

# A Brief Minireview of poly-triazole: Alkyne and Azide Substrate Selective, Metal-catalyst Design

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**ABSTRACT.** Organic compounds that contain poly-triazole are very important intermediates in pharmaceutical and chemical industry. Click chemistry is one of essential reactions that can form C-N bond with high atom economy. The research progress in metals catalyzed Click chemistry of azides and alkynes from the perspective of reaction mechanism is categorized and summarized.

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## **1. Introduction**

Click chemistry is one of the research frontiers and hotspots in polymer chemistry.<sup>1,2</sup> In recent years, copper-catalysed azide-alkyne cycloadditions (CuAAC) have attracted more and more attention, generating poly-1,2,3-triazole.<sup>3,4</sup> It is extraordinary convenient to insert alkynyl or azide groups into biological molecules, applying for biomedicine and functional materials.<sup>5,6</sup>

Since 2001, Sharpless has reported by Cu (I) catalysis, alkynyl and azide-based reaction rate can be improved as much as 104 times, also found in the price of copper ion catalytic.<sup>7, 8</sup> Huisgen 1, 3-dipolar cycloaddition reaction possess a large number of advantages, including under mild conditions, highly productive yield.<sup>9, 10</sup> It doesn't even need for special separation, purification, accounting for alkyne groups coordination with copper, so as to improving the reactivity of alkynyl.<sup>11, 12</sup> Along with high regioselectivity, carbon atoms are coordinated on the electron cloud density change without end group of copper ion catalytic acetylene and azide.<sup>13, 14</sup> In most cases, the 3-dipole ring addition reaction is not regionally selective and the reaction is slow.<sup>15, 16</sup> Biomolecules have hardly reacted with azide and alkyne group, due to the weak polarity of the latter two ones.<sup>17, 18</sup> Significantly, those groups are easily connected with each other. More importantly, click reaction has a high degree of chemical selectivity, employing for modifying highly functional biological molecules, such as polypeptides, *etc.*<sup>19-21</sup> Moreover, generating poly-triazole group is relatively stable in the sequent reaction, remaining permanent under the conditions of acid, base and redox.<sup>22-24</sup>

As for those merits, it is widely used in medical medicine and scientific materials for their versatility and reliability of synthetic reactions.<sup>25</sup> In this review, we will mostly focus on recent developments in the effects of different substrates containing azide and alkyne. Based on our research,<sup>26-31</sup> usage of the term click reaction is not only including the substrate classes of mono-alkyne, diyne, triyne, fourfold-yne, mono- azide, diazide, triazide and fourfold-yne, but extended to structurally related compounds with selective, reactivity and productive yield, *etc.* Moreover, marco-molecular click reactions will be mentioned as well if they are necessary for the discussion or might act as springboard for future research.

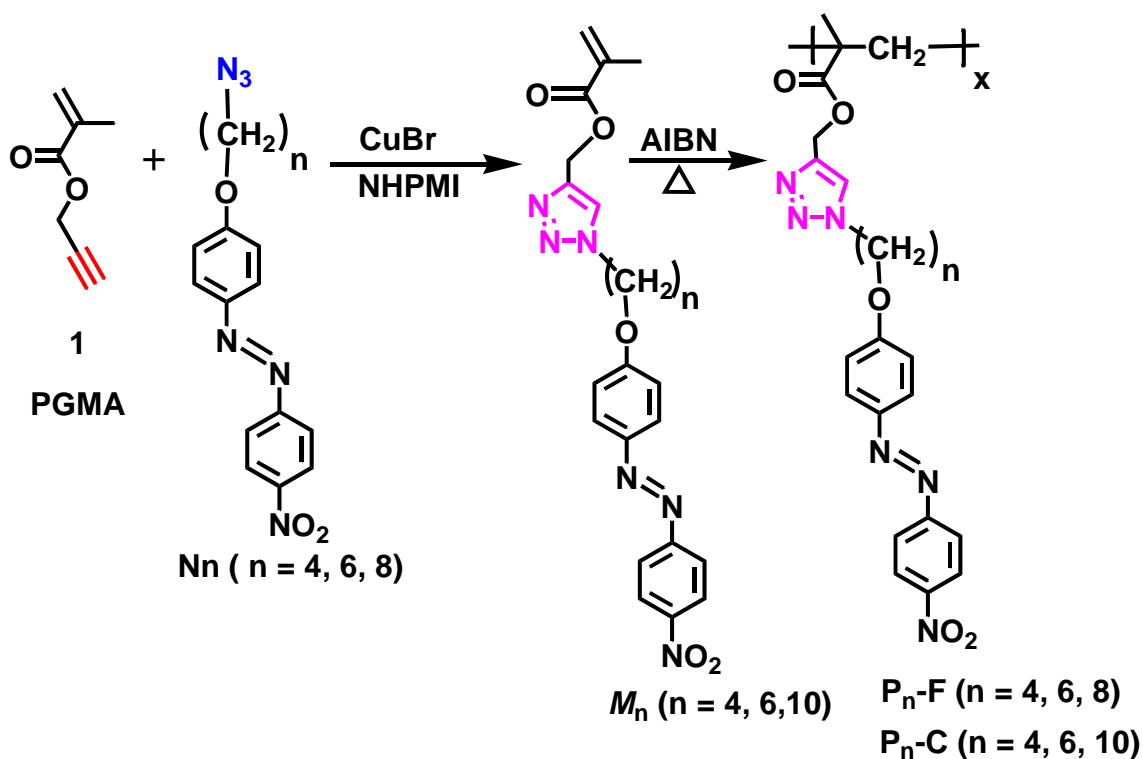
## 2. The effects of different compounds containing alkyne

Alkynes are classified as a new material, pharmaceutical intermediates, nanometer molecular devices as well as the important to build the skeleton in natural product synthesis.<sup>32, 33</sup> One of the most commonly used synthetic macromolecular triazole is a method of terminal alkynes and sodium azide as raw material, the Cu (I) catalytic Click reaction to finish.<sup>34, 35</sup> The method can get high yield of target product, so the alkyne class substrates play a very important role in the middle of the Click reaction.<sup>36, 37</sup>

### 2.1 Mono-alkyne

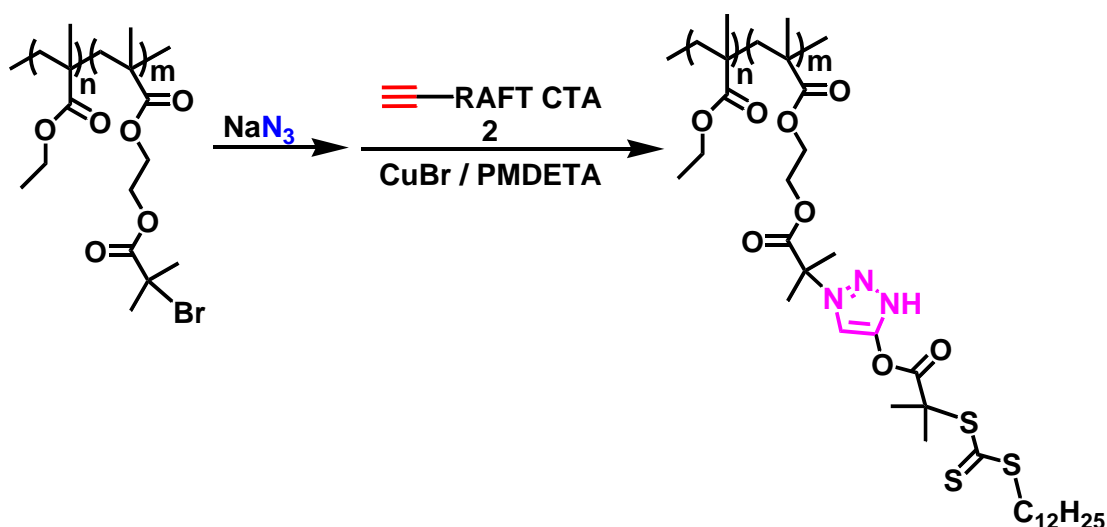
Mono-alkynes have broad application prospects in the Click reaction.<sup>38</sup> At the same time, single alkynes compounds are also a kind of plant secondary metabolites to resist various diseases and pests.<sup>39</sup> Thousands of alkynes compounds have been isolated from 19 families of higher plants and basidiomycetes of lower plants, among which PGMA is a typical representative.<sup>40</sup>

Zhang et al<sup>41</sup> under the action of catalyst CuBr/NHPMI success, will be the end of the containing side chain containing azobenzene azide with mono-alkyne **1** (PGMA, **Scheme 1**) through efficient Click reaction, side chain was synthesized at room temperature of liquid crystal polymer containing azobenzene, molecular weight can be as high as 303000 Da, also found that such a large molecular weight almost does not affect the height of the polymer solution reversible photosensitivity, they predicted that is widely used because of its high molecular weight and optics and has very good mechanical performance of optoelectronic devices



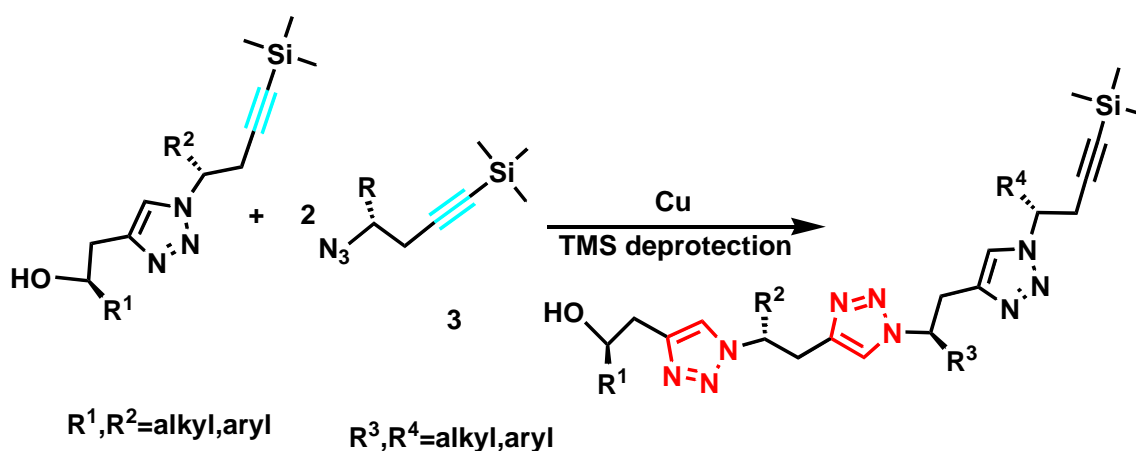
Scheme 1

For example, Zhao et al<sup>42</sup> used the CuBr/PMDETA catalytic system, which enables the end-group acetylene **2** (Scheme 2) containing multi-functional methyl methacrylate to carry out the click reaction efficiently at room temperature.



### Scheme 2

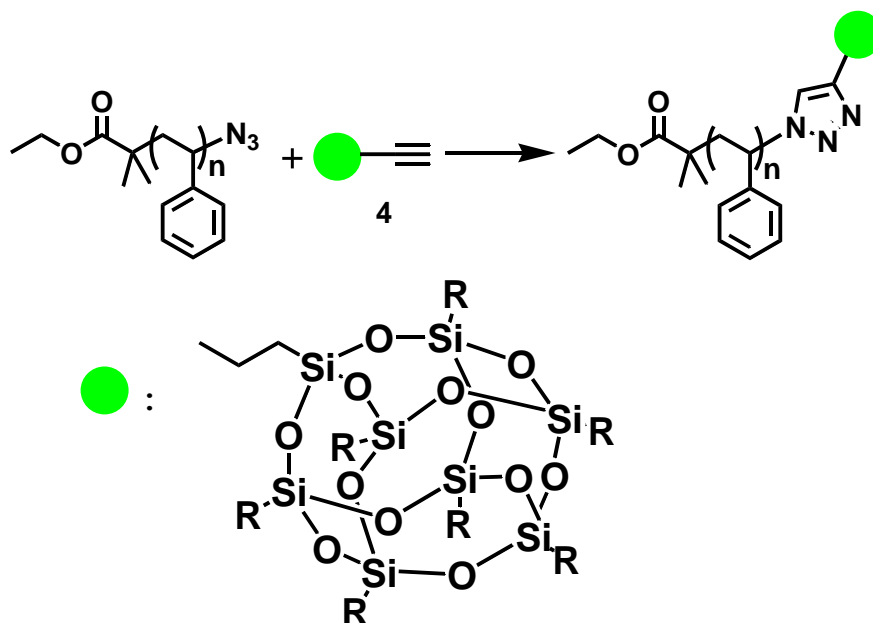
On the other hand, Hughes et al<sup>43</sup> by comparing with Cu (I) catalysts in the 1, 3-dipolar cycloaddition click chemistry based on substrate **3** (Scheme 3), found with Cu catalyst and after <sup>t</sup>BuOH under the condition of H<sub>2</sub>O is 1 : 2, the triazole dimerization product rate is the highest, and on this condition, can further to maximize the efficiency of aggregate into a series of racemic oligomer, the 1, 2, 3-triazole polymers is expected to become a potential peptide analogues, widely used in biological materials.



### Scheme 3

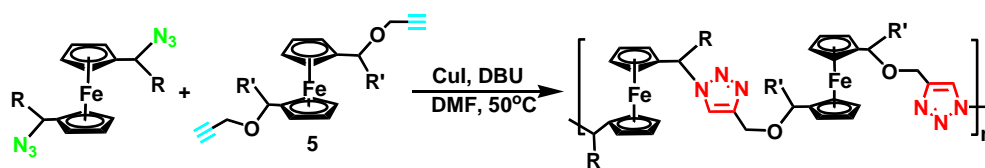
Click chemistry in recent years showed a good compatibility between functional groups and can be performed at room temperature, Muller team<sup>44</sup> is further combined with the ATRP technology used to successfully prepared a series of linear or branched chain containing half siloxane star or telechelic triazole polymer, among them, the more difficult is half as many as one of the substrate **4** containing siloxane acetylenic compounds, the synthesis of Muller using ATRP technology has been successfully synthesized, etc. Due to the unique nanocage structure and

excellent solubility of the side chain containing sesquioxide, these triazole polymers are currently widely used in the field of materials science.



Scheme 4

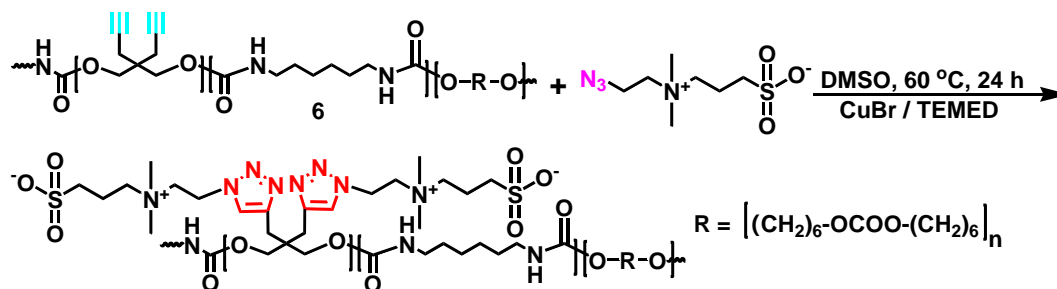
Recently, owollik et al<sup>45</sup> reported the CuI/DMF catalytic system, can make the end group containing modular conjugate ferrocene acetylene **5** (Scheme 5) effectively for the Click reaction under 50 °C, the liquid phase synthesis of the triazole derivatives were obtained can be used as high temperature resistant adhesive materials.



Scheme 5

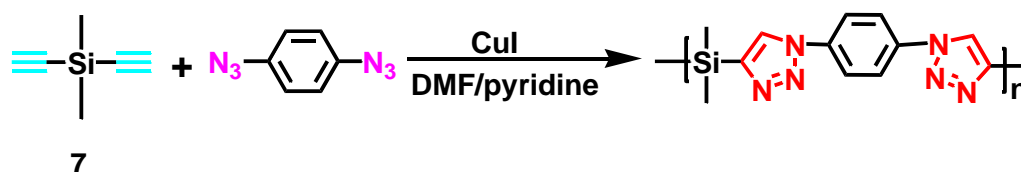
Xu et al<sup>46</sup> has been successful in catalyst under the catalysis of CuBr-TEMED/DMSO will contain diyne **6** (Scheme 6) and zwitterionic monomer DMPS-N<sub>3</sub> by click reaction under N<sub>2</sub> by

using a novel and efficient synthesis under 60 °C the triazole macromolecules. Due to its zwitterionic groups, it is expected to be used in biomedical applications.



**Scheme 6**

Feng et al<sup>47</sup> successfully synthesized poly-triazole macromolecules containing silyl and phenylene by using CuI as catalyst in a polar solvent DMF and pyridine mixture by click reaction of 1, 4-azapenzene and diethylenyl silane **7** with a quantum yield ranging from 0.19 to 0.37. This synthesis method provides a mild and low-cost way to obtain optical polymer materials containing organosilicon

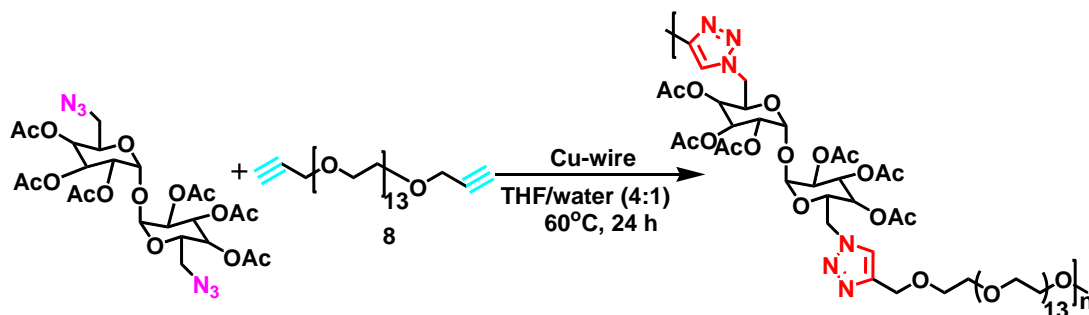


**Scheme 7**

In 2010, Khosravi et al<sup>48</sup> with Cu wire as catalyst, in a mixture of 4:1 tetrahydrofuran is mixed with water and solvent, the hydrophobic functional two azide trehalose and chain terminal for two polyethylene glycol (peg) click on the polymerization reaction of diyne **8**, reaction conditions for the reaction under 60 °C for 24 hours, get the new type of intelligent temperature response

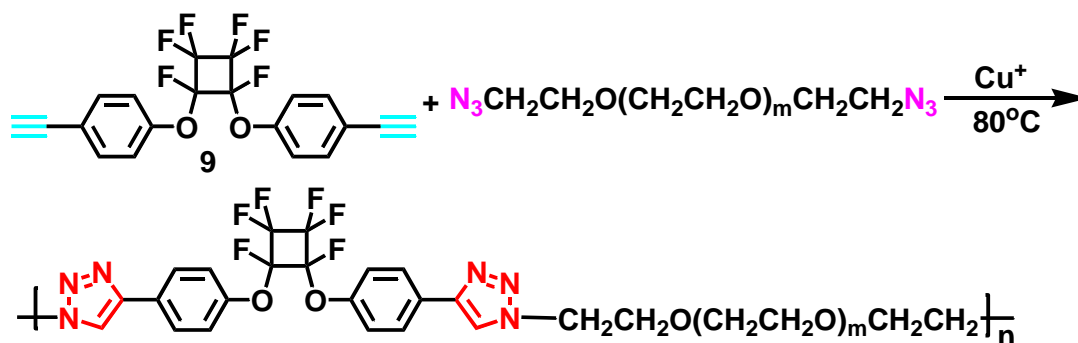


three azole linear sugary polymer, the temperature response of the polymer is mainly applied to medical materials (Scheme 8).



Scheme 8

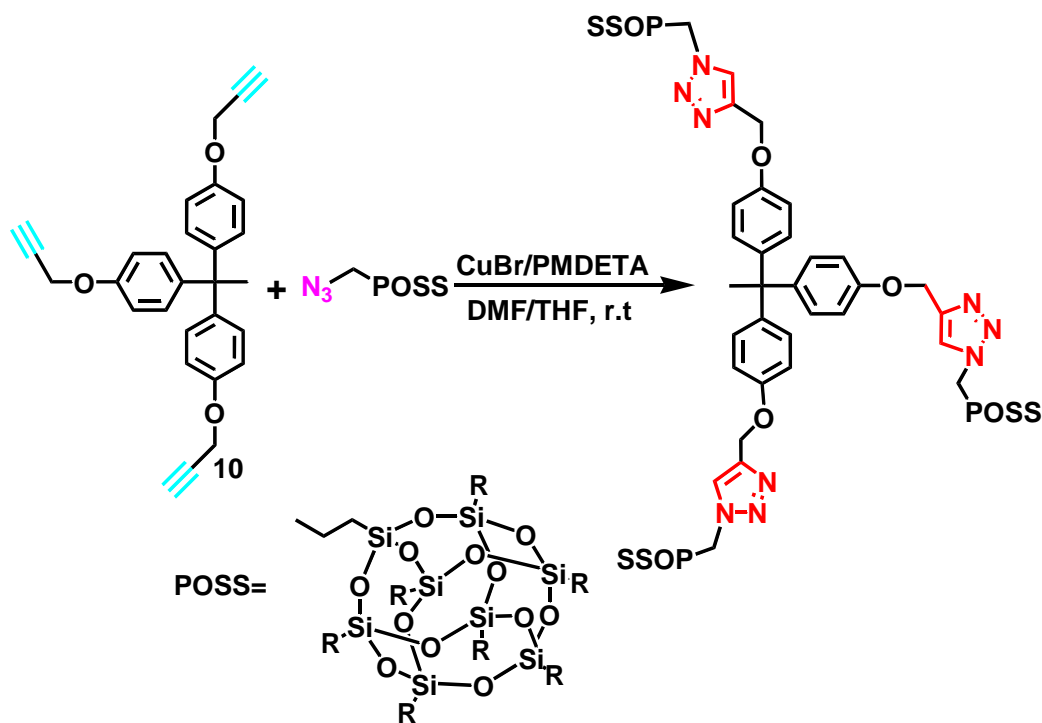
In 2008, the Qing et al<sup>49</sup> Cu<sup>+</sup> as catalyst, make more glycol 2 azide with diyne **9** (Scheme 9) containing eight fluorine cyclobutane reaction completely under temperature of 80 °C, generate more triazole fluoropolymer, high production rate, thermal stability is strong, in the most polar solvent with good solubility, but this is the most polymers are crystal shape. This fluoro-polytriazole polymer has attracted extensive interest in advanced heat, oxidation, chemical corrosion, and insulation materials



Scheme 9

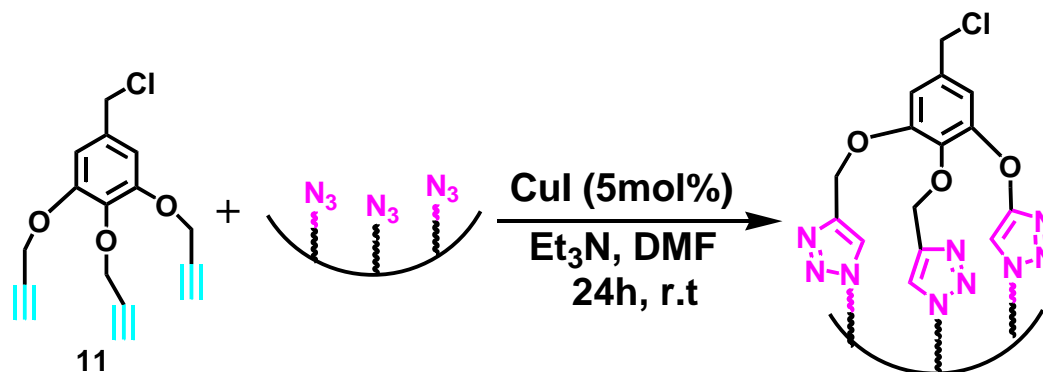
## 2.2 Triyne

Tunca et al<sup>50</sup> using CuBr/PMDETA catalytic system, in the mixed solvent of DMF and THF, with many functional groups can make three phenyl propyl ether of acetylene compound **10** with polyhedral oligomeric times half siloxane single-ended base azide efficiently for the click reaction at room temperature (**Scheme 10**), its liquid phase synthesis of the triazole derivatives products rate is as high as 94%, can be used in the field of biological materials



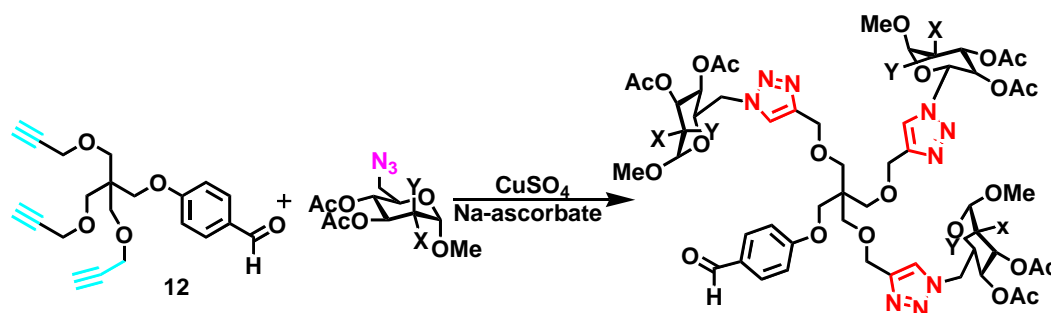
Bhaumik et al<sup>51</sup> took advantage of 5 mol % CuI catalytic system, in the mixed solvent of DMF and Et<sub>3</sub>N, can make the arc three azide and cup-type mesoporous triacetylene **11** (**Scheme 11**) compounds containing multiple functional groups and efficiently for the click reaction at room temperature, the liquid phase synthesis of mesoporous pyrrolidine triazole derivatives were molecular weight is not very big, but it continued to react with 4-aminopyridine can make its chain growth, and generate the threeazole mesoporous molecular, now can be used as a new type

of non-metallic organic catalysts applied in the Michael addition reaction, It is an important research direction of sustainable chemical synthesis in the future.



Scheme 11

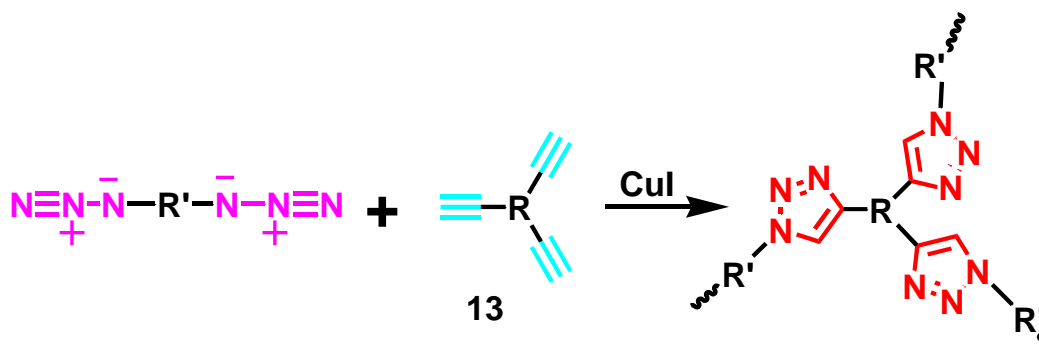
Lonnberg et al<sup>52</sup> used  $\text{CuSO}_4$ ·sodium asorbate/1, 4-dioxane catalytic system, which can make the triacetylene **12** (Scheme 12) containing benzaldehyde and tetraether react with glycoazide by Click at room temperature. The yield of triazole glycocluster synthesized by the system reached 57%, which can be applied in the field of medical medicine.



Scheme 12

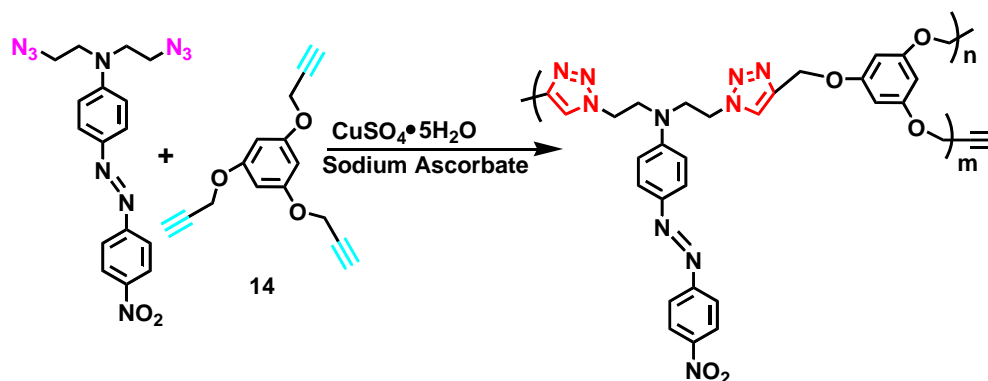
Tang et al<sup>53</sup> studied a lot of the literature of Click chemistry, deformation of small molecules found in the development of new polymerization is a valuable resource, for example by CuI catalytic system, can make the tri-acetylene compound **13** (Scheme 13) and Permian nitrogen

compounds to efficiently to click polymerization at room temperature, generating more than rules of linear macromolecular triazole, but they found the nonmetal catalyst polymerization, great progress has been made in recent years, this kind of catalyst is more advantageous to the rules of the functional structure of linear macromolecular synthesis. They play an important role in the synthesis of functional materials.



**Scheme 13**

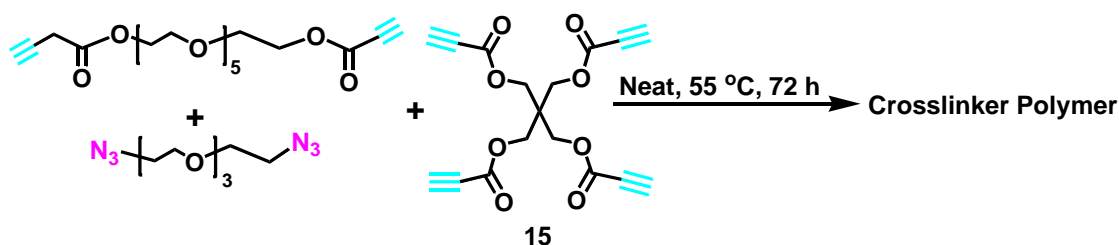
Shen et al<sup>54</sup> the  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and sodium ascorbic acid as catalyst, at room temperature, make the Permian nitrogen amino nitro azide ethyl benzene and benzene ether base three propiolic **14** (**Scheme 14**) click reaction efficiently, of the liquid-phase synthesis of the second order of the groups of linear optical many-branched triazole production rate of 59.2%, more than the corresponding linear triazole molecule low 9.1%, the molecular weight of 7400, a linear low of 600, but in common organic solvents has good solubility and thermal stability, the three dimensional space and more independent branch structure and ethynyl crosslinking structure at the end, Therefore, it is likely to play an important role in nonlinear optical materials in the future.



Scheme 14

### 2.3 Fourfold-yne

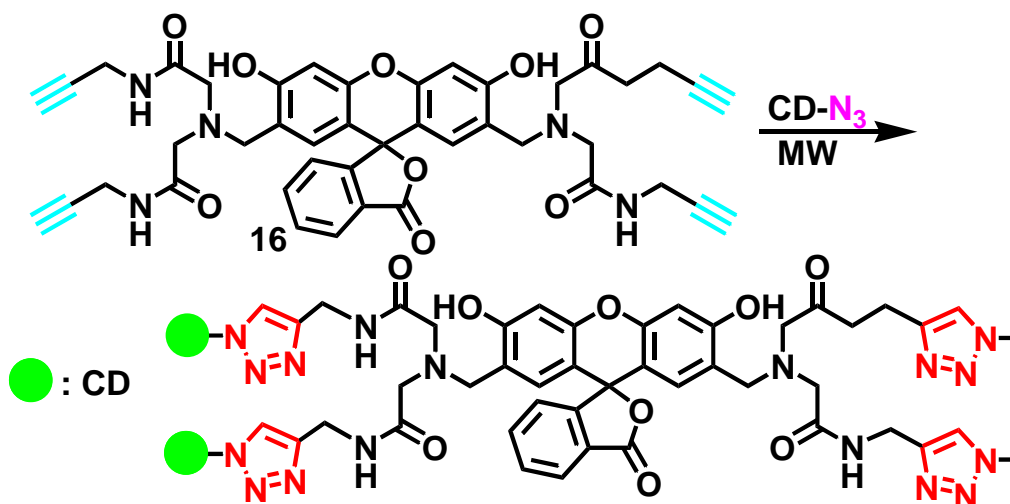
Duran<sup>55</sup> in the absence of water environment, such as the choice of different filler agent, the cross-linking agent for acetylene derivatives **15** (Scheme 15) to propiolic acid methyl ester and the Permian nitrogen compounds in the click reaction under 55 °C, the synthesis of three azole macromolecules can be applied to a potential rocket propellant binder and different proportions of stuffing agent for generating crosslinking different mechanical properties of polymers, and has a filler agent processing properties of polymers and the coefficient is better than that of the packless agent, especially in alumina filler agent is preferred.



Scheme 15

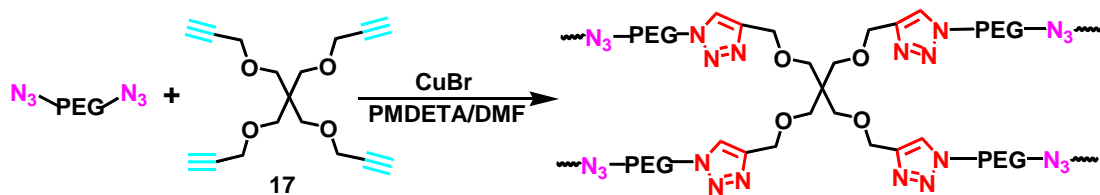
Kolb<sup>56</sup> reported, CuSO<sub>4</sub>/ascorbic acid sodium/DMF catalytic system, the cyclodextrin azide and fourfold alkyne **16** (Scheme 16) under microwave radiation to 90 °C in the click

polymerization for an hour, the liquid phase synthesis of three azole macromolecular production rate is as high as 74%, the molecular weight of 5409.79, can further and adamantane calcein compound reaction, preparation of new fluorescent wire at the same time can also be applied in the field of fluorescent dyes.



Scheme 16

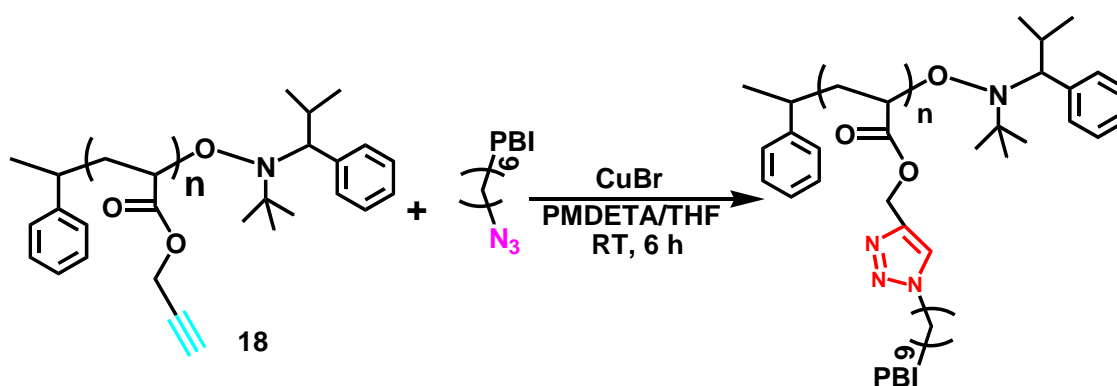
Lin<sup>57</sup> used CuBr/PMDETA DMF catalytic system, make fourfold alkyne **17** derivatives containing ether bond (Scheme 17) and polyethylene glycol (peg) Permian nitrogen compounds and methyl acrylate click and atom transfer radical polymerization reaction at the same time, the liquid phase synthesis with interpenetrating polymer network structure of triazole macromolecules are more likely to be more used in biological gene carrier and medical drugs.



Scheme 17

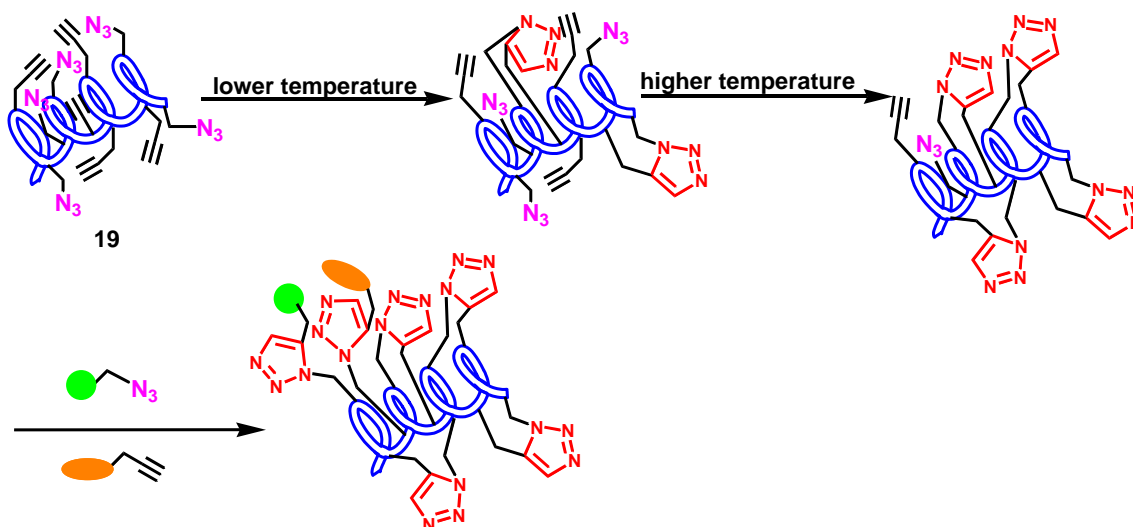
## 2.4 Other alynls

Thekkatt et al<sup>58</sup> used Cu(I)Br/PMDETA/THF catalytic system to perform a 6-hour click reaction between polyalkylene **18** containing multifunctional groups (**Scheme 18**) and polybenzimidazole azide compound at room temperature. The liquid phase synthesis of polytriazole macromolecule molecular weight up to 15800 can be applied to semiconductor materials.



**Scheme 18**

Hawker<sup>59</sup> use CuBr/PMDETA/DMF catalytic system, make fourfold alkyne **19** derivatives containing ether bond (**Scheme 19**) and polyethylene glycol (peg) Permian nitrogen compounds and methyl acrylate click and atom transfer radical polymerization reaction at the same time, the liquid phase synthesis with interpenetrating polymer network structure of triazole macromolecules are more likely to be more used in biological gene carrier and medical drugs.



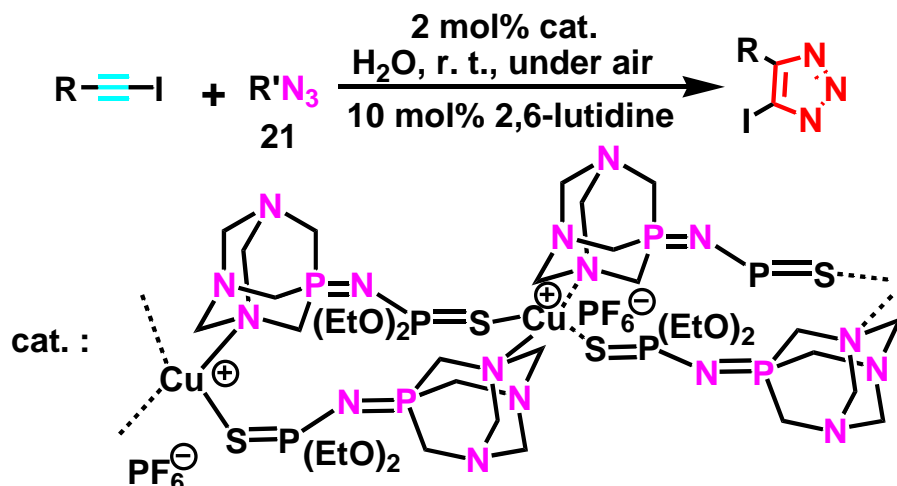
Scheme 19

### 3. The effects of different compounds containing azide

#### 3.1 mono-azide

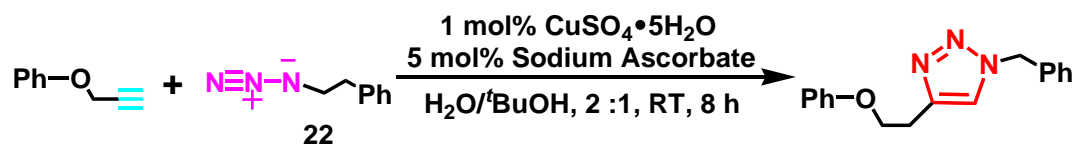
Gimeno<sup>60</sup> took advantage of 2 mol % Cu (I) complex/2, 6-dimethyl pyridine solution catalytic system, the mono azide **21** containing multifunctional group (Scheme 21) with multifunctional group's built-in single alkynes containing compound effectively the click reaction at room temperature, the liquid phase synthesis of iodine instead of triazole macromolecular yield above ninety percent, this new type of Cu (I) complex not only normal temperature stability, and is suitable for the mild reaction conditions, the catalyst click chemistry provides a new research direction.





Scheme 21

Sharpless<sup>61</sup> group based on 1 mol %  $\text{CuSO}_4$  and 5 mol % sodium ascorbate catalytic system,  $\text{H}_2\text{O}$  and  $t\text{BuOH}$  volume ratio of 2:1 in the mixed solvent, the single pile of azide **22** containing methylene phenyl (Scheme 22) and single alkynes containing phenyl methyl ether bond compounds at room temperature for 8 hours of the click reaction, the liquid phase synthesis of triazole macromolecular production rate is as high as 91%.

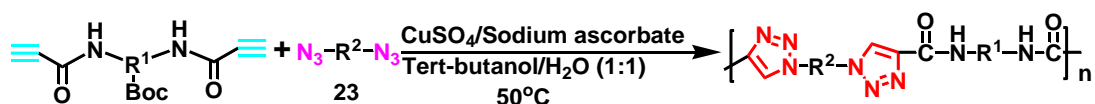


Scheme 22

### 3.2 Per-azide

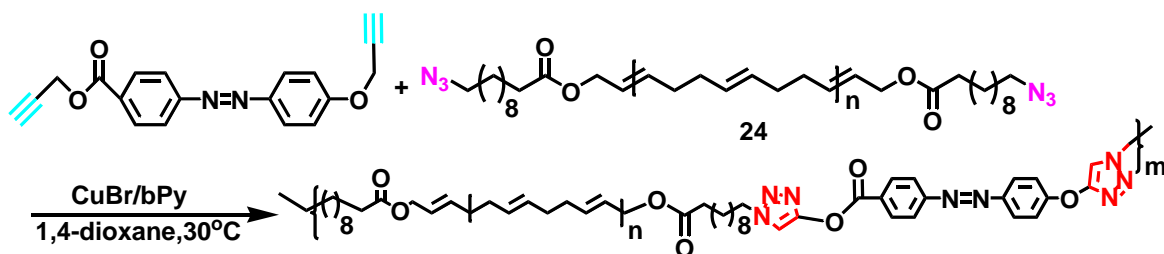
Although mono-azide compounds have been used in triazole synthesis, few reports have been reported on polymeric triazole. Therefore, the main influence of different azide compounds on Click synthesis of polymer triazole is per-azide compounds. For example, Zhang<sup>62</sup> reported other

per-azide **23** (Scheme 23) containing ester key polyene key compounds under 30 °C and alkynes efficient Click reaction of triazole macromolecular yield up to 98.6% more, molecular weight, the multi-functional team more triazole macromolecules can be widely applied to the adhesive materials, decoration materials, emulsifier, insulation material, gene transfer and drug synthesis, etc.



Scheme 23

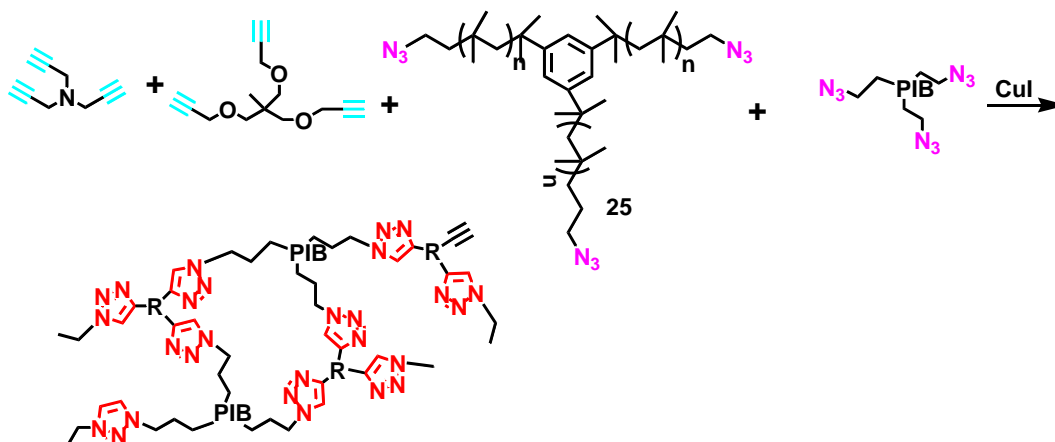
Li et al<sup>63</sup> demonstrated CuSO<sub>4</sub>/ascorbic acid catalytic system, soluble in first four butyl alcohol and water mixed solvent volume ratio of 1: 1, heating to 50°C response after 24 hours, in methylene chloride and trifluoroacetic acid solvent volume ratio of 1: 1, the azide-compound **24** (Scheme 24) and diynes containing amide efficient Click reaction of the synthesis of triazole macromolecules, because has good biological compatibility, can be used as the carrier of gene transfer



Scheme 24

Binder<sup>64</sup> and others members showed CuBr(PPh<sub>3</sub>)<sub>3</sub>/DMSO catalytic system, and makes the low molecular weight compounds two tri-alkynes with a liquid more valence three arm type tri-azide

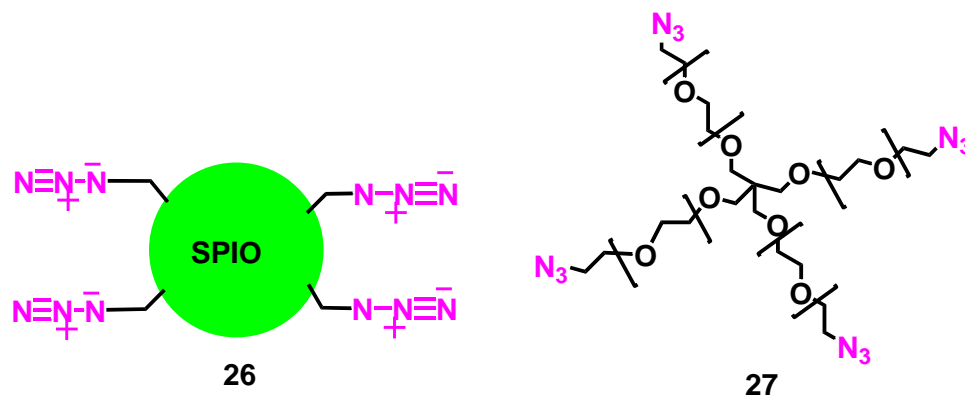
polymer **25** (Scheme 25) effectively click reaction, liquid phase synthesis of triazole macromolecular molecular weight can be as high as 250000 Da, and the network are triazole is a kind of macromolecule material with characteristics of self-healing.



Scheme 25

### 3.3 fourfold-azide

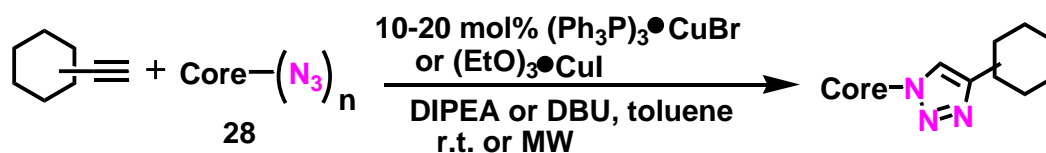
Tsourkas<sup>65</sup> and others using CuSO<sub>4</sub>/sodium ascorbate catalytic system, made by the fourfold-azide **26** (Figure 1) modified superparamagnetic iron oxide nanoparticles with a single group of alkyne and by fluorescent penetrant modified human epidermal growth factor receptor for directional click reaction at room temperature, in this paper, the synthetic triazole macromolecular compounds and no further and more alkynes continue to generate much triazole macromolecules, so the molecular weight is not big, but the study found that the greater the concentration of this single triazole molecule of synthetic its fluorescence intensity, the greater the and it contains a variety of functional groups, Based on this, it can be applied in the field of diagnostic imaging and tumor drug delivery.



**Figure 1** Some fourfold-azides applying for polymeric synthesis *via* Click chemistry

Kopecek<sup>66</sup> and others using CuBr, L- ascorbic acid/DMF catalytic system, make similar to the end of the four arms containing more than fourfold azide **27** (**Figure 1**) based on polyethylene glycol (and its molecular weight is 2100 and 8800 Da) have base of alkyne polypeptide on both sides with high efficiency under the room temperature anaerobic reaction, click find of synthesis of this kind of many of the hydrogel swelling degree and degree of papain solution depends on the molecular weight of polyethylene glycol (peg), may be the future be manipulation of the mechanical performance and digestion performance of the design direction of hydrogel, Hydrogels were the first biomaterials to be used in clinical applications, followed by tissue engineering, drug delivery, sensing materials, diagnostics and microfluidics.

Zhao et al<sup>67</sup> used a 10-20 mol%  $(\text{Ph}_3\text{P})_3\cdot\text{CuBr}$  or  $(\text{EtO})_3\text{P}\cdot\text{CuI}/\text{DIPEA}$  or DBU, toluene catalytic system to make the click reaction between glycine alkyne and terminal polyazides **28** (**Scheme 26**) efficiently at room temperature. The yield is usually up to 80%.



## Scheme 26

### 4. Conclusion and outlook

In summary, click chemistry has been widely used in the research fields of polymer, surface modification and nanomaterials.<sup>68, 69</sup> It has been proved that click chemistry provided a powerful research tool for the design and development of new materials with its own characteristics of insensitivity to oxygen and water, good stereoselectivity of products and high yield.<sup>70-72</sup> However, there are still some problems to be solved and the work to be done in the future aftermentioned.<sup>73-77</sup>

- (i) Currently, the click reaction by cyclic acetylene and azide are relying on ring tension.
- (ii) The catalytic system produces a certain degree of cytotoxicity, Cu(I) catalyst could result in aggregating nano-dispersion, limiting its application in vivo and nanometer.
- (iii) CuAAC itself needs to be further studied and improved. What kind of solvent, temperature should be selected as the better reaction system? The problem with the source of Cu<sup>+</sup> in the reaction is that it's still online.

### ASSOCIATED CONTENT

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Shu-ni Wang was born in Heyuan, Guangdong China, in 2000. He received his bachelor's degree from Foshan University in 2021. His research focuses on the synthesis and activity of *N-H* compounds



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### **Author Contributions**

Both †J. Huo and D. Chen were equally to this work. J. Huo, S. Wang, X. Hu, Q. Deng and D. Chen have designed and prepared the manuscript. All authors read and approved the final manuscript.

### **Notes**

The authors have declared no competing financial interest.

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