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Editorial

Introduction: Click Chemistry

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Click chemistry, as first articulated by Sharpless and colleagues in 2001,[1] was born of a desire to harness the power of molecular assembly for the widest possible range of applications. The logic behind click chemistry is simple: (i) new molecular properties are needed everywhere; (ii) such properties can emerge from the joining of small molecular building blocks; (iii) scientists and engineers not trained in synthetic chemistry often lack the skills and equipment needed to perform such connecting operations reliably; and (iv) chemical methods exist, and more can be developed, that make molecular connections easily.

The "click" in click chemistry was meant to convey the type of convenience and satisfaction one is afforded by snapping objects together with a luggage strap connector. It does not matter what the pieces are; if the two ends of the buckle can reach each other, the linkage is made. This powerful idea—that good chemistry can enable impactful chemical entities to be created by anyone—has motivated or supported an enormous range of endeavors in many fields including materials science, surface science, analytical chemistry, chemical biology, and drug development. And since methods for the selective and reliable making of bonds are actually quite difficult to discover, the sibling fields of click and bioorthogonal chemistry have synergistically led to the development of new sophisticated chemical reactions along with the highest level of mechanistic insight.

The foundational reactions of click chemistry were all venerable ones in the history of organic synthesis, including conjugate addition, strained ring opening, acylation/sulfonylation, aldehyde capture by α-effect nucleophiles, and cycloaddition. It is often forgotten that the copper-mediated azide−alkyne cycloaddition[2,3] (mechanistically not a cycloaddition at all) had yet to be discovered when click chemistry was first introduced. But an understanding of the potential power of such reactions—the real lasting value of the click chemistry concept—was certainly a motivator in Sharpless' search for a fast azide−alkyne ligation process. Its success, along with that of its biocompatible predecessors, the Staudinger[4] and native chemical ligation[5] reactions, got the field off to a rocket-fueled start.

Two decades later, we are now in the midst of a new wave of click chemistry, featuring both the continuous development of reaction methods and their ever-faster adoption across scientific disciplines. While not intended to represent a comprehensive survey of the entire field, this thematic issue of *Chemical Reviews* contains 14 accounts of different aspects of click chemistry reaction types and applications. Among the former, the reader will find insightful discussions of two types of polarized cycloaddition components, by Pezacki (nitrones) and Taran (mesoionic compounds such as sydnones). Dove provides a wide-ranging overview of nucleophilic addition to activated alkynes in a variety of situations, and Raines gives us an illuminating insight into recent chemistry with an old actor, cyclopentadiene. Prescher likewise provides an update on Staudinger-like processes, and Franzini summarizes other metal-free click reactions, such as tetrazine ligations, that have transformed chemical biology by being compatible with biological systems.

Since click reactions are usually characterized by high energy content in one or more reactants, building in such driving force is often the difficult step. Three contributors provide timely coverage of different ways to accomplish this, with light (Bowman and Lin) and oxidation (Albada). Implicit but not explored in the original image of the clicking luggage buckle was also the ability to disconnect on command. Johnson reviews this subject, dubbed "clip chemistry", since breaking bonds can be as important as making them.

Since biology is the most complex arena in which molecular synthesis can make an impact, we are also pleased to include reviews of four types of biomolecular applications of click chemistry. Brown surveys the use of click reactions with nucleic acids, and Paegel reviews the use of a variety of reactions in the presence of DNA, the key chemical requirement to harness the power of DNA-encoded libraries. The modification of lipids (Distefano) and carbohydrates (Tiwari, future issue, DOI: 10.1021/acs.chemrev.0c00920) by fast and selective reactions (mostly of the azide−alkyne variety) completes the tour.

As highlighted in the title of its first description in 2001, *function* is the point of click chemistry. Its success can be judged by how well it allows chemists and nonchemists alike to harness the power of molecular manipulation for the discovery and optimization of useful properties. But for those of us who are fortunate enough to be able to study molecular reactivity in

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its own right—for whom the behavior of molecules rises to the level of personality—click chemistry is also the pursuit of profound beauty. In other words, for both fundamental and practical reasons, it is great fun.

We are supremely grateful to the authors for their scholarship and insights. We hope that the readers derive as much pleasure from these reports as we do.

Neal K. Devaraj orcid.org/0000-0001-8247-3108
M. G. Finn orcid.org/0000-0002-8033-9973

AUTHOR INFORMATION

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.chemrev.1c00469

Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

Biographies

Neal K. Devaraj is a Professor and Murray Goodman Endowed Chair of Chemistry and Biochemistry at the University of California San Diego (UCSD), where he has been since 2011. He received a dual B.S. in Chemistry and Biology from the Massachusetts Institute of Technology in 2002 and a Ph.D. in Chemistry from Stanford University in 2007. A major research thrust of his lab involves understanding how nonliving matter, such as simple organic molecules, can assemble to form materials with emergent lifelike properties. Along these lines, his research group has developed approaches for the in situ synthesis of synthetic cell membranes by using selective bioconjugation reactions to "stitch" together lipid fragments. For his research contributions, he has been recognized by several awards including the American Chemical Society Award in Pure Chemistry, a Guggenheim Fellowship in the Natural Sciences, and being named a Blavatnik National Laureate in Chemistry.

M. G. Finn is the James A. Carlos Family Chair for Pediatric Technology and Chair of the School of Chemistry and Biochemistry at the Georgia Institute of Technology. He received a B.Sc. degree in Chemistry from Caltech in 1980 and a Ph.D. degree in 1986 from MIT working with Prof. K. B. Sharpless, followed by an NIH postdoctoral fellowship with Prof. J. P. Collman at Stanford University. He joined the faculty of the University of Virginia in 1988 and moved to the Department of Chemistry and The Skaggs Institute for Chemical Biology at The Scripps Research Institute in 1998 and then to Georgia Tech in 2013. The current interests of the Finn laboratory include the use of virus particles as molecular and catalytic building blocks in vaccines and functional materials, the development of click reactions for organic and materials synthesis, polyvalent interactions and advanced linker technologies in drug targeting, and the use of evolution for the discovery of chemical function. He is currently the Chief Scientific Officer of the Children's Healthcare of Atlanta Pediatric Technology Center. Prof. Finn was the first recipient of the annual Scripps Outstanding Mentor Award and a 2017 Arthur C. Cope Scholar award and was Editor-in-Chief of the journal *ACS Combinatorial Science*.

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