Click Chemistry

DOI: 10.1002/anie.200604050

1,3-Dipolar Cycloadditions of Azides and Alkynes: A Universal Ligation Tool in Polymer and Materials Science

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Keywords:
biotechnology · click chemistry · cycloaddition · materials science · polymers

In 2001, Sharpless and co-workers introduced "click" chemistry, a new approach in organic synthesis that involves a handful of almost perfect chemical reactions. Among these carefully selected reactions, Huisgen 1,3-dipolar cycloadditions were shown to be the most effective and versatile and thus became the prime example of click chemistry. Hence, these long-neglected reactions were suddenly re-established in organic synthesis and, in particular, have gained popularity in materials science. The number of publications dealing with click chemistry has grown exponentially over the last two years. The Minireview discusses whether click chemistry is a miracle tool or an ephemeral trend.

1. Introduction

Most of the major scientific challenges of the 21st century require nanomaterials with a high degree of structural order and defined properties. To meet this demanding level of complexity often necessitates the design of novel organic or inorganic molecules using sophisticated multistep experimental procedures. In this context, the discovery and selection of simpler and universal synthetic methods is essential. Indeed, the palette of chemical reactions developed within the last 100 years is extremely broad; however, many of these established reactions show significant limitations within a contemporary scientific context.

Selecting the most versatile chemical tools is the essence of "click" chemistry, an appealing concept proposed by Sharpless and co-workers.[1] Click chemistry is not a scientific discipline but rather a synthetic philosophy inspired by the simplicity and efficiency of the chemistry that takes place in nature. Indeed, highly complex biological systems rely on a modest library of monomers linked together by a few, but efficient, organic reactions. Similarly, the objective of click chemistry would be to establish an ideal set of straightforward and highly selective reactions in synthetic chemistry. For instance, the archetypal example of click chemistry is undoubtedly the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes.[2,3,6,7,93] In the absence of an appropriate catalyst, this reaction is usually quite slow as alkynes are poor 1,3-dipole acceptors. However, in the presence of copper(I), which can bind to terminal alkynes, cycloaddition reactions are dramatically accelerated, regioselective, and highly efficient (yields are often above 95%). Moreover, the copper-catalyzed azide–alkyne cycloaddition (CuAAC) can be performed in various solvents (including water) and in the presence of numerous other functional groups.[6,7]

Although click chemistry was initially postulated as a general concept for organic synthesis, this strategy also has an enormous potential in materials science.[8,9] The first report that illustrated this point appeared in mid-2004 by Hawker, Fokin, Sharpless, and co-workers.[10] Afterwards, the popularity of click chemistry within the materials science community grew considerably and has been, in particular, significantly boosted by the influential works of Hawker, Fréchet, and Finn.[10–24] As a result, the number of publications in this field has increased dramatically within the last two years. The target of this Minireview is to analyze and categorize this recent scientific trend.

2. Design of Novel Polymer Materials

Huisgen cycloadditions have been recently investigated as ligation tools for synthesizing linear polymers, dendrimers,

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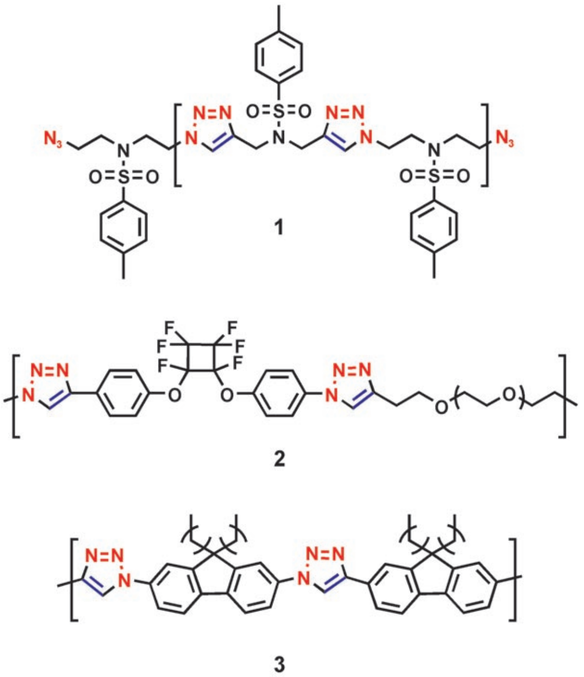
and rotaxanes.[10,11,14,22,25–27] Such structures containing multiple triazole or tetrazole repeating units constitute a novel class of macromolecules with potentially interesting properties. Hawker, Fokin, Sharpless, and co-workers explored first the CuAAC of various molecular building blocks for the convergent synthesis of dendrimers.[10] Overall, this method was found to be a straightforward strategy for the large-scale synthesis of triazole-based dendrimers. Shortly after, Finn and co-workers studied the click cycloaddition of azide- and alkyne-functionalized monomers for the preparation of either linear polymer chains (Scheme 1, **1**) or three-dimensional polymer networks.[11] The latter were investigated as novel adhesives for copper surfaces, as triazole rings have a strong ability to coordinate transition metals.



Scheme 1. Examples of linear polymer structures obtained by click polycycloaddition of azide- and alkyne-functionalized monomers.[11,25,27]

Novel conjugated polymers may also be prepared using CuAAC. The groups of Reek and Bunz both reported the preparation of poly(fluorenylene-triazolene) through the reaction of diazidofluorene monomers with various diynes (Scheme 1, **3**).[25,28] Interestingly, Bunz and co-workers additionally showed that these monomers could be locally polymerized, in the absence of a copper catalyst, by using a heated atomic force microscopy tip.[28]

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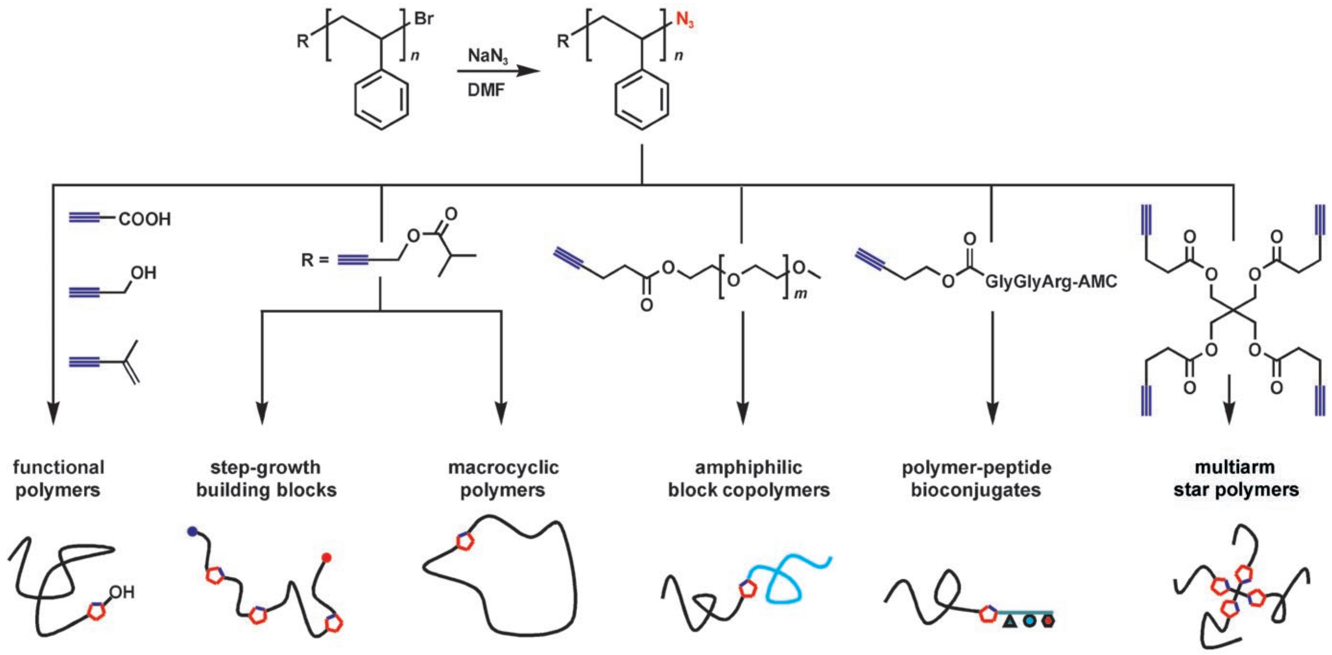
Qing and co-workers prepared poly(alkyl aryl) ethers containing 1,2,3-triazolyl and perfluorocyclobutyl units (Scheme 1, **2**) through click polycycloaddition.[27] These novel macromolecules exhibited a rather interesting thermal stability and melting fluidity. In comparison, polymers containing tetrazole units were found to be less thermoresistant. Matyjaszewski and co-workers synthesized polymers containing multiple tetrazole side groups by treating well-defined polyacrylonitrile precursors with sodium azide.[29] Their study indicated that tetrazole functionalities start to decompose at temperature as low as 120 °C.

Overall, Huisgen cycloadditions appear to be straightforward and efficient reactions for building novel polymer structures. However, so far, synthesis has been the prime focus of the aforementioned reports. Further studies are needed to assess comprehensively the physical behavior of these novel triazole- or tetrazole-containing polymers. Nonetheless, some of these early reports already suggested some interesting properties (e.g. solubility, swelling, and metal adhesion).

3. Macromolecular Engineering

Macromolecular engineering can be generally defined as the fabrication of complex macromolecular structures with defined composition, microstructure, functionality, and architecture (e.g. telechelic polymers, block copolymers, macromolecular brushes, stars, and networks) using covalent chemistry approaches.[30] Click reactions, and in particular Huisgen cycloadditions, were recently shown to be extremely versatile tools for such advanced macromolecular design. For instance, during the last two years, the 1,3-dipolar cycloaddition of azide and terminal alkynes has been investigated as a complementary tool for most of the major synthetic polymerization techniques such as cationic or anionic ring-opening polymerization (ROP),[31–34] ring-opening metathesis polymerization (ROMP),[35] polycondensation,[36] conventional free-radical polymerization,[12,37] nitroxide-mediated polymerization (NMP),[13,16] reversible addition–fragmentation chain-transfer polymerization (RAFT),[38] and atom-transfer radical polymerization (ATRP).[21,29,39–55] However, to date, the latter method has involved CuAAC more often than any of the others. Indeed, ATRP is a facile and versatile polymerization technique and therefore probably one of the most employed tools in modern polymer chemistry.[30,56] Nevertheless, the range of macromolecular engineering possibilities of ATRP can be further broadened by click chemistry (Scheme 2).

The first important application of CuAAC in polymer chemistry is undeniably the synthesis of functionalized polymers (either end-functionalized or side-functionalized). The post-functionalization of synthetic polymers is an im-

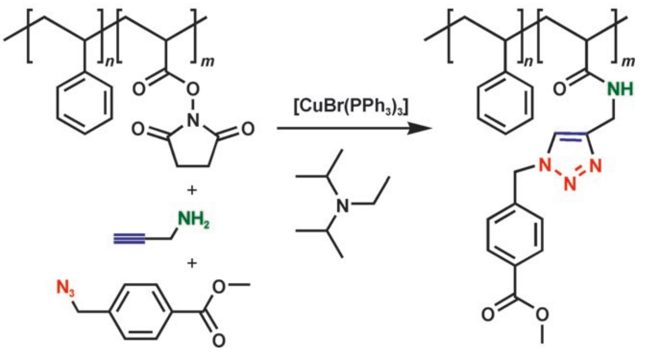


Scheme 2. Variations on a simple theme: examples of macromolecular architectures recently obtained by click modification of well-defined polystyrene prepared by ATRP.[39,42,44,46,48,51]

portant feature of macromolecular engineering, as many polymerization mechanisms are rather sensitive to bulky or functional groups. For example, telechelic polymers (i.e. polymers with defined chain ends) can be efficiently prepared through a combination of ATRP and CuAAC. The halogen end groups of polymers prepared using ATRP can be easily transformed into azide moieties and subsequently used in Huisgen cycloadditions with functional alkynes (Scheme 2).[40,42,46,53,54] Alternatively, azide- or alkyne-functionalized initiators can also be utilized.[43,44,46]

Polymers with multiple functional side chains have been prepared by CuAAC using precursors built with alkyne-functionalized monomers.[12,16,31,34,36] For example, Fréchet and co-workers constructed dendronized polymers (i.e. linear polymer chains with bulky side dendrons) through cycloaddition of the side chains.[12] Hawker and co-workers explored this concept even further and reported some very elegant examples of cascade side-chain functionalization of macromolecules (Scheme 3).[16] Azide-containing monomers and related polymer precursors have also been studied for the preparation of macromolecules with functional side groups.[32,35,37,45] However, although efficient, such strategies are experimentally risky (like any approach involving low-molecular-weight azides or macromolecules with a high density of azide groups) owing to the potentially explosive character of organic azides and should be investigated with extreme care.[57,58]

Besides the preparation of functional macromolecules, click reactions were also shown to be very useful tools for building polymers of defined architecture. The first example of architectural control using click chemistry was reported by van Hest and co-workers, who synthesized amphiphilic block copolymers by coupling azide- and alkyne-functionalized segments (Scheme 2).[44] Such a ligation strategy has been shown to be quite efficient for linking homopolymers of various nature. Grayson and co-workers recently described an elegant strategy for preparing macrocycles (i.e. polymer rings, which are often rather difficult to prepare) based on the self-ligation of well-defined α-alkyne-ω-azido-telechelic polystyrenes (Scheme 2).[51] Additionally, other nonlinear architectures such as stars,[33,48] miktoarm stars,[47,55] graft copolymers,[54,59] and networks[17,21] were constructed using click chemistry. All these studies relied on the Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes, with the exception of the approach reported by Yagci and co-workers for preparing graft copolymers which involved anthracene–maleimide Diels–Alder chemistry.[59]



Scheme 3. Example of cascade functionalization (amide formation and cycloaddition) of synthetic macromolecules.[16]

As mentioned above, CuAAC was explored for preparing triazole-containing dendrimers. Alternatively, Huisgen cycloadditions were studied for functionalizing the outer shells of various dendrimers or for linking preformed dendrons of various chemical nature (e.g. polyamidoamine- or polyester-based dendrons).[15,19,60,61] The latter reaction is an interesting route for preparing unsymmetrical dendrimers with distinct hemispheres.[19]

4. Bioconjugation

An important advantage of Huisgen cycloadditions is undoubtedly their very high degree of selectivity. For instance, the copper-catalyzed reaction of organic azides with terminal alkynes is tolerant to a wide variety of chemical functions.[6] This particular feature makes these reactions particularly attractive for modifying highly functional biomolecules. For example, CuAAC was investigated for modifying biological polymers such as nucleic acids or polysaccharides. (The strategies for functionalizing biopolymers are conceptually similar to those described above for synthetic polymers.)[62–64] Moreover, the Huisgen cycloaddition of azides and alkynes was shown to be very useful for preparing polymer bioconjugates (i.e. hybrid macromolecules composed of distinct synthetic and biological moieties). For instance, several reports indicated that sequence-defined oligopeptides can be linked to synthetic macromolecules using click ligation.[31,39,53,65] In particular, Nolte and co-workers described the synthesis and self-assembly in aqueous medium of bio-hybrid amphiphiles composed of a hydrophobic polystyrene segment coupled to a hydrophilic oligopeptide (Figure 1).[39] Besides peptide bioconjugation, Huisgen cycloadditions were also explored for functionalizing linear or dendritic synthetic macromolecules with carbohydrates (e.g. mannose, galactose, fucose, or lactose moieties).[19,50,66]

More complex biological entities such as proteins, enzymes, viruses, bacteria, and cells may also be transformed using azide–alkyne chemistry.[67–72] For example, Finn and co-workers efficiently modified the surface of the cowpea mosaic virus using CuAAC.[70] Indeed, such reactions can be performed under experimental conditions that are compatible with biological environments (e.g. aqueous medium and room temperature). However, such chemical modifications of biological assemblies should be cautiously characterized as many reactants or catalysts may induce denaturation or disassembly.[70] Additionally, Nolte and co-workers reported some interesting examples of protein conjugation (either transport proteins such as bovine serum albumin or enzymes such as lipases) using CuAAC.[39,73] In particular, they reported efficient procedures for linking proteins with manmade materials such as synthetic polymers or inorganic nanoparticles.

Other elegant examples of protein functionalization using CuAAC have been reported by the groups of Schultz and Tirrell.[67,68,72,74] Their modification approach relies on the use of nonnatural amino acids containing azide functions (e.g. *para*-azidophenylalanine, azidohomoalanine, azidonorvaline, and azidonorleucine), which can be incorporated into mutant proteins using either genetic engineering or the metabolic replacement of a natural amino acid by a noncanonical substitute.[67,75] The formed azido-functionalized proteins can be subsequently reacted with various functional alkynes. Such ligations can even be directly performed on cell surfaces if membrane proteins are mutated.[68,72] Moreover, the click strategy of Tirrell and co-workers was recently applied for distinguishing new proteins from old proteins in mammalian cells.[76] In this approach, only the newly synthesized proteins contain azidohomoalanine and can therefore be selectively labeled by an alkyne affinity tag.

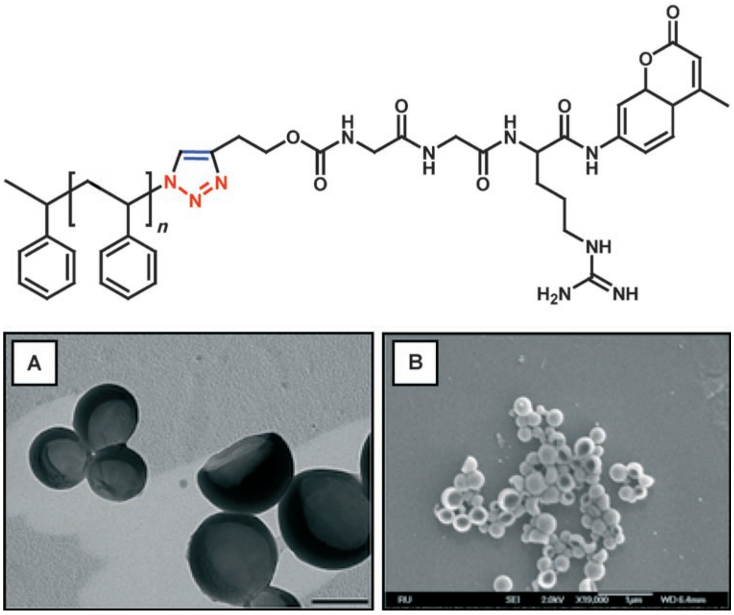


Figure 1. Top: Molecular structure of an amphiphilic polymer bioconjugate polystyrene-*b*-oligopeptide synthesized partly by click chemistry. Bottom: Visualization by electron microscopy of its aggregates in water: A) TEM and B) SEM. Reproduced from reference [39] with permission from the Royal Society of Chemistry.

5. Functional Nanomaterials

Highly efficient and selective click reactions have an enormous potential in nanoscience. Indeed, as opposed to molecular products obtained by covalent means, modern nanomaterials are often fragile supramolecular constructions, which cannot be easily purified or isolated. In this context, straightforward in situ reactions are rather valuable in materials science. Thus, the copper-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes, which can be performed at room temperature in multiple solvents and with stoichiometric amounts of reactants, has recently received increased attention from several research groups focusing on material design.

First, CuAAC has been shown to be a versatile tool for functionalizing or cross-linking colloidal objects such as polymer, lipid, or inorganic nanoparticles.[13,77–81] For example, Wooley and co-workers obtained shell-cross-linked polymer micelles by reacting alkyne moieties present in the hydrophilic outer shell of the micelles with azide-functionalized first-generation dendrimers.[13] The groups of Schuber and Kros reported elegant pathways for functionalizing liposomes (i.e. lipid vesicles).[77,79] Both approaches utilized alkyne-functionalized surfactants, which can be incorporated in the lipid bilayers and further reacted with azide-containing molecules. Their studies revealed that the lipid membranes are not damaged during this functionalization process and that only the outer surface of the vesicles are modified.[77,79] Moreover, a few routes have been reported recently for the click functionalization of inorganic nanoparticles.[80,81] In particular, Turro and co-workers coated the surface of maghemite particles with either azide- or alkyne-functionalized ligands, which were shown to be highly versatile platforms for further functionalization.[81] Besides spherical particles, anisotropic objects such as nanotubes were also modified by click chemistry. Adronov and co-workers reported an elegant pathway for functionalizing carbon nanotubes with polymers and thus for promoting colloidal dispersion of the resulting nanotubes in organic solvents (Figure 2).[41]

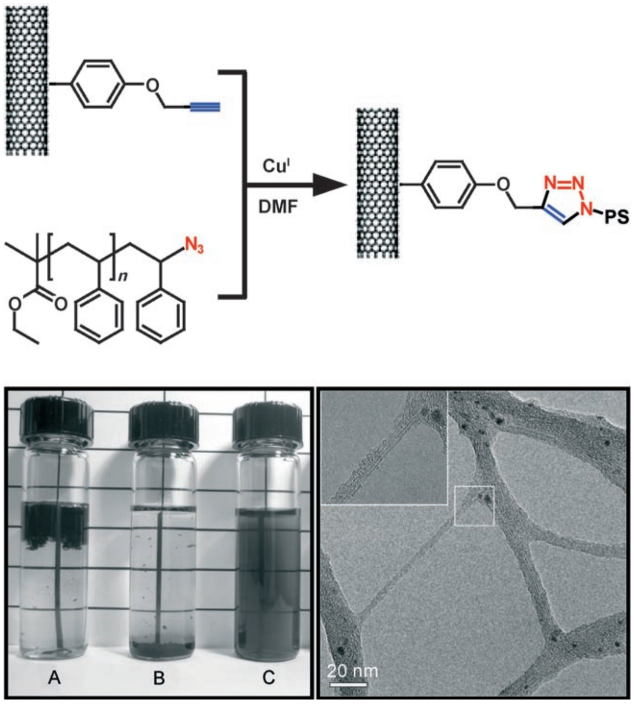


Figure 2. Top: Preparation of polystyrene-modified single-walled carbon nanotubes using click chemistry. Bottom left: THF solutions of pristine (A), alkyne-functionalized (B), or polymer-modified (C) carbon nanotubes. Bottom right: Transmission electron micrographs of the polymer–nanotube organic–inorganic hybrid structures (the inset shows a magnified view of the area within the white square). Adapted from reference [41] with permission from the American Chemical Society.

The azide/alkyne ligation was also studied for preparing various types of bulk materials.[17,18,20,23,82] The groups of Hawker and Hilborn reported the synthesis of poly(ethylene glycol) or poly(vinyl alcohol) hydrogels cross-linked by triazole rings.[17,82] Similar chemistry was used for attaching ligands on gel beads that are utilized in affinity chromatography or electrophoresis.[18,23]

Moreover, CuAAC has been shown to be an unprecedented tool for functionalizing flat surfaces. Pioneers in this area are undoubtedly Collman and Chidsey, who reported several important examples of self-assembled monolayers (SAMs) functionalized by triazole linkages.[84–87] Their work primarily focused on gold surfaces, but was extended by other groups to different types of substrates such as silicon wafers or glass slides.[88,89] Overall, a very wide variety of functional molecules (synthetic or biological) have already been attached to SAMs using an azide/alkyne strategy, thus opening a wide range of opportunities for applications such as molecular electronics, catalysis, or biosensors.[84,85,88–91] Besides the functionalization of SAMs, the Huisgen cycloaddition of alkynes and azides was also utilized for constructing polymer-modified surfaces. For example, Caruso and co-workers developed a click layer-by-layer technology (i.e. using alternating layers of alkyne- and azide-functionalized polymers) for constructing defined polymer films on either quartz, silicon, or gold surfaces.[38]

Two recent reports described the spatial control of click cycloadditions on flat surfaces by using microcontact printing.[83,92] Lahann and co-workers prepared defined biotin-functionalized patterns with the help of a poly(dimethylsiloxane) (PDMS) stamp inked with a solution of copper sulfate, which catalyzed locally the cycloaddition of an adsorbed alkyne polymer and biotin azide.[92] Alternatively, Reinhoudt and co-workers utilized an alkyne-inked PDMS stamp for creating various functional patterns on azido SAMs (Figure 3).[83] Interestingly, this approach did not necessitate a metal catalyst. Owing to the high local concentration of reactants in the confined regions between the stamp and the substrate, the azide/alkyne cycloaddition occurred spontaneously within a short period of time.

6. Summary and Outlook

Huisgen cycloadditions have become major ligation tools in material science in the past few years and have recently

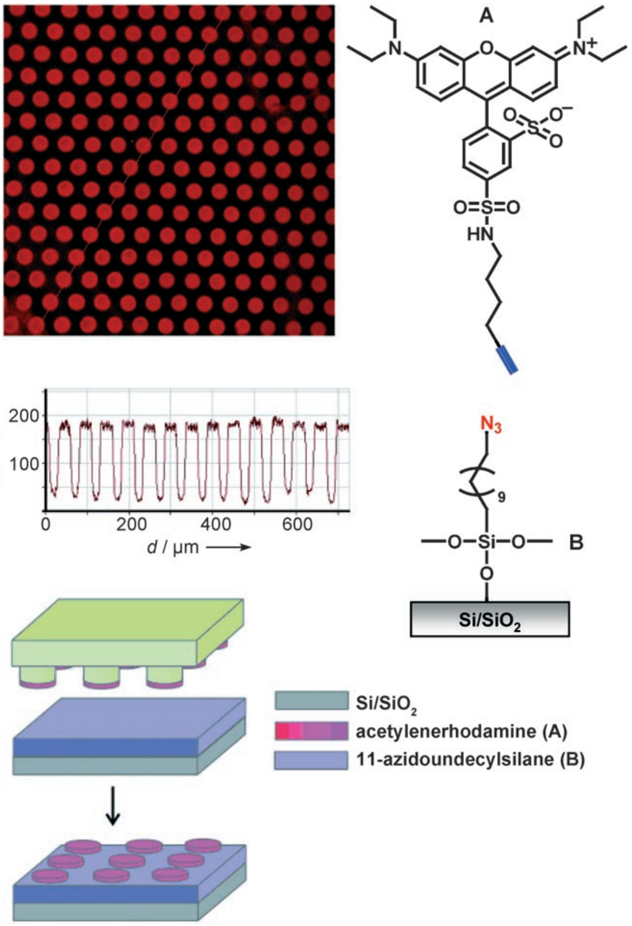


Figure 3. Example of click chemistry by microcontact printing in the absence of a copper catalyst. Top left: Visualization by fluorescence microscopy of the surface pattern (image width is 700 µm). Adapted from reference [83].

been shown to be useful in areas as diverse as polymer science, molecular biology, or nanoelectronics. However, Huisgen cycloadditions and click chemistry should be distinguished. Most of the reports described above used the dipolar cycloaddition of azides and alkynes, but did not necessarily follow the strict concept of click chemistry. Indeed, in many studies, scientific motivations and experimental conditions are often far from those initially promoted by Sharpless and co-workers. However, paradoxically, although the concept of click chemistry has often been misunderstood, it has been validated. Nowadays, Huisgen cycloadditions appear as universal ligation reactions, which compare in versatility with some of the most essential chemical reactions in nature.

Nevertheless, the 1,3-dipolar click cycloaddition of organic azides and terminal alkynes still presents some limitations. For instance, the use of a copper-based catalyst remains a drawback in some delicate applications. Thus, the development of optimized catalytic methods, either metal-free or involving other transition metals, is an important issue in this field. Moreover, the tantalizing concept of click chemistry should not be exclusively limited to Huisgen cycloadditions. The search for alternative versatile click reactions and ultimately for a complete toolbox of click reactions should press on.

The Fraunhofer society, Deutsche Forschungsgemeinschaft (project LU 1195/1-1), and the Federal Ministry of Education and Research (BMBF programs NanoforLife and NanoChem) are acknowledged for financial support. Moreover, J.F.L. thanks professor André Laschewsky (Universität Potsdam) for fruitful discussions and Juliane Kristen (Universität Potsdam) for the German translation.

Received: October 2, 2006

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