Introduction

The azide/alkyne ‘click’ reaction\(^1\) (also termed the Sharpless ‘click’ reaction) is a recent re-discovery of a reaction fulfilling many requirements for the affixation of ligands onto polymers by post-modification processes, which include a) often quantitative yields, b) a high tolerance of functional groups and solvents, as well as moderate reaction temperatures (25–70 °C). The present review assembles recent literature for applications of this reaction in the field of polymer science (linear polymers, dendrimers, gels) as well as the use of this and related reactions for surface modification on carbon nanotubes, fullerenes, and on solid substrates, and includes the authors own publications in this field. A number of references (>100) are included.
molecules in a general, fast, and efficient process. Critical for the broad application of the reaction as a click-type reaction is the discovery that the central, purely thermal Huisgen process can be extremely accelerated by the addition of various metal species (Ru, Ni, Pt, Pd), but mostly by CuI species, within the reaction system (see Scheme 2).

Whereas the purely thermal 1,3-dipolar cycloaddition reaction between aryl/alkyl azides and strongly activated alkynes (i.e., acyl- and sulfonyl cyanides as well as acyl-alkynes) was proposed (and investigated) by Sharpless and co-workers in 2001 [1,4] as a click-type reaction, Meldal and co-workers published a paper in 2002 [5] that describes the acceleration of this process by CuI salts, which leads to a reaction at 25 °C in quantitative yields, first mentioning the higher regioselectivity (1,4-triazole formation versus 1,5-triazole) with respect to the purely thermal process. Later, Sharpless and co-workers published a paper in 2002 [6a] where the formation of 1,2,3-triazoles by the CuI-catalyzed Huisgen reaction between nonactivated alkynes and alkyl/aryl azides was described. A catalytic cycle based on a concerted mechanism via a Cu acetylide intermediate was proposed, which has been recently revised to include a binuclear reaction mechanism on the basis of several observations [6b]. The critical ‘invention’ of this process is the transformation of a purely thermal 1,3-dipolar cycloaddition process to a 1,3-dipolar cycloaddition process catalyzed by metal salts (mostly CuI salts, but recently also Ru, Ni, Pd, and Pt salts) which runs at ambient temperature, is nearly solvent insensitive, and with an extremely high tolerance of functional groups. In the following chapter, a short mechanistic review will precede the recent applications of this reaction in various fields of science, most of all materials science, polymer chemistry, and biological applications. A survey of mostly recent literature related to the polymer science and

![Scheme 1.](image)

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materials fields will draw a line to other previous reviews\cite{1,7–9} describing the azide/alkyne click reaction,\cite{1} in general, for application in organic chemistry,\cite{8} as well as for drug discovery and biolabeling.\cite{9}

### Mechanistic Details/Catalysts

The basic process of the Huisgen 1,3-dipolar cycloaddition\cite{2,10,11} is depicted in Scheme 2, generating 1,4- and 1,5-triazoles, respectively. Nearly all functional groups are compatible with this process, except those that are a) either self reactive, or b) able to yield stable complexes with the CuI metal under catalyst deactivation. Thus the functional groups depicted in Scheme 3a are not compatible with the azide/alkyne-type click reaction, placing the thermal Huisgen 1,3-dipolar cycloaddition process as the most important side reaction. The main interfering functional groups are strongly activated azides (i.e., acyl- and sulfonyl azides) as well as cyanides, which are able to compete in purely thermal cycloaddition processes (Scheme 3a).

Double bonds are tolerated to a certain extent, given that they are neither electronically activated (i.e., by electron withdrawing substituents) nor embedded into substrates of appropriate ring strain.\cite{12} Thus the reactivity of phenylacetylene with phenylazide (reaction rate $k = 0.29 \times 10^7 \text{dm}^3 \cdot \text{M}^{-1} \cdot \text{s}^{-1}$) is comparable to that of hept-1-ene, styrene, and isoprene. Other alkenes and cycloalkenes display faster reactions with phenylazide (e.g., norbornene $k = 188 \times 10^7 \text{dm}^3 \cdot \text{M}^{-1} \cdot \text{s}^{-1}$, N-phenyl maleimide: $k = 27.60 \times 10^7 \text{dm}^3 \cdot \text{M}^{-1} \cdot \text{s}^{-1}$, and acetylene carbonic acid dimethyl ester : $k = 25.40 \times 10^7 \text{dm}^3 \cdot \text{M}^{-1} \cdot \text{s}^{-1}$). Therefore, the reaction with strained and electronically activated alkenes represents an important competitive reaction partner in the thermal process. Similar reasoning is also applicable for the rate-accelerating effect of electron-withdrawing substituents on the azido molecule as determined by Hammett correlations.\cite{13}

A variety of catalytic systems have been used to effect the 1,3-dipolar cycloaddition process. In case of the azide/acyetylene process, mostly CuI catalysts have been used (see Scheme 3b) and require about 0.25–2 mol-% of the catalysts. Most methods use CuI salts directly, other methods generate the copper(I) species by reduction of CuII salts using sodium ascorbate or metallic copper. Recently, the use of copper clusters of Cu/Cu oxide nanoparticles, sized 7–10 nm,\cite{14} as well as copper clusters of diameter ≈2 nm, with a specific surface area of 168 m$^2 \cdot \text{g}^{-1}\cite{15}$ have been described, although with contradicting explanations for their catalytic activity. Whereas in the former case the presence of CuI/CuII species in a ratio of 1:3 was made responsible for the strong catalytic activity, the latter publication claims the catalytic activity of the Cu0 species. Both publications claim a positive influence of the alkylamine ligand present on the nanoparticle surface as an additional factor for activity enhancement. Besides the copper catalyst, 1–5 equivalents of base are added, mechanistically for promoting the formation of the copper(I)-acetylide. Solvents and bases are listed in Scheme 3b/3c, which features most of the known solvents as applicable for this reaction. In addition, biphasic reaction systems (water/alcohol or water/toluene) can be applied with excellent results. The bases used (Scheme 4) are mostly triethylamine, 2,6-lutidine, and N,N-diisopropylethylamine (DIEA), as well as N,N,N’,N’-pentamethylethylenetetramine (PMDETA) or 2,2’-bipyridine. Besides the copper(I) catalyst

![Scheme 2](image2)

![Scheme 3](image3)
and the base, triazoles have been shown to accelerate the reaction.\cite{16a} Some of the ligands are indicative of a complexation of the copper(I), which leads to a stabilization of the copper(I) oxidation state, thus prevents coupling reactions such as the Ullman,\cite{17} and Cadiot-Chodkiewicz couplings.\cite{18b} Moreover, tris-triazolyl ligands inhibit the Cu\textsuperscript{II}-catalyzed oxidative coupling reactions of terminal alkynes to diynes under otherwise standard conditions.\cite{18b} Other systems use tris(carboxyethyl)phosphine (TCPE) as a ligand. Recently, the systematic investigation of catalytic systems for the Sharpless click reaction has been achieved by parallel methods by a fluorescence-quenching assay.\cite{16b} It should be mentioned that besides Cu\textsuperscript{I} salts, other metals that promote the dipolar cycloaddition reaction of terminal acetylenes and azides have been reported recently. Thus Sharpless and co-workers found that a variety of Ru complexes (CpRuCl(PPh\textsubscript{3}), [Cp\textsubscript{2}RuCl\textsubscript{2}], Cp’RuCl(NBD), and Cp’RuCl-(COD)) promote the azide/alkyne click reaction.\cite{19a} Interestingly, not only the 1,4-adduct is favored by some catalysts (i.e., Ru(OAc)\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}), but also the 1,5-adducts by other Ru catalysts. A catalytic cycle that relies on a pathway similar to the cyclotrimerization reaction of alkynes via a six-membered ruthenacycle has been proposed. Matyjaszewski and co-workers have recently published the use of Ni, Pd, and Pt salts to catalyze this reaction, although a mechanistic description is not provided.\cite{19b}

Strong effects of alternative synthetic methodologies have been observed within the click reaction. Thus Fokin and co-workers\cite{20} and others\cite{21} have investigated the reaction under action of microwave irradiation. They used a combination of nucleophilic displacements starting from benzyl halides and sodium azide directly linking the present phenylacetylene in a single step. The reaction was strongly enhanced by the action of microwave irradiation, and furnished the corresponding triazoles in yields between 86–93%. Similar observations have been described with click reactions on polymers and dendrimers. Another approach\cite{22} starts from the initial observation that ammonium salts can act as co-catalysts for the 1,3-dipolar cycloaddition process when using solely metallic copper as the catalyst. Thus ammonium salts directly promote the formation of Cu\textsuperscript{I} species, which enables an efficient reaction to yield the cycloaddition products in >95% yields.

A mechanistic picture of the copper catalyzed reaction was first proposed by Meldal and co-workers\cite{5} and Sharpless and co-workers\cite{6} and has later been verified by computational methods.\cite{23,24} However, the proposed catalytic mechanism (calculated by density functional theory (DFT) calculations) that relied on the initial formation of a Cu acetylide between the Cu\textsuperscript{I} species and the terminal alkyne which subsequently proceeded by an initial \(\pi\)-complex formation between the Cu\textsuperscript{I} and the

\[\text{Scheme 4.}\]

\[\text{Scheme 5.}\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Polymer/substrate</th>
<th>( M_n )</th>
<th>Polymerization method</th>
<th>Catalyst/conditions for ‘click’ reaction</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>18 400</td>
<td>ATRP</td>
<td>CuBr/r.t.</td>
<td>[29]</td>
</tr>
<tr>
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<td></td>
<td>ATRP</td>
<td>N-alkyl-2-pyridylmethanimine-CuBr/70 °C</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2 700/6 850</td>
<td>ATRP</td>
<td>CuBr/THF/r.t.4, 4’-di-(5-nonyl)-2, 2’-bipyridine</td>
<td>[31]</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>39 540</td>
<td>ATRP</td>
<td>NaN₃/ZnCl₂/120 °C</td>
<td>[28]</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td>ATRP</td>
<td>NaN₃/ZnCl₂/120 °C</td>
<td>NaN₃/ZnCl₂/120 °C</td>
<td>[28]</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>2 010</td>
<td>ATRP</td>
<td>CuBr/PMDETA/r.t.</td>
<td>[32]</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2 590</td>
<td>ATRP</td>
<td>CuBr/DMF/r.t.</td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>ATRP</td>
<td>Cu¹/DBN/THF/35 °C</td>
<td>[34]</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>4 150</td>
<td>ATRP</td>
<td>CuBr/PMDETA/THF/35 °C</td>
<td>[35]</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>31 900</td>
<td>nitroxide living-radical polymerization</td>
<td>CuBr(Ph₃)₃/DIPEA [42a,42b]</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>16 200</td>
<td>RAFT</td>
<td>CuBr(Ph₃)₃/DIPEA/THF/H₂O/r.t./3 d</td>
<td>[42b]</td>
</tr>
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Table 1. Overview of click reactions with polymers.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Polymer/substrate</th>
<th>$M_n$</th>
<th>Polymerization method</th>
<th>Catalyst/conditions for ‘click’ reaction</th>
<th>Ref.</th>
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<td><img src="image1.png" alt="Image" /></td>
<td>4200</td>
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<td>1400–18 100</td>
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<td>Cu(0)/CuBr or Cu$^+$Br/PMDETA/DMF/r.t.</td>
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</tr>
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<td>2 620–10 930</td>
<td>ROMP</td>
<td>Cu$^+$[Ph$_3$]$^+$Br/DIPEA/DMF/50 °C</td>
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<td>$\leq 33 400$</td>
<td>ROMP</td>
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<td>living cationic ring-opening polymerization</td>
<td>CuSO$_4$, SH$_2$O, water/t-BuOH</td>
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<tr>
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<td>3 100</td>
<td>quasi-living cationic polymerization of isobutene</td>
<td>Cu$^+$[Ph$_3$]$^+$Br/DIPEA/toluene</td>
<td>[48]</td>
</tr>
<tr>
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<td><img src="image7.png" alt="Image" /></td>
<td>14 100</td>
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<td>CuBr/PMDETA/sodium ascorbate/DMF</td>
<td>[51]</td>
</tr>
<tr>
<td>18</td>
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<td></td>
<td>Cu$^+$/CH$_3$CN</td>
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<td>free-radical polymerization</td>
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<tr>
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<td><img src="image10.png" alt="Image" /></td>
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<td></td>
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</tr>
<tr>
<td>20b</td>
<td><img src="image11.png" alt="Image" /></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry</td>
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<td>$M_n$</td>
<td>Polymerization method</td>
<td>Catalyst/conditions for ‘click’ reaction</td>
<td>Ref.</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>-------</td>
<td>-----------------------</td>
<td>------------------------------------------</td>
<td>-----</td>
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<tr>
<td>21</td>
<td></td>
<td>12 565</td>
<td>polyaddition</td>
<td>CuSO$_4$·5H$_2$O/sodium ascorbateH$_2$O/t-BuOH = 1:1/r.t.</td>
<td>[50]</td>
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<tr>
<td>22</td>
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<td>&lt;396 000</td>
<td>polyaddition</td>
<td>Cu/Cu(OAc)$_2$/TBTATHF/CH$_3$CN</td>
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</tr>
<tr>
<td>23</td>
<td></td>
<td>24 000</td>
<td>polyaddition</td>
<td>CuSO$_4$·5H$_2$O/sodium ascorbate</td>
<td>[57]</td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td>CVD polymerization</td>
<td>CuSO$_4$·5H$_2$O/sodium ascorbate H$_2$O/t-BuOH = 2:1</td>
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</tr>
<tr>
<td>25</td>
<td></td>
<td>8 300–17 600</td>
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<td>Cu(Br)(Ph$_3$I)/DIPEA</td>
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</tr>
<tr>
<td>26</td>
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<td>8 200</td>
<td>ATRP</td>
<td>Cu(Br)(Ph$_3$I)/DIPEA</td>
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</tr>
<tr>
<td>27</td>
<td></td>
<td>9 300</td>
<td>anionic ring-opening polymerization</td>
<td>CuSO$_4$·5H$_2$O/sodium ascorbate/100 °C</td>
<td>[59]</td>
</tr>
<tr>
<td>28</td>
<td></td>
<td>3 700–27 000</td>
<td>sequential stepwise solid-phase synthesis</td>
<td>Cu/I/ascorbic acid/DIPEA butan-2-ol/DMF/pyridine</td>
<td>[61]</td>
</tr>
</tbody>
</table>
alkyne,[25,26] to lead to a lowering of the pKₐ of the terminal acetylene by up to 9.8 units, thus enabling the attack onto the C–H bond, especially in aqueous systems, has been recently revised[6b] in favor of a binuclear mechanism as shown in Scheme 5.

Support for this hypothesis, which is similar to the monometallic mechanism proposed by Sharpless and co-workers[23,24] by calculation is based on the observation that the rate of catalysis is second order with respect to copper, but with increasing concentration of copper, less reactive species are observed. Overall, this results in a rate acceleration of 10⁵ and an absolute regioselectivity of the Cu I-catalyzed process.[27] Thus both the high regioslectivity and the rate acceleration are accounted for this mechanism. Similar results are obtained when calculating the Cu I-catalyzed cycloaddition reaction of azides to nitrile-oxides, for which a similar rate enhancement of the copper-catalyzed reaction in comparison to the purely thermal reaction was observed.

### Click Reactions on Linear Polymers and Gels

Since many known polymerization reactions in macromolecular chemistry require the absence of specific functional groups, there is considerable interest in the fixation of ligands onto polymers and gels after a successful polymerization reaction has been conducted. This is most important when living polymerization mechanisms are used, since especially the highly sophisticated chemical mechanism and equilibria of (quasi-)living polymerization reactions are often highly substrate specific and, therefore, strongly affected by even small amounts of functional groups or the respective coupling agents required for affixation. Another issue concerns the binding of large numbers of ligands onto polymers (i.e., sidechain-modified polymer) or dendrimers, which require highly efficient coupling reactions to this purpose as well. Further interest is directed towards the heterogeneous functionalization of polymers in solvent mixtures. Because of the limited solubility of many polymers, reactants for post-functionalization reactions cannot always be applied in homogeneous solution with the derivatized polymer. In these cases, highly efficient reactions acting in heterogeneous reaction media are desired. Thus it is not surprising that the Sharpless click reaction has been brought into the limelight recently because of its high efficiency, often reaching yields of >99% irrespective of the ligand structure, even in inhomogeneous reaction systems.

Table 1 lists the hitherto known click reactions on various polymers, oligomers, biopolymers, and gels. The nature of the initial polymerization reaction (if known) as well as the structure of the initial, starting polymers are given. Many of the controlled polymerization reactions derive from atom-transfer radical polymerization (ATRP), ring-opening metathesis polymerization (ROMP), and quasi-living cationic polymerization, some are from nitroxide-mediated polymerization (NMP), radical addition-fragmentation transfer (RAFT), or polycondensation reactions. Only a few examples of living anionic polymerization and free radical polymerization reactions have
been described up to now in junction with the click reaction. The catalytic systems used for the click-type reaction are also given, the vast majority with a focus on the copper-catalyzed azide/alkyne click reaction. In general it can be stated that only relatively low-molecular-weight polymers ($M_n < 30 000$ g mol$^{-1}$) are used, where a good characterization of the final polymer (in relation to the initial functionalization) is possible. High molecular weights are obtained in only a few cases, where the click reactions are used to build-up polymers with the triazole moiety within the main chain.

**Living Radical Polymerizations (ATRP, NMP, and RAFT)**

ATRP has been used extensively in conjunction with the azide/alkyne click reaction, and also represent the first, intensely exploited examples of a combination between a (quasi-)living polymerization reaction and the azide/alkyne click chemistry. Three different strategies have been described to combine these two reactions: a) using azido-telechelic macromonomers, b) via alky-telechelic macromonomers, and c) using azido or acetylenic moieties within the sidechain.

A combination between ATRP and an azide/alkyne click reaction has been demonstrated by Matyjaszewski and co-workers$^{[28]}$, using the reaction between pendant nitri- moieties and sodium azide (Scheme 6). In this variant of the Huisgen 1,3-dipolar cycloaddition reaction, the azide can be fixed onto the sidechains of polycrylonitrile (PAN, $M_n = 39 450$ g mol$^{-1}$) or poly(acrylonitrile-styrene) block copolymers ($M_n = 8 460$ g mol$^{-1}$). All polymers were prepared with low polydispersities ($M_w/M_n < 1.10$) using ATRP methods. The addition of the azide anion is catalyzed by SnCl$_2$ or ZnCl$_2$ to yield the corresponding tetrazole polymers in excellent yields. The addition reaction is reversible, thus liberating nitrogen from the polymers upon heating to temperatures from 120–190 °C.

Sidechain-modified polymers made by an initial ATRP reaction, subsequently followed by an azide/alkyne click reaction were described using 3-azidopropyl methacrylate as the monomer (Scheme 7)$^{[29]}$. This monomer yielded a good ATRP reaction, furnishing polymer 2 in good yields and acceptable polydispersity ($M_n = 18 400$ g mol$^{-1}$, $M_w/M_n = 1.33$). Copolymerization to the block copolymer 3 could be achieved, as well as the click reaction with various terminal acetylenes to give the final polymer 4 in yields higher than 95%, using Cu$^{II}$Br in $N,N$-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) solutions. Despite higher steric hindrance in polymer 2 as compared to the free monomer 1, the click reaction proceeded faster on the polymer, as judged by NMR spectroscopic investigations. Similar to the results obtained with tributyltin acrylate (TBTA)$^{[16a]}$, an anchimeric assistance of the reaction by already formed triazoles was proposed.

End-group modified polymers obtained by an ATRP strategy have been described by several authors.$^{[29–37]}$ An elegant method that places the azido moiety at the initiator part has been demonstrated by Haddleton and co-workers$^{[30]}$ with the initiators 5 (see Scheme 8), acting as initiator for the ATRP of methyl methacrylate via the $N$-alkyl-$2$-pyridyldimethanimine Cu$^{II}$Br-initiating system, to yield polymer 6. The initiating efficiency of 5b was found to be higher than those of 5a, presumably because of steric effects. Subsequent click reaction upon addition of terminal alkynes furnished the final polymers 7 in quantitative yields, thus relying on the residual Cu$^{II}$ catalyst present from the ATRP reaction. A related approach, which relied on the nucleophilic substitution reaction to introduce the azido-moiety after the ATRP process, has been reported by Lutz et al. (see Scheme 9)$^{[31]}$. The polystyrene (PS) polymer ($M_n = 2 700$ g mol$^{-1}$, $M_w/M_n = 1.11$) was prepared by ATRP (Cu$^{II}$Br/PMDETA), featuring a terminal bromine end-group 8 after the polymerization reaction. Subsequent nucleophilic substitution exchanged the bromine against the azide to furnish the final azido-telechelic polymer 9 by use of sodium azide in DMF as solvent within 3 h at room temperature. The click reaction with various terminal acetylenes (propargylic alcohol, propiolic acid, 2-methylbut-1-en-3-yne) was then conducted on these polymers using the Cu$^{II}$Br/4,4’-di-(5-nonyl)-2,2’-bipyridine catalytic system in tetrahydrofuran (THF) as solvent. Again, the reaction proceeded smoothly as judged by NMR spectroscopy to furnish the final polymers 10 in quantitative yields.

A similar strategy that relies on a combination of nucleophilic displacement of the bromine end-group in PS polymers has been achieved by Matyjaszewski and co-workers$^{[32]}$. As shown in Scheme 10, a bivalent $\alpha$, $\alpha$-dibromo-telechelic PS 11 ($M_n = 2 340$ g mol$^{-1}$, $M_w/M_n = 1.08$) was prepared by ATRP, using 2,6-dibromoheptanoate as initiator and Cu$^{II}$Br/PMDETA as the catalytic system. As in Lutz’s work,$^{[31]}$ a bromine/azide exchange was conducted to generate the diazido-telechelic polymer 12 quantitatively. Again, click reactions were performed on this bivalent polymer using propargylic alcohol as the acetylenic component. Since two modes of addition processes are possible, gradient polymer elution chromatography (GPEC) was used to separate the
mono- and disubstituted polymers 13 and 14. This method can separate polymers with similar molecular weight, albeit different polarity by changing the elution-solvent from a poor to a good solvent, which leads to an elution of the chains with the weaker column interactions first. A follow-up of the individual concentrations of the polymers 13 and 14 with time was possible, which led to an individual determination of the apparent rate constants of the click reactions with values of $3.2 \times 10^{-4}$ and $1.1 \times 10^{-4}$ s$^{-1}$, respectively. Therefore, the second click reaction was slower by a factor of 3 than the first one. Obviously, the decreased mobility of the chain overcomes the sometimes observed (usually positive) autocatalytic effect of multiple substitution reactions within the azide/alkyne click reactions.

The $\alpha$-alkyne-$\omega$-azido-terminated PS 16 (prepared by ATRP and subsequent bromine/azide exchange from polymer 15, $M_n = 2590$ g·mol$^{-1}$; $M_w/M_n = 1.11$) formed the platform for a step-growth process on the basis of the click reaction (see Scheme 11). A direct click reaction in the sense of an addition polymerization directly from the ATRP/substitution mixture was accomplished, which generated the Cu$^+$ catalyst by a simple addition of ascorbic acid. After 116 h of reaction time at room temperature, the addition polymer 17 ($M_n = 21500$ g·mol$^{-1}$; $M_w/M_n = 4.85$) was obtained. However, despite this relatively high molecular weight, about 18% of unreacted telechelic precursor 16 remained in the reaction mixture. A similar synthetic strategy using the acetylene-telechelic macromonomer 19 in reaction with an $\alpha$-azido-poly(ethylene glycol) 18 (see Scheme 12) was reported by Opsteen and van Hest. The use of the CuI/1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) catalytic system afforded the poly(methyl methacrylate)-block-poly(ethylene glycol) (PMMA-b-PEG) diblock copolymer 20 as well as the PMMA-b-PS block copolymers in high yields.

The coupling between a peptidic sequence or even a full protein and a telechelic PS-azide to generate biohybrid amphiphiles was described by Cornelissen and co-workers (see Scheme 13). The azido-telechelic PS 21 ($M_n = 4150$ g·mol$^{-1}$; $M_w/M_n = 1.15$) was directly coupled to the 3-butylnyl-linked peptide 22, which carried a coumarin dye as fluorophore. The coupling-reaction was achieved with CuBr/PMDETA in THF as solvent. Proof of the efficiency of the coupling reaction in the resulting biohybrid amphiphile 23 was achieved by matrix-assisted laser desorption-ionization (MALDI) mass spectrometry, which clearly demonstrated the shift in molecular weight upon addition of the peptidic sequence. Consequently,
whereas the conventional aqueous CuSO₄/ascorbate catalytic system failed with substrates 21 and 22 in THF/water mixtures, the conjugation of 21 to appropriately functionalized BSA (bovine serum albumin) was successful.

The syntheses of star polymers by ATRP/click methodology has been described by Gao and Matyjaszewski starting from telechelic azido-PS polymers (see Scheme 14).[36] A series of PSs 24 (molecular weights ranging from \( M_n = 1400 \) g mol\(^{-1}\)) was reacted with the bi-, tri-, and tetravalent alkynes 25, 26, and 27 respectively, to furnish the final star-type polymers 28, 29, and 30. A small but significant influence of added Cu⁰ species was found with respect to the reaction yield and efficiency, which led to an improvement of the reaction upon addition of small quantities of Cu⁰ species. However, reaction efficiencies decreased with increasing molecular weights, which ranged from 95 (\( M_n = 1400 \) g mol\(^{-1}\)) to 80% (\( M_n = 18100 \) g mol\(^{-1}\)). The method represents a highly universal approach towards star-type polymers with various polymeric sequences and structures.

The formation of macrocyclic polymeric rings has been demonstrated by Laurent and Grayson using the telechelic polymer 31 (see Scheme 15).[37] As known from organic synthesis, large rings are obtained with only some selected macrocyclization reactions, mostly under high-dilution methods. Since the azide/alkyne click reaction is a highly efficient reaction that works under moderate reaction conditions and, most importantly, involves a template effect by the Cu intermediate, a cyclization approach is highly interesting. Thus the starting PS polymer bearing terminal acetylenic and bromine moieties 16 (prepared by ATRP, \( M_n = 4200 \) g mol\(^{-1}\); \( M_w/M_n = 1.06 \)) was transformed into its azido-analogue 31. Despite the use of the ultrahigh dilution conditions usually required for these types of macrocyclization reactions, a continuous addition of the substrate by a syringe pump to a solution that contained the CuBr/bipyridine catalyst in DMF (0.1 × 10\(^{-3}\) m) was performed. The successful cyclization to yield 32 was accomplished as proven by NMR measurements (32: \( M_n = 4170 \) g mol\(^{-1}\)) upon inspection of the triazole resonances at 4.3–4.8 and 5.3–5.7 ppm, respectively. This demonstrates the high efficiency of the click reaction for the future preparation of macro(polymeric)cycles by a simple ring-closure reaction.

The attachment of carbohydrates to sidechain-modified polymethylacrylates has been demonstrated by Haddleton and co-workers (see Scheme 16).[38] Starting from the sidechain-modified PMMA 33, which bears multiple acetylenic moieties, a number of carbohydrates can be affixed (e.g., 1-azidosugars, 6-azidosugars). In accordance with previous investigations on carbohydrates[39,40] and cyclodextrins,[41] the carbohydrates can be either fully protected or, alternatively, can be used in the unprotected state with (Ph₃)₃CuBr and diisopropylethylamine (DIPEA) in DMSO as the catalytic system. As an elegant application, the generation of a library of mannose- and galactose-containing polymers 35 and 36 by a ‘co-clicking’ approach was reported. The relative amounts of the two different carbohydrates were varied and the reaction checked for the selective mannose/concanavalin A interaction in relation to the achieved ligand density. Significant effects between the ligand densities and the binding efficiencies were observed.

Recently there have been a few examples for the combination of NMP and the azide/alkyne click reaction (Scheme 17).[42] Various copolymers (e.g., the water-soluble terpolymer 37) were prepared by NMP to enable the direct...
introduction of the terminal acetylenic moieties after deprotection with tetrabutylammonium fluoride (TBAF). Subsequent attachment of azido-moieties \( \text{38} \) was effected using \([\text{Ph}_3]_3\text{CuBr}\) and DIPEA to furnish a large variety of different polymers \( \text{40} \) in high yields (\( \approx 98\% \) coupling efficiency) as judged by HPLC and NMR methods. A combination of RAFT and the azide/alkyne click reaction has been reported,\(^{[42b]}\) taking advantage of the RAFT polymerization process, since the corresponding NMP process did not succeed in maintaining the corresponding terminal acetylenic moieties. However, even in the RAFT process, protection of the terminal acetylene moiety as a trimethylsilyl derivative was required. The final click reaction furnished the corresponding coumarin derivative within a block-copolymeric micelle.

A polycondensation approach was first reported by Krasla and Steinke\(^{[43]}\) using bivalent azides and alkynes as building blocks for polymers (Scheme 18). The 1,3-dipolar cycloaddition process between the acetylene \( \text{41} \) and the azide \( \text{42} \) in this case was catalyzed by cucurbituril according to a previous report by Mock et al.,\(^{[44]}\) who demonstrated the efficiency of this catalytic system in the synthesis of polyrotaxanes. The cucurbituril in this case acts as a bridge between the alkyne and the acetylene, thus easing the linkage forming the 1,3-dipolar cycloaddition process by a preorganized structure to yield the rotaxane \( \text{43} \) as well as the polymeric rotaxane \( \text{44} \).

### ROMP, Cationic Polymerization, and Anionic Polymerization

Few examples have been reported that combine ROMP and (quasi-)living cationic polymerization with click reactions. Thus Binder et al.\(^{[45]}\) (Scheme 19) have developed efficient attachment strategies of supramolecular receptors (hydrogen-bonding structures) onto poly(oxy-norbornenes).\(^{[45a]}\) Thus either norbornene monomers \( \text{45, 46} \) as well as sidechain-derivatized polymers \( \text{47} \) bearing azido or acetylenic moieties can be used to effect efficient linking strategies to yield the final derivatized polymers \( \text{48} \). The critical point in the combination of poly(oxy-norbornene) chemistry and click chemistry lies in the control and thus suppression of the concurring thermal addition of azides onto the norbornene double bond. Thus only oxy-norbornene monomers can be used, because of their reduced ring strain with respect to norbornenes and thus reactivity in the non-catalyzed process. By developing the concept either from the monomer or the post-modification of the final polymers, a large variety of homo\(^{[45a,45b]}\) and block copolymers\(^{[45d,45e]}\) can be prepared using only a small set of starting monomers. Advantageous in this respect is the possibility to generate polymeric libraries from only a small set of precursor polymers. Another strategy using ROMP in conjunction with Diels-Alder-type cycloaddition reactions has been described by Paton and co-workers,\(^{[46]}\) which relies on nitrooxide addition onto the norbornene double bond. This highly efficient reaction runs in the absence of copper or other metal salts at moderate conditions, which enables the attachment of various carbohydrates onto the poly(norbornene) backbone. A conventional anthracene/maleimide click reaction that relies on a highly efficient, purely thermal Diels-Alder reaction has been recently reported by several authors.\(^{[47]}\)

Two examples for the combination of cationic polymerization reactions with click reactions have been described. One example describes the fixation of supramolecular ligands onto mono-, bi-, and trivalent telechelic...
polyisobutylmethyl methacrylate, prepared by quasi-living cationic polymerization ($M_n = 3 \times 10^5$ g mol$^{-1}$; $M_w/M_n = 1.10$).[48]}

The reaction has been performed in biphasic reaction systems, which feature toluene/water solvent mixtures and CuBr as the catalyst, and lead to yields above 94% (Scheme 20). Thus the reaction works satisfyingly at the interface, which enables the attachment of water-soluble substrates onto water-insoluble polymers, such as the trivalent polyisobutylene 49, to result in a large variety of trivalent substituted polyisobutylmethyl methacrylates 50. Another example of cationic polymerization has been demonstrated by the living cationic polymerization of poly(1, 3-oxazolines) using 2-(pent-4-ynyl)-2-oxazoline as the monomer.[49a] The attachment of some functional groups onto the sidechain-functionalized poly(1-oxazoline) was demonstrated by MALDI, which revealed the high fidelity of this derivatization reaction. A recent example of the combination of anionic polymerization with click reactions has been reported.[49b] 1-Ethyl-4-hydroxybenzene has been used as a monomer in several block copolymers (e.g., PMMA, PS) and subsequently transformed into the corresponding oxypropynes by classical Williams or Mitsunobu strategies. The click reactions could then be performed on these substrates.

![Scheme 13.](image1)

![Scheme 14.](image2)
Certainly, the click reaction opens an interesting prospect for crosslinking reactions, to furnish gels and networks as the resulting materials. A low temperature, combined with a high efficiency, may satisfy the mild reaction conditions required for gel-formation or templating processes.

The first contribution for the in-situ polymerization of azides and alkynes into networks has been contributed by Sharpless and co-workers.\textsuperscript{[50]} Two approaches were conducted to generate polymeric structures: bivalent azides and bivalent acetylenes were polymerized using CuI and sodium ascorbate in a \textit{t}-butyl alcohol/water mixture to furnish polycondensates with molecular weights below 12 500 g mol\(^{-1}\). This approach was taken as a starting point to prepare resin-type structures derived from bi- and trivalent azides and alkynes (Scheme 21). A large variety of trivalent acetylenes as well as trivalent azides were used in this condensation approach to yield a crosslinked resin material. The crosslinking process was used to link metallic structures (i.e., copper plates) by non-covalent interactions exerted by the acetylenes and formed triazoles, respectively. This method provides a new way to glue planar metallic plates by an efficient crosslinking process reminiscent of epoxy resins.

Another type of crosslinking reaction has been described by Turro and co-workers.\textsuperscript{[51]} Bivalent, \(\alpha,\alpha\)-diazido-telechelic poly(\(t\)-butyl acrylates) 51 (\(\bar{M}_n = 14\ 100\) g mol\(^{-1}\); \(M_w/M_n = 1.12\)), prepared by ATRP methods, were crosslinked into gels 52 by reaction with tri- and tetravalent acetylenes, such as 53 (see Scheme 22).

Gels and Networks
The optimal (and fastest) reaction conditions were found with a reaction system that consisted of CuBr/PMDETA with sodium ascorbate in DMF as solvent, and required ≈5 min for a complete crosslinking reaction. The fidelity of the crosslinking reaction was proven by ozonolysis of the central double bond in polymer 52, which enabled control of the destroyed polymer networks by gel permeation chromatography (GPC) analysis as a result of a significant molecular weight shift to $M_n = 7300$ g·mol$^{-1}$ with $M_w/M_n = 1.21$. Since hardly any initially present polymer 51 was detected, the crosslinking reaction was said to be complete, and reflected a direct transformation of the theoretical crosslinking density into the actual one. The high efficiency of the crosslinking reaction also enables the crosslinking of highly preorganized, supramolecular systems. Finn and co-workers[52] report a process wherein a network of hydrogen-bonding systems forms fibers, and subsequently organogels (see Scheme 23). Terminal acetylenic groups were affixed to the hydrophobic end-groups of the ordered system 54, and subsequently crosslinked by a short, bivalent $\alpha,\omega$-diazide, to yield the crosslinked gel 55. Each reaction was performed in acetonitrile, with a gelator concentration of 3% and a gelator/crosslinker ratio of 10:1, using CuII as the catalyst system. Several features are important in the final, crosslinked products: a) the structure of the fibers initially present in 54 are fully transformed into a fiber structure in the crosslinked structure 55, b) the crosslinked gels 55 retain their stability up to temperatures even above the boiling point of acetonitrile, and c) the storage moduli $G'$ increased significantly during crosslinking, which clearly demonstrated the formation of a rigid gel from the previously dynamic organogel 54.

Crosslinking of statistically substituted poly(vinyl alcohol)s has been recently described by Ossipov and Hilborn.[53] Two differently substituted poly(vinyl alcohols), derivatized by carbamate linkages to give polymer 56 and 57, respectively (see Scheme 24) were prepared. Crosslinking was achieved using the CuII$/$sodium ascorbate coupling reaction in aqueous systems. Upon systematically varying the amount of CuII in solution, a minimum of 20 mol-% with respect to the functional groups concentration was detected, which formed hydrogels of the general structure 58. This hints at incomplete crosslinking reactions at lower CuII concentrations, and thus at a minimum amount of Cu in order to effect gel formation. A similar approach, albeit with different monomeric and oligomeric components has been described by Hawker and co-workers.[54] As shown in Scheme 25, a telechelic poly(ethylene oxide) 59 ($M_n = 3400$–10 000 g·mol$^{-1}$) was crosslinked with a tetravalent azide 60, to yield crosslinked hydrogels 61. Compared to gels with similar structure, crosslinked via photochemical activation, the click crosslinked gels display strongly enhanced tensile stress and strain stabilities. The reasoning states that in contrast to radically crosslinked gels (where often dense clusters are surrounded by a weakly crosslinked matrix), perfectly crosslinked structures are obtained by the click
reactions, since the perfection is high because of the high efficiency of the crosslinking reaction.

This high dimensional stability of the gels that result from the azide/alkyne click reaction has prompted the generation of molecularly imprinted reactors for the 1,3-dipolar cycloaddition reaction as reported by Mosbach and co-workers.\cite{55} Catalytic effects with respect to the regioselectivity of the cycloaddition reaction were observed.

**Click Reactions on Other Polymers**

The click reaction has been used in a variety of other polymerization reactions not related to living or quasi-living polymerizations. Thus a new strategy aimed at the synthesis of new conjugated polymers based on poly(fluorene)s was developed (see Scheme 26).\cite{56} Starting from a 4,4'-disubstituted fluorene building block 62 and another 4,4'-diacetylenic fluorene 63, a click reaction in the sense of a polyaddition process was conducted. Finally
the polymers 64, with molecular weights up to $M_n = 13,000 \, \text{g} \cdot \text{mol}^{-1}$ with a $M_w/M_n = 1.61$ were obtained. However, because of the presence of the triazole moieties, a poor electronic communication between the individual $\pi$-systems was observed, which resulted in a poor conductivity. Bunz and co-workers\[57\] have demonstrated the importance of the click reaction for the construction of poly($p$-phenyleneethynylene)s (see Scheme 27).

Sidechain-modified poly(phenyleneethynylene)s 65 that bear terminal silyl-acetylenic moieties were subjected to an initial deprotection to furnish the free acetylenes, and were subsequently subjected to a click reaction to yield the substituted polymers 66. This enabled the introduction of a large variety of sidechain modifications into these polymers, leaving the main-chain acetylenic bond entirely unaffected. A related reaction that relied on terminal acetylenes in poly[$(4$-ethynyl-$p$-xylylene)-co-$(p$-xylylene)] is shown in Scheme 28.\[58\] The polymer was prepared as a thin film by chemical vapor deposition (CVD) of ethynyl[2,2]paracyclophane, which resulted in a film thickness of $\approx 50 \, \text{nm}$. Subsequently, a layer of biotinazide as well as sodium ascorbate was applied to the film, which resulted in an even distribution of the two components inside the polymer matrix. Conventional microcontact printing supplied Cu$\left(\text{SO}_4\right)_2$ to specific regions of the polymer film to result in a local click reaction between the biotin and the sidechain acetylenic components. The binding of biotin was monitored by a labeled streptavidin/dye conjugate, which proved the generation of patterns in the $50 \, \mu\text{m}$ range. This example demonstrates the fine applicability of this reaction onto polymer films by a direct printing approach.

Other sidechain modifications of polymers\[59\] have been reported using azido- or acetylene-functionalized polymers or oligomers. An example for an aliphatic co-polyester with pendant acetylenic groups has been described by Emrick and co-workers\[59a\] and Jerome\[59b,59c\] (Scheme 29). Thus the co-polyester 67 (prepared by Sn$\left(\text{OTf}\right)_2$-mediated polymerization of the respective lactones), was reacted with oligomeric, $\alpha$-azido(ethylene glycols) 68 to furnish the final grafted polymers 69. In addition, small peptidic sequences that consisted of hexynoylamido-functionalized RGDS 52 were click-reacted with the polymers 51 to furnish the final grafted polymers 53.
(Arg-Gly-Asp-Ser) sequences were successfully reacted, to yield biocompatible polymers for tissue engineering purposes.

There are many examples of coupling reactions onto biomolecules, in particular proteins, nucleic acids, as well as whole-cell systems. Furthermore, affinity based protein profiling (ABPP), as well as the application of the click reaction has been used in combinatorial chemistry. Since a full description of these issues would be beyond the scope of this article, the reader is referred to recent reviews in the area. In this article, only defined oligomeric structures will be discussed.

Reverse reaction onto synthetically prepared peptides that bear sidechain-modified acetylenic sequences was reported by Kirschbaum and co-workers. In this work, defined sequences of oligopeptides were generated by a stepwise synthetic approach, including pendent azido groups of acetylenic moieties. Subsequent azide/alkyne click reactions under copper catalysis furnished the final, sidechain-modified oligopeptides in high yield.

Polysaccharides have been used recently as scaffolds for the azide/alkyne click reaction as reported by Shinkai and co-workers [62] (see Scheme 30). 6-Azido-6-deoxycurdlan 70 was prepared in a short reaction sequence, featuring bromination and subsequent azide exchange. A large variety of different substrates 71a–71e, bearing terminal acetylenes, was then coupled by use of CuBr2/ascorbic acid/propylamine as a catalytic system to yield 72. Both ammonia as well as propylamine were found to strongly accelerate the coupling reaction, which reached conversions of the azide after ≈1 h. Another example reporting the synthesis of pseudo-oligosaccharides, which relied on triazole linkages, has been reported recently [63].

Several examples for click chemistry on oligonucleotides were reported [64–67]. The purely thermal 2,3-thermal Huisgen reaction was used by Ju and co-workers [65] to link a rhodamine dye to the end of oligonucleotides. The starting azido-tagged oligonucleotide was subjected to the thermal dipolar cycloaddition process at 80°C with an acetylene-modified rhodamine dye. The reaction was not highly regioselective and both the 1,3- and 1,4-regioisomers of the dye-labeled oligonucleotide were obtained. This method, if conducted under action of CuI, may definitely represent a low-temperature variant of the reported thermal labeling procedure. A highly versatile approach was reported by Carell and co-workers [66]. As shown in Scheme 31, an alkyne-sidechain-modified 16-mer DNA 73 was prepared and subjected to azide/
Scheme 24.

Scheme 25.
alkyne click reactions to yield the modified DNA 74. The synthesis of 73 relied on the incorporation of the unnatural nucleobases 75 and 76 into the DNA-strand by chemical synthesis on the solid phase. Subsequently, dyes and/or carbohydrates could be bound to the DNA using the classical CuI/TBTA catalytic system. Furthermore, dendrites could be added to these DNA sequences, enabling the binding of metal salts and the subsequent metallization of the DNA by Ag deposition. [67]

Rotaxanes, p-Cyclophanes and Calixarenes

The linking of large molecular fragments is an important synthetic challenge in supramolecular chemistry to generate, e.g., cyclic structures and interlocked molecules. Therefore, the click reaction on larger organic molecules touches upon classical polymer chemistry and is included in this review. Ryu and Zhao[41a] have studied the click reaction on calixarenes modified with five terminal azido moieties. Using the CuI/NaWO4/sodium ascorbate system, d-glucamine residues were bound to the lower rim of the calixarene, thus providing extremely simple access to functionalized calix[4]arenes. A similar approach has been undertaken by Santoyo-Gonzales and co-workers[41b] to generate multivalent neoglycoconjugates by the addition of 1-O-propargyl-glycosides onto 1-O-(β-azidoethyl)-glycosides. The addition onto multivalent substrates (e.g., cyclodextrins) has also been reported.[41b]

The formation of [2]-, [3]- and [4]-rotaxanes is another example for the high efficiency of the click reaction. Starting from a previous discovery[68,69] that either preorganizational effects as well as the cationic nature of cucurbituril can effect an efficient azide/alkyne click process, Tuncel and Steinke[70] have prepared rotaxanes wherein the cucurbituril moiety serves either as catalyst as well as a rotaxane-part during an azide/alkyne click reaction. Higher rotaxanes are also accessible using bifunctional building blocks as well as under generation of rotaxanes with a pH-responsive moiety.[71] Another example of supramolecular compounds has been reported by Stoddart and co-workers.[72] The critical step in the formation of interlocked structures is the fixation of the intermediate supramolecular complexes. Thus, usually after self assembly, large ‘stoppers’ are applied to the end-groups, which allow the final locked systems to fix the interlocked bundles. A simple approach using 1,3-dipolar cycloaddition chemistry was developed. The ‘locking-in’ of the complex was accomplished by a (thermal) 1,3-dipolar cycloaddition reaction using di-tert-butylacetylene dicarboxylate at 40–80°C, and then furnishing the final rotaxane. This reaction is faster than the conventional thermal Huisgen process because of the preorganization of the ligands. Thus, this reaction can be performed in preorganized samples without CuI catalysis with good efficiency. A recent similar example of Sauvage and co-workers[73] uses a preorganizational stoppering method that relies on metal complexation. Despite the fact that this method will be only applicable to a limited number of structurally diverse rotaxanes, the mechanism demonstrates the efficiency of this linkage reaction.

![Scheme 26.](image)

![Scheme 27.](image)
The literature on applications of the azide/alkyne click reaction for the modification of dendrimers has expanded considerably during the past two years. Because of the high yields promoted by click chemistry, the application on multiple reaction sites can be easily derived. Thus in order to fully substitute a generation-3 dendrimer with 96 chain ends using a reaction with 99% yield, only 38% of the fully substituted product can be obtained. Thus dendrimeric systems are an important field of investigation, since the click reaction is not only a very high yielding reaction, insensitive to most functional groups present in the reaction partners, but also allows reaction in sterically hindered environments. Thus the fixation of dendrons onto polymeric backbones, the synthesis of dendrimers and hyperbranched polymers, and finally the derivatization of the dendrimer’s surface is an important field for click reactions.

The surface functionalization of dendrimers derived from 3, 5-dihydroxybenzoic acid using a large variety of surface-bound peptides has been achieved. As shown in Scheme 32, starting from a dendrimer with a surface bearing multiple acetylenic moieties, a variety of amino acids, as well as undecameric peptides and cyclic peptides, have been immobilized onto the dendrimer surface to furnish the final products 77. Using the catalytic system of CuSO₄/sodium ascorbate in DMF mixtures, yields between 43–56% were achieved. Upon applying microwave irradiation, the reaction yields were increased to 96%, which demonstrated the high impact of microwaves on the (positive) reaction progress. Hawker and co-workers have reported similar effects upon reaction of 3,5-dioxybenzyl ether dendrimers with p-(azidomethyl)benzoic acid methyl ester, which yielded the fully substituted dendrimer upon microwave irradiation with Cu(PPh₃)₃Br as catalyst in more than 96% yield as proven by MALDI measurements (Scheme 33). Other dendrimers (such as DAB polyamine dendrimer or Boltorn resin) yielded similar good results under these conditions. Therefore, the method can be used to prepare structurally highly diverse dendritic libraries.

The linking of dendrons up to the 4th generation using click chemistry has been described by Lee et al. (Scheme 34). Frechet-type dendrons could be linked to the bivalent core or another azido-substituted dendron in yields ranging from 84 to 95%, using 5 mol-% of CuSO₄/sodium ascorbate in a DMF/water mixture. The trivalent dendrimer or the bivalent dendrimers could be obtained by this reaction, which provides an easy approach to link complexes and, more importantly, large structures. The method can be extended to link two different dendrons together by a click reaction (Scheme 35).

The generation of quasi ‘diblock’-dendrons that consisted of a poly(amidoamine) (PAMAM)- and a Frechet-type dendrimer has thus become possible, by the coupling of different dendrons of various size and, of course, with strongly differing properties into one dendritic molecule. The method has been extended to the preparation of symmetrical and asymmetrical PAMAM dendrimers (Scheme 36), available by coupling the precursor dendrimer with the bivalent azide. A related approach to bivalent dendrimers has been reported by Fokin and co-workers (Scheme 37). Starting from the dendron, where two coumarin dyes are affixed onto a dendron that consists of a Boltorn dendrimer, the carbohydrate building block is attached to the core of the dendrimer, to result in 16 carbohydrate units on the dendrimer surface in 92.
Frechet and co-workers\cite{79} have used the click reaction to fix dendrons onto polymers displaying terminal acetylenes (Scheme 38). Thus poly(vinyl acetylene) 93 was used as a scaffold for the fixation of dendrons type 90 to yield the dendronized polymer 95. The reaction works quantitatively for dendrons in the 1st and 2nd generation, and yields coupling products of the 3rd generation in more than 98% yield. Thus this process demonstrates the high steric tolerance of the click reaction even for dendritic structures. From here, certainly it is not far to combine polycondensation processes and click chemistry for the synthesis of dendrimers. Using Frechet’s convergent approach for the synthesis of dendrimers (see Scheme 39)\cite{80} the repeated condensation of bivalent acetylene 97 with various azides 96 yields the core-building block 98. Simple nucleophilic substitution to the azide yields the ‘double-edged’ building block 99, which in turn can be condensed with 97 to yield dendrimer 100. The formation of higher generations is achieved by repeating the steps, both of which are 100% reactions with respect to yield. Thus dendrimers up to the 4th generation can be constructed, and allow a subsequent end-group modification after the final coupling step.

A similar coupling strategy, which yielded dendrimers with triazoles in the main chain, has been reported by Hawker and co-workers.\cite{81} As shown in Scheme 40, the divergent approach was used to generate the dendron 101, which could be reacted with an excess of the ‘monomer’ to generate the dendrimer 102. Subsequent transformation of the terminal hydroxymethyl-moieties by nucleophilic substitution furnished the octa-azido compound 103, which can be extended using the same reaction sequence. Dendrimers with purities of 95% could thus be obtained, which is an astonishing number, since divergent methods
are usually much poorer in their efficiency and fidelity. This again demonstrates the high efficiency of the azide/alkyne click reaction.

The methodology of self-coupling of azido and acetylenic building blocks has been used by Voit and co-workers\[82\] as well as Smet et al.\[83\] to generate hyperbranched polymers (the so called simple variant of the stepwise-produced dendrimers) (Scheme 41a and 41b). Surprisingly, both authors used the same branched building block 104 as the basic structure for the thermal self-condensation in the sense of a Huisgen-1,3-dipolar cycloaddition process. When 104 is subjected to the thermal process, the hyperbranched polymer 105 \( (M_n = 10,000 \text{ g mol}^{-1}, \text{which corresponds to} \approx 30 \text{ units}) \) is generated. The copper-catalyzed process has been described by Voit and co-workers\[82\] for another, self-condensing monomer, namely compound 106, which upon use of the Cu\(n\)/sodium ascorbate couple generates a hyperbranched polymer 101. These processes represent an extremely simple variant to produce dendrimer-like molecules by a simple procedure.

To summarize, the application of the click reaction for the synthesis and derivatization of dendrimers is a highly valuable process, which widens the prospect of structural polymer chemistry. Thus this method will have a large impact in the supramolecular chemistry of polymers as well as their application as central building blocks in material science.

Click Reactions on Surfaces (Including Carbon Nanotubes and C\(_{60}\) )

One of the very important applications of the azide/alkyne click reaction is its high reactivity in heterogeneous reaction systems, which leads to the prospect of a high efficiency for the derivatization of surfaces and resin materials. In order to run the reaction, the initial key reaction involves an efficient and simple reaction to allow derivatization of a surface functionalized with azido or terminal acetylenes. Table 2 provides an overview of the different surfaces used in conjunction with azide/alkyne click reaction as well as the individual (Cu\(n\))-catalytic systems. Since the reactions have to be conducted heterogeneously, the exact nature of the solvent system is of importance. In the following context several surfaces are discussed, in which click reactions have been conducted: a) planar surfaces such as self assembled monolayers (SAMs) and glass surfaces, b) polymeric surfaces, c) nanoparticles, and d) micelles and vesicles, as well as e) the functionalization of crosslinked resins bearing terminal azido/alkyne moieties. The subsequent azide/alkyne click reaction then offers an excellent approach to various surfaces exposing functional groups.

Collmann et al.\[84\] (Scheme 42) were the first to describe the application of SAMs on gold surfaces and the subsequent azide/alkyne click reaction to attach ferrocenes onto the Au surface. They prepared an azido-
Scheme 33.
functional SAM by adsorption of 11-azidoundecanethiol in a mixture with decanethiol. The subsequent click reaction of the ferrocene-alkynes afforded the corresponding ferrocene-derivatized surfaces. Functionalization was proven by grazing-angle infrared spectroscopy and cyclic voltammetry. The surface coverage was measured as 17% when starting from a monolayer with a coverage of 30%. The density of the final monolayer was dependent on the initial amount of azido moieties present at the surface, thus offering a substrate-size-independent derivatization strategy. In a related publication, the same authors have extended their approach to mixed SAMs on planar Au surfaces [85] in addition to previously used methods (IR spectroscopy and ellipsometry). X-ray photoelectron spectroscopy (XPS) was used to prove the presence of the attached species. Moreover, a direct, time-resolved measurement of the click reaction onto the electrode surface was achieved. To this purpose, in-situ electrochemical measurements of a ferrocene derivative at a low electrode coverage allowed the determination of the reaction constant of the click reaction as \( k = 1 \times 10^3 \text{ M}^{-1} \cdot \text{s}^{-1} \), revealing an extremely high reaction rate in comparison to other, rapid surface reactions (e.g., the reaction of immobilized cyclopentene and benzoquinone \( k = 220 \text{ M}^{-1} \cdot \text{s}^{-1} \)), as recently reported by Gawalt and Mrksich [86]. A similar example by the same authors [87] demonstrates the determination of single electron transfer rates upon variation of the linker between the ferrocene unit and the corresponding Au surface of the SAM (see Scheme 43).

Using the click chemistry approach with the CuI/TBTA couple, a large variety of ligands with varying spacer length as well as different ligand densities could be affixed to the electrode surfaces, thus enabling a reliable and fast determination of the electron transfer rates.

Choi and co-workers [88] (Scheme 44) have used the inverse approach by presenting an SAM bearing terminal acetylenic moieties. They too applied the click reaction in aqueous reaction systems using CuI\( \text{SO}_4 \) and sodium ascorbate as the catalytic system. The attachment of the azides 108, 109, and 110 was proven by polarized infrared external reflection spectroscopy (PIERS) and XPS. Most importantly the attachment of the azido-modified nucleoside 109 onto the surface was demonstrated, thus proving the ability to attach molecules of biological significance onto SAM surfaces.

An example of a purely thermal Huisgen 1,3-dipolar cycloaddition has been reported by Lummerstorfer and Hoffmann [89] using chemistry on SAMs derived from silicon and silica surfaces (Scheme 45). Since no catalysts were used, the reaction needs a temperature of 70 °C in order to obtain a significant attachment of functional moieties onto the surface. An advantage of this uncata-
alyzed process is the attachment of the bisubstituted, activated acetylene dicarbonic acid and its derivatives onto the SAM.

A recent example of the click reaction onto SAM surfaces was reported by Binder and co-workers [90] (Scheme 46) which demonstrated the attachment of highly polar hydrogen-bonding systems 111 onto the ω-azido ligand 112 bound to SAMs. Again, the reaction scales with the amount of azido moieties bound to the surface, thus demonstrating the broad applicability of this reaction for the attachment of supramolecular receptors. A coverage of the SAM with the functional moiety 111 could thus be achieved, and ranged from only a few mol-% up to a full coverage, as determined by atomic force microscopy (AFM) detection of the supramolecular ligand sticking out of the planar surface. The system described works in aqueous as well as non-aqueous environments using CuBr(PPh$_3$)$_3$ as catalyst. A critical point concerned the use of a minimal amount of triphenyl phosphine, which can also act in a competing reaction that leads to a destruction of the azido moieties in a Staudinger-type reaction. The supramolecular ligand in turn could be used to assemble nanoparticles and other nanometer-sized objects onto the surface by a specific supramolecular interaction. The method has been extended for the immobilization of various complex carbohydrates onto Au surfaces by SAMs (see Scheme 47) [91]. After first immobilizing a ω-acetylenic substrate onto the SAM, various azido sugars 113 as well as the azido glycol 114 were reacted onto the surface using CuSO$_4$/sodium ascorbate/ethanol/water mixtures. Chaikof and co-workers [91b] have used silicon substrates and an additional, reversible Diels-Alder linker, able to be cleaved reversibly by thermal activation. In both cases, the ligand attachment was proven by antibody binding onto the carbohydrate moieties by surface plasmon resonance (SPR), which provides an important platform for the development of sensor-based detection and screening systems.

Two recent examples have combined the microcontact-printing of Au SAMs with the click reaction. One example has been mentioned already in the above polymer section, and relies on terminal acetylenes in poly[[4-(ethynyl-p-xylylene)-co-(p-xylylene)] as shown in Scheme 28. [58] The polymer was prepared as a thin film by CVD of
ethynyl[2,2]paracyclophane, which resulted in an \( \approx 50 \) nm thick film. Conventional microcontact printing supplied CuSO\(_4\) to specific regions of the polymer film, to result in a local click reaction between an \( \alpha \)-azido-biotin and the sidechain acetylenic moieties of the polymer. A similar example on silicon dioxide surfaces has been demonstrated by Reinhoudt and co-workers.\(^{[92a]}\) As shown in Scheme 48, the initial SAM of the \( \alpha \)-bromo-siloxane monolayer \( 115 \) was reacted with sodium azide in DMF at 70 °C, furnishing the azido-modified SAM, similar to the work reported by Lummerstorfer and Hoffmann.\(^{[89]}\) A silicon stamp (bearing line features, immersed with \( 5 \times 10^{-3} \) M octadec-1-yne) was then applied directly to the wafer \( 116 \) for 15 min at room temperature with a load of 35 g \textit{without the use of a copper catalyst}. As judged by AFM (by detecting the height differences as a result of the applied alkyne) as well as by XPS (by relating the intensities of the C 1s peak versus the N 1s peak), the attachment of the alkyne to yield surface \( 117 \) was proven. This, therefore, represents the first example of a low temperature, very fast attachment reaction without coupling reactions. Moreover, it demonstrates that the azide/alkyne click reaction is working at moderate reaction temperatures simply as a result of the close proximity of the azide and alkyne reactive functionality. An important example of a click reaction mediated by an AFM tip has been reported by Bunz and co-workers.\(^{[92b]}\) Most importantly, the reaction between a bivalent dialkyne derivative and a bivalent diazide has been accomplished by heating a specific region of a film by action of an AFM tip to \( \approx 250 \) °C, thus inducing the formation of conjugated fluorescent polymers within a lithographic process.

The direct, non-oxidative modification of pure Si(1,1,1)-surfaces by click reactions has been achieved by Heath and co-workers.\(^{[93a]}\) Thus a Si surface that presented terminal acetylenes was prepared by a short reaction sequence featuring PCl\(_5\) activation (to yield a chloro-functional surface) and a subsequent nucleophilic displacement.
reaction by sodium acetylide, to result in the surface 118 (see Scheme 49). The click reaction [Cu^II/ascorbate/DMF/12 h] in turn enabled the attachment of electroactive benzoquinones 119 to yield surfaces 120. The benzoquinones could be cleaved off electrochemically, to enable the subsequent derivatization of the so-obtained amino-functionalized surfaces with other ligands (e.g., ferrocenes). Another report[^94] on the modification of porous silicon started from a Si-H surface and a subsequent attachment of 1-vinylhept-6-yne, which in turn enabled the click reaction of various biologically important molecules. Both methods open an interesting pathway to functionalize silicon wafers in their native, pure silicon state. Using layer-by-layer (LbL) deposition, Caruso and co-workers[^93b] have reported a similar example to sequentially deposit sidechain-modified acetylenic and azido-modified polymers onto a surface, by ‘clicking’ them under formation of the triazole bridge.

Certainly, there is only a small difference between planar surfaces and curved surfaces, putting nanoparticles, as well as vesicles and other, related colloidal structures in the limelight of the click-based derivatization process. Two recent examples have demonstrated the versatility of the click reaction on nanoparticles (NPs), namely on Au NPs[^95] as well as on CdSe NPs and polyhedral oligomeric silsesquioxanes (POSS).[^96] The transformation of the conventional Au monolayer chemistry to those of NPs is demonstrated in Scheme 50. Thus a conventional ω-azido-alkyl ligand is generated on Au NPs (diameter ≈2.0 nm) by a nucleophilic displacement reaction (bromo-methyl/azidomethyl exchange) and
Scheme 39.

Scheme 40.
subsequent click reaction with acyl-activated acetylene ligands 121. The surface attachment was proven by IR spectroscopy as well as by cyclic voltammetry.

Click reactions on micelles and vesicles (liposomes) constitute another issue, addressed recently by several authors. The derivatization of both systems in an easy, room temperature-controlled process with (biorelated) ligands is important, mainly because of their dynamic properties, which prevents reactions at higher temperatures. Hawker and co-workers 97 have reported on the modification of block-copolymeric micelles (BCP micelles) by use of the click reaction. A diblock copolymer consisting of a hydrophilic shell and a hydrophobic, PS interior was prepared by NMP. After micelle formation, the outer, carboxylic acid moieties were reacted with either propargylamine or 3-azido-propylamine to yield the corresponding alkyne- or azide-modified BCP micelles. The derivatization process was subsequently performed on these micelles to yield the correspondingly modified BCP micellar surfaces.

Vesicular bilayers represent another surface whose derivatization is important. Two different examples have been described, both retaining the (usually fragile) structure of the vesicles. Schuber and co-workers 98 have used small unilamellar vesicles (SUVs), composed of dipalmitoyl phosphatidyl choline (DPPC), dipalmitoyl phosphatidyl glycerol (DPPG), and cholesterol (Scheme 51) with an outer shell of terminal acetylenes, achieved by incorporation of the unnatural lipid 125 in amounts of 10 mol-%. Using the classical click conditions, carbohydrate-bearing substrates (e.g., 122) were coupled to the SUV’s surface with the Cu(I)/SO₄/sodium ascorbate couple at a pH of 6.5. Despite an ~50-fold increase in diameter of the derivatized vesicles 124 in size during the coupling reaction, no leakage of the liposomes was observed, proving the mildness of the reaction without disturbance of the bilayer membrane. The other example has been reported by Kros and co-workers 99a using a dioleoylphosphatidyl ethanolamine (DOPE)-modified lipid 126 with an acetylenic head group (see Scheme 52). Fluorescence resonance energy transfer (FRET) methods were used to prove the attachment of ligand 128 by CuBr-catalysis onto the surface of the liposome, which enabled the transfer of energy between the attached dye and another dye incorporated.
### Table 2. Overview of click reactions on surfaces.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Surface/type</th>
<th>Chemical structure on surface</th>
<th>Investigated catalytic systems</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SAM on Au/planar</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>( \text{CuSO}_4\cdot\text{H}_2\text{O}/\text{sodium ascorbate/H}_2\text{O/EtOH} )</td>
<td>[84]</td>
</tr>
<tr>
<td>2</td>
<td>SAM on SiO(_2)/planar</td>
<td>( \overset{\cdots}{-(CH_2)_4-N} )</td>
<td>thermal/70 °C/neat</td>
<td>[89]</td>
</tr>
<tr>
<td>3</td>
<td>SAM on Au/planar</td>
<td>( \overset{\cdots}{-(CH_2)_n-(OCH_2CH_2)_nO} )</td>
<td>( \text{CuSO}_4\cdot\text{H}_2\text{O/sodium ascorbate/H}_2\text{O/EtOH} )</td>
<td>[88]</td>
</tr>
<tr>
<td>4</td>
<td>SAM on Au/planar</td>
<td>( \overset{\cdots}{-(CH_2)_4-N} )</td>
<td>( \text{CuSO}_4\cdot\text{H}_2\text{O/sodium ascorbate and (Ph}_3\text{Cu(I)Br/H}_2\text{O/EtOH} )</td>
<td>[90]</td>
</tr>
<tr>
<td>5</td>
<td>SAM on Au/planar</td>
<td>( \overset{\cdots}{-(CH_2)_n-16-N} )</td>
<td>( \text{CuSO}_4\cdot\text{H}_2\text{O/sodium ascorbate/H}_2\text{O/EtOH and DMSO/H}_2\text{O} )</td>
<td>[85]</td>
</tr>
<tr>
<td>6</td>
<td>SAM on SiO(_2)/planar</td>
<td>( \overset{\cdots}{-(CH_2)_4-N} )</td>
<td>no catalyst/r.t./µ-contact printing</td>
<td>[92a]</td>
</tr>
<tr>
<td>7</td>
<td>Si(111) surface/planar</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>( \text{CuSO}_4/\text{sodium ascorbate/DMF/r.t.} )</td>
<td>[93a]</td>
</tr>
<tr>
<td>8</td>
<td>layer by layer (LbL) film of polymer</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>( \text{CuSO}_4/\text{sodium ascorbate/pH = 3.5} )</td>
<td>[93b]</td>
</tr>
<tr>
<td>9</td>
<td>SAM on Au/planar</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>TBTA CuBF(_4/\text{hydroquinone/DMSO/H}_2\text{O} )</td>
<td>[87]</td>
</tr>
<tr>
<td>10</td>
<td>porous Si</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>CuSO(_4/\text{ascorbic acid, MeCN/tris-buffer/pH = 8.0, r.t.} )</td>
<td>[94]</td>
</tr>
<tr>
<td>11</td>
<td>SAM on Au/planar</td>
<td>( \overset{\cdots}{-(CH_2)_n-\text{NH}} )</td>
<td>CuSO(_4/\text{sodium ascorbate/H}_2\text{O/EtOH} )</td>
<td>[91a]</td>
</tr>
<tr>
<td>12</td>
<td>SAM on glass</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>CuSO(_4\cdot\text{H}_2\text{O, TBTA,TCEP/PBS-buffer/t-BuOH, 4 °C} )</td>
<td>[91b]</td>
</tr>
<tr>
<td>13</td>
<td>SAM on Au NPs 1.8 ± 0.4 nm</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>dioxane/hexane/r.t.</td>
<td>[95]</td>
</tr>
<tr>
<td>14</td>
<td>crosslinked BCP micelle by NMP</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>CuSO(_4\cdot\text{H}_2\text{O/sodium ascorbate/H}_2\text{O} )</td>
<td>[97]</td>
</tr>
<tr>
<td>15</td>
<td>SUV 90–130 nm</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>CuSO(_4/\text{sodium ascorbate/HEPES-buffer/pH = 6.5} )</td>
<td>[98]</td>
</tr>
<tr>
<td>16</td>
<td>SUV 110–120 nm</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>CuBr/H(_2\text{O} )</td>
<td>[99]</td>
</tr>
<tr>
<td>17</td>
<td>CdSe NP</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>CuBr</td>
<td>[96]</td>
</tr>
<tr>
<td>18</td>
<td>polymer layer</td>
<td>( \overset{\cdots}{-(CH_2)_n-N} )</td>
<td>AFM-tip/225 °C</td>
<td>[92b]</td>
</tr>
</tbody>
</table>
into the membrane itself. Both examples demonstrate that liposome surfaces in future may be broadly derivatized using this method, moreover allowing the exclusive modification of the outer side of the liposomal surface.

Another important development concerns the attachment of ligands for the subsequent solid phase synthesis of peptides and their corresponding ligation products with carbohydrate ligands. Thus Meldal and co-workers\[5\] have attached a variety of ligands onto resins modified with acetylenic ligands. A hydroxymethylbenzoic acid (HMBA)-modified poly(ethylene glycol acrylamide) (PEGA$_{800}$) resin was modified with a peptidic anchor bearing a terminal propargylglycine moiety. Subsequently a large variety of azides (e.g., 2-deoxy-2-azido carbohydrates, α-azido acids\[100\], adamantane, and carboxylic acids\[100\]) were coupled to the resin in yields $>95\%$. The chemistry was shown to be compatible with conventional amino acid protecting groups. In addition, a high 1,4-regioselectivity was observed on using the Cu$^\text{i}$ catalyst. A related concept has been developed by Gmeiner and co-workers\[101\] starting from a conventional Merrifield resin [(chloro-methyl)styrene] treated with sodium azide, thus furnish-
ing the azido-functionalized resin. This was linked to several formyl-aryloxypropynes to generate the corresponding 1,2,3-triazoles in more than 95% yield using CuII/DIPEA in THF at 35 °C. This allows a traceless-linker approach to generate fixed amide libraries, which can be cleaved from the resin using trifluoroacetic acid (TFA). This opens a new approach to traceless linkers onto Merrifield resins and demonstrates the high efficiency of the click chemistry approach. A related approach for the generation of linkers sensitive to conditions employed under MALDI measurements was developed by Finn and co-workers,[102] which relied on a combination of cycloreversion processes and click reactions.

An interesting application of 1,3-dipolar cycloaddition reactions has been demonstrated using carbon nanotubes and C60.[103] As discovered recently, the use of highly reactive dipolarophiles (such as azomethine ylides,[104] nitrile imines,[105] and nitrile oxides[106]) leads to cycloaddition reactions onto the surface of single-walled carbon nanotubes (SWCNTs).[107] However, slow reactions are often observed, which lead to reaction times in the range of several days. Therefore, the use of the azide/alkyne click reaction has been applied to fix a telechelic PS polymer by a grafting-to approach onto the surface of SWCNTs (see Scheme 53).[108] Since a direct, thermally induced reaction between the azide and the extended π-system of the SWCNT by nitrene-mediated addition is to be avoided, the CuI-mediated process was investigated, using an azido-telechelic PS polymer (prepared by ATRP according to previously mentioned methods). SWCNTs functionalized with terminal acetylenic moieties (prepared by a solvent free method that employed a diazotation reaction) were reacted with the azido-telechelic PS[129] (Mn = 2 010 to 8 620 g · mol⁻¹ with Mn/Mw = 1.09 to 1.13) by use of the CuBr/bipyridine system. As demonstrated extensively by solubility changes and thermogravimetric analysis, a significant attachment of the PS polymer was achieved. The structural integrity of the SWCNTs was also proven by Raman spectroscopy to reveal the absence of thermally induced nitrene reactions. In comparison to SWCNTs prepared by the nitrene-insertion methods, enhanced solubility as a result of the absence of the highly reactive nitrene moieties (which leads to additional, non-selective crosslinking) was observed.

To summarize, the click reaction works excellently on planar (two-dimensional) as well as on crosslinked three-dimensional (resin-type) surfaces, to furnish an efficient...
Scheme 46.

Scheme 47.
and general approach for their functionalization. A large number of surfaces, however, have not been investigated up to now, thus leaving an ample field for further investigations on the versatility of this reaction.

Click Reactions onto Biomolecules, Cells, and Viruses

Certainly the click reaction is particularly apt for the ligation of artificial ligands onto biomolecules, since this reaction is especially useful to work under conditions in which the structural integrity of peptides, proteins, carbohydrates, and assemblies derived there from is preserved. Thus besides conventional linking methods (e.g., disulfide exchange, amide linkage, reductive aminations, Staudinger-type ligations), this method definitely is an important contribution for biological labeling. Recent reviews deal with this topic therefore, the focus here is on new literature. One of the first examples to demonstrate the practicability of the azide/alkyne click reaction was provided by Meldal and co-workers who used the click reaction on peptides during solid-phase synthesis. Based upon this knowledge, Ghadiri and co-workers used the click reaction to generate cyclic peptides.

The purely thermal 2,3-thermal Huisgen reaction was used by Ju and co-workers to link rhodamine dyes to the end of oligonucleotides. The starting oligonucleotides displayed a terminal amino group, which in turn could be subjected to the thermal dipolar cycloaddition process at 80°C with an acetylene-modified rhodamine dye. An impressive example of the completeness and versatility of the azide/alkyne click reaction has been presented by Finn and co-workers upon modifying all sixty positions of the tobacco mosaic virus. After the generation of a virus-derivative displaying sixty azido, or acetylenic bonds, the final coupling with a rhodamine B dye yields the attachment of sixty moieties onto the surface of the labeled virus. The catalyst system used was based on CuSO4/tris(carboxyethyl) phosphine (TCEP)/catalyst/CuO. Both systems yielded an attachment efficiency of 100% in a solvent system based on phosphate buffer (plus 5% t-butyl alcohol) at a pH of 8.0.

The bio-labeling in living systems was demonstrated by Tirell and co-workers by incorporating the unnatural amino-acids azido-alanine, azidohomoalanine, azidonorvaline, and azidonorleucine into living cells. Reporting and quantification of the incorporation was subsequently done by ‘clicking’ an acetylene-modified biotin ligand onto the surface of the E-coli bacteria, which displayed the azido moieties. Ultrapure CuBr (purity 99.999%) was found to be superior in catalyzing the click reaction. A related approach to the use of activity based protein profiling (ABPP) has been reported by Cravatt and co-workers, which relied on ABPP as a chemical proteomic method, which employs active site-directed probes to simultaneously visualize the changes in activity of proteins in a cellular environment. To summarize, the combination of azide/alkyne click chemistry demonstrates a new approach to the profiling of enzymatic active sites as well as the search for new binding structures onto active protein sites. Clearly, an absolutely randomized approach (without knowledge of the enzyme’s active site) as well as an at least partially directed
Scheme 51.

Scheme 52.
approach is viable, to screen dynamic combinatorial libraries. Therefore, this method points to the future for studying associative phenomena, possibly also in supramolecular chemistry and materials science.

Conclusion and Outlook

During the past several years, click reactions have already demonstrated their efficiency and use in material chemistry and science, in particular in the field of polymer science. A plethora of chemists, tired of the extensive use of protecting-group strategies and insufficient reaction progress, have been searching for click-type reactions for decades. Now, with the advent of the azide/alkyne-1,3-dipolar cycloaddition click reaction, at least a visible step in this direction has been achieved, which explains the enormous impact this reaction has already had in its infancy. With respect to polymeric substrates, the reaction definitely speeds up the use of polymers with defined functional ligands, positioned either in the main chain or the respective sidechains. Most importantly, control of ligand density within polymers and surfaces is accessible by this simple method, which enables the study of molecular recognition in more detail. Certainly, new and other click-type reactions will emerge in the future, placing strong, hands-on chemical tools in the hands of the preparative material scientist, with the prospect to build matter in a brick-type fashion by simple chemical reactions.

Keywords: carbon nanotubes; ‘click’-reaction; 1,3-dipolar cycloaddition; dendrimers; polymers; surfaces


