

Nobel Prizes in Chemistry (2022) for the Development of Click Chemistry and Bioorthogonal Chemistry

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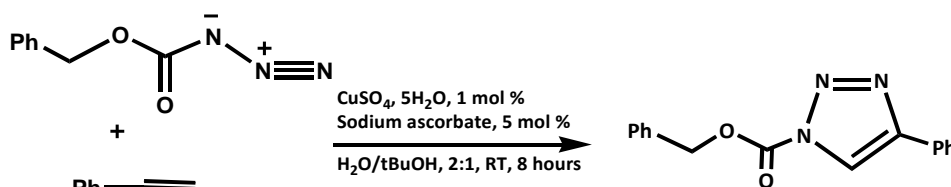
Abstract

In 2022, the Nobel Prize was awarded in the fields of click chemistry and bioorthogonal chemistry. The chemistry was developed by Sharpless, Meldal, and Bertozzi. Click chemistry has been extensively utilized in catalysis, solid-state peptide synthesis, and functionalizing large molecules. Bioorthogonal chemistry has been utilized in treating cancer of living cells and other medicinal diseases.

KEYWORDS: Nobel Prize, Sharpless, Click Chemistry, Bioorthogonal Chemistry, Triazole

INTRODUCTION

The Nobel Prize is highly regarded in the global scientific community. In 2022, Sharpless, Meldal, and Bertozzi were awarded the Nobel Prize for their work in click chemistry and bioorthogonal chemistry. Sharpless, a Nobel Prize winner in 2001, was a pioneer in asymmetric catalysis and chirally catalyzed alkene oxidation. In the same



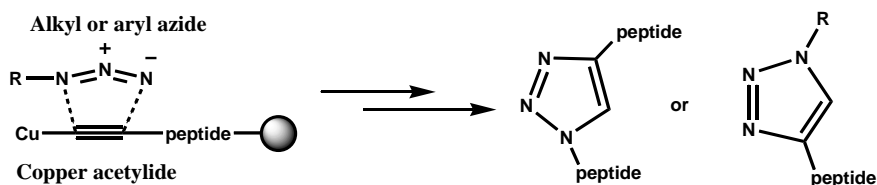
Scheme 1: Copper-catalyzed click chemistry

year, he introduced click chemistry, earning the Nobel Prize in this field 20 years later, making him the fifth person to receive two Nobel Prizes in chemistry. Click chemistry involves a reaction between substituted azide and phenylacetylene, resulting in a 1,4 substituted 1,2,3 triazole compound with CuSO₄·5H₂O as a cost-effective catalyst and sodium ascorbate as a reductant (Scheme 1). The conversion was efficient in tert-buOH, ethanol, and water solvents at room temperature.

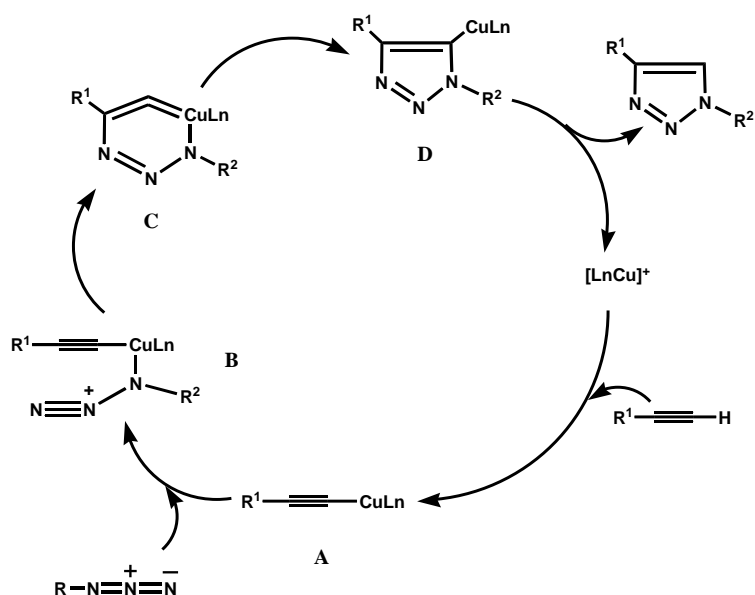
From an early age, he was a passionate and curious individual about chemistry. Born in 1941, he earned a B.A. from Dartmouth College and a Ph.D. in organic chemistry from Stanford University in 1968, under Eugene E. Van Tamelen's supervision. After

completing his postdoctoral work, he began his independent career at MIT and Stanford University and later became a professor at the Scripps Research Institute.

Morten Peter Meldal developed the same chemistry in the same year. The 1,3-dipolar



Scheme 2: Copper-catalyzed click chemistry in solid-state peptide

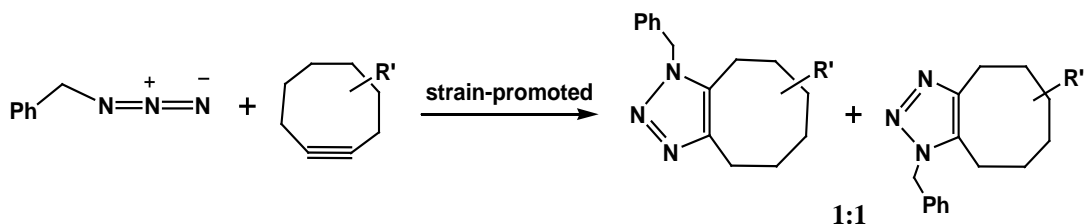


Scheme 3: Mechanism of Copper-catalyzed click chemistry

cycloaddition product 1,4-substituted [1,2,3]-triazole was demonstrated in the reaction of terminal alkynes and azide using a copper (I) catalyst (Scheme 2). The conversion rate is over 95% and it operates at solid-state peptide synthesis at 25°C. This reaction connects peptide and carbohydrate in solid support, proving useful in biology, medicinal chemistry, and functionalizing large molecules.

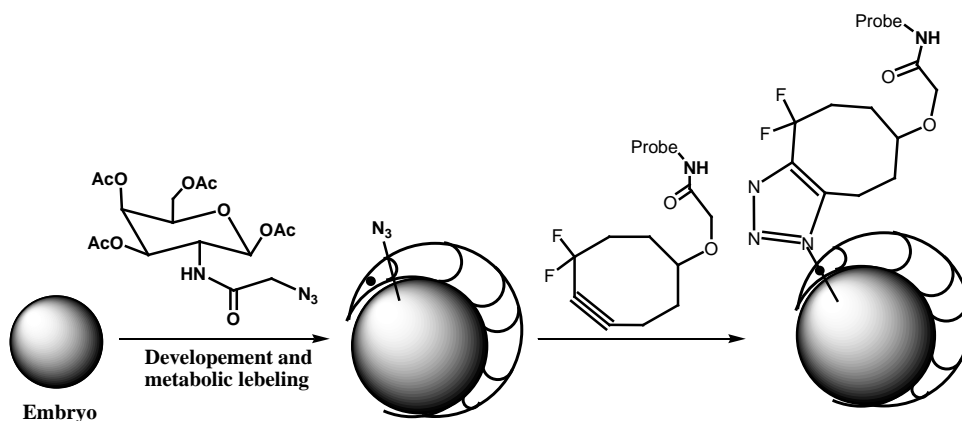
The reaction mechanism was thoroughly examined and confirmed through DFT calculation (Scheme 3). The copper complex reacts with substituted acetylene to form a Cu acetylide intermediate, followed by nitrogen from the substituted azide,

forming intermediate B. Triazole products are subsequently produced via intermediates C and D.



Scheme 4: Strain promoted [3 + 2] cycloaddition reaction

Meldal, a Danish chemist, initially worked as an engineer before transitioning to the organic chemistry field. Born in 1954 in Denmark, he earned a Ph.D. in synthetic chemistry of carbohydrates from the Technical University of Denmark (DTU). After completing his postdoctoral work, he became a professor at the DTU and later at the Carlsberg Laboratory.



Scheme 5: Imaging experiment with zebrafish embryos

Bertozzi's groundbreaking work demonstrated click chemistry in biological and living cells. Bioorthogonal chemistry is the study of the reactions of biomolecules and cell diseases. Bertozzi pioneered the application of click chemistry in living biological cells and pioneered the development of bioorthogonal chemistry. In 2007, she conducted a strain-promoted [3 + 2] cycloaddition reaction between cyclooctyne derivative and substituted azide (Scheme 4). However, the reaction was conducted in living cells, resulting in the production of two regioisomeric triazole products in equal amounts without any physiological toxicity.

In 2008, a peracetylated N-azidoacetylgalactosamine (Ac4GalNAz) organic reagent was applied to zebrafish embryos for this chemistry. The cell was injected with DIFO-fluorophore conjugates, allowing noninvasive imaging of glycans in the cell. Bioorthogonal chemistry has been applied to cancer cells, and a trial method is currently being conducted in human cells. Bertozzi, born in 1966, graduated from Harvard University, earned a Ph.D. from the University of California at Berkeley, and served as a faculty member there. In 2015, she became a professor at Stanford University and became the eighth woman to win the Nobel Prize in chemistry.

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