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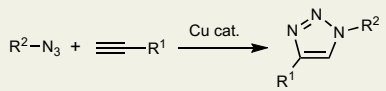
Simple connections take the prize

Click chemistry and bioorthogonal chemistry have finally been recognized with the Nobel Prize in Chemistry.

The 2022 Nobel Prize in Chemistry was awarded to Carolyn Bertozzi, Morten Meldal and Barry Sharpless "for the development of click chemistry and bioorthogonal chemistry"[1]. The prize celebrates not only the practical advance afforded by click reactions in the field of chemistry but the remarkable spread of click and bioorthogonal reactions into materials, pharmaceutical and life-sciences research. The Nobel Prize-winning trio share the great merit of having found simple and efficient ways in which molecules can be connected in a wide variety of conditions, making chemical manipulation easily accessible to the entire scientific community.

In general, organic chemists work with complex reactions, which are often multistep and demand tight control of multiple experimental parameters, including the concentration of reagents, temperature and solvents, and of the environment in which the reactions take place. Moreover, most traditional reactions can be time consuming and have relatively low yields, requiring post-purification processes to separate the product of interest from undesired by-products. In a pivotal review in 2001[2], Sharpless advocated for the simplification of chemical conjugation and coined the term 'click chemistry' to describe a handful of modular reactions that lead to materials composed of smaller building blocks joined together with heteroatom linkages (C–X–C) that are simple, fast and reliable, having few to no by-products. At the time, possibilities included nucleophilic ring opening reactions, non-aldol carbonyl chemistry, additions and cycloadditions involving unsaturated structures, such as hetero-Diels–Alder reactions and 1,3-dipolar cycloadditions. However, although versatile, these reactions still require chemists to exert control over the experimental conditions or suffer from slow kinetics at room temperature, which limits their applicability.

Copper-catalysed azide–alkyne cycloaddition
Minimal size, readily accessible, broadly useful



Reaction scheme of the copper-catalysed azide–alkyne cycloaddition. Figure reproduced with permission from ref. [7], Springer Nature Ltd.

In 2002, Meldal[3] and Sharpless[4] found out, independently from each other, that the azide–alkyne cycloaddition reaction, then termed the 'click' reaction, could be greatly accelerated and made almost quantitative by using copper(I) catalysts. This breakthrough discovery facilitated and encouraged innovative research in multiple disciplines as non-specialists now had a simple and fast click chemistry tool that generated almost exclusively the product of interest at room temperature and in an aqueous environment and standard atmosphere. In parallel, Bertozzi managed to transfer the 'orthogonal' principle, that is, the capability of compounds to react exclusively with each other independently from the presence of other reagents, to biological systems[5,6]. As copper is toxic to cells, Bertozzi found alternative catalyst-free ways to efficiently modulate the reaction kinetics of the azide–alkyne cycloaddition by chemically modifying the alkyne moieties, exploiting ring strain and electron-withdrawing groups. By setting up a range of 'bioorthogonal' reactions, her group managed to perform chemistry in living cells and living organisms, opening new capabilities in the fields of biomaterials and biomedical research.

Indeed, click chemistry has now become widespread across different fields of science. For the materials science community, this technology represents an exceptionally useful set of accessories to modulate materials' structure and properties in a controlled manner. By incorporating click reactants into polymer backbones, materials scientists now routinely exploit click chemistry to synthesize and functionalize polymers with controlled architecture, including polymer networks, block polymers, dendrimers, micelles and gels. Click chemistry has been exploited for microporous organic polymer synthesis, DNA arrays and nanomaterial functionalization. 'Photo-click' chemistry, that is, the combination of click chemistry with light control, has been used for surface photopatterning and to build photoresponsive materials. In biomaterials research, copper-free click chemistry is widely used to build functional materials meant for biomedical applications, such as drug delivery, and for the manipulation of biomaterials and living materials. Bioorthogonal photoreactions have been used for protein patterning in three-dimensional gels and for cell encapsulation in cytocompatible hydrogels. Copper-free click chemistry has been used to build controlled colloidal self-assemblies and to functionalize microrobots for antibiotic delivery. In synthetic biology, bioorthogonal reactions have been used to assemble protocells into thermoresponsive prototissues. In vivo, copper-free click chemistry has been used to manipulate processes in situ, such as to immunomodulate dendritic cells.

Although click chemistry and bioorthogonal strategies might not be the central focus of every materials science paper, in the span of 20 years, these strategies have become indispensable tools for materials researchers and have transversally impacted multiple subfields. This huge impact has only been possible thanks to the extreme simplicity and reliability of the click and bioorthogonal approaches.

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