7

Click Chemistry on Supramolecular Materials

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7.1 Introduction

A plethora of materials has been generated in the past decades, often built from molecules in highly defined configurations and conformations. Additionally, many modern functional materials rely on defined arrangement of molecular aggregates, in which the arrangement of molecules dictates the use of the underlying material,[1] thus putting supramolecular structure and ordering in the limelight.[2] Thus the use of optoelectronically active materials is strongly influenced by their arrangement in crystals or semicrystals, controlling band-overlap or charge-transport. As examples, the ordering of sexithiophenes in solar-cell devices strongly influences their ability to harvest photons and convert them into excitons; the conjugation length of oligo-(phenylene-vinylenes) strongly influences their absorption spectrum and thus their use in organic-light emitting diods; push–pull liquid crystalline molecules are ordered into liquid-crystalline phases via dipole–dipole interactions, which can be switched by external electrical fields from one liquid crystalline phase into another, thus changing the reflection of light as required in LCDs. Similarly, materials for use in biochemical applications are strongly influenced by noncovalent bonds acting through space, making hydrogen bonds or dipolar interactions the main directing forces for the spatial arrangement of biochemical receptors (Figure 7.1).

These examples demonstrate the close proximity of material science and supramolecular chemistry,[3] which are connected via the proper spatial and orientational positioning of intermolecular forces and interaction within molecular building blocks. Thus, often a molecular (= functional) scaffold needs to be oriented in space via appropriately affixed

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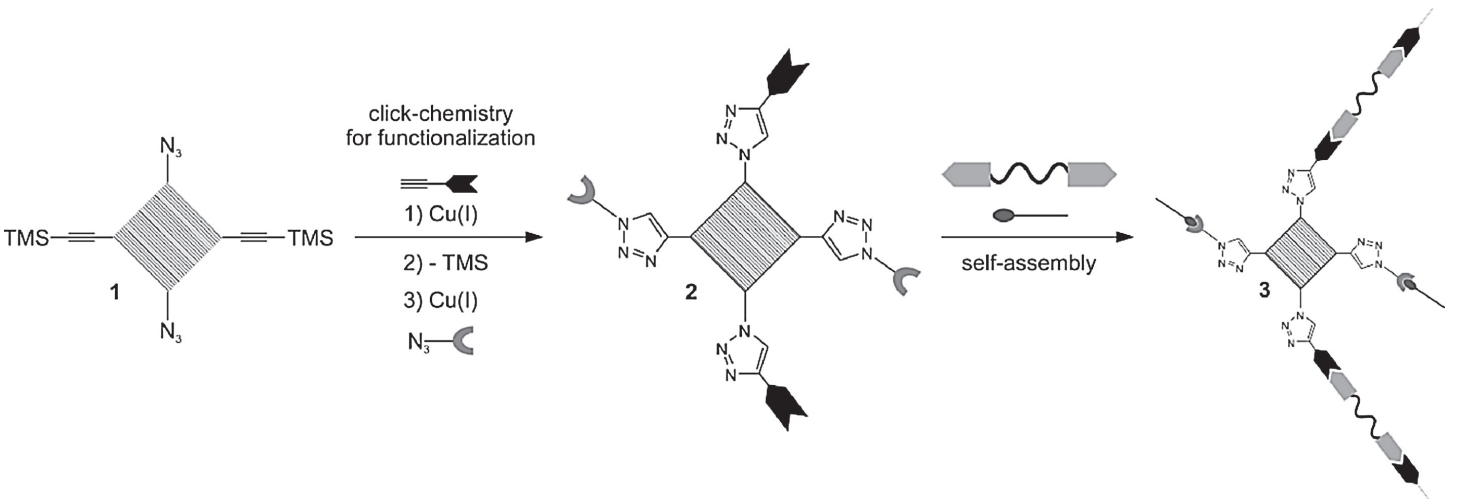
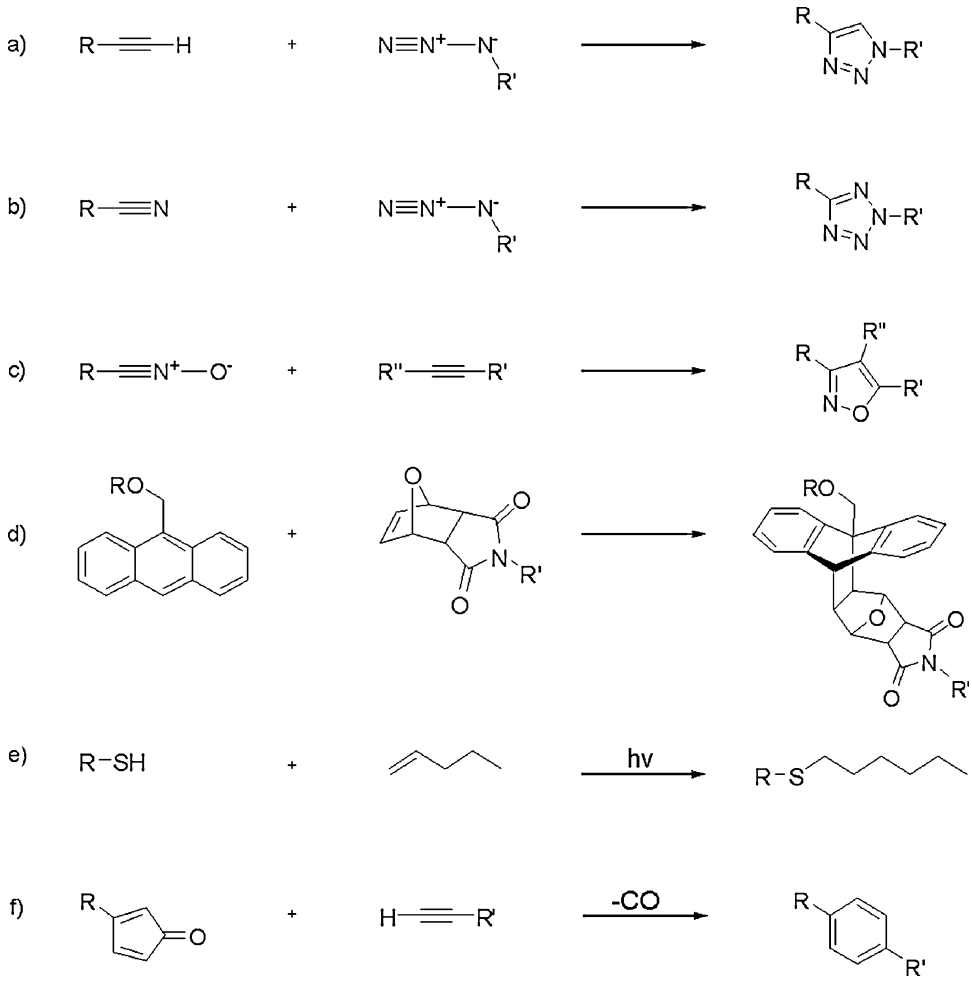


Figure 7.1 *Concept for the integration of azide–alkyne click chemistry into supramolecular science: highly efficient functionalization of the scaffold (1) is achieved with two different supramolecular receptors, furnishing the supramolecule (2), which assembled into aggregates (3).*

supramolecular interactions, which must be properly fixed and arranged around the molecule of interest. This often requires considerable synthetic force, since the molecules used are multifunctional, and thus multistep pathways are necessary – with all the disadvantages of modern synthetic organic chemistry. Thus, as most of the mentioned structures require tedious synthetic pathways, the approach to a specific structure is often limited by long-step syntheses and purification issues, often hampered by incomplete and insufficient chemical reactions. Moreover, as the molecular weights approach the limit of oligomeric and polymeric structures, the defined functionalization of such materials becomes problematic, as purification of incompletely reacted starting materials from their final products is difficult due to similar chemical structures or comparable size.

Universal chemical reactions, which are able to link many molecular species without protecting groups, offer high yields and provide an inherent insensitivity to chemical structure and solvents, are an important step forward in supramolecular material science. Moreover, as the energy of assembly in many supramolecular structures is close to the thermal energy, such a universal reaction in the ideal case would be of catalytic nature, not requiring strong acceleration by temperature increases, thus keeping supramolecular assemblies in place during reaction. Click chemistry is a proponent set of reactions, able to act as universal chemistry within supramolecular (material) science. According to the definition of Sharpless *et al*.,[4] a 'click reaction' is defined by a gain of thermodynamic enthalpy of at least 20 kcal mol^{-1}, thus opening way to a high-yielding and thus nearly substrate-insensitive reaction. This type of reaction was found most of all in the azide–alkyne click reaction,[4–6] which represents a metal-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition reaction[7,8] between CC triple, CN triple bonds[9] and alkyl-/aryl-/sulfonyl azides. The relevant outcomes of this reaction are (a) tetrazoles,[5,10] (b) 1,2,3-triazoles[11–14] or (c) 1,2-oxazoles, respectively. Briefly, the basic process of the Huisgen 1,3-dipolar cycloaddition[2,10,11] generates 1,4- and 1,5-triazoles, respectively (Scheme 7.1). The main metal salts used to accelerate this (at room-temperature rather slow) reaction are copper (I) salts [Cu(I)Br, Cu(I)I, in amounts of approximately 0.25–2 mol% with respect to the azide or alkyne substrate], aqueous regenerative systems [i.e. Cu(II) salts–ascorbic acid] as well as various copper clusters (Cu–Cu-oxide nanoparticles, sized 7–10 nm[15] or ~4 nm[16]), metallic $Cu^{(O)}$clusters[16–18] and copper–charcoal.[19] Recently, the use of a Cu(I)-free variant using the ring-strain of substituted 1,1,-difluoro-cyclooctynes to promote the dipolar cycloaddition process has been described, enabling mild reactions on living (cellular) systems.[20] Besides copper, other metals employed include Ru complexes[21] {[$CpRuCl(PPh_3)$, $[Cp*RuCl_2]_2$, Cp*RuCl(NBD) and Cp*RuCl(COD) favouring 1,5-addition [i.e. with $Ru(OAc)_2(PPh_3)_2$]}, and Au(I),[22] Ni, Pd[23] and Pt salts, although with much less catalytic activity.[24]

The mechanism of the reaction is different from that of a purely thermal 1,3-dipolar cycloaddition. According to Sharpless *et al*.,[11] modified by Finn *et al*.[25,26] by computational methods,[27,28] and finally revised by Bock *et al*.,[29] the metal-catalyzed reaction involves: (a) an up to 10^5th-rate acceleration and an absolute 1,4-regioselectivity of the Cu(I)-catalyzed process; (b) a kinetic feature of the reaction indicating at least second-order kinetics with respect to the concentration of the copper species,[26] thus involving at least two copper centers within the catalytic cycle, presumably linking two acetylenes via a μ-bridge;[30] (c) a significant autoacceleration if multiple triazoles are formed,[31] revealing intermolecular ligands effects; and (d) a significant rate-reduction with strongly increasing amount of copper. A basic feature, however is the formation of a copper-acetylide, resulting in the



Scheme 7.1

lowering of the pK_a-value of the Cu-acetylide by up to 9.8 units as calculated[28] via DFT-calculations.

Thus a relatively complex supramolecular assembly (**3**) can be generated from the supramolecule with two different receptor structures (**2**) (Figure 7.1) (representing different supramolecular interactions) in a two-step procedure, using the central azide- or alkyne-modified starting molecule (**1**), as nearly all functional groups are compatible with this process, except those that are (a) self-reactive or (b) able to yield stable complexes with the [Cu(I)-metal] under catalyst deactivation. The main interfering functional groups are terminal azides and alkynes,[32] strongly activated cyanides,[5,6,10] free (= accessible) thiol-moieties (R-SH) via the Staudinger reaction as well as strained or electronically activated alkenes.[8,33] However, the possibility to use free-thiols prior to an azide–alkyne click reaction has been demonstrated on polymers[34] and surfaces,[35] thus enabling the

use of free thiols despite the often interfering azide–amine reduction by the free thio-moiety. Most known solvents and biphasic reaction systems (mixtures of water–alcohol to water–toluene) can be applied with excellent results. Cocatalytic systems[31] often used include amino-bases[17,36] [mono- and multivalent triazoles[36], but also phosphines such as tris(carboxyethyl)phosphine (TCPE)]. Many reviews describe the azide–alkyne click reaction in general,[4,29] for application in polymer chemistry,[37–43] dendrimers,[40,44] carbohydrate chemistry,[45–47] materials-chemistry[37,38] and organic chemistry,[42,48] as well as for peptides[49] and drug discovery.[50] The following review focuses on the use of the azide–alkyne click reaction for the synthesis and assembly of multifunctional molecules in supramolecular (material) science.

7.2 Click Reactions on Rotaxanes, Cyclodextrines and Macrocycles

Rotaxanes, cyclodextrines and macrocycles are among the 'oldest' supramoelcular molecules developed. They are highly defined, and there has been intense research during recent decades. The azide–alkyne click reaction has promoted research in this area, as many synthetic approaches have become simpler and more effective.

7.2.1 Click with Rotaxanes

The basic approach to rotaxanes mediated via click reactions is shown in Figure 7.2.[51–57] Thus interlocked structures by (a) stoppering-reactions, (b) 'click polymerization or (c) macrocyclization have been achieved. A recent review has focused on this topic, describing rotaxanes and catenanes via click chemistry.[52] Two classical 'click stoppering' approaches have been described by Sauvage *et al*.[54] and Stoddart *et al*.[55] recently (see Figures 7.3 and 7.4).

Thus the assembly of the molecules is driven first by noncovalent interactions generating the complex (**4**), and subsequently the 'stoppers' fix the corresponding rotaxanes (**5**) in yields above 80%. An interesting example of 'click stoppering' by Sauvage *et al*.[54] (see Figure 7.4), generated the Cu-complexed molecule (**7**) via the click reaction. As the copper(I)-species is directly linked to the central rotaxane-core, thus acting not only as scaffold-forming metal, but also as catalyst in the subsequent click reaction, Leigh *et al*.[56] have formulated a highly interesting mechanism for the catalytic cycle as shown in Figure 7.4. Thus the copper-species interlocks molecule (**8**) and forms the catalytic species to add the propargylic alcohol (**6**) and the azido alcohol (**9**) to furnish the species (**10**) in catalytic amounts. Thus only a small amount of copper is needed to effect the efficient formation of the rotaxane (**7**). A similar formation of [3]-rotaxanes has been described furnishing the interlocked molecule (**11**) (see Figure 7.5).

One of the oldest examples of rotaxane formation was described before the discovery of Cu(I) catalysis by Steinke *et al*.,[57,58] focusing on the reaction of cucurbiturils into rotaxanes via 'click polymerization'. This approach has recently been revived,[53] generating pseudo-polyrotaxanes (**12**) threading cucurbit[7]uril and β-cyclodextrine in an alternating fashion onto the respective polymer, which is generated by a polyaddition process. As the click reaction is highly moderate in its reaction condition, the simple synthesis of such molecules is only possible via this strategy (Figure 7.6).

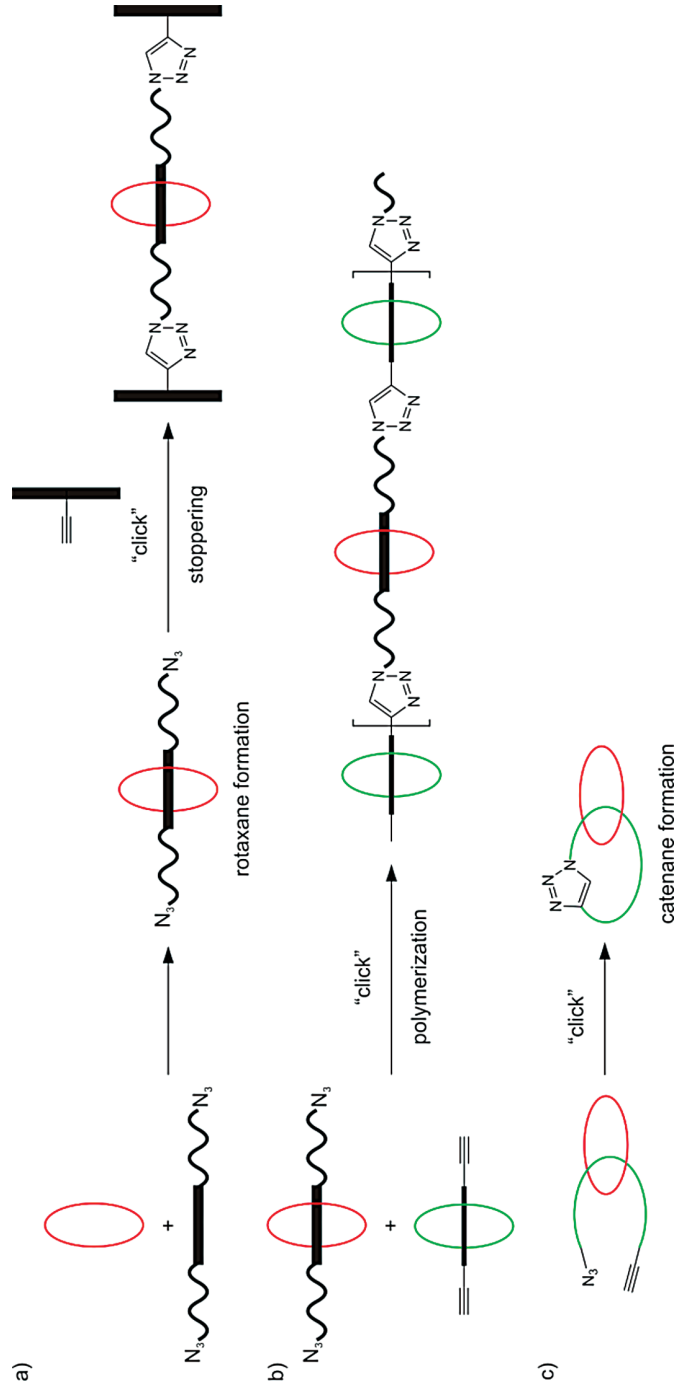


Figure 7.2 *Concept for the generation of rotaxanes via azide–alkyne click reactions.*

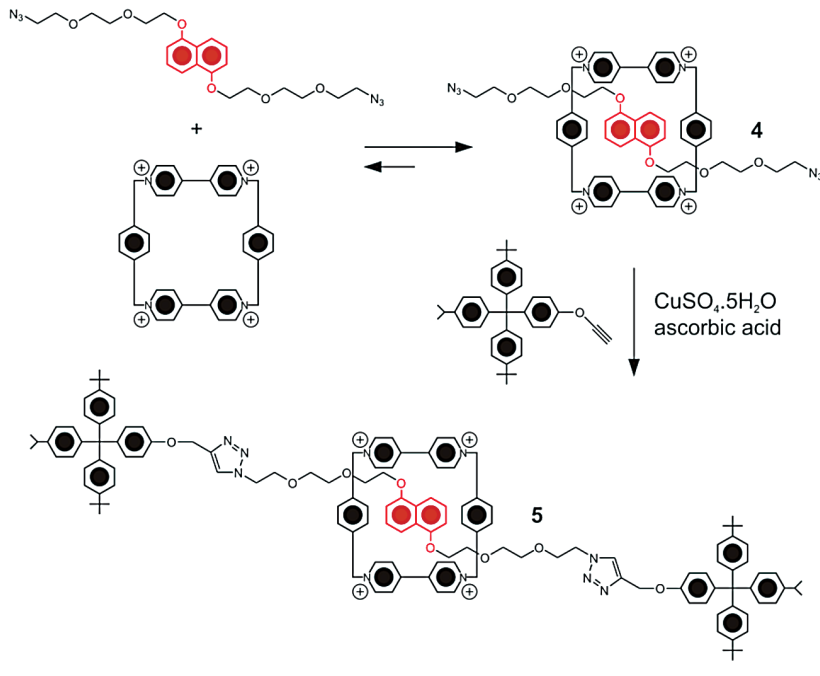


Figure 7.3 *Formation of rotaxanes via click stoppering.*

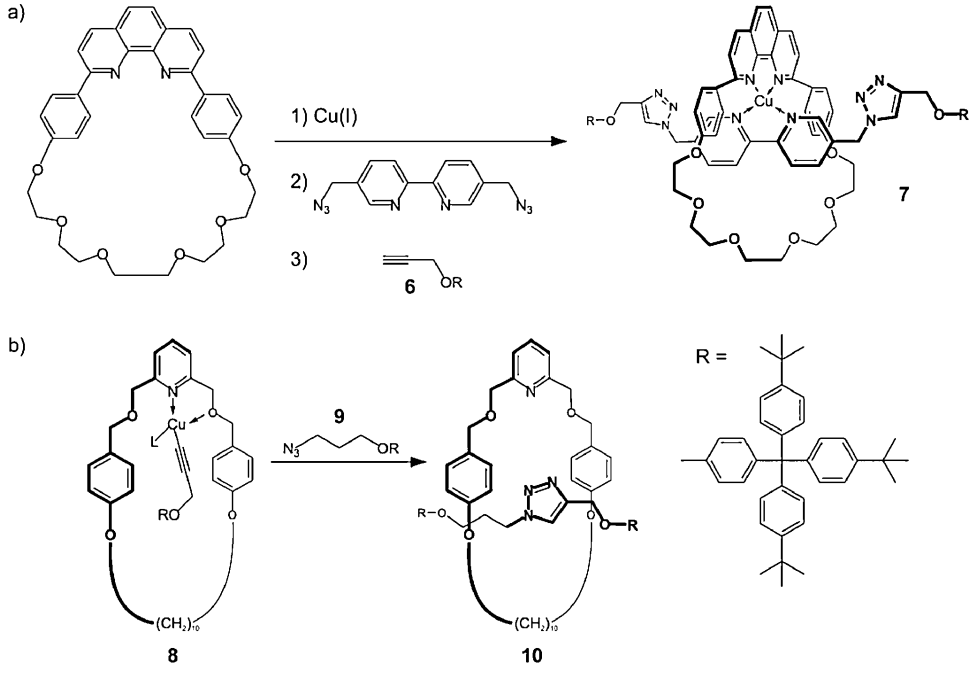


Figure 7.4 *Formation and mechanistic considerations for the generation of roatxane (**7**).*

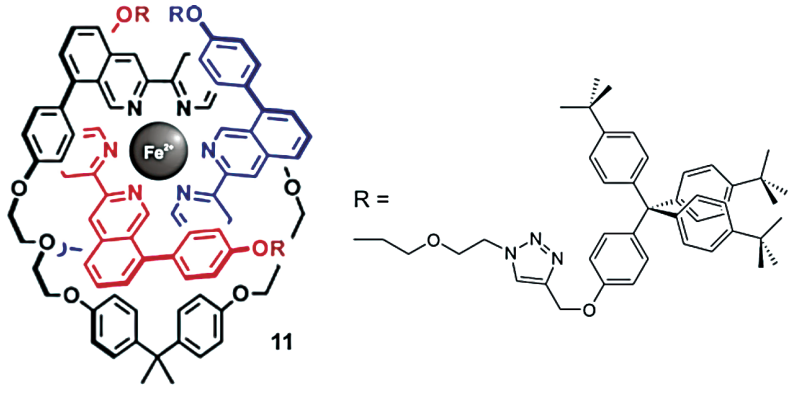


Figure 7.5 *Formation of interlocked structures (**11**).*

7.2.2 Click on Cyclodextrines

As the azide–alkyne click chemistry has been strongly applied to carbohydrates[45,46,59] due to their multifunctional nature and the excellent compatibility of the azide–alkyne click reaction with multihydroxy moieties; also cyclodextrines as well as the logically related calixarenes[60] have been functionalized via this reaction. Cyclodextrines are important supramolecular molecules, with a highly defined hydrophobic cavity and a hydrophilic exterior, allowing the complexation of hydrophobic guest within their interior, controlled by substituents on the outer rim. The functionalization of the outer rim via their 6′-hydroxy-moieties thus is an important point, often hampered by steric constraints or insufficient reactions that can nicely be accomplished vie the azide–alkyne click reaction, as shown in Figure 7.7.[53,61–69] The transformation of the 6′-hydroxylmoieties into azido-moieties can be achieved via direct reactions, thus opening the possibility for the

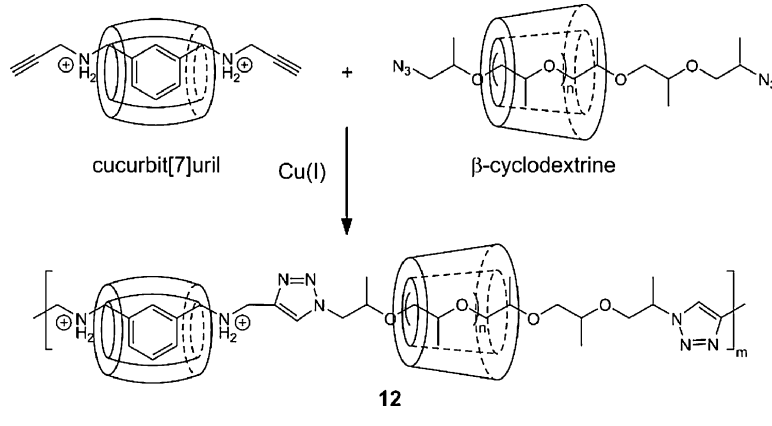


Figure 7.6 *Formation of alternating copolymers (**12**) consisting of rotaxanes made from b-cyclodextrin and cucurbit[7]uril.*

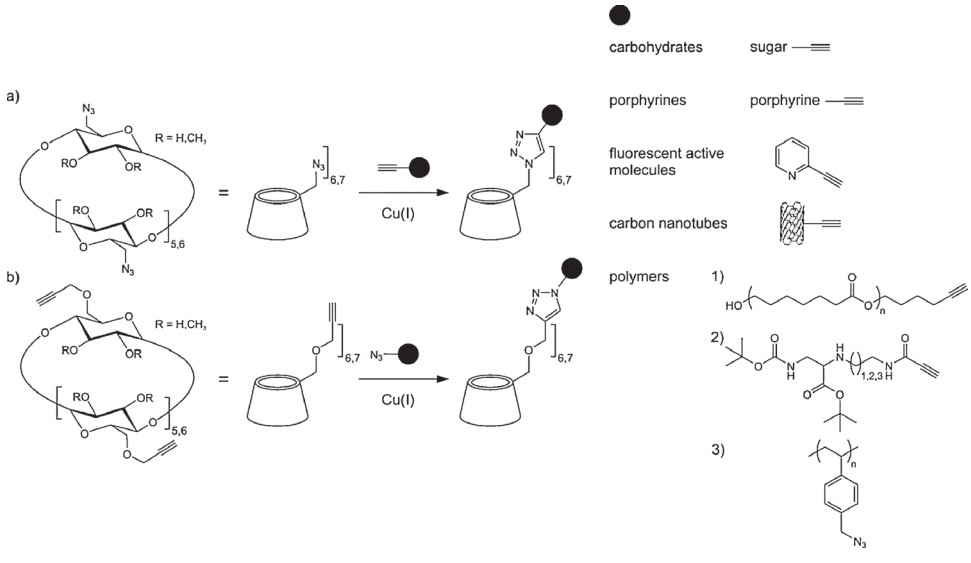


Figure 7.7 *Generation of modified cyclodextrines by azide–alkyne click reaction.*

attachment of other carbohydrates,[66,68] porphyrines,[64] other cyclodextrines,[63] fluorescent-labels,[67] carbon-nanotubes[65] and a variety of polymers.[62,69]

An excellent example for the use of the azide–alkyne click reaction has been recently described by Liu *et al*.[64] by attaching 6′-mono-azido-cyclodextrine moieties onto all four edges of porphyrine-molecules, thus generating brick-type structures as shown in Figure 7.8. The resulting structures [either the methoxylated structures (**13**) or the hydroxylated structures (**14**)] can self-assemble into highly regular structures using porphyrines with four phenyl groups, able to insert into the cyclodextrine cavities. Thus highly organized nanostructures can be built from these easily available associates within a one-step synthetic procedure.

Hoogenboom *et al*.[69] have attached seven poly(caprolactones) to the 6-positions of a β-cyclodextrin-derivative [see Figure 7.9(a)], generating a polymer-modifed cyclodextrin (star-shaped polymer **15**). As the steric demand of such polymeric chains is fairly large, the result is important and could not have been achieved by other method.

Another modification of cyclodextrines with polymers has been reported by attaching cationic polyimine polymers to a β-cyclodextrine-derivative.[62] The resulting star-polymer (**16**) can self-assemble into aggregates of about 50–100 nm and complex DNA due to its highly poly(cationic) nature. The molecules are highly efficient, nontoxic delivery agents for nucleic acids into HELA cells due to their complex formation and masking of the DNA within their assemblate structure.

Modification of carbon-nanotubes has been reported with cyclodextrines. Similar to the method employed previously with PS polymers,[70] an alkyne moiety was introduced via a nitrene addition onto the carbon nanotube backbone. Subsequently, the monofunctionalized cyclodextrine was attached to the carbon nanotubes, leading to uniformly labeled CD nanotubes (**17**), visible using TEM methods (Figure 7.10).

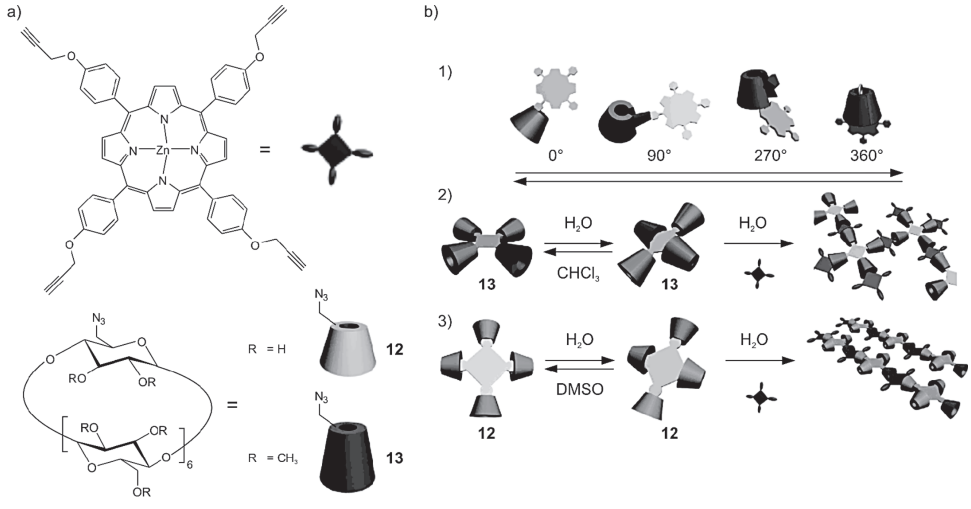


Figure 7.8 *Assembly of cyclodextrine-modifed porphyrines* ***12*** *and* ***13*** *into regular grids via key/lock-type interactions. Reprinted with permission from Y. Liu* et al.*, (2008), Complexation-induced transition of nanorod to network aggregates: alternate porphyrin and cyclodextrin arrays,* J. Am. Chem. Soc.*,* ***130*** *(2), 600–605. Copyright 2008 American Chemical Society.*

7.2.3 Click on Macrocycles

Macrocycles are important supramolecular structures – early examples include crown-ethers or cryptands; later examples are often related to membrane-spanning channels,[71,72] defined amphiphilic macrocycles[73] or cyclic polymers.[74] The engineering of such structures is difficult, since supramolecular interactions and defined rigid/flexible segments are

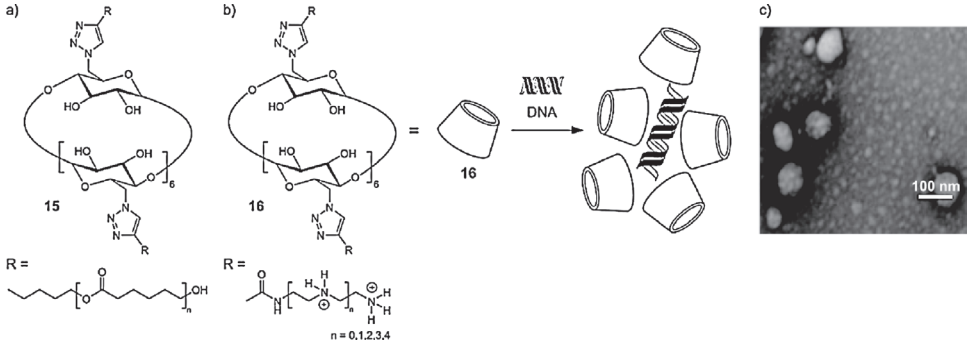


Figure 7.9 *(a) Generation of DNA–cyclodextrine complexes via attachment of cationic polymers onto the outer rim, yielding cyclodextrine* ***16****. (b) TEM-micrograph of the complexes formed between DNA and* ***16****. Reprinted with permission from S. Srinivasachari* et al.*, (2008), Polycationic beta-cyclodextrin click clusters: monodisperse and versatile scaffolds for nucleic acid delivery,* J. Am. Chem. Soc.*,* ***130****, 4618–4627. Copyright 2008 American Chemical Society.*

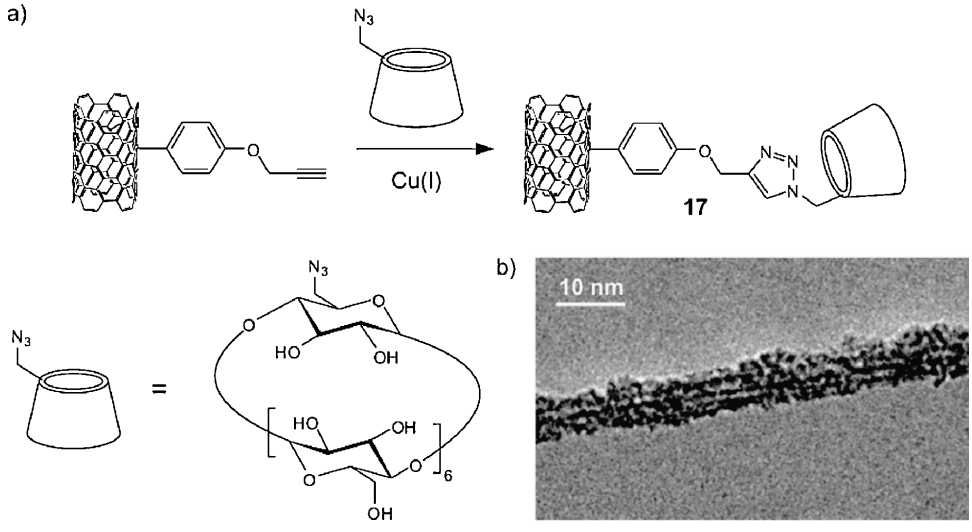


Figure 7.10 *(a) Attachment of cyclodextrines onto carbon-nanotubes. (b) TEM-micrograph of the formed-CD/nanotube structure. Reprinted with kind permission from Z. Guo* et al.*, (2008), Covalently β-cyclodextrin modified single-walled carbon nanotubes: a novel artificial receptor synthesized by click chemistry,* J. Nanopart. Res.*, **10** (6), 1077–1083. Copyright 2008 Springer Science and Business Media.*

difficult to be introduced into large cycles due to the poor efficiency of the cyclization reaction, whose efficiency declines with increasing chain length and steric constraints[75] (cyclization efficiency $\sim 1/N^{3/2}$ (N = chain length of the linear structure).[76] As the topic has been reviewed recently, only selected examples are provided in this review.

Cyclic polymers have been generated via the α,ω-end group functionalization PS (**18**),[77] PNIPAM (**20**, **22**)[78,79] and poly(ε-caprolactones)[80] with azide and alkyne groups. After macrocyclization, this strategy yields the corresponding cyclic polymers **20**, **22** in yields of ~80% efficiency (see Figure 7.11). starting from their linear precursor-structures **19** or **21**.

This method is a highly efficient method to generate cyclic polymers with higher molecular weights from their linear counterparts. As the properties of cyclic polymers are very different from those of the corresponding linear structures in terms of chain-conformation, crystallization and supramolecular ordering, this simple approach to cyclic polymers will definitely be a landmark for further investigations.

Haridas *et al.*[81] have described the synthesis of macrocycles **23** and **24**, starting from the open-bisacetylene via ring-closure reaction. (Figure 7.12). The generated macrocycles (triazolophanes) display a nonclassical hydrogen bonding system, as solvent molecules (i.e. acetonitrile) can be embedded in the interior of the cycle via these nonclassical hydrogen bonds. Currently, the macrocycle is investigated for its ionophoric properties due to this hydrogen-bonding ability.[81]

Another example of such nonclassical hydrogen bonds for ionophoric abilities has been reported by Flood *et al.*,[82] generating macrocycle **25** with four triazole-rings in its cavity. A dynamic equilibrium is observed upon addition of chlorine ions, which can be complexed to the interior, furnishing the ioniphore **26** with an association constant of $K_{assn} \approx 130\,000\ \text{M}^{-1}$.

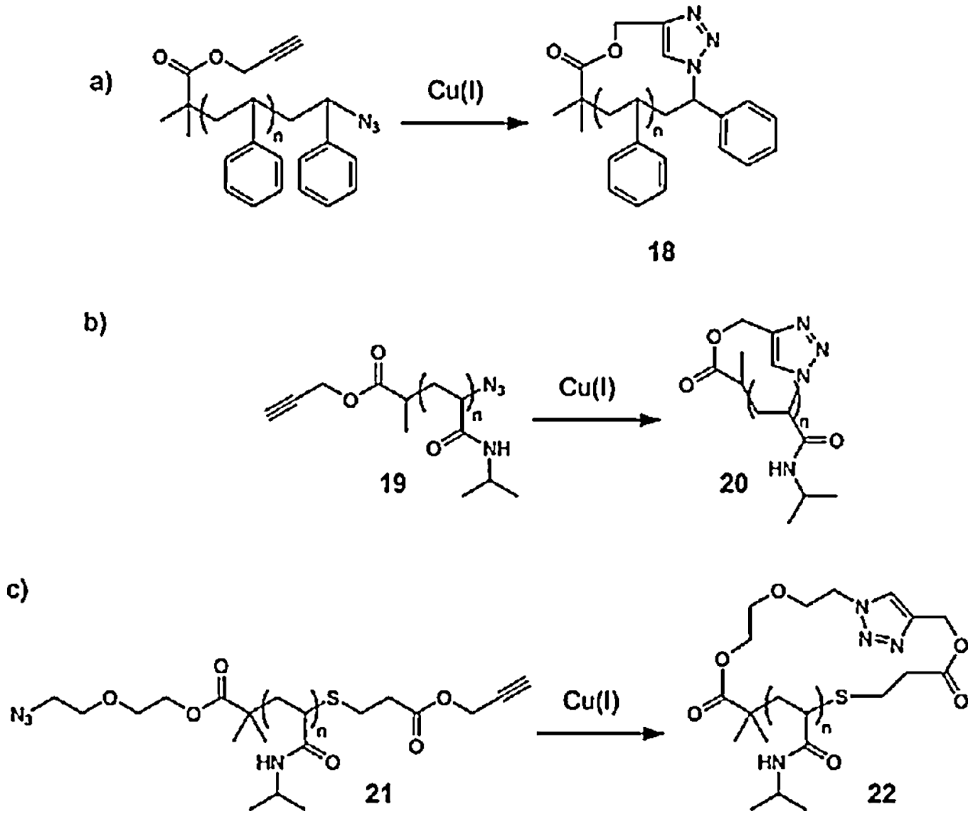


Figure 7.11 *Macrocyclization reactions of α,ω-modified polymers: (a) formation of cyclic-poly(styrene) (PS)* ***18****; (b, c) macrocyclic poly(*N*-isopropylacrylamides)* ***20*** *and* ***22****.*

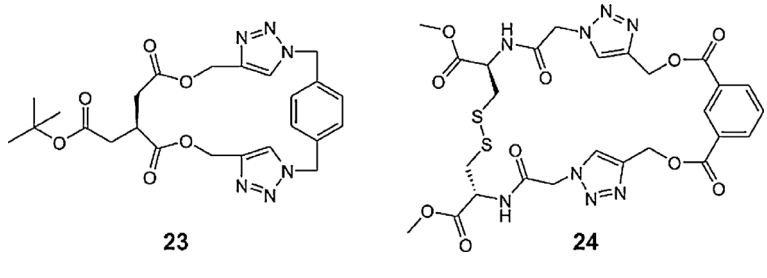


Figure 7.12 *Macrocycles* ***23*** *and* ***24****.*

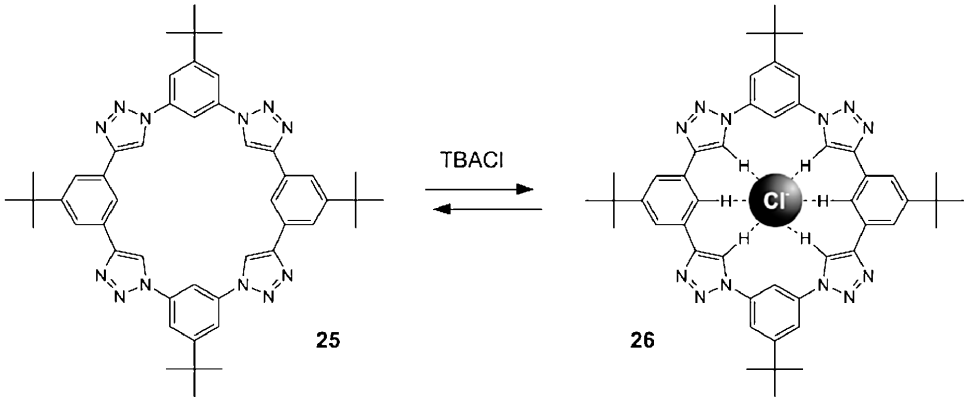


Figure 7.13 *Ionophoric activity of the macrocycle **25** via its chlorine-form **26**.*

Again, such structures are difficult to make via conventional pathways, thus opening new supramolecular macrocycles via the azide–alkyne click reaction (Figure 7.13).

Cyclic peptides for membrane-spanning,[72] helical peptides[72,83] or as binding domains for SH2 domains[84] have been prepared by the azide–alkyne click reaction. Thus the starting peptide **27** has been reacted with Cu(I)–ascorbate system in aqueous media, generating the SH2-binding macrocycle **28** as well as the dimeric macrocycle **29**. Both were found to exhibit increased affinities towards the Sh2-domain in sub-μM concentrations (Figure 7.14).

Cyclic carbohydrate molecules have been generated via click reactions (see Figure 7.15). Thus the dimerization of the trisachharide **30** furnishes the macrocycle **31** in nearly 80% yield.[68] As slightly different strategy has been used relying a combination of ring closing metathesis (RCM) and the azide–alkyne click reaction:[85] thus the macrocycles **32**, **33** and **34** containing the hexo- and pentopyranoses within their ring structure have been prepared in yields between 73 and 95% (Figure 7.15).

7.3 Click Reactions on DNA

It is unquestionable that DNA and RNA represent some of the best-studied supramolecular systems, as several types of supramolecular interactions are present and can be used for

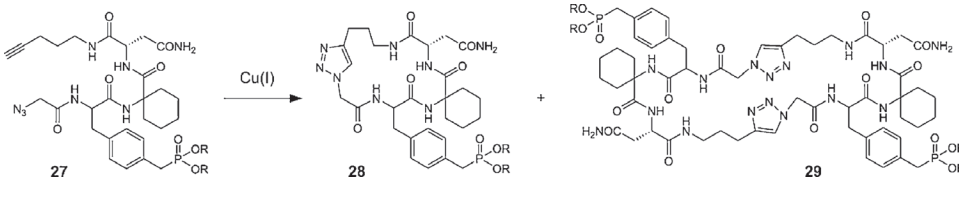


Figure 7.14 *Dimerization of the peptide **27** into monomeric cycle **28** and the dimer **29**.*

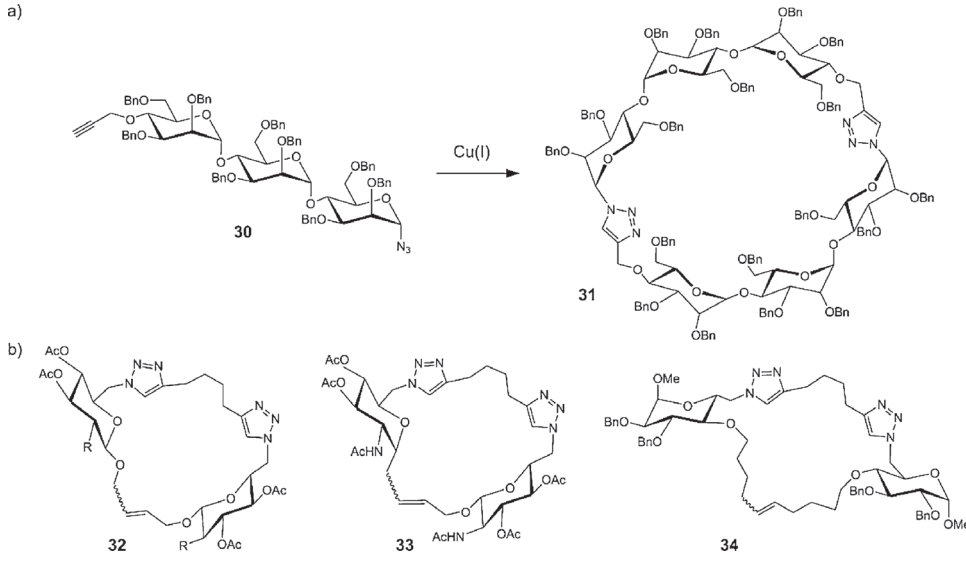


Figure 7.15 *Formation of macrocyclic carbohydrates. (a) Dimerization of **30** yielding **31**. (b) Various carbohydrate containing macrocycles formed by a combination of RCM and click.*

scaffolding. The hybridization of DNA and the subsequent PCR and other detection methods are the most prominent, followed by triplex formation (via Hogsteen-base-paring), cyclic DNA and cross-linking. As evident by the large number of publications, the azide–alkyne click reaction has had a strong impact on DNA modification and the subsequent use of DNA in supramolecular recognition processes (see Figure 7.16):[86–102] thus labeling of DNA with terminal azide–alkyne moieties in the side chain or at the chain end can be either achieved via chemical synthesis (phosphoamidite-method),[90,95] the cellular DNA-polymerases[87] or PCR,[90,91,93,94,97,99,100] as well as via chemical labeling of the respective end groups.[96,98,102] Thus unnatural nucleosides or nucleotides **35a–f** are required as shown in Figure 7.16, displaying purine and pyrimidine bases with attached alkynes or azides,[86,90,91,93,94,97,99,100] which subsequently can be incorporated into the DNA. It has been demonstrated that the structure of the incorporated nucleoside has a pronounced impact on the efficiency of the click reaction[93] (Figure 7.16). Thus both nucleosidic structures **35b** and **35c** were incorporated in the DNA via PCR and their click reaction in single- and double-stranded DNA subsequently investigated. It could be demonstrated that nucleoside **35b** is more efficient than nucleoside **35c**, presumably due to steric effects, since the alkyne moiety in dsDNA of nucleoside **35b** is sterically less hindered within the major groove of the DNA molecule.[88,93]

The method of side chain modification of DNA has been intensely investigated towards DNA metallization by Carell *et al.*,[99] as shown in Figure 7.17. Thus the side chain of DNA was modified with aldehyde residues via the click reaction, and subsequently metalized with Ag ions via the Tollens reaction by reaction with the pendant aldehydes. It was demonstrated that the attachment of poly-hydroxylated dendrimers yields a higher

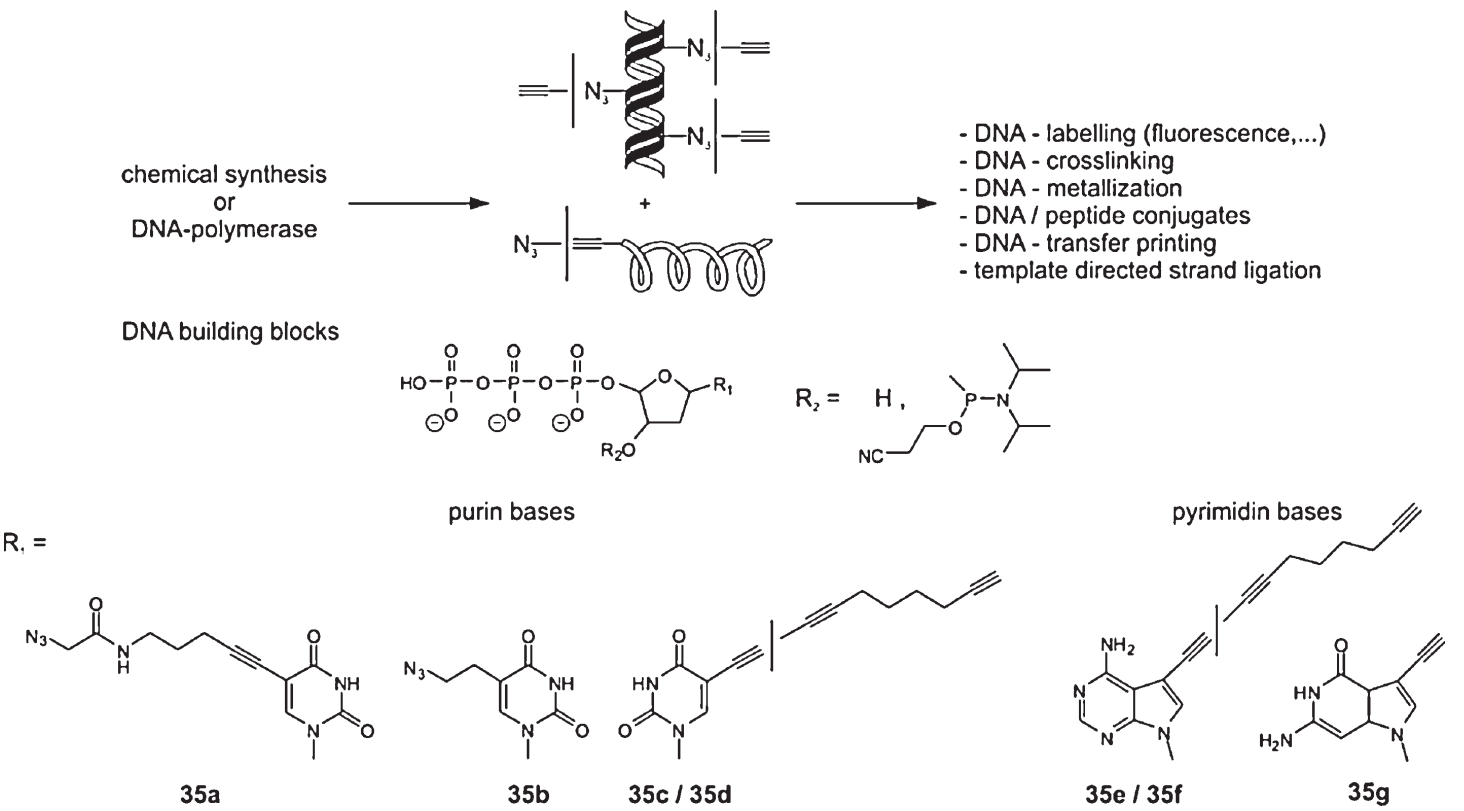


Figure 7.16 *Strategy for the incorporation of click concepts with DNA.*

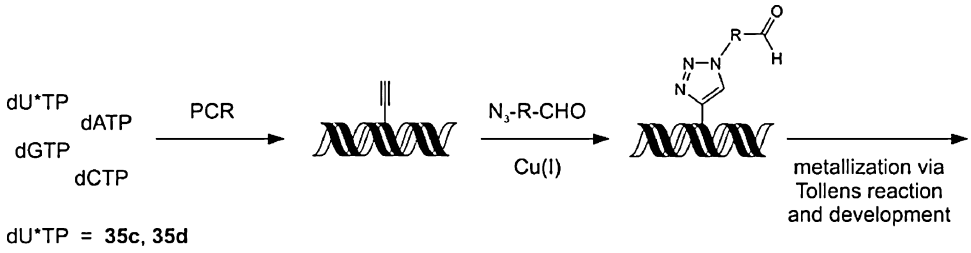


Figure 7.17 *Formation of alkyne modified DNA via PCR using the modified nucleotides **35c**, **d** and their metallization via attached aldehydes using the Tollens reaction.*

density of aldehyde moieties on the DNA strand during the Tollens reaction, followed by an easier metallization reaction of the DNA due to the increased presence of reducing moieties.

An enormous improvement of assaying methods of DNA has been developed by incorporating nucleotide **35c** directly into DNA within living cells [see Figure 7.18(a)].[87,92] After incorporation of **36c** by the DNA polymerases within the cells, the DNA is visualized by addition of a fluorescein derivative, attached to the labeled DNA via the click reaction. Thus whole amounts of large tissues or organ explants can be labeled via this method in minutes, which represents an enormous improvement over the conventionally used techniques. Moreover, the labeling can be achieved in live cells, thus enabling the assaying of *in-situ*-gene activity.

A slightly different approach for DNA detection *in vitro* used a process derived from photography for 'naked-eye'-DNA-detection [Figure 7.18(b)].[97] Thus DNA was labeled with alkyne moieties as described before, using PCR and the nucleosides **35b**, **c** and a pinacyanol dye was linked to the DNA via the azide–alkyne click reaction. Subsequent spotting generated strongly diluted DNA, which – after incubation with Ag^{+}-ions – generated dark-spots, which allow the selective detection of DNA after conventional hybridization down to 600 fmol by the naked eye.

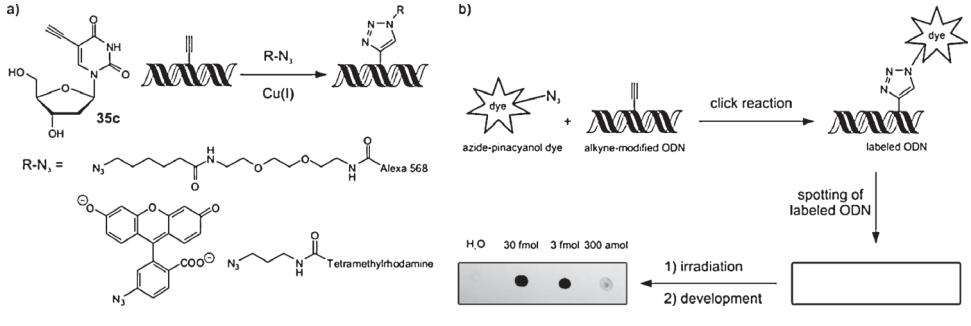


Figure 7.18 *(a) DNA-assaying in vivo by incorporation of **35c** and subsequent attachment of fluorescein-dye. (b) DNA-assaying for the 'naked-eye'. Reprinted with permission from D.M. Hammond* et al.*, (2007), DNA photography: an ultrasensitive DNA-detection method based on photographic techniques,* Ang. Chem. Int. Ed.*, **46** (22), 4184–4187. Copyright 2007 Wiley-VCH.*

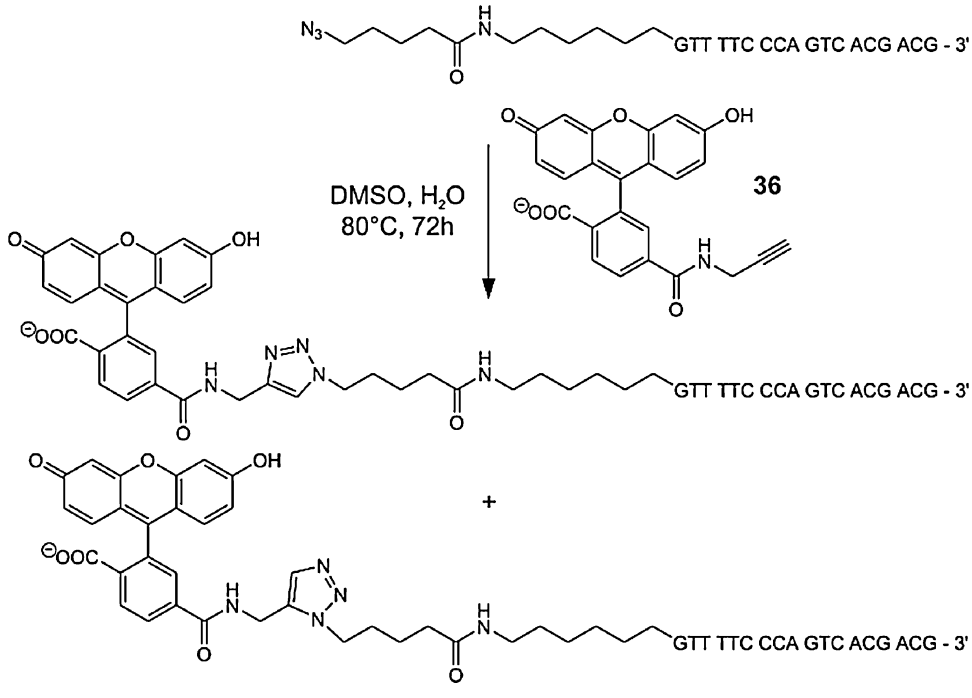


Figure 7.19 *DNA labeling at the end using the fluoresceine-molecule* ***36****.*

The classical attachment of fluorescent dyes to the end of DNA has been reported as one of the first examples for DNA labeling (see Figure 7.19).[102] MALDI-TOF methods were used to verify the completeness of the ligation-reaction with the fluorescent dye **36**, and the labeled DNA was directly used without further purification for the DNA sequencing via capillary electrophoresis due to the high efficiency of the azide–alkyne click reaction.

DNA cross-linking has been use as demonstrated the proximity effect of the azide–alkyne click reaction in adjacent DNA-strands (see Figure 7.20).[88] Thus exactly one nucleotide with an azide–alkyne moiety was incorporated into the DNA strands and subsequently hybridized. After hybridization, the addition of Cu(I) salts led to the cross-linking of the adjacent moieties under triazol formation. Nucleotides with longer side chains (i.e. octydiynyl **37**, **38** vs ethinyl **35c**) gave better cross-linking for steric reasons, as already described by Carell *et al.*[93] for the attachment of other groups to alkyne labeled DNA.

The transfer-printing of DNA onto azide-terminated glass surfaces is an important method to attach DNA in a simple process to surfaces for use in biochip-technology (Figure 7.21).[94] A method reported previously on polymeric surfaces via microcontact printing[103] or AFM tips[104] has thus been transferred to DNA: alkyne-labeled DNA (side chain- or end group-labeled) was stamped via a dendri-stamp onto a glass surface and modified with azido-moieties. The dendri-stamp presents multiple functional groups in order to improve the adhesion process by multivalent binding effects. Because of the

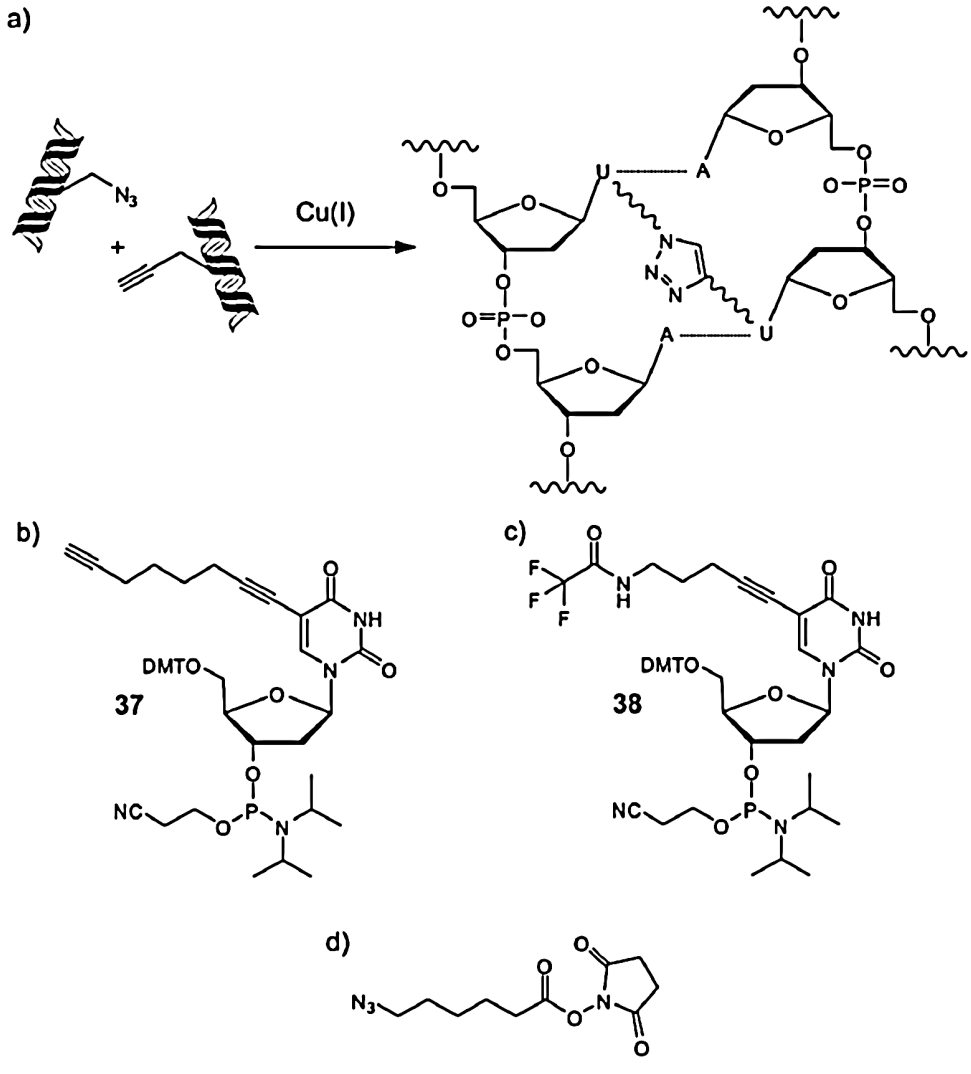


Figure 7.20 *(a) Crosslinking of DNA using the click reaction. (b) Incorporated* ***37*** *and* ***38*** *used for DNA-cross-linking.*

multiply-present reactive groups between the DNA (alkynes) and the surface (azides), no Cu(I) ions were required, just a contact time of approximately 1 h while applying a load of 120 g. Subsequent hybridization experiments demonstrated the effectiveness of the method for DNA recognition and assaying methods.

A combined method of DNA labeling and methylation has been described using the azide–alkyne click reaction [see Figure 7.22(a)].[101] An alkyne-labeled nucleoside **39** able to methylate DNA was incubated with DNA and a methyltransferase. During methyltransferase reaction, the azide–alkyne click reaction took place, thus demonstrating the

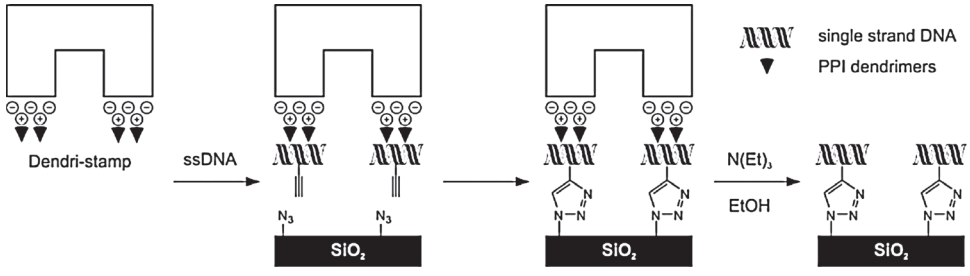


Figure 7.21 *Attachment of DNA to surfaces via stamping-methods.*

possibility to conduct both reactions within the active center of the methyltransferase enzyme.

A template-directed ligation process has been described, linking two DNA-fragments to yield a cyclic-structure (Figure 7.22).[96] Thus labeled DNA (3′-azide and a 5′-alkyne) was hybridized and incubated with Cu(I) ions, furnishing either a template-directed ligation into linear structures, or a nontemplated cyclization yielding cyclic DNA. The latter is very difficult to achieve by other methods and thus represents the first example of such a reaction to cyclic DNA.

Finally, DNA can be used for the assembly of nanoparticles, if corresponding additional supramolecular interactions are affixed to it (Figure 7.23).[91] Thus alkyne moieties were incorporated via PCR-methods, yielding DNA with a high density of alkyne moietes in the major groove. Au nanoparticles, equipped with high densities of azide moieties, can be assembled on the DNA strand, and subsequently fixed covalently after addition of Cu(I) salts via the triazole-linkages. Thus a stable adhesion and binding of nanoparticles can be effected on the DNA without the use of a reduction process directly.

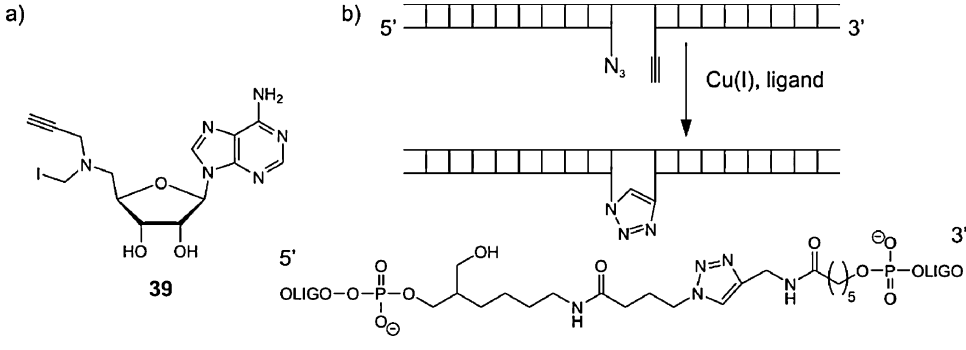


Figure 7.22 *(a) Chemical structure of **39** used for DNA-methylation. (b) Formation of cyclic DNA.*

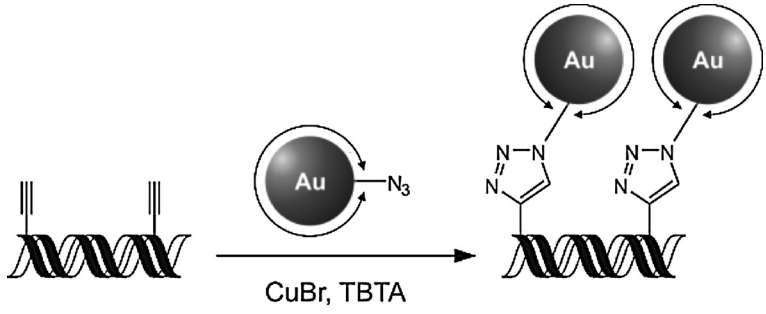


Figure 7.23 *DNA-metallization by use of alkine-modified-DNA and subsequent nanoparticle-attachment. Reproduced with permission from M. Fischler, U. Simon, H. Nir* et al.*, (2007), Formation of bimetallic Ag–Au nanowires by metallization of artificial DNA duplexes,* Small, ***3*** *(6), 1049–1055; G. A. Burley, J. Gierlich, M. R. Mofid* et al.*, (2006), Directed DNA metallization,* J. Am. Chem. Soc., ***128*** *(5), 1398–1399.*

7.4 Click Reactions on Supramolecular Polymers

Supramolecular polymers[105–107] are an increasingly important class of polymeric materials, where noncovalent bonds mediate the adhesion of oligomers or polymers. As supramolecular interactions in polymers can be tuned very efficiently (i.e. hydrogen-bonds ranging from ~7 to ~40 kJ/mol),[107] the molecular interaction between the chains can be tuned in high precision. Thus polymeric materials with highly dynamic properties can be generated, allowing the generation of dynamics polymers (so called 'dynamers'),[108] self-healing materials,[109] microphase-separated polymer blends[110] and gels[111] with tunable properties, or new biomaterials[112] and nanocomposites.[105]

As the topic of the azide–alkyne click reaction has had enormous impact on polymer chemistry and synthetic macromolecular chemistry,[43,113] it is not surprising that the field of supramolecular polymer chemistry has been strongly influenced by this reaction as it allows the affixation of supramolecular interactions at specific sites of a polymer chain. As one of the most prosperous combinations, many living polymerization methods have been combined with the azide–alkyne click reaction (for a recent reviews see Binder and Sachsenhofer[43,113]).

We were the first to exploit the use of the azide–alkyne click chemistry for the attachment of supramolecular entities onto the backbone of polymers prepared by living polymerization methods.[35,38,114–123] One of the first examples concerned the combination of ROMP with click chemistry,[114,116,117,123] thus achieving a controllable density of supramolecular entities in homopolymers **40**,[114] statistical copolymers[117] **41** and blockcopolymers **42**.[116,123] As shown in Figure 7.24(a–c), the possibility to 'first-click-then-ROMP' or 'first-ROMP-then-click' proved useful for the synthesis of an enormous number of different ROMP polymers with nearly any thinkable architecture. The method represents a universal scaffold for the attachment of many supramolecular entities, e.g. **43** (Hamilton-receptor–barbituric acid interaction), since the click chemistry is nearly substrate insensitive and allows the easy attachment of even complex supramolecular entities.

The scaffolds can be used to take advantage of two highly defined supramolecular interactions upon spreading as films, as shown in Figure 7.24 (d–f):[116,117]one the one hand

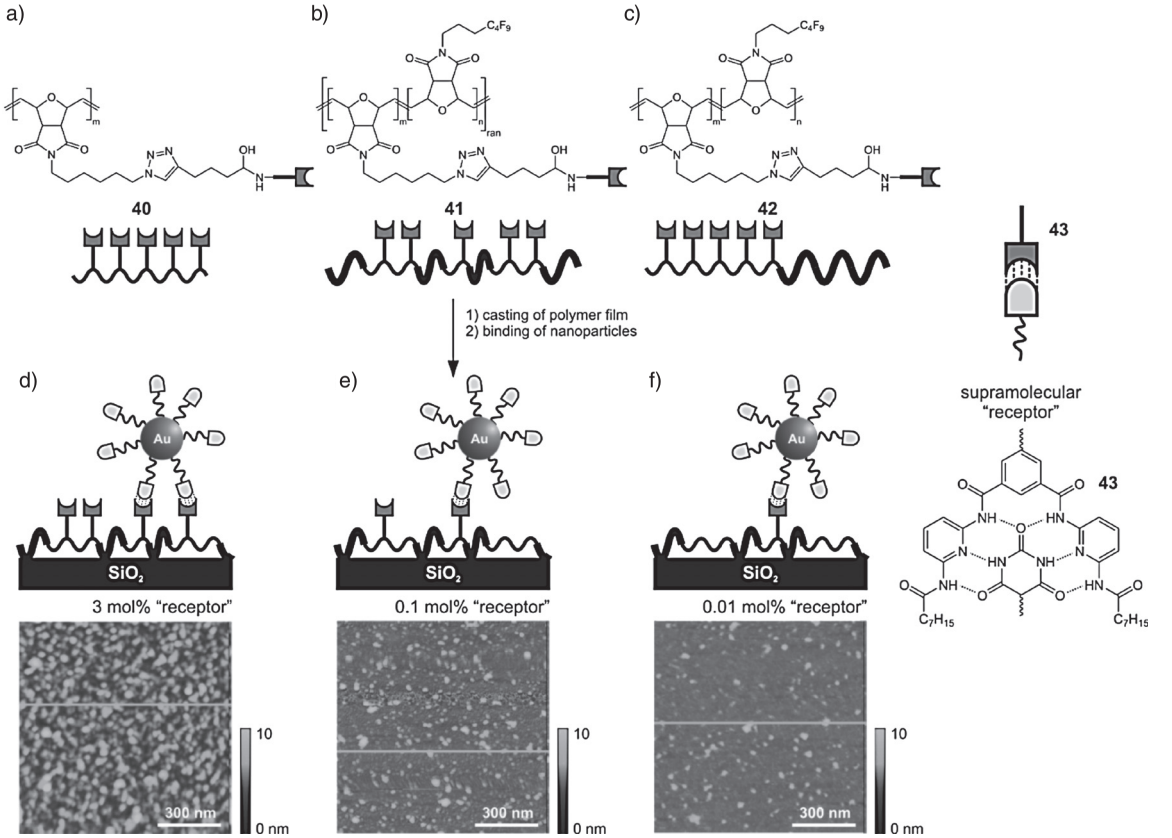


Figure 7.24 *Synthesis of polymers via ROMP/click methods, attaching supramolecular moiety* ***43*** *to the side chain, thus controlling the density of the supramolecular interaction. (a) Homopolymer* ***40****; (b) statistical copolymer* ***41****; (c) block-copolymer* ***42****. (d–f) The polymers can be cast into films, used for the attachment of nanoparticles via the selective hydrogen bond* ***43****.*

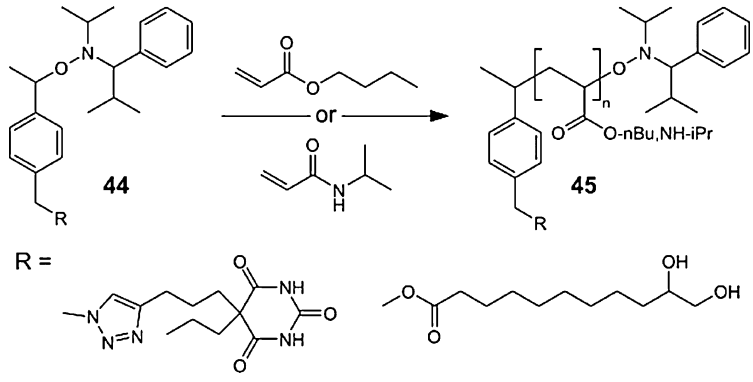


Figure 7.25 *Combining nitroxide-mediated polymerization (NMP) with click chemistry for the attachment of the supramolecular structures to the Haker-type-initiator* ***44****, yielding the monofunctional supramolecular polymers* ***45****. Reprinted with permission from W. Binder* et al.*, (2007), Magnetic and temperature-sensitive release gels from supramolecular polymers,* Adv. Func. Mat.*,* ***17*** *(8), 1317–1326. Copyright 2007 Wiley-VCH.*

microphase separation of block copolymers takes place if immiscible blocks exist and the supramoelcular entities are affixed to different blocks of the blockcopolymers, and on the other hand hydrogen-bonding interactions that can be presented by the polymer are useful to attach nanoparticles to the surface via supramolecular recognition. Thus statistically distributed hydrogen bonds shown in Figure 7.24(e) yield the correspondingly statistically distributed nanoparticles on the polymer film,[117] whereas the block copolymers yield controlled aggregates of the nanoparticles on the polymeric surface.[116] Thus the density and distribution of the nanoparticles can be controlled by use of the underlying polymeric scaffold. Without azide–alkyne click reaction it is nearly impossible to modify the density of such interactions on a polymeric chain without enormous synthetic effort.

Another combination of living polymerization and azide–alkyne click reactions has been reported by us, combing nitroxide-mediated polymerization (NMP) with click chemistry (Figure 7.25).[124] Thus the supramolecular entities (hydrogen bonds) have been affixed by use of a modified Hawker-type-nitroxide initiator **44**. Subsequent NMP of *n*-butylacrylate or *N*-isopropylacrylamide furnished the correspondingly mono-functional polymer chains **45**, as proven by MALDI-TOF-analysis. The method was further extended to the grafting-from reaction of NIPAM from iron-oxide-nanoparticle surfaces. The telechelic PNIPAM used was then incorporated into supramolecular gels, achieving an additional element of thermoresponsiveness into the material.[125]

The combination of living carbocationic polymerization of poly(isobutene) with the azide–alkyne click reaction allows the generation of star[111] and block copolymers[126,127] functionalized with hydrogen bonding end groups (Figure 7.26). Thus the three-arm star-poly(isobutylene) **46** was prepared with the respective multiple hydrogen bonds affixed to its end group moieties. MALDI-TOF and NMR-spectroscopy have been used to prove the generated structures, which in turn can be combined into highly temperature-sensitive amphiphilic gels by mixing with their . Superparamagnetic iron-oxide nanoparticles can be incorporated into these gels, yielding responsive materials with two-sensitivities: (a) those

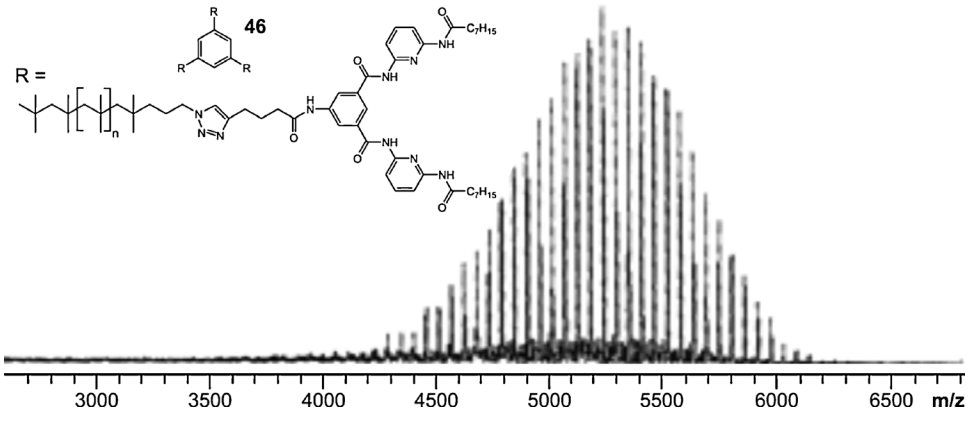


Figure 7.26 *Synthesis of three-arm-star polyisobutylene (PIB) with three attached supramolecular hydrogen bonding receptors* ***46****. Shown is the corresponding MALDI spectrum, demonstrating the effectiveness of the synthetic method.*

induced by the reversibility of the hydrogen bond and another (b) induced by an oszillating magnetic field, heating up the iron-oxide nanoparticles and stimulating the breakup of the gel. Moreover, the gel is self-healing as it assumes its original shape after mechanical deformation, as proven by rheological experiments.

The binding of nanoparticles to surfaces made from self-assembled monolayers (SAMs) has been achieved by the use of hydrogen-bonding systems between surface-modifed nanoparticles and SAMs with the matching interaction [see Figure 7.27(a, b)].[35,119] Thus a controlled density of hydrogen bonds (multiple-hydrogen bonds) was attached to mixed self-assembled monolayers via the azide–alkyne click reaction. As the molar ratio of the mixed SAM could be adjusted perfectly, surfaces with a defined density of molecular 'stickiness'[128] were prepared.[35] Thus a large variety of nanoparticles, surface modified with a similar strategy[119,129,130] (i.e. ligands modified via the azide–alkyne click reaction) could be deposited selectively onto the SAM-surface. Thus CdSe,[119] iron-oxide[124,129,131] and Au nanoparticles[35,116,117] were bound to the respective surfaces, allowing control of the layer thickness, morphology and density of the underlying layers.

A fine example of supramolecular poymer organization has been described by Hecht *et al.*,[132] taking advantage of selective chain-folding (see Figure 7.28). Thus pyridine units have been linked by triazoles, generating the helical structure **47**. Upon addition of metal ions, the helically folded chains are transformed into gels due to the bridging of the chains into networks.

The functionalization of styrene polymers with a supramolecular metal complex (iridium complexes) has been described using the click reaction (Figure 7.29). As these metallo-supramolecular structures may be important for the light-harvesting and charge-transfer in solar cells, these systems represent another contribution towards chain-organization via the polymeric backbones.

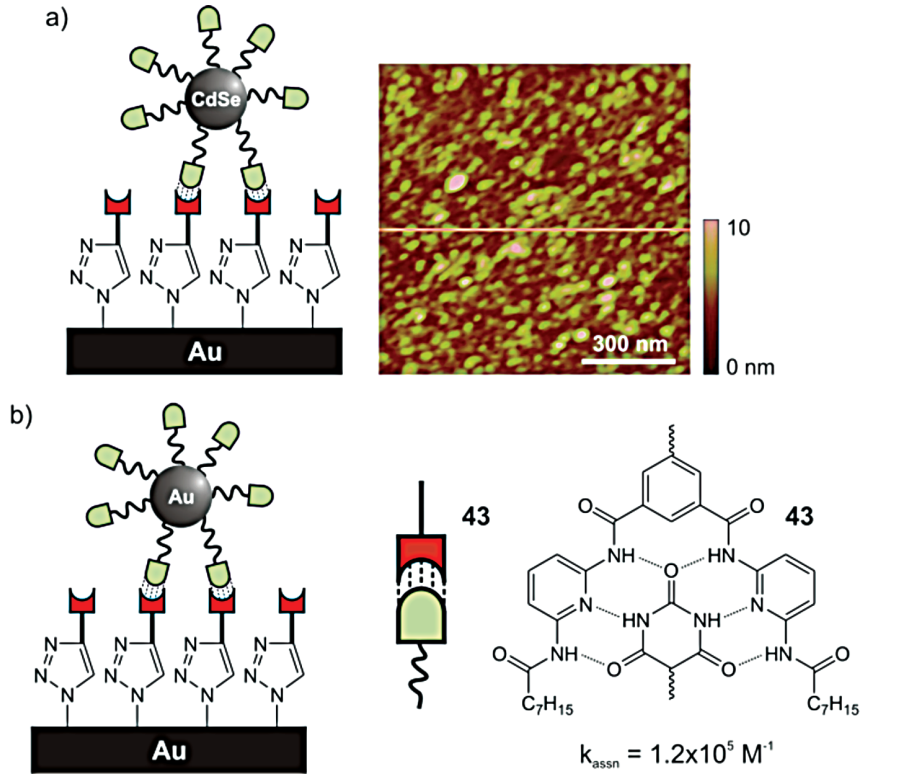


Figure 7.27 *(a) Modifications of surfaces via the azide–alkyne click reaction yielding controllable densities of supramolecular interactions using the Hamilton-receptor* ***43****. (b) CdSe and Au nanoparticles binding via the Hamilton receptor* ***43****. Reprinted with permission from W. H. Binder, R. Sachsenhofer, C. J. Straif* et al.*, (2007), Surface-modified nanoparticles via thermal and Cu(I)-mediated click chemistry: generation of luminescent CdSe nanoparticles with polar ligands guiding supramolecular recognition,* J. Mater. Chem.*,* ***17*** *(20), 2125–2132. Copyright 2007 Royal Society of Chemistry.*

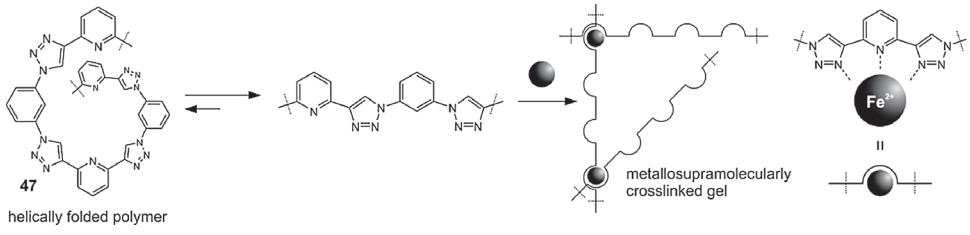


Figure 7.28 *Reversible folding of helical polymers* ***47*** *into gels by addition of iron-(II)-salts.*

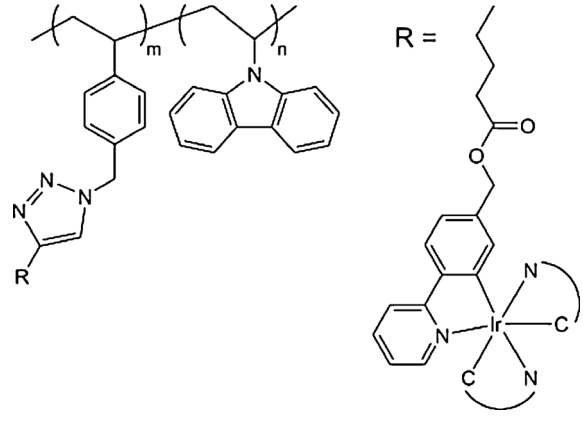


Figure 7.29 *Formation of block copolymers with attached iridium complexes.*

7.5 Click Reactions on Membranes

Biological membranes are highly organized assemblates of lipid molecules, being present either as closed lipid bilayer structures (called liposomes, vesicles) or as (artificial) monolayer systems (Langmuir layers).[133] Usually, biological membranes display a variety of physical effects (liquid crystalline transition temperatures, mixing/demixing effects),[134] which are highly dynamic in nature and reflect the lability of biological membranes, whose stability is limited by temperature, pressure and mechanical deformation. Another type of membrane consists of polymers, called polymersomes, where phase-separation phenomena between polymer chains (microphase-separation) or differential solubility (selective solubility) of polymer chains generate closed membranes.[135] These membranes represent a small fraction of the overall phase structures and are kinetically labile structures. However, when compared with their lipid counterparts, their stability is significantly higher and the membrane thickness scales with the length of the polymer chains.[136] In both cases (polymersomes and liposomes), modifications of the outer surface are important and crucial to effect molecular recognition at the outside of the membranes, thus studying, e.g., membrane-binding processes, membrane transport,[71] nanoparticle–membrane interaction[126,137] or encapsulation and triggered release.[138] Modification of polymersomes or liposomes thus is an important point for studying such processes, but often hampered by the inhereint lability of the underlying structures, especially with liposomes. As the azide–alkyne click reaction works under relatively mild reaction conditions (low temperature with high efficiency), it is a useful alternative to other methods such as thiol addition, disulfide reactions or *N*-hydroxysuccinimide additions to effect the modification of polymersomal–liposomal structures.[82,139–143]

We have described the self-assembly of hydrophilic and hydrophobic nanoparticles into liposomal[137] and polymersomal membranes[126] (see Figure 7.30). One of the best systems for this purpose proved to be a diblock copolymer made by linking PEO and PIB chains via a click reaction.[126] These blockcopolymers can be assembled into polymersomes, if the

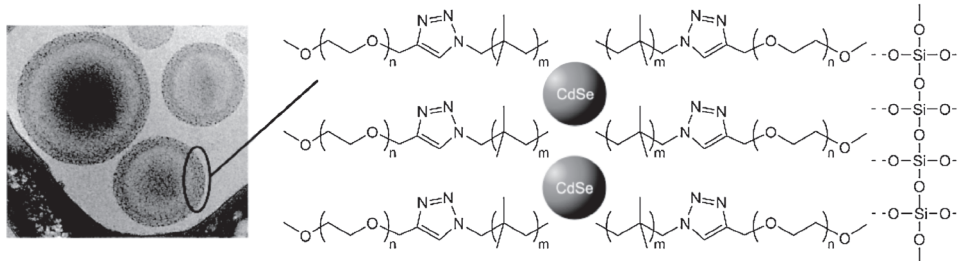


Figure 7.30 *Incorporation of CdSe nanoparticles into polymersome membranes made from PEO–PIB blockcopolymers and silicification of their outer shell via sol–gel-processes.*

ratio between the PEO and the PIB-block is appropriate. The simple testing of different systems can be achieved via generation of a library of different telechelic PIB-N_3/PEO-alkyne systems, clicked together in a simple manner. Thus the formation of the respective polymersomes could be acheived, whose membrane was subsequently used to incorporate hydrophobic nanoparticles into their hydrophobic interior. Furthermore, the outer shell was stabilized by sol–gel processes, yielding stable capsules with the embedded nanoparticles as a highly organized, supramolecular system.

The direct modification of polymersomal outer layers has been achieved via two different routes [see Figure 7.31(a, b)].[82,140] The use of a blockcopolymer (PS-PEG) with alkyne end groups allowed the generation of polymersomes with pendant alkyne moieties in multiple fashion.[82] The Cu(I)-mediated azide–alkyne click reaction can be subsequently conducted, enabling the fixation of azide-modified candida-lipase (CalB) onto the surface of the polymersome.

The analogous pathway has been described, using an endlabeled PS-*b*-PAA diblock-copolymer, which – after assembly into polymersomes – presents multiple azido-moieties [Figure 7.31(b)].[140] These were used for the reaction with either a fluorescence label (dansyl-dye) or the attachment of green-fluorescent protein onto the surface of the polymersome. A similar reaction pathway, reporting on the attachment of dendritic moieties onto the surface of PBD-PEO-polymersomes, is reported [Figure 7.31(c)].[143] Again, an appropriately functionalized PBD–PEO–N_3 diblock copolymer forms the scaffold for the polymersome, which is then decorated with azido moieties for further reaction with alkyne-modified dendrimers. The click reactions were carried out in aqueous systems, taking advantage of the regenerative system ($CuSO_4$–sodium ascorbate), thus nearly working under physiological conditions.

With liposomes, two examples of a direct azide–alkyne click reaction have been described (see Figure 7.32).[142,144] Using a DOPE alkyne [Figure 7.32(a)], the outer surface of a liposomal membrane was decorated with about 50% of alkyne moieties, embedded into a membrane consisting of DOPC.[142] The resulting liposomes were then incubated with an oxazole dye, which was attached covalently to the outer surface under Cu(I) catalysis. The presence of the oxazole dye was proven by FRET-measurements between a dye already present within the membrane.

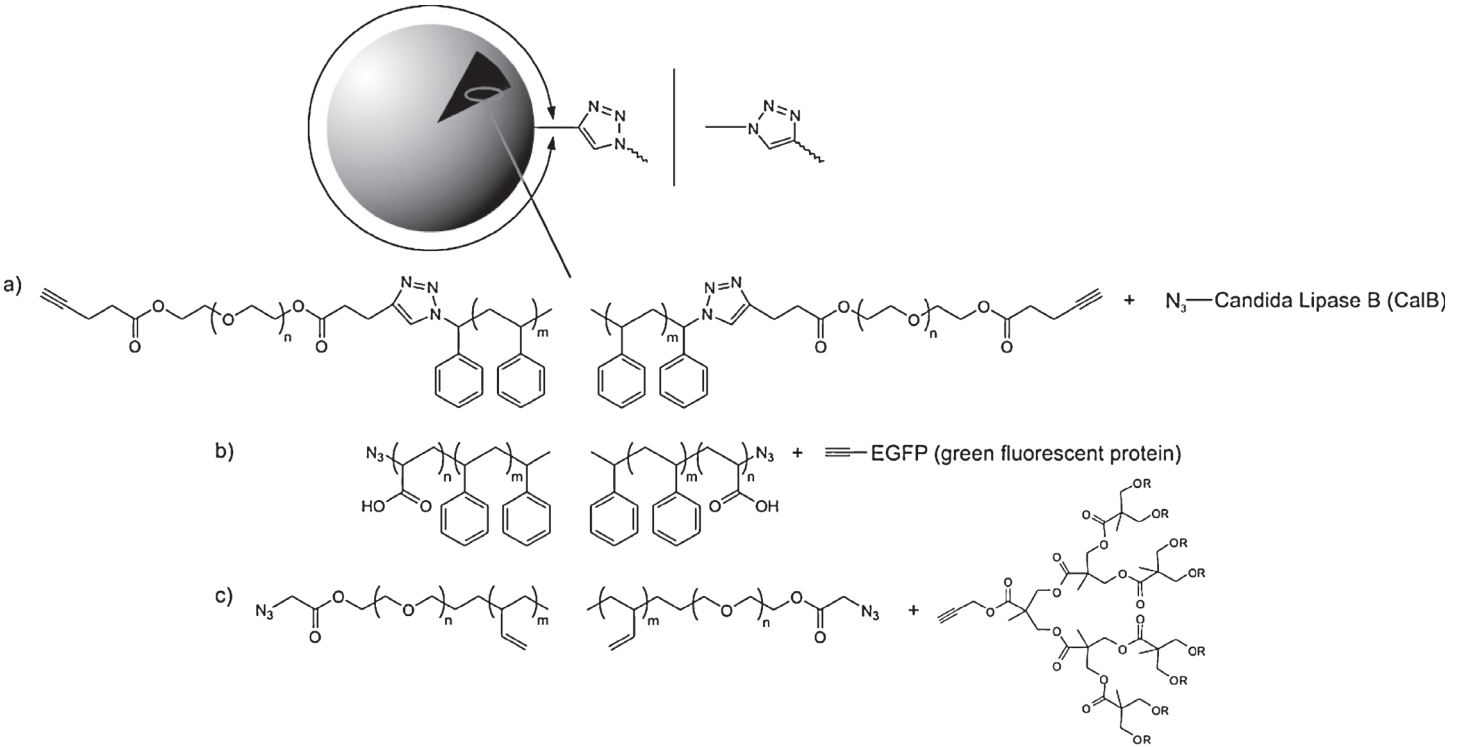


Figure 7.31 *Modification of polymersomal surfaces via the azide–alkyne click reaction: (a) modification of azide-modified polymersomes (polymer: PEG) with candida lipase (CalB); (b) PS polymersomes modified with green fluorescent protein (EGFP); (c) PS–PEO blockcopolymers within polymersomes and their modification with dendrimers.*

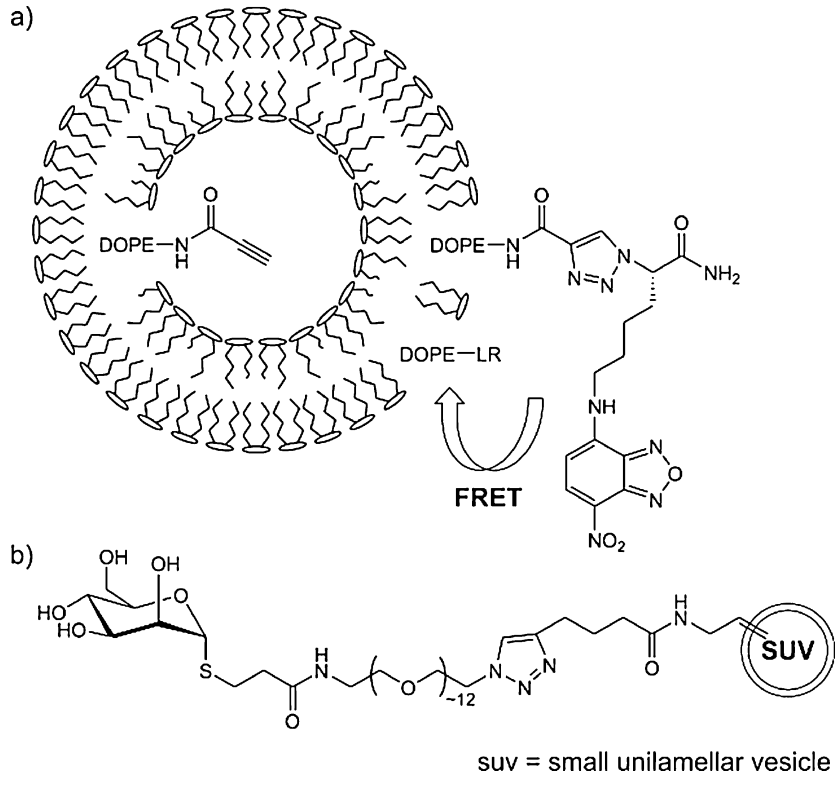


Figure 7.32 *Azide–alkyne click reactions using liposomes (a) using DOPE lipid; (b) using a small unilamellar vesicle (SUV) attaching a carbohydrate ligand to the outer surface.*

A similar strategy for labeling the outer surface of liposomes has been used relying on a glycerol-anchored lipid with a terminal alkyne moiety added to a conventional liposome-forming lipid mixture in 5–10 mol% [Figure 7.32(b)].[144] After liposome formation, the attachment of a mannose conjugate bearing a terminal azide moiety was investigated. It turned out that the efficiency of the reaction was strongly enhanced, if an appropriate bathophenanthrolinedisulfonic acid ligand for complexing copper ions was present. Only under these conditions could a complete surface functionalization be achieved, as proven via subsequent agglutination assays, which allow for a quantification of the attached mannose units to the liposomal surface.

Finally, it should be mentioned that the Cu(I)-mediated reactions are not useful for living (i.e. cellular) systems, owing to the toxicity of the Cu ions, which inhibit cell growth. Bertozzi *et al.*[20] have therefore developed a copper-free variant of the azide–alkyne click reaction, which relies on the use of highly strained substituted cyclooctynes, whose release of ring strain promotes the dipolar cycloaddition process without the use of Cu species. This method is now the method of choice for the labeling of cellular surfaces via incorporation of artificial amino-acids into membrane proteins.

7.6 Click Reactions on Dendrimers

The usefulness of the azide–alkyne click reaction is well demonstrated in the build-up of larger polymeric structures, in particular the generation of dendrimers. As dendrimers are important scaffolds for assembly into higher-ordered supramolecular structures, the value of the azide–alkyne click reaction is high. A recent review has been focussing on this combination, especially on the use of high-yielding, high-energy reactions for this purpose.[44] Besides the synthesis and functionalization of dendrimers,[38,41,44,46,145–158] hyperbranched polymers[44,158–161] can also be prepared using this methodology. Briefly, dendrimers can be generated by convergent or divergent methods, using the azide–alkyne click reaction as internal bond for the synthesis. This can lead to hyperbranched polymers either in one step or via sequential reaction. Additionally, whole dendron structures may be assembled via the azide–alkyne click reaction, using appropriately functionalized dendrons. Another issue concerns the generation of surface-modified dendrimers, which generates dendrimers with a high density of outer azide–alkyne moieties, which subsequently are then reacted with the appropriate functional groups, thus attaching a large number of these moieties onto the outer shell of the respective dendrimer. A large variety of different dendrimers, such as PAMAM-type dendrimers,[147,162] benzyl-type,[155] PS/PMDETA dendrimers,[152] triazole-containing dendrimers (in each generation)[149,163] and polyester-type dendrimers have been prepared via convergent methods, where the buildup of the central structure has been achieved by linking azide–alkynes.[148] Dendron attachment (i.e. divergent synthetic methodologies) to the side chain of poly(vinylacetylenes)[164] and inorganic ruthenium oligomers have been described.[165] Moreover, the generation of hyperbranched polymers in a one step-procedure, given that the starting material is present sufficiently pure and sterically not too crowded. This strategy has been used by several authors, generating medium-branched hyperbranched polymers in good yields.[159,166]

The surface of a large variety of different dendrimers can be modified generating, e.g., ferrocenyl-modified triazolyl-silane dendrimers,[146] dendritic peptides,[150] surface-modified polybenzyl and Boltorn dendrimers,[158] PEG-modified carbamate-dendrimers[167] and carbohydrate modified Boltorn dendrimers.[151] All these surfaces are more or less designed to act as recognition or organization sites for some supramolecular activity on the dendritic surface, whether it is a pure steric effect of organization or a defined key/lock-recognition.

The strategy to run multiple azide–alkyne click chemistry has been also transferred to the synthesis of polymer-brushes[168,169] or cross-linked capsules.[170] Similar to dendrimers, these structures display a high density of functional groups at their surface, thus requiring highly efficient linking-reaction for their functionalization.

7.7 Click Reactions on Gels and Networks

Gels and networks[62,79,120,171–184] have been formed additionally via azide–alkyne click reactions. This strategy has been proven useful as a simple cross-linking strategy, but also for the formation of highly sensitive gel and network structures not accessible by other methods.[174] As gels and networks are often either highly defined structures (e.g. fibers, organized by supramolecular interactions between small and medium-sized organic

molecules or block-copolymeric micelles linked into gels) or relatively rough-organized systems (weakly cross-linked gels, networks formed by covalent cross-linking), their structural definition is sometimes vague. This makes the following rather an assembly of gels, where the main structural definition has been achieved by use of the azide–alkyne click reaction, or where this reaction is a main structural element of the final material generated (see Figure 7.33). Thus multuivalent azide **48** and alkynes **49** (Figure 7.33) can be directly reacted, generating networks with a high level of cross-linking density due to the high efficiency of the azide–alkyne click reaction. By appropriate choice of the corresponding building block (examples of small monomer, oligomeric or polymeric) azides–alkynes as given in Figure 7.33(b, c), the corresponding properties of the networks, such as swelling character, hydrophobic/hydrophilic properties, density or functionality, can be nicely controlled.

Highly dense networks have been used extensively as scaffolds for synthetic reactions. Thus a large number of investigations have been carried out using highly cross-linked resins and support, mostly in the field of organic chemistry.[13,29,72,185] In these cases, the highly cross-linked Rink, Wang or Merrifield resins serve as a (porous) solid phase, presenting terminal azido- or alkyne moieties able to attach substrates via the azide–alkyne click reaction.

As supramolecularily preorganized molecules often tend to disintegrate upon thermal treatment, the azide–alkyne click reactions represent an important step towards stable networks of defined cross-linking density, thus 'freezing-in' a specific supramolecular structure.[175,179] Thus block copolymer micelles can be easily cross-linked using the azide–alkyne click reaction after assembly of the block copolymers (BCPs) into the respective micelles, yielding the well-known cross-linked BCP-micelles,[154,157,186–188] with a highly defined degree of cross-linking within their core- or corona-structure.

Besides the work of Wooley *et al.*[157,186,187], who used the azide–alkyne click reaction for the cross-linking of BPC-micellar core, a highly innovative example for cross-linking the shell of a BCP micelle has been described by Meier *et al.*[180] (Figure 7.34). Thus a diblockcopolymer **50** generated via ROMP, whose one block was modified via a highly cationic moiety via the azide–alkyne click reaction. The BCP was able to incorporate DNA, generating particles sized 20–120 nm, able to deliver DNA. The particles display a highly dendritic structure on their outside, thus presenting a high cationic charge to the outside of the carrier nanoparticle.

An approach to highly sophisticated and smart networks has been descriebd by Turro *et al.*[175,181] (see Figure 7.35). Thus telechelic macromolecules (P^{t}BuA, PMA) were prepared via ATRP methods, and finally equipped with terminal azido–alkin-moieties. Because of the presence of a photocleavable linker (*o*-nitrobenzyl-unit; Figure 7.35) or internal double bonds, the corresponding networks can be cleaved either by UV irradiation or via ozonolysis. As the initial chain length of the polymers is highly defined, the density of the networks has been adjusted with high precision.

Other examples of defined networks with relatively controllable network densities have recently been reported, derived from PEGs,[171] polyvinylacohols,[177] hyaluronic acids[182] or cross-linked hydrophilic polymer beads.[183]

A fine example of a liquid crystalline polymer via click reaction has been reported by Grubbs *et al*. by using an endfunctionalized bitelechelic ROMP-polymer **51** with pendant

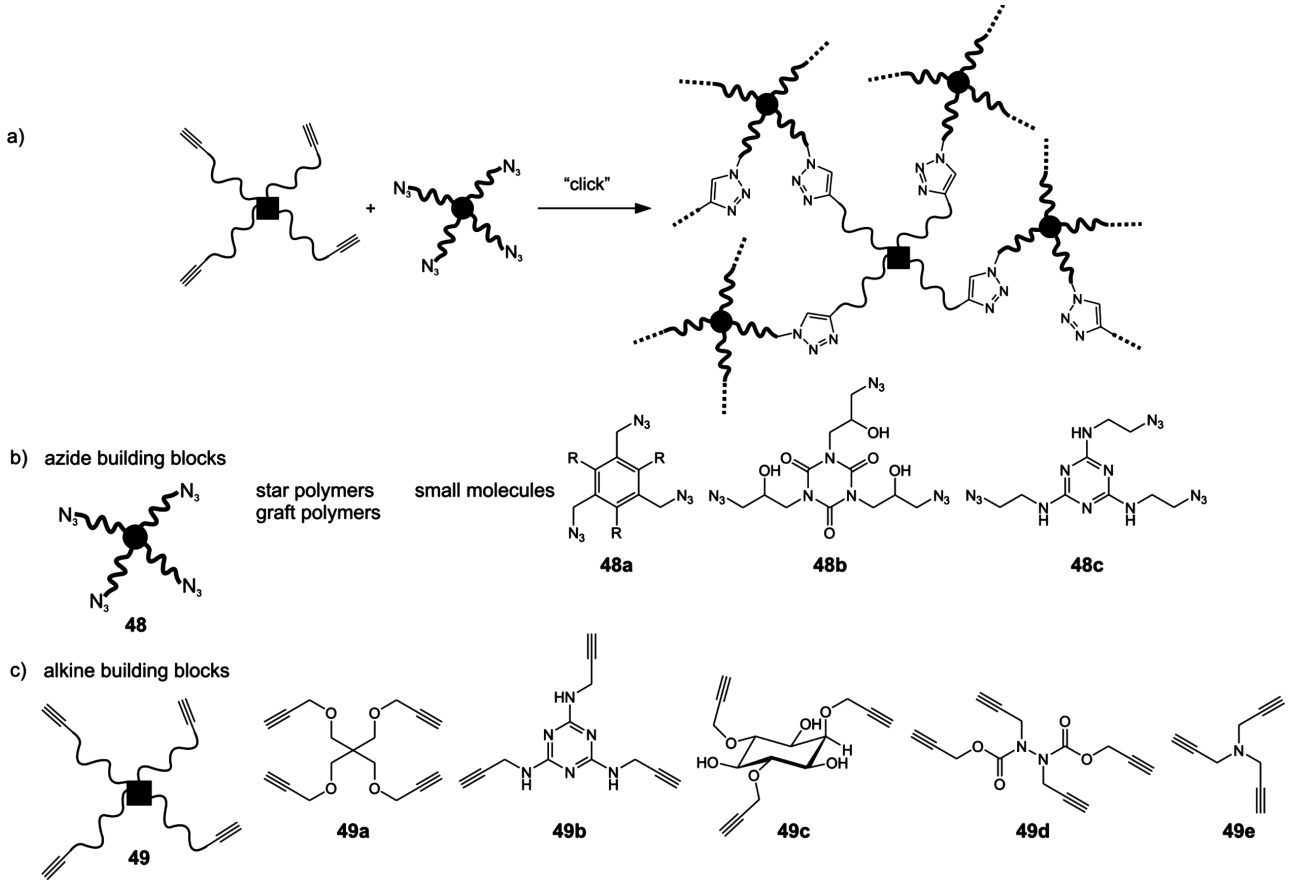


Figure 7.33 *Formation of networks using the azide–alkyne click reaction via multivalent building blocks* ***48*** *and* ***49*** *(selected examples).*

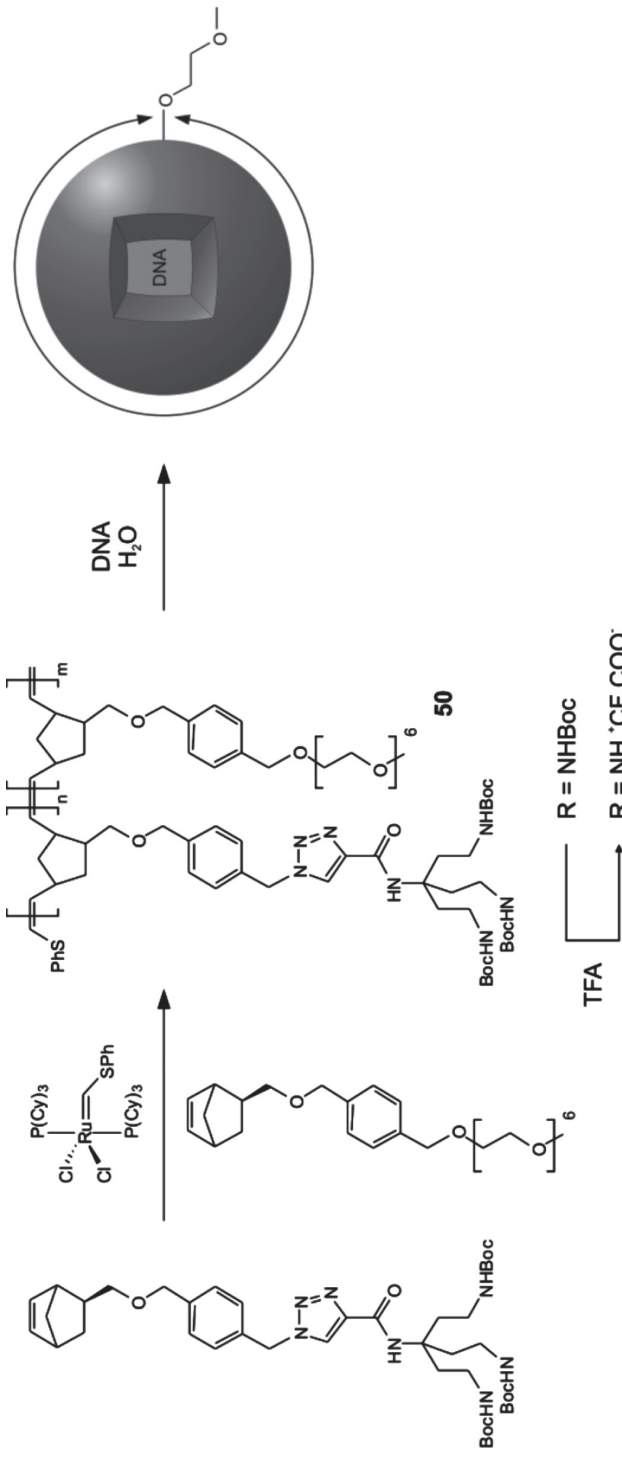


Figure 7.34 *Formation of DNA block copoylmeric micelles using the ROMP polymer* ***50****.*

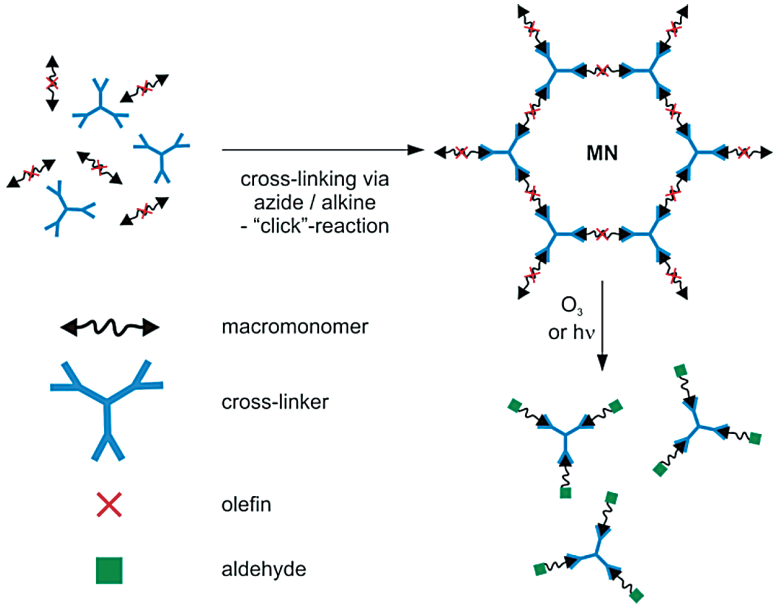


Figure 7.35 *Formation of photo- and ozone-cleavable networks via the azide–alkyne click reaction. Reprinted with permission from Y. Xia* et al.*, (2008), Well-defined liquid crystal gels from telechelic polymers,* J. Am. Chem. Soc.*, **130** (5), 1735–1740. Copyright 2008 American Chemical Society.*

liquid crystalline moieties (see Figure 7.36).[178] The final structure was cross-linked with a trivalent alkyne moiety, thus generating a highly defined network **52**, allowing study of the influence of network density on the orientation and nature of the liquid crystallinity.

Supramolecular gels are often generated from the interplay between hydrogen-bonding systems and hydrophobic interaction, often well balanced by solvent effects. The stabilization of such structures is difficult, but can be achieved using the azide–alkyne click reaction. Thus Finn *et al.*[184] and Diaz *et al.*[179] have reported on gels formed from amidic-bond networks, subsequently stabilized by the azide–alkyne click reaction (Figure 7.37)

We have reported on the generation of supramolecular gels built from multiple hydrogen bonds, attached to star-like PIB or PEG-poylmer (see Figure 7.38).[111,125] Thus trivalent star-PIBs **53** were prepared by a combination of living cationic polymerization and azide–alkyne click chemistry, being able to control the chain length of the (hydrophobic) PIB polymer. Upon assembly with matching hydrogen bonds **43** (supplied via end group-modified PEGs **54**), gel formation was observed, resulting in highly thermoreversible gels.[111] Furthermore, suprerparamagnetic nanoparticles or PNIPAM[111] could be incorporated into the gel, enabling strong thermoreversibility. The nanoparticles are located selectively within the hydrophobic cavities provided by the PIB-polymer, thus leading to a microphase-induced segregation of the nanoparticles.

The most picturesque example of network formation via the azide–alkyne click reaction has been provided by Finn *et al.*[172,173,189] in a series of publications (see Figure 7.39). The simplicity correlates to the effectiveness in the buildup of mechanically highly stable thermosets. Thus small molecules, multivalent in their azide–alkyne structures, were

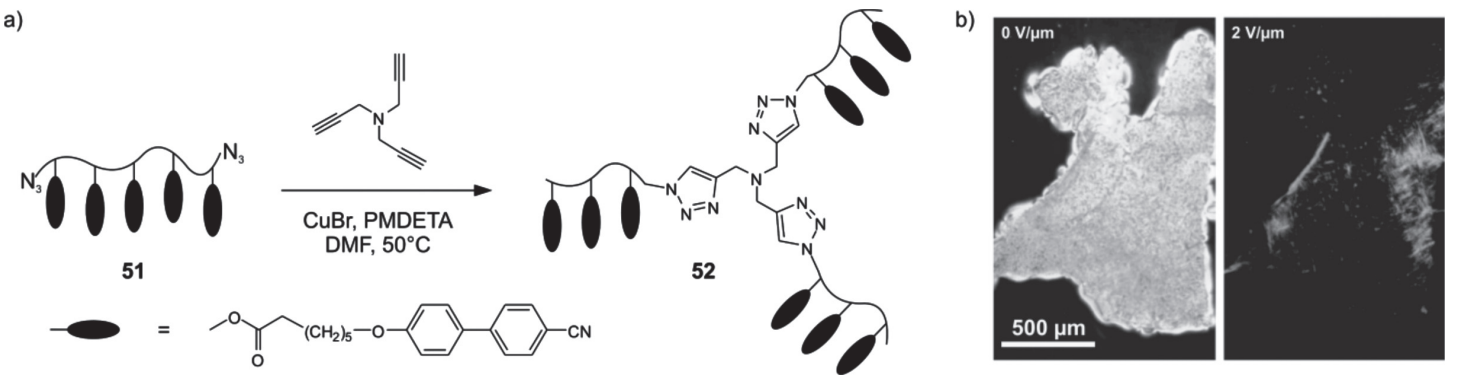


Figure 7.36 *Formation of cross-linked networks from liquid crystalline polymers. (a) Synthesis the network via cross-linking of* ***51*** *into the network* ***52****. (b) TEM micrograph of the cross-linked liquid crystalline gel.*

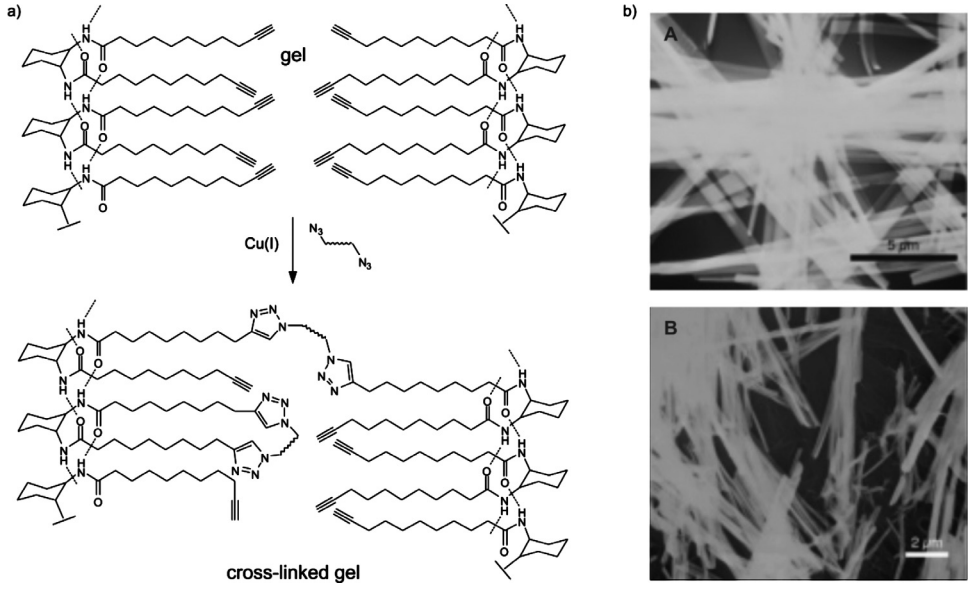


Figure 7.37 *Crosslinking of transient fibers, formed via amid-bond-assembly (organic gelators). (b) TEM micrograph of the fibers before (top) and after cross-linking (bottom), indicating the preservance of the fiber's-integrity. Reprinted with permission from D. D. Diaz* et al.*, (2006), Click chemistry in a supramolecular environment: stabilization of organogels by copper(I)-catalyzed azide–alkyne [3 + 2] cycloaddition,* J. Am. Chem. Soc.*, **128** (18), 6056–6057. Copyright (2006) American Chemical Society.*

mixed, and subsequently cross-linked between metal plates, i.e. metallic copper. Because of the high efficiency of the azide–alkyne click reaction, enormous hardness and glue strength could be achieved, representing the first directly applicable example of the click reaction. It furthermore shows, that often the most simple approach may be the most effective.

7.8 Click Reactions on Self-assembled Monolayers

Surfaces and interfaces often are not counted to supramolecular chemistry. However, as self-assembled monolayers or nanoparticle surfaces are highly organized structures, they are included in this review chapter. The chemistry on surfaces is as manifold as the chemistry on polymers or other materials; therefore the present data cannot be discussed in full detail, as they would represent a chapter on their own. An interesting aspect of the azide–alkyne click reaction lies in the fact that a reduced or enforced distance between the reaction partners leads to a strongly enhanced reaction rate. This effect has been demonstrated in the azide–alkyne click reaction within the pocket of enzymes (activity-based protein profiling, ABPP)[14,32,190] by direct microcontact printing[103,191] or via AFM-tips,[192] thus opening the chance for a sufficiently complete reaction at an interface.

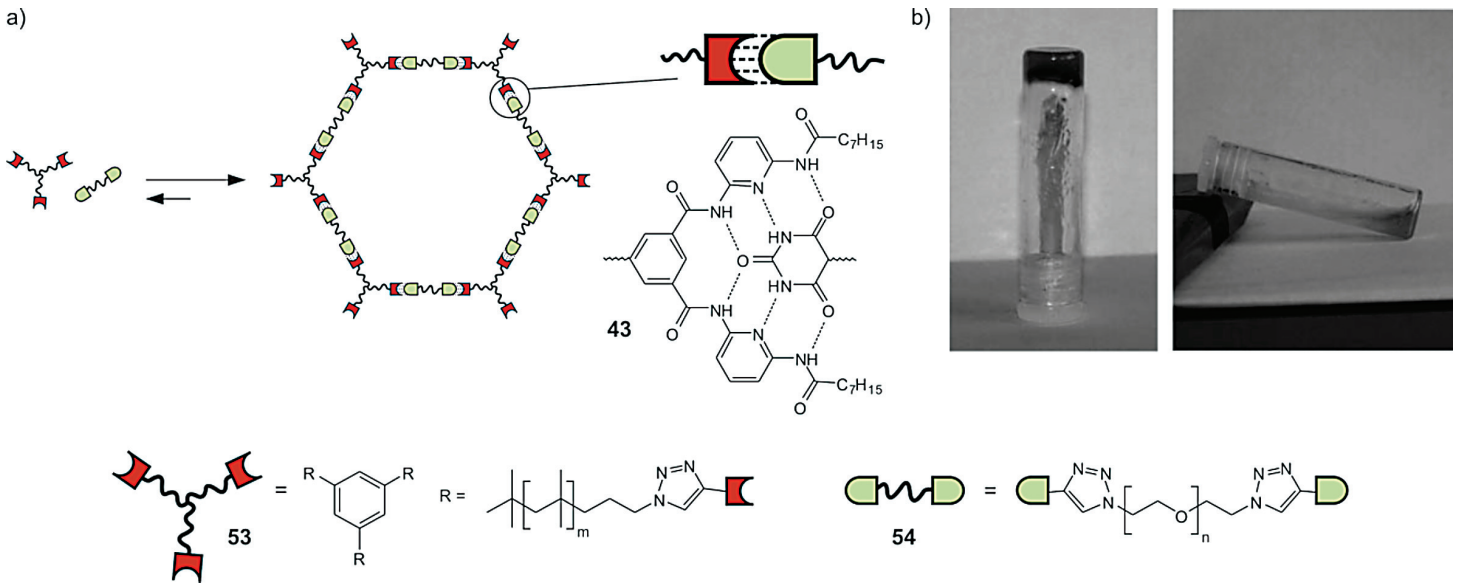


Figure 7.38 *(a) Formation of supramolecular gels by noncovalent interactions (hydrogen bonds) using a three-arm star PIB and a PEG-polymer, equipped with hydrogen bonds* ***43****. (b) Thermoreversibility of the gel by heating from room temperature (left) to 40 °C (right).*

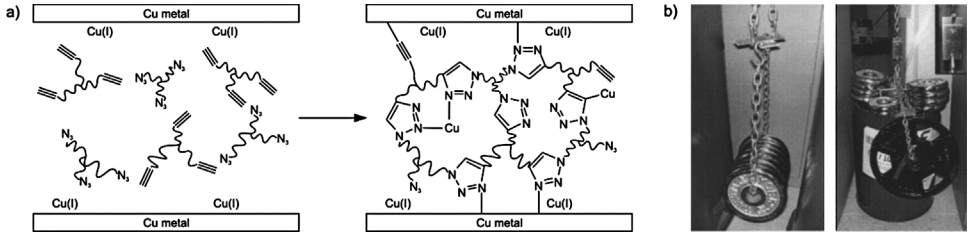


Figure 7.39 *Thermoset-formation by cross-linking via the azide–alkyne click reaction. (a) Linking of Cu plates by small-molecule-network-formation (b) Load tests demonstrating the effectiveness of the final thermoset. Reprinted with permission from D. D. Diaz* et al.*, (2004), Click chemistry in materials synthesis. 1. Adhesive polymers from copper-catalyzed azide–alkyne cycloaddition,* J. Polym. Sci., Part A: Polym. Chem.*, **42** (17), 4392–4403. Copyright (2004) John Wiley and Sons, Inc.*

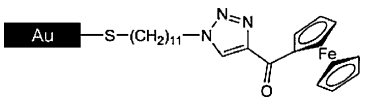
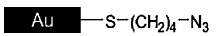
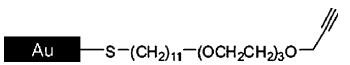
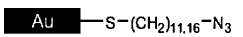
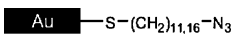
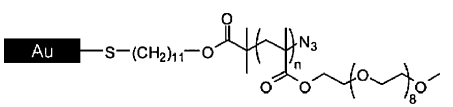
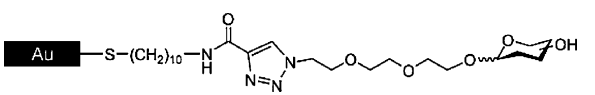
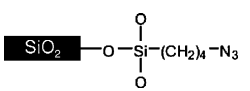
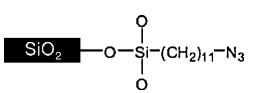
Table 7.1 gives an overview on the most relevant click reactions on surfaces. One of the most important aspects is the generation of the corresponding azide–alkyne modifed surfaces, which is a prerequisite for the subsequent azide–alkyne click reaction.

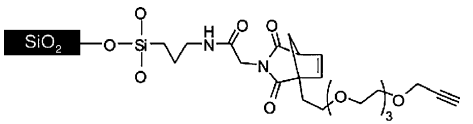
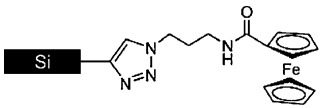
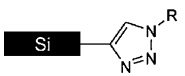
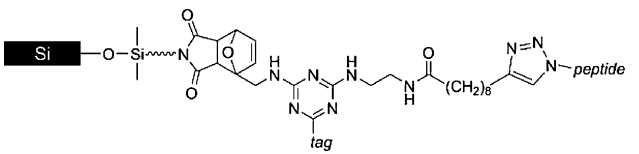
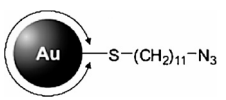
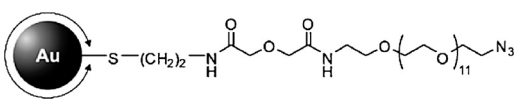
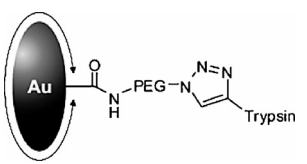
In the case of SAMs, the use of appropriately azide-[35,193–197] or alkyne-functionalized[156,198–202] surfaces by direct ligand-adsorption has been described. Alternatively, *in-situ*-generation of terminal azides by bromide–azide-exchange directly on the ω-bromoalkyl-functional monolayer can be effected,[196,203] eliminating the pressing instability of ω-azido-1-thioalkanes prior to the SAM-formation process. Thus a large variety of click reactions on SAMs,[35,118,156,169,193–196,198–203] polymeric surfaces[191,204–210] or Langmuir–Blodget layers (LbL layers),[160,206] has been reported .

Similar to SAMs, the surface of nanoparticles can be modified with the azide–alkyne click reaction.[118,121,122,124,211–214] Thus a large variety of nanoparticles (Au,[118,211,212,214] CdSe,[121] Fe_2O_3[122,124,213] and SiO_2[197]) as well as viruses[215] and Au nanorods[216] have been surface-functionalized with this method. Mostly, the attached ligands serve as recognition sites to direct the location of such nanosized objects onto materials via defined or nonspecific interactions. Selected examples of such recognition processes rely, e.g., on hydrogen bonding moieties, which allow the corresponding nanoparticles to be directed to a SAM surface,[35,119]a polymeric surface,[116,117] a liquid–liquid-interface[217] or a block-copolymeric phase or interface.[218] The interested reader is referred to the references for further reading.[35,116,117,119,217–219]

Finally, an important point has been observed upon comparing the Cu(I)-catalyzed reaction with the uncatalyzed, purely thermal, click reaction on CdSe nanoparticles.[121] Since copper ions interfere with the fluorescence properties in semiconductive nanoparticles, the use of Cu(I)-species is not advantageous for their surface modification. Thus without the use of the Cu(I) catalyst, the photoluminescence of the final, surface-modified CdSe nanoparticles remains nearly unchanged, whereas under Cu(I) catalysis a significant drop in the quantum yields is observed. Therefore, the purely thermal azide–alkyne reaction may be sometimes advantageous over the metal-catalyzed click process. Compared with conventional surface-modification methods, the azide–alkyne-methodology enables an elegant, fast and efficient approach to functionalized nanoparticles in a simple mode.

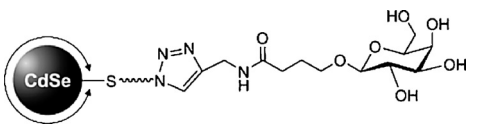
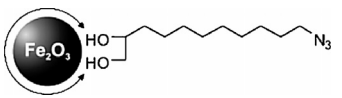
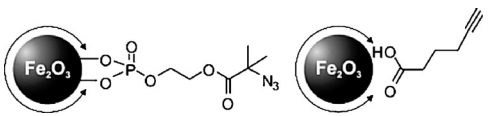
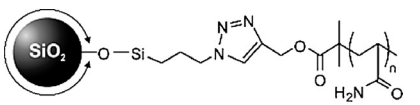
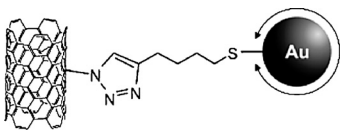
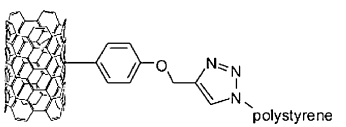
Table 7.1 *Azide–alkyne click reactions on surfaces, nanoparticles and interfaces*

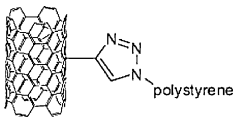
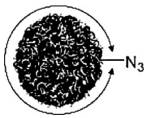
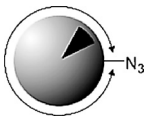
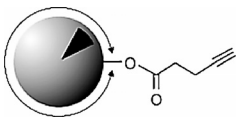
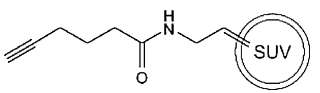
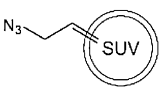
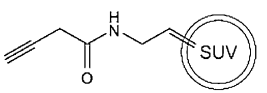
Entry	Polymer/substrate	Surface	Catalyst/conditions	Reference
1		SAM on Au	$CuSO_4{\cdot}5H_2O$/sodium ascorbate/H_2O/EtOH	193
2		SAM on Au	$CuSO_4{\cdot}5H_2O$/sodium ascorbate and $Cu(Ph_3)_3Br/H_2O$/EtOH	35
3		SAM on Au	$CuSO_4{\cdot}5H_2O$/sodium ascorbate/H_2O/EtOH	198
4		SAM on Au	$CuSO_4{\cdot}5H_2O$/sodium ascorbate/H_2O/EtOH and DMSO/H_2O	194
5		SAM on Au	TBTA $CuBF_4$/ hydroquinone/DMSO/ H_2O	195
6		SAM on Au	$CuSO_4{\cdot}5H_2O$/sodium ascorbate/r.t.	205
7		SAM on Au	$CuSO_4$/sodium ascorbate/H_2O:EtOH = 1:1	201
8		SAM on SiO_2	Thermal/70 °C/neat	196
9		SAM on SiO_2	$CuSO_4{\cdot}5H_2O$/sodium ascorbate	203

10		SAM on SiO_2	$CuSO_4 \cdot 5H_2O$/TBTA/TCEP/PBS-buffer/^{t}BuOH/4 °C	202
11		SAM on Si	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/DMF	199
12	 R = PEG, PMMA, PS	SAM on Si	$Cu(PPh_3)_3Br$/DIPEA/THF	169
13		Porous Si	$CuSO_4$/ascorbic acid,MeCN/tris-buffer/pH = 8.0/r.t.	200,220
14		SAM on Au nanoparticles	Dioxane/hexane/r.t.	211
15		SAM on Au nanoparticles	Cu(I)/r.t.	212
16		SAM on Au nanorods	$CuSO_4$/ascorbic acid/4 °C	216

(*Continued*)

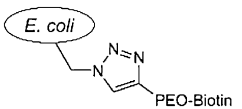
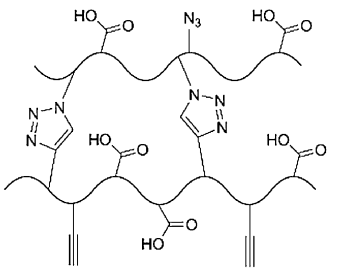
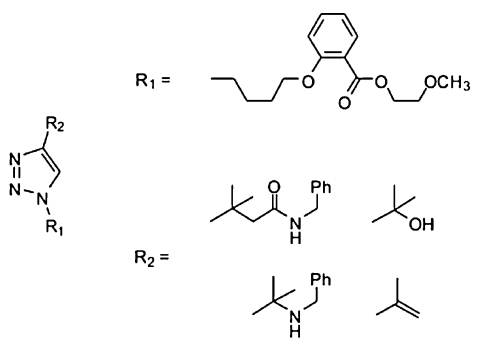
Table 7.1 *Azide–alkyne click reactions on surfaces, nanoparticles and interfaces (Continued)*

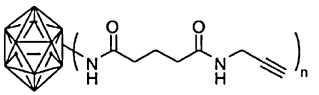
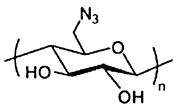
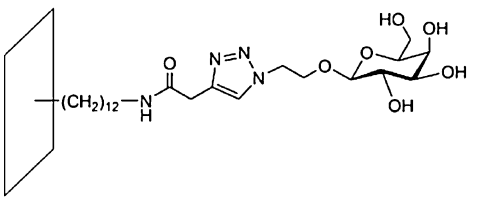
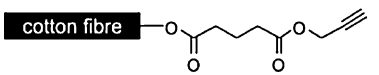
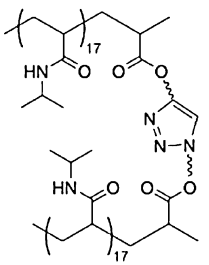
Entry	Polymer/substrate	Surface	Catalyst/conditions	Reference
17		SAM on CdSe nanoparticles	CuBr/TBTA/DIPEA or ΔT	118,121
18		SAM on CdSe nanoparticles	$CuSO_4$/sodium ascorbate/^{t}BuOH:H_2O=1:1	221
19		SAM on Fe_2O_3 nanoparticles	ΔT/toluene	122
20		SAM on Fe_2O_3 nanoparticles	$CuSO_4$	213
21		SAM on SiO_2 nanoparticles	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/DMSO/ 50 °C	197
22		SWNT-nanocomposites	Cu(I)	214
23		SWNT-nanocomposites	Cu(I)/DMF	70

24		SWNT-nanocomposites	Cu(I)	222
25		Surface-functionalized micelles	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/H_2O/r.t.	187
26		Surface-functionalized polymersomes	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/TBTA	140
27		Surface-functionalized polymersomes	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/ bathophenanthroline/ 4 °C	82
28		Surface-functionalized liposomes	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/H_2O	141
29		Surface-functionalized liposomes	$CuSO_4$/sodium ascorbate/HEPES-buffer/pH = 6.5	223
30		Surface-functionalized liposomes	CuBr/H_2O	142

(*Continued*)

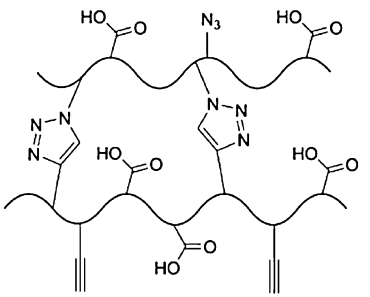
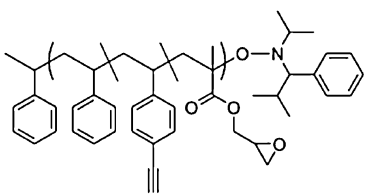
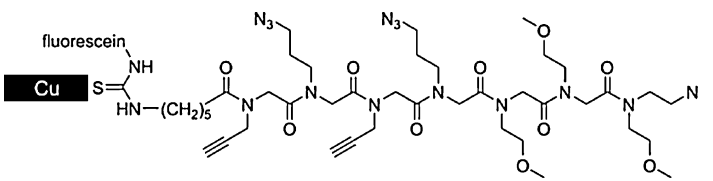
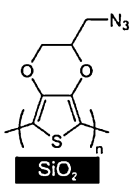
Table 7.1 *Azide–alkyne click reactions on surfaces, nanoparticles and interfaces (Continued)*

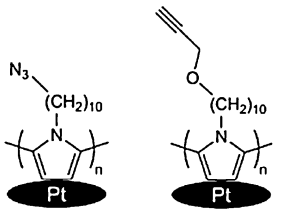
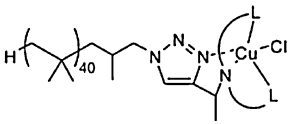
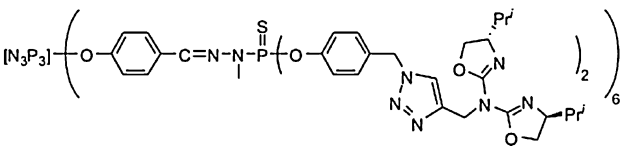
Entry	Polymer/substrate	Surface	Catalyst/conditions	Reference
31		Cell surface	$CuSO_4$/TCEP	224
32		Responsive polymer capsules	$CuSO_4 \cdot 5H_2O$/sodium ascorbate	206
33		pH sensitive releasing systems	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/^{t}BuOH:H_2O = 1:1	225

34		Surface-functionalized bionanoparticle	CuBr/PCDS	215
35		Polysaccharides	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/DMSO/r.t.	208
36		Sugar arrays in microtiter plate	CuI/DIPEA/toluene	226
37		Surface-functionalized cotton fibers	CuBr/*N*-(*n*-propyl)-2-pyridylmethanimine/toluene/70 °C	227
38		Layer by layer (LbL)	$CuSO_4 \cdot 5H_2O$/sodium ascorbate/H_2O	160

(*Continued*)

Table 7.1 *Azide–alkyne click reactions on surfaces, nanoparticles and interfaces (Continued)*

Entry	Polymer/substrate	Surface	Catalyst/conditions	Reference
39		Layer by layer (LbL)	$CuSO_4 \cdot 5H_2O$/sodium ascorbate	204
40		Polymer film	$CuSO_4$/sodium ascorbate/DIPEA/ H_2O/THF/r.t.	228
41		Polymer film	TEA.HCl/45 °C	229
42		Conductive polymers	$CuSO_4$/sodium ascorbate/DMF/r.t.	230

43		Conductive polymers	$CuCl_2$/sodium ascorbate/^{t}BuOH:H_2O=2:1/r.t.	209
44		Self-separating homogeneous Cu(I) catalysts	CuCl/heptanes/EtOH	207
45			CuI/$N(C_2H_5)_3$/THF	153

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