Obituary: David A. Evans

"Loving your work represents the best concrete approximation to happiness on earth"

Primo Levi

I first heard of Prof. David Evans as an undergraduate student in the mid 1980's at the University of Illinois at Urbana-Champaign. At the time, I was working in the group of Prof. S. E. Denmark, and I had taken the advanced organic synthesis course where the very latest advances in stereoselective synthesis were regularly discussed. Having seen an advertisement indicating that Prof. David Evans was delivering one of the weekly seminars at the University of Chicago, I took the opportunity to travel with friends and colleagues to my hometown so as to listen to a lecture on exciting new developments in stereoselective alkylation and aldol addition reactions. These were made possible because of Evans' discovery of the eponymous oxazolidinone auxiliary. It goes without saying my life was never the same afterwards. I suspect this is true for many who had the good fortune of interacting with Dave. There was a clarity to his presentation that was clearly guided by a desire to understand chemical phenomena at a very fundamental level coupled with a passion for teaching. Upon arriving in graduate school at Harvard University in fall of 1984, I was fortunate to join his group of trailblazing doctoral students and post-doctoral associates. It was a unique era in the Evans group, a time of transition, as the group was largely composed of students who had travelled cross-country from Caltech in Pasadena, CA to inaugurate the Evans Laboratories in Cambridge, MA. It was an electrifying time when the Evans aldol and alkylation methods were being implemented in the synthesis of some of the most complex polyketide natural products found in nature. It was also a time that saw parallel developments made possible by the auxiliary (also known as the 'done-pronounced as in drone) in diastereoselective Diels–Alder cycloadditions along with enolate hydroxylation, azidation, and halogenation, which in turn enabled syntheses of targets such as vancomycin, echinocandin D, and diphthamide. Given the breadth of Dave's program, it was also the period that saw development of directed reactions (olefin and hydroxy ketone reductions, hydroboration) and the early stages of what became a vibrant and highly productive program in asymmetric catalysis. From my vantage point, it was the best of times; yet in fact the period is but a snapshot that captures what is actually the entirety of Dave's high impact science and a phenomenal career that spanned early days at UCLA, almost a decade at Caltech, and then Harvard. I would hardly do it justice to attempt to cover the opus of Evans' career given the space limitations. As such, I have chosen a personal perspective that provides a moment in time, namely 1984–1990.

Dave's pioneering studies in the late 1970's inaugurated profound understanding of stereoselective transformations of enolates. This paved the way for design and development of the most successful chiral controlling group, or auxiliary, that to this day remains in wide use, some 50 years later! Dave's pioneering work in this area established the guiding principles for auxiliary design, and they have been further implemented in the design of catalysts for asymmetric synthesis. The design of the oxazolidinone auxiliary represent the apotheosis of understanding non-bonding interactions and engineering stereocontrol. Although it was initially developed for stereoselective enolate alkylations, the acyl oxazolidinones subsequently proved useful for range of other transformations. In particular, it is the development of the aldol addition reaction by Dave that revolutionized the field.

The disclosure of Evans' asymmetric aldol additions is a key point in time that demarcates a revolution in the synthesis of natural products, specifically, stereochemically complex polyketides. The synthesis of polyketides was never the same thereafter; access to polyketides was substantively altered at the level of tactics and strategy. As brilliant as work on stereoselective polyketide synthesis had been prior to the Evans aldol and alkylation reactions, generally useful stereocontrolled access routes to access acyclic fragments commonly found in polyketides was simply an unsolved problem. Most syntheses of complex polyketides had previously documented impressively creative ways around the problem by reformulating the challenge of acyclic stereocontrol as a problem in the stereocontrolled synthesis of rings that would subsequently be cleaved open.

Evans' oxazolidinone has had pronounced impact in discovery programs in academia and industry. Among the numerous representatives, the best-known cases entail syntheses of spongistatin, bafilomycin, discodermolide, and epothilone. These are examples of polyketides that had been targeted by numerous pharmaceutical research programs in industry as well as academia, because of their anticancer activities. The implementation of the Evans aldol addition reaction made possible multi-gram syntheses of these complex secondary metabolites. The material produced synthetically enabled in-depth study of their biology, providing insight for the generation of life saving anticancer drugs. Equally compelling stories may be found in access routes to other bioactive polyketides, such as rapamycin and FK 506. Enabled by the methods conceived and

developed by Evans, ready access to these compounds revolutionized understanding of cellular signaling pathways.

In the later stages of his career, Evans added a new direction or layer to his research group, namely research in asymmetric catalysis. This led to the development of a wide variety of catalysts based on optically active oxazoline-based ligands with a range of metals spanning the periodic table. The reactions found use in a broad range of transformations, including cyclopropanation, aziridination, Diels–Alder, and conjugate addition reactions, among others. Once again Evans drove the discipline, specifically asymmetric synthesis of reactions leading to C–C bond construction, and the pioneering work set high standards of scope and selectivity for catalytic asymmetric synthesis.

Beyond the impactful advances in synthesis, those of us that were fortunate to work with Dave Evans learned many important lessons that would be useful as practitioners of science and life in general. Dave's passion for synthesis always was reflected in his emphasis on the enduring value of organic syntheses both on its own merits as a discipline and through its ability to impact a wide range of other scientific endeavors. The practice of natural products total synthesis in the Evans group represented an ideal forum for reaction discovery and in-depth study of reaction mechanism and scope. Dave always emphasized that quality science has lasting value and as such great science speaks for itself without the need for overselling. As someone who took great pleasure in the latest advances in instrumentation, Dave taught his co-workers not to fear new technologies. Accordingly, the Evans group was the beneficiary of the latest available separation technologies and computational tools (Silicon Graphics) along with ChemDraw and Chem3D.

No disquisition on David Evans can be complete without highlighting his dedication to teaching. He held the view that mentoring and education of the young were paramount to the scientific enterprise. This was evident both in his dedication to the courses he taught as well as his personal relationship with the doctoral students and postdoctoral associates in his group. Dave dedicated countless hours to preparing undergraduate lectures and fostering engagement with the students. One can find numerous handouts on university websites today that follow the outlines of his own class notes. Additionally, Dave developed a collection of nearly 800 problems in organic chemistry that was made readily available to the community on the web with detailed solutions and citations. Dave's passion for education was also underscored at the weekly group meetings. Although the science was first and foremost, front and center, the weekly sessions emphasized the associated narrative, capturing the story of discovery, and conveying the evolution of a challenge from problem formulation to solution was critical to the promulgation of science. The Evans style in publications is characterized by succinct, clear description of science with beautifully rendered graphics that effectively convey the important lessons. The combination of world-class science and brilliant exposition is reflected in some rather interesting statistics: by 2006 there were at least three new articles published every day that cited Evans' work, and to date Evans' publications have been downloaded over one million times. Dave can also be credited with the training and education of a large cohort of individuals, who have gone on to be highly successful in their careers, as leaders in industry and academia. This important aspect of Evans' legacy will impact the evolution of the chemical sciences for future generations.

Dave will be remembered by the broader scientific community for his insights into chemical reactivity; by synthetic chemists for the numerous reactions and reagents he developed throughout his prodigious career in the service of synthesis; by former group members for his mentoring along with the rigor and energy he brought to the practice of science; by students enrolled in his lectures for his dedication, superb teaching style, and unbridled enthusiasm in the classroom; and by me for his unwavering support throughout my career. Dave will be sorely missed.

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