

# ABSTRACTS



**INVITED LECTURES**



**CLICK CHEMISTRY AND ATRP: A SIMPLE ROUTE FOR THE PREPARATION OF FUNCTIONAL MATERIALS**

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**Abstract**

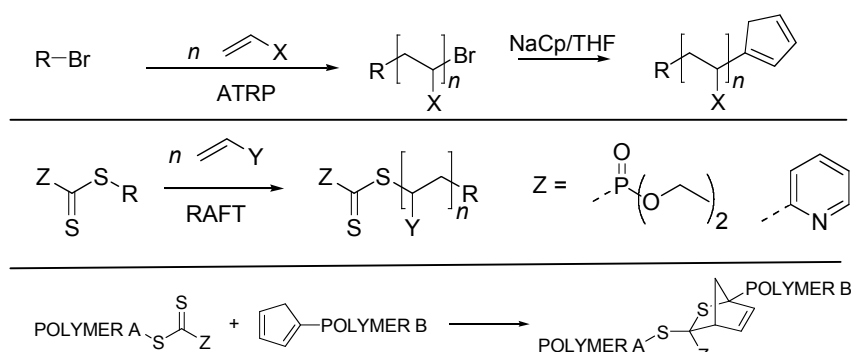
The CuI-catalyzed azide – alkyne cycloaddition, aka. “click chemistry” has been employed in many polymer functionalization and materials synthesis, especially in conjunction with controlled radical polymerization methods, such as ATRP. This click chemistry works so well with ATRP, due to the ease of incorporating clickable functionality into polymers prepared by ATRP and the use of the same catalyst in each process. The combination of these two powerful techniques has greatly expanded the range of available functional materials.

ULTRA-RAPID *CLICK* CONJUGATIONS AT AMBIENT TEMPERATURE

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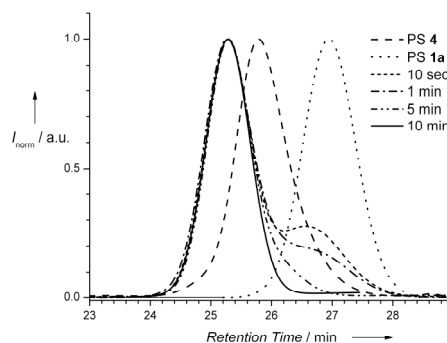
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The *lego*-like preparation of complex macromolecular designs under extremely mild reaction conditions is a desirable synthetic scenario. Ideally, no toxic catalysts should be employed and the conjugation reaction should be complete within a few minutes. With regard to the copper (I) azide-alkyne cycloaddition (CuAAC), the vast majority of publications report reaction times of several hours at temperatures ranging from ambient to 50 °C. However, in the synthesis of star polymers via a *click* coupling method, Gao and Matyjaszewski report a 97 % conversion of all azide moieties into the 1,2,3-triazole groups within 3 h at ambient temperature (using 1:1 stoichiometry).<sup>[1]</sup> Moreover, van Camp *et al.* report the completion of a *click* reaction between azide functionalized poly(isobornyl acrylate) and 2 equivalents of alkyne functionalized poly(1-ethoxyethyl acrylate) in just 5 minutes



**Scheme 1:** Preparation of Cp capped polymer chains from ATRP derived macromolecules (top); preparation of polymer chains carrying electron-deficient dithioesters (RAFT) (middle); ultra-rapid HDA click conjugation of Cp and dithioester capped polymers.

under ambient conditions.<sup>[2]</sup> It is therefore apparent that the rate of the CuAAC can be influenced by using an excess of one of the reactants, however this is undesirable in the majority of cases as further purification strategies are necessary. We have recently introduced an alternative *click* methodology, employing polymers prepared via reversible addition fragmentation chain transfer (RAFT) polymerization followed by a hetero Diels-Alder (HDA) reaction with a suitable diene.<sup>[3]</sup> The current lecture presents a further refinement of the RAFT-HDA concept as the catalyst free, ambient temperature *click* conjugation of individual polymer strands becomes possible via the use of novel ATRP derived cyclopentadienyl capped polymers in an extremely rapid hetero Diels-Alder cycloaddition (at reaction times of less than a few minutes) with macromolecules equipped with electron-deficient dithioester end-groups.<sup>[4]</sup> This development makes the RAFT-HDA concept attractive for the conjugation of temperature sensitive biological entities as well as for the rapid surface modification of nano- and micro-sized objects. Scheme 1 depicts the synthetic strategy that is followed. The conjugation reaction can proceed within minutes at ambient temperature and is correlated with a rapid decolorization of the reaction mixture. Figure 1 shows a series of SEC elugrams of Cp and



**Figure 1:** Overlay of SEC traces showing the progress of the HDA reaction between Cp and dithioester functionalized polystyrene. Note that the reaction proceeds at ambient temperature and with no added catalyst

dithioester capped polystyrenes as well as their conjugate. It is clearly visible that within 10 s the majority of the polymer chains have reacted and formed a block copolymer. The lecture will introduce the ultra rapid RAFT-HDA methodology on several examples (including the modification of surfaces) and explore its strengths and limitations.

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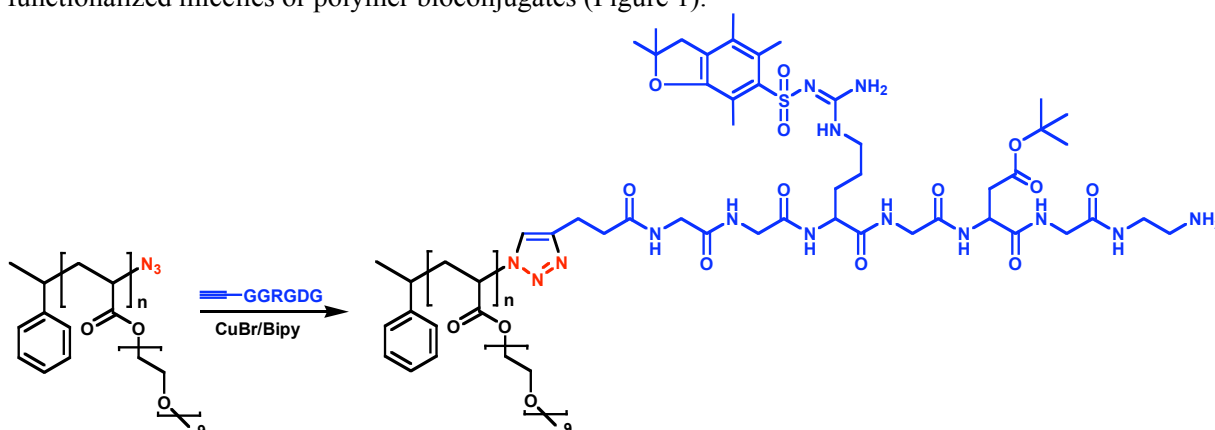
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## CLICK CHEMISTRY IN POLYMER SCIENCE: FROM REVOLUTION TO ESTABLISHMENT

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Reactions of the "click"-type have become, within the last five years, extremely popular in polymer chemistry.<sup>[1]</sup> In particular, copper-catalyzed azide-alkyne Huisgen cycloadditions (CuAAC) have been extensively studied for macromolecular engineering. Numerous examples of functional polymeric materials (e.g. colloids, surfaces) or advanced macromolecular architectures (e.g. block copolymers, macromolecular brushes, stars, miktoarm stars) have been prepared using CuAAC.<sup>[2, 3]</sup> For instance, our research group investigated the combination of CuAAC and atom transfer radical polymerization (ATRP). This dual strategy was found to be very efficient for preparing telechelic polymers, functionalized micelles or polymer bioconjugates (Figure 1).<sup>[2]</sup>



**Figure 1.** Selective ligation of biocompatible polymers with RGD cell-adhesion motifs via "click" 1,3 dipolar cycloaddition of azides and terminal alkynes.<sup>[4]</sup>

However, the last two years seem to be the calm after the storm in this field of research. Indeed, several hundreds of research articles have been published and overall creativity seems to slow down. The goal of this presentation is to examine this new situation. In particular, the next exciting steps in this field of research will be analyzed. For example, areas of polymer science where CuAAC has been neglected will be mentioned. Additionally, new generations of metal-free "click" reactions such as thiol-ene additions or strain-promoted azide-cyclooctyne cycloadditions will be discussed.<sup>[5, 6]</sup>

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## GLYCOPOLYMERS VIA CATALYTIC CHAIN TRANSFER POLYMERISATION AND DOUBLE CLICK REACTIONS

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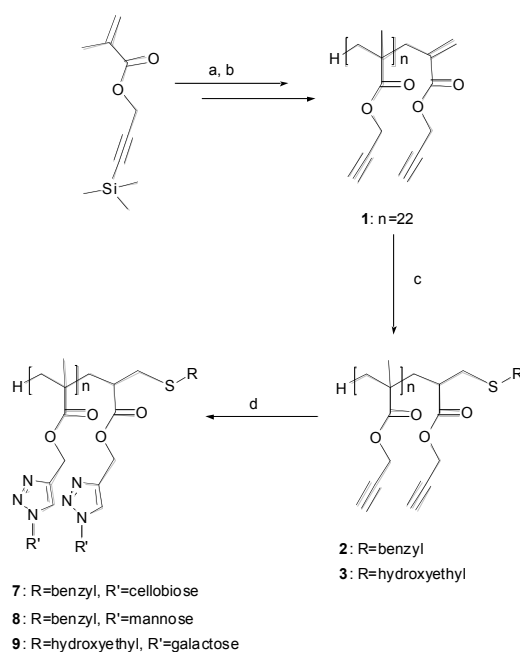
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Click chemistry as a concept of simplifying synthesis is very useful in polymer science to produce complex macromolecular structures, functional polymers and protein conjugates. The Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) has been the most widely studied and employed of the available click reactions. Recently, there has been an increasing interest in using the well-known addition of thiols to alkenes as a click process, so called thiol-ene click chemistry. Although thiol-ene click coupling has mainly been focused on a radical-mediated version to non activated alkenes, this reaction can also proceed via Michael addition, especially when the vinyl group is alpha to an electron withdrawing moiety.

Synthetic glycopolymers containing pendent sugar moieties have been shown to interact multivalently with carbohydrate-binding proteins, lectins, in a similar manner to natural glycoproteins. These biomimetic properties have caused significant interest in the synthesis of glycopolymers, and a number of different strategies have been employed to obtain the required multivalent carbohydrate ligands.

In our group, we have previously combined copper(I) mediated living radical polymerisation (often called ATRP) and CuAAC to produce glycopolymers by post-functionalisation of well-defined "clickable" polyalkyne scaffolds with sugar azides. An established, but dormant, method of obtaining end-functional polymers available for click-reactions is catalytic chain transfer polymerisation (CCTP). This is an extremely efficient process to produce vinyl terminated methacrylic oligomers. In this present study we have used CCTP to give alkyne-functional oligomers available for both CuAAC and thio-Michael addition reactions. Post-functionalisation of the oligomers with these dual click reactions results in end-functionalised glycopolymers in a very convenient manner.



**AZIDE-ALKYNE AND THIOL-ENE REACTIONS: VERSATILE TOOLS IN THE SYNTHESIS OF COMPLEX POLYMER STRUCTURES**

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We report the use of click reactions for a number of synthetic tasks forming interesting polymer structures.

First the copper-catalyzed Huisgen 1,3-dipolar azide-alkyne cycloaddition was used to synthesize cyclic polymers. To this end, an azido group modified 4-cyanopentanoic acid dithiobenzoate was employed as the chain transfer agent in the RAFT mediated polymerization of styrene. The thiocarbonyl thio endgroup was replaced by an alkyne bearing function. The cyclization was performed between the heterotelechelic chain ends of the polymers and it was proven by chromatography and viscometry.

In a second approach we functionalized crosslinked polydivinylbenzene (pDVB) microspheres using both thiol-ene chemistry and azide-alkyne click reactions. RAFT polymerization was carried out to synthesize SH-functionalized poly(*N*-isopropylacrylamide) (pNIPAAm) and utilized to generate pNIPAAm surface-modified microspheres via thiol-ene modification. The accessible double bonds on the surface of the microspheres allow the direct coupling with thiol-end functionalized pNIPAAm. In a second approach, pDVB microspheres were grafted with poly(2-hydroxyethyl methacrylate) (pHEMA). For this purpose, the residual double bonds on the microspheres surface were used to attach azide groups via the thiol-ene approach of 1-azido-undecane-11-thiol. In a second step, alkyne endfunctionalized pHEMA was used to graft pHEMA to the azide-modified surface via azide-alkyne click-chemistry.

Finally, we demonstrate the usefulness of thiol-ene chemistry for the crosslinking of butadiene blocks in the generation of Janus particles as well as core-shell cylinders from block co- and terpolymers.

**‘CLICKED’ MICROCAPSULES, BEADS AND MULTILAYERS: AZIDE-ALKYNE VERSUS THIOL-ENE AND THIOL-YNE APPROACH**

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Recently, besides the copper-catalyzed cycloaddition ‘click’ reaction, also the metal- and azide-free photopolymerisation of a mixture of thiols with -ene or -yne containing compounds was explored as an efficient method for the rapid production of novel materials. While the metal catalysed click reaction was employed by us as a novel approach for the synthesis of biodegradable, dextrane-containing microcapsules and multilayers<sup>(1,2)</sup>, we extended our research to several types of ‘thiol-click’ reactions for the straightforward formation of highly cross-linked, monodisperse polymeric beads by using UV in a micro-fluidic system under mild conditions. For this purpose, a wide range of multifunctional thiols have been clicked with multifunctional -enes or -ynes, using a photoinitiator, in a simple home-made micro-fluidic set-up. In the same way, biodegradable polymeric microcapsules were prepared by making use of several biopolymers modified with clickable functional groups such as -enes and -ynes. Their composition could be varied with the molar ratio of thiols to -enes or -ynes. Also, beads containing a variety of functional groups (such as hydroxyl, carboxylic, amine, etc.) were prepared by using appropriate functional thiols or -enes or -ynes in the thiol ‘click’ reaction system. To show the potential use of biodegradable microcapsules as carriers in delivery applications, the capsules were encapsulated with a fluorescent marker as a model drug and their release rate was observed under physiological conditions. The amount of drug loading and release rate can be controlled by tailoring the degree and nature (azide-alkyne, thiol-ene or thiol-yne) of clickable functional substitutions in the biopolymer as well as degradable linkages in the microcapsules. This work demonstrates the applicability of the thiol ‘click’ coupling reaction as a clean reaction and a powerful tool for a synthetic pathway towards diverse functional materials.

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## AZIDE + ALKYNE CLICK CHEMISTRY BY MICROCONTACT PRINTING

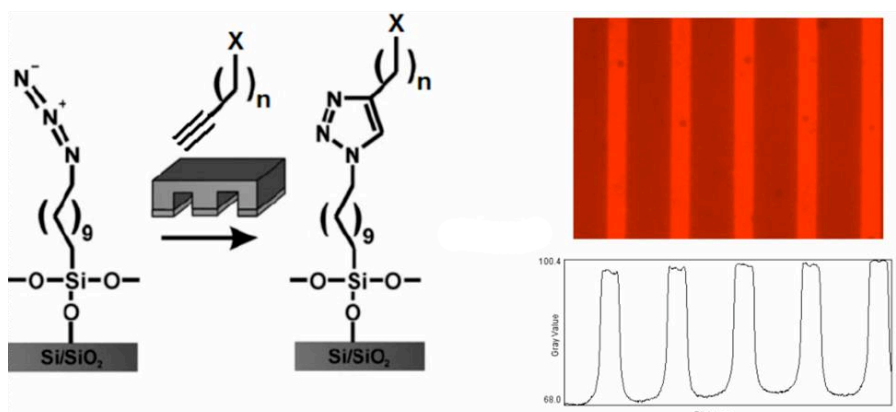
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Microcontact printing (mCP) is commonly used to pattern self-assembled monolayers (SAMs) as etch resists or chemical templates on solid substrates such as gold or silicon oxide. mCP is based on the transfer of a molecular ink in the contact area between an elastomer stamp and a solid substrate. However, we have recently found that mCP can also be used for chemical synthesis in the nanoscale confinement between stamp and substrate.

Also azide + alkyne click chemistry can be efficiently induced and directed with mCP. mCP of alkynes on azide-terminated SAMs leads to microarrays of the cycloaddition product within a few minutes, without a Cu(I) catalyst, and under mild conditions. This lecture will cover an investigation of the kinetics of azide + alkyne click chemistry by mCP as well as its application in the preparation of carbohydrate and DNA microarrays. In particular for the immobilization of biomolecules it is advantageous to exclude the toxic Cu catalysts.



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## **COMBINING EFFICIENT SYNTHETIC TOOLS TO PREPARE COMPLEX MACROMOLECULAR ARCHITECTURES**

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Combining the utility of controlled radical polymerization with the versatility of other recently expanded synthetic techniques allows facile tailoring of new polymers with specific macromolecular features. We have prepared a variety of responsive materials by employing reversible addition-fragmentation chain transfer (RAFT) polymerization and highly efficient postpolymerization modification methods that proceed with high conversion and selectivity. In addition to copper-catalyzed azide-alkyne cycloaddition (CuAAC), Diels-Alder and thiol-ene reactions were used to derivatize the well-defined polymers prepared by RAFT. For instance, chain transfer agent-derived thiocarbonylthio end groups were reduced to thiols and subsequently reacted with bismaleimides. The resulting maleimido terminated polymers demonstrate significant chemical versatility and readily undergo coupling to low molecular weight and polymeric thiols while also being susceptible to Diels-Alder reactions with dienes. This method is a means to conjugate RAFT-generated polymers to other thiol-containing compounds to yield functional telechelics, modular block copolymers, and biocomposites. Additionally, the specific combination of RAFT and CuAAC has been employed to make thermoresponsive hyperbranched copolymers, polymer-modified surfaces, cancer targeting micelles, and polymer-protein conjugates.

## CLICK CHEMISTRY – A POWERFUL TOOL TO CONSTRUCT DENDRITIC ARCHITECTURES WITH CONTROLLED FUNCTION

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With future cutting-edge applications requiring evermore complex polymeric architectures that express precise functions, scientists are constantly on the lookout for newly developed synthetic reactions. Consequently, the Click concept introduced by K. B. Sharpless, has emerged as a powerful synthetic methodology that can undertake present technological challenges.<sup>1</sup> One of the most important features of the Click concept is the extraordinary selective nature of these reactions. For instance, azides and primary acetylenes in the popular copper catalyzed 1,3-dipolar cycloaddition reaction (CuAAC) can coexist with other reactive groups without competitive interference. As a result, the construction of a wide range of functional polymeric materials have been reviewed including linear<sup>2</sup> and dendritic polymers.<sup>3</sup> This presentation will highlight click chemistry as a robust methodology to obtain advanced dendritic macromolecules by taking advantage of this selectivity, Figure 1. One approach efficiently describes an  $AB_2+CD_2$  strategy which allows an accelerated growth of dendrimers without the need of any activation steps.<sup>4</sup> In another approach,  $AB_2C$  dendrimers with click-active interior and hydroxyl functional exterior were successfully constructed with great efficacy.<sup>5</sup> Finally, one-pot postfunctionalizations strategy is presented as benign route to obtain fully tailored dendritic frameworks.

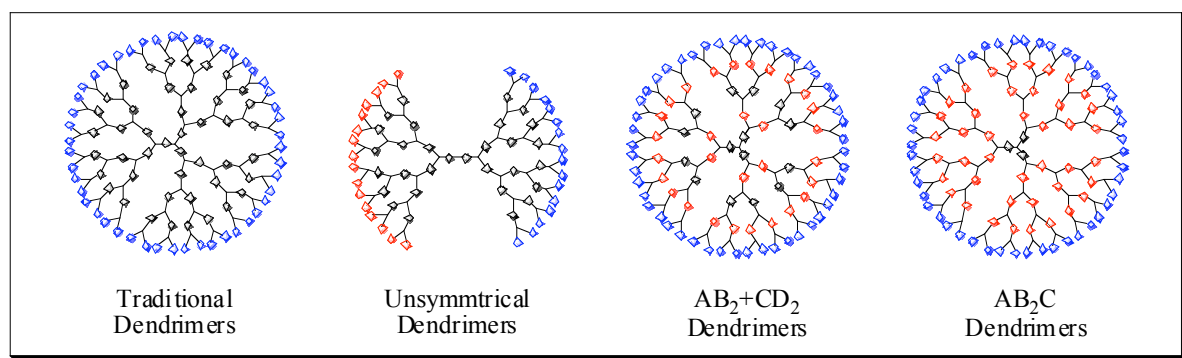


Figure 1. Dendritic structures obtained via the Click concept.

### References

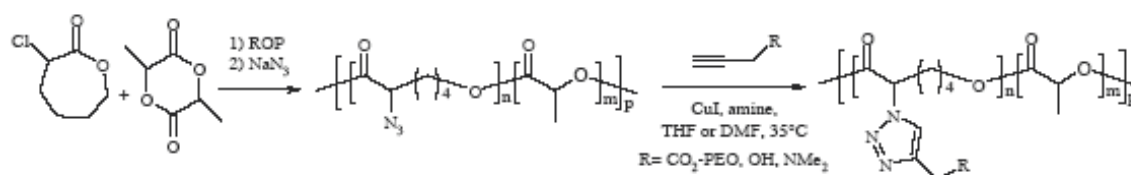
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## NEW DEVELOPMENTS IN THE FUNCTIONALIZATION OF ALIPHATIC POLYESTERS BY "CLICK" COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITION

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Nowadays, biodegradable and biocompatible aliphatic polyesters are widely used as environmentally friendly thermoplastics and biomaterials. Nevertheless, the absence of any pendant functional group is a severe limitation for the development of novel applications. Our strategy aiming at functionalizing aliphatic polyesters relies on the "click" copper-catalyzed cycloaddition (CuAAC) of alkynes duly substituted by functional groups or even chains onto PCL bearing pendant azides.<sup>1,2</sup> The aliphatic polyesters bearing pendant azides have been very efficiently synthesized by a straightforward approach, which relies on the ring-opening copolymerization of  $\alpha$ Cl $\epsilon$ CL (or  $\gamma$ Br $\epsilon$ CL) and  $\epsilon$ CL (or lactide) followed by reaction with sodium azide to convert pendant chlorides or bromides into azides.



The alternative reported by Emrick et al. is based on the CuAAC reaction of azides substituted by any functional group onto copolyesters of poly( $\epsilon$ -caprolactone) bearing pendant alkynes.<sup>3</sup>

Interestingly enough, Emrick et al. carried out the CuAAC reaction in water at 80°C. Unfortunately, it turned out, at least in our hands, that these conditions can not be extended to the derivatization of more sensitive aliphatic polyesters because degradation was then unavoidable. Nevertheless, we found out that degradation can be minimized whenever the CuAAC reaction is carried out in an organic solvent at lower temperature. Typically, the CuAAC reaction was carried out in DMF or THF at 35°C. Recently, it was shown that supercritical carbon dioxide can be used as a more environmentally friendly solvent than DMF or THF.

The contamination by catalytic residues of aliphatic polyesters functionalized by the CuAAC reaction is a severe limitation in view of future applications, especially in the biomedical field. In the last part of this talk, a special attention will be paid on our current efforts to get rid of copper residues.

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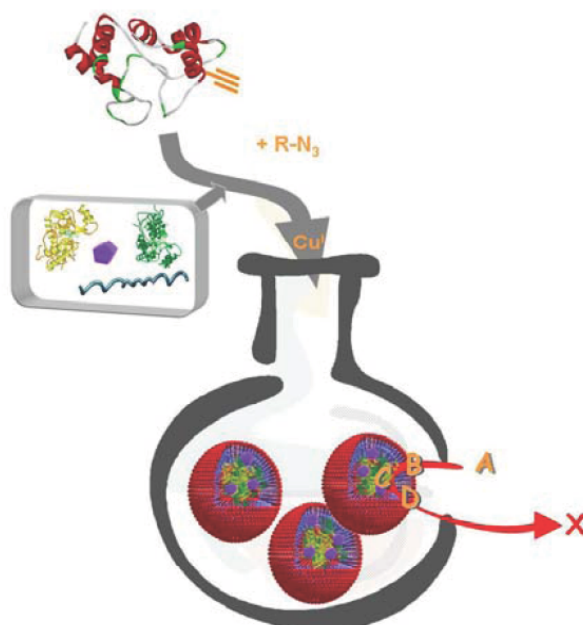
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## CLICK-CHEMISTRY FOR FUNCTIONAL PROTEIN-POLYMER BIOHYBRIDS. SYNTHETIC APPROACHES AND APPLICATIONS

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Due to their widespread utility in medical applications, biotechnology, and nanotechnology, polymer-protein conjugates are in the forefront of chemical research. During the last decades these bioconjugates have been prepared by conjugation of pre-functionalized polymers to biomolecules through covalent and/or bioaffinity bindings. These approaches often involve multiple steps of synthesis, chemical modification and tedious purification limiting therefore further studies concerning their functionality and applications.



**Figure 1:** Schematic representation of the "click" chemistry based synthetic approaches toward Giant Amphiphiles and the concomitant formation of bionanoreactors.

Synthesized to mimic natural superstructures, *Giant Amphiphiles*, the subclass of protein-polymer conjugates in which the hydrophobicity of the polymer conveys an overall amphiphilic character to the biohybrid, exhibit interesting aggregation properties and enormous potential in bio- and nanotechnology. To overcome the intrinsic limitations caused by either the synthetic approaches or the amphiphilic nature of such bioconjugates, we developed novel approaches for their synthesis based on the copper(I)-catalyzed 1,3-dipolar-azide/alkyne "click" cycloaddition.<sup>1,2,3</sup> The successful, facile and high yielding application of these alternative approaches leading to the synthesis of families of *Giant Amphiphiles* will be presented. More importantly, the construction of functional, hierarchically assembled bionanoreactors by the efficient one-pot incorporation of guest proteins within the formed superstructures and applications will be discussed.

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