William Standish Knowles (1917–2012)

Bill Knowles passed away on June 13, 2012 at his home in Chesterfield, Missouri at the age of 95. His Nobel Prize brought the importance of industrial and applied chemistry to the forefront.

William was born on June 1, 1917 in Taunton, Massachusetts and grew up in nearby New Bedford. His father was the owner of a cotton mill and he could have gone into the family business but didn't want to do that. He was educated at private schools and thinking that he was too young to go to college, spent a year at Phillips Academy in Andover, Massachusetts, where he won the Boylston prize (US$50) in chemistry. After this, Knowles went to Harvard where he specialized in organic chemistry, even though his ability to do mathematics had led his advisors to suggest a physical chemistry pathway. Louis Fieser was the main influence in the move to organic chemistry. He obtained his AB degree in 1939.

Bill obtained his PhD from Columbia University in 1942, working on steroid chemistry with Robert Elderfield. While performing one experiment, which required the distillation of diazomethane, he had an explosion that destroyed a hard-fought intermediate and he had to remake it. The war aided the short time to get his degree.

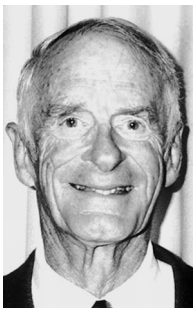
He then joined the Monsanto Company at their facility in Dayton, Ohio, moving to St. Louis in 1944. The reason he chose Monsanto was because it was the farthest west of the companies that offered him a job. Chemists were in short supply during the war. The work at Monsanto covered many topics, starting with the manufacture of hexamethylenetetramine for the explosive cyclonite and mite repellents, and benzyl benzoate for soldier's clothing. Another project involved the synthesis of vanillin from catechol, and this was to have an influence later in Bill's career, even though this chemical route was superseded by an isolation of lignin from paper waste. He also studied a manufacturing route to the antibiotic chloramphenicol, which was taken off the market because of aplastic anaemia developing in a few patients. However, this did not stop him from mixing some of this antibiotic with an ointment of other drugs that were being administered to his dog suffering from a fungal infection. The dog was better in two days and lived to be 17. Monsanto also looked at the synthesis of cortisone, and Bill was nominated to join this effort from his PhD work on steroids. This allowed him to return to Harvard and work in the labs of Professor R. B. Woodward, whom he grew to admire for his encyclopedic knowledge of chemistry and ability to look at problems from new angles. The first manufacturing project Bill had that involved a hydrogenation was the reduction of *para*-nitrophenetol. Nickel was the catalyst being used but the reaction was capricious owing to the hydrogen supply. The use of the more expensive palladium on carbon gave a much more reliable reaction, which was cheaper in the long term.

The research area that led to the Nobel Prize was asymmetric hydrogenation. Monsanto became interested in the manufacture of the Parkinson's drug L-Dopa, and to make it as a single enantiomer. Even in the 1960s, it was realized that the D-isomer was inactive and just baggage for the patient to take. As noted in his Nobel Lecture, naivety can be useful and lead to inventions. In a rather academic investigation, a new PhD, Jerry Sabacky, was given the task of reducing α-phenylacrylic acid in a homogeneous hydrogenation reaction with rhodium and a chiral phosphine. The resultant enantiomeric excess was 15%. At this time, Monsanto was selling vanillin to Hoffman–LaRoche, who then made racemic Dopa and resolved it. Knowles found out that the method being used involved the Erlenmeyer azlactone procedure, something in the public domain, but not simple to find out through "official" channels. As he put it, "*the less you have to hide, the more secretive you become.*" Use of the rhodium catalyst with the CAMP ligand gave an 88% *ee* of the amino acid derivative, and this was good enough to use in a commercial process, as the unwanted enantiomer was rejected in downstream purifications.

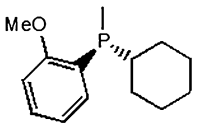
Kagan's work with DIOP led to an investigation where the phosphines were dimerized, and this led to DIPAMP. As this was easier to make than CAMP, gave a higher *ee* in the Dopa synthesis (95%), and was a crystalline air-stable solid, the manufacturing process moved to the use of [Rh-(DIPAMP)], which is still used today on a commercial scale.

The reduction of enamides to make a variety of α-amino acids and esters was continued by NSC Technologies, part of Monsanto, to make a wide variety of intermediates used in the pharmaceutical industry. Bill regretted the fact that he did not push harder to get Monsanto to make L-phenylalanine by an asymmetric hydrogenation, as this is a key component of the sweetener aspartame. NutraSweet was the parent company of NSC Technologies, and some of Bill's colleagues, especially Billy Vineyard, were key in working out a crystallization for the isolation of the correct isomer of aspartame at commercial scale.

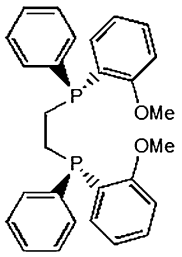
After retiring in 1986, Bill continued to act as a consultant and interacted with many of us who were looking to apply asymmetric hydrogenations on an industrial scale to a variety of compounds. These included a new route to the NSAID, naproxen, and the synthesis of unnatural amino acids using, what was then affectionately known as Knowles' catalyst. John Talley was very impressed



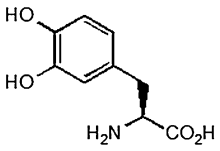
W. S. Knowles



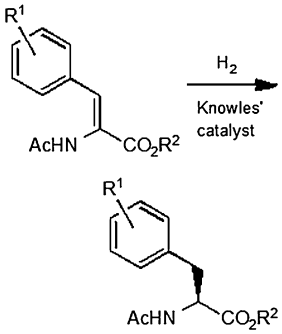
CAMP



(*R*,*R*)-DIPAMP



L-Dopa



that he saw this retired scientist sitting in the Monsanto library still reading the literature and making notes on 3 × 5 cards.

Working in industry, interactions on research are not as public as in academia. There is not the turnover of students and many workers can spend a considerable time on a single project. Bill was a gentle but challenging mentor with an easygoing attitude. He did like to challenge the management. He was excited to talk about science and new possibilities during these consulting sessions. Dr Scott Laneman, who was a postdoc at Monsanto at the time, cherishes one of these sessions where he and Knowles were discussing possible new phosphine ligands on a chalkboard. Both were covered in chalk dust with the lab radio blasting out AC/DC. This "older generation meets young" illustrates that Bill was interested in the science and working with others to solve a problem and was not put off by other, albeit rather loud, factors.

Bill chose to follow the technical ladder, rather than the managerial one, and was a Monsanto Distinguished Fellow. This acknowledged not only his contributions to the scientific field but also his contributions in making products for the company. Even after retirement, he continued to provide expertise on projects and provide insight into the area of asymmetric hydrogenations. He took pride in the knowledge that he had helped start an important and useful area of chemistry. In his own words, "*industry does too little exploratory research.*" His group's Nobel Prize-winning project on asymmetric catalysis is "*an excellent example of how a modest and inexpensive exploratory effort in industry can produce significant results.*" Indeed much of the early work was just done just by Jerry Sabacky. Billy Vineyard then became a member of the team. Their work was recognised by Monsanto in 1981 when they won the Charles A. Thomas & Carroll A. Hochwalt Award. Of course, many others were involved in moving the technology into the plant and this was highlighted when Bill was not invited to the plant celebration when the millionth pound of L-Dopa was produced.

Even before the Nobel Prize, the asymmetric hydrogenation work had gained the attention of academics. Jack Halpern (University of Chicago) and John Brown (University of Oxford) both studied the mechanism of the hydrogenation reaction. Even Barry Sharpless, who won the Nobel Prize along with Knowles and Noyori, said that Knowles had inspired him to work in the area of asymmetric catalysis.

Bill was a keen outdoorsman, even though he admitted he was terrible at athletics while growing up. He was raised by the sea and took a trip to Europe on a sailing ship before starting his undergraduate work at Harvard. The trip ended up in Stockholm, but not before getting arrested in Tallinn, Estonia. His return to Stockholm many years later certainly saw a different form of travel and no arrest.

He enjoyed fly-fishing, hiking, and cycling. The Knowles family spent time in their cabin in Jackson Hole, Wyoming, which is ideal for skiing and summer activities. The love of a challenge showed up in his recreational pursuits. Professor Albert Chan remembers being taught how to ski in Colorado where Bill, who was over 70 at the time, took him to the more difficult black diamond slopes. Although this was a large challenge for Albert, on getting down, he felt more confident with himself and fell in love with skiing. The lesson was to be well prepared all of the time for meaningful challenges.

Bill Knowles was able to look back on his career and at what is being done now. Asymmetric hydrogenation is now a key tool for the manufacture of molecules used in the life science industry. He saw monodentate phosphorus ligands being used for asymmetric hydrogenations after a hiatus of over 30 years. His vanillin method was surpassed by an extraction method from a cheap, renewable resource; with the move to green this trend seems to be continuing. He was allowed to perform independent research in an industrial environment that paid back manyfold over. As former employees of the Monsanto group of companies, we will cherish the memories of our interactions with him. Bill knew that it took a team to solve a problem and move a project forward. Overall, he was a jolly good fellow who will be sadly missed but never forgotten.

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