Post-Polymerization Modification

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Synthesis of Functional Polymers by Post-Polymerization Modification

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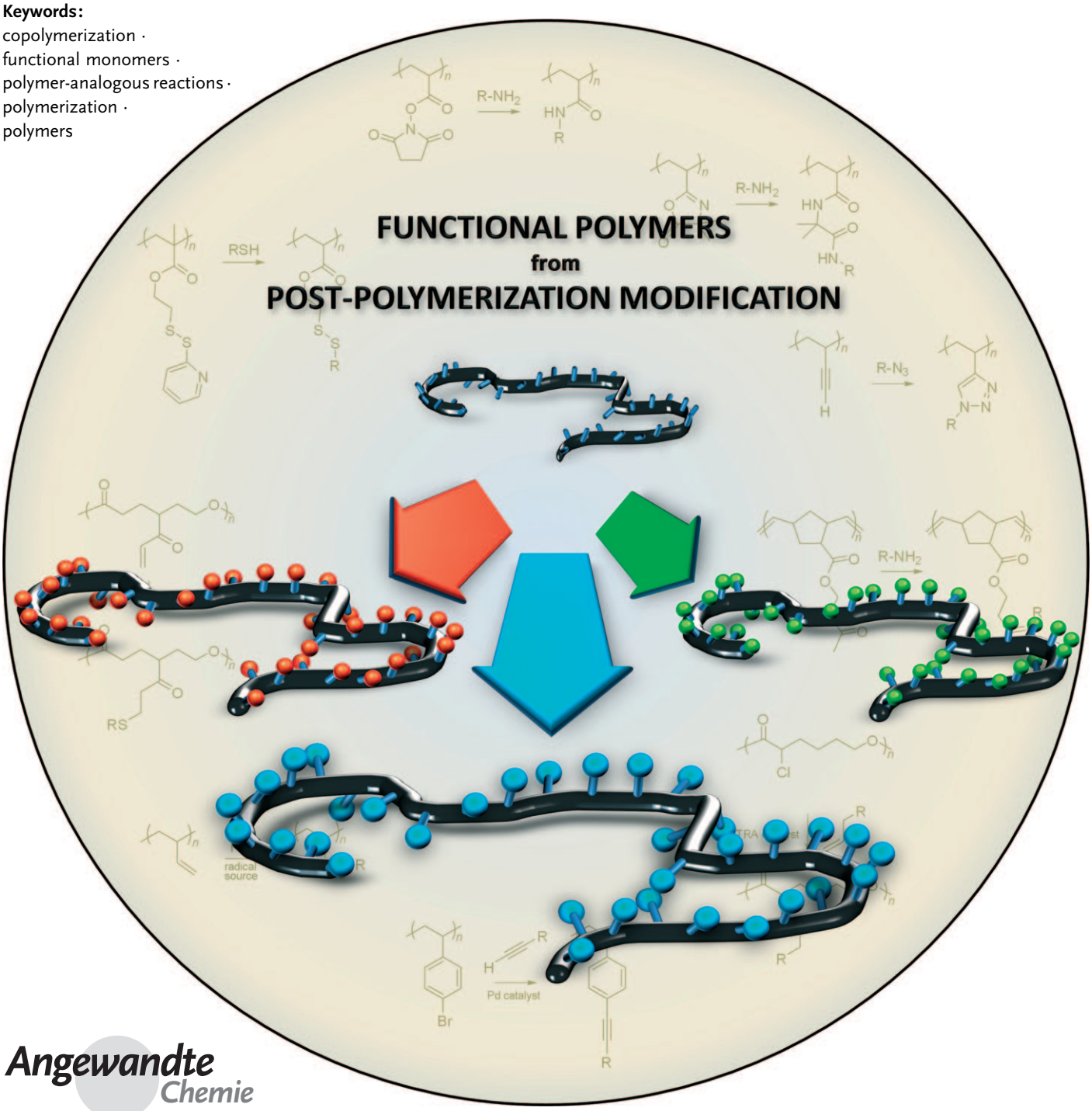
copolymerization · functional monomers · polymer-analogous reactions · polymerization · polymers



Post-polymerization modification is based on the direct polymerization or copolymerization of monomers bearing chemoselective handles that are inert towards the polymerization conditions but can be quantitatively converted in a subsequent step into a broad range of other functional groups. The success of this method is based on the excellent conversions achievable under mild conditions, the excellent functional-group tolerance, and the orthogonality of the post-polymerization modification reactions. This Review surveys different classes of reactive polymer precursors bearing chemoselective handles and discusses issues related to the preparation of these reactive polymers by direct polymerization of appropriately functionalized monomers as well as the post-polymerization modification of these precursors into functional polymers.

From the Contents

1. Introduction

The polymer-chemistry toolbox currently includes a variety of controlled, or "living", polymerization methods that allow the synthesis of polymers with precise control over molecular weight, composition, and architecture. The synthesis of functional polymers with precisely defined molecular weight, composition, and architecture, however, can still pose a significant challenge. Functional polymers may be prepared by polymerization of appropriately protected monomers, although the additional deprotection step may not necessarily proceed to completion and may also affect the structural integrity of the polymer backbone. Direct polymerization of functional monomers clearly is a more attractive strategy. The traditional living anionic and cationic polymerization techniques, however, only offer very limited possibilities for the direct polymerization of monomers containing functional groups. This situation has improved with the development of controlled ("living") radical polymerization techniques as well as with advances in catalytic polymerization, which have resulted in polymerization reactions with higher functional-group tolerance. In spite of these improvements, there is still a broad range of side-chain functionalities that cannot be introduced by direct polymerization using any currently available controlled polymerization techniques. Such functional groups may either completely prevent controlled polymerization or may participate in side reactions that can lead to loss of control over the polymerization reaction. Post-polymerization modification, also known as polymer-analogous modification, is an attractive approach for the synthesis of functional polymers that can overcome the limited functional-group tolerance of many controlled "living" polymerization techniques.

The synthesis of functional polymers through post-polymerization modification is schematically illustrated in Scheme 1 and is based on the polymerization of monomers with functional groups that are inert towards the polymerization conditions but which can be quantitatively converted in a subsequent reaction step into a broad range of other functional groups. Apart from the fact that post-polymerization modification allows access to functional polymers that cannot be prepared by direct polymerization of the corresponding functional monomers, this strategy is also highly attractive for combinatorial materials discovery. As a single reactive polymer precursor can be used to generate a diverse library of functional polymers with identical average chain lengths and chain-length distributions, the post-polymerization modification approach greatly facilitates the establishment of structure–property relationships.

In this Review, we provide a survey of different classes of reactive polymer precursors that can be prepared and discuss the different reactions that can be used to convert these precursors into functional polymers. Emphasis is placed on the chemoselectivity and orthogonality of the discussed reactions, in the hope of offering new impetus for the design of functionally complex materials. This Review is subdivided into nine sections, which successively highlight several important reactions that are available for post-polymerization modification. These reactions have been carefully selected on the basis of their ability to modify the side chains of polymers

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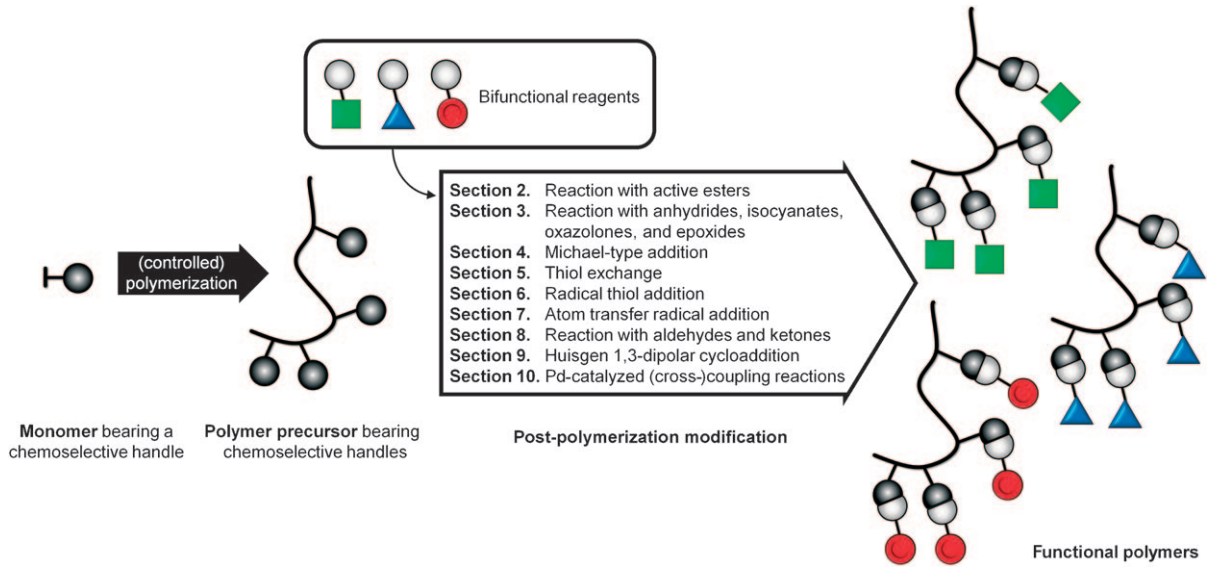


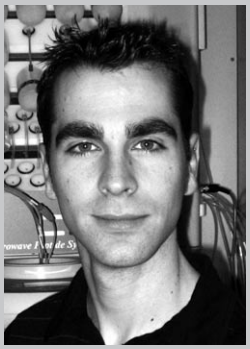
Scheme 1. Synthesis of polymers by post-polymerization modification.

1) in a single reaction step (following polymerization), 2) in high yield, and 3) with sufficient chemoselectivity and orthogonality to prepare polymers bearing many different functional groups. Minor exceptions to this scope that are of particular interest have been included. A compilation of monomers bearing functional groups appropriate for post-polymerization modification through these reactions and that may be directly polymerized in an unprotected form is provided in Table 1. Whenever possible, monomers suitable for modern controlled polymerization methods are highlighted in the text.

2. Modification of Polymeric Active Esters

The concept of post-polymerization modification of polymers bearing activated carbonyl compounds such as acid chlorides has been around for some time.[1] The nucleophilic substitution of polymeric active esters has become the most common form of post-polymerization modification since the introduction of these polymers by the groups of Ferruti[2] and Ringsdorf.[3] Polymeric active esters can be obtained from a variety of monomers using both (controlled) radical polymerization as well as metal-catalyzed polymerization techniques (Table 1). The most common monomers used to prepare side-chain *N*-hydroxysuccinimide (NHS) ester polymers are NMAS and NAS. A drawback of polyNAS and polyNMAS is that they are only soluble in DMF and DMSO. The solubility of active-ester-based polymer precursors can be improved by copolymerization[4] or by replacing the NHS ester group with other activating groups,[5] such as 2,4,5-trichlorophenol ester,[5] *endo*-*N*-hydroxy-5-norbornene-2,3-dicarboxyimide,[5] or pentafluorophenol ester groups, as shown by Théato and co-workers.[6,7] Another interesting active ester monomer is diNAS, which is a bis(active ester) monomer that was isolated as a byproduct from the synthesis of NAS.[8] This monomer can be copolymerized under free-radical conditions and leads to polymers with two reactive sites per repeat unit.

Generally, amines are reacted with active esters because of their good nucleophilicity compared to other functional groups (such as alcohols), which provides selectivity without the need for protecting groups. NHS esters have good hydrolytic stability,[9] which makes them attractive for the



Marc A. Gauthier was born in 1979 and received his B.Sc. in chemistry from the Université de Montréal (Canada) with distinctions. He received fellowships from the Natural Science and Engineering Council of Canada and the Fonds Québecois de la Recherche sur la Nature et les Technologies and was awarded his Ph.D. in 2007 for his work with T. H. Ellis and X. X. Zhu. He is currently a postdoctoral fellow at the Swiss Federal Institute of Technology Lausanne with H.-A. Klok and is working on peptide/protein–polymer conjugation.

Matthew I. Gibson was born in Stockport (England) in 1980. He graduated with an M.Chem degree (First Class honors) in 2003 from the University of Durham. He then remained in Durham to undertake a Ph.D. with N. R. Cameron working on the synthesis of novel materials by the polymerization of N-carboxyanhydrides until November 2006. In January 2007 he began a postdoctoral position at the Swiss Federal Institute of Technology Lausanne with H.-A. Klok on nanoparticle delivery technology.

Harm-Anton Klok was born in 1971 and studied chemical technology at the University of Twente (Enschede, The Netherlands) from 1989 to 1993. He received his Ph.D. in 1997 from the University of Ulm (Germany) after working with M. Möller. After postdoctoral research with D. N. Reinhoudt (University of Twente) and S. I. Stupp (University of Illinois at Urbana-Champaign, USA), he joined the Max Planck Institute for Polymer Research (Mainz, Germany) in early 1999 as a project leader in the group of K. Müllen. In November 2002, he was appointed to the faculty of the Swiss Federal Institute of Technology Lausanne.

biofunctionalization of polymers in aqueous or mixed aqueous media. Thiazolidine-2-thione reactive groups have been reported to combine similar low susceptibility to hydrolysis with a high rate of aminolysis in aqueous media.[10] The efficiency of the modification reaction is dependent on pH value, temperature, polymer concentration, and water content.[11] Smith et al. observed that the extent of grafting of an RGD peptide onto polyNAS decreased with increasing pH value and temperature owing to promotion of hydrolysis.[11] Cline and Hanna have noted that the reactivity of various amines towards aminolysis of *p*-nitrobenzoyl-*N*-hydroxysuccinimide in anhydrous dioxane correlated strongly with the basicity of the amino group, though steric hindrance within the investigated set of amines caused certain deviations

Table 1: Monomers suitable for preparing polymer precursors for post-polymerization modification by direct (co)polymerization.

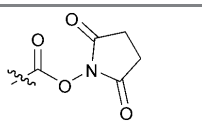
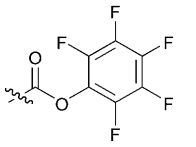
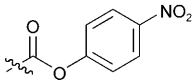
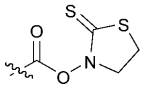
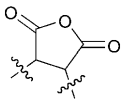
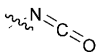
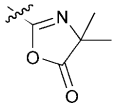
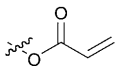
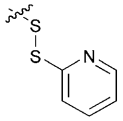
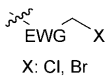
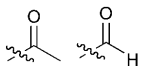
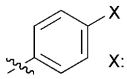
Section	Functional group	Polymerization method							
		FRP	ATRP	NMP	RAFT	Anionic	CROP	ROP	ROMP
2		NAS[11,16] diNAS[8]	NAS[18] NMAS[9,15,19]	NAS[20] NSVB[20]	NAS[4,13] NMAS[21,22] NSVB[23]				NNHS[24]
		PFA[6] PFMA[6] PFVB[25]			PFMA[26]				NPF[7]
		NPA[27]	NPMA[28]		NPA[29] NPMA[30]				
		MAPTT[10]							
3		MA[17]		MA[31]	MA[32]				
		MVI[17,33] VI[33]			TMI[34]				
		VDM[35,36]	VDM[37]	VDM[38] VPDMO[38] IDMO[38]					
		GMA[39]	GMA[40] 4-ES[41]	GMA[42] GA[43]	GMA[44]	GMA[45]			
4								γAεCL[46,47]	
5		PDSA[48,49] PDTEMA[50]	PDSM[19]						
6		DVB[51]	AMA[52]			BD[53,54]	2-BOx[55]	AVL[56]	
7	 X: Cl, Br							αClεCL[57,58]	

Table 1: (Continued)

Section	Functional group	Polymerization method							
		FRP	ATRP	NMP	RAFT	Anionic	CROP	ROP	ROMP
8			MVK[59]		VBA[60] MVK[61] PVK[61] DAA[22]				N-4-OBE[62] *N*-3-OBE[62]
9, 10		2-, 3-, and 4-PES[63]		4-PES[64]		4-DMBS 4-HBS 4-PES[65]	PynOx[66]	αPεCL[67]	N-PDCM[68]
			3-APM[69]				2-APOx[70]	αAεCL[71]	
10	 X: Br, $B(OR)_2$	4-BS[72] VPB[73]	4-BS[74] MBpin[75]	4-BS[76]	MBpin[77]	4-BS[78]			

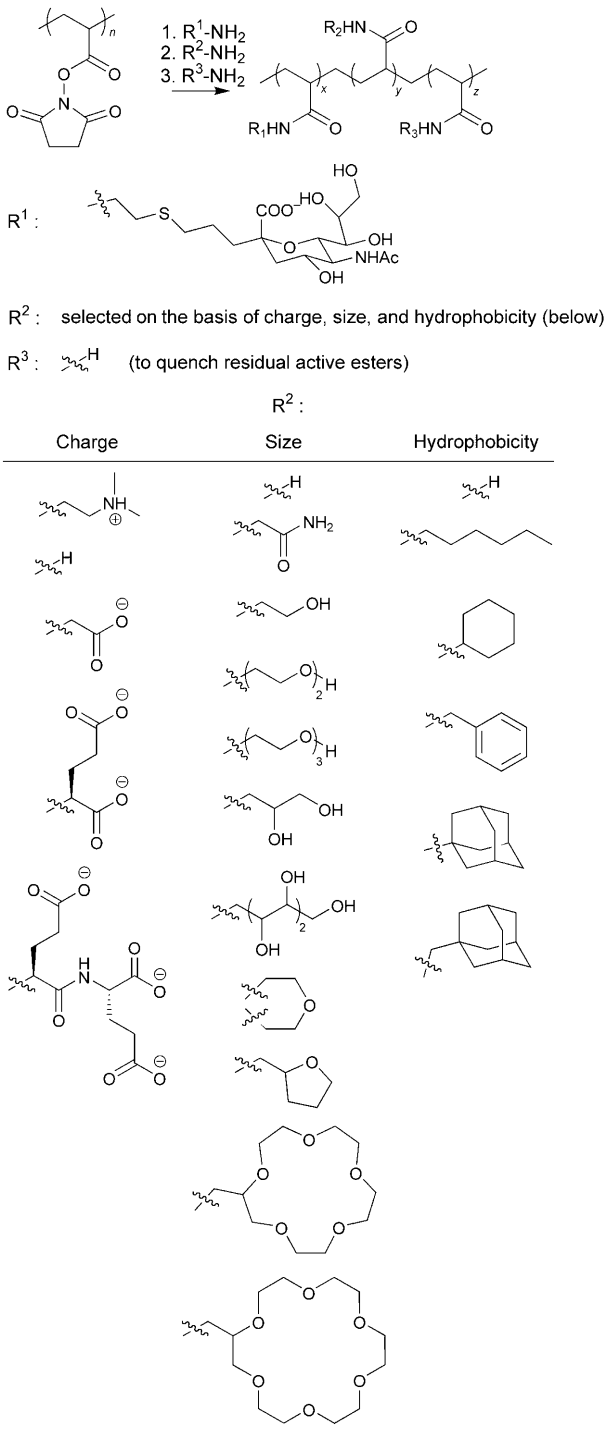
[a] α-azido-ε-caprolactone (αAεCL); γ-acryloyloxy-ε-caprolactone (γAεCL); allyl methacrylate (AMA); 3-azidopropyl methacrylate (3-APM); 2-(4-azidophenyl)oxazoline (2-APOx); atom transfer radical polymerization (ATRP); α-allyl(valerolactone) (AVL); 1,3-butadiene (BD); 2-(3-butenyl)-2-oxazoline (2-BOx); bromostyrene (BS); α-chloro-ε-caprolactone (αClεCL); cationic ring-opening polymerization (CROP); *N*-(1,1-dimethyl-3-oxobutyl)acrylamide (DAA); 2-methylenepentanedioic acid bis(2,5-dioxopyrrolidin-1-yl)ester (diNAS), 4-(3,3-dimethyl-1-butynyl)styrene (4-DMBS); divinylbenzene (DVB); 4-epoxystyrene (4-ES); electron-withdrawing group (EWG); free-radical polymerization (FRP); glycidyl acrylate (GA); glycidyl methacrylate (GMA); 4-(1-hexynyl)styrene (4-HBS); 2-isopropenyl-4,4-dimethyl-5-oxazolone (IDMO); maleic anhydride (MA); 3-(3-methacrylamidopropanoyl)thiazolidine-2-thione (MAPTT); 4-pinacolatoborylstyrene (MBpin); 1-methyl-vinylisocyanate (MVI); methyl vinyl ketone (MVK); *N*-acryloxysuccinimide (NAS); *N*-methacryloxysuccinimide (NMAS); nitroxide-mediated polymerization (NMP); bicyclo[2.2.1]hept-5-ene-*exo*-2-carboxylic acid *N*-hydroxysuccinimide ester (NNHS); *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 3-oxobutyl ester (N-3-OBE); *exo*-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 4-oxobutyl ester (N-4-OBE); *p*-nitrophenyl acrylate (NPA); *exo*-*N*-prop-2-ynyl-7-oxabicyclo[2.2.1]-hept-5-ene-2,3-dicarboximide (N-PDCM); *p*-nitrophenyl methacrylate (NPMA); *exo*-norbornene-5-pentafluorophenylester (NPF); α-propargyl-ε-caprolactone (αPεCL); *N*-succinimide *p*-vinyl benzoate (NSVB); pyridyldisulfide propylacrylate (PDSA); pyridyldisulfide propylmethacrylate (PDSM); *N*-[2-(2-pyridyldithio)]ethyl methacrylamide (PDTEMA); (phenylethynyl)styrene (PES); pentafluorophenylacrylate (PFA); pentafluorphenylmethacrylate (PFMA); pentafluorophenyl 4-vinylbenzoate (PFVB); phenyl vinyl ketone (PVK); 2-(pent-4-ynyl)-2-oxazoline (PynOx); reversible addition–fragmentation chain transfer (RAFT); ring-opening metathesis polymerization (ROMP); ring-opening polymerization (ROP); *m*-isoproprenyl-α,α′-dimethylbenzyl isocyanate (TMI); 4-vinylbenzaldehyde (VBA); 2-vinyl-4,4-dimethyl-5-oxazolone (VDM); vinyl isocyanate (VI); *p*-vinylphenyl boronic acid (VPB); 2-(4′-vinyl)phenyl-4,4-dimethyl-5-oxazolone (VPDMO)

from the otherwise linear trend.[12] This kinetic selectivity also allows selective attachment of lysine-containing peptides through their N-terminal amino group owing to the different basicity of this amino group ($pK_a \approx 8$) versus that of the lysine side chain ($pK_a \approx 11$).[11] In the absence of amino groups, conversion of active esters with hydroxy groups is possible, though elevated temperatures and activating agents such as *N*,*N*-dimethylaminopyridine may be required.[13] Polymers bearing NHS ester side chains can suffer from side reactions such as ring opening of the succinimide group and formation of N-substituted glutarimides by ring-closing attack of amides on neighboring active esters.[14] Suppression of these side reactions may be achieved by carrying out the post-polymerization reaction in DMSO at 75 °C for 24 h in the presence of five equivalents primary amine nucleophile.[15] Starting from a single batch of polyNAS, Mammen et al. prepared an extended library of sialic acid modified poly(acrylamide)s, which were used to screen the influence of side-chain functionality on influenza inhibitory properties (Scheme 2).[16]

3. Modification of Polymeric Anhydrides, Isocyanates, Oxazolones, and Epoxides

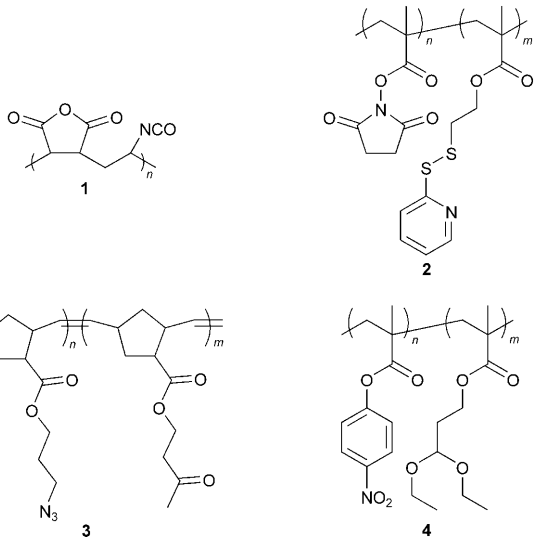
Reactive polymer precursors containing anhydride functionalities can be prepared from maleic anhydride, while polymers containing isocyanate groups can be synthesized from VI, MVI, or TMI (Table 1). These monomers have in common that they do not homopolymerize readily, but they can be copolymerized with various monomers using conventional or controlled radical polymerization techniques. Copolymers based on maleic anhydride or MVI usually have an alternating microstructure. A particularly interesting case is the copolymerization of maleic anhydride with MVI, which results in alternating copolymers with two chemical handles for further modification (**1** in Scheme 3).[17] Amines have been reported to react with anhydride groups of poly(styrene-*co*-maleic anhydride) up to near quantitative conversion in mixed DMSO/0.5 M $NaHCO_3$ buffer in 3 h.[79] Isocyanates can react with both alcohols and amines, but under very different conditions. Primary and secondary amines react with polymeric isocyanates quantitatively in a few minutes at 60 °C under stoichiometric conditions. Quantitative modification of the same isocyanate groups with alcohols, in contrast, requires the use of a large excess of alcohol or a catalyst such as dibutyltin dilaurate.[33]

In contrast to the monomers discussed above, vinyl-functionalized oxazolones such as 2-vinyl-4,4-dimethyl-5-oxazolone (VDM) and epoxide-functionalized monomers such as glycidyl methacrylate (GMA) can not only undergo copolymerization but also readily homopolymerize both under conventional and controlled radical polymerization conditions (Table 1). VDM-containing polymers react rapidly



Scheme 2. Evaluation of side-chain charge, size, and hydrophobicity on the potency of polymeric inhibitors of influenza virus.[16]

and quantitatively with amines such as benzylamine at room temperature to produce the corresponding amide-functional polyacrylamides.[38] The modification of oxazolones with amine nucleophiles can even be performed in aqueous media without significant competitive hydrolysis.[35] Reactions of oxazolone groups with alcohols are catalyzed by either acid or base; the best catalysts are trialkylphosphines and cyclic amidines.[80] As they can react with a broad range of

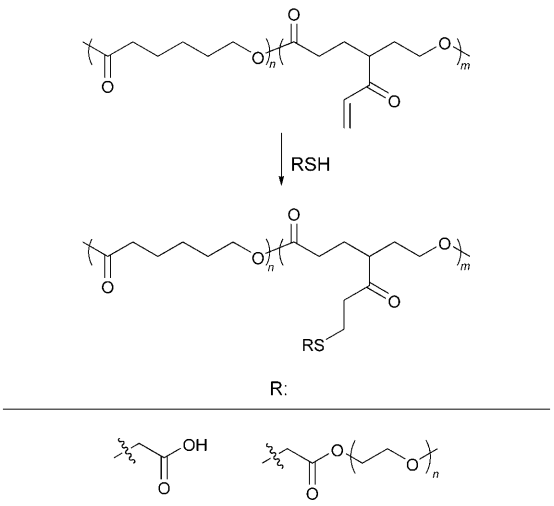


Scheme 3. Bifunctional polymer precursors with orthogonal reactive handles.[17,19,30,62]

functional groups, including carboxylic acids, alcohols, amines, thiols, and anhydrides, epoxide-functionalized polymers represent a versatile platform for post-polymerization modification.[39] An issue that needs to be considered in the post-polymerization modification of epoxide-functionalized polymers with primary amines is that ring opening of the epoxide group generates a secondary amine that may react with another epoxide group, leading to cyclic structures or cross-linked networks.[40]

4. Modification of Polymers by Michael-Type Addition Reactions

The Michael-type addition reaction between thiols and activated alkenes is an attractive tool for post-polymerization modification, as it proceeds readily in aqueous media under mild conditions.[81] At neutral pH values, Michael addition of thiols is one order of magnitude faster than that of amines,[81] highlighting the potential for preparing polymers with pendant amino groups by means of bifunctional reagents bearing both amino and thiol groups. Jérôme and co-workers have studied Michael-type addition post-polymerization modification of acrylate-functionalized polyesters.[46,47] Aliphatic copolyesters containing γ-acryloyloxy-ε-caprolactone units were modified with various functional groups by addition of 10 equivalents thiol reagent and 15 equivalents pyridine (catalyst) in THF (Scheme 4).[47] Conversions of 65–70% were achieved without compromising backbone integrity. Although polyesters with acrylate side-chain functionalities can be prepared by ROP,[46] functional groups that can act as Michael acceptors are generally incompatible with radical and ionic polymerization methods. Polymers susceptible to Michael-type post-polymerization modification can, however, be prepared by polymerization of monomers containing masked maleimide functionalities.[82] Maleimide functionalities can be protected/deprotected through the



Scheme 4. Michael-type addition of thiols to polyesters containing γ-acryloyloxy-ε-caprolactone groups.[47]

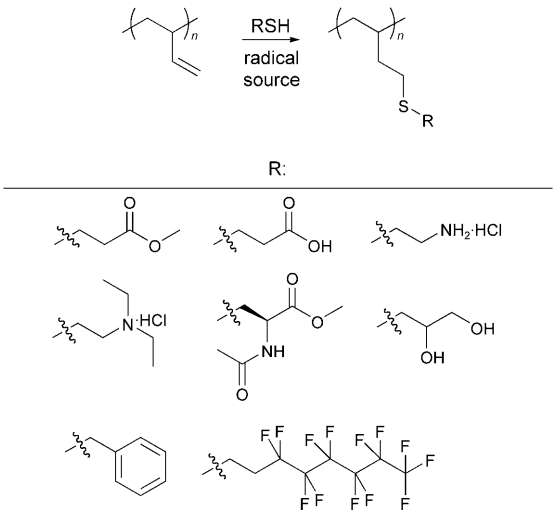
reversible [4+2] Diels–Alder cycloaddition reaction, for example with furan. These masked maleimides are compatible with radical polymerization conditions.[82] The retro-Diels–Alder reaction to release the maleimide functionalities proceeds quantitatively under relatively mild thermal conditions (125 °C in vacuum; 60 °C in solution).[82,83] This strategy was successfully used by Bailey and Swager to prepare rhodamine-modified poly(phenyleneethynylene)s.[83]

5. Modification of Polymers by Thiol Exchange

Disulfides are attractive chemical handles for post-polymerization modification, as they are readily exchanged in high yields with thiol compounds of interest. For this purpose, various pyridyldisulfide-functionalized acrylates and methacrylates have been developed that can be polymerized using conventional free-radical polymerization as well as ATRP (Table 1) and that are stable towards hydrolysis and aminolysis below pH 8.[50] A particular advantage of the pyridyldisulfide group is that thiol exchange generates 2-pyridinethione, which is an inert leaving group and has a characteristic UV/Vis absorbance spectrum that is distinctly different from that of the pyridyldisulfide functionality.[50] Terpolymers (copolymers made from three different monomers) containing pyridyldisulfide propylacrylate units have been modified with peptides bearing a free cysteine group to 86 and 35% (relative to pyridyldisulfide units) at pH 6 and 10, respectively.[48] This difference has been ascribed to protonation of the nitrogen atom on the pyridine group at lower pH values, which makes it a better leaving group. Using ATRP, Ghosh et al. have prepared a copolymer of *N*-hydroxysuccinimide methacrylate and 2-(2-pyridyldithio)ethyl methacrylate (**2** in Scheme 3).[19] This copolymer is highly attractive for post-polymerization modification, as it contains two orthogonal handles that are reactive towards amines and thiols.

6. Modification of Polymers by Radical Thiol Addition

The radical addition of thiols to polymeric alkenes such as 1,2-butadiene and natural or synthetic rubber has been known for some time,[84–89] and it has recently been revived as a means of modifying polymers. In the presence of a suitable radical source or under UV irradiation, thiols undergo addition to alkenes predominantly in anti-Markovnikov fashion.[51] Schlaad and Justynska have demonstrated that poly(1,2-butadiene) can be used as a platform to create different side-chain-functionalized polymers.[53] This reaction is tolerant towards a wide range of functional groups, including carboxylic acids, amines, and alcohols (Scheme 5).[54] It was found, however, that the number of

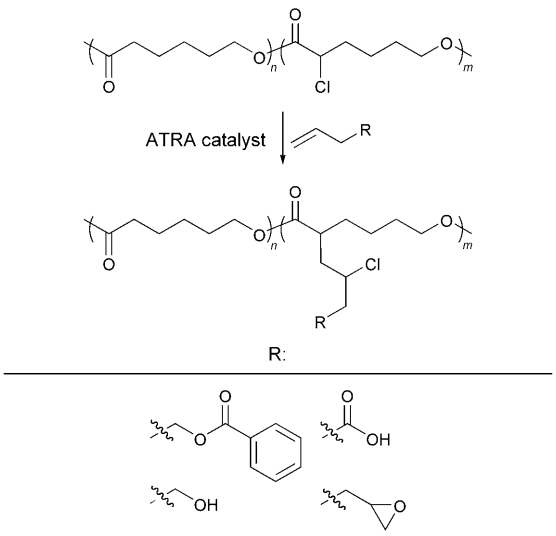


Scheme 5. Radical thiol addition to poly(1,2-butadiene).[54]

functional thiols that may be added to poly(1,2-butadiene) is generally less than the total number of double bonds available, owing to a side reaction in which the radical formed by addition of an RS radical to a double bond adds to another double bond in its vicinity, leading to the formation of a six-membered cyclic structure.[54] This side reaction can be effectively suppressed by increasing the distance between pendant alkenyl groups, as was demonstrated by the modification of poly(2-(3-butenyl)-2-oxazoline).[55]

7. Modification of Polymers by Atom Transfer Radical Addition

Atom transfer radical addition (ATRA) is a transition-metal-catalyzed reaction between alkyl halides and alkenes.[90] Jérôme and co-workers have extensively studied the ATRA post-polymerization modification of polyesters containing α-chloro-ε-caprolactone repeat units (Scheme 6). This process was successfully used to prepare polyesters modified with a broad range of functional groups, including alcohols, esters, epoxides, and poly(ethylene glycol).[57,58]



Scheme 6. Atom transfer radical addition to polyesters containing α-chloro-ε-caprolactone units.[58]

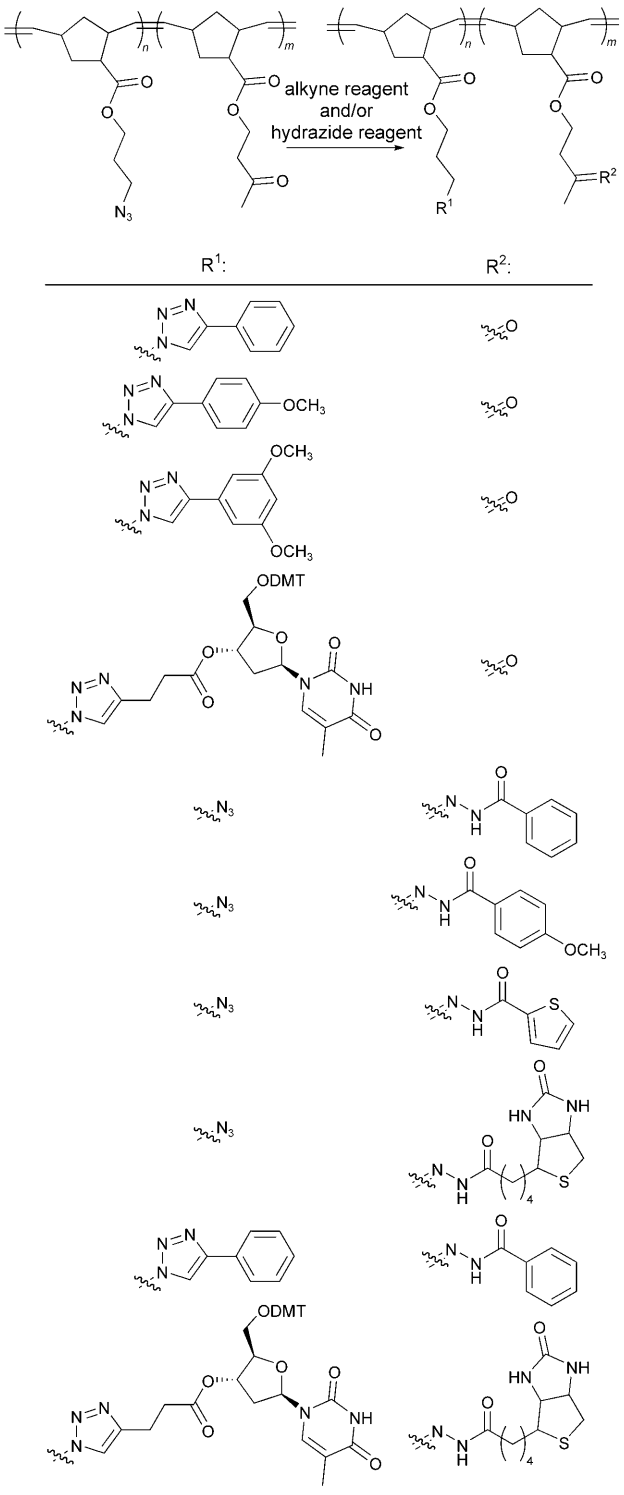
Post-polymerization modification with 3-butenyl benzoate or 3-buten-1-ol was found to proceed to essentially quantitative conversion in 90–240 min in DMF at 60 °C using CuBr/tris[2-(dimethylamino)ethyl]amine (Me_6TREN) as catalyst.[58,91] Attempts to carry out ATRA of vinylacetic acid and 1,2-epoxyhex-5-ene using these conditions were unsuccessful. The post-polymerization modification with these olefins could be achieved using the CuBr/1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) catalyst system, but at 32–42 % conversion. At 60 °C the ATRA process did not appear to compromise backbone integrity, though post-polymerization modification with 3-buten-1-ol was found to lead to a decrease in molecular weight, presumably owing to transesterification reactions.[58]

8. Modification of Polymers Bearing Aldehydes and Ketones

Aldehydes and ketones are electrophilic groups that can react selectively with amines, alkoxyamines, and hydrazides to form imines, oximes, and hydrazones, respectively. Imines are hydrolytically labile and must be reduced, a process referred to as reductive alkylation, to improve their stability. This reduction is generally accomplished using $NaBH_4$ or $NaCNBH_3$, which react optimally at basic or neutral pH values, respectively.[92] Oximes and hydrazones are hydrolytically stable between pH 2–7 and 5–7, respectively, but they decompose rapidly above pH 9.[93,94] Aldehyde-functionalized polymers can be conveniently prepared from 3,3′-diethoxypropyl methacrylate, which can be polymerized using free-radical polymerization[95] as well as under ATRP[96] and RAFT[97] conditions. After polymerization, the acetal protecting group can be removed with trifluoroacetic acid. 4-Vinylbenzaldehyde has been directly homopolymerized using RAFT conditions.[60] Coordination to the copper catalyst has been reported to prevent ATRP of methyl vinyl ketone, though its reverse ATRP copolymerization with methyl methacrylate was shown to be possible.[59] Methyl and phenyl vinyl ketone can be homopolymerized in a controlled fashion under RAFT conditions.[61] In several instances, aldehyde-functionalized monomers have been copolymerized using controlled polymerization conditions with a second monomer containing an orthogonal reactive side-chain functionality to afford copolymers that can be modified with two different functional groups in a one-pot reaction (**3** and **4** in Scheme 3).[30,62] Scheme 7 gives an overview of different copolymers prepared by Yang and Weck by one-pot dual functionalization of random copolymers obtained by ROMP of azide- and aldehyde-containing norbornene derivatives.[62]

9. Modification of Polymers by the Huisgen 1,3-Dipolar Cycloaddition Reaction

The Cu^I-mediated Huisgen 1,3-dipolar cycloaddition reaction ("click chemistry") has been extensively used for post-polymerization modification, because it gives high yields under mild conditions in aqueous and in organic media.[98] This approach requires the preparation of polymers containing azide or alkyne functional groups, which can be obtained by various (controlled) polymerization techniques (Table 1).[98] A number of side reactions can hamper the controlled polymerization of azide- or alkyne-containing monomers, however. It has been noticed, for example, that acidic protons adjacent to alkynes may cause termination of anionic polymerization.[65] ATRP of propargyl methacrylate proceeds with poor control, presumably owing to radical addition to the alkynyl group and coordination of the monomer and polymer alkynyl groups to the ATRP catalyst, among other things.[69] The broad molecular-weight distributions for polymers obtained from *N*-propargyl-7-oxynorbornene by ROMP are also thought to result from competing reactivity of the acetylenic moiety with the ROMP catalyst.[68] These problems may be overcome by trimethylsilyl protection of the alkynyl group on the monomer.[99] Whereas aliphatic azides are thought to interfere with the CROP of 2-oxazolines,[66] Binder and Gruber have successfully polymerized 2-(4-azidophenyl)oxazoline.[70] An attractive feature of post-polymerization modification using the Huisgen 1,3-dipolar cycloaddition reaction is that nearly all functional groups have been reported to be tolerant to this reaction, except for those that are self-reactive (e.g. azides and alkynes) or that form complexes with the catalyst (leading to deactivation).[98] Furthermore, azides are susceptible to reduction by thiols, although reactions between thiols and alkyl azides require relatively harsh conditions (100 °C for several hours) or a catalyst.[100] The orthogonality and potential of the Huisgen 1,3-dipolar cycloaddition reaction for the preparation of functional polymers was clearly demonstrated by Yang and Weck, who performed the one-pot modification of the azido groups on a dual-reactive polymer bearing both azide and ketone side chains (**3** in Scheme 3).[62] Quantitative conversion of the azide groups to triazoles was achieved with various alkyne reagents in 5–24 h using 5 mol % $CuSO_4 \cdot 5H_2O$ and 10 mol % sodium ascorbate in either THF or DMF (Scheme 7).



Scheme 7. One-pot modification of a dual, orthogonally reactive copolymer with alkyne and hydrazide reagents. DMT = dimethoxytrityl.[62]

10. Modification of Polymers by Pd-Catalyzed Coupling and Cross-Coupling Reactions

The palladium-mediated Heck, Sonogashira, Suzuki, and Stille reactions produce stable C–C bonds in high yield under relatively mild conditions with excellent functional-group tolerance and even in heterogeneous media.[101] Post-polymerization modification using one of these reactions requires polymers with alkyl or aryl halide, alkene, alkyne, boronic acid or ester, or organotin functional handles. *p*-Bromostyrene can be polymerized by controlled radical and anionic polymerization (Table 1). The anionic polymerization, however, requires judicious choice of initiator and temperature and the absence of light to proceed without side reactions.[78] Polymers containing boronic acid and boronic ester functionalities can be prepared in a controlled fashion using ATRP[75] and RAFT polymerization.[77] In spite of the generally excellent functional-group tolerance of palladium-catalyzed cross-coupling reactions, post-polymerization modification may be hindered owing to catalyst poisoning by thiols in the Suzuki reaction[102] or homocoupling of alkynes (Glaser coupling) in the Sonogashira reaction.[103] Sessions et al. have recently investigated the optimization of reaction conditions for the modification of poly(*p*-bromostyrene) with phenylacetylene and 1-hexyne by Sonogashira coupling.[76] Use of $[PdCl_2(PhCN)_2]$ as catalyst and tri-*tert*-butylphosphine as additional ligand allowed the room-temperature coupling of these compounds (present as 1.5 equiv relative to bromostyrene units) to poly(*p*-bromostyrene) ($8300\ g\,mol^{-1}$) at up to 89 and 99% conversion (for 1-hexyne and phenylacetylene, respectively) after 96 h. Modification of higher-molecular-weight poly(*p*-bromostyrene) ($71\,400\ g\,mol^{-1}$) with 1-hexyne led to cross-linking and gelation. Li et al. have prepared a 19-member library of poly(4-hexylthiophene)s by the Suzuki, Stille, and Heck reactions (Scheme 8).[104] The degrees of conversion of these transformations were estimated by ^1H NMR spectroscopy and were generally excellent.

11. Summary and Outlook

Post-polymerization modification is an attractive approach for the synthesis of functional polymers that overcomes problems related to the limited functional-group tolerance of a number of polymerization strategies. Post-polymerization modification is also a useful tool for combinatorial materials discovery, as it generates functionally diverse libraries of polymers with identical chain lengths and chain-length distributions from a single master batch of an appropriate polymer precursor. This Review has highlighted several selected reactions that can be used to introduce a range of functional groups into appropriate polymer precursors with very high conversion. Many of these precursors can be obtained using controlled "living" polymerization techniques. A number of recent reports have described the copolymerization of two monomers that contain orthogonal reactive groups. This is an interesting new development, which allows the one-pot synthesis of multifunctional polymers and which could provide new impetus for the development of new polymer materials and combinatorial materials discovery.

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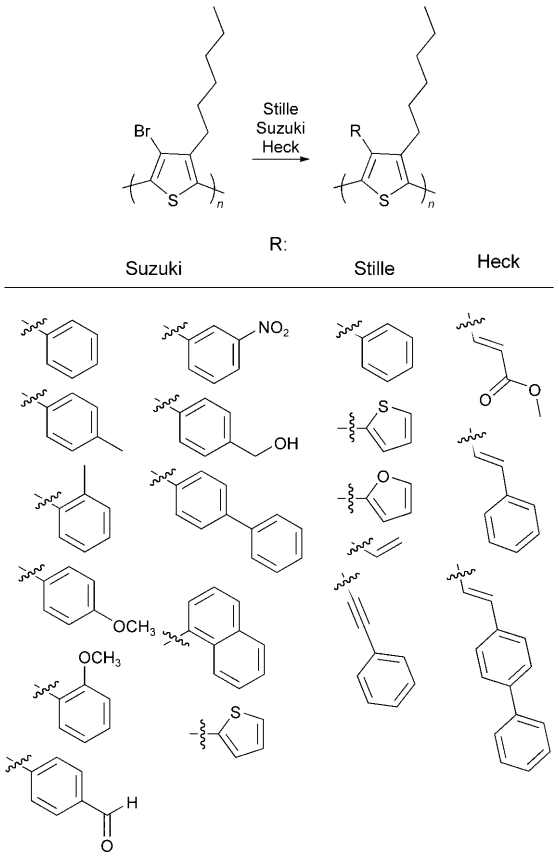

Scheme 8. Functional thiophenes produced by Pd-catalyzed post-polymerization modification.[104]

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