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Review Article

Modern Advances in Click Reactions and applications

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ABSTRACT

A mechanism of surface fictionalization, often referred to as click reaction, is the most widely used and accepted synthetic pathways in chemical processes today. This reaction has been used in a variety of synthesis and molecular modification applications, including biosciences, polymer sciences, material sciences, drug delivery, and the list is endless. The azide-alkyne 'click' reaction catalyzed by a metal is the most essential component to this early milestone. It is no exaggeration to claim that click chemistry has prepared the way for modern civilization in chemistry, and is thus an eye opener to current scientific practice. This paper outlines some of the key elements that have contributed to the clicks' character, as well as how they provide certain elements of perspective for scientific applications. As a result, the findings of this study imply that the chemistry of click reactions has emerged as a useful tool in biological and material chemistry.

***Keywords*:** Click reaction; Bio conjugation; Drug synthesis; Macromolecules, Surface fictionalization.

1. Introduction

Most macromolecules were previously produced and used without any modifications to contain relevant functional groups. The majority of old synthetic routes produce a huge number of by-products, some of which have negative consequences. The ability to functionalize the surface of these macromolecules in a technique called "click reaction,"

which was earlier invented by Dr. Barry Sharpless in 2001 [1] as an attempt to explain bio conjugation of molecules, was one of the most important early milestones in the field of chemistry. This method involves reactions that are orthogonal to other organic synthesis reactions and allows for the attachment of a substrate to a specific macromolecule. It is characterized by accelerated thermodynamic conditions that increase specificity and selectivity, and thus obey certain axioms such as mild reaction conditions and non-sensitivity to water and oxygen, high yield with non-toxic by-products, one-pot process, stereospecific and regiospecific, and simple isolation and purification processes [1].

Click chemistry is a synthetic ritual pushed by nature for its efficiency, selectivity, and simplicity, and it does not end with organic reactions. A click reaction is any reaction that allows for the effective ligation of smaller units to macromolecules in a one-pot procedure with simplified reaction conditions. The term "click" refers to reactions that can be carried out without chromatographic purification in safe and easily removed solvents. Click reactions can include a wide range of reactions with different mechanisms as long as they follow a common reaction path [2]. The generations of ureas, oxymes, and hydrazones, as well as addition reactions of unsaturated organic species, are all examples of carbon heteroatom bond building reactions that have been shown eligible to be dubbed click reations. The cycloaddition of alkynes to azides to give 1,2,3-triazoles is the only reaction that meets the criteria for click status, and is hence considered "the cream of the crop" and the best example of click reaction [2].

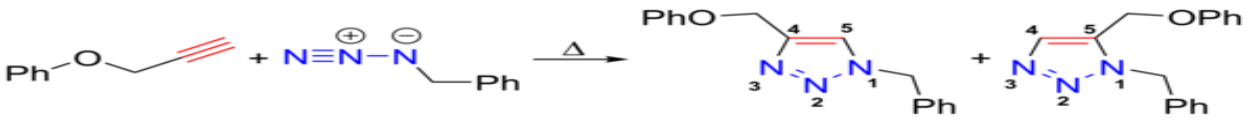


Fig 1. Cycloaddtition reaction of alkyne with azides

By reacting a terminal alkyne with azides, a mixture of 1,4-adduct and 1,5-adduct is generated in the above reaction. Morten claimed that a Cu (I) catalyst is inserted into the system to acquire the regioisomer as the lone product in order to obtain a single product of 1,2,3-triazole. Since its invention, click chemistry has paved the way for the synthesis of a diverse range of products. Its tentacles have spread across a variety of fields, including biosciences, polymer science, material science, drug delivery, and so on. This review will discuss some of the most significant breakthroughs in click chemistry and how they affect society.

2. Features of Click Reactions

i. Highly selective, fast, irreversible, thermodynamically driven reactions (> 20 kcal/mol), reaction "spring-loaded" towards the desired product only, usually exothermic
ii. Mild reaction conditions required (ideally non sensitive to oxygen and water)
iii. No solvent, benign solvent (e.g. water) or easily removed solvent
iv. One-pot process
v. Stereospecific and regiospecific
vi. Quantitative yields, non-toxic by-products
vii. Simple product isolation, ideally no purification required, or use of non-chromatographic methods (e.g. crystallization or distillation)

3. Click Chemistry in Action

3.1 Cycloaddition Reaction

The most common pericyclic reactions in chemical synthesis are cycloaddition reactions. These reactions include the breaking of two bonds and the formation of two bonds by cyclical electron movements in a concerted process involving two systems. Retrocycloaddition reactions are the inverse of cycloaddition processes. Both cycloadditions and cycloreversions take place in cyclic transition states, in which the interacting molecules exchange electrons continuously (Biswanath, 2017). The number of electrons involved in each reacting molecule is used to classify these reactions. To put it another way, Cycloaddition is the act of joining two separate species involving cyclic electron movement and resulting in the production of a new ring via a concerted process [3] .

Because of their tendancy to form several bonds in a single step and as well engender multiple steregenic centres with expected stereo chemical results, cyclo addition reaction is one among the prominent bond-making reactions in organic chemistry. Due to their complexity, cyclo addition reactions have been intensively explored in recent years [4-9] resulting in interesting and contentious disputes.

3.2 Classes of Cycloaddition Reactions

The most prominent cycloaddition reactions are grouped in to three classes as outlined below.

(a) The Diels-Alder (4+2)-Cycloaddition Reaction:

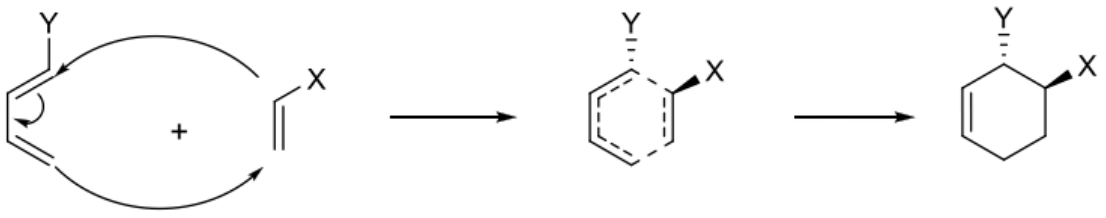


Fig 2. Formation of 6-member ring

(b) The (3+2)-Cycloaddition of 1,3-Dipolar-Compounds

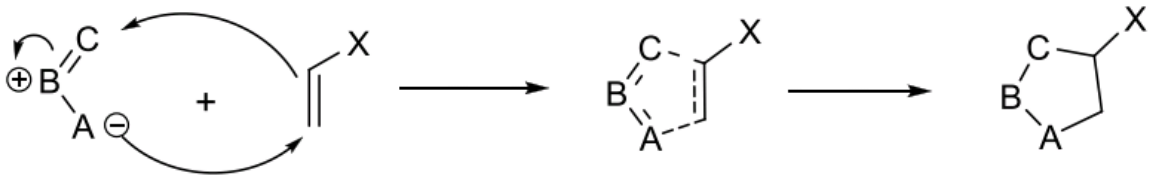


Fig 3. Formation of 5-member ring

(c)The (2+2)-Cycloaddition Reaction:

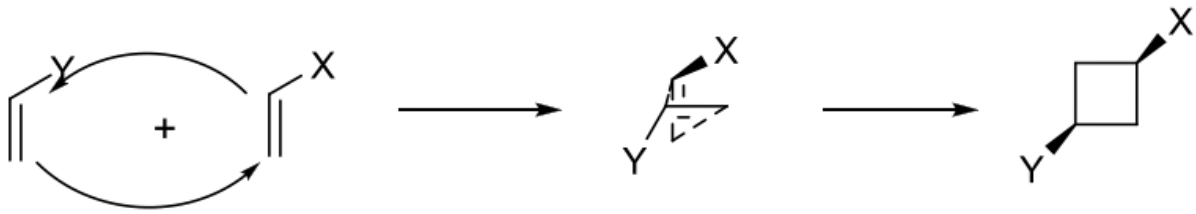


Fig 4. Formation of 4-member ring

Interphase between cycloaddition and Click Chemistry

Cycloaddition reactions are closely related to click chemistry because, like cycloaddition, click reactions require two functional groups to commence the conjugation, which can proceed with or without the involvement of a copper catalyst. The most common click responses are:

Copper (I)-catalyzed Azide-Alkyne Cycloaddition (CuAAC)

Copper (I)-catalyzed reactions CuAAC (CuAcid-Alkyne Cycloaddition) is a classic click reaction discovered and characterized independently by Sharpless and Medal in 2002. An azide and an alkyne are the functional groups involved, which combine to produce a 5-membered ring triazole. Depending on the primary product required, the reaction may or may not be catalyzed. Copper (I) catalysis is essential for increasing the otherwise low reactivity of the functional groups involved and obtaining just the 1,4-regioisomer [10] .

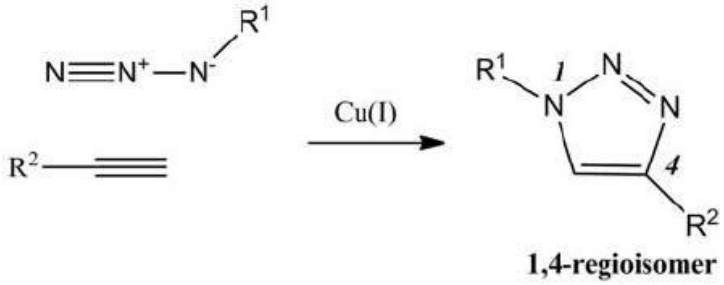


Fig 5. Copper(I)-catalyzed Azide-Alkyne Cycloaddition

When utilizing asymmetric alkynes, the non-catalyzed reaction creates a mixture of 1,4- and 1-5-regioisomers, requires high temperatures and extended reaction periods, and hence

cannot be considered a click reaction. While this is a Huisgen 1,3-dipolar cycloaddition, the copper (I) catalyzed click form does not fit into this category because it is not concerted [11].

Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC)

Bertozzi and colleagues invented the Strain-promoted Azide-Alkyne Cycloaddition (SPAAC) as the first copper-free bio-orthogonal click reaction to solve the cytotoxicity difficulties associated with copper ions in living systems. An azide and an alkyne are inserted into a stretched ring in this click reaction. Because cyclooctyne has the smallest stable alkyne ring, it's usual to use cyclooctyne-based reagents in click chemistry [10] .

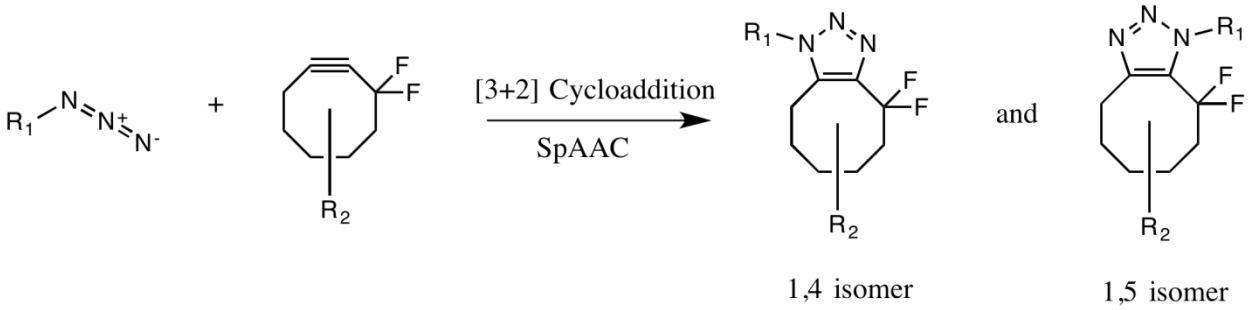


Fig 6. Strain-Promoted Azide-Alkyne Cycloaddition

The enthalpic release of ring-strain, rather than the copper (I) catalyst, drives the click reaction. The system is transformed from a ring-strain to a more favorable fused ring system with a low activation energy (E = 8.0 kcal/mol). In the absence of a catalyst, SPAAC reactions have a second order reaction rate constant of roughly 0.1 M–1 s–1, making them slower than CuAAC reactions [12] .

SPAAC reactions are extremely convenient since they may be used in a living system (both in vitro and in vivo) and do not induce cytotoxicity. SPAAC reactions, on the other hand, lack regioselectivity, resulting in a mixture of 1,4-substituted products. Furthermore, cyclooctyne reagents cost more than linear alkynes. The fact that cyclooctyne derivatives react with reduced cysteine via a thiol-yne mechanism is another disadvantage. Preincubation with iodoacetamide is recommended as a partial solution to this problem [13].

Strain-Promoted Alkyne-Nitrone Cycloaddition (SPANC)

A click reaction between a nitrone (acyclic or endocyclic) and a diaryl-strained-cyclooctynes, such as DIBO, is known as the Strain-Promoted Alkyne-Nitrone Cycloaddition (SPANC). N-alkylated isooxazoline is the end product [10].

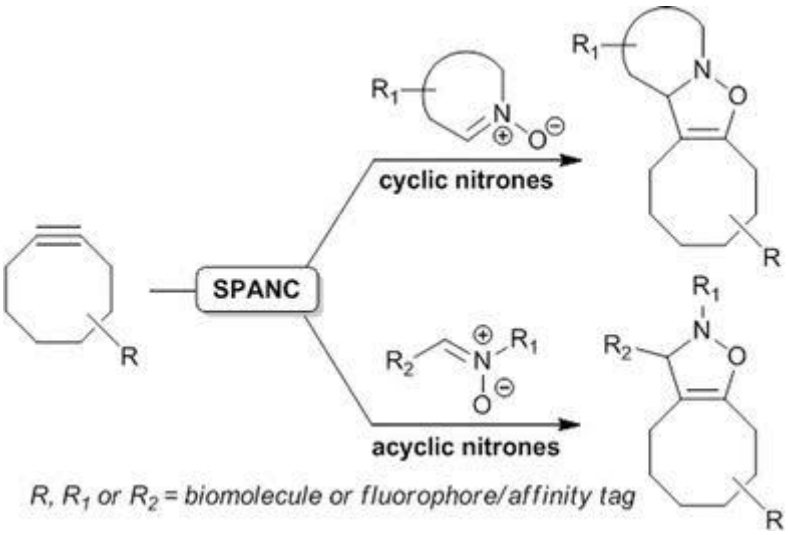


Fig 7. Strain-Promoted Alkyne-Nitrone Cycloaddition

The reaction is bio-orthogonal, which means it is compatible with living systems because no catalyst is required. As with SPAAC, the driving force is the enthalpic release of a ring-strain. With bimolecular rate constant (k2) values as high as 60 M–1 s–1, the reaction is quicker than CuAAC and SPAAC. It has been discovered that when cyclic nitrones are utilized, reaction rates are faster than when acyclic nitrones are used. The reagents, particularly endocyclic nitrones, are stable in biological environments and can be adjusted by functionalizing the nitrone dipole's carbon or nitrogen atom. Because of the comparatively low temperature stability of the N=O bond associated with the system, several cycloadduct products are prone to rearrangement [10].

[3+2] cycloaddition of alkene and azide

An activated alkene, such as norbornene, is first reacted with an azide in the alkene and azide [3+2] cycloaddition. The [3+2] cycloaddition produces an intermediate that is retro-Diels–Alder reacted to produce a mixture of 1,2,3- and 1,4,5-triazoles. The reaction is slower and non-chemoselective than SPAAC. Oxanorbornadiene has the benefit of being easier to synthesize than the cyclooctyne derivatives in SPAAC [14] .

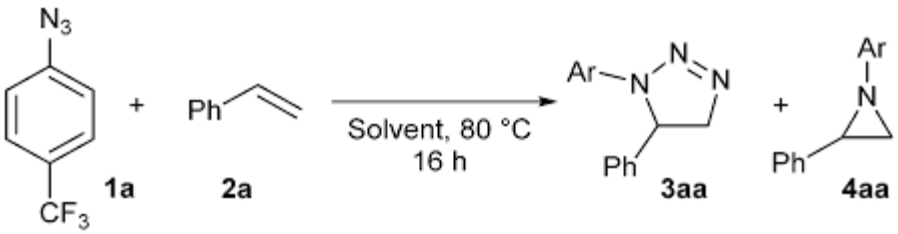


Fig 8. [3+2] cycloaddition of alkene and azide

Inverse-Electron-Demand Diels–Alder (iEDDA)

The inverse-Electron-Demand Diels–Alder (iEDDA) reaction involves a tetrazine and either a strained cyclooctene or an activated alkene. Trans-cyclooctene, unlike cis-cyclooctene, is extremely reactive due to ring tension. After forming an intermediate, nitrogen extrusion and tautomerisation produce the final product quickly. The most significant benefit is that the reaction rate is orders of magnitude faster than any other Cu-free click chemistry reaction. Photoisomerization may, however, occur with this system. Another strained alkene used in this click reaction is methylcyclopropene, which has the benefit of being tiny. Methylcyclopropene is hence valuable in enzymatic applications [15] .

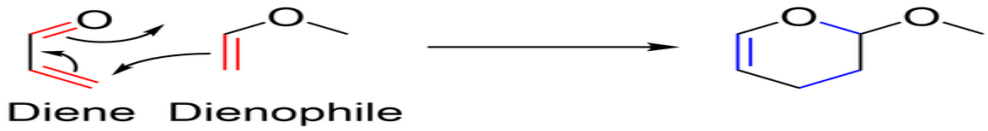


Fig 9. Inverse-Electron-Demand Diels–Alder (iEDDA) [16] (Mark Ondari 2017).

Photo-click reaction with alkene and tetrazole

Huisgen described the photo-click reaction between alkene and tetrazole as a dipolar addition. Unless conjugated with a carbonyl group, terminal alkenes are tiny and inert. When UV light activates tetrazoles, they produce nitrogen gas and a nitrile imine, which rapidly combines as a 1,3-dipole with the alkene to form a pyrazoline cycloadduct in a cycloaddition reaction [2] .

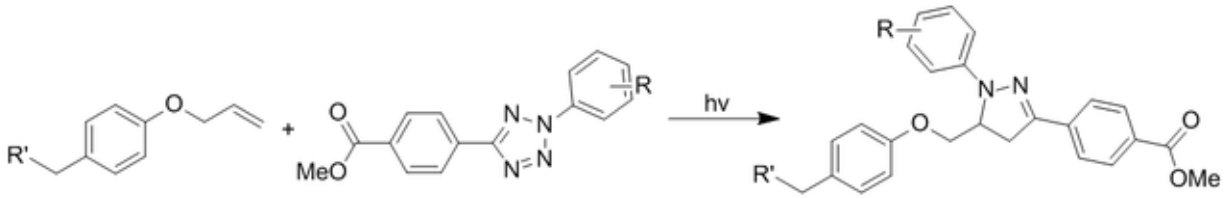


Fig 9. Photo-click reaction with alkene and tetrazole [17]

Because the intermediate synthesis is quick and UV light is only required for a brief time, it is compatible with living systems, as prolonged UV exposure causes cellular damage. The pyrazoline product is luminous, which is a desirable property for reactions carried out in biological systems [2] .

Thiol Chemistry in Relation to the Click Reaction

In the periodic table, sulfur and oxygen are in the same group. As a result, sulphur-containing molecules should exhibit characteristics comparable to oxygen compounds. The chemistry of the SH function, on the other hand, is very different from that of the OH

function. Organic molecules containing the SH group are called thiols in the IUPAC system, or mercaptans in earlier terminology [18,19] .

Thiols interact with several compounds as well as a variety of functional sites. These interactions often yield high product and it is of cause simple to initiate. A lot of these processes are performed in a safe environment and have been used in ordinary organic synthesis, surface functionalization and polymerization Thiols' wide spectrum of reactivity makes them excellent conjugation tools, but it also leaves them vulnerable to a variety of side reactions. Thiols, particularly low-molecular-weight compounds, have a bad odor and poor self-stability. Most of the downsides may be avoided with proper substrate selection and treatment, leaving thiols as useful components of the click chemistry toolbox [19]. Categoricaly, thiol’s interaction with other compounds can be grouped into two: radical reactions and nucleophilic reactions. Under specific reaction conditions, radical reactions are selective for some groups and at same time, considering a huge number of other functional groups [18,19].

Thiols' Radical Click Reactions

Photoactive or light initiated reactions of alkenes and alkynes are often observed to follow a smooth path. This reaction which is often preferable for surface functionalisation applicable in bioconjugation, do not require any transition metals as catalysts. Extreme pH conditions, and reducing tendencies do not break down thioether bonds formed in these processes. These processes have been used to tailor solid surfaces with specific characteristics, immobilize macromolecules like proteins, and perform surface engineering and patterning. Srinivasan [19].

Radical Click Reaction of Thiol–Ene

The anti-Markovnikov addition of a thiol to an alkene to generate a thioether, also known as alkene hydrothiolation, was used in this reaction. The initiation stage is triggered by direct irradiation of thiols with a UV rays, ideally at 254 nm, the reactions can be started. When thiols are irradiated, the S–H link is homolyzed, leading to the formation of the thiyl as a radical [18] . Cramer and coworkers were the first to report that UV light of low wavelengths causes thiols to self-initiate radical reactions. Thiyl radicals react with alkenes in a regioselective manner that allows for a variety of functional groups. The reaction specifications are mild whereas water and oxygen are both acceptable. These traits, as well as the self-initiation behaviors of thiols have allowed the thiol–ene reaction to be a very useful tool for click reactions [19].

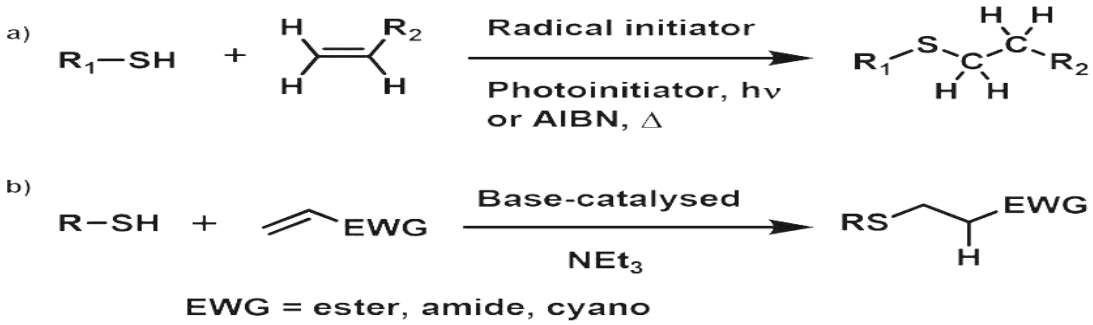
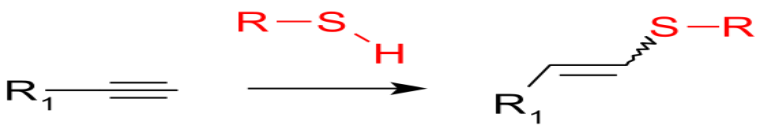


Fig 10. Radical Click Reaction of Thiol–Ene [20]

Through radical recombination events, thiol–ene radical reactions can sometimes produce undesirable by-products. The reversibility of the thiyl radical-olefins addition reaction can only be distorted by the extraction of a hydrogen radical from another thiol by the free radical product created, resulting in the formation of a another product called thioether thereby, spreading the radical reaction [21]. Even though it is preferable to trigger the initiation process by irradiating thiols directly, the reaction rates are generally slow due to the slow rate of radical generation. Using a mixture of light and a photoinitiator can greatly boost therates. The usage of hydrogen-abstracting initiators like benzophenone was used in the early investigations and applications [19].

Radical Click Reaction Thiol–Yne

The thiol-yne reaction, also known as alkyne hydrothiolation, is an organic interaction that occurs when a thiol reacts with an alkyne, analogous to the thiol-ene reaction. An alkenyl sulfide is the reaction result. The reaction was first described in 1949 [22 and was rediscovered in 2009. [23] It's employed in click chemistry and polymerization, especially with dendrimers [24]. The starting step for thiol–yne radical reactions is identical to that of thiol–ene reactions. After adding a thiol to the alkyne and forming a vinyl radical or a sulfanyl radical species. The addition mode is anti-Markovnikov. Secondary reactions such as cyclisation can be initiated by the radical intermediate [25] . The 1,2-disulfide or 1,1-dithioacetal develops after diaddition. Triethylborane, indium(III) bromide, and AIBN have all been reported as catalysts for radical additions. Cationic rhodium and iridium complexes, as well as thorium and uranium complexes, have been observed to catalyze the process [26].



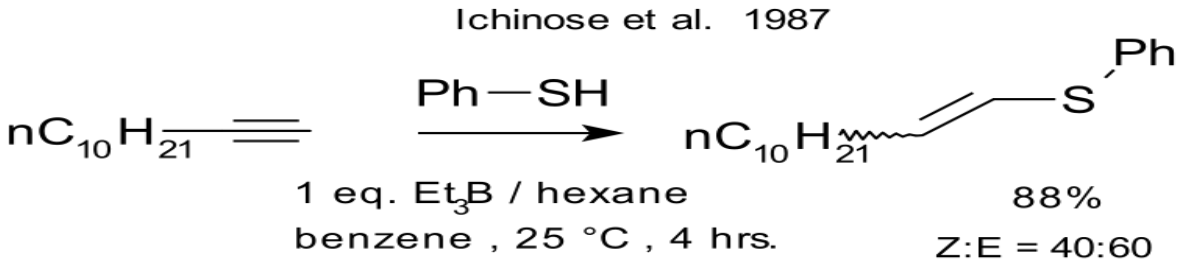


Fig 10. Radical Click Reaction Thiol–Yne

Thiol Nucleophilic Addition Click Reactions

Nucleophiles thiols and thiolate anions are excellent. A lot of reactions with the clicks status that rely on the nucleophilic reactions between thiols and electrophilic substrates such epoxides, halides, isocyanates, and Michael acceptors have been devised. The photoinitiation process depend on Bases, which are synthesis and introduced in catalytic amounts. The pace of these reactions is determined by the substrates' natural susceptibility to thiol and thiolate ion assault. This section goes over the numerous click reactions that have been designed using this principle [19].

Nucleophilic Thiol–Halogen Substitution

The exchange of outgoing specie carrying substrates by thiols, a mild nucleophile, is otherwise an illustration of click reaction of thiol [27]. Trialkylamines which is a mild base, help these reactions go more smoothly. The halogen salts generated via the dislodgment processes is of cause removed easily as precipitates. The most prominent of this technique, is the displacement of bromine by different thiols via SN2 nucleophilic substitution. Due to the higher nucleophilicity of thiols and thiolates, these reactions occur efficiently even in the presence of alcohols and amines as organic nucleophiles [19].

Click Reactions of the Thiol–Michael Addition

Unlike the thiol–ene radical reaction (occurring with practically any olefin), thiol Michael addition reactions necessitate activated carbon–carbon double bonds in conjunction with a EWG. In the presence of trialkylamine bases such as NEt3, the reaction proceeds smoothly, yielding very high yields of addition products [19]. Thiolate anions and triethylammonium cations are produced when thiols are deprotonated by a base such as NEt3. Because the thiolate anion is a powerful nucleophile, it attacks the olefin which is an electron-deficient electrophilic -carbon and produces a carbon-centered anion as an intermediate. Because the strong nature of this anion, it can extract proton from a thiol to regioselectively form a thioether. [19].

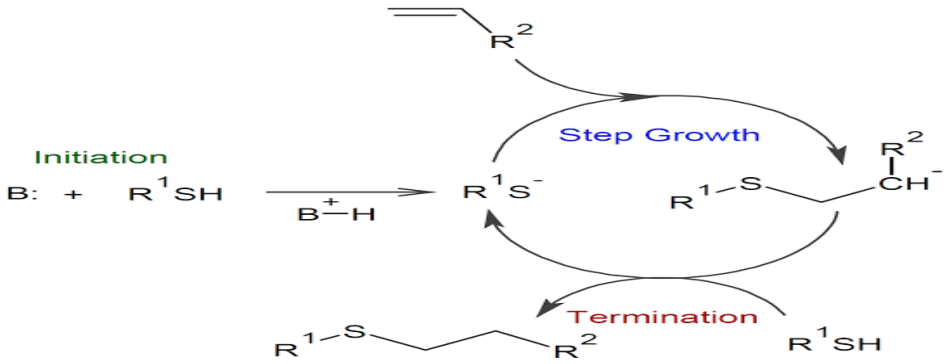


Fig 11: The Thiol–Michael Addition

Click Reactions of Thiol–Isocyanate

A lot of compounds such as Alcohols, amines, and thiolate ions quickly react with isocyanates. Isocyanates react with thiols to produce thiocarbamates in huge amount. This reaction has established itself in materials, organic and polymer science, and it meets a good number of requirements to be classified as a click reaction. The reaction offers a lot of tricks for modular surface functionalization and engineering applications [28] .

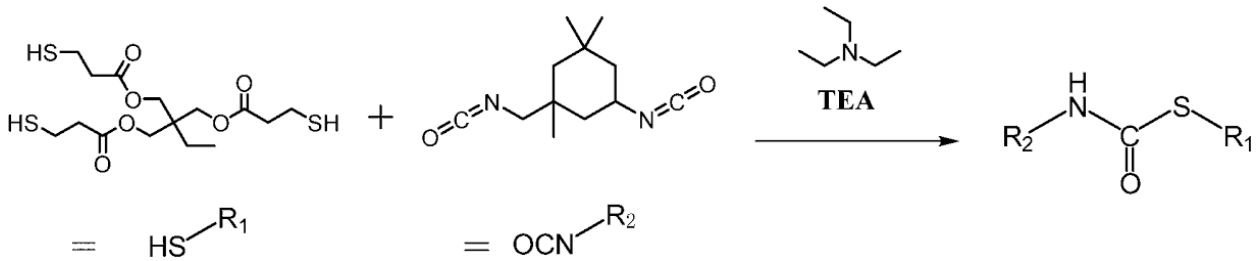


Fig 12. Click Reactions of Thiol–Isocyanate

Click Reactions of Thiol–Epoxide

Epoxides are stretched compounds that, in the presence of nucleophiles, perform ring opening events. The epoxide becomes more electrophilic by protonation, or powerful anions are used in these reactions. With the help og dilute basic solutions, thiols, which are significantly more acidic than water and alcohols, quickly deprotonate to yield thiolate ions [29]. The bases utilized in this case are tertiary amines for the production of thiolate ions. Following an SN2 reaction route, thiolate ions interact quickly and successfully with epoxides, giving alkoxide anions with side chain -thioether. The nucleophilic assault normally occurs on the epoxide's less modified carbon. The alkoxide ions can be protonated in two ways, either by a protonated base that started the reaction or by a thiol molecule, which produces an anion that propagates the reaction [19].

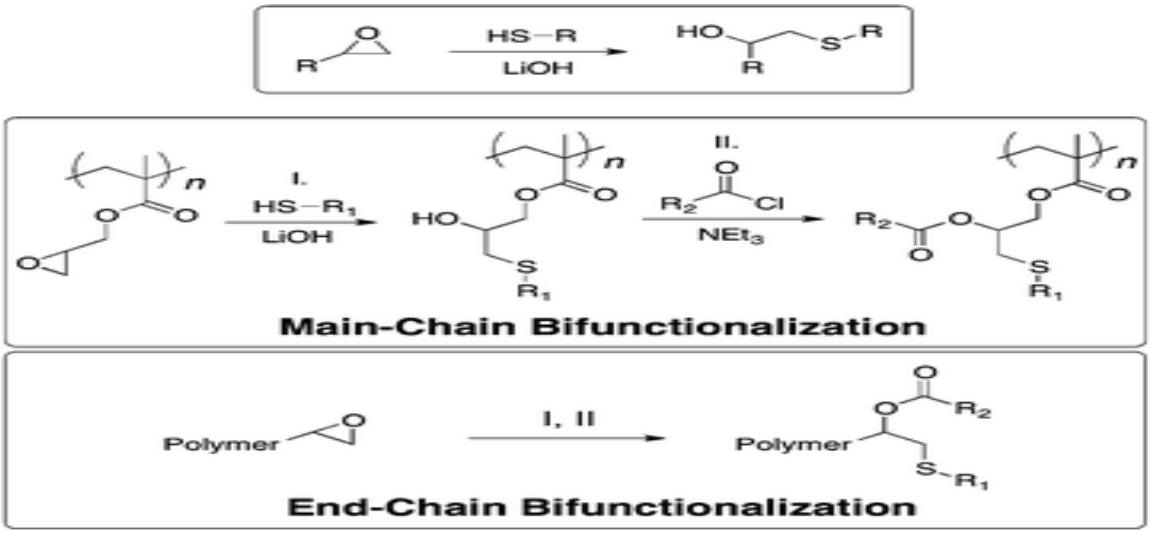


Fig 13. Click Reactions of Thiol–Epoxide

Nucleophilic Ring Opening

Sharpless classified a lot of ring-opening nucleophilic reactions as click reactions. Because of the increased reactivity caused by the tension in the ring structures, they are called spring-loaded reactions. Examples of such compounds that undergo nucleophilic ring opening reactions include epoxides, aziridines, and so on.

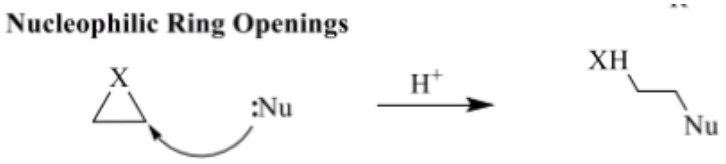


Fig 14. Nucleophilic Ring Opening

Carbonyl Chemistry of Non-Aldols

Click reactions involving non-aldol carbonyls, such as the creation of hydrazones, oximes, amides, ureas, and isoureas, are also successful. A new study shows that oxime-based click reactions can be used to make hydrogels [30] . To make an oxime-linked hydrogel, an eight-armed aminooxy poly(ethylene glycol) was treated with glutaraldehyde. This hydrogel can be utilized to assist cell adhesion and has customizable mechanical properties. Many researchers have employed the Staudinger process for bioorthogonal ligation and radiopharmaceutical production. Benny et al. published another paper in 2011 that included a unique hydrazide/hydrazone click reaction. The significant of these processes for tagging biological molecules with 99mTc (CO)3 is highlighted in this report. Due to the stability of the hydrazone moiety at physiological pH and instability under extreme pH conditions, it can be effectively used in medication administration [31] .

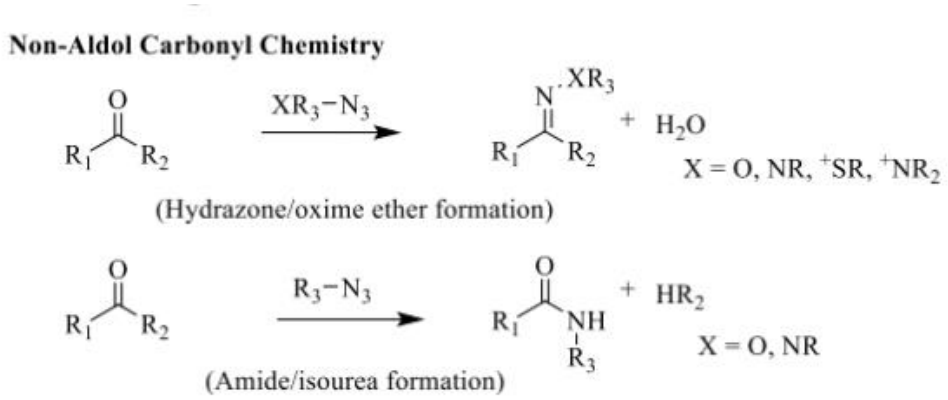


Fig 15. Carbonyl Chemistry of Non-Aldols

Multiple carbonyl bonds Addition

Click reactions include add to carbon–carbon multiple bonds that result in the formation epoxides, aziridins, which are mostly three membered ring. dihydroxylations, nitrosyl–halide addition, sulfenyl–halide addition, and a few Michael additions are also considered as reactions with the click status [19].

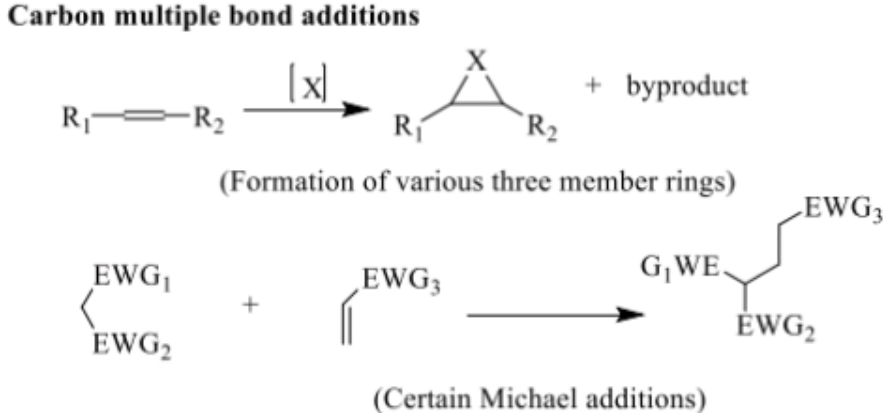


Fig 16. Multiple carbonyl bonds Addition

4. Click Chemistry in Practice

Bioconjugation

Bioconjugation is a vast field of study relating the production of covalent bonds between bio-molecules and synthetic pathways at the intersection of chemistry and molecular biology. It entails selective, rapid, and high-yielding biocompatible reactions that link substrates to biomolecules [32]. Surface functionalisation of a tiny molecular probe to a biological polymer or coupling an intricate carbohydrate with a proteins are examples of covalently linking two molecular entities that molecular biologists and chemists face when researching biological systems. Because of the wide range of functional reactivity and structural complexity, specific ligation reactions must be discovered to facilitate the connection functional groups in a solution under specified conditions [33]. For effectiveness within the

complex environment of living cells, the functional groups must be bio-compactable with each other and of cause the living system.

Exosomal Bioconjugation

Exosomes are membrane vesicles with a diameter of 30 to 100 nanometers that are released by cells and found in most, if not all, bodily fluids, such as blood, urine, and saliva. They are thought to aid communication between cells because of the believe that they carry functional information/cargo such as proteins, mRNA, and miRNA to recipient cells [34]. Exosome surface functionalization has been recorded via Click Chemistry in recent years. Due to quick reaction speeds, metal catalysed azide alkyne cycloaddition has been considered as an excellent tool for clicking small compounds and macromolecules to the surface of exosomes, according to [35]. The size of exosomes did not alter after conjugation, nor did the level of exosome interaction with recipient cells, implying that the specifications were both structurally and functionally friendly on the exosomes [35].

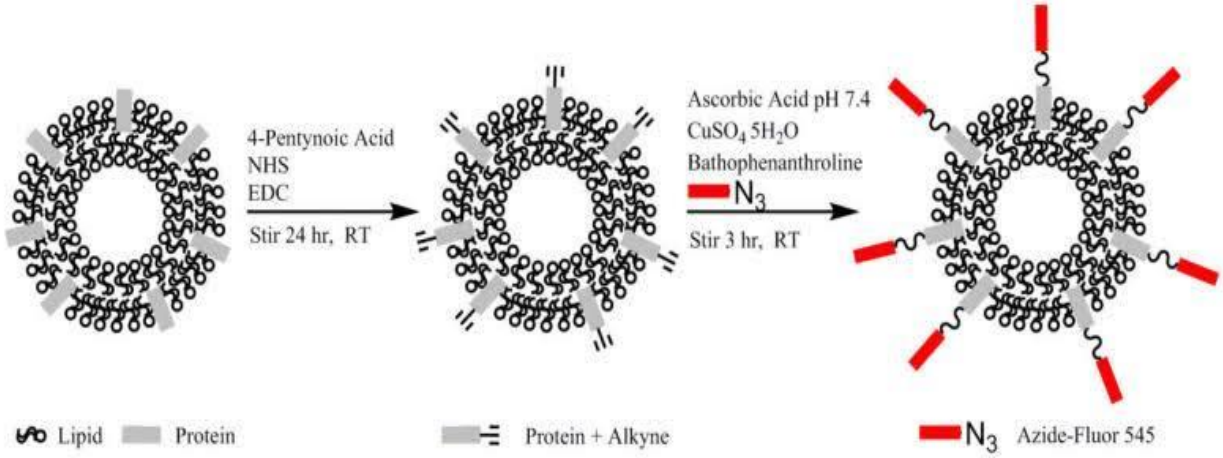


Fig 16.Mechanism of Exosomal Bioconjugation

Additional Interests

Sina Elahipanah and colleagues devised a pattern for high-yielding, and robust reactions of the clicks nature, which hanged on the smart and effective attack on amine active side by a functionalized dialdehyde group [36]. This click reaction occurred with high stability and yield initited by dialdehyde reagent and dialdehyde click conjugates in a solution containing organic solvents under mild situation. This reaction occurs in the absence of a catalyst or dialdehyde group which is activating in nature, and the only result is water.

Yuan Liu and colleagues used colloidal nanoparticles to develop a thiol-ene reaction which is cysteine-selective in nature hence, a bioconjugation with the clicks status [37].The thiol-

ene-based enzyme nanoconjugates and aptamer that resulted both have outstanding enzymatic activity and target binding capabilities.

Bioconjugates made from nanomaterial reactions have immense potential in sectors like materials science and biology. The thiol–stability ene's and high selectivity make it a promising option for use in various aspect of nanotechnology bioimaging, bioanalysis, and so on.

The pattern for coupling smaller units to larger biological molecules has changed dramatically, thanks to bioorthogonal processes. Low-molecular-weight chemicals cannot elicit a subsequent, adaptive immune response by themselves therefor, the coupling of various epitopes convaying helper T-cells resulting in the formation of IgG [38]. Proteins like as globulins, albumins, and hemocyanins, as well as viruslike particles and toxoids, are the most prevalent carriers.

The most extensive protocol for bioconjugation of tiny molecules has been the existence of the possibilities to bind an amine to hepten under mild reaction conditions [39]. Daniel and colleagues reported that CuAAC reaction is the most prominent way for combining protein and hapten together which can be employed in the formation of appropriate antibodies for immune-diagnosis [40]. These findings show that the triazole moiety's role in antibody interaction is less important than previously thought and hence, paved the way for the development of very important biotechnological immunoreagents for additional relevant substances such as biotoxins, antibiotics, and medicines using hitherto unexplored chemical methods incorporating novel attachable linkers and functionalized hepten sites. Further research will undoubtedly help to clarify the generalizability of the technique described here. Most of the binding sites as well as the nucleophilic and basic properties utilized in these reactions are of cause crucial to the primary amine. [41].

Some of the techniques used for the surface functionalisation of a biological molecule by an amine active group have contributed to the millstones we see today in various field of applied sciences hence, the synthesis of compounds containing primary amines, as well as approaches for devising chemical processes to react with primary amines, have received a lot of attention. The ligation of primary amine to various biological molecules has become so promising and useful, as we can see with various metabolites, amino acids, and so on. Credit to the ubiquity of the amine active group [42].

Material science and polymer chemistry

Polymer modification has been used to transform natural occurring materials into product with highly esteemed characteristics since the dawn of human technological development.

From the time of civilization, polymers from petroleum by-products undoubtedly became prevalent in a wide range of technological applications. Developments in polymer enhancement have attracted a lot of interest to imbue industrial polymers with various and largely favorable qualities [43]. The qualities of polymer material fabrications today hang on the extent of polymer modification which is of cause a function of click reaction in the long run. As this tends to increase the modulus and mechanical tolerance of various polymeric materials. In this regard, effective chemical techniques are always important when covalently manipulating polymer substrates to impart desired features. Polymer enhancement to meet certain features after polymerization reaction is one of the crucial tasks performed in macromolecular and material science. The click reaction involving azide and alkyne which is metal catalyzed is the most significant contributor to this goal. [44] defined polymer modification as "the chemical manipulation of polymers to produce functional variety." Chemical couture of a polymer structure is typically done to give the processed material better qualities like reactivity, stability to heat, resistance chemical and biological attacks and so on. Polymer modification is a field of science that spread its tentacles to a lot of disciplines such as materials chemistry, chemical engineering, physics, biology, and medical sciences to improve current qualities for on-demand end-goal applications [45].

Click chemistry techniques are a collection of chemical reactions that share several key characteristics, which makes them to be simple, orthogonal, economical, ragioselective and sterioselective in nature. Various reactions products have similar properties with this reactions but the most potent of all these is the product obtained from the cycloaddition reaction invoving alkyne and azide which have gained wide usage in chemistry of polymers. These reactions can be catalyzed by transition metals which can be referred to as copper(I)-catalyzed alkyne–azide cycloaddition or may be due to ring strain of cyclic alkynes also called strain-promoted alkyne–azide cycloaddition.

A lot of polymeric materials have been fabricated using the copper (I)-catalyzed alkyne–azide cycloaddition click reactions. This make the reaction to gain a lot of acceptance in various aspect of material technology [46] therefor, functionalization of polymer is of enermouse advantage as it specified and enhance most of the properties of the polymer material required for application in sectors like construction, automobile, and so on.

The cycloaddition of a diene and a dienophile otherwise called a Diels–Alder reactions is crucial for equivalents carbon–carbon bond forming processes, which are fundamental features of click technique. Because of the advantage attached to this reaction as well as it

efficiency, mild conditions and its reversibility activated by heat, this reaction have been exhaustively applied in diverse surface modification of polymeric materials. [47].

Thiol-X reactions, which can infer thiol interactions with alkenes, alkynes, halo compounds, or epoxides, have gained popularity in polymer science, resulting in quick and resilient methods [48]. Surface modification of the polymer architecture, nanoparticles coated with polymers, as well as crosslinked materials are among the many uses of these processes. The click techniques used in polymer science aren't just for these frequent reactions. Other reactions for the production and modification of macromolecular structures include hydrazone and oxime-based carbonyl chemistry, as well as sulfur(VI) fluoride exchange reactions [49]. The click chemistry notion appears to be a continuing chemical phenomenon that perpetually proposes novel chemical reactions, with polymer science showing potential for its use.

Drug Distribution

Today, click chemistry plays a significant role in addressing the demands of chemical research, particularly in drug production. It makes use of two of active sites which react quickly and either regioselectively or sterioselectively (click's behavior) with one another in both aqueous and organic solvents. The selectivity, reactivity, biocompatibility, and stability of each click reaction are all factors in their selection [2]. By making it simple to synthesize building blocks for novel chemical entities, click chemistry has considerably aided the overall drug development process (NMEs). Despite the fact that it has not completely replaced traditional drug synthesis approaches, it has enhanced and expanded them by assisting with excellent invention, discovery and maximization of the process [2].

Nano-systems that release cancer treatments in response to external stimuli have distinct benefits over traditional carriers, which release their payload passively. Drug loading and release applications have been demonstrated to be optimal for reduced graphene oxide (rGO) nanosheets with restored sp2 networks. (Teodorescu and colleagues, 2015) Because effective covalent modification of the rGO depends on, the non-covalent - stacking modification approach of scaffold which have been widely investigated [50]. This method, in one way or the other has proven to be efficient for molecules that can create effective non-covalent interactions. It's difficult to conjugate compounds that can't form such interactions with rGO.

The azide-alkyne-based modification of rGO was successful, however employing copper metal could be problematic as a catalyst for medical applications because any trace of copper can increase the cytotoxicity of nanostructures. This involves creating click reactions that

exclude the use of any form of catalyst during the modification process hence, the use of strain-promoted azide-alkyne cycloaddition (SPAAC) has been explicitly encouraged [51].
In bio-conjugations, nucleophilic thiol-ene based processes using the thiolmaleimide functional group dyad have been widely used. This clickable-rGO construct is an appealing contender for a variety of practical applications due to its ease of manufacture and functionalization to quickly produce a functional material in a modular form. A strain-promoted click chemistry-based metal-free "click" conjugation process was investigated as a simple and quick tool for surface modification of encapsulated drugs, micro bubbles, nanoparticles, siRNA-encapsulated micelles, protein molecules the list is endless [51]. The use of copper-free click chemistry in conjunction with metabolic labeling has opened up new medication delivery possibilities.

Alcaraz and colleagues investigated whether cubosomes modified with azide or DBCO functional groups could perform copper-free click reaction using strained cyclooctyne or azide, respectively [52]. Phytantriol-based cubosomes were functionalized with azide or DBCO-containing phospholipids. The efficacy of "click ability" was determined by reacting cubosomes with a complimentary dye and using size exclusion chromatography to determine bound and unbound dye [52]. Haichang Ding and colleagues reported a unique dual pH- and thermo-responsive hydrogel system [53]. Under UV irradiation, the thiol groups in PNIPAM and the allyl groups in OAL-CS may quickly construct a crosslinking hydrogel network using "thiol-ene" click chemistry. Temperature and pH could be used to adjust the swelling ratio of the OAL-CS/PNIPAM hydrogel. Finally, vanillin release tests were performed to demonstrate the bio based materials' potential for drug delivery applications [53].

5. Conclusion

This versatile reaction is expected to have a long life in the context of the synthesis of complex and functional molecular architectures. The utilization of click chemistry provides an efficient an acceptable evidence of its contribution towards surface modification in organic chemistry, and polymer research during the last few years. For decades, chemists frustrated by the widespread and usage of protecting group techniques were attracted towards inventing new processes that could aid their synthesis hence, the search for reactions with the click's status. At least a noticeable step in this direction has now been made with the introduction of the azide-alkyne bioconjugation reaction, which specifies the immense influence this reaction already had in its early days. This reaction has been cleverly used to make a variety of compounds easier to make. Additional click chemistry reactions are being researched more

and more, which is beneficial in broadening the variety of accessible binding sites that can be used during chemical reactions. Hence, click chemistry is considered valid for application in biological and material chemistry.

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