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Click Chemistry

Light-Induced Click Reactions

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cycloaddition · Diels–Alder reaction · hybrid materials · photochemistry · polymers

Spatial and temporal control over chemical and biological processes, both in terms of "tuning" products and providing site-specific control, is one of the most exciting and rapidly developing areas of modern science. For synthetic chemists, the challenge is to discover and develop selective and efficient reactions capable of generating useful molecules in a variety of matrices. In recent studies, light has been recognized as a valuable method for determining where, when, and to what extent a process is started or stopped. Accordingly, this Minireview will present the fundamental aspects of light-induced click reactions, highlight the applications of these reactions to diverse fields of study, and discuss the potential for this methodology to be applied to the study of biomolecular systems.

1. Introduction

Since the birth of modern chemistry, chemists have tried to identify chemical reactions that involve minimum work-up, limited side reactions, precise chemical connections, and high yields. In 2001, Sharpless and co-workers introduced a new synthetic strategy, termed "click chemistry", which focuses on easy-to-make chemical compounds and materials derived from modular blocks.[1] The definition of click chemistry states that "*the reactions must be modular, wide in scope, give very high yields, generate only inoffensive by-products that can be removed by nonchromatographic methods, and be stereospecific (but not necessarily enantioselective).*"[1]

The most commonly employed click reactions that have been adapted to fulfill these criteria are: 1) cycloaddition reactions (most commonly the Huisgen 1,3-dipolar cycloaddition,[2] and also the Diels–Alder reaction[3]), 2) nucleophilic ring-opening reactions of strained heterocyclic electrophiles (including epoxides, aziridines, and aziridinium ions),[4] 3) reactions of non-aldolcarbonyl compounds (involving ureas, oximes, and hydrazones),[5] and 4) additions to carbon–carbon multiple bonds (especially thiol-ene chemistry, and also Michael additions).[6]

Applications of click reactions have had a profound effect on diverse areas of research. For example, over 5000 scientific articles have been published since 2001 regarding the use of click reactions for preparative organic synthesis, bio-conjugation, drug discovery, polymer and material sciences, and nanotechnology. From these studies, it is clear that novel polymeric materials may be fabricated from new monomers, for example, monomers differing in chemical nature from "classical" monomers. Because most "classical" monomers are inexpensive and readily available, their utilization for the production of novel materials deserves intense consideration from a practical point of view. In addition, click chemistry has attracted worldwide interest for its potential to embed desired properties into conventional polymers, particularly when combined with controlled/living polymerization processes. However, in some applications that feature surface patterns or three-dimensional scaffolds, these reactions may not be adequate, particularly when spatial and temporal controls are also required.[7]

Light drives many important processes in nature, including photosynthesis and ozone production in the atmosphere.[8] Light-induced chemical reactions involve the absorption of light to generate highly reactive molecules, which then undergo chemical changes. For example, unimolecular reactions,[9] such as ionization, dissociation, and isomerization reactions, as well as bimolecular reactions,[10] such as cycloaddition and intermolecular electron transfer, can be activated by light.[11]

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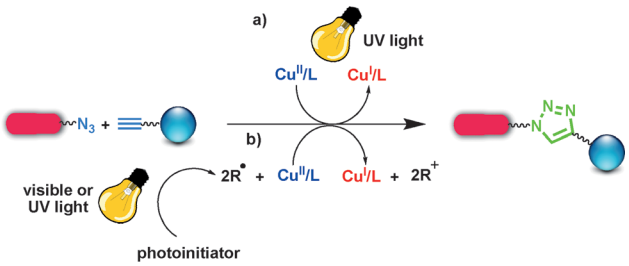
Light-induced reactions can also be spatially and temporally controlled by focusing photons onto a given area and by varying exposure time, wavelength, and intensity as needed. This level of control is not possible with conventional thermal reactions.[12] Light-induced click reactions also effectively combine the classical benefits of click reactions with the advantages of a photochemical process. For example, these reactions can be activated at specific times and locations, resulting in a powerful method for chemical synthesis, bioorthogonal conjugation, and tailored material fabrication. Additionally, light-induced reactions are developed to fulfill the click criteria, including photoinitiated thiol-ene/thiol-yne coupling,[6d] the photoinduced 1,3-dipolar cycloaddition reaction of alkenes and nitrile imines,[12a] strain-promoted cycloaddition reactions of photochemically generated cycloalkynes and azides,[12b,c,13] photoinduced ester formation reactions of benzodioxinones with alcohols,[14] and photoinduced Diels–Alder reactions[15] (Table 1). It is also important to note that not all of the light-induced reactions that have been reported completely meet the strict click criteria.[16] However, this does not diminish the importance of such studies, although it may be more appropriate to refer to these reactions as "coupling" reactions.

Herein, we will focus on the advantages of newly developed, light-induced click reactions versus thermally activated click reactions. In particular, we will discuss the ability of the former to overcome existing problems and challenges in surface chemistry, biology, and materials science. The historical development, mechanistic aspects, limitations, and potential applications of these reactions will also be presented along with selected examples. In addition, we will place special emphasis on work performed in our group concerning the utilization of photoinduced benzodioxinone and electron-transfer reactions as click pathways.

2. Light-Induced Cycloaddition Reactions

Cycloadditions are a broad class of reactions in which unsaturated species combine to form cyclic adducts. These reactions can be activated by a variety of stimuli, including heat, light, ultrasound, and metal catalysts. Moreover, the reactants are typically nonreactive to acids, alcohols, and amines, and many other functional groups. Thus, extra protection/deprotection steps are not necessary. Unlike other addition reactions, cycloadditions are not usually influenced by molecular oxygen to give undesired side reactions, and they proceed quantitatively in both aqueous and organic media.[17] However, polar solvents and Lewis acids often accelerate the rate of reaction.[16,18] Furthermore, in contrast with condensation reactions, cycloaddition reactions do not produce by-products with low molar mass. Therefore, most cycloaddition reactions are classified as click reactions. In particular, copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reactions between azides and terminal alkynes (developed by the groups of Sharpless[2a] and Meldal[2b]) have become the most popular click reactions to date. These reactions are versatile, regiospecific, and exhibit a high efficiency under mild reaction conditions. Moreover, several methods are available for generation of the Cu^{I} catalyst required for CuAAC reactions. These methods involve the in situ reduction of Cu^{II} to Cu^{I} by 1) various reducing agents,[8c] 2) photochemical[19] and 3) electrochemical[20] redox processes, and 4) copper-containing nanoparticles.[21] In addition, Yagci[22] and Bowman[23] have recently developed a new photochemical protocol for the in situ generation of Cu^{I} from a Cu^{II} complex using light to catalyze a CuAAC reaction between azides and alkynes. The desired Cu^{I} can be generated by either direct irradiation of Cu^{II} or indirect reduction of Cu^{II} using a photoinitiator (Scheme 1). In direct photolysis, the absorption of UV light by a ligand of the Cu^{II} centre promotes an intramolecular electron transfer from the π-system of the ligand to the central ion, resulting in the transformation of a Cu^{II} ion into Cu^{I}, and transformation of the ligand into a radical species. Alternatively, in the indirect approach, a photoinitiator absorbs light in the UV-visible region, where



Scheme 1. Photoinduced CuAAC click reactions mediated by a) direct and b) indirect reduction of Cu^{II} to Cu^{I}.

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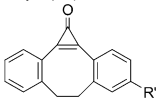
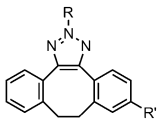
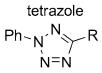
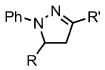
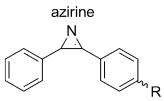
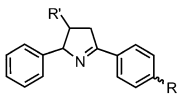
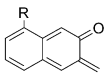
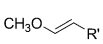
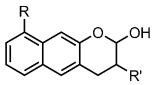
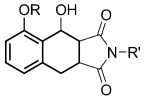
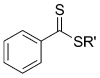
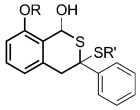
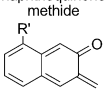
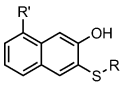
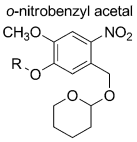
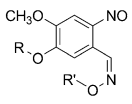
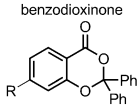
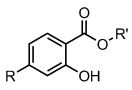
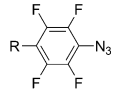
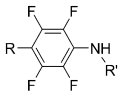
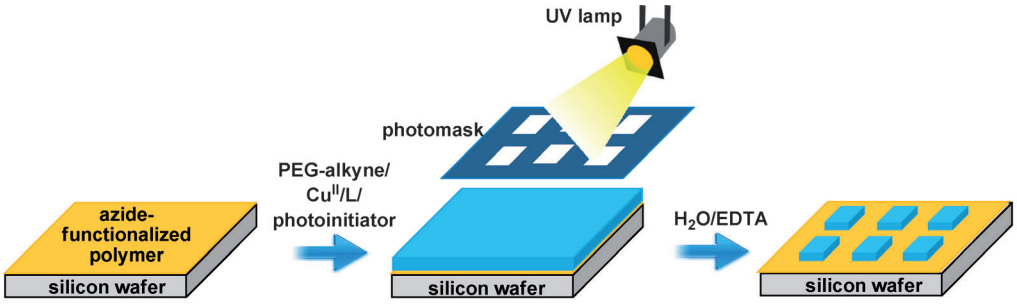
Table 1: Selected light-induced click and coupling reactions.

Reagent A	Reagent B	Adduct	*t*	Conditions
azide $R-N_3$	alkyne $\equiv-R'$		< 1 h	UV light and no additional reagent, or visible light and a photoinitiator[23]
azide $R-N_3$	cyclopropenone 		< 2 h	UV light (350 nm), in aqueous media[12b,c]
tetrazole 	alkene 		< 10 min	UV light (300–365 nm), in aqueous media with N_2 as the only by-product[12a]
azirine 	alkene 		< 10 min	UV light (302 nm), in aqueous media[35]
naphthoquinone methide 	vinyl ether 		< 15 min	UV light (300–350 nm), in aqueous media[15]
o-quinodimethane 	maleimide 		< 15 min	UV light (300–350 nm), in aqueous media[37a,b]
o-quinodimethane 	dithioester 		< 15 min	UV light (300–350 nm), in aqueous media[37c]
thiol $R-SH$	alkene  or alkyne 		< 2 h	UV or visible light and a photoinitiator[6]
thiol $R-SH$	naphthoquinone methide 		< 15 min	UV light (300–350 nm), in aqueous media[40]
o-nitrobenzyl acetal 	alkoxyamine $R'-ONH_2$		3 min and overnight in the dark	UV light (370 nm), under inert atmosphere[42]
benzodioxinone 	alcohol $R'-OH$ or amine $R'-NH_2$		< 24 h	UV light (300–350 nm), under N_2 atmosphere[14]
perfluorophenylazide 	alkane  or alkene 		< 10 min	UV light (240–400 nm), under N_2 atmosphere[45]
aldehyde 	alkene 		ca. 48 h	UV light (254 nm), under N_2 atmosphere[51]

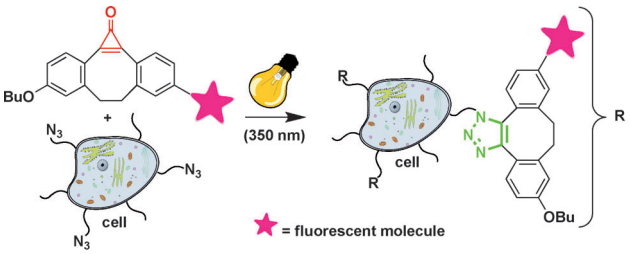


Scheme 2. Photolithographical patterning of a PEG-based hydrogel onto an azide-functionalized polypropylene using a photomask. EDTA = ethylendiaminetetraacetate.

the copper complex is colorless, and forms reactive intermediates, such as free radicals or carbocations. These intermediates then strongly promote the photoreduction of Cu^{II} to Cu^{I}. The nature of the photochemically generated radicals and the redox properties of the copper complex are crucial for the success of CuAAC reactions.

Light-induced CuAAC reactions were initially investigated using FT-IR and ^{1}H NMR spectroscopy and ESI^+ mass spectrometry of model compounds. All of these techniques confirmed that a triazole product was formed, and that the azide and alkyne molecules were consumed. Spatial control of the CuAAC reaction was then explored by the synthesis or in situ modification of hydrogels. Regarding the latter, irradiation through a photomask was used to generate Cu^{I}, which then catalyzed a light-induced CuAAC reaction between multifunctional alkynes and azide-functionalized monomers, or between an azide-bearing fluorophore and a pendant alkyne-functionalized polymer network. The result was a spatially defined fluorescent pattern within the hydrogels (Scheme 2).[23,24]

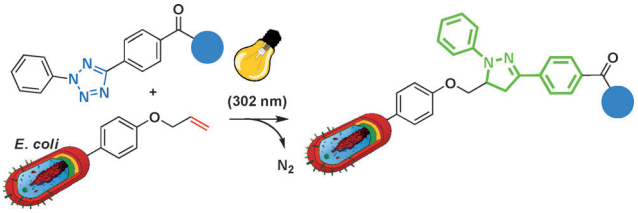
Light-induced CuAAC reactions can be temporally controlled because the activating light beam can be turned on and off as desired. Furthermore, the overall rate of the click reaction can be altered by light intensity, irradiation time, and photoinitiator concentration. Detailed kinetic investigations have suggested that Cu^{I} is not rapidly consumed during the reaction in the dark, and this may be a result of the disproportionation of Cu^{I} to Cu^{II} and Cu^{0}, which presumably leads to the regeneration of Cu^{I}.[25] This feature allows a reaction to be completed with a minimal amount of UV irradiation and copper catalyst. On the other hand, a light-induced CuAAC reaction can be stopped at any time by simply bubbling air into the reaction mixture, which leads to an irreversible oxidation of the catalyst by molecular oxygen.[26] Visually, the color of the solution turns green, implying that photogenerated Cu^{I} complexes have reoxidized to Cu^{II} complexes. Interestingly, however, this inhibition process is completely reversible. For example, when the reaction mixture is purged with argon gas and then subjected to UV irradiation for 15 min, the click reaction regains momentum and proceeds at the same rate as before. These results suggest that light is a powerful stimulus for gaining spatial and temporal control of a CuAAC reaction. Moreover, these features make light-induced CuAAC reactions a promising method for applications in both biological and materials science. However, the toxicity of the metal catalyst is a deterrent for its wider use in biological systems. Therefore, Bertozzi and co-workers[27] used a family of strained alkynes, called cyclooctynes, to achieve a strain-promoted cycloaddition of alkynes and azides. In this reaction, an alkyne group is located in a strained cyclooctyne ring with additional fluorine atoms in propargylic positions, and this greatly increases the reaction rate such that it is comparable to the CuAAC reaction. Following this work, Popik and co-workers[12b,c] reported a light-induced strategy for the in situ generation of a dibenzocyclooctyne from a photochemically masked cyclopropenone. Such cyclopropenone derivatives do not react with azides under ambient conditions in the dark. Thus, the activation of cyclopropenones by light is particularly efficient. In addition, the quantitatively strained alkynes that are produced then undergo facile, catalyst-free cycloadditions with the azides to produce the corresponding triazoles. Notably, this reaction makes it possible to visualize azido-labeled biomolecules in model organisms or tissues by employing dye-functionalized alkynes (Scheme 3). As such, light-induced, strain-promoted cycloaddition reactions offer exciting opportunities to label living organisms in a temporally and spatially controlled manner, and this may facilitate the preparation of microarrays.



Scheme 3. Light-induced, strain-promoted cycloaddition reaction of a cyclopropenone-containing fluorescent molecule and an azide-functionalized cell.

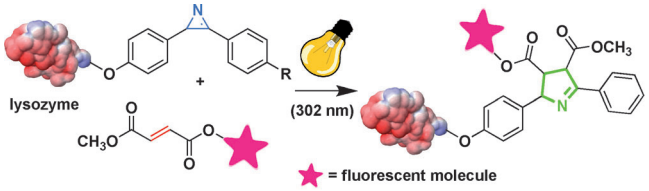
Apart from CuAAC click reactions, there is another type of cycloaddition that belongs to the same family and is referred to as a light-induced 1,3-dipolar cycloaddition of a tetrazole and an alkene. The concept was first reported by Huisgen and Sustmann[28] as early as 1967, and was re-investigated by Lin and co-workers in 2008.[29] The click reaction of interest involves light-induced decomposition of

tetrazoles at 302 nm to release molecular nitrogen. A highly reactive nitrile imine intermediate is then generated, which chemoselectively reacts with various electron-deficient and unactivated terminal alkenes and alkynes through a 1,3-dipolar cycloaddition to yield stable pyrazoline adducts.[30] Compared to other click reactions, this light-induced 1,3-dipolar cycloaddition presents several advantages: 1) it is simple to implement because tetrazole-based molecules only require two steps for their synthesis, and only a simple UV lamp is required for activation (because of high photolysis quantum yields), 2) a metal catalyst is not needed, 3) the reaction proceeds rapidly, 4) the reaction has bio-orthogonality, and 5) monitoring of the reaction is convenient because of the formation of fluorescent pyrazoline cycloadducts. In addition, because the process does not require an activated alkene, it is more easily employed for the labeling of proteins in both biological media and living cells.[12a,31] A light-induced tetrazole-ene cycloaddition reaction can also be successfully applied to the functionalization of polymer surfaces.[31c,32] For example, tetrazole structures can be optimized using long-wavelength sensitive (365 nm) and highly reactive tetrazole reagents so that the reaction can be induced with a brief, low-energy irradiation step, which also minimizes photodamage to biomolecules.[33] With nonfluorescent starting materials, the fluorescence of the pyrazoline product facilitates direct detection of the reaction within a biological system.[33b] Accordingly, the utility of this chemistry for in vivo labeling of proteins was examined in proof-of-principle experiments performed using *E. coli* cells (Scheme 4). Overall, light-induced tetrazole–alkene cycloaddition reactions represent a promising new click reaction that is characterized by excellent solvent and water compatibility, functional group tolerance, regioselectivity, and yield.[34] In recent studies, the use of activated alkenes and cyclopropenes was evaluated, and a higher rate of cycloaddition was achieved without Michael addition side reactions usually occurring with unactivated alkenes.[34] Furthermore, compared to previous studies, cyclopropene-directed, light-induced click chemistry exhibited rapid reaction kinetics and labeling of proteins (ca. 2 min).



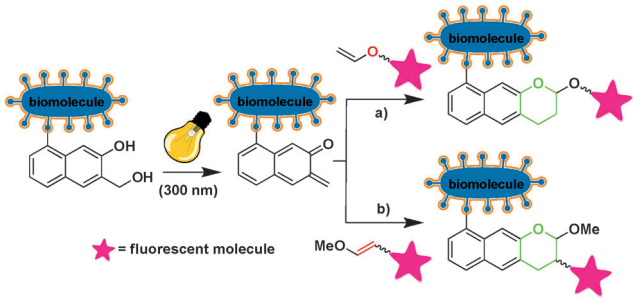
Scheme 4. Cycloaddition of an activated alkene with a nitrile imine dipole that is photogenerated in situ from a tetrazole.

Lim and Lin have developed another light-induced azirine–alkene cycloaddition reaction for the efficient protein conjugation in a biological medium at neutral pH and room temperature.[35] In this transformation, an azirine is irradiated with light to create a highly reactive nitrile ylide, which then reacts spontaneously with an activated alkene to yield a pyrroline product. The nitrile ylides generated in situ appear to be more reactive than nitrile imines generated from tetrazole precursors in the presence of water, which then require highly electron-deficient dipolarophiles, such as fumarate, to achieve an efficient click reaction. This light-induced azirine–alkene cycloaddition reaction was successfully applied to the bio-conjugation of an azirine-containing lysozyme with dimethylfumarate-linked monodisperse poly(ethylene glycol) (PEG) at room temperature (Scheme 5).



Scheme 5. Light-induced azirine–alkene cycloaddition reaction.

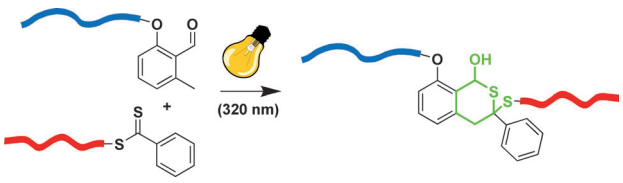
Sharpless and co-workers recognized the well-known Diels–Alder [4+2] cycloaddition as another click reaction. This reaction occurs between an electron-rich diene and an electron-poor dienophile, and the driving force behind this ring-forming reaction arises from the formation of σ-bonds. These σ-bonds are more energetically stable than the π-bond with the four π-electrons of the diene and the two π-electrons of the dienophile. Therefore, Diels–Alder click reactions usually do not require catalysts, produce high yields under mild conditions, and do not produce any by-products. However, in some cases, Lewis acids are used as a catalyst to increase both the regioselectivity and the rate of the reaction.[2b,3a–c] In these cases, the Diels–Alder cycloaddition reactions could be light-induced, thereby providing spatial control of the process. Accordingly, Popik and co-workers explored the cycloaddition of in situ photogenerated *ortho*-quinone methides and vinyl ethers to yield benzochroman products as a light-induced click reaction.[15,36] Photochemical dehydration of 3-hydroxy-2-naphthalene methanol derivatives produced the very reactive heterodiene *o*-naphthoquinone methide, which rapidly couples with unactivated alkenes, such as vinyl ethers, to produce stable or hydrolytically labile linkages. *Ortho*-naphthoquinone methide reacts very selectively in aqueous solution and only unactivated alkenes produce Diels–Alder adducts. Furthermore, it appears that a significant amount of the *o*-naphthoquinone methide is quenched by water, essentially resulting in the regeneration of starting material.[36b] The Diels–Alder reaction then proceeds well with vinyl ether at either the oxygen or carbon atoms (Scheme 6a). A unique feature of this reaction is that the choice of vinyl ether dictates the stability of the final product. For example, if the reaction occurs through an oxygen linkage, the resulting benzochroman contains an acetal linkage, and this is stable in neutral and basic solutions, yet is unstable in strongly acidic solutions. This can be advantageous for bio-conjugation applications, such as the elution of captured proteins from (strept)avidin resin. Alternatively, if a stable product is desired, the reaction can occur at the β-carbon atom of the vinyl ether (Scheme 6b).



Scheme 6. Light-induced hetero-Diels–Alder reactions between *ortho*-quinonemethides and vinyl ethers.

In this context, photoenols are highly reactive dienes that can be used with activated alkenes (e.g., *N*-maleimide derivatives) in other Diels–Alder-based reactions for polymer–polymer conjugation[37] or biocompatible surface modifications.[38] The efficiency and speed of photoenol chemistry has been demonstrated in a wide range of solvent systems, as well as on surfaces with covalently attached molecules. In the surface modification, a small-molecule ATRP initiator, poly(ethylene glycol), and a peptide were incorporated.[38] Various complex (co)polymers (e.g. stars or block-copolymers) may be readily synthesized using simple UV irradiation by reacting polymers capped with *o*-methylphenyl ketone or aldehyde moieties.[37a] Moreover, photoenol chemistry has been successfully applied to surface patterning using different maleimide derivatives with high resolution.[38]

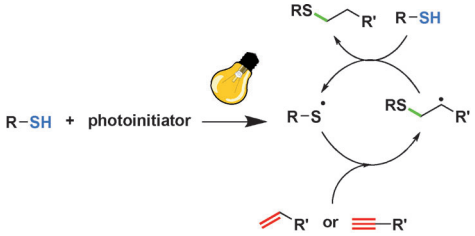
With the use of photoenol chemistry, it is also possible to use certain conventional polymers prepared by reversible addition/fragmentation chain-transfer polymerization (RAFT) as dienophiles for the synthesis of block copolymers.[36b] For example, a RAFT polymer with a non-activated dithioester terminus can be readily coupled to photoenol-functionalized polymers using a light-induced Diels–Alder reaction at ambient temperature without a catalyst (Scheme 7).[37c] In addition, this reaction is orthogonal to both thermally induced Diels–Alder cycloaddition and CuAAC reactions, thereby enabling sequential click derivatizations to be performed in one pot for the synthesis of ABC triblock copolymers.[37a]



Scheme 7. Synthesis of block copolymers through a photoenol-based, light-induced hetero-Diels–Alder cycloaddition reaction.

3. Light-Induced Thiol-Ene/Yne Reactions

Similar to cycloaddition reactions, thiol–alkene/alkyne reactions also exhibit characteristics of click chemistry, for example, orthogonality with other common synthetic procedures (a key aspect), very mild reaction conditions, benign catalysts and solvents, high reaction rates, insensitivity to water and (often) molecular oxygen, complete regioselectivity (anti-Markovnikov selectivity), both thiols and enes/ynes are readily available, work-up is straightforward, and (usually) high yields are achieved. Although other coupling reactions involving thiols and alkenes/alkynes proceed through a nonradical pathway (e.g., nucleophilic substitution or Michael addition), they are also considered click reactions. In particular, the radical thiol-ene/yne reaction is one of the most widely explored systems, and the radical mechanism involves the free radical addition of a thiol to an ene/yne bond through a thermal or photochemical process. The result is a thioether product that exhibits a high degree of anti-Markovnikov selectivity (Scheme 8). The rate of the thiol-ene



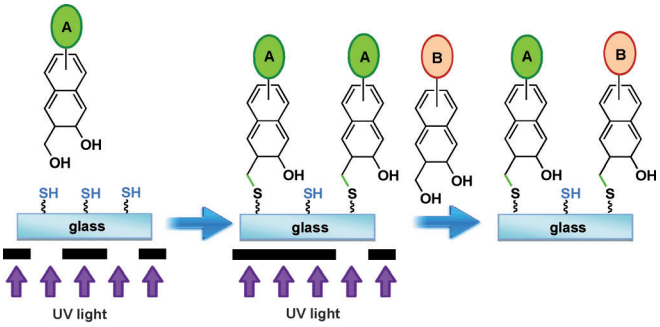
Scheme 8. Light-induced thiol-ene/yne click reactions.

reaction also depends strongly on the chemical structure of the alkene, with electron-rich and/or strained alkenes reacting more rapidly than electron-poor alkenes (e.g., norbornene > vinyl ether > alkene > vinyl ester > allyl ether > acrylate > N-substituted maleimide > methacrylate > conjugated dienes). While both heat and light can be used to generate radicals to initiate the thiol-ene/yne reaction, photoinitiation allows the process to be controlled by the wavelength, intensity, dosage, and duration of the light applied.

Use of the thiol-ene/yne click reaction has increased over the past few years as a result of its simplicity and efficiency. In addition, the tolerance of this reaction to a wide range of functional groups, as well as its orthogonality to various types of chemistry, make this reaction an ideal and broadly applicable method for organic synthesis, bio-conjugation, surface modification, and photolithography. The light-induced version of the thiol-ene/yne reaction can proceed at room temperature in the absence of a metal catalyst and tolerates a number of functional groups, including alcohols, amines, amino acids, carbohydrates, carboxylic acids, and fluorinated compounds. Because the reaction is typically initiated by visible light, which is not harmful to biomolecules, and proceeds well under mild reaction conditions (it tolerates molecular oxygen and water), this reaction is also an ideal and broadly applicable method specifically for bio-conjugation. The application of thiol-ene/yne reactions to the synthesis and functionalization of a diverse set of materials has been thoroughly discussed in a number of recent reviews and is therefore not described herein.[6c,d,39]

Another click reaction involves the Michael addition of photochemically generated *o*-naphthoquinone methides with thiols.[40] For example, a thiol-functionalized glass slide is immersed in an aqueous solution of 3-(hydroxymethyl)-2-naphthol derivatives. A mask is then placed over the slide,

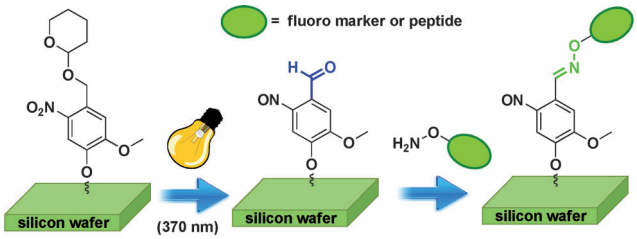
and the 3-(hydroxymethyl)-2-naphthol moieties are exposed to a fluorescent lamp that emits at 350 nm for 2 min in order to induce efficient photochemical dehydration. The reactive *o*-naphthoquinone methide species that are formed then induce an addition reaction with the thiol groups present on the surface. These reactive naphthols can be reused numerous times without loss of efficiency, because very little of the reagent is consumed and the unreacted naphthoquinone methides are quenched with water to recover the initial compound. Moreover, this feature prevents migration of *o*-naphthoquinone methides from the site of irradiation, and provides spatial control. The resulting thioether linkage is also stable under ambient conditions, yet can be cleaved by UV irradiation to regenerate the free thiol. The unique reversibility of *o*-naphthoquinone methide/thiol click chemistry not only allows various substrates to undergo patterned immobilization on a surface, but also provides a light-directed release or replacement of the immobilized substances (Scheme 9). Furthermore, the high stability and robustness of the reactive groups and the compatibility of the reaction with aqueous solutions makes this chemistry suitable for biological applications.



Scheme 9. Immobilization and replacement of 3-hydroxymethyl-2-naphthol derivatives on a thiol-functionalized surface. Adapted from Ref. [40].

4. Light-Induced Oxime Reactions

The formation of an oxime bond by the reaction of an aldehyde and an alkoxyamine is an different form of click chemistry that is inexpensive and does not require the synthesis of a library of building blocks. As a result, reaction products are generated with sufficient purity and biocompatibility for direct biological evaluation. Recently, several groups have reported that light-induced click chemistry may confer spatial and temporal control to oxime-based reactions.[41] These reactions occur in two steps, with a rapid and mild photodeprotection of an aldehyde or an alkoxyamine followed by oxime formation with the counterpart. Moreover, this chemistry has been successfully applied to the formation of micropatterned substrates (Scheme 10).[42] For example, photopatterning of *o*-nitrobenzylacetal-functionalized silicon wafers was achieved by applying UV-A radiation to a mask for 3 min. When the mask was removed, the silicon wafers were treated with a solution of a fluoro marker (*O*-[(perfluorophenyl)methyl]-hydroxylamine hydrochloride) or



Scheme 10. Functionalization of silicon wafer surfaces through light-induced oxime-based click reactions. Adapted from Ref. [42].

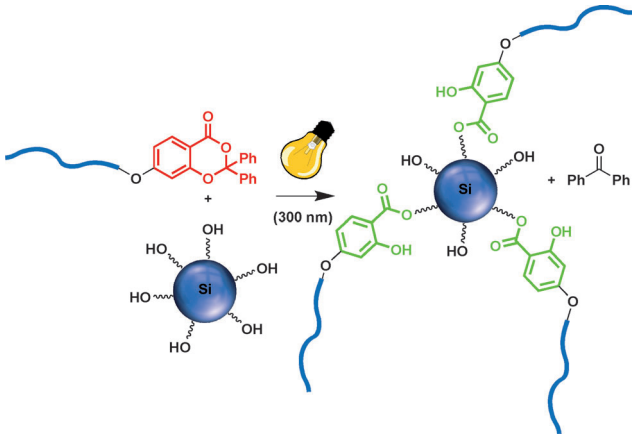
a peptide ((2-aminooxy)-acetamido Gly-Arg-Gly-Ser-Gly-Arg). Using this strategy, site-specific immobilization of biomolecules, dyes, or other functional groups can be achieved without the need for a catalyst that may be toxic or difficult to remove.

5. Other Light-Induced Coupling Reactions

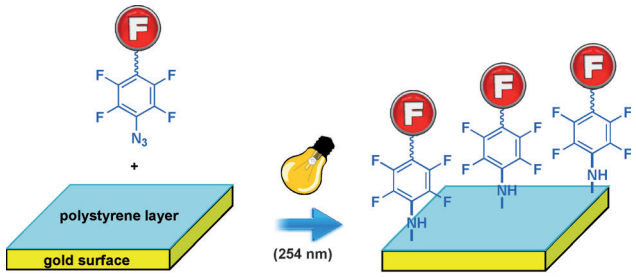
Recently, ketene chemistry has been recognized as a promising route for the modification of macromolecular structures with significant yields. Ketenes are intermediates that are very reactive toward unsaturated compounds and produce a [2+2] cycloadduct. Alternatively, ketenes can react with nucleophiles such as alcohols, amines, and acids to produce esters, amides, and anhydrides, respectively. Ketenes are derivatives of carboxylic acids with two consecutive double bonds, and can be produced thermally[43] or photochemically[14a–c,44] from dialkyl Meldrum's acid or benzodioxinone, respectively. In the latter case, benzodioxinones can be incorporated into either monomers or polymers as photolytic precursors of ketene to allow coupling reactions to occur.[14d–f,44c] By taking advantage of ketene chemistry, a novel route has been described for the incorporation of polymers onto silica particle surfaces under mild conditions and in the absence of a catalyst or an additional reagent. In comparison, existing photografting methods require multistep reactions for the same grafting process (Scheme 11).

Phenyl azides are popular light-sensitive compounds because of their high reaction efficiencies, rapid kinetics, excellent storage stability, and ease of preparation.[45] Upon activation by light, the fluorinated phenylazide moiety decomposes to an electron deficient perfluorophenyl nitrene that can subsequently undergo C–H insertion and/or C=C addition reactions.[46] Light-induced perfluorophenyl azide chemistry has proven to be useful for the conjugation of less reactive functional groups, such as polyolefins and carbon materials, and provides highly robust and stable linkages (Scheme 12). This method can also be used for the immobilization of carbohydrate structures to a variety of nanomaterials, including polymers,[47] silicon wafers,[48] gold,[47b,49] iron oxide,[45c] and silica nanoparticles.[45d,e,50]

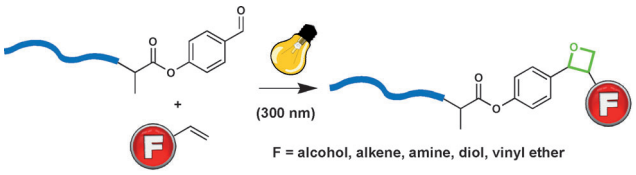
Light-induced [2+2] cycloaddition of carbonyl compounds to olefins, also known as the Paterno–Büchi reaction, has recently been described as a coupling reaction, and provides functionalization of polymers (Scheme 13).[51] Compared to typical click reactions, the cycloaddition reaction



Scheme 11. Synthesis of polymer-supported silica particles through light-induced ketene chemistry. Adapted from Ref. [44c].



Scheme 12. Modification of polymer surfaces through light-induced perfluorophenyl azide chemistry.



Scheme 13. End-group modification of polymers with aldehyde termini through light-induced [2+2] cycloaddition.

may not fulfill the stringent criteria of the click concept, as reaction times are generally too high and a relatively large excess of the alkene compound is required to achieve a complete conversion of aldehyde compounds. Nevertheless, the light-induced Paterno–Büchi cycloaddition reaction is a convenient way to prepare synthetically useful oxetanes based on the wide variety, accessibility, and relative inertness of the required starting materials. The use of [2+2] and [4+4] photocycloadditions in organic chemistry, polymer chemistry, and materials science has recently been reviewed elsewhere, and therefore is not described herein.[48a]

6. Conclusion

The versatility of click chemistry has been broadly exploited by photochemical methods, in which the reaction of interest is defined by when and where light is delivered in a system. Furthermore, light-induced click reactions have a broad range of adjustable parameters (e.g., wavelength and intensity of light, duration of irradiation, and spatial and temporal control) that can be optimized to suit a given application. The method is also universal and applicable to a wide variety of materials surfaces and combines the advantages of click chemistry and photolithography processes. Considering its mild reaction conditions, rapid throughput, and compatibility with orthogonal methods, this methodology provides numerous opportunities for its application in chemistry-related fields such as chemical biology and medicinal chemistry. Furthermore, any limitations of the method, such as orthogonality and toxicity, can be efficiently managed by selecting a reaction that is appropriate for a specific set of conditions. Current research is directed toward further increasing the level of performance, developing new light-induced click systems in a modular fashion, and eliminating metal toxicity.

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