Chemistry of Organo-Hybrids: Synthesis and Characterization of Functional Nano-Objects

ARTICLE *in* MACROMOLECULAR RAPID COMMUNICATIONS · MAY 2013

Impact Factor: 4.94 · DOI: 10.1002/marc.201300017 · Source: PubMed

4 AUTHORS, INCLUDING:

Anja S Goldmann
Karlsruhe Institute of Technology
36 PUBLICATIONS **829** CITATIONS
SEE PROFILE

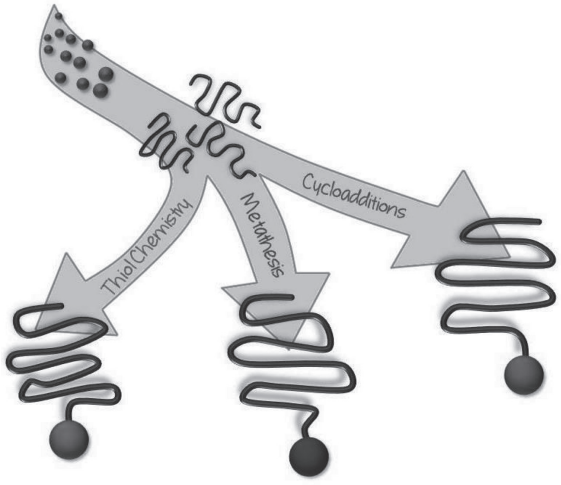
Mathias Glassner
Ghent University
26 PUBLICATIONS **352** CITATIONS
SEE PROFILE

Post-Functionalization of Polymers via Orthogonal Ligation Chemistry

Anja S. Goldmann,* Mathias Glassner, Andrew J. Inglis, Christopher Barner-Kowollik*

This article is adapted from a chapter appearing in "Chemistry of Organo-Hybrids: Synthesis and Characterization of Functional Nano-Objects" (Eds: E. Lacôte, B. Charleux, C. Copéret), Wiley-VCH, 2013

The establishment of advanced living/controlled polymerization protocols allows for engineering synthetic polymers in a precise fashion. Combining advanced living/controlled polymerization techniques with highly efficient coupling chemistries facilitates quantitative, modular, and orthogonal functionalization of synthetic polymer strands at their chain termini as well as side-chain functionalization. The review highlights the current status of selected post-functionalization techniques of polymers via orthogonal ligation chemistries, major characteristics of the specific transformation chemistry, as well as the characterization of the products.



1. Introduction

The modification of synthetic polymer strands at their chain termini after the completion of the polymerization is, in many cases, the prerequisite for their use in a wide variety of advanced applications as well as for their employment in subsequent modular construction efforts. The firm establishment of advanced living/controlled polymerization protocols allows for the generation of extremely well-defined polymer architectures from a wide monomer range under mild conditions. These protocols form the basis for the subsequent polymer modification.

While several excellent reviews have appeared in the field of polymer (end group) modification—often addressing the end-group modification possibilities associated with a specific polymerization protocol[1–5]—we provide herein a true user's guide to polymer post-modification. To achieve a highly accessible review article, we collated the key information regarding the synthetic process, the reaction conditions required as well as characterization data that evidence a successful transformation in an encompassing tabular format. The accompanying text briefly highlights the major characteristics of the specific transformation chemistry as well as some additional background information. Many of the chemistries collated in the tables have been tested

Dr. A. S. Goldmann, Dr. M. Glassner, Dr. A. J. Inglis, Prof. C. Barner-Kowollik
Preparative Macromolecular Chemistry, Institut für Technische Chemie und Polymerchemie, Karlsruhe Institute of Technology (KIT), Engesserstraße 18, 76131 Karlsruhe, Germany
E-mail: anja.goldmann@kit.edu; christopher.barner-kowollik@kit.edu

DOI: 10.1002/marc.201300017

in our laboratories, while others were selected for their transformational power. The selection presented in the present review article is a critical one, implying that not every possible transformation is listed, but only those which we have judged to be most useful in a synthetic context, i.e., feature high conversions, mild conditions, and readily removable by-products. The astute reader will notice that we make only sparing use of the term "click chemistry,"[6,7] based on the fact that many of the presented transformations can, under specific conditions, fulfill click criteria, yet only a very few reaction types fulfill these criteria consistently. In terms of the chemical scope, we have focused on cycloaddition reactions, thiol-based chemistry, metathesis reactions, i.e., ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis (ADMET), oxime transformations as well as Pd-catalyzed coupling reactions.

2. Cycloaddition Reactions

Post-polymerization modifications of synthetic polymers demand efficient processes, i.e., reactions that reach high conversions under mild conditions tolerating a wide range of functional groups. Cycloaddition reactions thus represent an attractive class of reactions for this purpose. In particular, some 1,3-dipolar and Diels–Alder cycloadditions can fulfill the stringent requirements for post-polymerization modifications. Only few examples exist for [2+2] cycloadditions, e.g. Conradi and Junkers[8] reported polymer end-group modifications via photo-induced [2 + 2] Paterno–Büchi reactions of aldehyde end groups with various alkenes. However, nearly all cycloadditions that have been employed for post-polymerization modifications belong to the class of 1,3-dipolar or Diels–Alder cycloadditions. The following section will provide an overview of these reactions that can be used for post-polymerization functionalizations. Details concerning the individual reactions are outlined in Tables 1 and 2.

2.1. 1,3-Dipolar Cycloadditions

2.1.1. Overview

The extensive investigations of cycloaddition reactions between 1,3-dipoles and dipolarophiles by Huisgen[32,33] in the 1960s have laid the foundation for the development of such reactions into a universal method for the synthesis of five-membered heterocycles.[34] The high efficiency that is inherent to some of these reactions renders them powerful tools for the post-functionalization of polymers. The most widely used 1,3-dipolar cycloadditions in polymer chemistry (Scheme 1) that will be discussed within the present section are the:

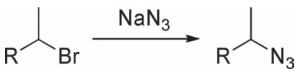
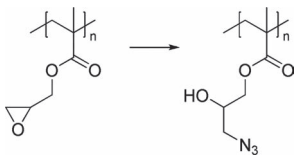
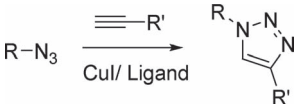
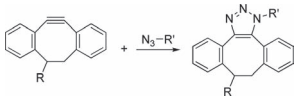
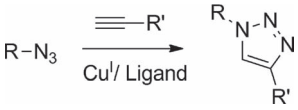
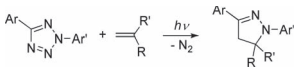
Anja S. Goldmann studied Polymer- and Colloid Chemistry at the University of Bayreuth and completed her Ph.D. in 2010 under the supervision of Prof. Axel H. E. Müller (University of Bayreuth). Her research projects during her Ph.D. thesis focused on click chemistry and its application in complex macromolecular architecture and surface modification. Since 2010, Dr. Goldmann is the research manager in the Barner-Kowollik team at the Karlsruhe Institute of Technology (KIT). Her research interests include novel efficient ligation techniques, synthetic approaches to complex macromolecular designs, functional polymers, synthetic biomimetic molecules, and the application of those to (bio)surface modification, particle modification, and material science.

Mathias Glassner studied chemistry at the University of Karlsruhe and completed his Ph.D. thesis under the supervision of Prof. Barner-Kowollik at the Karlsruhe Institute of Technology (KIT) in 2012. His dissertation research focused on modular Diels-Alder conjugations for the design of polymer architectures and materials. His research interests include controlled/living polymerizations, functional polymers, mild modular conjugation protocols, reversible Diels-Alder systems, light-triggered ligation techniques, and surface modifications. Mathias is currently a postdoc in the group of Prof. Richard Hoogenboom at Ghent University.

Andrew J. Inglis studied engineering at the University of New South Wales, specializing in industrial chemistry. He has almost 2 years experience working in the chemical industry in Australia and received the University Medal upon completion of his undergraduate studies. He attained his Ph.D. with *summa cum laude* at the Karlsruhe Institute of Technology (KIT) under the supervision of Prof. Christopher Barner-Kowollik in 2010. Andrew is currently studying medicine and surgery at the University of Sydney. His research interests include the application of novel macromolecular and synthetic chemistry technologies to the biomedical and surgical sciences.

Christopher Barner-Kowollik completed a Ph.D. in Physical Chemistry at the University of Göttingen, before joining the Center for Advanced Macromolecular Design at the University of New South Wales, where he led a research team as a full professor, after holding ranks from research associate to associate professor. He is currently a full professor of macromolecular chemistry at the Karlsruhe Institute of Technology (KIT). His main research interests range from the synthesis of complex macromolecular systems, their applications and material properties, the design of nano- and microstructured biofunctional surfaces, the development of novel (light triggered) and bioorthogonal pericyclic conjugation chemistries, the development of polymer and surface conjugation as well as polymerization protocols, mass spectrometry on polymer systems coupled with chromatographic techniques, to polymer reaction kinetics.

Table 1. Synthesis of azide - functionalized polymers and 1,3-dipolar cycloaddition reactions.

Transformation	Reaction conditions[a)]	User notes	Ref.	Characterization
	N_3:Br 5:1 DMF, RT, overnight	Incompatible with other leaving groups that can be substituted by N_3	[1]	^{1}H NMR: Disappearance of the signal according to C*H*Br (≈4 – 5 ppm), appearance of the signal according to C*H*N_3 (≈ 3 – 4 ppm) ESI-/MALDI-MS: shift in *m/z* value and change of the isotopic pattern
	Epoxide:N_3:NH_4Cl 1:3:3 DMF, 50 °C, 26 h		[9]	^{1}H NMR: Disappearance of signal according to the epoxide (≈ 4.4 and 3.9 ppm (two protons from CO_2CH_2), 3.2 ppm (C*H*-O from the epoxide ring), and 2.8 and 2.7 ppm (CH_2-O from the ring). Appearance of new signals ≈ 3.9 – 4.2 ppm (CO_2CH_2 and C*H*OH) and 3.6 and 3.4 ppm (CH_2N_3) IR: Appearance of azide vibration (≈2100 cm^{-1})
	Typical: N_3:Alkyne 1:1 Cu^I/Ligand/DMF or $CuSO_4 \cdot 5H_2O$/sodium ascorbate/H_2O, 2 – 24 h at RT	Numerous conditions are described in the literature. For a detailed collection of various reaction conditions, see ref. [10].	[10–13]	^{1}H NMR: Disappearance of the signals associated with the terminal alkyne and C*H*N_3. Appearance of signals associated with the triazole. ESI-/MALDI-MS: shift in *m/z* value. IR: Disappearance of alkyne (≈3300 cm^{-1}) and azide (≈2090 cm^{-1}) vibrations
	N_3:Alkyne 1:1. 3 h at RT		[14–16]	As above for the CuAAC
	Oxime:Alkyne 50:1. Alkyne/oxime/aq. $NaHCO_3$/EtOH/chloramine-T. 16 h at RT or i) oxime/CH_2Cl_2/pyridine/*N*-chlorosuccinimide; 1 h at RT ii) alkyne/NEt_3 16 h at RT	Nitrile oxide is generated in situ from oxime precursor via hydroxyimidoyl chloride intermediate	[17,69]	^{1}H NMR: Disappearance of the signals associated with the terminal alkyne. Appearance of signals associated with the isoxazole moiety (4-H ring proton at ≈6.50 ppm)
	Tetrazole:Alkene 1:1. 25 min UV irradiation at RT	A hand-held 302 nm or 254 nm UV lamp is used as a light source	[18,19]	^{1}H NMR: Appearance of signals associated with the pyrazoline cycloadduct. ESI-/MALDI-MS: as above. Fluorescence spectroscopy: Variable emissions of the pyrazoline product in the region of 487–538 nm, depending on the structure of the dipolarophile

[a)]The stoichiometry closest to equimolar ratios described in the literature is given, even if there are examples where an excess of small molecules towards polymer end/side groups was employed.

- copper-catalyzed azide-alkyne cycloaddition (CuAAC)
- strain-promoted azide-alkyne cycloaddition (SPAAC)
- nitrile oxide-alkyne cycloaddition (NOAC)
- nitrile imine-mediated tetrazole-ene cycloaddition (NITEC)

2.2. Azide–Alkyne Cycloadditions (CuAAC and SPAAC)

The formation of substituted 1,2,3-triazoles by thermally induced cycloadditions of organic azides and alkynes was first reported by Michael in 1893.[35] In the absence of a

Table 2. Diels – Alder cycloaddition reactions and synthesis of Cp-functionalized polymers.

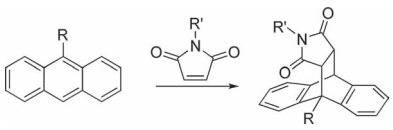
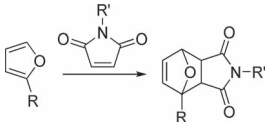
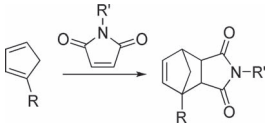
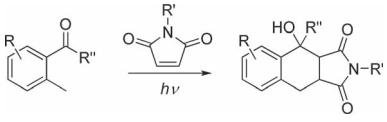
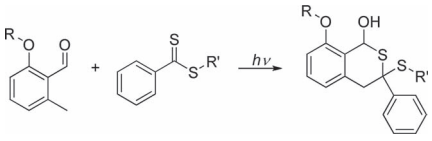
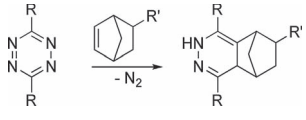
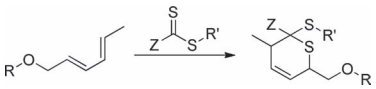
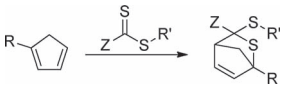
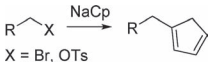
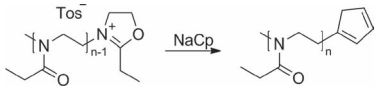
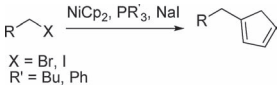
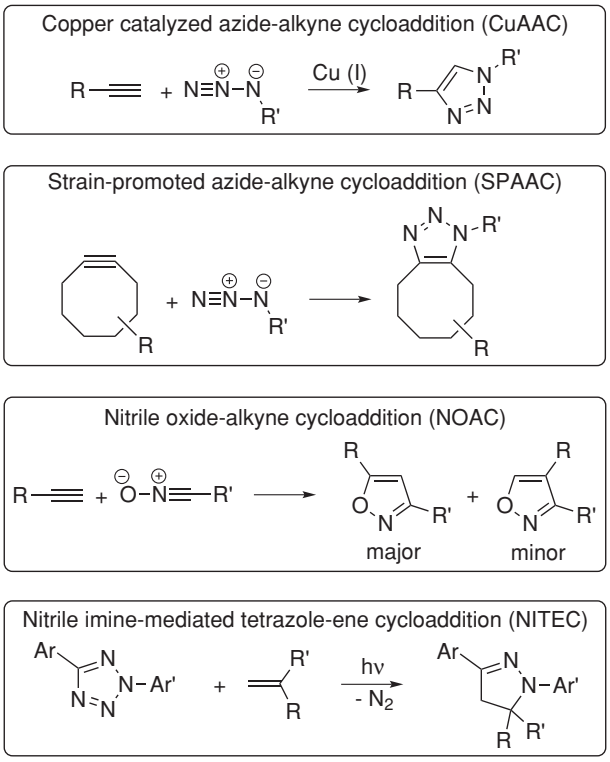
Transformation	Reaction conditions[a)]	User notes	Ref.	Characterization
	Anthracene:Maleimide 1:1. 36 – 48 h at 110 – 120 °C	Often in situ deprotection of furan - protected maleimide precursors. Incompatible with other groups that are reactive towards maleimides, e.g., thiols	[20]	^{1}H NMR: Disappearance of the signals associated with anthracene. Appearance of signals associated with the cycloadduct. ESI-/MALDI-MS: as above. UV–Vis: Disappearance of the absorbance corresponding to the anthracene moiety (five-finger absorbance from 300 to 400 nm)
	Furan:Maleimide 1:1. 25–120 °C	Reaction is thermally reversible. Incompatible with other groups that are reactive towards maleimides, e.g., thiols.	[21]	^{1}H NMR: Disappearance of the signals associated with furan and maleimide moieties. Appearance of signals associated with the cycloadduct. ESI-/MALDI-MS: as above
	Maleimide:Cp 1:1. 1 h at RT	Reaction is thermally reversible. Incompatible with other groups that are reactive towards maleimides, e.g., thiols	[22]	^{1}H NMR: Disappearance of the signals associated with Cp and maleimide moieties. Appearance of signals associated with the cycloadduct. ESI-/MALDI-MS: as above
	Photoenol-precursor:Maleimide 1:1. 15 min – 2 h UV irradiation (λ_{max} = 320 nm) at RT. Degassed solution	Incompatible with other groups that are reactive towards maleimides, e.g., thiols.	[23,24]	^{1}H NMR: Disappearance of the signals associated with maleimide and the photoenol precursor. Appearance of signals associated with the cycloadduct. ESI-/MALDI-MS: as above
	Photoenol precursor: Dithioester 1:1. 10 min UV irradiation (λ_{max} = 320 nm) at RT. Degassed solution	The deoxygenation method has an influence on the overall kinetics. The execution of three freeze–pump–thaw cycles yielded faster reactions than those after deoxygenation by nitrogen bubbling	[25]	^{1}H NMR: Disappearance of the signals associated with the dithioester and the photoenol-precursor. Appearance of signals associated with the cycloadduct. ESI-/MALDI-MS: as above. UV/Vis: Disappearance of the absorbance corresponding to the C = S moiety. ($\pi \rightarrow \pi^*$: ~300 nm, $n \rightarrow \pi^*$: ~510 nm).
	Tetrazine:Norbornene 1:1. 2 – 12 h at RT		[26]	^{1}H NMR: Disappearance of the norbornenyl signals. Appearance of signals associated with the cycloadduct. ESI-/MALDI-MS: as above. UV/Vis: Disappearance of the absorbance corresponding to the tetrazine moiety (≈546 nm).

Table 2. Continued

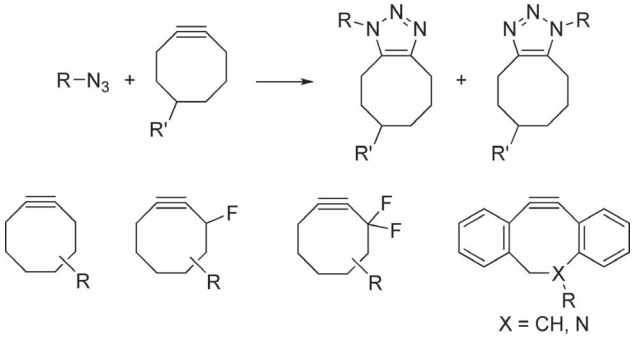
Transformation	Reaction conditions[a)]	User notes	Ref.	Characterization
	Diene:Dithioester 1:1. 24 h at 50 °C in $CHCl_3$ + $ZnCl_2$ for Z = $P(O)(OEt)_2$ or TFA for Z = py. For Z = $P(O)(OEt)_2$: 4 h at RT in H_2O	A mixture of stereo/regio-isomers is generated.	[27,28]	^1H NMR: Disappearance of the diene signals. Appearance of signals associated with vinylic protons of the cycloadduct. ESI-/MALDI-MS: as above. UV/Vis: Disappearance of the absorbance corresponding to the C = S moiety ($\pi \rightarrow \pi^*$: ~ 325 nm, $n \rightarrow \pi^*$: ~525 nm)
	Diene:Dithioester 1:1. 10 min at RT in $CHCl_3$ (+TFA for Z = py) or H_2O (+ HCl for Z = py).	Reaction is thermally reversible at $T > 90$°C. A mixture of stereo/regio-isomers is generated.	[28,29]	As for previous entry
	X:NaCp 1:3. THF, 0°C→RT overnight, degassed solution	Works for PEG and PS. Incompatible with esters. A mixture of the 1- and 2-isomer is generated	[29]	^1H NMR: Appearance of signals associated with the Cp group (vinylic ≈ 5.9- 6.7, bridge head ≈ 2.9 ppm). ESI-/MALDI-MS: shift in *m/z* value and change of the isotopic pattern for X = Br
	Oxazoline$^+$:NaCp 1:3. 0 °C→RT overnight, degassed solution	One-pot synthesis. NaCp acts as termination agent. A mixture of the 1- and 2-isomer is generated	[22]	^1H NMR: Appearance of signals associated with the Cp group (vinylic ≈ 5.9-6.7, bridge head ≈ 2.9 ppm). ESI-/MALDI-MS: as above
	X:Cp:PR_3:NaI 1:4:2:6 (R = Bu, Ph). No NaI required for X = I. THF, RT overnight, degassed solution. Toluene/THF, 90 °C, 4 h for polyethylene	Compatible with a wide range of monomers such as (meth)acrylates and acrylamides. A mixture of the 1- and 2-isomer is generated	[30,31]	^1H NMR: Appearance of signals associated with the Cp group (vinylic ≈ 5.9-6.7, bridge head ≈ 2.9 ppm). ESI-/MALDI-MS: shift in *m/z* value and change of the isotopic pattern

[a)]The stoichometry closest to equimolar ratios described in the literature is given, even if there are examples where an excess of small molecules towards polymer end/side groups was employed. TFA = trifluoroacetic acid, py = 2-pyridine.

catalyst, the reaction requires elevated temperatures and produces a mixture of 1,4- and 1,5-regioisomers. A drastic enhancement of the reaction rate and regioselectivity towards the 1,4-substituted ring by Cu(I) catalysis was described in 2002 by the groups of Meldal[36] and Sharpless.[37] Since then the CuAAC reaction has rapidly evolved into one of the most popular reactions within the concept of click chemistry.[7,38] The enormous impact of the click idea on polymer and materials science[3–4,39,40] turned the CuAAC reaction into an ubiquitous strategy in this research area.[10–13] The use of CuAAC reactions requires the synthesis of alkyne and azide functional polymers. A general strategy is the utilization of functional initiators or transfer agents.[41] The most common method for the generation of azide functional macromolecules is the substitution of a leaving group, e.g., a halogen from atom transfer radical polymerization (ATRP) with an azide.[1,42,43] Quantitative transformation is usually realized by reaction with an excess of NaN_3 in DMF at ambient temperature overnight. An alternative route for the incorporation of azide groups into a polymer is the ring opening of epoxides in poly(glycidyl methacrylate) with NaN_3.[9] The CuAAC has been employed for the construction of virtually any imaginable macromolecular architecture



Scheme 1. 1,3-dipolar cycloadditions that have been employed for the efficient post-functionalization of polymers.



Scheme 2. The SPAAC reaction and cyclooctyne derivatives that have been used for SPAAC reactions.

including end-/side-functional polymers,[44–49] block copolymers,[43,50–53] polymer bioconjugates,[54–57] dendrimers,[58–61] networks,[62–64] step-growth,[65,66] graft,[67–69] cyclic,[70–73] and (miktoarm) star[74–77] polymers (refer to Figure 1).

The toxicity of copper catalysts has resulted in a strong demand for the design of metal-free click reactions for biological applications.[78] Wittig and Krebs reported a catalyst-free cycloaddition of azides with cyclooctyne in 1961.[79] The strain-promoted azide–alkyne cycloaddition (SPAAC) of cyclooctyne derivatives was developed into an efficient tool for bioconjugations by Bertozzi and co-workers.[14–16] The SPAAC reaction of unsubstituted cyclooctyne is considerably slower compared with CuAAC reactions. Therefore, derivatives bearing electron-withdrawing groups, particularly fluorine, have been synthesized to decrease the HOMO–LUMO gap (highest occupied molecular orbital–lowest unoccupied molecular orbital) and consequently enhance the reactivity.[80] An alternative strategy utilized by Boons and co-workers[81] to increase the reaction rate is to impose additional ring strain by the introduction of aromatic rings to either side of the alkyne (Scheme 2).

2.3. Nitrile Oxide–Alkyne Cycloaddition

An alternative strategy to achieve a transition metal catalyst-free 1,3-dipolar cycloaddition is the utilization of dipoles with enhanced reactivity. Nitrile oxides are capable of undergoing a cycloaddition with non-activated alkynes at ambient temperatures thus providing an attractive tool for polymer- and bioconjugation reactions.[82] Heaney and co-workers[17] reported the end-group modification of alkyne-terminated polymers with various small molecule nitrile oxides that were generated in situ from the oxime precursor and chloramine-T as a dipole generating agent

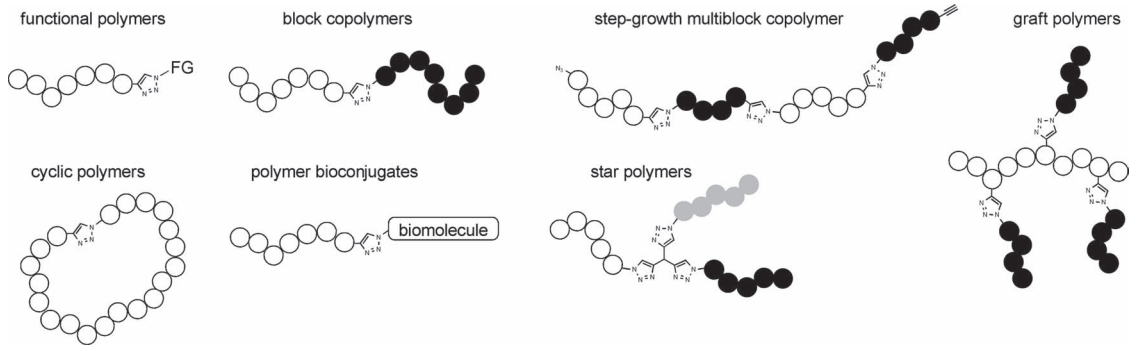
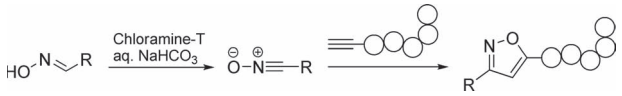


Figure 1. Schematic representations of macromolecular architectures synthesized by CuAAC. FG = functional group.



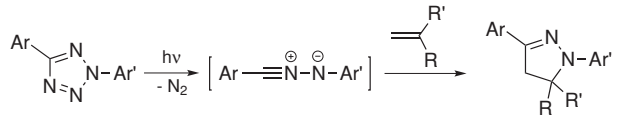
Scheme 3. End-group modification of alkyne-terminated polymers via cycloaddition of nitrile oxides.

(Scheme 3). It was demonstrated in a successive publication that the NOAC reaction is orthogonal to the CuAAC reaction.[83]

2.4. Nitrile Imine-Mediated Tetrazole-Ene Cycloaddition

Upon irradiation with UV light, 2,5-diaryl tetrazoles undergo a rapid cycloreversion releasing nitrogen and yielding the corresponding nitrile imines, which can react with suitable dipolarophiles such as alkenes (Scheme 4).[84]

Lin and co-workers[18] employed the NITEC reaction for the modification of tetrazole functionalized proteins. Polymer–polymer coupling via the NITEC approach was demonstrated by Barner-Kowollik and co-workers[19a] who also demonstrated its ability for (bio)surface functionalization utilizing maleimide-functionalized polymers as the dipolarophile.[19b,85] The fact that the pyrazoline cycloadducts show strong fluorescence facilitates the direct visualization of the reaction success and allows monitoring of the conversion by fluorescence spectroscopy.



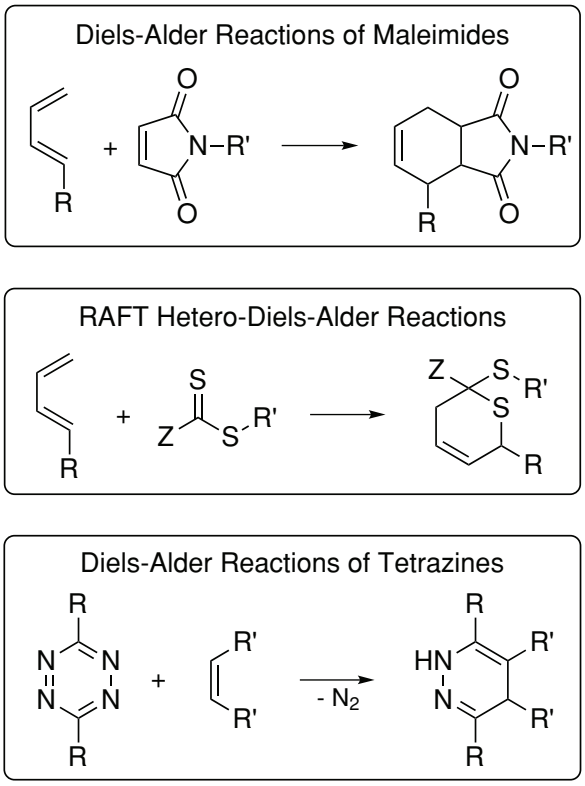
Scheme 4. The photo-induced nitrile imine-mediated tetrazole-ene cycloaddition (NITEC).

2.5. Diels–Alder Reactions

2.5.1. Overview

The discovery of the [4 + 2] cycloaddition between a diene and an ene (the dienophile) by Otto Diels and Kurt Alder[86] was a pioneering result that was honored with the Nobel Prize in 1950. Diels–Alder (DA) reactions belong to the most widely used reactions in organic synthesis.[87–89] The high efficiency of many DA reactions makes them an appropriate tool for polymer post-functionalization. The most common DA reactions in polymer science that that will be discussed within this section are (Scheme 5):

- DA reactions with maleimide as dienophile
- Hetero DA (HDA) reactions of dithioester end groups generated by reversible addition–fragmentation chain transfer (RAFT) polymerization
- Inverse electron-demand DA reactions of tetrazines

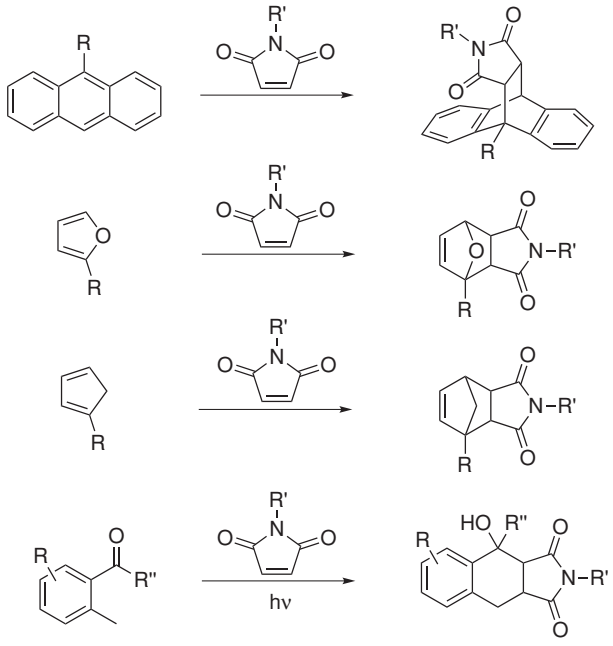


Scheme 5. Generalized representation of Diels–Alder reactions that have been employed for polymer post-functionalization.

2.6. Diels–Alder Reactions Involving Maleimides

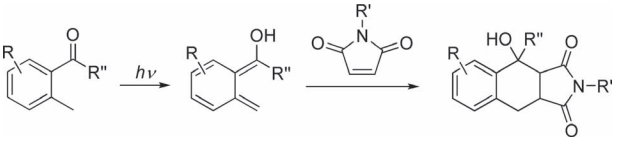
In *normal* DA reactions,[90] an electron-rich diene is reacted with an electron-poor dienophile. Maleimides represent an attractive moiety for this reaction type because of their electron-poor C=C double bond and the possibility to attach various substituents to the nitrogen atom. A range of dienes has been used in polymer and material science for DA conjugations with maleimides including anthracene, furan, cyclopentadiene (Cp), and photo-generated *ortho*-quinodimethanes (photoenols) as shown in Scheme 6.

The DA reaction between maleimides and anthracenes has been successfully employed for polymer end group[91] and backbone functionalization[92,93] as well as for the construction of macromolecular architectures such as block copolymers,[20,94] brush copolymers,[95,96] (miktoarm) stars,[97–100] cyclic,[101] dendronized,[102] and H-shaped[103] polymers. The reaction is typically carried out at elevated temperatures (>110 °C) for an extended time (36–120 h) without a catalyst. In some cases, the maleimide functionality is generated in situ by deprotection of a furan-protected precursor via a retro-DA reaction. The strong UV absorbance of anthracenes can be utilized to monitor the DA reaction via UV/Vis spectroscopy.[20] The temperature-dependent cycloaddition–cycloreversion equilibrium between maleimides and furans[21,104] is



Scheme 6. Examples of Diels–Alder reactions of maleimides in polymer and material science.

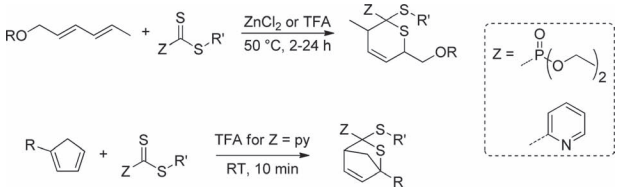
a widely used tool for the synthesis of thermoreversible dendrimers,[105–108] hydrogels,[109–111] networks,[112–118] and self-healing materials.[119–124] An alternative strategy is to utilize cyclopentadienyl groups that are able to react quantitatively with maleimides at ambient temperature.[22,125] Barner-Kowollik and co-workers recently reported the DA trapping of photo-generated *o*-quinodimethane end groups with maleimide-capped polymers (Scheme 7).[23,85] The light-induced reaction was shown to be orthogonal to thermally induced DA reactions.[24]



Scheme 7. UV-light-induced formation of *o*-quinodimethanes and subsequent DA reactions with maleimides.

2.7. RAFT Hetero Diels–Alder Reactions

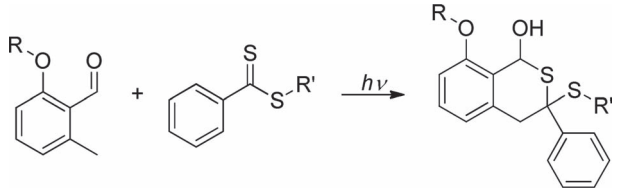
The groups of Barner–Kowollik and Stenzel pioneered the utilization of dithioester-capped polymers that are readily accessible by RAFT polymerization as dienophiles in HDA cycloadditions. Different dithioesters bearing an electron-withdrawing group were identified, which can act as controlling agents in RAFT polymerization and react quantitatively with hexadienoyl-based dienes at 50 °C in the presence of an appropriate catalyst (Scheme 8).[27] The potential



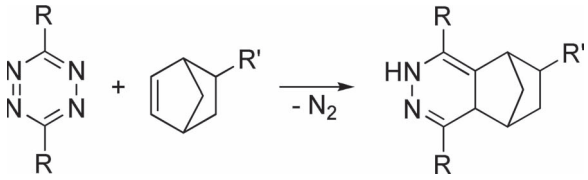
Scheme 8. RAFT–HDA cycloadditions of electron-deficient dithioesters.

of the RAFT–HDA concept was demonstrated by construction of various macromolecular architectures including block copolymers,[27] star polymers,[126] star-shaped block copolymers,[127] and combs.[128]

Employing Cp-capped polymers as a diene, block copolymer formation can be achieved at ambient temperature within 10 min reaction time.[29] The fact that the Cp-adduct may undergo a complete retro-HDA reaction at elevated temperatures (90 °C) makes it an interesting tool for the construction of smart materials,[129–131] yet should also be kept in mind when employing the reaction for polymer post-functionalizations. UV/Vis spectroscopy enables a facile monitoring of the HDA and the retro-HDA reaction by utilizing the strong $\pi \rightarrow \pi^*$ (≈325 nm) or the weak $n \rightarrow \pi^*$ (≈ 525 nm) transition of the dithioester moiety.[28,129] Cp-functional polymers can be synthesized by substitution of an appropriate leaving group such as a tosylate or bromide with sodium cyclopentadienide (NaCp) or the much milder and broadly applicable strategy using nickelocene ($NiCp_2$) as the Cp source.[30] An alternative route is to utilize NaCp as a termination agent for the cationic ring-opening polymerization of oxazolines.[22] It was demonstrated in a recent publication[28] that quantitative RAFT–HDA conjugation of hexadienoyl-derived dienes can be realized at ambient temperature without a catalyst in an aqueous solution. Furthermore, a recent study revealed that photoenols derived from 2-methoxy-6-methylbenzaldehyde undergo a DA reaction with dithiobenzoate functional polymers as shown in Scheme 9.[25] Consequently, block copolymers can be constructed employing polymers synthesized by RAFT polymerization with a conventional, non-electron-deficient transfer agent such as 2-cyanopropyl dithiobenzoate as the dienophile.



Scheme 9. Photo-induced RAFT–HDA cycloaddition of non-electron-deficient dithioesters.



Scheme 10. The tetrazine–norbornene DA_{inv} reaction.

2.8. Inverse Electron-Demand Diels–Alder Reactions of Tetrazines

Inverse electron-demand DA reactions (DA_{inv}) are attractive candidates for irreversible post-functionalizations. The DA_{inv} reaction between tetrazines and strained alkenes or alkynes has been successfully employed for bioconjugation reactions.[132–135] O'Reilly and co-workers[26] recently reported the utilization of the tetrazine-norbornene DA_{inv} reaction depicted in Scheme 10 for the post-functionalization of synthetic polymers. The high efficiency of the catalyst-free reaction at ambient conditions was demonstrated by block copolymer formation.

The progress of the reaction can be conveniently followed by UV/Vis spectroscopy by observing the decrease of the weak absorbance of the tetrazine at ≈546 nm.[26]

3. Thiol Chemistry

Of all the methods by which the physical and chemical properties of synthetic polymeric materials may be modified through efficient processes, namely *click* chemistries or efficient conjugations,[6] those that make use of thiols are arguably the least labor intensive and offer the greatest versatility in terms of the number of functional moiety pairings that enable efficient conjugation capabilities. Such pairings include the use of thiols with terminal alkenes (*thiol-ene*), terminal alkynes (*thiol-yne*), organic bromides (*thio-bromo*), isocyanates (*thio-isocyante*), pentafluorostyrene groups and with epoxides to effect a conjugation via a ring-opening mechanism.

Of particular practical importance is the relative simplicity and commercial availability of the above-mentioned functional groups. It is for this basic reason that when considering a chemical pathway to *"post-functionalize"* synthetic polymers, the gamut of thiol-based chemistries should be included as part of the *powerful* options to achieve one's needs.

The following section will provide an overview of the various ways in which thiols can be used to achieve polymeric post-functionalization, with an emphasis placed upon (i) the ways in which the polymeric materials are prepared to include the required functionality for conjugation, and (ii) the conditions with which the actual conjugation is carried out. For convenience and readability, pertinent information concerning the chemical transformations dealt with is tabulated. Given that the thiol group itself is common to all the discussed transformations, the use of such functionality in post-polymerization functionalization will be dealt with in isolation, with the following sections 3.2 (from Section 3.2.) detailing the usage of the complimentary functionality.

3.1. The Thiol Group

In many instances, the goal for many synthetic polymers is to alter their chemical/physical properties by covalently attaching a variety of small molecules either to the polymer's end group or at multiple positions along its backbone. A search of the Sigma–Aldrich catalogue[136] reveals the commercial availability of nearly 2000 thiol-related products. Such diversity has certainly been a motivating force for many researchers to tailor their synthetic strategies to make use of such readily available compounds. Indeed, considering the additional chemistry that may be performed on small molecular thiols, there is essentially very little limitation in what type of functional properties can be introduced to polymeric structures.

There are a number of strategies that one may make use of to incorporate thiol functionality into the polymer itself. The broad techniques that will be discussed here are (i) de-protection, (ii) substitution, and (iii) a combination of the two. An overview of these strategies is provided in Table 3.

3.1.1. De-protection

What has been proven to be perhaps the most straightforward method by which the thiol function is incorporated into the polymeric structure is the conversion of the dithioester moiety inherent to polymers prepared via RAFT polymerization into a thiol through a process such as aminolysis. In this case, the dithioester end group is regarded as a "masked" or "protected" thiol that is in need of de-protection before being of use in conjugation chemistry. Such a technique is reliant upon an effective polymerization procedure that maximizes the chain-end fidelity of its product, i.e., the dithioester functionality.

There are many variations of the aminolysis reaction that may be employed on RAFT polymers. The general requirements are, naturally, a small molecular weight amine such as triethylamine (TEA) or hexylamine (HexAM) and a reducing compound that prevents, or at least limits, the oxidative disulfide formation from the resulting thiol-capped polymers (e.g., Me_2PPh,[i] Bu_3P[ii]). The thiocarbonylthio group may also undergo a reduction reaction to yield the required thiol. For example, polymers

[i] Dimethyl phenylphosphine.
[ii] Tributylphosphine.

Table 3. Pathways to equipping polymers with thiol functionality.[a)]

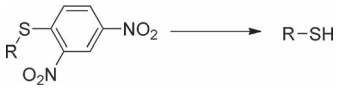
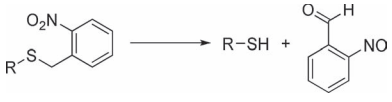
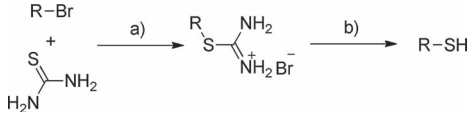
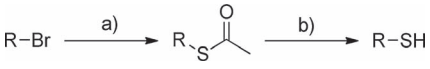
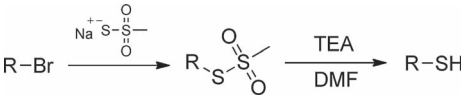
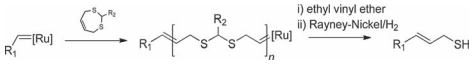
Transformation	Reaction conditions	Ref.	Characterization
	Polymer-RAFT:N_2H_4:Me_2PPh 1:5:1. CH_2Cl_2, RT, overnight under N_2	[137]	UV/Vis: successful transformation is indicated by the disappearance of the absorbance of the thiocarbonylthio group, typically occurring at $\lambda = 290 - 320$ nm[138]
	Polymer-RAFT:TEA:Bu_3P 1:10:1. 1,4-dioxane, RT, 2 h under N_2	[91]	FT-IR Spectroscopy: observing the loss of the C=S stretching band ($\approx$1000 – 1200 cm^{-1})[91,139]
	Polymer-RAFT:$P(OEt)_3$:HexAm 1:10:9.5. DMF, RT, 3 h under Argon	[140]	^{1}H NMR: loss of signals that are characteristic of the Z-group of the RAFT agent used.
	(i) Polymer-RAFT:methylamine 1:3. benzene, RT, 3 h. (ii) Addition of TCEP, RT, 2 h	[141]	^{13}C NMR: loss of the characteristic signal for the thiocarbonyl carbon (typically at $\delta > 200$ ppm)
	(i) Polymer – RAFT + 0.5 M $NaBH_4$	[142]	SEC: useful only in ensuring no oxidative coupling has occurred. Alternatively, in the case of symmetrical trithiocarbonates, successful cleavage is indicated by a shift to lower molecular weight.
	(ii) Dialysis in H_2O, RT		
	(iii) Treatment with TCEP prior to use in conjugation reactions.		
	Polymer – Disulfide:DTT ~ 1:80	[143]	SEC: used to ascertain that the molecular weight of the product shifts to lower values.
	DMF, 60 °C, 50 h		
	Polymer + TEA	[144–146]	^{1}H NMR: disappearance of protons of the dinitrophenyl group ($\delta = 7.77$, 8.41, and 9.09 ppm).
	Mercaptoethanol/propanethiol, pH 8, RT, 15 h		Raman Spectroscopy: Appearance of a signal at 2600 cm^{-1} corresponding to stretching of the S–H bond.
	Polymer in CH_2Cl_2, 0.01 eq. Me_2PPh	[147,148]	UV/Vis: Disappearance of the strong absorbance of the *o*-nitrosobenzaldehyde group at $\lambda = 345$ nm.
	UV irradiation ($\lambda_{max} = 320$ nm), RT, 16 h, N_2		^{1}H NMR: Disappearance of characteristic protons of the *o*-nitrosobenzaldehyde group at $\delta = 8.0$ and 7.37 – 7.60 ppm
	Polymer in acetonitrile		ESI-MS: Shift in *m/z* to lower values of all polymer peaks by the mass of the *o*-nitrosobenzaldehyde group (m/z = 135.03).

Table 3. Continued

Transformation	Reaction conditions	Ref.	Characterization
	UV irradiation (λ_{max} = 320 nm) (8W), RT, 2.5 h, N_2		
	a) Polymer-Br: thiourea 1:10, DMF, 100 °C, 24 h	[149,150]	^{1}H NMR: Shift of the signal from the α-bromo proton from 4.6 to 3.15 ppm.
	b) 10 eq. NaOH, 110 °C, 24 h		
	a) Polymer-Br: potassium thioacetate (1:3), acetone, reflux, 4 h	[151]	H NMR: appearance of a new signal at δ = 2.01 ppm due to the $SCOCH_3$ group.
	b) Hydrolysis with NaOMe (3 eq.)		^{13}C NMR: appearance of new signals at 31.32 and 206.9 ppm due to the $SCOCH_3$ group.
	a) Polymer-Br:sodium methansulfonate (1:1.5,1:3,1:5), DMF, 40 °C, 14 h	[152]	^{1}H NMR: appearance of new signal at δ = 3.2 ppm due to the–S-CH_3 group.
	b) Hydrolysis: DMF (with traces of water), TEA, 70 °C, 2 h		^{13}C NMR: appearance of new signal at 51.5 ppm due to the–S-CH_3 group.
			ESI-MS: Changes in the *m/z* values of the polymer peaks corresponding to a substitution of Br for methanethiosulfonate groups.
	Polymer dissolved in CH_2Cl_2 and reacted with H_2 in the presence of a Raney-Nickel slurry in methanol (14 h at 8 bar H_2 pressure)	[153]	^{1}H NMR: appearance of a new signal at δ = 3.4–3.7 ppm corresponding to the $–CH_2SH$ end group.
			^{13}C NMR: appearance of a new signal at δ = 27.38, attributable to the $–CH_2SH$ end group.
			MALDI-TOF MS: used to correlate *m/z* values from calculated structures with experimental data.

[a] Bu_3P = tributylphosphine, DMF = ***N,N***-dimethylformamide, DTT = 2,3-dihydroxy-1,4-butanethiol, HexAm = hexyl amine, Me_2PPh = dimethyl phenylphosphine, NaOMe = sodium methoxide, $P(OEt)_3$ = triethylphosphite, Polymer-Br = polymer bearing bromide functionality, Polymer-RAFT = polymer bearing dithioester functionality; RT = room temperature, TCEP = tris(2-carboxyethyl)phosphine, TEA = triethylamine.

prepared with trithiocarbonate RAFT agents may be treated with $NaBH_4$ to effect the transformation.[142] It is important to note that it is common practice to perform the aminolysis reaction in situ of the subsequent coupling reaction in a convenient one-pot process. However, there may be instances in which it is desired, or indeed necessary to first isolate the thiol-capped polymer. Selected examples from the literature in such circumstances are highlighted in Table 3.

An alternative strategy is to incorporate other protected or "masked" thiols into polymers either as part of the initiator used to generate the polymer or as a post-polymerization modification. Disulfide moieties may produce reactive thiols through a post-polymerization

reduction. The use of a bis-functional ATRP initiator bearing a central disulfide linkage enables the formation of a polymer structure that retains the disulfide linkage as a mid-chain functionality.[143] Subsequent treatment with 2,3-dihydroxy-1,4-butanethiol (DTT) affects a reduction of the disulfide linkage, generating two polymer chains (of half the original molecular weight) bearing thiol end groups. This technique may also be extended to generating polymers bearing thiol side-chain functionality through the use of disulfide-containing monomers.[154]

Equipping a polymer chain with an α-(2,4-dinitrophenylthio) moiety through esterification,[144,145] or incorporating such species into a ring-opening polymerization (ROP)[145,146] or ATRP initiator[146] allows the resulting polymers to attain thiol functionality through an exchange reaction using a large excess of a small-molecular-weight thiol such as mercaptoethanol or propanethiol. Depending upon the solubility of the polymers in question, the small-molecular-weight thiol may serve as the solvent for the exchange reaction. Nicolaÿ[155] describes a simple methodology to prepare well-defined polythiol copolymers by RAFT polymerization. A methacrylate monomer carrying a S-alkyl-*O*-ethyl xanthate moiety as a thiol protecting group was prepared in two high yielding steps. Polythiol copolymers were subsequently obtained by aminolysis of the xanthate protecting groups at ambient temperature. Patton and co-workers[156] equipped polymer brush backbones with photolabile *o*-nitrobenzyl and *p*-methoxyphenacyl thioethers for a post-polymerization surface modification approach. Application of light affords spatial control of reactive thiol functionalities and enables thiol-mediated transformations for functional polymer surfaces.

Perhaps the most convenient route by which a polymer's thiol function is released from its protected form is the photo-triggered transformation of 2-nitrobenzyl thioether moieties as recently demonstrated by Barner-Kowollik and co-workers.[147,148] Such structures have been proven to be chemically inert and withstand the conditions imposed upon it during radical polymerization. However, it must be noted that the photochemical mechanism of the deprotection step is strongly dependent upon pH and the solvent used.[157] For the purposes of performing conjugation chemistry with the resulting thiol function, attempts to perform in situ thiol-ene reactions (either via the Michael-addition or radically mediated routes) resulted in numerous side products, including homopolymerization of the added alkene, and even complete failure of the deprotection step in the presence of TEA.[147] A catalytic amount of Me_2PPh, however, is a recommended addition in the prevention of disulfide formation of the resulting thiols.

3.1.2. Substitution

ATRP is one of the most convenient polymerization techniques for the generation of a versatile array of materials that may be conveniently modified in post-polymerization processes. The central feature that allows for this is the inherent terminal halide functionality (most typically a bromide). It has already been described in the present review that the halide terminus may be substituted for an azide function for use in the CuAAC. However, this synthetic handle may also be transformed into a thiol function in a number of different ways, all of which contain at least two synthetic steps to achieve the desired functionality.

One method involves reacting the halide-functional polymer with thiourea to generate an isothiouronium salt intermediate. Subsequent treatment with a base such as sodium hydroxide facilitates cleavage to yield the desired thiol.[149,150] Similar methods involve treatment of the halide-functional polymer with potassium thioacetate[151] or sodium methanethiosulfonate[152] followed by hydrolysis into the desired thiol function. It is noteworthy that in the last example, the methanethiosulfonate polymer intermediate has a versatility that is not matched by other substitution methods. In addition to being hydrolyzed into a thiol, it may also be used to perform an in situ thiol-ene reaction (as the conditions of the hydrolysis also permit the Michael-addition of the resultant thiol to alkenes) and also may undergo thiol exchange reactions, thus enabling a route to a reversible redox polymer functionalization that is independent of thiol-type *click* chemistries.

The successful transformation of RAFT polymers into thiol-capped species can be determined by a number of different methods. A technique that may be universally applied to all RAFT polymers is UV/Vis spectroscopy. The thiocarbonyl group weakly absorbs visible light (due to a forbidden $n \rightarrow \pi^*$ transition) thus giving its color, however such moieties undergo a strong absorption in the UV region of the spectrum (due to an allowed $\pi \rightarrow \pi^*$ transition). Thus, the progress of an aminolysis reaction may be qualitatively monitored by observing the discoloration of the polymer solution as the thiocarbonyl group is replaced by a thiol. However, for quantitative measurements, it is the UV absorbance profile of the reaction mixture that must be measured. The strong absorptivity of the $\pi \rightarrow \pi^*$ transition means that the UV spectrum is highly useful for high molecular weight polymers, in which the concentration of thiocarbonyl end groups is very small. The majority of dithioester compounds utilized as RAFT agents absorb in the 290–310 nm range.[138]

FT-IR spectroscopy may also be used to monitor the aminolysis reaction by observing the loss of the C=S stretching band (≈1000–1200 cm^{-1}).[91,139] ^1H NMR s-y has been used in certain cases, however its use depends upon

the structure of the polymer and the RAFT agent, as well as the molecular weight:end-group ratio of the polymer. The FT-IR technique is only useful if the Z-group of the RAFT agent used (and thus being present as a polymer end group) bears chemically distinct protons from those of the polymer backbone. Furthermore, ^{1}H NMR spectroscopy is limited to those polymers in which the molecular weight: end group ratio is small, typically, a linear polymer chain of $\overline{M}_n < 5000–10\,000$ gmol^{-1}. For example, the aminolysis of poly(*N,N*-diethylacrylamide) prepared using 1-cyano-1-methylethyl dithiobenzoate may be monitored by observing the disappearance of the aromatic protons of the Z-group.[141]

The quantitative measurement of the thiol moiety may also be determined by titration with 2,2′-dithiopyridine disulfide.[152] The reaction between these two compounds results in the formation of pyridinethione, which produces a strong absorbance at 370 nm in acetonitrile. The use of size-exclusion chromatography (SEC) is not used to determine the efficiency of the conversion, but to ensure that no oxidative coupling has taken place.

The final example, by which the thiol functionality may be incorporated as a polymer end group, involves the concept of sacrificial synthesis in ring-opening metathesis polymerization (ROMP). Hilf and Kilbinger[153] elegantly demonstrated that by performing a chain-extension reaction on a polymer that had been prepared via ROMP with thioacetal monomers, a post-polymerization hydrogenation reaction that cleaved or sacrificed the second block yielded the targeted homopolymer bearing a reactive thiol end group. In the world of ROMP, this provides a synthetic route, which is well suited to thiol-ene reactions, given that the typical polymer prepared via ROMP bears terminal ene functionality.

3.2. Thiol-Ene

In terms of polymeric conjugation chemistry with thiols, their reaction with terminal alkenes in the so-called thiol-ene reaction has certainly taken center stage. Aside from using small-molecular-weight alkenes (either directly commercially available or readily synthesized), terminal *ene* functionality may be imparted to the polymer structure. The following will briefly highlight selected examples in which polymeric materials may be functionalized; next, discussion will proceed onto the various methods by which the thiol-ene reaction may be performed.

3.2.1. The *Ene* Functionality

Perhaps the most straightforward approach for generating ene functional polymers is the initial synthesis of appropriately ene functional polymerization initiators or indeed monomers. For example, allyl amine may be used as an initiator for the ROP of ε-caprolactone[158] to yield the corresponding polymer bearing a single ene function at the chain terminus. Alternatively, 6-allyl-ε-caprolactone may be co-polymerized with ε-caprolactone to yield appropriate ene functionality along the polymer backbone to varying degrees.[159] If it is a radical-based polymerization mechanism that is required (such as ATRP), then initiators or indeed monomers may be equipped with an ene function, provided that the structure of the ene has a substantially lower rate of polymerization than the polymerizable component of the monomer to not only avoid loss of the ene function, but to also prevent crosslinking of the final polymer. An alternative strategy is the so-called high temperature macromonomer synthesis,[160] in which a degassed solution of acrylate monomer in hexyl acetate solution is heated to high temperature (140 °C) in the presence of a thermally activated radical initiator (such as azobisisobutyronitrile). If it is a simple ene functional polymer for use in a proof of concept model reaction, a convenient route to take is the functionalization of commercially available polyethylene glycol monomethyl ether with allyl bromide in a Williamson ether synthesis.[159] Examples of the above routes are depicted in Figure 2.

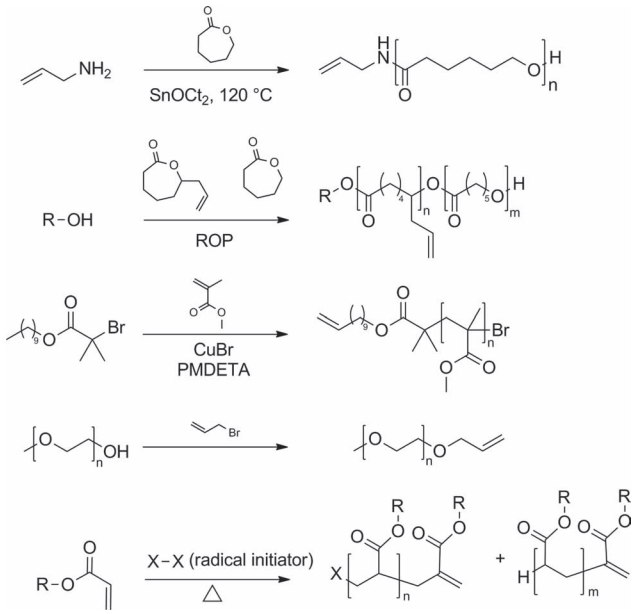


Figure 2. Convenient strategies for the incorporation of ene functionality onto the end groups of polymers (ROP: ring-opening polymerization; PMDETA: *N,N,N′,N″,N‴*-Pentamethyldiethylenetriamine).

3.2.2. The Thiol-Ene Reaction

The reaction of thiols with enes may be performed via two distinct pathways: (i) radical mediated, in which a generated thiyl radical adds across the carbon double bond of

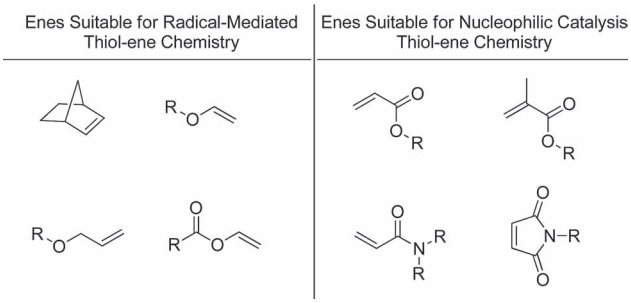


Figure 3. Examples of enes suitable for radical-mediated, and nucleophilic catalysis thiol-ene chemistry.

the ene; and (ii) nucleophilic catalysis, which promotes the Michael-type addition of thiols across the carbon double bond of the ene. The choice of which route to take is largely driven by factors such as a) the structure of the ene utilized; and b) the nature of the conjugation to be performed (polymer–polymer conjugation, polymer–small molecule conjugation, or convergent–polymer conjugation to achieve well-defined branched structures. Figure 3 depicts examples of enes suitable for radical-mediated, and nucleophilic catalyzed thiol-ene chemistry.

There are some excellent reviews dealing specifically with thiol-related conjugation chemistries that provide details of the mechanisms and uses of thiol-ene chemistry,[161–164] however, as a rule of thumb, it may be stated that the reactivity of the ene toward the addition of thiyl radicals generally decreases as the electron density of the C=C bond decreases.[iii] Conversely, in order for the Michael-addition of thiols to enes to bear an efficiency that is demanded by *click* chemistry, the ene must be rendered electron deficient through an electron-withdrawing substituent. Figure 2 depicts select examples of the various ene structures that are suitable for thiol-ene chemistry.

The following will provide information on the two mechanistic/catalytic systems used to effect successful thiol-ene coupling. For a convenient overview of the specific details concerning the various reactions, the reader is directed to the relevant section in Table 4.

3.2.3. Radical-Mediated Pathways

When thiol-ene ligation chemistry was initially introduced into the literature, it was of the radical chemistry variant. Schlaad and co-workers[177,178] made use of such chemistry for the efficient modification of well-defined polymeric materials and surfaces. It was shown by Hawker and co-workers[165] that radical thiol-ene chemistry could be used for the preparation of fourth-generation dendrimers with unprecedented efficiency. Hawker and colleagues then went on to complete a more comprehensive investigation into the radical-based thiol-ene reaction, in which a variety of ene functional polymers were reacted with a range of commercially available, low-molecular-weight thiols either under thermal initiation, in the presence of 2,2′-azobis(2-methylproprionitrile) or photoinitiation, in the presence of trace amounts of (2,2-dimethoxy-2-phenylacetophenone (DMPA).[159] The photo-initiated reactions (all performed at ambient temperature) achieved completion within a 30 min to 2 h timeframe, significantly outperforming thermally initiated reactions.

It is important to note that all examples in which the radical-based thiol-ene reaction is shown to perform very well involved, at least one component being a small molecule (typically the thiol). An equimolar stoichiometry between ene and thiol is not sufficient for effective coupling. A unique publication, which compiled the individual efforts of the groups of Barner-Kowollik and Du Prez, demonstrated that radical thiol-ene chemistry has rather severe limitations when its use is aimed at effecting polymer–polymer ligations or convergent macromolecular synthesis.[179] The array of side products, incomplete conversion and the requirement for uneven stoichiometries in such purely macromolecular systems means that such a strategy cannot be reliably called upon for the construction of well-defined macromolecular materials and falls outside the realm of *click* chemistry.[6]

3.2.4. Nucleophilic Catalysis

Effecting a thiol and ene coupling through the use of a Michael-type mechanism has certainly expanded the applicability of such a pathway in macromolecular modification. The most common catalysts or activating systems involved are nitrogen bases such as TEA and HexAM. The advantage of such compounds lies in their concurrent use in the aminolysis of polymers prepared via RAFT polymerization, thus releasing the reactive thiol for the conjugation reaction. The point of which the user of this reaction must be aware is the high propensity of the macromolecular thiols to undergo oxidative coupling. Oxidative coupling can usually be observed by the presence of a shoulder to smaller elution volumes in the SEC trace of the thiol-functional polymer. To overcome the problem, two strategies are used (mostly in combination). The first is to perform the desired coupling reaction in situ with the aminolysis of the dithioester group of the polymer (as this is the most common source of macromolecular thiols in the literature). Concomitantly, a reductive agent is also added to the

[iii]Exceptions include the rapid addition of thiyl radicals to norbornene, and the subsequent hydrogen abstraction of the generated carbon-centred radical to complete the conjugation (which is also rapid). Also, the addition of thiyl radicals to methacrylate, styrene or conjugated double bonds exemplifies this exception. In this case, the initial addition of the thiyl radical is very fast, however the resulting radicals (methacrylic, benzylic or allylic) are stable to the extent that hydrogen abstraction to complete the reaction is impeded.

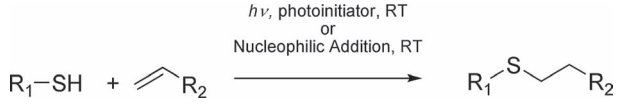
Table 4. Conjugation reactions involving thiols.[a)]

Transformation	Reaction conditions[b)]	User notes	Ref.	Characterization
Thiol-ene	MTS_{poly}:$acrylate_{SM}$ 1:1.5. Catalytic TEA. DMF (traces of H_2O), 70 °C, 2 h	One-pot hydrolysis, followed by thiol-ene.	[152]	ESI-MS/MALDI-TOF MS: may be used to verify that conjugation has been successful by observing the appropriate shift in *m/z* value of the polymer peaks.
	Ene_{poly}:SH_{SM} 1:5-10. 0.2 eq. DMPA, Ar, 365 nm, RT, 25 min-2 h	Reactions performed in the minimal amount of solvent to solubilize components. Deoxygenation required. Primary ene-functional ATRP initiators compatible.	[159,165]	^{1}H NMR Spectroscopy: related to signals that are characteristic of the conjugated species, or a disappearance of signals from vinylic protons.
	Ene_{poly}:SH_{SM} 1:5-10. 0.5 eq. AIBN, N_2, 80 °C, 3 – 24 h	This thermally initiated process is much less efficient than the comparable UV-initiated process above (conversions ranged from 17% – 100%).	[159]	SEC: to observe shifts to higher molecular weight in cases where macromolecular – macromolecular couplings or hyperbranched species are obtained. FT-IR Spectroscopy:
	Ene_{SM}:SH_{poly} 1:1.5-15. HexAM or TEA/Me_2PPh, N_2, RT, 5 min – 15 h	The HexAM is added to carry out the in situ conversion of dithioester end group to thiol. The function of the Me_2PPh is twofold: to act as a reducing agent to prevent disulfide formation and to catalyze the nucleophilic thiol-ene reaction. The SH, ene and Me_2PPh should be pre-mixed and then the HexAM should be added for best results.	[166,167, 148]	disappearance of alkene C-H bending vibrations at ~1000-650 cm^{-1} and disappearance of S-H stretching vibrations at ~ 2600–2550 cm^{-1}.
	Ene_{SM}:SH_{poly}1:3.2.14eq. $P(OEt)_3$, 3 eq. HexAM, 3 eq. TEA, 21 h, RT	A mixture of the SH_{poly}, $P(OEt)_3$ and HexAM is prepared in DMF and stirred for 3 h at RT. A solution of the ene and TEA in DMF is added to the reaction mixture and allowed to react for a further 18 h at RT.	[140]	
Thiol-yne	Alkyne:SH 1:10. DMPA, N_2, 365 nm, DMF RT, 10 min	Note that for this reaction, 2 SH moieties react with a single alkyne.	[168]	ESI-MS/MALDI-TOF MS: as above.
	Alkyne:SH 1:32. DMPA, N_2, 364 nm CH_2Cl_2/MeOH, RT, 10 min		[169]	^{1}H NMR Spectroscopy: disappearance of signals associated with alkyne protons.
	Surface-bound alkyne + SH_{SM}. Solvent-free conditions, DMPA, 365 nm, ambient air, 8 min.	Disappearance of C–H signal at 3288 cm^{-1}, triple bond signal at 2131 cm^{-1}	[170]	SEC: as above
	Bis-function alkyne-SH. DMPA, DMF, 365 nm, RT, 2 h	The bis-functional reactant takes full advantage of the "2 for 1" mechanism of thiol-yne chemistry to achieve hyper-branched structures.	[171]	FT-IR Spectroscopy: disappearance of alkyne C–H stretching vibrations at ≈2140 – 2100 cm^{-1} and disappearance of S–H stretching vibrations at ≈2600–2550 cm^{-1}.
Thio-bromo	SH:bromoester 1.2:1. 1.2 eq. TEA, ACN, RT, 5 min – 15 h	These examples involve the synthesis of highly branched structures and the variation in reaction time is a reflection on performing the same reaction on molecules that are geometrically increasing in size.	[172,173]	ESI-MS/MALDI-TOF MS: as above.

Table 4. Continued

Transformation	Reaction conditions[b)]	User notes	Ref.	Characterization
	SH:bromoester 1:1. 2 eq. HexAM, 2 eq. TEA, ACN, 30 min–20 h	Faster reaction times achieved with secondary α-bromoesters. These reactions are compatible with a one-pot aminolysis procedure of RAFT-derived polymers. The wide range of reaction times reflects the slower kinetics of the thio-bromo reaction on very large and sterically hindered molecules.	[174]	^{1}H NMR Spectroscopy: related to signals that are characteristic of the conjugated species. SEC: as above.
Thio-isocyanate	SH_{poly}:NCO_{SM} 1:2. ~2 eq. TEA, N_2, THF, RT, overnight	Reaction is not orthogonal to the base - catalyzed Michael addition of thiols to enes. Reaction must be performed in the absence of water and compounds bearing hydroxyl or amine functionality.	[141]	GATR-FT-IR Spectroscopy: disappearance of isocyanate signals at ≈2275 cm^{-1} and appearance of signals associated with the relevant thiol species. ^{1}H NMR Spectroscopy: as above. UV/Vis Spectroscopy: for end-group analysis where the modified end group bears a characteristic absorbance profile.
Thio-pentafluorostyrene	PFS_{poly} + 1.2 eq. SH_{SM} (with respect to PFS groups). 3 eq. TEA, DMF, RT/overnight or 40 °C/60 min	Quantitative conversion data is readily achieved through ^{19}F NMR spectroscopy.	[175]	^{19}F NMR Spectroscopy: disappearance of signal from F atom in the *para* position.
Thio-epoxide	$RAFT_{poly}$/Epoxide/$NaBH_4$/Me_2PPh. 1:50:2:1. N_2/THF, RT, 72 h	A one-pot procedure involving the in situ conversion of dithioester to thiol and subsequent thiolysis of oxiranes resulted in quantitative conversion. Use of DBU as a catalyst for thiol-epoxide reactions yielded significant coupling side-reactions. $ZnCl_2$ may also be used as a reagent to effect the thiol-epoxide reaction, however quantitative conversions were not achieved.	[137]	^{1}H-NMR Spectroscopy: as above
	SH_{SM}/$Epoxide_{poly}$/LiOH 1:2:1. THF, RT, 12 h	The LiOH should be added to an ice-chilled solution of the thiol and expoxide.	[176]	UV/Vis Spectroscopy: as above

[a)]MTS = methanesulfonate, TEA = triethylamine, DMF = ***N,N***–dimethylformamide, DMPA = 2,2-dimethoxy-2-phenylacetophenone, AIBN = azobisisobutyronitrile, HexAM = hexylamine, Me_2PPh = dimethyl phenylphosphine, RT = room temperature, $P(OEt)_3$ = triethoxyphosphite, MeOH = methanol, AN = acetonitrile, PFS = pentafluorostyrene, THF = tetrahydrofuran, DBU = 1,8-diazabicyclo [5.4.0] undec-7-ene, SEC = size-exclusion chromatography, ESI-MS = electrospray ionization-mass spectrometry, MALDI-TOF/MS = matrix assisted laser desorption ionization-time of flight/mass spectrometry, FT-IR spectroscopy = Fourier transform-infrared spectroscopy, GATR = grazing-angle attenuated total reflection; [b)]The $suffix_{poly}$ denotes that the indicated functional group is found on a polymer; The $suffix_{SM}$ denotes that the indicated functional group exists as an isolated small molecule.



Scheme 11. The thiol-ene reaction.

reaction mixture, most typically a phosphine derivative such as Me_2PPh. Importantly, Lowe and co-workers[167,180] showed that Me_2PPh not only serves as a reducing agent, but also serves as a potent catalyst for the thiol-ene reaction itself.

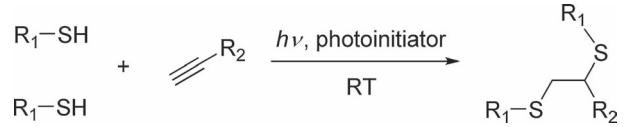
3.3. Thiol-yne

Where thiol-ene chemistry has been predominantly carried out utilizing a nucleophilic mechanism, thiol-yne chemistry makes use of a radical pathway. Alkynes have mainly been used in the CuAAC for polymer modification, yet the use of thiols as the conjugating partner allows for a double addition, i.e., a single alkyne unit may play host to the addition of two thiol species in the single "two-step" conjugation reaction.

Under UV irradiation, and in the presence of a UV radical initiator such as DMPA, the thiol-yne reaction can achieve >90% conversion in just 1.5 min.[169] Unfortunately, the thiol-yne reaction is not orthogonal to the radical-based thiol-ene reaction. Therefore, if it is desired to perform both reactions to achieve selective functionalization of a material, the nucleophilic-type thiol-ene reaction should be performed first.

Due to its "two for one" mechanism, the thiol-yne reaction is ideally suited for the generation of hyperbranched materials such as dendrimers. Stenzel and co-workers[168] reported this very elegant concept that nicely correlates the methodology with that used by Hawker to produce well-defined dendritic structures using the radical thiol-ene pathway.[165] In both examples, the efficiency of the conjugation reactions in building up the dendritic structure is observed to be independent of the generation of branching, with only 10 min required under UV irradiation (in the presence of DMPA) to achieve quantitative conversions. Perrier and co-workers[171] also took advantage of the heightened branching capabilities of thiol-yne chemistry to access functional, hyperbranched polymers from small molecules that beared both thiol and alkyne functionality.

When alkyne moieties are incorporated into the backbone of a polymer chain (via polymerizing the corresponding functional monomer), the thiol-yne reaction is very capable in modifying the chemical functionality of such polymers. Patton and co-workers[170] demonstrated this concept in the modification of surface-tethered, alkyne-functional polymeric brushes. Here, the application of a photomask enabled the spatial selectivity of the reaction sites, enabling surface patterning via sequential functionalization with variant thiol species.



Scheme 12. The radical thiol-yne reaction.

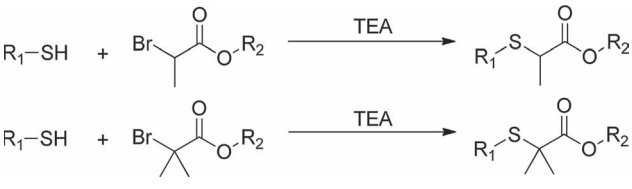
3.4. Thio-Bromo

Perhaps one of the most common end groups of polymers formed via ATRP is the α-bromoester. When the ideals of *click* chemistry found their way into polymer chemistry,[6] the nucleophilic substitution of such bromo-functional polymers with azides arguably served as the inspiration to adapt other forms of highly efficient chemical transformations to make direct use of the inherent bromide functionality. Under base-activation (typically TEA), thiols may react with α-bromoesters to form a thio-ether linkage.

Percec and co-workers[172] utilized nucleophilic bromine substitution advantageously in the generation of up to G4 dendrimers through sequential thio-bromo and acylation reactions. Using a 1.2-fold excess of thioglycerol (and 1.2 eq. TEA) with respect to the secondary α-bromoester functionality on a synthesized G1 scaffold, the G2 dendrimer was achieved in high yield in 5 min at ambient temperature. It should be noted, however, that increasing reaction times were required as higher generation dendrimers were targeted.

Also presented by the same group, the thio-bromo reaction was implemented in a novel "branch and grow" strategy for generating dendritic macromolecules.[173] Single-electron transfer living radical polymerization (SET-LRP) was used to generate linear macromolecules bearing the required bromoester terminus. Under similar conditions used previously, the thio-bromo reaction was performed using thioglycerol, thus introducing two hydroxyl functionalities, which could subsequently be converted into alkyl-bromide functionality to serve as an initiator for a subsequent round of polymerization, hence "branch and grow."

Making use of the "masked" thiol functionality of polymers prepared via a RAFT process, Davis and co-workers[174] reported the synthesis of dithiobenzoate-based RAFT agents that bear bis-bromoester functionality on the R residue. Polymerization therefore yielded polymers with α-bis-bromoester functionality and, ultimately ω-thiol functionality. Using a HexAM/TEA activating system, an in situ



Scheme 13. The thio-bromo reaction.

aminolysis followed by the thio-bromo reaction yielded the generation of highly branched materials. It is noteworthy that the type of polymer was shown to influence the success of the thio-bromo reaction. When poly(methyl acrylate) was used, conjugation efficiencies of only 73%–80% were achieved. The efficiency was boosted to >95% when poly(*N*-isopropylacrylamide) was used. Overall, it is recommended that secondary α-bromoesters be used in place of their tertiary counterparts due to the significantly greater reactivity toward the thio-bromo reaction.

3.5. Thio-Isocyanate

3.5.1. The Isocyanate Functionality

Until recently, isocyanates were only found in polymer structures as intermediate end groups in the preparation of poly(thiourethanes) through the step-wise addition of thiol and isocyanate containing "pre-polymers."[181,182] However, it has been demonstrated that these highly sensitive functionalities may be incorporated along a polymer's backbone or indeed as an end group with a view to be utilized in subsequent thiol couplings.

Patton and co-workers[183,184] demonstrated that an isocyanate-containing monomer, 2-isocyanatoethyl methacrylate (ICEMA), may undergo polymerization from a surface-bound UV-initiator to yield the required isocyanate-functional polymer. The presence of the targeted functionality could be confirmed through the use of grazing-angle attenuated total reflection FT-IR (GATR-FT-IR) spectroscopy by the presence of a signal at 2275 cm^{-1}, corresponding to the asymmetric stretching vibration of the isocyanate group. Interestingly, the reactive isocyanate group was inert to the radical polymerization and no special handling was necessary prior to thiol coupling. Furthermore, the isocyanate-functional and surface-bound polymers were able to be stored for 2 weeks under nitrogen without any appreciable reduction in reactivity. Perrier and co-workers[185] have also demonstrated that isocyanate-containing monomers (namely ICEMA and dimethyl *meta*-isopropenyl benzyl isocyanate (IBI)) could be co-polymerized (in a sequential fashion) with methyl methacrylate and styrene respectively in a RAFT process to achieve the desired isocyanate-functional block copolymers. A useful take-home message from this work is that while ICEMA has a higher reactivity for conjugation reactions, it is also more susceptible to side reactions during the polymerization process and the work-up. Conversely, the more sterically hindered isocyanate function of IBI lowers its reactivity such that side reactions are suppressed without necessarily impacting upon the efficiency of subsequent conjugation or *click* reactions.

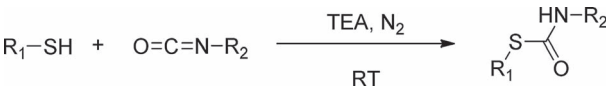
In the only example of providing well-defined α-isocyanate end-functional polymers, Perrier and co-workers[186] developed an elegant process in which a carbonyl-azide functional RAFT agent generates an isocyanate function through an in situ Curtius rearrangement during the actual polymerization process. Such a RAFT agent was shown to be compatible for the polymerization of acrylate, methacrylate, acrylamide, and styrene derivatives and also coupling with amine and alcohol derivatives were quantitatively achieved. Importantly, the isocyanate that is formed was shown to be sufficiently stable so as to eschew the use of anhydrous and oxygen-free conditions in the post-polymerization modification reactions. At this stage, however, reaction with thiols in this system has not been reported.

3.5.2. Thiol-Isocyanate Reaction

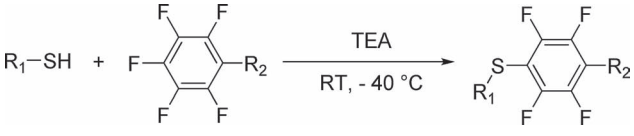
Lowe and co-workers[141] demonstrated the post-polymerization modification of polymers prepared via the RAFT process with an array of commercially available isocyanates. The dithioester end group of poly(*N,N*-diethylacrylamide) was converted into a reactive thiol through aminolysis and subsequent couplings with isocyanate derivatives were achieved in overnight reactions performed at ambient temperature and oxygen-free conditions. As outlined in Table 4, a twofold excess of isocyanate was required for the TEA-catalyzed reaction. Importantly, the thiol-isocyanate reaction is not orthogonal to the nucleophilic thiol-ene reaction (although it is more selective towards thiocarbamate formation). However, such chemistry is orthogonal to thiol-yne chemistry, as demonstrated by Patton and co-workers[184] in their surface-bound polymer brushes work. Furthermore, by investigating a variety of commercially available thiols with their isocyanate-functional surface bound polymers, Patton and co-workers showed that while quantitative conversion was accomplished within several hours with TEA as the catalyst, the same conversions could be achieved within minutes with 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) as the catalyst.

3.6. Thio-Pentafluorostyrene

The propensity of *para*-fluorine substituents of pentafluorophenyl groups to undergo nucleophilic substitution reactions with compounds such as primary amines and thiols was exploited by Becer



Scheme 14. The thio-isocyanate reaction.



Scheme 15. The thio-pentafluorostyrene reaction.

et al.[175] in the post-polymerization functionalization of polymers prepared by copolymerization of styrene and pentafluorostyrene.

Under relatively benign conditions (40 °C with TEA in dimethylformamide (DMF) solution), 90% conversion of the *para*-fluoro moieties of a poly(pentafluorostyrene) homopolymer with a thiol was achieved within 30 min, with quantitative conversion in less than 1 h. It is noteworthy that due to the strong hydrophobicity of pentafluorostyryl units, incorporation of such units to a significant degree in low-molecular-weight materials will require solvent/catalyst systems to be optimized. This was clearly demonstrated by Becer et al. in conjugation reactions of poly(styrene)–poly(pentafluorostyrene)-*co*-polymers. In such instances, a common solvent for both blocks is required to achieve maximum conjugation efficiency, something that is not always easy (or indeed feasible) to accomplish.

3.7. Thio-Epoxide

Taking advantage of the ring strain of epoxides, the nucleophilic ring-opening addition of thiols to such compounds provides yet another route to post-polymerization modification. Traditionally, epoxides have served as monomers in ROP, however when present as functionality in their own right within a polymer structure, they allow for the addition of a thiol-species to effect a conjugation while also releasing a further-modifiable hydroxyl-functionality.

3.7.1. The Epoxide Functionality

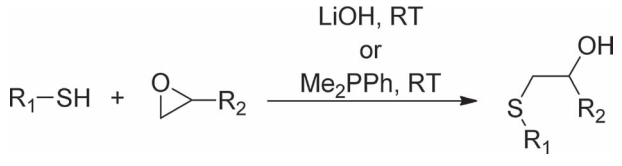
Thus far epoxides have been demonstrated, in thiol-conjugations, as both end group and backbone functionalities in polymers. De and Kahn explored both pathways by preparing polymers from synthesized epoxide-containing methacrylates (to provide backbone functionality) and also through the use of commercially available poly(ethylene glycol) diglycidyl ether.[176] Furthermore, multi-functional epoxide-containing molecules (many of which are commercially available) may be used as linkers in building up larger structures from linear homopolymer chains,[137] which will be discussed in the following section.

3.7.2. The Thio-Epoxide Reaction

In a preliminary study, Harvison and co-workers[137] explored the thio-epoxide reaction by utilizing a one-pot in situ reduction of dithioester-bearing polymers synthesized via RAFT polymerization with a variety of small-molecular weight and commercially available epoxides. An initial strategy in which thiol-functional poly(styrene) was first isolated and then reacted with epoxide (under either DBU or $ZnCl_2$ catalysis) resulted in successful conjugation, however in non-quantitative yields (<88%).

A more successful strategy was demonstrated in which a RAFT polymer was reduced with $NaBH_4$ (releasing the thiol function) and subsequently reacted with epoxide (catalyzed by Me_2PPh) in a one-pot process. This technique gave quantitative conversions in the majority of cases, all of which made use of a large excess of epoxide. Higher molecular weight structures were also successfully generated through the use of di- and tri-functional epoxide species, however the use of the tri-functional species (to generate three-arm stars) resulted in significant amounts of lower molecular weight side products.

Providing a reciprocal example, in which small-molecular-weight thiols were conjugated to epoxide-containing polymers, De and Kahn obtained quantitative thiol-epoxide coupling in the presence of LiOH and a twofold excess of thiol.[176] Advantage was then taken of the hydroxyl functionality that is generated through the ring-opening reaction and esterified to impart additional functionality. Specifically, amphiphilic structures were obtained through the introduction of a hydrophilic component through the thiol-driven reaction and a hydrophobic component through esterification of the generated hydroxide.



Scheme 16. The thio-epoxide reaction.

4. Metathesis

4.1. Ring-Opening Metathesis Polymerization (ROMP)

ROMP is a functional-group tolerant polymerization mechanism among the various "living" polymerization techniques. The reactivity of the particular catalyst must be adapted to the development of the specific end group functionalizations. Nevertheless, the preservation of the carbon double bonds during the polymerization is a unique feature of ROMP. The employment of (functional) cyclic olefins such as bi- or oligo-cyclic structures (e.g., norbornenes, cyclooctenes, and cyclobutadienes) gives access to highly functional polymers. In the present section, we highlight some elegant examples for the preparation of functional polymers by ROMP via post-modification (refer also to Table 5 for selected examples).

Functionalization of ROMP polymers in general can be introduced at three different stages of the polymerization, (i) initiation of the polymerization with a metal complex that bears a functional carbene, (ii) addition of a termination agent added at the end of the polymerization allowing the transfer of a functional group to every polymer chain that contains an active metal carbene site and (iii) polymerization of a second monomer onto

Table 5. End-group functionalization of ROMP polymers.

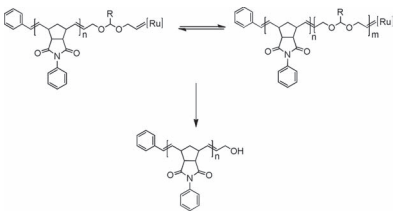
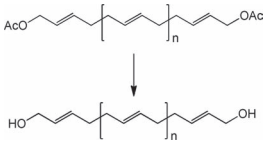
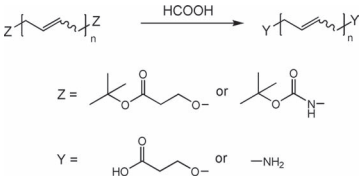
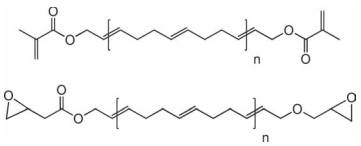
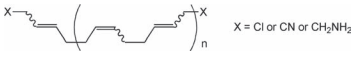
Transformation	Reaction conditions	User notes	Ref.	Characterization
	Poly(PNI-*b*-dioxepin), $CHCl_3$; methanol, 6N HCl, 14 h, RT	The total degree of functionalization was determined by comparing the integral of the ^{1}H NMR signal of the functional end group to the integrals of the styryl end group introduced by the initiator.	[200]	^{1}H NMR: 4.16 ppm (m, 2H, CH_2-O end group); 5.2-5.5 ppm (m, 2H, olefin end group); 6.3-6.4 ppm (m, 1H, double bond, CH_2-OH end); SEC
	$AcOCH_2CH$ $CHCH_2OAc$; 1,5-cyclooctadiene; methylene chloride solution; NaOMe, MeOH, THF; 45 – 50 °C; argon atmosphere	Structure was found to be consistent with perfect 1,4-HTPBD containing allylic alcohol end groups.	[192]	^{1}H NMR in $CDCl_3$: proton of CH_2-group adjacent to OH-group: 4.16 (d, *J* 7 Hz, H cis), 4.06 (d, *J* 5 Hz, H trans), ^{13}C NMR in $CDCl_3$: -*C*H_2-OH: 63.8 ppm (trans), 58.6 ppm (cis)
	Polymerizations were run neat at 45 °C for 24 h with $[COD]/(PCy_3)_2Cl_2Ru=CHPh$; The ester groups on PBD with $\overline{M}_n$ = 1700 – 8500 gmol^{-1} and PBD with $\overline{M}_n$ = 1800 – 8000 gmol^{-1} were removed with excess of formic acid to give the corresponding bis(carboxyl)-functionalized telechelic PBDs or bis(amino)-functionalized telechelic PBDs	Ruthenium catalyst is tolerant towards functional groups (i.e. amines, carboxylic acids); however in the presence of 3-hexenedioic acid or 1,4-diamino-2-butene, its activity is diminished over the time scale of the polymerization; efficiency of deprotection depended on the molecular weight of the starting material.	[193]	The resonances of functionalized termini and terminal methylenes were clearly present in ^{1}H NMR and ^{13}C NMR spectra. Unpublished results; SEC
	General polymerization procedure: nitrogen-filled drybox; CTA; cyclooctadiene (COD); for reactions involving the methacrylate CTA, aluminum foil was wrapped around the reaction vessel to prevent photo-induced cross-linking; ethyl vinyl ether	Synthesis of cross-linkable telechelic poly(butenylene)s	[195]	^{1}H NMR: determination of molecular weight assuming F_n = 2.0 (degree of functionalization). ^{13}C NMR, IR spectroscopy, SEC, DSC, and TGA: evidence for the cross-linking reaction
	Typical two-stage polymerization procedure: second-generation Grubbs precatalyst; 1,4-dicyano-2-butene; COD; CH_2Cl_2; N_2 atmosphere; RT		[196]	^{1}H NMR: monitoring the disappearance of COD (5.7 ppm (CH=C); 2.2 ppm (CH_2), ^{13}C NMR

Table 5. Continued

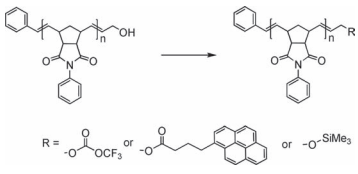
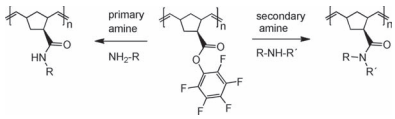
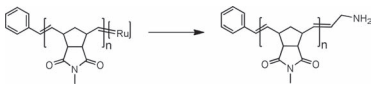
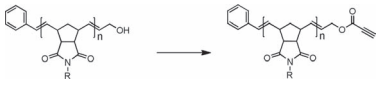
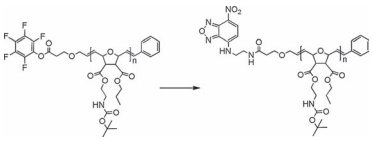
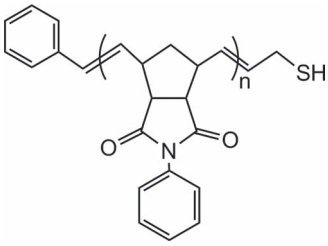
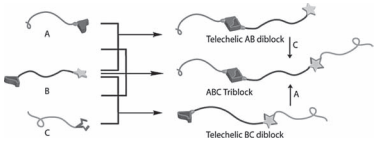
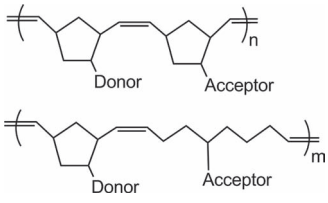
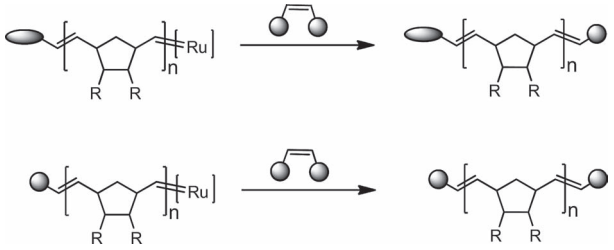
Transformation	Reaction conditions	User notes	Ref.	Characterization
	*Esterification of mono hydroxy-functional polymer with trifluoroacetic anhydride*: OH-functional PNI in dichloromethane-d2 in a NMR tube; trifluoroacetic anhydride. *Esterification of mono hydroxy-functional polymer with pyrenebutyric acid:* pyrenebutyric acid; oxalyl chloride, dry THF; stirred over night. OH-functionalized PNI in dichloromethane was added dropwise; after 3 h triethylamine was added; over night. *Reaction of mono hydroxy-functional polymer with TMS-Cl*: OH-functional PNI in dichloromethane; trimethylsilyl chloride; triethylamine; over night		[198]	*Trifluoroacetic anhydride functionalized PNI:* ^{1}H NMR: shifted signals to OH-functional PNI: 4.82 ppm (m, CH_2-O end group). ^{19}F NMR: δ[ppm]: -75.66; SEC. *Pyrene-functional PNI:* A SEC experiment with UV detection at λ = 340 nm (characteristic for pyrenebutyric acid derivatives). *TMS-Cl functionalized PNI*: ^{1}H NMR: additional signals to OH-functional PNI: 0.17 (s, 9H, $SiMe_3$-endgroup). ^{29}Si NMR (79.49 MHz in $CDCl_3$): 18.25 ppm; SEC
	ROMP: first - generation Grubbs catalyst in dichloromethane	All polymers were soluble in many organic solvents such as chlorinated hydrocarbons, aromatic hydrocarbons, diethyl ether and THF, acetone, DMF and DMSO, but insoluble in *n*-hexane, methanol, and water	[205]	ROMP: ^{1}H NMR; ^{19}F NMR: three broad peaks at 153.46, 158.52, and 162.84 ppm; FT-IR spectroscopy: 1777 cm^{-1} assigned to the carbonyl bond of the monomer
	acidic hydrolysis using 10% HCl in acetone		[194]	FT-ICR mass spectrometry; a complete shift of the molecular weight distribution was observed in the FT-ICR mass spectra of the amine end-functionalized polymers
	*Synthesis of PHNI-OH*: *N*-hexyl-*exo*-norbornene-2,3-dicarboximide (HNI); degassed by repeated; CH_2Cl_2; Grubbs' first - generation catalyst ($RuCl_2(CHC_6H_5)[P(C_6H_{11})_3]_2$); triphenylphosphine; ca. 4 h for 3000 g mol^{-1} and ca. 7 h for 5000 g mol^{-1}; 2-isopropyl-dihydro-1,3-dioxepine was added and allowed to react for another 15 h; ethyl vinyl ether; HCl (6M), methanol; RT; 10 h. *Esterification of hydroxy-functional polynorbornenes with propiolic acid, PPNI-CCH, and PHNI-CCH*: mono-hydroxy-polynorbornene; dicyclohexyl carbodiimide (DCC); DMAP; propiolic acid; dry DCM; 12 h.		[201]	^{1}H NMR: (2.9–3.1 ppm (m, 2H, 3.3–3.5 ppm (m, 2H, N-CH_2); C(O)CH); 4.16 ppm (m, 2H, CH_2-O endgroup); 5.5–5.9 ppm (m, 2H, double bonds polymer); 6.3–6.4 ppm (m, 1H, double bond; CH_2-OH endgroup). ^{1}H NMR: For PPNI-CCH and PHNI-CCH: 6.3–6.4 ppm (m, 1H, double bond at alkyne terminus)

Table 5. Continued

Transformation	Reaction conditions	User notes	Ref.	Characterization
	End-functionalized polymer; amine-free ***N,N***-dimethyl formamide; amine-functionalized NBD-dye; RT, 3 day	Polymer utilized for surface functionalization studies	[204]	^{1}H NMR: 2.51 (t, J = 6.5 Hz, 0.1 H, N-CH_2CH_2-NH-Ar from endgroup), 2.95 (br t, 0.1 H, O-CH_2CH_2 from endgroup), 3.67 (t, J = 6.4 Hz, 0.1 H, N-CH_2CH_2-NHAr from endgroup), 3.84 (t, 0.1 H, O-CH_2CH_2 of endgroup), 5.61 (br s, 1H, NH), 5.90 (br m, 1H, H1 and H1' trans)
	Polymer dissolved in CH_2Cl_2 and reacted with H_2 in the presence of a Raney-Nickel slurry in methanol (14 h at 8 bar H_2 pressure)		[153]	^{1}H NMR: appearance of a new signal at δ = 3.4-3.7 ppm corresponding to the–CH_2SH end-group. ^{13}C NMR: appearance of a new signal at δ = 27.38 ppm, attributable to the–CH_2SH end-group. MALDI-TOF MS: used to correlate ***m/z*** values from calculated structures with experimental data.
 Reprinted with permission from Ref. [207]. Copyright 2010, American Chemical Society.	General polymerization procedure: monomer; anhydrous, degassed CH_2Cl_2; argon atmosphere, initiator in CH_2Cl_2; 25 °C; 8 h.	Complementary H-bonding groups: *N,N'*-bis[6-(alkanoylamino)pyridin-2-yl] isophthalamide (often referred to as the Hamilton receptor or Wedge) and 2,7-diamido-1,8-naphthyridine (DAN); cyanuric acid (CA)- ureidoguanosine (UG) end-groups	[207]	^{1}H NMR; 2D NOESY; Isothermal Titration Calorimetry (ITC) to prove orthogonal nature of the Wedge-CA and DAN-UG pairs; SEC
	General polymerization procedure: monomer; anhydrous, degassed $CHCl_3$; argon atmosphere. Grubbs' first generation initiator in $CHCl_3$; 25 °C; 1 h. Upon completion of the polymerization, ethyl vinyl ether was added, 25 °C; 1 h	Side-chains consist of electron-rich 1,5-dialkoxynaphthalene and electron-deficient 1,2,4,5-benzenetetracarboxylic dianhydride (pyromellitic dianhydride)	[211]	^{1}H NMR; ^{13}C NMR with inverse gated ^{1}H decoupling showing integrations of the polymer signals (at 132.2 ppm and 127.3 ppm) and poly-4-(6-Decyl-1,3,5,7-tetraoxo-6,7-dihydropyrrolo[3,4-f] isoindol-2- (1H,3H,5H)-yl)butylcyclooct-4-enecar-boxylate signals (between 129 ppm and 131 ppm); SEC, UV/Vis: for random copolymers a signal was detected at ~450 nm

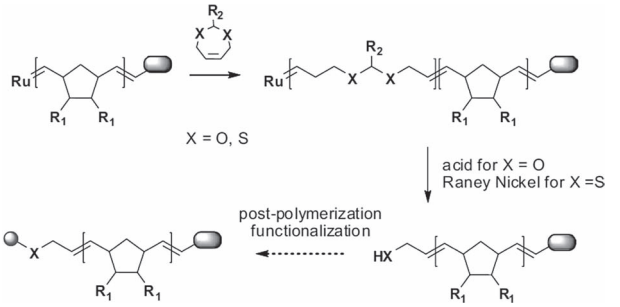


Scheme 17. Synthesis of semitelechelic and telechelic polymers using a chain transfer agent.

the first block that leaves after the decomposition of the second block a functional group at the end of the first polymer chain.[187]

ROMP leads to a polymer with an active metal carbene at one end and is therefore a good starting point to convert the reactive terminus into other useful chemical groups. Generally speaking, the functionalization of ROMP polymers can be performed on one chain (semitelechelic) and on both sides (telechelic) (Scheme 17). Use of an acyclic chain-transfer agent allows the synthesis of telechelic polymers that bear functional groups on both chain ends as demonstrated by Goethals et al.[188,189] Detailed information on the vast field of modification strategies are published in the excellent reviews by Hilf and Kilbinger,[190] Slugovc and co-workers[187] as well as in the recently published book of Theato and Klok.[191] Hilf and Kilbinger summarized the methods available for functionalization and classified the methods according to functional groups, catalyst, polymer type, number of functional groups, and the degree of functionalization. The feature article of Slugovc and co-workers[187] gives a well-structured overview of the state of research until 2010 regarding the synthesis of functional polymeric materials.

The utilization of chain transfer agents (CTAs) in Ruthenium-catalyzed ROMP is one method to attach reactive groups onto polymer chain ends. Unprotected functional groups such as hydroxyl,[192] amines,[193,194] carboxylic acids,[193] halides, pseudo-halides, methacrylates,[195] and epoxides[195] were introduced. Halides, pseudo-halides,[196] methacrylates, and epoxides[195] can serve as initiation sites for radical polymerization techniques, i.e., free-radical polymerizations, ATRP, or ionic polymerizations. In 2009, catalyst development made a considerable step forward regarding reactivity and selectivity when Grubbs and co-workers[197] impressively showed the increase of the number of polymer chains per catalyst molecule. Kilbinger and co-workers[198] demonstrate in several publications post-modification procedures to introduce functional groups, i.e., -OH, -SH, alkyne, aldehydes, or carboxylic acid groups. The team published an innovative approach for preparing polymer chains with one chemical group attached at the end, with excellent



Scheme 18. Preparation of end-group-functional polymers as demonstrated by Kilbinger and co-workers.[153,198] The second block of a diblock copolymer is sacrificed to obtain a monofunctionalized metathesis polymer with a hydroxy end group. By incorporation of a dioxepine unit into the copolymer, a breaking point is created between the block to be end functionalized and the block to be sacrificed. Reprinted with permission.[187] Copyright 2010, American Chemical Society.

control over the chain length. They described the monofunctionalization of the chain end of ruthenium-catalyzed metathesis polymers, which can be carried out in the presence of residual monomer. They synthesized block copolymers from *exo-N*-phenylnorbornene-2,3-dicarboximide and cleaved the second block that can be eliminated by a subsequent deprotection step to obtain an OH-functional polymer for an additional modification with several functional groups (i.e., trifluoroacetic anhydride; pyrenebutyroyl chloride; trimethylsilyl chloride)[198] (Scheme 18). The proposed strategy offers two advantages. First, side reactions such as the reaction of the metal carbene with double bonds in the polymer chains[199] can be avoided. Second, block copolymers can easily be purified, thus leading to high yield of polymers with a single chemical group at their chain ends.

The same team demonstrated that the substituents for the ROMP macroinitiation of poly(*exo-N*-phenyl-2,3-norbornene dicarboximide) with various dioxepine derivatives and Grubbs' first-generation catalyst are important for functionalization efficiency, in the order phenyl > isopropyl > methyl.[200] They demonstrated that the estimation of the value of k_i/k_p for macroinitiations for new sacrificial monomers is possible by analyzing one or two functionalization reactions thus providing an easy tool for the rapid screening and evaluation of new sacrificial monomers. As described already in the section *Thiol Chemistry*, Hilf and Kilbinger[153] demonstrated the preparation of a homopolymer bearing a reactive thiol end group. Additionally, the team prepared highly functional monohydroxy end-functionalized ROMP polymers and in a subsequent step, they attached an alkyne moiety for the conjugation of polyethylene glycol in a 1,3-dipolar cycloaddition to yield amphiphilic diblock copolymers.[201] The synthetic route allow for the preparation of block copolymers that are not accessible by

conventional chain extension procedures. Norbornene-terminated polymers were synthesized from OH-functional polymers.[202] This approach gives access to highly functional graft copolymer architectures. Aldehyde and carboxylic acid groups were introduced by end-capping with living ruthenium carbene chain ends using single-turnover olefin metathesis substrates.[203] Vinylene carbonate and 3*H*-furanone are introduced as functionalization and termination agents for the Ruthenium-initiated ROMP leading directly to the formation of functional polymer end groups without further chemical transformation steps.

Madkour et al.[204] described the synthesis of two terminating agents and their possible uses to end-functionalize living ROMP polymers. Two allyl-based terminating agents were presented that can be used to end-functionalize living polymer chains (that have activated ester groups) obtained by ROMP using Grubbs' third-generation catalyst. A fluorescent dye was coupled to the end-functionalized polymer and demonstrated the coupling of polymers with antimicrobial activity.

Vogel and Theato[205] obtained polymers from *exo*-5-norbornene-2-carboxylic acid pentafluorophenyl ester by ROMP. In a subsequent step, they obtained polymeric active esters that could be used for the preparation of multifunctional polymers. The precursor polymers reacted quantitatively with primary and secondary amines.

ROMP provides a platform to synthesize end-functionalized polybutadiene. Macosko and co-workers[196] prepared high-molecular-weight (up to 200 000 Da) telechelic polybutadiene by utilizing difunctional chain transfer agents.[196] Grubbs and co-workers[193,195] prepared polybutadiene bearing COOH, NH_2, methacrylate, or epoxide functionalities. An efficient strategy for the synthesis of monoamine end-functionalized living polymers using ROMP with Ruthenium initiators was reported by Kilbinger and co-workers[194] Amine end functionalization is rather difficult in ROMP due to the possibility of the coordination of the free amino groups to the Ruthenium catalyst.[206] A new cyclic olefin, 2-phenoxy-2,3,4,7-tetrahydro-1H-1,3,2-diazaphosphepine 2-oxide was synthesized that led to amine-functional *exo*-*N*-methylnorbornene imide polymers.

In 2010, Weck and co-workers[207] prepared a supramolecular ABC triblock copolymer based on hydrogen bonding by utilization of a functionalized initiator and subsequent end-group functionalization with a Hamilton wedge and at the other terminus a 2,7-diamido-1,8-naphthyridine. In solution, a supramolecular block copolymer was formed by the addition of homopolymers with the complementary hydrogen-bonding moieties. For earlier publications related to the preparation of the supramolecular ABC triblock copolymer, the reader is referred to the indicated publications[208–210].

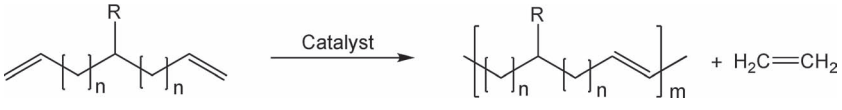
The Weck team also introduced a set of living donor/acceptor side-chain-functionalized monomers (electron-rich 1,5-dialkoxynaphthalene and electron-deficient 1,2,4,5-benzenetetracarboxylic dianhydride) via ROMP to generate a variety of homo- and copolymers such as block copolymers, random copolymers, and alternating copolymers.[211] Characterization of the polymers by UV/Vis spectroscopy shows a charge-transfer absorption band for the random and alternating copolymers. It was elucidated that intrachain and not interchain interactions between the donor and acceptor side-chain units are the reason for the charge-transfer band.

4.2. Acyclic Diene Metathesis

ADMET, like ROMP, is an attractive synthetic tool for polymer synthesis since it can be performed under mild- and user-friendly conditions. ADMET polymerization is a step-growth polymerization driven by the release of a condensate, usually ethylene,[212] and is typically performed on α,ω-dienes to produce well-defined and strictly linear polymers with unsaturated polyethylene backbones (Scheme 19).

Functionalization of ADMET polymers is feasible because of the discovery of the Schrock and Grubbs metathesis catalysts and ongoing improvements regarding their selectivity. A wide range of polymeric architectures, such as block copolymers, stars, and telechelic polymers that are difficult to synthesize via other approaches are thus accessible through this approach. Linear polyethylenes as well as functionalized polyethylenes (i.e., alkyl branched or graft copolymers) are also accessible through ADMET polymerization. By advancing the development of metathesis catalysts, the spectrum of functional polymers is broadened.

Mutlu et al.[213] published in 2011 an excellent review providing a detailed overview of representative examples of materials with defined architectures applying ADMET polymerization. The critical review provides detailed information about the history of ADMET polymerization, its functional group tolerance and serves as an overview of different strategies for the preparation of defined architectures and the synthesis of hyperbranched, conjugated, or crosslinked polymers. The present section will provide



Scheme 19. ADMET polymerization.

a selection of recent methods in which ADMET can be used for polymeric post-functionalization.

The key to improved functional group tolerance in olefin metathesis was the development of catalysts that react preferentially with olefins in the presence of heteroatom functionalities. Grubbs and co-workers developed well-defined Ruthenium-catalyst systems that have been used to polymerize monomers containing ketones,[214] alcohols,[215,216] esters,[217,218] ethers,[219] silyl chlorides, siloxanes,[220] amides,[221,222] carboxylic acids,[218] acrylates,[223,224] and amino acid containing monomers.[222] So far, most research has been focused on the copolymerization of ethylene with (polar) monomers to create novel polymeric materials with a wide range of applications. However, the drawback of the ADMET technique is the inherent difference in reactivity between ethylene and other vinyl monomers during chain polymerization, which results in copolymers with low polar monomer incorporation and side reactions with polar and/or protic functionalities (i.e. branching).[225] Valenti and Wagener[226] have provided several examples of model polyethylene copolymers via ADMET polymerization, i.e., poly(ethylene)/poly(vinyl alcohol) or ethylene-vinyl acetate (EVA) copolymers.[227] Furthermore, Wagener et al.[228] prepared a series of ADMET polyethylene analogues containing randomly placed alcohol and acetate groups. Schwendeman and Wagener[229] prepared amorphous, hydrophobic telechelic hydrocarbon diols using ADMET. The hydrocarbon backbone is based on a polymer of a *gem*-dimethyl-substituted α,ω-diene followed by hydrogenation of the polymer's repeat unit. These diols can be used in hydrolysis and UV resistant polyurethanes.

The team of Meier advanced the preparation of functional polymers based on from ADMET polymerization. Several studies of the development of new (functional) polymers from renewable resources have been published by his group.[216,223,230–232] Polymers from renewable resources have the great advantage that the properties profit from biocompatibility and biodegradability. Even though the direct polymerization via ADMET is only possible for some feedstocks, i.e., plant oils, several functional monomers can be prepared from natural occurring monomers. For example, methyl-10-undecanoate was modified via thiol-ene chemistry to obtain functional monomers ready for ADMET polymerization.[232] Linear and hyperbranched polyesters were obtained that contain also thioether linkages. Furthermore, the Meier team prepared poly-α,ω-unsaturated aldehydes and poly(allyl alcohols) from castor oil-derived monomers (i.e., 10-undecenal).[230] 10-Undecenal was nearly quantitatively transformed into the corresponding aldol condensation product. The ADMET approach with different Ruthenium-based metathesis initiators allowed the generation of poly-α,ω-unsaturated aldehydes with high molecular weights up to 11 kDa under solvent-free conditions. The subsequent reduction with sodium borohydride to allyl alcohols were accomplished successfully.

In a collaborative project with the group of Barner-Kowollik, a triblock copolymer was prepared by two orthogonal photo-induced polymer–polymer conjugation reactions through the use of an acrylate end-functionalized polymer, derived from ADMET polymerization.[224] On the one hand, the 2-formyl-3-methylphenoxy (FMP) moiety (a second-generation photoenol precursor) was employed for orthogonal polymer–polymer conjugations using terminal acrylates of diblock copolymers synthesized via ADMET polymerizations to directly prepare triblock copolymers. On the other hand, complex triblock copolymers were synthesized via a sequential one-pot approach utilizing the extraordinary orthogonality of the photo-induced DA reaction. The generated ADMET polymers contain internal α,β-unsaturated ester functions and acrylate end-moieties, allowing for their post-polymerization functionalization via photo-induced DA reaction. Please refer to the Section 1, *Cycloadditions,* for detailed information about photo-induced DA reactions.

Selected examples from the literature including post-modification of ADMET polymers are highlighted in Table 6.

5. Oxime Chemistry

Oxime ligation is an attractive chemistry as it is compatible with biomolecules. Thus, employing oxime formation in conjugation chemistry is an interesting area for many researchers. Stable oxime formation features reactions of an alkoxyamine with an electrophilic aldehyde or ketone (Scheme 20).

The transformation is orthogonal to many organic functional groups as well as high yielding, which enables the rapid synthesis of a large library of compounds. Oxime ligation produces site-specific conjugates thus providing stability under physiological conditions and is therefore an important method for preservation of bioactivity.[233]

The ability to assemble biomolecules under physiological conditions motivated the development of chemoselective ligation, which led chemists and biologists to search for reactive functional groups under mild, orthogonal, and aqueous conditions. Protein chemists started exploring unique chemoselective reactions that can tolerate the presence of other functional groups (orthogonality). In the present section, we will not summarize all biological chemoselective strategies as several excellent reviews and articles exist that fulfill that aim.[233–235] Moreover, there are many examples of immobilization of biomolecules on surfaces via oxime ligation since peptide

Table 6. Selected pathways to equipping ADMET polymers with a functionality.

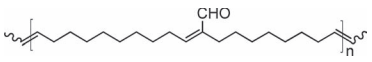
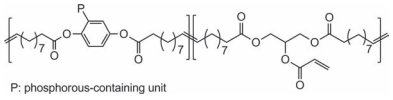
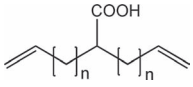
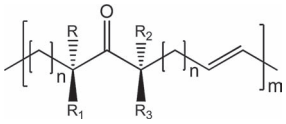
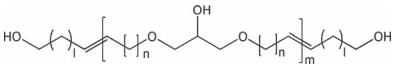
Transformation	Reaction conditions	Ref.	Characterization
	General procedure: monomer (Z)-2-(non-8-enyl)trideca-2,12-dienal; 1,4-benzoquinone, 60–100 °C; nitrogen atmosphere. Grubbs catalyst, 4 h.	[230]	^{1}H NMR: difficult to determine the exact degree of polymerization (DP) by integral because the terminal double bonds were not detectable, even in high enhancement. In order to determine the DP by NMR, a very useful approach should be the addition of methyl-10-undecenoate as a chain stopper. As an example, the ^{1}H NMR spectrum of 10-undecanoate - functionalized polymer has a dominant methyl ester signal at 3.67 ppm
 P: phosphorous-containing unit	1,2-Di-10-undecenoylglycerol, Hoveyda-Grubbs 2nd generation catalyst; 80 °C, N_2: 12 h.	[231]	Synthesis of block copolymers with different block ratios; T_g (and T_m) was determined by DSC; FT-IR (cm^{-1}): 3540 (O–H), 1742 (C=O), 1142 (C–O); ^{1}H NMR; ^{13}C NMR
	General procedure: Argon dried drybox, monomer: catalyst (400:1 molar ratio; 65 °C with magnetic agitation under reduced pressure. Alternately, the reaction may be conducted in a pressure tube fitted with a vacuum valve via Teflon bushing, thereby eliminating the need to transfer the ADMET polymer to another vessel for hydrogenation. Polymer/catalyst mixture was combined with silica gel, toluene, hydrogen pressure was applied as quickly as possible, 90 °C.	[218,227]	^{1}H NMR; ^{13}C NMR; SEC, elemental analysis
	Ketodienes were dried over CaH_2, filtered through Celite; argon atmosphere or pumped continuously under high vacuum for 24 h just prior to polymerization. E.g., poly[1 -oxo-2,2,11,11-tetramethyl-6-undecenylene]. in a Schlenck tube in a dry box; nitrogen atmosphere, catalyst; 6,6,8,8-tetramethyl-1,12-tridecadiene-7-one; reaction was allowed to stir until it became too viscous; addition of toluene as diluent. Reaction at a vacuum line; 8 h.	[214]	^{1}H NMR; ^{13}C NMR; IR: CO, 1709 cm^{-1}.
	*Synthesis of the polyols*: 1,3-di-10-undecenoxy-2-propanol; 10-undecenol; 0.1% of catalyst per mol of double bond; 80 °C; 5 h. *Synthesis of the polyurethanes:* polyol; anhydrous toluene (50% solution); argon atmosphere, 50 °C; the solution was homogenized and casted over silanized glass preheated at 90 °C for 2 h and 130 °C for 3 h.	[216]	^{1}H NMR; ^{13}C NMR; determination of the mmol of hydroxyl groups per gram of polyol

Table 6. Continued

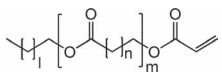
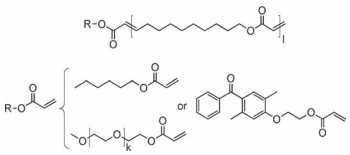
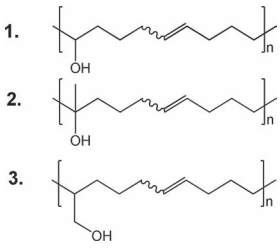
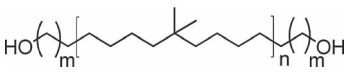
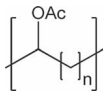
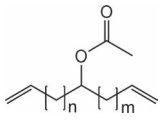
Transformation	Reaction conditions	Ref.	Characterization
	10-undecenoyl acrylate; dichloromethane; Hoveyda–Grubbs second - generation catalyst; 40°C; 5 h	[223]	By adding a selective chain stopper with increasing $\overline{M}_n$, ^{1}H NMR showed a slight decrease in the head-to-tail selectivity, resulting in a somewhat smaller end group accuracy. ^{13}C NMR; synthesis of star and block copolymers
	General procedure for ADMET polymerizations: undec-10-enyl acrylate; selected chain-stopper; DCM; Hoveyda–Grubbs second generation; 40 °C; 24 h; yields ranged from 85% to 95%.	[224]	SEC analysis revealed homogeneous molecular weight distributions and PDIs close to 2; synthesis of triblock copolymers
	General metathesis conditions: All glassware flame-dried under vacuum before use; monomers vacuum fractionally distilled; monomers were placed over 4 Å molecular sieves; monomers degassed (freeze-pump-thaw cycles) under high vacuum. All metathesis reactions were initiated in the bulk, inert atmosphere. A few drops of dry $CDCl_3$ were added on occasion in order to facilitate reaction initiation; catalyst, RT until the viscosity increased then increase to 70 °C.	[226]	**1.** ^{1}H NMR in $CDCl_3$: 1.09 ppm (br, 8H), 1.35 ppm (br, 1H), 1.71 ppm (br, 4.4H), 3.19 ppm (br, 1.9H), 4.67 ppm (br, 0.04H end group), 5.15 ppm (br, 2H), 5.60 ppm (br, 0.003H end group); IR (neat, cm^{-1}) 3341, 3005, 2926, 2856, 1726, 1457, 1440, 1036, 967, 511. elemental analysis; SEC. **2.** ^{1}H NMR in $CDCl_3$: 1.45 ppm (br, d, 9H), 2.00 (br, 4H), 3.55 ppm (br, 0.7H), 4.98 ppm (br, 0.29H end group), 5.40 ppm (br, 2H), 5.80 ppm (br, m, 0.04H end group); ^{13}C NMR (ppm) 24.8 – 33.4 (multiple signals), 36.4, 71.0, 129.5 – 130.5 ppm (multiple signals); elemental analysis; SEC. **3.** ^{1}H NMR in $CDCl_3$: 1.12 ppm (s, 3H), 1.40 ppm (br, 8H), 1.99 ppm (br, 4H), 4.94 ppm (br, m, 0.25H end group), 5.39 ppm (br, 2H), 5.79 ppm (br, m, 0.09H end group); ^{13}C NMR (ppm) 23.90, 26.94, 27.67, 33.01, 41.37, 72.72, 129.92, 130.42 ppm; elemental analysis; SEC
	Argon atmosphere; dry box; toluene; monomer; chain transfer reagent; Grubbs second - generation catalyst; 6.5 h. After another 15 h, the mixture was very viscous; temperature was increased to 60 °C; stirring for another 22 h till no bubbles were observed.	[229]	^{1}H NMR in $CDCl_3$: d 0.82 ppm (s), 1.15–1.30 ppm (m), 1.57 ppm (t, end group), and 3.64 ppm (t, endgroup). The ^{13}C NMR has many peaks due to an olefin isomerization; side reaction, so they will not be listed. ^{1}H NMR determined $\overline{M}_n$ = 2400 $gmol^{-1}$. Complete disappearance of the acetoxy end-group resonances at 2.05 and 4.05 ppm, and appearance of a new hydroxyl end-group resonance at 3.64 ppm. The ^{13}C NMR has many peaks due to an olefin isomerization side reaction; SEC

Table 6. Continued

Transformation	Reaction conditions	Ref.	Characterization
	Prepared by the tandem homogeneous ADMET/heterogeneous hydrogenation approach. Acetoxy-functional diene monomer; catalyst $Cl_2(Cy_3P)_2$-RuCHPh; 45–65 °C; 48 h; reaction mixture was combined with silica; olefin hydrogenation in toluene at 90 °C.	[227]	^{1}H NMR experiments indicate that the reaction is complete in 5–6 h, hydrogenations were conducted over a period of 24 h to ensure maximum reduction; ^{1}H NMR for 11-Acetoxy-1,20-heneicosadiene 4.83 (1H); 2.02 (s, 3H); 1.50 (br, 4H); 1.23 (br, 32H). ^{13}C NMR (ppm): 170.9, 74.45, 34.15, 29.71, 29.58, 29.37, 25.33, 21.28. $\overline{M}_n$ (SEC): 4.0×10^4 (PDI = 1.8).
	Representative ADMET procedure: Functionalized diene monomer; degassed under high vacuum over night; 25 – 60 °C (depending on monomer); 1,9-decadiene; Ruthenium catalyst; 60 – 70 °C; argon atmosphere; several days	[228]	^{1}H NMR; ^{13}C NMR (ppm): 21.7 (CH_3O); 25.7; 34.6; 74.4; 170.7 (C=O); SEC-LS. Synthesis of several linear functional ethylene copolymers, i.e., hydroxyl, ketone, butylacrylate, methacrylate, and acrylic acid

and protein arrays are widely used in the fields of medicine, biomaterials, and biotechnology for cell and tissue engineering. However, we will not focus in detail on surface functionalization to chemically attach proteins or immobilize biomolecules on surfaces by oxime chemistry. We rather focus specifically on synthetic polymer/protein- or polymer/polymer-ligations as well as end-group and side-chain functionalization.

In 2003, Kochendoerfer and co-workers[236] demonstrated the conjugation of a synthetic polymer and a protein [synthetic erythropoiesis protein, (SEP)]. They showed that polymer-modified proteins have full biological effects and increased half-lives in vivo. The same group developed a synthetic route that allows the effective protection of the aminooxy group during peptide synthesis, peptide ligation, and protein folding.[237] They demonstrated that the mild deprotection of the resulting proteins, here a synthetic CCL-5 (RANTES) analogue, in solution occurs without interference with the native folded structure for subsequent specific attachment of, for example, PEG. The approach permits the site-specific attachment at any stage of the synthesis.

Several research groups have reported the synthesis of polymers capable of oxime formation by introducing terminal aldehyde, ketone, or alkoxyamine groups.[238–241] Electrophilic groups such as aldehydes and ketones can selectively react with amines, alkoxyamines, and hydrazides to form imines, oximes, and hydrazones, respectively. As demonstrated by Maynard and co-workers,[242,243] aldehyde end- or side-group functional polymers can be conveniently prepared from 3,3′-diethoxypropyl methacrylate using free-radical polymerization,[242] ATRP,[244] and RAFT[243] polymerization. The acetal protecting group is removed after the polymerization with trifluoracetic acid (TFA). Wooley and co-workers[245] prepared aldehyde-containing polymers by utilizing RAFT polymerization of 4-vinylbenzylaldehyde.

The same team prepared poly(methyl vinyl ketone) and poly(phenyl vinyl ketone) under RAFT conditions.[246] Maynard and co-workers[247] as well as the group of Weck[248] prepared copolymers with reactive aldehyde or ketone functional monomers, respectively, ready for an orthogonal reaction. Maynard utilized RAFT polymerization whereas the group of Weck prepared random copolymers based on ROMP.

In addition to the end-group modification of polymer strands, side-chain functional polymers have also been reported to obtain oxime functionality.[236,240,243,244,249,250] An alternative strategy to incorporate alkoxyamines in a polymer chain is the polymerization of monomers with latent alkoxyamine functionalities.[251] Sumerlin and co-workers[251] demonstrated the RAFT polymerization of styrenic monomers with pendant phthalamide-protected O-(4-vinylbenzyl)-hydroxylamine and subsequent deprotection to obtain styrenic alkoxyamine polymers. After the cleavage, coupling with small-molecule aldehydes and ketones was accomplished, proceeding to near-quantitative conversion.

Scheme 20. Oxime bond formation.

Maynard and co-workers[240,243,244,249] demonstrated different approaches to obtain alkoxyamine side-chain and end-group functional polymers, i.e., synthesized by RAFT polymerization[241] or ATRP.[238,243] Boc-protected aminooxy end-functionalized pNIPAAm was synthesized by RAFT polymerization utilizing a Boc-protected aminooxy trithiocarbonate chain transfer agent (CTA).[241] Protein–polymer conjugates were prepared by conjugation of levulinyllysine-modified BSA to the aminooxy–pNIPAAm. The polymer could be utilized to form thermoresponsive bioconjugates with other proteins modified with aldehydes or ketones as they showed that the conjugate could be thermally precipitated owing to the conveyance of the thermoresponsive nature of the polymer to the protein. Heredia et al.[238] reported a straightforward approach to prepare polymers with narrow polydispersity and R-aminooxy functionality via ATRP. PolyPEGMA, polyHEMA, and polyNIPAAm were prepared in a range of molecular weights with narrow polydispersities utilizing Boc-aminooxy ATRP initiators. Oxime bond formation between levulinyl-modified BSA and aminooxy end-functionalized polyNIPAAm is demonstrated.

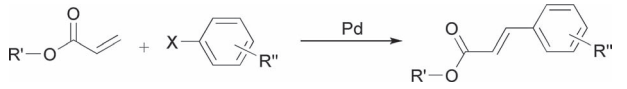
Maynard and co-workers[252] synthesized bio-functionalized hydrogels that encapsulate stem cells (3-D) or support adherence of the cells (2-D) by oxime bond formation. Aminooxy poly(ethylene glycol) (PEG) was mixed with glutaraldehyde to form oxime-linked hydrogels. By adjusting the weight percent of the aminooxy–PEG and the stoichiometric ratio of aldehyde to aminooxy groups, the mechanical properties, the water absorption, and the swelling ratio of the system was tuned. The authors showed that gels containing the integrin ligand arginine-glycine-aspartic acid (RGD) supported mesenchymal stem cell (MSC) incorporation.

Barner-Kowollik and co-workers[253] introduced a light-induced transformation process to allow not only for the quantitative and extremely rapid photo release of aldehyde functionalities but also the spatial control over the *click*-type oxime ligation using mild conditions. The method proceeds at low-energetic wavelengths (UVA). The authors translated the process to the fabrication of biopatterned silicon surfaces.

For a convenient overview of the specific details concerning the various syntheses of functional polymers and selected examples of oxime ligations on polymer strands, the reader is directed to the Tables 7 and 8.

6. Pd-Catalyzed Coupling and Cross-Coupling Reactions

Prominent among carbon–carbon coupling processes in organic synthesis are the Pd-catalyzed reactions, namely the Suzuki-Miyaura coupling, Stille coupling, Negishi coupling, Kumada coupling, Hiyama coupling, Sonogashira coupling, Heck reaction, Buchwald-Hartwig coupling, Pd-catalyzed cyanation, and the Pd-catalyzed carbonylation. The most commonly applied Pd-catalyzed carbon–carbon bond formation reactions are the Heck, Stille, Suzuki, Sonogashira, and the Negishi reaction. Over the last decade, cross-coupling reactions, i.e., the Pd-catalyzed coupling reactions found their way into polymer science. The reason for this trend lies in the high yield and the relatively mild reaction conditions with which such reactions may be performed, in addition to their excellent functional group tolerance and the possibility to perform these transformations in heterogeneous media.[259]



Scheme 21. Cross coupling reactions: i.e., Pd-catalyzed coupling reaction of acrylates (R′, R″: polymer chains, X: i.e. halide).

RAFT polymerization[260] and ATRP[261] have been utilized to prepare polymers containing boronic acid and boronic ester functional groups in a controlled fashion. Sumerlin and co-workers[260] described the synthesis of well-defined water-soluble boronic acid-containing macromolecules from boron-containing monomers. Homopolymers bearing organoboron segments were prepared from 4-pinacolatoborylstyrene (BSt) and block copolymers containing poly (*N,N′*-dimethylacrylamide) PDMA and pBSt.

Jäkle and co-workers[261] reported the efficient synthesis of organo vinyl(co)polymers via ATRP from organoboron monomers or from borylated precursors by using also BSt as the monomer. Chain extension for the preparation of block copolymers was carried out with poly(styrene). Two routes for the preparation of boron-containing block copolymers were investigated. First, the direct ATRP of BSt and subsequent chain extension with poly(styrene) and second, the transformation of trimethylsilyl-functionalized polystyrene by selective boron-silicon exchange with tribromoborane (BBr_3).

Li et al.[262] described the synthesis of poly(thiophenes) carrying aryl, vinyl, and alkynyl side groups via Suzuki, Stille, and Heck coupling. A library of 19 poly(4-hexylthiophene)s was prepared with an excellent degree of conversion (>99% in most cases). The method demonstrates the construction of poly(thiophene)s possessing more complex structures from poly(3-alkylthiophene) precursors.

Barner-Kowollik, Meier and co-workers[224] introduced a modular and very efficient method to introduce functional groups ready for Heck-coupling to prepare block copolymers. The reaction conditions were performed under Jeffery's conditions,[263,265] allowing the use of

Table 7. Pathways to equipping polymers with end-groups capable for oxime conjugation.

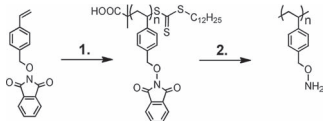
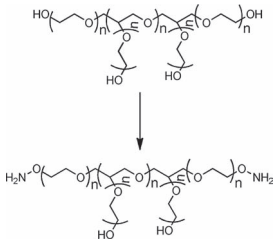
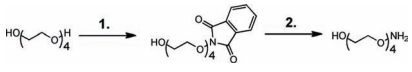
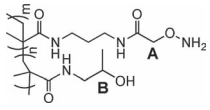
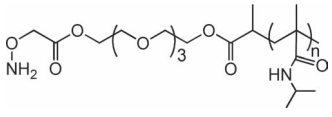
Transformation	Reaction conditions	Ref.	Characterization
Alkoxyamines			
	RAFT polymerization. 1. DMP, AIBN, dioxane, 80 °C. 2. N_2H_4, THF, 60 °C. Alternative: phthalimide protected groups cleaved prior to isolation: THF, hydrazine monohydrate (10 eq. per monomer); 60 °C, 4 h or RT, 24 h	[251]	^{1}H NMR: monitoring of conversion and confirmation of deprotection of polymer (disappearance of aromatic phthalimide groups at 7.8 –7.2 ppm; appearance of a peak at 5.9 ppm (–O–NH_2); methylene protons to alkoxyamine group shift from 4.9 to 4.4 ppm. SEC
	***N***-hydroxyphthalimide, PPh_3, diisopropyl azodicarboxylate, 16 h, 23 °C. Cleavage of the ***N***-phthalimide: addition of anhydrous hydrazine in dry acetonitrile, 30 min	[252,254]	^{1}H NMR in $CDCl_3$: 3.83–3.48 ppm (m, PEG signals). Percent substitution was calculated from the ***N***-hydroxyphthalimide-8-arm PEG by comparison of the integrations of the ***N***-hydroxyphthalimide end group proton peaks at 7.83 and 7.75 ppm with the integrations of the PEG proton peaks at 4.37, 3.86 – 3.47 ppm assuming the molecular weight of the PEG as 20.000. Substitution of 97%.
	1. ***N***-hydroxyphthalimide, PPh_3, diisopropyl azodicarboxylate, 16 h, 23 °C. 2. Cleavage of the ***N***-phthalimide: addition of anhydrous hydrazine in dry acetonitrile, 12 h, 23 °C.	[252]	^{1}H NMR in $CDCl_3$: 3.89 – 3.88 ppm (m, 2H, CH_2ONH_2), 3.76 – 3.72 ppm (m, 12H, ethylene glycolprotons), 3.67 – 3.65 (m, 2H, CH_2OH) ppm; ^{13}C NMR in $CDCl_3$: oxime carbon at 154 ppm.
	Aminooxy-methacrylamide-*co*-HPMA: AIBN, 50:50 molar ratio of 2-(3-(2-methylprop-2-enamido)propylamino)-2-oxoethoxycarbamate: ***N***-(2-hydroxypropyl)methacrylamide (HPMA) weight percent (12.5:0.6:86.9 monomers: AIBN: CH_3OH); methanol; 50 °C; 24 h	[250]	*tert*-butyl 2-(3-(2-methylprop-2-enamido)propylamino)-2-oxoethoxycarba-mate: TLC, ^{1}H NMR, High-resolution mass spectrometry (fast-atom bombardment) HRMS(FAB); integration of peaks A:B to be 1.0:0.55 confirming an equimolar ratio of monomers
	ATRP of polyPEGMA and polyHEMA: 1:1:2 of initiator:CuBr:bipy, MeOH, 22 °C, monomer to initiator ratios of 50:1. ATRP of polyNIPAAm: 1:2:2 of initiator:CuCl:Me_6TREN, DMSO, 22 °C; 1:50 molar ratio of initiator:NIPAAm. For the synthesis of aminooxy-functionalized ATRP Initiators please refer to Ref.[238]; *i.e.* deprotection of Boc-aminooxy polyNIPAAm: Boc-protected; 50% (v/v) TFA/$CHCl_3$ solution; 30 min	[238]	^{1}H NMR: 4.75 ppm ($NOCH_2$ end-group), SEC

Table 7. Continued

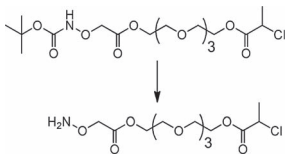
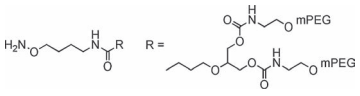
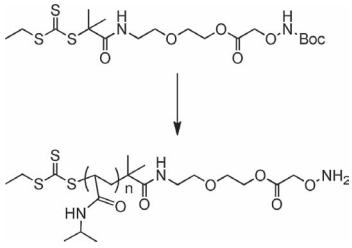
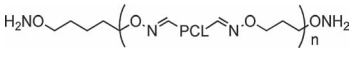
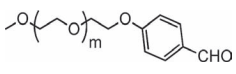
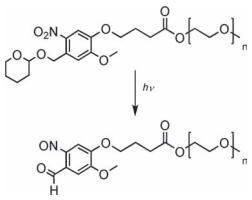
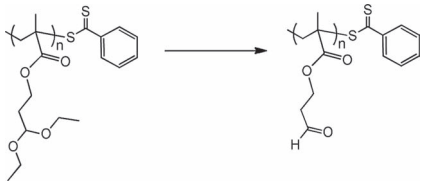
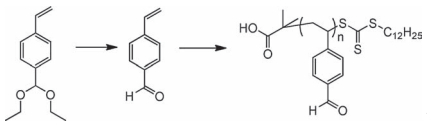
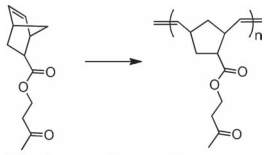
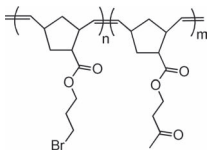
Transformation	Reaction conditions	Ref.	Characterization
	50% (v/v) solution of TFA/$CHCl_3$; 30 min; solvent was removed by bubbling with argon	[238]	^{1}H NMR: deprotection of the end-group disappearance of the *tert*-butyl protons at 1.42 ppm; methylene protons to the aminooxy group shifted from 4.40 to 4.67 ppm.
	2,5-dioxopyrrolidin-1-yl-4-(2-(*N*-(20 kDa mPEGyl)carbamoyloxy)-1-(*N*-(20 kDa mPEGyl)carbamoyloxymethyl) ethoxy)butanoate, ethyldiisopropylamine, CH_2Cl_2, *N*-(4-aminobutoxy)carbamic acid *tert*-butyl ester, 16 h, RT	[255]	not stated
	RAFT polymerization. 1. NiPAAm, AIBN; DMF, 70 °C. 2. TFA, $CHCl_3$, 30 min. Purification of Boc-aminooxy-functionalized CTA: reverse phase HPLC (acetonitrile:water (55:45) mixture)	[241]	CTA characterization: ^{1}H NMR, MALDI-MS; presence of the trithiocarbonate group confirmed by UV/Vis: maximum absorbance at 308 nm ($\pi \rightarrow \pi^*$). Polymer characterization: ^{1}H NMR; IR: N–H stretch of amide (3292 cm^{-1}), C–H stretch sp^3 carbons (≈2972 cm^{-1}), C= O stretch amide (1630 cm^{-1}), CNH vibration (1540 cm^{-1}), UV/Vis spectroscopy: trithiocarbonate end group: maximum absorbance at 307 nm; SEC
	polycaprolactone, terephthalaldehydic acid, anhydrous THF; DCC, DMAP, N_2, RT, 48 h	[256]	^{1}H NMR in $CDCl_3$: ratio of the methylene signal in the OPCL backbone (-CH_2OCO- 3.9–4.2 ppm) to the methoxyl signal in the PEG terminals (CH_3O–, 3.35 ppm); thermal properties analyzed by DSC and TGA techniques: T_m = 38 °C of PEG-OPCL-PEG; $T_{decomp\ (PEG)}$ ≈ 318 °C (With 10% weight loss); TGA residual weight percent at 700 °C is 4.2%; amphiphilic PEG-OPCL-PEG displays a good solubility in common organic solvent, like THF, DMF, and DMSO; spontaneously aggregate in aqueous media SEC: $\overline{M}_n$ = 3800 $gmol^{-1}$, $\overline{M}_w$ = 4200 g mol^{-1}
	Poly(ethylene glycol) monomethyl ether ($\overline{M}_n$ = 1000 $gmol^{-1}$) p-toluenesulfonate (MPEG-OTs); 4-hydroxybenzaldehyde; anhydrous potassium carbonate; dry acetonitrile; 85 °C; N_2; 2 days	[257]	^{1}H NMR in $CDCl_3$ (ppm): 3.34 (s, 3H, –OCH_3), 3.50 – 4.17 (t, ≈100H, –CH_2CH_2O), 6.98 (d, 2H, J = 8.61, Ar), 7.78 (d, 2H, J = 8.61, Ar), 9.84 (s, 1H, –CHO); ^{13}C NMR in $CDCl_3$ (ppm): 59.26 (–OCH_3), 72.15 – 67.99 (–OCH_2), 115.07, 122.55, 142.16, 166.20 (phenyl), 191.00 (CHO).

Table 7. Continued

Transformation	Reaction conditions	Ref.	Characterization
	NOTP-containing poly(ethylene glycol): 4-(2-methoxy-5-nitro-4-(((tetrahydro-2H-pyran-2-yl)oxy) methyl)phenoxy)butanoic acid) poly(ethylene glycol) methyl ether ($\overline{M}_n$ = 2000 gmol^{-1}; DCC; dry DCM; DMAP; RT; overnight. Aldehyde is formed under photo-activation ($h\nu$, λ_{max} = 370 nm), photodeprotection of NOTP-containing poly(ethylene glycol), CH_2Cl_2, low-pressure fluorescent lamp (Osram Delux L Blue UVA 18 W/78) emitting at 370 nm; 3 min; RT	[253]	NOTP-containing poly(ethylene glycol): SEC/ESI-MS analysis revealed a clean reaction. product; photodeprotection: SEC/ESI-MS: -102.07 Da tetrahydro-*2H*-pyran-2-ol; UV/Vis spectroscopy: after irradiation; λ_{max} = 370 nm
	pDEPMA; CH_2Cl_2; trifluoroacetic acid (TFA) and. H_2O (1:1); 20 min; 23 °C; for synthesis procedure of pDEPMA please refer to Ref. [244]	[244]	^{1}H NMR: the aldehyde proton peak at 9.69 ppm was observed after deprotection; the acetal proton peaks at 3.66, 3.51, and 1.25 ppm were no longer visible. UV–Vis: λ_{max} = 551 nm: spectrophotometric assay with Purpald® was used to confirm the results. The dye reacts only with aldehydes to form a purple product; maximum absorption wavelength of 551 nm indicating the presence of side-chain aldehydes
	*S*-1-dodecyl-*S*×-(α,α′-dimethyl-α″-acetic acid)trithiocarbonate (DDMAT); 4-vinylbenz-aldehyde; AIBN, 75 °C, N_2 atmosphere; either 1,4-dioxane or 2-butanone was used as the polymerization solvent (2-butanone better than 1,4-dioxane)		^{1}H NMR: the integration area ratio of aldehyde. protons vs. aromatic protons in PVBA is 1.00:2.12:2.03; SEC
Ketone functional polymers			
 Block copolymers i.e. 	*exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 3-bromopropyl ester; *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 4-oxobutyl ester anhydrous, degassed CH_2Cl_2, Grubbs' first-generation initiator,[215] Argon atmosphere. For the synthesis of block copolymers including aldehyde functionality please refer to Ref. [248]	[248]	^{1}H NMR in $CDCl_3$ (ppm): 6.13 (m, 2H), 4.23 (t, *J* = 6.5 Hz, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 3.03 (s, 1H), 2.93 (s, 1H), 2.19 (m, 3H), 1.91 (m, 1H), 1.51 (m, 1H), 1.38 (m, 2H). ^{13}C NMR (ppm): 175.8, 137.9, 135.5, 62.1, 46.7, 46.4, 43.1, 41.7, 31.8, 30.5, 29.6. Anal. Calculated for $C_{11}H_{15}BrO_2$: C, 50.98; H, 5.83. Found: C, 50.97; H, 5.80. ESI-MS *m/z*: calculated for $C_{11}H_{15}BrO_2$, 258.0255; found, 258.0232.

2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid (DMP); 2,2,0-azobisisobutyronitrile (AIBN); triphenylphosphine (Ph_3P); poly(ethyleneglycol methacrylate) (PEGMA); poly(hydroxy ethylene methacrylate) (polyHEMA); dicyclohexyl carbodiimide (DCC); dimethylaminopyridin (DMAP); 2-[(4,5-dimethoxy-2-nitrobenzyl)oxy]tetrahydro-2H-pyranyl (NOTP); diethoxypropyl methacrylate (DEPMA).

Table 8. Conjugation reactions involving oximes.

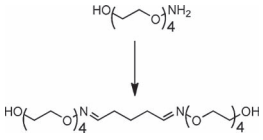
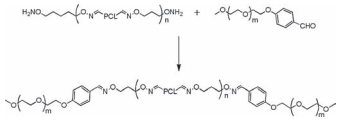
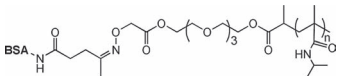
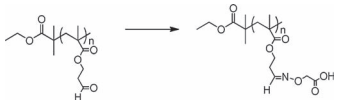
Transformation	Reaction conditions	User notes	Ref.	Characterization
Endgroup transformation				
	Precision polymer (PP) and peptide segments SEP-D, SEP-A: a molar ratio of 1:1.2 to 1.5 in 50% aqueous acetonitrile	Refer to Ref. [236] for chemical structure of PP and peptides; Segment SEP-A: APPRLICDSR VLERYLLEAK EAEK(*N*ε-levulinyl) ITTGCA EH(Dnp)- thioester. Segment SEP-D: CAIS PPDAAK(*N*ε-levulinyl) AAPL RTITADTFRK LFRVYSNFLR GKLKLYTGEA C(picolyl) RTGDR- carboxylate	[236]	Preparative reversed-phase HPLC using a linear water/acetonitrile gradient. SEP-D-PP and SEP-A-PP, respectively, were identified by ESI-MS and/or analytical RP-HPLC, pooled, and lyophilized
	Glutaraldehyde. D_2O	gels containing the integrin ligand arginine-glycine- aspartic acid (RGD) supported mesenchymal stem cell (MSC) incorporation	[252]	^{1}H NMR: oxime peak (*syn* and *anti*): 7.6 ppm and 6.9 ppm. ^{1}H NMR: disappearance of the signal at 9.7 ppm associated with the aldehyde moiety. ^{13}C NMR: appearance of the signal at 164 ppm associated with the oxime carbon
	Aldehyde - terminated PEG; polycaprolactone anhydrous DMSO, 37 °C, 48 h;	Yield 28% (low yield might result from the dynamic equilibrium of oxime bonds)	[256]	^{1}H NMR: 8.1 and 7.7 ppm (1H, -*H*C–NO)
	Levulinyl lysine-modified BSA; deprotected. polyNIPAAm; 50/50 (v/v) ACN/Milli-Q H_2O; 30 min	Isolation of the polyNIPAAm-BSA conjugate, 150 µL of the solution was warmed above 32 °C. PNIPAAm undergoes a reversible hydrophobic collapse above its lower critical solution temperature (LCST) of 32 °C	[238]	Bioconjugate formation was demonstrated with polyNIPAAm. Complete removal of the Boc group was evidenced by the disappearance of the *tert*-butyl protons at 1.42 ppm and the characteristic shift of the R-aminooxy protons to 4.75 ppm in the ^{1}H NMR spectrum
Side-chain transformation				
	Poly(3,3′-diethoxypropyl methacrylate) (PDEPMA), CH_2Cl_2, solution of H_2O/TFA (50:50), neutralization with $NaHCO_3$; NaOAc in MeOH (pH 5) and O-(carboxymethyl)hydroxylamine, 2 h, RT	SEC analysis was not performed because of the insolubility in DMF and THF; T_g = –18.6 °C.	[243]	^{1}H NMR, IR: stretch of the methacrylate carbonyl (1721 cm^{-1}); asymmetric carboxylate anion (1595 cm^{-1})

Table 8. Continued

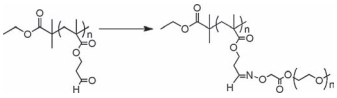
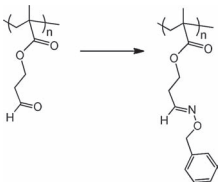
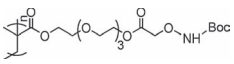
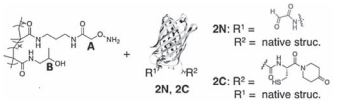
Transformation	Reaction conditions	User notes	Ref.	Characterization
	PDEPMA, CH_2Cl_2, solution of H_2O/TFA (50:50), neutralization with $NaHCO_3$; NaOAc in MeOH (pH 5) and O-(carboxymethyl)hydroxylamine, aminooxy-functionalized tetra(ethylene glycol), 2 h, RT	SEC in 0.1 M LiBr in DMF at 40 °C; T_g = –24.5 °C.	[243]	^{1}H NMR, SEC IR: the oxime (C–N) stretch was observed as a weak peak at 1639 cm^{-1}, while the carbonyl stretch of the methacrylate and PEG side chain was seen at 1728 cm^{-1} and 1757 cm^{-1}
	Poly(3-formyl ethyl methacrylate) (FEMA); O-benzylhydroxylamine hydrochloride; sodium acetate; MeOH, 45 °C; 2 h	Synthesis also made with addition of methoxyamine hydrochloride resulting in a block copolymer with two different oxime ligations. The ratio of benzyl hydroxylamine to methoxyamine in the final polymer was 36 to 64 from the ^{1}H NMR spectrum and oxime ligation of FEMA with aminooxy – RGD was performed	[244]	^{1}H NMR: oxime hydrogen clearly visible in the NMR spectrum (6.7-6.8 ppm); ***syn*** and ***anti*** isomers were apparent in a 60:40 ratio; SEC
	AIBN, toluene, 75 °C	Refer to Ref. [258] for synthesis of the monomer (Boc-aminooxy tetra(ethylene lycol) methacrylate)	[249]	Poly(Boc-aminooxy tetra (ethylene glycol) methacrylate): ^{1}H NMR in (MeOH-d4): 4.37 ppm (bs, 2H, $NHOCH_2CO_2$), 4.28 ppm (bm, 2H, $NHO-CH_2CO_2CH_2$), 4.07 ppm (ms, 2H, $CO_2CH_2CH_2O$), 3.70 – 3.61 ppm (bm, 12H, CH_2OCH_2), 1.93 – 1.81 ppm (bm, 2H, (CH_2 polymer backbone), 1.42 ppm (s, 9H, $C(CH_3)_3$), 1.02 – 0.87 (bm, 3H, CH_3 polymer backbone); SEC: $\overline{M}_n$ = 102 600 Da, PDI = 2.59; FT-IR
 Reprinted with permission from Ref. [250]. Copyright 2008, American Chemical Society	Alkoxyamine-*co*-HPMA, in phosphate buffer (pH 6.5) (80 mg mL^{-1}) mixture with meGFP 1:1; 16 h	Synthesis of *tert*-butyl 2-(3-(2-methylprop-2-enamido) propyl amino)-2-oxoethoxy carbamate: refer to Ref. [250]	[250]	Aminooxy-methacrylamide-*co*-HPMA: ^{1}H NMR: integration of peaks A:B to be 1.0:0.55 confirming an equimolar ratio of monomers; peak A: 4.1 – 4.2 ppm; peak B: 3.8 – 3.9 ppm

Table 8. Continued

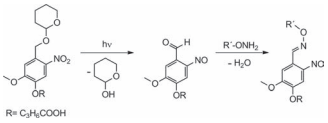
Transformation	Reaction conditions	User notes	Ref.	Characterization
	Photo-triggered deprotection of *o*-nitrobenzyl acetal: at 370 nm with a low-cost compact fluorescent lamp (λ_{max} = 370 nm, 14 mWcm^{-2}, 18 W); DCM, hydroxylamine; hydrochloride, RT, over night	Model reactions were performed in solution on a poly(ethylene glycol) methyl ether (PEG) functionalized with 2-[(4,5-dimethoxy-2-nitrobenzyl) oxy]tetrahydro-2H-pyranyl for photo-induced oxime linkage; NOTP-functionalized were linked with a solution of (2-aminooxy) acetamido Gly-Arg-Gly-Ser-Gly-Arg peptide	[253]	SEC/ESI-MS: +15.01 Da after oxime ligation Surface analysis: XPS, TOF-SIMS: to verify efficient spatially controlled photopatterning only the non-irradiated zone showed the presence of nitrite (NO_2^-) and tetrahydro-2H-pyranyl. ($C_5H_9O^+$) ions (treatment with (2-aminooxy) acetamido Gly-Arg-Gly-Ser-Gly-Arg peptide (GRGSGR): presence of $CH_3N_2^+$ and $C_4H_8N^+$ ions (characteristic secondary ions for arginine-containing peptides)

Table 9. Pd-catalyzed coupling and cross-coupling reactions.

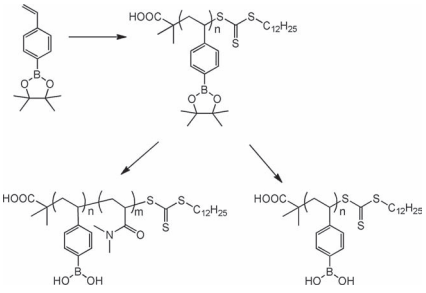
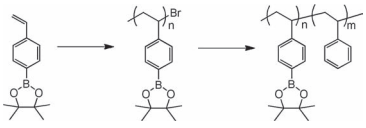
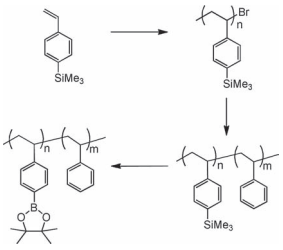
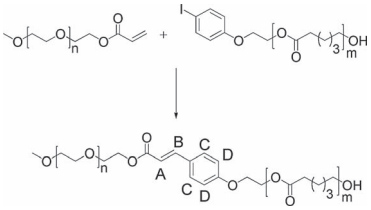
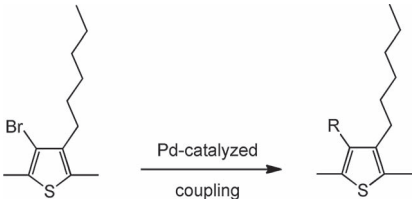
Transformation	Reaction conditions	Ref.	Characterization
	For monomer synthesis refer to Ref. [260] Homopolymer synthesis: pBSt; DMP; AIBN; 70 °C; 9 h; Block copolymer synthesis: ***N,N***-dimethylacrylamide (DMA); pBSt macro CTA; AIBN; anisole; 70 °C; 6 h Deprotection of polymeric pinacol ester to yield boronic acid polymers: PBSt; excess amount (×9) of polystyrene-supported boronic acid acetonitrile/2 vol.% trifluoroacetic acid; refluxing for 24 h	[260]	SEC; block copolymer molecular weights were determined by *in-situ* calculation of *dn/dc*, assuming 100% mass recovery
	Homopolymer synthesis: ratio of monomer:initiator:catalyst:ligand of 100:1:2:4 at 90 °C. Monomer MBpin; 1-phenylethylbromide; CuBr; PMDETA; anisole. Chain extension of the resulting organoboron polymer PSBP in in bulk at 110 °C	[261]	SEC; SEC-LS; TGA; DSC: T_g's of PSBpin-*b*-PS at ca. 110 and 201 °C (onset); data correlate well with those of the respective homopolymers: PS = 107 °C; PSBpin = 197 °C
	Homopolymer synthesis: Monomer MSi; 1-phenylethylbromide; CuBr; PMDETA; anisole; 110 °C	[261]	SEC; SEC-LS; TGA; DSC (onset, 20 °C min^{-1}; second heating curve): 97 °C; TGA (20 °C min^{-1}; N_2): T_{dec} = 418 °C (onset, 100% weight loss).

Table 9. Continued

Transformation	Reaction conditions	Ref.	Characterization
	PEG-acrylate: Poly(ethylene glycol) methyl ether; $CHCl_3$; acryloyl chloride; Et_3N; 16 h, RT. Aryliodide functional poly(ε-caprolactone): 2-(4-iodophenoxy); TBD; ε -CL; ethanol; 1 h; 50 min; 25 °C. Heck coupling: acrylic-substrate; aryliodide functional substrate; $Pd(OAc)_2$; $NaHCO_3$; tetrabutylammonium-chloride (TBA-Cl); DMF; 48 h; 30 °C, Argon atmosphere; no additional phase-transfer catalyst was necessary when the higher molecular weight PEG-acrylate ($\overline{M}_{n,SEC}$ = 8200 Da) was used. PEG acts as a phase-transfer agent	[224]	^{1}H NMR: proton A: 6.3–6.4 ppm; proton B: 7.6-7.7 ppm; protons C: 7.4-7.5 ppm; protons D: 6.9–7.0 ppm; SEC
	A library of all synthesized compounds are found in Ref. [262] ***Suzuki coupling***: 2% eq. $Pd(PPh_3)_4$; 3.3 eq. Na_2CO_3; 1.5 eq. $RB(OH)_2$; THF, 80 °C, 48 h. ***Stille reaction:*** 2% or 4 eq. $Pd(PPh_3)_4$; 1.5 eq. $RSnBu_3$; 110 °C; toluene; 24 – 120 h. ***Heck coupling***: investigated using methyl acrylate, styrene, and 4-vinylbiphenyl; 2% eq. $Pd(PPh_3)_4$; 2.0 eq. vinyl compound; 5 eq. Et_3N, toluene, 125 °C, 72 h	[262]	^{1}H NMR: ***Suzuki coupling***: aromatic protons at 7.27 and 7.15 ppm; all protons of the hexyl group shifted upfield; R-methylene protons shifted from 2.72 to 2.26 ppm. ***Stille coupling***: ^{1}H NMR, IR. ***Heck coupling***: Under the reaction conditions employed only 29% – 51% of the Br groups were substituted. UV/Vis spectra in THF solution showed an increase in the absorption maximum (λ_{max}: 355–403 nm) for aryl-(phenyl, naphthyl, thienyl, and furyl) and phenylethynyl-substituted polymers

equimolar amounts of both polymers and low reaction temperatures. The coupling process is based on the reaction of acrylate-terminated polymers with aryliodide-terminated polymers. Therefore, ADMET homo- and diblock (co)polymers carrying acrylate end groups were coupled to aryliodide-functional PEG and PCL. Examples of the above routes are depicted in Table 9.

Acknowledgements: C. B.-K. is grateful for continued financial support from the Karlsruhe Institute of Technology (KIT).

Received: January 9, 2013; Published online: April 29, 2013; DOI: 10.1002/marc.201300017

Keywords: click chemistry; modular and orthogonal ligation; post-functionalization; polymers

[1] V. Coessens, T. Pintauer, K. Matyjaszewski, *Prog. Polym. Sci.* **2001**, *26*, 337.
[2] M. A. Gauthier, M. I. Gibson, H.-A. Klok, *Angew. Chem. Int. Ed.* **2009**, *48*, 48.
[3] R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade, C. J. Hawker, *Chem. Rev.* **2009**, *109*, 5620.
[4] B. S. Sumerlin, A. P. Vogt, *Macromolecules* **2010**, *43*, 1.
[5] H. Willcock, R. K. O'Reilly, *Polym. Chem.* **2010**, *1*, 149.
[6] C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad, W. Van Camp, *Angew. Chem. Int. Ed.* **2011**, *50*, 60.
[7] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
[8] M. Conradi, T. Junkers, *Macromolecules* **2011**, *44*, 7969.
[9] N. V. Tsarevsky, S. A. Bencherif, K. Matyjaszewski, *Macromolecules* **2007**, *40*, 4439.
[10] W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2008**, *29*, 952.
[11] R. A. Evans, *Aust. J. Chem.* **2007**, *60*, 384.
[12] J.-F. Lutz, *Angew. Chem. Int. Ed.* **2007**, *46*, 1018.

[13] M. Meldal, *Macromol. Rapid Commun.* **2008**, *29*, 1016.
[14] J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16793.
[15] S. T. Laughlin, J. M. Baskin, S. L. Amacher, C. R. Bertozzi, *Science* **2008**, *320*, 664.
[16] J. A. Codelli, J. M. Baskin, N. J. Agard, C. R. Bertozzi, *J. Am. Chem. Soc.* **2008**, *130*, 11486.
[17] I. Singh, Z. Zarafshani, J.-F. Lutz, F. Heaney, *Macromolecules* **2009**, *42*, 5411.
[18] W. Song, Y. Wang, J. Qu, M. M. Madden, Q. Lin, *Angew. Chem. Int. Ed.* **2008**, *47*, 2832.
[19] a) M. Dietrich, G. Delaittre, J. P. Blinco, A. J. Inglis, M. Bruns, C. Barner-Kowollik, *Adv. Functional Mater.* **2012**, *22*, 304; b) G. Delaittre, M. Dietrich, J. P. Blinco, A. Hirschbiel, M. Bruns, L. Barner, C. Barner-Kowollik, *Biomacromolecules* **2012**, *13*, 1700.
[20] H. Durmaz, B. Colakoglu, U. Tunca, G. Hizal, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 1667.
[21] A. Gandini, *Prog. Polym. Sci.* **2013**, *38,* 1.
[22] M. Glassner, K. Kempe, U. S. Schubert, R. Hoogenboom, C. Barner-Kowollik, *Chem. Commun.* **2011**, *47*, 10620.
[23] T. Gruendling, K. K. Oehlenschlaeger, E. Frick, M. Glassner, C. Schmid, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2011**, *32*, 807.
[24] M. Glassner, K. K. Oehlenschlaeger, T. Gruendling, C. Barner-Kowollik, *Macromolecules* **2011**, *44*, 4681.
[25] K. K. Oehlenschlaeger, J. O. Mueller, N. Heine, M. Glassner, N. K. Guimard, G. Delaittre, F. G. Schmidt, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2013**, *52*, 762.
[26] C. F. Hansell, P. Espeel, M. M. Stamenović, I. A. Barker, A. P. Dove, F. E. Du Prez, R. K. O'Reilly, *J. Am. Chem. Soc.* **2011**, *133*, 13828.
[27] S. Sinnwell, A. J. Inglis, T. P. Davis, M. H. Stenzel, C. Barner-Kowollik, *Chem. Commun.* **2008**, 2052.
[28] M. Glassner, G. Delaittre, M. Kaupp, J. P. Blinco, C. Barner-Kowollik, *J. Am. Chem. Soc.* **2012**, *134*, 7274.
[29] A. J. Inglis, S. Sinnwell, M. H. Stenzel, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2009**, *48*, 2411.
[30] A. J. Inglis, T. Paulöhrl, C. Barner-Kowollik, *Macromolecules* **2010**, *43*, 33.
[31] E. Espinosa, M. Glassner, C. Boisson, C. Barner-Kowollik, F. D'Agosto, *Macromol. Rapid Commun.* **2011**, *32*, 1447.
[32] R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565.
[33] R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 633.
[34] A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, John Wiley & Sons, New York **2002**.
[35] A. Michael, *J. Prakt. Chem.* **1893**, *48*, 94.
[36] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.
[37] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
[38] M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952.
[39] C. Barner-Kowollik, A. J. Inglis, *Macromol. Chem. Phys.* **2009**, *210*, 987.
[40] C. Barner-Kowollik, F. E. Du Prez, P. Espeel, C. J. Hawker, T. Junkers, H. Schlaad, W. Van Camp, *Angew. Chem. Int. Ed.* **2011**, *50*, 60.
[41] M. A. Tasdelen, M. U. Kahveci, Y. Yagci, *Prog. Polym. Sci.* **2011**, *36*, 455.
[42] K. Matyjaszewski, Y. Nakagawa, S. G. Gaynor, *Macromol. Rapid Commun.* **1997**, *18*, 1057.
[43] J. A. Opsteen, J. C. M. van Hest, *Chem. Commun.* **2005**, 57.
[44] H. Gao, G. Louche, B. S. Sumerlin, N. Jahed, P. Golas, K. Matyjaszewski, *Macromolecules* **2005**, *38*, 8979.
[45] J.-F. Lutz, H. G. Börner, K. Weichenhan, *Macromol. Rapid Commun.* **2005**, *26*, 514.
[46] A. P. Vogt, B. S. Sumerlin, *Macromolecules* **2006**, *39*, 5286.
[47] X.-Y. Wang, A. Kimyonok, M. Weck, *Chem. Commun.* **2006**, 3933.
[48] B. S. Sumerlin, N. V. Tsarevsky, G. Louche, R. Y. Lee, K. Matyjaszewski, *Macromolecules* **2005**, *38*, 7540.
[49] W. H. Binder, C. Kluger, *Macromolecules* **2004**, *37*, 9321.
[50] D. Quémener, T. P. Davis, C. Barner-Kowollik, M. H. Stenzel, *Chem. Commun.* **2006**, 5051.
[51] W. Agut, D. Taton, S. Lecommandoux, *Macromolecules* **2007**, *40*, 5653.
[52] M. Urien, H. Erothu, E. Cloutet, R. C. Hiorns, L. Vignau, H. Cramail, *Macromolecules* **2008**, *41*, 7033.
[53] S. F. M. van Dongen, M. Nallani, S. Schoffelen, J. J. L. M. Cornelissen, R. J. M. Nolte, J. C. M. van Hest, *Macromol. Rapid Commun.* **2008**, *29*, 321.
[54] J.-F. Lutz, H. G. Börner, K. Weichenhan, *Macromolecules* **2006**, *39*, 6376.
[55] A. J. Dirks, S. S. van Berkel, N. S. Hatzakis, J. A. Opsteen, F. L. van Delft, J. J. L. M. Cornelissen, A. E. Rowan, J. C. M. van Hest, F. P. J. T. Rutjes, R. J. M. Nolte, *Chem. Commun.* **2005**, 4172.
[56] V. Ladmiral, G. Mantovani, G. J. Clarkson, S. Cauet, J. L. Irwin, D. M. Haddleton, *J. Am. Chem. Soc.* **2006**, *128*, 4823.
[57] A. J. Link, D. A. Tirrell, *J. Am. Chem. Soc.* **2003**, *125*, 11164.
[58] J. W. Lee, J. H. Kim, B.-K. Kim, J. H. Kim, W. S. Shin, S.-H. Jin, *Tetrahedron* **2006**, *62*, 9193.
[59] M. Malkoch, K. Schleicher, E. Drockenmuller, C. J. Hawker, T. P. Russell, P. Wu, V. V. Fokin, *Macromolecules* **2005**, *38*, 3663.
[60] P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed.* **2004**, *43*, 3928.
[61] E. Fernandez-Megia, J. Correa, I. Rodríguez-Meizoso, R. Riguera, *Macromolecules* **2006**, *39*, 2113.
[62] J. A. Johnson, D. R. Lewis, D. D. Díaz, M. G. Finn, J. T. Koberstein, N. J. Turro, *J. Am. Chem. Soc.* **2006**, *128*, 6564.
[63] D. D. Díaz, S. Punna, P. Holzer, A. K. McPherson, K. B. Sharpless, V. V. Fokin, M. G. Finn, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4392.
[64] M. Malkoch, R. Vestberg, N. Gupta, L. Mespouille, P. Dubois, A. F. Mason, J. L. Hedrick, Q. Liao, C. W. Frank, K. Kingsbury, C. J. Hawker, *Chem. Commun.* **2006**, *26*, 2774.
[65] N. V. Tsarevsky, B. S. Sumerlin, K. Matyjaszewski, *Macromolecules* **2005**, *38*, 3558.
[66] A. Qin, J. W. Y. Lam, B. Z. Tang, *Macromolecules* **2010**, *43*, 8693.
[67] R. Riva, S. Schmeits, F. Stoffelbach, C. Jerome, R. Jerome, P. Lecomte, *Chem. Commun.* **2005**, 5334.
[68] H. Gao, K. Matyjaszewski, *J. Am. Chem. Soc.* **2007**, *129*, 6633.
[69] M. Hong, J.-Y. Liu, B.-X. Li, Y.-S. Li, *Macromolecules* **2011**, *44*, 5659.
[70] B. A. Laurent, S. M. Grayson, *J Am. Chem. Soc.* **2006**, *128*, 4238.
[71] A. S. Goldmann, D. Quémener, P.-E. Millard, T. P. Davis, M. H. Stenzel, C. Barner-Kowollik, A. H. E. Müller, *Polymer* **2008**, *49*, 2274.
[72] D. E. Lonsdale, C. A. Bell, M. J. Monteiro, *Macromolecules* **2010**, *43*, 3331.
[73] J. Xu, J. Ye, S. Liu, *Macromolecules* **2007**, *40*, 9103.

[74] M. R. Whittaker, C. N. Urbani, M. J. Monteiro, *J. Am. Chem. Soc.* **2006**, *128*, 11360.
[75] O. Altintas, G. Hizal, U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5699.
[76] H. Gao, K. Matyjaszewski, *Macromolecules* **2006**, *39*, 4960.
[77] R. Hoogenboom, B. C. Moore, U. S. Schubert, *Chem. Commun.* **2006**, 4010.
[78] C. R. Becer, R. Hoogenboom, U. S. Schubert, *Angew. Chem. Int. Ed.* **2009**, *48*, 4900.
[79] G. Wittig, A. Krebs, *Chemische Ber.* **1961**, *94*, 3260.
[80] D. H. Ess, G. O. Jones, K. N. Houk, *Org. Lett.* **2008**, *10*, 1633.
[81] X. Ning, J. Guo, M. A. Wolfert, G.-J. Boons, *Angew. Chem. Int. Ed.* **2008**, *47*, 2253.
[82] F. Heaney, *Eur. J. Org. Chem.* **2012**, *2012*, 3043.
[83] I. Singh, Z. Zarafshani, F. Heaney, J.-F. Lutz, *Polym. Chem.* **2011**, *2*, 372.
[84] J. S. Clovis, A. Eckell, R. Huisgen, R. Sustmann, *Chemische Ber.* **1967**, *100*, 60.
[85] T. Pauloehrl, G. Delaittre, V. Winkler, A. Welle, M. Bruns, H. G. Börner, A. M. Greiner, M. Bastmeyer, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2012**, *51*, 1071.
[86] O. Diels, K. Alder, *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.
[87] F. Fringuelli, A. Taticchi, *The Diels-Alder Reaction: Selected Practical Methods*, Wiley, West Sussex, UK **2002**.
[88] K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.
[89] L. Tietze, G. Kettschau, *Topics Curr. Chem.* **1997**, *189*, 1.
[90] J. Sauer, R. Sustmann, *Angew. Chem. Int. Ed.* **1980**, *19*, 779.
[91] M. Li, P. De, S. R. Gondi, B. S. Sumerlin, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 5093.
[92] T.-D. Kim, J. Luo, Y. Tian, J.-W. Ka, N. M. Tucker, M. Haller, J.-W. Kang, A. K. Y. Jen, *Macromolecules* **2006**, *39*, 1676.
[93] Z. Shi, J. Luo, S. Huang, Y.-J. Cheng, T.-D. Kim, B. M. Polishak, X.-H. Zhou, Y. Tian, S.-H. Jang, J. D. B. Knorr, R. M. Overney, T. R. Younkin, A. K. Y. Jen, *Macromolecules* **2009**, *42*, 2438.
[94] K. Masutani, S. Kawabata, T. Aoki, Y. Kimura, *Polym. Int.* **2010**, *59*, 1526.
[95] B. Gacal, H. Durmaz, M. A. Tasdelen, G. Hizal, U. Tunca, Y. Yagci, A. L. Demirel, *Macromolecules* **2006**, *39*, 5330.
[96] A. Dag, H. Sahin, H. Durmaz, G. Hizal, U. Tunca, *J. Polym. Sci. Part A: Polym. Chem.* **2011**, *49*, 886.
[97] O. Altintas, G. Hizal, U. Tunca, *Des. Monomers Polym.* **2009**, *12*, 83.
[98] A. Dag, H. Durmaz, G. Hizal, U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 302.
[99] H. Durmaz, F. Karatas, U. Tunca, G. Hizal, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 499.
[100] H. Durmaz, A. Dag, A. Hizal, G. Hizal, U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 7091.
[101] H. Durmaz, A. Dag, G. Hizal, U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 5083.
[102] M. Tonga, N. Cengiz, M. M. Kose, T. Dede, A. Sanyal, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 410.
[103] E. Gungor, G. Hizal, U. Tunca, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3409.
[104] A. Sanyal, *Macromol. Chem. Phys.* **2010**, *211*, 1417.
[105] M. L. Szalai, D. V. McGrath, D. R. Wheeler, T. Zifer, J. R. McElhanon, *Macromolecules* **2007**, *40*, 818.
[106] J. R. McElhanon, D. R. Wheeler, *Org. Lett.* **2001**, *3*, 2681.
[107] M. M. Kose, G. Yesilbag, A. Sanyal, *Org. Lett.* **2008**, *10*, 2353.
[108] A. Vieyres, T. Lam, R. Gillet, G. Franc, A. Castonguay, A. Kakkar, *Chem. Commun.* **2010**, *46*, 1875.
[109] H.-L. Wei, Z. Yang, H.-J. Chu, J. Zhu, Z.-C. Li, J.-S. Cui, *Polymer* **2010**, *51*, 1694.
[110] H.-L. Wei, Z. Yang, L.-M. Zheng, Y.-M. Shen, *Polymer* **2009**, *50*, 2836.
[111] C. M. Nimmo, S. C. Owen, M. S. Shoichet, *Biomacromolecules* **2011**, *12*, 824.
[112] S. A. Canary, M. P. Stevens, *J. Polym. Sci., Part A: Polym. Chem.* **1992**, *30*, 1755.
[113] E. Goiti, M. B. Huglin, J. M. Rego, *Eur. Polym. J.* **2004**, *40*, 219.
[114] K. Inoue, M. Yamashiro, M. Iji, *J. Appl. Polym. Sci.* **2009**, *112*, 876.
[115] B. J. Adzima, H. A. Aguirre, C. J. Kloxin, T. F. Scott, C. N. Bowman, *Macromolecules* **2008**, *41*, 9112.
[116] C. Goussé, A. Gandini, P. Hodge, *Macromolecules* **1998**, *31*, 314.
[117] Y.-L. Liu, C.-Y. Hsieh, Y.-W. Chen, *Polymer* **2006**, *47*, 2581.
[118] R. Gheneim, C. Perez-Berumen, A. Gandini, *Macromolecules* **2002**, *35*, 7246.
[119] A. A. Kavitha, N. K. Singha, *ACS Appl. Mater. Interfaces* **2009**, *1*, 1427.
[120] A. M. Peterson, R. E. Jensen, G. R. Palmese, *ACS Appl. Mater. Interfaces* **2010**, *2*, 1141.
[121] J. A. Syrett, G. Mantovani, W. R. S. Barton, D. Price, D. M. Haddleton, *Polym. Chem.* **2010**, *1*, 102.
[122] X. Chen, M. A. Dam, K. Ono, A. Mal, H. Shen, S. R. Nutt, K. Sheran, F. Wudl, *Science* **2002**, *295*, 1698.
[123] X. Chen, F. Wudl, A. K. Mal, H. Shen, S. R. Nutt, *Macromolecules* **2003**, *36*, 1802.
[124] J. S. Park, K. Takahashi, Z. Guo, Y. Wang, E. Bolanos, C. Hamann-Schaffner, E. Murphy, F. Wudl, H. T. Hahn, *J. Composite Mater.* **2008**, *42*, 2869.
[125] M. Glassner, J. P. Blinco, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2011**, *32*, 724.
[126] A. J. Inglis, S. Sinnwell, T. P. Davis, C. Barner-Kowollik, M. H. Stenzel, *Macromolecules* **2008**, *41*, 4120.
[127] S. Sinnwell, A. J. Inglis, M. H. Stenzel, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2008**, *29*, 1090.
[128] A. Bousquet, C. Barner-Kowollik, M. H. Stenzel, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 1773.
[129] T. Paulöhrl, A. J. Inglis, C. Barner-Kowollik, *Adv. Mater.* **2010**, *22*, 2788.
[130] A. J. Inglis, L. Nebhani, O. Altintas, F. G. Schmidt, C. Barner-Kowollik, *Macromolecules* **2010**, *43*, 5515.
[131] M. Glassner, J. P. Blinco, C. Barner-Kowollik, *Polym. Chem.* **2011**, *2*, 83.
[132] M. L. Blackman, M. Royzen, J. M. Fox, *J. Am. Chem. Soc.* **2008**, *130*, 13518.
[133] N. K. Devaraj, S. Hilderbrand, R. Upadhyay, R. Mazitschek, R. Weissleder, *Angew. Chem. Int. Ed.* **2010**, *49*, 2869.
[134] N. K. Devaraj, R. Upadhyay, J. B. Haun, S. A. Hilderbrand, R. Weissleder, *Angew. Chem. Int. Ed.* **2009**, *48*, 7013.
[135] N. K. Devaraj, R. Weissleder, S. A. Hilderbrand, *Bioconjugate Chem.* **2008**, *19*, 2297.
[136] Sigma Aldrich Catalogue, www.sigmaaldrich.com/germany.html (accessed: 07/10/2012).
[137] M. A. Harvison, T. P. Davis, A. B. Lowe, *Polym. Chem.* **2011**, *2*, 1347.
[138] K. Skrabania, A. Miasnikova, A. M. Bivigou-Koumba, D. Zehm, A. Laschewsky, *Polym. Chem.* **2011**, *2*, 2074.
[139] R. M. Silverstein, F. X. Webster, D. J. Kiemle, *Spectrometric Identification of Organic Compounds*, 7 ed., John Wiley & Sons, Inc., NJ **2005**.
[140] H. Hien, The, M. E. Levere, S. Pascual, V. Montembault, J.-C. Soutif, L. Fontaine, *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 1657.

[141] H. B. Li, B. Yu, H. Matsushima, C. E. Hoyle, A. B. Lowe, *Macromolecules* **2009**, *42*, 6537.
[142] C. W. Scales, A. J. Convertine, C. L. McCormick, *Biomacromolecules* **2006**, *7*, 1389.
[143] N. V. Tsarevsky, K. Matyjaszewski, *Macromolecules* **2002**, *35*, 9009.
[144] M. Trollsas, C. J. Hawker, J. L. Hedrick, G. Carrot, J. Hilborn, *Macromolecules* **1998**, *31*, 5960.
[145] G. Carrot, J. G. Hilborn, M. Trollsas, J. L. Hedrick, *Macromolecules* **1999**, *32*, 5264.
[146] G. Carrot, J. Hilborn, J. L. Hedrick, M. Trollsas, *Macromolecules* **1999**, *32*, 5171.
[147] T. Pauloehrl, G. Delaittre, M. Bastmeyer, C. Barner-Kowollik, *Polym. Chem.* **2012**, *3*, 1740.
[148] G. Delaittre, T. Pauloehrl, M. Bastmeyer, C. Barner-Kowollik, *Macromolecules* **2012**, *45*, 1792.
[149] L. Garamszegi, C. Donzel, G. Carrot, T. Q. Nguyen, J. Hilborn, *React. Funct. Polym.* **2003**, *55*, 179.
[150] M. Uygun, M. A. Tasdelen, Y. Yagci, *Macromol. Chem. Phys.* **2010**, *211*, 103.
[151] M. Liras, O. Garcia, I. Quijada-Garrido, R. Paris, *Macromolecules* **2011**, *44*, 1335.
[152] C. Boyer, A. H. Soeriyadi, P. J. Roth, M. R. Whittaker, T. P. Davis, *Chem. Commun.* **2011**, *47*, 1318.
[153] S. Hilf, A. F. M. Kilbinger, *Macromolecules* **2009**, *42*, 4127.
[154] L. Li, X. Jiang, R. Zhuo, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 5989.
[155] R. Nicolaÿ, *Macromolecules* **2011**, *45*, 821.
[156] R. M. Hensarling, E. A. Hoff, A. P. LeBlanc, W. Guo, S. B. Rahane, D. L. Patton, *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 1079.
[157] Y. V. Il'ichev, M. A. Schworer, J. Wirz, *J. Am. Chem. Soc.* **2004**, *126*, 4581.
[158] Y.-J. Wang, C.-M. Dong, *J. Polym. Sci., Part A: Polym. Chem.* **2012**, *50*, 1645.
[159] L. M. Campos, K. L. Killops, R. Sakai, J. M. J. Paulusse, D. Damiron, E. Drockenmuller, B. W. Messmore, C. J. Hawker, *Macromolecules* **2008**, *41*, 7063.
[160] A.-M. Zorn, T. Junkers, C. Barner-Kowollik, *Macromol. Rapid Commun.* **2009**, *30*, 2028.
[161] C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540.
[162] C. E. Hoyle, T. Y. Lee, T. Roper, *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 5301.
[163] A. B. Lowe, *Polym. Chem.* **2010**, *1*, 17.
[164] P. J. Roth, C. Boyer, A. B. Lowe, T. P. Davis, *Macromol. Rapid Commun.* **2011**, *32*, 1123.
[165] K. L. Killops, L. M. Campos, C. J. Hawker, *J. Am. Chem. Soc.* **2008**, *130*, 5062.
[166] J. W. Chan, B. Yu, C. E. Hoyle, A. B. Lowe, *Chem. Commun.* **2008**, 4959.
[167] J. W. Chan, B. Yu, C. E. Hoyle, A. B. Lowe, *Polymer* **2009**, *50*, 3158.
[168] G. J. Chen, J. Kumar, A. Gregory, M. H. Stenzel, *Chem. Commun.* **2009**, 6291.
[169] J. W. Chan, C. E. Hoyle, A. B. Lowe, *J. Am. Chem. Soc.* **2009**, *131*, 5751.
[170] R. M. Hensarling, V. A. Doughty, J. W. Chan, D. L. Patton, *J. Am. Chem. Soc.* **2009**, *131*, 14673.
[171] D. Konkolewicz, A. Gray-Weale, S. Perrier, *J. Am. Chem. Soc.* **2009**, *131*, 18075.
[172] B. M. Rosen, G. Lligadas, C. Hahn, V. Percec, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3931.
[173] B. M. Rosen, G. Lligadas, C. Hahn, V. Percec, *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3940.
[174] J. Xu, L. Tao, C. Boyer, A. B. Lowe, T. P. Davis, *Macromolecules* **2010**, *43*, 20.
[175] C. R. Becer, K. Babiuch, D. Pilz, S. Hornig, T. Heinze, M. Gottschaldt, U. S. Schubert, *Macromolecules* **2009**, *42*, 2387.
[176] S. De, A. Khan, *Chem. Commun.* **2012**, *48*, 3130.
[177] A. Bertin, H. Schlaad, *Chem. Mater.* **2009**, *21*, 5698.
[178] N. ten Brummelhuis, C. Diehl, H. Schlaad, *Macromolecules* **2008**, *41*, 9946.
[179] S. P. S. Koo, M. M. Stamenovic, R. A. Prasath, A. J. Inglis, F. E. Du Prez, C. Barner-Kowollik, W. Van Camp, T. Junkers, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 1699.
[180] J. W. Chan, C. E. Hoyle, A. B. Lowe, M. Bowman, *Macromolecules* **2010**, *43*, 6381.
[181] E. Klemm, C. Stöckl, *Makromol. Chem.* **1991**, *192*, 153.
[182] J. Shin, H. Matsushima, J. W. Chan, C. E. Hoyle, *Macromolecules* **2009**, *42*, 3294.
[183] R. M. Hensarling, S. B. Rahane, A. P. LeBlanc, B. J. Sparks, E. M. White, J. Locklin, D. L. Patton, *Polym. Chem.* **2011**, *2*, 88.
[184] S. B. Rahane, R. M. Hensarling, B. J. Sparks, C. M. Stafford, D. L. Patton, *J. Mater. Chem.* **2012**, *22*, 932.
[185] J. Moraes, T. Maschmeyer, S. Perrier, *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 2771.
[186] G. Gody, C. Rossner, J. Moraes, P. Vana, T. Maschmeyer, S. Perrier, *J. Am. Chem. Soc.* **2012**, *134*, 12596.
[187] A. Leitgeb, J. Wappel, C. Slugovc, *Polymer* **2010**, *51*, 2927.
[188] E. J. Goethals, *Makromol. Chem. Macromol Symposia* **1986**, *6*, 53.
[189] E. J. Goethals, P. van Caeter, F. E. Du Prez, M. F. Dubreuil, *Macromol. Symposia* **1995**, *98*, 185.
[190] S. Hilf, A. F. M. Kilbinger, *Nat. Chem.* **2009**, *1*, 537.
[191] P. Theato, H.-A. Klok, *Functional Polymers by Post-Polymerization Modification: Concepts, Guidelines, and Applications*, Wiley-VCH, Weinheim **2012**.
[192] M. A. Hillmyer, S. T. Nguyen, R. H. Grubbs, *Macromolecules* **1997**, *30*, 718.
[193] T. Morita, B. R. Maughon, C. W. Bielawski, R. H. Grubbs, *Macromolecules* **2000**, *33*, 6621.
[194] A. A. Nagarkar, A. Crochet, K. M. Fromm, A. F. M. Kilbinger, *Macromolecules* **2012**, *45*, 4447.
[195] B. R. Maughon, T. Morita, C. W. Bielawski, R. H. Grubbs, *Macromolecules* **2000**, *33*, 1929.
[196] S. Ji, T. R. Hoye, C. W. Macosko, *Macromolecules* **2004**, *37*, 5485.
[197] J. B. Matson, S. C. Virgil, R. H. Grubbs, *J. Am. Chem. Soc.* **2009**, *131*, 3355.
[198] S. Hilf, E. Berger-Nicoletti, R. H. Grubbs, A. F. M. Kilbinger, *Angew. Chem. Int. Ed.* **2006**, *45*, 8045.
[199] *Handbook of Metathesis,* Vol. *3* (Ed: R. H. Grubbs), Wiley-VCH, Weinheim **2003**.
[200] S. Hilf, R. H. Grubbs, A. F. M. Kilbinger, *Macromolecules* **2008**, *41*, 6006.
[201] S. Hilf, N. Hanik, A. F. M. Kilbinger, *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 2913.
[202] S. Hilf, A. F. M. Kilbinger, *Macromol. Rapid Commun.* **2007**, *28*, 1225.
[203] S. Hilf, R. H. Grubbs, A. F. M. Kilbinger, *J. Am. Chem. Soc.* **2008**, *130*, 11040.
[204] A. E. Madkour, A. H. R. Koch, K. Lienkamp, G. N. Tew, *Macromolecules* **2010**, *43*, 4557.
[205] N. Vogel, P. Theato, *Macromol. Symposia* **2007**, *249–250*, 383.

[206] C. Slugovc, S. Demel, S. Riegler, J. Hobisch, F. Stelzer, *J. Mol. Catal. A: Chem.* **2004**, *213*, 107.
[207] S. K. Yang, A. V. Ambade, M. Weck, *J. Am. Chem. Soc.* **2010**, *132*, 1637.
[208] A. V. Ambade, C. Burd, M. N. Higley, K. P. Nair, M. Weck, *Chem.–A Eur. J.* **2009**, *15*, 11904.
[209] A. V. Ambade, S. K. Yang, M. Weck, *Angew. Chem. Int. Ed.* **2009**, *48*, 2894.
[210] S. K. Yang, A. V. Ambade, M. Weck, *Chem.–A Eur. J.* **2009**, *15*, 6605.
[211] J. Romulus, S. Patel, M. Weck, *Macromolecules* **2012**, *45*, 70.
[212] T. Baughman, K. Wagener, in *Metathesis Polymerization*, Vol. *176* (Ed.: M. Buchmeiser), Springer, Berlin, Heidelberg **2005**, pp. 1.
[213] H. Mutlu, L. M. de Espinosa, M. A. R. Meier, *Chem. Soc. Rev.* **2011**, *40*, 1404.
[214] K. B. Wagener, J. T. Patton, M. D. E. Forbes, T. L. Myers, H. D. Maynard, *Polym. Int.* **1993**, *32*, 411.
[215] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2000**, *34*, 18.
[216] E. del Rio, G. Lligadas, J. C. Ronda, M. Galià, M. A. R. Meier, V. Cádiz, *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 518.
[217] M. D. Watson, K. B. Wagener, *Macromolecules* **2000**, *33*, 3196.
[218] M. D. Watson, K. B. Wagener, *Macromolecules* **2000**, *33*, 8963.
[219] K. B. Wagener, K. Brzezinska, J. D. Anderson, T. R. Younkin, K. Steppe, W. DeBoer, *Macromolecules* **1997**, *30*, 7363.
[220] K. R. Brzezinska, K. B. Wagener, G. T. Burns, *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 849.
[221] T. E. Hopkins, J. H. Pawlow, D. L. Koren, K. S. Deters, S. M. Solivan, J. A. Davis, F. J. Gómez, K. B. Wagener, *Macromolecules* **2001**, *34*, 7920.
[222] T. E. Hopkins, K. B. Wagener, *Macromolecules* **2004**, *37*, 1180.
[223] L. Montero de Espinosa, M. A. R. Meier, *Chem. Commun.* **2011**, *47*, 1908.
[224] M. Winkler, L. Montero de Espinosa, C. Barner-Kowollik, M. A. R. Meier, *Chem. Sci.* **2012**, *3*, 2607.
[225] G. Odian, *Principles of Polymerization*, 3rd ed., Wiley, New York **1991**.
[226] D. J. Valenti, K. B. Wagener, *Macromolecules* **1998**, *31*, 2764.
[227] M. D. Watson, K. B. Wagener, *Macromolecules* **2000**, *33*, 5411.
[228] S. E. Lehman, K. B. Wagener, L. S. Baugh, S. P. Rucker, D. N. Schulz, M. Varma-Nair, E. Berluche, *Macromolecules* **2007**, *40*, 2643.
[229] J. E. Schwendeman, K. B. Wagener, *Macromol. Chem. Phys.* **2009**, *210*, 1818.
[230] O. Kreye, T. Tóth, M. A. R. Meier, *Eur. J. Lipid Sci. Technol.* **2011**, *113*, 31.
[231] L. Montero de Espinosa, M. A. R. Meier, J. C. Ronda, M. Galià, V. Cádiz, *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 1649.
[232] O. Türünç, M. A. R. Meier, *Macromol. Rapid Commun.* **2010**, *31*, 1822.
[233] H. D. Maynard, R. M. Broyer, C. M. Kolodziej, in *Click Chemistry for Biotechnology and Materials Science* (Ed: J. Lahann), John Wiley & Sons, Ltd, West Sussex, UK **2009**, pp. 53.
[234] C. P. R. Hackenberger, D. Schwarzer, *Angew. Chem. Int. Ed.* **2008**, *47*, 10030.
[235] G. G. Kochendoerfer, *Curr. Opin. Chem. Biol.* **2005**, *9*, 555.
[236] G. G. Kochendoerfer, S.-Y. Chen, F. Mao, S. Cressman, S. Traviglia, H. Shao, C. L. Hunter, D. W. Low, E. N. Cagle, M. Carnevali, V. Gueriguian, P. J. Keogh, H. Porter, S. M. Stratton, M. C. Wiedeke, J. Wilken, J. Tang, J. J. Levy, L. P. Miranda, M. M. Crnogorac, S. Kalbag, P. Botti, J. Schindler-Horvat, L. Savatski, J. W. Adamson, A. Kung, S. B. H. Kent, J. A. Bradburne, *Science* **2003**, *299*, 884.
[237] H. Shao, M. M. Crnogorac, T. Kong, S.-Y. Chen, J. M. Williams, J. M. Tack, V. Gueriguian, E. N. Cagle, M. Carnevali, D. Tumelty, X. Paliard, L. P. Miranda, J. A. Bradburne, G. G. Kochendoerfer, *J. Am. Chem. Soc.* **2005**, *127*, 1350.
[238] K. L. Heredia, Z. P. Tolstyka, H. D. Maynard, *Macromolecules* **2007**, *40*, 4772.
[239] A. W. Jackson, D. A. Fulton, *Macromolecules* **2009**, *43*, 1069.
[240] J. T. Kopping, Z. P. Tolstyka, H. D. Maynard, *Macromolecules* **2007**, *40*, 8593.
[241] V. Vázquez-Dorbatt, Z. P. Tolstyka, H. D. Maynard, *Macromolecules* **2009**, *42*, 7650.
[242] K. L. Christman, H. D. Maynard, *Langmuir* **2005**, *21*, 8389.
[243] R. C. Li, R. M. Broyer, H. D. Maynard, *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5004.
[244] J. Hwang, R. C. Li, H. D. Maynard, *J. Controlled Release* **2007**, *122*, 279.
[245] G. Sun, C. Cheng, K. L. Wooley, *Macromolecules* **2007**, *40*, 793.
[246] C. Cheng, G. Sun, E. Khoshdel, K. L. Wooley, *J. Am. Chem. Soc.* **2007**, *129*, 10086.
[247] R. C. Li, J. Hwang, H. D. Maynard, *Chem. Commun.* **2007**, 3631.
[248] S. K. Yang, M. Weck, *Macromolecules* **2007**, *41*, 346.
[249] K. L. Christman, R. M. Broyer, E. Schopf, C. M. Kolodziej, Y. Chen, H. D. Maynard, *Langmuir* **2010**, *27*, 1415.
[250] A. P. Esser-Kahn, M. B. Francis, *Angew. Chem. Int. Ed.* **2008**, *47*, 3751.
[251] M. R. Hill, S. Mukherjee, P. J. Costanzo, B. S. Sumerlin, *Polym. Chem.* **2012**, *3*, 1758.
[252] G. N. Grover, J. Lam, T. H. Nguyen, T. Segura, H. D. Maynard, *Biomacromolecules* **2012**, *13*, 3013.
[253] T. Pauloehrl, G. Delaittre, M. Bruns, M. Meißler, H. G. Börner, M. Bastmeyer, C. Barner-Kowollik, *Angew. Chem. Int. Ed.* **2012**, *51*, 9181.
[254] K. L. Christman, E. Schopf, R. M. Broyer, R. C. Li, Y. Chen, H. D. Maynard, *J. Am. Chem. Soc.* **2008**, *131*, 521.
[255] B. Peschke, M. Zundel, S. Bak, T. R. Clausen, N. Blume, A. Pedersen, F. Zaragoza, K. Madsen, *Bioorg. Med. Chem.* **2007**, *15*, 4382.
[256] Y. Jin, L. Song, Y. Su, L. Zhu, Y. Pang, F. Qiu, G. Tong, D. Yan, B. Zhu, X. Zhu, *Biomacromolecules* **2011**, *12*, 3460.
[257] L. Zhu, Y. Shi, C. Tu, R. Wang, Y. Pang, F. Qiu, X. Zhu, D. Yan, L. He, C. Jin, B. Zhu, *Langmuir* **2010**, *26*, 8875.
[258] K. L. Christman, R. M. Broyer, Z. P. Tolstyka, H. D. Maynard, *J. Mater. Chem.* **2007**, *17*, 2021.
[259] S. Bräse, J. H. Kirchhoff, J. Köbberling, *Tetrahedron* **2003**, *59*, 885.
[260] J. N. Cambre, D. Roy, S. R. Gondi, B. S. Sumerlin, *J. Am. Chem. Soc.* **2007**, *129*, 10348.
[261] Y. Qin, V. Sukul, D. Pagakos, C. Cui, F. Jäkle, *Macromolecules* **2005**, *38*, 8987.
[262] Y. Li, G. Vamvounis, J. Yu, S. Holdcroft, *Macromolecules* **2001**, *34*, 3130.
[263] T. Jeffery, *J. Chem. Soc., Chem. Commun.* **1984**, 1287.
[264] A. Gress, A. Völkel, H. Schlaad, *Macromolecules* **2007**, *40*, 7928.
[265] T. Jeffery, *Tetrahedron Lett.* **1985**, *26*, 2667.