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Functional biodegradable polymers *via* ring-opening polymerization of monomers without protective groups

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Biodegradable polymers are of current interest and chemical functionality in such materials is often demanded in advanced biomedical applications. Functional groups often are not tolerated in the polymerization process of ring-opening polymerization (ROP) and therefore protective groups need to be applied. Advantageously, several orthogonally reactive functions are available, which do not demand protection during ROP. We give an insight into available, orthogonally reactive cyclic monomers and the corresponding functional synthetic and biodegradable polymers, obtained from ROP. Functionalities in the monomer are reviewed, which are tolerated by ROP without further protection and allow further post-modification of the corresponding chemically functional polymers after polymerization. Synthetic concepts to these monomers are summarized in detail, preferably using precursor molecules. Post-modification strategies for the reported functionalities are presented and selected applications highlighted.

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1. Introduction

Biodegradable polymers are of great current interest for biomedical applications, *e.g.* for drug and gene delivery systems, bioengineering scaffolds or as bioadhesives. They employ binding motifs within their backbone, inspired by natural biopolymers, *e.g.* polysaccharides, polyhydroxyalkanoates, polypeptides or (deoxy)-ribonucleic acids (DNA and RNA). A broad range of synthetic biodegradable polymer classes has been developed so far, including polyesters, polyamides, polycarbonates, poly(phosphoester)s, polyphosphazenes, poly(ester amide)s, poly(ester-ether)s, poly-(ester-anhydride)s, poly(ester urethane)s, poly(ester urea)s, polyacetals, polyorthoesters, polydioxanones and polyiminocarbonates, which can be obtained by step-growth polycondensation or -addition or chain-growth polymerization.[1] Especially, when it comes to advanced applications, chemical functionality in such materials is demanded, *e.g.* to attach labels or other molecules along the backbone.

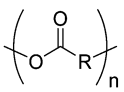
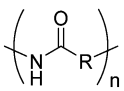
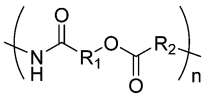
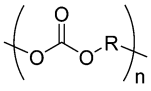
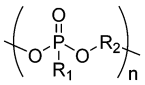
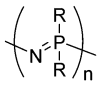
With a plethora of modern catalysts, the chain growth approach has a higher control over polymer molar masses and dispersities. Different mechanisms are available, including cationic, anionic, enzymatic, coordinative and radical ring-opening polymerization (ROP). Copolymerization of different cyclic monomers with pendant alkyl or aryl groups gives access to a variety of polymeric materials with a broad range of different physical properties, *e.g.* varying hydrophilicity/hydrophobicity, crystallinity, solubility, mechanical strength, degradation behavior or thermal stability. Such degradable polymers are also important for the future of sustainable polymers and plastics.[2] Properties and features, as well as their advantages and drawbacks of the different classes of synthetic biodegradable polymers, are beyond our scope and are extensively discussed in several reviews.[2–6]

While copolymerization of alkylated and arylated monomers adjusts the materials properties, fine-tuning of the polymers is often demanded for specific applications: additional attachment of bioactive molecules, redox- or pH-sensitive functionalities or cross-linkable groups might be required for their applications. On the one hand, (especially) ionic ROP might be sensitive to impurities and tolerates only certain chemical functionalities. The sensitivity to moisture and thereby the exclusion of water as reaction solvent is a drawback. On the other hand, also bioactive molecules (*e.g.* carbohydrates, peptides or proteins) can be sensitive or undergo side-reactions that they do not tolerate the polymerization process or conditions, *e.g.* organic solvents, high temperatures or required catalysts. Great effort has been made in the last decades, developing cyclic monomers with orthogonal chemical functions, which do not interfere the polymerization process. These monomers can be divided into two groups: (I) orthogonally reactive groups that do not interfere with the polymerization but can be post-modified afterward; (II) active groups, *e.g.* photo- or redox-active.

In this review, we summarize synthetic strategies to orthogonally reactive cyclic monomers reported in the literature that allows subsequent post-polymerization modification. We highlight the general concepts, preferably using precursor molecules, which can be used to prepare these monomers and thereby chemically functional biodegradable polymers by ROP (Table 1). A comparison on the synthetic ease of the different monomer classes will be given, that helps to choose the polymer class of choice for the desired application. We further display post-modification strategies with selected applications.

The scope of the review is to be a handbook on the preparation of orthogonally reactive cyclic monomers to deliver a "toolbox" on how functional synthetic biodegradable polymers

Table 1 Overview of the monomers and polymer classes discussed in this review

Polymer class	General structure	Cyclic monomers
Polyesters		Lactone Macrolactone Glycolide Lactide Hemilactide *O*-Carboxyanhydride (OCA)
Polyamides		Lactam α-*N*-Carboxy anhydride (α-NCA) γ-*N*-Carboxy anhydride (γ-NCA)
Poly(ester amide)s		Esteramide
Polycarbonates		Trimethylene carbonate (TMC)
Polyphosphoesters		Phosphate Phosphite Phosphonate
Polyphosphazenes		Hexachlorophosphazene

are prepared and post-modified. Tables after each section summarize the monomers discussed in the text, together with literature references and some comments.

All the herein discussed polymer classes are potentially degradable or biodegradable, due to certain linkages in the backbone. The degradation profile is one of the most important features of these polymers, depending on their area of application. Several of the examples given in this review are claimed to be degradable, due to labile ester or amide linkages in the backbone, although degradation behavior was not studied in detail. Degradation is possible by acidic, alkaline, enzymatic, microbial or oxidative cleavage of ester/amide bonds. The comparison of degradation rates and conditions is difficult, as the degradation profiles depend on various factors: the hydrophilicity or hydrophobicity, water-solubility, crystallinity, glass transition, and/or glass transition temperature, processing, size, geometry (in bulk, as foams, thin fibers, nanoparticles, micelles, in solution, *etc.*), porosity and water diffusion (Table 2). In addition, the degree of polymerization, sterics of any substituents, polymer architecture, and solubility of degradation products have a strong impact on the degradation rates as well. Another factor that makes the comparison even in one polymer class difficult are additional post-modifications, *e.g.* with hydrophobic, polar or charged groups that further alter the degradation profiles.

The protocols for polymer degradation are diverse and lack standardized conditions, which makes most degradation studies non-comparable with each other (detailed information can be found in a recent review).[7] Most common degradation mechanism for the polymers discussed herein is hydrolysis of the polymer backbone. In most cases either acidic or basic hydrolysis are conducted under non-physiological conditions, *i.e.* at very low or high pH values that do not occur in natural environments. Furthermore, the chemical nature of the buffer solution, buffer-capacity, temperature, and concentration of polymer (if water-soluble) or shape of the specimen is different for most studies. For the enzymatic degradation, different enzymes can be applied, which may stem from different organisms and vary in their activity. Even batch-to-batch variations of the very same enzyme makes standardization of *in vitro* degradations difficult (overview of parameters shown in Table 1).

Trying to summarize some general aspects of degradation profile, herein we give some examples of non-functionalized polymers. Hydrolysis or enzymatic degradation are the typical degradation mechanism for such materials, with kinetics being very dependent on the environment and the chemical structure and/or crystallinity of the polymers. While polycaprolactone shows rather a slow degradation rate (within 2–3 years), due to its crystallinity, polylactide (depending on the chirality and composition) undergoes loss of mass within 6–16 months; polyglycolide (45–55% crystallinity) is known to lose mass within 6–24 months. Copolymers of poly(D,L-lactide-*co*-glycolide) are reported to degrade faster, depending on the composition ratio, within 5–6 months. Polyesters hydrolyze under acidic and basic conditions;[8] in contrast, some polyphosphoesters can be very stable under acidic conditions but degrade in the presence of a base. For polyphosphates, a typical water-soluble example is poly(methyl ethylene phosphate); while being stable at low pH, degradation of triester to diester bonds occurs under alkaline conditions within 5 h (at pH 12.3) to 21 months (pH 7.3). (Note: these are degradation times for 50% cleavage of the ester bonds in the main chain of the polymer.)[9] Polyphosphonates with the P–C bond in the side chain show similar degradation profiles under neutral and basic conditions. Complete degradation was observed after 1 hour at pH 12.[10] Contrary, polyphosphoramidates undergo hydrolysis in basic and acidic media.[11–15] While hydrolysis almost exclusively proceeds at the P–N bond under acidic and nearly neutral conditions, P–O, as well as P–N bond cleavage, occurs under basic conditions, still with a higher probability for P–N cleavage.[14] 94% cleavage of main-chain polyphosphoramidates to diesters has been shown at pH 3.0 within 12.5 days.[11] The degradation profile of polyphosphazenes strongly depends on the substituents and ranges from hydrolytically stable (with hydrophobic, bulky alkoxy side groups) to hydrolytically unstable (with hydrophilic amino substituents). Degradation of the P=N-backbone is commonly accelerated in acidic media, but they are rather inert under basic conditions.[16,17] The biodegradation of synthetic aliphatic

Table 2 Overview of parameters influencing the degradability of polymers and polymeric materials

	Influencing parameters of the...		
Degradation	Polymer	Sample	Procedure
– Hydrolytic: • Acidic • Basic – Enzymatic – Microbial – Oxidative	– Hydrophilicity/hydrophobicity – Water-solubility – The degree of polymerization – The glass transition temperature – Crystallinity – Sterics of substituents – Architecture (linear/branched/cross-linked) – The solubility of degradation products – Post-modifications	– Processing – Size/geometry: • Bulk • Foam • Fibers • Nanoparticles • Micelles • In solution – Porosity – Water diffusion	– Choice of enzyme: • Origin • Activity • Selectivity – Physiological/non-physiological conditions – pH: • Acidic • Basic • Molarity – Buffer: • Buffer-system • Capacity – Concentration – Temperature – *In vitro/in vivo*

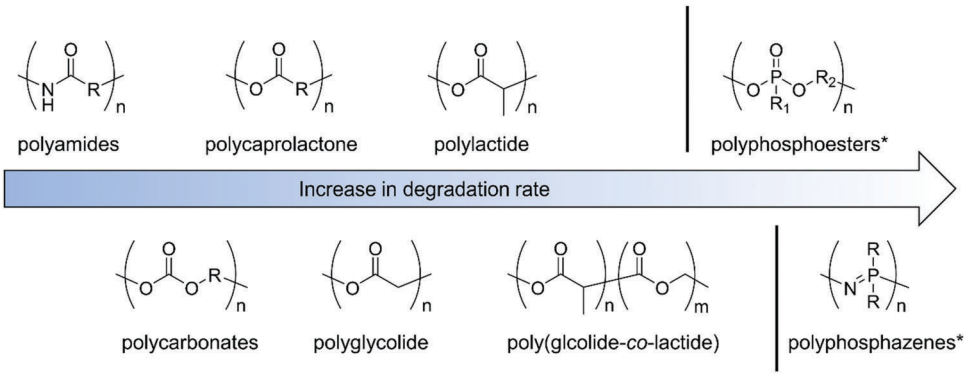


Fig. 1 Overview of the systematic order of degradability of the discussed polymer classes. * Note: degradation profiles of polyphosphazenes and polyphosphoesters depend strongly on the nature of the substituents.

polyamides is known to be low due to high crystallinity. Enzymatic or microbial degradation has been shown.[18] Fig. 1 gives a rough overview of the systematic order of degradability of the discussed polymer classes, however, the data has to be taken as an estimation only, as many factors as mentioned above may influence absolute values. A recent review summarizes the degradation of polylactides.[19] We refer the interested reader to separate reviews concentrating on the degradation of synthetic polymers.[3,4,16,17,20–23]

2. Overview of orthogonally reactive groups

ROP only tolerates some additional chemical functionalities in the monomers. Since alcohols, thiols, amines or carboxylic acids interfere with the propagation and serve as initiators or terminating agents, they need to be protected before polymerization. Commonly used protecting groups, *e.g.* benzyl, benzoyl, ethers, silyl ethers, acetals, urethanes, sulfonamides or esters are applied in cyclic monomers for ROP. Removal of protection groups is conducted after the polymerization under alkaline or acidic conditions, or by hydrogenation and often demands harsh conditions, which might also degrade the polymer backbone. We do not further consider these protected monomers in the review and concentrate exclusively on orthogonally reactive functionalities (Fig. 2). For protected monomers, we refer to other reviews, specializing in the respective polymer class.[24–28] The same functional groups can also be installed into the initiator structure, in order to prepare end-functionalized polymers (telechelics).[29,30]

For the orthogonal functions, alkynes and alkenes are by far most frequently reported in the literature and are used in the monomers and initiator structures. Alkynes undergo the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC, Huisgen 1,3-dipolar cycloaddition) with azides or can react in a thiol–yne reaction with thiols in often quantitative yield and mild conditions. Also, azides as the ''counterpart'' are reported as functionality in monomers. Besides CuAAC, they can be additionally modified with DBCO derivatives in a strain-promoted alkyne–azide cycloaddition (SPAAC),[31] which turns the reaction into a copper-free functionalization and is especially interesting for biomedical applications. Alkenes are accessible for probably the most modification reactions: besides thiol–ene reaction and Michael addition, epoxidation (*e.g.* by *m*CPBA), dihydroxylation, hydroboration, ozonolysis, hydrazination, hydrogenation, bromination, hydrobromination, and others are applicable. Especially epoxidation opens a platform for diverse further reaction. Also, few monomers are reported that directly carry an epoxide, which under certain conditions does not interfere with ROP. Epoxides can cross-link the materials, react with thiols, be dihydroxylated or further polymerized. If alkene functions are vinylidenes, the cyclic monomers are bifunctional for radical polymerization or can serve as cross-linkers as well. They furthermore can be used for olefin cross-metathesis or Suzuki coupling. Acrylate, methacrylate and styrenic functions likewise can be radically polymerized, cross-link the materials, undergo thiol–ene reaction and Michael addition or are accessible for olefin cross-metathesis. Cinnamoyl groups serve as cross-linkers. Likewise, methylidene functions can be polymerized or cross-link materials and undergo thiol–ene reaction, which can be also achieved with norbornene groups, additionally suitable for 1,3-dipolar cycloadditions and ring-opening metathesis polymerization (ROMP). Completing the group of double bond-containing functionalities, internal double bonds are accessible for epoxidation, dihydroxylation, and cross-metathesis, while vinyl ethers are interesting reaction partners for thiol–ene reaction, acetal- and thioacetalisation.

Halogenated monomers are a second important category, especially with bromide or chloride substituents. Nucleophilic substitution *e.g.* with sodium azide and quaternization of tertiary amines or phosphines has been reported, as well as dehydrohalogenation or boration. Iodide substituted monomers play a minor part, but can also be used for nucleophilic substitution and quaternization of amines, or are used as a radioopaque function, *e.g.* for contrast agents. Such halogenated polymers have also been used extensively as initiators for atom transfer radical polymerization (ATRP) to prepare graft or brush (co)polymers. Several bromo isobutyrate-containing monomers were developed for the same purpose, as well as trithiocarbonate

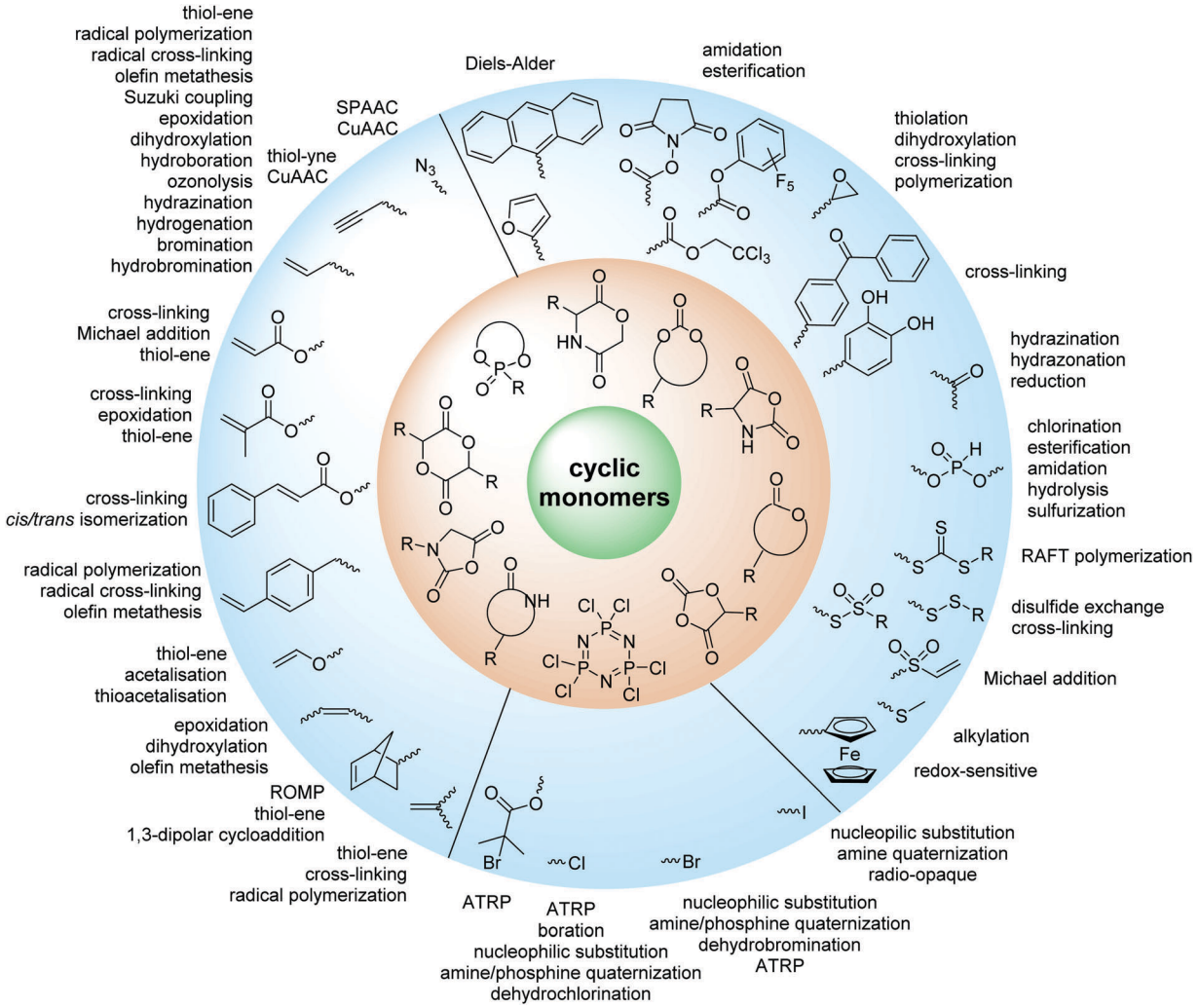


Fig. 2 Overview on cyclic monomers discussed in the review with orthogonally reactive groups.

monomers for reversible addition–fragmentation chain transfer polymerization (RAFT).

A third category includes more exotic, but at the same time very interesting and partly unexpected chemical functionality: besides the trithiocarbonate-containing monomers for RAFT polymerization, several further sulfur-containing monomers are introduced, bearing disulfide or *S*-sulfonyl groups. The functional groups do not interfere with ROP and can be considered as "protected thiols". Functionalization is achieved with thiols by disulfide exchange reaction without any prior deprotection reaction: dynamic and redox-responsive cross-linking are accessible. Methyl-thioether functions can undergo reversible alkylation reaction, additionally implementing cationic charges. Vinyl sulfonyl moieties can react in Michael addition reactions. P–H bonds of cyclic H-phosphonate monomers are suitable for modification by esterification, amidation (after chlorination), hydrolysis and sulfurization. The P–H bond has not been reported yet in pendant chains. Ketones within the ring the cyclic monomer are accessible for reduction, hydrazination, and hydrazonation reactions. Benzophenone groups can be used as photo-cross-linkers by a C,H-insertion crosslinking reaction (CHic mechanism[32,33]) with CH groups. Cross-linking can also be achieved by catechol functions (1,2-dihydroxybenzene), either reversible by metal ion complexation or covalently by reaction with amine, thiols or other catechols after oxidation to quinone intermediates. In addition, active ester-containing monomers have been reported, such as trichloroethyl-, NHS- (*N*-hydroxysuccinimide) and pentafluorophenyl-ester groups, which undergo amidation and esterification reactions with alcohols or amines after polymerization.[34,35] Finally, anthracene and furan derivatives are suitable for [4+2] cycloaddition Diels–Alder reactions. However, reports on this thermally reversible modification by additive/catalyst-free cycloaddition are rare, which might be a further potential for future applications.

In general, also orthogonal reactions have limitations. This starts with the degree of conversion, which is not always quantitative and leaves non-reacted groups behind. In addition, polymerization conditions of functional monomers need to be carefully selected. For instance, pentafluorophenyl esters can only be polymerized using acid catalysis, thiol derivatives in some cases are complicated to work with (for example due to formation of disulfides), catechol-functionalized compounds

should be handled under oxygen-free atmosphere to avoid oxidation, and epoxides can also be ring-opened during the polymerization, if not carefully handled (*e.g.* at elevated temperatures). Moreover, the effectiveness of the post-functionalization methods can vary.[36] Radical thiol–ene and thiol–yne reactions often need a large excess of the thiol to prevent unwanted crosslinking reactions. For click reactions, the removal of the copper catalyst needs to be taken into account, *etc.* Such issues need always to be considered and are sometimes not clearly mentioned in publications. We refer to some general reviews about post-polymerization modifications that can be considered as additional reading.[25,36–38]

3. Polyesters

Aliphatic polyesters from ROP probably display the broadest group of fully synthetic biodegradable polymers. A variety of lactones with different ring sizes are available resulting in poly(ε-caprolactone)s, poly(δ-valerolactone)s, poly(γ-butyrolactone)s, poly(β-butyrolactone)s, poly(β-propiolactone)s, and poly(α-propiolactone)s. Macrolactone monomers are likewise polymerizable. Furthermore, cyclic diesters (lactides, glycolides and *O*-carboxy anhydrides (OCAs)) produce the commercialized poly(α-hydroxy acid)s (PAHAs) polylactides (PLAs) and polyglycolides (PGAs) (Table 3). Several reviews about functional aliphatic poly(ester)s have been published and might be considered for further reading.[26,39,40]

A less explored synthetic route to polyesters is the radical ring-opening polymerization (RROP) of cyclic ketene acetals (CKAs), which was summarized recently[41] and is not further considered in this review. However, as radical polymerization is interesting also on the industrial scale, this strategy might be used also for the development of degradable functional polyesters. To the best of our knowledge, only methylidene-functionalized or chlorinated monomers are reported so far,[41] resulting in halogenated polyesters or polymers with internal double bonds, but no postmodification was reported. In addition, less explored are poly(ester-ether)s and polythioesters. Five-, six- as well as seven-membered cyclic lactone ethers have been polymerized *via* ROP to poly(ester-ether)s. Reported substituents are mainly alkyl- or aryl chains or protected functions. To the best of our knowledge, orthogonally reactive monomers are not available so far but should be considered as a further development of lactone monomers. ε-Thiolactones and β-thiolactones can be polymerized by a base-catalyzed ring-opening polymerization to polythioesters. However, no functional reactive monomers have been reported to the best of our knowledge.[42] The combination of polyaddition and ring-opening of different cyclic monomers offers a further strategy to novel functional materials with tunable properties: the reaction of lactone monomers with diamines has been reported.[43] Polyesters can also be obtained by alternating ring-opening copolymerization (ROCOP) of epoxides and anhydrides. We exclude the technique of polyaddition of orthogonally reactive epoxides or anhydrides and point to several recent reviews.[39,44,45]

3.1 Lactones

3.1.1 ε-Caprolactones. Functional ε-caprolactones ε-(CL) can be divided into three subgroups, substituted in α-, β or γ-position, depending on the synthesis strategy for each monomer (overall yields: 19–70%). CLs are commonly polymerized with 2,2-dibutyl-2-stanna-1,3-dioxepane (DSDOP) as catalyst (in toluene at 20 °C for 24 h[46] or at 60 °C for 2 h) or with tin(II) 2-ethyl hexanoate ($SnOct_2$) in bulk or solution at 100–140 °C for 4–24 h (Scheme 1). For detailed polymerization conditions of lactones and lactides/glycolides and applied catalysts, we refer to separate literature.[47]

3.1.1.1 α-Substituted-ε-caprolactones. α-Halogenated caprolactones can be prepared by the Baeyer–Villiger oxidation of 2-halogenated-cyclohexanone with *meta*-chloroperoxybenzoic acid (*m*CPBA) (yield: 45–70%, Scheme 2A).[46] Mohamod and coworkers[48] polymerized α-fluoro caprolactone (**A1**) as homo- or copolymer with caprolactone. α-Chloro- (**A2**)[46] and α-bromocaprolactone (**A3**)[49] was polymerized and substituted with azides, which allowed further postmodification with alkynes in a Huisgen 1,3-dipolar cycloaddition.[49] These graft-polymers were used as macroinitiators for ATRP of methyl methacrylate (MMA)[50] or hydroxyethyl methacrylate (HEMA)[51] with the chlorides or bromides as initiating sites. Azide-functional poly(ε-CL) was also directly synthesized by an α-azido-ε-CL (**A4**),[52] which was prepared by substitution of **A2** or **A3** with sodium azide.

A further general strategy is the functionalization of the α-position of ε-caprolactone by deprotonation with LDA (lithium diisopropylamide) and subsequent reaction with an electrophile (Scheme 2B). α-Iodo-caprolactone (**A5**) was obtained in this way by iodination with ICl (yield: 29%).[53] The authors claimed the resulting copolymers to exhibit radio-opacity properties with potential application in temporary reconstructing material or drug delivery because of visualization *via* routine X-ray radioscopy.

α-Alkene and -alkyne functionalized caprolactones are used for the purpose of thiol–ene reaction and click reaction, introducing charged functionalities or bulky molecules, such as dyes or sugars. Following the described strategy, deprotonated ε-caprolactone reacts with allyl bromide, propargyl bromide or propargyl chloroformate to yield α-allyl-ε-caprolactone (**A6**, yield: 65%),[54] α-propargyl-ε-caprolactone (**A7**)[55] and α-propargyl carboxylate-ε-caprolactone (**A8**).[56] After copolymerization of **A6** with ε-CL, Coudane and coworkers[54] attached Boc-protected-amines as the pendant chains by the radical thiol–ene reaction. They proved deprotection of the amine without degradation of the backbone and subsequent reaction with fluorescein isothiocyanate (FITC). They claimed the water-soluble cationic polyesters as interesting materials for gene delivery. Maynard and coworkers[57] recently reported trehalose- and carboxybetaine-substituted poly(CL) and used it as a polymeric excipient for the stabilization of the therapeutic protein G-CSF for storage at 4 °C and at heat stressor temperatures of 60 °C. Copolymers of **A7** were functionalized with the clinically used diethylene-triaminepentaacetic acid (DTPA)/Gd^{3+} complex, resulting in

Table 3 Orthogonally functional cyclic monomers for the synthesis of polyesters

Monomer	R =	No.	Post-modification	Ref.
ε-Caprolactones				
α-Substituted				
	F	**A1**	– No modification	48
	Cl	**A2**	– Nucleophilic substitution with sodium azide and click chemistry – ATRP macroinitiator for "grafting from" of MMA	46 and 50
	Br	**A3**	– Nucleophilic substitution with sodium azide and click chemistry – ATRP macroinitiator	49 and 51
	I	**A5**	– Radio-opaque properties	53
	N_3	**A4**	– Click chemistry	52
		A7	– Click reaction with cyclodextrin or Gd^{3+}-complexes	55, 58 and 59
		A8	– Click reaction to core-cross-linked micelles	56
		A6	– Thiol–ene reaction with amines, dyes, sugars or zwitterions	54 and 57
		A9	– End-chain cross-linker for macrocyclic polyester	60
	=	**A10**	– No modification	61
ε-Substituted				
		A7b	– Click reaction to couple cyclodextrin	55 and 59
β-Substituted				
		A11	– No modification	63
		A12	– Epoxidation and thiol–ene reaction to cross-link	64
γ-Substituted				
	Cl	**A13**	– Nucleophilic substitution with sodium azide and click chemistry with a cholesterol derivative for cell scaffolds and foams – Quaternization with pyridine	65
	Br	**A14**	– Elimination, epoxidation, and ring-opening to diols – Nucleophilic substitution with sodium azide and click chemistry	66–68
	=O	**A15**	– Hydrazination or hydrogenation – Reduction to alcohols and use as macroinitiator or coupling of maleic anhydride	69–71, 151 and 152
		A16	– Bifunctional polymerization – Electrografting onto metal surfaces – 2D- and 3D-microstructured resins – Michael-addition of thiols	72–75
		A17	– Photo-cross-linking	73 and 76
	Br	**A18**	– ATRP initiator or macroinitiator	77
		A19	– Photo-cross-linking	78
δ-Valerolactones				
		A20	– Dihydroxylation with NMO/OsO_4	80 and 85
		A22	– Click chemistry with PEG-, GRGDS-, phosphorylcholine or benzophenone-azides	79, 82, 84 and 85
		A21	– Dihydroxylation and PEG "grafting to"	81
	=	**A23**	– Radical copolymerization with methacrylates to form networks	86
	Fe	**A24**	– No polymerization	87
	Fe	**A25**	– No polymerization	87
	Fe	**A26**	– No polymerization	87
γ-Butyrolactones				
	=	**A27**	– Copolymerization with CL and cross-linking with methacrylate	92 and 93

Table 3 (*continued*)

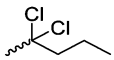
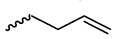
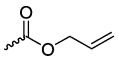
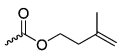
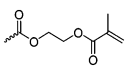
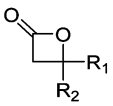
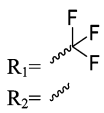
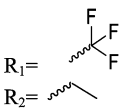
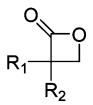
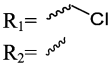
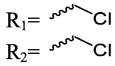
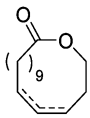
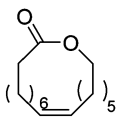
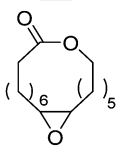
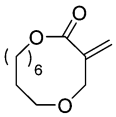
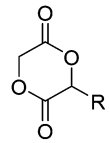
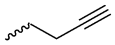
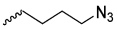
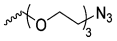
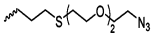
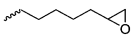
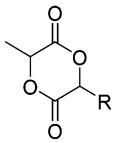
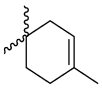
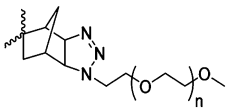
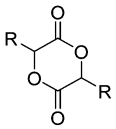
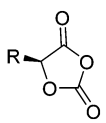
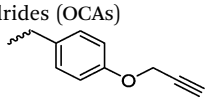
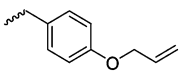
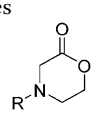
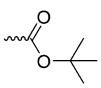
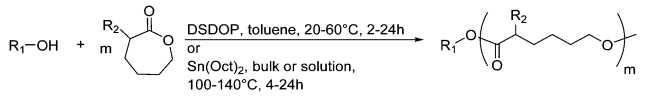
Monomer	R =	No.	Post-modification	Ref.
		**A28**	– Co- and terpolymerization with CL or TMCs and grafting from of methacrylates	95
β-Propiolactones				
		**A29**	– Tacticity studies	96
		**A30**	– Tacticity studies	96
		**A31**	– Tacticity studies	96 and 98
		**A32**	– Tacticity and property studies	98
		**A33**	– Tacticity and property studies	99
		**A34**	– Tacticity and property studies	99
		**A39**	– Selective polymerization studies	103
		**A40**	– Selective polymerization studies	103
		**A41**	– Selective polymerization studies	103
		**A42**	– Hydroboration or olefin cross metathesis	104–107
		**A43**	– Epoxidation and sulfonation to polymers inducing bone formation; thiol–ene reaction to macroinitiator for "grafting from"	108 and 110–112
		**A44**	– Epoxidation	108
		**A45**	– No modification	109
β-Butyrolactones				
		**A35**	– Tacticity and property studies	97
		**A36**	– Tacticity and property studies	97
		**A37**	– Quaternization with pyridine	100 and 101
		**A38**	– Polymerization studies	102
		**A46**	– Radical cross-linking or thiol–ene reaction	113 and 114
Macrolactones				
		**A47**	– Thiol–ene reaction for functionalization with pendant chains, cross-linking or functionalization with ATRP initiators for "grafting from" of *tert*-butyl acrylate	119 and 122
		**A48**	– Epoxidation	125
		**A49**	– No modification	125

Table 3 (*continued*)

Monomer	R =	No.	Post-modification	Ref.
		**A50**	– Radical cross-linking	126
Mono-substituted glycolides				
		**A51**	– Epoxidation, dihydroxylation	127
		**A54**	– Click chemistry with PEG–azide	128
Mono-substituted hemilactides				
		**A52**	– Thiol–ene reaction with amines for gene delivery – Photo-cross-linking of nanoparticles/capsules	133 and 135
		**A55**	– Click chemistry with PEG-/palitaxcel-azide	129
		**A58**	– Click chemistry with dansyl-azide	138
		**A59**	– Click chemistry with dansyl-alkyne	138
		**A60**	– Click chemistry with dansyl-alkyne	138
		**A61**	– Click chemistry with dye/cell internalizing peptide – Staudinger condensation with Tap-GRGDS	139 and 140
		**A53**	– Cross-linking	134
		**A62**	– ROMP – Click reaction with tetrazine derivatives	130 and 131
		**A64**	– No modification	142
		**A65**	– No modification	142
		**A63**	– No modification	141
Di-substituted glycolides				
		**A56**	– Click chemistry with azide derivatives	136
		**A57**	– Formation of double bonds – Thiol–ene reaction	137
O-Carboxyanhydrides (OCAs)				
		**A66**	– Cross-linking with di-azides to redox- or light-responsive micelles – Thiol–yne reaction to form polyelectrolytes for gene delivery	145 and 147–149
		**A67**	– No modification	146
Morpholinones				
			– R = *N*-acyl morpholin-2-ones polymerize readily, but the *N*-aryl or *N*-alkyl substituted morpholin-2-ones do not polymerize.	144
		**A68**	– After removal of BOC group water-soluble.	144

MRI-visible polymers as a hydrophobic contrast agent.[58] PEG-block copolymers of α-propargyl carboxylate-ε-caprolactone formed micelles, which were core-cross-linked by a difunctional azide-cross-linker.[56] An alternative strategy to produce α-propargyl-ε-caprolactone (**A7**, yield: 14%) starts with deprotonation of cyclohexanone and subsequent substitution with

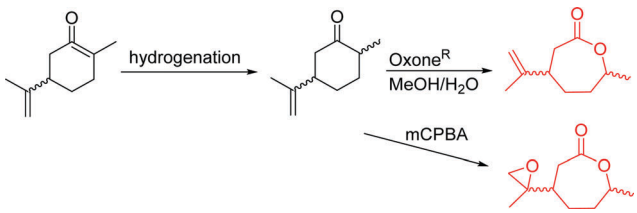


Scheme 1 General polymerization scheme of caprolactones to polyesters (R_1 and R_2 represent non-specified alkyl or aryl substituents).

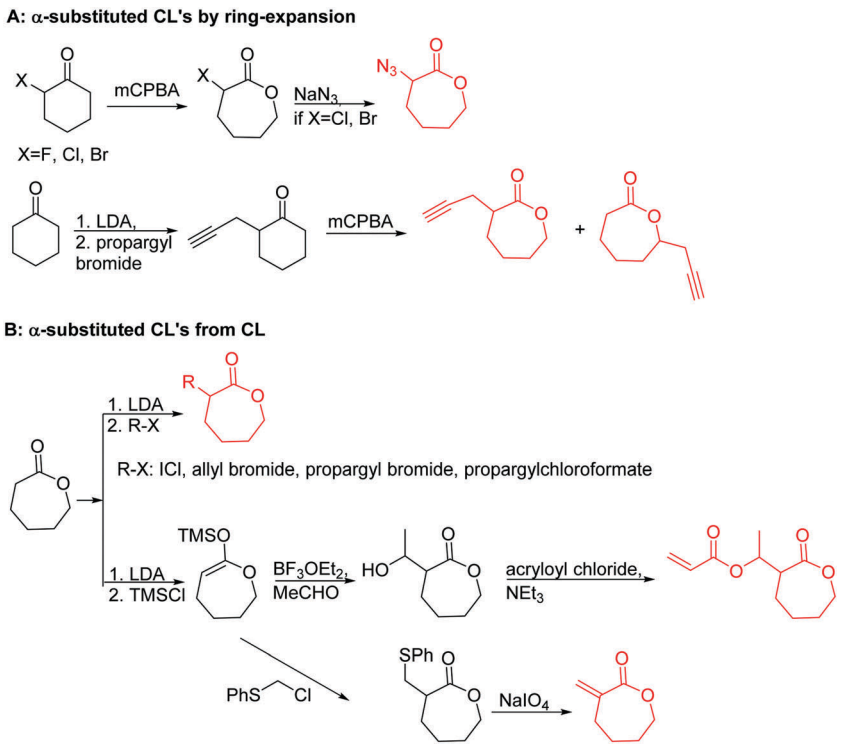
propargyl bromide, followed by the Baeyer–Villiger oxidation to expand the ring to ε-caprolactone (Scheme 2A).[59] However, a mixture of α- and ε-substituted caprolactones (**A7** and **A7b**, isomeric mixture yield: 30/70) were obtained. Ritter and coworkers prepared polymers and attached cyclodextrins *via* click reaction to form supramolecular organogels.[55]

Lecomte and coworkers[60] reported an acrylate-substituted CL (**A9**) using it as end chain comonomer to form macrocyclic polyesters. The macrocycles were formed by UV-crosslinking of the acrylates. **A9** was synthesized in three steps (Scheme 2B): deprotonation of caprolactone and addition of trimethylsilyl chloride formed a trimethylsilylketene acetal, which further reacted in a Mukaiyama aldol reaction with acetaldehyde. Esterification of the formed hydroxylactone with acryloyl chloride yielded the final monomer α-(1-acryloyloxyethyl)-ε-caprolactone (**A9**). Ritter and coworkers[61] reported the ROP of α-methylidene-ε-caprolactone (**A10**), while the monomer has been polymerized at the vinyl functionality before. Homopolymerization yielded only low molar masses, copolymerization with caprolactone clearly higher molecular weight polymers. They claimed the polymers to be radically cross-linkable, however, did not report on further details. The monomer was synthesized by *O*-silylation, followed by thioalkylation with α-chloro thioanisole and completed by oxidative sulfur (Scheme 2B) removal (overall yield: 39%).[62]

3.1.1.2 β-Substituted-ε-caprolactones. Hillmyer and coworkers reported two β-substituted CLs derived from natural carvone: 7-methyl-4-(2-methyl oxirane-2-yl)oxepan-2-one (**A11**)[63] and dihydrocarvide (**A12**)[64] (Scheme 3). **A11** was synthesized in two steps: hydrogenation of carvone resulted dihydrocarvone; epoxidation and ring-expansion yielded the final monomer (second step 25% yield). The monomer was homo- and copolymerized with CL, however, both rings reacted under the reported polymerization conditions (in bulk or solution, 20–120 °C, diethylzinc ($ZnEt_2$) or tin(II) 2-ethyl hexanoate ($SnOct_2$) catalyst). To obtain polymers with epoxides as pendant groups, monomer **A12** was obtained by ring-expansion of dihydrocarvone using Oxone® (triple salt $2{\cdot}KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$).[64] Poly(dihydrocarvide-*co*-carvomenthide) was subsequently epoxidized and crosslinked with a dithiol to prove the possibility of post-modification.



Scheme 3 Synthetic route to β-substituted CLs from carvone.



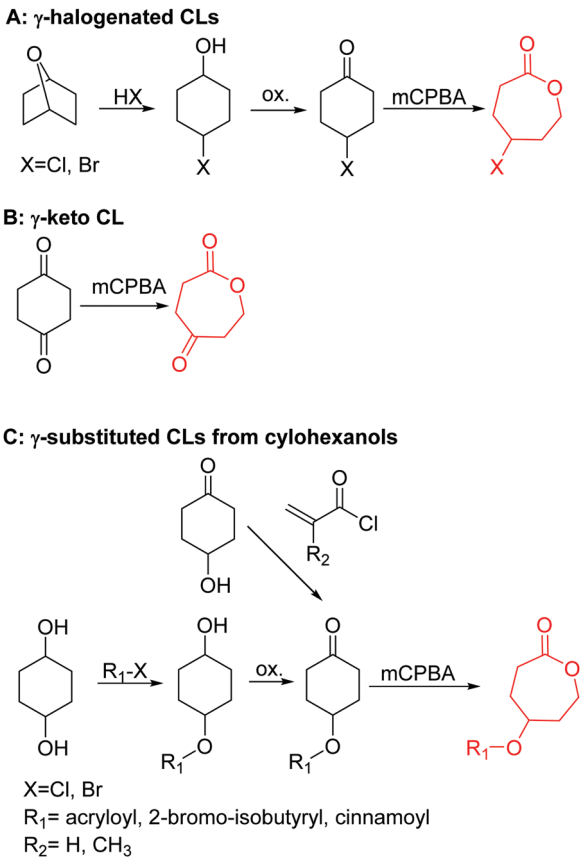
Scheme 2 Synthetic strategies for the synthesis of α-substituted ε-caprolactones: (A) by ring-expansion *via* the Baeyer–Villiger oxidation of cyclohexanones; (B) by substitution of ε-caprolactone.

3.1.1.3 γ-Substituted-ε-caprolactones. γ-Halogenated caprolactones are synthesized starting from 4-halogenated-cyclohexanol (obtained by halogenation of 7-oxabicyclo[2.2.1]heptane); the alcohol was oxidized to a cyclic ketone to yield the monomer γ-chloro-ε-caprolactone (**A13**)[65] or γ-bromo-ε-caprolactone (**A14**)[66] after a Baeyer–Villiger oxidation (yield for the last step: 62%; Scheme 4A). Hegmann and coworkers[65] used **A13** in a copolymerization with caprolactone and lactide, substituted the chloride with an azide and attached cholesterol derivatives. The copolymers were used as cell scaffolds and foams. Jérôme and coworkers[67] quaternized copolymers of caprolactone and **A14** with pyridine, applied a debromination or epoxidation, and subsequent ring-opening to obtain hydrophilic poly(CL) substituted with diols in the backbone. P(**A14**) was substituted by an azide and amine-groups were then coupled by click chemistry to obtain pH-sensitive star-shaped polyesters.[68] A γ-azide-ε-caprolactone has not been reported yet to the best of our knowledge. γ-Keto-ε-caprolactone (**A15**) was reported by the same group,[69] obtained by ring extension of 1,4-cyclohexanedione (Scheme 4B). Qiao and coworkers[70] functionalized the keto groups by hydrazine chemistry to introduce hydroxyl groups and coupled 4-nitrophenyl chloroformate. The activated ester was reacted with primary amines, *e.g.* of the cell adhesive peptide GRGDS. Lang and coworkers[71] reduced the carbonyl group in copolymers to hydroxyl groups, using them as a macroinitiator for further grafting of lactide.

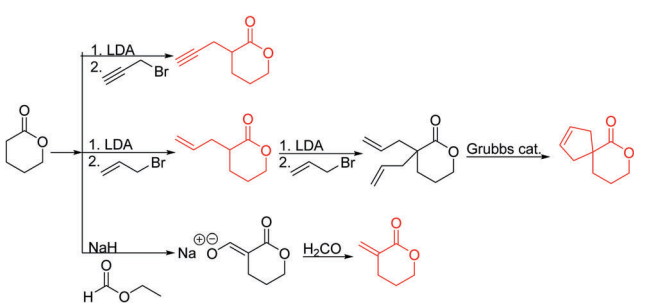
γ-Acryloyloxy ε-caprolactone (**A16**), a bifunctional monomer for ROP and radical polymerization,[72] was prepared in two or three steps (Scheme 4C): 1,4-cyclohexanediol reacted with acryloyl chloride. The resulting monoalcohol was oxidized and the ring extended to yield the monomer (in an overall yield of 36%). A shorter alternative strategy started with the reaction of acryloyl chloride with 2-hydroxycyclohexan-1-one and subsequent ring extension (overall monomer yield 24%).[73] Besides using the monomer for both ROP and ATRP, copolymers were grafted onto metal surfaces,[74] used as 2D or 3D microstructured resins[73] or were post-modified by Michael-addition of thiols.[75] A similar monomer, γ-methacryloyloxy-ε-caprolactone (**A17**), was prepared by the same method, using methacryloyl chloride instead (overall monomer yield 29%),[73] which were cross-linked upon UV-irradiation *e.g.* to form microparticles.[76] γ-(2-Bromo-2-methyl propionate)-ε-caprolactone (**A18**) carries a classical ATRP initiating group and was presented by Hedrick and coworkers.[77] A γ-cinnamate-modified caprolactone (**A19**) was recently reported by Budhlall and coworkers,[78] which can undergo *cis*/*trans* isomerization and [2+2] cycloaddition upon UV-irradiation. Homo- or copolymers were used as thermoresponsive and semicrystalline networks after photochemical cross-linking.

3.1.2 δ-Valerolactones. Poly(δ-valerolactone)s have been much less studied compared to poly(ε-caprolactone)s and the number of orthogonally reactive δ-valerolactone monomers is very limited to a few examples of α-substituted δ-valerolactone. Examples for substitution in other positions are only available for alkylated substituents. δ-Valerolactones are polymerized under similar conditions as caprolactones, *e.g.* with and an alcohol as initiator and $Sn(Oct)_2$ as a catalyst in bulk at 100 °C for 16 h,[79] or with $Sn(OTf)_2$ as a catalyst in bulk or THF at room temperature for 24 h.[80]

Emrick and coworkers[80] reported the first functionally substituted monomer, α-allyl-δ-valerolactone (**A20**), synthesized by the same strategy as α-substituted ε-caprolactones: lithiation of δ-valerolactone in α-position with LDA and subsequent reaction with allyl bromide yielded **A20** in one step (yield: 71%, Scheme 5). **A20** was copolymerized with ε-caprolactone or δ-valerolactone, as well as homopolymerization obtained polymers in good conversion and narrow molecular weight distributions. The alkenes were quantitatively dihydroxylated with NMO/OsO_4 to obtain more hydrophilic poly(ester)s. The group



Scheme 4 Synthetic strategies for the synthesis of γ-substituted ε-caprolactones: (A) for γ-halogenated CLs; (B) for γ-keto CL; (C) for γ-substituted CLs from cyclohexanols.



Scheme 5 Synthetic strategy for the synthesis of substituted δ-valerolactones.

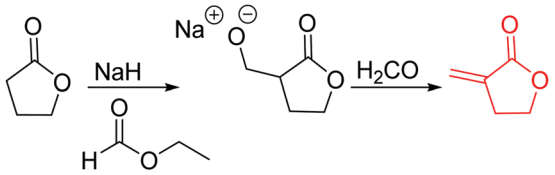
also introduced a α-cyclopentene-δ-valerolactone (**A21**):[81] **A20** was lithiated and allylated to yield α,α-diallyl-δ-valerolactone. Ring-closing metathesis using a Grubbs catalyst gave **A21**. The cyclopentene substituted lactone was not able to homopolymerize; copolymerization with ε-caprolactone was realized with the incorporation of *ca.* 20% of **A21**. The pendant group was converted to *cis*-1,2-diols by dihydroxylation with OsO_4 and showed longer bench-life stability compared to the diol-containing poly(ester)s from pendant allyl groups probably due to the higher rigidity of the monomer units. PEG was grafted onto the copolymers. Finally, Emrick and coworkers[82] also used α-propargyl-δ-valerolactone (**A22**)[83] (synthesized by the same strategy as **A21**) and obtained homo- as well as copolymers with ε-caprolactone. They functionalized the polymers by click chemistry with a PEG–azide, an oligopeptide-azide (GRGDS-N_3), a phosphorylcholine derivative[84] or a benzophenone group, to produce photopatternable aliphatic polyester.[79] Harth and coworkers[85] used **A20** and **A22** to form multifunctional polyester nanoparticles.

α-Methylidene-δ-valerolactone (**A23**) has usually been polymerized as "vinyl monomer". Ritter and coworkers[86] reported the first polymerization by ring-opening. Formylation of δ-valerolactone, subsequent formyl transfer and elimination of a carboxylate anion yielded **A23** (yield: 57%, Scheme 5). The monomer was copolymerized with δ-valerolactone, and networks obtained by free radical polymerization of the methylidene functionality with different methacrylates.

Diaconescu and coworkers reported a series of three different α-ferrocenyl-δ-valerolactones (**A24–A26**) and six ferrocenyl-substituted trimethylene carbonate (TMC) monomers (**C5–C10**), all obtained by click chemistry of azide-functionalized ferrocene to **A22**, 5-(propynyl)-1,3-dioxane-2-one and propargyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (**C11**) (see also below).[87] While all TMC monomers were polymerizable with DBU/TU as the catalyst (1,8-diazabicycloundec-7-ene and 1-(3,5-bis(trifluoromethyl)-phenyl)-3-cyclohexyl thiourea), **A24–A26** were not able to be polymerized neither as homo- nor copolymers.

3.1.3 γ-Butyrolactones. γ-Butyrolactone is often considered to be the "non-polymerizable" lactone, due to its low ring strain.[88] It can oligomerize using a lipase catalyst[89] or under high pressure (20 000 atm) and can be copolymerized with other lactone monomers.[90] Chen and coworkers[91] recently successfully obtained poly(γ-butyrolactone) *via* ROP with a La[$N(SiMe_3)_2$]$_3$/R–OH catalyst system at −40 °C in THF with a number molecular weight of 30 kg mol^{-1}, 90% monomer conversion and control over linear or cyclic topology.

Since polymerization of γ-butyrolactone remains difficult, only a few functional monomers have been reported so far. α-Methylidene-γ-butyrolactone (**A27**) is widely used as vinyl-comonomer; Ritter and coworkers[92] reported copolymerization with caprolactone in a ROP for the first time, Chen and coworkers[93] recently reported homopolymerization. They used the methylidene function for crosslinking of the polymers with a methacrylate to transparent polyester networks. The monomer was synthesized in two steps by the same strategy as **A23** (Scheme 6): formylation of γ-butyrolactone, subsequent formyl transfer and elimination of a carboxylate anion yielded **A27**.[94] Albertsson and coworkers[95] recently reported the copolymerization of α-bromo-γ-butyrolactone (**A28**), which is commercially available at Sigma Aldrich. Due to the high selectivity and reactivity of modern organocatalysts at ambient reaction temperatures, the authors were able to polymerize co- and terpolymers, with trimethylene carbonate (TMC), **C47** or ε-caprolactone with an alcohol as the initiator and diphenyl phosphate (DPP) as the catalyst at 30 °C for 48 h. Grafting of methyl acrylate *via* Cu(0)-mediated CRP (controlled radical polymerization) on the copolymers was demonstrated.

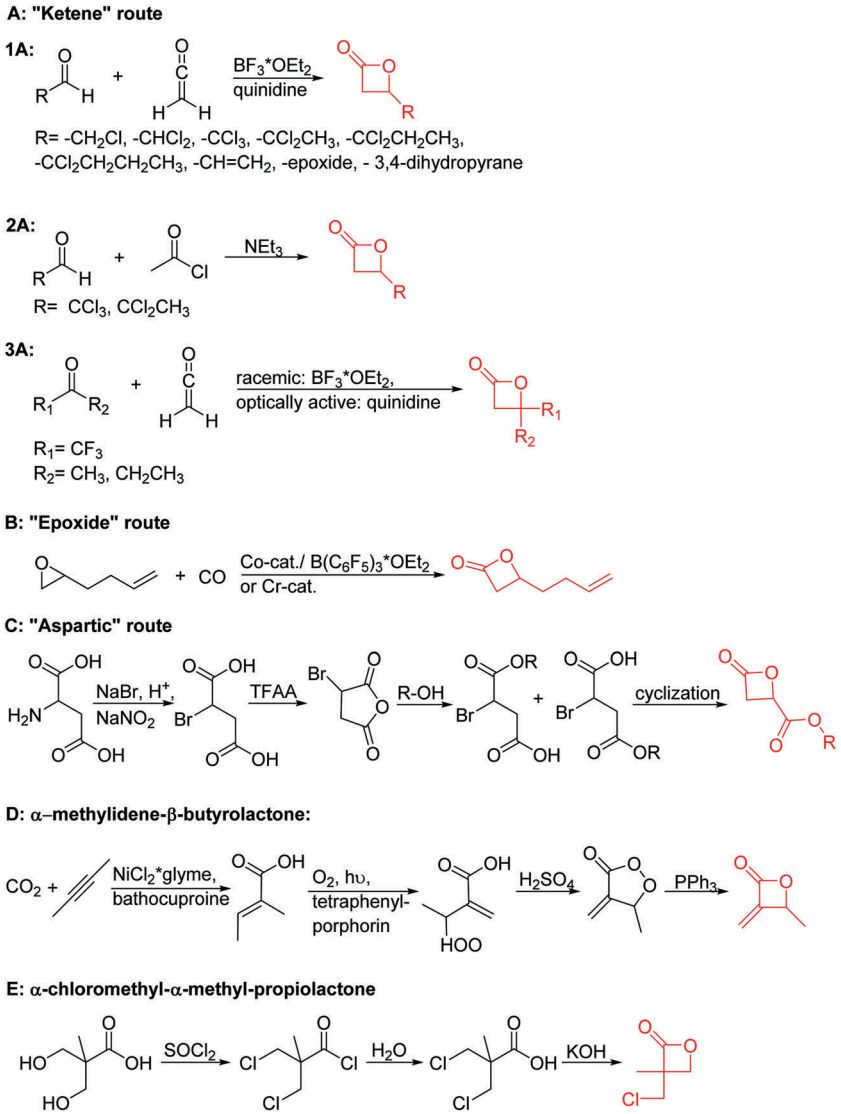


Scheme 6 Synthetic strategy for the synthesis of α-methylidene-γ-butyrolactone.

3.1.4 β-Propiolactones and β-butyrolactones. Substituted β-propiolactones and β-butyrolactones are synthesized by three general synthetic strategies, following a "ketene", "epoxide", or "aspartic" route (Scheme 7).

Mono-, di-, and tri-halogenated propiolactones and their polymerization are reported extensively in the literature. Modification after polymerization has not been reported so far. Tani and coworkers[96] synthesized β-chloromethyl- (**A29**), β-dichloromethyl- (**A30**) β-trichloromethyl-β-propiolactone (**A31**) by [2+2] cycloaddition from ketene and the corresponding mono-, di- or trichlorinated acetaldehyde and intensively investigated in their polymerization behavior and tacticity of obtained polymers (Schemes 7, 1A). Prud'Homme and coworkers further introduced several chlorinated and fluorinated propiolactones (**A32–A36**),[97–99] partially being β-disubstituted at the lactone ring (Scheme 7, 1A–3A). For racemic mixtures of the monomers, they used the corresponding halogenated aldehyde (or halogenated acetone or butanone for β-di substituted lactones), acetyl chloride and triethylamine, for optically active monomers they used the synthetic route using ketene and the chiral catalyst quinidine. Li and coworkers[100,101] copolymerized α-chloromethyl-α-methyl-propiolactone (**A37**) with caprolactone (Scheme 7, E). Quaternization with pyridine resulted in polymers with increased hydrophilicity. Chlorination of 2,2′-bis(hydroxymethyl)propionic acid with thionyl chloride, hydrolysis of the formed acyl chloride and cyclization under basic conditions yielded the monomer. A α,α-bis-chloromethyl-propiolactone monomer (**A38**) has been reported by Kuriyama and coworkers[102] and copolymerized with β-propiolactone. Post-modification has not been shown.

Cherdron and coworkers[103] presented several β-substituted lactones, carrying pendant groups suitable for other polymerization techniques (epoxide (**A39**), 3,4-dihydropyrane (**A40**), vinyl (**A41**)). They showed selective lactone polymerization, but also did not use the further functionality for post-modification reactions. They followed the general synthetic strategy using ketene and a corresponding aldehyde (Scheme 7, 1A).



Scheme 7 Synthetic strategies to substituted of β-propio- and β-butyrolactones: (A) ''ketene'' route, *e.g.* for halogenated lactones; (B) ''epoxide'' route yielding β-heptenolactone; (C) ''aspartic'' route; (D) synthesis of α-methylene-β-butyrolactone; (E) synthesis of an α-disubstituted propiolactone.

The polymerization of β-heptenolactone (**A42**) (or also called allyl-β-butyrolactone) is only rarely reported in the literature, which is probably due to an inconvenient synthetic route of the monomer or use of special zinc or yttrium catalysts for polymerization. But-3-en-1-yl-epoxide reacted with carbon monoxide in the presence of a Co-based catalyst at 6.2 MPa/80 °C[104] or an active Cr-catalyst at 1 atm/22 °C[105] to the monomer (Scheme 7, B). While Guillaume and coworkers[106] functionalized poly(β-heptenolactone) by hydroboration, Shaver and coworkers[107] recently post-modified the polymer by olefin cross-metathesis with 15 different alkene cross-partners producing a whole library of poly(ester)s with different functionalities.

Guérin and coworkers[108,109] developed three functional monomers for unsaturated poly(β-maleic acid) derivatives: allyl malolactonate (4-allyloxycarbonyl-2-oxetanone, **A43**), 3-methyl-3-butenyl malolactonate (4-[3-methyl-3-butenyloxycarbonyl]-2-oxetanone, **A44**) and 2-methylethenoyloxyethyl malolactonate (4-[2-methylethenoyloxyethyl-oxycarbonyl]-2-oxetanone, **A45**). While the ketene route gave only low yields, the ''aspartic route'' was applied (Scheme 7, C): aspartic acid was brominated and bromosuccinic acid anhydride formed. Esterification with an appropriate alcohol (allyl alcohol, 3-methyl-3-buten-1-ol or 2-hydroxyethyl methacrylate) opened the anhydride and formed a mixture of the corresponding mono-bromo succinic acid esters, and the major product was lactonizable. Epoxidation and subsequent sulfonation have been carried out. The copolymers were able to induce new bone formation and muscle regeneration in *in vivo* models.[110,111] Thiol–ene reactions with mercaptoethanol converted the copolymers into macroinitiators to ''graft from'' polycaprolactone.[112]

Lu and coworkers[113] recently reported a novel methylene functionalized monomer, α-methylidene-β-butyrolactone (**A46**), synthesized from carbon dioxide and 2-butyne in four steps (Scheme 7, D). After formation of tiglic acid, catalyzed by

$NiCl_2$*glyme and bathocuproine, an allylic peroxide was formed by photooxygenation. Dehydration formed a peroxylactone, which yielded **A46** after deoxygenation. The vinylidene functional group was used for radical cross-linking or thiol–ene reaction.[114]

3.1.5 Macrolactones. Mainly two macrolactones, globalide (**A47**) and ambrettolide (Am, **A48**) are used to prepare long-chain aliphatic polyesters by ROP. **A47** is a natural unsaturated 16-membered lactone, **A48** a 17-membered lactone used in the fragrance industry. 14–19-membered lactones can be extracted from natural sources including angelica plant root. The ring-strain is the driving-force for ROP of smaller cycles and increases from 5- to 7-membered lactones, exhibiting the maximum for ε-caprolactone.[115,116] Macrolactones have a low ring-strain and their ROP is entropy-driven instead of enthalpy-driven, as for the strained lactones.[116] Macrolactones can be polymerized enzymatically by lipases, *e.g.* Novozyme 435 (Candida Antarctica lipase B (CALB) immobilized on acrylic resins).[117] For further details we refer to excellent reviews of Kobayashi[117,118] and the work of the Heise group.[119–124]

Heise and coworkers functionalized the olefins in polyglobalide *via* thiol–ene reaction with different thiols.[120,122] In another study, dithiol-cross-linked polyglobalide films were further reacted with mercaptohexanol to attach ATRP initiators.[119] Such films were further grafted with *tert*-butyl acrylate and proteins were conjugated to the deprotected grafts. Möller and coworkers[125] polymerized **A48** and oxidized the internal double bonds by Baeyer–Villiger oxidation using *m*CPBA to the epoxides. They showed, that a strategy *vice versa* is also possible: after epoxidation of **A48**, the monomer **A49** (AmE) was polymerized with Novozyme 435, while the epoxides remained intact. Kobayashi and coworkers[126] reported already in 2001 the enzymatic ROP of 2-methylene-4-oxa-12-dodecanolide (**A50**) by lipase and subsequent radical crosslinking of the polymers.

3.2 Cyclic diester monomers

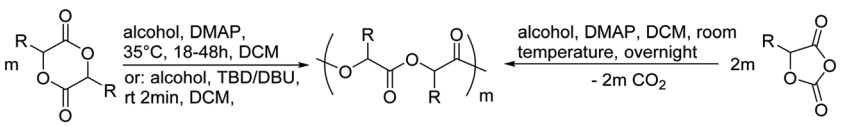
Poly(α-hydroxy acid)s (PAHAs) are obtained from cyclic diester monomers (Scheme 8). Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers (PLGA) are accessible from renewable resources. They are typically prepared by ROP of the cyclic dimers of lactic and glycolic acid (lactides and glycolides). However, the lack of structural diversity of lactides and glycolides limits the preparation of functional poly(α-hydroxy acid)s. Synthesis of substituted 1,4- dioxane-2,5-diones can be complicated and reactivity in ROP is often poor. They are usually polymerized with $Sn(Oct)_2$ at 110–130 °C for 2–24 h in bulk[127] or toluene,[123] with 4-dimethylamino pyridine (DMAP) at 35 °C for 18–48 h in DCM,[128,129] or with TBD or DBU at room temperature for 2 min to 24 h in DCM,[122,130,131] using primary alcohols as initiator.

O-Carboxy anhydrides (OCAs) are suitable alternatives for the preparation of functionalized PAHAs under mild conditions and were recently summarized in an excellent article.[132]

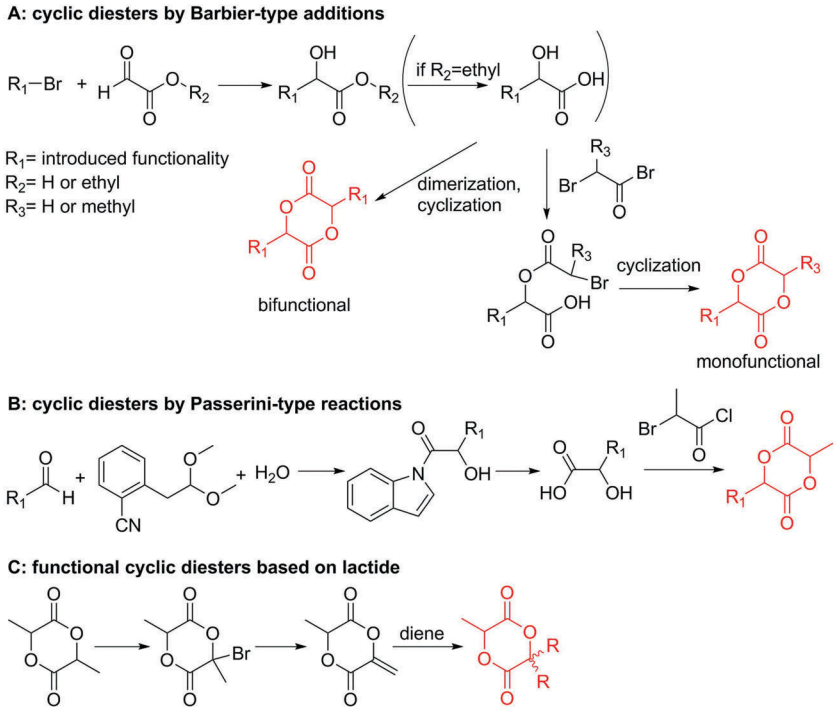
3.2.1 Lactide and glycolide monomers. A general synthetic procedure to mono- or difunctional orthogonally reactive glycolide or lactide monomers was reported by Hennink and coworkers[127] in three steps (Scheme 9A). Starting from an appropriate alkyl bromide (*e.g.* propargyl bromide), a Barbier-type addition to glyoxylic acid/ester (and cleavage of the ester, if used) resulted in a glycolic acid derivative which further reacted with 2-bromoacetyl bromide (or 2-bromopropanoyl bromide in case of a lactide monomer[129,133–135]). Intramolecular cyclization in diluted solution yielded the monomer (yields typically 15–45%). Difunctional monomers can be formed by dimerization and cyclization of the glycolic acid derivative.[136]

Hennink and coworkers[127] polymerized an allyl functional glycolide (**A51**) and showed epoxidation with NMO/OsO_4 and subsequent hydrolysis to diols. The allyl lactide analog **A52** has been reported by Cheng and coworkers.[133] They photochemically crosslinked PEG–PLA block copolymers *via* thiol–ene reaction with a dithiol-crosslinker to obtain nanoparticles. Pfeifer and coworkers[135] used cationic modified PEG–PLA-block copolymers for gene delivery. The monomer was also further functionalized by olefin cross-metathesis with an epoxy alkene and further hydrogenated to the saturated epoxy lactide (**A53**).[134] An orthogonal reactive iron-based catalyst was applied for the polymerization of **A53**, which selectively polymerizes the diester cycle if the catalyst is in the iron(II) form. The oxidized catalyst (iron(III)-species) instead selectively polymerizes the epoxide. The bifunctional epoxy diester was selectively polymerized to an epoxy-functional polyester (Fig. 3). After oxidation of the catalyst and removal of solvent, the epoxy-functions were polymerized to cross-link the polymers.

Coudane and coworkers[128] reported an alkyne functional glycolide (3-(2-propynyl)-1,4-dioxane-2,5-dione, **A54**), and modified PLGA-copolymers with PEG–azides. Cheng and coworkers[129] reported the analogous alkyne lactide **A55**. They grafted PEG–paclitaxel–azide conjugates onto PLA-copolymers. A disubstituted alkynated glycolide (**A56**) has been used by Baker and coworkers[136] for the polymerization of homopolymers and random or block copolymers, which were functionalized by click chemistry with PEG550–azide and azidododecane, to obtain thermoresponsive materials exhibiting lower critical solution temperatures (LCST) from room temperature to >60 °C. A facilitated synthesis of difunctional halogenide monomers was reported by Collard and



Scheme 8 General scheme for the polymerization of lactides/glycolides and *O*-carboxy anhydrides (OCAs) to poly(α-hydroxy acid)s (PAHAs) (for definition of R-group, please see the main manuscript).



Scheme 9 Synthetic strategies to functional lactides and glycolides: (A) by a Barbier-type addition; (B) by a Passerini-type reaction, (C) by functionalization of lactide.

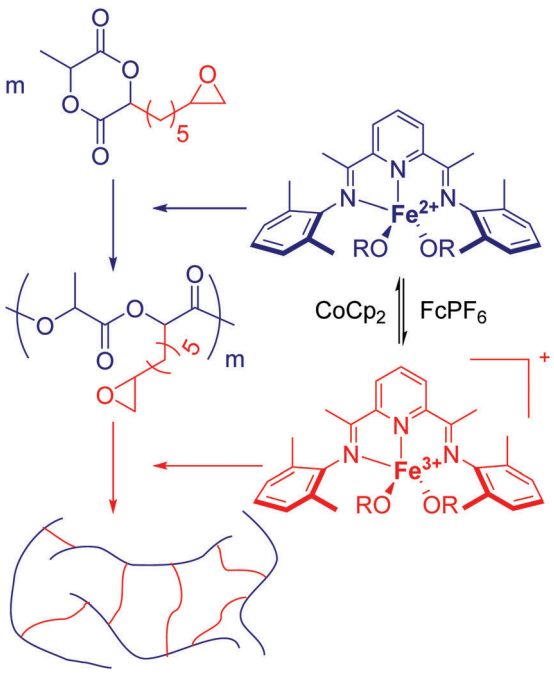
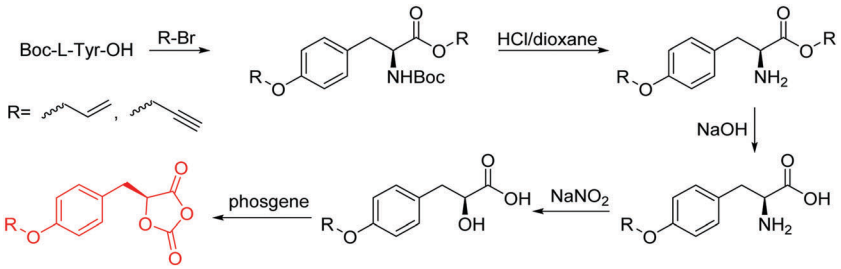


Fig. 3 Selective polymerization of a bifunctional monomer by the redox-controlled iron catalyst. Reproduced from ref. 134 with permission from The Royal Society of Chemistry, Copyright 2016.

coworkers to yielding 3,6-bis(chloromethyl)-1,4-dioxane-2,5-dione (**A57**):[137] 3-chloropropane-1,2-diol was oxidized to the glycolic acid derivative and subsequently dimerized and cyclized. Polymers were modified by dehydrochlorination to methylidene functions and further reacted with thiol derivatives by radical or nucleophilic thiol addition.

Yang and coworkers[138] reported a further alkyne-functionalized lactide **A58**, synthesized by an alternative route: several commercially available aldehydes were reacted in a Passerini-type condensation to obtain the glycolic acid derivative (Scheme 9B). PLA-copolymers of **A58** were modified with dansyl-azide as prove of concept. They additionally reported two azide-functionalized monomers (**A59** and **A60**), synthesized by the same route. Copolymers were modified with dansyl alkyne. Overall yields for the synthetic strategy of **A58–A60** were 6–16%. Weck and coworkers[139] introduced an azido-tri(ethylene glycol) functional lactide (**A61**). Polymers were modified with a fluorescent dye (7-nitrobenzoxadiazole, NBD) and a cell internalization peptide gH625 by click chemistry, and proved cellular uptake. The group as well showed modification by Staudinger condensation with Tap-GRGDS.[140]

Modification of lactides without ring-opening is rare. Hillmyer and coworkers[131] realized a bifunctional norbornene/lactide monomer (**A62**) suitable for ROP as well as ROMP by bromination and elimination of a lactide with an overall yield of 35% (Scheme 9C). The formed alkene reacted in a Diels–Alder reaction with cyclopentadiene and formed the bifunctional monomer. Dove and coworkers[130] showed that the norbornenes in such copolymers were able to react with tetrazine derivatives. The norbornene-tetrazine reaction allowed post-modification under mild conditions at room temperature and without the addition of a catalyst or additives. The monomer was further functionalized with azide derivatives (**A63**), *e.g.* PEG-N_3[141] and polymerized. Two more lactides were realized by the same strategy using



Scheme 10 Synthetic route to *O*-carboxy anhydrides (OCAs) from amino acids.

cyclohexa-1,3-diene (**A64**) and isoprene (**A65**) as diene for the Diels–Alder reaction, but the corresponding polymers were not further post-modified.[142]

3.2.2 *O*-Carboxyanhydrides (OCAs). In 1976, the first *O*-carboxy anhydride (OCA), 5-methyl-5-phenyl-1,3-dioxolan-2,4-dione, has been thermally polymerized.[143] OCAs are readily available monomers from α-hydroxy acids (with yields up to 28–75%, depending on the number of synthesis steps) and are a suitable alternative to lactides and glycolides, yielding PAHAs. Preparation of OCA monomers follows a general synthetic strategy: α-hydroxy acids are carbonylated using phosgene, di- or triphosgene as a carbonylating agent. In case of the latter two agents, activated charcoal is often used to promote the decomposition to phosgene and a tertiary amine is added as an acid scavenger (Scheme 10). Thermodynamically the ROP of OCAs is favored compared to lactide, both enthalpically and entropically. During the ROP, CO_2 is released by decarboxylation from every monomer unit and thus polymerization is more entropically driven than by release of ring strain.[144] Bases and nucleophiles like pyridine, DMAP, NHCs or zinc complexes (with an external protic initiator) are able to promote the polymerization of OCAs in organic solvents as dichloromethane at room temperature in a few minutes to several hours, acid catalysts fail. Enzymatic polymerization showed higher polymerizability for OCAs than for lactides (polymer molar masses up to 10^4 g mol^{-1} within 24 h at 80 °C for OCAs, and 5–7 days at 80–130 °C for lactide).[132]

The class of monomer has mainly been explored in the last decade and two orthogonally reactive OCAs have been reported so far: L-Tyr-alkynyl- (**A66**)[145] and L-Tyr-allyl-OCA (**A67**).[146] Cheng and coworkers used boc-protected L-Tyr-OH and reacted it with propargyl bromide to introduce the alkyne (or allyl bromide for the analogs alkene, Scheme 10).[145] After the release of the amine group and formation of the α-hydroxy acid by diazotation with sodium nitrite, carbonylation, and cyclization yielded the final monomer. PEG-block copoly(ester) of **A66** were core-crosslinked with a di-azide-cross-linker to redox-[147] or light-responsive[148] poly(ester) micelles; homopolymers were post-modified by thiol–yne reaction with cysteamine to polyelectrolytes for gene delivery and cell-penetration.[149] L-Tyr-allyl-OCA (**A67**) has not been used for post-modification so far.

3.2.3 Morpholinones. Waymouth and coworkers prepared *N*-substituted morpholin-2-ones by the oxidative lactonization of *N*-substituted diethanolamines with the Pd catalyst $[LPd(OAc)]_2^{2+}[OTf^-]_2$.[150] The organocatalytic ring-opening polymerization of *N*-acyl morpholin-2-ones occurs readily to generate functionalized poly(amino esters) with *N*-acylated amines in the polyester backbone. The thermodynamics of the ring-opening polymerization depends sensitively on the hybridization of the nitrogen of the heterocyclic lactone. *N*-Acyl morpholin-2-ones polymerize readily to generate polymorpholinones, but the *N*-aryl or *N*-alkyl substituted morpholin-2-ones do not polymerize. Experimental and theoretical studies reveal that the thermodynamics of ring opening correlates to the degree of pyramidalization of the endocyclic *N*-atom. However, so far orthogonal monomers have not been prepared to the best of our knowledge. The deprotection of the poly(*N*-Boc-morpholin-2-one) (**A68**) produced a water-soluble, cationic polymorpholinone. We believe this area will continue to grow for future functional polymers.

4. Polyamides

Polyamides from cyclic monomers can be obtained from cyclic lactams (polyamide-3 to polyamide-6), from α-*N*-carboxy anhydrides (NCAs) (polypeptides or polyamide-2) and *N*-substituted glycine *N*-carboxy anhydrides (NNCAs) (polypeptoids), or from cyclic diamides and ester amides (Table 4). Besides synthetic polypeptides, most of them exhibit only poor biodegradability, but under harsh alkaline conditions or in the presence of special microorganisms can be degraded.

4.1 Lactams

β-Lactam (2-azetidinone), γ-butyrolactam (2-pyrrolidone), δ-valerolactam (2-piperidone) and ε-caprolactam (2-azepanone) are the main unsubstituted lactams used in the ROP. The number of orthogonally reactive lactam monomers is very limited so far. This might be attributed to the low solubility of the products in most common organic solvents, due to H-bonding or crystallization. ε-Caprolactam is typically polymerized in anionic ROP in bulk at temperatures of 140 °C above the melting point of the monomer (70 °C) within 15 min, with the polymer precipitating from the melt (Scheme 11).[153] *N*-Acyl or *N*-carbamoyl lactams as activators like hexamethylene-1,6-dicarbamoyl-caprolactam are commonly added to promote the polymerization. For more details, we refer to an excellent book chapter.[154]

Vinyl lactam monomers are reported for all lactams, however, were only used for polymerization of the vinyl functionality.

Table 4 Orthogonally functional cyclic monomers for the synthesis of polyamides and poly(ester amide)s

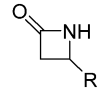
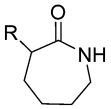
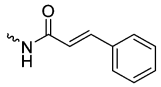
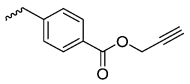
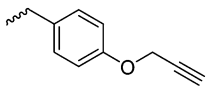
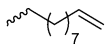
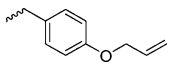
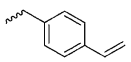
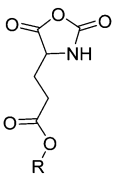
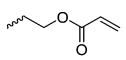
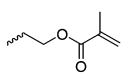
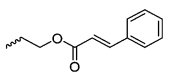
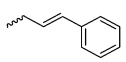
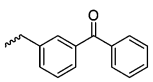
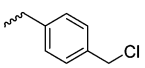
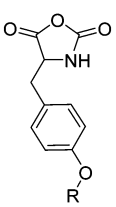
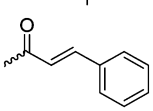
Monomer	R =	No.	Post-modification	Ref.
Lactams				
		**B1**	– No modification	155 and 156
		**B2**	– Thermal or photochemical cross-linking	153
Glutamic acid-based NCAs				
		**B3**	– Click chemistry with PEG-, carbohydrate-, amine- or cyclodextrin-azides; photochemical thiol–yne reaction to introduce carboxy groups	165–169
		**B4**	– Click chemistry to introduce alkyl chains of different lengths	170
		**B5**	– Click reaction with amine/guanidines for gene delivery	171
		**B6**	– Epoxidation and cross-linking; oxidation to carboxy functionalities; photochemical thiol–ene reaction to introduce carboxy groups	172 and 173
		**B7**	– Epoxidation and cross-linking – Oxidation to carboxy functionalities	172
		**B8**	– Thiol–ene reaction with cysteamine to elongate the distance between charged groups and backbone	174
		**B9**	– Radical cross-linking – Ozonolysis to alcohols and aldehydes and hydroamination – Oxidation to diols and carboxy groups – Olefin metathesis – Suzuki coupling	175–178
		**B10**	– Formation of films by photo-cross-linking	179
		**B11**	– Formation of films by photo-cross-linking	179
		**B12**	– Formation of films by photo-cross-linking	179
		**B19**	– Photo-cross-linking to stable micelles for drug delivery	180 and 181
		**B20**	– No modification	182
		**B21**	–ATRP macroinitiator – Quaternization with diamines to form nanogels for drug delivery	183 and 184
		**B22**	– Derivatization with NaN_3 and click chemistry with carbohydrates, arginine or imidazolium – Quaternization of phosphine and pyridinium salts	185–189
		**B23**	– Derivatization with NaN_3 and click chemistry with arginine – Quaternization of phosphine and pyridinium salts	186, 188 and 190
		**B24**	– Derivatization with NaN_3 and click chemistry with arginine	186
		**B25**	– Nucleophilic substitution with 1-alkylimidazolium salts to LCST- and UCST-type polypeptides	191
		**B26**	– Amidation with amines for gene delivery	192 and 193
Tyrosine-based NCAs				
		**B13**	– Formation of films by photo-cross-linking	179
		**B14**	– Formation of films by photo-cross-linking	179
		**B15**	– Formation of films by photo-cross-linking	179

Table 4 (*continued*)

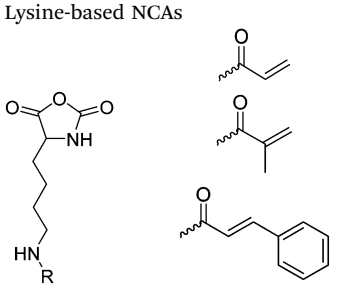
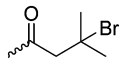
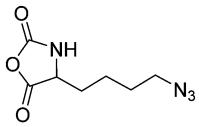
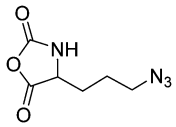
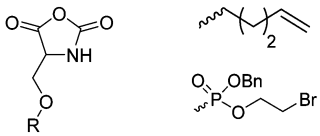
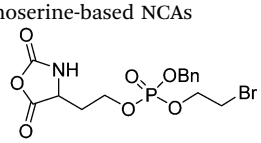
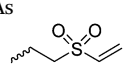
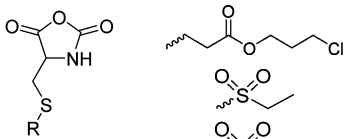
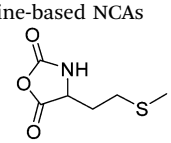
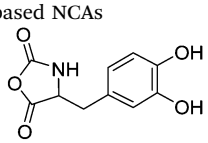
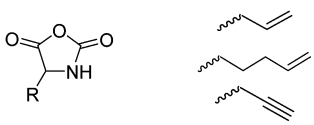
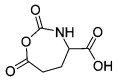
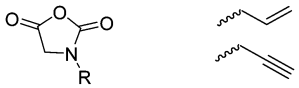
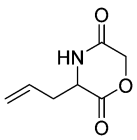
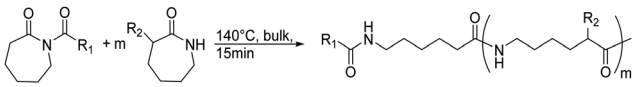
Monomer R =	No.	Post-modification	Ref.
Lysine-based NCAs			
	**B16**	– Formation of films by photo-cross-linking – Thiol–ene reaction for cross-linking	179 and 194
	B17	– Formation of films by photo-cross-linking – Thiol–ene reaction	179 and 195
	B18	– Formation of films by photo-cross-linking	179
	**B28**	–ATRP macroinitiator	196
	**B29**	– Click chemistry	197
Ornithine-based NCAs			
	**B30**	– Click chemistry	197
Serine-based NCAs			
	**B31**	– Thiol–ene reaction with cysteamine to cell-penetrating peptides	198
	B32	– Modification degrades the polymer	199
Homoserine-based NCAs			
	**B33**	– Amination to form poly(L-phosphorylchloline homoserine)	199
Cysteine-based NCAs			
	**B34**	– Michael-type addition of polar-, charged- or carbohydrate-thiols forming glycopeptides, coatings, and hydrogels	200
	**B35**	– Nucleophilic substitution with imidazolium salts	201
	B36	– Reaction with thiols to form asymmetric disulfides	202 and 203
	B37	– Reaction with thiols to form asymmetric disulfides	202
Methionine-based NCAs			
	**B38**	– Alkylation with bromide, iodide and triflate derivatives and triggered dealkylation with sulfur nucleophiles – Oxidation to sulfoxides causing a change of copolymer conformation – Reaction with epoxides to β-alkyl-β-hydroxyethyl sulfonium products	204–207
DOPA-based NCAs			
	**B39**	– Oxidative cross-linking and tissue adhesion	194, 210 and 211
Unnatural amino acid-based NCAs			
	**B40**	– Reduction or bromination – Glycosylation by thiol–ene reaction	212–214
	B41	– No modification	215
	B42	– Glycosylation by click chemistry – Photochemical thiol–yne reaction	214 and 216–219

Table 4 (*continued*)

Monomer	R =	No.	Post-modification	Ref.
γ-NCAs		**B27**	– No modification	160
NNCAs		**B43**	– Thiol–ene reaction with thioglycerol and –glucose	224 and 225
		B44	– Click chemistry with PEG–azide – Thermal cross-linking	226 and 227
Cyclic esteramides		**B45**	– Thiol–ene reaction with charged or polar thiols	223

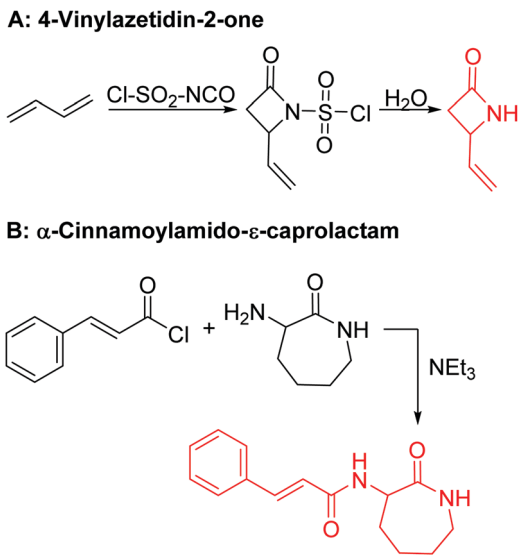


Scheme 11 General polymerization protocol for caprolactams to poly(amides)s with an *N*-acyl lactam as an activator (R_1 and R_2 represent non-specified alkyl substituents).

4-Vinylazetidin-2-one (**B1**) is the only bifunctional monomer, whose anionic ROP was reported (in DMSO with potassium 2-pyrrolidone, at 25–30 °C, 2 h).[155] **B1** was synthesized by reaction of 1,3-butadiene with chlorosulfonyl isocyanate and subsequent saponification (Scheme 12A).[156] However, no post-modification has been reported so far.

While a few protected functional ε-caprolactam monomers (with an amine, carboxy, and carbonyl groups) are reported, Carlotti and coworkers[153] synthesized a reactive monomer, bearing a cinnamoyl functionality. α-Cinnamoylamido-ε-caprolactam (**B2**) was synthesized in one step from cinnamoyl chloride and α-amino-ε-caprolactam (yield: 80%) (Scheme 12B). Copolymers with ε-caprolactam were cross-linked thermally (at 140 °C) or photochemically (at 364 nm) and again de-cross-linked photochemically (at 254 nm). α-Amino-ε-caprolactam might be an interesting precursor for future ε-caprolactams with other functional groups, *e.g.* to tailor the degradation rates. Polyamides can also be post-modified at the amide group by *N*-alkylation with formaldehyde,[157] by epoxides or 2-bromoethylamine,[158] isocyanates or acid chlorides.[159]

An interesting approach might be the synthesis of monomers from natural and renewable sources, *e.g.* macrolactones or carbohydrates. However, only a limited number of such examples is available up to date. Only a few functional OCA monomers for the synthesis of polyesters are reported, and expansion the monomer class is promising.

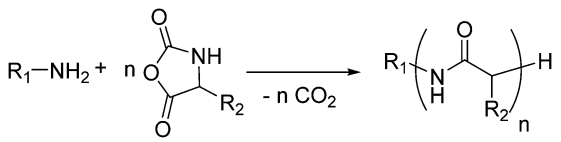


Scheme 12 Synthetic route to functional lactams: (A) 4-vinylazetidin-2-one **B1** and (B) α-cinnamoylamido-ε-caprolactam **B2**.

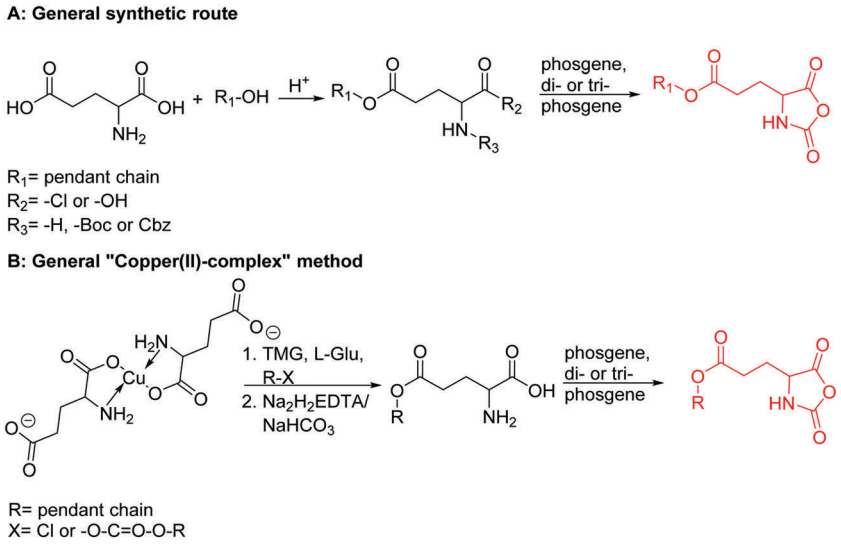
4.2 *N*-Carboxyanhydrides

Synthetic polypeptides are accessible by ROP of *N*-carboxy anhydrides (Leuchs' anhydrides, NCAs), which are *N*-analogs to poly(α-hydroxy acid)s from *O*-carboxy anhydrides (OCAs). α-NCAs (5-membered rings) dominate the literature, while β-NCAs (6-membered rings) are only reported without additional functional groups to date. A single functional γ-NCA monomer (7-membered ring) has been reported in 1978,[160] bearing a pendant carboxyl moiety (see below and Scheme 15).

A variety of protected, functionalized, and orthogonally reactive α-NCA monomers are reported. They are excellently summarized in two recent reviews.[161,162] Primary amines are the common initiators[163] for the ROP of NCAs, but also



Scheme 13 General protocol for the polymerization of NCAs to polypeptides with amines as the initiator (R_1 and R_2 represent non-specified substituents).



Scheme 14 General synthetic routes to functional NCAs, depicted with glutamic acid.

alcohols can be applied (as the initiation of the OH-group is slower than that of an amino-group, either the alcohol needs to be activated or broad molecular weight distributions will be obtained)[164] (Schemes 13 and 14).

4.2.1 Glutamic acid- and tyrosine-based NCAs. The majority of orthogonally functional NCA monomers are based on glutamic acid. Hammond and coworkers[165] reported γ-propargyl-L-glutamate NCA (**B3**), with homopolymers being functionalized by click chemistry with PEG–azides of different chain lengths to form grafted brushes,[165] different azide-functionalized carbohydrates,[166] primary to quaternary amines to form antimicrobial polypeptides,[167] or with cyclodextrin.[168] Chen and coworkers[169] introduced carboxy groups by the photochemical thiol–yne reaction. The polymers were used to control biomineralization of calcium carbonate.[169] Tang and coworkers[170] reported a second alkyne functionalized monomer, γ-(4-(propargoxycarbonyl)-benzyl)-L-glutamate NCA (**B4**), synthesized by the Cu(II)-complex method, using 4-(chloromethyl)benzoyl chloride (Scheme 14B). Obtained polypeptides were functionalized by click chemistry with alkyl chains of different lengths and the UCST-behaviour extensively analyzed in aqueous mixtures. Cheng and coworkers[171] reported a similar monomer, γ-(4-propargyloxybenzyl)-L-glutamate NCA (**B5**), also obtained by the Cu(II)-complex method, using 4-propargyloxybenzyl chloride. The polypeptides were amine/guanidine functionalized by click chemistry and their transfection efficiency for gene delivery examined.

Several alkene-functionalized NCAs have been reported to date. Daly and coworkers[172] prepared γ-allyl-L-glutamate (**B6**) and γ-(9-decenyl)-L-glutamate NCA (**B7**) and studied their homo- and copolymerization and epoxidation of the double bonds with *m*CPBA. Gelation was obtained by cross-linking of the epoxides with TFA, oxidation to carboxylic acids was shown with $KMnO_4/NaHCO_3$. Zhang and coworkers[173] used **B6** in copolymers for photochemical thiol–ene reaction and introduction of carboxy groups. γ-(4-Allyloxylbenzyl)-L-glutamate NCA (**B8**) has been reported by Cheng and coworkers,[174] using the copper(II)-complex method and 4-allyloxylbenzyl chloride. Thiol–ene reaction in homopolymers of **B8** with cysteamine to poly(γ-(4-aminoethylthiopropoxyl)benzyl-L-glutamate) exhibited a charge-backbone distance of 17 σ-bonds. Remarkably high helicity of 81% was observed for polypeptides with a DP of 10 at pH 2. Compared to the polymer with an elongated charge-backbone distance of 17 σ-bonds, poly(γ-(4-(1-hexanol-6-aminomethyl))benzyl-L-glutamate) with a DP of 10 and a charge-backbone distance of 11 σ-bonds showed mixed conformation of β-sheets and only 26% α-helices. γ-(4-Vinyl benzyl)-L-glutamate NCA was introduced by the group of Schouten.[175] The olefins were used for radical cross-linking of terpolymer surface-grafted films,[175] or transformation by ozonolysis into alcohols[176] or aldehydes[177] and subsequent hydroamination with primary amines, to yield polypeptides suitable for gene transfection.[178] Oxidation to diols or carboxy functionalities by osmium tetroxide, olefin metathesis reaction with *cis*-1,4-dichlorobutene and Suzuki coupling were shown by Cheng and coworkers.[176]

Kamogawa and coworkers[179] reported already in 1975 a whole library of photoreactive glutamic acid, tyrosine and lysine based NCAs with pendant acryloyl, methacryloyl and cinnamoyl groups (**B10–B18**). They showed polymerization of all NCAs and photochemical cross-linking of films, whereas the photosensitivity decreased for acryloyl ≈ methacryloyl > cinnamoyl, and polyglutamate > polylysine > polytyrosine. A further photo-cross-linkable monomer, also containing a cinnamoyl function, γ-cinnamoyl-L-glutamate NCA (**B19**), was already reported before by Iwakura and coworkers in 1974.[180] Jing and coworkers[181] photochemically crosslinked self-assembled polypeptide-*block*-PEG micelles of **B19**, loaded with paclitaxel as stable drug carriers. Iwakura and coworkers reported a further potentially photoactive benzophenone-containing NCA, γ-*p*-benzoyl benzyl-L-glutamate NCA and its homo- and copolymerization with γ-*p*-benzyl-L-glutamate NCA (**B20**).[182] They studied the orientation of benzophenone groups in the side chains and conformation

of polymers. The further photochemical reaction of the pendant groups has not been shown so far.

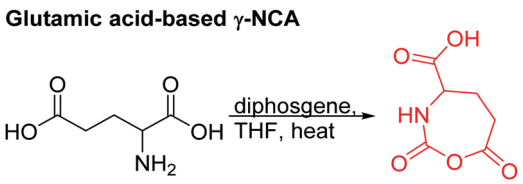
Several chlorinated monomers with varying length of alkyl spacers and suitable for nucleophilic substitution were reported: homo- and copolymers of a γ-(2-chloroethyl)-L-glutamate NCA (**B21**) were used as ATRP macroinitiator to graft oligoethylene methacrylate or to form nanogels for drug delivery.[183] Cross-linking of the gels was achieved through quaternization reaction of 2,2′-dithiobis(*N,N*-dimethyl ethylamine) (dTbDEA) with the chloride functionalities.[184] Polymers with the analogous γ-(3-chloropropyl)-L-glutamate (**B22**), γ-(6-chlorohexyl)-L-glutamate (**B23**), and γ-(8-chlorooctyl)-L-glutamate NCA (**B24**) were further derivatized to the respective azides and modified with carbohydrates,[185] arginine,[186] or imidazolium[187] derivatives by click chemistry. These poly(arginine) mimics with hydrophobic side chains of different lengths exhibited helix-related cell-penetrating properties and high DNA and siRNA delivery efficiencies in various mammalian cells. Quaternization of the chloride substituted polypeptides with triethylphosphine yielded cell-penetrating peptides,[188] quaternization with pyridinium salts UCST-type polypeptides,[189] and with 1-methyl benzimidazole helical antimicrobial polypeptides.[190] Tang and coworkers[191] reported γ-(4-chloromethyl benzyl)-L-glutamate NCA (**B25**), synthesized by the copper(II) complex strategy. These chloride-substituted polypeptides were modified with 1-alkyl imidazolium (methyl or *n*-butyl) and various counter-anions (*i.e.* Cl^-, F^-, BF_4^-). The polypeptides exhibited LCST- or UCST-type behavior in organic solvents or in water. Poly(peptide)s of an active ester functionalized monomer, γ-trichloroethyl-L-glutamate NCA (**B26**)[192] were post-modified by amidation with different amine derivatives and their properties examined as gene delivery vectors.[193] Higashi and coworkers reported already in 1978 a carboxylated γ-NCA (**B27**),[160] after the reaction of the glutamic acid with diphosgene (Scheme 15). They proved successful polymerization by viscosity measurements and characteristic amide signals in IR spectra, which are also observed for Nylon-4. Modification of the carboxyl function has not been reported.

4.2.2 Lysine- and ornithine-based NCAs. Besides the photoreactive investigations of **B16–B18** from Kamogawa[179] (see above), Lei and coworkers[194] recently used **B16** for complex mussel-inspired thermoresponsive polypeptide-Pluronic copolymers as surgical adhesives and for hemostasis. Chen and coworkers[195] prepared copolymers of **B17** (Scheme 16A) and **B3**. Both groups applied thiol–ene reaction with high efficiency for post-modification.

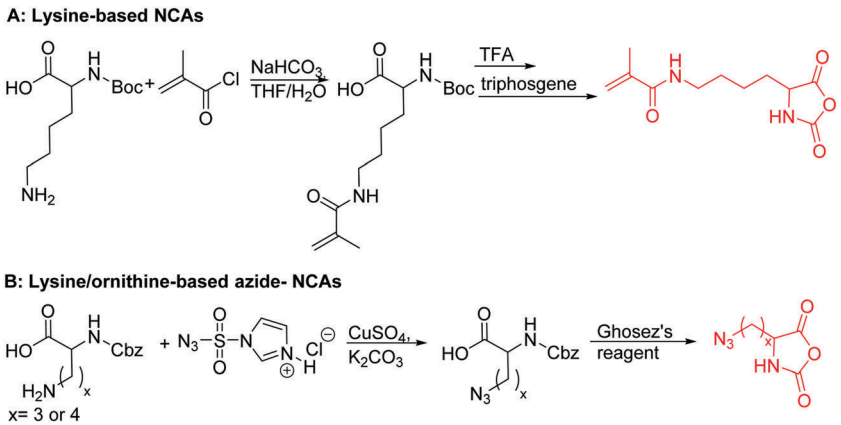
Polymers of ε-*N*-bromoisobutyryl-L-lysine NCA (**B28**) were used as ATRP macroinitiators by Li and coworkers,[196] and two polypeptide bottlebrushes with polystyrene or poly(oligoethylene glycol methacrylate) prepared, exhibiting an α-helical conformation in appropriate solvents.

Deming and coworkers[197] reported azide-containing monomers: azido-norleucine (**B29**) and azido-norvaline NCAs (**B30**). α-*N*-Carboxybenzyl lysine or ornithine was reacted with imidazole-1-sulfonyl-azide·HCl, $CuSO_4$, and K_2CO_3 to form the azide derivative (Scheme 16B). The derivatives were converted to NCAs, using the Ghosez's reagent (1-chloro-*N,N′*-2-trimethyl-1-propenylamine). Various alkyne derivatives were attached to azide-substituted pol(peptide)s through click chemistry with >95% conversion.

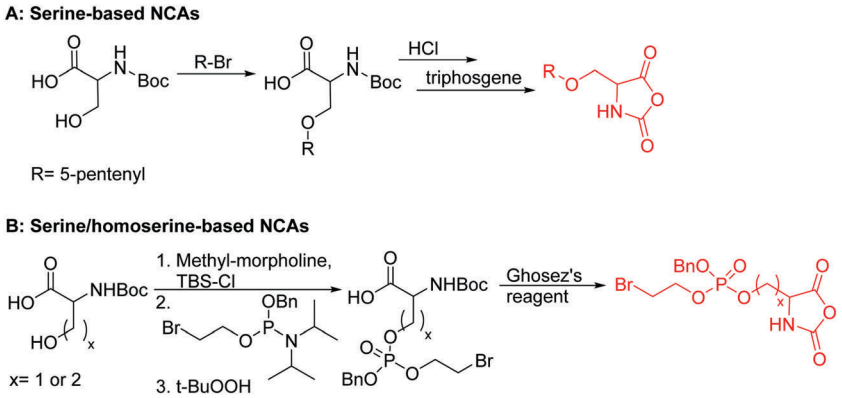
4.2.3 Serine- and homoserine-based NCAs. Cheng and coworkers[198] synthesized *O*-pentenyl-L-serine NCA (**B31**) (Scheme 17A) and prepared block copolymers with PEG. Modification by thiol–ene reaction with cysteamine gave water-soluble copolymers with elongated and charged side chains exhibiting cell-penetrating properties. Deming and coworkers[199] reported two phosphate containing monomers, *O*-2-bromo ethyl-benzylphospho-L-serine NCA (**B32**) and *O*-2-bromo ethyl-benzylphospho-L-homoserine NCA (**B33**) (Scheme 17B). While poly(L-phosphorylcholine serine) was not obtained after amination of the bromides in polymer P(**B32**) due to β-elimination



Scheme 15 Synthetic strategy to a glutamic acid-based γ-NCA **B27**.



Scheme 16 Synthetic routes to lysine/ornithine-based NCAs.



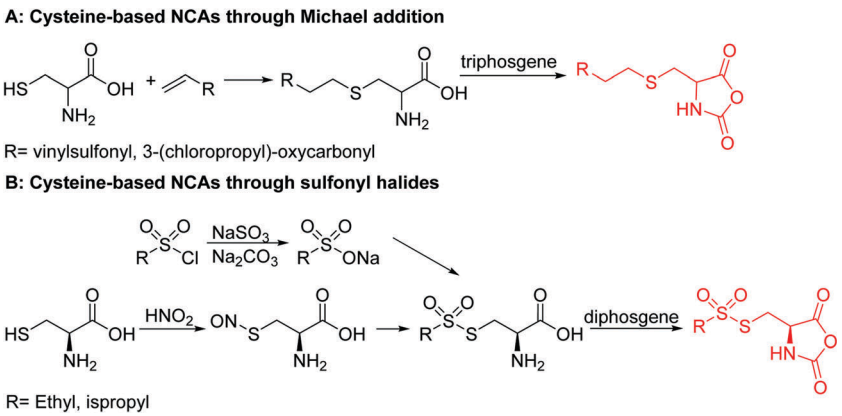
Scheme 17 Synthetic routes to serine/homoserine-based NCAs.

and chain degradation, the use of poly(L-phosphorylcholine homoserine) overcame the side reaction. Both deprotection and amination were achieved in one step. **B32** and **B33** were synthesized from homoserine or serine and benzyl (2-bromo ethyl)diisopropylphosphoramidite. Cyclization was achieved by Ghosez's reagent.

4.2.4 Cysteine-based NCAs. A vinyl sulfone-substituted L-cysteine NCA (**B34**) was reported by Zhong and coworkers,[200] synthesized from divinyl sulfone and L-cysteine hydrochloride (Scheme 18A). Post-modification of vinyl sulfone-functionalized polypeptides with different thiols (polar, charged, carbohydrates) through nucleophilic addition produced glycopolypeptides, functional polypeptide coatings, or hydrogels. Tang and coworkers[201] reported an *S*-(2-(3-chloropropoxycarbonyl)ethyl)-L-cysteine NCA (**B35**) from 3-chloropropyl acrylate. The polypeptides were substituted with imidazolium salts and their UCST-behavior was investigated.

Barz and coworkers[202] recently reported two interesting *S*-sulfonyl based NCA monomers: *S*-(ethylsulfonyl)-L-cysteine NCA (**B36**) and *S*-(isopropylsulfonyl)-L-cysteine NCA (**B37**) (Scheme 18B). Disulfides are reversible and therefore attractive for biomedical applications. They are stable under extracellular conditions, but cleavable inside of cells. Usually, disulfide formation has been achieved by oxidation of thiols (with long reaction times, often not 100% conversion and the lack of formation of asymmetric disulfides) or by the formation of reactive thiols (chlorinated or nitroso-thiols). A major drawback of activated thiols is the limited stability against aminolysis and hydrolysis. The group of Barz introduced two monomers with a protective and at the same time activating group, which was stable during ROP. Asymmetric disulfide formation was chemoselectively achieved by post-modification with appropriate thiols. An alkyl sulfonyl chloride was hydrolyzed to an alkyl sulfinic acid sodium salt and reacted with *S*-nitrosocysteine (generated *in situ* from L-cysteine) forming a thiosulfonate, which reacted with diphosgene to yield the final NCAs (**B36** and **B37**) (Scheme 18B). Quantitative post-modification of polymers from **B36** with benzylmercaptan was proven within 60 s, without degradation or side reactions. The approach opens a way to reversible conjugation of drugs as well as cross-linking to form nanostructures.[203]

4.2.5 Methionine-based NCAs. Deming and coworkers[204] reported L-methionine NCA (**B38**). Beneficially, L-methionine NCA was synthesized in one step with high yield (91%)[204] proceeding from L-methionine. L-Methionine is readily available and the amino acid with the highest production rate due to its use in animal feed. Methionine in homo- and polypeptides were chemoselectively and efficiently (>90%) alkylated with a broad range of bromide, iodide, triflate, and epoxide[205] (pH < 3) derivatives yielding stable sulfonium or β-alkyl-β-hydroxyethyl sulfonium products. Polymethionine was compatible with the



Scheme 18 Synthetic protocols for cysteine-based NCAs.

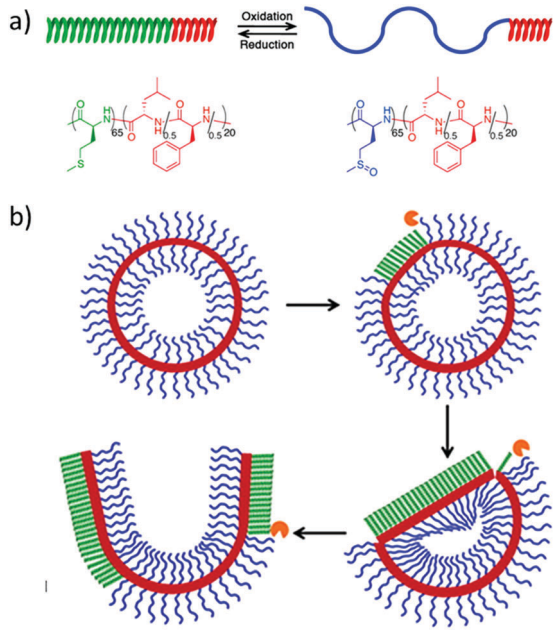


Fig. 4 The enzyme-triggered release of cargos from methionine sulfoxide containing vesicles: (a) structure and redox properties of poly(L-methionine)-*b*-poly(L-leucine-*stat*-L-phenylalanine) peptides, (b) the possible effect of enzymatic reduction of vesicle surface of sulfoxide segments to methionine segments for a change of conformation and cause of vesicle ruptures. Adapted from ref. 207 with permission from the American Chemical Society, Copyright 2017.

deprotection of other functional groups. Sulfur nucleophiles dealkylated the polypeptides again and triggered the release of therapeutics or tagged protein digests from affinity columns were achieved.[206] Oxidation of sulfur in poly(L-methionine) to poly(L-methionine sulfoxide) or poly(L-methionine sulfone) influences the conformation of the polypeptides: poly(L-methionine) is hydrophobic forming an α-helix, poly(L-methionine sulfoxide) is water-soluble with a disordered conformation (Fig. 4); poly(L-methionine sulfone) exhibits a slightly water-soluble mainly α-helical structure. Deming and coworkers[207] designed poly(L-methionine)-*b*-poly(L-leucine-*stat*-L-phenylalanine) copolymers and the oxidized sulfoxide copolymers self-assembled to stable vesicles. Upon reduction of the sulfoxides by methionine sulfoxide reductase A and B (MSR enzymes, found within human cells) and DTT as surrogate reductant, the hydrophilic disordered segments became hydrophobic and changed to rigid α-helical conformation. Change of conformation stiffened the vesicle membranes by forming a crumpled sheet-like morphology and eventually caused vesicle membrane rupture. Triggered release of an encapsulated model cargo (Texas Red labeled dextran) by enzymatic reduction of the sulfoxides segments has been demonstrated.

4.2.6 DOPA-based NCAs. In recent years, catechol-containing polymers, inspired by mussel foot proteins (MFP) gained increasing interest for biomedical applications. Catechols complex metal-ions pH-dependently and reversible with high binding affinities, react with amines and thiols or covalently cross-link with each other under oxidizing conditions. *O*,*O*′-Dicarbobenzyloxy-[208] and *O*,*O*′-acetyl-protected[209] L-DOPA NCAs were reported in the literature. The unprotected L-dihydroxyphenylalanine NCA (**B39**) was introduced from the group of Qiao[210] by reaction of L-DOPA with triphosgene. They stated, that the phenolic hydroxyl groups did not initiate ROP of NCAs, however, used the NCA immediately after synthesis for polymerization, probably due to instability during storage. Block copolymers of L-glutamic acid and **B39** showed reversible vesicle formation with ellipsoidal morphology at pH 3 and hollow vesicles at pH 12. Oxygen-mediated oxidation of DOPA groups at pH 12 stabilized the vesicles by cross-linking. Lei and coworkers[194,211] recently applied the **B39** in L-arginine- and L-DOPA-containing polypeptides as surgical adhesives.

4.2.7 Synthetic amino acid-based NCAs. In 1945, Schlögl *et al.*[212] already introduced D,L-allylglycine NCA (**B40**) and its polymerization. Post-modification at that time was only conducted *via* hydrogenation, hydrobromination, and bromination. Schlaad and coworkers[213,214] showed glycosylation by radical and photochemical thiol–ene reaction to enhance helical stability and solubility of poly(D,L-allylglycine) and poly(D,L-allylglycine-*co*-L-glutamate). A further unsaturated NCA, 5-pentenyl-D,L-glycine NCA (**B41**), was reported by Blanch and coworkers,[215] postpolymerization modification has not been reported. In 1960, Schlögl *et al.*[216] reported the synthesis of D,L-propylglycine NCA (**B42**) from D,L-propylglycine, and phosgene, and its polymerization. Post-modification was only reported decades later in 2010 by Heise and coworkers[217] with glycosylation by click chemistry,[218] and in 2012 by Schlaad and coworkers[214] with glycosylation by the photochemical thiol–yne reaction. Bioactivity of the polymers, micelles or polymersomes was proven by selective lectin binding by the groups of Heise and Schlaad. Block copolypeptides with one glycosylated segment were found to be efficient stabilizers (completely based on renewable building blocks) in the emulsion polymerization of styrene.[219]

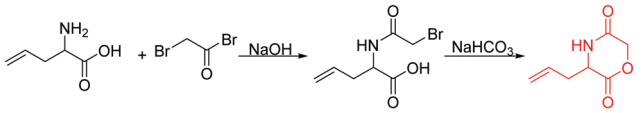
Alkene- or alkyne-substituted NCAs from unnatural amino acids compared to analog NCAs from natural amino acid display the distinct benefit, that ester or amide linkages are absent in the pendant chains. Pendant chains in polypeptides from naturally amino acid-based NCAs might be cleaved by hydrolysis or aminolysis at these linkages and thereby molecules introduced by post-modification detached. A challenging drawback of unnatural amino acid-based NCAs is the synthesis of the needed amino acids, which might be the reason for only a few reported monomers in literature.

4.3 Cyclic diamide monomers

To the best of our knowledge, no orthogonally functional cyclic diamides suitable for ROP have been reported so far. They are usually used for polycondensation reaction, where the ring remains in the backbone of the polymer. Elias and coworkers copolymerized the unfunctionalized monomer 2,5-dioxopiperazine (DOP) with caprolactam,[220] Hildgen and coworkers with allyl glycidyl ether.[221]

4.4 Cyclic ester amide monomers

Morpholine-2,5-diones, resulting in polydepsipeptides, have been functionalized with different alkyl chains or protected groups.



Scheme 19 Synthetic strategy to functional morpholino-2,5,-dione monomer (**B45**).

However, they are less reactive as lactides.[222] To the best of our knowledge, Klok and coworkers[223] reported the only orthogonally reactive ester amide monomer, L-allylglycine-morpholine-2,5-dione (**B45**). Further functional morpholine-2,5-diones employ protecting groups. A recent review summarizes the properties of poly(ester amide)s.[43] The synthetic strategy is analog to the synthesis of functional glycolides and lactides: a corresponding α-amino acid and 2-bromo acetyl bromide reacted and the final monomer was realized by intramolecular cyclization of the intermediate in 13% yield (Scheme 19). Klok and coworkers showed modification by thiol–ene reaction with different fluorinated, carboxylated, aminated or dihydroxylated thiols with conversions between 15–100%.

5. Polycarbonates

Aliphatic polycarbonates find broad application in biomedical devices and drug delivery. They are typically prepared by phosgene condensation or ester exchange, by addition polymerization of epoxides with carbon dioxide in ring-opening copolymerization (ROCOP)[228] or by ROP of 6-membered cyclic carbonates, *i.e.* trimethylene carbonate (TMC). Poly(trimethylene carbonate) (PTMC) and poly(dimethyl trimethylene carbonate) (PDTC) display poor hydrophilicity and slow degradation rates. A broad range of functional TMCs, which we present here, has been explored to alter these properties and increase hydrophilicity and degradation. Polymerization of the five-membered cyclic carbonates is thermodynamically unfavorable.[229] Polymerization above 150 °C results in poly(ether-carbonate)s and decarboxylation. Five-membered vinylene carbonate[230] and vinylethylene carbonate[231] are radically polymerized at the vinyl function, while the cyclic carbonate remains unaffected. Polymerization of seven-membered rings is possible but less relevant. Reported functional monomers are limited to alkyl- or aryl-pendant chains, or protected functionalities; reactive functionalities have not been reported up to date. For more details, we also refer to a review of Rokicki.[229] The copolymerization of epoxides with anhydrides or carbon dioxide to polycarbonates is an attractive strategy. Functional epoxides and their synthetic protocols are well-established,[232] and the potential of the combination with carbon dioxide[228] or anhydrides[45] are exploited (Table 5).

5.1 Trimethylene carbonate

Various mono- and disubstituted trimethylene carbonate (TMC) monomers have been reported in the literature. Dove and coworkers published an excellent review about TMCs in 2013,[25] including general synthetic strategies, functional monomers, and their polymerization, as well as post-modification reactions and applications. Here, we restrict to general synthesis strategies for orthogonally-reactive monomers and selected some representative examples for further applications.

While homopolymerization of the most functional monomers is possible, often copolymerization with alkyl-chain containing TMCs is conducted to adjust the functional group density. Furthermore, disubstituted monomers mostly contain a methyl or ethyl substituent, which has an impact on the thermal properties and solubility of the products. Alcohols are commonly used as initiators. A variety of synthetic protocols for the polymerization of TMCs are reported, including the polymerization with tin(II) octoate in bulk at *ca.* 110–120 °C for 4–48 h. Modern synthesis protocols rely on organocatalysis with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in bulk or solution at temperatures between 25 and 110 °C for 1–3 days, with a catalytic system of DBU or sparteine with a thiourea cocatalyst *N*-cyclohexyl-*N*′-(3,5-bis(trifluoromethyl)phenyl)thiourea (TU) at room temperature and in solution for 2–4 h or with the more reactive base 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) in bulk or solution at temperatures ranging from 0–25 °C over a period of 1 min to 2 h (Scheme 20). Commonly used solvents are dichloromethane, chloroform or toluene, depending on the solubility of TMCs and applied reaction temperatures.

A variety of synthetic strategies has been reported for the synthesis of substituted TMCs, including 2–5 steps with overall yields between 17–70%. A synthetic strategy relies on 2,2-bishydroxy(methyl)propionic acid (bis-MPA) as feedstock (Scheme 21), which was esterified to introduce the functional group, *e.g.* with alkylhalogenides (Scheme 21, route I). Following cyclization with ethyl chloroformate under basic conditions produced the TMCs. Hedrick and coworkers[233] introduced an alternative route for a versatile precursor (5-methyl-5-carboxy-2-oxo-1,3-dioxane), yielding functional monomers in one further step (Scheme 21, route II). The carboxyl function of bis-MPA was protected with benzyl bromide, cyclization achieved, *e.g.* with triphosgene, and the carboxylic acid functionality deprotected again by hydrogenation (overall yield of precursor 59%). The precursor was either directly esterified again to introduce functionalities as pendant chains or transformed into a more reactive acid chloride and then esterified (overall yields: 15–41%). An alternative precursor, carrying a pentafluorophenyl ester protecting group,[34,234] was synthesized on a gram to kilogram scale, easily handled and stored (yield: 75% Scheme 21, route III). It was reacted with suitable nucleophiles, as alcohols or amines in a transesterification reaction to functional TMCs. A further alternative is the use of imidazole intermediates using 1,1′-carbonyl diimidazole (CDI) as a key reagent (yield of intermediate: 67% Scheme 21, route IV). The intermediates were robust and bench stable.[235] Alternatively, the hydroxyl functions of bis-MPA was first protected, *e.g.* with 2,2-dimethoxypropane (DMP) (Scheme 21, route V). Esterification of the carboxyl group introduced subsequently the pendant functionality. After deprotection of the hydroxyl groups, cyclization was achieved with ethyl chloroformate under basic conditions to yield the final monomers.

Another general route uses glycerol or trimethylolalkanes (such as trimethylolpropane) as feedstock (Scheme 22), which

Table 5 Orthogonally functional cyclic TMCs for the synthesis of polycarbonates

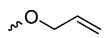
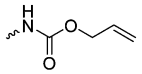
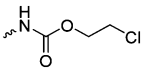
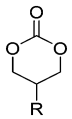
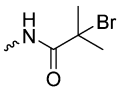
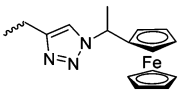
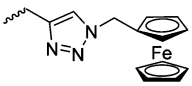
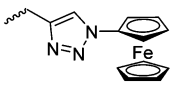
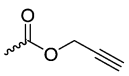
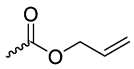
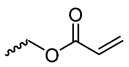
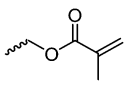
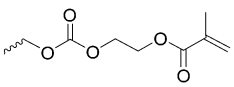
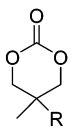
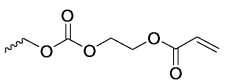
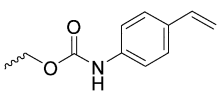
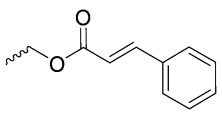
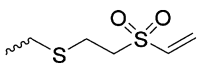
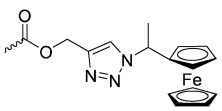
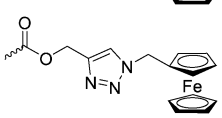
Monomer R =	No.	Post-modification	Ref.
5-Monosubstituted TMCs			
	**C1**	– Epoxidation with *m*CPBA, hydrazination and doxorubicin attachment for drug delivery – Photochemical thiol–ene reaction with mercaptoethanol	236 and 238–241
	**C2**	– No modification	237
	**C3**	– No modification	237
 	**C4**	– Macroinitiator for ATRP polymerization of HEMA	242
	**C5**	– Study of redox potential	87
	**C6**	– Study of redox potential	87
	**C7**	– Study of redox potential	87
Disubstituted TMCs			
	**C11**	– Click chemistry with carbohydrates, immobilization of TSP50 proteins or hemoglobin as oxygen carrier or reversible light-responsive micelles with spiropyran modification – Thiol–yne reaction – Functionalization with decaborane for BNCT – Epoxidation and hydrolyzation to diols or reaction with alcohols, amines or thiols	243–248
	**C13**	– Thiol–ene reaction to attach folic acid, nucleobases, for cross-linking and gelation – Ozonolysis and reduction to aldehydes and aldehyde-aminooxy click reaction	250–259
	**C14**	– Modification by Michael-addition with polar and charged groups – Photo-cross-linking to obtain micelles and fibers	260–262
	**C15**	– No modification	260
	**C16**	– No modification	263
 	**C17**	– No modification	263
	**C18**	– No modification	263
	**C19**	– Photo-cross-linking	264
	**C20**	– Michael-type reaction to attach polar or charged groups, GRGDC peptide or PEG-SH	265
	**C8**	– Study of redox potential	87
	**C9**	– Study of redox potential	87

Table 5 (*continued*)

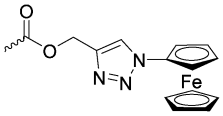
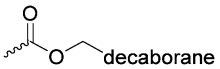
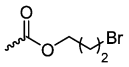
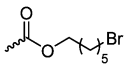
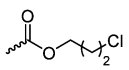
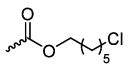
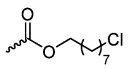
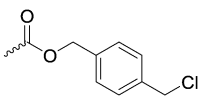
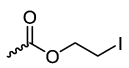
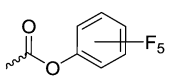
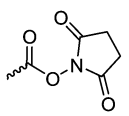
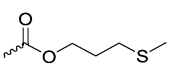
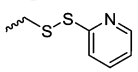
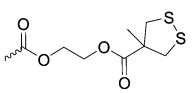
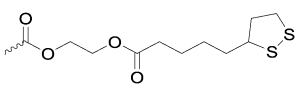
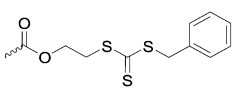
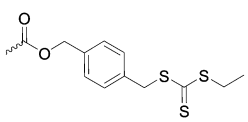
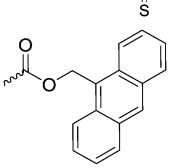
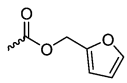
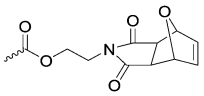
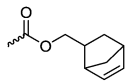
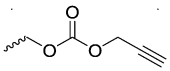
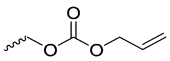
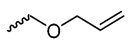
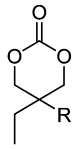
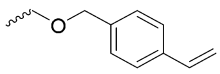
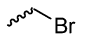
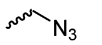
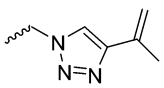
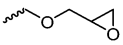
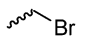
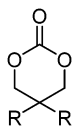
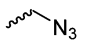
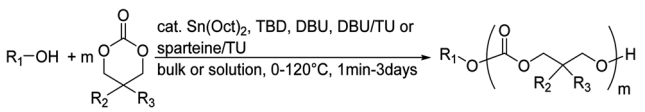
Monomer R =	No.	Post-modification	Ref.
	**C10**	– Study of redox potential	87
	**C12**	– PEG-copolymer nanoparticles as boron vector for BNCT	249
	**C21**	– No modification	266
	**C28**	– Nucleophilic substitution with bis-tertiary amines, pyridines or imidazoles as gene delivery vector and for antimicrobial applications	268, 269, 271, 272 and 274
	**C31**	– Nucleophilic substitution with pyridines or imidazoles for antimicrobial applications	272
	**C22**	– No modification	266
	**C27**	– Nucleophilic substitution with bis-tertiary amines, pyridines or imidazoles as gene delivery vector and for antimicrobial applications	268, 270, 272 and 273
	**C29**	– Nucleophilic substitution with pyridines or imidazoles for antimicrobial applications	272 and 273
	**C30**	– Nucleophilic substitution with primary amines for antimicrobial applications	273
	**C32**	– Nucleophilic substitution with primary amines for antimicrobial applications	274–277
	**C26**	– Nucleophilic substitution with bis-tertiary amines as gene delivery vector	268
	**C25**	– Click reaction with alkyne derivatives – No polymerization is shown of azide monomer	267
	**C33**	– Functionalization with different amines	277–281
	**C34**	– Functionalization with amines to introduce charged groups or bioactive molecules	282
	**C35**	– Functionalization with epoxide derivatives to introduce galactose, tocopherol or carbazols	283
	**C36**	– Thiol–disulfide exchange reaction with thiols to reduction-sensitive self-assembled micelles or nanoparticles	284 and 285
	**C37**	– Thiol–disulfide exchange reaction for formation of dynamic, stimuli-responsive and self-healing hydrogels	286 and 287
	**C38**	– Thiol–disulfide exchange reaction for formation of core-cross-linked micelles or hydrogels	287
	**C39**	– RAFT macroinitiator	288
	**C40**	– RAFT macroinitiator	289
	**C41**	– Diels–Alder reaction with maleimide-polymer derivatives to grafted copolymers	290

Table 5 (*continued*)

Monomer	R =	No.	Post-modification	Ref.
		**C42**	– Cross-linking with maleimide-comonomers by Diels–Alder reaction to materials for nanoimprinting	291
		**C43**	– Cross-linking with furfuryl-comonomers by Diels–Alder reaction to materials for nanoimprinting	291
		**C44**	– Click reaction with azides – Thiol–ene reaction – Inverse electron demand Diels–Alder reaction with tetrazines	292
		**C45**	– No modification	235
		**C46**	– No modification	235
		**C47**	– Thermal or photochemical cross-linking – Thiol–ene reaction with PEG-SH for the formation of LCST-type polycarbonates	293–295
		**C49**	– Cross-linking with styrene	297
		**C23**	– No modification	266
		**C24**	– No modification	266
		**C50**	– Click reaction with alkynes – No polymerization is shown of azide monomer	267
		**C51**	– No modification	267
		**C48**	– Functionalization with thiols or benzylamine	296
		**C52**	– Quaternization with tertiary amines for antimicrobial applications – Azidation and click reaction to form amphiphilic graft copolymers, micelles or nanoparticles for drug delivery	298–301
		**C53**	– Click reaction with alkynes core-cross-linked micelles or hydrogels for drug delivery or cell tissue engineering	302–304
		**C54**	– Self-cross-linking of micelles for drug delivery and intracellular de-cross-linking	305
		**C55**	– Epoxidation with *p*-CPBA	306 and 307

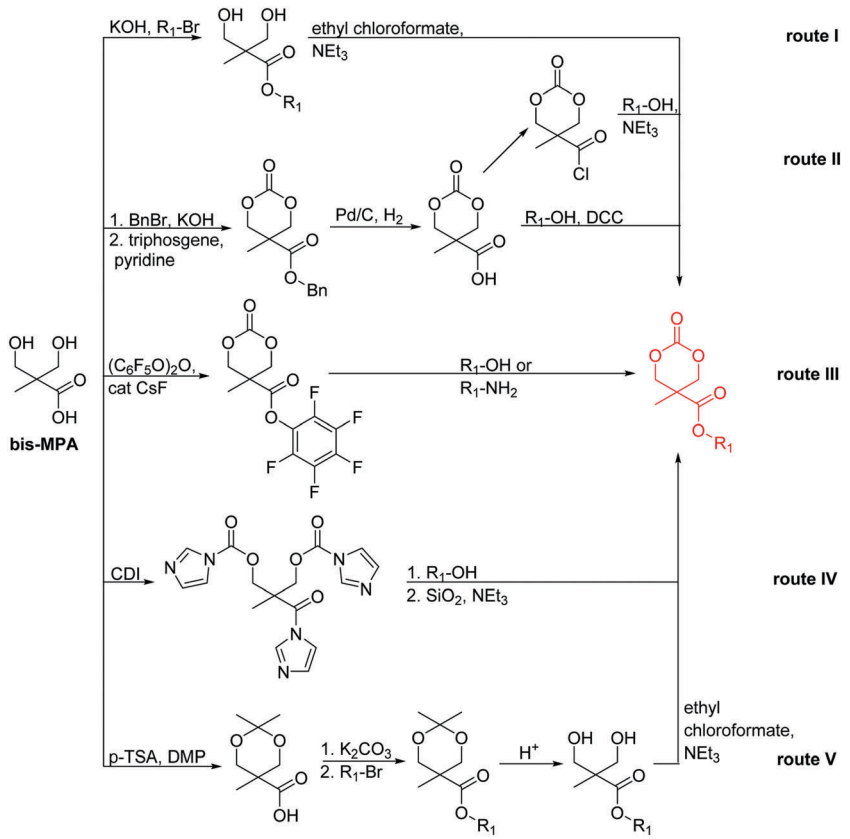


Scheme 20 General protocol for the organocatalytic polymerization of TMCs to poly(carbonates)s with alcohols as initiators.

are protected as acetals with benzaldehyde (Scheme 22, route VI), acetone, or 2,2-dimethoxypropane (DMP) (Scheme 22, route VII). The pendant hydroxyl group was substituted with alkylhalogenides or acid chlorides, the acetal hydrolyzed, and the final monomer formed by reaction with triphosgene or ethyl chloroformate under basic conditions.[236] Alternatively, the starting compound was either directly transformed to the cyclic carbonate and afterward esterified to introduce the pendant functionality (Scheme 22, route VIII) or first, an oxetane-ring was generated (Scheme 22, routes IX–XI). After halogenation of the remaining hydroxyl group and ring-opening of the oxetane, cyclization was achieved, *e.g.* with ethyl chloroformate or 1,1′-carbonyldiimidazole (CDI) (overall yield: 31–47%, Scheme 22, route IX). Alternatively, the alkyl halogenide was reacted with sodium hydrogen sulfide and the resulting thiol modified either by thiol–ene reaction or disulfide formation (Scheme 22, routes X (yield: 16%) and XI (yield: 16%)). For more details, we also refer to the review of Dove.[25]

Yang and coworkers[237] reported a strategy synthesizing monosubstituted TMCs from 2-aminopropane-1,3-diols (serinol) (Scheme 23, route XII; yields: 32–69%). Substitution of the amine with chloroformates, acyl halides or *N*-carbonyloxy succinimide derivatives introduced the pendant chain, followed by cyclization with ethyl chloroformate.

5.1.1 5-Monosubstituted trimethylene carbonates. Zhuo and coworkers[236,238,239] reported an allyl-containing monomer, 5-(allyloxy)-1,3-dioxan-2-one (**C1**). Homo- or amphiphilic block copolymers with PEG were functionalized by photochemical thiol–ene reaction with cysteamine[240] or by epoxidation,

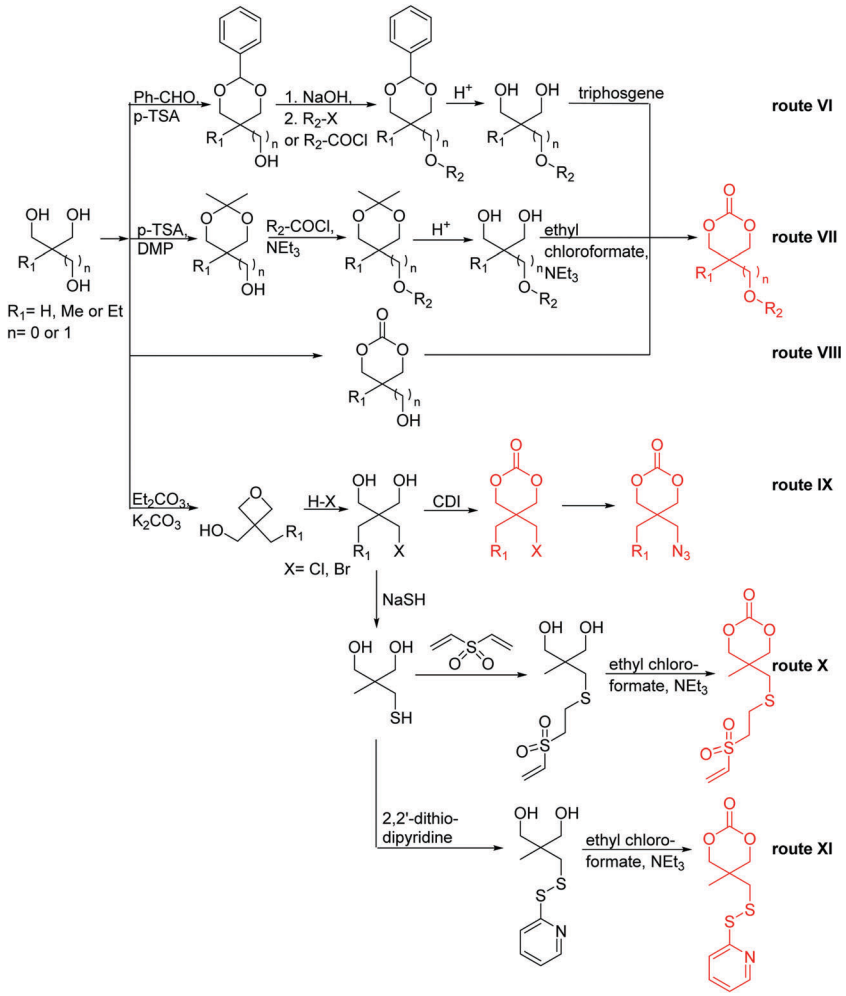


Scheme 21 Synthetic strategies to trimethylene carbonates (TMCs) from 2,2-bishydroxy(methyl)propionic acid (bis-MPA).

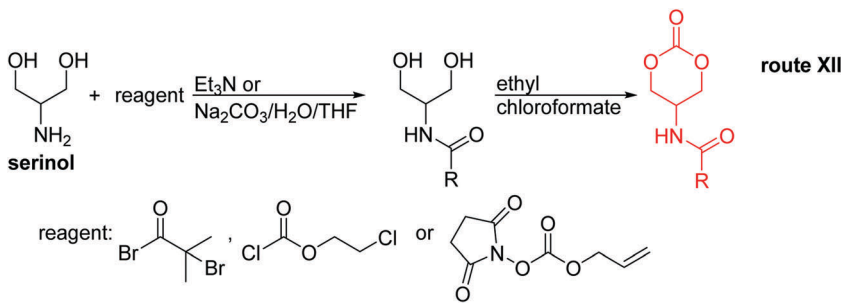
subsequent hydrazination and attachment of doxorubicin for drug delivery.[241] Yang and coworkers[237] reported allyl- (**C2**) and chloro- (**C3**) functional carbamate TMCs from serinol (Scheme 23, route XII), however, post-modification of polymers was not shown by the authors. Dai and coworkers[242] reported recently a monomer with an ATRP initiating group, 2-(2-bromoisobutyrylamido) trimethylene carbonate (**C4**), using an analogous route with 2-bromoisobutyryl bromide. Hydroxyethyl methacrylate (HEMA) was grafted from copolymers as macroinitiator, and the amphiphilic polymers self-assembled in micelles.

Diaconescu and coworkers[87] reported several ferrocene-containing TMCs (5-substituted (**C5–C7**) and 5-methyl-5′-substituted (**C8–C10**)), polymerized them and studied their redox potential for biological studies. Proceeding from 2-(prop-2-yn-1-yl)-propane-1,3-diol, cyclization was achieved with triphosgene. Ferrocene-azide derivatives were attached by click chemistry.

5.1.2 5-Methyl-5′-substituted trimethylene carbonates. A variety of alkyne-, alkene-, vinylidene-, and acrylate-functionalized 5-methyl-5′-substituted trimethylene carbonates (MTCs) has been reported with versatile applications so far. Jing and coworkers reported an alkyne monomer (**C11**), where lactide-copolymers were functionalized with sugars-azides[243] and lectin-interactions has been proved, the protein TSP50 has been immobilized on polymer fibers,[244] or amphiphilic triblock copolymers were self-assembled into core–shell micelles and conjugated with hemoglobin as artificial oxygen carriers.[245] Reversibly light-responsive polycarbonate micelles functionalized with an azide-modified spiropyran were shown by Xu and coworkers.[246] Dove and coworkers[247] additionally showed quantitative radical thiol–yne functionalization. Carborane-conjugated amphiphilic PEG-block copolymers nanoparticles were used as drug delivery platform for doxorubicin and boron neutron capture therapy (BNCT) at the same time.[248] The functionalization with decaborane was shown for the monomer (**C12**) and subsequent polymerization.[249] An analogous allyl monomer (**C13**) was reported by Storey and coworkers[250] and lactide-copolymers were epoxidized and hydrolyzed to diols, reacted with alcohols, polyethylenimine as gene delivery vector,[251] or with diamines/dithiols to nanosponges for potentially controlled release.[252] Thiol–ene reaction was applied to attach folic acid,[253] or nucleobases[254] (for core-crosslinking of micelles by base pairing)[255] for drug delivery applications, to cross-link hydrogels,[256] to microstereolithography resins as biocompatible 3D extracellular constructs,[257] or to attach dopamine for self-healing gels *via* Fe^{3+}-ion complexation.[258] Wooley and coworkers polymerized 5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one (**C13**) to allyl-functionalized polycarbonates. The allyl bond was transformed into aldehyde-functional polycarbonates *via* ozonolysis and reductive work-up. Ozone efficiently cleaved the double bonds without damage to the polycarbonate backbone. The resulting aldehydes were functionalized with aminooxy compounds under mild conditions. Also, polycarbonates with both alkene and aldehyde groups were prepared by partial ozonolysis and functionalized by consecutive aldehyde–aminooxy and thiol–ene modifications in an orthogonal fashion.[259]



Scheme 22 Synthetic strategies to trimethylene carbonates (TMCs) derived from trimethylolalkanes.



Scheme 23 Synthetic strategy to trimethylene carbonates (TMCs) derived from serinol.

Zhong and coworkers reported (meth)acrylated MTCs **C14** and **C15**. The acrylate was copolymerized with lactide or caprolactone and modified by Michael-addition with thiols of varying polar and charged groups,[260] or folate-conjugated paclitaxel-loaded PEG–PC–PLA-triblock copolymer micelles photo-crosslinked for drug delivery.[261] Amsden and coworkers[262] electrospun lactide-copolymers of **C14** and photo-crosslinked them yielding fibrous crimped scaffolds to culture cells. Hedrick and coworkers[263] introduced additional (meth)acrylated and styrene functionalized monomers (**C16–C18**), synthesized from the pentafluorophenyl ester precursor (Scheme 22, route III). They showed polymerization of **C16** and **C18**, but no further chemical modification. Jing and coworkers[264] introduced a cinnamate-functionalized monomer (**C19**), which was photo-crosslinked after the ROP. A vinyl sulfone monomer (**C20**) was synthesized by Zhong and coworkers[265] from 3-methyl-3-oxetanemethanol and divinyl sulfone (Scheme 22, route X). Copolymers and coatings were functionalized by selective Michael-type reaction with thiol-containing

molecules to introduce polar and charged groups, GRGDC peptide, or thiolated poly(ethylene glycol) (PEG-SH).

Bowden and coworkers[266] synthesized a series of 5-methyl or 5-ethyl-5′-halide-functional MTCs (halide = chloride or bromide, **C21–C24**) (Scheme 22, route IX), however, they did not perform post-functionalization. In another report, the bromide monomer **C21** was transformed to an azide monomer (**C25**)[267] and used as a precursor for modification by click reaction with alkyne derivatives and subsequent ROP. Hedrick and coworkers[268] further reported 2-iodo-ethyl (**C26**), 3-chloropropyl (**C27**) and 3-bromo-propyl (**C28**) MTC monomers, synthesized from the acid chloride MTC precursor (route II). Copolymers were functionalized with a bis-tertiary amine (TMEDA). While for the quaternization of the 3-chloropropyl substituted polymers from **C27** 90 °C was required, the 3-bromo-propyl (**C28**) and 2-iodo-ethyl (**C26**) substituted polymers were functionalized at room temperature in high conversion >90%. Chloride substituted polymers (**C27**) showed no gel formation because of the low reactivity of chlorine substituents. The iodide and bromide substituted polymers from **C26** and **C28** were more difficult to handle as undesired cross-linking occurred. Bromide-substituted copolymers from **C28** with 50% 5-methyl-5-ethyloxycarboxyl-1,3-dioxan-2-one comonomer instead did not show cross-linking. The cationic polycarbonate was able to bind and complex DNA for generating nanoparticles and application as a gene delivery vector were studied.[268] Coatings of surface grafted diblock copolymers of PEG and bromide substituted-polycarbonates from **C28**, quaternized with trimethylamine, exhibited antibacterial and antifouling properties and effectively killed Staphylococcus aureus (MSSA) and methicillin-resistant *S. aureus* (MRSA) on the coatings.[269] The polymer coating prevented blood protein adhesion and no significant hemolysis was observed. Nanoparticles of cationic polycarbonates disrupted microbial walls/membranes selectively and efficiently and thus inhibited the growth of Gram-positive bacteria (MRSA and fungi).[270] Galactose-functionalized cationic polycarbonates were applied for targeted gene delivery to hepatocytes.[271] Yang and coworkers investigated in different pyridines and imidazoles as quaternizing agents[272] for polycarbonates or the effect of hydrophobicity[273] of the polymers from 3-chloropropyl (**C27**), -hexyl (**C29**) or -octyl (**C30**) and 3-bromo propyl (**C28**) or -hexyl (**C31**) MTCs, and their impact on antimicrobial properties.[272] In other studies, cationic (co)polymers of a benzyl chloride-substituted MTC (5-methyl-5-(4-chloromethyl)benzyl carboxyl-1,3-dioxan-2-one, **C32**), again quaternized with different amines, were investigated with respect to their antimicrobial behavior,[274] activity, and selectivity.[275] Here, functionalization was faster compared to 3-bromo propyl substituted polymers from **C28**. Polymers were additionally functionalized by quaternization with phosphines, the chloride in polymers from **C32** was substituted with NaN_3 and subsequently clicked to various alkynes,[276] or functionalized with boronic acid derivatives.[277]

Besides the use of a pentafluorophenyl ester MTC (**C33**) as a precursor for preparation of functionalized monomers (Scheme 22, route III),[234] **C33** itself was polymerized to highly reactive PCs. Hedrick and coworkers proved post-modification with different amines[278,279] to use them *e.g.* as stealth materials,[280] with persistent radicals, or with boronic acid derivatives.[277] They self-assembled them to nanoparticles or used them as MRI agents.[281] Liu and coworkers[282] reported a further active ester MTC monomer, functionalized with a NHS ester (5-methyl-5′-(succinimide-*N*-oxycarbonyl)-1,3-dioxan-2-one, **C34**), which was copolymerized with caprolactone and the copolymers modified by aminolysis with ethylene diamine to yield hydrophilic amido-amine pendant chains. They proposed facilitated attachment of bioactive molecules, targeting ligands, and covalent incorporation of prodrugs for the active ester copolymers.

A thioether-substituted monomer **C35** was recently reported by Hedrick and coworkers,[283] that was incorporated into homo-, di- and triblock copolymers, which were functionalized with epoxides, yielding sulfonium-functionalized PCs. Alkene functionalities, polar groups, galactose, tocopherol, and carbazols were introduced in the pendant chains. Zhong and coworkers reported a pyridyl disulfide-functionalized monomer (**C36**, Scheme 22, route XI), which was copolymerized with caprolactone. The polymers were functionalized in a thiol–disulfide exchange reaction with PEG-SH[284] and self-assembled into reduction-sensitive micelles for active intracellular drug release or with thiolated lactobionic acid[285] to reduction-sensitive shell-sheddable glyconanoparticles for efficient hepatoma-targeting delivery of doxorubicin. Two dithiolane-functionalized monomers **C37** and **C38** were recently synthesized by Waymouth and coworkers from 5-methyl-5′-carboxylic acid-trimethylene carbonate, oxalyl chloride, and 2-hydroxyethyl 4-carboxylate-4′-methyl-1,2-dithiolane[286] (**C37**) or 2-hydroxyethyl-5-(1,2-dithiolan-3-yl)pentanoate (**C38**).[287] Water-soluble triblock PEG–PC-copolymers were cross-linked with dithiols or with each other by reversible ring-opening of the pendant 1,2-dithiolanes and dynamic hydrogels obtained,[286] or self-assembled into core-crosslinked (flower-bridged) micelles (Fig. 5).[287] Depending on the pendant dithiolane chains, the hydrogels were dynamic, adaptable, and self-healing or rigid, resilient, and brittle. Cross-linked flower micelles dissociated upon the addition of acetone. Micelles cross-linked by a thiol and capped with maleimide persisted in acetone, and micelles cross-linked by a thiol, capped with maleimide, and then treated with dithiothreitol dissociated in acetone. Two trithiocarbonate functionalized monomers **C39**[288] and **C40**[289] were reported, serving as RAFT macroinitiator after ROP. *N*-Isopropylacrylamide (NiPAAm) (or methyl acrylate and tetrahydropyran acrylate)[289] were grafted from the poly(carbonate)s.

Tunca and coworkers[290] reported an anthracene containing MTC monomer (**C41**), suitable for Diels–Alder reactions with dienophiles. Polymers were grafted with a furan-protected maleimide-terminated-poly(methyl methacrylate) or poly(ethylene glycol) or a mixture of both to yield well-defined polycarbonate graft or heterograft copolymers with an efficiency over 97%. Nelson and coworkers[291] chose a similar approach, using a furfuryl-containing TMC monomer (**C42**). They provided copolymers with a second counterpart monomer: a Diels–Alder-protected maleimide-containing comonomer (**C43**). The maleimide was

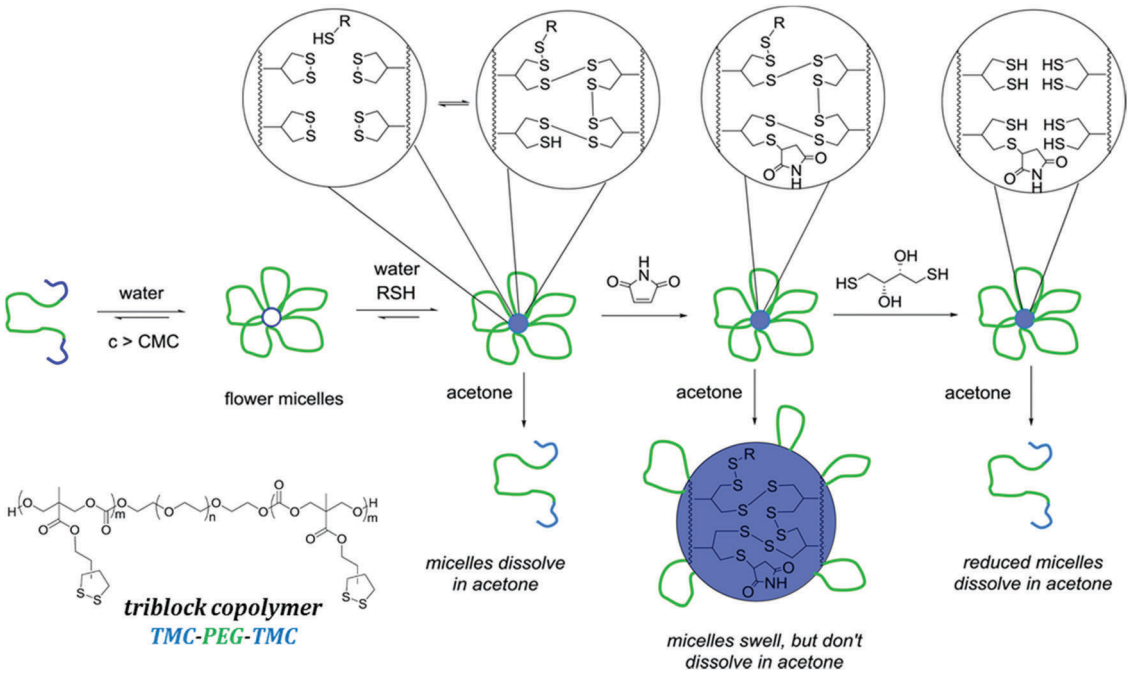


Fig. 5 Self-assembly of dithiolane-functionalized TMC–PEG–TMC block copolymers into flower micelles and thiol-initiated cross-linking of the micelles. Adapted from ref. 287 with permission from the American Chemical Society, Copyright 2017.

thermally deprotected and furan released at 130 °C. At 90 °C furfuryl functionalities in the copolymers reacted with the maleimide functions and covalently cross-linked the material. The polymer films were used for the thermally induced nanoimprinting process. Dove and coworkers[292] introduced a monomer with a norbornene-functionality (**C44**). They presented different post-modification reactions on the homopolymers: (i) functionalization with azides *via* a 1,3-dipolar cycloaddition, (ii) inverse electron demand Diels–Alder reaction with tetrazines and (iii) radical thiol–ene coupling.

5.1.3 5-Ethyl-5′-substituted trimethylene carbonates. Malkoch and coworkers[235] reported on alkyne- (**C45**) and alkene- (**C46**) functionalized 5-ethyl-5′-substituted TMCs, synthesized *via* imidazole intermediates (analog to Scheme 24, route IV with trimethylolpropane as starting material). They showed polymerization of the monomers, post-modification has not been reported so far. Höcker and coworkers[293] studied the polymerization of 5-allyloxymethyl-5′-ethyl TMC (**C47**), cross-linked the polymers and investigated their thermal behavior. Brandell and coworkers[294] used UV-cross-linked homopolymers as electrolytes in solid-state Li batteries. Dove and coworkers[295] modified homopolymers of **C47** *via* photochemical thiol–ene reaction, *e.g.* with PEG-SH of different chain lengths, and showed a linear increase of LCST in correlation with increasing length of PEG chains. They further transformed the monomer to an oxirane ether carbonate (**C48**) by epoxidation with *m*CPBA.[296] Homopolymers were functionalized in a thiol-epoxy reaction in presence of LiOH or DBU as a catalyst. While the degree of functionalization with aliphatic and benzylic thiols was rather low (<1–56%), thiophenol showed effective modification (50–94%) without polymer degradation in the presence of DBU as a catalyst. Functionalization with primary amines in the presence of Lewis acid catalysts was reported to be challenging because the Lewis acids promoted degradation of the polymers. Functionalization without a catalyst and increased temperature (50 °C) showed conversion >95% with benzylamine, but also the formation of some cross-linked material was observed. A styrene-functionalized TMC (**C49**) was introduced by Endo and coworkers,[297] polymerized and radically cross-linked in the presence of styrene. The cross-linked polymer network was cleaved under basic conditions with potassium *tert*-butoxide and linear, soluble polystyrene with TMC functionalities was obtained.

Bowden and coworkers[266] reported two 5-ethyl-5′-halide-functional TMCs (halogenide = chloride (**C23**) or bromide (**C24**)). **C24** was transformed to an azide functionalized monomer[267] (**C50**) allowing further click chemistry. The authors showed selected monomers to be polymerizable, *e.g.* a α-methyl vinyl triazole monomer (**C51**). However, the post-polymerization modification has not been shown so far.

5.1.4 5,5′-Disubstituted trimethylene carbonates. Shen and coworkers[298] reported a dibromo-substituted monomer (**C52**), obtained by transesterification between 2,2-bis(bromomethyl)-propane-1,3-diol and ethyl chloroformate. Caprolactone–carbonate copolymers were functionalized by quaternization with tertiary amines and their antimicrobial properties were examined.[299] Copolymers were quantitatively functionalized by azidation and click chemistry with PEG–alkyne of different chain length, to achieve amphiphilic graft copolymers with PEG as hydrophilic branches.[298] From such materials, aggregation[298,300] and paclitaxel-loaded redox-responsive core-crosslinked micelles for drug delivery were investigated.[301] In contrast to Shen

and coworkers, Zhuo and coworkers[302] reported only poor conversions for the azidation of bromide copolymers. They introduced a diazido-substituted TMC (**C53**, 2,2-bis(azidomethyl)trimethylene carbonate) by transesterification of 2,2-bis(azidomethyl)propane-1,3-diol with ethyl chloroformate. Functionalization of polymers with different alkynes was achieved in quantitative yields. Amphiphilic PEG-*b*-P(**C53**-*r*-DTC) copolymers were crosslinked with disulfide-containing dialkyne-crosslinkers. The core-crosslinked redox-responsive micelles were investigated with respect to their drug release of methotrexate (MTX).[303] Song and coworkers[304] prepared hydrogels from PEG–PC–PEG triblock copolymer, containing azide substituents, and crosslinked them *via* copper-free ring-strain driven click reaction (SPAAC). Encapsulated bone marrow stromal cells exhibited high cell viability in the hydrogels and they exhibited higher cytocompatibility than hydrogels cross-linked by methacrylate functionalities.

Meng and coworkers[305] introduced a dithiolane TMC (**C54**), synthesized from 2,2-bis(bromomethyl)-1,3-propanediol and NaSH and subsequent cyclization with ethyl chloroformate. PEG–PC copolymers self-assembled to micelles and crosslinked by disulfide exchange reaction, encapsulating doxorubicin (DOX). *In vivo* studies of the micelles in malignant **B16** melanoma-bearing C57BL/6 mice with a dosage of 30 mg DOX eq. per kg effectively suppressed tumor growth, prolonged mice survival time and did not cause systemic toxicity. The drug was released within the tumor cells after reductive cleavage by glutathione.

Gross and coworkers[306] reported 2,2-(2-pentene-1,5-diyl)-trimethylene carbonate (**C55**), synthesized in one step from cyclohexene-4,4-dimethanol and ethyl chloroformate. They extensively studied the polymerization behavior and showed epoxidation of the pendant vinyl group with pCPBA (22–95% conversion, $<2\%$ hydrolysis of epoxides to diols). They suggested further hydrolysis to diols, reaction with alcohols or amines or initiation of ring-opening polymerization.[307]

5.1.5 Other polycarbonates. Venkataraman *et al.* prepared polycarbonates from *N*-substituted functional eight-membered cyclic carbonates.[308] Organocatalytic ring-opening polymerization (ROP) produced well-defined polymers carrying different pendant groups at the in-chain tertiary amine. The copolymerization of the eight-membered monomers with 6-membered cyclic comonomers including commercially available L-lactide and trimethylene carbonate produced novel copolymers. Difunctional analogs produced antimicrobial hydrogels after quaternization of the amine groups using methyl iodide to confer antimicrobial properties. Stable hydrogels were obtained only when the bifunctional monomer concentration was equal to or higher than 12 mol%. *In vitro* and *in vivo* antimicrobial studies revealed that all quaternized hydrogels exhibited broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria and fungi, while the antimicrobial activity of the non-quaternized hydrogels was negligible. Moreover, the gels showed fast degradation at room temperature (4–6 days), which makes them ideal candidates for wound healing and implantable biomaterials.[309,310]

6. Polyphosphoesters

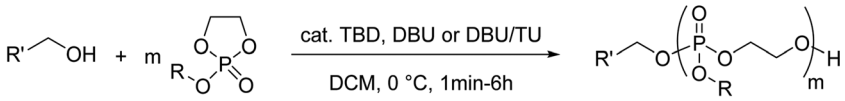
Polyphosphoesters (PPEs) have gained interest in the last two decades for biomedical applications due to their biocompatibility and -degradability. Depending on the number of methylene spacers in the backbone, PPEs with a broad range of hydrophobic to hydrophilic properties have been reported with various degradation behavior. The binding motif around the phosphorus atom (P–O, P–H, P–C or P–N) divides PPEs into further subclasses of polyphosphates, -phosphites, -phosphonates, or -phosphoramidates. The pentavalency of the phosphorus atom allows the facile introduction of alkyl-, aryl- or functional side chains and thus further tuning of the polymer properties. PPEs can be obtained by ROP from 5- and 6-membered cyclic phosphates, H-phosphonates, phosphonates or phosphoramidates (Table 6). Orthogonally functional cyclic phosphoramidates has not been reported so far. We refer to two recent reviews for detailed information on PPEs.[311,312]

6.1 Cyclic phosphates

PPEs can be prepared from 5-membered cyclic phosphates. Most monomers are prepared *via* 2-chloro-2-oxo-1,3,2-dioxaphospholane (COP) as the precursor. COP is either commercially available (but relatively expensive) or can be synthesized in two steps by the reaction of phosphorus trichloride with ethylene glycol, followed by oxidation (Scheme 26A). The oxidation procedure, however, was proven to be time-consuming and care has to be taken that the P–Cl-intermediate does not hydrolyze, *e.g.* if the oxygen gas is not dry. We recently optimized the reaction, using $CoCl_2$ as catalyst and oxygen from the dried air instead of elemental oxygen, making the synthesis process more convenient and shorten the reaction time from days to hours.[313] The final monomers are obtained by esterification of COP with an appropriate alcohol (yield for esterification step 30–70%). Their purification is sometimes challenging due to the high ring-strain: column chromatography over deactivated silica or distillation at reduced pressure are typical purification methods, but sometimes reduce the yields. If the starting COP is highly pure and the alcohol used in the final step can be removed *in vacuo*, the monomers are obtained pure enough without additional purification steps. Some orthogonally reactive monomers have been reported in literature up to date. Because of a growing interest in PPEs for biomedical applications, we expect the report of several further monomers in the common years.

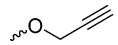
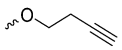
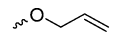
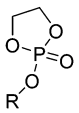
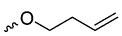
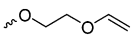
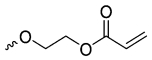
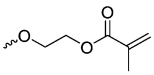
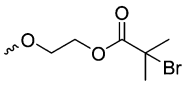
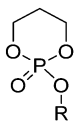
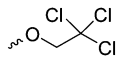
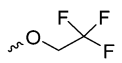
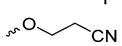
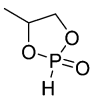
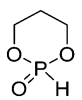
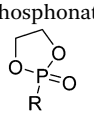
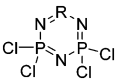
Modern polymerization techniques for PPEs rely on the use of organocatalysts such as TBD, DBU, or an additional use of a thiourea cocatalyst (TU), but also classical basic, acidic or metal-based catalysts ($Sn(Oct)_2$) may be applied.[314] Primary alcohols are typically used as the initiator. Depending on the reactivity of catalyst, polymerizations can be conducted in dichloromethane at 0 °C for a period of 1 min to several hours. The reaction is terminated after *ca.* 80% conversion of monomers to avoid transesterification side reactions during a later stage of polymerization (Scheme 24).

A propargyl-functionalized phosphate monomer (2-(prop-2-yn-1-yloxy)-2-oxo-1,3,2-dioxaphospholane, **D1**) was reported by



Scheme 24 The general protocol for the organocatalyzed ROP of cyclic phosphates to polyphosphoesters.

Table 6 Orthogonally functional cyclic phosphorus-containing monomers for the synthesis of polyphosphoesters or polyphosphazenes

Monomer	R =	No.	Post-modification	Ref.
Phosphates				
		**D1**	– Click chemistry with PEG–azide to self-assembled block copolymers	315
		**D2**	– Click chemistry or thiol–yne reaction to form charged micelles, silver- or paclitaxel-loaded nanoparticles, or block copolymers as a templating agent for calcium carbonate particles	316–325
		**D3**	– Thiol–ene reaction to attach cysteamine for siRNA delivery or subsequent attachment of doxorubicin by hydrazine chemistry and dimethyl maleic anhydride for pH-responsivity	326–328
		**D4**	– Thiol–ene reaction to conjugate paclitaxel with an acid-labile linker for drug delivery	314, 329 and 330
		**D5**	– Thiol–ene reaction, acetalization or thio-acetalization	331
		**D6**	– Michael-type addition of charged thiols	332
		**D7**	– Copolymers as cross-linker for copolymerization with 2-methacryloyloxyethyl phosphorylcholine (MPC) to hydrogels – Photo-cross-linking to hydrogels	333–336
		**D8**	–ATRP-macroinitiator to graft poly(2-methacryloyloxyethyl phosphorylcholine)	337 and 338
		**D9**	– No modification	339
		**D10**	– No modification	339
		**D11**	– No modification	339
H-Phosphonates				
		**D12**	– Oxidation with N_2O_4 to poly(phosphoric acid)s – Reaction with amines to poly(phosphoramidate)s as a gene carrier – Chlorination and reaction with alcohols to polyphosphates as a gene carrier	340–347
		**D13**	– Oxidation with N_2O_4 to poly(phosphoric acid)s – Chlorination and reaction with amines to polyphosphoramidates – Sulfurization to polyphosphorothioates	348–353
Phosphonates				
		**D14**	– Thiol–ene reaction with cysteine or 3-mercaptopropionic acid to form thermoresponsive terpolymers	10 and 354
Phostones		**D15**	– Potential for functional R groups (to date only ethyl and butyl have been reported)	357
				
Phosphazenes				
		**D16**	– Nucleophilic substitution with alcohols and amines	16 and 358
		**D17**	– Nucleophilic substitution with alcohols and amines	361 and 363
		**D18**	– Nucleophilic substitution with alcohols and amines	323 and 362
		**D19**	– Nucleophilic substitution with alcohols and amines	365 and 366
		**D20**	– Nucleophilic substitution with alcohols and amines	365 and 366

Wang and coworkers,[315] block copolymers with caprolactone were synthesized and PEG-N_3 clicked on the alkyne. The polymers self-assembled to nanoparticles with high biocompatibility. Contrary, Wooley and coworkers[316] reported the unsuccessful synthesis of **D1** with isolated yield $<20\%$ and suspected the reaction *via* a S_N2' mechanism to be responsible for decomposition of the monomer (nucleophilic attack at the acetylene proton and subsequent loss of the pendant chain at the phosphate group). They pointed out the absence or loss of the terminal acetylene proton in the ^{1}H-NMR spectra provided by Wang and coworkers and suggested loss or partial loss of the alkynyl functionality. Instead, Wooley *et al.* installed an additional methylene spacer and reported the butynyl monomer 2-(but-3-yn-1-yloxy)-2-oxo-1,3,2-dioxaphospholane (**D2**) with high yield and purity.[316] The monomer was polymerized (homopolymers or copolymers with caprolactone or cyclic phosphates) and post-modification by click chemistry or thiol–yne reaction was applied to prepare non-ionic, cationic, anionic, and zwitterionic micelles,[317,318] covalently labeled core–shell polymeric nanoparticles with fluorescent contrast agents for theranostic applications,[319] PEG-*b*-PPE-based paclitaxel conjugates for ultra-high paclitaxel-loaded multifunctional nanoparticles,[320,321] or silver-bearing degradable polymeric nanoparticles showing *in vitro* antimicrobial activity (Fig. 6).[322,323] For this purpose, silver cations were chelated into the corona or incorporated into the core using AgOAc, or SCC22 or SCC10. The placements of the silver species within the nanoparticle frameworks are proposed locations that have not been confirmed experimentally. Frank and coworkers used **D2** to form anionic hydrophilic PPE-copolymers as efficient templating agent for calcium carbonate particles.[324,325]

Wang and coworkers[326] reported a cyclic phosphate carrying an allyl pendant group (2-(prop-2-en-1-yloxy)-2-oxo-1,3,2-dioxaphospholane, **D3**), which was polymerized with a PEG-macroinitiator. The block copolymers self-assembled into nanoparticles and the allyl groups were post-modified by thiol–ene reaction with cysteamine and partially further reacted with dimethyl maleic anhydride to introduce pH-responsivity. Additionally, doxorubicine was conjugated to the polymers by hydrazine chemistry or the polymers were used for siRNA delivery.[327] In contrast, Lecomte and coworkers[328] used the pendant allyl chain of **D3** as a protective group to produce polyphosphodiesters after selective deprotection with 1.5 eq. sodium benzene-thiolate. Quantitative deprotection without degradation was reported within 2 h in DMF/H_2O (50 : 50, v/v) at room temperature. A butenyl monomer (2-butenoxy-2-oxo-1,3,2-dioxaphospholane, **D4**) was reported by Lecomte and coworkers[314] and block copolymers with 2-isobutoxy-2-oxo-1,3,2-dioxaphospholane were prepared to demonstrate the control over copolymerizations of cyclic phosphates. Further post-modification has not been shown. Wooley and coworkers[329] synthesized PEG-*b*-PPE of **D4** and conjugated Paclitaxel with acid-labile linkages by thiol–ene reaction for drug delivery. Junkers and coworkers[330] developed a flow microreactor to attach thiols upon UV-irradiation to butenyl-containing PPEs of **D4**. Wooley and coworkers[331] also introduced a monomer with a reactive vinyl ether moiety (**D5**), which was either reacted in a thiol–ene reaction, thio-acetalization with thiols or acetalization with alcohols. While they reported quantitative conversion for thiol–ene reaction, acetalization, and thio- acetalization resulted in rather low conversions of 18% and 8%, respectively. Ni and coworkers[332] reported a functional phosphate monomer carrying an acrylate group (**D6**, care has to be taken as the monomer undergoes quick radical polymerization during workup) and prepared block copolymers with caprolactone. The pendant acrylates were quantitatively functionalized by nucleophilic addition chemistry with thiols to introduce hydrophilic chains with hydroxyl, carboxyl, amine, and amino acid functionalities with low cytotoxicity. Stable micelles in aqueous solution, loaded with doxorubicin, opened the way to drug delivery carriers. While after 2 days at 37 °C, 30% release of cargo was observed in PBS-buffer (pH 7.4, 0.01 M), over 70% was reported in the presence of 0.2 mg mL^{-1} phosphodiesterase I. Iwasaki *et al.*[333] used a methacryloyl phosphate monomer (**D7**) to obtain copolymers with 2-isopropyl-2-oxo-1,3,2-dioxaphospholane. They were used as cross-linker and copolymerized with 2-methacryloyloxyethyl phosphorylcholine (MPC) to prepare hydrogels. 100% degradation of the PPE-crosslinker polymer was observed within 6 days at pH 11, and 50% within 15 days at pH 7.4. 50% of the hydrogels degraded after 44 days at pH 7.4 (PBS-buffer).[334] As highly porous hydrogels, they are suitable for 3D cell cultivation and increased proliferation of mouse osteoblastic cell (MC3T3-E1) was reported with increasing amount of PPEs in the hydrogels.[335] The methacrylates as well were photo-cross-linked to obtain hydrogels.[336]

Iwasaki *et al.*[337,338] copolymerized a cyclic bromoisobutylate phosphate (2-(2-oxo-1,3,2-dioxaphosphoroyloxyethyl-2-bromoisobutylate), **D8**) with 2-isopropyl-2-oxo-1,3,2-dioxaphospholane. The polymer was used as a macroinitiator for ATRP polymerization, to form amphiphilic PPEs with poly(2-methacryloyloxyethyl phosphorylcholine)-grafted chains.

6-Membered phosphate monomers are synthesized by a similar strategy, using 2-chloro-2-oxo-1,3,2-dioxaphosphorinane as the precursor, which is further substituted with an appropriate alcohol (Scheme 25B). Penczek and coworkers[339] reported in 1977 three potentially orthogonally reactive monomers with 2,2,2-trichloroethyl (**D9**), 2,2,2-trifluoroethyl (**D10**) or 2-cyanoethyl (**D11**) functionalities as pendant chains (yields were not reported), but did not further modified the corresponding polymers, which

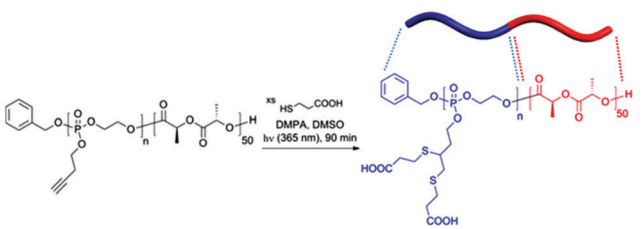
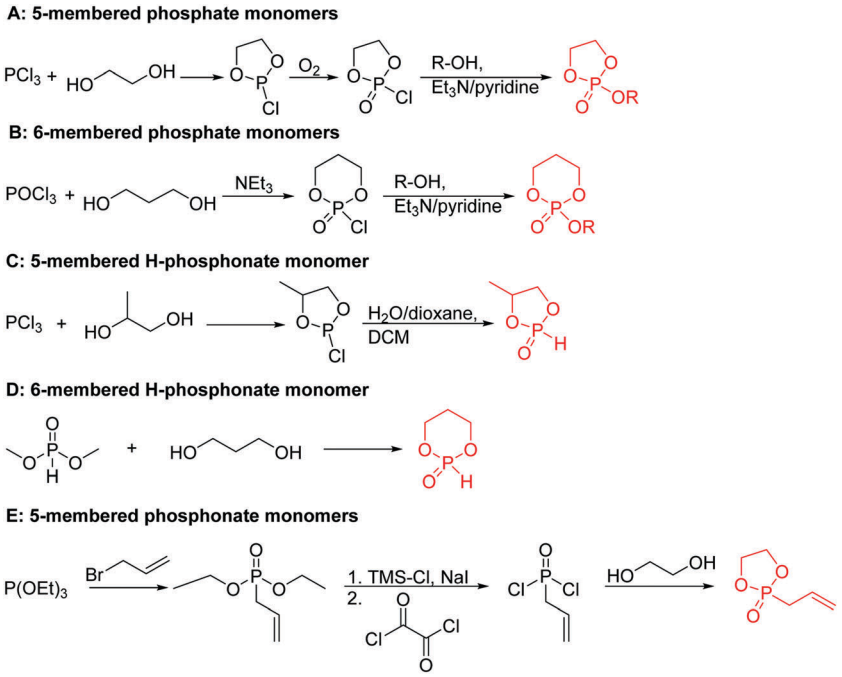


Fig. 6 Synthetic route to silver-bearing degradable polymeric nanoparticles: post-polymerization modification of alkyne-functionalized PPE-*b*-PLLA *via* thiol–yne "click" reaction to prepare anionic amphiphilic diblock copolymer, reproduced from ref. 322 with permission from the American Chemical Society, Copyright 2017.



Scheme 25 Synthetic strategies for cyclic phosphate, phosphonate, and H-phosphonate monomers.

were obtained by cationic polymerization in bulk. 6-Membered cyclic phosphates as monomers are less considered in the literature compared to 5-membered phosphates, due to a lower ring strain.

6.2 Cyclic H-phosphonates

A cyclic 5-membered H-phosphonate monomer, 4-methyl-2-oxo-2-hydro-1,3,2-dioxaphospholane (**D12**), was polymerized by Vogl and coworkers,[340] starting from 1,2-propandiol and PCl_3. 4-Methyl-2-chloro-1,3,2-dioxaphospholane was oxidized by a mixture of water/dioxane to obtain the phosphite (yield has not been reported) (Scheme 25C). The monomer was also synthesized from optically active propandiol. The polymer p(**D12**) was converted by various strategies to (i) poly(phosphoric acid)s by oxidation with dinitrogen tetroxide, (ii) poly(phosphoramidate)s[341,342] by an Atherton–Todd reaction with primary or secondary amine (30–60% conversion), and (iii) polyphosphates[343] by chlorination and subsequent substitution with an appropriate alcohol (quantitative conversion), *e.g.* to poly(2-aminoethyl propylene phosphate) (PPE-EA). Leong and Mao used the polyphosphates[343,344] and polyphosphoarmidates[342,345] (with charged groups[346]) in several reports as gene carrier and transfection agent, or to form plasmid-templated DNA-block copolymer nanoparticles.[347]

A 6-membered H-phosphonate monomer, 2-hydro-2-oxo-1,3,2-dioxaphosphorinane (**D13**),[348] was polymerized by Penczek and coworkers[349] (Scheme 25D). It was prepared by transesterification from dimethyl phosphite and 1,3-propylene glycol (yield: 79%[348]). Penczek showed conversion to poly(phosphoric acid)s by oxidation with dinitrogen tetroxide, to polyphosphoramidates by chlorination with gaseous chlorine and subsequent reaction with primary amines (*C*- or *N*-substituted imidazoles, adenine or uracil),[350–352] or to polyphosphorothioates[353] by sufurization with sulfur in the presence of lutidine.

6.3 Cyclic phosphonates

A 5-membered cyclic allyl phosphonate monomer (2-allyl-2-oxo-1,3,2-dioxaphospholane, **D14**) was recently reported by Wurm and coworkers.[10,354] For cyclic phosphonates the pendant group was introduced in the first step of a three-step reaction (Scheme 25E): after reaction of allyl bromide with triethyl phosphite, allyl phosphonic acid dichloride was formed by reaction with chlorotrimethylsilane and oxalyl chloride. Ring-closing reaction with ethylene glycol formed the final phosphonate monomer with an overall yield of 28% after distillation (as for cyclic phosphates, purification of the highly strained monomers can reduce the yield). Terpolymers were quantitatively modified with cysteine by a thiol–ene reaction and their thermoresponsive behavior analyzed.[354] PEG-*b*-PPEs were modified with 3-mercaptopropionic acid. The block copolymers exhibited UCST behavior and were self-assembled into temperature-dependent dynamic aggregates.[10] Polyphosphonates are prepared by using the organocatalyst DBU and primary alcohols as an initiator in dichloromethane at 0 °C for 16 hours with monomer conversions of 90–96%.[354–356] Very recently also phostones have been polymerized to polyphosphonates with the P–C bond in the main-chain, which might be extended to functional derivatives.[357] Their great benefit compared to the other cyclic phosphates or phosphonates is the relatively easy one-step synthesis, which might be expanded to allyl-functionalized phostones, for example (**D15**). It was proven that their degradation proceeds much slower than the corresponding side-chain polyphosphonates.

7. Polyorganophosphazenes

Polyorganophosphazenes are a polymer class of inorganic–organic hybrid polymers and exhibit a high diversity of properties due to the high versatility of possible organic substituents (Table 6). The phosphorus-nitrogen backbone is substituted by two organic side groups on the phosphorus atoms. Polymerization techniques and application of polyorganophosphazenes were recently summarized in excellent reviews.[16,358,359]

The most widely used method to prepare polyorganophosphazenes is the thermal ROP of hexachlorophosphazene (**D16**) with no control over the polymer molar mass and thus generally high molecular weights ($>10^6$ Da) and broad molecular weight distributions to the precursor polydichloro-phosphazene [$NPCl_2$]. Living cationic polymerization of trichlorophosphoranimine ($Cl_3PNSiMe_3$) with two equivalents of phosphorus pentachloride by a chain growth mechanism in solution at room temperature results in higher control of polymer molar mass *via* the feed monomer to initiator ratio with lower dispersities. We refer the reader to a separate review.[16]

D15 is commercially available (at Sigma Aldrich) or can be synthesized from phosphorous pentachloride and ammonium chloride and subsequent sublimation from a mixture of oligomers (Scheme 26). The precursor rapidly hydrolyzes in the presence of water but can be completely post-modified under dry conditions with amines, alcohols, thiols or alkylation agents such as RMgX or RLi. Mixed, stepwise substitution with two or more organic substituents on the same macromolecule was possible and gives access to a library of polymers with varied properties.[16] The complete modification is important to prevent uncontrolled cross-linking or degradation due to unreacted P–Cl groups. ROP was achieved with partially or completely substituted cyclophosphazene, but side reactions as ring expansion, decomposition or no reaction at all were observed. Generally, the probability for polymerization decreased with increasing number of organic substituents.[360]

Several further cyclic phosphazene monomers with a substitution of a phosphorus atom by carbon or sulfur were reported yielding cyclocarbophosphazene $N_3P_2CCl_5$ (**D17**) from phosphorous pentachloride, ammonium chloride and cyanamide (10% yield)[361] or cyclothiophosphazene $N_3P_2SCl_5$ (**D18**) (yield 40–50%).[362] Polychlorocarbophosphazenes[363] and polychlorothiophosphazenes[323] were obtained by thermal polymerization (120 °C, 4–6 h and 90 °C, 4 h, respectively), and were more reactive to nucleophilic substitution by aryloxides than classical polyphosphazene.[361,362,364] Polycarbophosphazenes exhibited higher glass transition temperatures than polyphosphazene analog due to less torsional mobility in the backbone,[361,364] polythiophosphazenes[362] less hydrolytic stability. Polymerization (165–180 °C, 4 h) of cyclothionylphosphazenes $N_3P_2SOCl_5$ (**D19**) and $N_3P_2SOFCl_4$ (**D20**) yielded hydrolytically stable polythionylphosphazenes.[365,366]

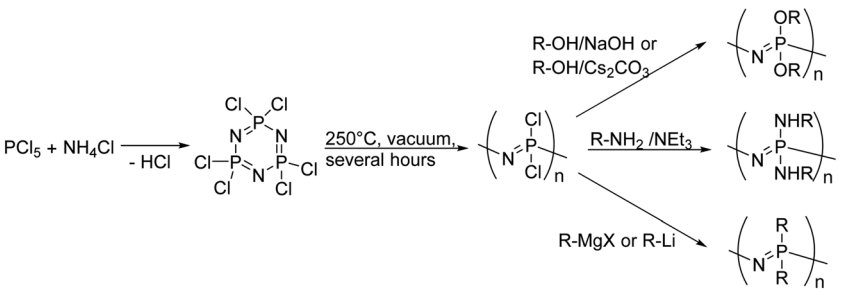
8. Summary & outlook

The ring-opening polymerization gives access to well-defined polymers with narrow molecular weight distributions. However, as the reaction conditions for ROP typically do not tolerate nucleophiles and need inert conditions (in most cases), many functional groups in the monomers need to be protected. The deprotection step after the polymerization can be challenging, when also the polymer backbone can be degraded. In contrast, orthogonally reactive groups that do not interfere with the polymerization conditions are efficient alternatives to protective group chemistry. They can be post-modified by efficient reactions, which do not degrade the polymer backbone. Typical functional groups are alkenes, alkynes, and halogens, but several further functions have been summarized in this review.

Most functional cyclic monomers are synthesized in several reaction steps: the orthogonal functional groups are mostly introduced in the first step, making the synthesis of most functional monomers lengthy with variable yields. The use of "precursor monomers" would be beneficial, introducing the desired functionality in the last reaction step, but such strategies are missing. It is however possible for the preparation of functional phosphate monomers, that rely on the commercially available precursor 2-chloro-2-oxo-1,3,2-dioxaphospholane. The design of similar precursor strategies for other material classes would give faster access to multifunctional polymers with tailored properties (such as solubility or degradation profile).

The presented general concepts of post-modifications can be used for all summarized polymer classes, which are:

– nucleophilic substitution of halides,
– alkyne–azide click chemistry,
– thiol–ene and –yne reactions
– Diels–Alder reactions



Scheme 26 Synthetic route to hexachlorophosphazene and polyorganophosphazenes.

They often yield quantitative conversion under mild conditions (*e.g.* excluding acidic or alkaline conditions or heavy-metal catalysts).

A broad variety of orthogonally reactive functionalities for cyclic monomers for the ROP and post-modification opportunities has been reported so far, which give access to diverse chemically functional biodegradable polymers and promising applications. There is still plenty of scope for further developments.

Conflicts of interest

There are no conflicts to declare.

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