Click Chemistry Approaches for the Synthesis and Functionalization of Macromolecules

Mesut Görür*

Department of Chemistry, Faculty of Arts and Science, Bursa Uludag University, 16059, Görükle, Bursa, Turkey

Abstract: Click chemistry methods are powerful tools in the hands of synthetic chemists. Cu(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition reaction (CuAAC) is accepted as "the cream of the crop" of click chemistry techniques due to its orthogonality and near-perfect yields in very mild conditions. Besides CuAAC, Diels–Alder (DA), thiol–ene, atom transfer nitroxide radical coupling (ATNRC), and aldehyde–aminooxy reactions are other effective ligation methods in terms of chemoselectivity and reaction yields at moderate conditions, thus they are also accepted as click chemistry reactions. Click chemistry and controlled polymerization techniques have been utilized extensively in the synthesis of well-defined and elegant macromolecular structures.

Keywords: Click chemistry, Functionalization of macromolecules, Orthogonal reactions.

1. INTRODUCTION

The introduction of new technologies has been demanding intelligently developed polymers with improved physical and chemical properties, such as tailor-made molecular structures and functionalities, well-defined molecular weight, and narrow molecular weight distribution. Various polymerization and ligation methods have been employed to tackle this challenge. Cu(I)-catalyzed 1,3-dipolar azide-alkyne cycloaddition reaction (CuAAC) [1], developed by Sharpless based on Huisgen dipolar cycloaddition reaction [2], is one of the most effective and widely used ligation methods in the synthesis of macromolecular compounds [3-7]. Therefore, nowadays this reaction is named as "Sharpless-type click reaction".

According to Sharpless, synthesis of reliable modular blocks with powerful and selective functional units is the key step for the efficient preparation of any molecules with desired chemical and structural properties [1]. This notion laid the foundations of "click chemistry" approach. There are some strict requirements for reactions to be regarded as a click chemistry technique. The reactions must be modular, tolerant to diverse functional groups other than the targeted one, require no or benign solvents, have high conversion rates at moderate conditions with high regioselectivity, and need simple and nonchromatographic purification methods [8].

The definition of "click chemistry" approach was later revised by Barner-Kowollik *et al*. [9]. According to the revised definition, stoichiometric amounts of the functional building modules should be attached in an acceptable time-scale with high conversion rates and the targeted product should be removed from the reaction mixture via simple large-scale purification methods.

Besides CuAAC, atom transfer nitroxide radical coupling (ATNRC), Diels–Alder (DA) cycloaddition, thiol–ene, thiol-yne, and aldehyde–aminooxy click reactions have been employed together with controlled polymerization (CRP) methods in the preparation of various tailor-made polymers with elegant molecular structures.

2. SHARPLESS-TYPE CLICK REACTION (CuAAC)

The Huisgen cycloaddition reactions between alkyne and azide moieties are conducted at relatively high thermal conditions, yielding 1,4- and 1,5-triazoles [10]. Later, Sharpless and Medlar independently developed this synthetic method and reported that the presence of Cu(I) salt provides this reaction with exclusive regioselectivity to produce 1,4-disubstituted 1,2,3-triazoles (Figure **1**) [11, 12]. Besides, CuAAC requires very mild reaction conditions and mostly performed at ambient temperature [13-16]. Due to the orthogonality and nearly perfect chemoselectivity of CuAAC, it is accepted as the "cream of crop" of the click reactions [17] and thus, there are copious amount of literature work reporting the use of CuAAC in the preparation of well-defined polymers with various topologies, including linear [18-22], star-shaped [23,

---

*Address correspondence to this author at the Department of Chemistry, Faculty of Arts and Science, Bursa Uludag University, 16059, Görükle, Bursa, Turkey: Tel: +90 (224) 275 50 94;
E-mail: mesutgorur@uludag.edu.tr

E-ISSN: 2311-8717/21

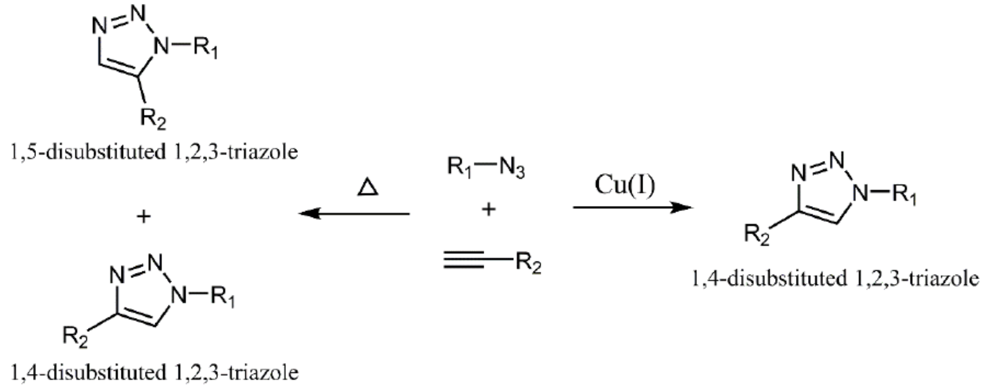

Figure 1: Huisgen (on the left) and Sharpless (on the right) type 1,3-dipolar azide-alkyne cycloaddition reactions.

24], miktoarm star [25, 26], graft [27-30], cyclic [31, 32], hyperbranched [33-35], and crosslinked [36] polymers.

In the reaction mechanism of CuAAC, proposed by Sharpless [37], coordination of Cu(I) to alkynes leads to copper-acetylide intermediate and then followed by the attachment of azide units, yielding a six membered Cu-containing metallacycle which is another intermediate species. Finally, the latter intermediate is transformed into triazole ring rapidly. The obtained 5-membered heteroatom triazole ring has high chemical stability and its large dipole moment (5D) imparts it hydrogen bond forming capacity [38, 39].

Atom transfer radical polymerization (ATRP) is one of the most used CRP method along with CuAAC conjugation technique. This polymerization technique attaches halogen atom to the end-groups of the produced polymer. Then, these alkyl-halide end-groups are easily converted into alkyl-azide units [40]. Various functional groups of monomers, small- or macromolecules can be transformed into azide or alkyne groups via suitable chemical modification techniques. Besides, due to chemical and thermal stability of azide or alkyne groups, various polymerization initiator molecules with these functionalities were used in the preparation of linear, star, and graft polymers via CRP techniques, such as ATRP [41], reversible addition-fragmentation chain transfer polymerization (RAFT) [42-44], ring opening polymerization (ROP) [42, 44-47], and nitroxide-mediated polymerization (NMP) [48].

The introduction of a small molecular compound with suitable functional units to a macromolecular structure is a relatively straightforward synthetic route and can be achieved via various ligation methods, including click chemistry methods [49]. However, combination of two or more macromolecules and isolation of the targeted polymer through simple large scale purification methods is a quite challenging procedure. Fortunately, CuAAC is an excellent combination method, even in the case of equimolar amount of the polymers with azide and alkyne functional polymers, to give exceptionally high conversion rates. In a typical example, PMMA-PSt-PtBA and PMMA-PSt-PEG miktoarm star terpolymers were prepared through CuAAC and CRP methods. Poly(MMA-b-St) having an alkyne functional moiety was synthesized by ATRP of methylmethacrylate (MMA) and NMP of styrene (St) employing an initiator molecule with alkyne, bromide and alkoxyamine functional groups. Subsequently, an equimolar amount of azide functional poly(tert-butylacrylate) (PtBA) was treated with alkyne functional Poly(MMA-b-St) copolymer through CuAAC reaction, yielding PMMA-PSt-PtBA miktoarm star terpolymer. Whereas, excess amount of azide functional poly(ethylene glycol) (PEG) was reacted with Poly(MMA-b-St) in the same manner, and then the crude product was precipitated in methanol to remove the unreacted PEG. The monomodal GPC curves indicated that only the targeted polymers were obtained, as well as the success of the performed CuAAC reactions [50].

The orthogonality (tolerance towards various functional groups other than the targeted one) of a ligation method becomes extremely important in one-pot reaction procedures. The most important advantage of the one-pot reaction procedures is that the purification methods are applied only to the targeted final polymers, not to the intermediates [51]. Zhang *et al.* reported tailor-made PSt-PCL-PDMA and PEO-PCL-PDMA miktoarm star polymers in a one-pot procedure [52]. The core molecule with alkyne, bromide and hydroxyl functional groups was attached to azide functional PSt (or PEG) via CuAAC reaction, yielding a macroinitiator with bromide and hydroxyl functional groups for simultaneous ATRP of 2-(dimethylamino)ethyl methacrylate (DMA) and ROP of ε-caprolactone (ε-CL), respectively. In this one-pot mechanism, the use of equimolar amount of core molecule and PSt (or PEG) is vitally important to produce well-define miktoarm star polymer.

The synthesis of block copolymers can be accomplished using living polymerization methods, such as ionic polymerization (cationic or anionic), ATRP, RAFT, and NMP. This approach necessitates to perform consecutive polymerization reactions. A single living polymerization method or combinations of them can be used to produce block copolymers, depending on the end-functional units of the precursor polymers. The polymer obtained from the first reaction is employed as a macroinitiator for another monomer in the next step to extend the polymer chain. This approach limits the type of monomers to be used in the preparation of block copolymers [53]. The polymerization initiator functional groups at the termini of the precursor chains dictate the type of the monomers of the next polymer blocks. Whereas macromolecular structures with azide and alkyne end-functional units can be efficiently attached to each other via CuAAC at quantitative and near-perfect conversion rates. Opsteen *et al*. [54] elegantly prepared linear diblock PMMA-*b*-PEG, PSt-*b*-PEG, PMMA-*b*-PSt, and triblock PEG-*b*-PSt-*b*-PEG via Cu(I)-catalyzed click reaction between alkyne and azide groups. GPC chromatograms of the synthesized block copolymers were observed to be monomodal. In another example, Quémener *et al*. [55] reported diblock PSt-*b*-PVAc copolymer through CuAAC of azide functional poly(vinyl acetate) (PVAc) and alkyne functional PSt which were obtained by RAFT polymerization of respective monomers. He *et al*. prepared diblock PEG-*b*-PSt copolymer via ATRP of St using bromide end-functional PEG as the macroinitiator. Following azidification of the bromide end groups of PEG-*b*-PSt, alkyne functional PCL was attached to the diblock copolymer via CuAAC reaction, yielding triblock PEG-b-PSt-*b*-PCL copolymer [56].

Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions were also used in the synthesis of various macromolecular structures in a step-growth manner [57]. Zhou *et al*. reported the synthesis of polytriazoleimides by CuAAC step-growth polymerization between dialkyne and diazide functional monomers [58]. Besset *et al*. prepared starch-based polytriazoles through CuAAC reactions between diazide and dialkyne functional dianhydrohexitol monomers [59].

3. DIELS–ALDER CLICK REACTIONS

Diels-Alder (DA) reaction mechanism was invented by two Nobel Laureates (1950), Otto Diels and Kurt Alder [60]. This reaction is a straightforward [4+2] cycloaddition reaction between a conjugated diene and dienophile, giving a stable cyclohexene moiety (Figure **2**) [61]. Conjugated dienes and dienophiles have 4π- and 2π-electron systems, respectively. The temperature requirements for these reactions depend on the selection of diene-dienophile pairs [4]. For example, cycloaddition of anthracene and maleimide occurs at relatively high temperatures around 110 °C, whereas furan-maleimide cycloaddition reactions can be conducted at relatively low temperatures. But the products obtained from the latter reaction is not thermally stable, retro-DA reaction of the furan-maleimide adduct is observed to take place above 60 °C in solutions [62]. Thermal reversibility of this reaction makes it suitable for the preparation of thermo-responsive materials [63,64]. Hetero Diels-Alder reactions between dithioester functional group and butadiene can be conducted around 50 °C [65], whereas cyclopentadiene can be coupled to dithioester unit at ambient temperatures. The adducts obtained from the reaction of dithioesters and cyclopentadiene are thermally stable up to 80 °C [4].

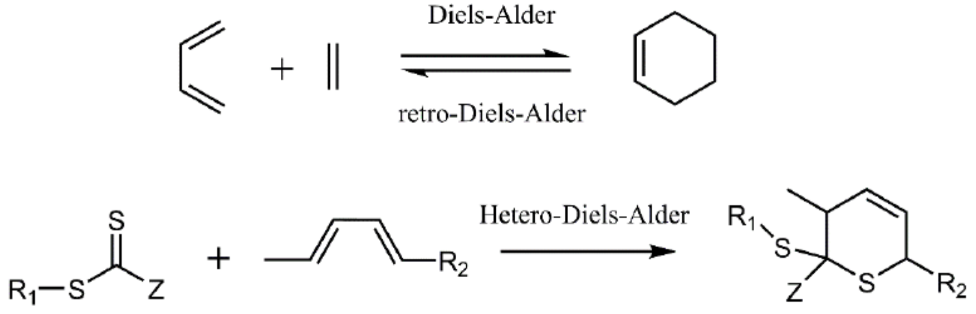

Figure 2: Diels-Alder, retro-Diels-Alder, and hetero-Diels-Alder reactions.

DA reactions do not require transition metal catalyst and have been employed in the synthesis of elegant macromolecular structures including homopolymers, dendrimers, star polymers, block and graft polymers. Durmaz *et al*. prepared linear triblock PEG-b-PSt-PMMA and PCL-b-PSt-b-PMMA copolymers via in situ (one-pot) CuAAC and Diels-Alder [4+2] reactions in an elegant way, demonstrating the orthogonality of these ligation mechanisms [51]. In some cases, maleimide group is protected with furan to prevent any side reactions and furan protecting unit can be removed by rising the temperature to over 100 °C in suitable reaction conditions. Tunca and Hizal group synthesized PEG and Jeffamine macrostructures with furan-protected maleimide groups at both ends and then removal of furan unit was carried out by refluxing in toluene. The maleimide end functional groups of the obtained polymers were reacted with anthracene moiety of a trifunctional compound. Then, nitroxy and bromide functional groups of the trifunctional compound were used as the initiators in consecutive NMP of St and ATRP of tert-BA, respectively, yielding heteroarm H-shaped terpolymers [66].

Bousquet *et al*. reported preparation of an elegant graft copolymer through RAFT polymerization and hetero-DA conjugation techniques. Firstly, random copolymer of St and trans, trans-2,4-hexadienylacrylate (ttHA) monomers was synthesized. Then, homopolymer of n-BA was prepared via RAFT polymerization and attached to P(St-r-ttHA) copolymer via hetero-DA click method, yielding P(St-g-^{n}BA) graft copolymer [67].

4. THIOL-ENE CLICK REACTIONS

Thiol-ene reaction is a hydrothiolation reaction of C=C double bond and has click-type characteristics (Figure **3**). Thiol-ene reactions are facile and versatile processes, can be performed under variety of conditions. In radical pathway, cleavage type (type I) photoinitiators, H-abstraction type photo-initiators, or thermal initiators can be used [68]. Although a wide range of olefinic compound can be used in this reaction, reaction rates considerably change depending on the reaction mechanism and substitutions around the C=C bond. Besides, selection of thiol compounds substantially affect the rate of the reaction depending on S–H bond strength and the cleavage pattern [69].

Thiol-ene click reaction has been employed in the preparation of various well-defined polymeric structures. Iskin *et al*. gave a good example in their report on the synthesis of an ABC-type miktoarm star polymer through thiol-ene, ROP, and CuAAC reactions. Firstly, they synthesized a core compound with allyl, hydroxyl, and azide functional groups. Then, thiol end-capped PSt was prepared via ATRP and suitable chemical functionalization methods. Thiol-funtional PSt and allylic compound were reacted in the presence of bis-(2,4,6-trimethylbenzoyl)-phenylphosphine oxide (BAPO), which is a cleavage type photoinitiator, yielding azide and hydroxyl functional PSt. Subsequently, the obtained PSt was employed in the ROP of ε-CL, giving PSt-*b*-PCL diblock copolymer with azide unit at the core. PSt-b-PCL was clicked with alkyne end-capped PEG, yielding PSt-PCL-PEG miktoarm star polymer [70].

Thiol-ene Michael addition reactions slightly differs from radical-mediated thiol-ene reactions. In these reactions, the abstraction of hydrogen with suitable bases produces an ion. Then, the thiolate anion is attached to an olefinic moiety (having an e-withdrawing unit) and then a carbanion intermediate is produced, which in turn takes a hydrogen from another thiol, yielding a new thiolate ion. The reaction goes on until all double bonds are used up [71].

Thiol-ene Michael reactions are very effective green conjugation techniques and used in many biochemical functionalization procedures and surface functionalization of biomaterials [72, 73]. Additionally, conjugation of polymers or of small molecules to polymers can be accomplished via nucleophile- and base-catalyzed thiol-ene Michael reactions even in very dilute systems without resulting in detrimental side products [74]. Yu *et al*. reported an elegant synthetic procedure for the preparation of sequence-ordered polymers via sequential thiol-ene Michael addition and radical mediated thiol–ene reactions in one-pot manner. The thiols which were produced by in situ ring-opening reactions of thiolactones readily reacted with electron-deficient methacrylate double bond of the allyl methacrylate (not the electron-rich allylic double bond) via thiol-ene Michael addition. Subsequent to the

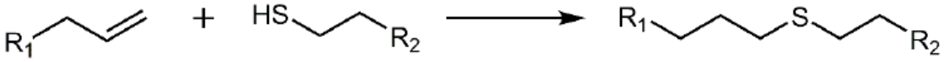

Figure 3: Thiol-ene click reaction mechanism.

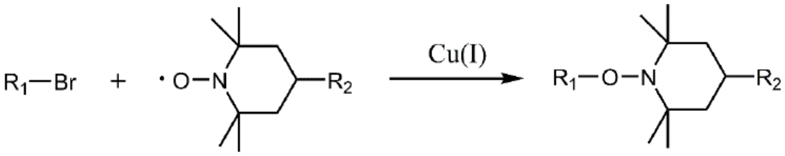

Figure 4: ATNRC click reaction procedure.

completion of the Michael addition and ring opening reactions, radical-mediated thiol-ene click reaction was performed under UV irradiation [75].

5. ATOM TRANSFER NITROXIDE RADICAL COUPLING (ATNRC) CLICK REACTIONS

Atom transfer nitroxide radical coupling is one of the strongest and the most selective ligation methods. Although it is only a ligation method, its mechanism resembles that of atom transfer radical polymerization and nitroxy-mediated polymerization (Figure **4**). Nitroxide radical cannot start polymerization by attacking olefinic bonds, instead it only couples with carbon-centered radicals at diffusion-controlled rates (k_t ~ 10^8 L mol^{-1} s^{-1}) [76]. Lin *et al* reported a very good example of ABC-type triblock linear copolymers via in situ CuAAC and ATNRC reactions. Azide end-capped PtBA, PSt with α-alkyne and ω-bromide functionalities, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) end-capped PEG and PCL polymers were prepared by living polymerization methods. PtBA-*b*-PSt-*b*-PEG and PtBA-*b*-PSt-*b*-PCL triblock copolymers were prepared via in situ CuAAC and ATNRC click reactions of corresponding homopolymers in the presence of CuBr/PMDETA catalyst system [77].

6. ALDEHYDE–AMINOOXY CLICK REACTIONS

Aldehyde-aminooxy reactions are accepted as biorthogonal click reactions and include condensation reactions of aldehydes or ketones with α-effect amines (hydrazides or aminooxy reagents) [78]. This reaction method was used for the preparation and chemical modification of different biologically important macromolecular structures [79].

Wu *et al*. synthesized PNIPAM-PEG miktoarm star polymer via RAFT polymerization of N-isopropylacrylamide (NIPAM) and aldehyde-aminooxy conjugation method (Figure **5**). PNIPAM macro-RAFT agent was prepared via RAFT polymerization of N-

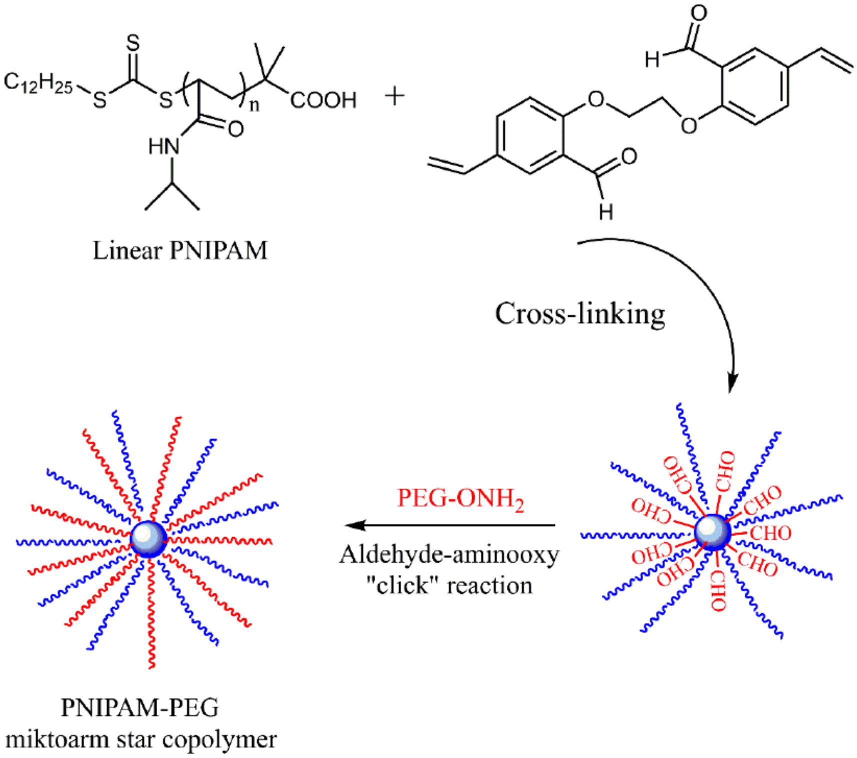

Figure 5: Synthesis of PNIPAM-PEG miktoarm star polymer via RAFT polymerization of poly(N-isopropylacrylamide) (PNIPAM) and aldehyde-aminooxy conjugation method.

isopropylacrylamide (NIPAM) using 2-(dodecylsulfanylthiocarbonylsulfanyl)-2-methylpropionic acid (DMPA) RAFT agent in the presence of 2,2'-azobisisobutyronitrile (AIBN). Then, it was used as the macroinitiator in the crosslinking reaction of the aldehyde functionalized divinyl compound. The obtained multiarm star polymer had a crosslinked core with aldehyde functional groups. Then, the aldehyde groups at the core were conjugated with aminooxy functional PEG, yielding miktoarm star with PNIPAM and PEG polymers chains [80].

7. CONCLUSION

Click chemistry techniques are very effective synthetic tools for the preparation of tailor-made elegant polymeric structures. Among them, Cu(I)-catalyzed azide-alkyne [3+2] dipolar cycloaddition reaction (CuAAC) was regarded as “the cream of the crop” due to its high tolerance to variety of functional units and near-perfect yields in very mild conditions. Whereas the use of transition metal catalyst is a major drawback limiting its use in biochemical applications. Since Diels-Alder, thiol-ene, and aldehyde-aminooxy click reaction methods do not involve metal catalyst species, they can be safely employed in the synthesis macromolecules for biological and biochemical applications.

REFERENCES

[1] Kolb HC, Finn MG, Sharpless KB. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. Angew Chemie Int Ed 2001; 40(11): 2004-21. https://doi.org/10.1002/1521-3773(20010601)40:11<2004::AID-ANIE2004>3.0.CO;2-5

[2] Huisgen R. 1,3-Dipolar Cycloadditions. Past and Future. Angew Chemie Int Ed English 1963; 2(10): 565-98. https://doi.org/10.1002/anie.196305651

[3] Terzic I, Meereboer NL, Loos K. CuAAC click chemistry: a versatile approach towards PVDF-based block copolymers. Polym Chem 2018; 9(27): 3714-20. https://doi.org/10.1039/C8PY00742J

[4] Durmaz H, Sanyal A, Hizal G, Tunca U. Double click reaction strategies for polymer conjugation and post-functionalization of polymers. Polym Chem 2012; 3(4): 825-35. https://doi.org/10.1039/C1PY00471A

[5] Meldal M. Polymer "Clicking" by CuAAC Reactions. Macromol Rapid Commun 2008; 29(12-13): 1016-51. https://doi.org/10.1002/marc.200800159

[6] Kolb HC, Sharpless KB. The growing impact of click chemistry on drug discovery. Drug Discov Today 2003; 8(24): 1128-37. https://doi.org/10.1016/S1359-6446(03)02933-7

[7] Fournier D, Hoogenboom R, Schubert US. Clicking polymers: a straightforward approach to novel macromolecular architectures. Chem Soc Rev 2007; 36(8): 1369-80. https://doi.org/10.1039/b700809k

[8] Moses JE, Moorhouse AD. The growing applications of click chemistry. Chem Soc Rev 2007; 36(8): 1249-62. https://doi.org/10.1039/B613014N

[9] Barner-Kowollik C, Du Prez FE, Espeel P, Hawker CJ, Junkers T, Schlaad H, *et al*. "Clicking" Polymers or Just Efficient Linking: What Is the Difference? Angew Chemie Int Ed 2011; 50(1): 60-2. https://doi.org/10.1002/anie.201003707

[10] Dabiri M, Kasmaei M, Salari P, Movahed SK. Copper nanoparticle decorated three dimensional graphene with high catalytic activity for Huisgen 1,3-dipolar cycloaddition. RSC Adv 2016; 6(62): 57019-23. https://doi.org/10.1039/C5RA25317A

[11] Patil JD, Patil SA, Pore DM. A polymer supported ascorbate functionalized task specific ionic liquid: an efficient reusable catalyst for 1,3-dipolar cycloaddition. RSC Adv 2015; 5(27): 21396-404. https://doi.org/10.1039/C4RA16481D

[12] Pan S, Yan S, Osako T, Uozumi Y. Batch and Continuous-Flow Huisgen 1,3-Dipolar Cycloadditions with an Amphiphilic Resin-Supported Triazine-Based Polyethyleneamine Dendrimer Copper Catalyst. ACS Sustain Chem Eng 2017; 5(11): 10722-34. https://doi.org/10.1021/acssuschemeng.7b02646

[13] Gorur M, Yilmaz F, Kilic A, Demirci A, Ozdemir Y, Kosemen A, *et al*. Synthesis, characterization, electrochromic properties, and electrochromic device application of a novel star polymer consisting of thiophene end-capped poly(ε-caprolactone) arms emanating from a hexafunctional cyclotriphosphazene core. J Polym Sci Part A Polym Chem 2010; 48(16): 3668-82. https://doi.org/10.1002/pola.24151

[14] Gorur M, Yilmaz F, Kilic A, Sahin ZM, Demirci A. Synthesis of pyrene end-capped A6 dendrimer and star polymer with phosphazene core via "click chemistry." J Polym Sci Part A Polym Chem 2011; 49(14): 3193-206. https://doi.org/10.1002/pola.24756

[15] Doganci E, Gorur M, Uyanik C, Yilmaz F. Synthesis of AB3-type miktoarm star polymers with steroid core via a combination of "Click" chemistry and ring opening polymerization techniques. J Polym Sci Part A Polym Chem 2014; 52(23): 3390-9. https://doi.org/10.1002/pola.27406

[16] Eren O, Gorur M, Keskin B, Yilmaz F. Synthesis and characterization of ferrocene end-capped poly(ε-caprolactone)s by a combination of ring-opening polymerization and "click" chemistry techniques. React Funct Polym 2013; 73(1): 244-53. https://doi.org/10.1016/j.reactfunctpolym.2012.10.009

[17] Huang D, Qin A, Tang BZ. CHAPTER 1 Overview of Click Polymerization. In: Click Polymerization The Royal Society of Chemistry; 2018. p. 1-35. https://doi.org/10.1039/9781788010108-00001

[18] Golas PL, Tsarevsky N V, Sumerlin BS, Matyjaszewski K. Catalyst Performance in "Click" Coupling Reactions of Polymers Prepared by ATRP: Ligand and Metal Effects. Macromolecules 2006; 39(19): 6451-7. https://doi.org/10.1021/ma061592u

[19] Hartwig S, Hecht S. Polypseudopeptides with Variable Stereochemistry: Synthesis via Click-Chemistry, Postfunctionalization, and Conformational Behavior in Solution. Macromolecules 2010; 43(1): 242-8. https://doi.org/10.1021/ma902018w

[20] Chen Y, Guan Z. Bioinspired Modular Synthesis of Elastin-Mimic Polymers To Probe the Mechanism of Elastin Elasticity. J Am Chem Soc 2010; 132(13): 4577-9. https://doi.org/10.1021/ja9104446

[21] Kumar A, Chhatra RK, Pandey PS. Synthesis of Click Bile Acid Polymers and Their Application in Stabilization of Silver Nanoparticles Showing Iodide Sensing Property. Org Lett 2010; 12(1): 24-7. https://doi.org/10.1021/ol902351g

[22] Tsarevsky N V, Sumerlin BS, Matyjaszewski K. Step-Growth "Click" Coupling of Telechelic Polymers Prepared by Atom

Transfer Radical Polymerization. Macromolecules 2005; 38(9): 3558-61.
https://doi.org/10.1021/ma050370d

[23] Lammens M, Fournier D, Fijten MWM, Hoogenboom R, Prez F Du. Star-Shaped Polyacrylates: Highly Functionalized Architectures via CuAAC Click Conjugation. Macromol Rapid Commun 2009; 30(23): 2049-55.
https://doi.org/10.1002/marc.200900494

[24] von der Ehe C, Kempe K, Bauer M, Baumgaertel A, Hager MD, Fischer D, *et al*. Star-Shaped Block Copolymers by Copper-Catalyzed Azide-Alkyne Cycloaddition for Potential Drug Delivery Applications. Macromol Chem Phys 2012; 213(20): 2146-56.
https://doi.org/10.1002/macp.201200307

[25] Doganci E, Tasdelen MA, Yilmaz F. Synthesis of Miktoarm Star-Shaped Polymers with POSS Core via a Combination of CuAAC Click Chemistry, ATRP, and ROP Techniques. Macromol Chem Phys 2015; 216(17): 1823-30.
https://doi.org/10.1002/macp.201500199

[26] Iskin B, Yilmaz G, Yagci Y. Synthesis of ABC type miktoarm star copolymers by triple click chemistry. Polym Chem 2011; 2(12): 2865-71.
https://doi.org/10.1039/c1py00352f

[27] Demirci G, Tasdelen MA. Synthesis and characterization of graft copolymers by photoinduced CuAAC click chemistry. Eur Polym J 2015; 66: 282-9.
https://doi.org/10.1016/j.eurpolymj.2015.02.029

[28] Doran S, Yagci Y. Graft polymer growth using tandem photoinduced photoinitiator-free CuAAC/ATRP. Polym Chem 2015; 6(6): 946-52.
https://doi.org/10.1039/C4PY01307G

[29] Acik G, Altinkok C, Tasdelen MA. Synthesis and characterization of polypropylene-graft-poly(l-lactide) copolymers by CuAAC click chemistry. J Polym Sci Part A Polym Chem 2018; 56(22): 2595-601.
https://doi.org/10.1002/pola.29241

[30] Tsarevsky N V, Bencherif SA, Matyjaszewski K. Graft Copolymers by a Combination of ATRP and Two Different Consecutive Click Reactions. Macromolecules 2007; 40(13): 4439-45.
https://doi.org/10.1021/ma070705m

[31] Hossain MD, Valade D, Jia Z, Monteiro MJ. Cyclic polystyrene topologies via RAFT and CuAAC. Polym Chem 2012; 3(10): 2986-95.
https://doi.org/10.1039/c2py20505j

[32] Lonsdale DE, Monteiro MJ. Various polystyrene topologies built from tailored cyclic polystyrene via CuAAC reactions. Chem Commun 2010; 46(42): 7945-7.
https://doi.org/10.1039/c0cc02904a

[33] Qin A, Lam JWY, Jim CKW, Zhang L, Yan J, Häussler M, *et al*. Hyperbranched Polytriazoles: Click Polymerization, Regioisomeric Structure, Light Emission, and Fluorescent Patterning. Macromolecules 2008; 41(11): 3808-22.
https://doi.org/10.1021/ma800538m

[34] Tang Y, Jim CKW, Liu Y, Ye L, Qin A, Lam JWY, *et al*. Synthesis and Curing of Hyperbranched Poly(triazole)s with Click Polymerization for Improved Adhesion Strength. ACS Appl Mater Interfaces 2010; 2(2): 566-74.
https://doi.org/10.1021/am9008727

[35] Wu W, Ye C, Yu G, Liu Y, Qin J, Li Z. New Hyperbranched Polytriazoles Containing Isolation Chromophore Moieties Derived from AB4 Monomers through Click Chemistry under Copper(I) Catalysis: Improved Optical Transparency and Enhanced NLO Effects. Chem - A Eur J 2012; 18(14): 4426-34.
https://doi.org/10.1002/chem.201102872

[36] Scheel AJ, Komber H, Voit BI. Novel Hyperbranched Poly([1,2,3]-triazole)s Derived from AB2 Monomers by a 1,3-Dipolar Cycloaddition. Macromol Rapid Commun 2004; 25(12): 1175-80.
https://doi.org/10.1002/marc.200400097

[37] Rostovtsev V V, Green LG, Fokin V V, Sharpless KB. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. Angew Chemie Int Ed 2002; 41(14): 2596-9.
https://doi.org/10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4

[38] Caballero A, Zapata F, González L, Molina P, Alkorta I, Elguero J. Discovery of anion-π interactions in the recognition mechanism of inorganic anions by 1,2,3-triazolium rings. Chem Commun 2014; 50(36): 4680-2.
https://doi.org/10.1039/C4CC00169A

[39] Romero T, Caballero A, Tárraga A, Molina P. A Click-Generated Triazole Tethered Ferrocene−Pyrene Dyad for Dual-Mode Recognition of the Pyrophosphate Anion. Org Lett 2009; 11(15): 3466-9.
https://doi.org/10.1021/ol901308z

[40] Ata S, Basak S, Mal D, Singha NK. Synthesis and self-assembly behavior of POSS tethered amphiphilic polymer based on poly(caprolactone) (PCL) grafted with poly(acrylic acid) (PAA) via ROP, ATRP, and CuAAC reaction. J Polym Res 2017; 24(2): 19.
https://doi.org/10.1007/s10965-016-1171-6

[41] Zhu J, Liu Y, Xiao L, Zhou P. Temperature-Sensitive (BA)(AC)2 Miktoarm Star Diblock Copolymer Based on PMMA, PPEGMA, and PNIPAm. Macromol Chem Phys 2016; 217(6): 773-82.
https://doi.org/10.1002/macp.201500449

[42] Vora A, Singh K, Webster DC. A new approach to 3-miktoarm star polymers using a combination of reversible addition-fragmentation chain transfer (RAFT) and ring opening polymerization (ROP) via "Click" chemistry. Polymer (Guildf) 2009; 50(13): 2768-74.
https://doi.org/10.1016/j.polymer.2009.03.054

[43] Harvison MA, Lowe AB. Combining RAFT Radical Polymerization and Click/Highly Efficient Coupling Chemistries: A Powerful Strategy for the Preparation of Novel Materials. Macromol Rapid Commun 2011; 32(11): 779-800.
https://doi.org/10.1002/marc.201100156

[44] Ye C, Zhao G, Zhang M, Du J, Zhao Y. Precise Synthesis of ABCDE Star Quintopolymers by Combination of Controlled Polymerization and Azide-Alkyne Cycloaddition Reaction. Macromolecules 2012; 45(18): 7429-39.
https://doi.org/10.1021/ma3015118

[45] Chu Y, Yu H, Zhang Y, Zhang G, Ma Y, Zhuo R, *et al*. Synthesis and characterization of biodegradable amphiphilic ABC Y-shaped miktoarm terpolymer by click chemistry for drug delivery. J Polym Sci Part A Polym Chem 2014; 52(23): 3346-55.
https://doi.org/10.1002/pola.27396

[46] Gungor FS, Kiskan B. One-pot synthesis of poly(triazole-graft-caprolactone) via ring-opening polymerization combined with click chemistry as a novel strategy for graft copolymers. React Funct Polym 2014; 75: 51-5.
https://doi.org/10.1016/j.reactfunctpolym.2013.12.005

[47] Tasdelen MA. Poly(epsilon-caprolactone)/clay nanocomposites via "click" chemistry. Eur Polym J 2011; 47(5): 937-41.
https://doi.org/10.1016/j.eurpolymj.2011.01.004

[48] Gozgen A, Dag A, Durmaz H, Sirkecioglu O, Hizal G, Tunca U. ROMP-NMP-ATRP combination for the preparation of 3-miktoarm star terpolymer via click chemistry. J Polym Sci Part A Polym Chem 2009; 47(2): 497-504.
https://doi.org/10.1002/pola.23166

[49] Senthamizhan A, Celebioglu A, Bayir S, Gorur M, Doganci E, Yilmaz F, *et al*. Highly Fluorescent Pyrene-Functional Polystyrene Copolymer Nanofibers for Enhanced Sensing Performance of TNT. ACS Appl Mater Interfaces 2015; 7(38): 21038-46.
https://doi.org/10.1021/acsami.5b07184

[50] Altintas O, Hizal G, Tunca U. ABC-type hetero-arm star terpolymers through "Click" chemistry. J Polym Sci Part A Polym Chem 2006; 44(19): 5699-707. https://doi.org/10.1002/pola.21633

[51] Durmaz H, Dag A, Altintas O, Erdogan T, Hizal G, Tunca U. One-Pot Synthesis of ABC Type Triblock Copolymers via in situ Click [3 + 2] and Diels−Alder [4 + 2] Reactions. Macromolecules 2007; 40(2): 191-8. https://doi.org/10.1021/ma061819l

[52] Zhang Y, Li C, Liu S. One-pot synthesis of ABC miktoarm star terpolymers by coupling ATRP, ROP, and click chemistry techniques. J Polym Sci Part A Polym Chem 2009; 47(12): 3066-77. https://doi.org/10.1002/pola.23388

[53] Barner-Kowollik C, Inglis AJ. Has Click Chemistry Lead to a Paradigm Shift in Polymer Material Design? Macromol Chem Phys 2009; 210(12): 987-92. https://doi.org/10.1002/macp.200900139

[54] Opsteen JA, van Hest JCM. Modular synthesis of block copolymers via cycloaddition of terminal azide and alkyne functionalized polymers. Chem Commun 2005;(1): 57-9. https://doi.org/10.1039/b412930j

[55] Quémener D, Davis TP, Barner-Kowollik C, Stenzel MH. RAFT and click chemistry: A versatile approach to well-defined block copolymers. Chem Commun 2006;(48): 5051-3. https://doi.org/10.1039/B611224B

[56] He X, Liang L, Xie M, Zhang Y, Lin S, Yan D. Synthesis of Novel Linear PEO-b-PS-b-PCL Triblock Copolymers by the Combination of ATRP, ROP, and a Click Reaction. Macromol Chem Phys 2007; 208(16): 1797-802. https://doi.org/10.1002/macp.200700153

[57] McBride MK, Gong T, Nair DP, Bowman CN. Photo-mediated copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) "click" reactions for forming polymer networks as shape memory materials. Polymer (Guildf) 2014; 55(23): 5880-4. https://doi.org/10.1016/j.polymer.2014.08.001

[58] Zhou X, Wan L, Hu Y, E Y, Huang F, Du L. Synthesis and characterization of novel polytriazoleimides by CuAAC step-growth polymerization. Polym J 2010; 42(3): 216-22. https://doi.org/10.1038/pj.2009.337

[59] Besset C, Pascault JP, Fleury E, Drockenmuller E, Bernard J. Structure−Properties Relationship of Biosourced Stereocontrolled Polytriazoles from Click Chemistry Step Growth Polymerization of Diazide and Dialkyne Dianhydrohexitols. Biomacromolecules 2010; 11(10): 2797-803. https://doi.org/10.1021/bm100872h

[60] Diels O, Alder K. Synthesen in der hydroaromatischen Reihe. Justus Liebigs Ann Chem 1928; 460(1): 98-122. https://doi.org/10.1002/jlac.19284600106

[61] Tasdelen MA. Diels-Alder "click" reactions: recent applications in polymer and material science. Polym Chem 2011; 2(10): 2133-45. https://doi.org/10.1039/c1py00041a

[62] Szalai ML, McGrath D V, Wheeler DR, Zifer T, McElhanon JR. Dendrimers Based on Thermally Reversible Furan−Maleimide Diels−Alder Adducts. Macromolecules 2007; 40(4): 818-23. https://doi.org/10.1021/ma062093w

[63] Vieyres A, Lam T, Gillet R, Franc G, Castonguay A, Kakkar A. Combined CuI-catalysed alkyne -azidecycloaddition and furan-maleimide Diels-Alder "click" chemistry approach to thermoresponsive dendrimers. Chem Commun 2010; 46(11): 1875-7. https://doi.org/10.1039/B924888A

[64] Farhat W, Venditti R, Becquart F, Ayoub A, Majesté JC, Taha M, *et al*. Synthesis and Characterization of Thermoresponsive Xylan Networks by Diels-Alder Reaction. ACS Appl Polym Mater 2019; 1(4): 856-66. https://doi.org/10.1021/acsapm.9b00095

[65] Inglis AJ, Sinnwell S, Stenzel MH, Barner-Kowollik C. Ultrafast Click Conjugation of Macromolecular Building Blocks at Ambient Temperature. Angew Chemie Int Ed 2009; 48(13): 2411-4. https://doi.org/10.1002/anie.200805993

[66] Durmaz H, Karatas F, Tunca U, Hizal G. Heteroarm H-shaped terpolymers through the combination of the Diels-Alder reaction and controlled/living radical polymerization techniques. J Polym Sci Part A Polym Chem 2006; 44(13): 3947-57. https://doi.org/10.1002/pola.21499

[67] Bousquet A, Barner-Kowollik C, Stenzel MH. Synthesis of comb polymers via grafting-onto macromolecules bearing pendant diene groups via the hetero-Diels-Alder-RAFT click concept. J Polym Sci Part A Polym Chem 2010; 48(8): 1773-81. https://doi.org/10.1002/pola.23943

[68] Doganci E, Gorur M, Yilmaz F. CHAPTER 4 Use of Click Chemistry as a Coupling Strategy for the Synthesis of Miktoarm Star Polymers. In: Miktoarm Star Polymers: From Basics of Branched Architecture to Synthesis, Self-assembly and Applications The Royal Society of Chemistry; 2017. p. 90-115. https://doi.org/10.1039/9781788010429-00090

[69] Lowe AB. Thiol-ene "click" reactions and recent applications in polymer and materials synthesis. Polym Chem 2010; 1(1): 17-36. https://doi.org/10.1039/B9PY00216B

[70] Iskin B, Yilmaz G, Yagci Y. ABC type miktoarm star copolymers through combination of controlled polymerization techniques with thiol-ene and azide-alkyne click reactions. J Polym Sci Part A Polym Chem 2011; 49(11): 2417-22. https://doi.org/10.1002/pola.24672

[71] Fairbanks BD, Love DM, Bowman CN. Efficient Polymer-Polymer Conjugation via Thiol-ene Click Reaction. Macromol Chem Phys 2017; 218(18): 1700073. https://doi.org/10.1002/macp.201700073

[72] Xu K, Cantu DA, Fu Y, Kim J, Zheng X, Hematti P, *et al*. Thiol-ene Michael-type formation of gelatin/poly(ethylene glycol) biomatrices for three-dimensional mesenchymal stromal/stem cell administration to cutaneous wounds. Acta Biomater 2013; 9(11): 8802-14. https://doi.org/10.1016/j.actbio.2013.06.021

[73] Stengelin E, Kuzmina A, Beltramo GL, Koziol MF, Besch L, Schröder R, *et al*. Bone Scaffolds Based on Degradable Vaterite/PEG-Composite Microgels. Adv Healthc Mater 2020; 9(11): 1901820. https://doi.org/10.1002/adhm.201901820

[74] Nair DP, Podgórski M, Chatani S, Gong T, Xi W, Fenoli CR, *et al*. The Thiol-Michael Addition Click Reaction: A Powerful and Widely Used Tool in Materials Chemistry. Chem Mater 2014; 26(1): 724-44. https://doi.org/10.1021/cm402180t

[75] Yu L, Wang L-H, Hu Z-T, You Y-Z, Wu D-C, Hong C-Y. Sequential Michael addition thiol-ene and radical-mediated thiol-ene reactions in one-pot produced sequence-ordered polymers. Polym Chem 2015; 6(9): 1527-32. https://doi.org/10.1039/C4PY01363H

[76] Yang D, Feng C, Hu J. Nitroxide radical coupling reaction: a powerful tool in polymer and material synthesis. Polym Chem 2013; 4(8): 2384-94. https://doi.org/10.1039/c2py20987j

[77] Lin W, Fu Q, Zhang Y, Huang J. One-Pot Synthesis of ABC Type Triblock Copolymers via a Combination of "Click Chemistry" and Atom Transfer Nitroxide Radical Coupling Chemistry. Macromolecules 2008; 41(12): 4127-35. https://doi.org/10.1021/ma702404t

[78] Baskin JM, Bertozzi CR. Bioorthogonal Click Chemistry: Covalent Labeling in Living Systems. QSAR Comb Sci 2007;

26(11-12): 1211-9.
https://doi.org/10.1002/qsar.200740086

[79] Wu Z-M, Liang H, Lu J, Deng W-L. Miktoarm star copolymers via combination of RAFT arm-first technique and aldehyde-aminooxy click reaction. J Polym Sci Part A Polym Chem 2010; 48(15): 3323-30.
https://doi.org/10.1002/pola.24116

[80] Wu Z, Liang H, Lu J. Synthesis of Poly(N-isopropylacrylamide)−Poly(ethylene glycol) Miktoarm Star Copolymers via RAFT Polymerization and Aldehyde−Aminooxy Click Reaction and Their Thermoinduced Micellization. Macromolecules 2010; 43(13): 5699-705.
https://doi.org/10.1021/ma100800b

Received on 07-08-2021 Accepted on 14-10-2021 Published on 19-11-2021

DOI: https://doi.org/10.12974/2311-8717.2021.09.05