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Reaction: Programmable chemputable click chemistry

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Melanie Guillén-Soler received her MS degree in organic chemistry in 2018 from Universidad Autónoma de Madrid (UAM) and her PhD in chemistry from Universidade de Santiago de Compostela (2023, USC), where she worked on the development of novel electrocatalyst materials for advanced energy-conversion technologies. Currently, she is a postdoctoral researcher in the Cronin group, working on automation of electrochemistry. Leroy (Lee) Cronin is the Regius Professor of Chemistry at the University of Glasgow and the founder and CEO of Chemify. He is known for his approach to the digitization of chemistry and developing digital-to-chemical transformation known as chemputing, which can turn code into reactions and molecules. He has also developed a new theory for evolution and selection called assembly theory, which aims to quantify and explain how selection can occur in chemistry before biology. Lee is also exploring how chemical systems can compute and what is needed for the evolution of intelligence, as well as designing a new type of computational system that uses information encoded in chemical reactions and molecules.

The authors argue that click chemistry, with its rapid, selective, and high-yielding reactions, has the potential to democratize synthesis, making it more accessible to a wider range of researchers and practitioners. Traditionally, the synthesis of complex molecules has been challenging, requiring specialized expertise and expensive equipment. However, click chemistry, with its modular and predictable nature, can enable even non-experts to engage in the process of molecular synthesis, and the limitation of the reaction is outweighed by the ease of the chemistry.

The authors posit that click chemistry holds the promise of further democratizing the field of synthetic chemistry. By reducing complex chemical reactions to reliable, modular processes, click chemistry lowers the barriers to entry for both individuals and organizations. This increased accessibility could catalyze broader participation in chemical synthesis, thereby fostering innovation and expanding the scope of potential scientific discoveries.[1] The paper's historical framing, which contextualizes click chemistry within the broader trend of technological democratization (e.g., the printing press), is important also within the context of progress made for the digitization of chemistry.[2–4] The parallels drawn to the printing press and the internet, both of which significantly transformed information dissemination and accessibility, are exciting if not slightly over generalized. The authors foresee a future where click chemistry allows both academic researchers and amateur scientists to actively participate in chemical synthesis. This vision aligns with contemporary efforts aimed at promoting inclusivity and participatory approaches within the scientific domain. A challenge is to see how a large enough library of clickable reagents could lead to a diverse enough chemical space, but in principle, something like this could be imagined.

There are challenges and risks when making synthetic chemistry more accessible. The authors emphasize the need for robust regulations and safety protocols to prevent unintended consequences from the widespread use of click chemistry. The authors also advocate for developing governance models and technological solutions to effectively mitigate these risks, enabling the benefits of democratization without compromising public safety and well-being. A report from the 2015 Royal Society of Chemistry provides valuable insights into the future of chemical sciences. The vision

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https://doi.org/10.1016/j.chempr.2024.07.032

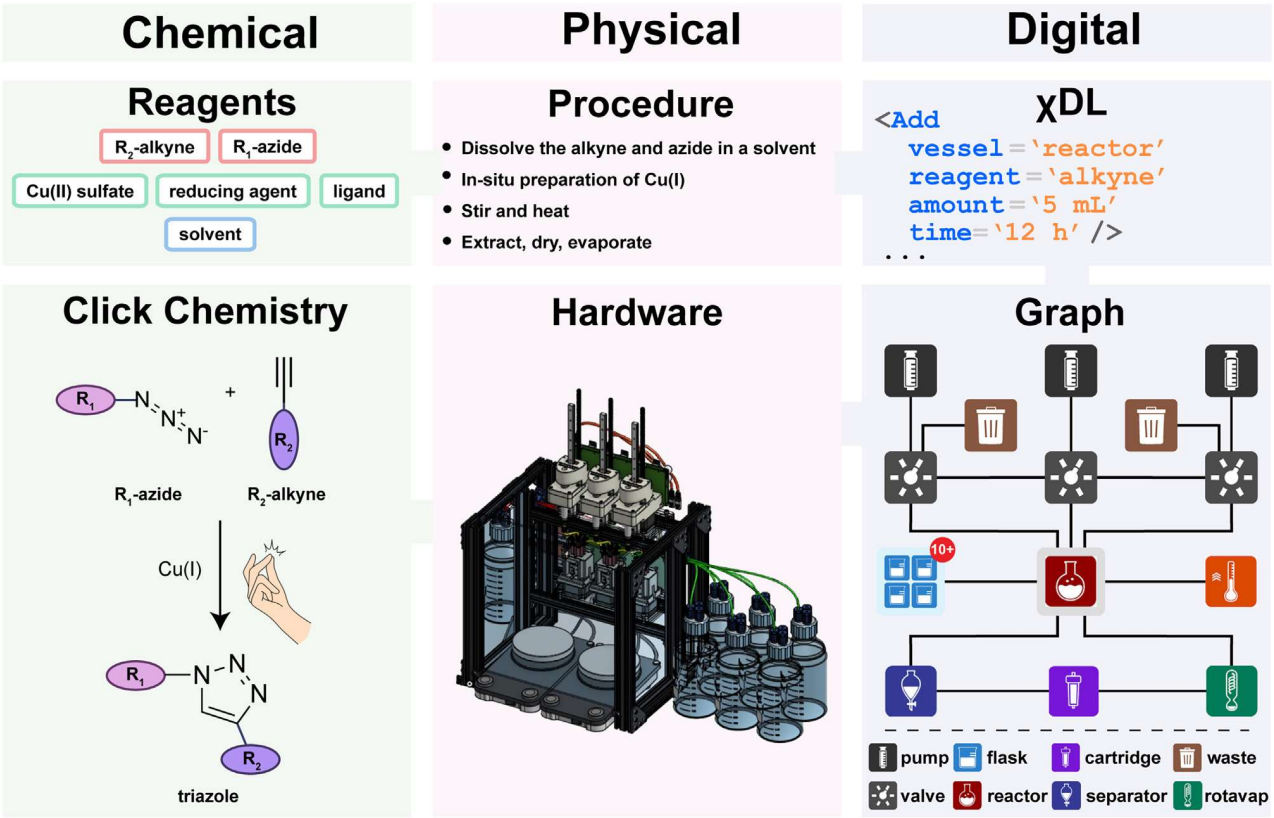

Figure 1. General workflow of chemputer-operated click chemistry

of "push-button chemistry," where remote synthesis and computer modeling become standard practices, illustrates the transformative potential of click chemistry in the field. While the paper recognizes that this vision is not yet fully actualized, it highlights ongoing efforts aimed at realizing this goal. The analogy to 3D printing further emphasizes the capacity of click chemistry to revolutionize manufacturing and other industries by enabling precise and automated synthesis procedures.[2]

The paper also highlights the importance of open-source data and digital platforms in democratizing chemistry. Examples like ChemRxiv and Reaxys are cited, which enable researchers to share findings and data. These platforms foster transparency and collaboration, which are crucial for a democratized scientific community. The emphasis on open-source initiatives reflects a wider trend toward greater accessibility and collaboration in science, breaking down traditional barriers to participation.

The paper highlights the development of automated synthesis platforms as a crucial step toward realizing the vision of push-button chemistry. The pioneering work of the Cronin Laboratory and the startup Chemify, in creating automated synthesis systems, serves as a notable example.[3,4] These innovative technologies harness machine learning and advanced robotics to enable complex chemical reactions, paving the way for a future where chemical synthesis becomes as accessible as operating a 3D printer. By automating the synthetic process and incorporating intelligent algorithms, these systems have the potential to make chemical synthesis more efficient, accurate, and scalable, further democratizing access to this critical scientific capability. The integration of these automated platforms with open-source data and digital platforms can empower a wider range of researchers and practitioners to engage in the pursuit of novel molecules and materials, accelerating scientific discoveries and innovations across various fields.[3]

The development of universal synthesis machines powered by AI and automation could potentially revolutionize the field of drug discovery. The research by Burke Lab exemplifies the capacity of automation and machine learning combined to expedite drug discovery, rendering the process more efficient and accessible.[5] The modular and predictable nature of click chemistry, combined with the power of AI-driven automation, could serve as an example to

revolutionize the drug discovery pipeline. Nevertheless, the development of the chemputer and chemputation promises to be a more universal approach.[3,4] The development of chemputation requires a programming language for chemistry that can be run on a universal chemical robot to carry out precise and reproducible synthesis tasks. Chemputation, like computation, is precise and verifiable and opens up a way to encode new chemical reactions, as well as well-known reactions like click chemistry (see Figure 1), allowing all chemistry to be digitally accessible. This is because chemputation allows *all* human-accessible chemistry currently known and unknown to be encoded. Like the invention of language and printing press technology, chemputation has universal reach. At the same time, by making the synthesis of diverse chemical compounds more streamlined and accessible, click chemistry could also enable a broader exploration of chemical space.

The paper presents a well-argued case for the potential of click chemistry in democratizing synthetic chemistry. Nonetheless, the authors stress the necessity for prudent governance frameworks and the creation of secure, trustworthy technologies to address potential risks, which could be collaboratively done with pioneers in the field like Cronin Lab. The authors' envisioned future of synthetic chemistry is one where innovation and accessibility coexist, forging a path toward a more inclusive and participatory scientific community.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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