Organic Syntheses

Site-Selective C-H Fluorination of Pyridines and Diazines with AgF_2

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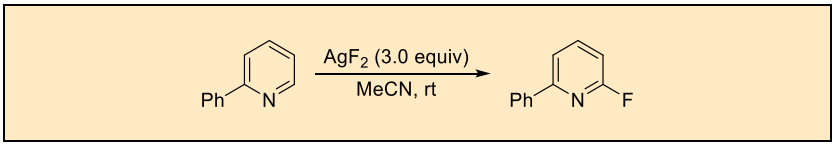

Procedure

A. *2-Fluoro-6-phenylpyridine (**1**).* To an oven-dried 1-L round-bottomed flask equipped with a 4.0 cm Teflon-coated magnetic stirbar is charged anhydrous MeCN (560 mL) (Note 1) via a graduated cylinder and 2-phenylpyridine via syringe (6.98 g, 45.0 mmol, 1.00 equiv) (Note 2). The flask is fitted with a rubber septum, nitrogen inlet (Note 3), and thermocouple. The flask is placed in an ambient temperature water bath (22–23 °C) and the stir rate is set to 700-900 rpm. Silver (II) fluoride (19.7 g, 135 mmol, 3.00 equiv) is weighed into a glass vial (Note 4), then charged in one portion to the reaction flask. The reaction mixture is aged at ambient temperature (Note 5) and monitored for conversion by TLC (Note 6). During the course of the reaction, the black AgF_2 is consumed as yellow AgF is formed (Figure 1). After 90 min the reaction is deemed complete, and the reaction mixture containing insoluble silver salts is filtered over Celite (50 g, wetted with MeCN) in a 500-mL disposable filter funnel, rinsing once with MeCN (100 mL). The light yellow filtrate is concentrated on a rotary

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Figure 1. Color change through course of reaction

evaporator (25–40 mmHg, 25–30 °C) to near dryness to afford approximately 15–20 grams of a yellow/brown residue. The residue is shaken well with a combination of MTBE (100 mL) and 1M HCl (50 mL). The resulting silver salts are removed by filtration with a 120 mL disposable filter funnel (Figure 2), rinsing with MTBE (50 mL). The filtrates are transferred to a 250 mL separatory funnel. The aqueous layer is discarded, and the organic layer is washed once with saturated aqueous NaCl (50 mL), dried over anhydrous $MgSO_4$ (20 g), filtered, and concentrated on a rotavap (110–140 mmHg, 25 °C) to afford an amber colored oil (approx. 7 g). This crude material is purified by flash chromatography on silica gel to afford **1** (6.14–6.36 g, 79–81%) as a colorless oil (Note 7).

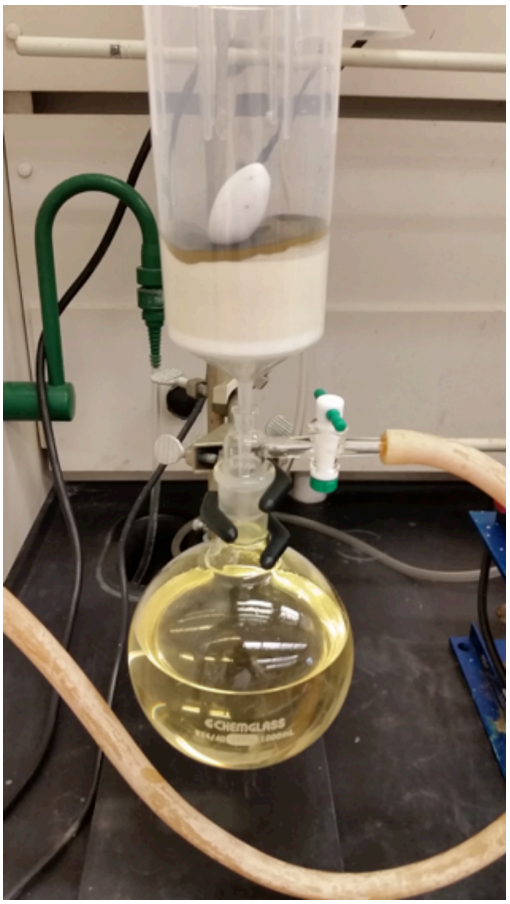

Figure 2. Filtration of Silver salts

Notes

1. Anhydrous MeCN was purchased from EMD Millipore (for HPLC Gradient Analysis, spectrophotometry and gas chromatography) and used as received. The water content was measured by Karl-Fischer titration to be 14 ppm.
2. 2-Phenylpyridine was purchased from Sigma-Aldrich and dried over 10 wt % 3 Å molecular sieves for >24 h prior to use. The water content was measured by Karl-Fischer titration to 1 ppm immediately prior to use.

3. The reaction is sensitive to moisture, but not to oxygen.
4. Silver (II) fluoride was purchased from Sigma-Aldrich and used as received. Silver (II) fluoride is a black, fine, crystalline solid that gently fumes in moist air. This reagent reacts with moisture and should be weighed quickly in air then immediately stored in a desiccator. Silver (II) fluoride handled and stored this way was used reproducibly in the title reaction on various scales over the course of 2-3 weeks. Notable discoloration of the black solid to a yellow/brown solid occurs after prolonged handling in air, at which time the reagent should be discarded.
5. The internal temperature of the reaction was measured to be 24–25 °C during the first 30 minutes, then 23–24 °C for the remainder of the reaction. In the absence of an ambient temperature water bath, the internal temperature rose to 30–32 °C during the first 30 minutes for a reaction performed on the same scale. A minimal impact on the reaction profile is observed in the absence of a water bath.
6. The reaction was monitored by silica TLC with 95:5 hexanes:ethyl acetate as the mobile phase. The R_f of **1** is 0.29.
7. The crude product was loaded onto a column (340 g biotage SNAP HP-Sil) equilibrated with 95:5 heptane/EtOAc. After 600 mL of initial elution, 50 mL fractions were collected. The desired product was obtained in fractions 18–33. A small impurity (2-3%) eluted immediately prior to the desired product and could be separated. The product fractions were combined and concentrated on a rotavap (40-50 mmHg, 25 °C for the bulk of the solvent; 5 mmHg, 25 °C for residual solvent) to provide **1** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ : 6.87 (dd, J = 8.0, 3.1 Hz, 1H), 7.47 (m, 3H), 7.63 (dd, J = 7.5, 2.6 Hz, 1H), 7.84 (dd, J = 8.2, 7.8 Hz, 1H), 8.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ : 107.6 (d, J = 37.7 Hz), 117.3 (d, J = 3.9 Hz), 126.9, 128.8, 129.6, 137.5, 141.6 (d, J = 7.8 Hz), 156.3 (d, J = 13.4 Hz), 163.4 (d, J = 238.0 Hz). HRMS (ESI-TOF) m/z calcd for $C_{11}H_8FN$ $(M + H)^+$ 174.0719, found 174.0712. Purity was determined by quantitative ^{1}H NMR using benzyl benzoate as an internal standard to be 100 wt%.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Fluorinated compounds are pervasive in all areas of organic chemistry and are especially prevalent in active pharmaceutical ingredients.[2] In drug discovery, the replacement of C-H bonds by C-F bonds is one of the most common tactics to tune the biological properties of a lead compound. However, the direct transformation of a C-H bond to a C-F bond is rarely used in drug discovery, due the harsh reaction conditions required and the

limited generality of existing methods. Thus, the use of pre-fluorinated building blocks and additional synthetic steps are typically required for the synthesis of each fluorinated derivative.

To help address the need for general methods to conduct direct C-H fluorination, we developed a reaction for the conversion of the C-H bond adjacent to nitrogen in pyridines and diazines to a C-F bond with high site-selectivity.[3] The reaction is highly tolerant of functional groups and variation of the electronic properties of the substrate. It is notable that the reactions occur at or near ambient temperature with a single, commercially available reagent. In addition to being valuable final products, the fluoropyridines and fluorodiazines are suitable electrophiles for S_NAr reactions with a broad range of nucleophiles, often reacting under mild conditions.[4] Thus, this methodology allows for tandem C-H fluorination and S_NAr as a simple approach to the late-stage diversification of complex heterocycles.

References

1. University of California, Department of Chemistry, 718 Latimer Hall, Berkeley, CA 94720-1460. E-mail: jhartwig@berkeley.edu
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3. Fier, P. S.; Hartwig, J. F. *Science* **2013**, *342*, 956–960.
4. Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10139–10147.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

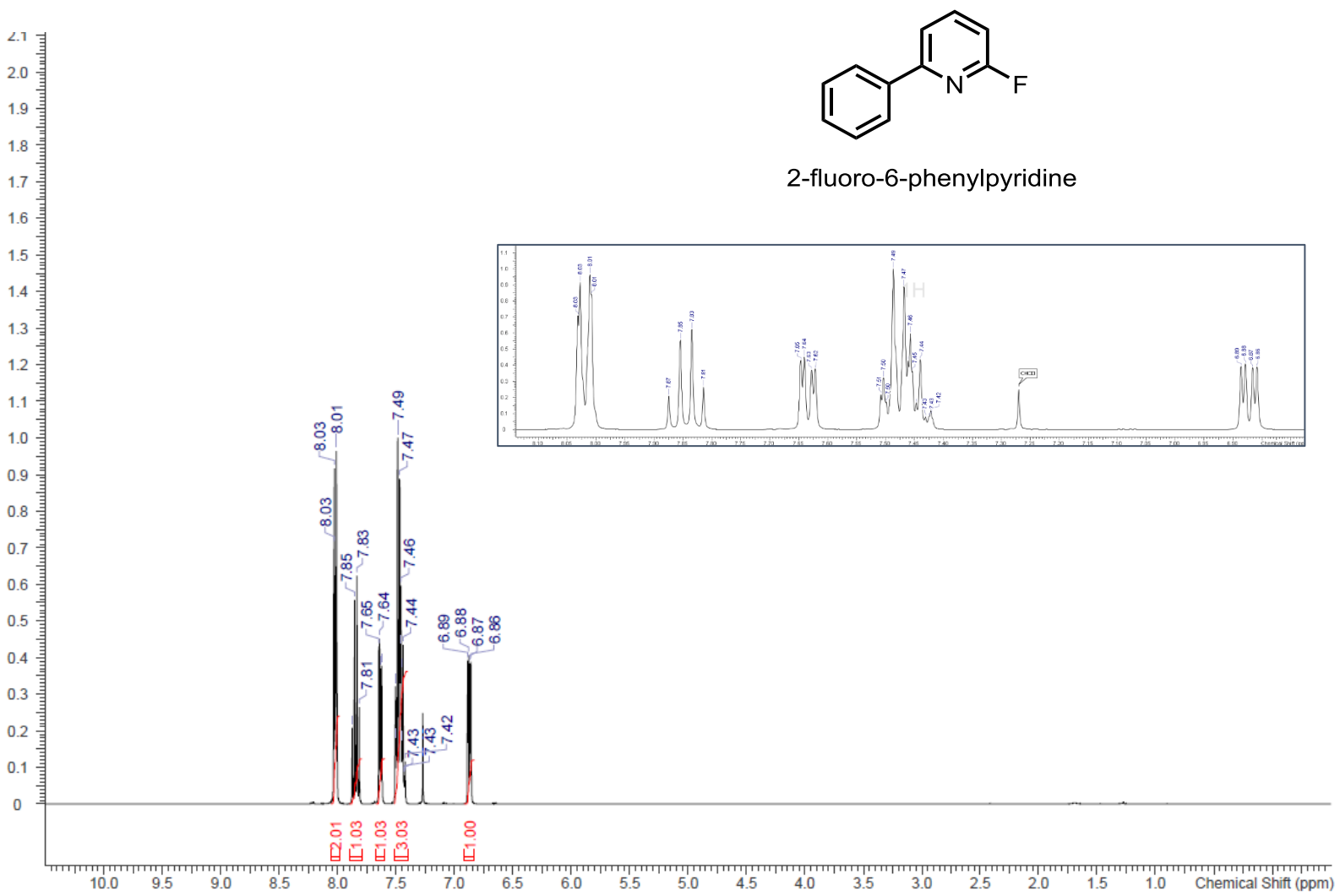
Silver (II) fluoride; (7783-95-1)
2-Phenylpyridine; (1008-89-5)
2-Fluoro-6-phenylpyridine (180606-17-1)

Patrick Fier was born and raised in Iowa, and received his B.S. degree in chemistry from the University of Northern Iowa. He then obtained his Ph.D. in the group of Prof. John Hartwig from the University of California, Berkeley in 2014. As a graduate student, he developed several methods for the introduction of fluorine and fluorinated groups into organic molecules. He is currently a Sr. Scientist in the Department of Process Chemistry at Merck in Rahway, NJ. His research interests include the development, study, and applications of novel organic transformations.

John F. Hartwig received a B.A. degree in 1986 from Princeton University, and a Ph.D. degree in 1990 from the University of California, Berkeley under the collaborative direction of Robert Bergman and Richard Andersen. After a postdoctoral fellowship with Stephen Lippard, he began an appointment at Yale University in 1992. In 2006, Professor Hartwig moved to the University of Illinois Urbana-Champaign, where he was named the Kenneth L. Rinehart Jr. Professor of Chemistry. In 2011, Professor Hartwig moved to his current position on the faculty at the University of California, Berkeley, where he is the Henry Rapoport Professor of Chemistry.

Matthew G. Beaver earned a Ph.D. from the University of California, Irvine (2010) under the guidance of Prof. Keith A. Woerpel where his research focused on the elucidation of factors that govern stereoselectivity in the reactions of oxocarbenium ion intermediates. In 2010, he joined Prof. Timothy F. Jamison's group as an NIH postdoctoral fellow where he made contributions to two distinct areas of research: the development of nickel-catalyzed C–C bond forming reactions and natural product synthesis utilizing *endo*-selective epoxide-opening cascades. In 2012, Matt began his industrial career in the Synthetic Technologies and Engineering group within Process Development at Amgen, where his work has focused on the development of improved synthetic processes for programs spanning from pre-clinical to commercial.

Christopher J. Borths earned a Ph.D. in synthetic organic chemistry from the California Institute of Technology in 2004 for developing novel organocatalytic methods with Prof. David MacMillan. After completing his graduate studies, he joined the Chemical Process Research and Development Group at Amgen where he is currently a Principal Scientist. He is a group leader in the Synthetic Technologies and Engineering group within the Pivotal Drug Substance Technology department where he works on the development of robust and safe manufacturing processes for the production of active pharmaceutical ingredients, including traditional synthetic small molecule drugs, antibody-drug conjugates, and bioconjugation technologies.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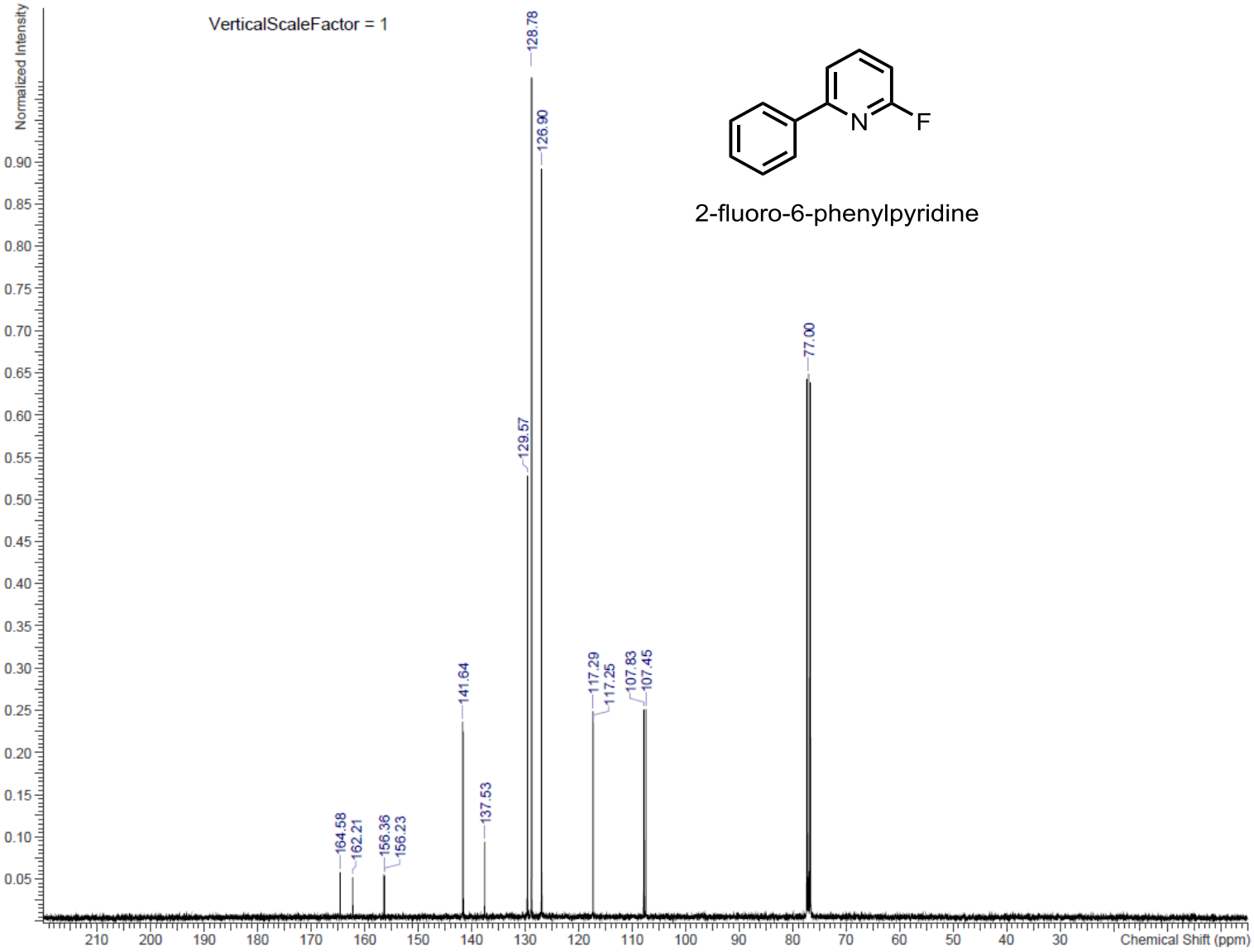
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