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Click Chemistry: Mechanistic and Synthetic Perspectives

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Search for reactions that can be used to link two or more diversely functionalized molecules with minimum effort and without the formation of side products has become increasingly important in the past 15 years. As organic molecules started to find their place as easily tunable and functional materials, the requirement of new conjugation reactions that can be used effectively by nonsynthetic organic chemists became unavoidable. Such a reaction should be easier to carry out, yield high selectivity, should be compatible with water and other protic solvents, and should lead to quantitative conversions. Click chemistry is a collection of such reactions that has evolved as an efficient tool for ligation, which gained quick acceptance in biotechnology, material and polymer science, medicinal chemistry, and so on. Among all the click reactions, copper-catalyzed 1,3-dipolar Huisgen cycloaddition (HDC) between a terminal alkyne and an azide is *the jewel in the crown*. Owing to its remarkable functional group tolerance, researchers can fearlessly introduce easily functionalizable groups such as hydroxyl, carboxyl, and amino groups into conjugate molecules using this reaction.

The concept of click chemistry was first introduced by Sharpless and coworkers in 2001 at the Scripps Research Institute [1]. Click chemistry is not limited to a set of organic reactions, but is a synthetic philosophy inspired by nature in terms of their efficiency, selectivity, and simplicity. Any reaction that can produce conjugate molecules efficiently from smaller units under simpler reaction conditions can be considered as a click reaction. The catchy term *click* refers to reactions that are modular in approach, efficient, selective, versatile in nature, give single product (high yielding), and can be performed in benign and easily removable solvents without the need for chromatographic purification. There are various reactions with different mechanisms that can be considered as click reactions, provided they follow a simple common reaction trajectory [1].

Sharpless first introduced the concept of click chemistry to provide an effective conjugation technique in drug discovery [2], but the concept and methodology were widely accepted, and click chemistry found its applications in almost all facets of research and technology, which employ organic molecules, such as

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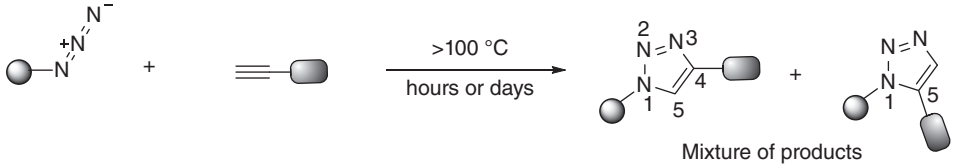
polymer science [3], nanoscience [4], bioconjugation [5], and development of sensors [6] .

In this chapter, we have provided a detailed account of various click reactions with emphasis on their mechanisms and synthetic details. The discussions are based on the following classification of click reactions.

1.1 Cycloaddition Click Reactions

1.1.1 Azide–Alkyne Huisgen 1,3-Dipolar Cycloaddition

The classical HDC reaction between an alkyne and an azide is the most discussed among click reactions. Both alkynes and azides are unreactive under physiological conditions and undergo a cycloaddition reaction only at elevated temperatures (Scheme 1.1) [7, 8]. Although both alkynes and azide functions can easily be introduced on to the substrates, the cycloaddition reaction is highly exothermic (ΔH^0 is between −50 and −65 kcal/mol) and has a high activation barrier of 25–26 kcal/mol (for methyl azide and propyne). Hence, the uncatalyzed reaction is generally slow and is not regioselective [9]. The difference between HOMO-LUMO energy levels of both azide and alkyne are comparable, thus both dipole HOMO and dipole LUMO pathways can operate in this reaction leading to a mixture of 1,4 and 1,5-triazole regioisomers. It is, however, observed that the use of electron-deficient terminal alkynes can impart 1,4-regioselectivity to a reasonable extent. These factors limit the use of uncatalyzed Huisgen cycloaddition as an effective conjugation technique.



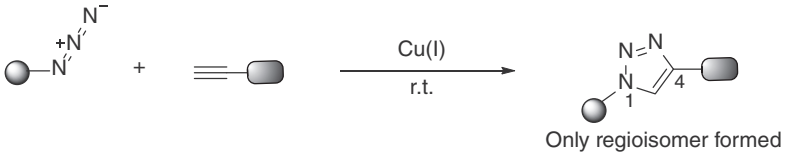
Scheme 1.1 Huisgen 1,3-dipolar cycloaddition between alkynes and azides.

1.1.2 Copper-Catalyzed Azide–Alkyne Cycloaddition (CuAAC) Click Reaction

Sharpless [9] and Meldal [10] independently reported a Cu(I)-catalyzed version of the cycloaddition reaction between azides and terminal alkynes, which is 10^7 times faster than the uncatalyzed reaction. The interaction between Cu(I) and terminal alkynes makes the latter a better 1,3-dipolarophile, enhancing its reaction

with azides. The Cu(I)-catalyzed reaction is highly regioselective and only the 1,4-adducts are formed. The Cu(I)-catalyzed reactions can be carried out at room temperature and at a much faster rate.

Sharpless reported the possibility of using *in situ* generated copper(I), obtained through the reduction of copper sulfate pentahydrate ($CuSO_4 \cdot 5H_2O$) with ascorbic acid, as an efficient catalyst for carrying out azide–alkyne conjugation reactions in solutions [9]. The reactions worked well when a mixture of water and an alcohol is used as the solvent. The solvent mixture allowed effective dissolution of the metal salt and the organic components needed to be conjugated. Meldal and coworkers reported a very practical application of azide–alkyne cycloaddition catalyzed with cuprous iodide in conjugating peptides through side chains or the backbone in solid phase [10]. Both reactions were selective for the formation of 1,4-disubstituted 1,2,3-triazoles and together revolutionized the concept of click reactions (Scheme 1.2).



Scheme 1.2 CuAAC click reaction.

In addition to being a stable linker, the triazole group has certain other advantages. On comparison with an amide bond, which was otherwise the most common linkage used, a triazole group exhibits certain interesting and unique properties. Unlike an amide bond, triazoles are not susceptible to hydrolytic cleavage. They cannot be reduced or oxidized under normal conditions. A triazole linkage, with an extra atom in its backbone, places the carbon atoms linked to 1- and 4-positions at a distance of 5.0 Å, while an amide linkage places the carbon atoms only at 3.8 Å apart from each other. The nitrogen atoms at 2- and 3-positions of the triazole have weak hydrogen-bond-accepting properties. The inherent dipole moment in a triazole ring leads to polarization of the C_5–H bonds, making them hydrogen bond donors and enabling C–H···X hydrogen bonds, similarly to an amide bond [11]. These properties also enabled Cu(I)-catalyzed triazole formation to gain attention as an effective conjugation method.

Conjugation of functional molecules through triazoles received immediate attention especially in drug discovery. Linhardt *et al*. synthesized some sialic acid conjugates using copper catalyzed azide–alkyne cycloaddition (CuAAC), which are potential neuraminidase inhibitors with good IC_{50} values (Figure 1.1) [12]. There are a large number of such examples of CuAAC being used effectively for assembling small molecular units to obtain more functional and useful molecules. An interesting example is the synthesis of the rigid macrocycle **C** (Figure 1.2) by Flood *et al*., in which triazole units function as rigid structural units and provide acidic hydrogens to interact and detect chloride ions in organic solvents [13]. In

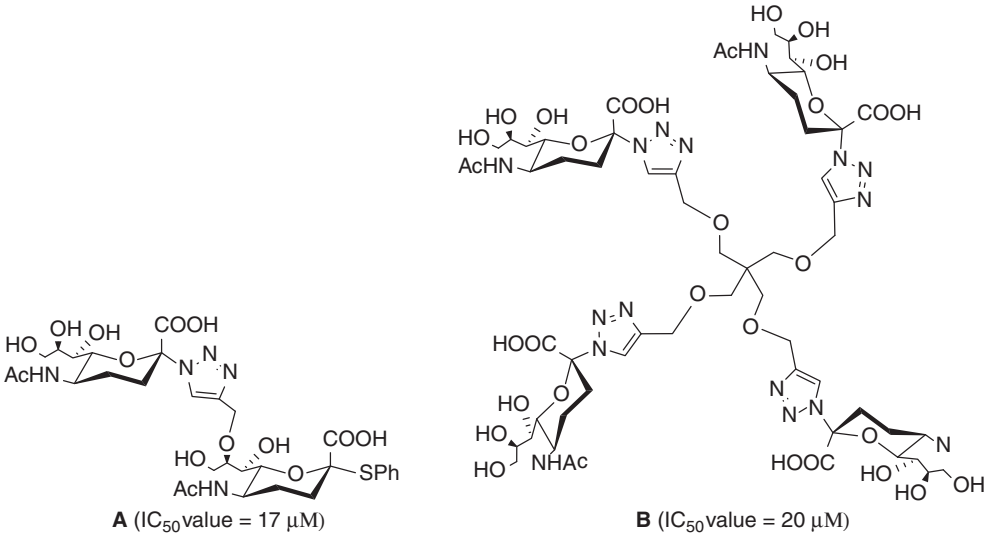


Figure 1.1 Sialic-acid-based neuraminidase inhibitors; a disaccharide mimic **A** and a dendrimer **B**.

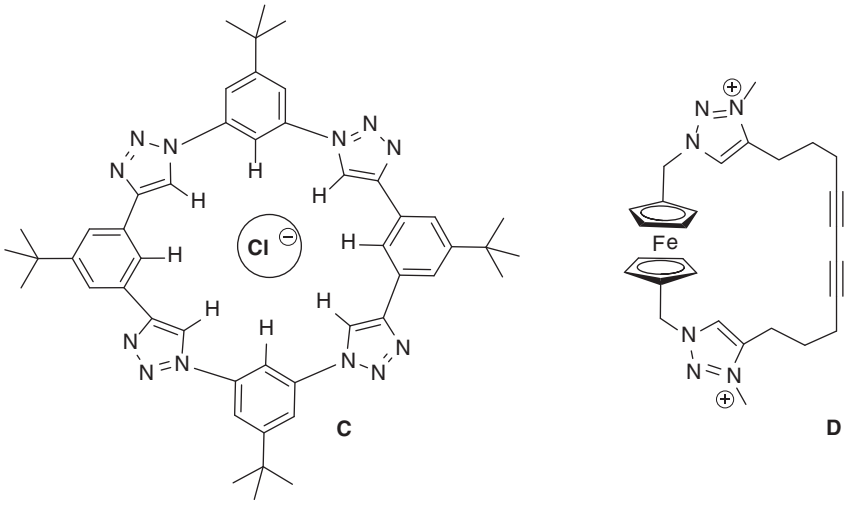
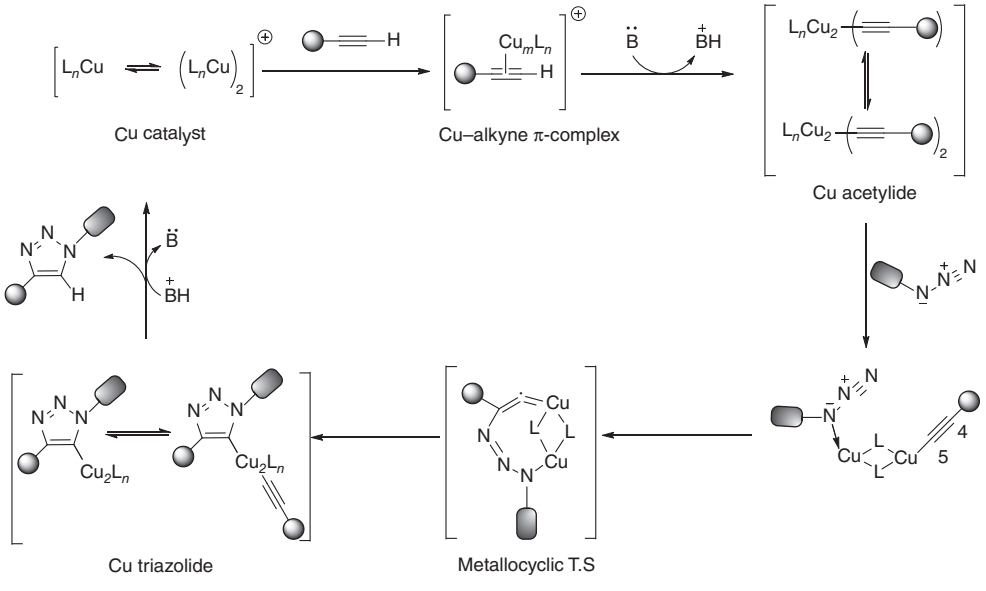


Figure 1.2 Triazole-containing macrocycles used for the detection of anions.

a similar attempt, Beer *et al*. have reported a ferrocene-containing bis(triazole) macrocycle **D** (Figure 1.2), in which they have increased the anion binding tendency of the C–H of triazole by converting triazole units to cationic triazolium moieties. Alkylation of a triazole increases its binding capability with anions such as chloride and benzoate ions even in polar organic solvents [14].

1.1.2.1 Mechanism of CuAAC Click Reactions

A detailed mechanistic analysis of CuAAC was reported by Jan H. van Maarseveen and coworkers in 2006 [15]. The report was based on comprehensive kinetic studies and DFT calculations. Studies showed that the Cu-catalyzed cycloaddition reaction proceeds through a stepwise mechanism and the activation energy is 11 kcal/mol less than that of the uncatalyzed reaction, which has an activation energy of 26 kcal/mol. However, a concerted mechanism involving Cu–acetylene π-complex and the azide was calculated to have a higher activation energy of 27.8 kcal/mol. The reaction begins with the formation of a Cu–alkyne π complex, which then forms a copper acetylide after deprotonation of the alkyne proton. Coordination of copper with the alkyne makes the acetylenic proton more acidic, increasing its acidity by up to 9.7 pH units, which allows the deprotonation to occur in aqueous media even in the absence of a base. The copper acetylide exists in equilibrium between a monomer and a dimer. One of the Cu ions in the dimer coordinates with the azide nitrogen and activates it. This complex then cyclizes to give a metallacycle via a nucleophilic attack of the terminal nitrogen of the azide group on the internal carbon of the alkyne. The metallacycle then undergoes a ring contraction through a transannular interaction between the lone pair of electrons on the substituted nitrogen of the azide and the C═Cu bond. This relatively faster step yields a Cu triazolide, which undergoes protonation to liberate the 1,4-disubstituted triazole and regenerates the Cu(I) catalyst (Scheme 1.3) [16].



Scheme 1.3 Mechanism of the CuAAC reaction as proposed by Jan H. van Maarseveen [15].

1.1.2.2 Catalysts used for CuAAC Click Reactions

The success achieved in CuAAC click reactions prompted researchers to look for better and more stable catalysts to carry out the azide–alkyne cycloaddition to triazoles. However, despite several efforts, Cu^{+1} is found to be the best catalyst. The unique activity of Cu^{+1} over other metal ions is due to its ability to involve the terminal alkynes in both σ and π interactions and the possibility of immediate replacement of the ligands in its coordination sphere (generally in aqueous medium). However, Cu^{+1} is thermodynamically unstable and oxidizes to Cu^{+2} or disproportionates to a mixture of Cu^{+2} and Cu under aerobic conditions. Cu^{+2} is catalytically inactive, and its generation halts the reaction.

The thermodynamic instability of Cu^{+1} places importance on its introduction to a reaction mixture. It is observed that Cu^{+1} species are relatively stable in organic solvents and in the absence of water and oxygen. Cu(I) salts such as CuI, CuBr, and $CuOTf{\cdot}C_6H_6$ have been found to be efficient catalysts in organic solvents. The use of Cu(I) salts in organic solvents is generally carried out with the addition of a tertiary amine base such as diisopropylethylamine (DIPEA) or 2,6-lutidine [17]. This is attributed largely to the requirement of a base to deprotonate the Cu–alkyne π complex, so as to generate the copper acetylide. It is also observed that amines and certain solvents such as acetonitrile [18] stabilize the Cu(I) species through coordination, preventing its degradation through oxidation or disproportionation.

When the reactions are carried out in aqueous media or in a mixture of water and an alcohol (most commonly *tert*-butanol), the degradation of Cu(I) salts is inevitable. It is found that the use of a Cu(II) salt such as $CuSO_4{\cdot}5H_2O$ along with reducing agents such as sodium ascorbate, hydrazine, or tris(2-carboxyethyl)phosphine (TCEP) generates Cu^{+1} *in situ*. This method, where the active catalyst is generated in the reaction mixture via reduction of Cu(II) salts, works well in aqueous solutions and even in the presence of oxygen [19]. Additionally, the ability of water to act as a base allows these reactions to be carried out in the absence of an external base such as DIPEA. The continuous presence of a reducing agent such as sodium ascorbate ensures the regeneration of Cu(I) even if the active catalysts is quenched by air [19b]. It is also advantageous that carrying out reactions in aqueous media with *in situ* generation of Cu(I) species allows the use of substrates with unprotected amino and hydroxyl functions.

A third but less explored method for introduction of Cu^{+1} into the reaction mixture is by vigorously shaking or by microwave irradiation of a solution containing metallic copper. While the amount of Cu^{+1} ions produced in solution by vigorous shaking is quite less leading to extended reaction times (12–48 h) [20], microwave irradiation completes the reaction in 10–15 min at elevated temperatures [21]. An advantage of this method is the isolation of products with negligible copper contamination. Various other forms of copper such as Cu(I)-modified zeolites, copper oxide nanoparticles [22], or copper nanoparticles adsorbed on charcoal [23] have all been utilized successfully for CuAAC reactions.

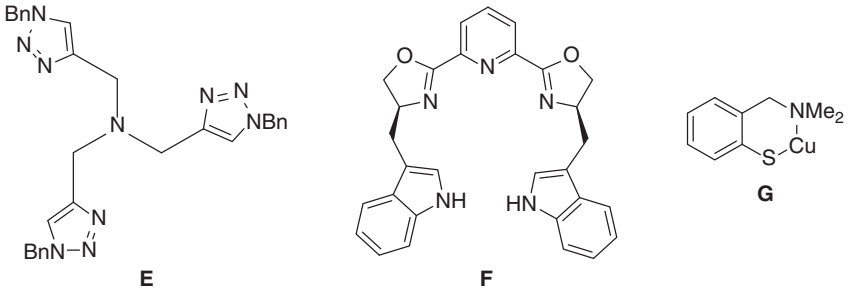


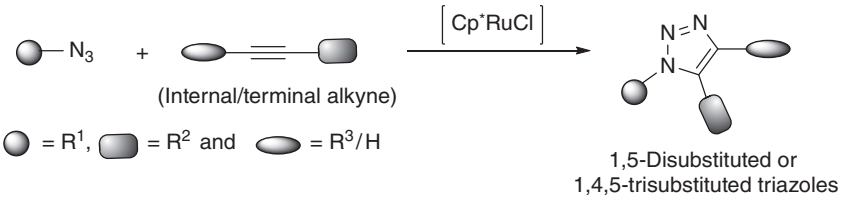
Figure 1.3 Ligands used in CuAAC click reactions.

1.1.2.3 Ligands used for CuAAC Click Reactions

Although CuAAC can be performed with Cu^{+1} generated *in situ* or provided as a Cu(I) salt in the absence of any ligands, certain ligands such as those that can form heterocyclic chelates with Cu^{+1} ions are shown to increase the rate of the reaction (Figure 1.3) [24]. The role of these ligands is assumed to be based on restraining Cu^{+1} from interactions, which lead to its degradation. Tris-(benzyltriazolylmethyl)amine (TBTA, **E**), a tetradentate ligand, is shown to be very efficient in increasing the rate of CuAAC click reactions [25]. Owing to its tetradentate-binding ability, it completely surrounds the Cu(I) center and does not provide any free binding sites for destabilizing interactions. The tertiary amino group in TBTA can also act as the required base, when reactions are carried out in organic solvents. Certain ligands are known to reduce the minimum catalyst loading by almost 10 times with no increase in reaction time [26]. Some common nitrogen-based ligands used in facilitating CuAAC are shown in Figure 1.3. Other than those based on nitrogen, ligands containing oxygen, phosphorous [27], carbon [28], and sulfur [29] as donor atoms are also reported.

1.1.3 Ruthenium-Catalyzed Azide–Alkyne Cycloaddition (RuAAC) Click Reactions

Among various other metal ions studied for catalyzing HDC between azides and alkynes, Ru(II) catalysts were found to be the most notable. The catalytic activity and regioselectivity of the reaction were found to be dependent on the ligand environment of the Ru center. Unlike the Cu(I)-catalyzed reactions, azide–alkyne cycloaddition reactions catalyzed by ruthenium complexes showed a preference for the formation of 1,5-disubstituted triazoles to the formation of 1,4-disubstituted triazoles (Scheme 1.4). Out of the various ruthenium complexes studied for catalysis of this cycloaddition reaction, the most successful catalysts are C_p^*RuCl, $C_p^*RuCl(PPh_3)_2$, $C_p^*RuCl(COD)$, and $C_p^*RuCl(NBD)$. The reactions are performed with 1–2 mol% of the catalyst in THF/dioxane or in any nonprotic solvent at temperatures ranging from ambient to 80 °C. Another salient feature of Ru-catalyzed reactions is the possibility to use internal alkynes for the reaction to obtain 1,4,5-trisubstituted triazoles as the products in good



Scheme 1.4 Formation of 1,5-disubstituted or 1,4,5-trisubstituted triazoles via Ru-catalyzed 1,3-dipolar cycloaddition reaction between azides and alkynes.

yields (Scheme 1.4) [30]. Other than Cu and Ru, attempts have been made to use other metals such as Ni, Fe, Sm, Ce, and Zn also as catalysts for HDC reactions, but none of them gave satisfying results to be used widely [31].

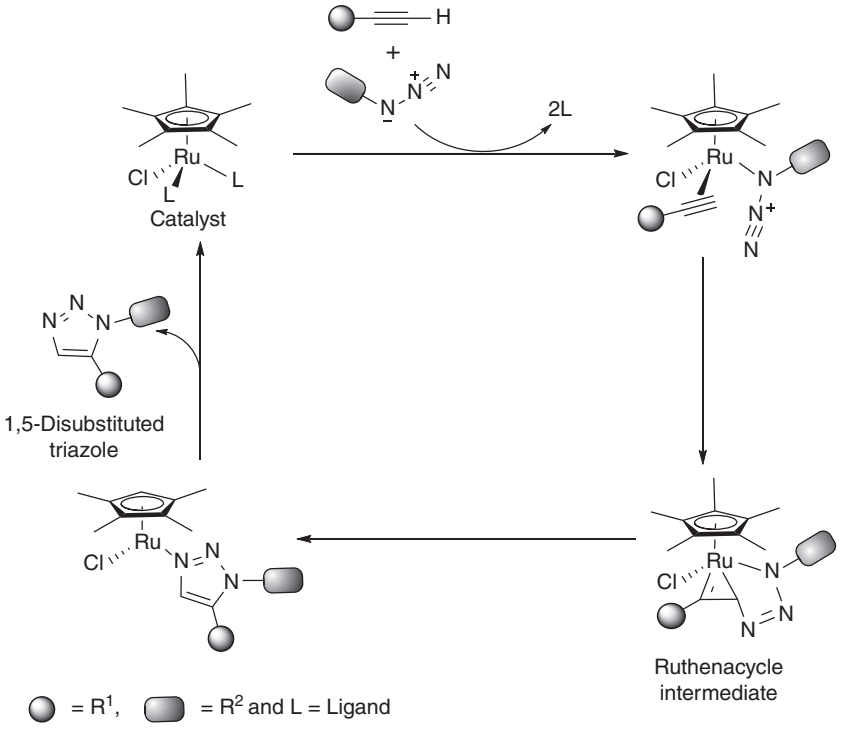
Unlike CuAAC reactions, the Ru-catalyzed version of HDC reactions was more dependent on the steric details of the azides than those of the alkyne components. Primary and secondary azides in the presence of catalytic amount of Ru complexes react with a wide range of terminal alkynes, but tertiary azides seem to be less reactive [24]. Electronic and steric properties of the alkynes too play a crucial role in these reactions, but not as much as those of the azides. Alkynes having H-bond donor groups such as propargyl alcohols and propargyl amines show high regioselectivity even for unsymmetrical alkynes. Strong H-bond between OH or NH_2 of the alkyne and Cl on the Ru complex is the driving force for the reaction. The new bond is always formed between β carbon of alkyne and terminal nitrogen of the azides.

1.1.3.1 Mechanism of RuAAC Click Reactions

Mechanistic insights into ruthenium-catalyzed azide–alkyne cycloaddition (RuAAC) reactions were provided by Fokin and coworkers in 2008, based on DFT calculations [32]. The mechanism is proposed to have two important steps. After the initial coordination of the alkyne and azide onto ruthenium, an irreversible oxidative coupling takes place, which also involves the formation of a C–N bond by the nucleophilic attack of the electronegative carbon of the activated alkyne on the terminal electrophilic nitrogen of the coordinated azide, forming a six-membered ruthenacycle intermediate. This cyclic intermediate then undergoes a rate-determining reductive elimination to give a triazolyl complex, which liberates a 1,5-disubstituted triazole product through ligand exchange (Scheme 1.5).

1.1.4 Strain-Promoted Azide–Alkyne Cycloaddition (SPAAC) Reactions

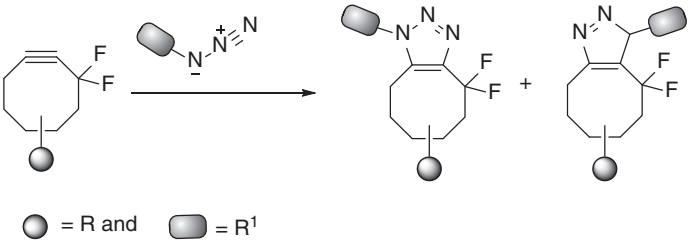
Apart from the applications in synthesizing drug molecules with a triazole linkage, azide–alkyne cycloaddition reactions have also been used for various biological applications such as site-specific protein/viruses modifications and functionalization of cell surfaces. Use of transition-metal-catalyzed reactions for



Scheme 1.5 Proposed mechanism of RuAAC click reactions.

such applications is not advisable as metal salts could be detrimental to living cells. Copper salts are known to degrade oligonucleotide strands, and copper is cytotoxic at higher concentrations. This has placed an importance on the search for click reactions that can be carried out without the use of metal catalysts.

Use of electron-deficient alkynes is a possible option for increasing the rate of an uncatalyzed azide–alkyne cycloaddition reaction. However, this requirement places a serious restriction on the nature of functionalities that can be incorporated on the alkyne. A rapid cycloaddition reaction between neat cyclooctyne, the smallest stable cycloalkyne, and phenyl azide to give a triazole product in high yields was reported as early as in 1961. The release of substantial ring strain of nearly 18 kcal/mol in the cyclooctyne was the driving force for this reaction. Bertozzi and coworkers explored the possibility of using this strain-promoted azide–alkyne cycloaddition (SPAAC) reaction as a click reaction for bioconjugation [33]. They introduced electron-withdrawing groups (EWGs) on to the cyclooctyne system to increase its reactivity toward cycloaddition reactions further. Mono- and difluorinated cyclooctyne derivatives were prepared, which have lower energy LUMO providing an increased second-order rate constants for cycloaddition reactions (Scheme 1.6) [34].



Scheme 1.6 An example for SPAAC click reaction.

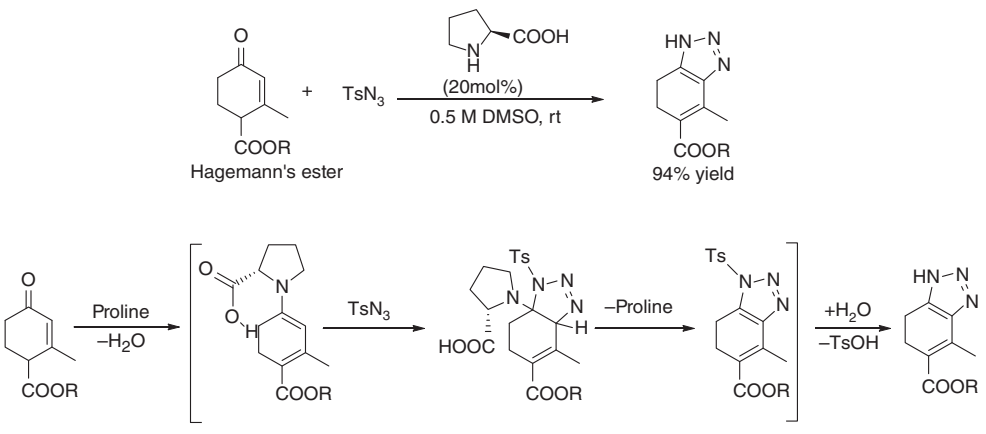
Boons and coworkers employed a different strategy and introduced benzyl groups adjacent to the alkyne function, thereby increasing the ring strain in the cyclooctyne molecule [35]. They succeeded in using these benzyl derivatives for reaction with azides and employed this strategy in visualizing labeled glycoconjugates metabolically in living cells.

Various other cycloaddition reactions including Diels–Alder reaction and hetero-Diels–Alder reactions have been employed as click reactions. However, all such reactions have found no or limited applications as conjugation methods.

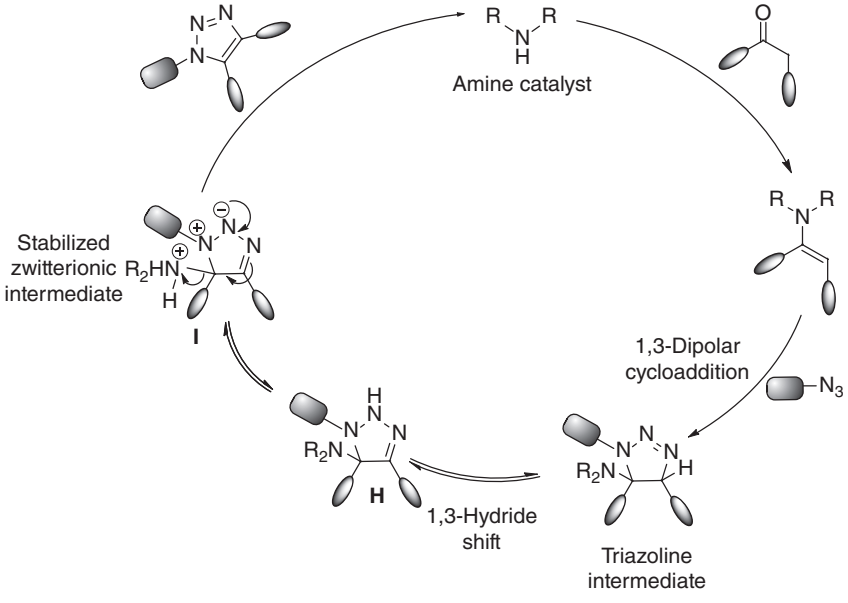
1.1.5 Organocatalytic Triazole Formation

As illustrated earlier, 1,2,3-triazoles have the potential to be very useful pharmacophores. This has placed some importance in methods leading to their formation even if they are not be used as click reactions for conjugation. One such approach that has gained recent attention is the synthesis of 1,2,3-triazoles through organocatalytic cycloaddition reactions. Compared to metal catalysts, organocatalysts are eco-friendly, insensitive to oxygen and water, and are easily available. Enolates and enamines can be easily produced by condensation of amine and aldehyde, so they have been explored by many researchers as dipolarophiles [36]. A representative example is the proline-catalyzed reaction between Hagemann's ester and tosyl azide to give fused triazoles, reported by Ramachary *et al*. [34b] (Scheme 1.7).

In general, such reactions begin with the *in situ* formation of an enamine by reaction between a carbonyl compound and a secondary amine, which also acts as the catalyst (Scheme 1.8). The enamine thus generated act as a dipolarophile, which reacts with the azide. The cycloaddition reaction between the dipolarophile and azide leads to the formation of a five-membered triazoline intermediate in equilibrium with other intermediates H and I. The protonated secondary ammonium ion I undergoes an elimination leading to the formation of a 1,2,3-triazole (Scheme 1.8). Other than enamines, enolates, peptidyl phosphoranes, vinyl sulfones, and iminolates are some examples that are frequently utilized as dipolarophiles. The dipolarophiles generated are categorized into two types: activated dipolarophiles (e.g., Hagemann's esters and β-ketoesters) and



Scheme 1.7 Proline-catalyzed synthesis of fused triazole from Hagemann's ester and tosyl azide.



Scheme 1.8 Mechanism for amine-catalyzed 1,3-dipolar cycloaddition between aldehydes and azides.

unactivated dipolarophiles (e.g., alkyl or allyl ketones and aldehydes). Among amine catalysts that have been found to catalyze these reactions, secondary amines (such as pyrrolidine, morpholine, and diethylamine) and amino acids (such as proline) are the most effective [37].

1.2 Thiol-Based Click Reactions

Thiols react with a wide range of substrates and with a number of different functional groups. Generally, the reactions are high yielding and easy to follow. Many of these reactions can be carried out under benign conditions and have been utilized for routine organic synthesis, polymerization, and surface functionalization. The wide range of reactivity of thiols makes them very good conjugation tools, but at the same time, this makes them very susceptible to many side reactions. Thiols, especially the low-molecular-weight molecules are foul-smelling and have low self-stability. Proper selection of substrates and careful handling can circumvent most of the disadvantages, leaving thiols as efficient members in the toolbox of click chemistry.

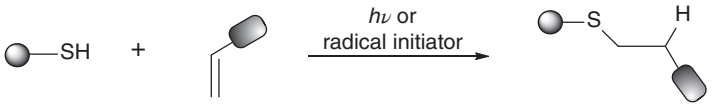
The history of sulfur-based cross-linking began as early as in 1839, when Goodyear used elementary sulfur to cross-link unsaturated polymers, and the technique is known as *vulcanization* [38]. Ever since then, sulfur and thiols are seen as easily available conjugation tools. The reactions of thiols can broadly be classified as radical reactions and nucleophilic reactions. Radical reactions in particular make them selective toward certain groups under specific reactions conditions, tolerating a large number of other functional groups.

1.2.1 Radical Click Reactions of Thiols

The reactions of thiols toward alkenes and alkynes proceed quite smoothly in the presence of light or a radical initiator. The reactions do not need any transition metals as catalysts and are highly preferred as a conjugation method for the preparation of functional molecules for biological applications. Thioether bonds generated in such reactions are stable to strong acids, strong bases, and reducing conditions. These reactions have found their applicability in tailoring solid surfaces with specific properties, immobilization of macromolecules such as proteins, and surface engineering and patterning.

1.2.1.1 Thiol–Ene Radical Click Reaction

The reaction of thiols with alkenes was first introduced by Posner in 1905 [39]. The reactions can be initiated either by using a radical initiator or directly by irradiating thiols with a UV source, preferably at 254 nm. Irradiation of thiols promotes homolysis of the S–H bond resulting in the formation of a thiyl radical [40]. The self-initiation of thiols leading to radical reactions on irradiation with UV light of low wavelengths was first reported by Cramer and coworkers. The reaction of thiyl radicals with alkenes is regioselective and tolerates a wide variety of functional groups. The reaction conditions are mild and are compatible with water and oxygen. These characteristics along with the self-initiation properties of thiols have provided the thiol–ene reaction the status of being a very useful click reaction. The reactions are often termed as *hydrothiolation* of an alkene (Scheme 1.9).

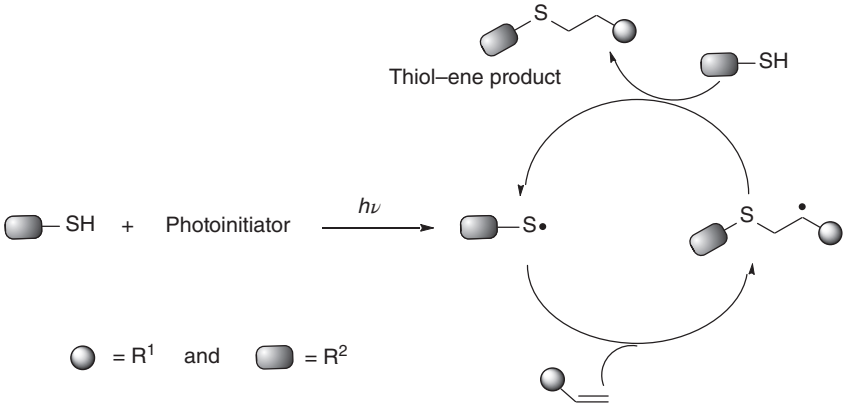


Scheme 1.9 The hydrothiolation of a C=C bond in the presence of hν or a radical initiator.

The thiol–ene radical reactions can sometime lead to the formation of unwanted by-products through radical recombination reactions. The addition of a thiyl radical to olefins is reversible, until the free radical product formed abstracts a hydrogen radical from another thiol giving a thioether product and propagating the radical reaction [41].

Although it is advantageous to initiate these reactions through direct irradiation of thiols, the reaction rates are often quite slow, resulting from a slow rate of radical formation. The rates can be improved considerably by using a combination light and a photoinitiator. Initial studies and applications were based on the use of hydrogen-abstracting initiators such as benzophenone. It was later found that the reaction rates increase tremendously on the use of Norrish type-1 photoinitiators such as dimethoxyphenylacetophenone (DMPA, for ultraviolet initiation) and phosphine oxide (for visible light initiation).

The mechanism of the reaction has three steps, similarly to all radical reactions. In the initiation step, the thiol or the photoinitiator is irradiated with a light of suitable frequency to generate a thiyl radical. The thiyl radical thus generated undergoes an anti-Markovnikov addition to the alkene to generate a carbon radical as intermediate. The carbon radical then reacts with another thiol molecule forming a thioether and another thiyl radical, and the reaction propagates to complete the radical cycle. The reaction terminates through recombination of thiyl radicals and carbon radicals with each other or between themselves (Scheme 1.10).



Scheme 1.10 The mechanism for the hydrothiolation of a C=C bond in the presence of a photoinitiator and light.

The formation of the carbon sulfur bond follows an anti-Markovnikov regioselectivity, which ensures the formation of the most stable carbon radical [42]. There are several reports establishing a general trend for the reaction of thiols with alkenes. Comprehensive reports in this regard were published by Hoyle *et al.* [43], where they compared the reaction of three families of thiols, namely alkyl-3-mercaptopropionates, alkyl thioglycolates, and alkyl thiols, with various alkenes. The reactivity order provided by them is as follows: norbornene > vinyl ethers > propenyl > alkenes ≈ allyltriazines ≈ allyl isocyanurates > acrylates > N-substituted maleimides > acrylonitrile ≈ methacrylates > styrene > conjugated dienes.

A general observation is that the reactivity of an alkene decreases with decrease in electron density of the double bond. Norbornene has an unusually high reactivity owing to a distorted double bond, and addition of thiyl radical leads to a decrease in ring strain. Conjugated olefins such as methacrylates, styrene, and 1,3-dienes have very low reactivity, which is attributed to a very low rate of abstraction of protons by the corresponding carbon radicals from thiol molecules. The decreased reactivity of such carbon radicals are a result of their increased stability achieved through conjugation. It is observed that terminal double bonds are more reactive to hydrothiolation than internal double bonds. Hoyle and coworkers have shown that 1-hexene is 8 times more reactive than *trans*-2-hexene and 18 times more reactive than *trans*-3-hexene [41a].

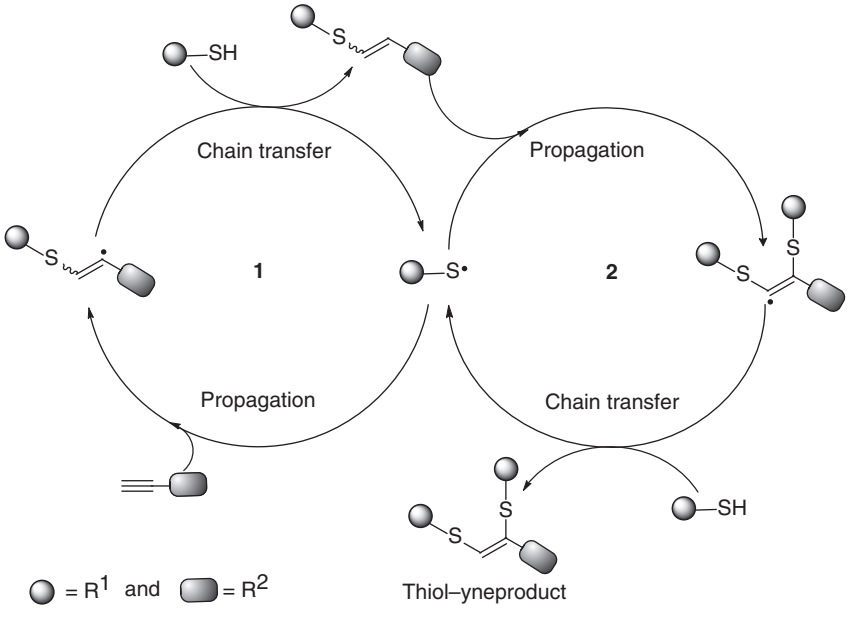
Among the various families of thiol that have been studied, propionates and glycolates are more reactive than alkyl thiols. This difference in reactivity is proposed to be resulting from the weakening of S–H bond through H-bonding with the carbonyl of the ester function and from polar effects [44].

1.2.1.2 Thiol–Yne Radical Click Reaction

Thiol–yne radical reactions follow a similar initiation step to that of thiol–ene reactions. After the initial addition of a thiol to the alkyne and formation of a vinyl radical with a β-thioether function, a hydrogen abstraction from another thiol molecule generates a new thiyl radical. Subsequent addition of a thiyl radical on the vinyl thioether forms another carbon radical, which abstracts a hydrogen from another thiol molecule to give a 1,2-dithioether, and the thiyl radical generated reenters the chain process (Scheme 1.11). The addition of the first thiol to the alkyne is the rate-limiting step, and the second thiol addition to the intermediate thiol–alkene is a faster step. Studies revealed that the second addition is approximately three times faster than the first addition [45].

In short, the thiol–yne radical click reaction is the formation of a 1,2-dithioether through double addition of thiols on to an alkyne. The reaction has largely been used to generate multifunctional polymer structures. Repetitive thiol–yne reactions are used to form multifunctional molecules, which are further used to make dendrimers [42] or hyperbranched polymers [46].

It has been found that the reactions of thiols with internal alkynes are slower than those with terminal alkynes. These reactions are generally very sensitive to steric crowding. Sulfanyl and related radicals are electron-deficient in nature and



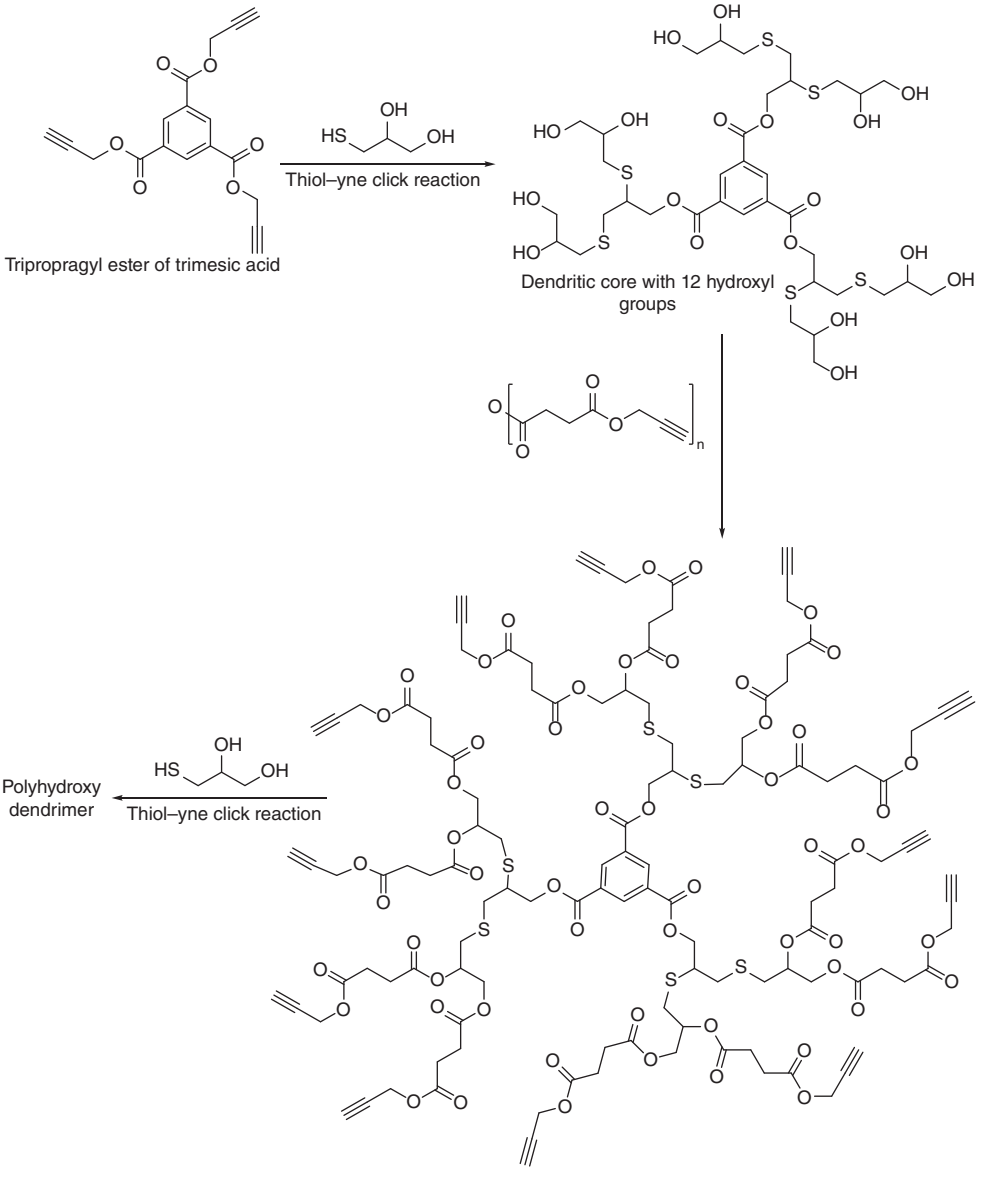
Scheme 1.11 The reaction mechanism of thiol–yne addition reaction.

are more prone to react with electron-rich alkynes. It is, however, possible to effect these reactions on strained internal alkynes, which are not necessarily electron-rich. In one such example, rapid reaction of thiols with cyclooctyne in the absence of radical initiation is reported. The driving force for this reaction comes from the release of strain in the cyclooctyne system [47].

An elegant example for the use of thiol–yne click reactions to form highly functionalized dendrimers was reported by Stenzel coworkers [42]. They used tripropargyl ester of trimesic acid as the core of a dendrimer, which was functionalized with 1-thioglycerol molecules to get 12 hydroxyl functions attached to the dendritic core. The hydroxyl groups were esterified with anhydride-bearing alkyne groups and were further functionalized with thiol–yne click reactions. The method was repeated to get a dendrimer with as many as 192 hydroxyl groups (Scheme 1.12).

1.2.2
Nucleophilic Addition Click Reactions of Thiols

Thiols and thiolate anions are very good nucleophiles. Various click reactions have been developed based on the nucleophilic attack of thiols on to the electrophilic substrates such as epoxides, isocyanates, halides, and Michael acceptors. The reactions are generally initiated by bases, which are added in catalytic amounts or are produced in catalytic amounts by photolatent bases that act as photoinitiators for these reactions [48]. The rates of these reactions are dependent on the substrates

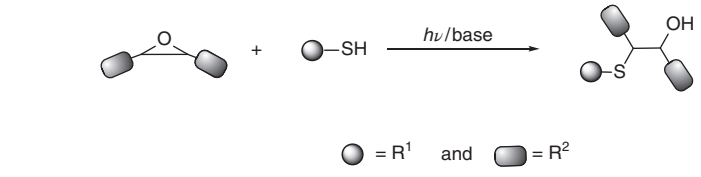


Scheme 1.12 Multistep thiol–yne mediated synthesis of a highly functional dendrimer.

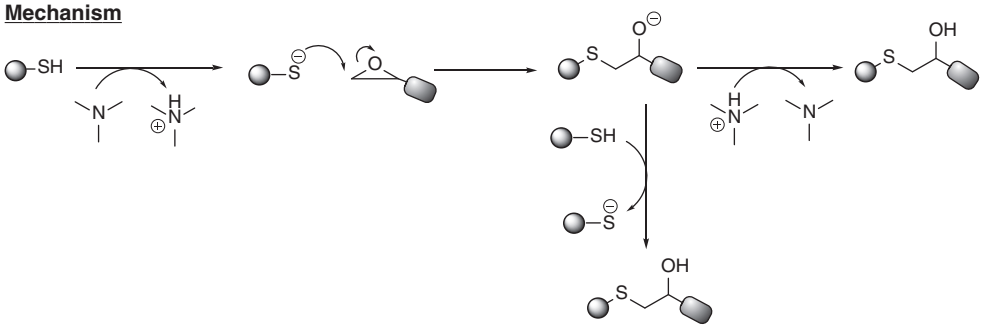
and their inherent susceptibility to attack by thiols and thiolate ions. This section discusses the various click reactions developed based on this concept.

1.2.2.1 Thiol–Epoxide Click Reactions

Epoxides are strained compounds that undergo ring opening reactions in the presence of nucleophiles. These reactions are carried out either in acidic medium, where the epoxide is protonated making it more electrophilic, or using strong anionic nucleophiles. Thiols, which are considerably more acidic (pK_a of RSH ~5–10 and pK_a of PhSH is 6.4) than water ($pK_a = 15.7$) and alcohols ($pK_a \sim 17$) are readily deprotonated to give thiolate ions in the presence of very dilute basic solutions [49]. In general, tertiary amines are used as bases for the generation of thiolate ions. Thiolate ions react immediately and effectively with epoxides following an S_N2 reaction pathway and yielding alkoxide anions with a β-thioether substituent. The nucleophilic attack usually happens on the less substituted carbon of the epoxide. The alkoxide ions are protonated either from a protonated base that was used to initiate the reaction or from a molecule of thiol, which generates another thiolate anion and propagates the reaction (Scheme 1.13) [50].



Mechanism



Scheme 1.13 Base catalyzed thiol–epoxy ring-opening click reaction.

Fringuelli and coworkers have explored the use of InCl3 (Lewis acid), TsOH (Brønsted acid), n-Bu3P (Lewis base), K2CO3 (Brønsted base), and so on, as catalysts in solvent-less conditions for thiol–epoxide click reactions [51].

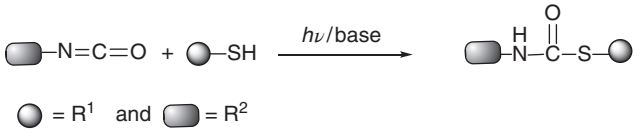
1.2.2.2 Thiol–Isocyanate Click Reactions

Isocyanates are very reactive compounds, which react readily with alcohols, amines, water, and thiols or thiolate ions. Reaction of isocyanates with thiols

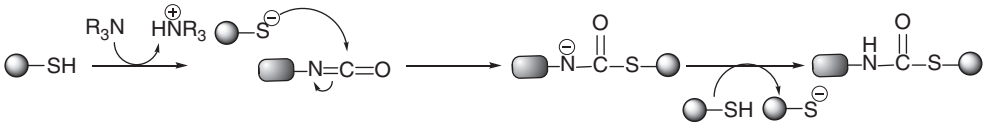
gives thiocarbamates in very high to quantitative yields. This reaction has found its place in organic and polymer chemistry and satisfies all the criteria required to term it as a click reaction. The reaction has a very good potential to be used for modular approaches in surface engineering [52].

Polyurethanes are extremely versatile polymeric materials due to their elasticity, responsive nature toward impact, stretchability, and other possible physical manipulations. They have been utilized in various fields to make optical devices, adhesives, coatings, and also in many biomedical applications. Thiol–isocyanate click reactions have been used to generate polythiourethanes, a sulfur analog of polyurethane, in a very efficient way and in high yields [50].

In the presence of catalytic amount of a base (such as triethylamine (NEt_3)), thiols are deprotonated to thiolate anions, which react with isocyanates forming thiourethanes. The thiol–isocyanate reaction is fast and proceeds readily without any side product even in the presence of water, alcohol, or amines. The most common base used for this reaction is 1,5-diazabicyclo(4.3.0)non-5-ene (*DBN*). The reaction has the potential to be used more often as a very effective conjugation method (Scheme 1.14).



Mechanism

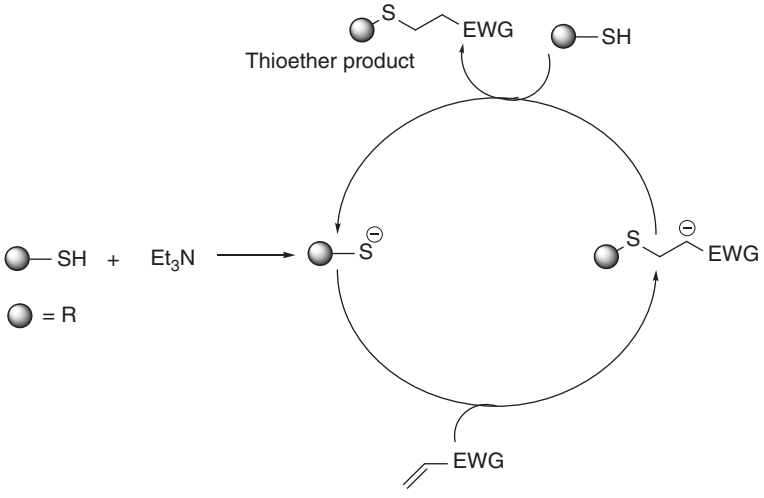


Scheme 1.14 Tertiary-amine-catalyzed thiol–isocyanate click reaction.

1.2.2.3 Thiol–Michael Addition Click Reactions

Hydrothiolation of C=C double bond can be performed in the presence of mild bases or using nucleophilic catalysis. Unlike thiol–ene radical reaction (which can proceed with almost all olefins), thiol Michael addition reactions require activated carbon–carbon double bonds, which are in conjugation with an EWG. In the presence of trialkylamine bases such as NEt_3, the reaction proceeds smoothly to give the addition products in very high yields. On deprotonation of thiols by base such as NEt_3, thiolate anions are formed along with triethylammonium cations. Since thiolate anion is a strong nucleophile, it attacks at the electrophilic β-carbon of the electron-deficient olefin and generates a carbon-centered anion as intermediate. This anion is a strong base thus abstracts proton from either a thiol or an ammonium cation and ultimately forms a thioether product regioselectively

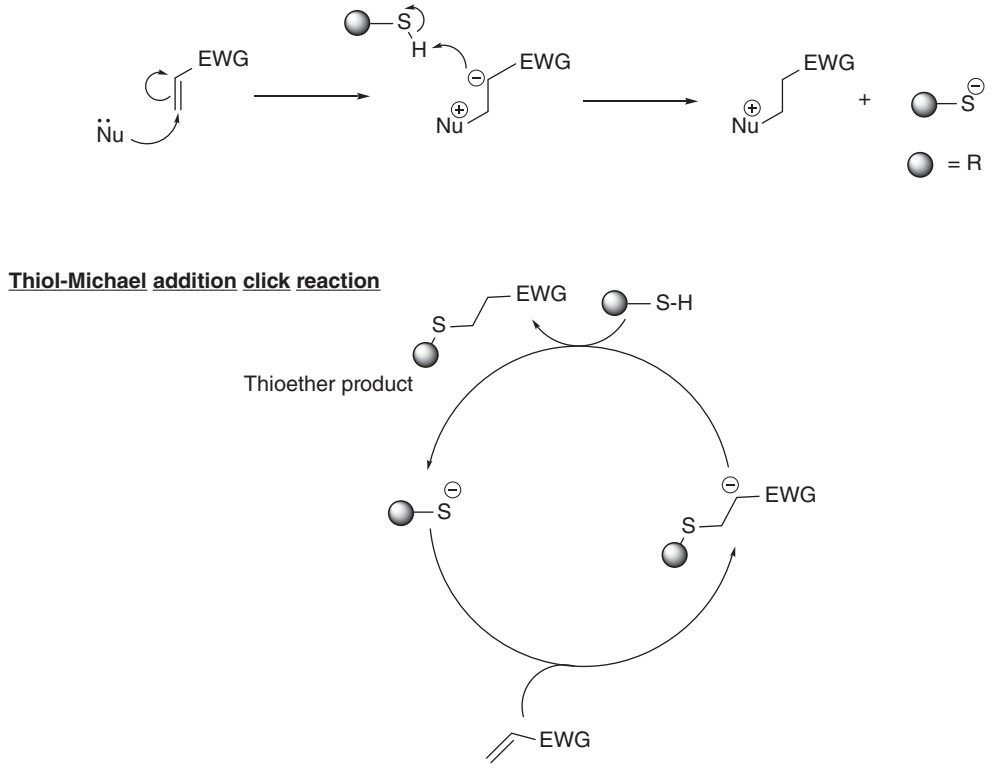
(Scheme 1.15). The final abstraction of proton is thermodynamically controlled and is a fast step. However, the attack of thiolate anion on the Michael acceptor is kinetically controlled. The overall rate and yield of these reactions can be altered by changing various factors such as solvent polarity, pH, strength of the base (catalyst), and nature of EWGs on the C=C bond [53–55].



Scheme 1.15 The base-catalyzed mechanism for the hydrothiolation of an activated C=C bond.

Apart from base catalysis, Michael addition of thiols can also be performed using nucleophilic catalysis. Primary and secondary amines and certain phosphines are the most commonly used catalysts. Nucleophile mediated thiol–Michael addition reactions have extensively been studied. The nucleophiles attack the Michael acceptors to generate a carbanion, which abstracts protons from thiols to generate thiolate anions, which in turn propagate the reaction (Scheme 1.16) [56]. Nucleophilicity of the catalyst plays a crucial role in the kinetics of the nucleophile-based thiol–Michael addition reactions, as stronger the nucleophile, more easily the thiolate anion will be generated.

Chan *et al*. studied bulk reaction of hexanethiol (5 mmol) with hexyl acrylate (5 mmol) in the presence of 0.43 M hexylamine ($pK_a = 10.56$), *n*-dipropylamine ($pK_a = 11$), and NEt_3 ($pK_a = 10.75$) under ambient condition for 500 s. After 500 s, reaction with hexylamine showed approximately 95% conversion, *n*-dipropylamine showed approximately 60% conversion, and NEt_3 showed less than 1% conversion. These amines have almost the same pK_a, but there is a huge difference in their kinetic profiles. Apart from these amines, they also studied various weak nucleophiles, which have varying basicity, such as pyridine ($pK_a = 5.14$), aniline ($pK_a = 9.34$), and 1,8-bis(dimethylamino)naphthalene (a proton sponge with $pK_a = 12.1$), and found that they yield less than 1% conversion. Based on these observations, the catalysis was attributed to the kinetic



Scheme 1.16 Nucleophilic catalysis of thiol–Michael addition reactions.

profile of the catalysts in nucleophilic reactions rather than to their basicity [56, 57]. Stewart *et al*. have reported nucleophilic catalysis of thiol–Michael addition reactions using phosphines [55a].

Owing to the low pK_a values of thiols, thiol–Michael addition reactions can be performed under ambient conditions in water or other protic solvents. However, both base- and nucleophile-catalyzed thiol–Michael addition reaction are affected to some extent by the presence of external protic species, especially the nucleophile-mediated pathway is more affected due to low catalytic concentration of nucleophiles compared to bases in these reactions.

1.2.2.4 Thiol–Halogen Nucleophilic Substitution Reaction

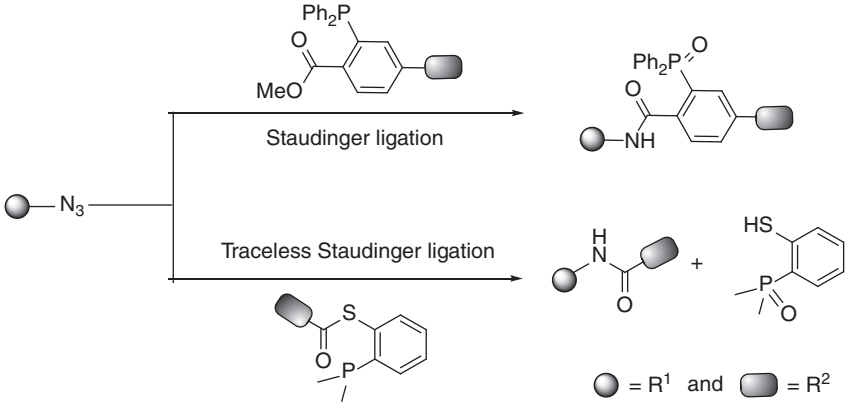
Another example of thiol click reaction is the rapid and efficient substitution of leaving group bearing substrates by thiols, a soft nucleophile [58]. These reactions proceed better in the presence of mild organic bases such as trialkylamines. The halide salts formed during this displacement reactions can be removed easily as precipitates in a very simple and effective manner.

Displacement of bromine by various thiols by S_N2 nucleophilic substitution is definitely one of the best examples of click reaction. These reactions proceed well even in the presence of other nucleophiles such as alcohols and amines, owing to the increased nucleophilicity of thiols and thiolates. 2-Mercaptoethanol and other aliphatic thiol–dialcohol molecules when added to polymers, end-functionalized by halogen atoms, result in selective thiol end-functionalization of polymer chains.

1.3
Miscellaneous Click Reactions

Other than the click reactions mentioned earlier, there are few others that can be included in this list [1].

1) Nucleophilic ring-opening reactions of epoxides, aziridines, aziridinium ions, episulfonium ions, and cyclic sulfates have been included by Sharpless under the category of click reactions. They are termed as *spring-loaded reactions* owing to their increased reactivity resulting from the strain in the ring systems.
2) Nonaldol carbonyl-type reactions such as formation of hydrazones, oximes, amides, ureas, and isoureas are also effective click reactions. A recent report demonstrates the use of oxime-based click reactions for the formation of hydrogels [59]. An eight-armed aminooxy poly(ethylene glycol) was reacted with glutaraldehyde to form oxime-linked hydrogel efficiently. This hydrogel has tunable mechanical properties and can be used to support cell adhesion. Staudinger reaction has also been used by many researchers for bioorthogonal ligation and for synthesis of radiopharmaceuticals (Scheme 1.17) [60–62].



Scheme 1.17 Staudinger and traceless Staudinger ligation click reactions.

Another report incorporating novel hydrazide/hydrazone click reaction was by Benny *et al*. in 2011. This report emphasizes on the high potential of these reactions for labeling biomolecules with $^{99m}Tc(CO)_3$. The hydrazone moiety is stable at physiological pH and unstable under strongly acidic and basic conditions, so can be used efficiently for drug delivery applications [63].

3) Addition to carbon–carbon multiple bonds leading to the formation of three-membered rings (epoxidations, aziridinations), dihydroxylations, nitrosyl–halide addition, sulfenyl–halide addition, and a few Michael additions are also grouped under click reactions [2].

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