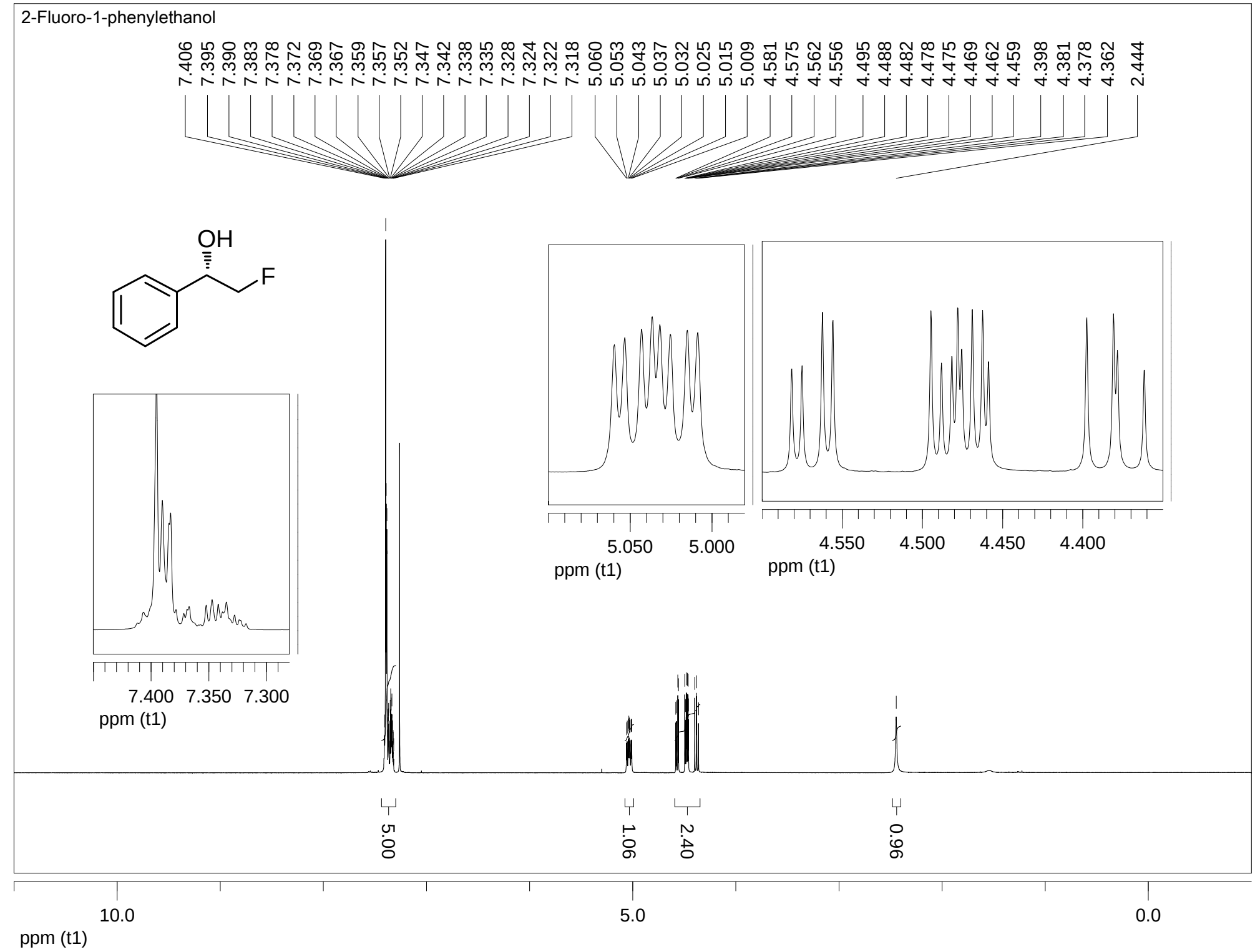
Abigail Doyle received her A.B. and A.M. summa cum laude in Chemistry and Chemical Biology from Harvard University in 2002. From 2003-2008, she was an NDESG and NSF graduate fellow working with Professor Eric Jacobsen at Harvard University. Her graduate research included the development of transition metal-catalyzed enantioselective alkylation reactions of enolates with alkyl halides. Abby began as an Assistant Professor in the Department of Chemistry at Princeton University in July 2008. Her research group is working in the area of catalysis and asymmetric synthesis. One area of interest is the use of transition metal catalysts to prepare chiral building blocks that contain stereogenic C–F bonds using nucleophilic fluorine sources.

Travis Shaw was born in 1987 in Corpus Christi, TX. He graduated from The University of Texas at Austin in 2010 with a B.S. in biochemistry. While at UT Austin he worked on the total synthesis of a sesquiterpene-neolignan natural product under the advisory of Professor Dionicio Siegel. Travis also spent a summer performing synthetic studies in alkaloid total synthesis in the lab of Professor Karl Gademann at the École polytechnique fédérale de Lausanne in Lausanne, Switzerland. He joined the Doyle group in the summer of 2010 and his research is currently focused on the asymmetric hydrohalogenation of olefins.

Julia Kalow was born in Newton, MA (US). She graduated from Columbia University in 2008 (B.A., Chemistry and Creative Writing), where she did undergraduate research in the laboratory of Professor James Leighton. She is currently pursuing her Ph.D. at Princeton University under the supervision of Professor Abigail Doyle, where her research focuses on the development of asymmetric catalytic methods for nucleophilic fluorination. Julia is a National Science Foundation Predoctoral Fellow and Bristol-Myers Squibb Endowed Graduate Fellow in Synthetic Organic Chemistry.

Forian Vogt was born in Feuchtwangen (Germany) in 1981 and studied chemistry at the Technical University Munich (Germany). He obtained his M.Sc. degree under the supervision of Prof. Thorsten Bach (Munich) and Prof. Martin Banwell (Australian National University) in 2006. He then joined the lab of Prof. Thorsten Bach as a Ph.D. student in June 2006 focusing on the synthesis of hydrogen bond mediated ligands and catalysts and their application in stereoselective synthesis. After receiving his Ph.D. degree in March 2010, he moved to California for postdoctoral studies with Prof. Brian Stoltz where his research interests include the development of catalytic, asymmetric methods and their utility in natural product total syntheses

2-Fluoro-1-phenylethanol



2-Fluoro-1-phenylethanol