HHS Public Access

Author manuscript

Chem Rev. Author manuscript; available in PMC 2022 June 23.

Published in final edited form as:

Chem Rev. 2021 June 23; 121(12): 6991–7031. doi:10.1021/acs.chemrev.0c00799.

Light-Triggered Click Chemistry

Gangam Srikanth Kumar, **Qing Lin***

Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14260-3000, United States

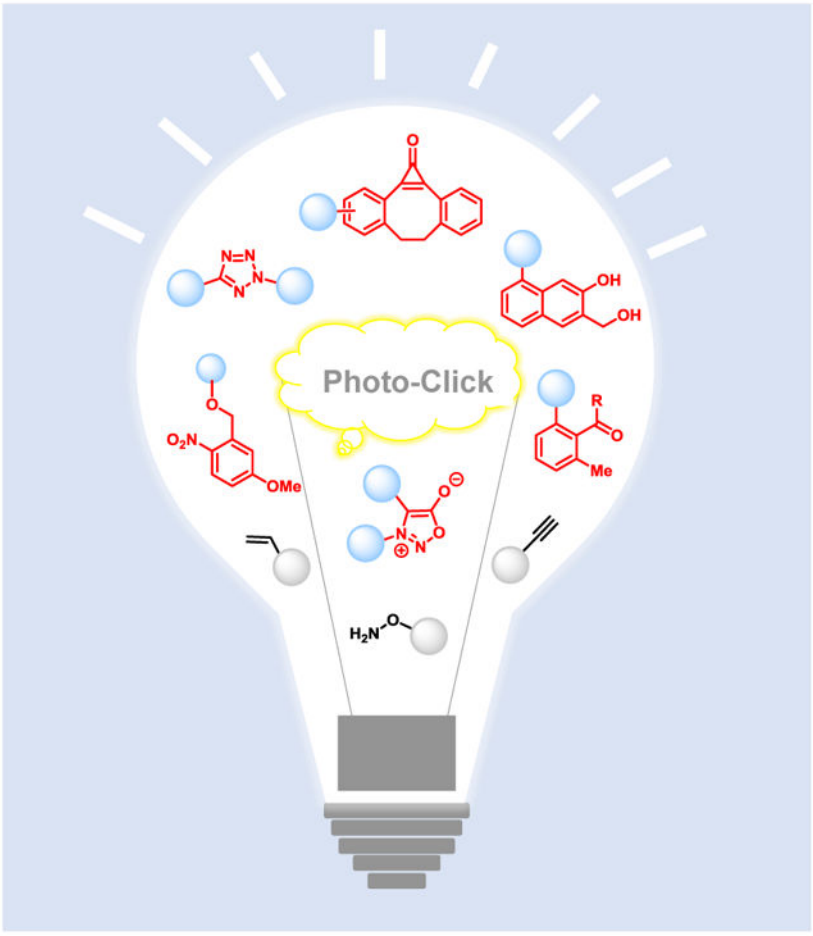
Abstract

The merging of click chemistry with discrete photochemical processes has led to the creation of a new class of click reactions, collectively known as photoclick chemistry. These light-triggered click reactions allow the synthesis of diverse organic structures in a rapid and precise manner under mild conditions. Because light offers unparalleled spatiotemporal control over the generation of the reactive intermediates, photoclick chemistry has become an indispensable tool for a wide range of spatially-addressable applications, including surface functionalization, polymer conjugation and crosslinking, and biomolecular labeling in the native cellular environment. Over the last decade, a growing number of photoclick reactions have been developed, especially those based on the 1,3-dipolar cycloadditions and Diels-Alder reactions owing to their excellent reaction kinetics, selectivity and biocompatibility. This review summarizes the recent advances in the development of photoclick reactions and their applications in chemical biology and materials science. A particular emphasis is placed on the historical contexts and mechanistic insights into each of the selected reactions. The in-depth discussion presented here should stimulate further development of the field, including the design of new photoactivation modalities, the continuous expansion of λ-orthogonal tandem photoclick chemistry, and the innovative use of these unique tools in bioconjugation and nanomaterial synthesis.

Graphical Abstract

***Corresponding author: Qing Lin** − Department of Chemistry, State University of New York at Buffalo, Buffalo, New York 14260-3000, United States; qinglin@buffalo.edu.

The authors declare no competing financial interest.



1. Introduction

In nature, many fundamental life processes, such as photosynthesis, use sunlight as energy to drive complex biochemical cascade reactions.[1,2] Inspired by nature, chemists have successfully harnessed light to trigger key chemical transformations in their efforts to synthesize complex molecules and biomolecular conjugates.[3–5] In contrast to the thermal process, the light-triggered reactions often display high yield and selectivity without the need for acids, bases, or transition metals for substrate activation. Thus, the photochemical strategy can considerably reduce the number of steps needed in the total synthesis of complex natural products.[3] Notably, aside from triggering the initial reaction, the light may not alter the subsequent chemical transformations (*vide infra*). From the application perspective, the use of light endows spatial and temporal control over the reaction, which makes them highly valuable in the realms of chemical biology and materials science.[5–9] The use of light as an external stimulus also allows chemical reactions to operate at the single-cell or even subcellular levels.

In 2001, Sharpless introduced the concept of click chemistry for facile synthesis of functional molecules from modular building blocks.[10] A set of efficiency criteria were put

forward for a reaction to be classified as “click reaction”: 1) the reaction must be operationally simple and have a broad substrate scope; 2) the reaction must be fast, high yielding, and selective; 3) the reaction must generate no or benign byproducts, which can be removed using non-chromatographic techniques; and 4) the reaction must be carried out under ambient conditions in non-hazardous solvents or neat. Many photochemical reactions satisfy these stringent criteria when suitable privileged substrates are used. The merging of click chemistry with benign photochemical processes has led to the creation of a new class of light-triggered click reactions, also known as photoclick chemistry, enabling synthesis of diverse molecular structures, conjugates, and networks in a spatiotemporally controlled manner in complex systems.[11,12]

A growing number of photoclick reactions have been reported in the literature over the last decade. The prominent examples include the photoinduced tetrazole-alkene cycloaddition,[13] the light-triggered hetero-Diels–Alder reactions,[14] the light-triggered azide–alkyne cycloadditions,[15] the photoinduced sydnone–alkene/alkyne cycloaddition,[16] the photoinduced azirine–alkene cycloaddition,[17] and the light-triggered oxime ligation reactions[18] (Scheme 1).

The photoclick reactions begin with the absorption of photons to generate the reactive species. Based on how light is harnessed, the photoclick chemistry can be classified into three types (Scheme 2). Type I involves irreversible photo-generation of a reactive intermediate with varying stability. In general, a precursor is ruptured under photochemical conditions to release N_2, CO_2, or a photo-protecting group and generate the reactive intermediate, which is then intercepted selectively by a cognate reaction partner (Scheme 2a). The light-triggered tetrazole–alkene cycloaddition, sydnone–alkene/alkyne cycloadditions, oxime ligation, and azirine–alkene cycloaddition depicted in Scheme 1 represent this type. Notably, the long half-lives of reactive intermediates may negatively affect the spatial control of the process. Type II involves photo-isomerization to generate a highly unstable reactive intermediate, which can either revert back to the starting materials or proceed to react with its partner to form a covalent adduct (Scheme 2b). The examples of this type include photoinduced hetero-Diels–Alder reactions based on *o*-naphthoquinone methide and *o*-quinodimethane. Type III reactions require a catalyst whose activation is mediated by light, e.g., light-triggered azide–alkyne cycloaddition and tetrazine ligation (Scheme 2c). Collectively, these photoclick reactions offer potent tools to many research fields, including biomolecular conjugation, drug discovery, polymer synthesis, lithography, and material sciences. Since several excellent reviews on thiol-ene photoclick reactions have appeared in the literature,[19–22] in this Review, we decided to focus on primarily the cycloaddition-based light-triggered click reactions and their myriad applications in chemical biology and materials sciences, with emphases on the historical context and mechanistic studies.

2. Tetrazole Photoclick Chemistry

2.1 History and Synthesis of Tetrazoles

Tetrazoles are an essential class of heterocycles comprised of a five-member ring with four nitrogen and one carbon atoms.[23] Unlike pentazoles, tetrazoles play a crucial role in drug

design because they are stable and bioisosteric to carboxylic acids. In 1885, J. A. Bladin reported the first synthesis of tetrazole by reacting dicyanophenylhydrazine with nitrous acid.[24] Later, Hantzsch and Vagt reported [3+2]-cycloaddition of azides with nitriles,[25] a method used widely for the synthesis of tetrazoles (Scheme 3a). Because of the widespread use of 2,5-diaryltetrazoles in bioorthogonal ligation and polymer synthesis, several synthetic approaches have been reported.[26,27] For example, Kakehi and coworkers reported the facile synthesis of 2,5-disubstituted tetrazoles by reacting phenylsulfonyl hydrazide with arene diazonium salts (Scheme 3b).[28] The advantages of this method include the use of readily available starting materials and good yields. However, this method employs hazardous reagents and suffers from laborious purification steps. Alternatively, the transition metal-catalyzed N^2-arylation of 5-substituted tetrazoles with diverse arylating reagents such diaryliodonium salts and aryl boronic acids have been developed.[29–35] Among these approaches, the Cu-catalyzed regioselective arylation of 5-substituted tetrazoles provides rapid access to 2,5-disubstituted tetrazoles under mild conditions (Scheme 3c).[32]

2.2 Generation and Structure of Nitrile Imines

In 1960, Huisgen and coworkers discovered the unique reactivity of tetrazole moiety in a photo-triggered 1,3-dipolar cycloaddition reaction of 2,5-diphenyltetrazole **9** with methyl crotonate.[36–38] Irradiation of 2,5-diphenyltetrazole with a mercury lamp led to the formation of a pair of pyrazoline regioisomers in a 3:1 ratio (Scheme 4a). A two-step reaction mechanism was proposed: upon absorption of light, the tetrazole undergoes fast cycloreversion to generate the reactive nitrile imine **10** with the extrusion of N_2; this nitrile imine then undergoes fast 1,3-dipolar cycloaddition with methyl crotonate to afford the pyrazoline product. The *in situ* generated nitrile imine species was confirmed by the reaction of a phenylhydrazonyl chloride with an alkene dipolarophile in the presence of a base *via* 1,3-dehydrochlorination, giving rise to the same cycloadduct. Following these initial studies, the reactivity of nitrile imines was explored in 1,3-dipolar cycloaddition reactions with various dipolarophiles as well as in intramolecular ring-closure reactions.[39–41]

Later, Holm and coworkers carried out a detailed study to investigate the formation of nitrile imines using spectroscopic techniques, including UV–vis, infrared, and MS-based fragmentation involving the ^{15}N-labeled tetrazoles.[42] The experimental studies revealed that 2,5-diaryltetrazoles underwent efficient ring rupture upon 290 nm UV irradiation with a quantum yield of 0.5~0.9 and that the electronic properties of substituents had minimal effect on ring rupture. Very recently, Barner-Kowollik and coworkers studied the wavelength-dependence and mechanism of the tetrazole-alkene cycloaddition reaction by using a combination of computational and experimental studies.[43,44]

Nitrile imines could also be generated by other means. Broggini and coworkers reported their generation from the hydrazonyl chlorides under aqueous conditions and their subsequent reactions with the various dipolarophiles (Scheme 4b).[45] The rate of cycloaddition was accelerated in aqueous media due to the hydrophobic effect. In the absence of dipolarophiles, tetrazine products were formed *via* dimerization of the nitrile imine. Recently, Carell and coworkers exploited the hydrazonyl chlorides for bioorthogonal protein modification in aqueous media.[46] The drawback of using hydrazonyl chloride as the

nitrile imine precursor is that the hydrazonyl chloride is prone to hydrolysis in aqueous media.[47] In contrast, tetrazoles exhibit excellent stability under aqueous conditions and provide rapid on-demand access to nitrile imines *via* photoirradiation.

In principle, the non-stabilized nitrile imines can adopt four possible electronic structures, including propargylic, allenic, 1,3-dipolar, and carbenic forms (Scheme 5a). A photo-crystallographic study of the tetrazole-Zn coordination complex at 90 K revealed a bent geometry for the *in situ* generated nitrile imine (Scheme 5b).[48] A separate water-quenching study confirmed that the twisted geometry represents the 1,3-dipolar form, a primary electronic structure likely responsible for its outstanding reactivity toward alkene dipolarophiles in aqueous media.

2.3 Mechanism of Nitrile Imine-Mediated Cycloaddition

Liu and coworkers studied the mechanism of the nitrile imine-mediated cycloaddition with alkenes.[49] In this work, they used hydrazonyl chlorides as the nitrile imine precursor to study the kinetics of the reactions. They found that the *p*H and the chloride concentrations have significant effects on reaction rate; the rate was higher under basic *p*H and in the absence of chloride ion, which they attributed to faster deprotonation and de-chlorination, respectively. Based on these results, they proposed a mechanism in which the generation of the nitrile imine from the hydrazonyl chloride is the rate-determining step of the overall reaction (Scheme 6).

Irrespective of how the nitrile imine is produced, scheme 6 shows a theoretical framework to consider the nitrile imine-mediated cycloaddition reactions as well as potential side reactions. Unlike other 1,3-dipoles such as azide and nitrones, nitrile imines are generally much less stable in an aqueous medium. In the absence of a suitable dipolarophile, they would react with water or other strong nucleophiles such as thiols to form the stable adducts, e.g., compounds **21** and **25** in Scheme 6.[50–53] Thus, to ensure that the 1,3-dipolar cycloaddition predominates among all the competing pathways, the nitrile imine and alkene reactivities need to be optimally tuned to increase the cycloaddition reaction rate while suppressing the competing ones.[54]

2.4 Enhancing Tetrazole Reactivity and Selectivity

In 2007, Lin and coworkers reported an efficient synthesis of diverse pyrazolines **29** *via* the photoinduced 1,3-dipolar tetrazole–alkene cycloaddition (Scheme 7).[55] A 302-nm handheld UV lamp commonly used for thin-layer chromatography was found to be sufficient for the tetrazole ring-rupture. The transformation displayed excellent functional group tolerance, outstanding regioselectivity, and high yield (Scheme 7). Remarkably, the reactions could be performed in protic solvents, including ethanol and EtOH/H_2O (7:1) mixture. This report offers the first glimpse into the desirable characteristics of the photoinduced tetrazole–alkene cycloaddition as a photoclick reaction, including its operational simplicity, functional group tolerance, mild reaction conditions tolerating water as a cosolvent.

To probe how substituents affect the rate of the tetrazole photoclick chemistry, Lin and coworkers prepared a series of 2,5-diaryltetrazoles carrying the electron-withdrawing or

electron-donating groups on the phenyl rings and determined the second-order rate constants, k_2, of the photoinduced cycloaddition reactions with 4-penten-1-ol (Scheme 8).[56] A plot of calculated HOMO energies, E_{HOMO}, of the corresponding nitrile imine versus log(rate of reaction) displayed a linear relationship, indicating that the rate enhancement is principally a result of HOMO-lifting effect, which decreases the HOMO (dipole)−LUMO (dipolarophile) energy gap in the transition state and thus accelerates the cycloaddition reaction.[57]

One of the most effective strategies to accelerate the click reactions is through substrate activation *via* ring strain, particularly for applications in biological systems. For tetrazole photoclick chemistry, the strained substrates offer faster cycloadditions without concurrent increases in the side reactions (Scheme 6). To this end, Lin and coworkers synthesized a series of conformationally constrained macrocyclic tetrazoles by placing a bridge between the two flanking phenyl rings (Scheme 9a).[58] Upon photoirradiation, macrocyclic tetrazoles produced the cyclic nitrile imines with reduced conformational flexibility, which lowers distortion energy in the cycloaddition reaction.[59,60] Compared to the acyclic analog, macrocyclic tetrazole **34** displayed enhanced reactivity in labeling a norbornene-modified lysozyme in PBS (Scheme 9b).

For enhanced selectivity for cycloaddition, An et al. prepared a series of sterically shielded tetrazoles containing structural pendants at the ortho positions of the C-aryl ring (Scheme 10a).[54] Among them, the di(*ortho*-2′-*N*-Boc-pyrrole)-substituted tetrazole **43** displayed an exquisite selectivity for the cycloaddition (Scheme 10b). The DFT calculations and structural studies revealed that *N*-Boc-pyrrole groups at *ortho*-positions of the C^5-aryl ring block nucleophilic addition, and as a result, increase the stability of nitrile imines with a half-life of 102 s in the aqueous medium. Moreover, the HOMO energy of the nitrile imine can be modulated through the substituent effect of the N-aryl group (Scheme 10c).[61] Owing to its excellent selectivity and fast kinetics, the sterically shielded tetrazole **43** was later successfully used to label a strained alkene-encoded membrane protein in live mammalian cells (*vide infra*).

2.5 Tuning Photoactivation Wavelength

Because a prolonged exposure of 302-nm UV light causes photodamage to cells, visible or NIR light-triggered tetrazole photoclick chemistry is more desirable in cellular applications. To this end, Lin and coworkers synthesized the substituted diaryltetrazoles that undergo ring rupture upon 365-nm photoirradiation (Scheme 11).[62] The substituents on the N-phenyl ring were found to be critical in determining absorption maxima; the presence of NH_2, NMe_2, and styryl groups led to a shift of absorption maxima to the longer-wavelength region and higher absorption coefficient at 365 nm (Scheme 11a). Notably, these substrates displayed similar reactivity in the photoinduced 1,3-dipolar cycloadditions with alkenes in organic solvents as well as in aqueous buffer. In addressing the photobleaching associated with the amino-containing pyrazolines products, a scaffold-hopping strategy was reported in the design of long-wavelength photoactivable tetrazoles consisting of chromophores such as naphthalene and coumarin (Scheme 11b).[63] Specifically, the naphthalene derived tetrazole

49 showed excellent reactivity in the photoinduced cycloaddition reaction with the alkene dipolarophiles under 365-nm photoirradiation.

In 2013, An et al. reported the design of laser-activatable tetrazoles with improved biocompatibility.[33] A series of oligothiophene based tetrazoles were synthesized through Cu-catalyzed N-arylation of substituted 5-(thiophen-2-yl)tetrazoles with phenyl(thiophen-2-yl)iodonium salts (Scheme 12a). Among them, tetrazole **53b** showed excellent reactivity in the photoinduced cycloaddition reaction with second-order rate constants approaching 619 ± 108 M^{-1} s^{-1} (Scheme 12b). Notably, the quantum yield for 405 nm laser triggered tetrazole ring rupture was determined to be 0.16, significantly higher than those of 365 nm photoactivable tetrazoles (Φ = 0.006 ~ 0.04).[62] A water-soluble tetrazole **53f** was then used to image microtubules in CHO cells in a spatially controlled manner. Additionally, the emission wavelength of oligothiophene pyrazoline products was tuned by introducing extended π-conjugation at the C^5- position of the tetrazole (Scheme 12c).[64] The pyrazoline products displayed solvent-dependent red fluorescence with emission maxima in the range of 575~644 nm, which could be useful in probing the polarity change in biological systems.

In 2015, the Barner-Kowollik group reported a visible light-triggered tetrazole photoclick chemistry by using a pyrene chromophore (Scheme 13).[65] The pyrene aryl tetrazole (PAT) **57** was synthesized in two steps from readily available starting materials. The pyrene-tetrazole displayed excellent reactivity towards a variety of dipolarophiles. The utility of this tetrazole was demonstrated in small-molecule ligation, design of block copolymers, and polymer end-group modification. The same group also reported an up-converting nanoparticles (UCNPs) assisted, NIR light-induced tetrazole photoclick chemistry (Scheme 13).[66] In this process, UCNPs (yttrium, tantalum, and ytterbium nanoparticles) were irradiated with the 974-nm NIR light to convert PAT to the nitrile imine, which then reacts with dipolarophiles. However, the cytotoxicity of the pyrene chromophore could potentially limit the broad use of these approaches in biological applications.

The two-photon excitation (2PE) induced process provides excellent spatiotemporal control over the single-photon process owing to the decreased light scattering of near-infrared (NIR) light and improved three-dimensional localization of excitation. Yu et al. reported 2PE-triggered tetrazole photoclick chemistry by taking advantage of strong two-photon absorption of naphthalene.[67] A femtosecond 700 nm NIR pulsed laser was used to generate the nitrile imines. A series of tetrazoles containing the auxochromic and oligo(ethylene glycol) groups at β-position of naphthalene were synthesized and tested in the 2PE-induced cycloaddition reaction (Scheme 14). The 2PE-triggered cycloaddition reaction of tetrazole **65** with acrylamide followed zero-order kinetics (k_0 = 0.067 ± 0.001 μM/min), indicating that the photoinduced tetrazole ring rupture is the rate-determining step. The two-photon absorption cross-section of tetrazole **65** was determined to be 12 GM (1 GM = 10^{-50} cm^4 s/photon), and the cycloaddition reaction cross-section was 3.8 GM. The utility of two-photon-triggered, fluorogenic photoclick reaction was demonstrated in a spatially controlled microscopic imaging of microtubules in live mammalian cells. The ability to generate nitrile imine species from photoactivable tetrazoles at different wavelengths enables the use of tetrazole photoclick reaction in conjunction with other photoclick reactions.[68–71] Recently, several λ-orthogonal photoligation strategies were presented for surface functionalization, in

which the photoactivable tetrazoles selectively activated in the presence of other photoactivable functionalities that undergo photoclick reactions.[69,70]

2.6 Dipolarophiles Other Than Alkenes

The tetrazole photoclick chemistry is not limited to alkenes; other dipolarophiles such as alkynes and quinones could also participate in the cycloaddition reactions.[72–74] Bochet and coworkers reported the synthesis of pyrazoles via 1,3-dipolar cycloaddition between the photogenerated nitrile imines and the alkynes (Scheme 15a).[72] Later, Yu and coworkers tuned the reactivity of nitrile imine by installing CF_3 group at *ortho*-positions of C^5-phenyl ring of the tetrazole for highly selective cycloaddition reaction with BCN (Scheme 15b).[73] The exquisite selectivity in light-triggered tetrazole-alkyne cycloaddition was attributed to the electrostatic shielding effect of the CF_3 groups. Exceptionally robust kinetics was observed for the tetrazole-BCN cycloaddition reaction, with k_2 values approaching 10^5 M^{-1} s^{-1}. In the absence of BCN, the oligothiophene moiety on the N^2-position of the tetrazole structure quenched the reactive nitrile imine to form the product **73**. The tetrazole-BCN photoclick reaction was later employed in protein bioconjugation under visible light. Separately, Ribagorda and coworkers reported the synthesis of pyrazoline-fused quinones *via* cycloaddition of tetrazoles with quinones (Scheme 15c).[74]

2.7 Applications in Bioorthogonal Protein Labeling

Over the last decade and a half, bioorthogonal chemistry has emerged as a powerful tool for visualizing multiple biomolecules including lipids, proteins, glycans and nucleic acids in their native cellular environment as well as manipulating biological processes in living systems.[75–77] In general, bioorthogonal chemistry comprises of two steps: 1) site-specific introduction of a chemical reporter into the target biomolecule; 2) bioorthogonal reaction between the chemical reporter and its reaction partner. Among a growing number of bioorthogonal reactions, tetrazole photoclick chemistry has generated a strong interest owing to its fast kinetics and spatiotemporal control.

In 2008, Lin and coworkers reported the first use of tetrazole photoclick chemistry for bioorthogonal protein modifications.[78] The initial study of the reaction between a tetrazole-modified peptide and acrylamide in PBS supports a two-step reaction mechanism involving the photoinduced generation of the nitrile imine followed by its subsequent cycloaddition with acrylamide. The second step is the rate-determining step that proceeds with a second-order rate constant of 11.0 M^{-1} s^{-1} (Scheme 16a). The selectivity of the reaction was verified through residue-specific modification of a tetrazole-modified lysozyme by acrylamide in PBS under a brief 302-nm photoirradiation (Scheme 16b). For site-specific protein modification, a tetrazole-containing enhanced green fluorescent protein (EGFP) prepared through intein-mediated chemical ligation and reacted with *N*-hexadecyl methacrylamide to produce the fluorescent EGFP-pyrazoline adduct after 1 min 302-nm photoirradiation (Scheme 16c).

In 2008, the Lin group demonstrated the suitability of tetrazole photoclick chemistry for fluorescent labeling of an *O*-allyl-tyrosine encoded Z-domain protein in *E. coli* cells (Scheme 17).[79] While light-triggered tetrazole ring rupture was rapid, the subsequent

cycloaddition with *O*-allylphenyl ether dipolarophile was slow (k_2 = 0.00202 M^{-1} s^{-1}) because of a large dipole HOMO-dipolarophile LUMO energy gap. Nonetheless, BL21(DE3) cells expressing the *O*-allyl-tyrosine-encoded Z-domain (alkene-Z) were selectively labeled by tetrazole **78** after photoirradiation at 302 nm for 4 min followed by overnight incubation (Scheme 17). Adding the electron-donating groups on the phenyl rings increases HOMO energies of the photogenerated nitrile imines, leading to faster reactions.[56] In particular, 2-(*p*-methoxyphenyl)-5-phenyltetrazole **79** displayed robust reactivity toward *O*-allylphenyl ether with k_2 value of 0.79 M^{-1} s^{-1}, about 200-fold faster than tetrazole **78**. With this improvement, tetrazole **79** allowed fluorescent labeling of the *O*-allyl-tyrosine encoded Z-domain protein in *E. coli* in one minute.[56]

To encode tetrazoles at any position in a protein structure for site-specific modification *via* photoclick chemistry, Lin and coworkers designed a series of photoreactive tetrazole amino acids in which the amino acid moiety was attached to either C^5 or N^2-aryl ring (Scheme 18a).[80] One of the amino acids, *p*-tetrazole-phenylalanine (*p*-Tpa, **82c**), was incorporated site-specifically into myoglobin using the amber codon suppression technique with an *M. jannaschii* amber suppressor *Mj*TyrRS mutant. Furthermore, *p*-Tpa served as a chemical reporter for fluorescent labeling of myoglobin via tetrazole photoclick chemistry (Scheme 18b).[81] Because *p*-Tpa lacks C-aryl ring, it exhibited slower reaction kinetics (k_2 = 0.082 M^{-1} s^{-1} towards dimethyl fumarate) and required 254 nm UV light for photoactivation.[81]

Since tetrazole amino acids are large, it is challenging to identify specific aminoacyl-tRNA synthetases to charge them into proteins for structural and functional studies. Therefore, it is preferable to encode their smaller reaction partners—alkenes—into proteins to minimize perturbation to protein structure. An early example of using tetrazole photoclick chemistry to image proteins in mammalian cells involved the metabolic incorporation of a methionine surrogate, homoallylglycine (HAG, **86**).[82] The advantage of this metabolic approach is its simplicity: no genetic manipulation is required for the introduction of the alkene chemical reporter. Indeed, β-galactosidase pre-tagged with HAG showed selective labeling by tetrazoles in both cell lysates and living mammalian cells. Because the adducts from tetrazole photoclick chemistry are fluorescent, HAG served as a robust chemical reporter for spatiotemporally controlled, fluorescent imaging of the newly synthesized proteins in HeLa cells.

Many synthetic alkene amino acids suitable for tetrazole photoclick chemistry have been incorporated site-specifically into proteins using the amber codon suppression technique (Scheme 19).[83,84] Whereas the earlier *O*-allyltyrosine **87** was a viable substrate for tetrazole photoclick chemistry in bacteria; it is not suitable for mammalian systems because the *Mj*TyrRS/$tRNA_{CUA}$ pair are not orthogonal to the mammalian synthetase/tRNA pairs. Because acrylamide is an excellent substrate for photoclick chemistry, the Liu and Wang groups independently reported the genetic encoding of an acrylamide-modified lysine (AcrK, **88**) for fluorescent protein labeling via tetrazole photoclick chemistry (Scheme 20a).[85,86] The advantages of using AcrK as a chemical reporter include its fast kinetics and minimum perturbation to the protein structure due to its small size. When AcrK was incorporated into FtsZ proteins in bacterial and mammalian cells, it allowed fluorescent labeling of FtsZ directly in intact cells (Scheme 20a).[86] To improve fluorescence turn-on

efficiency, Guo and coworkers reported the genetic encoding of styrene **89** as a dipolarophile for tetrazole photoclick chemistry (Scheme 20b).[87] The utility of this styrene-based alkene reporter was demonstrated by labeling the intracellular stress response protein HdeA in live cells (Scheme 20b).

While electron-deficient alkene amino acids are excellent reaction partners for tetrazoles, they are susceptible to Michael addition by thiols in biological systems. To avoid this problem, several groups have turned attention to the strained alkenes due to their excellent reactivity in the nitrile imine-mediated cycloaddition reactions and inertness in biological systems. For example, the Carell group reported the genetic encoding of a norbornene-modified Lys (NorK, **90**) into human polymerase j, which was further modified with hydrazonyl chlorides.[46] Similarly, the Lin group developed a cyclopropene amino acid (CpK, **91**) for fluorescent labeling of proteins inside mammalian cells *via* tetrazole photoclick chemistry (Scheme 21).[88] Compared to acrylamide and norbornene, 3,3-disubstituted cyclopropene **95d** exhibited faster kinetics owing to the partial release of the cyclopropene ring strain after the cycloaddition reaction (Scheme 21a). When CpK was incorporated site-specifically into EGFP in HEK293 cells, it directed rapid and selective labeling of EGFP by a 365-nm photoactivatable tetrazole **97** based on confocal microscopy (Scheme 21b).

To minimize steric repulsion between the C^3-substituent adjacent to the cyclopropene π-bond and the incoming nitrile imine in the transition state, Yu *et al.* reported the design of a highly reactive, yet stable spiro[2.3]hex-1-ene (Sph, **99**) for superfast photoclick reaction.[89] The crystal structure of Sph shows that the cyclobutane ring in Sph pulls C^3-substituents away from π-faces of the cyclopropene ring, resulting in a decreased bond angle of 92.3° compared to 113.5° for Cp **98** (Scheme 22a).

Kinetic analysis revealed that Sph is about 15 times more reactive than cyclopropene in the reaction with tetrazole **79**. When the spiro[2.3]hex-1-ene modified lysine (SphK, **92**) was incorporated site-specifically into superfolder GFP (sfGFP), it enabled rapid modification of sfGFP by a water-soluble tetrazole **100** with the second-order rate constant of 10,420 M^{-1} s^{-1} in Cl^--free phosphate buffer (Scheme 22b). SphK was then used in rapid fluorescent labeling of GCGR, a member of class B G protein-coupled receptors, in live HEK 293T cells with the sterically shielded tetrazole **101** (Scheme 22c).[54] Two nitrogen-containing spiroalkenes, azaspiro[2.3]hex-1-ene and azaspiro[2.4]hept-1-ene, were also synthesized, which show improved water solubility and reactivity in tetrazole photoclick chemistry with k_2 values as high as 33,200 M^{-1} s^{-1} in phosphate buffer/ACN (1:1) mixed solvent.[90]

2.8 Applications in Nucleic Acid Modification

The tetrazole photoclick chemistry was also used in post-synthetic modifications of nucleic acids.[91] Wagenknecht and coworkers reported the synthesis of a series of 2′-deoxyuridine building blocks containing diaryltetrazoles **102** as photoactivable groups (Scheme 23a).[92,93] The rapid photo-triggered modification of DNA was achieved by photoirradiation of the samples in aqueous medium at 365 or 405 nm (outside the absorption region of nucleic acids), with second-order rate constants up to 89 M^{-1} s^{-1}. Later, Zhou and coworkers

exploited an intramolecular photoclick reaction for fluorescent detection of DNA base variation (Scheme 23b).[94] Since the alkene moiety can be readily incorporated into nucleosides, the Rentmeister and Zhang groups designed the RNA and DNA building blocks bearing *O*-allyl group for post-synthetic modifications via the tetrazole photoclick chemistry.[95,96]

2.9 Chemosensors

Because tetrazole photoclick chemistry produces fluorescent cycloadducts, Yu *et al.* exploited this unique property and designed the photoactivatable fluorescent probes based on an intramolecular photoclick chemistry.[97] In a proof-of-concept study, they prepared a series of taxoid-tetrazoles conjugates by linking 7-β-alanyltaxol core with a tetrazole unit containing an *O*-allyl overhang at *N*-phenyl ring **104** (Scheme 24). Upon photoirradiation, the conjugates proceeded through an intramolecular photoclick reaction to form fluorescent pyrazoline adducts with fluorescence turn-on ratios as high as 112-fold for taxoid pyrazoline **105d**. The utility of this type of photoactivable fluorescent probes was demonstrated in spatially controlled fluorescent labeling of microtubules in live CHO cells.

Because fumarate is an excellent alkene substrate and the cycloadduct is fluorescent, Meier and coworkers designed a tetrazole probe **106** to detect the oncometabolite fumarate (Scheme 25a).[47] Owing to the efficient photochemical generation of nitriles imines, this approach provides improved sensitivity compared to the previously reported hydrazonyl chloride probes.[98] Similarly, An *et al.* developed a BODIPY-linked bithiophene-tetrazole **109** as an off-on fluorescence probe for the detection of hydrogen peroxide inside HeLa cells.[99] A drastic decrease of BODIPY fluorescence was observed for the meta-linked BODIPY-tetrazole after reaction with dimethyl fumarate. The BODIPY fluorescence was recovered after treatment with hydrogen peroxide (Scheme 25b). This unique fluorescence off-on was exploited for the detection of hydrogen peroxide inside HeLa cells using a water-soluble BODIPY-tetrazole **109**. Recently, Wittman and coworkers reported visualization of complex carbohydrates based on the reaction between the tetrazole and an acrylamide modified mannosamine.[100] Separately, Binco and coworkers designed a novel profluorescent nitroxide **113** via a tetrazole photoclick reaction to monitor the redox or radical processes (Scheme 25c).[101]

2.10 Applications in Materials Science

The ability to provide spatiotemporal control makes the tetrazole photoclick chemistry a powerful tool in materials science applications, including surface functionalization, polymer synthesis and cross-linking, and fullerene conjugation.[7,102,103] In 2011, Barner-Kowollik and coworkers demonstrated the utility of this photoclick reaction in surface functionalization by ligating a maleimide containing polymer chain to the tetrazole-functionalized silicon wafer surface (Scheme 26).[104] Later, they ligated poly(dopamine) (PDA) films with antifouling poly(MeOEGMA) brush polymers to control cell adhesion using tetrazole photoclick chemistry.[105] Similarly, Nallani and Liedberg reported the conjugation of the tetrazole-functionalized horseradish peroxidase with methacrylate-terminated ABA block copolymers.[106] Following these studies, numerous reports of nitrile imine-mediated surface patterning appeared.[7,107–115]

In 2014, the Barner-Kowollik group reported a facile approach for photolytic preparation of fluorescent polymers by employing polymerization of non-fluorescent photoreactive monomers based on tetrazole photoclick chemistry (Scheme 27a).[116,117] Later, they applied the photoclick reaction for the synthesis of extended linear polymers.[118] In this work, the selective reaction of a tetrazole-modified nitrile-butadiene rubber (NBR) **116** with a bis-maleimide linker **117** provided access to nitrile rubber of high molecular weight (Scheme 27b). Notably, tetrazole photoclick chemistry was used together with other photoclick reactions such as photo-enol chemistry for the synthesis of copolymers.[71]

The photoinduced cross-linking of polymers plays a vital role in tuning material properties such as solubility, viscosity, and optical properties. To this end, tetrazole photoclick chemistry has proven to be a valuable tool for polymer cross-linking owing to the precise control over photogeneration of the nitrile imines. Darkow and coworkers demonstrated a UV light-induced tetrazole-alkene reaction mediated cross-linking in membrane polymers.[119] Recently, the Barner-Kowollik group presented sunlight-induced cross-linking of 1,2-polybutadienes under ambient conditions employing a difunctional tetrazole **119** (Scheme 27c).[120] Several reaction parameters, including reaction time and concentration and light source, were optimized. They expanded the utility of tetrazoles as cross-linking agents to prepare fluorescent cellulose network,[121] as well as patterned surface and microparticles by direct laser writing.[122] Moreover, the quantification of ligation points in polystyrene networks was carried out by monitoring the fluorescence intensity of the cross-linked product.[123] On the other hand, single-chain nanoparticles (SCNPs) prepared via intramolecular cross-linking of single polymeric chains have found applications in chemosensors, catalysis, and drug delivery. In this regard, the intramolecular cycloaddition reactions between tetrazoles and alkene-functionalized polystyrenes were employed in the synthesis of SCNP.[124,125]

Fullerenes (C_{60}) are used widely in material and energy sciences due to their high electron affinity and excellent electron transfer properties. They are also known to undergo 1, 3-dipolar cycloaddition reactions with nitrile imines. Several examples of fullerene functionalization based on the cycloaddition chemistry have been reported.[126] Barner-Kowollik and coworkers developed an efficient method for fullerene functionalization based on tetrazole photoclick chemistry (Scheme 28).[127,128] The linear polymers such as tetrazole-functionalized polyethyleneglycol and poly(*tert*-butyl)acrylate were conjugated to fullerene to form the hybrid networks under UV irradiation.

2.11 Miscellaneous Applications

The intramolecular photoclick chemistry was also exploited for the synthesis of stapled peptides.[129] For example, Madden *et al.* used Balaram's 3_{10}-helix as a peptide helix model and appended the tetrazole and alkene groups at the side chain of i and $i + 4$ residues, respectively (Scheme 29). The resulting peptides were subjected to 302-nm photoirradiation to trigger the photoclick chemistry mediated peptide stapling. Peptide precursors with the lysine sidechain provided higher yields than those with the ornithine sidechain. Both tetrazole reactivity and alkene rigidity are crucial in determining macrocyclization yield

(Scheme 29). This intramolecular photoclick chemistry was further extended to the design of the potent stapled peptide-based dual inhibitors of Mdm2/Mdmx.[130]

By taking advantage of the spatiotemporal control, Zhong and coworkers employed the tetrazole photoclick chemistry to prepare hydrogels with unique features such as tunable gelation and high specificity (Scheme 30a).[131] These PEG-based hydrogels were used for the controlled release of therapeutic proteins. Similarly, Zhang and coworkers exploited the intramolecular photoclick chemistry to regulate self-assembly of supramolecular hydrogels (Scheme 30b).[132] The formation of the pyrazoline products led to the photodegradation of supramolecular hydrogels and the release of encapsulated biological materials such as cells and proteins.

3. Light-Triggered Azide–Alkyne Cycloadditions

3.1 Cu(I)-Catalyzed Azide–Alkyne Cycloadditions

The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) is of paramount importance in synthetic chemistry and widely regarded as a prototypic click reaction.[77,133–137] The research groups of Meldal and Sharpless independently reported the reactions between azides and alkynes to produce 1,2,3-triazoles with high regioselectivity and excellent yields (Scheme 31a).[138,139] Owing to its robustness and versatility, it has been extensively employed in biomolecular ligation, combinatorial synthesis, medicinal chemistry, surface functionalization, and polymer synthesis. In most CuAACs, active Cu(I) catalysts are generated *in situ* from Cu(II) salts through 1) the use of a reducing agent, 2) electrochemical generation of Cu(I),[140,141] 3) photochemical approaches,[142] and 4) copper-containing nanoparticles.[143] Among these approaches, reducing agents such as sodium ascorbate, quinone, and hydroquinone are the most commonly used. The photochemical generation of Cu(I) catalysts provides spatial and temporal control over the process, which could be advantageous for some biological and material science applications. To this end, König and coworkers reported the first example of light-triggered CuAAC reaction through photoirradiation of riboflavin tetraacetate **120** in the presence of Et_3N (Scheme 31b).[142] The resulting flavin reduces Cu(II) to Cu(I), which in turn catalyzes the reaction between the azide **123** and the alkyne **124**.

The light-induced formation of Cu(I) species can be carried out by either direct or indirect photolysis of Cu(II) catalytic system. The direct photolysis involves the absorption of UV light by a ligand of Cu(II), which leads to a ligand metal charge transfer for the reduction of Cu(II) complexes (Scheme 31c). To this end, Yagci and coworkers generated Cu(I) species by UV/Vis irradiation of $CuCl_2$ in the presence of the PMDETA ligand (Scheme 31d).[144] Similarly, Schubert and coworkers reported a photoinduced CuAAC reaction based on copper(II) acetate salt.[145] For direct reduction, amine ligands play a crucial role in the light-triggered CuAAc reactions. In addition to the stabilization of Cu(I) species, ligands also improve the solubility of catalytic systems in organic solvents. Tertiary amines such as triethylamine, PMDETA, tetramethylethylenediamine, and hexamethylenetetramine were among the most effective ligands.

On the other hand, indirect photolysis involves the absorption of UV-visible light through a photoinitiator to generate radical intermediates, which reduces Cu(II) to Cu(I) (Scheme 31c). Usually, indirect reduction approaches are faster than direct irradiation of Cu(II) complexes in the generation of Cu(I) species. To this end, Bowman and coworkers reported the light-induced CuAAc *via* photoinitiated Cu(II) reduction using a $CuSO_4{\cdot}5H_2O$ as a catalyst and a cleavage type photoinitiator Irgacure 2959 for the synthesis of hydrogels (Scheme 32).[146] Upon light irradiation (400–500 nm), the photoinitiator generates the radical species, which efficiently reduces Cu(II) to Cu(I).

A wide range of photoinitiators with distinct UV/visible absorption characteristics are available for light-induced CuAAc click reactions, including DBMP, titanocene, TMDPO, camphorquinone/benzyl alcohol, and phenothiazine (Scheme 33).[147,148] Based on the mechanism for the generation of radical species, these photoinitiators can be classified into two types: Type I (unimolecular) and Type II (bimolecular). Although both types are capable of reducing Cu(II) to Cu(I), Type I photoinitiators are more efficient than Type II in CuAAC reactions. The difference was attributed to the relatively low quantum yield of the bimolecular reaction process in generating radical species (Scheme 33).

Over the years, a large number of copper catalysts including $CuCl_2{\cdot}2H_2O$/sodium benzoate,[149] copper(II)(tris(2-aminoethyl)-amine)ketoprofenate,[150,151] copper(II)(N,N′-dimethylethylendiamine) ketoprofenate,[152] copper(II)phenyl-2,4,6-trimethylbenzoylphosphinate,[153] and others[154,155] have been successfully used in light-triggered CuAAC click reactions. To avoid photodecomposition under UV light exposure, numerous visible light-triggered CuAAC reactions were reported.[156–159]

In general, the efficiency of light-triggered CuAAC reactions depends on several factors, including irradiation time, light intensity, photoinitiator concentration. Studies have indicated that the photoinduced CuAAC reactions can proceed with the minimal amount of irradiation and the copper catalyst.[146] Importantly, the photoinduced CuAAC reactions provide temporal control over the process, as the reaction can be stopped at any time through bubbling of air into the system.[150] Upon introduction of air, re-oxidation of Cu(I) to Cu(II) occurs readily as the solution color changes to green. However, the inhibition of reaction is completely reversible; the reaction restarts by purging the solution with argon along with photoirradiation. Because of these features, the light-induced CuAAC reactions have been applied extensively to material sciences.[102,103,146,160–169]

3.2 Strain-Promoted Azide–Alkyne Cycloadditions

Despite the advantages of CuAAC reactions, the toxicity of copper limits the widespread adoption of CuAAC in biological applications. Bertozzi and coworkers reported the strain-promoted azide–alkyne cycloaddition (SPAAC) involving cyclooctynes without the use of a copper catalyst.[170] Following this pioneering work, a variety of strained alkynes including fluorinated cyclooctynes, dibenzocyclooctynes, and thiacycloalkynes have been designed for accelerated copper-free azide-alkyne cycloaddition.[171–173] In 2009, Popik and coworkers reported a photoinduced, copper-free azide–alkyne cycloaddition reaction using cyclopropenones **139** as the photo-masked alkyne precursors (Scheme 34).[15] These cyclopropenones were prepared in two steps: Friedel-Crafts alkylation of **137** with

trichlorocyclopropenium cation followed by selective hydrolysis to generate the cyclopropenones **139** (Scheme 34a).[15,174,175] The cyclopropenones display excellent thermal stability and do not react with azides under ambient conditions in the dark. However, upon irradiation at 350 nm cyclopropenones **139** rapidly generate the corresponding dibenzocylcooctynes **140**, which reacts with azides to form the cycloadducts **141** (Scheme 34b). The utility of this transformation was demonstrated through successful glycan labeling as well as surface immobilization. In these studies, the biotin-containing cyclopropenone **142** was used for cell labeling experiments, while the amino-terminated linker appended cyclopropenone **143** was used for immobilization on brush polymers (Scheme 34c).[15,176–178] The cyclopropenone-based photoinduced click chemistry was also applied to surface functionalization, hydrogel derivatization, functionalization of nanoparticles, and synthesis of hetero-bivalent agents.[178–183]

The Popik group employed a SPAAC-based sequential click strategy for cross-linking two discrete azide-tagged substrates (Scheme 35).[184] The heterobifunctional linker **144** contains a cyclopropenone-masked dibenzocyclooctyne group on one end (photo-DIBO) and an azadibenzocyclooctyne (ADIBO) group on the other. This design allows sequential catalyst-free ligations with two different azide substrates because the photo-DIBO moiety reacts with an azide-containing compound only after photoirradiation.

The dibenzo[a,e]cyclooctadiyne (Sondheimer diyne, **148**) represents a unique class of cross-linkers containing two strained triple bonds as reactive sites for double SPAAC reactions with two azides. This diyne has been successfully employed in cross-coupling numerous azide-functionalized partners from biomolecules to metal-organic frameworks.[185–188] However, the low stability and rapid decomposition of the DIBOD cross-linkers in aqueous solution limits its broader utility. To overcome this limitation, Popik and coworkers designed a novel photochemical precursor **147** for the DIBOD cross-linker, in which both alkynes are masked as cyclopropenones (Scheme 36a).[189] The photo-DIBOD **147** displayed high stability despite the presence of angle strain and an antiaromatic cyclooctatetraene core. Irradiation of photo-DIBOD with a 350 or 420 nm light in the presence of the azide resulted in the formation of a bis-triazole product. In this process, the addition of the second equivalent of azide to the diyne proceeds at a faster rate than that of the first azide addition. This rate difference in azide additions makes it challenging to achieve selective ligation with two different azides. To address this issue, the same group synthesized a mono-cyclopropenone-caged dibenzocyclooctadiynes (MC-DIBOD, **150**).[190] MC-DIBOD allows sequential SPAAC cross-linking of two different azides (Scheme 36b). MC-DIBOD was prepared by using selective monodecarbonylation of photo-DIBOD **147** or mono-cyclopropanation of dibenzo[a,e]cyclooctadiyne (DIBOD, **148**). Interestingly, the triazole-fused alkyne **152** displays excellent reactivity toward azides with k_2 values approaching 34 M^{-1} s^{-1}, thus representing the fastest SPAAC reaction in organic solvents (Scheme 36b).

Recently, Spitale and coworkers reported the first cellular application of cyclopropenone-based light-triggered click chemistry (photo-SPAAC) to label nascent azide-modified RNAs (Scheme 37a).[191] The cyclopropenone-caged oxa-dibenzocyclooctyne **155** displayed excellent stability even in the presence of high concentrations of thiols, and upon 350 nm irradiation, rapidly reacted with RNAs containing 2’-azidoadenosine (Scheme 37a). This

light-triggered strategy enabled fluorescence imaging and enrichment of RNAs in subpopulations of cells. To enhance the utility of this reaction in biological systems, the Popik group reported the SPAAC click reaction using near-infrared (NIR) radiation (Scheme 37b).[192,193] The photoinduced decarbonylation of cyclopropenone was achieved by nonresonant two- and three-photon excitation. The utility of this multiphoton SPAAC was demonstrated in cellular labeling in intact tissue as well as 3D patterning of hydrogels using **159b**. More recently, Kunishima and coworkers described a photocatalyst-promoted SPAAC reaction under blue light (450–500 nm) irradiation.[194]

Bertozzi and coworkers reported photo-generation of dibenzoselenacycloheptyne from irradiation of 4-selenabicyclo[5.1.0]-octatrienone, a highly strained alkyne designed for copper-free click reaction.[195] However, these compounds displayed low stability and reactivity as they underwent a hydrogen atom transfer from the solvent rather than cycloaddition. Following this study, Klán and coworkers developed click reactions based on a highly strained seven-membered dibenzosilacyclohept-4-yne **161** and azides or 1,2,4,5-tetrazines.[196] This reagent was readily generated from photoirradiation of the cyclopropenone precursor and displayed high stability and reactivity in click reactions with azides and tetrazines (Scheme 38a). Later, they reported a bioorthogonal “catch and photo-release” strategy involving a sequential [3+2] azide-alkyne cycloaddition and a photo-Favorskii rearrangement (Scheme 38b).[197]

Separately, Schnarr and coworkers reported a photoinitiated benzyne click reaction using 2-(3-acetyl-3-methyltriaz-1-en-1-yl)benzoic acid **168** as a benzyne precursor (Scheme 39a).[198] The benzyne photo precursor **168** can be synthesized in four steps and is stable under ambient conditions. The reaction was compatible with a variety of functional groups and completed in less than 5 min. Theoretical studies on cycloaddition involving strained alkenes showed that only trans-cyclooctene is capable of rapid cycloaddition with azides at room temperature.[199] Encouraged by this result, Weaver and coworkers harnessed photochemical energy and developed a visible-light triggered cycloaddition of alkyl azide with benzofused cycloheptene **170** (Scheme 39b).[200] The reaction involves a photocatalyst mediated light-induced isomerization of benzocycloheptene to the strained trans-cycloalkene, which then reacts rapidly with the azides. The reaction between the azide and benzocycloheptene occurs only in the presence of light and the photocatalyst **172**, thus providing a temporal control to the reaction. This transformation displays broad functional group tolerance and was employed in fast bioconjugation of azide-functionalized insulin. The shortcomings of this reaction include precipitation of photocatalyst under higher aqueous concentration and requirement of long irradiation time, which limit its utility in biological systems.

4. Light-Triggered Hetero-Diels–Alder Reactions

4.1 Hetero-Diels–Alder Reaction of Naphthoquinone Methides

The Diels–Alder reaction is a powerful reaction for building molecular complexity in the synthesis of natural products and molecules with biological significance.[201,202] Following the seminal work of Otto Diels and Kurt Alder in 1928, tremendous advancements have been made to improve the selectivity and yields of the reaction. The reaction rate can be accelerated by the use of lewis acids or *in situ* generated reactive dienes. The hetero-Diels–

Alder reaction is a variant of Diels-Alder reaction in which hetero atom containing dienes or dienophiles are involved in the bond formation step. Light can be used to generate reactive hetero-dienes, e.g., *o*-quinone methides and hydroxy-*o*-quinodimethanes (photenols), from appropriate precursors. Since light-induced Diels–Alder reactions proceed under physiological conditions without requiring a catalyst or producing side products and allow spatiotemporal control of the process, they have been extensively exploited in biological applications and material chemistry.

Popik and coworkers reported the photoirradiation of 3-(hydroxymethyl)-2-naphthol (NQMP, **173**) to generate reactive naphthoquinone-3-methides (oNQMs, **174**), which undergoes facile hetero-Diels–Alder reaction with the electron-rich olefins to afford photostable benzochroman **175** in high yields (Scheme 40a).[14,203] The photoactivation of NQMP can be carried out using a low-pressure mercury lamp or fluorescent tube (300 nm or 350 nm) with high quantum yields (Φ_{300} = 0.17 ± 0.02 for **173**). The reactions produce the benzochroman products exclusively with second-order rate constants up to 4×10^4 M^{-1} s^{-1}; the unreacted oNQMs **174** undergo rapid hydration ($k_{H2O} \sim 145$ s^{-1}) to regenerate the starting material **173** (Scheme 40a). The distinctive features of this transformation are fast kinetics and the use of only 1.5 equivalents of alkene dienophiles. Notably, oNQMs react with vinyl ethers and enamines, but not other alkenes such as methyl acrylate, 2,5-dihydrofurans, dimethyl maleate, and methylcyclohexane (Scheme 40b). For unreactive alkenes, the hydration process predominates, resulting in regeneration of the starting material. Importantly, the product stability is dependent on the pH of the solution; for example, the use of enamines as an alkene partner results in the formation of 2-hydroxybenzochroman under neutral aqueous conditions (Scheme 40c). Later, the Popik group demonstrated the utility of this transformation in the light-directed surface derivatization and patterning.[204,205]

The *in situ* generated *o*-NQMs **174** can be intercepted by a variety of nucleophiles, including thiols and azide ions (Scheme 41a).[206] The reaction between *o*-NQMs and thioethanolamine proceeds five times faster than the one with ethyl vinyl ether. The resulting thiol adducts are photolabile and can be converted into *o*-NQM during extended irradiation. This type of thiol–quinone methide photoclick chemistry has been exploited for various applications including selective and irreversible functionalization of proteins and patterned immobilization of biomolecules onto surfaces (Scheme 41b).[207,208]

4.2 Hetero-Diels–Alder Reaction of *o*-Methyl Phenyl Ketones and Aldehydes

The *o*-quinodimethanes (oQDM) display remarkable activity in the Diels-Alder reaction and proven to be versatile intermediates for the synthesis of cyclic scaffolds.[209,210] In recent years, photo-triggered Diels–Alder reaction based on *o*-quinodimethanes have been exploited in various applications,[211] including surface functionalization,[212,213] syntheses of sequence-defined macromolecules,[214] light-induced assembly of nanostructures,[215] 3D laser writing[216,217] and polymer-polymer conjugations.[218–222]

In 2011, Barner-Kowollik and coworkers reported a light-triggered Diels–Alder reaction for polymer conjugation based on photoinduced generation of o-quinodimethanes (photoenols) from 2-methylbenzophenones **183** (Scheme 42a).[223] The reaction involves the formation of

biradical **184**, which undergoes rearrangement to form highly reactive *E*- and *Z*-photoenols. The *E*-isomer **185** diplays excellent reactivity with the activated dienophiles such as maleimides in conjugating polymeric building blocks. However, the *Z*-isomer **186** may undergo a [1,5]-sigmatropic shift to deliver starting material (Scheme 42a). The efficiency and speed of the photoenol chemistry were demonstrated in the conjugation of polymeric building blocks containing *o*-methyl phenyl ketone and maleimide functionalities. The introduction of a hydrogen bond donor to the *ortho* position of the formyl group further enhanced the reactivity of photoenols (Scheme 42b).[212] This enhancement is attributed to the presence of hydrogen bonding in stabilizing the intermediate, leading to its longer lifetime and thus the amount of *Z*-isomer formed **189.**[224] The Barner-Kowollik group designed a 2-formyl-3-methyl phenoxy (FMP) substrate **188** as an efficient precursor of photoenol for light-triggered Diels–Alder reaction with a variety of dienophiles including the maleimide and acrylamide (Scheme 42b).[212] The transformation is compatible with a wide range of solvents, including dichloromethane, acetonitrile, DMF, and water; however, irradiation time varies depending on the solvent.

Recently, Barner-Kowollik and coworkers studied wavelength-dependency of the photoinduced click reaction between *o*-QDMs and dienophiles to understand the mechanism and photophysical properties of the reaction.[43] To apply the photoenol chemistry to biological applications, they presented a visible light-induced Diels–Alder transformation based on reactive *o*-quinodimethane thioethers **191** and electron-deficient alkenes.[225] The use of visible light for the generation of reactive dienes was achieved through a simple oxygen-to-sulfur switch within the *o*-methylbenzaldehyde (o-MBA) structure **191** (Scheme 42c), which lowers the energy gap for the $\pi \rightarrow \pi^*$ transition in the formation of o-QDMs and contributes to the red-shift in absorption. The visible-light-induced [4+2] ligation proceeds quantitatively in aqueous solution as well as in organic solvents.

Since 2-cyanopropyl dithiobenzoate (CPDB) based polymers (RAFT agents) and electron-deficient alkynes are compatible with the photoenol chemistry, hetero-Diels–Alder conjugation was used in the conjugation of the photoenol with the thioester terminus containing RAFT polymer under ambient conditions (Scheme 43a).[220] The use of electron-deficient alkynes as dienophiles in Diels–Alder reaction with photocaged dienes **188** and **191** leads to the formation of pro-fluorescent Diels–Alder product **195** (Scheme 43b).[226] Since the pro-fluorescent product **195** does not absorb light in the range of starting material, the photobleaching and other side reactions from competitive absorption were not observed. Interestingly, the pro-fluorescent product **195** was converted into fluorescent naphthalene **196** in the presence of a catalytic amount of acid *via* rapid E1 elimination (Scheme 43b). The controlled generation of the fluorescent product enables fluorometric evaluation of the ligation reaction.

4.3 Hetero-Diels–Alder Reaction of 9,10-Phenanthrenequinone with Alkenes

In 2018, Zhang and coworkers reported visible light-triggered photoclick reaction involving [4+2]-cycloaddition between 9,10-phenanthrenequinone (PQ) **197** and electron-rich alkenes such as vinyl ethers (VE) to form fluorescent adducts **199** (dione–vinyl ether photocycloaddition).[227] The reaction proceeds via photoinduced electron transfer (PeT)

pathway involving excitation of PQ functionality to PQ*. The electron transfer between the excited PQ* and vinyl ether (VE) moiety leads to the formation of a 1,6-biradical intermediate **198**, which undergoes intramolecular radical recombination to form [4+2] cycloadducts **199** (Scheme 44). This reaction displays high selectivity for the cycloaddition, and side reactions such as nucleophilic addition or cycloadditions with electron-deficient olefins were not observed. The authors demonstrated the utility of this photocycloaddition in orthogonal labeling of proteins together with strain-promoted azide-alkyne cycloaddition (SPAAC) or the tetrazole photoclick chemistry with monomethyl fumarate.

4.4 Tetrazine Ligation

The inverse electron-demand Diels–Alder cycloaddition (iEDDAC) of tetrazines with strained alkenes or alkynes, also known as tetrazine ligation, has emerged as an ideal tool for biomolecular labeling.[228–230] Fox and co-workers reported a tetrazine ligation involving a cyclopropane-fused trans-cyclooctene with a second-order rate constant of 10^6 M^{-1} s^{-1},[231,232] representing one of the fastest bioorthogonal reaction reported in the literature. Recently, light-induced tetrazine ligations (photo-iEDDAC) were developed based on *in situ* generations of one of the reaction partners.[233–236] For example, Fox and coworkers described a light-induced tetrazine ligation using visible light along with methylene blue photosensitizer for oxidation of dihydrotetrazine to tetrazine (Scheme 45a).[233] Irradiation of dihydrotetrazine **200** with 660-nm light in the presence of methylene blue generates the reactive tetrazine **201**, which then reacts with trans-cyclooctene to form cycloadduct **202** (Scheme 45a). The photocatalytic activation of tetrazine ligation has been used for the functionalization of polymeric materials. For example, Forsythe and coworkers used the light catalyzed tetrazine-norbornene iEDDAC reaction for polymer cross-linking to form the hydrogels.[234] Recently, the photoactivation of cyclopropenones to generate to cycloalkynes was also adopted in the light-triggered tetrazine ligation for site-specific protein labeling in live cells (Scheme 45b).[235] The cyclopropenone-caged BCN-based probe **204** displayed excellent reactivity towards tetrazine with rate constants of 50 M^{-1} s^{-1}. Similarly, Laughlin and coworkers reported a photocaged approach in cyclopropene–tetrazine ligation by masking the cyclopropene reactivity with a photo-protecting group (Scheme 45c).[236,237] Here, a unique caged spirocyclopropene derivative **208** was designed in which the presence of a bulky photo-protecting group prevents the cycloaddition reaction. Upon irradiation, the protecting group is removed to release the unhindered cyclopropene **209**, which readily reacts with the tetrazine **207**.

5. Light-Triggered Sydnone–Alkyne Cycloadditions

Sydnones are an important class of mesoionic heterocycles that have been studied extensively in synthetic chemistry due to their stability and facile synthesis.[238] Generally, sydnones are depicted in the form of resonance structure **211**, which is similar to the enolate structure. However, experimental studies suggested that the sydnones might not be aromatic; other representations such as **212** and **213** are in agreement with the spectral data (Scheme 46a).[239] Sydnones are synthesized in two steps: nitrosylation of an amino acid derivative followed by cyclodehydration in the presence of an acid (Scheme 46b).[240] Sydnones display excellent reactivity in 1,3-dipolar cycloadditions with a variety of dipolarophiles to form

pyrazoles. The reaction proceeds through the formation of a bicyclic intermediate **218** that undergoes spontaneous CO_2 loss via a retro-Diels–Alder process to afford the pyrazole product **219** (Scheme 46c). Over the years, tremendous advancements have been made with this transformation.[238,241] Among them, copper-mediated sydnone–alkyne cycloaddition (CuSAC) is the most significant, enabling its use as a click reaction for bioconjugation.[242] Recently, Cu-free sydnone–alkyne cycloadditions were reported using the strained alkynes bicyclo[6.1.0]non-4-yn-9-ylmethanol (BCN) and dibenzoazacyclooctyne with k_2 values of 0.054 M^{-1} s^{-1} and 1.46 M^{-1} s^{-1}, respectively.[243,244] Surprisingly, the reaction of 4-fluorosydnones with the strained alkynes improved reaction kinetics tremendously, with the second-order rate constants reaching 10^4 M^{-1} s^{-1}.[245,246]

The generation of nitrile imines species upon photoirradiation of sydnones and their use in cycloaddition reactions have been well-documented in literature.[247–251] Inspired by their unique reactivity, Yu and coworkers reported the first photoinduced diarylsydnone–alkene cycloaddition reaction with high efficiency and excellent fluorescence turn-on (Scheme 47a).[16] A series of diarylsydnones (DASyds) **220** were synthesized and screened in the photoinduced 1,3 dipolar cycloaddition reactions. Among them, diarylasydnone **220a** displayed excellent reactivity in the fluorogenic photoclick reaction towards various alkenes, including TCO, norbornene, methyl methacrylate, diethyl fumarate, and 5-vinyl-2'-deoxyuridine (VdU). Notably, the competitive thermal cycloaddition was extremely slow as there were no cycloadducts observed in the dark for 24 hours. Selective photoinduced fluorogenic labeling of TCO-appended proteins was achieved by using **220a**. Subsequently, they demonstrated fast photoclick reactions between the diarylsydnones and the strained alkynes (Scheme 47b).[252] Importantly, the reaction between **220d** and BCN was achieved under 405-nm photo illumination with high efficiency and selectivity. The competing cycloaddition products derived from the diarylsydnone–alkyne cycloaddition (DASAC) pathway were also observed; however, this pathway proceeds at a much slower rate compared to the photoclick one (Scheme 47b). Significantly, the adjacent *ortho*-diaryl units on the diarylsydnones (DASyd) twisted around the sydnone core, which presents steric repulsion towards the incoming dienophile and hinders the DASAC pathway. Kinetic studies indicated that the decarbonylation of 4,5-diaryl-2-oxa-1,5-diazabicyclo[2.1.0]pentan-3-one **221** might be the rate-determining step in the transformation. The biocompatibility of this reaction was demonstrated through selective protein labeling on A549 cell surface. The same group also designed the photoactivatable β-diarylsydnone-L-alanines for the fluorogenic tracing of peptides in live cells *via* photoclick cyclization.[253]

Recently, Yu and coworkers reported a visible-light accelerated bioorthogonal reaction of diarylsydnone **220** with the strained dibenzo[b,f][1,4,5]thiadiazepine (DBTD) (Scheme 48).[254] In addition to the generation of nitrile imine species, visible light irradiation also induces the isomerization of DBTD from *Z* to *E* to confer ring-strain onto the macrocyclic azobenzene. Kinetic studies revealed that (*E*)-DBTD **229** reacts 6.6-fold faster than that of (*Z*)-DBTD **228**. Notably, the cycloaddition between the N=N bond of (*E*)-DBTD **229** and the nitrile imine dipole was extremely fast, with k_2 of $(1.6 \pm 0.16) \times 10^5$ M^{-1} s^{-1}. The versatility of the DBTD reporter was demonstrated in selective fluorescence labeling of proteins.

6. Light-Triggered Azirine–Alkene Cycloadditions

Upon photolysis, 2*H*-azirines **230** generate reactive nitrile ylides that can react with a variety of dienophiles to form cycloadducts **234** (Scheme 49a).[255–257] Lin and coworkers reported a photoinduced azirine–alkene cycloaddition, or azirine ligation, for efficient protein modification in an aqueous medium.[17] The *in situ* generated nitrile ylides appear to be more reactive than the photogenerated nitrile imines and react with the electron-deficient alkenes such as dimethyl fumarate. The utility of azirine ligation was demonstrated in the selective functionalization of an azirine-modified lysozyme by PEG-modified fumarate (Scheme 49b). To expand the scope of azirine ligation, Barner-Kowollik and coworkers introduced a pyrene group on the azirine ring, leading to visible-light (>390 nm) triggered azirine ligation with the electron-deficient alkenes such as fumarates, acrylates, and maleimide under ambient conditions (Scheme 49c).[258]

7. Light-Triggered Oxime Ligation

In recent years, oxime ligation—the condensation of aldehydes with alkoxyamines—has been extensively studied owing to their high efficiency, selectivity, and operational simplicity.[259–261] The main advantages include the use of inexpensive starting materials with water being the only side product and compatibility with the aqueous medium, making this reaction attractive for biological and polymer applications. Light can be used as an external stimulus to generate one of the two reactants involved in an oxime click reaction. The Maynard and Yousaf groups reported the light-triggered oxime ligation reactions for immobilizing biomolecules based on the photochemical generation of the alkoxyamine species (Scheme 50a).[262,263] Owing to the inherent photochemical control, this reaction has been employed in micropatterning substrates.[18,264] Separately, Barner-Kowollik and coworkers reported a rapid generation of aldehydes through photo-deprotection of the o-nitrobenzyl acetal derivatives at 370 nm (Scheme 50b).[18] The utility of this light-triggered oxime reaction was demonstrated in surface patterning with a fluorophore as well as the GRGSGR peptide.

8. Miscellaneous Photochemical Reactions

Given the apparent advantages of photochemistry, several light-triggered reactions can be potentially turned into click reactions owing to the usefulness of the in situ generated reactive intermediates. In particular, photoinduced benzodioxinone-based ketene chemistry, photoinduced perfluorophenyl azide chemistry, and photoinduced [2+2] cycloaddition reactions have attracted significant interests in organic chemistry and material sciences.[11,102] Ketenes are a versatile class of intermediates with unique reactivity in synthetic chemistry and have proven to be highly reactive towards a variety of functional groups including amines, acids, alcohols, and unsaturated compounds.[265–267] Ketenes can be readily generated photochemically from irradiation of benzodioxinone **237** or dialkyl Meldrum's acid and react with alcohols rapidly in the synthesis of linear and cross-linked polymers (Scheme 51a).[268–278] Similarly, the photoinduced perflurophenyl azide chemistry has been widely exploited in surface functionalization and nanomaterial synthesis owing to its fast kinetics, high efficiency, and easy preparation.[279] Mechanistically, the reaction involves the

photochemical generation of electron-deficient perfluorophenyl nitrene **241**, which readily undergoes C-H or X-H insertion reactions (Scheme 51b). The utility of this reaction was demonstrated in the immobilization of carbohydrates to different nanomaterials such as silica wafer, gold substrates, and polymers.[280–284] Finally, the photoinduced reaction between a carbonyl compound and an alkene, commonly known as Paterno–Büchi reaction, is a photochemical reaction invaluable for the synthesis oxetanes and functionalization of polymers (Scheme 51c).[285–287] Similar to other click reactions, this reaction proceeds through a concerted mechanism with 100% atom economy. However, the reaction requires an excessive amount of the alkene reaction partner and proceeds rather slowly. Nevertheless, numerous applications based on [2+2]-photocycloaddition were well-documented in the literature.[287,288]

9. Conclusions and Outlook

In this Review, we have discussed three types of light-triggered click reactions, including mainly 1,3-dipolar cycloadditions, hetero-Diels-Alder cycloadditions, and oxime ligation, and their growing impact on diverse research fields such as chemical biology and material sciences. The use of light as external stimuli to trigger click reactions not only enhances the efficiency of the click reactions but also offers rapid access to diverse scaffolds and molecular architectures under mild reaction conditions. Furthermore, the “on-demand” nature of light-induced reactions has added a spatiotemporal control to the click reactions for a variety of critical applications, including surface functionalization, polymer chemistry, and bioorthogonal chemistry. Importantly, the efficiency of photoclick reactions can be refined by adjusting wavelength, light intensity, and photoirradiation time.

The field of the light-triggered click chemistry continues to expand in the last decade as a growing number of photoclick reactions have been reported based on the photochemical generation of reactive species without the use of toxic metal catalysts or reagents. Among them, tetrazole photoclick reaction and hetero-Diels-Alder photoclick reactions have received substantial attention from the research community owing to their concerted reaction mechanism and rapid reaction rate. More recently, the use of light to introduce ring strain into the substrates represents an emerging area within the photoclick chemistry arena with a potential to open up new opportunities for bioconjugation and nanomaterial synthesis.[200,254,289]

Since the majority of photoclick reactions are triggered by UV light, which may restrict their utility in biological systems, tremendous efforts have been devoted to the development of photo-triggered click reactions under visible and near-infrared (NIR) light. Significant advances have been made in recent years in tuning photoactivation wavelength, decreasing photoirradiation time, improving reactant stability in complex environments, and designing faster reactions. The availability of a sizeable photoclick reaction repertoire operating at varied but discrete wavelengths has made it possible to perform tandem λ-orthogonal photoclick reactions in materials science.[71] With additional photoactivation modalities, it should be possible in the future to employ multiple photoclick reactions in multiplexed manipulation of biomolecules in a spatiotemporally controlled manner in their native cellular environments. With the advancements mentioned here and continuing expansion of

the field, we envision that the powerful tools derived from the union of light with click chemistry will fuel a new age of molecular exploration in chemical biology and materials science in many years ahead.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Institutes of Health (R35GM130307) and National Science Foundation (CHE-1904558) for supporting our ongoing work on exploring orthogonal chemical reactivity in life processes. We thank the graduate students and postdoctoral fellows in Lin research group, past and present, for their diligent contributions, and our collaborators for pushing the boundaries of applications described in this manuscript.

Biographies

Gangam Srikanth Kumar received a Master's degree in Chemistry from Central University of Rajasthan in 2013 and a Ph.D. in organic chemistry from the Indian Institute of Science and Education Bhopal in 2018 under the guidance of Prof. Manmohan Kapur. His doctoral studies focused on the development and mechanistic insight of transition-metal catalyzed C-H functionalization methods for the synthesis of diverse heterocycles. After completing his Ph.D., he began his postdoctoral research in the group of Prof. Qing Lin at University at Buffalo, USA. He is currently working on the development and application of bioorthogonal methods based on the 1,3-dipolar cycloaddition reactions of nitrile imines.

Professor Qing Lin received his BS in Chemistry from the University of Science and Technology of China in 1994 and Ph.D. in Organic Chemistry from Yale University in 2000 under the direction of Professor Andrew Hamilton. After postdoctoral training in Professor Peter Schultz's lab at Scripps Research and a brief stay in the industry, he joined the faculty of the State University of New York at Buffalo in 2005, where he is now Professor of Chemistry. His research interests include the development of (i) bioorthogonal reaction-based tools and their use in elucidating molecular mechanisms of the class B G protein-coupled receptor-mediated signaling, and (ii) enabling chemical technologies for the design of next-generation peptide and protein therapeutics.

ABBREVIATIONS

Ac	acetyl
ACN	acetonitrile
AcrK	N^6-acryloyl-*L*-lysine
ADIBO	azadibenzocyclooctyne
AsphK	N^6-((2-oxo-2-(5-azaspiro[2.3]hex-1-en-5-yl)ethoxy)carbonyl)-L-lysine
BCN	bicyclo[6.1.0]nonyne
Boc	*tert*-butoxycarbonyl
BODIPY	boron-dipyrromethene

Bn	benzyl
Bz	benzoyl
CpK	N^6-(1-methylcycloprop-2-ene-1-carbonyl)-L-lysine
CQ	camphorquinone
CuAAc	copper-mediated azide alkyne cycloaddition
CuSAc	copper-mediated sydnone alkyne cycloaddition
CPDB	2-cyanopropyl dithiobenzoate
DASAC	diarylsydnone-alkyne cycloaddition
DASyd	diarylsydnones
DBMP	2-benzyl-2-(dimethylamino)-4′-morpholinobutyrophenone
DBTD	dibenzo[b,f][1,4,5]thiadiazepine
DCM	dichloromethane
DIBOD	dibenzo[a,e]cyclooctadiyne
DIC	differential interference contrast
DIO	3,3-dioctadecyloxacarbocyanine
DMF	*N*,*N*-dimethylformamide
DNA	deoxyribonucleic acid
DIBO	dibenzocyclooctyne
DMSO	dimethylsulfoxide
EDG	electrondonating group
EWG	electron withdrawing group
EtOAc	ethyl acetate
E. coli	Escherichia coli
EGFP	enhanced green fluorescent protein
FT-IR	Fourier-transform infrared spectroscopy
GFP	green fluorescent protein
GPCRs	G protein-coupled receptors
HdeA	(histone-like nucleoid structuring)-dependent expression A
HEK	human embryonic kidney

HOMO	highest occupied molecular orbital
iEDDAC	inverse electron-demand Diels–Alder cycloaddition
LUMO	lowest unoccupied molecular orbital
LC-MS	liquid chromatography-mass spectrometry
Mdm2	mouse double minute 2 homolog
MC-DIBOD	mono-cyclopropenone-caged dibenzocyclooctadiynes
***Mj*TyrRS**	*Methanocaldococcus jannaschii* tyrosyl-tRNA synthetase
MP-SPAAC	multiphoton-triggered SPAAC
NMR	nuclear magnetic resonance
NorK	N^6-((((1*S*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-en-2-yl)methoxy)carbonyl)-L-lysine
Ph	phenyl
eq	equivalents
HAG	homoallylglycine
Me	methyl
NBR	nitrile-butadiene rubber
NIR	near-infrared
NQMP	3-(hydroxymethyl)-2-naphthol
o-MBA	o-methylbenzaldehyde
***o*NQMs**	2-napthoquinone-3-methides
oQDM	o-quinodimethanes
PBS	phosphate-buffered salin
PBTA	poly(tertbutyl)acrylate
PDA	polydopamine
PEG	polyethylene glyco
2PE	two-photon excitation
PMDETA	*N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine
poly(MeOEGMA)	poly[oligo(ethylene glycol)methyl ether methacrylate
PQ	9,10-phenanthrenequinone

RAFT	reversible addition–fragmentation chain transfer
RNA	ribonucleic acid
rt	room temperature
sfGFP	superfolder green fluorescent protein
SCNPs	single-chain nanoparticles
SPAAC	strain-promoted cycloaddition
Sph	spiro[2.3]hex-1-ene
SphK	N^6-((spiro[2.3]hex-1-en-5-ylmethoxy)carbonyl)-L-lysine
StyrK	N^6-(((4-vinylbenzyl)oxy)carbonyl)-L-lysine
Tet	tetrazole
Titanocene	dicyclopentadienyl bis[2,6-difluoro-3-(1-pyrrolyl)phenyl]titanium
TMEDA	tetramethylethanediamine
TMDPO	trimethylbenzoyl)diphenylphosphine oxide
TLC	thin layer chromatography
TCO	trans-cyclooctene
UV	ultraviolet
UCNPs	up-converting nanoparticles
VE	vinyl ethers

References

(1). Stowell MHB; McPhillips TM; Rees DC; Soltis SM; Abresch E; Feher G Light-Induced Structural Changes in Photosynthetic Reaction Center: Implications for Mechanism of Electron-Proton Transfer. Science 1997, 276, 812–816. [PubMed: 9115209]

(2). Steinberg-Yfrach G; Rigaud J-L; Durantini EN; Moore AL; Gust D; Moore TA Light-Driven Production of ATP Catalysed by F0F1-ATP Synthase in an Artificial Photosynthetic Membrane. Nature 1998, 392, 479–482. [PubMed: 9548252]

(3). Hoffmann N Photochemical Reactions as Key Steps in Organic Synthesis. Chem. Rev 2008, 108, 1052–1103. [PubMed: 18302419]

(4). Kärkäs MD; Porco JA; Stephenson CRJ Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis. Chem. Rev 2016, 116, 9683–9747. [PubMed: 27120289]

(5). Holland JP; Gut M; Klingler S; Fay R; Guillou A Photochemical Reactions in the Synthesis of Protein-Drug Conjugates. Chem. Eur. J 2020, 26, 33–48. [PubMed: 31599057]

(6). Chatani S; Kloxin CJ; Bowman CN The Power of Light in Polymer Science: Photochemical Processes to Manipulate Polymer Formation, Structure, And Properties. Polym. Chem 2014, 5, 2187–2201.

(7). Delaittre G; Goldmann AS; Mueller JO; Barner-Kowollik C Efficient Photochemical Approaches for Spatially Resolved Surface Functionalization. Angew. Chem. Int. Ed 2015, 54, 11388–11403.

(8). Olson RA; Korpusik AB; Sumerlin BS Enlightening Advances in Polymer Bioconjugate Chemistry: Light-Based Techniques for Grafting to and from Biomacromolecules. Chem. Sci 2020, 11, 5142–5156. [PubMed: 34122971]

(9). Li J; Kong H; Zhu C; Zhang Y Photo-Controllable Bioorthogonal Chemistry for Spatiotemporal Control of Bio-Targets in Living Systems. Chem. Sci 2020, 11, 3390–3396. [PubMed: 34109018]

(10). Kolb HC; Finn MG; Sharpless KB Click Chemistry: Diverse Chemical Function from a Few Good Reactions. Angew. Chem. Int. Ed 2001, 40, 2004–2021.

(11). Tasdelen MA; Yagci Y Light-Induced Click Reactions. Angew. Chem. Int. Ed 2013, 52, 5930–5938.

(12). Kaur G; Singh G; Singh J Photochemical Tuning of Materials: A Click Chemistry Perspective. Mater. Today Chem 2018, 8, 56–84.

(13). Herner A; Lin Q Photo-Triggered Click Chemistry for Biological Applications. Top. Curr. Chem 2016, 374.

(14). Arumugam S; Popik VV Light-Induced Hetero-Diels-Alder Cycloaddition: A Facile and Selective Photoclick Reaction. J. Am. Chem. Soc 2011, 133, 5573–5579. [PubMed: 21417455]

(15). Poloukhtine AA; Mbua NE; Wolfert MA; Boons GJ; Popik VV Selective Labeling of Living Cells by a Photo-Triggered Click Reaction. J. Am. Chem. Soc 2009, 131, 15769–15776. [PubMed: 19860481]

(16). Zhang L; Zhang X; Yao Z; Jiang S; Deng J; Li B; Yu Z Discovery of Fluorogenic Diarylsydnone-Alkene Photoligation: Conversion of ortho-Dual-Twisted Diarylsydnones into Planar Pyrazolines. J. Am. Chem. Soc 2018, 140, 7390–7394. [PubMed: 29870240]

(17). Lim RKV; Lin Q Azirine Ligation: Fast and Selective Protein Conjugation via Photoinduced Azirine–Alkene Cycloaddition. Chem. Commun 2010, 46, 7993–7995.

(18). Pauloehrl T; Delaittre G; Bruns M; Meißler M; Börner HG; Bastmeyer M; Barner-Kowollik C (Bio)Molecular Surface Patterning by Phototriggered Oxime Ligation. Angew. Chem. Int. Ed 2012, 51, 9181–9184.

(19). Hoyle CE; Bowman CN Thiol–Ene Click Chemistry. Angew. Chem. Int. Ed 2010, 49, 1540–1573.

(20). Hoyle CE; Lowe AB; Bowman CN Thiol-Click Chemistry: A Multifaceted Toolbox for Small Molecule and Polymer Synthesis. Chem. Soc. Rev 2010, 39, 1355–1387. [PubMed: 20309491]

(21). Lowe AB Thiol–Ene "Click" Reactions and Recent Applications in Polymer and Materials Synthesis: A First Update. Polym. Chem 2014, 5, 4820–4870.

(22). Fuoco T; Finne-Wistrand A Synthetic Approaches to Combine the Versatility of the Thiol Chemistry with the Degradability of Aliphatic Polyesters. Polym. Rev 2020, 60, 86–113.

(23). Benson FR The Chemistry of the Tetrazoles. Chem. Rev 1947, 41, 1–61. [PubMed: 20257066]

(24). Bladin JA Ueber von Dicyanphenylhydrazin Abgeleitete Verbindungen. Ber. Dtsch. Chem. Ges 1885, 18, 1544–1551.

(25). Hantzsch A; Vagt A Ueber Das Sogenannte Diazoguanidin. Justus Liebigs Ann. Chem 1901, 314, 339–369.

(26). Ostrovskii VA; Popova EA; Trifonov RE Developments in Tetrazole Chemistry (2009–2016); Academic Press, 2017; Vol. 123, pp 1–62.

(27). Neochoritis CG; Zhao T; Dömling A Tetrazoles via Multicomponent Reactions. Chem. Rev 2019, 119, 1970–2042. [PubMed: 30707567]

(28). Ito S; Tanaka Y; Kakehi A; Kondo K-I A Facile Synthesis of 2,5-Disubstituted Tetrazoles by the Reaction of Phenylsulfonylhydrazones with Arenediazonium Salts. Bull. Chem. Soc. Jpn 1976, 49, 1920–1923.

(29). Koguro K; Oga T; Mitsui S; Orita R Novel Synthesis of 5-Substituted Tetrazoles from Nitriles. Synthesis 1998, 1998, 910–914.

(30). Fedorov AY; Finet J-P N-Phenylationof Azole Derivatives by Triphenylbismuth Derivatives/Cupric Acetate. Tetrahedron Lett. 1999, 40, 2747–2748.

(31). Beletskaya IP; Davydov DV; Gorovoy MS Palladium- and Copper-Catalyzed Selective Arylation of 5-Aryltetrazoles by Diaryliodonium Salts. Tetrahedron Lett. 2002, 43, 6221–6223.

(32). Li Y; Gao L-X; Han F-S Efficient Synthesis of 2,5-Disubstituted Tetrazoles via the Cu_2O-Catalyzed Aerobic Oxidative Direct Cross-Coupling of N–H Free Tetrazoles with Boronic Acids. Chem. Commun 2012, 48, 2719–2721.

(33). An P; Yu ZP; Lin Q Design of Oligothiophene-Based Tetrazoles for Laser-Triggered Photoclick Chemistry in Living Cells. Chem. Commun 2013, 49, 9920–9922.

(34). Livingstone K; Bertrand S; Jamieson C One-Pot Suzuki-Hydrogenolysis Protocol for the Modular Synthesis of 2,5-Diaryltetrazoles. J. Org. Chem 2020, 85, 7413–7423. [PubMed: 32392054]

(35). Onaka T; Umemoto H; Miki Y; Nakamura A; Maegawa T $[Cu(OH)(TMEDA)]_2Cl_2$-Catalyzed Regioselective 2-Arylation of 5-Substituted Tetrazoles with Boronic Acids Under Mild Conditions. J. Org. Chem 2014, 79, 6703–6707. [PubMed: 24962401]

(36). Huisgen R; Seidel M; Sauer J; McFarland J; Wallbillich G The Formation of Nitrile Imines in the Thermal Breakdown of 2,5-Disubstituted Tetrazoles. J. Org. Chem 1959, 24, 892–893.

(37). Huisgen R; Seidel M; Wallbillich G; Knupfer H Diphenyl-nitrilimin und Seine 1.3-Dipolaren Additionen an Alkene und Alkine. Tetrahedron 1962, 17, 3–29.

(38). Clovis JS; Eckell A; Huisgen R; Sustmann R 1.3-Dipolare Cycloadditionen, XXV. Der Nachweis des freien Diphenylnitrilimins als Zwischenstufe bei Cycloadditionen. Chem. Ber 1967, 100, 60–70.

(39). Garanti L; Sala A; Zecchi G Intramolecular 1,3-Dipolar Cycloadditions of Nitrile Imines Bearing an Alkenyl Substituent. J. Org. Chem 1977, 42, 1389–1392.

(40). Wentrup C; Damerius A; Reichen W Intramolecular Cyclization of Nitrile Imines. Synthesis of Indazoles, Fluorenes, and aza Analogs. J. Org. Chem 1978, 43, 2037–2041.

(41). Schmitt G; Laude B Intramolecular Cycloadditions of Nitrilimines on Olefins and Acetylenes. Tetrahedron Lett. 1978, 19, 3727–3728.

(42). Toubro NH; Holm A Nitrilimines. J. Am. Chem. Soc 1980, 102, 2093–2094.

(43). Menzel JP; Noble BB; Lauer A; Coote ML; Blinco JP; Barner-Kowollik C Wavelength Dependence of Light-Induced Cycloadditions. J. Am. Chem. Soc 2017, 139, 15812–15820. [PubMed: 29024596]

(44). Blasco E; Sugawara Y; Lederhose P; Blinco JP; Kelterer AM; Barner-Kowollik C Understanding Reactivity Patterns in Light-Induced Nitrile Imine Mediated Tetrazole-Ene Cycloadditions. ChemPhotoChem 2017, 1, 159–163.

(45). Molteni G; Orlandi M; Broggini G Nitrilimine Cycloadditions in Aqueous Media. J. Chem. Soc., Perkin Trans 1 2000, 3742–3745.

(46). Kaya E; Vrabel M; Deiml C; Prill S; Fluxa VS; Carell T A Genetically Encoded Norbornene Amino Acid for the Mild and Selective Modification of Proteins in a Copper-Free Click Reaction. Angew. Chem. Int. Ed 2012, 51, 4466–4469.

(47). Kulkarni RA; Briney CA; Crooks DR; Bergholtz SE; Mushti C; Lockett SJ; Lane AN; Fan TWM; Swenson RE; Linehan WMet al. Photoinducible Oncometabolite Detection. ChemBioChem 2019, 20, 360–365. [PubMed: 30358041]

(48). Zheng SL; Wang YZ; Yu ZP; Lin Q; Coppens P Direct Observation of a Photoinduced Nonstabilized Nitrile Imine Structure in the Solid State. J. Am. Chem. Soc 2009, 131, 18036–18037. [PubMed: 19928921]

(49). Wang XS; Lee YJ; Liu WSR The Nitrilimine-Alkene Cycloaddition is an Ultra Rapid Click Reaction. Chem. Commun 2014, 50, 3176–3179.

(50). Zhang Y; Liu W; Zhao Z Nucleophilic Trapping Nitrilimine Generated by Photolysis of Diaryltetrazole in Aqueous Phase. Molecules 2013, 19, 306–315. [PubMed: 24378969]

(51). Feng W; Li L; Yang C; Welle A; Trapp O; Levkin PA UV-Induced Tetrazole-Thiol Reaction for Polymer Conjugation and Surface Functionalization. Angew. Chem. Int. Ed 2015, 54, 8732–8735.

(52). Siti W; Khan AK; de Hoog H-PM; Liedberg B; Nallani M Photo-Induced Conjugation of Tetrazoles to Modified and Native Proteins. Org. Biomol. Chem 2015, 13, 3202–3206. [PubMed: 25673512]

(53). Zhao S; Dai J; Hu M; Liu C; Meng R; Liu X; Wang C; Luo T Photo-Induced Coupling Reactions of Tetrazoles with Carboxylic Acids in Aqueous Solution: Application in Protein Labelling. Chem. Commun 2016, 52, 4702–4705.

(54). An P; Lewandowski TM; Erbay TG; Liu P; Lin Q Sterically Shielded, Stabilized Nitrile Imine for Rapid Bioorthogonal Protein Labeling in Live Cells. J. Am. Chem. Soc 2018, 140, 4860–4868. [PubMed: 29565582]

(55). Wang Y; Rivera Vera CI; Lin Q Convenient Synthesis of Highly Functionalized Pyrazolines via Mild, Photoactivated 1,3-Dipolar Cycloaddition. Org. Lett 2007, 9, 4155–4158. [PubMed: 17867694]

(56). Wang Y; Song W; Hu WJ; Lin Q Fast Alkene Functionalization In Vivo by Photoclick Chemistry: HOMO Lifting of Nitrile Imine Dipoles. Angew. Chem. Int. Ed 2009, 48, 5330–5333.

(57). Houk KN; Sims J; Watts CR; Luskus LJ Origin of Reactivity, Regioselectivity, and Periselectivity in 1,3-Dipolar Cycloadditions. J. Am. Chem. Soc 1973, 95, 7301–7315.

(58). Yu Z; Lim RKV; Lin Q Synthesis of Macrocyclic Tetrazoles for Rapid Photoinduced Bioorthogonal 1,3-Dipolar Cycloaddition Reactions. Chem. Eur. J 2010, 16, 13325–13329. [PubMed: 21031376]

(59). Ess DH; Houk KN Distortion/Interaction Energy Control of 1,3-Dipolar Cycloaddition Reactivity. J. Am. Chem. Soc 2007, 129, 10646–10647. [PubMed: 17685614]

(60). Ess DH; Houk KN Theory of 1,3-Dipolar Cycloadditions: Distortion/Interaction and Frontier Molecular Orbital Models. J. Am. Chem. Soc 2008, 130, 10187–10198. [PubMed: 18613669]

(61). An P; Lin Q Sterically Shielded Tetrazoles for A Fluorogenic Photoclick Reaction: Tuning Cycloaddition Rate and Product Fluorescence. Org. Biomol. Chem 2018, 16, 5241–5244. [PubMed: 29995029]

(62). Wang Y; Hu WJ; Song W; Lim RKV; Lin Q Discovery of Long-Wavelength Photoactivatable Diaryltetrazoles for Bioorthogonal 1,3-Dipolar Cycloaddition Reactions. Org. Lett 2008, 10, 3725–3728. [PubMed: 18671406]

(63). Yu Z; Ho LY; Wang Z; Lin Q Discovery of New Photoactivatable Diaryltetrazoles for Photoclick Chemistry via ‘Scaffold Hopping’. Bioorg. Med. Chem. Lett 2011, 21, 5033–5036. [PubMed: 21570845]

(64). An P; Yu Z; Lin Q Design and Synthesis of Laser-Activatable Tetrazoles for a Fast and Fluorogenic Red-Emitting 1,3-Dipolar Cycloaddition Reaction. Org. Lett 2013, 15, 5496–5499. [PubMed: 24111736]

(65). Lederhose P; Wust KNR; Barner-Kowollik C; Blinco JP Catalyst Free Visible Light Induced Cycloaddition as An Avenue for Polymer Ligation. Chem. Commun 2016, 52, 5928–5931.

(66). Lederhose P; Chen Z; Mueller R; Blinco JP; Wu S; Barner-Kowollik C Near-Infrared Photoinduced Coupling Reactions Assisted by Upconversion Nanoparticles. Angew. Chem. Int. Ed 2016, 55, 12195–12199.

(67). Yu Z; Ohulchanskyy TY; An P; Prasad PN; Lin Q Fluorogenic, Two-Photon-Triggered Photoclick Chemistry in Live Mammalian Cells. J. Am. Chem. Soc 2013, 135, 16766–16769. [PubMed: 24168622]

(68). Hiltebrandt K; Pauloehrl T; Blinco JP; Linkert K; Börner HG; Barner-Kowollik C λ-Orthogonal Pericyclic Macromolecular Photoligation. Angew. Chem. Int. Ed 2015, 54, 2838–2843.

(69). Batchelor RR; Blasco E; Wuest KNR; Lu H; Wegener M; Barner-Kowollik C; Stenzel MH Spatially Resolved Coding of λ-Orthogonal Hydrogels by Laser Lithography. Chem. Commun 2018, 54, 2436–2439.

(70). Lederhose P; Abt D; Welle A; Müller R; Barner-Kowollik C; Blinco JP Exploiting λ-Orthogonal Photoligation for Layered Surface Patterning. Chem. Eur. J 2018, 24, 576–580. [PubMed: 29159967]

(71). Menzel JP; Feist F; Tuten B; Weil T; Blinco JP; Barner-Kowollik C Light-Controlled Orthogonal Covalent Bond Formation at Two Different Wavelengths. Angew. Chem. Int. Ed 2019, 58, 7470–7474.

(72). Remy R; Bochet CG Application of Photoclick Chemistry for the Synthesis of Pyrazoles via 1,3-Dipolar Cycloaddition between Alkynes and Nitrilimines Generated In Situ. Eur. J. Org. Chem 2018, 2018, 316–328.

(73). Jiang S; Wu X; Liu H; Deng J; Zhang X; Yao Z; Zheng Y; Li B; Yu Z Ring-Strain-Promoted Ultrafast Diaryltetrazole–Alkyne Photoclick Reactions Triggered by Visible Light. ChemPhotoChem 2020, 4, 327–331.

(74). Ortiz-Rojano L; Rojas-Martin J; Rodriguez-Diaz C; Carreno MC; Ribagorda M Light-Induced Tetrazole-Quinone 1,3-Dipolar Cycloadditions. Chem. Eur. J 2019, 25, 15050–15054. [PubMed: 31585021]

(75). Ramil CP; Lin Q Bioorthogonal Chemistry: Strategies and Recent Developments. Chem. Commun 2013, 49, 11007–11022.

(76). Carell T; Vrabel M Bioorthogonal Chemistry—Introduction and Overview. Top. Curr. Chem 2016, 374, 9.

(77). Kenry Liu, B. Bio-orthogonal Click Chemistry for *In Vivo* Bioimaging. Trends Chem. 2019, 1, 763–778.

(78). Song W; Wang Y; Qu J; Madden MM; Lin Q A Photoinducible 1,3-Dipolar Cycloaddition Reaction for Rapid, Selective Modification of Tetrazole-Containing Proteins. Angew. Chem. Int. Ed 2008, 47, 2832–2835.

(79). Song W; Wang Y; Qu J; Lin Q Selective Functionalization of a Genetically Encoded Alkene-Containing Protein via “Photoclick Chemistry” in Bacterial Cells. J. Am. Chem. Soc 2008, 130, 9654–9655. [PubMed: 18593155]

(80). Wang YZ; Lin Q Synthesis and Evaluation of Photoreactive Tetrazole Amino Acids. Org. Lett 2009, 11, 3570–3573. [PubMed: 19637915]

(81). Wang J; Zhang W; Song W; Wang Y; Yu Z; Li J; Wu M; Wang L; Zang J; Lin Q A Biosynthetic Route to Photoclick Chemistry on Proteins. J. Am. Chem. Soc 2010, 132, 14812–14818. [PubMed: 20919707]

(82). Song WJ; Wang YZ; Yu ZP; Vera CIR; Qu J; Lin Q A Metabolic Alkene Reporter for Spatiotemporally Controlled Imaging of Newly Synthesized Proteins in Mammalian Cells. ACS Chem. Biol 2010, 5, 875–885. [PubMed: 20666508]

(83). Liu CC; Schultz PG Adding New Chemistries to the Genetic Code. Annu. Rev. Biochem 2010, 79, 413–444. [PubMed: 20307192]

(84). Lang K; Chin JW Cellular Incorporation of Unnatural Amino Acids and Bioorthogonal Labeling of Proteins. Chem. Rev 2014, 114, 4764–4806. [PubMed: 24655057]

(85). Lee Y-J; Wu B; Raymond JE; Zeng Y; Fang X; Wooley KL; Liu WR A Genetically Encoded Acrylamide Functionality. ACS Chem. Biol 2013, 8, 1664–1670. [PubMed: 23735044]

(86). Li F; Zhang H; Sun Y; Pan Y; Zhou J; Wang J Expanding the Genetic Code for Photoclick Chemistry in E. Coli, Mammalian Cells, and A. thaliana. Angew. Chem. Int. Ed 2013, 52, 9700–9704.

(87). Shang X; Lai R; Song X; Li H; Niu W; Guo JT Improved Photoinduced Fluorogenic Alkene-Tetrazole Reaction for Protein Labeling. Bioconjugate Chem. 2017, 28, 2859–2864.

(88). Yu Z; Pan Y; Wang Z; Wang J; Lin Q Genetically Encoded Cyclopropene Directs Rapid, Photoclick-Chemistry-Mediated Protein Labeling in Mammalian Cells. Angew. Chem. Int. Ed 2012, 51, 10600–10604.

(89). Yu Z; Lin Q Design of Spiro[2.3]hex-1-ene, A Genetically Encodable Double-Strained Alkene for Superfast Photoclick Chemistry. J. Am. Chem. Soc 2014, 136, 4153–4156. [PubMed: 24592808]

(90). An P; Wu HY; Lewandowski TM; Lin Q Hydrophilic Azaspiroalkenes as Robust Bioorthogonal Reporters. Chem. Commun 2018, 54, 14005–14008.

(91). Krell K; Harijan D; Ganz D; Doll L; Wagenknecht H-A Postsynthetic Modifications of DNA and RNA by Means of Copper-Free Cycloadditions as Bioorthogonal Reactions. Bioconjugate Chem. 2020, 31, 990–1011.

(92). Arndt S; Wagenknecht H-A “Photoclick” Postsynthetic Modification of DNA. Angew. Chem. Int. Ed 2014, 53, 14580–14582.

(93). Lehmann B; Wagenknecht HA Fluorogenic “Photoclick” Labelling of DNA Using A Cy3 Dye. Org. Biomol. Chem 2018, 16, 7579–7582. [PubMed: 30307458]

(94). He Z; Chen Y; Wang Y; Wang J; Mo J; Fu B; Wang Z; Du Y; Zhou X A Rapidly Photo-Activatable Light-Up Fluorescent Nucleoside and Its Application in DNA Base Variation Sensing. Chem. Commun 2016, 52, 8545–8548.

(95). Holstein JM; Stummer D; Rentmeister A Enzymatic Modification of 5'-Capped RNA with a 4-Vinylbenzyl Group Provides a Platform for Photo-Click and Inverse Electron-Demand Diels-Alder Reaction. Chem. Sci 2015, 6, 1362–1369. [PubMed: 29560223]

(96). Wu YX; Guo GL; Zheng JD; Xing D; Zhang T Fluorogenic "Photoclick" Labeling and Imaging of DNA with Coumarin-Fused Tetrazole in Vivo. ACS Sens. 2019, 4, 44–51. [PubMed: 30540170]

(97). Yu Z; Ho LY; Lin Q Rapid, Photoactivatable Turn-On Fluorescent Probes Based on an Intramolecular Photoclick Reaction. J. Am. Chem. Soc 2011, 133, 11912–11915. [PubMed: 21736329]

(98). Zengeya TT; Garlick JM; Kulkarni RA; Miley M; Roberts AM; Yang Y; Crooks DR; Sourbier C; Linehan WM; Meier JL Co-opting a Bioorthogonal Reaction for Oncometabolite Detection. J. Am. Chem. Soc 2016, 138, 15813–15816. [PubMed: 27960310]

(99). An P; Lewandowski TM; Lin Q Design and Synthesis of a BODIPY-Tetrazole Based "Off-On" in-Cell Fluorescence Reporter of Hydrogen Peroxide. ChemBioChem 2018, 19, 1326–1333. [PubMed: 29385317]

(100). Schart VF; Hassenruck J; Spate AK; Dold JEGA; Fahrner R; Wittmann V Triple Orthogonal Labeling of Glycans by Applying Photoclick Chemistry. ChemBioChem 2019, 20, 166–171. [PubMed: 30499611]

(101). Lederhose P; Haworth NL; Thomas K; Bottle SE; Coote ML; Barner-Kowollik C; Blinco JP Design of Redox/Radical Sensing Molecules via Nitrile Imine-Mediated Tetrazole-ene Cycloaddition (NITEC). J. Org. Chem 2015, 80, 8009–8017. [PubMed: 26168007]

(102). Tasdelen MA; Kiskan B; Yagci Y Externally Stimulated Click Reactions for Macromolecular Syntheses. Prog. Polym. Sci 2016, 52, 19–78.

(103). Blasco E; Wegener M; Barner-Kowollik C Photochemically Driven Polymeric Network Formation: Synthesis and Applications. Adv. Mater 2017, 29, 1604005.

(104). Dietrich M; Delaittre G; Blinco JP; Inglis AJ; Bruns M; Barner-Kowollik C Photoclickable Surfaces for Profluorescent Covalent Polymer Coatings. Adv. Funct. Mater 2012, 22, 304–312.

(105). Rodriguez-Emmenegger C; Preuss CM; Yameen B; Pop-Georgievski O; Bachmann M; Mueller JO; Bruns M; Goldmann AS; Bastmeyer M; Barner-Kowollik C Controlled Cell Adhesion on Poly(dopamine) Interfaces Photopatterned with Non-Fouling Brushes. Adv. Mater 2013, 25, 6123–6127. [PubMed: 23999835]

(106). de Hoog H-PM; Nallani M; Liedberg B A Facile and Fast Method for the Functionalization of Polymersomes by Photoinduced Cycloaddition Chemistry. Polym. Chem 2012, 3, 302–306.

(107). Blasco E; Pinol M; Oriol L; Schmidt BVKJ; Welle A; Trouillet V; Bruns M; Barner-Kowollik C Photochemical Generation of Light Responsive Surfaces. Adv. Funct. Mater 2013, 23, 4011–4019.

(108). Tischer T; Rodriguez-Emmenegger C; Trouillet V; Welle A; Schueler V; Mueller JO; Goldmann AS; Brynda E; Barner-Kowollik C Photo-Patterning of Non-Fouling Polymers and Biomolecules on Paper. Adv. Mater 2014, 26, 4087–4092. [PubMed: 24719300]

(109). de los Santos Pereira A; Kostina NY; Bruns M; Rodriguez-Emmenegger C; Barner-Kowollik C Phototriggered Functionalization of Hierarchically Structured Polymer Brushes. Langmuir 2015, 31, 5899–5907. [PubMed: 25961109]

(110). Abt D; Schmidt BVKJ; Pop-Georgievski O; Quick AS; Danilov D; Kostina NY; Bruns M; Wenzel W; Wegener M; Rodriguez-Emmenegger Cet al. Designing Molecular Printboards: A Photolithographic Platform for Recodable Surfaces. Chem. Eur. J 2015, 21, 13186–13190. [PubMed: 26235994]

(111). Stolzer L; Vigovskaya A; Barner-Kowollik C; Fruk L A Self-Reporting Tetrazole-Based Linker for the Biofunctionalization of Gold Nanorods. Chem. Eur. J 2015, 21, 14309–14313. [PubMed: 26303592]

(112). Vonhören B; Roling O; Buten C; Körsgen M; Arlinghaus HF; Ravoo BJ Photochemical Microcontact Printing by Tetrazole Chemistry. Langmuir 2016, 32, 2277–2282. [PubMed: 26886297]

(113). Wendler F; Rudolph T; Görls H; Jasinski N; Trouillet V; Barner-Kowollik C; Schacher FH Maleimide-Functionalized Poly(2-Ethyl-2-Oxazoline): Synthesis and Reactivity. Polym. Chem 2016, 7, 2419–2426.

(114). Gegenhuber T; Abt D; Welle A; Oezbek S; Goldmann AS; Barner-Kowollik C Spatially Resolved Photochemical Coding of Reversibly Anchored Cysteine-Rich Domains. J. Mater. Chem. B 2017, 5, 4993–5000. [PubMed: 32264016]

(115). Wilke P; Abt D; Große S; Barner-Kowollik C; Börner HG Selective Functionalization of Laser Printout Patterns On Cellulose Paper Sheets Coated with Surface-Specific Peptides. J. Mater. Chem. A 2017, 5, 16144–16149.

(116). Mueller JO; Voll D; Schmidt FG; Delaittre G; Barner-Kowollik C Fluorescent Polymers from Non-Fluorescent Photoreactive Monomers. Chem. Commun 2014, 50, 15681–15684.

(117). Estupinan D; Gegenhuber T; Blinco JP; Barner-Kowollik C; Barner L Self-Reporting Fluorescent Step-Growth RAFT Polymers Based on Nitrile Imine-Mediated Tetrazole-Ene Cycloaddition Chemistry. ACS Macro Lett. 2017, 6, 229–234.

(118). Duerr CJ; Lederhose P; Hlalele L; Abt D; Kaiser A; Brandau S; Barner-Kowollik C Photo-Induced Ligation of Acrylonitrile-Butadiene Rubber: Selective Tetrazole-Ene Coupling of Chain-End-Functionalized Copolymers of 1,3-Butadiene. Macromolecules 2013, 46, 5915–5923.

(119). Darkow R; Yoshikawa M; Kitao T; Tomaschewski G; Schellenberg J Photomodification of a Poly(Acrylonitrile-Co-Butadiene-Co-Styrene) Containing Diaryltetrazolyl Groups. J. Polym. Sci., Part A: Polym. Chem 1994, 32, 1657–1664.

(120). Mueller JO; Guimard NK; Oehlenschlaeger KK; Schmidt FG; Barner-Kowollik C Sunlight-Induced Crosslinking of 1,2-Polybutadienes: Access To Fluorescent Polymer Networks. Polym. Chem 2014, 5, 1447–1456.

(121). Hufendiek A; Carlmark A; Meier MAR; Barner-Kowollik C Fluorescent Covalently Cross-Linked Cellulose Networks via Light-Induced Ligation. ACS Macro Lett. 2016, 5, 139–143.

(122). Wang C; Zieger MM; Schenzel A; Wegener M; Willenbacher J; Barner-Kowollik C; Bowman CN Photoinduced Tetrazole-Based Functionalization of Off-Stoichiometric Clickable Microparticles. Adv. Funct. Mater 2017, 27, 1605317.

(123). Estupiñán D; Barner-Kowollik C; Barner L Counting the Clicks in Fluorescent Polymer Networks. Angew. Chem. Int. Ed 2018, 57, 5925–5929.

(124). Willenbacher J; Wuest KNR; Mueller JO; Kaupp M; Wagenknecht H-A; Barner-Kowollik C Photochemical Design of Functional Fluorescent Single-Chain Nanoparticles. ACS Macro Lett. 2014, 3, 574–579.

(125). Offenloch JT; Willenbacher J; Tzvetkova P; Heiler C; Mutlu H; Barner-Kowollik C Degradable Fluorescent Single-Chain Nanoparticles Based On Metathesis Polymers. Chem. Commun 2017, 53, 775–778.

(126). Hirsch A; Brettreich M Fullerenes : Chemistry and Reactions; Wiley-VCH: Weinheim, 2005.

(127). Sugawara Y; Jasinski N; Kaupp M; Welle A; Zydziak N; Blasco E; Barner-Kowollik C Light-Driven Nitrile Imine-Mediated Tetrazole-Ene Cycloaddition as a Versatile Platform for Fullerene Conjugation. Chem. Commun 2015, 51, 13000–13003.

(128). Sugawara Y; Hiltebrandt K; Blasco E; Barner-Kowollik C Polymer-Fullerene Network Formation via Light-Induced Crosslinking. Macromol. Rapid Commun 2016, 37, 1466–1471. [PubMed: 27336692]

(129). Madden MM; Rivera Vera CI; Song W; Lin Q Facile Synthesiso of Stapled, Structurally Reinforced Peptide Helices via A Photoinduced Intramolecular 1,3-Dipolar Cycloaddition Reaction. Chem. Commun 2009, 5588–5590.

(130). Madden MM; Muppidi A; Li ZY; Li XL; Chen JD; Lin Q Synthesis of Cell-Permeable Stapled Peptide Dual Inhibitors of the P53-Mdm2/Mdmx Interactions via Photoinduced Cycloaddition. Bioorg. Med. Chem. Lett 2011, 21, 1472–1475. [PubMed: 21277201]

(131). Fan Y; Deng C; Cheng R; Meng F; Zhong Z In Situ Forming Hydrogels via Catalyst-Free and Bioorthogonal "Tetrazole–Alkene" Photo-Click Chemistry. Biomacromolecules 2013, 14, 2814–2821. [PubMed: 23819863]

(132). He M; Li J; Tan S; Wang R; Zhang Y Photodegradable Supramolecular Hydrogels with Fluorescence Turn-On Reporter for Photomodulation of Cellular Microenvironments. J. Am. Chem. Soc 2013, 135, 18718–18721. [PubMed: 24106809]

(133). Meldal M; Tornøe CW Cu-Catalyzed Azide-Alkyne Cycloaddition. Chem. Rev 2008, 108, 2952–3015. [PubMed: 18698735]

(134). Haldón E; Nicasio MC; Pérez PJ Copper-Catalysed Azide–Alkyne Cycloadditions (CuAAC): An Update. Org. Biomol. Chem 2015, 13, 9528–9550. [PubMed: 26284434]

(135). Tiwari VK; Mishra BB; Mishra KB; Mishra N; Singh AS; Chen X Cu-Catalyzed Click Reaction in Carbohydrate Chemistry. Chem. Rev 2016, 116, 3086–3240. [PubMed: 26796328]

(136). Meldal M; Diness F Recent Fascinating Aspects of the CuAAC Click Reaction. Trends Chem. 2020, 2, 569–584.

(137). Neumann S; Biewend M; Rana S; Binder WH The CuAAC: Principles, Homogeneous and Heterogeneous Catalysts, and Novel Developments and Applications. Macromol. Rapid Commun 2020, 41.

(138). Rostovtsev VV; Green LG; Fokin VV; Sharpless KB A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. Angew. Chem. Int. Ed 2002, 41, 2596–2599.

(139). Tornøe CW; Christensen C; Meldal M Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. J. Org. Chem 2002, 67, 3057–3064. [PubMed: 11975567]

(140). Hong V; Udit AK; Evans RA; Finn MG Electrochemically Protected Copper(I)-Catalyzed Azide–Alkyne Cycloaddition. ChemBioChem 2008, 9, 1481–1486. [PubMed: 18504727]

(141). Devaraj NK; Dinolfo PH; Chidsey CED; Collman JP Selective Functionalization of Independently Addressed Microelectrodes by Electrochemical Activation and Deactivation of a Coupling Catalyst. J. Am. Chem. Soc 2006, 128, 1794–1795. [PubMed: 16464070]

(142). Ritter SC; König B Signal Amplification and Transduction By Photo-Activated Catalysis. Chem. Commun 2006, 4694–4696.

(143). Pachón LD; van Maarseveen, J. H.; Rothenberg, G. Click Chemistry: Copper Clusters Catalyse the Cycloaddition of Azides with Terminal Alkynes. Adv. Synth. Catal 2005, 347, 811–815.

(144). Tasdelen MA; Yagci Y Light-Induced Copper(I)-Catalyzed Click Chemistry. Tetrahedron Lett. 2010, 51, 6945–6947.

(145). Sandmann B; Happ B; Vitz J; Hager MD; Burtscher P; Moszner N; Schubert US Photoinduced Polyaddition of Multifunctional Azides and Alkynes. Polym. Chem 2013, 4, 3938–3942.

(146). Adzima BJ; Tao Y; Kloxin CJ; DeForest CA; Anseth KS; Bowman CN Spatial and Temporal Control of the Alkyne–Azide Cycloaddition by Photoinitiated Cu(II) Reduction. Nat. Chem 2011, 3, 256–259. [PubMed: 21336334]

(147). Tasdelen MA; Yilmaz G; Iskin B; Yagci Y Photoinduced Free Radical Promoted Copper(I)-Catalyzed Click Chemistry for Macromolecular Syntheses. Macromolecules 2012, 45, 56–61.

(148). Yagci Y; Tasdelen MA; Jockusch S Reduction of Cu(II) by Photochemically Generated Phosphonyl Radicals to Generate Cu(I) as Catalyst for Atom Transfer Radical Polymerization and Azide-Alkyne Cycloaddition Click Reactions. Polymer 2014, 55, 3468–3474.

(149). Guan X; Zhang J; Wang Y An Efficient Photocatalyst for the Azide-Alkyne Click Reaction Based on Direct Photolysis of A Copper(II)/Carboxylate Complex. Chem. Lett 2014, 43, 1073–1074.

(150). Harmand L; Cadet S; Kauffmann B; Scarpantonio L; Batat P; Jonusauskas G; McClenaghan ND; Lastécouères D; Vincent J-M Copper Catalyst Activation Driven by Photoinduced Electron Transfer: A Prototype Photolatent Click Catalyst. Angew. Chem. Int. Ed 2012, 51, 7137–7141.

(151). Harmand L; Lambert R; Scarpantonio L; McClenaghan ND; Lastécouères D; Vincent JM A Photoreducible Copper(II)-Tren Complex of Practical Value: Generation of A Highly Reactive Click Catalyst. Chem. Eur. J 2013, 19, 16231–16239. [PubMed: 24127367]

(152). Beniazza R; Lambert R; Harmand L; Molton F; Duboc C; Denisov S; Jonusauskas G; McClenaghan ND; Lastécouères D; Vincent JM Sunlight-Driven Copper-Catalyst Activation Applied to Photolatent Click Chemistry. Chem. Eur. J 2014, 20, 13181–13187. [PubMed: 25171758]

(153). Gong T; Adzima BJ; Bowman CN A Novel Copper Containing Photoinitiator, Copper(II) Acylphosphinate, and Its Application in both the Photomediated CuAAC Reaction and in Atom Transfer Radical Polymerization. Chem. Commun 2013, 49, 7950–7952.

(154). Beniazza R; Bayo N; Molton F; Duboc C; Massip S; McClenaghan N; Lastécouères D; Vincent JM Effective Ascorbate-Free and Photolatent Click Reactions in Water Using a Photoreducible Copper(II)-Ethylenediamine Precatalyst. Beilstein J. Org. Chem 2015, 11, 1950–1959. [PubMed: 26664615]

(155). Dadashi-Silab S; Yagci Y Copper(II) Thioxanthone Carboxylate as a Photoswitchable Photocatalyst for Photoinduced Click Chemistry. Tetrahedron Lett. 2015, 56, 6440–6443.

(156). Arslan M; Yilmaz G; Yagci Y Dibenzoyldiethylgermane as a Visible Light Photo-Reducing Agent for CuAAC Click Reactions. Polym. Chem 2015, 6, 8168–8175.

(157). Yetiskin O; Dadashi-Silab S; Khan SB; Asiri AM; Yagci Y Visible-Light-Induced Copper(I)-Catalyzed Azide-Alkyne Cycloaddition Initiated by Zinc Oxide Semiconductor Nanoparticles. Asian J. Org. Chem 2015, 4, 442–444.

(158). Castro-Godoy WD; Heredia AA; Schmidt LC; Argüello JE A Straightforward and Sustainable Synthesis of 1,4-Disubstituted 1,2,3-Triazoles via Visible-Light-Promoted Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC). RSC Adv. 2017, 7, 33967–33976.

(159). Gong T; Adzima BJ; Baker NH; Bowman CN Photopolymerization Reactions Using the Photoinitiated Copper (I)-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) Reaction. Adv. Mater 2013, 25, 2024–2028. [PubMed: 23401189]

(160). Chen RT; Marchesan S; Evans RA; Styan KE; Such GK; Postma A; McLean KM; Muir BW; Caruso F Photoinitiated Alkyne-Azide Click and Radical Cross-Linking Reactions for the Patterning of Peg Hydrogels. Biomacromolecules 2012, 13, 889–895. [PubMed: 22332589]

(161). McBride MK; Gong T; Nair DP; Bowman CN Photo-Mediated Copper(I)-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) “Click” Reactions for Forming Polymer Networks as Shape Memory Materials. Polymer 2014, 55, 5880–5884. [PubMed: 25378717]

(162). Demirci G; Tasdelen MA Synthesis and Characterization of Graft Copolymers by Photoinduced CuAAC Click Chemistry. Eur. Polym. J 2015, 66, 282–289.

(163). Doran S; Yilmaz G; Yagci Y Tandem Photoinduced Cationic Polymerization and CuAAC for Macromolecular Synthesis. Macromolecules 2015, 48, 7446–7452.

(164). Kahveci MU; Ciftci M; Evran S; Timur S; Yagci Y Photoinduced in Situ Formation of Clickable Peg Hydrogels and Their Antibody Conjugation. Designed Monomers and Polymers 2015, 18, 129–136.

(165). Tinmaz HB; Arslan I; Tasdelen MA Star Polymers by Photoinduced Copper-Catalyzed Azide-Alkyne Cycloaddition Click Chemistry. J. Polym. Sci., Part A: Polym. Chem 2015, 53, 1687–1695.

(166). Maetz E; Croutxé-Barghorn C; Delaite C; Allonas X Combination of Photoinduced Copper(I) Catalyzed Click Chemistry and Photosol-Gel Reaction for the Synthesis of Hybrid Materials. Polym. Chem 2016, 7, 7383–7390.

(167). Konetski D; Gong T; Bowman CN Photoinduced Vesicle Formation via the Copper-Catalyzed Azide-Alkyne Cycloaddition Reaction. Langmuir 2016, 32, 8195–8201. [PubMed: 27443396]

(168). Williams MG; Teplyakov AV Indirect Photopatterning of Functionalized Organic Monolayers via Copper-Catalyzed “Click Chemistry”. Appl. Surf. Sci 2018, 447, 535–541. [PubMed: 29955204]

(169). Liang S; Guan Y; Zhang Y Layer-by-Layer Assembly of Microgel Colloidal Crystals via Photoinitiated Alkyne-Azide Click Reaction. ACS Omega 2019, 4, 5650–5660. [PubMed: 31459719]

(170). Agard NJ; Prescher JA; Bertozzi CR A Strain-Promoted [3 + 2] Azide-Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems. J. Am. Chem. Soc 2004, 126, 15046–15047. [PubMed: 15547999]

(171). Jewett JC; Bertozzi CR Cu-Free Click Cycloaddition Reactions in Chemical Biology. Chem. Soc. Rev 2010, 39, 1272–1279. [PubMed: 20349533]

(172). Dommerholt J; Rutjes FPJT; van DFL Strain-Promoted 1,3-Dipolar Cycloaddition of Cycloalkynes and Organic Azides. Top. Curr. Chem 2016, 374, 16.

(173). Pigge FC Strain-Promoted Cycloadditions for Development of Copper-Free Click Reactions. Curr. Org. Chem 2016, 20, 1902–1922.

(174). Starke F; Walther M; Pietzsch H-J A Novel Dibenzoazacyclooctyne Precursor in Regioselective Copper-Free Click Chemistry. An Innovative 3-Step Synthesis. ARKIVOC 2010, 350–359.

(175). McNitt CD; Popik VV Photochemical Generation of Oxa-Dibenzocyclooctyne (ODIBO) for Metal-Free Click Ligations. Org. Biomol. Chem 2012, 10, 8200–8202. [PubMed: 22987146]

(176). Kuzmin A; Poloukhtine A; Wolfert MA; Popik VV Surface Functionalization Using Catalyst-Free Azide-Alkyne Cycloaddition. Bioconjugate Chem. 2010, 21, 2076–2085.

(177). Orski SV; Poloukhtine AA; Arumugam S; Mao L; Popik VV; Locklin J High Density Orthogonal Surface Immobilization via Photoactivated Copper-Free Click Chemistry. J. Am. Chem. Soc 2010, 132, 11024–11026. [PubMed: 20698664]

(178). Laradji AM; McNitt CD; Yadavalli NS; Popik VV; Minko S Robust, Solvent-Free, Catalyst-Free Click Chemistry for the Generation of Highly Stable Densely Grafted Poly(ethylene glycol) Polymer Brushes by the Grafting to Method and Their Properties. Macromolecules 2016, 49, 7625–7631.

(179). Bjerknes M; Cheng H; McNitt CD; Popik VV Facile Quenching and Spatial Patterning of Cylooctynes via Strain-Promoted Alkyne-Azide Cycloaddition of Inorganic Azides. Bioconjugate Chem. 2017, 28, 1560–1565.

(180). Luo W; Gobbo P; McNitt CD; Sutton DA; Popik VV; Workentin MS “Shine & Click” Photo-Induced Interfacial Unmasking of Strained Alkynes on Small Water-Soluble Gold Nanoparticles. Chem. Eur. J 2017, 23, 1052–1059. [PubMed: 27727488]

(181). Sun L; Gai Y; McNitt CD; Sun J; Zhang X; Xing W; Li Z; Popik VV; Zeng D Photo-Click-Facilitated Screening Platform for the Development of Hetero-Bivalent Agents with High Potency. J. Org. Chem 2020, 85, 5771–5777. [PubMed: 32223160]

(182). Luo W; Legge SM; Luo J; Lagugne-Labarthet F; Workentin MS Investigation of Au SAMs Photoclick Derivatization by PM-IRRAS. Langmuir 2020, 36, 1014–1022. [PubMed: 31922420]

(183). Friscourt F; Fahrni CJ; Boons G-J A Fluorogenic Probe for the Catalyst-Free Detection of Azide-Tagged Molecules. J. Am. Chem. Soc 2012, 134, 18809–18815. [PubMed: 23095037]

(184). Arumugam S; Popik VV Sequential “Click” - “Photo-Click” Cross-Linker for Catalyst-Free Ligation of Azide-Tagged Substrates. J. Org. Chem 2014, 79, 2702–2708. [PubMed: 24548078]

(185). Kii I; Shiraishi A; Hiramatsu T; Matsushita T; Uekusa H; Yoshida S; Yamamoto M; Kudo A; Hagiwara M; Hosoya T Strain-Promoted Double-Click Reaction for Chemical Modification of Azido-Biomolecules. Org. Biomol. Chem 2010, 8, 4051–4055. [PubMed: 20657923]

(186). Hashimoto C; Nomura W; Narumi T; Fujino M; Nakahara T; Yamamoto N; Murakami T; Tamamura H CXCR4-Derived Synthetic Peptides Inducing Anti-HIV-1 Antibodies. Biorg. Med. Chem 2013, 21, 6878–6885.

(187). Wang Z; Liu J; Arslan HK; Grosjean S; Hagendorn T; Gliemann H; Bräse S; Wöll C Post-Synthetic Modification of Metal–Organic Framework Thin Films Using Click Chemistry: The Importance of Strained C–C Triple Bonds. Langmuir 2013, 29, 15958–15964. [PubMed: 24283622]

(188). Lau YH; Wu Y; Rossmann M; Tan BX; de Andrade P; Tan YS; Verma C; McKenzie GJ; Venkitaraman AR; Hyvönen Met al. Double Strain-Promoted Macrocyclization for the Rapid Selection of Cell-Active Stapled Peptides. Angew. Chem. Int. Ed 2015, 54, 15410–15413.

(189). Sutton DA; Yu S-H; Steet R; Popik VV Cyclopropenone-Caged Sondheimer Diyne (Dibenzo[A,E]Cyclooctadiyne): A Photoactivatable Linchpin for Efficient Spaac Crosslinking. Chem. Commun 2016, 52, 553–556.

(190). Sutton DA; Popik VV Sequential Photochemistry of Dibenzo[a,e]dicyclopropa[c,g][8]annulene-1,6-dione: Selective Formation of Didehydrodibenzo[a,e][8]annulenes with Ultrafast SPAAC Reactivity. J. Org. Chem 2016, 81, 8850–8857. [PubMed: 27635662]

(191). Nainar S; Kubota M; McNitt C; Tran C; Popik VV; Spitale RC Temporal Labeling of Nascent RNA Using Photoclick Chemistry in Live Cells. J. Am. Chem. Soc 2017, 139, 8090–8093. [PubMed: 28562039]

(192). Urdabayev NK; Poloukhtine A; Popik VV Two-Photon Induced Photodecarbonylation Reaction of Cyclopropenones. Chem. Commun 2006, 454–456.

(193). McNitt CD; Cheng H; Ullrich S; Popik VV; Bjerknes M Multiphoton Activation of Photo-Strain-Promoted Azide Alkyne Cycloaddition "Click" Reagents Enables in Situ Labeling with Submicrometer Resolution. J. Am. Chem. Soc 2017, 139, 14029–14032. [PubMed: 28925255]

(194). Mishiro K; Kimura T; Furuyama T; Kunishima M Phototriggered Active Alkyne Generation from Cyclopropenones with Visible Light-Responsive Photocatalysts. Org. Lett 2019, 21, 4101–4105. [PubMed: 31117705]

(195). Almeida G. d.; Townsend LC; Bertozzi CR Synthesis and Reactivity of Dibenzoselenacycloheptynes. Org. Lett 2013, 15, 3038–3041. [PubMed: 23734979]

(196). Martinek M; Filipova L; Galeta J; Ludvikova L; Klan P Photochemical Formation of Dibenzosilacyclohept-4-yne for Cu-Free Click Chemistry with Azides and 1,2,4,5-Tetrazines. Org. Lett 2016, 18, 4892–4895. [PubMed: 27624804]

(197). Madea D; Slanina T; Klan PA 'Photorelease, Catch and Photorelease' Strategy for Bioconjugation Utilizing a *p*-Hydroxyphenacyl Group. Chem. Commun 2016, 52, 12901–12904.

(198). Gann AW; Amoroso JW; Einck VJ; Rice WP; Chambers JJ; Schnarr NA A Photoinduced, Benzyne Click Reaction. Org. Lett 2014, 16, 2003–2005. [PubMed: 24625300]

(199). Schoenebeck F; Ess DH; Jones GO; Houk KN Reactivity and Regioselectivity in 1,3-Dipolar Cycloadditions of Azides to Strained Alkynes and Alkenes: A Computational Study. J. Am. Chem. Soc 2009, 131, 8121–8133. [PubMed: 19459632]

(200). Singh K; Fennell CJ; Coutsias EA; Latifi R; Hartson S; Weaver JD Light Harvesting for Rapid and Selective Reactions: Click Chemistry with Strain-Loadable Alkenes. Chem 2018, 4, 124–137.

(201). Franc G; Kakkar AK Diels–Alder "Click" Chemistry in Designing Dendritic Macromolecules. Chem. Eur. J 2009, 15, 5630–5639. [PubMed: 19418515]

(202). Nicolaou KC; Snyder SA; Montagnon T; Vassilikogiannakis G The Diels–Alder Reaction in Total Synthesis. Angew. Chem. Int. Ed 2002, 41, 1668–1698.

(203). Arumugam S; Popik VV Photochemical Generation and the Reactivity of o-Naphthoquinone Methides in Aqueous Solutions. J. Am. Chem. Soc 2009, 131, 11892–11899. [PubMed: 19650661]

(204). Arumugam S; Orski SV; Locklin J; Popik VV Photoreactive Polymer Brushes for High-Density Patterned Surface Derivatization Using a Diels-Alder Photoclick Reaction. J. Am. Chem. Soc 2012, 134, 179–182. [PubMed: 22191601]

(205). Arumugam S; Popik VV Patterned Surface Derivatization Using Diels-Alder Photoclick Reaction. J. Am. Chem. Soc 2011, 133, 15730–15736. [PubMed: 21861517]

(206). Arumugam S; Lin N; Nekongo E; Popik VV; Guo J; Mbua NE; Friscourt F; Boons G-J Selective and Reversible Photochemical Derivatization of Cysteine Residues in Peptides and Proteins. Chem. Sci 2014, 5, 1591–1598. [PubMed: 24765521]

(207). Arumugam S; Popik VV Attach, Remove, or Replace: Reversible Surface Functionalization Using Thiol-Quinone Methide Photoclick Chemistry. J. Am. Chem. Soc 2012, 134, 8408–8411. [PubMed: 22568774]

(208). Zlatic K; Antol I; Uzelac L; Mikecin Drazic A-M; Kralj M; Bohne C; Basaric N Labeling of Proteins by BODIPY-Quinone Methides Utilizing Anti-Kasha Photochemistry. ACS Appl. Mater 2020, 12, 347–351.

(209). Segura JL; Martín N o-Quinodimethanes: Efficient Intermediates in Organic Synthesis. Chem. Rev 1999, 99, 3199–3246. [PubMed: 11749515]

(210). Cuadros S; Melchiorre P Organocatalytic Strategies to Stereoselectively Trap Photochemically Generated Hydroxy-o-quinodimethanes. Eur. J. Org. Chem 2018, 2018, 2884–2891.

(211). Yang B; Gao S Recent Advances in the Application of Diels–Alder Reactions Involving o-Quinodimethanes, Aza-o-Quinone Methides and o-Quinone Methides in Natural Product Total Synthesis. Chem. Soc. Rev 2018, 47, 7926–7953. [PubMed: 29993045]

(212). Pauloehrl T; Delaittre G; Winkler V; Welle A; Bruns M; Boerner HG; Greiner AM; Bastmeyer M; Barner-Kowollik C Adding Spatial Control to Click Chemistry: Phototriggered Diels-Alder Surface (Bio)functionalization at Ambient Temperature. Angew. Chem., Int. Ed 2012, 51, 1071–1074.

(213). Vigovskaya A; Abt D; Ahmed I; Niemeyer CM; Barner-Kowollik C; Fruk L Photo-induced Chemistry for the Design of Oligonucleotide Conjugates and Surfaces. J. Mater. Chem. B 2016, 4, 442–449. [PubMed: 32263208]

(214). Zydziak N; Konrad W; Feist F; Barner-Kowollik C; Zydziak N; Konrad W; Feist F; Barner-Kowollik C; Afonin S; Weidner S Coding and Decoding Libraries of Sequence-Defined Functional Copolymers Synthesized via Photoligation. Nat. Commun 2016, 7, 13672. [PubMed: 27901024]

(215). Chen L; Xu M; Hu J; Yan Q Light-Initiated in Situ Self-Assembly (LISA) from Multiple Homopolymers. Macromolecules 2017, 50, 4276–4280.

(216). Quick AS; Rothfuss H; Welle A; Richter B; Fischer J; Wegener M; Barner-Kowollik C Fabrication and Spatially Resolved Functionalization of 3D Microstructures via Multiphoton-Induced Diels–Alder Chemistry. Adv. Funct. Mater 2014, 24, 3571–3580.

(217). Mueller P; Zieger MM; Richter B; Quick AS; Fischer J; Mueller JB; Zhou L; Nienhaus GU; Bastmeyer M; Barner-Kowollik Cet al. Molecular Switch for Sub-Diffraction Laser Lithography by Photoenol Intermediate-State Cis–Trans Isomerization. ACS Nano 2017, 11, 6396–6403. [PubMed: 28582617]

(218). Glassner M; Oehlenschlaeger KK; Gruendling T; Barner-Kowollik C Ambient Temperature Synthesis of Triblock Copolymers via Orthogonal Photochemically and Thermally Induced Modular Conjugation. Macromolecules 2011, 44, 4681–4689.

(219). Winkler M; Mueller JO; Oehlenschlaeger KK; Montero de Espinosa L; Meier MAR; Barner-Kowollik C Highly Orthogonal Functionalization of ADMET Polymers via Photo-Induced Diels-Alder Reactions. Macromolecules 2012, 45, 5012–5019.

(220). Oehlenschlaeger KK; Mueller JO; Heine NB; Glassner M; Guimard NK; Delaittre G; Schmidt FG; Barner-Kowollik C Light-Induced Modular Ligation of Conventional RAFT Polymers. Angew. Chem. Int. Ed 2013, 52, 762–766.

(221). Glassner M; Oehlenschlaeger KK; Welle A; Bruns M; Barner-Kowollik C Polymer Surface Patterning via Diels-Alder Trapping of Photo-Generated Thioaldehydes. Chem. Commun 2013, 49, 633–635.

(222). Tischer T; Claus TK; Bruns M; Trouillet V; Linkert K; Rodriguez-Emmenegger C; Goldmann AS; Perrier S; Boerner HG; Barner-Kowollik C Spatially Controlled Photochemical Peptide and Polymer Conjugation on Biosurfaces. Biomacromolecules 2013, 14, 4340–4350. [PubMed: 24127628]

(223). Gruendling T; Oehlenschlaeger KK; Frick E; Glassner M; Schmid C; Barner-Kowollik C Rapid UV Light-Triggered Macromolecular Click Conjugations via the Use of o-Quinodimethanes. Macromol. Rapid Commun 2011, 32, 807–812. [PubMed: 21469243]

(224). Mellows SM; Sammes PG Stereoselective Trapping of a Photo-Enol. J. Chem. Soc. D, 1971, 21–22.

(225). Feist F; Menzel JP; Weil T; Blinco JP; Barner-Kowollik C Visible Light-Induced Ligation via o-Quinodimethane Thioethers. J. Am. Chem. Soc 2018, 140, 11848–11854. [PubMed: 30137988]

(226). Feist F; Rodrigues LL; Walden SL; Krappitz TW; Dargaville TR; Weil T; Goldmann AS; Blinco JP; Barner-Kowollik C Light-induced Ligation of o-Quinodimethanes with Gated Fluorescence Self-reporting. J. Am. Chem. Soc 2020, 142, 7744–7748. [PubMed: 32293171]

(227). Li J; Kong H; Huang L; Cheng B; Qin K; Zheng M; Yan Z; Zhang Y Visible Light-Initiated Bioorthogonal Photoclick Cycloaddition. J. Am. Chem. Soc 2018, 140, 14542–14546. [PubMed: 30351919]

(228). Wu H; Devaraj NK Inverse Electron-Demand Diels–Alder Bioorthogonal Reactions. Top. Curr. Chem 2015, 374, 3.

(229). Oliveira BL; Guo Z; Bernardes GJL Inverse Electron Demand Diels–Alder Reactions in Chemical Biology. Chem. Soc. Rev 2017, 46, 4895–4950. [PubMed: 28660957]

(230). Wu H; Devaraj NK Advances in Tetrazine Bioorthogonal Chemistry Driven by the Synthesis of Novel Tetrazines and Dienophiles. Acc. Chem. Res 2018, 51, 1249–1259. [PubMed: 29638113]

(231). Blackman ML; Royzen M; Fox JM Tetrazine Ligation: Fast Bioconjugation Based on Inverse-Electron-Demand Diels-Alder Reactivity. J. Am. Chem. Soc 2008, 130, 13518–13519. [PubMed: 18798613]

(232). Selvaraj R; Fox JM Trans-Cyclooctene—A Stable, Voracious Dienophile for Bioorthogonal Labeling. Curr. Opin. Chem. Biol 2013, 17, 753–760. [PubMed: 23978373]

(233). Zhang H; Trout WS; Liu S; Andrade GA; Hudson DA; Scinto SL; Dicker KT; Li Y; Lazouski N; Rosenthal Jet al. Rapid Bioorthogonal Chemistry Turn-on through Enzymatic or Long Wavelength Photocatalytic Activation of Tetrazine Ligation. J. Am. Chem. Soc 2016, 138, 5978–5983. [PubMed: 27078610]

(234). Truong VX; Tsang KM; Ercole F; Forsythe JS Red Light Activation of Tetrazine-Norbornene Conjugation for Bioorthogonal Polymer Cross-Linking across Tissue. Chem. Mater 2017, 29, 3678–3685.

(235). Mayer SV; Murnauer A; von Wrisberg M-K; Jokisch M-L; Lang K Photo-induced and Rapid Labeling of Tetrazine-Bearing Proteins via Cyclopropenone-Caged Bicyclononynes. Angew. Chem. Int. Ed 2019, 58, 15876–15882.

(236). Jiang T; Kumar P; Huang W; Kao W-S; Thompson AO; Camarda FM; Laughlin ST Modular Enzyme- and Light-Based Activation of Cyclopropene-Tetrazine Ligation. ChemBioChem 2019, 20, 2222–2226. [PubMed: 30990967]

(237). Kumar P; Jiang T; Li S; Zainul O; Laughlin ST Caged Cyclopropenes for Controlling Bioorthogonal Reactivity. Org. Biomol. Chem 2018, 16, 4081–4085. [PubMed: 29790564]

(238). Decuypère E; Plougastel L; Audisio D; Taran F Sydnone–Alkyne Cycloaddition: Applications in Synthesis and Bioconjugation. Chem. Commun 2017, 53, 11515–11527.

(239). Wiechmann S; Freese T; Drafz MHH; Hübner EG; Namyslo JC; Nieger M; Schmidt A Sydnone Anions and Abnormal N-Heterocyclic Carbenes of O-Ethylsydnones. Characterizations, Calculations and Catalyses. Chem. Commun 2014, 50, 11822–11824.

(240). Earl JC; Mackney AW 204. The Action of Acetic Anhydride on N-Nitrosophenylglycine and Some of Its Derivatives. J. Chem. Soc 1935, 899–900.

(241). Hladikova V; Vana J; Hanusek J [3 + 2]-Cycloaddition Reaction of Sydnones with Alkynes. Beilstein J. Org. Chem 2018, 14, 1317–1348. [PubMed: 29977399]

(242). Kolodych S; Rasolofonjatovo E; Chaumontet M; Nevers M-C; Créminon C; Taran F Discovery of Chemoselective and Biocompatible Reactions Using a High-Throughput Immunoassay Screening. Angew. Chem. Int. Ed 2013, 52, 12056–12060.

(243). Narayanam MK; Liang Y; Houk KN; Murphy JM Discovery of New Mutually Orthogonal Bioorthogonal Cycloaddition Pairs through Computational Screening. Chem. Sci 2016, 7, 1257–1261. [PubMed: 29910881]

(244). Wallace S; Chin JW Strain-Promoted Sydnone Bicyclo-[6.1.0]-Nonyne Cycloaddition. Chem. Sci 2014, 5, 1742–1744. [PubMed: 25580211]

(245). Plougastel L; Koniev O; Specklin S; Decuypere E; Créminon C; Buisson D-A; Wagner A; Kolodych S; Taran F 4-Halogeno-Sydnones for Fast Strain Promoted Cycloaddition with Bicyclo-[6.1.0]-Nonyne. Chem. Commun 2014, 50, 9376–9378.

(246). Liu H; Audisio D; Plougastel L; Decuypere E; Buisson D-A; Koniev O; Kolodych S; Wagner A; Elhabiri M; Krzyczmonik Aet al. Ultrafast Click Chemistry with Fluorosydnones. Angew. Chem. Int. Ed 2016, 55, 12073–12077.

(247). George MV; Angadiyavar CS Photochemical Cycloadditions of 1,3-Dipolar Systems. I. Additions of *N,C*-Diphenylsydnone and 2,5-Diphenyltetrazole. J. Org. Chem 1971, 36, 1589–1594.

(248). Gotthardt H; Reiter F Photolyse der Sydnone in Gegenwart von Mehrfachbindungssystemen. Tetrahedron Lett. 1971, 12, 2749–2752.

(249). Märky M; Hansen H-J; Schmid H Photochemisches Verhalten von 3,4-Diarylsydonen. Vorläufige Mitteilung. Helv. Chim. Acta 1971, 54, 1275–1278.

(250). Pfoertner K-H; Foricher J Photoreaktionen Des 3-Methyl-4-Phenylsydnons. Helv. Chim. Acta 1980, 63, 653–657.

(251). Butković K; Vuk D; Marinić Ž; Penić J; Šindler-Kulyk M Synthesis and Photochemistry of 3-(O-Stilbeneyl)-4-H/Me/Ph-Sydnones; Intramolecular Cyclization To 1,2-Benzodiazepines and/Or Quinolines. Tetrahedron 2010, 66, 9356–9362.

(252). Zhang XC; Wu XT; Jiang SC; Gao JS; Yao ZJ; Deng JJ; Zhang LM; Yu ZP Photo-Accelerated "Click" Reaction between Diarylsydnones and Ring-Strained Alkynes for Bioorthogonal Ligation. Chem. Commun 2019, 55, 7187–7190.

(253). Yao Z; Wu X; Zhang X; Xiong Q; Jiang S; Yu Z Synthesis and Evaluation of Photo-Activatable β-Diarylsydnone-L-Alanines for Fluorogenic Photo-Click Cyclization of Peptides. Org. Biomol. Chem 2019, 17, 6777–6781. [PubMed: 31268077]

(254). Gao J; Xiong Q; Wu X; Deng J; Zhang X; Zhao X; Deng P; Yu Z Direct Ring-Strain Loading for Visible-Light Accelerated Bioorthogonal Ligation via Diarylsydnone-Dibenzo[b,f] [1,4,5]Thiadiazepine Photo-Click Reactions. Commun. Chem 2020, 3, 29.

(255). Padwa A; Smolanoff J Photocycloaddition of Arylazirenes with Electron-Deficient Olefins. J. Am. Chem. Soc 1971, 93, 548–550.

(256). Padwa A Azirine Photochemistry. Acc. Chem. Res 1976, 9, 371–378.

(257). Albrecht E; Mattay J; Steenken S [3 + 2] Cycloadditions and Protonation by Alcohols of Photochemically Generated Nitrile Ylides from 2H-Azirines. Formation and Reactivities of Azaallenium Cations. J. Am. Chem. Soc 1997, 119, 11605–11610.

(258). Mueller JO; Schmidt FG; Blinco JP; Barner-Kowollik C Visible-Light-Induced Click Chemistry. Angew. Chem. Int. Ed 2015, 54, 10284–10288.

(259). Ulrich S; Boturyn D; Marra A; Renaudet O; Dumy P Oxime Ligation: A Chemoselective Click-Type Reaction for Accessing Multifunctional Biomolecular Constructs. Chem. Eur. J 2014, 20, 34–41. [PubMed: 24302514]

(260). Kölmel DK; Kool ET Oximes and Hydrazones in Bioconjugation: Mechanism and Catalysis. Chem. Rev 2017, 117, 10358–10376. [PubMed: 28640998]

(261). Yang Y; Zhang J; Liu Z; Lin Q; Liu X; Bao C; Wang Y; Zhu L Tissue-Integratable and Biocompatible Photogelation by the Imine Crosslinking Reaction. Advanced Materials 2016, 28, 2724–2730. [PubMed: 26840751]

(262). Christman KL; Broyer RM; Tolstyka ZP; Maynard HD Site-Specific Protein Immobilization Through N-Terminal Oxime Linkages. J. Mater. Chem 2007, 17, 2021–2027.

(263). Park S; Yousaf MN An Interfacial Oxime Reaction To Immobilize Ligands and Cells in Patterns and Gradients to Photoactive Surfaces. Langmuir 2008, 24, 6201–6207. [PubMed: 18479156]

(264). DeForest CA; Tirrell DA A Photoreversible Protein-Patterning Approach for Guiding Stem Cell Fate in Three-Dimensional Gels. Nat. Mater 2015, 14, 523–531. [PubMed: 25707020]

(265). Tidwell TT The First Century of Ketenes (1905–2005): The Birth of a Versatile Family of Reactive Intermediates. Angew. Chem. Int. Ed 2005, 44, 5778–5785.

(266). Leibfarth FA; Hawker CJ The Emerging Utility of Ketenes in Polymer Chemistry. J. Polym. Sci., Part A: Polym. Chem 2013, 51, 3769–3782.

(267). Allen AD; Tidwell TT New Directions in Ketene Chemistry: The Land of Opportunity. Eur. J. Org. Chem 2012, 2012, 1081–1096.

(268). Soltani O; De Brabander JK Synthesis of Functionalized Salicylate Esters and Amides by Photochemical Acylation. Angew. Chem. Int. Ed 2005, 44, 1696–1699.

(269). Kumbaraci V; Talinli N; Yagci Y Photoinduced Synthesis of Oligoesters. Macromolecules 2006, 39, 6031–6035.

(270). Kumbaraci V; Talinli N; Yagci Y Photoinduced Crosslinking of Polymers Containing Pendant Hydroxyl Groups By Using Bisbenzodioxinones. Macromol. Rapid Commun 2007, 28, 72–77.

(271). Tasdelen MA; Kumbaraci V; Talinli N; Yagci Y Photoinduced Cross-Linking Polymerization of Monofunctional Vinyl Monomer without Conventional Photoinitiator and Cross-Linker. Macromolecules 2007, 40, 4406–4408.

(272). Tasdelen MA; Kumbaraci V; Jockusch S; Turro NJ; Talinli N; Yagci Y Photoacid Generation by Stepwise Two-Photon Absorption: Photoinitiated Cationic Polymerization of Cyclohexene Oxide by Using Benzodioxinone in the Presence of Iodonium Salt. Macromolecules 2008, 41, 295–297.

(273). Durmaz YY; Kumbaraci V; Demirel AL; Talinli N; Yagci Y Graft Copolymers by the Combination of ATRP and Photochemical Acylation Process by Using Benzodioxinones. Macromolecules 2009, 42, 3743–3749.

(274). Kumbaraci V; Aydogan B; Talinli N; Yagci Y Naphthodioxinone-1,3-Benzodioxole as Photochemically Masked One-Component Type II Photoinitiator for Free Radical Polymerization. J. Polym. Sci., Part A: Polym. Chem 2012, 50, 2612–2618.

(275). Yilmaz G; Kumbaraci V; Talinli N; Tatar P; Demirel AL; Yagci Y Photoinduced Grafting of Polystyrene onto Silica Particles by Ketene Chemistry. J. Polym. Sci., Part A: Polym. Chem 2012, 50, 2517–2520.

(276). Aydogan C; Ciftci M; Kumbaraci V; Talinli N; Yagci Y Hyperbranced Polymers by Photoinduced Self-Condensing Vinyl Polymerization Using Bisbenzodioxinone. Macromol. Chem. Phys 2017, 218, 1700045.

(277). Arslan M; Motallebzadeh A; Kiskan B; Demirel AL; Kumbaraci IV; Yagci Y Combining Benzoxazine and Ketene Chemistries for Self-Healing of High Performance Thermoset Surfaces. Polym. Chem 2018, 9, 2031–2039.

(278). Alkan Goksu Y; Kumbaraci V; Yagci Y Modular Photoinduced Grafting Onto Approach by Ketene Chemistry. J. Polym. Sci., Part A: Polym. Chem 2019, 57, 274–280.

(279). Liu L-H; Yan M Perfluorophenyl Azides: New Applications in Surface Functionalization and Nanomaterial Synthesis. Acc. Chem. Res 2010, 43, 1434–1443. [PubMed: 20690606]

(280). Yan M; Ren J Covalent Immobilization of Ultrathin Polymer Films by Thermal Activation of Perfluorophenyl Azide. Chem. Mater 2004, 16, 1627–1632.

(281). Yan M; Ren J Covalent Immobilization of Polypropylene Thin Films. J. Mater. Chem 2005, 15, 523–527.

(282). Liu L; Engelhard MH; Yan M Surface and Interface Control on Photochemically Initiated Immobilization. J. Am. Chem. Soc 2006, 128, 14067–14072. [PubMed: 17061889]

(283). Pei Y; Yu H; Pei Z; Theurer M; Ammer C; André S; Gabius H-J; Yan M; Ramström O Photoderivatized Polymer Thin Films at Quartz Crystal Microbalance Surfaces: Sensors for Carbohydrate-Protein Interactions. Anal. Chem 2007, 79, 6897–6902. [PubMed: 17705448]

(284). Wang H; Li L-L; Tong Q; Yan M-D Evaluation of Photochemically Immobilized Poly(2-ethyl-2-oxazoline) Thin Films as Protein-Resistant Surfaces. ACS Appl. Mater 2011, 3, 3463–3471.

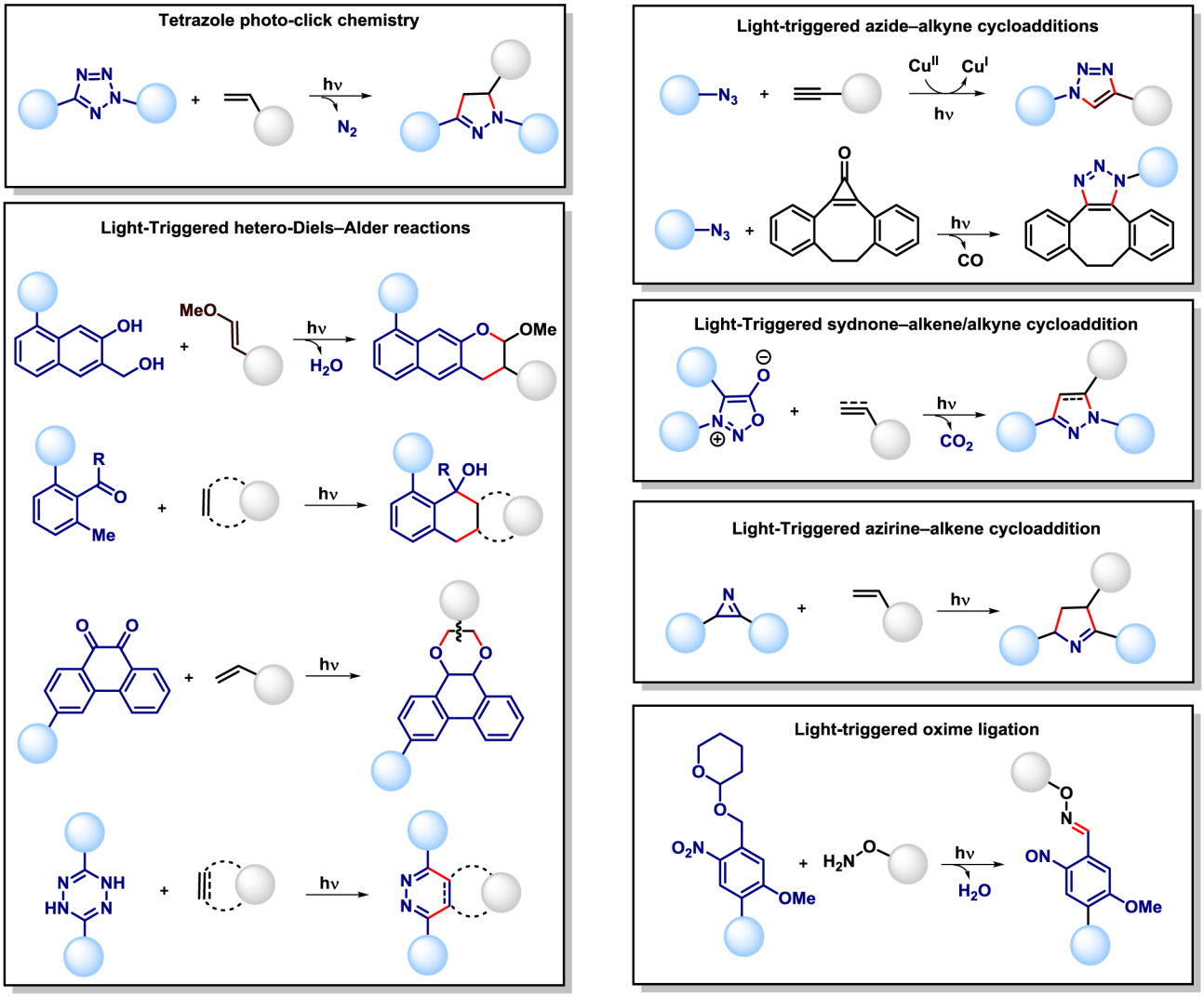
(285). Conradi M; Junkers T Photoinduced Conjugation of Aldehyde Functional Polymers with Olefins via [2 + 2]-Cycloaddition. Macromolecules 2011, 44, 7969–7976.

(286). D'Auria M; Racioppi R Oxetane Synthesis through the Paternò-Büchi Reaction. Molecules 2013, 18, 11384–11428. [PubMed: 24043139]

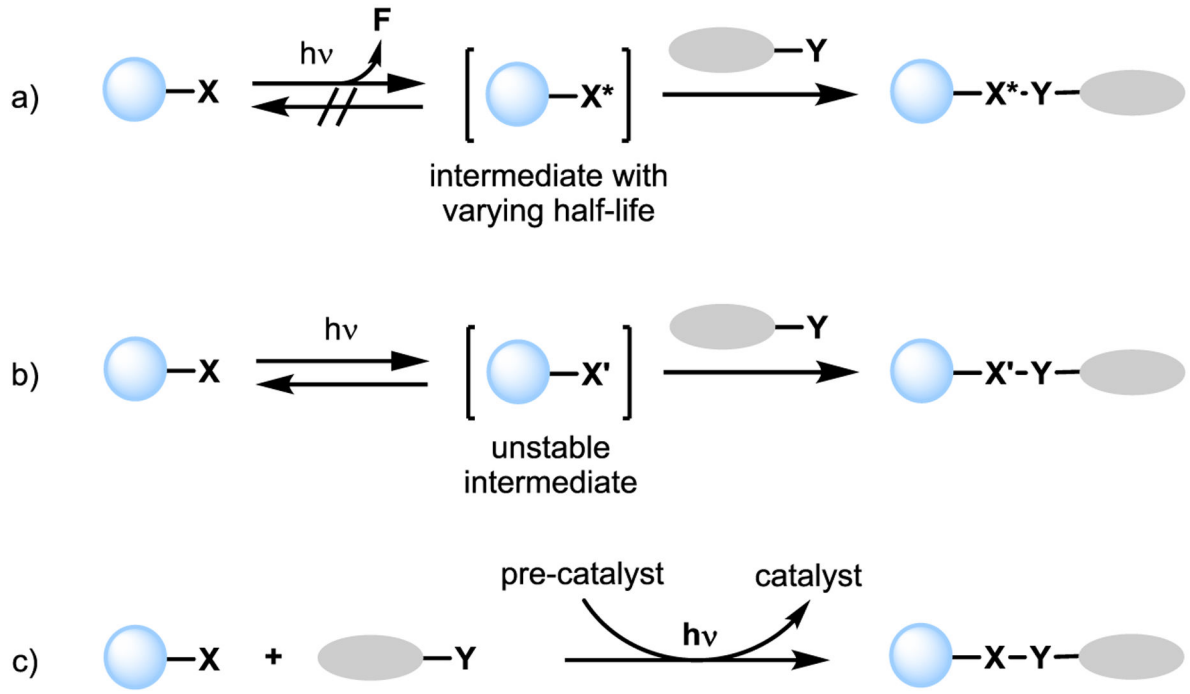
(287). D'Auria M The Paternò–Büchi Reaction – A Comprehensive Review. Photochem. Photobiol. Sci 2019, 18, 2297–2362. [PubMed: 31273370]

(288). Fréneau M; Hoffmann N The Paternò-Büchi reaction—Mechanisms and application to organic synthesis. J. PhotoChem 2017, 33, 83–108.

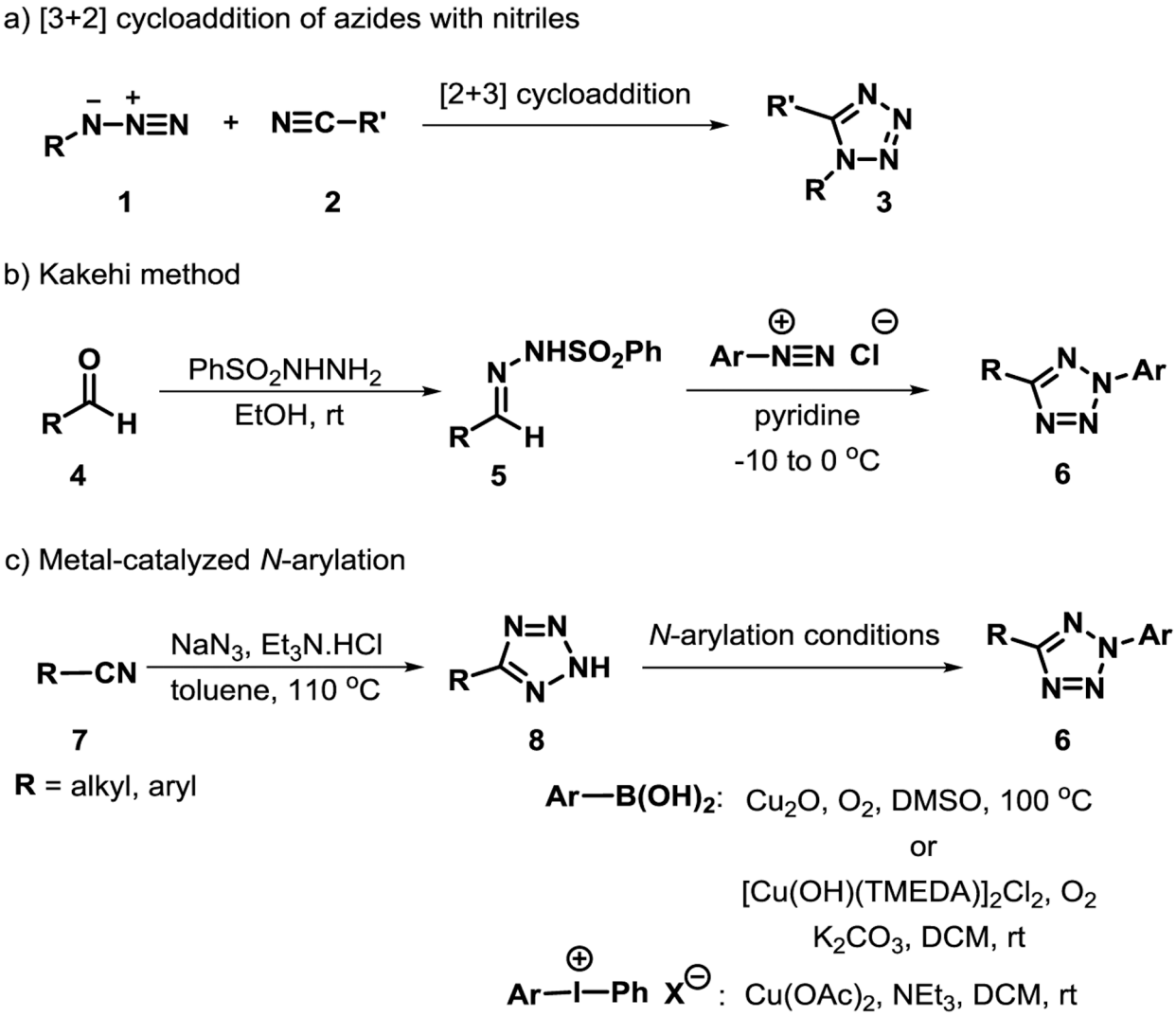
(289). Day JI; Singh K; Trinh W; Weaver JD Visible Light Mediated Generation of trans-Arylcyclohexenes and Their Utilization in the Synthesis of Cyclic Bridged Ethers. J. Am. Chem. Soc 2018, 140, 9934–9941. [PubMed: 30001489]



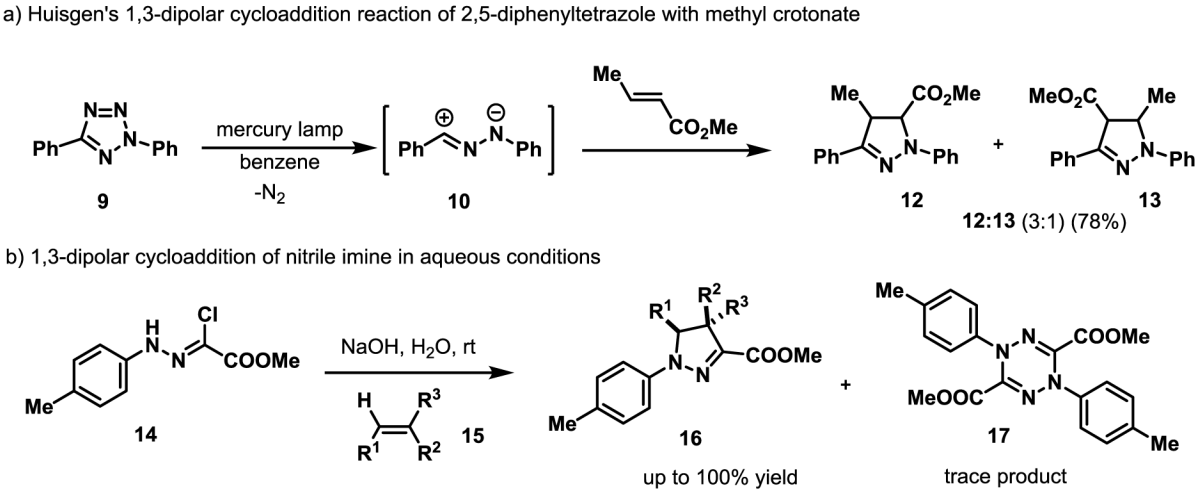
Scheme 1:
Representative examples of photoclick reactions



Scheme 2:
Three types of photoclick reactions: a) type I; b) type II; c) type III



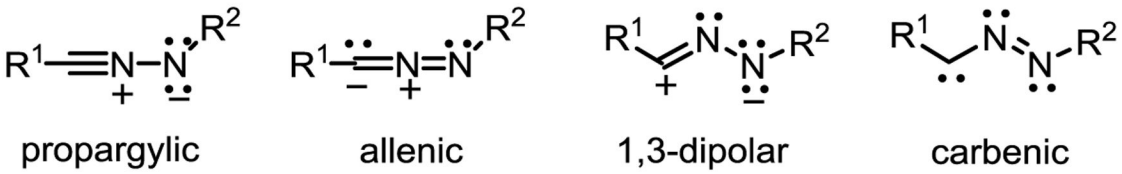
Scheme 3:
Synthesis of tetrazoles



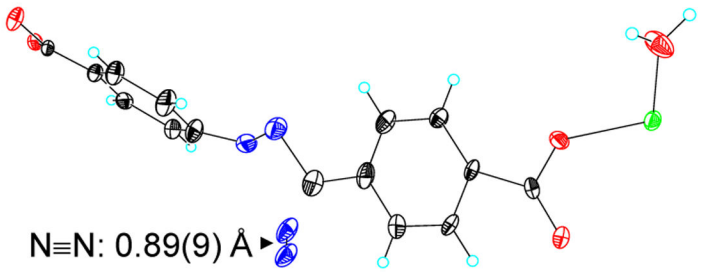
Scheme 4:

Early reports of nitrile imine-mediated 1,3-dipolar cycloaddition reactions

a)

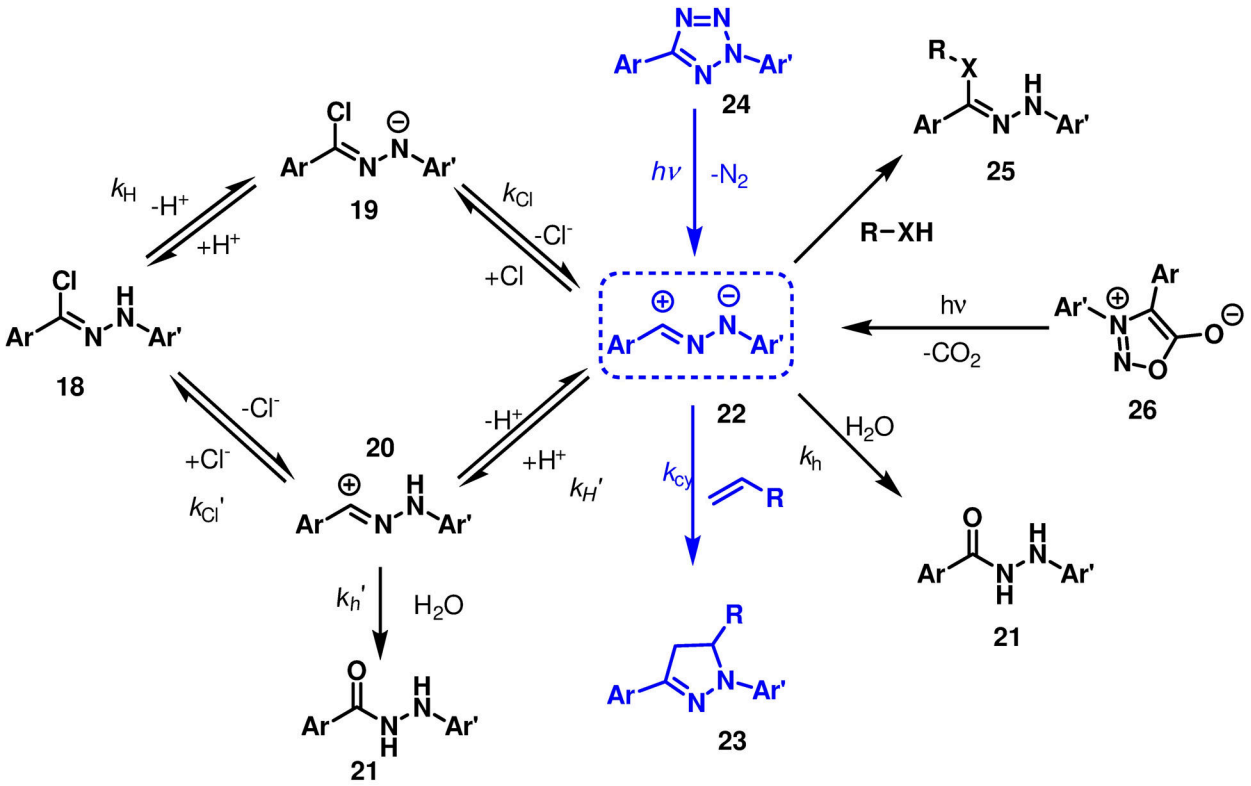


b)



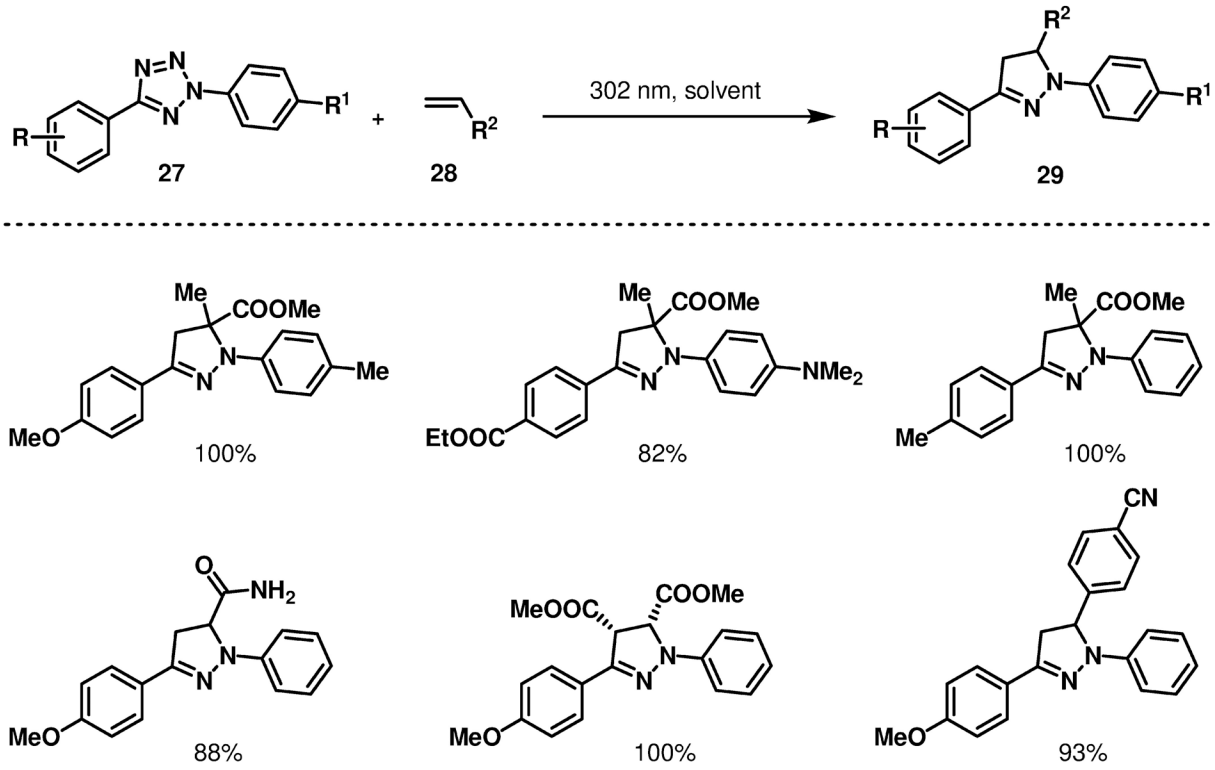
Scheme 5:

a) Electronic structures of the nitrile imine; b) direct observation of the bent nitrile imine 1,3-dipolar structure in the solid-state. Adapted from ref 48. Copyright 2009 American Chemical Society.

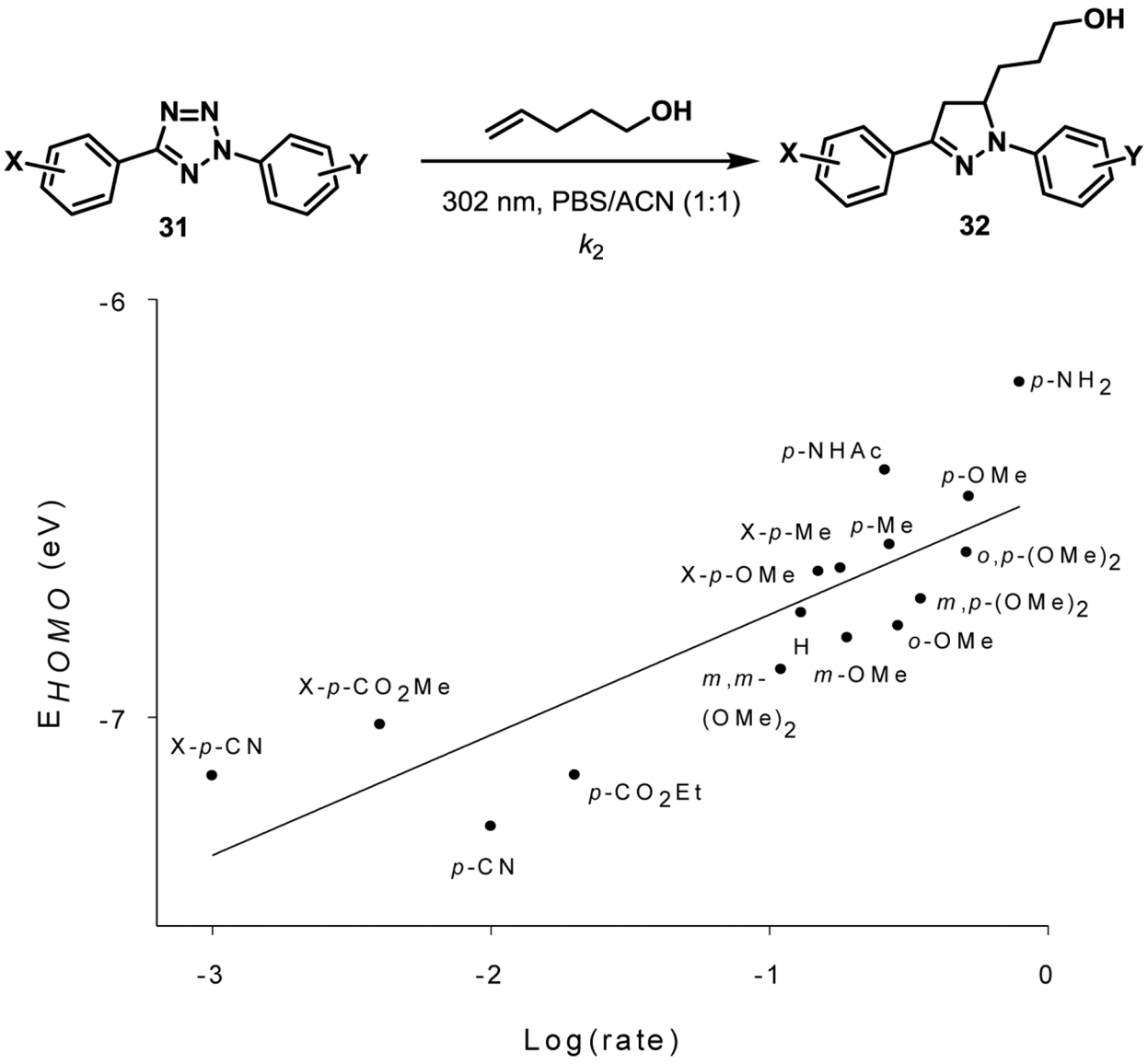


Scheme 6:

A theoretical framework to account for the nitrile imine generation and all the nitrile imine mediated reactions including 1,3-dipolar cycloaddition (highlighted in blue)

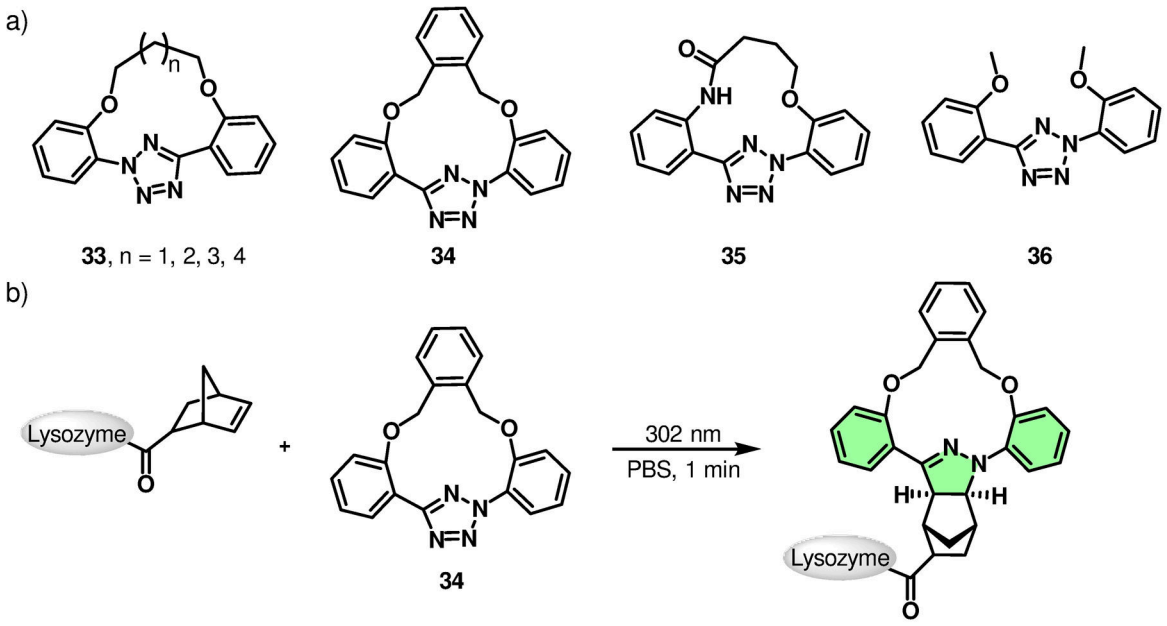


Scheme 7:
Photoinduced 1,3-dipolar cycloaddition for the synthesis of pyrazolines



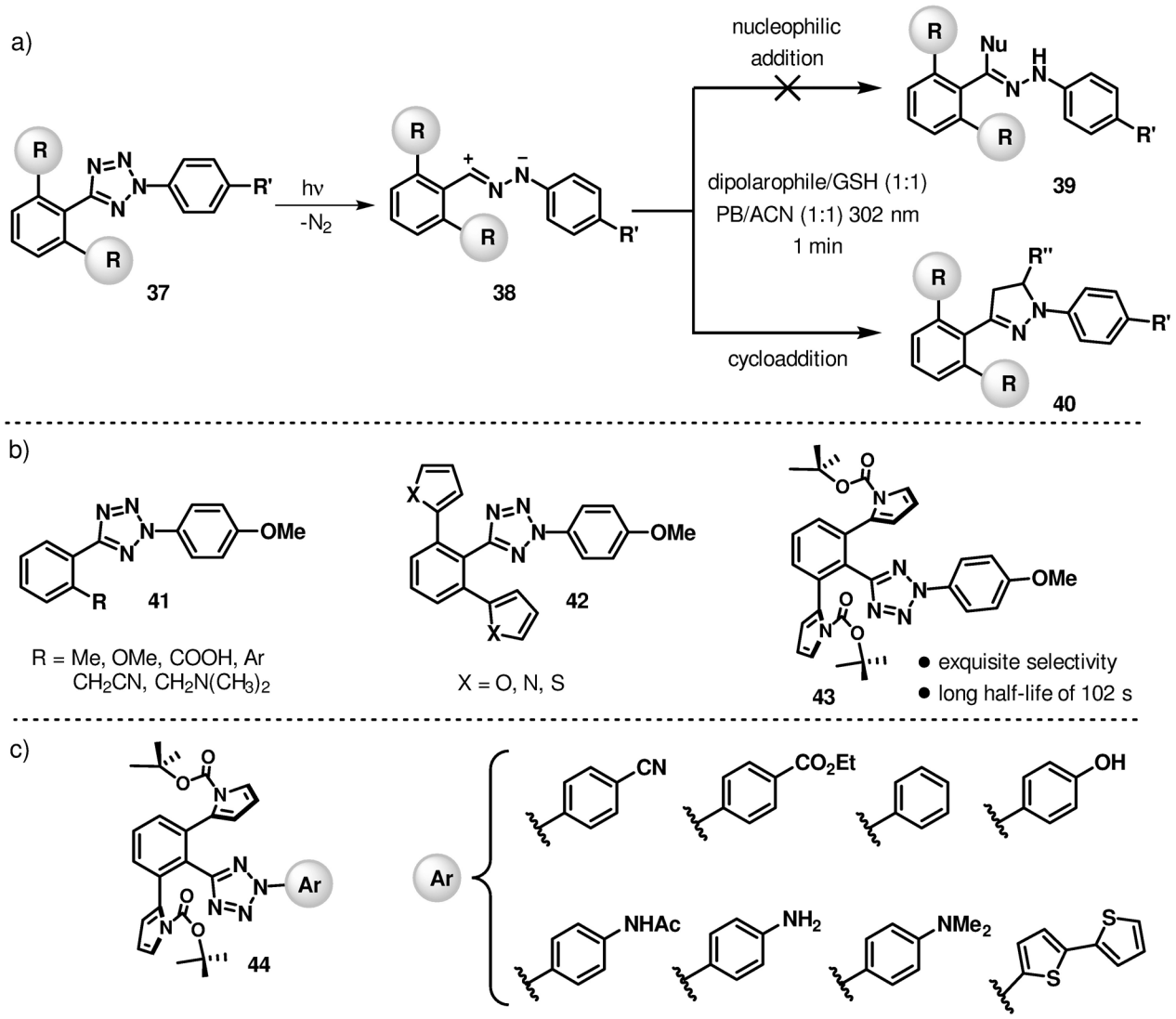
Scheme 8:

Plot of E_{HOMO} vs. log(rate) reveals HOMO-lifting effect in tetrazole photoclick chemistry. Reproduced with permission from ref 56. Copyright 2009 John Wiley & Sons,Inc.



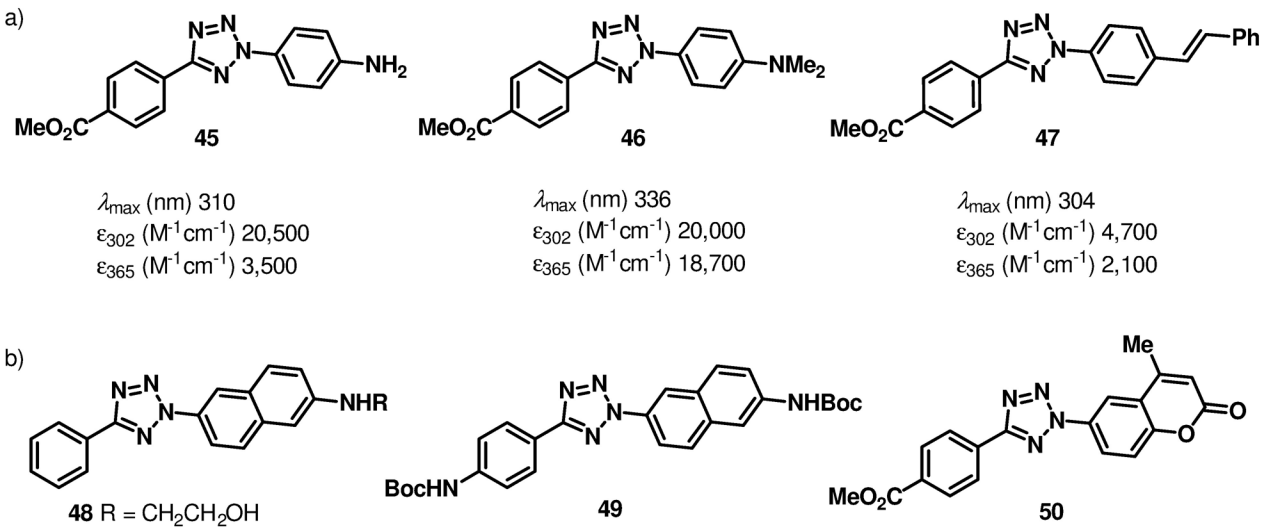
Scheme 9:

a) Design of macrocyclic tetrazoles; b) Application of macrocyclic tetrazole in protein labeling



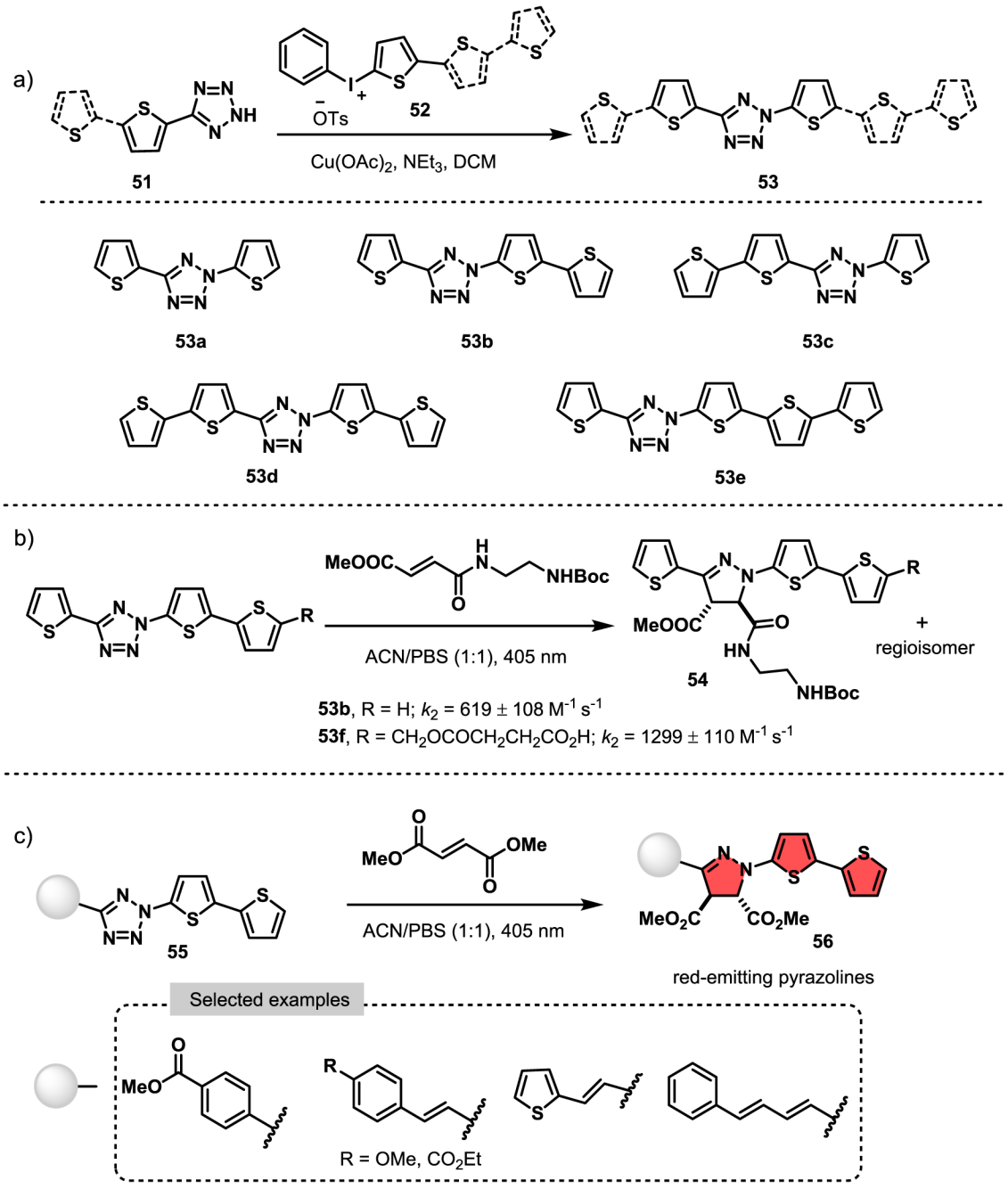
Scheme 10:

Sterically shielded tetrazoles for bioorthogonal cycloaddition reaction



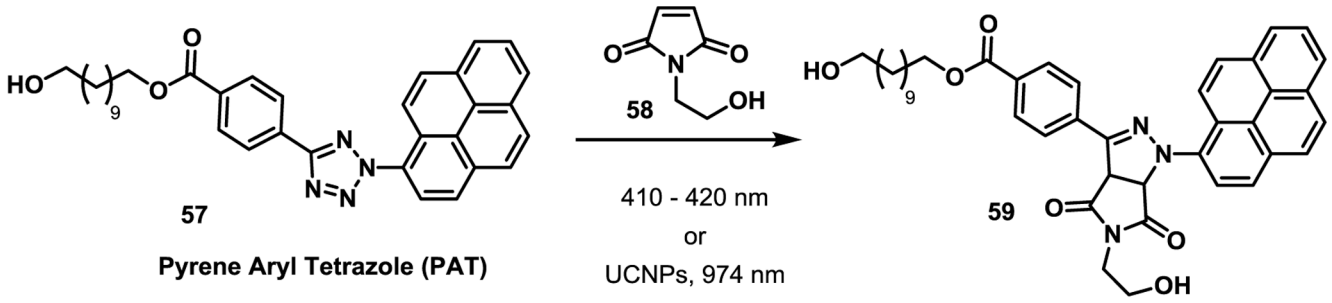
Scheme 11:

Tetrazole photoclick reactions under 365-nm photoirradiation

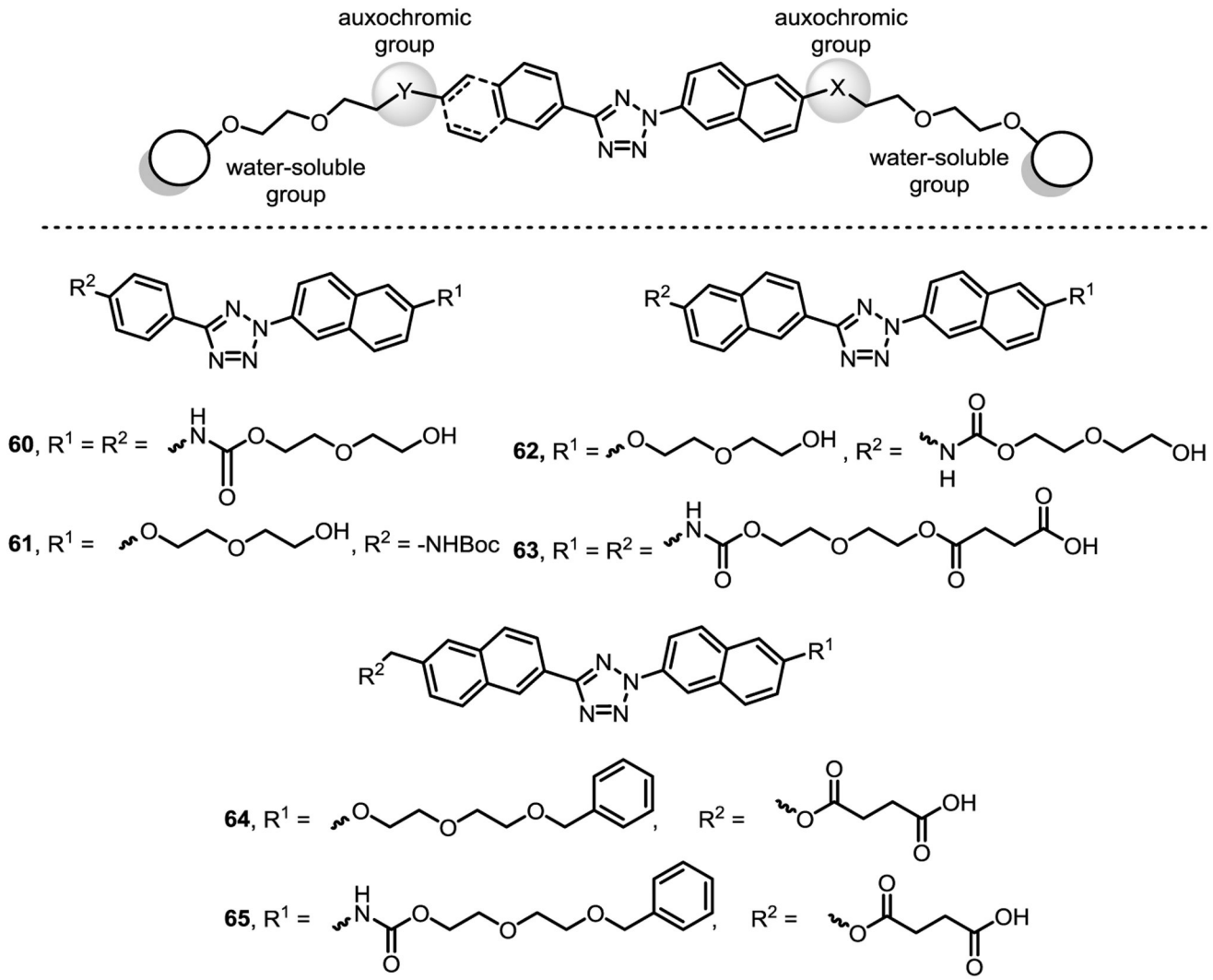


Scheme 12:

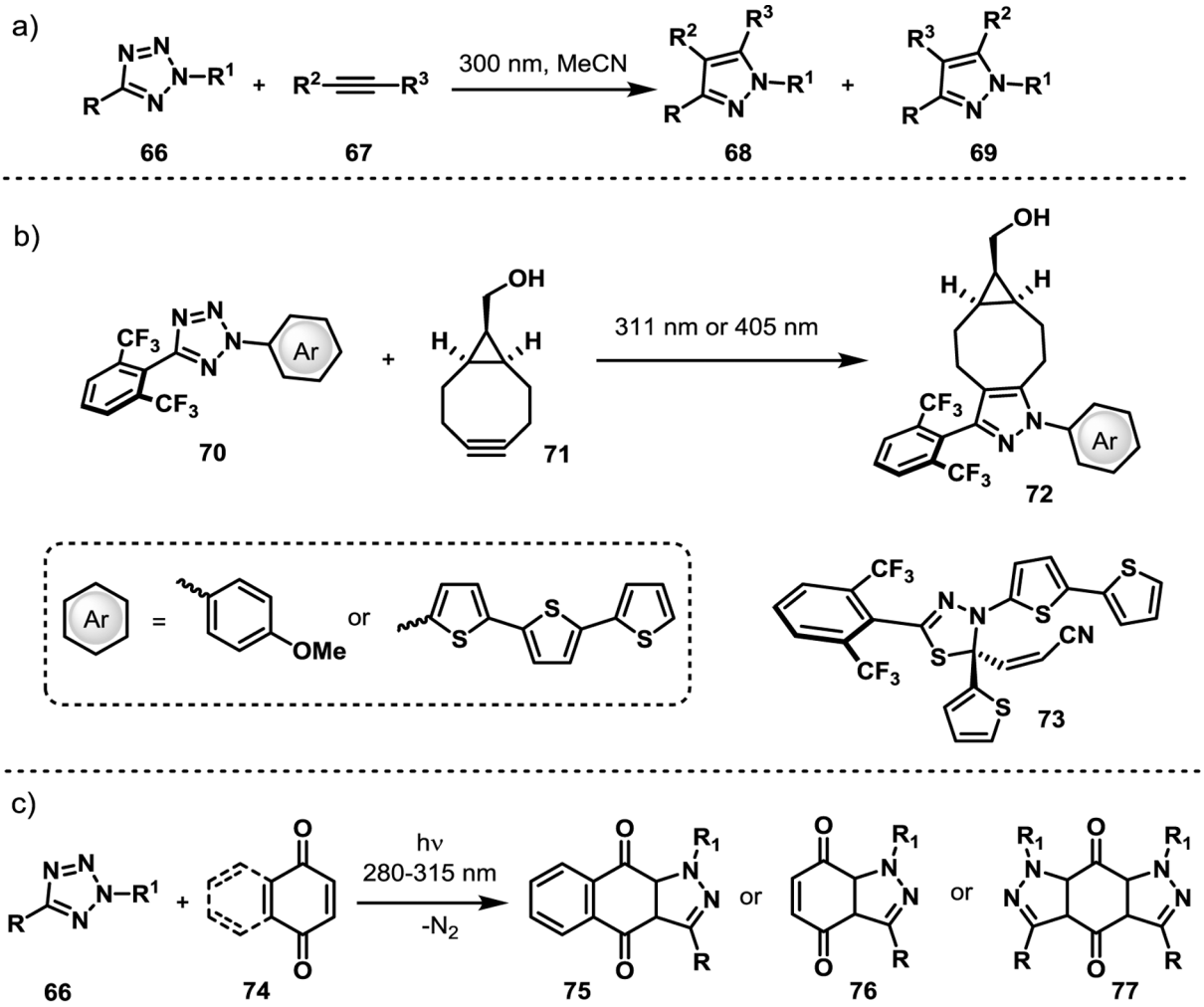
a) Synthesis of oligothiophene-based tetrazoles; b) Kinetic characterization of the oligothiophene-based tetrazoles in 405 nm laser-triggered photoclick chemistry; c) Laser-activatable tetrazoles with the extended π-system



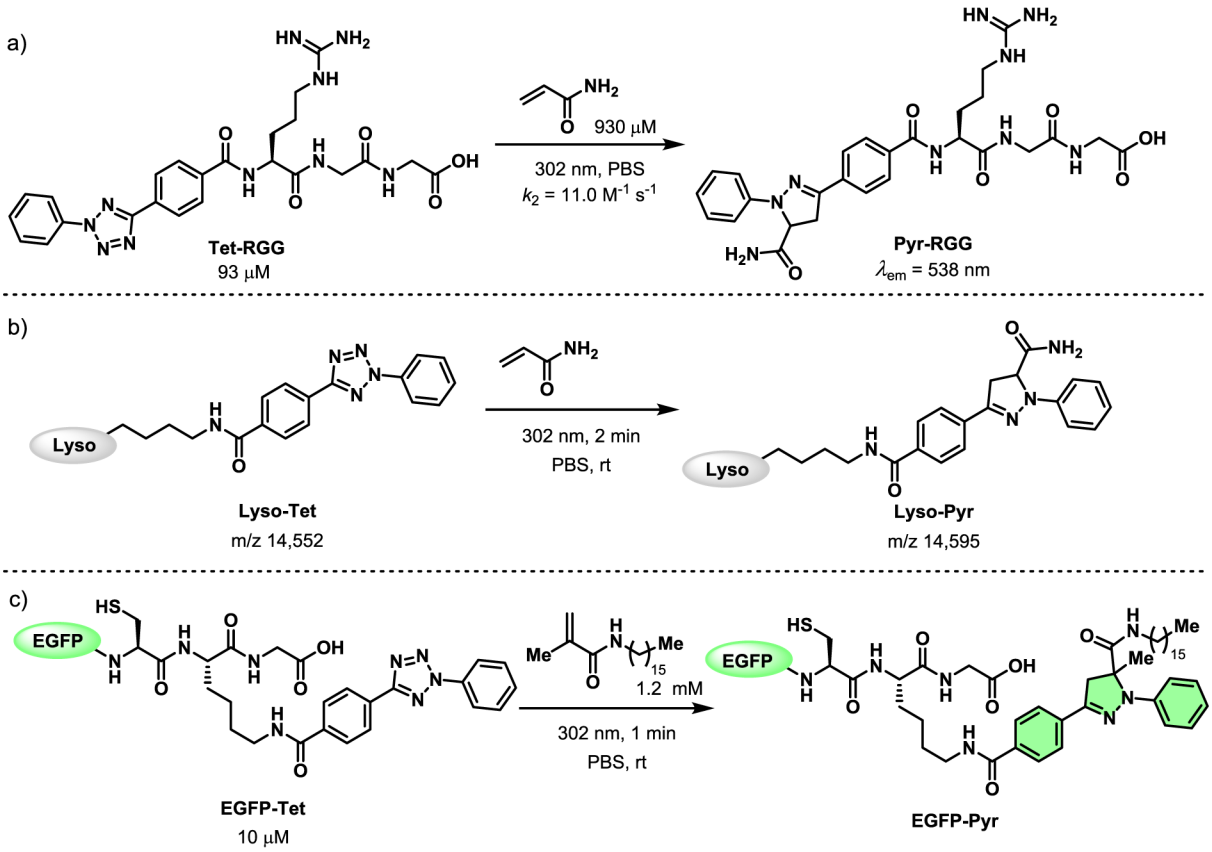
Scheme 13:
Visible or NIR light-induced cycloaddition based on Pyrene Aryl Tetrazole (PAT)



Scheme 14:
Design of naphthalene-tetrazoles for two-photon triggered photoclick chemistry

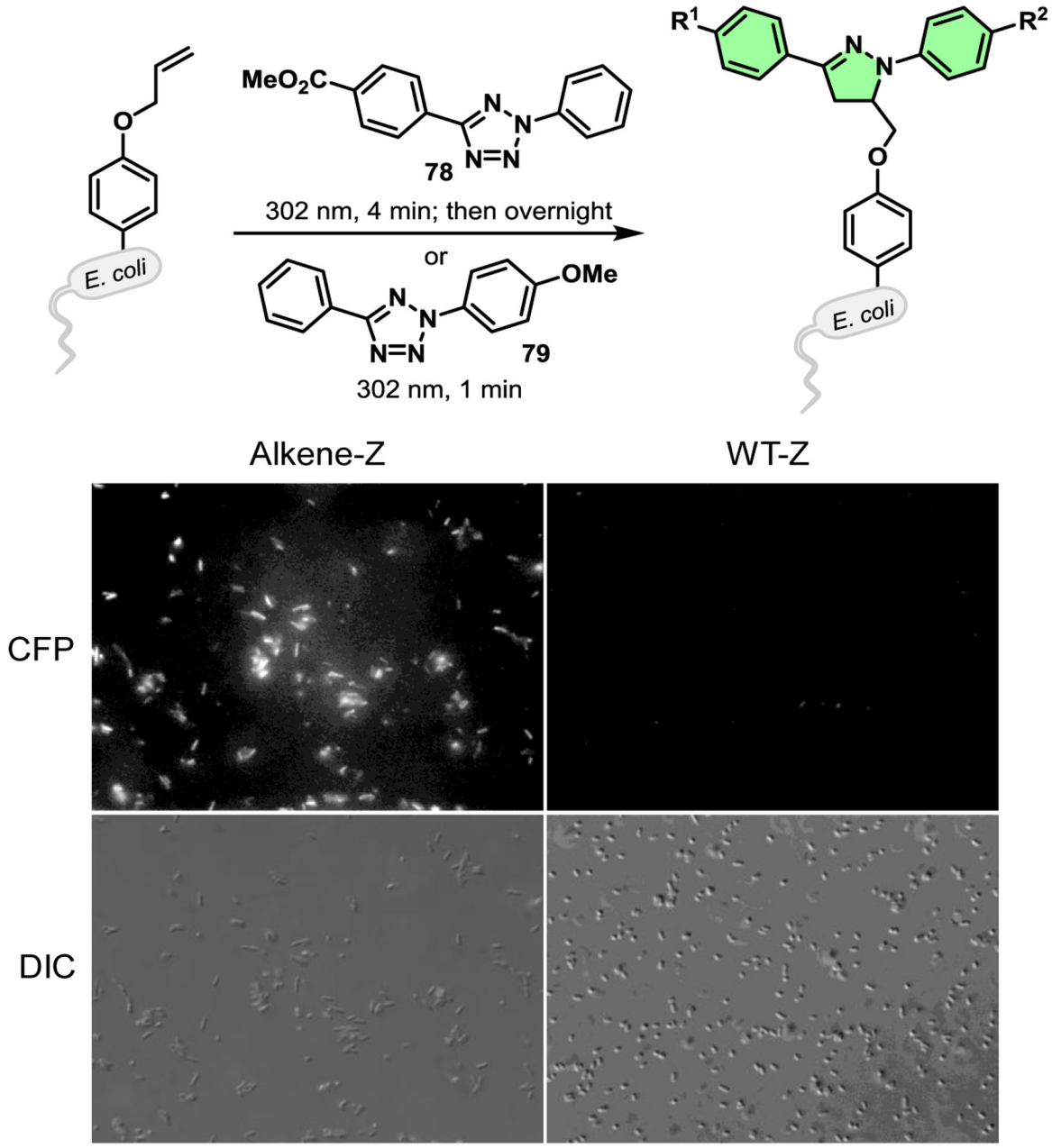


Scheme 15:
Tetrazole photoclick reaction with various dipolarophiles



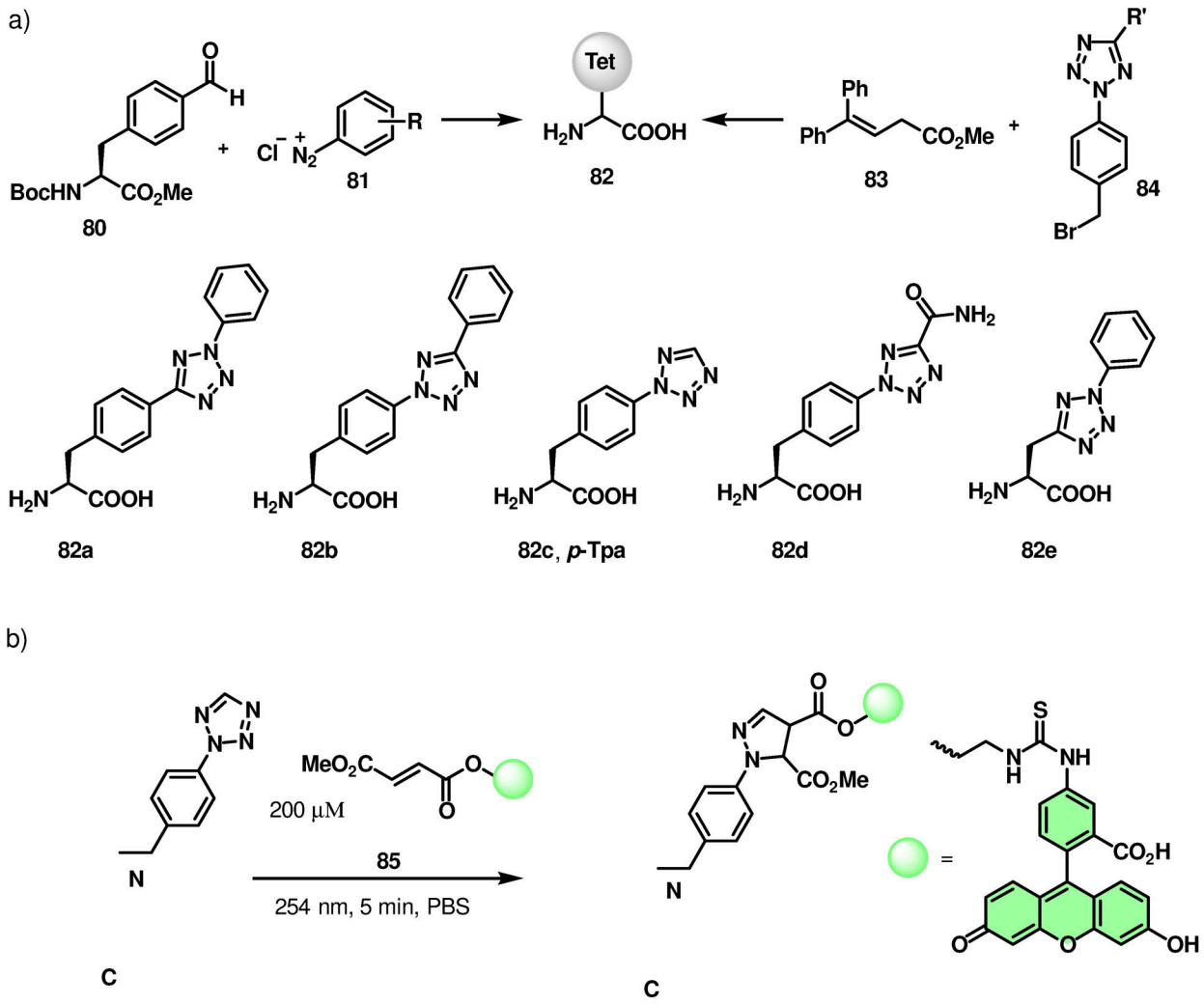
Scheme 16:

Photoclick chemistry mediated bioorthogonal labeling of a) a tetrazole-modified peptide; b) a tetrazole-modified lysozyme; and c) a tetrazole-containing EGFP



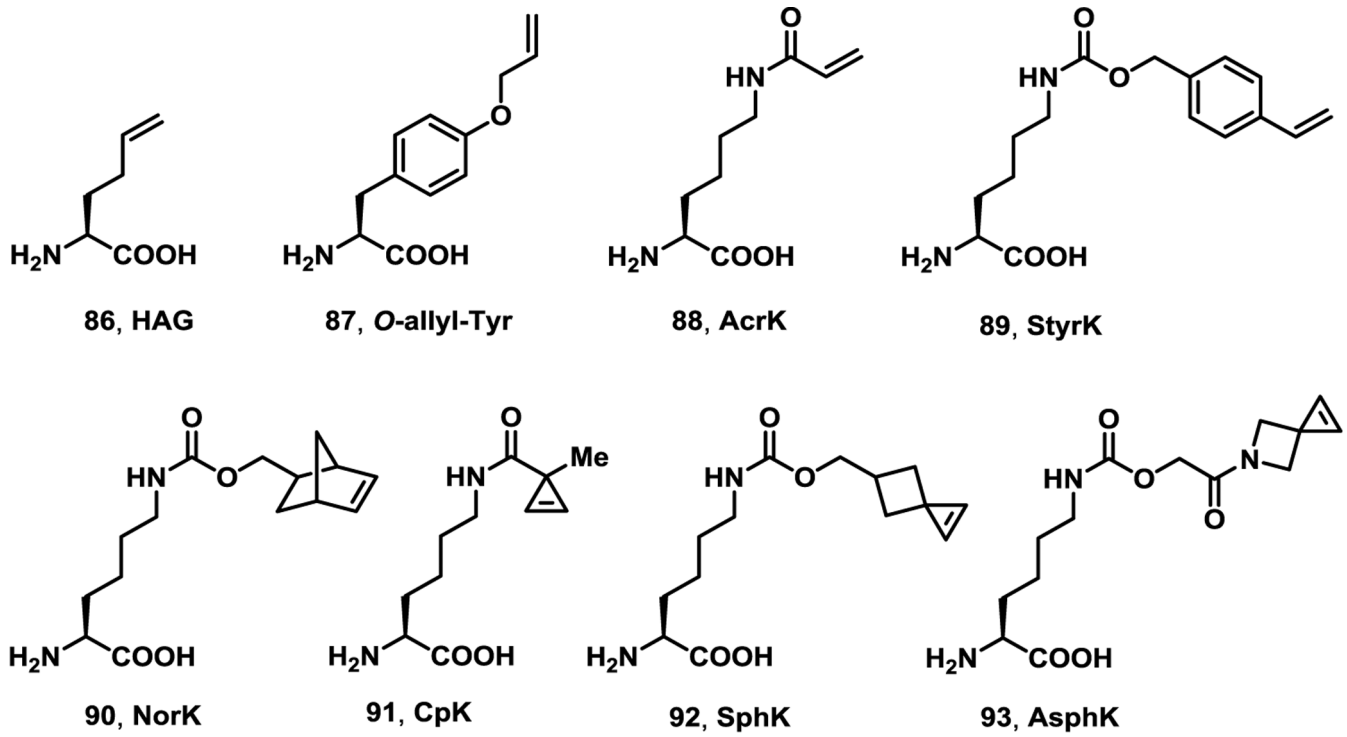
Scheme 17:

Fluorescent labeling of alkene-encoded proteins in *E. coli* via tetrazole photoclick chemistry. Reproduced from ref 79. Copyright 2008 American Chemical Society.

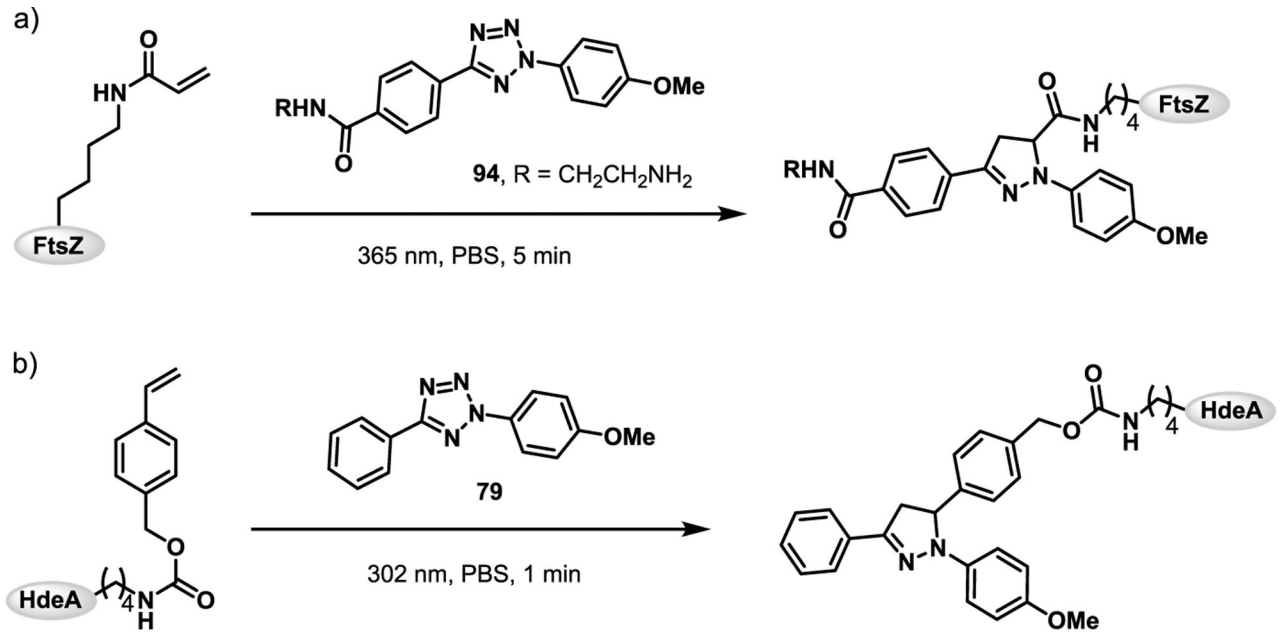


Scheme 18:

a) Synthesis of photoreactive tetrazole amino acids; b) Selective fluorescent labeling of the *p*-Tpa-encoded myoglobin via tetrazole photoclick chemistry. Adapted from ref 81. Copyright 2010 American Chemical Society.

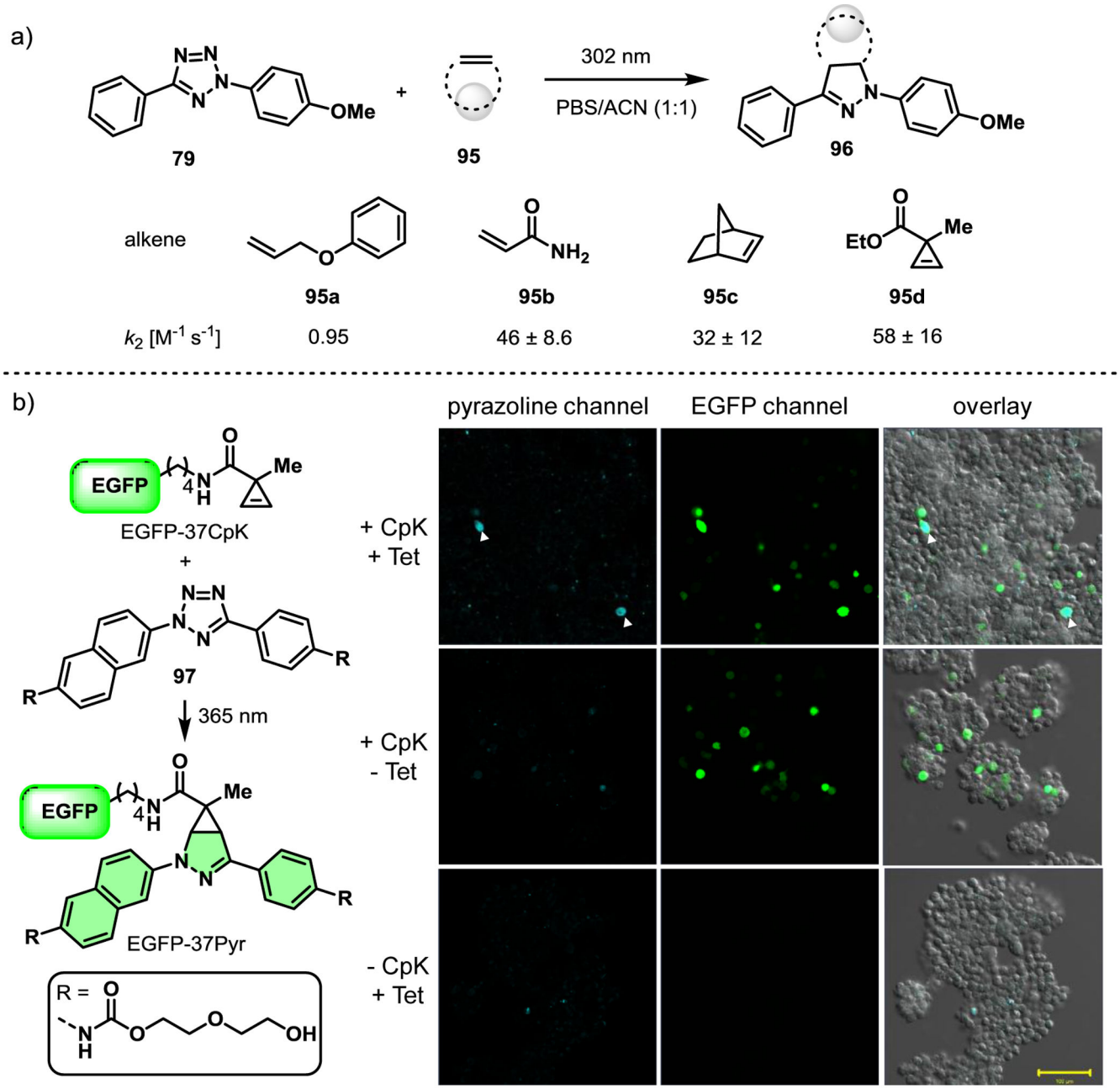


Scheme 19:
Genetically encoded alkene amino acids for bioorthogonal protein labeling



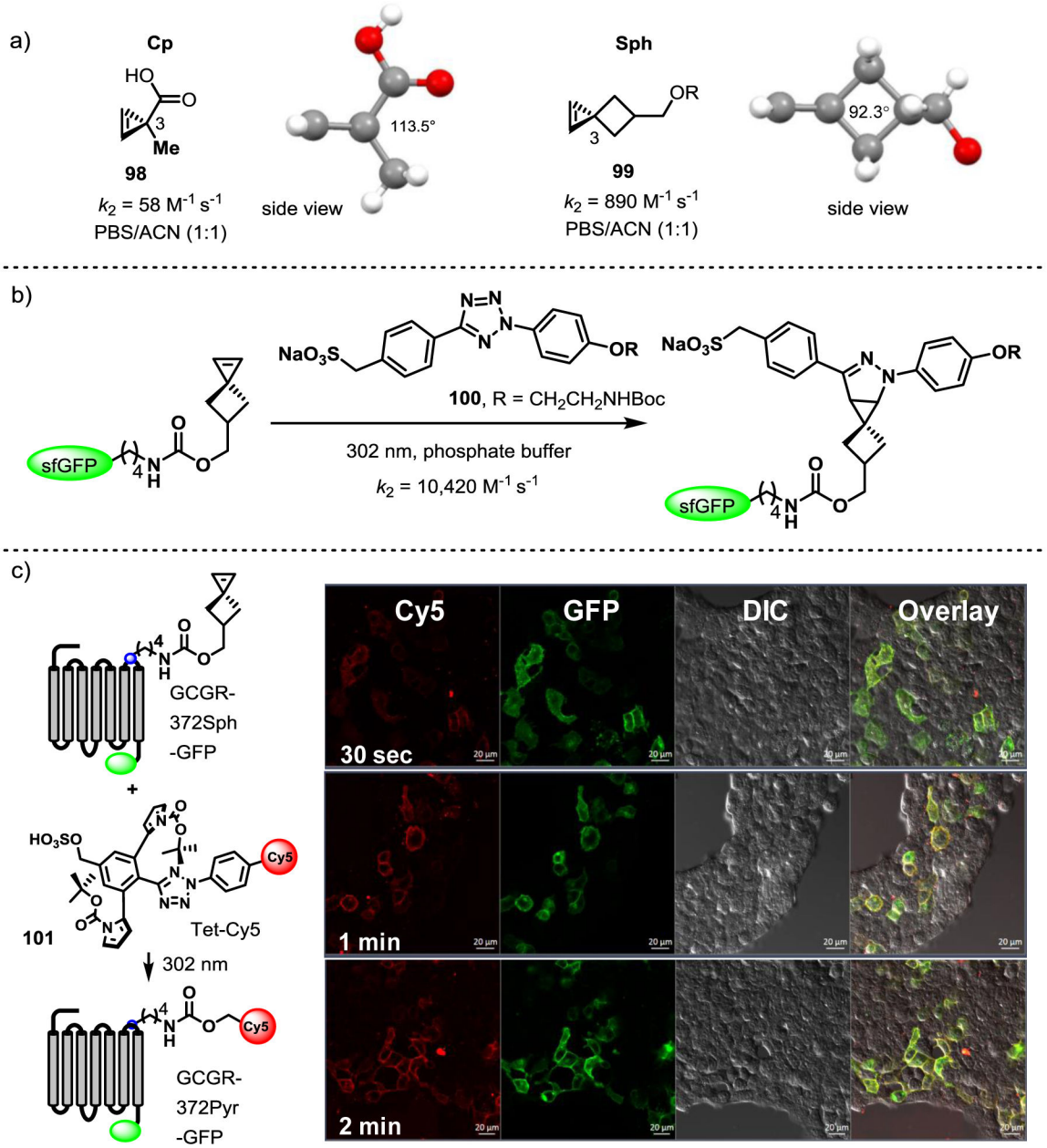
Scheme 20:

Bioorthogonal protein labeling in live cells via tetrazole photoclick chemistry with a genetically encoded a) acrylamide or b) styrene-containing amino acid



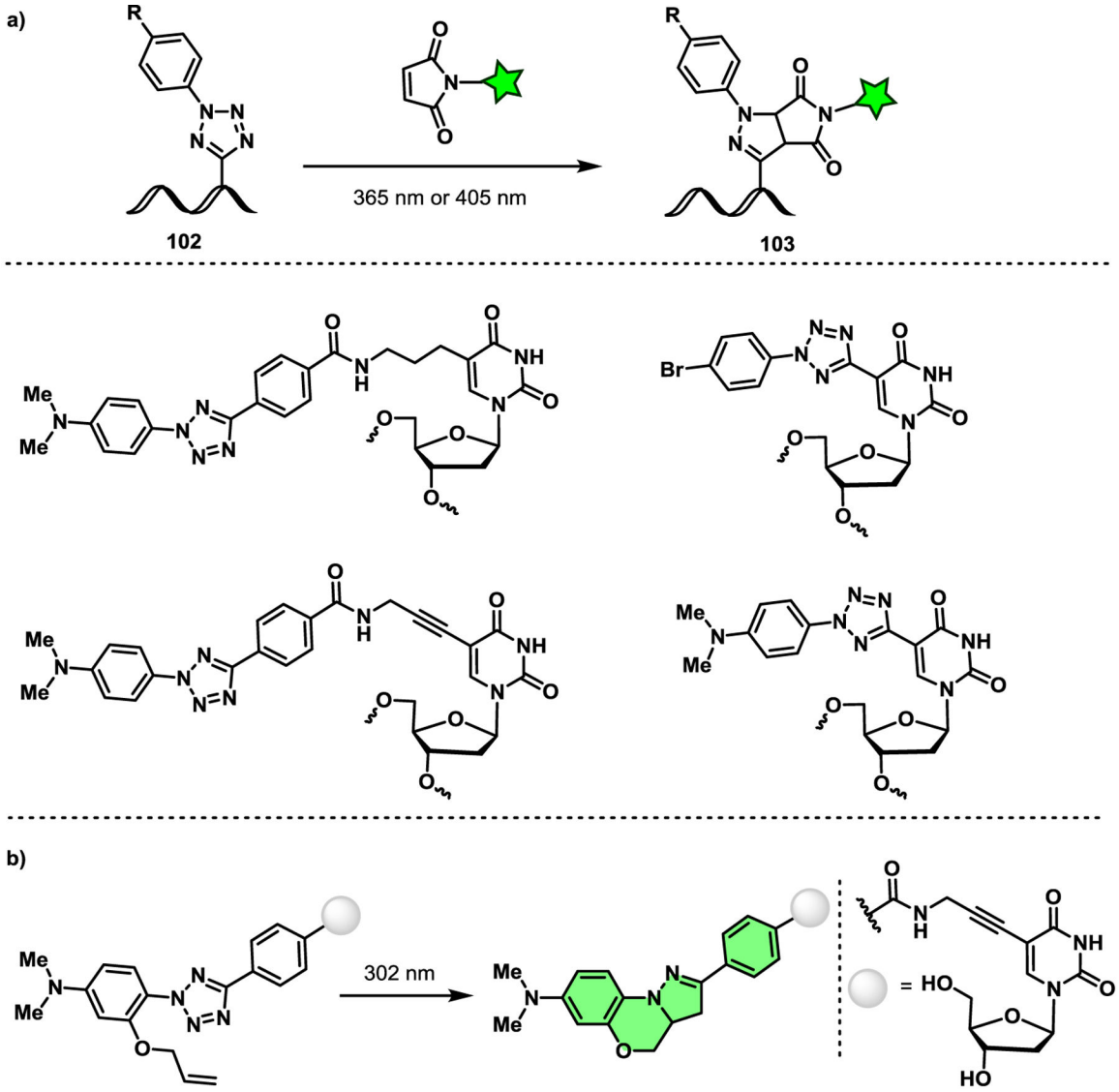
Scheme 21:

A cyclopropene amino acid (CpK) for bioorthogonal labeling of proteins: a) kinetic studies; b) selective labeling of CpK-encoded EGFP in HEK293 cell via tetrazole photoclick chemistry. Adapted and reproduced with permission from ref 88. Copyright 2009 John Wiley & Sons,Inc.



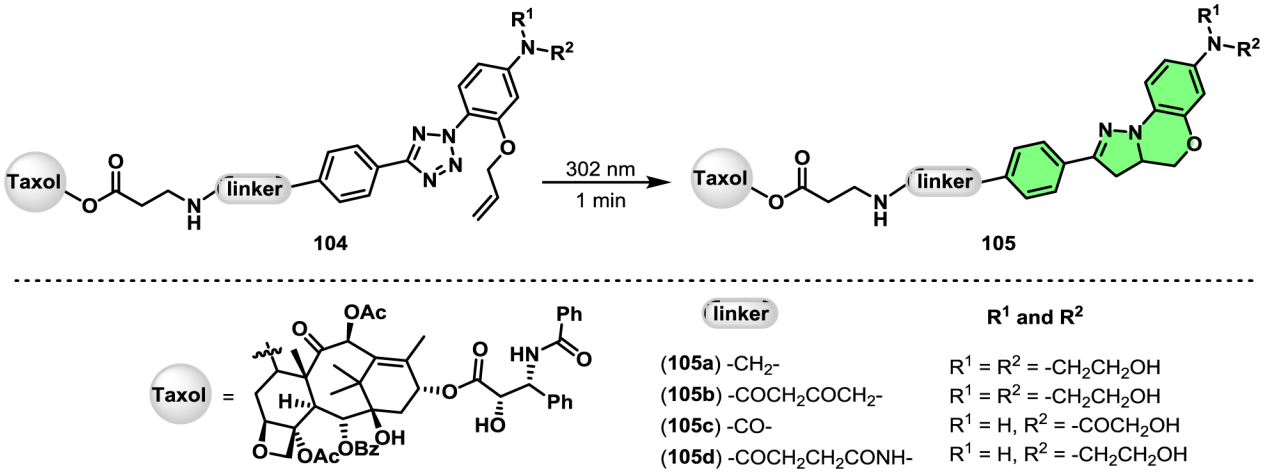
Scheme 22:

Design of spiro[2.3]hex-1-ene for superfast photoclick chemistry: a) crystal structure of Sph vs. Cp; b) genetic encoding of SphK into sfGFP; c) bioorthogonal labeling of GCGR in live cells. Adapted and reproduced from ref 54. Copyright 2018 American Chemical Society.



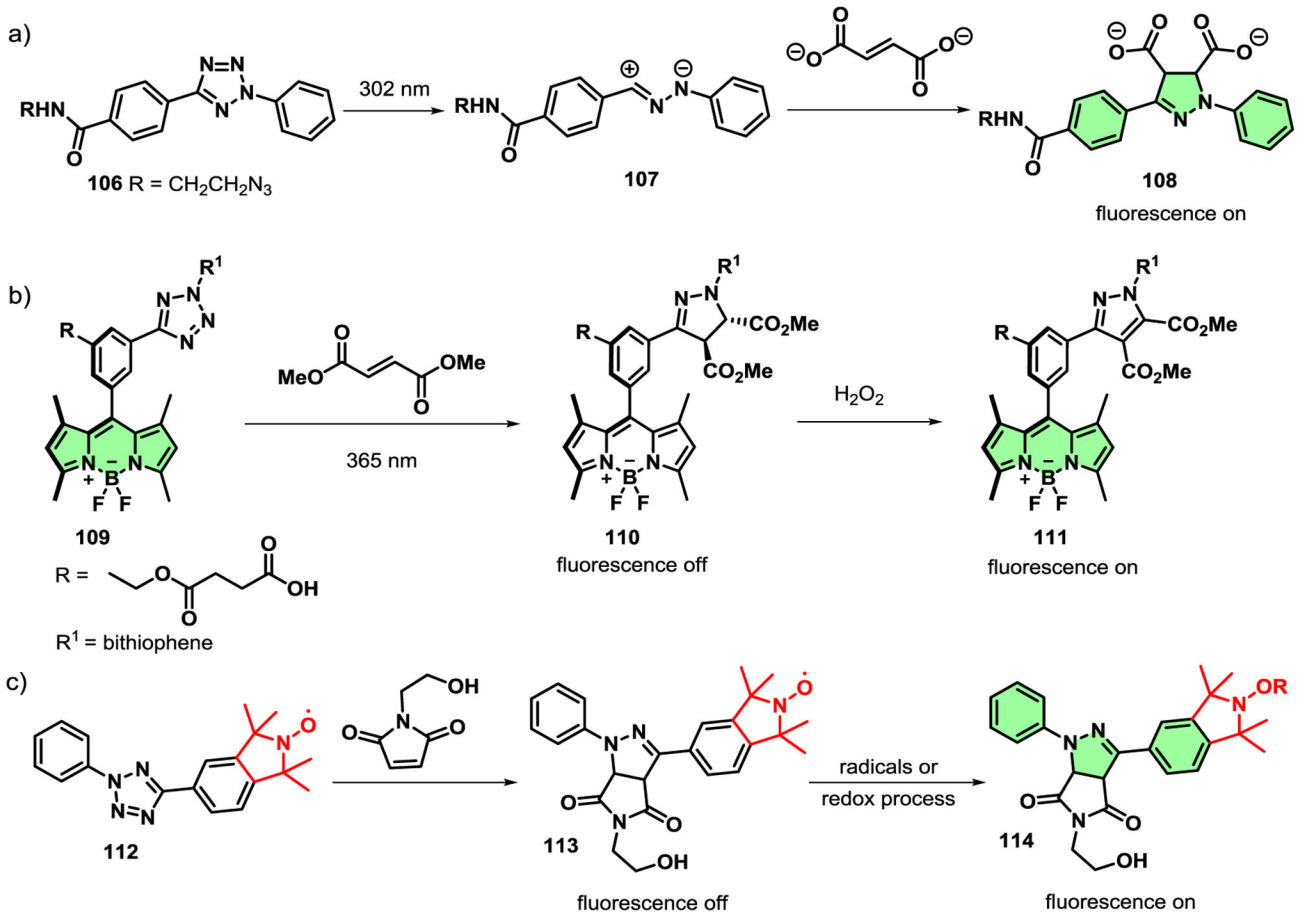
Scheme 23:

a) Tetrazole photoclick chemistry for post-synthetic modifications of DNA; b) Intramolecular photoclick reaction for fluorescent detection of DNA base variation



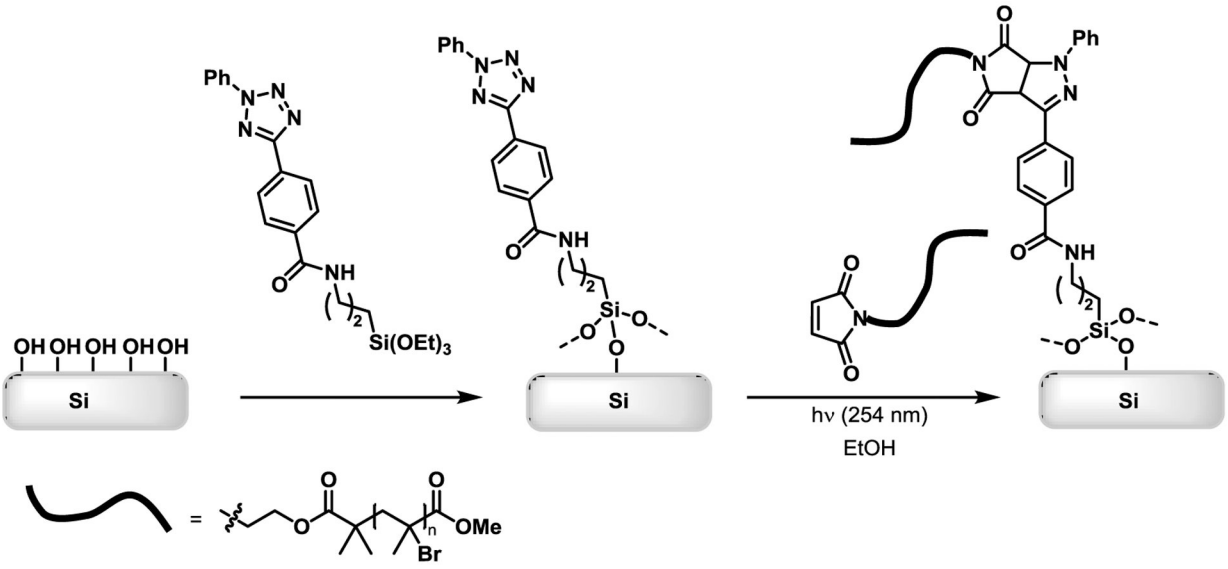
Scheme 24:

Design of photoactivatable turn-on fluorescent microtubule probes based on an intramolecular photoclick chemistry

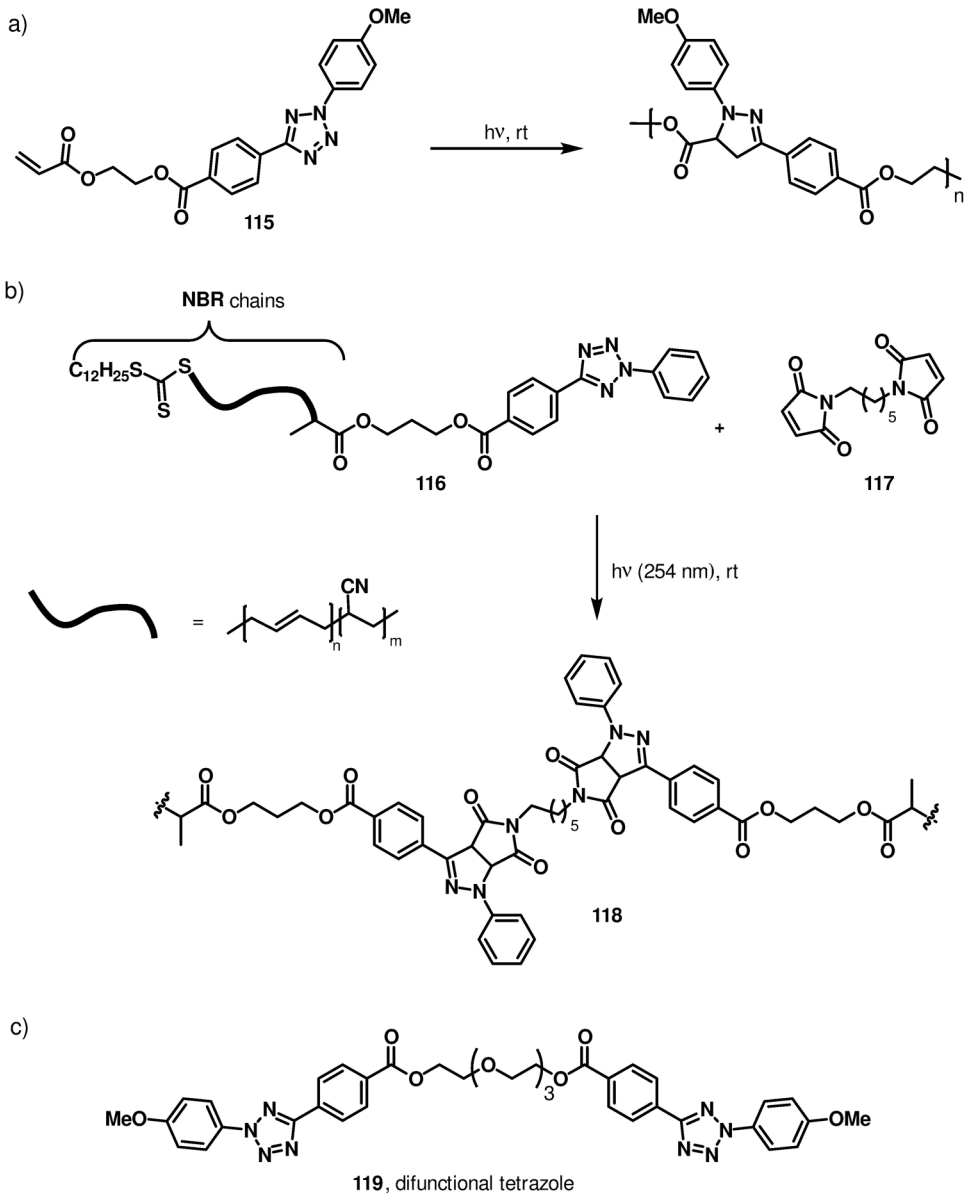


Scheme 25:

a) Photoinducible detection of the oncometabolite fumarate; b) Design of a BODIPY-tetrazole based fluorescence reporter of hydrogen peroxide; c) Design of redox/radical sensing molecules

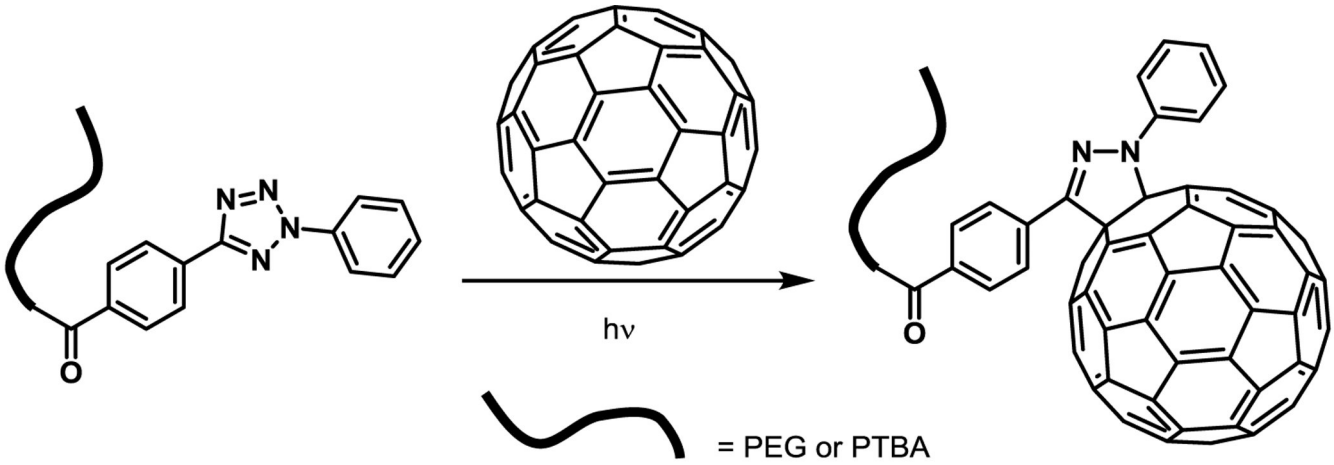


Scheme 26:
Preparation of a poly(methyl methacrylate) grafted silicon wafer

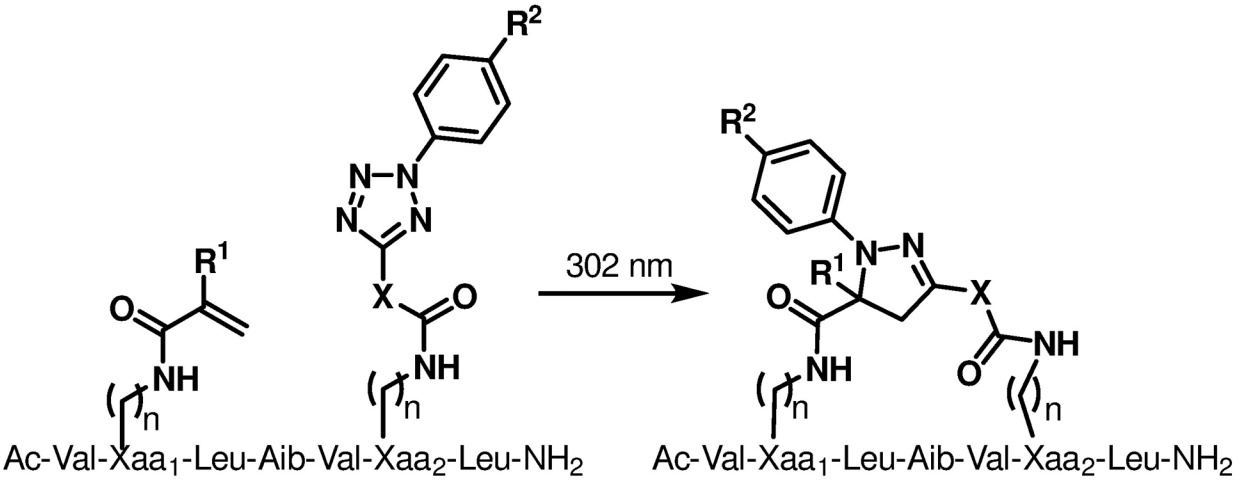


Scheme 27:

a) Tetrazole-alkene based polymerization using a monomer of the A-B type; b) Light-induced ligation of NBR building blocks to obtain high molecular weight nitrile rubber; c) Reagent employed for cross-linking of a butadiene polymer

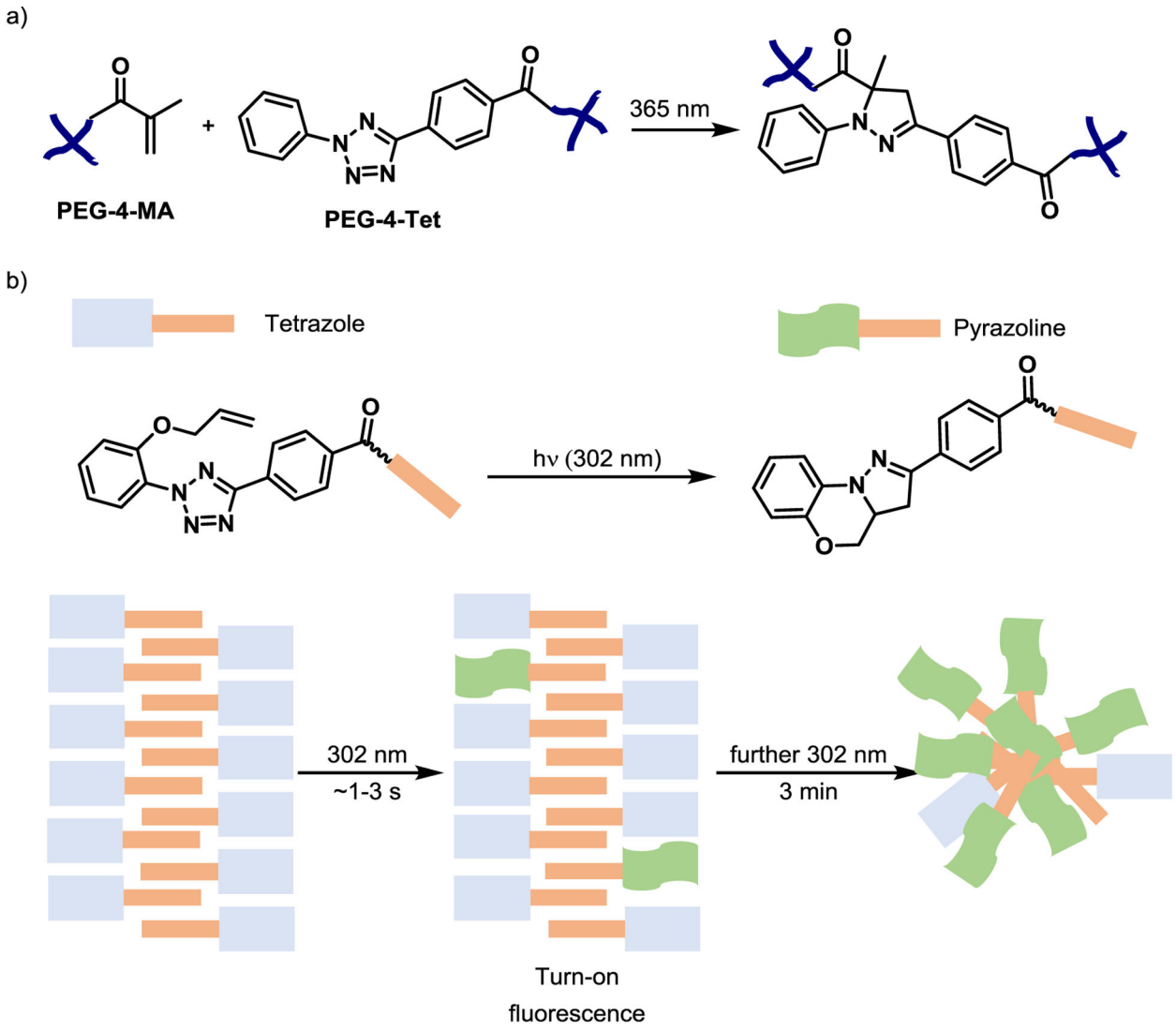


Scheme 28:
Tetrazole photoclick chemistry for fullerene conjugation



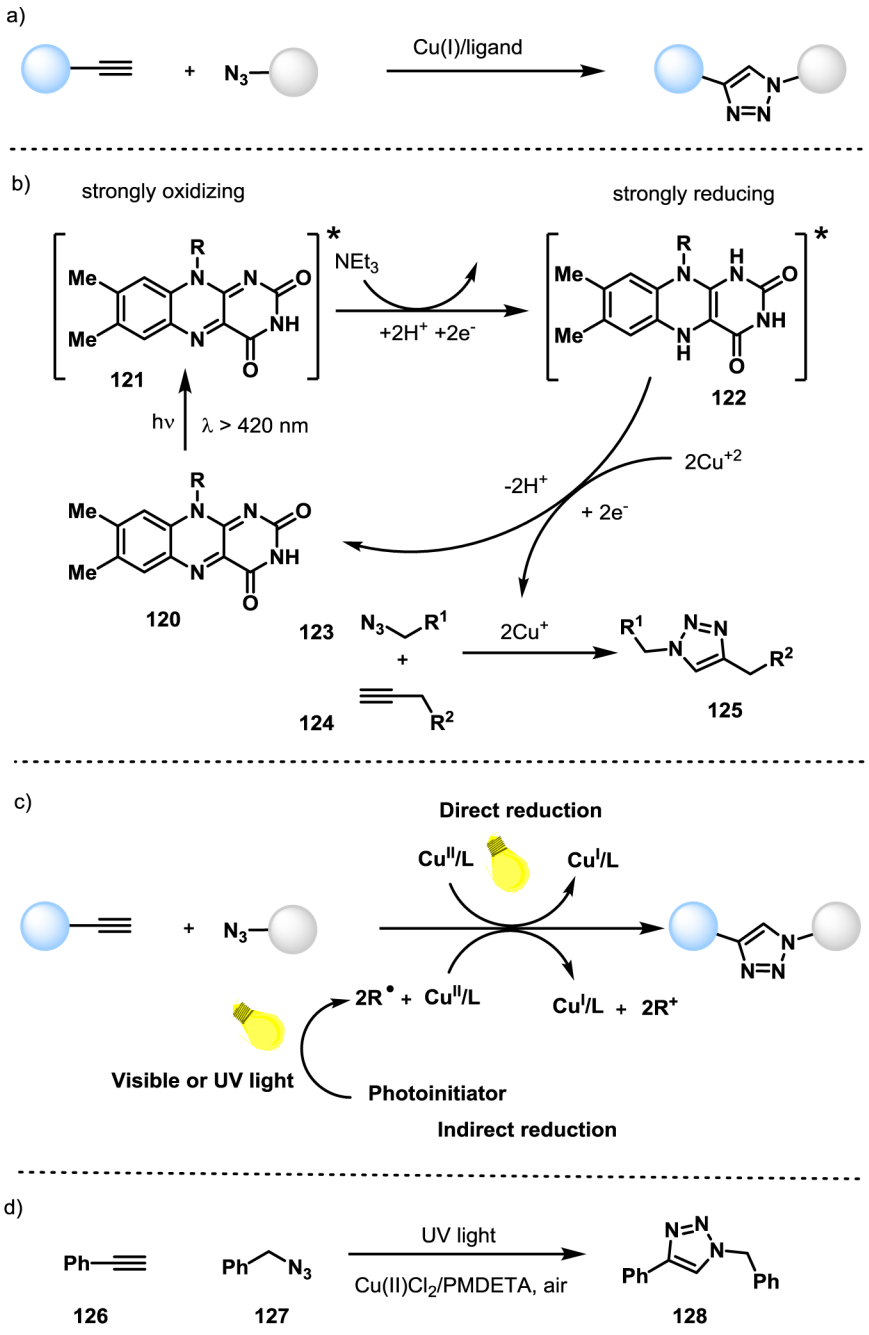
n	X	R^1	R^2	Yield (%)
3	–	Me	H	15
3	-Ph-	Me	H	15
4	–	Me	H	41
4	-Ph-	Me	H	38
4	–	H	OMe	64
4	–	Me	OMe	53
4	–	H	NMe_2	63
4	–	Me	NMe_2	94

Scheme 29:
Synthesis of stapled peptides via intramolecular photoclick chemistry

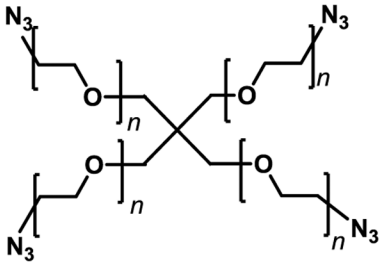


Scheme 30:

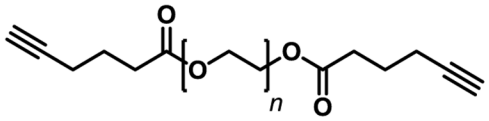
Tetrazole photoclick chemistry for the preparation of (a) hydrogels and (b) photodegradable supramolecular hydrogels. Adapted and Reproduced from ref 132. Copyright 2013 American Chemical Society.



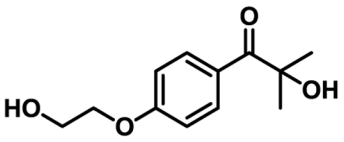
Scheme 31:
Light-triggered CuAAC click reactions



129, 10K PEG-tetraazide



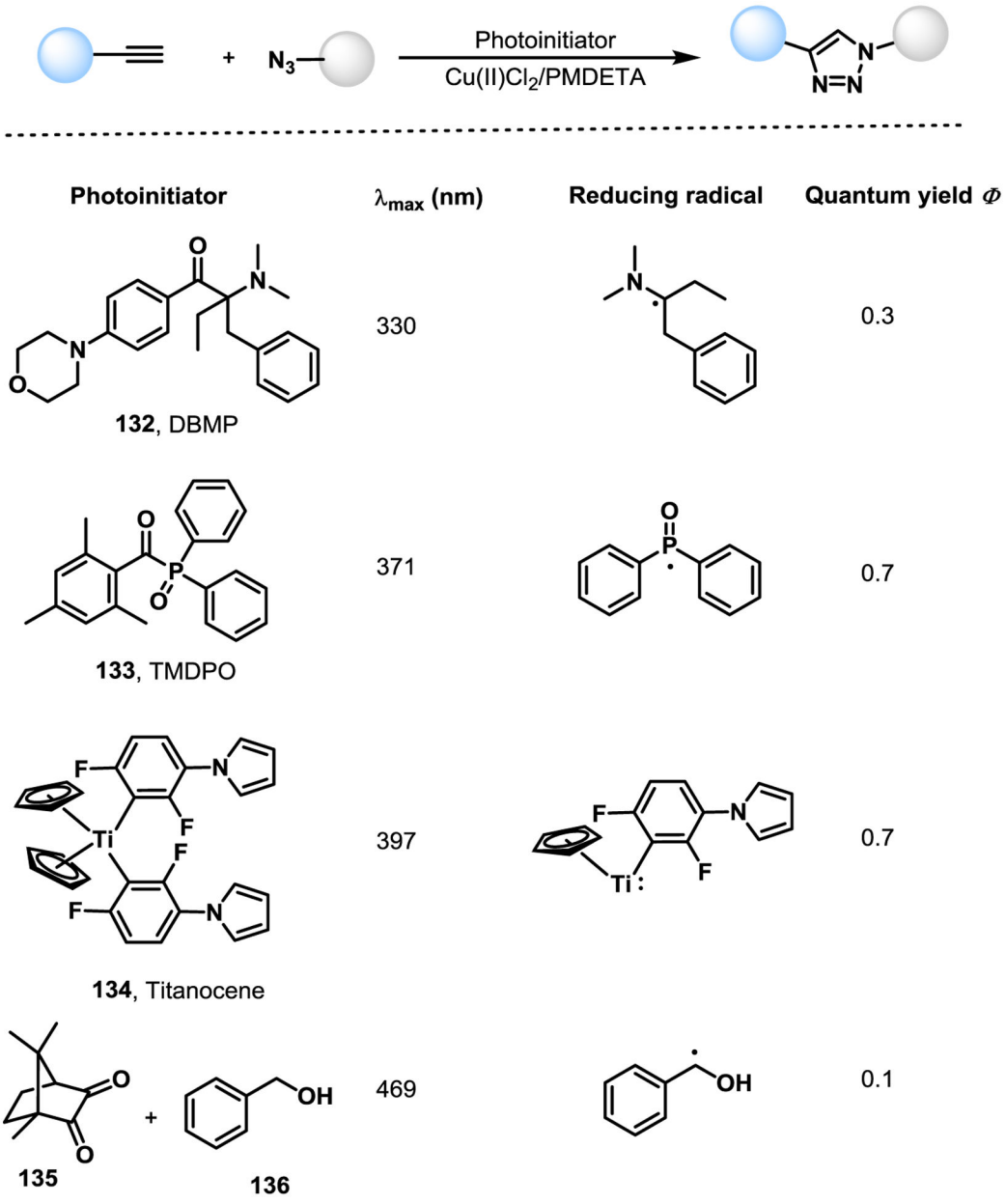
130, 3K PEG-dialkyne



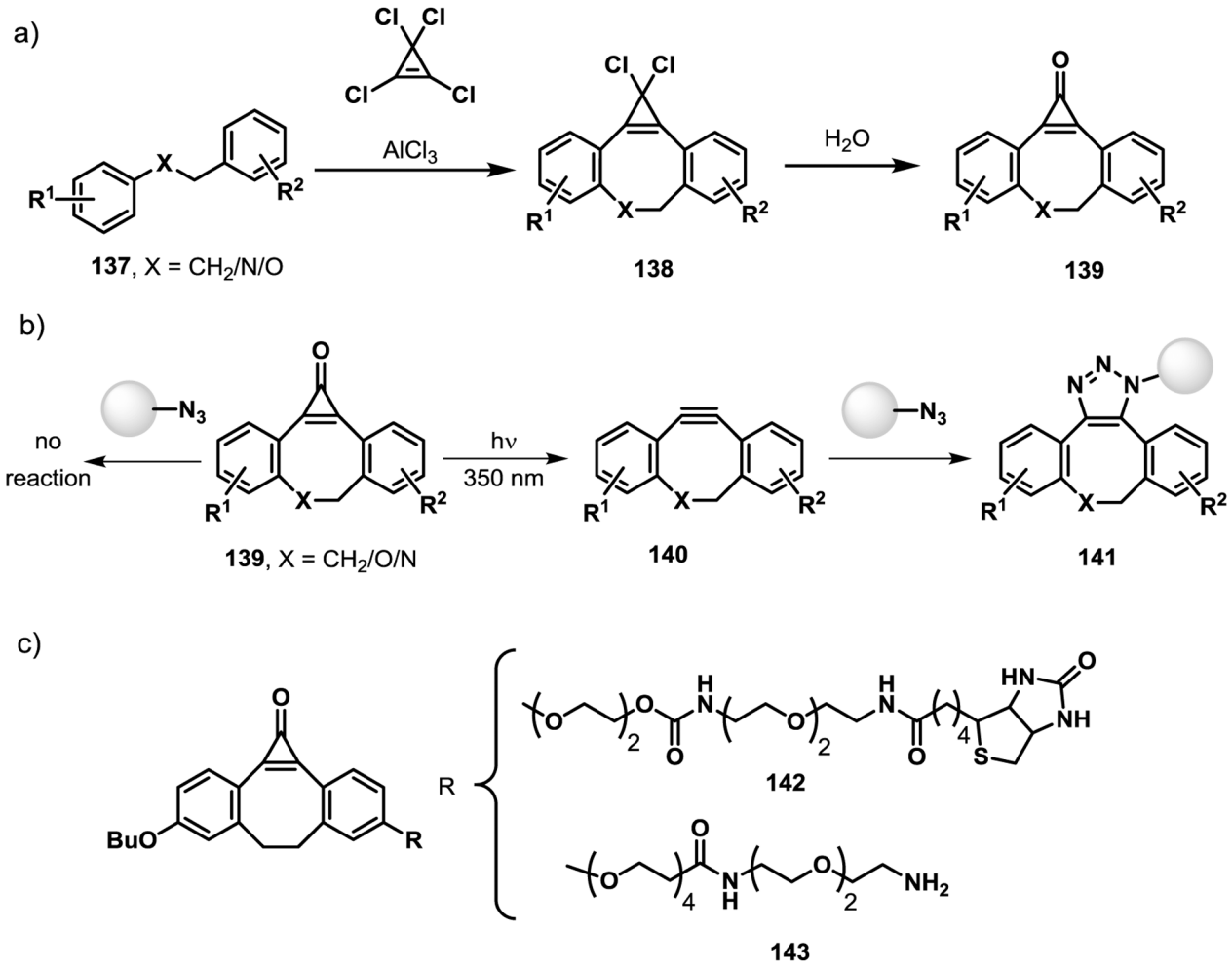
131

Scheme 32:

Substrates used in light-triggered CuAAc reaction for hydrogel formation

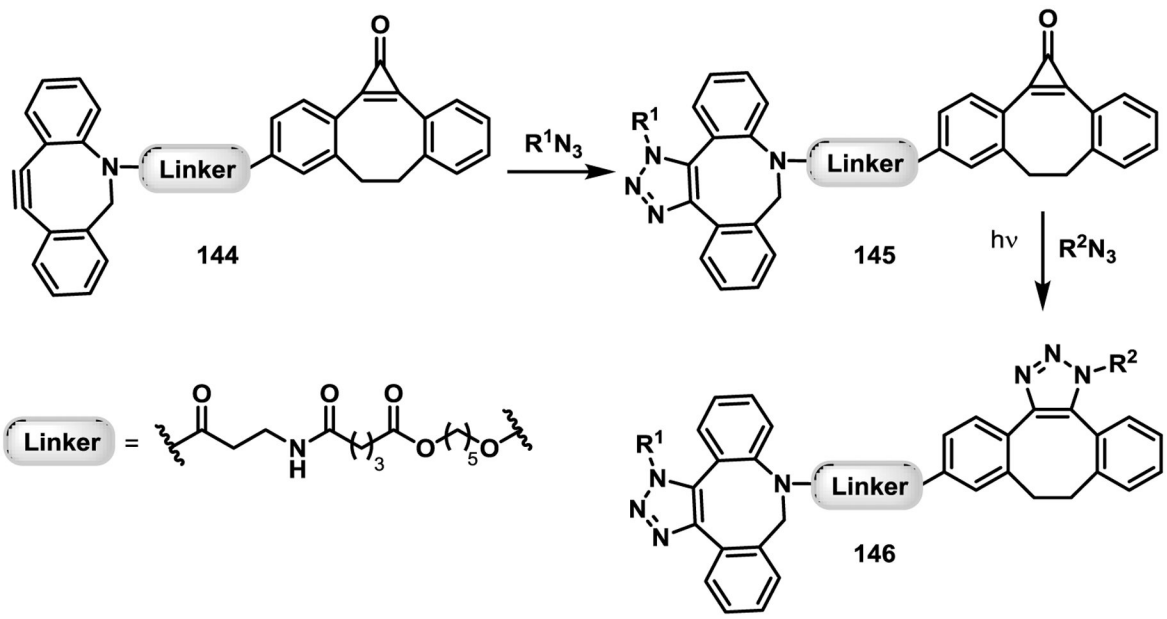


Scheme 33:
Photoinduced CuAAC click reaction using free radical photoinitiators

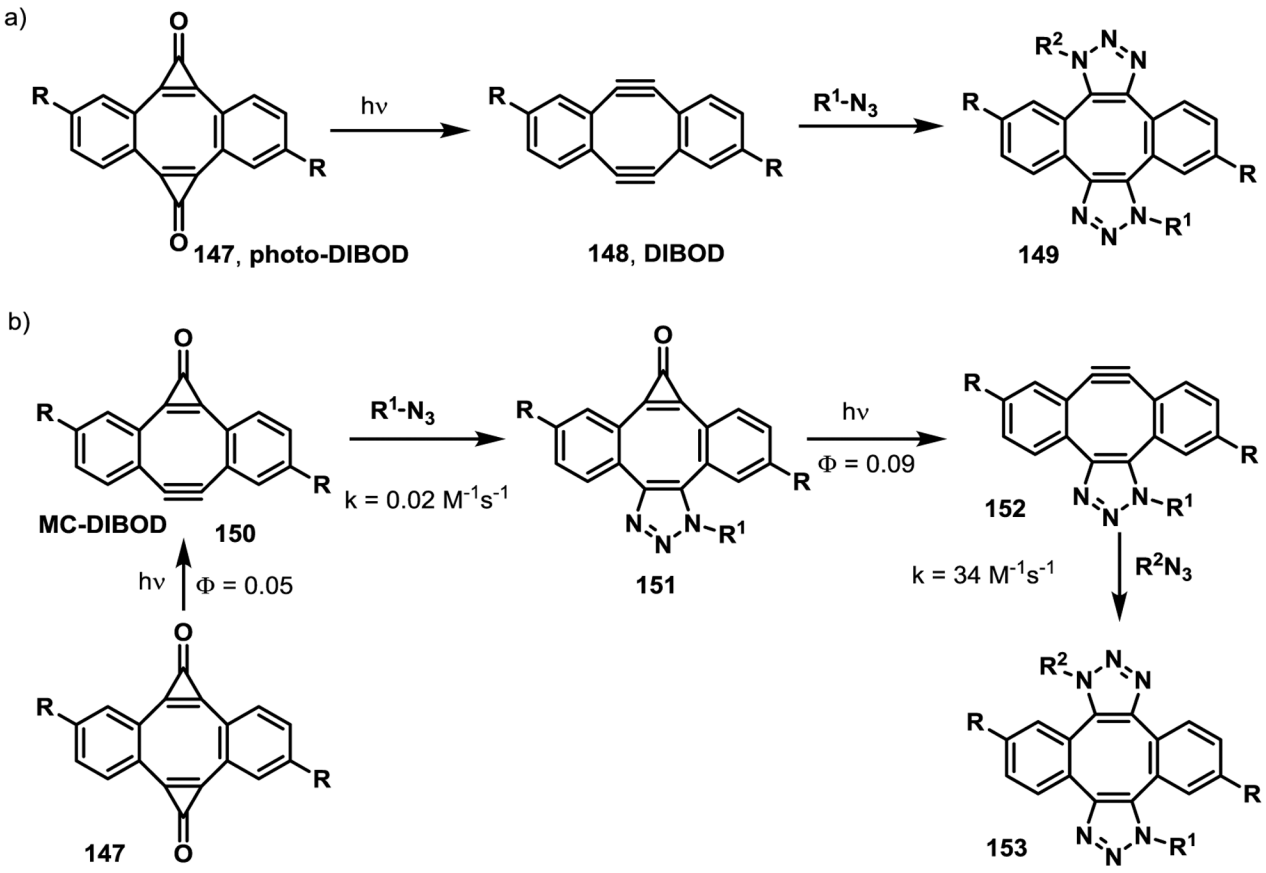


Scheme 34:

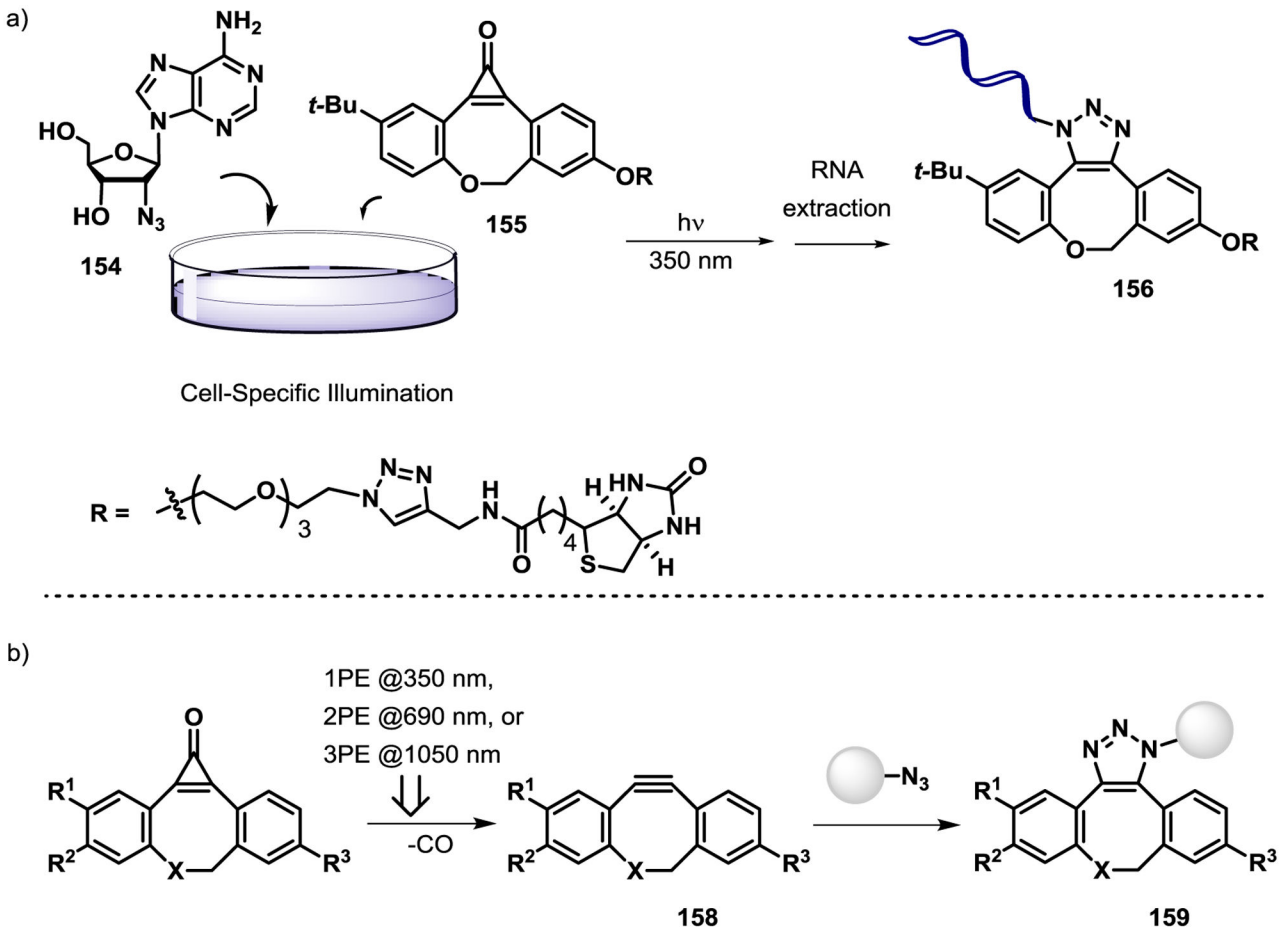
a) synthesis of cyclopropenones; b) Light-induced strain-promoted cycloadditions between azides and alkynes; c) cyclopropenone substrates used in for cell labeling experiments and immobilization on brush polymers



Scheme 35:
Sequential photoinduced SPAAC reactions

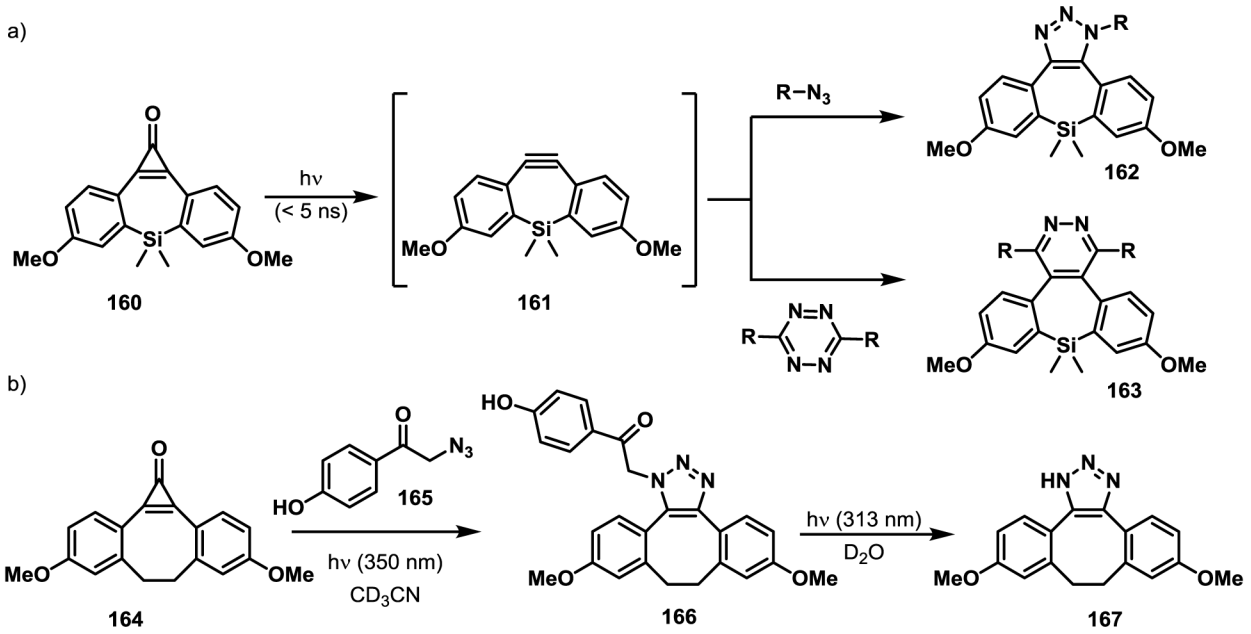


Scheme 36:
Double SPAAC of two azides with a) photo-DIBOD and b) MC-DIBOD



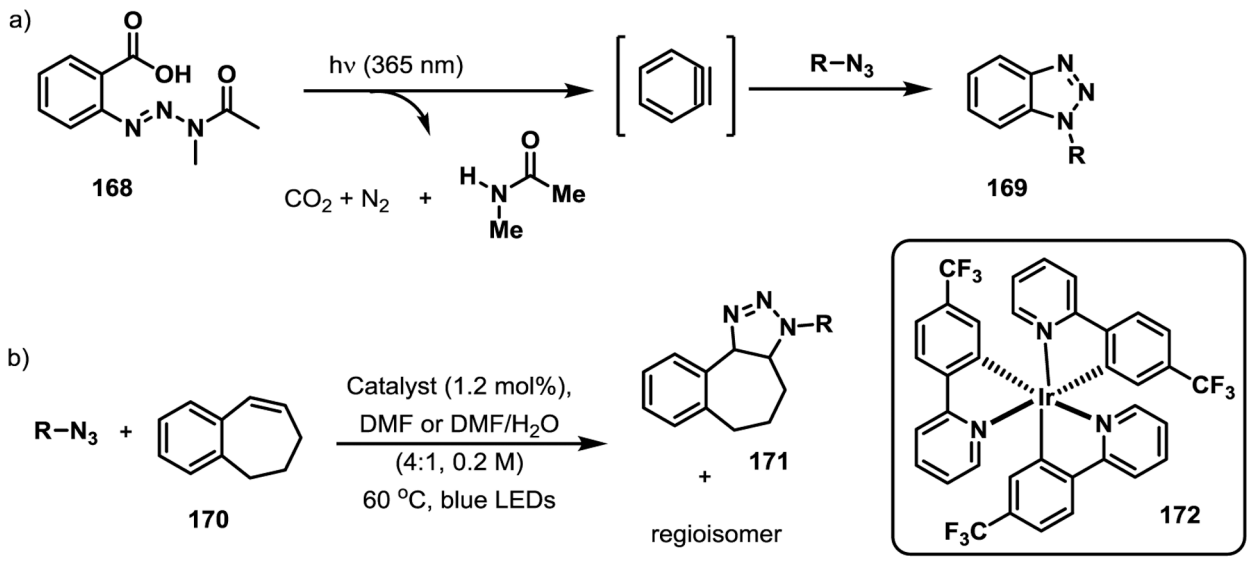
157a, X = O, R^1 = *t*-Bu, R^2 = H, R^3 = $(OCH_2CH_2)_4OH$
157b, X = O, R^1 = *t*-Bu, R^2 = H, R^3 = $(OCH_2CH_2)_4ONHS$
157c, X = CH_2, R^1 = H, R^2 = OMe, R^3 = $(OCH_2CH_2)_4OH$

Scheme 37:
a) Photo-SPAAC rection for temporal labeling of nascent RNAs; b) MP-SPAAC click reactions



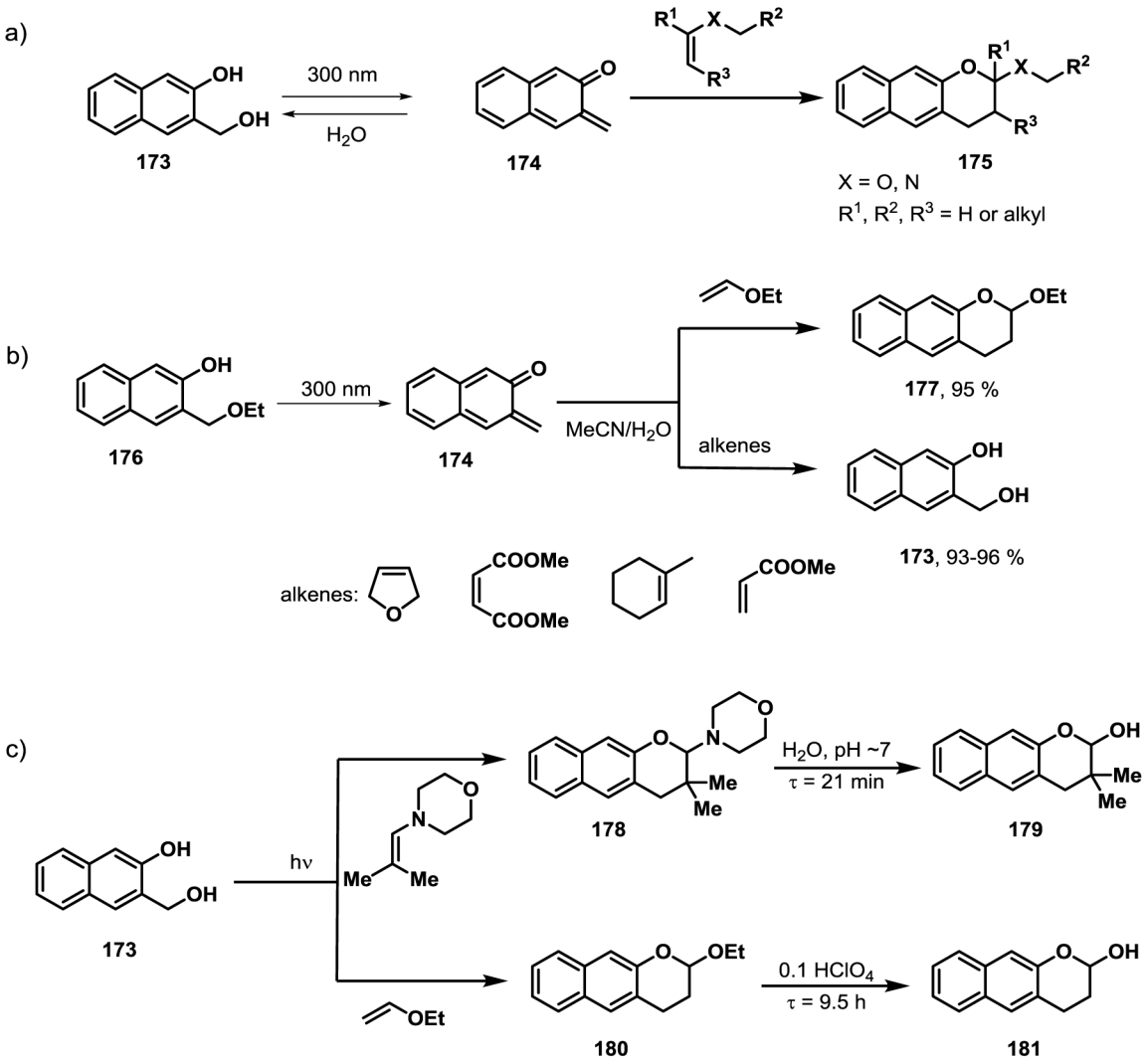
Scheme 38:

a) Click reactions based on dibenzosilacyclohept-4-yne; b) Bioorthogonal “catch and photo-release” strategy based on light-triggered, strain-promoted cycloaddition



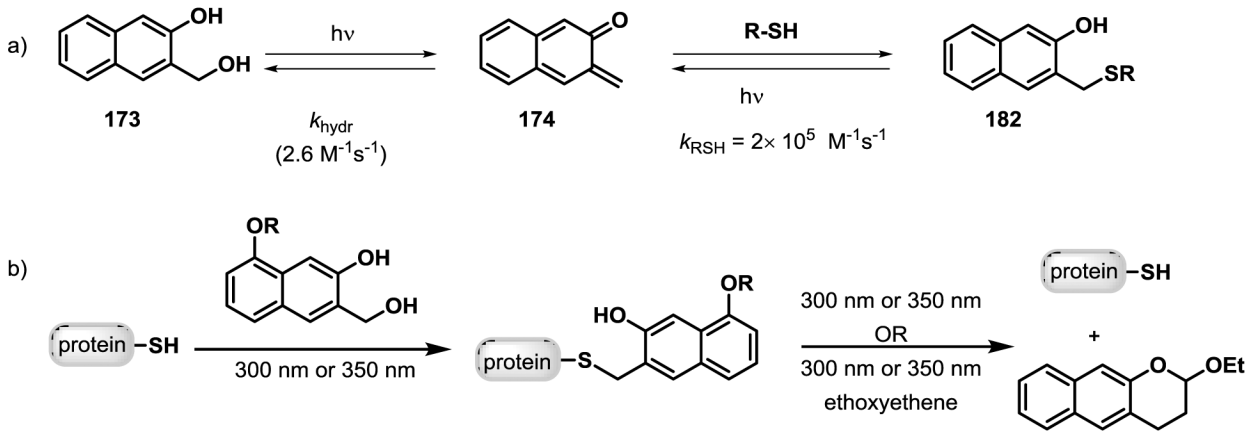
Scheme 39:

a) Photo-triggered benzyne click reaction; b) Visible-light mediated [3 + 2]-cycloaddition of azides with alkenes

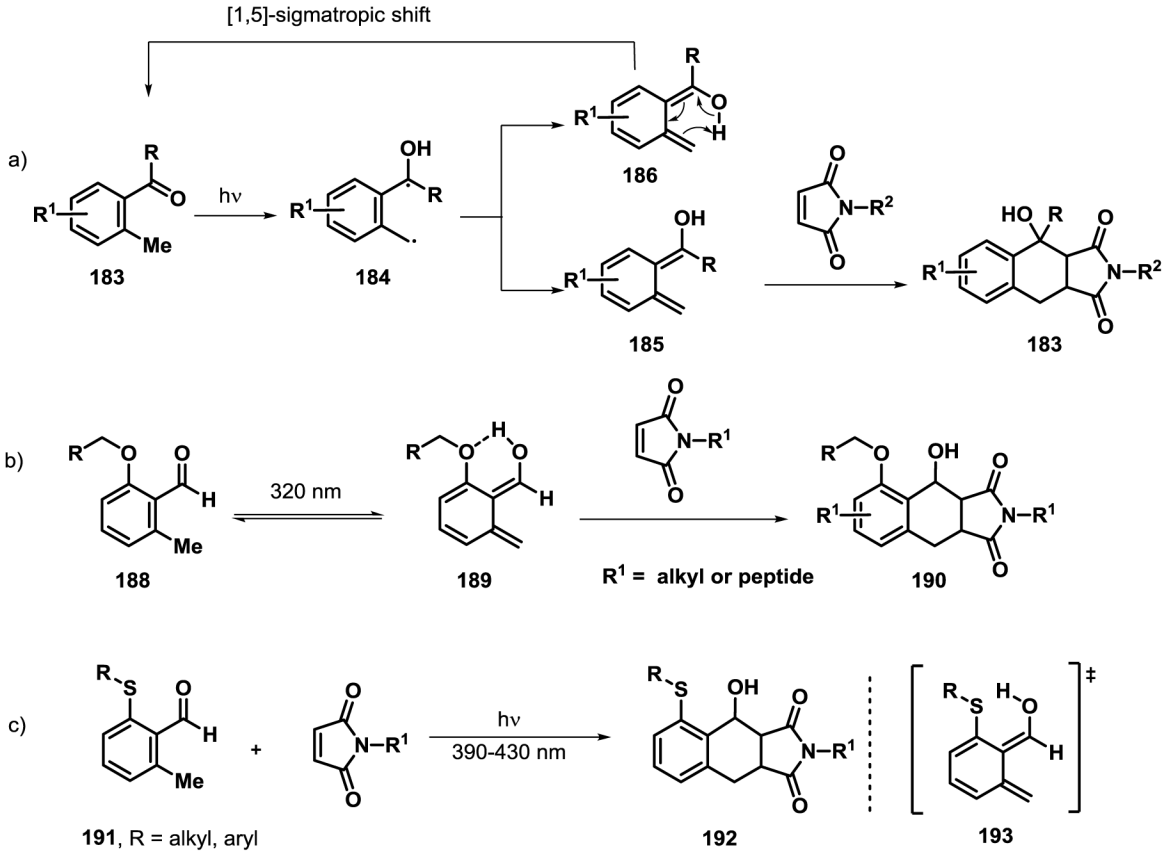


Scheme 40:

Photoactivation of NQMP to generate *o*NQM for hetero-Diels-Alder cycloaddition

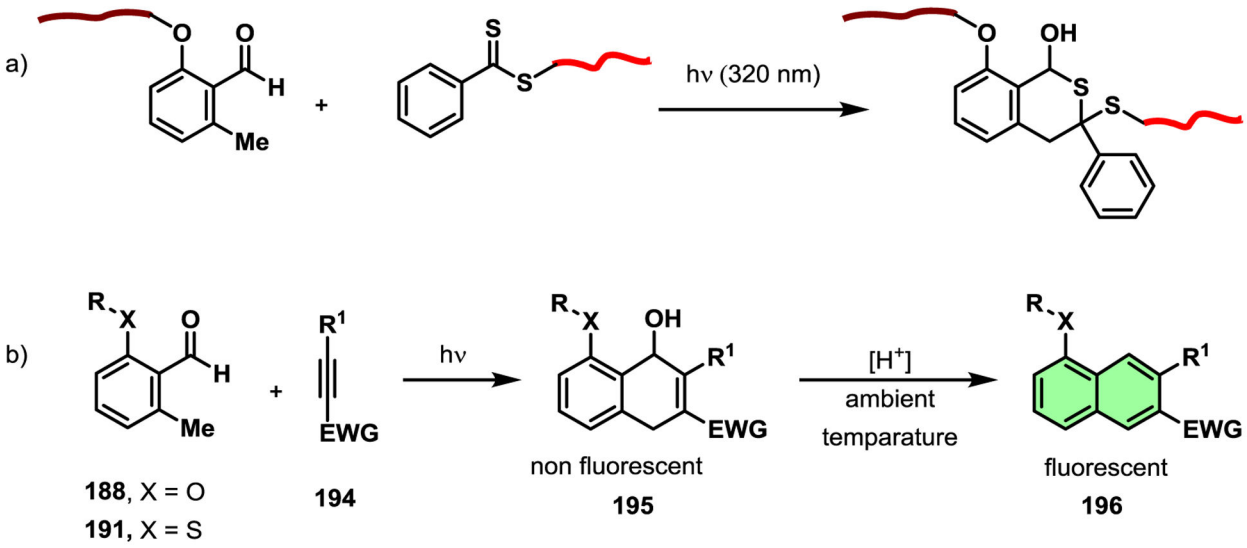


Scheme 41:
Thiol–quinone methide photoclick reactions



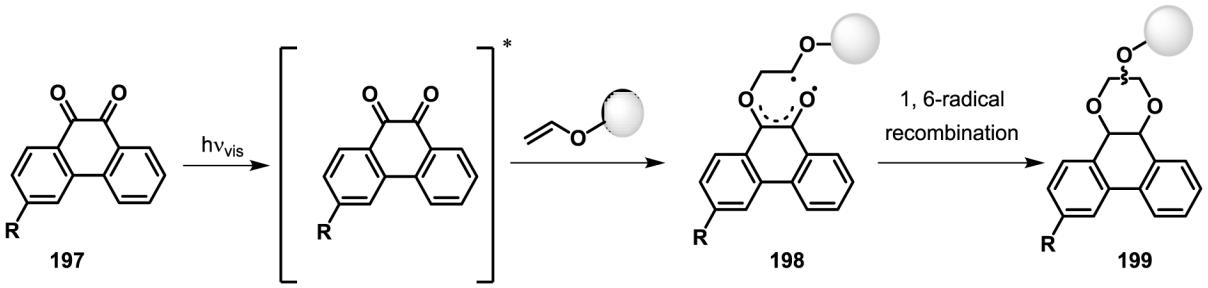
Scheme 42:

Light-triggered hetero-Diels–Alder reaction of *o*-methyl phenyl ketones and aldehydes

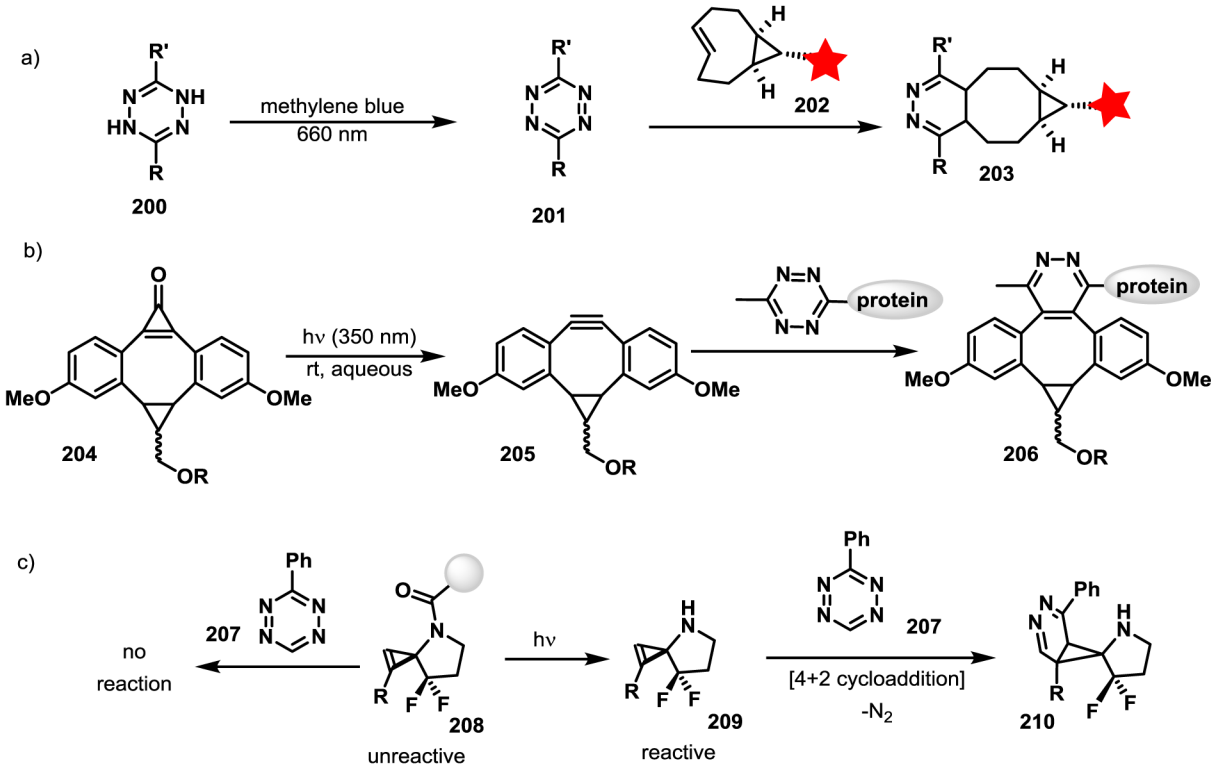


Scheme 43:

a) Light-induced hetero-Diels–Alder conjugation of photoenols with non-activated dithioester; b) Light-induced hetero-Diels–Alder reaction with alkynes

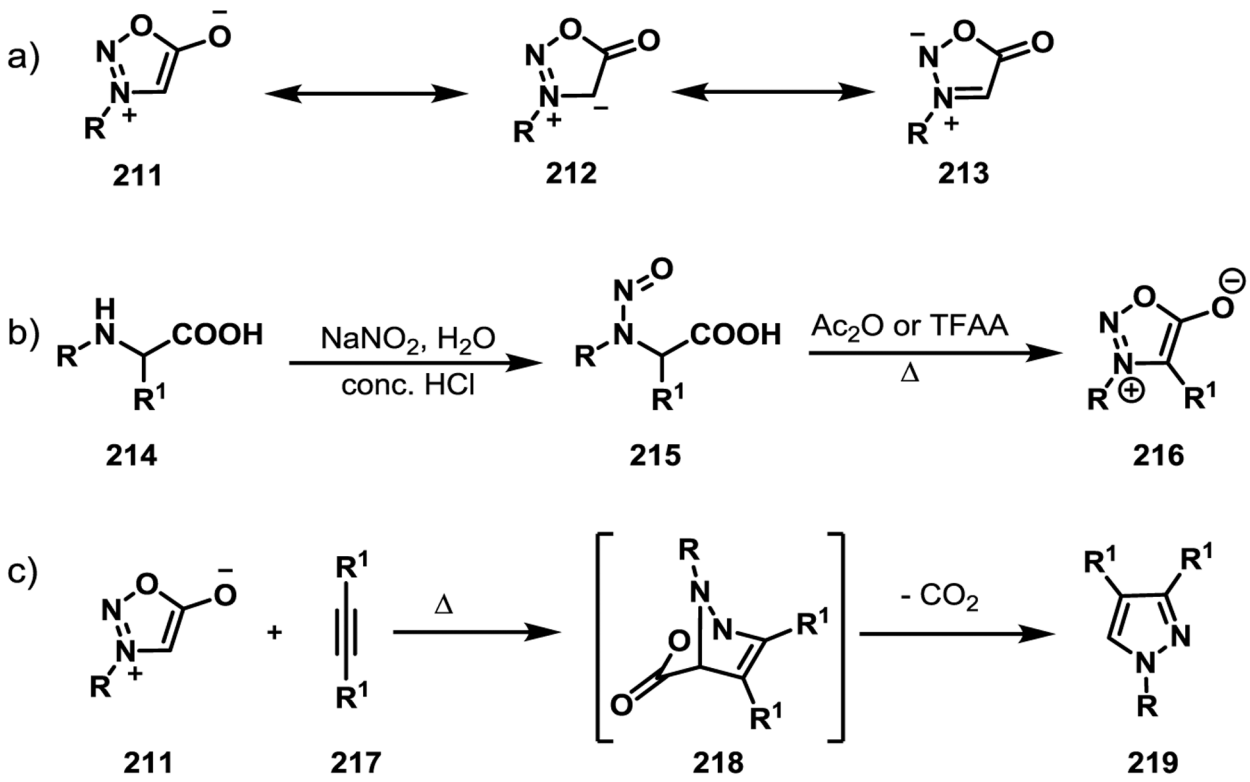


Scheme 44:
Visible light-triggered photoclick cycloaddition



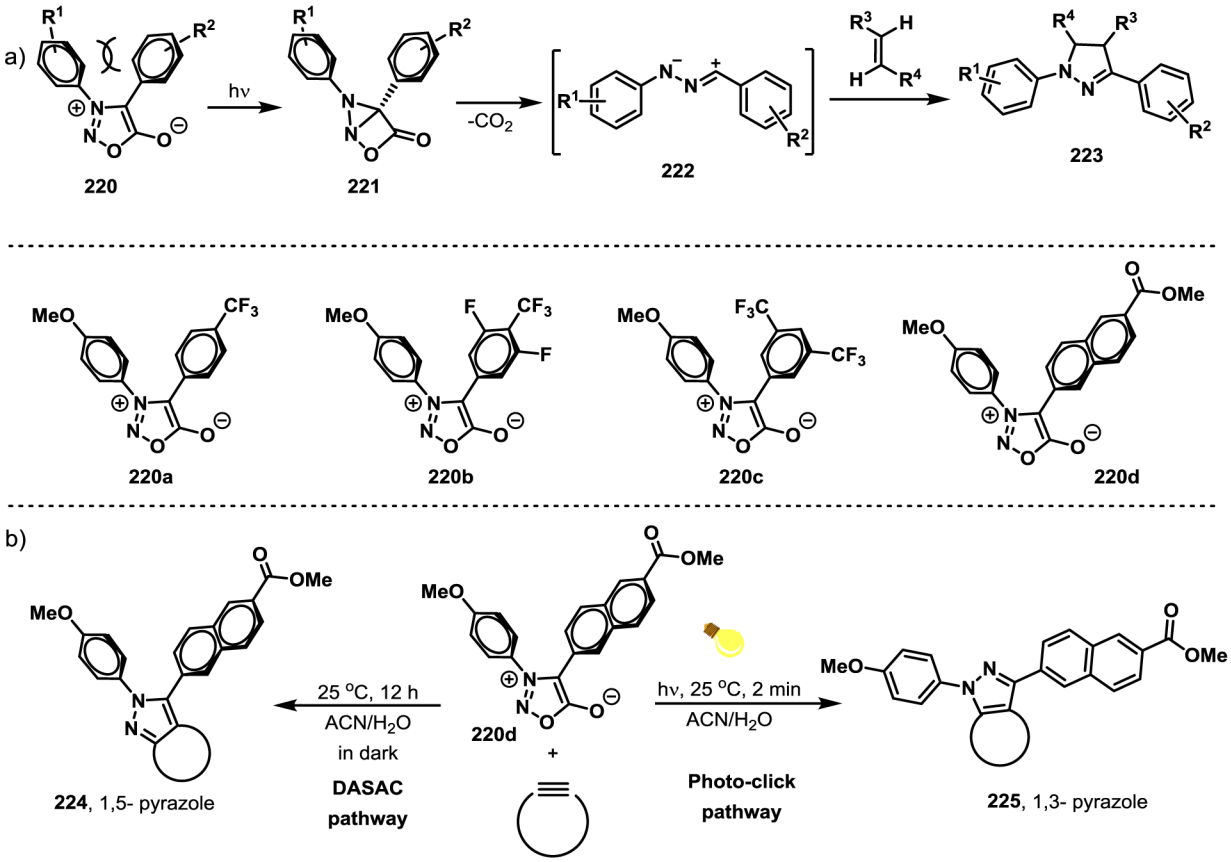
Scheme 45:

a) Visible light-induced tetrazine ligation; b) Cyclopropenone-caged bicyclononynes for light-triggered tetrazine ligation; c) Caged cyclopropenes for light-triggered tetrazine ligation

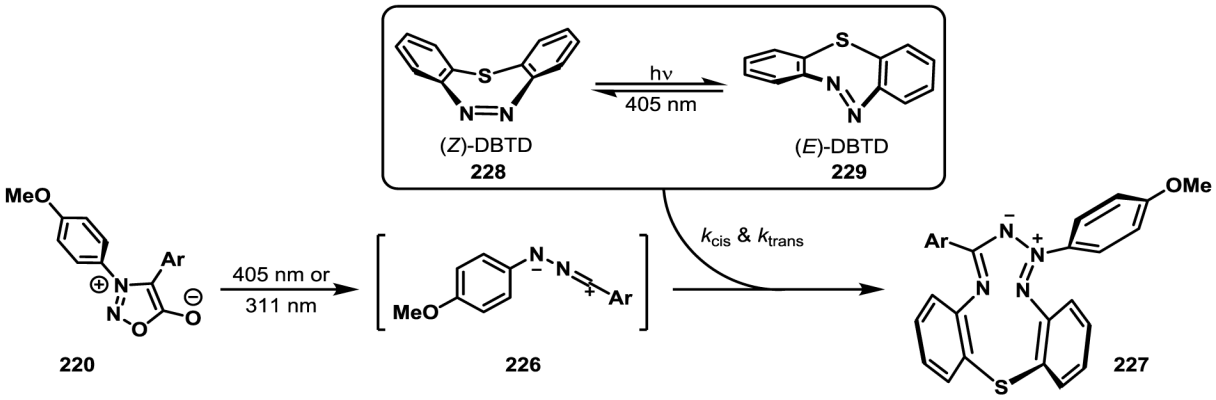


Scheme 46:

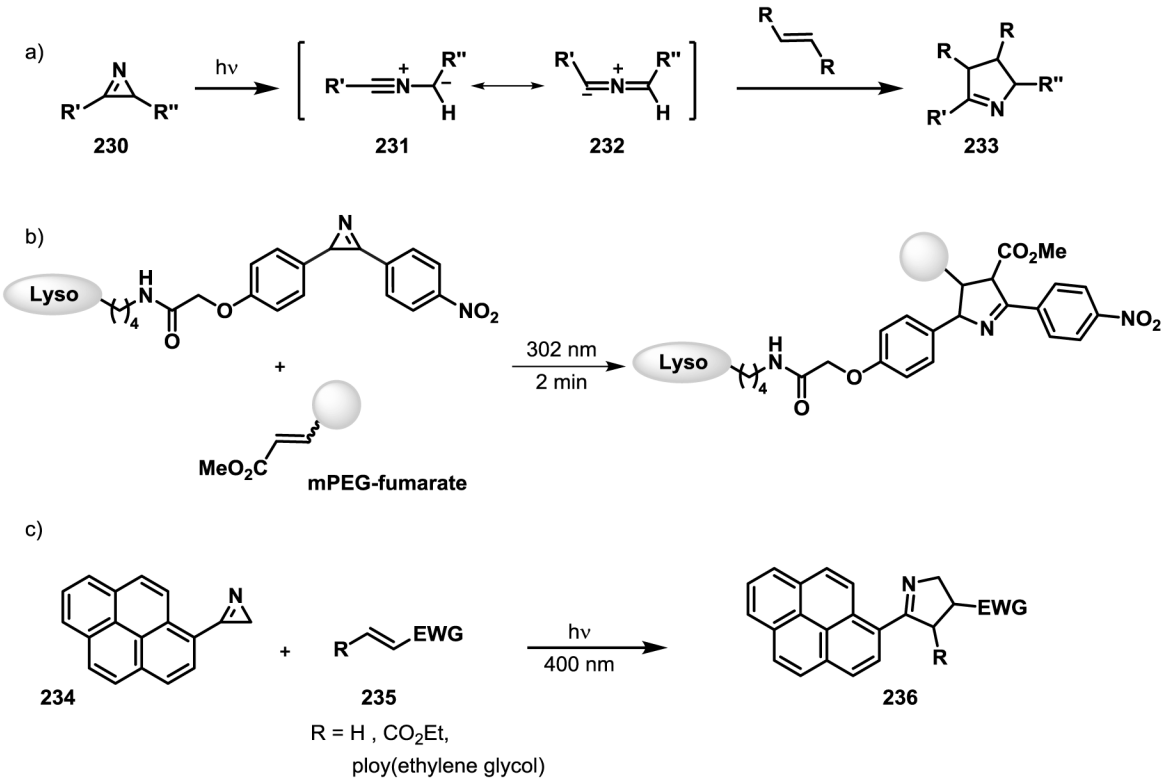
a) Sydnone resonance structures; b) Synthesis of sydnones; c) Cycloaddition reaction between sydnones and alkynes



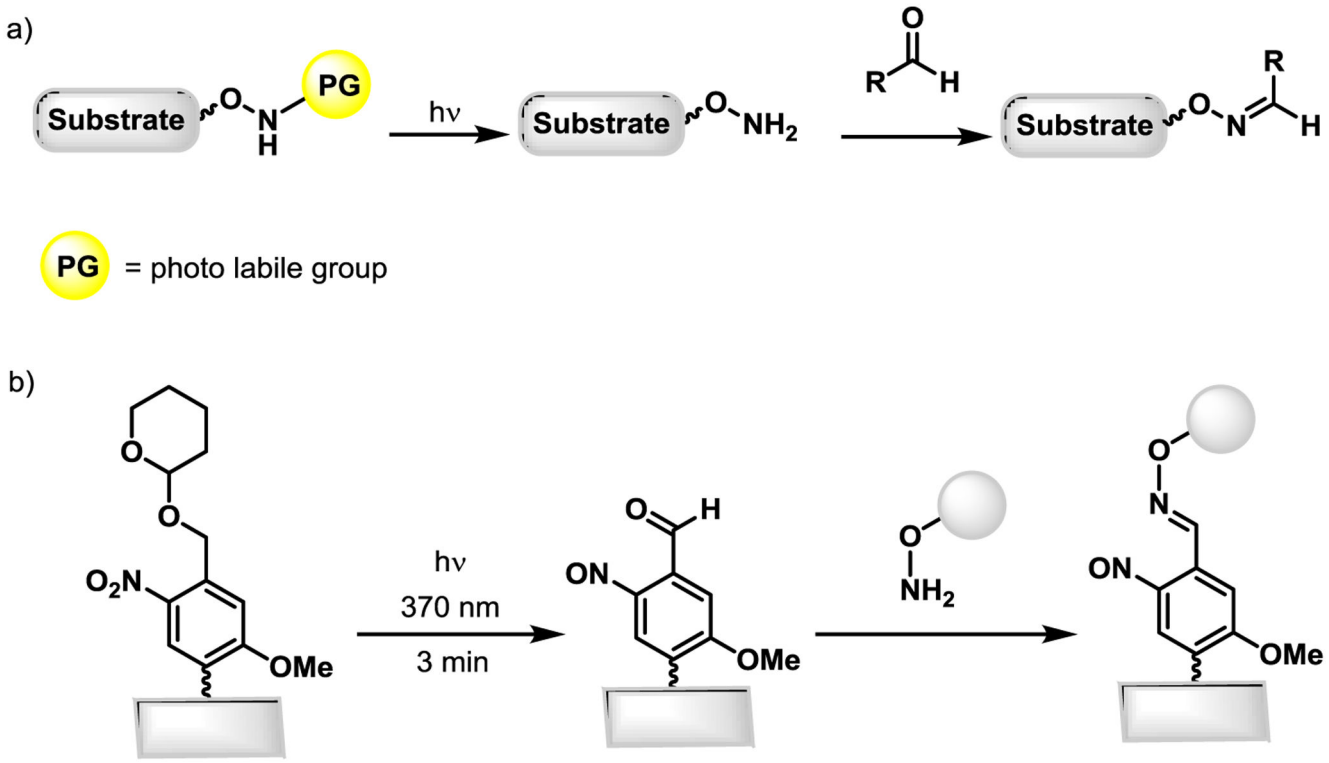
Scheme 47:
Photo-triggered sydnone–alkene/alkyne cycloadditions



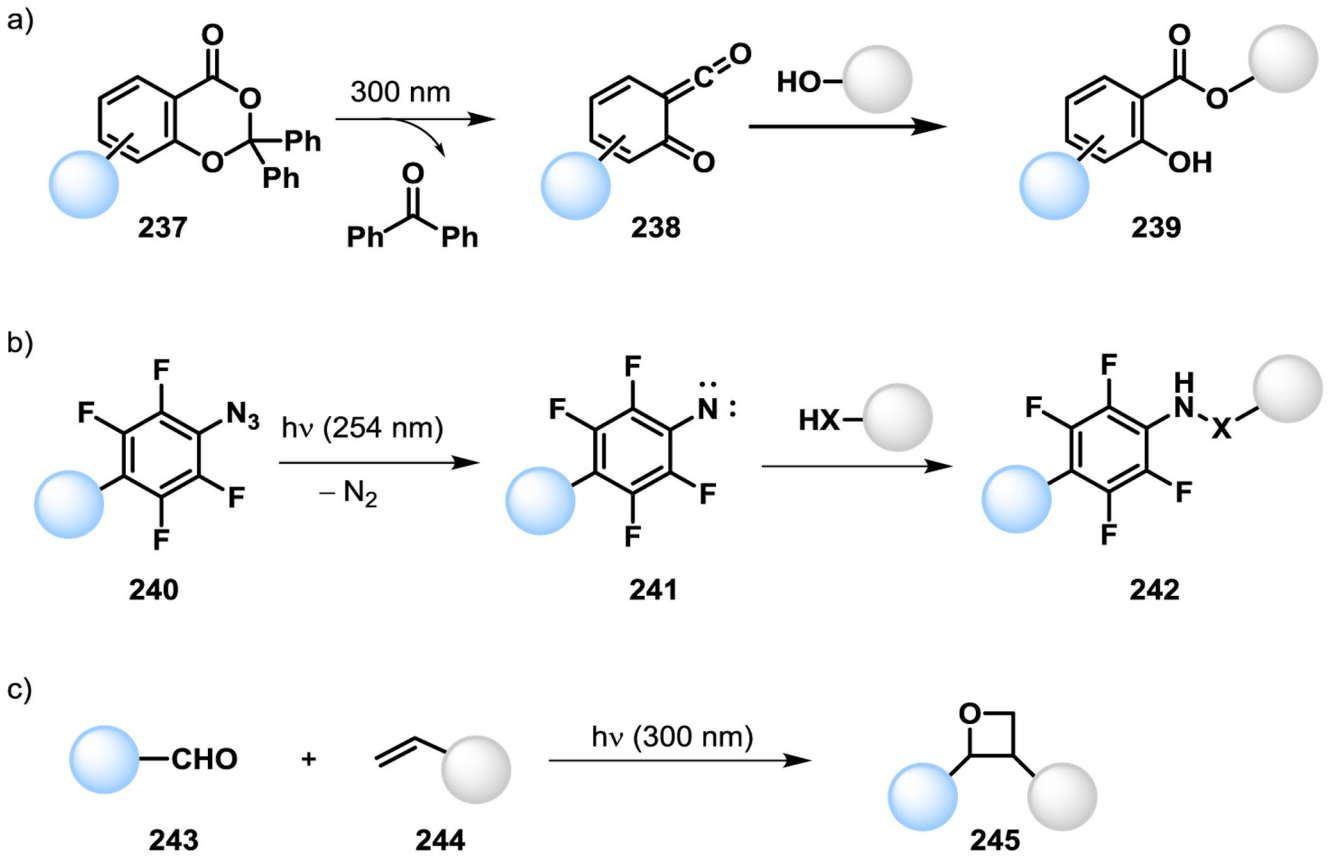
Scheme 48:
DASyd-DBTD photoclick reaction



Scheme 49:
Photoinduced azirine–alkene cycloadditions



Scheme 50:
Light-induced oxime ligation reactions



Scheme 51:
Light-triggered a) ketene chemistry; b) perfluorophenyl azide chemistry; and c) [2+2] cycloaddition