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REVIEW

Ugi Reaction in Polymer Chemistry: Syntheses, Applications and Prospectives

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The Ugi reaction, one of the most famous multicomponent reaction, has recently been introduced into polymer chemistry as a novel, efficient and useful tool to prepare multifunctional polymers. In this review, recent progress on the utilization of the Ugi reactions in polymer chemistry, including monomer synthesis, polycondensation, post-polymerization modification (PPM) etc. has been be summarized. Meanwhile, the applications of multifunctional polymers synthesized *via* the Ugi reaction and the future development of the Ugi reaction in polymer chemistry have also been discussed.

Introduction

'Macromolecular chemistry is the youngest branch of organic chemistry…….'

------Hermann Staudinger

Exploring efficient organic reactions and introducing them into polymer chemistry to prepare new monomers, discover new polymerization approaches, and modify polymer chain-ends or side chains through the post-polymerization modification (PPM) strategy are the even-lasting theme for polymer chemists. With the increasing applications of new functional polymers in biology, energy, medicine and environment areas, polymer preparation has entered the precise-synthesis era, requiring the synthesized polymers have highly controllable structures and multiple functions through greener synthesis process. Thus, deeper investigation and utilization of delicate organic reactions to prepare elegant polymers for multipurpose application are crucial for the development of the modern polymer chemistry.

Although firstly described by K. B. Sharpless and co-workers in 2001, the click reactions have actually attracted broader attentions since the application in polymer chemistry[1-6]. Due to their 'click' properties, such as highly efficient, atom-economic, modular, easy operation and purification etc., click reactions have been welcomed in many research areas outside organic chemistry, such as material science, life science, chemical biology and polymer chemistry[7-13]. The introduction of click reactions, such as the copper-catalyzed azide–alkyne cycloaddition (CuAAC), thiol–ene/yne free-radical addition, (hetero) Diels–Alder reaction, etc., has led a rapid research storm in polymer chemistry[2, 14-20]. For example, when used in the PPM methods which are normally difficult through

traditional coupling reactions, the high efficient click reactions make it possible to efficient link small molecules on the main chain of polymer precursors or even completely stitch macromolecules together to achieve copolymers, demonstrating the progress in polymer chemistry by introducing highly efficient organic reactions. Besides the successful introducing two component click reactions into polymer chemistry, more and more other charming organic reactions have been reassessed from the angle of polymer synthesis and introduced in the polymer chemistry. Among them, the multicomponent reactions (MCRs) show unique values.

MCRs are those reactions to combine more than two reactants in a sequential manner to give highly selective products that retain majority of the atoms of the starting materials. Although known for over 150 years in organic chemistry, only recently, with Meier's introducing tri-component Passerini reaction into polymer chemistry[21, 22], a series of multicomponent reactions (MCRs) such as Ugi reaction, Biginelli reaction, Kabachnik-Fields (KF) reaction, thiolactone-based reactions etc., have been reconsidered from the perspective of polymer chemistry and ultilized to prepare delicated polymers[23-25]. Different from traditional two-component coupling reactions (click reactions etc.), MCRs can efficiently compress three or more reactants into a single product, thus, three or more functional groups might be simply linked together in one step, which will probably lead to polymers with sophisticated structures or multiple functions.

As one of the most famous MCRs, Ugi reaction has been verified a highly efficient and atom-economic organic reaction for total synthesis of natural products. The Ugi reaction is named after Ivar Karl Ugi, who first reported this reaction in 1959[26, 27]. The Ugi reaction is a four-component reaction involving a ketone or aldehyde, an amine, a carboxylic acid and an isocyanide to form a bis-amide while only losing one water as the byproduct. First, an imine is formed from the aldehyde and amine components. The imine is then protonated by the carboxylic acid. And the isocyanide reacts in the α-addition

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with the activated (protonated) imine and carboxylate to form the corresponding imidate. Subsequent Mumm rearrangement yields the final Ugi product (Fig. 1)[28]. Recently, Ugi reactions have been introduced in polymer chemistry, and proven a good tool for macromolecular architecture design[29]. Here, in this mini review, we will summarize the recent progress on the usage of Ugi reactions in polymer chemistry, including monomer synthesis, polycondensation, PPM etc., and we will also make a brief introduction on the applications of multifunctional polymers synthesized via Ugi reaction and discuss about the future development of Ugi reaction in polymer chemistry.
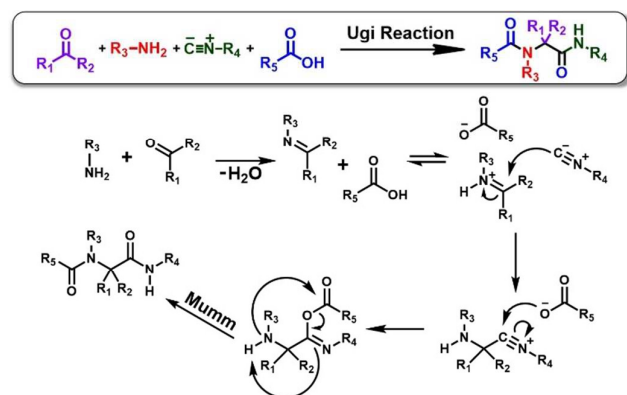

Fig. 1 Reaction mechanism of Ugi reaction.

Monomer Synthesis

In polymer chemistry, the most direct and easiest way to prepare polymers with diverse structures is to synthesize monomers with diverse structures and polymerize them. In 2003, Wright et al. introduced Ugi reaction in the synthesis of norbornenyl monomers for the first time (Fig. 2)[30]. Four different monomers, either starting from a norbornenyl acid or an aldehyde derivative, were prepared via the Ugi reaction. And then, the monomers were converted to the corresponding polymers by a ring-opening metathesis polymerization (ROMP) in the presence of the second-generation Grubbs' catalyst. Polymers with molecular weight up to 50 kDa could be obtained. Besides, the enantiomerically pure reactants have also been used to get chiral monomers via Ugi reaction, but the diastereoselectivity ratio was only 1.7:1 and chromatographic separation of the diastereomers was necessary. Afterwards, polymers with chiral peptide-structures as side chains were obtained via ROMP using those chiral monomers. In this research, the four-component Ugi reaction united four separate units into a single molecule to make diverse monomers and corresponding polymers. Moreover, the structure of Ugi product is similar with dipeptide, thus polymers constructed from these types of monomers may similar with polypeptide or proteins.
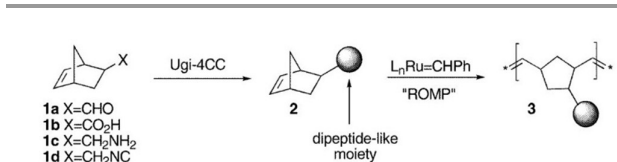

Fig. 2 An Ugi/ROMP Strategy for Diversity-Driven Polymer Synthesis. Reprinted with permission from ref.30. Copyright © 2003, Kluwer Academic Publishers

In 2012, Meier et al. introduced Ugi reaction in the synthesis of α,ω-diene monomers, promoting the application of Ugi reaction in the monomer synthesis once again (Fig. 3)[31]. The 10-undecenoic acid and 10-undecenal (derivatives from castor-oil) reacted with several primary amines and isocyanides through the Ugi reaction to form a library of different α,ω-diene monomers. The obtained monomers were then polymerized through the acyclic diene metathesis (ADMET) polymerization, as well as the thiol–ene addition polymerization to obtain diverse polymers with different molecular weights and polydispersity indices (PDIs). The possibility of versatile post-modification of functional groups in the side chains of the corresponding polymers should be of considerable interest to generate new polymer materials[32].
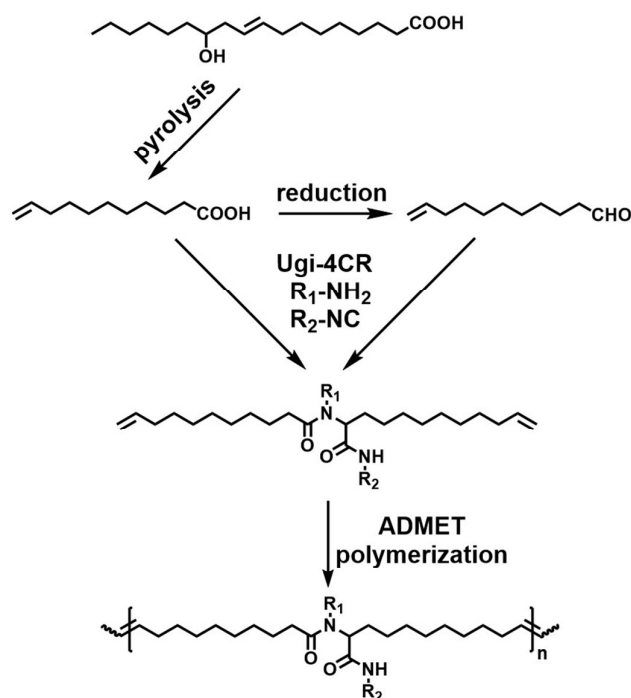
Fig. 3 Synthetic route of diene monomer via Ugi reaction, and the subsequent ADMET polymerization to obtain diverse polymers.

In 2015, a novel class of acrylamide monomers was synthesized via the Ugi reaction[33]. The application of acrylic acid and a variety of amines, aldehydes, and isocyanides as reactants resulted in a set of diversely substituted acrylamides in a highly straightforward one-pot procedure. Those acrylamides were subjected to free radical polymerization to yield amorphous polymers with various designable side-chains. Subsequently, the synthesized polyacrylamides were tested for their biological

activity by a modified Japanese Industrial Standard Z 2801:2000 protocol. All tested polymers showed high tolerance toward Gram-negative *Escherichia coli* and *Pseudomonas fluorescens* as well as Gram-positive *Bacillus subtilis* bacteria, thus suggesting those "easy to tune" polymers for applications requiring biocompatibility.

Polycondensation

Polycondensation, a form of step-growth polymerization, is a process by which two molecules join together, resulting in loss of small molecules which are often water[34-38]. In the modern synthetic strategy, newly emerging efficient reactions are being introduced as polycondensation tools, such as several famous click reactions[39-45]. For another example, as a milestone of new polycondensation methodology, Meier *et al.* introduced a tricomponent Passerini reaction into polymer chemistry to prepare multicomponent polycondensates, opening a door for synthesizing new condensed polymers[21, 46]. From then on, more and more MCRs, including Ugi reaction, Biginelli reaction, Kabachnik-Fields reaction *etc*., have been explored for polycondensate syntheses[47-55].

In 2014, Meier et al. demonstrated a very efficient and modular polycondensation approach to synthesize diversely substituted polyamides via the Ugi four-component reaction (Ugi-4CR) for the first time (Fig. 4)[48]. All six possible monomer combinations of two bifunctional AA-type components and two monofunctional components were investigated to prepare diversely substituted polyamides. A mixed solution of methanol and tetrahydrofuran (THF) was used to ensure the smooth Ugi reaction and the solubility of the obtained polymers, resulting in the Ugi-type condensed polymers with molecular weight up to 18 kDa. Besides, 5-hexynoic acid was also applied in this polycondensation system, to prepare polyamides with alkynyl groups, which can be subsequently modified via CuAAC click reaction. It is notable that, in order to avoid side reactions of the Ugi reaction and get polymers with high molecular weight, the aldehyde component must have a blocked α-position, such as in benzaldehyde or isobutyraldehyde, which does not allow (or does not favor) deprotonation due to a lack of or low α-CH-acidity. By similar approach, in 2014, Luxenhofer et al. also prepared diverse condensed polymers using aromatic monomers via the Ugi reaction[56]. N-methyl-2-pyrrolidone (NMP) was used as solvent in the presence or absence of water. As the result, GPC analysis of the precipitated product hints water might accelerate the polymerization since the Ugi-4CR has been reported to benefit from the presence of water, but not lead to higher molecular weight polymers. Those results are complementary to Meier's results, broadening the synthetic scope of Ugi reaction in polycondensation.
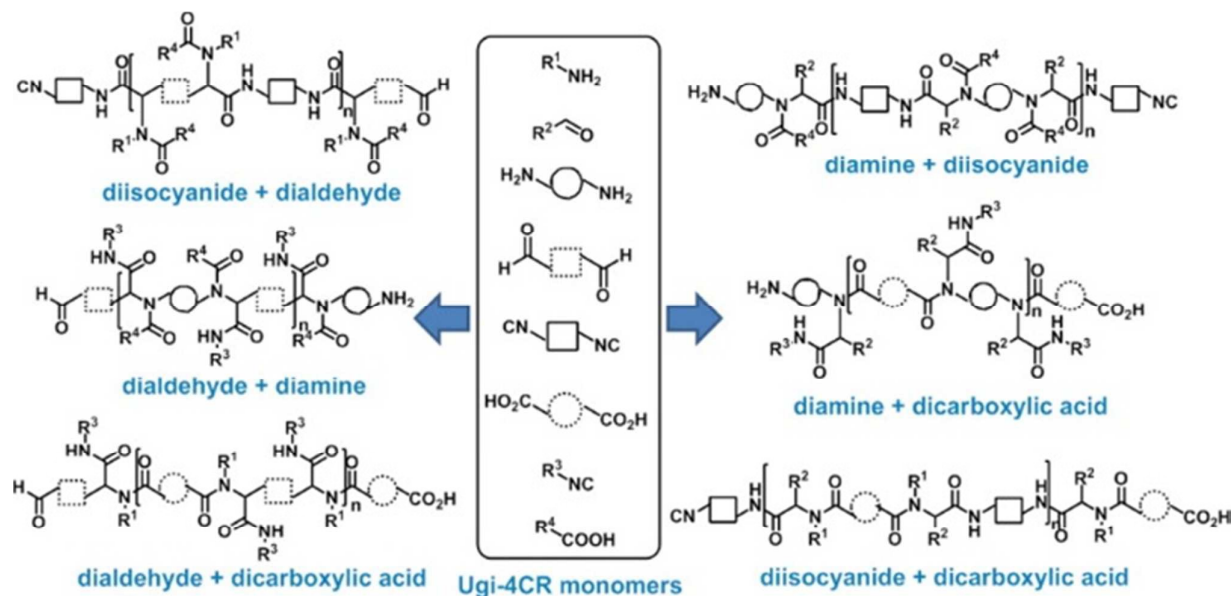

Fig. 4 Polycondensation via Ugi reaction using bifunctional components. Reprinted with permission from ref.48. Copyright © 2014, American Chemical Society.

As a upgraded version, the Ugi five-component condensation (Ugi-5CC) containing carbon dioxide, an alcohol (mostly methanol), an isocyanide, an oxo-component (aldehyde or ketone), and a primary amine to yield N-(alkoxycarbonyl)amino amides has also been developed[57-59]. In 2014, Meier *et al.* applied the Ugi-5CC into polymer synthesis using carbon dioxide as the reactant. Polymers with molecular weight about 20 kDa were facilely prepared via the Ugi-5CC following the polycondensation process[60]. This approach offers a novel route for the incorporation of carbon dioxide into polymers and enable the synthesis of different structural motifs, such as polyurethanes and polyhydantoins in a catalyst-free fashion, paving a new way for a new class of polymers which might not be achievable by other MCRs in a straightforward way.

Post-polymerization modification (PPM)

Modifications of the side or chain-end groups of polymers are common approaches to prepare functional (co)polymers. Among them, stitching two polymer chain-ends together to get a block copolymer can be regarded as a special PPM. However, due to the inherent steric hindrance of the polymer chains, conventional modification reactions are usually slow and inefficient, leading to unsatisfied partially modified polymers. Click reactions are the solution to this thorny problem because of their high efficiency and almost quantitative yields, some copolymers have been successfully prepared through click reactions[61-63]. The traditional click reactions are two-component coupling reactions, thus, the obtained block copolymer is hardly further modified to get multifunctional polymers. To improve this process, the Ugi reaction has been used to prepare middle functionalized copolymers.

In 2014, Tao et al. applied Ugi reaction in the polymer conjugation process (Fig.5)[64]. A benzaldehyde terminated polymethylmethacrylate (PMMA-CHO, $M_{nNMR} \sim 8800$, $M_{nGPC} \sim 24200$, PDI: 1.08) through atom transfer radical polymerization (ATRP) and an aniline terminated methoxypolyethylene glycol (mPEG-NH$_2$, $M_n \sim 5000$, $M_{nGPC} \sim 28000$, PDI: 1.03) were prepared, respectively, and used as parent polymers. Commercially available cyclohexyl isocyanide was chosen as the isocyanide component and different carboxylic acids were used to add various functions to the achieved block copolymers. The molar ratio of the two parent polymers is 1:1, and the reaction was conducted in methanol under room temperature without external added catalyst. The coupling process is almost complete ($\sim$ 100%) in 0.5 h, confirming the high efficiency of Ugi reaction. The ^{1}H NMR spectrum of the purified PMMA-*b*-mPEG copolymer illustrated the Ugi building blocks (CHO & NH$_2$) at two parent polymer chain ends disappeared while the characteristic -NCHCO- peak of the Ugi structure can be clearly observed. The integral ratio between -NCHCO- and ester methylene is 0.50 (theoretical value = 0.5), indicating the complete Ugi reaction between parent polymer chain ends. Meanwhile, the characteristic peaks of the fluorescent moiety in the carboxylic acid can also be clearly observed in the purified copolymer, confirming the successful polymer-polymer coupling via four-component Ugi reaction among mPEG-NH$_2$, PMMA-CHO, carboxylic acid and isocyanide. Meanwhile, the natural property of MCRs results in the middle functionalized block copolymer steming from the functional groups on the carboxylic acids. Thus, using the Ugi reaction as the coupling tool, block copolymers with fluorescent or other reactive groups in the chain middle have been facilely prepared. Furthermore, block copolymer with chain transfer agent (CTA) group in the middle has been used as the macro-CTA in reversible addition-fragmentation chain transfer (RAFT) polymerization to simply prepare miktoarm star copolymer. Those results suggest Ugi reaction can not only behave like traditional two-component click reactions to efficiently stitch two different polymers together to quantitatively generate copolymers, but also facilely implant new functions to the

products due to its unique multicomponent nature. The Ugi reaction, along with other efficient MCRs, might be the new type of click reactions, and lead a new trend of PPM to prepare multifunctional (co)polymers.
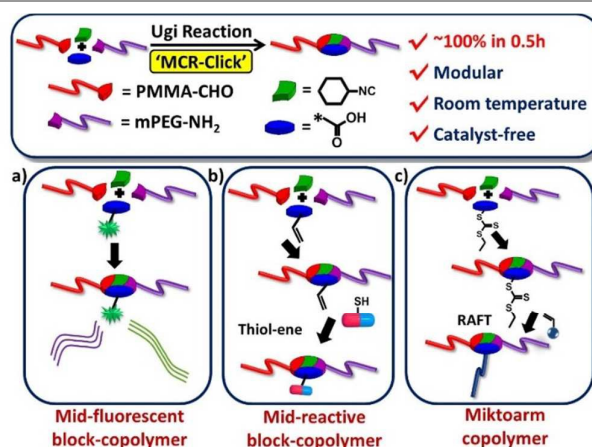

Fig 5. Polymer conjugation via Ugi reaction and the obtained mid-functional block copolymers. a) Mid-fluorescent block copolymer. b) Mid-reactive block copolymer and subsequent modification through thiol-ene click reaction. c) Miktoarm star copolymer by the collaboration of Ugi-type polymer conjugation and RAFT polymerization. Reprinted with permission from ref.64. Copyright © 2014, Royal Society of Chemistry.

Besides, the Ugi reaction has also been applied in the modification of polymer side chains by Meier et al.[65]. The modification allowed a straightforward adjustment of the properties of the random poly(2-oxazoline). Importantly, control over the cloud point and glass transition temperatures were possible by simple variation of the substrates in the multicomponent grafting approach.

Applications

By using the Ugi reaction in polymer synthesis, multifunctional polymers which are desired in many areas, such as materials science, chemical biology, etc. can be facilely prepared.

In 2014, the Ugi reaction was applied in the synthesis of PEGylation agents for the first time by Tao et al. (Fig. 6)[66]. PEGylation, the process of covalent attachment of poly(ethylene glycol) (PEG) chains to therapeutic proteins/peptides, can significantly improve the pharmacological and biological properties of therapeutic proteins/peptides[67-72]. With the rapid development of PEGylation technology, the new generation PEGylation agents have been proposed, i.e., the protein and polymer should cooperate mutually as a whole, the polymer should be not only a cloak, but a partner of the therapeutic protein to promote diagnosis and therapy process. For example, incorporation of tracing element into PEGylation might make the circulation and working site of therapeutic proteins directly visible, leading to more rapid and efficient clinical trial. However, the synthesis of the new generation PEGylation agent is complicated through traditional two-component coupling reactions, which need link functional groups one after another. The usage of Ugi reaction provides a rational solution to this problem. By using functional

modules as raw materials, PEG can be modified with multifunctions in one shot *via* the Ugi reaction. The modification efficiency is more than 90% in 2 h at ambient temperature without any catalyst. Thus, PEG with both protein reactive group and fluorescent group has been facilely prepared as a multifunctional PEGylation agent. The obtained agent was subsequently react with protein to obtain protein-polymer conjugates. Due to the fluorescent group on the PEGylation agent, the conjugates are fluorescent visible, making it possible to be observed directly under UV. The usage of Ugi reaction, both highly efficient and multicomponent, makes the synthesis process much easier to achieve multifunctional product, thus, PEGylation agents with other desired structures and multiple functions are hopefully prepared in the near future.
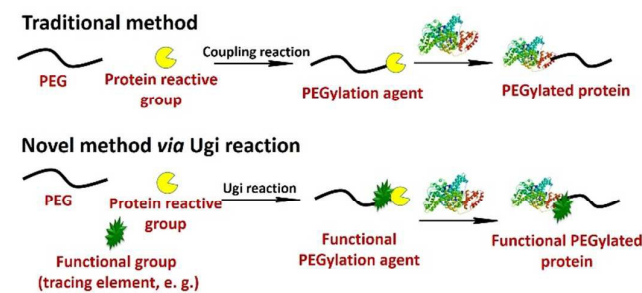

Fig. 6 Synthesis of PEGylation agents using traditional method and novel method *via* Ugi reaction.

Another example is in material science. In 2014, Tao et al. introduce Ugi reaction in the surface modification of carbon nanotubes (CNTs) (Fig. 7)[73]. CNTs, cylindrical nanostructure allotrope of carbon, have been found many potential applications because of their superb mechanical and electrical properties[74-76]. However, the poor solubility of CNTs in both aqueous and organic solvents hampers its real application. Plenty of methods have been developed to solve this problem, including the conjugation of solubilizer on the CNT surface ('grafting to' method), in-situ polymerization on CNT surface ('grafting from' method), etc.[77-84]. However, most of those methods do suffer from tedious processes, harsh reaction conditions or unsatisfactory solubilization effect. Besides, only one kind of polymer can be modified on CNT surface by either approach, limiting the function and application of the obtained CNT-polymer complex. The Ugi reaction has been employed to solve those problems due to its multicomponent nature. In Tao's research, the Ugi reaction, RAFT polymerization and π-π stacking have been conducted in a one pot manner to modify pristine CNTs. A trithiocarbonate (for RAFT) containing a carboxylic group was chosen as the carboxylic source for Ugi reaction; 1-pyrenecarboxaldehyde was used for π-π stacking and as the aldehyde source of Ugi reaction; aniline and commercially available cyclohexyl isocyanide acted as the amine and the isocyanide moieties in Ugi reaction, respectively. All abovementioned compounds were mixed with 2,2'-azobis(2-methylpropionitrile) (AIBN, initiator for RAFT), N-isopropylacrylamide (NIPAAm, monomer for RAFT) and the CNT in a Schlenk tube (methanol as solvent). After 30 min

degass and 20 h polymerization, the CNTs can be well dispersed in methanol, primarily indicating the formation of CNT-PNIPAAm complex through this simple one-pot strategy. The Fourier Translation Infrared Spectroscopy (FT-IR), thermal gravimetric analysis (TGA), transmission electron microscopy (TEM) image and even the Nuclear Magnetic Resonance (NMR) spectra further confirmed the successfully fabrication of CNT-PNIPAAm. The obtained CNT-PNIPAAm can disperse well in common solvents for weeks. Meanwhile, PNIPAAm conjugated on CNT surface remained its thermosensitivity, thus that CNT-PNIPAAm composite can dissolve in cold water and precipitate in hot water. Furthermore, by replace aniline with mPEG-NH$_2$, PNIPAAm and PEG can be simultaneously modified on CNT surface via the one-pot system. This one-pot system can really be regarded as the hybrid of 'grafting-from' and 'grafting-to' methods, making it possible to simply modify carbon material with different polymers.
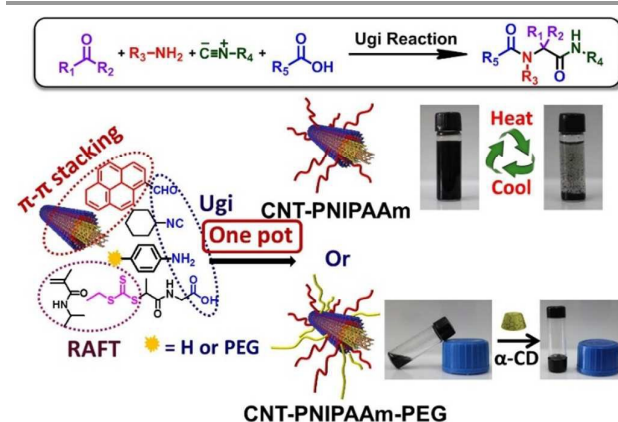

Fig. 7 (Co)polymer modification of CNT surface through one-pot strategy combining Ugi reaction, π-π stacking and RAFT polymerization. Reprinted with permission from ref.73. Copyright © 2014, Royal Society of Chemistry.

Conclusions and perspectives

MCRs have been looked as the possible 'click 2.0 reactions' for new polymer syntheses[85]. In this mini review, we have summarize the recent utilization of Ugi reaction in polymer chemistry, including monomer synthesis, polycondensation, PPM, *etc.*. Due to its high efficiency and multicomponent nature, multifunctional polymers can be facilely prepared via the Ugi reaction. Thus, the introduction of Ugi reaction will benefit many research areas requiring multifunctional polymers. In this review, it has also been briefly described the preliminary applications of multifunctional polymers steming from that Ugi reaction in the chemical biology and material science. Compared with traditional methods, novel methods using Ugi reaction can bring multiple functions in a much easier and greener operation process.

Since the amazing properties of Ugi reaction, it will play a more and more important role in polymer chemistry and other research areas. High molecular weight polymers with dendritic architectures or sequent structures will hopefully be obtained using this fantastic reaction. Multifunctional polymers

synthesized via Ugi reaction will also extend its application range. Despite the success application of the Ugi reaction in the preparation of functional polymers, there are still some limitations that must be concerned about the Ugi reaction. The unbearable smell and relatively high price of isocyanide limit its application for large scale manufacture. And the common used solvent of the Ugi reaction, methanol, is a poor solvent to many polymers, which also limit the application of the Ugi reaction. Besides, the functional modification of isocyanide is difficult, which also limit multifunctional modification of polymers. Fortunately, in addition to the Ugi reaction, there are still many other MCRs can be chosen, such as the Biginelli reaction, mercaptoacetic acid locking imine (MALI) reaction, *etc.* for different purpose applications. For example, Biginelli reaction has been used in surface modifation of CNTs[83], the obtained CNT-polymer composites possessing characteristic properties of anchored polymer can be well dispersed in general solution to expand CNTs' application realm. Besides, more and more MCRs have been introduced in polymer chemistry, and they all play important roles by taking advantage of their own features[23, 86]. The synthesis will become easier to facilely prepare delicated polymers by using these MCRs.

Acknowledgements

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Table of Contents

Ugi Reaction in Polymer Chemistry: Syntheses, Applications and Prospectives

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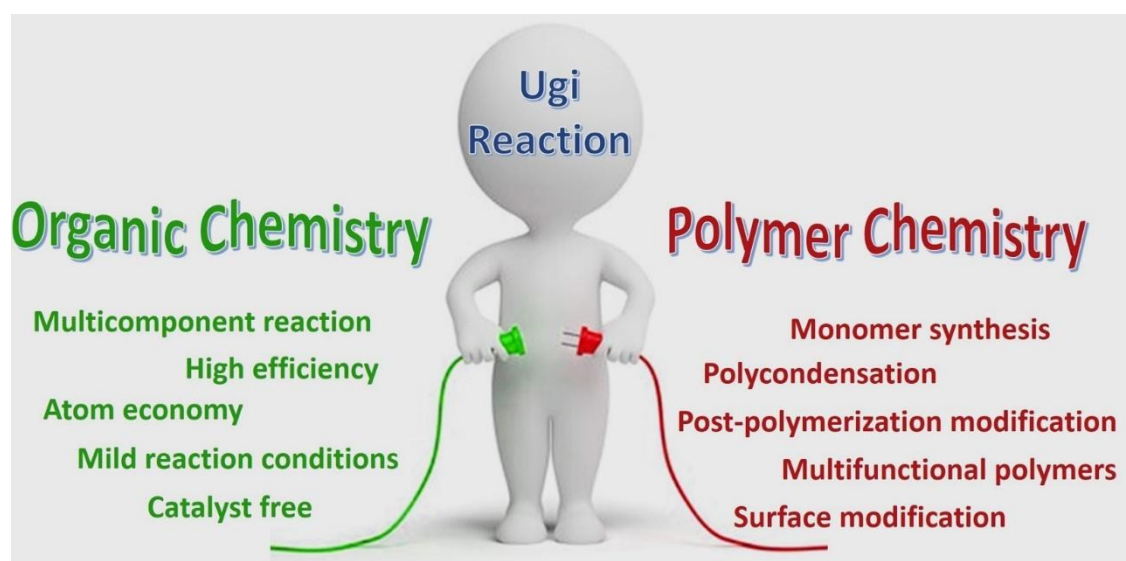
The well-known Ugi reaction is becoming a novel, efficient and useful tool to prepare multifunctional polymers.