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Thiol–Yne Chemistry: A Powerful Tool for Creating Highly Functional Materials**

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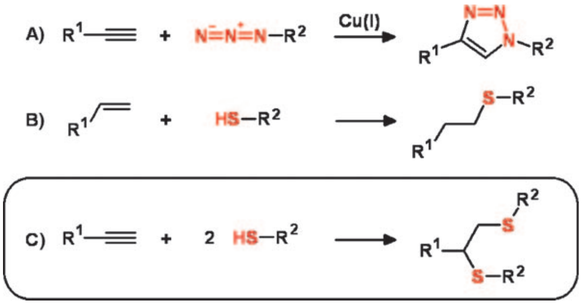
click chemistry · dendrimers · polymers · radical reactions

The introduction of the click chemistry concept by Sharpless and co-workers in 2001 revolutionized all fields of chemistry.[1] Click reactions were defined to be modular, stereospecific, wide in scope, and to have the potential to give high product yields and only inoffensive by-products, if any. Furthermore, click reactions can be performed using simple reaction conditions and allow easy product isolation. The large impact of click chemistry does not come from the novelty of the coupling procedures, but lies in the rediscovery of forgotten coupling procedures by chemists who improve the procedures using contemporary methods and science. The most widely used click method is the copper(I)-catalyzed azide–alkyne cycloaddition (Scheme 1 A), which is an improved version of the Huisgen azide–alkyne dipolar cycloaddition. In recent years, a large number of metal-free click reactions have been introduced to avoid the use of toxic metal catalysts.[2] The radical-mediated thiol–ene coupling procedure (Scheme 1 B) seems to be the most promising metal-free click reaction, which employs readily available starting materials as well as simple reaction conditions comprising either a chemical radical source or UV irradiation; for the latter, placing the flask in the sunlight is sufficient to get a fast and complete reaction.[3] However, notably, this radical coupling procedure is not always efficient for polymer–polymer conjugation, therefore the nucleophilic thiol–ene addition might be preferred.



Scheme 1. Copper(I)-catalyzed azide–alkyne cycloaddition (A), radical thiol–ene coupling (B), and radical thiol–yne reaction (C).

The ever increasing complexity of polymeric materials requires better and better control over polymer structure with regard to architecture and functionality. Therefore, combining the best available organic and polymer synthetic methods is required to open new avenues to complexity, which explains the importance of click chemistry in materials science.[4] As a result, a variety of new click chemistry coupling procedures have been developed by polymer chemists. In 2009 the radical-mediated thiol–yne coupling procedure was introduced for the development of highly cross-linked polymer networks by Bowman and co-workers,[5] who were inspired by almost forgotten reports on multiple radical additions of thiols to alkynes.[6] The beauty of this thiol–yne coupling procedure is that it combines the readily available building blocks of the copper(I) azide–alkyne click reaction and the thiol–ene chemistry to create multifunctional materials under mild reaction conditions: Two thiols are coupled to one alkyne using either a chemical radical source, UV irradiation, or sunlight at ambient temperature (Scheme 2). The radical mechanism of the thiol–yne reaction makes it very robust and versatile method that tolerates a variety of functional groups; the presence of oxygen should, however, be avoided.

Since the thiol–yne reaction allows simple addition of two thiols to an alkyne, it appears to be perfectly suited to create multifunctional polymer structures. Indeed, the thiol–yne reaction could be used to introduce a large number of functional groups onto poly(propargyl methacrylate) brushes, resulting in functional surfaces as reported by Patton and co-workers.[7] The versatility of the thiol–yne approach to polymer-brush modification was demonstrated by creating pH-responsive surfaces as well as surfaces with patterned functionalities using UV-induced thiol–yne reactions in combination with a photomask. The orthogonality of the radical thiol–yne reaction with a nucleophilic thiol–ene reaction, employing an activated alkene, was demonstrated by Chan, Hoyle, and Lowe.[8] Thiol-functionalized substrates could be modified with propargyl acrylate using a phosphine-catalyzed nucleophilic thiol–ene reaction, thereby leaving the alkyne intact. Subsequent addition of a second thiol allowed the introduction of two functional groups per alkyne using the

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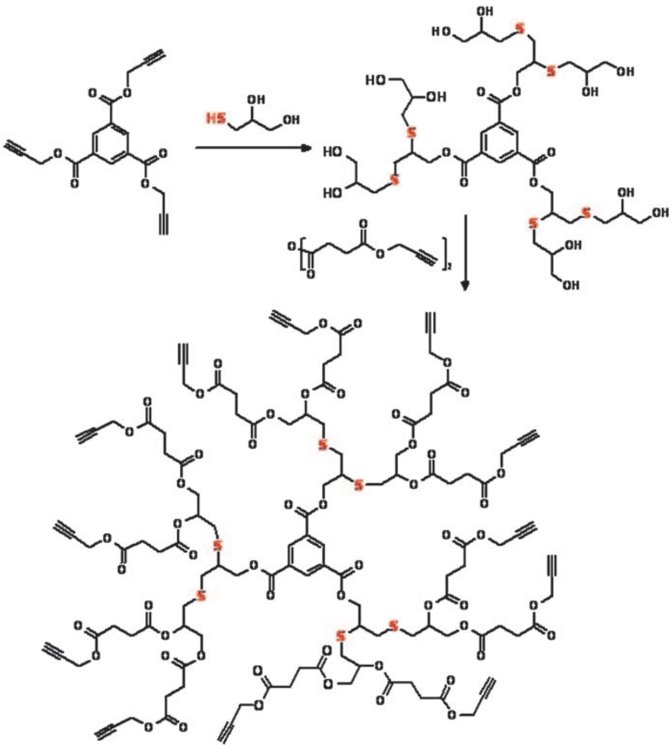
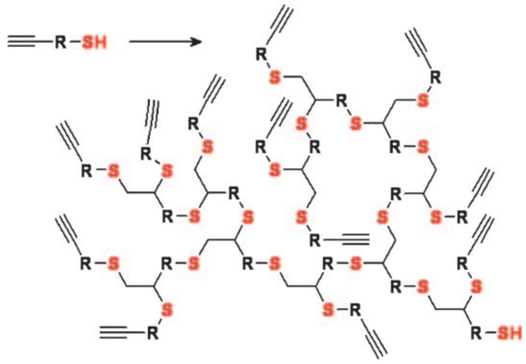


Scheme 2. Multistep thiol–yne mediated synthesis of highly functional dendrimers.



Scheme 3. One-pot thiol–yne mediated synthesis of highly functional hyperbranched polymers.

radical thiol–yne reaction. Even though these studies utilize thiol–yne reactions to get a high degree of functionalization, the full potential of repetitive thiol–yne reactions to exponentially increase the number of functional groups was not yet explored.

The full potential of repetitive thiol–yne chemistry for the construction of highly functional macromolecules was recently exploited for the synthesis of dendrimers[9] and hyperbranched polymers.[10] Stenzel and co-workers employed a trifunctional alkyne as a core molecule to add six 1-thiolglycerol molecules, by using the thiol–yne radical addition, to generate a first generation dendrimer having 12 hydroxy groups at the periphery (Scheme 2).[9] Subsequent esterification of the hydroxy groups with an acetylene anhydride (Scheme 2) and then thiol–yne coupling of 1-thiolglycerol provided the second generation dendrimer with 48 hydroxy groups. Repetition of these steps successfully yielded the third generation dendrimer having 192 hydroxy groups. As such, highly functional monodisperse dendrimers were obtained by thiol–yne branching at the expense of a laborious multistep synthetic procedure including chromatographic purification steps.

Perrier and co-workers exploited the branching power of thiol–yne chemistry to generate hyperbranched polymers.[10] Bifunctional thiol-alkynes were used as AB_2 type monomers where the thiol is the A unit and a single alkyne represents the two B units. As such, highly functional hyperbranched polymers could be obtained in a simple one-step procedure (Scheme 3). The most striking result of this study is the fact that the degree of branching (DB) of the polymers is nearly equal to one, which is what is expected for a perfect dendrimer. In other words, each alkyne is either present as an unreacted functional group or has reacted twice with a thiol and, therefore the hyperbranched polymers do not contain intermediate alkenes. This result implies that the addition of the first thiol to the alkyne is the rate-limiting step, which is then followed by a fast second thiol addition to the intermediate thiol-alkene. Although a few other hyperbranched polymers with $DB \approx 1$ have been reported,[11] the thiol–yne approach is significantly more elegant and straightforward. The versatility of this thiol–yne method was demonstrated by varying the R group on the thiol and the alkyne from a short spacer to an oligomeric poly(styrene), both resulting in highly functionalized hyperbranched polymers with $DB \approx 1$ within three hours.

This simple one-pot thiol–yne radical addition route towards hyperbranched polymers having $DB \approx 1$ opens up a completely new platform for highly functional polymers. The spacer length and composition in between the alkyne and thiol appears to be unlimited, allowing accurate tuning of the size as well as properties of the hyperbranched polymers. Furthermore, the large number of terminal alkyne units at the periphery can be readily modified using copper(I) azide–alkyne click chemistry or thiol–yne reactions to introduce more functional groups. In fact, a second polymer shell could be introduced using the hyperbranched polymer as a starting material for a second thiol–yne reaction with a different oligomeric thiol-alkyne to generate core-shell hyperbranched polymers bearing terminal alkyne groups at the periphery. The main challenge for this chemistry will be to control the molar-mass distribution as well as the size of the hyperbranched polymers since the reported examples have polydispersity indices up to 16, preventing their use in many biomedical applications. In addition, the availability of a large variety of thiol-yne monomers as well as the efficiency for polymer–polymer conjugation are important topics to be addressed.

In summary, thiol–yne chemistry is an exciting new 'click' method that is especially promising for the preparation of multifunctional and (hyper)branched polymer structures.

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