1
History of Post-polymerization Modification

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1.1
Introduction

The history of post-polymerization modification, also known as *polymer analogous modification*, is arguably as long as the history of polymer science. As early as 1840, Hancock and Ludersdorf independently reported the transformation of natural rubber into a tough and elastic material on treatment with sulfur [1]. In 1847, Schönbein exposed cellulose to nitric acid and obtained nitrocellulose [2], which was later employed as an explosive. In 1865, Schützenberger prepared cellulose acetate by heating cellulose in a sealed tube with acetic anhydride. The resulting material has found widespread use as photographic film, artificial silk, and membrane material, among others [3]. Although the post-polymerization modification of these natural polymers was widely used in the late nineteenth and early twentieth centuries, the nature of these materials and their modification reactions were only poorly understood. This comes as no surprise, as it was at the same time that Staudinger [4], one of the pioneers of modern polymer science, was struggling to gain acceptance for the notion of the existence of macromolecules. Staudinger [5] also coined the term *polymer analogous reaction* and studied these reactions as an attractive approach to fabricate functional materials.

The general acceptance of the concept of macromolecules also marked the beginning of an increased use of post-polymerization modification reactions to engineer synthetic polymers. Serniuk *et al.* [6] reported the functionalization of butadiene polymers with aliphatic thiols via thiol–ene addition in 1948. Chlorinated polystyrene–divinylbenzene beads were first used in the 1950s as ion exchange resins [7] and later by Merrifield to develop solid-state peptide synthesis [8]. The modification of halogenated or lithiated poly(meth)acrylates was first investigated in the early 1960s [9, 10] and followed by Iwakura's studies on the post-polymerization modification of polymers bearing pendant epoxide groups [11–13]. Although many of the early developments in polymer science can be attributed to the utilization of post-polymerization modifications, the variety of chemical reactions that was available for post-polymerization modification was relatively limited (Figure 1.1). This, however, rapidly changed in the early 1990s with the emergence

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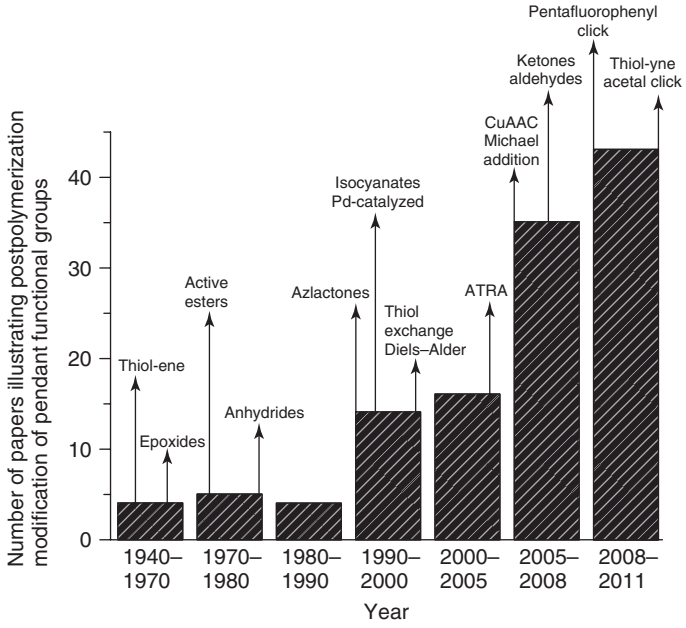
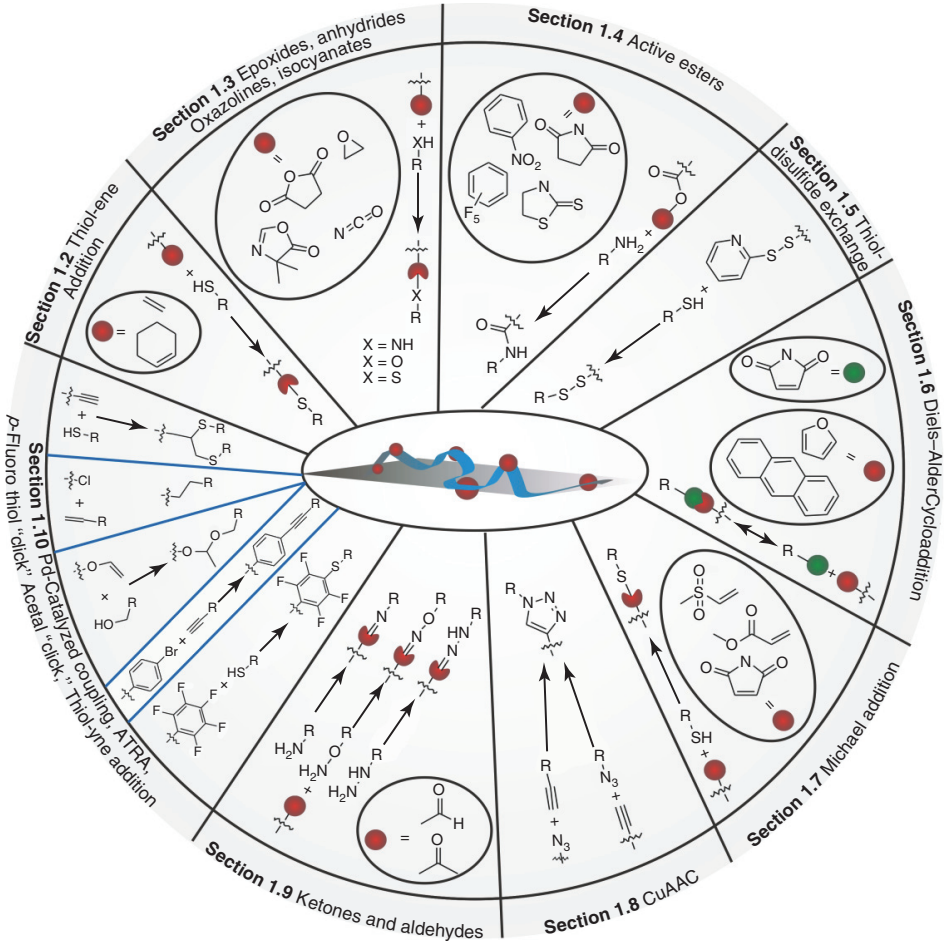


Figure 1.1 Historical overview of the development of post-polymerization modification. The work on post-polymerization modification increased with a skyrocketing pace starting from the late 1990s as a result of development of functional-group-tolerant (controlled radical) polymerization techniques combined with the (re)discovery of highly efficient coupling chemistries. This figure was prepared based on the articles cited in this chapter and last updated in September 2011.

of living/controlled radical polymerization techniques such as atom-transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT), and nitroxide-mediated polymerization (NMP) [14–16]. The improved functional group tolerance of these methods as compared to conventional polymerization techniques allowed the fabrication of well-defined polymers bearing a wide variety of functional groups that can be quantitatively and selectively modified using relatively mild conditions without any side reactions.

The emergence of living/controlled radical polymerization techniques coincided with the discovery/revival of several chemoselective coupling reactions such as copper-catalyzed azide/alkyne cycloaddition (CuAAC), thiol–ene addition, and many others, which are now commonly referred to as *click* reactions. Together, these two developments provided the basis for the explosive growth in use and versatility of post-polymerization reactions since the 1990s. The aim of this chapter is to give a historical account of the development of nine main classes of post-polymerization modification reactions (Scheme 1.1). For the selection of these reactions, strategies that involve the use of, for example, poorly controlled nucleophilic substitution reactions and the modification of relatively inert groups, such as alcohols and carboxylic acids, were not considered. Instead, emphasis was placed on readily



Scheme 1.1 Nine different classes of reactions that can be used for the preparation of functionalized polymers via post-polymerization modification.

available reactive groups that do not require an additional deprotection step before post-polymerization modification.

1.2
Post-polymerization Modification via Thiol-ene Addition

The anti-Markovnikov addition of thiols to alkenes is usually mediated by a radical source or by ultraviolet (UV) irradiation [17]. One of the earliest systematic studies regarding the post-polymerization modification of polyBu via radical thiol addition was reported by Serniuk and coworkers in 1948 [6]. They proposed that only the vinyl

groups generated by 1,2-addition of butadiene units (i.e., pendant vinyl groups) were functionalized, which was later confirmed by Romani and coworkers [18]. Since these early studies, thiol–ene post-polymerization modification has developed into a powerful synthetic tool. Table 1.1 provides an overview of different alkene functional polymers that have been used as substrates for post-polymerization modification.

A drawback of thiol–ene addition to poly(1,2-Bu) is that because of the close proximity of the neighboring vinyl groups, the radical formed after the addition of the thiol may attack an adjacent vinyl group, leading to an intramolecular cyclization [20]. One possibility to suppress this side reaction is to carry out the post-polymerization modification at low temperature and at relatively high concentrations [24]. Schlaad and coworkers further illustrated that, by increasing the distance between pendant alkene groups, intramolecular cyclization could also be supressed, which revolutionized the via thiol–ene post-polymerization modification [22]. This was demonstrated by the post-polymerization modification of poly2Box, which was quantitatively modified using 1.2–1.5 equivalents thiol under mild conditions (radicals generated with UV light at room temperature).

Radicals that mediate the thiol–ene addition can either be generated by thermal or photochemical initiation. Hawker and coworkers illustrated that, although both initiation pathways lead to the complete conversion of pendant alkenes, milder conditions and shorter reaction times are sufficient when photoinitators are used (Scheme 1.2) [23]. Furthermore, they also demonstrated the orthogonality of the radical thiol addition and CuAAC and the compatibility of the alkene group with controlled radical polymerization (CRP) techniques.

Recently, Heise reported the preparation of an unsaturated polyester (polyGI) via enzymatic ring-opening polymerization (ROP) of the corresponding cyclic ester monomer containing backbone alkene groups. He demonstrated that these backbone alkene groups are also susceptible to post-polymerization modification via thiol–ene addition, but near-quantitative conversion of these groups is only possible when a high excess of thiol is used, as these backbone alkene groups have decreased reactivity compared to pendant alkenes [31].

1.3 Post-polymerization Modification of Epoxides, Anhydrides, Oxazolines, and Isocyanates

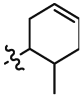
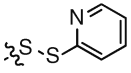
Epoxides, anhydrides, oxazolines, and isocyanates represent a class of reactive groups that have a relatively long history in polymer science. A common feature of these groups is that they are tolerant toward radical-based polymerization techniques, which explains why polymers containing these groups were extensively used for the fabrication of functional polymers via post-polymerization modification already since the 1960/1970s. Table 1.2 provides an overview of polymers bearing epoxide, anhydride, oxazoline, and isocyanate groups that have been used for post-polymerization modification.

Table 1.1 Post-Polymerization modification of (co)polymers via radical thiol addition.

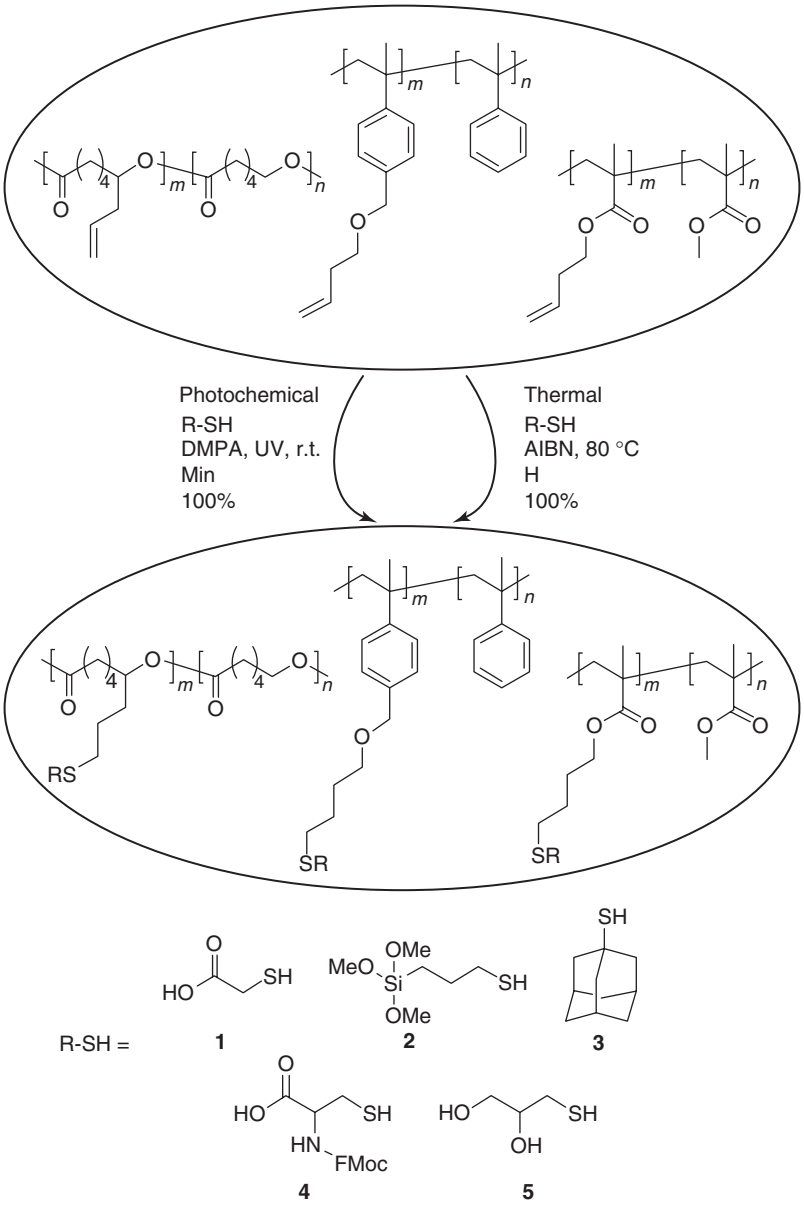
Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Conversion (%)	Comments
	Bu	St	FRP	Thioglycolic acid, air, r.t. 3–144 h	38–47	Only the vinyl double bonds (generated by 1,2-addition) were assumed to undergo functionalization [6]
		AN		C_8–C_{16} chain length mercaptans (2.0 equivalents), 180–200 °C	35–52	
	Bu	St	FRP	Thioglycolic acid, ethyl mercaptoacetate, AIBN, or benzoyl peroxide, 90–100 °C, 2.5 h	24–40	Post-Polymerization modification only proceeds from the vinyl double bonds. Side reactions are possible [18]
	V4 V1D2	D3	ROP	1-Octanethiol, 2-(4-pyridyl)ethanethiol (2.0–3.0 equivalents), AIBN (0.12–0.26 equivalents), 65 °C, 2–24 h	100	Excess thiol was used to suppress the side reactions [19]
	1,2-Bu	EO	AP	A library of thiols (5.0–40.0 equivalents), AIBN (0.3 equivalents), 70 °C, 24 h	70–86	Side reactions are possible [20, 21]
	2BOx	2EOx	CROP	A library of thiols (1.2–1.5 equivalents), UV, 24 h	96–100	Mild reaction conditions. No side reactions. Radical thiol addition was proposed as a click reaction [22]
	B3MA	MMA	ATRP	Library of thiols (5.0–10.0 equivalents), DMPA (0.2 equivalents), UV, r.t., 0.5–2 h	46–100	Photochemical initiation warrant access to greater yields at milder conditions compared to thermal initiation. Orthogonality of the thiol–ene and CuAAC reactions was demonstrated [23]
	αAlεCL	εCL	ROP	Library of thiols (5.0–10.0 equivalents), AIBN (0.2 equivalents), 80 °C, 3–24 h	17–100	
	BMVB	St	RAFT			
	1,2-Bu	—	—	Methyl 3-mercaptopropionate (2.0 equivalents), UV, −35 °C, 24 h	86	Carried out in concentrated media and at low temperature to suppress side reactions [24]
	MAC	—	—	A library of thiols (2.0 equivalents), AIBN (0.1 equivalents), 90 °C, 24 h	Quantitative	Excess thiol was used to suppress side reactions [25]
	U($ArAll_3$-HMDI)	—	PA	2-Mercaptoethanol (47 equivalents), AIBN (2.0 equivalents), 80 °C, 24 h	Quantitative	Polymer bears three allyl groups per repeating unit [26]
	AGE	EO	AROP	A library of thiols (20.0 equivalents), AIBN (0.75 equivalents), 75 °C, overnight	90–98	Excess thiol was used to suppress the side reactions [27]
	EVGE	EO	AROP	Benzyl mercaptan (0.5–10.0 equivalents), AIBN (0.75 equivalents), 75 °C, 12 h	Quantitative	No side reactions [28]
	DecEnOx	2EOx	CROP	Ac_4GlcSH (1.2 equivalents), DMPA (0.2 equivalent), UV, 6 h	100	Polymer contains three chemoselective handles allowing sequential functionalization [29]

(*continued overleaf*)

Table 1.1 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	CHMFS	—	RAFT	$C_{12}H_{25}SH$ (3.0 equivalents), DMPA (2 mol%), UV, 30 min	85	[30]
	GI	—	ROP	6-Mercapto-1-hexanol, butyl-3-mercapto propionate, *N*-acetylcysteamine (excess), AIBN, 80 °C	75–95	Excess thiol is necessary for high degree of functionalization [31]
	PDSM	—	RAFT	PEG_{2000}-acrylate (1.2 equivalents), DMPA (0.20 equivalent), TCEP (1.0 equivalents), UV, 1 h	68	Side reactions are possible [32]

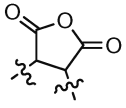
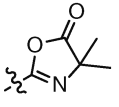
AIBN, 2,2′-Azobis(2-methylpropionitrile); AP, anionic polymerization; CROP, cationic ring-opening polymerization; DMPA, 2,2-dimethoxy-2-phenylacetophenone; and AROP, anionic ring-opening polymerization.
For each functional group/substrate, entries are listed in chronological order.



Scheme 1.2 Post-Polymerization modification of polymers bearing alkene groups via thiol–ene addition either mediated by photochemical or thermal initiation [23].

Table 1.2 Post-Polymerization modification of (co)polymers bearing epoxide, anhydride, oxazoline, and isocyanate groups.

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Conversion (%)	Comments
	GA	AN	FRP	Di-*n*-butylamine, diethanolamine (4.0 equivalents), 70 °C, 10–14 h	45–80	Conversion depends on copolymer composition [11, 12]
	GMA	MMA	FRP	Di-*n*-butylamine, *N*-butylhexylamine (1.0 equivalent), 70 °C, 2.5 h	20–35	[13]
	GMA	St	FRP	A library of amines and carboxylic acids (excess), 80 °C, 20 h	20–80	Addition of TEA improved the rate of post-polymerization modification with carboxylic acids [33].
	GMA	MMA	FRP	NPC, NNC (1.0 equivalent), base (1.0 equivalent), 90–130 °C, 24 h	35–95	Side reactions are possible [34].
	GMA	MMA	FRP	4-Hydroxy-4′methoxybiphenyl (1.3 equivalents), Na (1.3 equivalents), refluxed in 1,4-dioxane, 6 h	75–100	Copolymer is more reactive than homopolymer [35]
	GMA	MMA	SI-ATRP	Octylamine (1.0 M), 60 °C, 4 h	58	Cross-linking occurs between neighboring chains [36]
	GMA	DEAEMA	SI-ATRP	A library of primary amines (0.5–1.0 M), r.t., 48 h	10–79	Tertiary amine groups of DEAEMA catalyzes the reaction [37]

	MAn	St	FRP	Neocarzinostatin (0.2 equivalent), 4 °C, pH 8.5, 24 h	97 (Amino group)	MAn is partially hydrolyzed. Polymer–drug conjugate was prepared (SMANCS) [38, 39]
	MAn	St	FRP	Octylamine, 0–40 °C, 3 h	90	Functionalization with sterically hindered amines is not possible [40]
	MAn	St	FRP	4-Aminobenzoic acid (1.5 equivalents), TEA (2.0 equivalents), 90 °C, 48 h	Quantitative	Near-quantitative functionalization with aromatic amines is possible. Conversion of MAn with amines is greater compared to alcohols [41]
	MAn	St	—	A library of amine-functionalized sugars (2.0 equivalents), r.t., 3 h	54–94	Obtained glycopolymers showed improved hepatic cell adhesion compared to hydrolyzed Ma_n-*alt*-St [42]
	MAn	St	FRP	Propylamine, butylamine, pentylamine, r.t., 5 h	Quantitative	[43]
	VDM	MMA	FRP	4-Methoxy-4′-(β-aminoethoxy) biphenyl (1.1 equivalents), 70 °C, 24 h	65–90	No side reactions [44]
	VDM	AAm EdMA St	SI-FRP	Benzylamine (0.3 equivalent), 30 min	100	Functionalized porous disks were developed to scavenge excess amines from the reaction mixtures [45]
	VDM	—	FRP	Benzylamine, Jeffamine M600®, DBz_{10}, 40 °C, 72 h	Quantitative	Aqueous post-polymerization modification [46]
	VDM	St	NMP	Benzylamine, morpholine (1.2 equivalents), r.t., 24 h	Quantitative	[47]
	NBAz	—	ROMP	Glycine methyl ester hydrochloride (1.5 equivalents), TEA (1.5 equivalents), r.t., 20 h Diethylamine (1.1 equivalents), r.t., 20 h	Quantitative	[48]
	VDM	St	SI-ATRP	Benzylamine (1.0 equivalent), r.t., 24 h	66–98	M_n of the copolymer influences the extent of post-polymerization modification [49]

(*continued overleaf*)

Table 1.2 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Conversion (%)	Comments
	TMI	St	FRP	PEG_{750}-OCH_3, hydroxymethyl(benzo-18-crown-6) (5.0 equivalents), DBTDL (catalyst), 85 °C, 20 h	Quantitative	Post-Polymerization modification of a cross-linked network [50]
	MVI	MA	FRP	A library of hydroxyl-functionalized hemicyanines (0.3 equivalent), 40 °C, 3 d	30–35	Allows the fabrication of polymeric multilayers containing nonlinear optical (NLO) chromophores [51]
	MVI	MI	FRP	A library of undemanding alcohols and hydroxyl-functionalized chromophores (1.0 equivalent), DBTDL (0.02 equivalent), 50 °C, 1–2 d	Quantitative	Reactivity of isocyanates toward alcohols and amines were demonstrated in different reaction conditions [52]
	VI			A library of amines (1.0 equivalent), 50 °C, 2–3 h	80–100	
	TMI	St	ATRP	9-Methyl-(aminomethyl) anthracene, r.t., 4 h	Quantitative	[53]
	AOI	—	RAFT	Hexanol (1.5 equivalents), 0.1% (wt) DBTDL, overnight Hexylamine (1.0 equivalent), overnight Hexanethiol (1.0 equivalent), 0.5% (wt) TEA, overnight	Quantitative	Reactivity and chemoselectivity of isocyanates toward alcohols, amines, and thiols were demonstrated in different reaction conditions [54]
	AOI	—	SI-PP	A library of thiols, DBU (0.2 mol% with respect to thiol), r.t., minutes	Quantitative	Proposed as a click reaction. Faster functionalization when DBU was used as a catalyst compared to TEA [55]

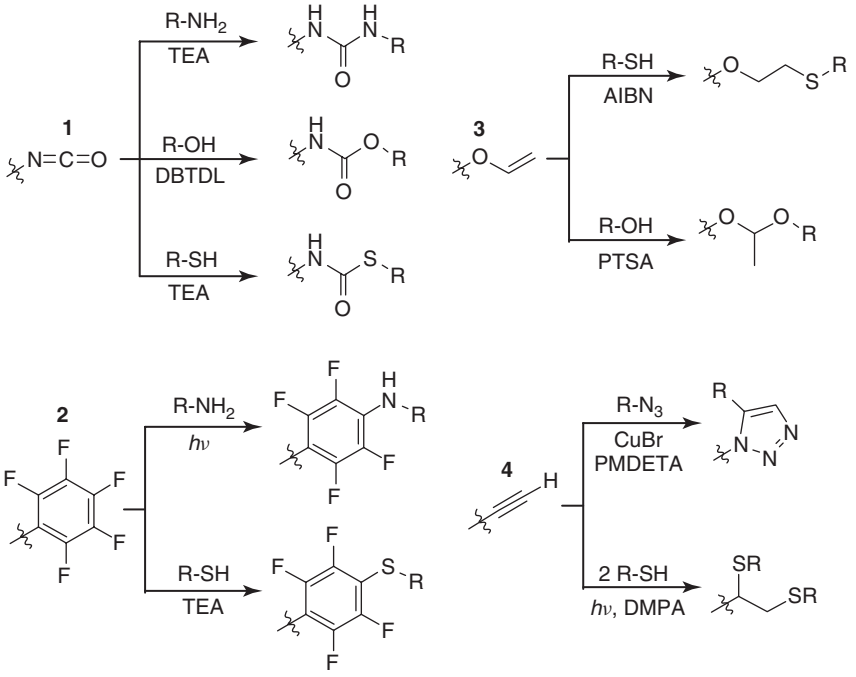
SI-ATRP, surface-initiated atom-transfer radical polymerization; SI-FRP, surface-initiated free-radical polymerization.
For each functional group/substrate, entries are listed in chronological order.

Although thermosetting epoxy resins were already being used in the 1950s for many applications such as tissue embedding for electron microscopy [56] or as dental restoratives [57], it was only in the 1960s that Iwakura and coworkers for the first time systematically studied the post-polymerization modification of polymers containing epoxide groups, such as polyGA and polyGMA. They reported that the post-polymerization modification of polyGA or polyGMA with simple secondary amines (1.0–4.0 equivalents of amine) proceeded with low to moderate yields [11–13]. In 1974, Kalal [33] illustrated that the post-polymerization modification via epoxide ring opening can be catalyzed by a tertiary amine (TEA) and reported up to 80% conversion of epoxide groups of polyGMA with carboxylic acids in the presence of TEA. More recently, Barbey and Klok [37] exploited the catalytic effect of the TEA groups on epoxide ring opening by preparing polyGMA-*co*-polyDMAEMA brushes, which contained pendant TEA groups that were demonstrated to accelerate the rate of post-polymerization modification via epoxide ring opening with amines in aqueous media at room temperature. A drawback of epoxide-functionalized polymers is that they are prone to cross-linking on modification with primary amines because of the reaction between the secondary amines formed after the epoxide ring opening with another unreacted epoxide group [36]. While amines are most frequently employed for the post-polymerization modification of polymers bearing epoxide groups, epoxide groups themselves are reactive toward, for example, alcohols and carboxylic acids [33, 35].

Maleic anhydride (MAn) copolymers have attracted significant attention since the late 1970s and early 1980s with the work carried out by Maeda and coworkers [38, 39], who prepared the anticancer agent poly(styrene-*co*-maleic anhydride) conjugated neocarzinostatin (SMANCS). Functionalization of MAn copolymers with undemanding primary amines was reported to proceed almost quantitatively at ambient temperatures [40, 42, 43], whereas N-substituted maleimide (MI) formation was observed at elevated temperatures on ring closure of the maleamic acid (i.e., amine-modified MAn) [58, 59].

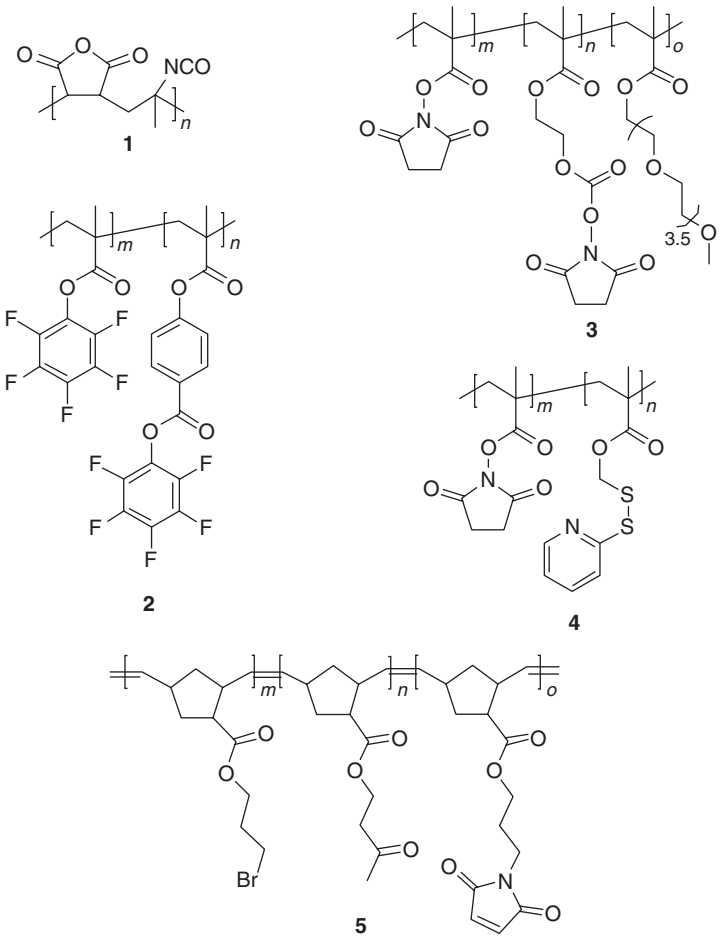
Polymers bearing pendant oxazoline groups can be prepared by the polymerization of 2-vinyl-4,4-dimethyl-5-oxazoline (VDM), which was first illustrated by Taylor and coworkers in the early 1970s [60]. Similar to MAn copolymers, quantitative modification of polyVDM with amines is possible at room temperature [47, 48]. Furthermore, the hydrolytic stability of the oxazoline group allows aqueous post-polymerization modification without side reactions [46]. For instance, this selectivity toward amines in aqueous media was utilized for rapid and high-density immobilization of protein A onto polyVDM-functionalized beads at pH 7.5 [61].

The isocyanate group is another attractive handle that allows post-polymerization modification with amines, alcohols, and thiols. While the modification of isocyanates with amines or thiols proceeds rapidly and quantitatively and can be further facilitated by the addition of TEA or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), quantitative conversion with alcohols is only possible in the presence of a catalyst such as dibutyltin dilaureate (DBTDL) (**1** in Scheme 1.3) [51, 54]. *m*-Isopropenyl-α-α-dimethylbenzyl isocyanate (TMI), vinylisocyanate (VI), and



Scheme 1.3 Polymers bearing isocyanate, *n*-alkyl pentafluorophenyl, allyl ether, and alkyne groups that can be quantitatively modified with various reagents, but under different reaction conditions [28, 51, 54, 65, 66].

1-methylvinylisocycanate (MVI) are examples of commonly employed monomers for the synthesis of isocyanate-containing (co)polymers (Table 1.2). A special feature of these isocyanate monomers, which they share with MAn, is that their homopolymerization is more demanding compared to their copolymerization. While the homopolymerization of VI by conventional polymerization techniques can be accompanied by a variety of side reactions because of the competing reactivity of the vinyl double bond and isocyanate group [62], TMI homopolymerization does not yield high-molecular-weight polymer because of the steric hinderance imposed by the α-methyl group to the radical propagation site [63, 64]. Beyer and coworkers [51] synthesized MVI-*alt*-MAn, in which the isocyanate and anhydride groups were sequentially modified with an alcohol and amine, respectively (**1** in Scheme 1.4). More recently, Flores *et al*. reported that a novel isocyanate-containing monomer (2-(acryloyloxy)ethylisocyanate, AOI) can be readily homopolymerized via RAFT polymerization [54] unlike VI, TMI, and MI, and Hensarling and coworkers [55] demonstrated the quantitative modification of polyAOI with thiols within minutes at room temperature.

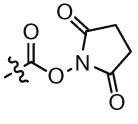


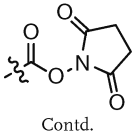
Scheme 1.4 Polymers bearing multiple orthogonal and chemoselective handles that allow either sequential or one-pot post-polymerization modification with different functional groups [51, 67–70].

1.4 Post-polymerization Modification of Active Esters

The synthesis and post-polymerization modification of active ester polymers was pioneered by Ferruti and Ringsdorf in the 1970s [71, 72]. Since then, a broad variety of active ester polymers has been developed utilizing essentially the complete spectrum of available polymerization techniques (Table 1.3). The reaction of active ester polymers with amines is probably the most frequently used post-polymerization modification strategy. Amines are most often used for the post-polymerization modification of active ester polymers since they can react selectively even in the presence of weaker nucleophiles, such as alcohols.

Table 1.3 Postpoymerization modification of (co)polymers bearing active ester groups.

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	NAS	—	FRP	Piperidine, allylamine, r.t., 4 h	Quantitative	Side reactions are possible [72]
	NMAS	—		*N*-Butylamine, 60 °C, 6 h		
	NAS	—	FRP	Cyclohexylamine (2.0 equivalents), r.t., 5 d	60–70	PolyNAS is more reactive than polyNMAS [71]
	NMAS	—				
	NAS NSVB	St	NMP	[G-4]-NH_2 (1.1 equivalents), heat, 24 h	50–100	Side reactions are possible. Conversion depends on copolymer composition [73]
	NHNS		ROMP	Aminoethyl mannoside (1.2 equivalents), NMM (1.1 equivalents), 24 h, followed by the addition of DIC (1.0 equivalent) to the reaction mixture, overnight	—	Post-Polymerization modification yielded polymers with greater biological activity compared to the polymer generated by prefunctionalization strategy [74]

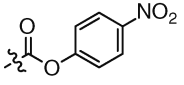


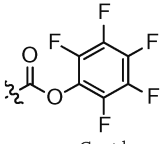
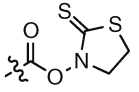
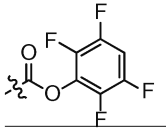
Contd.

NMAS	—	ATRP	H-Gly-Gly-β-naphthylamide·HBr·0.6H_2O (0.10 equivalent), TEA (0.2 equivalent), 50 °C, 2.5 h, followed by the addition of 1-amino-2-propanol (2 equivalents) to the reaction mixture, 50 °C, 1.25 h	Quantitative	Well-defined polymer–drug conjugates were synthesized [75]
NMAS	—	ATRP	A library of primary aliphatic amines bearing charged groups, r.t., overnight	Quantitative	Sequential modification with two different charged amines yielded pH-responsive polymers [76]
NAS	—	ATRP	Galactosamine (0.2 equivalent), TEA (2.0 equivalents), 60 °C, 6 h	Quantitative	[77]
NMAS	HPMA	RAFT	Peptide Ac-HTSTYWWLDGAPK-Am (130.0 equivalents), TEA (excess), 50 °C, 24 h	14	Polymer peptide conjugate exhibits 3 orders of magnitude higher affinity toward antrax toxin compared to the unbound peptide [78]
MAC_2AE	—	SI-FRP	A library of *n*-alkylamines (C_3-C_{18}), biomolecules, dyes, complexing agents, PEG-NH_2 (50 mg or 50 µl), TEA (50 µl), 40 °C, 16 h	34–100	The relationship between the polymer brush thickness and the molar mass of the polymer repeating unit was demonstrated [79]
NSVB	—	RAFT	Terpy-NH_2 (2.5 equivalents), 50 °C, 16 h	95–99	No side reactions [80]
NSVB	—	SI-ATRP	1-Amino-methylpyrene, octadecylamine (0.12 M), TEA, 40 °C, overnight	Quantitative	[81]
NMAS	PEGMA AHMA SCEMA	FRP	Allylamine (5.0 equivalents), TEA (5.0 equivalents), r.t., 18 h	Quantitative	Polymers bearing multiple chemoselective handles allowing orthogonal functionalization [68]

(*continued overleaf*)

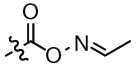
Table 1.3 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Post-Polymerization modification: Conversion (%)	Post-Polymerization modification: Comments
	NPA	St	FRP	Benzyloxyamine, 120–140 °C, 25 h	Quantitative	Harsh conditions. Side reactions are possible [82]
	NPA NPMA	HPMA	FRP	*t*-Butylamine, diisopropylamine (100.0 equivalents), 25 °C	75–100	Polymers are more reactive than the monomers toward diisopropylamine [83]
	NPMA	St	ATRP	*N*-Butylamine (9.0 equivalents), 50 °C, 24 h	Quantitative	[84]
	NPMA	—	RAFT	Glycine methyl ester (10.0 equivalents), TEA, 50 °C, 12 h	86	[85]
	PFMA PFA	—	FRP	Hexylamine, *n*-hexylmethylamine (1.0 equivalent), base (1.0 equivalent), 50 °C, 24 h	65–99	PolyPFA is more reactive than polyPFMA. Functionalization with secondary amines is not possible [86]
	PFMA	—	PPP	1,6-Diaminohexane (0.01 M) in 10.0 mM PBS, 10 min	Quantitative	High-energy process. Side reactions and hydrolysis are possible [87]

 Contd.	PFPNorb	—	ROMP	Hexylamine, *n*-hexylmethylamine (2.0 equivalents), 50 °C, 24 h	Quantitative	[88]
	PFMA	—	RAFT	Library of primary aliphatic amines (2.0 equivalents), TEA (2.0 equivalents), 50 °C, 16 h	47–100	Steric effects limit the extent of post-polymerization modification [89]
	PFVB	—	FRP	A library of primary, secondary and cyclic amines (2.0 equivalents), r.t., 12 h Aniline (2.0 equivalents), 50 °C, 12 h	100	More reactive than polyPFA and polyPFMA. Functionalization with aromatic amines is possible [90]
	PFVB	PFMA	RAFT	A library of aromatic amines, 60 °C, 6 d	100	Sequential functionalization of the copolymer was achieved. Functionalization with secondary aromatic amines is not possible [67]
	MAPTT	HPMA	FRP	1-Amino-2-propanol, methyl esters of amino acids (2.0 equivalents), 25 °C, 1–60 min	Quantitative	Aqueous post-polymerization modification is possible. Side reactions in the copresence of amines and thiols [91]
	TFPMA	DMAEMA	ATRP	Benzylamine, cyclohexylamine (2.0 equivalents), 60 °C, 6 h *t*-Butylamine (3.0 equivalents), 80 °C, 24 h	Quantitative	Less reactive than pentafluorophenyl ester polymers [92].

(*continued overleaf*)

Table 1.3 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Conversion (%)	Comments
	AOA	—	FRP RAFT NMP	Diisopropylamine (0.19 equivalent), 50 °C, 48 h followed by ammonia (excess), 50 °C, 24 h	Quantitative	polyAOA partially modified with diisopropylamine exhibits an LCST [93]
	AOA	—	RAFT	Hydrazide (10.0 equivalents), 0 °C, 1 h	Quantitative	Hydrazide-functionalized polyAOA employed as an intermediate for the covalent immobilization of a glycan library [94]

PBS, phosphate-buffered saline.
For each functional group/substrate, entries are listed in chronological order.

The most frequently employed active ester polymers are *N*-hydroxysuccinimide derivatives (NHS), such as polyNAS and polyNMAS. A drawback of these polymers, however, is that their solubility is limited to DMF and DMSO. Furthermore, the post-polymerization modification of these active ester polymers can be accompanied by side reactions, such as succinimide ring-opening or the formation of N-substituted glutarimide groups [95]. These side reactions can be suppressed by using an excess of amine or proton acceptor, such as TEA or DMAP [96].

Polymers bearing pentafluorophenyl (PFP) ester groups are attractive alternatives to NHS ester polymers, as polyPFMA was demonstrated to have higher reactivity and better hydrolytic stability and is soluble in a wide range of solvents as compared to polyNMAS [86]. Nevertheless, similar to NHS, PFP ester homopolymers are insoluble in water and thus cannot be functionalized in aqueous media.

Another class of active ester polymers that form an interesting alternative to polyNAS and polyNMAS are those that contain thiazolidine-2-thione (TT) groups. Subr and Ulbrich [91] reported that polymers bearing TT groups allow rapid aminolysis in aqueous media while displaying good hydrolytic stability. The difference between the rates of aminolysis and hydrolysis was found to be greatest between pH 7.4 and 8.0. A drawback of TT esters is that they display low selectivity between amines and thiols under identical reaction conditions.

Active ester polymers based on 4-vinyl benzoate (VB) often exhibit higher reactivity compared to their (meth)acrylates. For instance, Hawker *et al.* [73] used polyNSVB to fabricate dendrimer-functionalized polymers with high yields. Theato and Nilles [90] illustrated that, unlike polyPFMA and polyPFA, polyPFVB can quantitatively react with less nucleophilic aromatic amines. In a subsequent study, the same authors prepared statistical and block copolymers from pentafluorophenyl 4-vinyl benzoate (PFVB) and pentafluorophenyl methacrylate (PFMA) and demonstrated that these polymers could be sequentially modified with an aromatic and aliphatic amine, respectively (**2** in Scheme 1.4) [67].

An alternative strategy toward orthogonally functionalizable active ester-based polymers was developed by Sanyal and coworkers [68]. These authors prepared copolymers of *N*-methacryloxysuccinimide (NMAS) with PEGMA and the carbonate functional monomer 2-(N-succinimidylcarboxyoxy)ethyl methacrylate (SCEMA) (**3** in Scheme 1.4). Exposure of this copolymer to allylamine in THF at room temperature led to complete conversion of the carbonate groups with near-quantitative preservation of the active ester moieties, which could be subsequently modified by adding an excess of propargylamine at 50 °C.

1.5
Post-polymerization Modification via Thiol-Disulfide Exchange

Thiol–disulfide exchange is ubiquitous in biology where it is involved in a variety of processes such as modulation of enzyme activity [97], viral entry [98], and protein folding [99]. Although this reaction has been known since the 1920s from a study of Lecher on alkalisulfides/alkalithiols [100] as well as from the work of Hopkins on

the biochemistry of glutathione [101], it was not until the late 1990s that Wang and coworkers first demonstrated that polymers bearing pyridyl disulfide groups could be employed as an appealing platform for post-polymerization modification via thiol–disulfide exchange, as it could proceed quantitatively and selectively in mild conditions and in aqueous media below pH 8 [102]. Table 1.4 gives an overview of various pyridyl disulfide-containing polymers that have been used as substrates for post-polymerization modification.

Thiol–disulfide exchange post-polymerization modification is strongly pH dependent. There are opposing claims, however, regarding the optimum pH for quantitative functionalization. While Wang and coworkers [102] first illustrated that the rate of post-polymerization modification was highest between pH 8 and 10, Bulmus *et al.* [103] later reported higher conversions of pyridyl disulfide groups with terminal cysteine residues at pH 6 compared to pH 10.

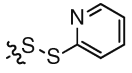
One of the assets of the thiol–disulfide exchange reaction is that it allows the introduction of functional groups via a disulfide bond that is reversible and can be cleaved, either via reduction or with an exchange with another thiol. For instance, Langer [104] first demonstrated the reduction of pyridyl disulfide-containing poly(β-amino ester)s modified with glutathione in intracellular media, which led to a 50% decrease in the DNA binding capacity of the polymer. Ghosh *et al.* [69] later illustrated the quantitative release of incorporated thiols from the polymer backbone on reduction of the newly formed disulfide bonds by DTT. Furthermore, they also illustrated the orthogonality of thiol–disulfide exchange and aminolysis of active esters (**4** in Scheme 1.4).

1.6 Post-polymerization Modification via Diels-Alder Reactions

The cycloaddition reaction between a diene and a substituted alkene (dienophile), which was discovered in 1928 by Diels and Alder and distinguished with a Nobel Prize in Chemistry in 1950 [106], emerged as an attractive tool for post-polymerization modification in the 1990s [107, 108]. The Diels–Alder reaction fulfills the ''click'' criteria [109], as it can proceed with quantitative yields without any side reactions, is tolerant to a wide variety of functional groups, and is orthogonal with many other chemistries, such as CuAAC [110, 111]. Furthermore, many Diels–Alder reactions are reversible and the Diels–Alder adduct can decompose into the starting diene and dienophile at higher temperatures as compared to the temperature required for the forward reaction [112]. The reversibility of the Diels–Alder reaction has been extensively utilized to prepare thermoresponsive macromolecular architectures such as gels [107, 113–116], as well as in the synthesis of dendrimers [117] and smart copolymers [118].

Polymers that can be postmodified using Diels–Alder chemistry can be prepared either via a precursor route based on the deprotection of masked MI groups following polymerization of the corresponding monomers [116, 119] or by direct

Table 1.4 Post-Polymerization modification of (co)polymers via thiol–disulfide exchange.

Polymerization				Post-Polymerization modification		
Functional group(s)	**Monomer**	**Comonomer**	**Polymerization method**	**Reagents – reaction conditions**	**Conversion (%)**	**Comments**
	PDTEMA	HPMA	FRP	Peptide pAntp-SH (0.1 equivalent), pH 3–8, min Oligo-SH (0.1 equivalent), pH 9, 5 min	Quantitative 50	Extent of post-polymerization modification is highly pH dependent. PDTEMA content in copolymer: 8.3 mol% [102]
	PDSA	MAA	FRP	Peptide 5-FAM-$(Gly)_3$-Cys (excess), overnight	100	Extent of post-polymerization modification is highly pH dependent. PDSA content in copolymer: 3–8 mol% [103]
		*n*BA		Peptide $(Lys)_6$-$(Gly)_3$-Cys (0.53–0.90 equivalent), pH 6 or 10, r.t., 16 h	35–86	
				Oligo-SH (0.30–1.0 equivalent), pH 7.4 or 9.0, r.t., 16 h	27–50	
	PDA(β-amino ester)	—	PA	Mercaptoethylamine (excess), r.t., 0.5 h Peptide RGDC (2 equivalents), r.t. 28 h	Quantitative	Biodegradable polymer bearing thiol-reactive handles [104]
	PDSM	NMAS	ATRP	1-Undecanethiol, thiomethylanthracene (1.2 equivalents), AcOH (catalyst), r.t., 4 h	Quantitative	Reversibility of the reaction was demonstrated. Synthesized polymer bears two chemoselective handles allowing simultaneous functionalization [69]
	PDSM	—	RAFT	A library of thiols (0.06–1.0 equivalent), r.t, 14 h	65–100	Simultaneous functionalization with two different thiols is possible [105]

For each functional group/substrate, entries are listed in chronological order.

polymerization of the monomers containing unmasked dienes, such as furan or anthracene groups (Table 1.5). In an early example, Laita and coworkers demonstrated the post-polymerization modification of various furan-containing polyurethanes in which the furan group was either incorporated in the backbone or in the side chain of these polymers. While modification of the pendant furans with MIs proceeded to completion, conversion of backbone furan groups was limited to 30–60% at 40 °C using 3.0 equivalents of MI [120]. Jones *et al.* [114] later reported higher conversions (60–85%) of the post-polymerization modification of backbone anthracene groups with MIs in stoichiometric conditions when the reaction temperature was increased to 120 °C. Kim and coworkers [121] prepared copolymers bearing pendant anthracene groups, which were quantitatively modified with relatively bulky MI-functionalized chromophores at 120 °C by using stoichiometric amount of MI.

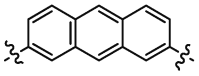
Another interesting class of functional groups for the Diels–Alder post-polymerization modification is pyridinedithioesters. These are attractive since they can act both as a chain transfer agent in RAFT polymerization [124] as well as a heterodienophile in [4 + 2] cycloaddition [125, 126]. Bousquet and coworkers [123] exploited this unique feature to quantitatively modify poly*tt*HA at 50 °C by using 4.0–5.0 equivalents of poly*t*BA (M_n = 3500–13500 g/mol), which was prepared by RAFT polymerization by using benzyl pyridine-2-yl dithioformate as a chain transfer agent.

1.7
Post-polymerization Modification via Michael-Type Addition

Michael-type addition reactions have been frequently employed in polymer science starting from the early 1970s to fabricate a variety of macromolecular architectures including step-growth polymers, dendrimers, and cross-linked networks [127]. However, it is only more recently that this reaction has found use in preparing side-chain functional polymers, as only CRP techniques enable the preparation of polymers bearing Michael acceptors, such as acrylates, MIs, and vinyl sulfones. Table 1.6 gives an overview of different polymers that have been used in Michael-type post-polymerization modification. Post-polymerization modification of these polymers with thiols is particularly attractive, as this reaction can proceed quantitatively and selectively in aqueous media at room temperature [128].

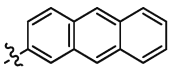
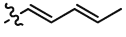
Jérôme and coworkers [129] first demonstrated the synthesis of acrylate-bearing polyesters via ROP. Quantitative functionalization of these polymers without any backbone degradation was achieved in the presence of a large excess of thiol and pyridine (10.0–25.0 equivalents) at room temperature. Weck and coworkers showed that unmasked MI groups are compatible with ring-opening metathesis polymerization (ROMP) conditions. Quantitative modification of MI-bearing poly(norbornene)-based terpolymers was achieved when 2.0 equivalents of the thiol was used at 25 °C. Furthermore, these authors also demonstrated that Michael-type addition, CuAAC, and hydrazone formation are orthogonal chemistries that allow both sequential as well as one-pot modification with different functionalities

Table 1.5 Post-Polymerization modification of (co)polymers via Diels–Alder reactions.

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Conversion (%)	Comments
 or 	A library of Fu-PU	—	PC	*N*-Methylmaleimide, *N*-phenylmaleimide (3.0 equivalents), 40 °C, 4–5 h	30–100	The extent of modification of pendant furan groups is greater compared to the ones in the backbone [120]
	FMA	—	FRP	A library of maleimides and bismaleimides (1.0 equivalent), 55 °C, 48 h	60–85	Reversibility of the reaction was demonstrated. Post-Polymerization modification generated two different stereoisomeric Diels–Alder adducts [115]
	ADC	ET	PC	*N*-Phenylmaleimide (1.0 equivalent), 120 °C, 12 h *N*-Phenylmaleimide (1.0 equivalent), 250 °C (melt), 5–10 min	94 23–51	[114]

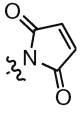
(*continued overleaf*)

Table 1.5 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	PAMA	MMA	FRP	A library of maleimide-functionalized chromophores, 120 °C, 3 h	Quantitative	Bulky substituents were incorporated [121]
	APMOS	St	CuAAC	Poly*t*BA-MI (M_n = 2300 g mol^{-1}), PEG-MI (M_n = 750 g mol^{-1}) (1.3 equivalents), 110 °C, 48 h	92–96	Comb-shaped polymers were synthesized [122]
	ttHA	St	RAFT	Poly*n*BA-BP2TF (M_n = 3500–13000 g mol^{-1}) (4.0–5.0 equivalents), TFA (2 equivalents), 50 °C, 12–24 h	75–100	Hetero Diels–Alder reaction. Comb-shaped polymers were synthesized [123]

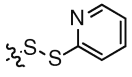
PC, polycondensation.
For each functional group/substrate, entries are listed in chronological order.

Table 1.6 Post-Polymerization modification of (co)polymers via Michael-type addition.

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification: Reagents – reaction conditions	Conversion (%)	Comments
	γAεCL	εCL	ROP	Mercaptoacetic acid (10 equivalents), Py (15 equivalents), r.t., 75 h	100	No backbone degradation [129]
				PEG_{900}-SH (20 equivalents), Py (25 equivalents), r.t., 60 h	80	
	AC	εCLLA	ROP	A library of thiols (10 equivalents), Py (10 equivalents), r.t., 2–3 d	30–100	Post-Polymerization modification with thiols bearing neighboring carboxylic acid groups proceed with low yields [130]
				Peptide RGDC (1.0 equivalents), Py (10 equivalents), 7 d	58	
	IBBL	GPE	AROP	Dodecanethiol, benzylmercaptan (1.0 equivalent), $AlCl_3$ (0.1 equivalent), r.t., 24 h	97–100	Mild reaction conditions [131]
	PMNorb	OBNorb BPNorb	ROMP	Benzenethiol (2.0 equivalents), 25 °C, 18 h	Quantitative	Polymer bears three chemoselective handles warrant access to orthogonal functionalization [70]

(*continued overleaf*)

Table 1.6 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	PDSM	—	RAFT	$PEG_{(454–2000)}$-acrylate (1.2 equivalents), ethylamine (0.03 equivalent), TCEP (1.0 equivalent), overnight	70–73	Side reactions are possible. Steric effects limit the extent of post-polymerization modification [32]
	VSC	εCL LA TMC	ROP	A library of thiols (2.0 equivalents), r.t., 24 h	Quantitative	Quantitative post-polymerization modification with bulky thiols is possible [132]

For each functional group/substrate, entries are listed in chronological order.

(**5** in Scheme 1.4) [70]. Polyesters bearing α,β unsaturated ketone groups have recently been prepared by the copolymerization of glycidyl phenyl ether and bicyclic bis(δ-butyrolactone) monomers by Ohsawa and coworkers. These polyesters contain pendant isopropenyl groups that were shown to react quantitatively with thiols in stoichiometric conditions when $AlCl_3$ was used as a catalyst at room temperature [131]. Wang *et al*. prepared vinyl sulfone-functionalized poly(ester carbonate)s by ring-opening copolymerization of a vinyl sulfone carbonate monomer with ε-caprolactone, L-lactone, or trimethylene carbonate. Post-polymerization modification was reported to proceed quantitatively even with bulky thiols (2.0 equivalents of the thiol used) at room temperature [132].

1.8
Post-polymerization Modification via Azide Alkyne Cycloaddition Reactions

The discovery that the Huisgen 1,3-dipolar cycloaddition (CuAAC) reaction between azides and alkynes can be carried out at mild conditions and in regioselective manner when Cu(I) salts are used as catalyst can be considered as the origin of what is now commonly referred to as *click chemistry*. As already predicted by Sharpless and Meldal in 2002 [133, 134], the scope of the CuAAC reaction turned out to be enormous. CuAAC often proceeds with quantitative yields both in aqueous and organic media under mild conditions and is orthogonal with almost any type of functionalization strategy. Table 1.7 gives an overview of azide- and alkyne-functionalized polymers that have been postmodified using CuAAC.

In 2004, Binder reported that the ROMP of oxynorbonenes bearing unmasked alkyne groups proceeds with poor control owing to the competing reactivity of the alkyne group with the ROMP catalyst. This problem was circumvented by preparing alkyne-bearing polymers via a precursor route that involves side-chain modification of a precursor poly(norbornene) via alkylation with propargy bromide. These authors also prepared azide-bearing poly(oxynorbonene)s via another precursor route based on the modification of pendant alkyl bromide chains with sodium azide [158]. In 2005, Parrish and coworkers first demonstrated the compatibility of the alkyne groups with ROP by copolymerizing αPδVL with ε-caprolactone. Quantitative modification of the alkyne groups was achieved with an azide-functionalized poly(ethylene glycol) (PEG) ($M_n = 1100\ \mathrm{g\,mol^{-1}}$) in stoichiometric conditions at 80 °C when $CuSO_4{\cdot}5H_2O/Na_{asc}$ was used as catalyst [143]. Matyjaszewski illustrated that, while an azide-containing monomer (3-azidopropyl methacrylate, AzPMA) can be successfully polymerized with ATRP, polymerization of propargyl methacrylate proceeded with poor control presumably owing to the side reactions involving the pendant acetylene group. Modification of polyAzPMA proceeded quantitatively with a library of alkynes (1.1 equivalents of the alkynes used) at room temperature in the presence of CuBr [135]. Riva and coworkers reported the compatibility of the azide groups with ROP by preparing copolymers of an azide-functionalized caprolactone ($\alpha N_3\varepsilon$CL) with ε-caprolactone, which reacts quantitatively with propargyl

Table 1.7 Post-Polymerization modification of (co)polymers via azide/alkyne cycloaddition reactions.

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	AzPMA	DMAEMA	ATRP	A library of alkynes (1.1 equivalents), CuBr (0.5 equivalent), r.t., 2 h	Quantitative	polyAzPMA is more reactive than AzPMA [135]
	$\alpha N_3 \varepsilon CL$	εCL	ROP	Propargyl benzoate (1.2 equivalents), CuI (0.1 equivalent), DBU, or TEA (0.1 equivalent), 35 °C, 2 h	Quantitative	Terminal hydroxyl group was esterified to prevent side reactions before post-polymerization modification [136]
	AzEMA	—	RAFT	Phenyl acetylene (1.1 equivalents), CuI (0.1 equivalent), r.t., overnight	Quantitative	Copper catalyst is difficult to remove [137]
	AzHMA	—	SI-RAFT	Phenylacetylene, oligoaniline-alkyne, PS-alkyne (2.0 equivalents), CuBr/PMDETA (0.5 equivalent), r.t., 20 min	50–90	Steric effects have a greater impact to the extent of reaction for polyAzHMA brush compared to free polyAzHMA in solution [138]
	CAA	MA	RAFT	PEG_{750}-SAE-Propargyl (1.1 equivalents), $CuSO_4 \cdot 5H_2O/Na_{asc}$ (0.07/0.14 equivalent), 50 °C	Quantitative	[139]
	N_3MPA	—	RAFT	α-GP-alkyne (1.5 equivalents), $CuSO_4 \cdot 5H_2O/Na_{asc}$ (0.1/4.0 equivalents), r.t., 18 h	Quantitative	[140]
	ADTC	DTC	ROP	A library of alkynes (1.2 equivalents), CuBr/TEA (1.0 equivalent) 35 °C	Quantitative	Polymer bears two alkyne groups per repeating unit [141]
	AzDXO	LA	ROP	(1)5-hexyn-1-ol (17.6 equivalents), CuBr, r.t., 24 h. (2)DBCO-NHS (3 equivalents), r.t. 12 h	Quantitative	Cu-free functionalization via SPAAC was achieved. Polymer bears two azide groups per repeating unit [142]

	αPδVL	εCL	ROP	PEG_{1100}-N_3 (1.0 equivalent), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.1/0.2 equivalent), 80 °C, 10–12 h Peptide GRGDS-N_3 (0.05 equivalent), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.5/0.8 equivalent), 80 °C, 10–12 h	Quantitative	No backbone degradation [143]
	PynOx	2MOx	CROP	TMS-N_3, Ac-N_3 (7.3–13.7 equivalents), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.3–0.8/0.5–1.4 equivalents) r.t., overnight	Quantitative	Quantitative modification in aqueous media [144]
	αPδVL	εCL	ROP	Camptothecin-N_3 (0.2 equivalent), DIEA (0.08 equivalent), $CuBrPPh_3$ (0.04 equivalent), r.t., 48 h, followed by the addition of PEG_{1100}-N_3 (1.1 equivalents), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.4 equivalent), 80 °C, overnight	Quantitative	No backbone degradation. Improved solubility of the polymer-drug conjugate on functionalization with PEG [145]
	PCDO	LA	ROP	Azide-functionalized sugars (1.0 equivalent), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.9/1.8 equivalents), 80 °C, 5 h	Quantitative	[146]
	PgMA	PEGMA	RAFT	Pyrenyl-N_3 (1.2 equivalents), CuBr/PMDETA (0.2 equivalent), r.t., 24 h	Quantitative	Comb-shaped polymers assembling into electron donor–acceptor (EDA) supramolecules were synthesized [147]
	dPGL	LA	ROP	1-Azidodecane, PEG_{550}-N_3 (3.0 equivalents), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.05 equivalent), r.t., 3 h	Quantitative	No backbone degradation [148]
	U-PBM U-DPPD	—	PA	A library of azides (2.0 equivalents), CuBr/PMDETA (0.1 equivalent), or $CuSO_4{\cdot}5H_2O/Na_{asc}$ (0.05/0.1 equivalent), 50 °C, overnight	Quantitative	PolyU-DPPD bears two alkyne groups per repeating unit [149]
	U-MPPD	—	PC	Benzyl azide, PEG_{550}-N_3 (2.0 equivalents), CuBr/PMDETA (0.2–1.0 equivalent), 50 °C, 2–600 min	Quantitative	[150]
	ProDOT-P	ProDOT-H	OP	A library of azides (9.0–24.5 equivalents), $CuSO_4{\cdot}5H_2O/Na_{asc}$ (7.0/24.0 equivalents), 80 °C, 5 d	Quantitative	Low atom economy. Improved solubility of the polymer on functionalization [151]

(*continued overleaf*)

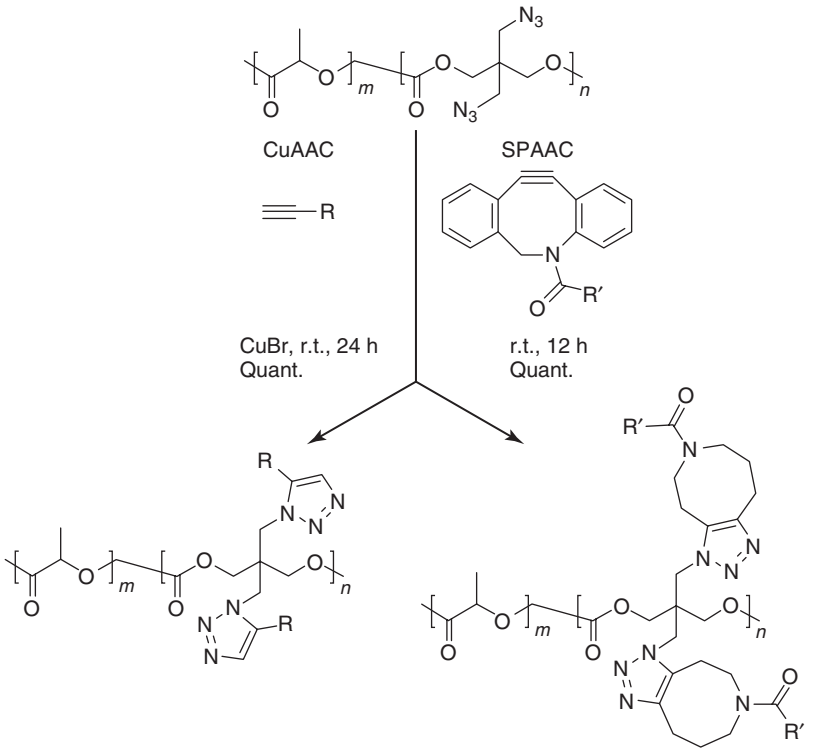
Table 1.7 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
Contd.	PLG	—	ROP	$PEG_{750-5000}$-N_3 (1.0–2.0 equivalents), CuBr/PMDETA (0.3 equivalent)	95–99	Conformation of the polymer allows quantitative functionalization with PEG [152]
	αPεCL	εCL	ROP	polyDMAEMA$_{6500}$-N_3, CuBr/PMDETA, r.t., 24 h	Quantitative	Comb-shaped polymers were synthesized [153]
	αPεCL	εCL	ROP	β-CD-N_3 (5.0 equivalents), $CuSO_4 \cdot 5H_2O/Na_{asc}$ (0.05/0.10 equivalent), 95 °C, 24 h	90–100	Polymer was end-capped to prevent side reactions before post-polymerization modification [154]
	PGL	LA	ROP	PEG_{2000}-PTXL-N_3 (0.50 equivalent), CuBr/PMDETA (0.6 equivalent), 35 °C, 24 h	95	A biodegradable polymer–drug conjugate was synthesized [155]
	NPME	Ethylene	EOP	PEG_{1700}-N_3, PS_{2600}-N_3 (1.8 equivalents), CuBr/PMDETA (0.9/2.7 equivalents), 80 °C, 12–24 h	91–100	[156]
	PgMA	—	SI-FRP	A library of azides, CuBr/PMDETA, 80 °C, 8 h	70	[157]

For each functional group/substrate, entries are listed in chronological order.

benzoate (1.2 equivalents) at 35 °C when CuI was used [136]. The possibility to synthesize azide-/alkyne-functionalized polymers via direct polymerization of the corresponding monomers, as demonstrated in these last three examples, marked the beginning of an explosive growth of the use of CuAAC post-polymerization modification strategy (Table 1.7).

A drawback of the CuAAC post-polymerization modification reaction is that removal of the copper catalyst can be demanding, as it can form complexes with the triazole ring, which hampers the solubility of the functionalized polymer [137]. Furthermore, toxicity of the copper catalyst to cells limits the applicability of CuAAC reaction in biological media [159, 160]. An attractive, copper-free functionalization strategy is the *strain-promoted azide alkyne cycloaddition* (SPAAC) reaction [161]. Recently, Song and coworkers [142] demonstrated that the functionalization of pendant azide groups of polyAzDXO via SPAAC reaches quantitative conversion at shorter reaction times compared to CuAAC and at lower equivalents of the cyclooctyne/alkyne used (Scheme 1.5).



Scheme 1.5 Post-Polymerization modification of polyAzDXO via CuAAC and SPAAC reaction [142].

1.9 Post-polymerization Modification of Ketones and Aldehydes

Ketones and aldehydes can selectively react with primary amines, alkoxyamines, and hydrazines to form imines, oximes, and hydrazones, respectively. While imines are usually prone to hydrolysis, oximes and hydrazones are hydrolytically stable between slightly acidic to neutral pH [162, 163]. Nevertheless, imines can be further converted to stable secondary amines via reductive amination in the presence of a reducing agent, such as borohydride derivatives [164, 165]. Table 1.8 gives an overview of aldehyde and ketone functional polymers that have been modified via post-polymerization modification.

Although the preparation of polymers bearing pendant ketone groups was already reported by Overberger and Tsurata in the 1960s [171, 172], these polymers have only recently found use as a platform for post-polymerization modification. Bertozzi and coworkers [166, 173] prepared copolymers containing vinylmethylketone (VMK) and isopropenyl methyl ketone (IMK) both via free-radical polymerization (FRP) as well as via RAFT polymerization and demonstrated that the resulting polymers could be quantitatively modified with aminoxy-functionalized sugars at 95 °C when 2.8 equivalents of the sugar was used (Table 1.8). Yang and Weck [70, 167] reported the synthesis of aldehyde- and ketone-functionalized polynorbornenes via Ru-catalyzed ROMP of the corresponding aldehyde- and ketone-substituted norbornene monomer. Post-polymerization modification of the ketone-substituted polymer with a library of hydrazines proceeded quantitatively at 25 °C. Barrett and Yousaf prepared a library of poly(ketoester)s that contain ketone groups as part of the backbone of the polymer. Modification of these backbone ketone groups proceeded quantitatively with a library of oximes (1.5 equivalents used) at room temperature (Scheme 1.6) [170].

The first example of the polymerization of monomers containing aldehyde groups was reported as early as in 1950s by Wiley and Hobson [174] as well as by Schulz *et al*. [175]. The research activities of the latter authors concentrated on poly(acrolein), which was obtained via redox polymerization, and also included first studies on the post-polymerization modification of these polymers. Polymerization of unprotected aldehyde monomers by conventional polymerization techniques, however, can be accompanied by a variety of side reactions, because of the competing reactivity between the vinyl double bond and the aldehyde group [176]. To overcome these problems, precursor routes based on deprotection of masked aldehyde functionalities, such as acetal or dioxolane groups, following polymerization of the corresponding monomers by oxidation were employed to prepare well-defined aldehyde-bearing polymers starting from 1980s [85, 177–180]. In 2007, Wooley *et al*. [181], for the first time, reported the direct RAFT polymerization of an unprotected aldehyde-containing monomer (vinylbenzaldehyde, VBA). Fulton demonstrated that polyVBA prepared via RAFT polymerization could be quantitatively modified using an excess of various acylhydrazides. Furthermore, Fulton demonstrated the dynamic nature of the reaction between an aldehyde and *n*-acylhydrazone, and therefore, probed the potential of polyVBA as a platform

Table 1.8 Post-Polymerization modification of (co)polymers bearing ketone and aldehyde groups.

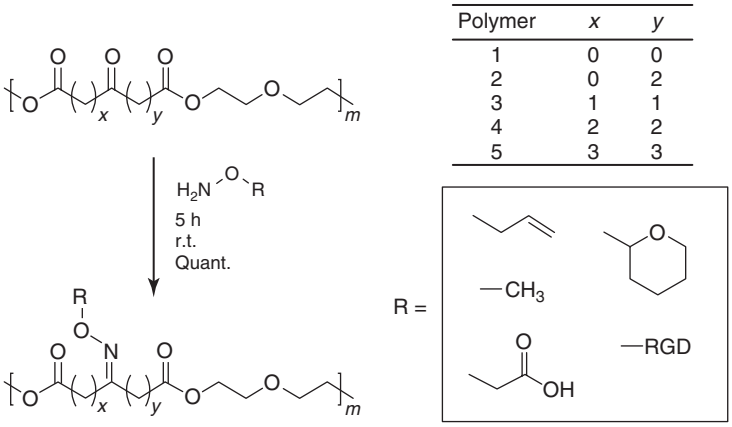
Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	VMK	DAPA	FRP	α-Aminoxy GalNac (2.8 equivalents), AcOH (0.1%), 95 °C, 96 h	96–100	Conformation of the polymer changed on post-polymerization modification [166]
	IMK		RAFT	α-Aminoxy GalNac (1.03 equivalents), pH 5.5, 50 °C, 20 h	80	
	OBNorb	BPNorb	ROMP	A library of hydrazides, 25 °C, 2–24 h	97–99	Orthogonality of the hydrazone formation and CuAAC was demonstrated. Aldehyde derivative of the polymer is insoluble in common organic solvents [167]
	OBNorb	BPNorb PMNorb	ROMP	Benzylhydrazide (2.0 equivalents), 25 °C, 4 h	98	Polymer synthesized bears three chemoselective handles warrant access to orthogonal functionalization [70]

(*continued overleaf*)

Table 1.8 (*continued.*)

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
	VBA	—	RAFT	*N*-Acylhydrazides (C_5,C_{10},C_{17}, 100.0 equivalents), TFA (catalyst), 2 h	Quantitative	Low atom economy. Reversible post-polymerization modification [168]
	FVFC	PEGMA	RAFT	*O*-Benzylhydroxylamine hydrochloride (1.2 equivalents), 25 °C, 12 h	Quantitative	[169]
	A library of PKE's	—	CP	A library of alkoxyamines (1.5 equivalents), r.t, 5 h	Quantitative	Direct functionalization of the backbone. Mild reaction conditions. Biocompatible polymer [170]

For each functional group/substrate, entries are listed in chronological order.



Polymer	x	y
1	0	0
2	0	2
3	1	1
4	2	2
5	3	3

Scheme 1.6 Quantitative modification of various poly(keto esters) via a library of alkoxyamines [170].

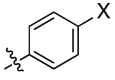
for the construction of combinatorial libraries [168]. Xiao *et al.* [169] reported the preparation of polyFVFC-*co*-polyEGMA, which could be quantitatively modified with 1.2 equivalents of *O*-benzylhydroxylamine at 25 °C.

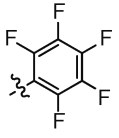
1.10
Post-polymerization Modifications via Other Highly Efficient Reactions

In the previous sections, we attempted to summarize the emergence and historical development of eight of the most prominent reactions that are used for post-polymerization modification. In addition to these more established post-polymerization modification reactions, there are also other reactions that have received less attention or which have been developed more recently. This final section provides an overview of several of these reactions (Table 1.9) and discusses their potential for post-polymerization modification.

The discovery of the catalytic effect of organopalladium compounds for the formation of stable C–C bonds with high yields and at milder conditions compared to many other coupling strategies, which was rewarded with the Nobel Prize in Chemistry in 2010, has enormously expanded the scope of organic synthesis as well as polymer science. Although palladium-catalyzed coupling reactions tolerate a wide variety of functional groups including halides, alkenes, alkynes as well as organoboron and organotine compounds [189–192], the post-polymerization modification of polymers bearing pendant phenyl halide groups with alkynes (Sonogashira coupling) has been investigated most extensively (Table 1.9). Stephens and Tour [182] reported that the conversion of brominated poly(*p*-phenylene) with various alkynes proceeds with moderate to high yields at elevated temperatures when phenylphosphine-based palladium catalysts were used. Grubbs later demonstrated near-quantitative functionalization of low-molecular-weight polyBrS

Table 1.9 Post-Polymerization modification of (co)polymers via Pd-catalyzed coupling, ATRA, *p*-fluoro thiol, acetal, and thiol–yne reactions.

Functional group(s)	Monomer	Comonomer	Polymerization method	Post-Polymerization modification		
				Reagents – reaction conditions	Conversion (%)	Comments
 X : Br, I	bPP	PPh	HMPA-Promoted	A library of alkynes (3.5 equivalents), diisopropylamine (3.5 equivalents), CuI (0.04 equivalent), $PdCl_2(PPh_3)_2$, or $Pd(PPh_3)_4$ (0.04 equivalent), 60–100 °C, 5–10 h	56–84	Polymer does not have a well-defined structure. Cross-linking is possible [182]
	BrS	VPSt	NMP	Phenylacetylene, 1-hexyne (1.5 equivalents),diisopropylamine (1.7 equivalents), CuI (0.04 equivalent), $[PdCl_2(PhCN)_2]$ (0.08 equivalent), r.t., 96 h	47–99	High-molecular-weight polyBrS cross-links on moderate functionalization with 1-hexyne [183]
	HB-I(PV-PE)	—	Pd-catalyzed	A diverse library of alkynes, CuI, $PdCl_2(PPh_3)_2$, r.t., overnight	85–95	Polymerization and post-polymerization modification was carried under identical conditions [184]

	αClεCL	εCL	ROP	3-Butenyl benzoate (4.0 equivalents), CuBr (1.0 equivalent), Me_6TREN, 60 °C, 90–240 min	Quantitative	No backbone degradation [185, 186]
	αClεCL	εCL	ROP	PEG_{750}-alkene (4.0 equivalents), CuBr (1.0 equivalent), Me_6TREN (1.0 equivalent), 60 °C, 240 min	19	Side reactions are possible [187]
	PFS	St	NMP	$GlcAc_4$-SH (1.2 equivalents), TEA (3.0 equivalents), 40 °C, 30–60 min	Quantitative	Thiol bearing molecules selectively react with the *para*-fluorine position [66]. Functionalization with amines is also possible [65]
	PFS	OEGMA	NMP	Thiophenol (0.2 equivalents), TEA (1.2 equivalents), r.t., 15 h	Quantitative	Quantitative functionalization with aromatic thiols is possible [188]
	EVGE	EO	AROP	Benzyl alcohol (10.0 equivalents), PTSA (0.01 equivalent), r.t., 10 min	Quantitative	Acetal-click reaction [28]
	PgMA	—	SI-FRP	A library of thiols, DMPA, 28 °C, 1 h	80	Thiol–yne reaction proceeds faster than CuAAC [157]

For each functional group/substrate, entries are listed in chronological order.

at room temperature when the reaction was mediated by $[PdCl_2(PhCN)_2]$. However, cross-linking of high-molecular-weight polyBrS was observed on modification with 1-hexyne [183]. Bunz *et al.* [184] extended the Pd-catalyzed post-polymerization modification to the functionalization of various hyperbranched polyI(PV-PE) copolymers.

Another attractive reaction for the post-polymerization modification of polymers is atom-transfer radical addition (ATRA), which takes place between alkyl halides and alkenes in the presence of a transition-metal catalyst and can be considered as a predecessor of ATRP [193]. Jérome and coworkers [185, 186] prepared poly(αClεCL-*co*-εCL) and investigated the modification of this polymer with various alkenes (Table 1.9). They demonstrated that, although ATRA post-polymerization modification is tolerant to many functional groups, such as alcohols, esters, epoxides, and carboxylic acids, the extent of modification can be limited by the competing reduction of C–Cl bonds to C–H bonds [187].

The development of the CuAAC reaction has stimulated the search for alternative ''click reactions.'' Examples of ''click'' reactions that have recently emerged and which have found use for post-polymerization modification include the PFP click [194], the acetal-click, and the thiol–yne addition reactions (Table 1.9) [195]. A common feature of these reactions is that they proceed very rapidly and quantitatively at mild conditions. Schubert and coworkers extensively studied the modification of polyPFS copolymers via PFP click reactions. Quantitative substitution of the *p*-fluoro position can be rapidly achieved both with amines and thiols, but milder conditions are sufficient when thiols are used (**2** in Scheme 1.3) [65, 66]. Furthermore, quantitative modification with less nucleophilic aromatic thiols was also achieved at longer reaction times [188]. Recently, Wurm and coworkers [28] prepared a polyether derivative bearing pendant vinyl ether groups (polyEVGE, ethoxy vinyl glycidyl ether), which was not only susceptible to modification via radical thiol addition but could also be functionalized with alcohols to form side-chain acetal groups (**3** in Scheme 1.3). These authors reported quantitative conversion of vinyl ether groups within 10 min in the presence of the *p*-toluene sulfonic acid (PTSA) catalyst with an excess of benzyl alcohol at room temperature. Although the reaction between alkynes and thiols in the presence of a radical source has already been known since the1930s [196], it was only recently that it was revived as a ''click'' reaction and started to find widespread use for the fabrication of macromolecular architectures [195, 197–199]. Hensarling and coworkers [200] illustrated that the post-polymerization modification of polyPgMA brushes with a library of thiols proceeded quantitatively within minutes under UV irradiation and a photoinitiator at ambient conditions. Cai and coworkers [157] showed that quantitative functionalization of polyPgMA brushes can be achieved both via thiol–yne and CuAAC reactions, whereas milder conditions are sufficient when thiol–yne modification was employed (**4** in Scheme 1.3).

1.11
Concluding Remarks

Many of the early developments in polymer science can be attributed to the use of post-polymerization modification reactions. The (re)discovery of many highly efficient and orthogonal chemistries, combined with the development of various functional-group-tolerant living/controlled polymerization techniques, has enormously expanded the scope of post-polymerization modification and resulted in an enormous increase in the use of this approach to synthesize functional polymers. Looking at the developments in this field from an historical perspective, the aim of this chapter was to highlight the significant advances and breakthroughs and to provide the reader with a flavor of what has been accomplished and all the possibilities that are yet to be explored.

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