Abstracts

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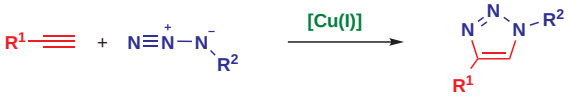
2.1 Introduction to CuAAC

F. F. Ort and F. P. J. T. Rutjes

The basic principles of the copper-catalyzed azide–alkyne cycloaddition reaction (CuAAC), widely considered to be the first click reaction, are described. This involves amongst others the concept of click reactions, the mechanism of CuAAC, the synthesis and reactivity of organic azides and acetylenes, an overview of most commonly used copper(I) catalysts and ligands, the properties of 1,2,3-triazoles and their resemblance to amides, and a general overview of the scope and limitations of this reaction.



Keywords: click chemistry · copper-catalyzed azide–alkyne cycloaddition (CuAAC) · azides · alkynes · dipolar cycloaddition · Huisgen cycloaddition · amide isostere · 1,2,3-triazoles · copper catalysts

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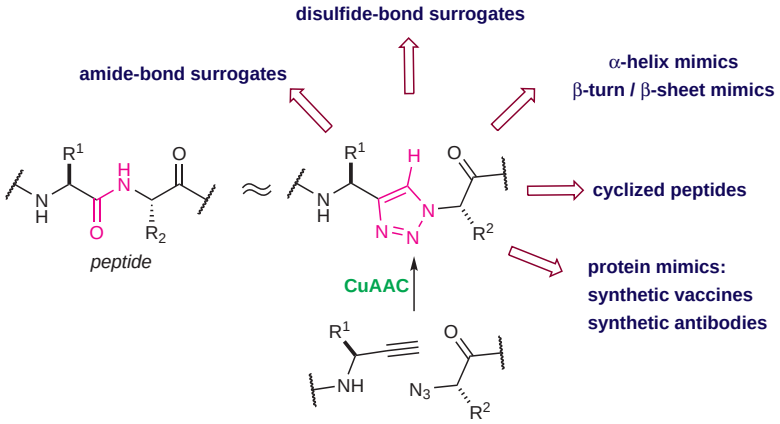
2.2 CuAAC in Peptidomimetics and Protein Mimics

T. J. Meuleman and R. M. J. Liskamp

The tremendous recent developments in click chemistry, including the impressive developments of strain-promoted cycloaddition reagents, all started with the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction conceived by Meldal et al. and Sharpless et al. This led to a revolution of extremely important applications in the chemical, biological, medical, and materials sciences. It is fair to state that, especially in the synthesis of multifunctional and complex small-to-large biomolecular constructs, CuAAC has been indispensable. This has been particularly evident in the area of peptides, peptidomimetics, and protein mimics. These biomolecules play key roles in the various peptide–peptide, peptide–protein, and protein–protein interactions that are involved in many diseases and disorders, and peptide-based therapeutics can be important in this context. However, it is often important to improve the bioactivity and overall stability, and modulate the spatial structure, of peptide-based therapeutics. The incorporation of the 1,4-disubstituted 1,2,3-triazole moiety as a non-native structural element using CuAAC is explored in this chapter. The resulting incorporated triazole moiety can lead to structural surrogates of the amide bond and disulfide bond. As a consequence, CuAAC can be utilized toward introducing conformational constraints and stabilizing secondary structures of α-helices, β-sheets/turns, or loop-like structures. In addition, CuAAC can be used to combine various peptide sequences with molecular scaffolds to develop protein mimics that can find applications as synthetic vaccines and antibodies.



Keywords: click chemistry · copper-catalyzed azide–alkyne cycloaddition (CuAAC) · 1,2,3-triazoles · peptidomimetics · protein mimicry · structural surrogates · α-amino alkyne analogues · conformational constraints · synthetic vaccines · synthetic antibodies · α-helixes · β-sheets · β-turns

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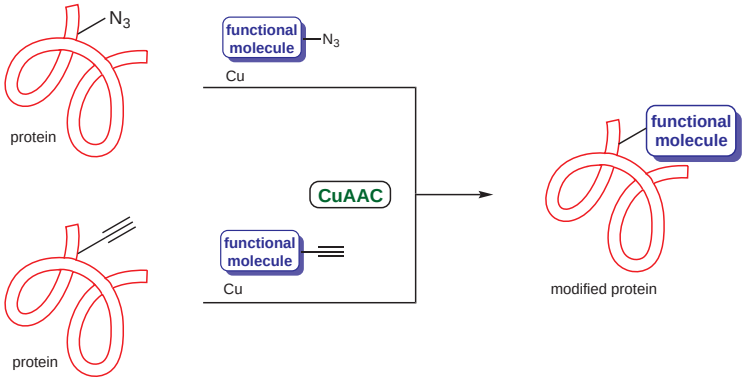
2.3 CuAAC in Protein Conjugation

A. La Venia, A. Kovalová, and M. Vrabel

This chapter summarizes the use of the copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction in the synthesis of peptide and protein conjugates. The different reaction conditions used for construction of the conjugates and their application in various disciplines are covered. Synthetic strategies for the introduction of the click groups (azide or alkyne) into the peptide backbones are included as well.

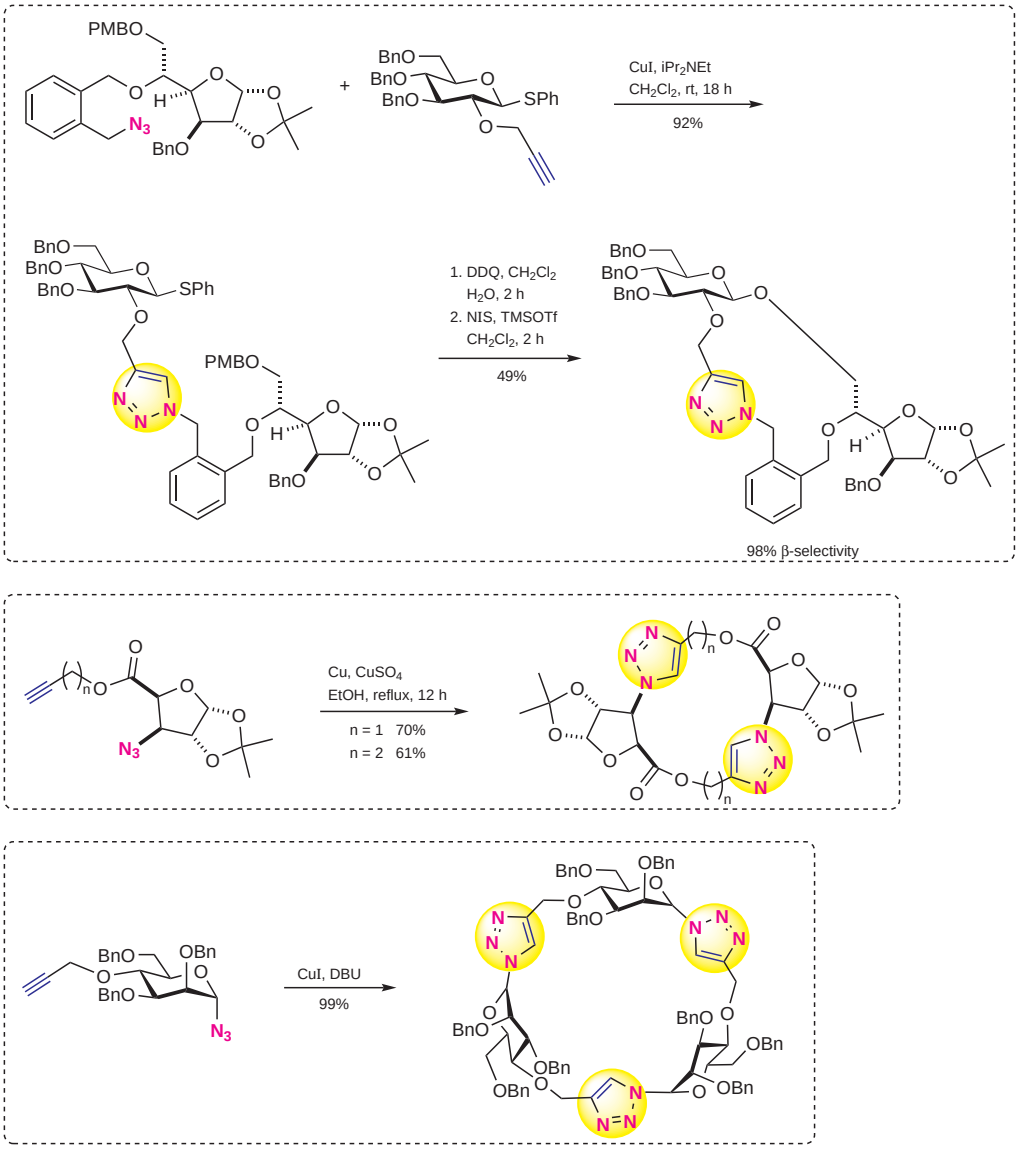


Keywords: click chemistry · copper-catalyzed azide–alkyne cycloaddition (CuAAC) · alkynes · azides · copper catalysts · dipolar cycloadditions · peptide modification · protein modification · triazoles

2.4 CuAAC in Carbohydrate Conjugation

A. K. Agrahari, A. Mishra, and V. K. Tiwari

Copper(I)-catalyzed azide–alkyne cycloaddition reactions (CuAAC), as a versatile, reliable, and modular strategy, have been widely investigated in the area of glycoscience during the last 20 years. Herein, we presented a brief overview of CuAAC click approaches for easy access to diverse simple and complex triazole-appended carbohydrate-containing molecular architectures. Both intermolecular and intramolecular CuAAC conjugation of glycosylated azides and terminal alkynes have been widely employed for the regioselective triazole-forming reaction under standard click conditions.



Keywords: click chemistry · copper-catalyzed azide–alkyne cycloaddition (CuAAC) · alkynes · azides · copper catalysis · triazoles · carbohydrates · conjugation

Science of Synthesis Reference Library
Click Chemistry

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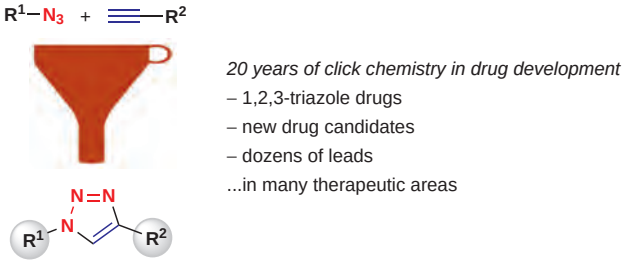
2.5 CuAAC and Metal-Free 1,3-Dipolar Huisgen Cycloadditions in Drug Discovery

K. M. Kacprzak, I. Skiera, and J. Rutkowski

Proclaimed by Sharpless in 2001, the manifesto of click chemistry philosophy shifted the focus from target-oriented to drug-like-oriented synthesis, and has enormously accelerated the drug-discovery process over the last two decades. Copper(I)-catalyzed and metal-free versions of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes have become the reference click chemistry synthetic tools. These processes are adaptable to various drug-design modes such as kinetic target guided synthesis (in situ click chemistry assembling; KTGS), combinatorial chemistry/high-throughput-screening approaches, or structure-based rational projecting. Moreover, the facile click chemistry derivatization of natural or synthetic products, linking molecules or improving the stability of leads by installation of 1,2,3-triazoles, is another important stream of bioactivities. This review is intended to provide a general overview of click-chemistry-powered drug design, with dozens of successful examples resulting in the discovery of nanomolar-active 1,2,3-triazoles in every stage of drug development.



Keywords: alkynes · azides · click chemistry · combinatorial chemistry · copper-catalyzed azide–alkyne cycloaddition (CuAAC) · dipolar cycloaddition · drug design · kinetic target guided synthesis (KTGS) · lead compounds · 1,2,3-triazoles

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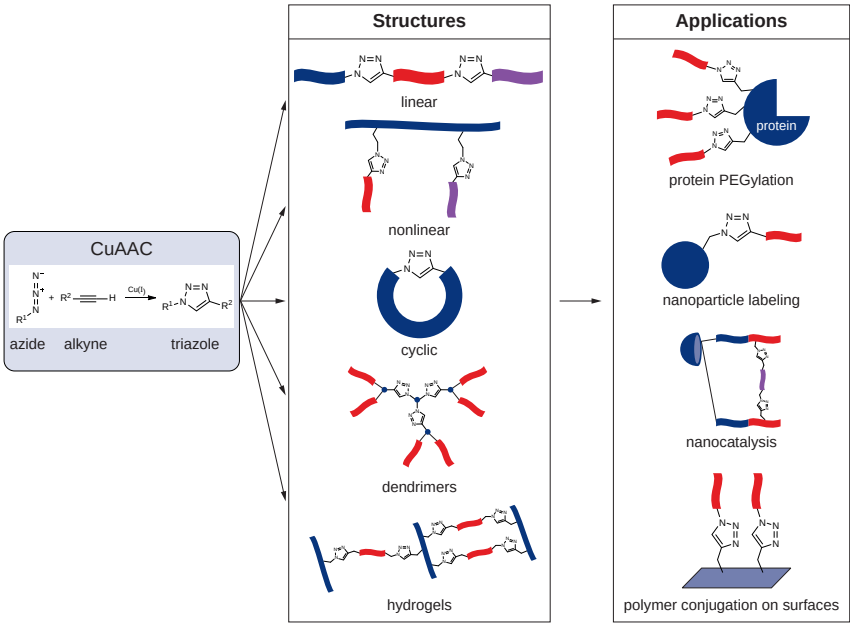
2.6 CuAAC Applications in Macromolecules, Polymers, Nanoparticles, and Supramolecular Chemistry

C. Zhang, K. M. Page, and J. C. M. van Hest

In this chapter we describe applications of copper-catalyzed azide–alkyne cycloaddition (CuAAC) in macromolecular synthesis and polymer functionalization. This entails the synthesis of polymers with different architectures and the conjugation of polymers to surfaces and particles.



Keywords: click chemistry · copper-catalyzed azide–alkyne cycloaddition (CuAAC) · alkynes · azides · biomimetic synthesis · copper catalysts · cycloaddition · dendrimers · macrocycles · medicinal chemistry · nanostructures · polymerization · polymers · supramolecular chemistry

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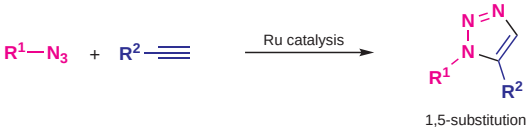
3 Ruthenium-Catalyzed Azide–Alkyne Cycloaddition (RuAAC)

A. J. Paterson, T. Beke-Somfai, and N. Kann

Under ruthenium catalysis, 1,5-disubstituted 1,2,3-triazoles can be accessed with high selectivity from terminal alkynes and organic azides via a ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC) reaction. These conditions also allow the use of internal alkynes, providing access to 1,4,5-trisubstituted 1,2,3-triazoles. This chapter reviews the scope and limitations of the RuAAC reaction, as well as selected applications. A brief mention of azide–alkyne cycloaddition reactions catalyzed by other metals is also included.



Keywords: click chemistry · RuAAC · cycloaddition · triazoles · ruthenium catalysts · carbon—nitrogen bonds · nitrogen heterocycles · alkynes · azides

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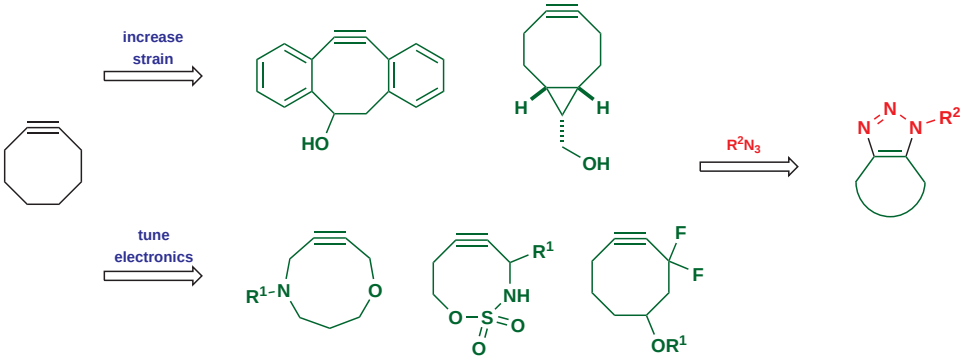
4.1 Strain-Promoted Azide–Alkyne Cycloaddition (SPAAC): Background, Substrate Preparation, and Reactivity

T. Harris and I. V. Alabugin

This chapter discusses the creative synthetic approaches to azides and cycloalkynes, provides the rationale for controlling SPAAC reactivity through tuning cycloalkyne and azide backbone modifications, and highlights research on nitrone cycloadditions with cycloalkynes. This synthetic and knowledge toolset will help in the design of better cycloalkynes and their partners to answer challenging research questions and aid the development of new applications.



Keywords: click chemistry · alkynes · azides · cyclization · cycloadditions · cycloalkynes · eight-membered rings · fragmentation · hyperconjugation · nitrones · ring formation · ring expansion · strain-promoted azide–alkyne cycloaddition (SPAAC) · strain-promoted azide–nitrone cycloaddition (SPANC)

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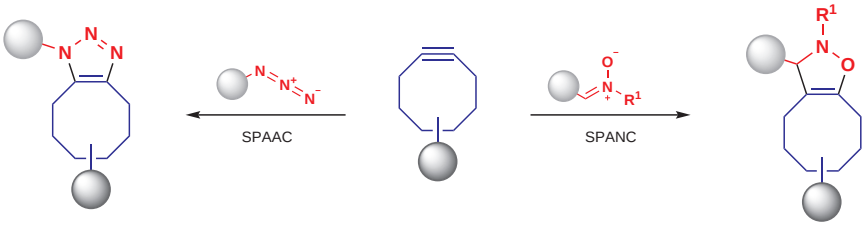
4.2 Applications of SPAAC and SPANC in Life Sciences

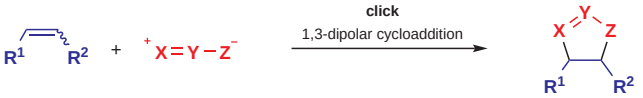
L. J. N. Janssen and D. Blanco-Ania

The bioorthogonal, strain-promoted azide–alkyne cycloaddition (SPAAC) and the strain-promoted alkyne–nitrone cycloaddition (SPANC) reactions have been used for conjugation with high affinity and specificity. In contrast to the cytotoxic copper-catalyzed cycloaddition, both SPAAC and SPANC are inert in biological environments. This chapter reviews the developments and applications of SPAAC and SPANC in life sciences reported since 2004, when Bertozzi et al. published the first bioorthogonal reaction.



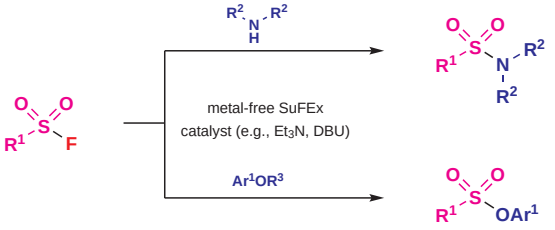
Keywords: click chemistry · strain-promoted azide–alkyne cycloaddition (SPAAC) · alkynes · azides · bioorthogonality · cycloaddition · cyclooctynes · nitrones

Click reactions between 1,3-dipoles and alkenes are appealing due to their versatility, which goes beyond simple conjugation applications and the synthesis of five-membered heterocycles. Leveraging various 1,3-dipoles and alkenes, photoactivatable, highly reactive, and "click to release" systems have been developed. In this article, we explore the wide range of reactivities, selectivities, and applications offered by this class of cycloadditions.



Keywords: 1,3-dipoles · alkenes · click reactions · click chemistry · cycloadditions

Sulfur **F**luoride **Ex**change (SuFEx) click chemistry is a new generation technology for creating stable molecular connections with absolute reliability under metal-free conditions. SuFEx builds upon the fundamental principles of click chemistry by exploiting a unique blend of stability and latent reactivity of high oxidation state sulfur fluoride [e.g., S(VI)] functionalities to forge stable covalent linkages at connective SuFEx hubs. In this review, we focus mainly on the SuFEx hubs, sulfuryl fluoride (SO_2F_2), thionyl tetrafluoride (SOF_4), ethenesulfonyl fluoride (ESF), 1-bromoethene-1-sulfonyl fluoride (BESF) and, 2-substituted alkyne-1-sulfonyl fluorides (SASFs). We describe each connector's unique reactivity and their application to SuFEx click chemistry.



R^1 = aryl or alkyl; R^2 = aryl or alkyl; R^3 = H, TMS, TBDMS

Keywords: sulfur fluoride exchange (SuFEx) · click chemistry · connective hubs · sulfuryl fluoride · thionyl tetrafluoride · ethenesulfonyl fluoride · 1-bromoethene-1-sulfonyl fluoride · 2-substituted alkyne-1-sulfonyl fluorides · diversity-oriented click reactions · sulfur fluorides

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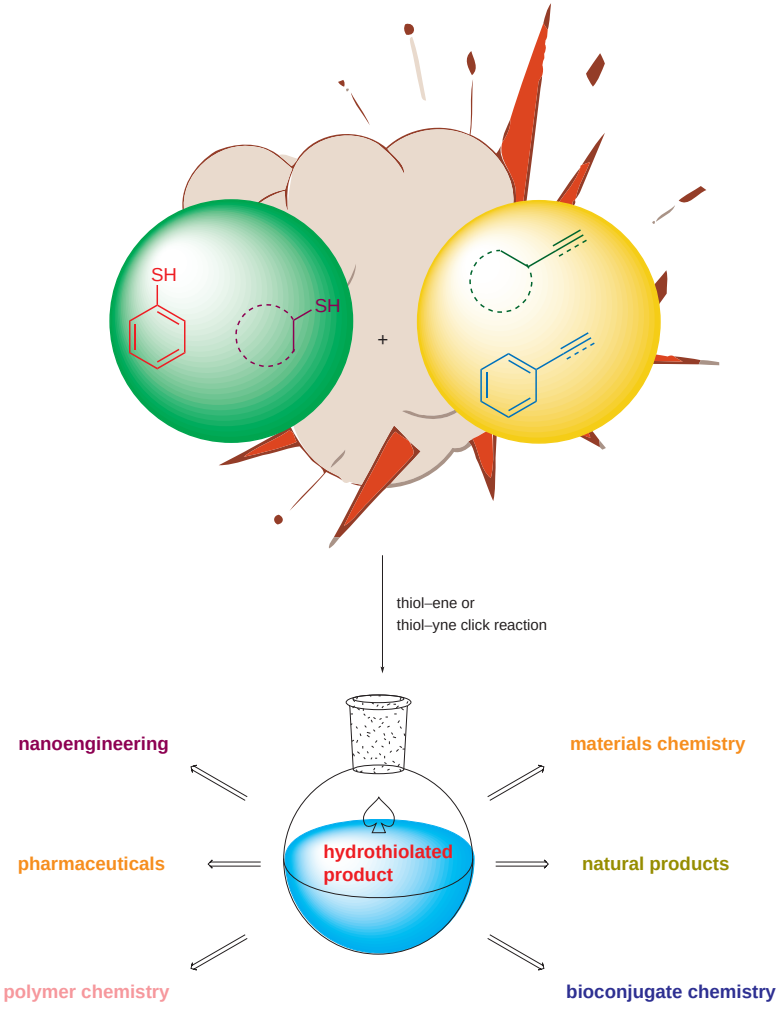
6.1 Thiol–Ene/Yne Click Reactions: A Powerful Tool Toward Diversity-Oriented Synthesis

A. K. Sinha and R. Singh

The clickable addition reaction between thiols and unsaturated compounds leading to the generation of (branched/linear) thioethers or (branched/linear) vinyl sulfides is known as the hydrothiolation reaction. Based upon the nature of unsaturation, i.e. double bond or triple bond, hydrothiolation reactions are classified as thiol–ene and thiol–yne click reactions, respectively. These reactions have emerged as a powerful and widely used strategy for the generation of carbon–sulfur bonds due to several associated benefits including versatile synthetic procedures, wide functional-group tolerance, high atom economy with few to no byproducts, and simple purification. The hydrothiolation reactions have numerous trapping applications in the fields of polymer chemistry, nanoengineering, pharmaceuticals, natural products, and perhaps most importantly in medicinal chemistry for the synthesis of many drugs and bioactive molecules.



Keywords: hydrothiolation · click chemistry · thiol–ene reactions · thiol–yne reactions · anti-Markovnikov reaction · Markovnikov reaction

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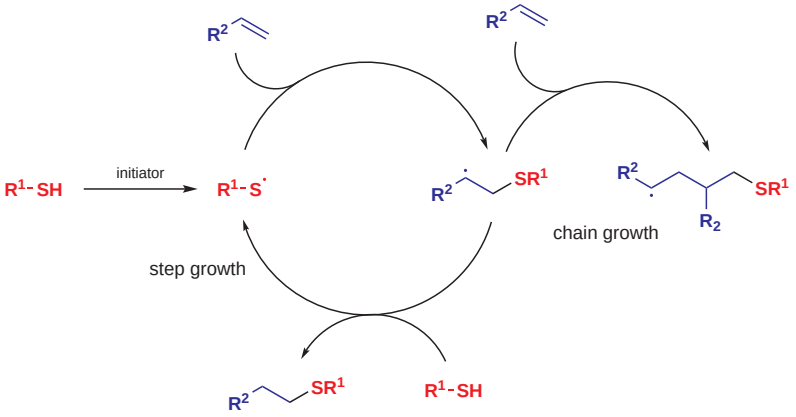
6.2 Hybridization of Thiol–Ene Chemistry Hydrogels for Biomedical Applications

Z. Xu and K. M. Bratlie

Light-triggered thiol–ene polymerization is a powerful tool for synthesizing hydrogels that are aimed to be applied in situ or used as 3D scaffolds. Thiol–ene reactions are a class of click transformations that involve free-radical-mediated addition of electron-rich thiol groups to electron-poor carbon–carbon double bonds. When tuned with homopolymerization of the carbon–carbon double bonds, the resultant hydrogel properties can be finely adjusted. In this review, commonly used methods for modifying polymers with thiol groups or double bonds are discussed, and strategies to overcome flaws in thiol–ene hydrogels are provided. Emphasis is given to the application and outlook of thiol–ene crosslinked hydrogels.



Keywords: click chemistry · thiol–ene polymerization · hydrogels · natural polymers · synthetic polymers · free radicals · light initiators · step growth · chain growth · methacrylic anhydride · norbornene

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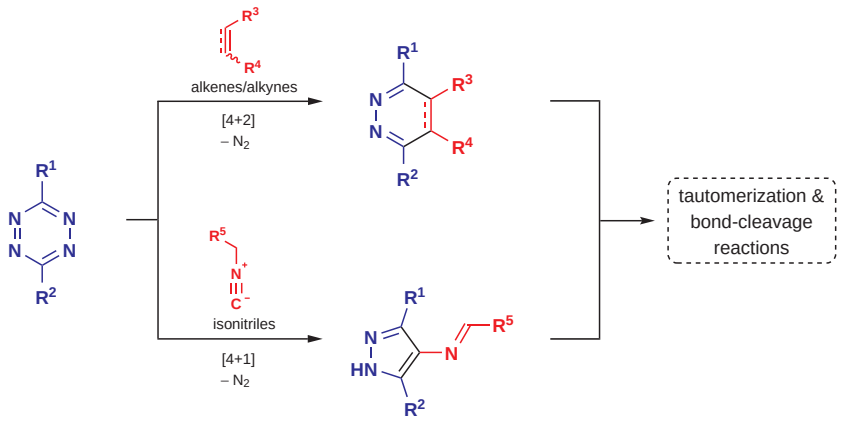
7 Tetrazine-Based Cycloadditions in Click Chemistry

W. Kuba, M. Wilkovitsch, J. C. T. Carlson, and H. Mikula

The spontaneous cycloaddition of tetrazines with a number of different dienophiles has become a powerful tool in chemical biology, in particular for the biocompatible conjugation and modification of (bio)molecules. The exceptional reaction kinetics made these bioorthogonal ligations the methods of choice for time-critical processes at very low concentrations, facilitating controlled molecular transformations in complex environments and even in vivo. The emerging concept of bond-cleavage reactions triggered by tetrazine-based cycloadditions enabled the design of diagnostic and therapeutic strategies. The tetrazine-triggered activation of prodrugs represents the first bioorthogonal reaction performed in humans, marking the beginning of the era of clinical translation of bioorthogonal chemistry. This chapter provides an overview of the synthesis and reactivity of tetrazines, their cycloadditions with various dienophiles, and transformations triggered by these reactions, focusing on reaction mechanisms, kinetics and efficiency, and selected applications.



Keywords: click chemistry · bioorthogonal chemistry · inverse-electron-demand Diels–Alder · dienophiles · *trans*-cyclooctenes · cyclooctynes · cyclopropenes · isonitriles · reaction kinetics · bioorthogonal bond-cleavage · click-to-release · tetrazines · dihydropyridazines · pyridazines · aminopyrazoles

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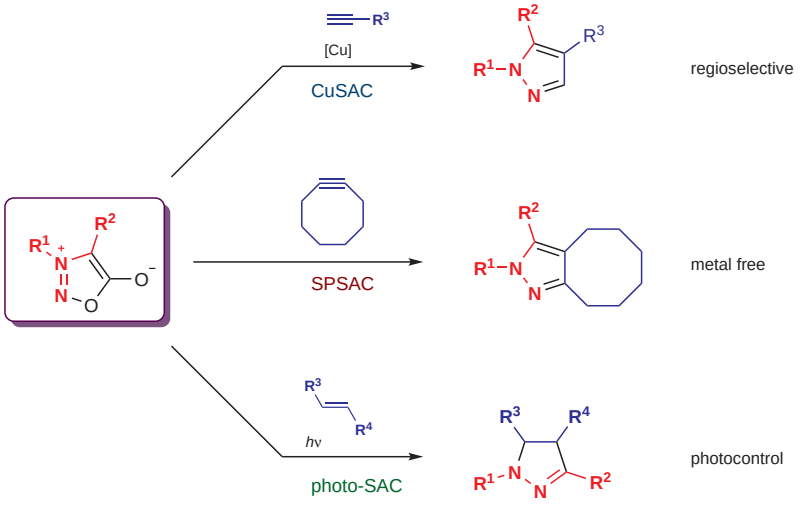
8 **Sydnone-Based Cycloadditions in Click Chemistry**

F. Friscourt

The 1,3-dipolar cycloaddition of sydnones (1,2,3-oxadiazolium-5-olates) with dipolarophiles, such as alkynes, has recently emerged as a versatile click reaction, with applications ranging from the mild and regioselective preparation of polysubstituted pyrazoles for drug discovery to the metal-free bioorthogonal ligation of biomacromolecules in living cells. This chapter reviews the importance of metal catalysis for controlling the regioselectivity of the copper-mediated reaction (CuSAC), as well as the development of fluorogenic probes, the click and release strategy, and photo-triggered ligations based on strain-promoted sydnone–alkyne cycloadditions (SPSAC).



Keywords: 1,3-dipoles · sydnones · cycloaddition · pyrazoles · cyclooctynes · click chemistry · bioconjugation · fluorogenic reactions · bioimaging