Synthesis of a Phosphorous Sulfur Incorporating Reagent for the Enantioselective Synthesis of Thiophosphates


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Procedure (Note 1)

A. Triethylammonium bis-(pentafluorothiophenol)phosphorousdithioate (3). A dry 1 L, four-necked [middle neck size = 29/32 for overhead stirrer; size of other three necks = 24/29], round-bottomed flask is equipped with a 4 cm Teflon-coated overhead mechanical stirrer, a temperature sensor (thermocouple), an addition funnel (size = 24/29) connected with a nitrogen inlet and bubbler, and an outlet connected to an empty gas tube which is
vented into a 500 mL round-bottomed flask half-filled (250 mL) with 10 wt% aqueous bleach solution (Figure 1).

Figure 1. Reaction set up (photo provided by submitters)

Toluene (150 mL) (Note 2) is charged into the flask followed by phosphorus pentasulfide 2 (28 g, 0.13 mol, 1.0 equiv) (Note 3) under a nitrogen atmosphere. The resulting pale-yellow slurry is stirred, then 2,3,4,5,6-pentafluorothiophenol 1 (50 g, 0.25 mol, 2.0 equiv) (Note 4) is added through an addition funnel, followed by another charge of toluene (100 mL) to rinse down the vessel wall. The slurry is cooled to an internal temperature of 10–15 °C using an ice-water bath, and then triethylamine (35.5 mL, 0.26 mol, 2.05 equiv) (Note 5) is charged to the addition funnel and added dropwise to the reaction mixture over a period of 30 min. During this addition, the internal temperature of the reaction mixture increased to ~30 °C, and the solution becomes homogeneous, turning to a golden yellow color. After completion of the addition, the ice-water bath is removed, and the solution is allowed to reach ambient temperature (22–26 °C). After
stirring for 4–5 h, the reaction mixture becomes a pale-yellow heterogeneous slurry (Figure 2).

Figure 2. Reaction appearance after 4 h (photo provided by submitters)

The slurry is stirred at ambient temperature (22–26 °C) for a total of ~30 h under a nitrogen atmosphere and then sampled for reaction completion by UPLC (Note 6). The reaction mass is filtered over a Celite bed (20 g) prepared on top of a Büchner funnel and subsequently washed using toluene (100 mL) (Figure 3A). The combined filtrate is taken into a 1 L separatory funnel and washed with water (2 × 250 mL), followed by a 20 wt% aqueous brine solution (100 mL) (Figure 3B) (Note 7). The organic layer is transferred into a 1 L single-necked round-bottomed flask and concentrated to a final volume of ~100 to 150 mL on a rotary evaporator (bath temperature: 45–50 °C, 38 mmHg) (Figure 3C).
The solution becomes a white suspension during concentration. The suspension is cooled to ambient temperature (25–35 °C), then methanol (100 mL) (Note 8) is added, forming a pale-yellow solution, which is transferred into a 1 L four-necked, round-bottomed flask equipped with a 4 cm Teflon-coated overhead mechanical stirrer, a temperature sensor (thermocouple), and a 250 mL addition funnel, and a glass stopper. The top of the addition funnel is fitted with a nitrogen inlet. An additional charge of methanol (75 mL) is used to completely transfer the material from the 1 L single-necked, round-bottomed flask.  n-Heptane (175 mL) (Note 9) is added directly to the solution, resulting in a biphasic mixture. After stirring the biphasic mixture for ~5 min, a hazy suspension forms (Figure 4A). Water (150 mL) is charged to the addition funnel and is added over a period of 20 min to the white, hazy mixture, while maintaining an internal temperature of 25–35 °C. After the addition of water is complete, crystals form (Note 10) and the slurry thickens. Stirring is continued for 16 h at the same temperature. The crystals are filtered through a Büchner funnel fitted with a 30 μm filter cloth. The round-bottomed flask is washed with an aqueous methanol solution (3:2 v/v, water/methanol, 75 mL) and the rinse is passed through the filter cake (Figure 4B). The filter cake is washed with water (2 × 90 mL) then with n-heptane (2 × 45 mL). The wet cake is deliquored on
the filter for 3 h. The white cake is placed into a vacuum oven (50 °C, 600 mmHg) and dried for 18 h. The oven-dried material is unloaded to give 66.07 g (89%) of compound 3 as a white crystalline solid with 99.7% purity (Notes 11, 12, and 13) (Figure 4C).

**Figure 4.** A) Slurry formation, B) Filtration, C) Isolated cake (photos provided by submitters)

B. (2R,3aR,6S,7aR)-3a-methyl-2-((perfluorophenyl)thio)-6-((prop-1-en-2-yl)hexahydrobenzo[d][1,3,2]oxathiaphosphole 2-sulfide (5). A 1 L, four-necked, round-bottomed flask is equipped with a 4 cm Teflon-coated overhead mechanical stirrer, a temperature sensor (thermocouple), rubber septum and a 50 mL addition funnel connected with a nitrogen inlet and bubbler. 1,2-Dichloroethane (300 mL) (Note 14) is charged into the flask followed by compound 3 (50 g, 83.80 mmol, 99.8 mass%) under a nitrogen atmosphere affording a yellow, homogeneous solution. Di-n-butyl phosphate (20.8 mL, 111 mmol, 1.32 equiv) (Note 15) is added followed by cis-(-)-limonene oxide (19.2 g, 126.2 mmol, 1.5 equiv) (Note 16). An additional charge of 1,2-dichloroethane (75 mL) is used to rinse the vessel wall. Dichloroacetic acid (17.5 mL, 212 mmol, 2.53 equiv) (Note 17) is charged into the 50 mL addition funnel and added dropwise over a period of 30 min. with a concomitant internal temperature rise to ~30 °C. The reaction mixture is stirred for 2 h at 50–55 °C under a nitrogen atmosphere (Figure 5A). After 2 h a homogenous, dark yellow solution is formed. The reaction is monitored by UPLC (Note 18). Upon completion of the reaction after 2 h, the mixture is cooled to 25–30 °C (Figure 5B) and transferred to a 2 L single-necked, round-bottomed
flask and concentrated on a rotary evaporator (bath temperature: 40–45 °C, 30 mmHg) until an approximate final volume of 250–300 mL is reached.

Figure 5. A) Initial reaction setup, B) Final reaction appearance (photos provided by submitters)

Methanol (500 mL) is charged into the flask and the solution is concentrated to an approximate final volume of 250–300 mL. This process is repeated a total of five times (Figure 6) to remove 1,2-dichloroethane (Note 19) and the thin slurry is transferred to a 1 L four-necked, round-bottomed flask equipped with a 4 cm Teflon-coated overhead mechanical stirrer, a temperature sensor (thermocouple), and a 100 mL addition funnel. Additional methanol (50 mL) is used to rinse and assist the transfer to the 1 L four-necked, round-bottomed flask containing the slurry.
Water (25 mL) is added through the addition funnel over a period of 10 min into the reaction mixture while maintaining an internal temperature of 25–35 °C. A white precipitate forms, and the slurry is stirred for 2 h at the same temperature (Figure 7A). The solids are collected by filtration over a Büchner funnel fitted with a 30 μm filter cloth (Figure 7B). The filter cake is washed using 1:1 mixture of methanol/water (250 mL). The wet cake is deliquored on the filter for 1 h. The filtered solid is unloaded to afford 22.91 g of crude compound 5 as a white solid (Figure 8) (Notes 20 and 21). This solid is subjected to a further recrystallization to improve the purity.
Compound 5 (21 g) is added to a 1 L, single-necked, round-bottomed flask. Dichloromethane (21 mL) (Note 22) is charged into the flask and the solid dissolves immediately to give a clear solution. n-Heptane (42 mL) is
added and the mixture is concentrated on a rotary evaporator under reduced pressure (bath temperature: 45–50 °C, 550 mmHg) to a final volume of ~ 40–45 mL. The addition of n-heptane and the concentration are repeated twice more, whereupon a slurry forms. The mass is cooled to room temperature and transferred to a 1 L, three-necked, round-bottomed flask, fitted with an overhead mechanical stirrer and temperature sensor (thermocouple), and a glass stopper. n-Heptane (42 mL) is charged slowly into the round-bottomed flask, and the mass is stirred for 2 h at room temperature. The crystals of 5 that formed are collected by filtration over a Büchner funnel fitted with a 30 μm filter cloth, followed by washing with n-heptane (21 mL), and the crystals are deliquored for 2 h. The wet crystals are dried in a vacuum oven (45 °C, 600 mmHg) for 6 h. The material is unloaded from the oven to give 19.8 g (51%) of compound 5 as a white crystalline solid (Notes 23, 24, and 25).

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with phosphorous pentasulfide, 2,3,4,5,6-pentafluorophenol, toluene, n-heptane, methanol, dichloroethane, dichloromethane, triethylamine, (+) or (-)-limonene.
oxide, di-n-butyl phosphate, dichloroacetic acid and Celite, as well as the proper procedures for handling malodorous chemistry.

2. Anhydrous toluene (99.8%) was purchased by the checkers from Sigma-Aldrich and used as received. Dry toluene (100 mass%) was purchased by the submitters from Sonia Industries, India and used as received.

3. Phosphorous pentasulfide (98+%) was purchased by the checkers from ACROS Organics and used as received. Phosphorous pentasulfide (100 mass%) was purchased by the submitters from Leonid Chemicals Private Ltd., India and used as received. Fresh lots of high quality phosphorous pentasulfide should be used. Lower quality and/or older lots of this material can lead to variable conversion and isolated yields.

4. 2,3,4,5,6-Pentafluorothiophenol (100 mass%) was purchased by the checkers from Apollo Scientific and used as received. 2,3,4,5,6-Pentafluorothiophenol (100 mass%) was purchased from Spectrochem, China and used as received.

5. Triethylamine (99%) was purchased by the checkers from Fisher Scientific and used as received. Triethylamine (99.8 mass%) was purchased by the submitters from Sonia Industries, India and used as received.

6. A supernatant aliquot (0.5 mL) was withdrawn from the reaction mixture. Approximately 100 mg was diluted to 10 mL with acetonitrile and submitted as such for UPLC analysis. The UPLC analysis indicated that relative area percent of pentafluorothiophenol versus product <5%. UPLC Conditions are as follows. Column: Agilent Poroshell 120, EC-C18(50 x 2.1 mm, 1.9 μm particle size). Flow rate: 0.8 mL/min. Injection Volume: 1.0 μL. Detector Wavelength: 210 nm. Column temperature: 40 °C. Sample Temperature: 25 °C. Run Length: 5 min. Mobile Phase “A”: 0.1% H₃PO₄ in water. Mobile Phase “B”: Acetonitrile. Gradient (Time, %B): (0.00 min, 5%), (4.00 min, 95%), (5.00 min, 95%). Pentafluorothiophenol retention time is 2.441 min, product 3 retention time is 2.814 min. UPLC Conditions are as follows. Column: Waters Acquity CSH C18 (100 x 2.1 mm, 1.7 μm particle size).

7. The filtrate was washed with water to remove excess Et₃N. If this step is omitted and the filtrate is directly concentrated, a sharp exotherm is observed in the crystallization. This is due to residual Et₃N.

8. Methanol (Optima, 99.9%) was purchased by the checkers from Fisher Chemical and used as received. Methanol (Laboratory Grade) was purchased by the submitters from Sonia Industries, India and used as received.
9. \(n\)-Heptane (ReagentPlus\textsuperscript{®} 99%) was purchased by the checkers from Sigma Aldrich and used as received. \(n\)-Heptane (Laboratory Grade) was purchased by the submitters from Sonia Industries, India and used as received.

10. Occasionally, unseeded crystallization, as written, does not happen instantaneously. Upon prolonged, vigorous stirring (~30 min) it will begin to self-nucleate and crystallize.

11. Triethylammonium bis(pentafluorothiophenol)phosphorousdithioate (3) has the following characterization properties: mp 95.0 °C. \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 1.42 (t, \(J = 7.3\) Hz, 9H), 3.26 (qd, \(J = 7.3, 5.3\) Hz, 6H), 8.89 (s, 1H); \(^{13}\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\): 8.7, 46.7, 109.4 (t, \(J = 18.0\) Hz), 128.7 (d, \(J = 101.8\) Hz), 136.7 (t, \(J = 15.6\) Hz), 138.7 (t, \(J = 15.2\) Hz), 141.2 (t, \(J = 15.5\) Hz), 143.2 (t, \(J = 15.5\) Hz), 147.1 (d, \(J = 10.1\) Hz), 149.1 (d, \(J = 9.8\) Hz).

\(^{31}\)P NMR (202 MHz, CDCl\textsubscript{3}) \(\delta\): 99.42 (s, br).

\(^{19}\)F NMR (470 MHz, CDCl\textsubscript{3}) \(\delta\): –128.65 (d, \(J = 17.8\) Hz), –150.96 (td, \(J = 21.1, 7.2\) Hz), –161.68 (t, \(J = 20.4\) Hz); FTIR (film): 2997, 1636, 1469, 1389, 1090, 979 cm\(^{-1}\).


qNMR: 24.9 mg of 3 and 28.9 mg of acenaphthene (99%, Sigma Aldrich) were dissolved in 3.0 mL of CDCl\textsubscript{3}.

12. Triethylammonium was assayed by UPLC for purity (sample concentration: 0.3 mg/mL in acetonitrile) (see Note 6 for UPLC conditions), which was determined to be >99.9% by area. Quantitative \(^1\)H NMR using 24.9 mg of 3 and 28.9 mg of acenaphthene (99%, Sigma Aldrich) as an internal standard provided a purity assessment of >99.9% by weight.

13. A second reaction performed on similar scale provided 66.09 g (88%) of compound 3 in 99.6% purity as determined by qNMR.

14. Anhydrous 1,2-dichloroethane (99.8%) was purchased by the checkers from Sigma-Aldrich and used as received. Dry 1,2-dichloroethane (100 mass%) was purchased by the submitters from Sonia Industries, India and used as received.

15. Dibutyl phosphate (97%) was purchased by the checkers from Oakwood Chemical and used as received. Dibutyl phosphate (100 mass%) was purchased by the submitters from Changzhou Sinowa Chemicals, China and used as received.

16. Cis-Limonene oxide (100 mass%) was purchased from Keminentek Laboratories, India and used as received. Cis-Limonene oxide can also be prepared as in Reference 6. The reaction profile and isolated yield is highly dependent on the quality of limonene oxide used.
17. Dichloroacetic acid (99%) was purchased by the checkers from Oakwood Chemical and used as received. Dichloroacetic acid (100 mass%) was purchased by the submitters from Sigma-Aldrich and used as received.

18. An aliquot (~0.5 mL) was withdrawn from reaction mass. Approximately 100 mg was diluted to 10 mL with acetonitrile and submitted as such for UPLC analysis. For UPLC conditions see Note 6.

19. The submitters reported that GC could be used to monitor 1,2-dichloroethane content, which should be no more than 0.5 ppm.

20. Compound 5 was assayed by UPLC for purity (sample concentration: 0.2 mg/mL in acetonitrile) (please see note 6 for UPLC conditions). Purity, as determined by area, was assessed at 98.3%, with 1.7% of the isomer.

21. A second run on similar scale provided 23.04 g of the same material before recrystallization. UPLC was used to assess purity of 97.5%, with 2.5% of the isomer.

22. Anhydrous dichloromethane (99.8%) was purchased by the checkers from Sigma-Aldrich and used as received. Dichloromethane (100 mass%) was purchased by the submitters from Sonia industries and used as received.

23. Characterization of 5: mp 108.6 °C; 1H NMR (500 MHz, CDCl₃) δ: 1.67 (s, 3H), 1.71–1.79 (m, 1H), 1.81 (s, 3H), 1.86–2.07 (m, 4H), 2.31–2.38 (m, 1H), 2.60 (s, 1H), 4.28 (ddd, J = 12.7, 4.8, 3.7 Hz, 1H), 4.86 (s, 1H), 5.02 (d, J = 0.5 Hz, 1H); 13C NMR (126 MHz, CDCl₃) δ: 22.1, 22.6, 23.5, 27.8 (d, J = 14.7 Hz), 33.8 (d, J = 9.0 Hz), 39.0, 65.7, 86.7 (d, J = 3.3 Hz), 105.3–104.7 (m), 111.8, 137.2–136.7 (m), 139.2–138.7 (m), 142.3–141.8 (m), 144.4–143.9 (m), 145.1, 147.0 (dt, J = 11.0, 4.2 Hz), 149.0 (dt, J = 10.9, 4.2 Hz); 31P NMR (202 MHz, CDCl₃) δ: 99.6–99.7 (m); 19F NMR (470 MHz, CDCl₃) δ: −129.27 −−130.30 (m), −148.02 (dt, J = 21.0, 7.5, 3.8 Hz), −158.32 −−160.28 (m). FTIR (film): 2967, 1636, 1511, 1482, 1090, 973 cm⁻¹. HRMS: ESI [M + H] calcd for C₁₆H₁₇F₅OPS₃: 447.0094. Found: 447.0074.

24. Compound 5 was assayed by UPLC for purity (sample concentration: 0.3 mg/mL in acetonitrile) (see Note 6 for UPLC conditions), which was determined to be 99.9% by area. Quantitative 1H NMR using acenaphthene (99%, Sigma Aldrich) as an internal standard provided a purity assessment of 95.5% by weight.

25. Recrystallization of the reaction product from a second reaction (described in Notes 13 and 21) provided 20.49 g (54%) of compound 5 in 99.9% UPLC area percent purity and 98.8 wt% purity as assessed by qNMR.
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](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

The replacement of a single oxygen atom with a sulfur atom is a common modification found in antisense oligonucleoside research. This modification can affect the properties of the molecule, for example by improving its stability to metabolic cleavage.\(^2\) This single atom modification now creates a chiral center at phosphorous, the consequences of which are currently under investigation by practitioners in the field. Currently, the method of choice by which this functionality is constructed is through the use of P(III)
phosphoramidites which are loaded with chiral auxiliaries based on, for example, proline. This phosphoramidite is coupled with another nucleoside with a specific activator, then the phosphorous is oxidized with a sulfur source. While typically a high yielding methodology, there are some challenges that can be encountered. This chemistry is highly water sensitive owing to the reactivity of the phosphoramidite and strict care must be taken to limit moisture. Additionally, the chiral auxiliary must be prepared often times in multiple steps. To circumvent these issues, we sought to devise a system that would be more tolerant to water, be more readily accessible and be isohypsic with respect to the final phosphorous oxidation state. Drawing inspiration from the oxathiaphospholane work originating with Stec, we developed the phosphorous-sulfur incorporation reagents (stylized as psi or Ψ) as a stable, and easily prepared reagent that links two entities (e.g. nucleosides) affording a chiral thiophosphate with excellent levels of stereocontrol. This is operationally carried out by loading the reagent on the first nucleoside with DBU (Scheme 1). This loaded nucleoside can be purified by chromatography, crystallization, or precipitation.

Scheme 1. Loading a nucleoside

The loaded nucleoside is then coupled with the next nucleoside, again with DBU (Scheme 2).
Both enantiomers of the reagents are commercially available through Sigma-Aldrich (the P(R) PSI reagent, i.e., 5 catalog number ALD00604 and the enantiomeric P(S) PSI reagent, i.e. ent-5 catalog number ALD00602). The availability of the reagents and ease of use compare favorably to the current art.

References

1. Chemical Development and API Supply, Biocon Bristol-Myers Squibb Research and Development Center, Biocon Park, Jigani Link Road, Bommasandra IV, Bangalore-560099, India. Chemical and Synthetic Development, Bristol-Myers Squibb, 1 Squibb Dr. New Brunswick, NJ 08903. Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.


**Appendix**

\textbf{Chemical Abstracts Nomenclature (Registry Number)}

- Phosphorous Pentasulfide: Phosphorous Sulfide; (1314-80-3)
- 2,3,4,5,6-Pentafluorothiophenol: 2,3,4,5,6-Pentafluorobenzenethiol; (771-62-0)
- Triethylamine: N,N-Diethylethanamine; (121-44-8)
- Cis-(-)-Limonene oxide: (15,45,6R)-1-Methyl-4-(1-methylethenyl)-7-oxabicyclo[4.1.0]heptane; (32543-51-4)
- Dibutyl Phosphate: Phosphoric Acid, Dibutyl Ester; (107-66-4)
- Dichloroacetic acid: 2,2-Dichloroacetic Acid; (79-43-6)
- Celite: Diatomaceous earth; (68855-54-9)
- (2R,3aR,6S,7aR)-3a-Methyl-2-((perfluorophenyl)thio)-6-(prop-1-en-2-yl)hexahydrobenzo[d][1,3,2]oxathiaphosphole 2-sulfide (5):
- (2R,3aR,6S,7aR)-Hexahydro-3a-methyl-6-(1-methylethenyl)-2-[(2,3,4,5,6-pentafluorophenyl)thio]-1,3,2-Benzoxathiaphosphole; (2245335-71-9)

Prantik Maity obtained his M.Sc. degree from IIT Madras, Chennai. After acquiring his Ph.D. at University of Regensburg, Germany in the laboratory of Prof. Burkhard König, 2008, he commenced two postdoctoral research at University of Freiburg and University of Delaware under Prof. Bernhard Breit and Prof. Mary P Watson respectively. In 2014, he joined at Biocon Bristol Myers Squibb Research and Development Center (BBRC), where currently he holds the position of Principal Investigator in the department of Chemical Development and API Supply.
Amitha Anandamurthy was born in Shivamogga Karnataka, India in 1992 and acquired her M.Sc. in Chemistry in 2014. She had previous work experience with Rentokil PCI as Research Associate. She is currently working with Biocon Bristol Myers Squibb Research and Development Center (BBRC) as a senior Research Associate.

Vijaykumar Shekarappa was born in Karnataka, India in 1985 and acquired his M.Sc. in Organic Chemistry in 2008 from Kuvempu University, India. He worked as a Research Associate in R&D centre, The Himalaya Drug Company, Bangalore. Currently he is working with Biocon Bristol Myers Squibb Research and Development Center (BBRC) as a Senior Associate Scientist.

Rajappa Vaidyanathan was born in Madras, India. He completed his Ph.D. in 1998 from the University of California, Irvine working in the laboratories of Prof. Scott Rychnovsky. After a post-doctoral appointment at Eli Lilly and Company, he joined the Chemical Process R&D group of Pharmacia Corporation, Kalamazoo, MI, and subsequently Pfizer in Groton, CT. During this period, he led several inter-disciplinary teams in the discovery and development of practical, environmentally responsible processes for New Chemical Entities, three of which were commercialized as approved drugs. He is currently Group Director and Head of Chemical Development and API Supply at Bristol Myers Squibb in Bangalore, India.
Bin Zheng received his Ph.D. from the University of Toledo. After postdoctoral studies at Caltech under the supervision of Professor Andrew Myers, he joined the Process R&D group of Bristol Myers Squibb in New Brunswick, NJ, where he is currently a Principal Scientist in Chemical Process Development.

Jason Zhu obtained his Master's Degree in 1993 from Boston University. After working at a CRO for 3 years, he then joined the Process R&D group of Bristol Myers Squibb in New Brunswick, NJ, where he is currently a Research Scientist in Chemical Process Development.

Michael Schmidt obtained his Ph.D. in 2008 from the Massachusetts Institute of Technology working in the group of Professor Mohammad Movassaghi in the area of alkaloid total synthesis. Thereafter, he joined Bristol Myers Squibb where he is currently a Principal Scientist in Chemical Process Development.
Richard (Rich) Fox completed his Ph.D. in 2006 from the University of Pennsylvania working in the group of Professor Amos B Smith, III. After a post-doctoral appointment at the University of California, Berkeley with Professor Robert Bergman, he joined the Process R&D group of Bristol Myers Squibb in New Brunswick, NJ, where he is currently a Principal Scientist in Chemical Process Development.

Kyle Knouse was born in Pennsylvania and received his B.S in Chemistry from Temple University in Philadelphia (2011). He is currently undergoing his graduate studies at the Scripps Research Institute under the guidance of Professor Phil S. Baran.

Julien Vantourout completed his Ph.D. in 2018 from the collaborative program between the University of Strathclyde and GlaxoSmithKline, UK, where he studied in the laboratories of Dr. Allan Watson. Thereafter, he started a post-doctoral appointment at Scripps Research with Prof. Phil Baran. He is currently a staff scientist in the Baran lab.
Phil S. Baran was born in New Jersey in 1977 and received his undergraduate education from New York University in 1997. After earning his Ph.D. at TSRI in 2001, he pursued postdoctoral studies at Harvard University until 2003, at which point he returned to TSRI to begin his independent career. He was promoted to the rank of Professor in 2008 and is currently the Darlene Shiley Professor of chemistry. The mission of his laboratory is to educate students at the intersection of fundamental organic chemistry and translational science.

Martin Eastgate completed his Ph.D. in 2002 from the University of Cambridge, UK, where he studied in the laboratories of Dr. Stuart Warren. After a post-doctoral appointment at the University of Illinois Urbana-Champaign, with Prof. Scott Denmark, he joined the process chemistry team at Bristol Myers Squibb, where he is currently Head of Chemical Research in Chemical Process Development.

Álvaro Gutiérrez-Bonet was born in Madrid (Spain) in 1989. He received his Ph.D. from the ICIQ (Institute of Chemical Research of Catalonia) working in the laboratories of Professor Ruben Martin. After postdoctoral studies at the University of Pennsylvania under the supervision of Professor Gary Molander, he joined the Process R&D group of Merck, in West Point, PA, where he is currently a Senior Scientist in Discovery Process Chemistry.