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Review Article

TRENDS OF CLICK SYNTHESIS: A REVIEW

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ABSTRACT

Click chemistry has become a unique and efficient modern chemistry technique for chemical synthesis of complex molecules. Click chemistry must wide in scope giving high yield with a variety of starting materials. It must be easy to perform, be insensitive to Oxygen or Water, and use only readily available reagents. Reaction work-up and product isolation must be simple, without requiring chromatographic purification. Several reaction are fit the concept of click chemistry better than others. Such types of reaction like Cycloadditions of unsaturated species, especially 1,3-dipolar cycloaddition reactions, Diels-Alder reaction Nucleophilic substitution-ring-opening reactions such as epoxides, Carbonyl chemistry of the non-aldol type, Additions to carbon- carbon multiple bonds, such as epoxidation and Thiol-ene click reactions.

Keywords: chromatographic purification, cycloaddition, nucleophilic.

INTRODUCTION

The concept of click chemistry introduced by Professor K. B. Sharpless is similar to quickly assembling (clicking) small building blocks together to make a larger structure. K Barry Sharpless and his co-workers have discovered and developed many widely used catalytic oxidation processes including the first general methods for stereoselective oxidation the Sharpless reactions for asymmetric epoxidation, dihydroxylation, and aminohydroxylation of olefins. His mentors at Dartmouth College Stanford University (PhD in 1968 and postdoctoral research) and Harvard University (further postdoctoral research) and Prof. T. A. Spencer, Prof. E. E. van Tamelen, Prof. J. P. Collman, and Prof. K. Bloch, respectively.

Before 1990, when he became W. M. Keck Professor of Chemistry at The Scripps Research Institute, Prof. Sharpless was a member of faculty at the Massachusetts Institute of Technology (MIT) and Stanford University. Prof. Sharpless's honors include the Chemical Sciences Award of the National Academy of Sciences (of which he is a member), the Roger Adams and Arthur C. Cope Awards from the American Chemical Society, the Tetrahedron Award, the King Faisal Prize, the Prelog Medal, the Wolf Prize, and honorary doctorates from five American and European universities.

The Sharpless research group involved in search for new homogeneous oxidation catalysts and for transition metal catalyzed asymmetric processes. Click chemistry is a chemical philosophy introduced by K. Barry Sharpless in 2001and describes chemistry tailored to generate substances quickly and reliably by joining small units together. This is inspired by the fact that nature also generates substances by joining small modular units.

To generate substances by joining small units together with heteroatom links (C-X-C). The goal is to develop an expanding set of powerful, selective and modular blocks that work reliably in both small- and large-scale applications. Sharpless termed the foundation of this approach click chemistry.

Click chemistry in combination with combinatorial chemistry, high-throughput screening and building chemical libraries speeds up new drug discoveries by making each reaction in a multistep synthesis fast, efficient and predictable. Click chemistry is not a specific reaction; it is a concept that mimicks nature [1].

Classification of Click Chemistry

Click chemistry can be classified as follows according to the nature of the reaction or type of reaction.

1. **Cycloadditions** reaction of unsaturated species, especially 1, 3-dipolar cycloaddition reactions.
2. **Nucleophilic substitution reaction**, particularly ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridiniumions, and episulfoniumions.
3. **Carbonyl** chemistry of the non-aldol type such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides.
4. **Additions** reaction, carbon- carbon multiple bonds, especially oxidative cases such as epoxidation, dihydroxylation, aziridination, and sulfenyl halide addition, but also Michael additions of Nu-H reactants.
5. **Thiol-ene** click reactions.

Reaction in Click Chemistry

Click chemistry deals with beautifully represented among cycloaddition reactions involving heteroatoms, such as hetero Diels-Alder and especially 1, 3-dipolar cycloadditions. These modular fusion reactions unite two unsaturated reactants and provide fast access to an enormous variety of interesting five and six membered heterocycles. Huisgen dipolar cycloaddition of azides and alkynesas the 'cream of the crop'. However, probably because of concerns about the safety of the azide moiety, medicinal chemists have not given these transformations the special attention as they deserve. The actual cycloaddition step may be as reliable for other types of reactions, but the azide group is by far the most convenient of the 1,3-dipolar components to introduce and to carry until needed. It may be the only one which is stable toward dimerization and hydrolysis. While azides were widely valued for their ease of introduction and reduction to primary amino groups, the remarkable stability (orthogonality) of aliphatic azides to a wide variety of other standard organic synthesis conditions [2].

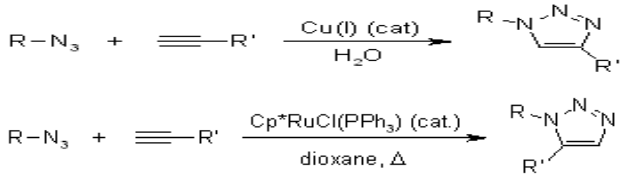
In above paragraph we shortly give the information about the name reaction which is carried out under the name of click chemistry.

Rhuthenium catalysed azide alkyne cycloaddition reaction

Many of the starting monosubstituted alkynes and organic azides were available commercially. Many others can easily be synthesized with a wide range of functional groups and their cycloaddition reaction selectively gives 1, 2, 3-triazoles [3].

The thermal Huisgen 1, 3-Dipolar Cycloaddition (classic 1,3-dipolar cycloaddition) of alkynes to azides requires elevated temperatures and often produces mixtures of the two regioisomers when using asymmetric alkynes. In this respect, the classic 1, 3-dipolar cycloaddition fails as a true click reaction. A copper-catalyzed

variant that follows a different mechanism can be conducted under aqueous conditions, even at room temperature. Additionally, whereas the classic Huisgen 1, 3-dipolar cycloaddition often gives mixtures of regioisomers, the copper-catalyzed reaction allows the synthesis of the 1, 4-disubstituted regioisomers specifically. By contrast a later developed ruthenium-catalyzed reaction gives the opposite regioselectivity with the formation of 1, 5-disubstituted triazoles. These catalyzed reactions comply fully with the definition of click chemistry and have put a focus on azide-alkyne cycloaddition as a prototype click reaction [4].



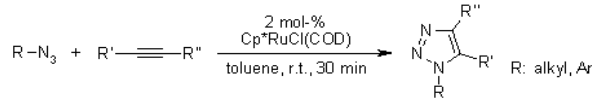
1. Huisgen Azide Alkyne 1, 3-Dipolar Cycloaddition

This reaction was highly exothermic, but the high activation barrier was responsible for a very low reaction rate, even at elevated temperature. Another drawback was the formation of regioisomers, as the two possible HOMO-LUMO interactions of the substrates are closely related in terms of energy. The thermal reaction therefore, often gives approximately 1:1 mixtures of both the 1, 4-substituted and the 1, 5-substituted regioisomers. Thus the neat reaction between ethynylphenylether and benzyl azide gives mixture of 1,4 and 1,5-triazole.

2. Copper-Catalyzed Azide Alkyne Cycloaddition (CuAAC)

As one of the best click reactions to date, the copper-catalyzed azide-alkyne cycloaddition features an enormous rate acceleration of 10^7 to 10^8 compared to the uncatalyzed 1,3-dipolar cycloaddition. It succeeds over a broad temperature range, is insensitive to aqueous conditions and a pH range over 4 to 12, and tolerates a broad range of functional groups. Pure products can be isolated by simple filtration or extraction without the need for chromatography or recrystallization. The active Cu (I) catalyst can be generated from Cu (I) salts or Cu (II) salts using sodium ascorbate as the reducing agent. Addition of a slight excess of sodium ascorbate prevents the formation of oxidative homocoupling products. Disproportionation of a Cu (II) salt in presenc of a Cu wire can also be used to form active Cu (I). Instead, a copper acetylide forms, after which the azide displaces another ligand and binds to the copper. Then, an unusual six-membered copper (III) metallacycle was formed. The barrier for this process has been calculated to be considerably lower than the one for the uncatalyzed reaction [5].

The calculated rate at room temperature is 1 s^{-1} which is quite reasonable. Ring contraction to a triazolyl-copper derivative is followed by protonolysis that delivers the triazole product and closes the catalytic cycle. Copper catalysed azide alkyne



cycloaddition reaction cannot be carried out on internal alkynes to get fully substituted 1, 2, 3-triazols.

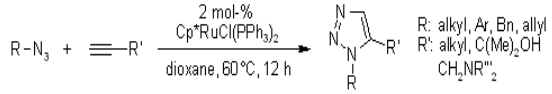
3. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition (RuAAC)

A search for catalysts revealed that pentamethylcyclopentadienyl ruthenium chloride [CpRuCl] complexes are able to catalyze the cycloaddition of azides to terminal alkynes regioselectively leading to 1, 5-disubstituted 1, 2, 3-triazoles. In addition, RuAAC can also be used with internal alkynes, providing fully substituted 1, 2, 3-triazoles, which contrasts with CuAAC. The ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) appears to proceed via oxidative coupling of the azide and the alkyne to give a six-membered ruthenacycle, in which the first new carbon-nitrogen bond is formed between the more electronegative carbon of the alkyne and the terminal, electrophilic nitrogen of the azide. This step was followed by reductive elimination, which forms the triazole product. DFT calculations support this mechanistic proposal and indicate that the reductive elimination step is rate-determining [6].

Solid-Phase Synthesis by Click chemistry:

Use of click reactions in combinatorial style to generate molecules of highly diverse structure and function. Much of the enormous effort in library synthesis currently pursued in academic and industrial laboratories makes use of polymeric supports for the stepwise construction of products. Solid-phase organic synthesis is popular precisely because it allows reactions that fall short of click status to be employed as click reactions, that is in situations where extremely high yields and simple purification procedures were required [7]. These attributes were achieved by using a large excess of the reactants in the mobile phase.

While this approach had been very effective for the synthesis of large libraries, the final products tend to be too lipophilic to probe the full range of biological interactions. The hydrophobic character of these collections may, in part, be due to the absence of by stander protic functional groups, which tend to be omitted intentionally or otherwise, to avoid extra protection or deprotection steps. Most importantly the solid-phase approach was ill suited to process-driven discovery: it was very expensive and highly wasteful of reagents and solvents; it is difficult to make large amounts of products and when such large-scale syntheses were attempted the yield per unit volume was poor intermediates bound to polymeric supports are difficult to analyze directly by standard spectrometric methods; and another layer of chemical technology the installation and cleavage of a linker was required. In other words, since solid phase combinatorial approaches to the discovery of biologically



active compounds ignore most of the issues that constrain practical organic syntheses and the most likely outcome is a trend toward drugs that are even harder to manufacture [8].

Click chemistry and drug discovery:

Click chemistry was being used increasingly in biomedical research, ranging from lead discovery and optimization to tagging of biological systems such as proteins, nucleotides and whole organisms.

Synthesis of lead discovery libraries

Over the course of five years, click chemistry laboratories at Coelacanth Corporation have employed solution-phase chemistry to produce a variety of screening libraries, containing a total of 200 000 individual compounds each more than 85% pure and available in 25–50mg amounts. In line with the click chemistry philosophy each library compound was produced in only one or two synthetic steps from key building block reagents using automated liquid handling workstations [9]. Despite the short synthetic sequences much compound diversity and novelty was achieved by starting with noncommercial building block reagents prepared in-house on multi-gram or even kilogram scales. Some examples as follows:

1. 'Spring-loaded' epoxides and aziridines for the formation of 1, 2-difunctionalized compounds by nucleophilic opening.
2. Imidoesters for the generation of five-membered aromatic heterocycles
3. Azides for the synthesis of 1, 2, 3-triazolederived libraries via 1,3-dipolar cycloaddition with β- ketoesters.
4. And 3-aminoazetidines for the preparation of non-aromatic heterocyclic libraries.
5. Targeted libraries were made one of which led to the discovery of potent Peroxisome Proliferator-Activated Receptor γ (PPAR-γ) agonists.

6. The copper-(I)-catalyzed formation of 1, 2, 3-triazoles has recently been used to prepare functionalized resins for the solid phase synthesis of a library of dopaminergic arylcarbamides.
7. In another resin-based approach (Yli-Kauhaluoma et al) prepared 1, 2, 3 triazoles via thermal 1,3-dipolar cycloaddition of polymer-bound azides to alkynes followed by cleavage from the solid support with TFA.
8. Drug discovery approaches based on the copper-(I)-catalyzed formation of triazoles from azides and acetylenes.

With the ~106-fold rate acceleration of the copper-(I)-catalyzed variant of Huisgen's 1, 3-dipolar cycloaddition reaction, the generation of screening libraries had reached a new level of simplicity. Two subunits were reliably joined together by formation of a 1,4-disubstituted 1,2,3-triazole linkage [10]. This ligation process works best in aqueous media without requiring protecting groups for any of the most common functional groups, enabling compound screening straight from the reaction mixtures (i.e. without prior purification). Specific example where in such ligation process employed.

Synthesis of neoglycoconjugates

Carbohydrates play a central role in metabolism, cell–cell interaction and cell migration processes and pathogen defence offering a host of attractive drug discovery opportunities Carbohydrates make poor lead compounds, owing to their notoriously modest affinities for the respective receptors or enzymes, poor pharmacological properties, and difficult syntheses. Click chemistry, the copper-(I) catalyzed ligation of azides and acetylenes, promises to greatly simplify and accelerate the discovery of high-affinity carbohydrate mimetics. Santoyo Gonzalez and co-workers prepared a series of multivalent, triazole-linked neoglycoconjugates, using the robust copper-catalyzed coupling of carbohydrate-derived acetylenes and azides. Complete regiochemical control and yields of greater than 80% were achieved using organic-soluble copper-(I) complexes as catalysts. Microwave irradiation considerably shortened the reaction times from several hours to a few minutes at room temperature. 'Disaccharides' derived from mannose were prepared and multiple mannose units were linked to aromatic and heteroaromatic cores. Even heptavalent manno-β-cyclodextrins were accessible with this approach [11].

Fucosyl transferase inhibitors:

Cell surface glyco-proteins and glyco-lipids bearing the sialyl Lewisx and sialyl Lewisa tetrasaccharide epitopes mediate a variety of crucial cell–cell recognition processes, such as fertilization, embryogenesis, and lymphocyte trafficking, immune response and cancer metastasis. The final step in the biosynthesis of these carbohydrates catalyzed by fucosyltransferases involves the transfer of an L-fucose moiety from guanosine diphosphate β-L-fucose (GDP-fucose) to a specific hydroxyl group of sialyl N-acetyl-lactosamine. Selective inhibitors of these enzymes might provide drugs by blocking the synthesis of fucosylated end-products and the pathology they trigger. Wong et al. identified nanomolar inhibitors from a compound library that was prepared by linking GDPderived acetylene to a library of azides using the copper- (I) catalyzed triazole formation. The excellent yields and the absence of protecting groups allowed 85 test compounds to be rapidly prepared in water and screened straight from the reaction mixture [12]. Hit follow-up, conducted on purified compounds against a panel of fucosyl and galactosyl transferases and kinases, revealed biphenyl derivative as the most potent inhibitor of human α-1,3-fucosyltransferase VI that has been found to date and it was also revealed to be selective for this one enzyme.

Non azide 1, 3- Cycloaddition Reactions as click reaction:

A wide variety of alkynes engage in such reactions, with electron-deficient cases usually being the most reactive. Azide 1 reacts with the cyanoacetylene equivalent, 2-chloroacrylonitrile, to give only one regioisomer of triazole 2, which retains its isolated olefins for further decoration. Non-azide 1, 3-dipolar cycloaddition processes provide interesting five-membered heterocycles. The sequence started with addition of hydrazine to the aziridinium intermediate generated from **a**. The resulting cyclic hydrazide **b** then undergoes condensation with aromatic aldehydes to give azomethine ylides **c**, which react with a variety of unsaturated components to give [3.2] cycloadducts. The rich array of functionality displayed by these products provides opportunities for the creation of unique combinatorial libraries [13].

In situ click chemistry:

Mock's discovery of a dramatic rate acceleration of the azide alkyne cycloaddition by sequestering the two components inside a host structure, prompted Sharpless *et al*. to investigate a new paradigm for drug discovery, which was dependent on irreversible target-guided synthesis of high affinity inhibitors from reagents that are inert under physiological conditions. By contrast other approaches employ highly reactive reagents (e.g. aldehydes and hydrazines; thiols and chloroketones etc.) and reversible reactions for the in situ assembly of inhibitors inside a target's binding pocket. Acetylcholine esterase (AChE) was chosen as the target. Its inhibitors have been employed for over a century in various therapeutic regimens and to investigate the role of acetylcholine in neurotransmission. The enzyme's active site was located at the base of a narrow gorge ~20 Å in depth. A second peripheral binding site exists at the rim of the gorge near to the enzyme surface. The concerted thermal 1, 3-dipolar cycloaddition reaction between azide and acetylene reagents (which carry active-site and peripheral- site binding groups via flexible spacers) was selected for this study for several reasons [14].

1. First, the reaction is extremely slow at room temperature.
2. Second, it does not involve components that might disturb the binding sites (external reagents, catalysts, by-products).
3. The reactants are bio-orthogonal.

Substantial rate acceleration was observed for certain azide acetylene reagent combinations in the presence of the enzyme. From 49 building block combinations, the enzyme selected the TZ2/PA6 pair, leading to the formation of a sole reaction product in a highly regioselective fashion: the TZ2PA6 syn 6 triazole. By contrast, chemical synthesis in the absence of enzyme provided a roughly 1:1 mixture of synand anti-6 regioisomers. Both are respectable inhibitors, but the syn-6 isomer, with a 100- fold greater affinity and a sub-picomolar dissociation constant for certain acetylcholine esterases, has potency greater than all known non-covalent organic AChE inhibitors. Thus AChE itself served as the reaction vessel, synthesizing its own inhibitor by equilibrium-controlled sampling of various possible pairs of reactants in its gorge until the irreversible cycloaddition between azide and acetylene essentially 'froze' the pair that fits best into the binding pocket. A recent X-ray crystallographic analysis of both the syn-6- and anti-6- mouse AChE complexes at 2.45–2.65 Å resolution reveals that the former has effectively trapped the enzyme in a previously unknown conformational state. If this 'open' conformer is in facile equilibrium with the ground state it might help to explain the enormous turnover rates of acetylcholine esterases similar to a breathing motion that is in pace with the catalytic cycle. In addition, this study revealed that the 1, 2, 3-triazole cores interact strongly with the protein through hydrogen bonding to N2 and N3 and through their large dipole moments (~5 Debye).

Polymer chemistry:

In polymer chemistry, systems have been described based on addition polymerization with 1,4-benzenedithiol and 1, 4-diethynylbenzene in the synthesis of dendrimers in star polymers in graft polymerisation, block copolymers and in polymer

networks. Another reported application was the synthesis of macrocycles via dithiol coupling[15].

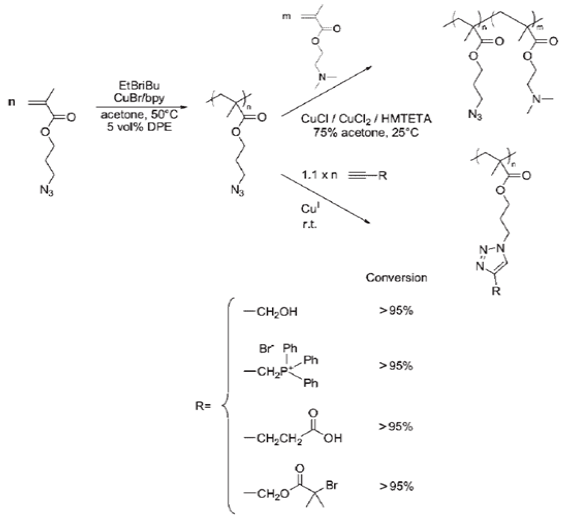
Click Reactions on Linear Polymers and Gels:

1. Since many known polymerization reactions in macromolecular chemistry require the absence of specific functional groups, there was considerable interest in the fixation of ligands onto polymers and gels after a successful polymerization reaction had been conducted.
2. This was most important when living polymerization mechanisms were used since especially the highly sophisticated chemical mechanism and equilibria of (quasi-) living polymerization reactions are often highly substrate specific and therefore, strongly affected by even small amounts of functional groups or the respective coupling agents required for affixation.
3. Another issue concerns the binding of large numbers of ligands onto polymers (i.e., sidechain-modified polymers) or dendrimers, which require highly efficient coupling reactions to this purpose.
4. Further interest is directed towards the heterogeneous functionalization of polymers in solvent mixtures.
5. Because of the limited solubility of many polymers reactants for post-functionalization reactions cannot always be applied in homogeneous solution with the derivatized polymer. In these cases, highly efficient reactions acting in heterogeneous reaction media are desired.
6. Thus the Sharpless click reaction had been brought into the limelight recently because of its high efficiency, often reaching yields of >99% irrespective of the ligand structure even in in homogeneous reaction systems [16].

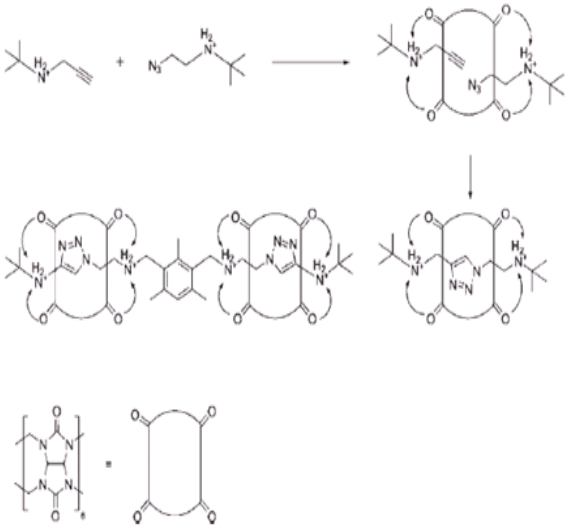
The nature of the initial polymerization reaction (if known) as well as the structure of the initial, starting polymers is given. Many of the controlled polymerization reactions derive from:

1. Atom-transfer radical polymerization (ATRP).
2. Ring-opening metathesis polymerization (ROMP).
3. Quasi-living cationic polymerization.
4. Nitroxide-mediated polymerization (NMP).
5. Radical addition- fragmentation transfer (RAFT) [17].

Living Radical Polymerizations (ATRP, NMP, and RAFT):



Sidechain-modified polymers made by an initial ATRP reaction subsequently followed by an azide or alkyne click reaction were described using 3-azidopropyl methacrylate 1 as the monomer. This monomer yielded a good ATRP reaction furnishing polymer 2 in good yields and acceptable polydispersity [18]. Copolymerization to the block copolymer (c) could be achieved, as well as the click reaction with various terminal acetylenes to give the final polymer (d) in yields higher than 95%, using CuIBr in N,N-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) solutions. Despite higher steric hindrance in polymer (b) as compared to the free monomer (a), the click reaction proceeded faster on the polymer, as judged by NMR spectroscopic investigations. Similar to the results obtained with tributyltin acrylate (TBTA), an anchimeric assistance of the reaction by already formed triazoles was proposed. Recently there have been a few examples for the combination of NMP and the azide/alkyne click reaction. Various copolymers (e.g., the water-soluble terpolymer 37) were prepared by NMP to enable the direct 'Click' Chemistry in Polymer and Materials Science. A polycondensation approach was first reported by Krasla and Steinke using bivalent azides and alkynes as building blocks for polymers [19]. The 1, 3-dipolar cycloaddition process between the acetylene and the azide. In this case was catalyzed by cucurbituril according to a previous report by Mock et al, who demonstrated the efficiency of this catalytic system in the synthesis of polyrotaxanes.



Applications

Click chemistry has widespread applications. Some of them are:

1. Preparative organic synthesis of 1, 4-substituted triazoles.
2. Modification of peptide function with triazoles.
3. Modification of natural products and pharmaceuticals.
4. Drug discovery.
5. Macrocyclizations using Cu(I) catalyzed triazole couplings.
6. Modification of DNA and nucleotides by triazole ligation.
7. Drug discovery.
8. Supramolecular chemistry: calixarenes, rotaxanes, and catenanes.
9. Dendrimer design.
10. Carbohydrate clusters and carbohydrate conjugation by cu(1) catalyzed triazole ligation reactions.
11. Polymers and Material science.
12. Nanotechnology and
13. Bioconjugation, for example, azidocoumarin.

The reactions in Click chemistry must (or would be desirable):

1. Be modular
2. Be wide in scope
3. Give very high chemical yields
4. Generate only inoffensive by products
5. Stereospecific

6. Physiologically stable

7. Exhibit a large thermodynamic driving force > 84 kj/mol to favour a reaction with a single reaction product. A distinct exothermic reaction makes a reactant "spring loaded".

8. High atom economy [20].

Potential Limitations of Click Chemistry:

1. In spite of the undisputable success of the concept of click chemistry within just a few years there are still a few limitations associated with the concept. Because of the stringent criteria that were used to identify click reactions, chemical diversity was intrinsically limited. As a matter of fact, the CuAAC reaction is still by far the most widely used click reaction.
2. However, copper is believed to be cytotoxic and demonstrated side effects associated with excessive copper intake include hepatitis,Alzheimer's disease and neurological disorders. Click reactions to be used in contact with living systems, the copper catalyst must be completely removed or alternatives, such as Staudinger ligation or strain-promoted [3 + 2] heterocycloadditions, must be employed.
3. Azides, among the prime reactants for Huisgen's 1, 3-dipolar cycloaddition reaction, are also often associated with potential toxic side effects and certain azides may bear a very real explosive potential.
4. Finally a more practical limitation is that the supply of clickable starting materials often cannot keep up with the demands of the rapidly emerging application space in materials science and biotechnology. Meanwhile, many of the researchers that work in these fields are not synthetic chemists, who can easily synthesize appropriate starting materials, but must rely on commercial sources for obtaining access to these chemicals. However as the click chemistry philosophy continues to spread through the area of materials science, polymers and biotechnology, more and more clickable building blocks can be expected to become easily available [21].

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