Advances in Polymer Science 269

Patrick Theato *Editor*

Multi-Component and Sequential Reactions in Polymer Synthesis

Springer

269
Advances in Polymer Science

Aims and Scope

The series Advances in Polymer Science presents critical reviews of the present and future trends in polymer and biopolymer science. It covers all areas of research in polymer and biopolymer science including chemistry, physical chemistry, physics, material science.

The thematic volumes are addressed to scientists, whether at universities or in industry, who wish to keep abreast of the important advances in the covered topics.

Advances in Polymer Science enjoys a longstanding tradition and good reputation in its community. Each volume is dedicated to a current topic, and each review critically surveys one aspect of that topic, to place it within the context of the volume. The volumes typically summarize the significant developments of the last 5 to 10 years and discuss them critically, presenting selected examples, explaining and illustrating the important principles, and bringing together many important references of primary literature. On that basis, future research directions in the area can be discussed. Advances in Polymer Science volumes thus are important references for every polymer scientist, as well as for other scientists interested in polymer science - as an introduction to a neighboring field, or as a compilation of detailed information for the specialist.

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Patrick Theato
Editor

Multi-Component and Sequential Reactions in Polymer Synthesis

With contributions by

J.-P. Dilcher · F.E. Du Prez · P. Espeel · R. Hu · H. Jürgens · R. Kakuchi · A. Khan · G.A. Luinstra · M.A.R. Meier · F. Moldenhauer · A. Sehlinger · M.C. Stuparu · B.Z. Tang · L. Tao · P. Theato · Y. Wei · Y. Zhao · C. Zhu

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ISSN 0065-3195 ISSN 1436-5030 (electronic)
Advances in Polymer Science
ISBN 978-3-319-20719-3 ISBN 978-3-319-20720-9 (eBook)
DOI 10.1007/978-3-319-20720-9

Library of Congress Control Number: 2015944327

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface

The synthesis of functional polymers is currently seeing a revival. Within the last decade, numerous new polymerizations and functionalization routes for the synthesis of polymers have been described. This is an extremely positive development, considering the ever increasing demand of novel and complex polymeric materials in advanced applications.

Within the present series on "Multi-Component and Sequential Reactions in Polymer Synthesis", I have the honor to compile recent developments in multi-component reactions (MCRs) or sequences of reactions that are used for the synthesis of polymers or the post-modification of polymers. From the early times on, polymer synthesis has been inspired by novel organic reactions. However, it took usually several decades until new and efficient organic reactions found their way into polymer synthesis. This relatively slow trend has changed recently – likely due to the faster access to interdisciplinary information – and it can be observed that modern organic reactions now find their use in polymer synthesis within a couple of years after their discovery. Noteworthy, the fundamental requirement for a reaction to be useful for the synthesis of polymers is efficiency. Reactions must proceed in high conversions without the formation of any side products via side reactions. After the advent of "click-reactions" in polymer synthesis, a second generation of highly efficient reactions employing multiple components in one step or in defined sequences of steps has found use in polymer synthesis. Consequently, one could easily speak in modern terms of "click 2.0" reactions. I do not claim this book to be a comprehensive compilation of all ongoing synthetic developments in this area, but rather an inspiring source providing a first overview on numerous ongoing advances.

Thankfully, numerous experts have kindly agreed to provide up-to-date chapters on several aspects in the area, thereby contributing to a collection of recent developments. In the first chapter, Ryohei Kakuchi discusses the use of metal-catalyzed MCRs for the synthesis of polymers. Special attention is laid to Cu-catalyzed developments. In the second chapter, Rongrong Hu and Ben Zhong Tang summarize developments of multi-component polymerizations of alkynes and

it beautifully complements the first chapter. Additionally, they highlight fascinating properties of the synthesized polymers, which include aggregation-induced/-enhanced emission, light refractivitiy, photopatternability, or magnetism. In the third chapter, Lei Tao and coworkers review the Biginelli MCR for the synthesis of polymers, which can be used in coupling reactions or the post-polymerization modification. The fourth chapter, written by Ansgar Sehlinger and Michael A.R. Meier covers the intensively utilized Passerini and Ugi multi-component reactions in polymer science. Mihaiela C. Stuparu and Anzar Khan highlight in fifth chapter sequential thio-epoxy and esterification reactions. Although based on relatively old reactions, it is the simplicity of this approach that makes it a very potent reaction sequence. Pieter Espeel and Filip E. Du Prez elaborate on the one-pot multi-step reaction based on thiolactones in sixth chapter. Thiolactones can be ring-opened with amines, expressing a thiol, which can be converted in a subsequent reaction in a thiol-X reaction. The seventh chapter by Fenja Moldenhauer and Patrick Theato summarizes numerous other sequential reactions for the synthesis and modification of polymers. Last but not least, the eighth chapter by Gerrit A. Luinstra and coworkers focuses on the industrial relevant modification of polybutadiene with sequential reactions, thereby providing an insight into demands for industrial relevant materials and their synthesis.

Experts in the respective fields wrote these chapters for chemists working in academia or industry. I sincerely hope that chemists, biochemists, material scientists or simply any researcher interested in modern polymer synthesis will find this book and its chapters useful. May it be an inspiring source or reference!

Hamburg, Germany Patrick Theato
April 2015

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Adv Polym Sci (2015) 269: 1–16
DOI: 10.1007/12_2014_300

Published online: 6 January 2015

Metal-Catalyzed Multicomponent Reactions for the Synthesis of Polymers

Ryohei Kakuchi

Abstract Despite the chemical complexity of multicomponent reactions (MCRs), the dawn of MCRs was fairly early in the history of organic chemistry. After lagging behind successful utilization of MCRs in combinatorial chemistry, the integration of MCRs with polymer chemistry has very recently started, which offers new possibilities in polymer synthesis. In spite of a large number of MCRs available for organic transformation reactions, this chapter describes metal-catalyzed MCRs in the area of polymer chemistry.

Keywords Multicomponent reactions · Organometallic catalysts · Polymer synthesis

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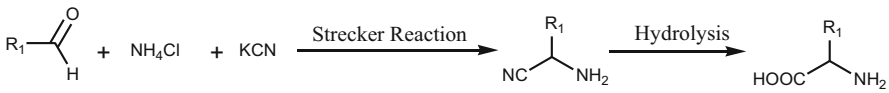
Abbreviations

A^3-coupling	Metal-catalyzed three-component reactions between alkynes, amines, and aldehydes
CuAAC	Cu(I)-catalyzed cycloaddition reaction between terminal alkynes and azides
CuMCR	Cu(I)-catalyzed multicomponent reaction between terminal alkynes, sulfonyl azides, and nucleophiles
CuSeq	Sequential Cu(I)-catalyzed cycloaddition reaction between alkynes and azides and metal-catalyzed cross-coupling reaction of triazole derivatives
IMCR	Isocyanide-based multicomponent reaction
MC-MCR	Metal-catalyzed multicomponent reaction

1 Introduction

Despite the chemical complexity of multicomponent reactions (MCRs), the dawn of MCRs was fairly early in the history of organic chemistry. The first MCR was the so-called Strecker reaction discovered in 1850 [1, 2], which generates amino acids via a three-component reaction between amines, aldehydes (or ketones), and hydrogen cyanide (Scheme 1). Since then, organic chemists have devoted much effort to the discovery of additional MCRs. Thus, we now can find a number of MCRs, including the Biginelli reaction [3], the Gewald reaction [4], the van Leusen three-component reaction [5], the Hantzsch reaction [6], the Mannich reaction [7], the Kabachnik–Fields reaction [8, 9], the Passerini reaction [10], the Ugi reaction [11, 12] and numerous variations thereof [13].

In spite of the relatively long history of MCRs, the utility of MCRs in organic chemistry was not recognized as main stream for many years. The turning point in the history of MCRs was in the 1990s when combinatorial chemistry [14] (i.e., library synthesis) underwent explosive growth [15–26]. Largely triggered by a strong demand for an astronomical number of chemical compounds for use in drug discovery [27–29], MCRs have attracted increasing attention from a variety of scientists. Because MCRs proceed with three or more reactants to generate a single product, the chemical diversity of the final products can be drastically improved by simply changing the starting chemical compounds. The use of



Scheme 1 Strecker amino acid synthesis

MCRs in combinatorial approaches allowed the creation of diverse organic molecules, leading to rapid developments in pharmaceutical chemistry.

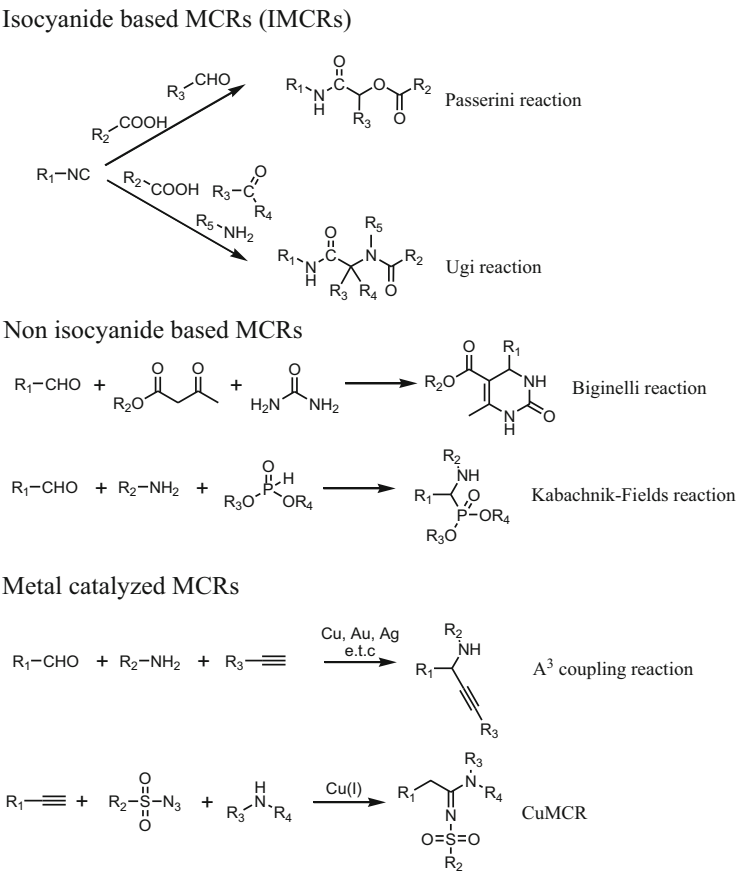
In polymer science, a clear transition occurred from simple plastic production to the generation of diverse functional materials targeted for use in applications such as electronic devices, nanomaterials, and medical treatments [30–37]. In this context, highly efficient linking reactions (so-called click chemistry) have played an indispensable role in polymer science since the 2000s when the concept and philosophy of click reactions was first proposed by Sharpless and coworkers [38]. Click reactions usually refer to thiol-ene [39], thiol-maleimide [35], isocyanate-nucleophile [35], and activated ester-amine reactions [40], as well as Cu(I)-catalyzed [32, 34, 41] and metal-free [36] 1,3-dipolar cycloaddition reactions between organo-azides and acetylenes. Despite a number of available click reactions, Cu(I)-catalyzed 1,3-dipolar cycloaddition reactions between organo-azides and acetylenes (CuAAC) have played a dominant role in the synthesis of functional polymers. Although the use of click reactions in polymer chemistry is undoubtedly effective for material scientists, well-established click reactions show some inevitable drawbacks: (1) the installation of a clickable reactive unit within the desired functional compounds is mandatory, (2) only one functional unit per clickable unit can be installed, and (3) required reagents are often not available commercially. Therefore, the direct use of readily available functional compounds without any organic transformation is highly desirable in order to accelerate interdisciplinary application of such polymers.

The employment of MCRs is expected to overcome the drawbacks of click reactions because many MCRs proceed with common functional compounds such as aldehydes, ketones, and amines, which are commercially available in most cases. Hence, polymer chemists are currently examining and starting to take advantage of the synthetic utility of MCRs for polymer synthesis [42, 43]. Although the main MCRs used in polymer science are isocyanide-based reactions such as the Passerini and Ugi reactions, this chapter will focus on metal-catalyzed MCRs in the area of polymer chemistry.

2 Classification and Comparison of MCRs

Prior to discussing the current state of MCRs in polymer synthesis, the classification of MCRs should be addressed. In spite of the large number of MCRs, these reactions can be divided into three groups: (1) isocyanide-based MCRs (IMCRs), (2) non-isocyanide-based MCRs, and (3) metal-catalyzed MCRs (MC-MCRs). The MCR classification and a few examples are listed in Scheme 2.

Isocyanide derivatives are undoubtedly the most important reactants in MCRs because they show both nucleophilic and electrophilic characters within a single functionality. For example, IMCRs include the Ugi four-component reaction (Ugi-4CR) [11, 12], the Passerini three-component reaction (Passerini-3CR) [10], the Groebke–Blackburn–Bienaymé reaction [44–46], the van Leusen three-



Scheme 2 Classification of MCRs and representative reactions

component reaction [5], and numerous modified synthetic methodologies based on these IMCRs.

The next important class comprises non-isocyanide-based MCRs. In contrast to IMCRs, non-isocyanide-based MCRs do not rely on the unique properties of isocyanides, but rather rely in most cases on the reactivity of imines generated in situ from amines and aldehydes. This class includes the Gewald reaction [4], the Hantzsch reaction [6], the Biginelli reaction [3], the Petasis reaction [47–49], the Kabachnik–Fields reaction [8, 9], the Povarov reaction [50], and the Doebner reaction [51].

The last category is the class of MCRs catalyzed by organometallic species (MC-MCRs). MC-MCRs include the palladium-catalyzed multicomponent reaction of vinyl compounds [52], the three-component Sakurai allylation reaction [53], metal-catalyzed three-component reactions between alkynes, amines, and

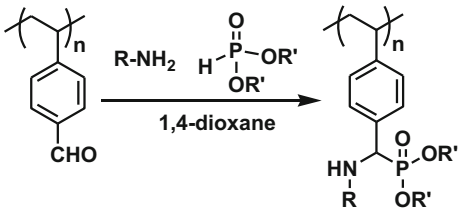
aldehydes (A^3-coupling) [54], and Cu(I)-catalyzed three-component reactions between alkynes, nucleophiles, and sulfonyl azides (CuMCR) [55].

Generally, IMCRs have played an indispensable role in the history of MCRs because the majority of MCRs rely on the intrinsic reactivity of isocyanides, thereby not restricting the reactant scope of the reaction. However, IMCRs face distinct and inevitable drawbacks owing to the nature of isocyanides. As clearly stated by Ugi, isocyanide derivatives possess strong odors, therefore there is huge demand for *odorless* isocyanide derivatives [56]. In addition, there are only a limited number of synthetic protocols for isocyanides, with most of them being quite time-consuming [57]. To be precise, isocyanides are usually synthesized from parental amine derivatives. First, amines are converted into the corresponding formamide derivatives, followed by dehydration of the obtained formamides to afford isocyanide derivatives [57]. Therefore, caution and time are needed to conduct IMCRs, especially because of the extreme odor of isocyanides, which limits IMCRs in practical applications, such as in materials science where non-experts need to handle chemicals. In this context, non-isocyanide MCRs are very attractive to many scientists who do not wish to handle isocyanides. Unfortunately, the number of non-isocyanide MCRs is rather limited. In addition, the reaction mechanisms of both IMCRs and non-isocyanide MCRs are strictly governed by the selected reactant, which in turn limits the fine-tuning of MCRs.

Metal-catalyzed MCRs are advantageous for their easy handling and variety of available reactants. In contrast to other MCRs, the reaction process and reactants can be fine-tuned by metal catalyst and ligand design. In addition, many reactants, catalysts, and ligands can be recycled and reused from the well-established metal-catalyzed cross-coupling chemistry [58–60]. These features are crucially important, not only for polymer and materials chemists, but also for a wide range of interdisciplinary researchers who do not have strong chemical backgrounds.

3 The State of MCRs in Polymer Chemistry

Although the Strecker reaction was discovered almost 160 years ago, the integration of MCRs into polymer chemistry was only initiated recently [42, 43]. In the early 2000s, several reports describing monomer preparation via MCRs and subsequent polymerization thereof were reported. The most important landmark in the area of MCRs in polymer chemistry was established by the group of Meier in 2011 [61]. Briefly, they demonstrated that the Passerini-3CR could be successfully employed for monomer preparation, step-growth polymerization, and post-polymerization functionalization. Along with the successful demonstration by the group of Meier, the striking utility of the Passerini-3CR was further demonstrated by other research groups [62]. In addition to successful use of MCRs in polymerization techniques, Li et al. utilized Passerini-3CR for sequence-controlled polymer synthesis [63], which is recognized as an important scientific subject, as recently emphasized by Lutz and coworkers [64–66]. In addition to the Passerini reaction,



Scheme 3 Kabachnik–Fields post-polymerization modification reaction

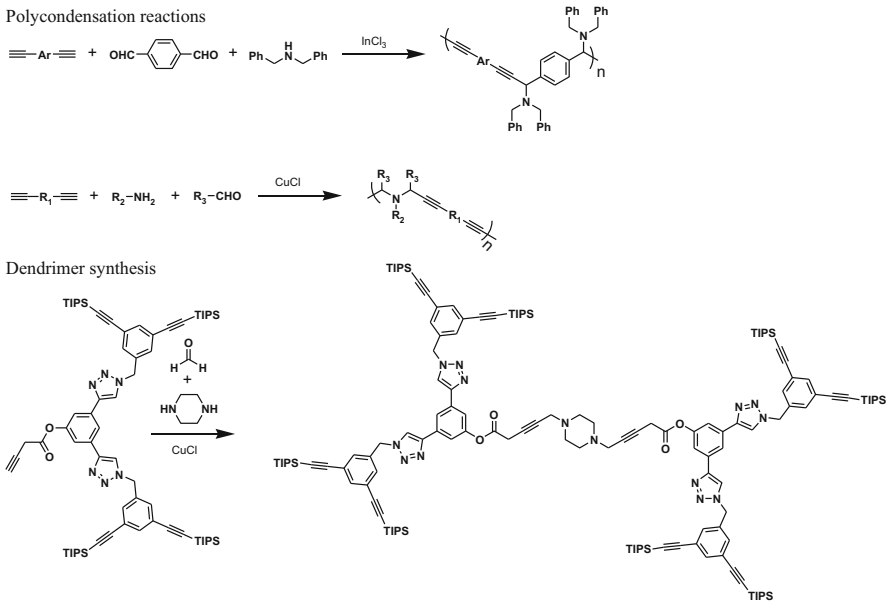
the Ugi four-component reaction (Ugi-4CR) was employed for polymer synthesis independently by the Meier and Tao groups [67, 68]. Because this chapter deals with MC- MCRs, research based on IMCRs such as Passerini and Ugi reactions are not discussed in detail. For precise discussions on the synthetic possibilities of IMCRs, in another chapter of this book Sehlinger and Meier describe recent advances in polymer chemistry based on IMCRs such as the Passerini and Ugi reactions [69].

To furnish a convenient reaction platform, polymer chemists have explored the utility of non-isocyanide-based MCRs in order to avoid the use of isocyanides. For example, Tao and coworkers focused intensively on the employment of non-isocyanide MCRs such as the Biginelli reaction [70] and the three-component reaction between aldehydes, amines, and mercaptoacetic acid [71]. In addition, the utility of the Kabachnik–Fields reaction was demonstrated independently by the groups of Theato [72] and Tao [73]. To be precise, Kakuchi and Theato showed that the Kabachnik–Fields post-polymerization modification reaction on poly(4-vinyl benzaldehyde) with amines and phosphites proceeded very efficiently to afford polymers featuring α-amino phosphonate pendant groups (Scheme 3) [72]. Furthermore, the group of Tao succeeded in synthesizing polymeric α-amino phosphonates via concurrent Kabachnik–Fields reactions of vinyl compounds and RAFT polymerization of the vinyl monomers in a one-pot process [73].

Despite the above-mentioned pioneering studies of non-isocyanide MCRs, their diversity and applications are rather limited mainly because of the limited number of non-isocyanide MCRs. Therefore, there is a huge demand for research on the use of isocyanide-free MCRs in polymer chemistry because it would be beneficial to a variety of scientists.

4 Metal-Catalyzed MCRs in Polymer Chemistry

Considering the practical importance of isocyanide-free MCRs, metal-catalyzed multicomponent reactions (MC-MCRs) are ideal candidates for polymer synthesis. Among the growing number of MC-MCRs, the three-component reaction between amines, aldehydes, and acetylenes (A^3-coupling) should be addressed. A^3-coupling

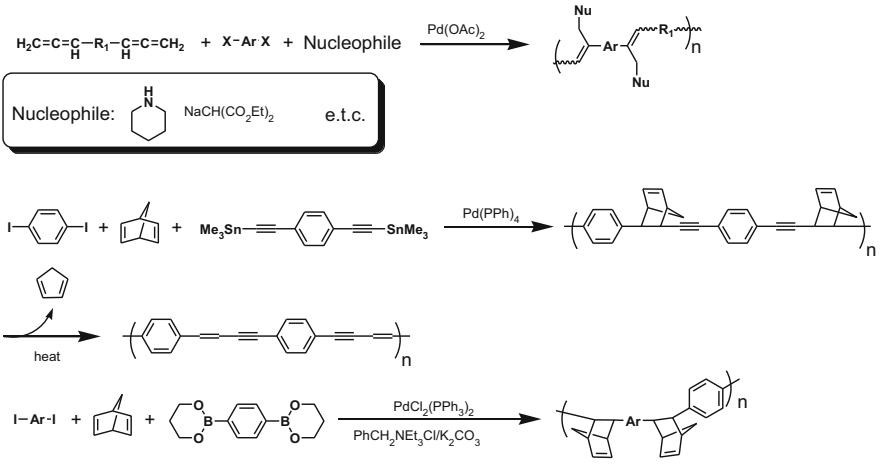


Scheme 4 Polymer synthesis based on A^3-coupling reactions

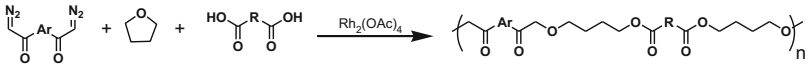
reactions accept various organo-metallic catalysts and thus provide a robust and reliable reaction platform (Scheme 4) [54]. In 2013, the group of Tang successfully employed an indium-catalyzed A^3-coupling reaction for the polycondensation of bisaldehydes, bisacetylenes, and *sec*-amines to afford the corresponding polymers without structural defects at high efficiency (Scheme 4) [74]. More recently, the group of Tang also succeeded in constructing polymers based on A^3-coupling polyaddition with a CuI catalyst (Scheme 4) [75]. Along with this successful demonstration by the group of Tang, the group of Kakkar demonstrated an A^3-coupling reaction for the synthesis of dendrimers, which they employed in biological applications (Scheme 4) [76].

In addition to the A^3-coupling reaction, additional MC-MCRs have been reported to produce polymers with unique properties (Scheme 5) [77–82]. The group of Endo has successfully shown that the palladium-catalyzed three-component reaction between bisallenes, aryl dihalides, and nucleophiles can afford the corresponding polymers with high efficiency and chemical selectivity (Scheme 5) [77]. For example, they conducted a three-component polycondensation reaction between 1,2,10,11-dodecatetraene, 4,4′-diiodobiphenyl, and sodium diethyl malonate in the presence of $Pd(OAc)_2$ and 1,2-bis(diphenylphosphino)ethane in 1,4-dioxane at 80°C for 2 days to afford the corresponding polymers with high molecular weight ($M_n = 1.1 \times 10^4$ g mol^{-1}) in practically quantitative yields (97%) [77]. Endo, Tomita and colleagues expanded this synthetic strategy to the preparation of π-conjugated polymers [79]. Specifically, they conducted a

Palladium catalyzed three component polycondensation reactions



Rhodium catalyzed three component polycondensation reactions



Scheme 5 Polymer synthesis based on palladium and rhodium catalyzed MCRs

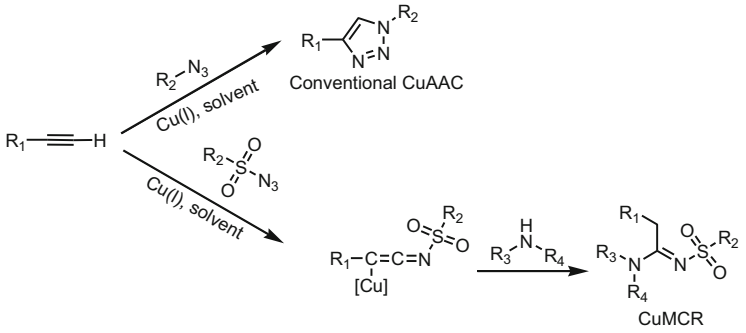
palladium-catalyzed three-component polycondensation reaction between 1,4-diallenylbenzene, 4,4′-diiodobiphenyl, and diethyl malonate salt to afford poly(arylene-vinylene) derivatives (Scheme 5) [79]. Interestingly, Tomita and Nakagawa employed this synthetic strategy to produce poly(*p*-phenylene-vinylene)s with highly ordered chiral structures via a palladium-catalyzed three-component reaction between *p*-bromophenylallene and sodium di-(–)-menthyl methylmalonate as the chiral source [82]. In addition to the above-mentioned reaction based on allene derivatives, a palladium-catalyzed three-component polycondensation was reported between *p*-diiodobenzene, norbornadiene, and organotin [80] or organo-boronate [81] reagents to afford the corresponding polymers with reasonable molecular weights (Scheme 5). Importantly, the obtained polymers were revealed to undergo thermal retro-Diels Alder reaction, affording fully conjugated polymers (Scheme 5). In 2011, the group of Ihara succeeded in a facile utilization of a rhodium-catalyzed three-component polycondensation reaction between bis(diazoketone) derivatives, dicarboxylic acids, and THF in the presence of $Rh_2(OAc)_4$ to produce poly(ester ether ketone)s with moderate molecular weights (up to $M_n = 2.5 \times 10^4$ g mol^{-1}) (Scheme 5) [83].

5 The Evolution of Click Chemistry: From CuAAC to Multicomponent Reactions

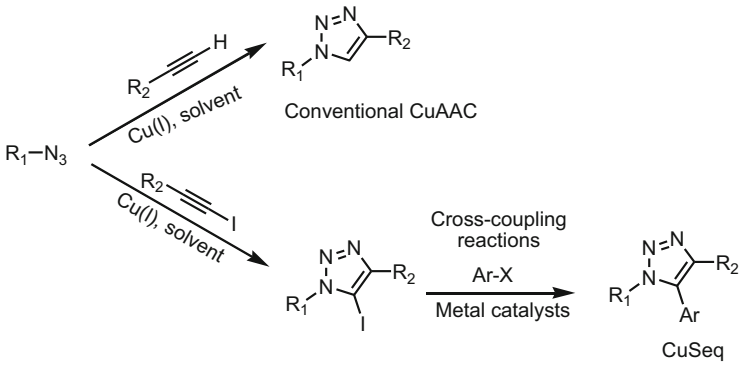
The reaction between organo-azides and alkynes, called the Huisgen cycloaddition reaction, was reported many years ago [84]. However, intense attention has been given to this reaction only recently. In 2001, the groups of Fokin and Sharpless [85] and Meldal [86] independently discovered that a catalytic amount of Cu(I) drastically increased the reactivity and regioselectivity of the reaction. This discovery sparked intensive efforts on the integration of CuAAC in interdisciplinary research.

Along with application of CuAAC in many research fields, increasing attention has been given to an innovation of CuAAC itself [55, 87–89]. The reaction between organo-azides and alkynes is known to proceed via a [3 + 2] cycloaddition reaction pathway affording 1,2,3-triazole compounds as products. Chemical modification of 1,2,3-triazole is promising because the triazole structure possesses three successive nitrogen atoms and is expected to be chemically unstable because of the possibility of N_2 being released from the structure [90]. Therefore, many organic chemists have been devoting themselves to innovations in CuAAC, while interdisciplinary scientists have been focusing on applications of CuAAC in many research fields [91].

In 2005, the group of Chang reported a very important reaction in which the reaction mode of CuAAC could be fine-tuned through reaction design [55]. To be precise, the Cu(I)-catalyzed cycloaddition reaction between terminal alkynes and sulfonyl azides was revealed to produce ketenimine species via nitrogen release from the in-situ generated 1,2,3-triazole derivatives (Scheme 6). Additionally, the generated ketenimine moiety was then nucleophilically trapped by co-existing amines in situ to yield *N*-sulfonylamidines with excellent conversions, regioselectivity, and tolerance towards co-existing functional groups (Scheme 6). Furthermore, in 2006, the group of Fokin also reported utilization of a similar CuMCR between terminal alkynes, sulfonyl azides, and water to produce amide



Scheme 6 Reaction modes of the reaction between organic azides and terminal alkynes



Scheme 7 CuAAC and the Cu(I)-catalyzed sequential type of multicomponent reaction

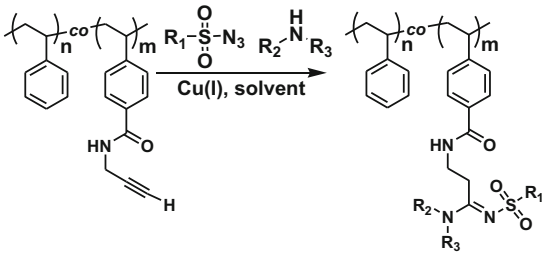
derivatives via ketenimine generation and subsequent ketenimine trapping by water [92]. Along with the successful three-component reaction between terminal alkynes, sulfonyl azides, and amines (CuMCR), the group of Chang intensively explored new reactant partners for ketenimines and has proposed a new class of MCRs [88, 89]. Notably, both sulfonyl azides [93] and terminal alkynes are readily available. Thus, CuMCR is easy to conduct even by non-experts because none of the components (alkynes, amines, sulfonyl azides, and copper catalysts) have to be synthesized.

In addition to one-pot and one-step CuMCRs, a new class of CuAACs comprising sequential reactions between 1-iodo alkynes and organic azides, followed by metal-catalyzed cross-coupling reactions on the generated 5-iodo 1,2,3-triazole moieties (CuSeq), was developed [94]. In 2009, the group of Fokin reported that 1-iodo alkynes can participate in CuAAC reactions in the presence of copper catalysts in the same manner as terminal alkynes (Scheme 7) [94]. The generated 5-iodo 1,2,3-triazole derivatives behaved similarly to iodo-aromatic compounds, allowing further chemical modification of 5-iodo 1,2,3-triazole derivatives using metal-catalyzed cross-coupling reactions such as the Suzuki–Miyaura cross-coupling reaction (Scheme 7) [60]. It is worth noting here that a number of reactants for CuSeq are readily available because of the well-established cross-coupling reactions, including not only the Suzuki–Miyaura cross-coupling reaction but also the Heck reaction, the Sonogashira reaction, and the Still reaction [58, 59, 95]. In addition, CuMCR and CuSeq are completely free from the use of isocyanides, making them ideal candidates for use by non-experts.

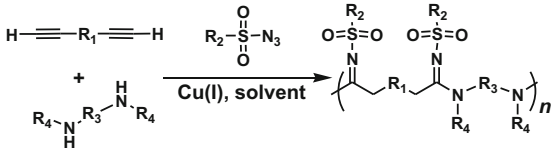
6 Integration of Cu-Catalyzed Multicomponent Reactions into Polymer Chemistry

As mentioned previously, the integration of highly efficient and reliable modification reactions into polymer chemistry has been a long-lasting and highly demanding goal. Based on the happy marriage of CuAAC and polymer chemistry, the employment of CuMCRs (a different reaction mode of CuAAC) in polymer chemistry seems natural (Scheme 8). In 2013, the group of Theato validated the synthetic utility of CuMCR for post-polymerization modification of polymers featuring acetylene moieties with amines and sulfonyl azides in the presence of a catalytic amount of $Cu(PPh_3)_3Br$ (Scheme 8) [96]. In addition to the post-polymerization modification reaction, the group of Choi proposed a new polycondensation reaction by using CuMCR [97]. The three-component polycondensation of diamines, bis-terminal alkynes, and sulfonyl azides was conducted in DMF in the presence of 10 mol% Cu(I)Cl at 70°C to afford polymeric *N*-sulfonylamidines, whose molecular weights reached 7.5×10^4 g mol^{-1} (Scheme 8). These examples clearly show the advantages of CuMCRs in polymer synthesis because of the high efficiency and reliability of the reaction with a broad variety of compounds and practically no structural defects in the obtained polymers. As a direct consequence

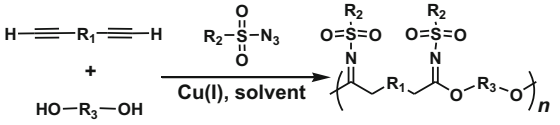
Post-polymerization modification



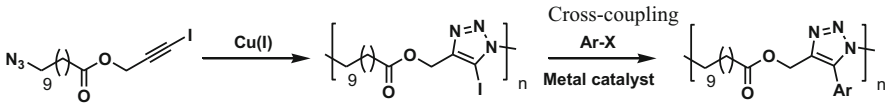
CuMCR polycondensation affording polymeric *N*-sulfonylamidines



CuMCR polycondensation affording polymeric *N*-sulfonylimidates



Scheme 8 Polymer synthesis based on CuMCR



Scheme 9 Polymer synthesis based on CuSeq

of the mechanism of the CuMCR, applicable nucleophiles are not limited to amines. Under basic conditions, alcohols are also known to behave as facile nucleophiles in Cu-catalyzed three-component reactions between sulfonyl azides, terminal alkynes, and nucleophiles [87]. In 2014, the group of Choi employed CuMCR between sulfonyl azides, terminal alkynes, and alcohols for a step-growth polymerization, essentially affording polymeric *N*-sulfonylimidates (Scheme 8) [98]. They succeeded in synthesizing poly(*N*-sulfonylimidates) featuring diverse functional units by simply changing the chemical structure of the starting materials. It is worth emphasizing here that CuMCR proceeds via a reaction mode different to that of CuAAC. Thus, it is possible to re-use and take advantage of the reactants used in CuAAC (i.e., organo-azides and terminal alkynes), making CuMCR a promising candidate for a wide range of applications.

Not only CuMCR but also CuSeq were successfully integrated into polymer chemistry [99]. In 2011, the group of Fokin demonstrated the striking utility of CuSeq in polymer synthesis (Scheme 9). They demonstrated that the CuAAC polyaddition reaction of a monomer featuring azide and 1-iodo alkyne moieties within a single monomeric structure afforded polymeric 5-iodo 1,2,3-triazole derivatives. The obtained polymeric 5-iodo triazole derivatives were further modified via metal-catalyzed cross-coupling reactions including the Suzuki–Miyaura and Heck reactions, which successfully afforded functionalized polymers via sequential modifications [99]. Thus, the synthetic utilities of CuMCRs and CuSeq can provide not only polymer chemists but also a range of interdisciplinary scientists with a useful and highly efficient synthetic toolbox, with which functional polymers are accessible starting from readily available compounds without time-consuming chemistries.

7 Summary and Outlook

The advantages of metal-catalyzed MCRs include not only their broad compatibility with various functionalities and high reliability of reaction yields, but also easy handling of reactions. In addition, MCRs allow chemists to install two or more functionalities into polymer structures simultaneously. Metal-catalyzed MCRs are in most cases free from isocyanides, which is crucially advantageous for non-experts who wish to employ MCR-based functionalization techniques. This particular advantage of MCRs over classical click reactions should be addressed in the field of polymer chemistry. Although a number of metal-catalyzed MCRs have

been reported, only a few examples are gradually becoming integrated into polymer chemistry and only very recently. In this context, the combination of metal-catalyzed MCRs and polymer synthesis has just initiated the first scientific contact. I believe that a number of MCRs will become integrated into polymer chemistry, which should lead to a new generation of polymer syntheses.

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Adv Polym Sci (2015) 269: 17–42
DOI: 10.1007/12_2014_303

Published online: 8 February 2015

Multicomponent Polymerization of Alkynes

Rongrong Hu and Ben Zhong Tang

Abstract Multicomponent reactions (MCRs) are a group of unique reactions with a number of advantages such as atom economy, high efficiency, and simple procedure. These convenient reactions, especially MCRs based on alkyne monomers, are widely studied and extensively reported. However, polymerization methods based on MCRs of alkynes have rarely been developed to benefit the preparation of macromolecules. In this paper, up-to-date progress in the development of multicomponent polymerizations (MCPs) based on alkyne monomers is summarized, including MCP of alkynes, aldehydes and amines; MCP of alkynes, azides and amines/alcohols; and multicomponent tandem polymerization of alkynes, carbonyl chloride and thiols. Efforts in monomer screening, polymerization condition optimization, and structural characterization of the resultant polymer have generated a series of functional polymer materials with fascinating properties such as aggregation-induced/enhanced emission, light refractivity, photopatternability, and magnetism.

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Keywords Multi-component polymerization · Tandem polymerization · Alkyne polymerization · Aggregation-induced emission

Contents

1 Introduction

Multicomponent reactions (MCRs) have attracted much attention in the past decade because of advantages such as high atom economy, simple procedure, and high efficiency. [1] Because of their ability to generate complex structures economically and efficiently [2], numerous MCRs have been developed and widely studied, such as the Cu-catalyzed three-component reactions [3–6], Mannich reactions [7, 8], Passerini reactions [9, 10], and A3-coupling reactions [11]. Of these, multicomponent alkyne reactions have become quite popular recently and abundant literature has been published regarding the various MCRs of alkynes with all sorts of reactants [12, 13].

Most synthetic polymers have random structures because the preparation of regular polymers is difficult and requires skill-demanding techniques such as living polymerization. It is thus of great interest to develop programmable polymerization reactions for the synthesis of polymers with well-defined structures, ordered sequences of monomer units, unique material properties, and potential practical applications [14]. Because of the high efficiency and well-defined product structure of the convenient MCRs, multicomponent polymerizations (MCP) are highly desirable for the synthesis of a wide range of polymer structures that are difficult to obtain by other methods [15]. However, the development of MCPs is challenging because of their narrow monomer scope, low conversion, low molecular weight (M_w) polymer products, low solubility, and various side reactions that can lead to defects in the polymer structure [16]. Despite all the difficulties, scientists have made great endeavors to developed efficient MCPs. For example, Li and colleagues reported step-growth polymerization of a dialdehyde, a diisocyanide, and a carboxylic acid with various functionalities in a mild, clean, and simple process without protection-deprotection procedures [17]. Such a one-pot Passerini reaction can easily afford polyamides with various functional side groups. Later, the same group reported the first example of four-component polymerization of a dicarboxylic acid, a dialdehyde, a diisocyanide, and a monocarboxylic acid for the preparation of highly branched functional polymers [18]. Another efficient and

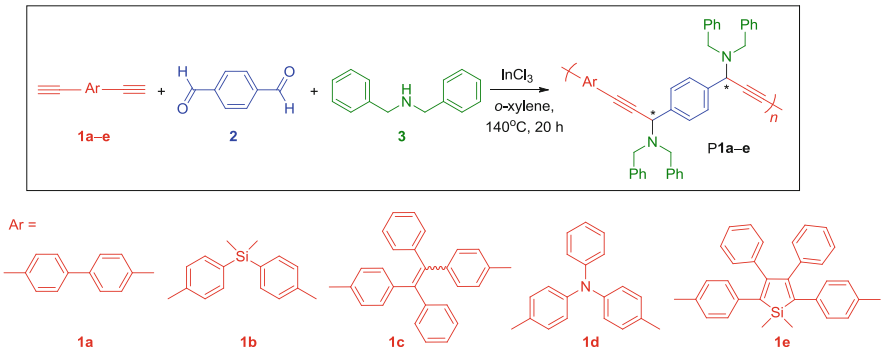
modular approach was reported by Meier and coworkers for the preparation of diversely substituted polyamides. Four-component Ugi polymerizations of isocyanohexanes, aldehydes, acids, and amines were realized from two bifunctional and two monofunctional monomer components with six different monomer combinations [19].

Alkyne-based MCPs are rarely reported, despite the rich chemistry of alkynes. Compared with traditional polymers, polymers prepared from alkyne monomers generally contain a conjugated polymer backbone and hence possess optoelectronic properties, enabling advanced functionalities of the polymer materials. However, their rigid structure can lead to poor solubility and limit the exploration of efficient polymerization methods [20]. In this review, the most up-to-date progress in the development of alkyne-based MCPs is introduced, including MCPs of alkynes, aldehydes, and amines; MCPs of alkynes, azides, and amines/alcohols; and multicomponent tandem polymerization of alkynes, carbonyl chloride, and thiols.

2 Multicomponent Polymerization of Alkynes, Aldehydes, and Amines

Of the many MCRs, the transition-metal-catalyzed reaction of an alkyne, aldehyde, and amine is a representative example [21]. Recently, Wang and coworkers reported an efficient indium-catalyzed A3-coupling. Through C–H bond activation, the reaction proceeded smoothly to afford the corresponding product in nearly quantitative yield, atom-economically without any cocatalyst or activator [22]. Attracted by the advantages of this MCR, the potential of developing the three-component coupling reaction of alkyne, aldehyde, and amine into a versatile alkyne-based polymerization technique was explored for the synthesis of novel polymers with structural regularity and advanced functionality [23].

A group of functional diynes **1a–e** were used to explore one-pot A3-coupling polymerizations with commercially available terephthalaldehyde **2** and dibenzylamine **3** (Scheme 1). In particular, tetraphenylethene (TPE)-containing diyne **1c** and dimethyltetraphenylsilole (DMTPS)-containing diyne **1e** were designed because TPE/DMTPS core structures are well-known fluorophores with unique aggregation-induced emission (AIE) characteristics. Such propeller-shaped luminogenic molecules as TPE and hexaphenylsilole (HPS) are nonemissive in solution but emit intensely in the aggregated state [24]. In solution, the intramolecular rotation of AIE compounds serves as a nonradiative pathway for the decay of excitons. In the aggregated state, such rotation is restricted, which blocks the relaxation channels and thus turns on the light emission of the luminophore [25]. Integration of an AIE moiety into the monomer structure endows the resultant polymer with AIE or aggregation-enhanced emission (AEE) features [26]. Meanwhile, the twisted structure of TPE or HPS significantly inhibits the close packing of the polymer chains and enlarges the intermolecular distance, resulting in satisfactory solubility of the polymer product.



Scheme 1 Indium-catalyzed polycoupling of diynes **1a–e**, dialdehyde **2**, and secondary amine **3**

The MCP of diynes **1a**, terephthalaldehyde **2**, and dibenzylamine **3** was first carried out in the presence of indium(III) chloride at high temperature for 20 h under inert atmosphere. The polymerization conditions, including solvent, temperature, and concentration of catalyst and monomers, were optimized. The solvent exerts a strong effect on the reaction. Of the tested solvents, benzene, 1,2-dichloroethane, and toluene afforded satisfactory results, whereas acetonitrile and 1,4-dioxane produced poor polymerization results. *o*-Xylene was the most suitable medium for the polycoupling reaction, giving a soluble polymeric product with the highest molecular weight (17,400 g/mol) in 99% yield. Temperature also plays an important role in this MCP. Only when the reaction temperature was close to the boiling point of *o*-xylene, at about 140°C, could high M_w polymer be obtained. Furthermore, the catalyst loading ratio and monomer concentration were optimized at $[InCl_3] = 0.013$ M, $[\mathbf{1}] = [\mathbf{2}] = 0.067$ M. A slight excess of **3** with a concentration of 0.147 M afforded a soluble polymer in 97% yield with M_w of 19,500 g/mol and polydispersity index (M_w/M_n) of 2.5. All polymerizations of other monomers **1b–e** also proceeded smoothly under the optimized conditions, giving polymers P**1b–e** in high yields (up to 95%) with high M_w (up to 51,200 g/mol).

Model compound **4** (Fig. 1) was synthesized to assist characterization of the polymer structure. In the IR spectra, the absorption bands at 3,237, 1,693, and 3,326 cm^{-1}, associated with the ≡C–H, C=O, and N–H stretching vibrations of the monomers, respectively, were absent in the spectra of **4** and P**1a**. Similarly, three new peaks emerged at δ 4.96, 3.81, and 3.57 in the ^{1}H NMR spectra of **4** and P**1a**, associated with resonance of the methylene protons next to the nitrogen atom. The resonances of the alkyne proton of **1a**, aldehyde proton of **2**, and amine proton of **3** at δ 3.14, 10.14, and 3.74, respectively, were not present, suggesting that the alkyne, aldehyde, and amine functional groups were completely consumed and that the polymerization had taken place (Fig. 1). In the ^{13}C NMR spectra, no resonance peak of a carbonyl group could be observed and new peaks representing the methylene carbons next to the nitrogen atom emerged, demonstrating the desired structure of the polymer.

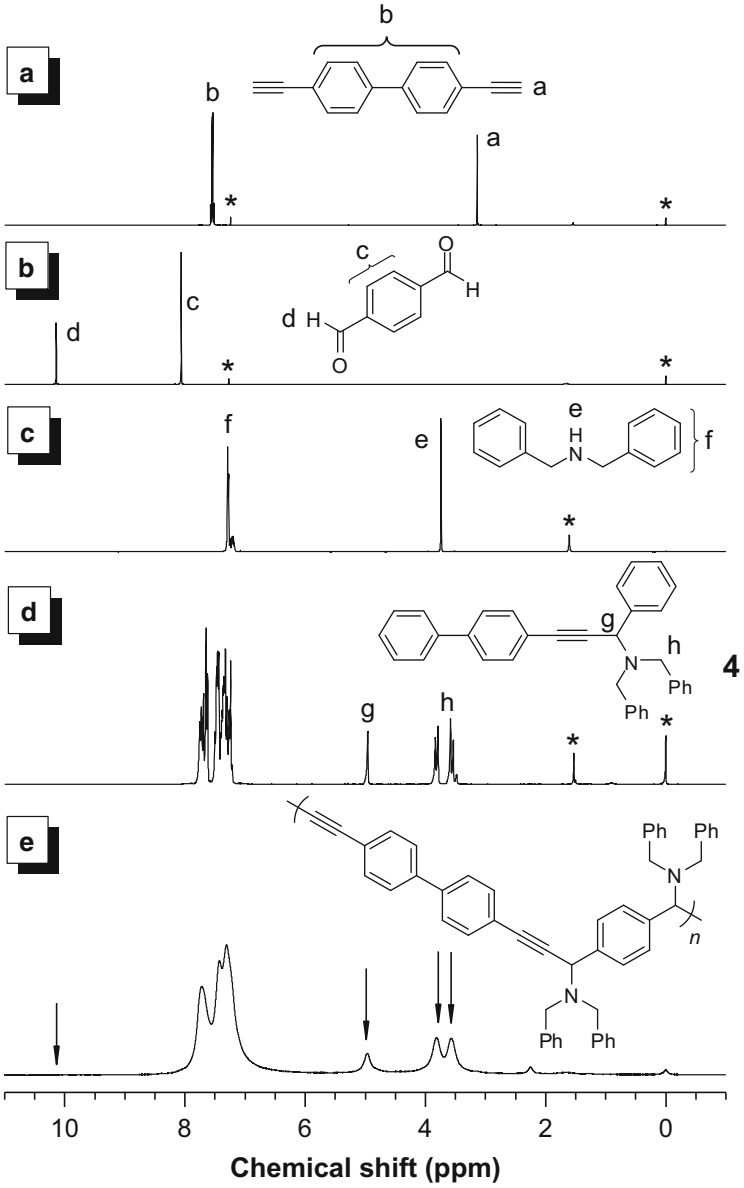


Fig. 1 ^{1}H NMR spectra of (**a**) **1a**, (**b**) **2**, (**c**) **3**, (**d**) **4**, and (**e**) P**1a** in deuterated chloroform. The solvent peaks are marked with asterisks

P**1a–e** possess good solubility in normal organic solvents, including dichloromethane, chloroform, tetrahydrofuran (THF), and dioxane. They also enjoy high thermal stability with 5% weight loss at 249–281°C and carbonize in moderate yields of up to 50%, even when heated to 800°C. Moreover, they can be

readily prepared as tough thin films by spin-coating or static-casting processes. The polymers generally consist of polarizable aromatic rings, acetylene units, and heteroatoms; their thin films thus exhibit large refractive index (RI) values of up to 1.7443−1.6200 in the visible to IR region, which are higher than those of conventional polymers such as polystyrene, poly(methyl methacrylate), and polycarbonate [27]. Their low optical aberrations, high optical transparency, and light refractivity enable these polymers to find technological applications as coating materials in advanced optical display systems [28].

The photophysical properties of P**1a–e** were also studied. The absorption spectra of P**1a–e** peaked at 301–377 nm and their photoluminescence (PL) spectra in dilute THF solution peaked at 385–509 nm. Conventional luminescent polymers generally suffer from strong interchain interaction in the aggregated state, which quenches and shifts their light emission bathochromically [29]. P**1c** and P**1e** with AIE-active moieties embedded in the polymer backbone behave differently. As shown in Fig. 2a, b, P**1c** emitted a bluish-green light at 503 nm in dilute THF solution. Gradual addition of water, a poor solvent of the polymer, into its THF solution progressively enhanced its emission, with little change in the spectral profile. The fluorescence quantum yields of the solution and solid thin film state of P**1c** were 1.5% and 14.3%, respectively, demonstrating an AEE feature. A similar phenomenon was observed for P**1e** (Fig. 2c, d) except that when the water content was above 80 vol%, the suspension of P**1e** became unstable and large precipitates were formed, which lowered the effective concentration of the solution and, hence, the PL intensity. In contrast to the small-molecule AIE compounds, the TPE/silole units are linked together by covalent bonds in the polymer structures, which partially restrict their intramolecular rotation and therefore render the polymers faintly emissive in THF solutions.

There are plenty of internal C≡C bonds in the polymer backbones of P**1a–e**, which can serve as versatile ligands in organometallic chemistry. These triple bond-containing polymers can thus be readily metallified through complexation with organometallic compounds [30, 31]. When P**1a–e** were treated with octacarbonyldicobalt at room temperature, cobalt-containing polymers P**2a–e** were obtained, whose chemical structures were confirmed by IR spectra (Scheme 2). For P**2a**, for example, strong bands of typical cobalt carbonyl absorption peaks appeared at 2,089, 2,051, and 2,025 cm^{-1} in the IR spectrum, indicative of the integration of metallic species into the polymer structure at the molecular level. The organometallic polymers P**2a–e** could be further pyrolyzed at 1,000°C under nitrogen to furnish magnetic ceramics MC**a–e** containing nanoscopic cobalt species. The nanostructured ceramics MC**a–e** generally possessed high saturation magnetization (M_s) and low hysteresis loss. MC**a**, with the highest content of ferromagnetic Co nanocrystallites, possessed the highest M_s value of 81 emu/g, which is impressively high considering that the M_s value of maghemite is 74 emu/g (Fig. 3) [32].

When the catalyst and reaction conditions of the MCRs are altered, even with the same functional groups of the monomers, totally different product structures can be acquired. The above-discussed indium-catalyzed three-component polymerization is limited by the expensive $InCl_3$ catalyst and harsh polymerization conditions; the

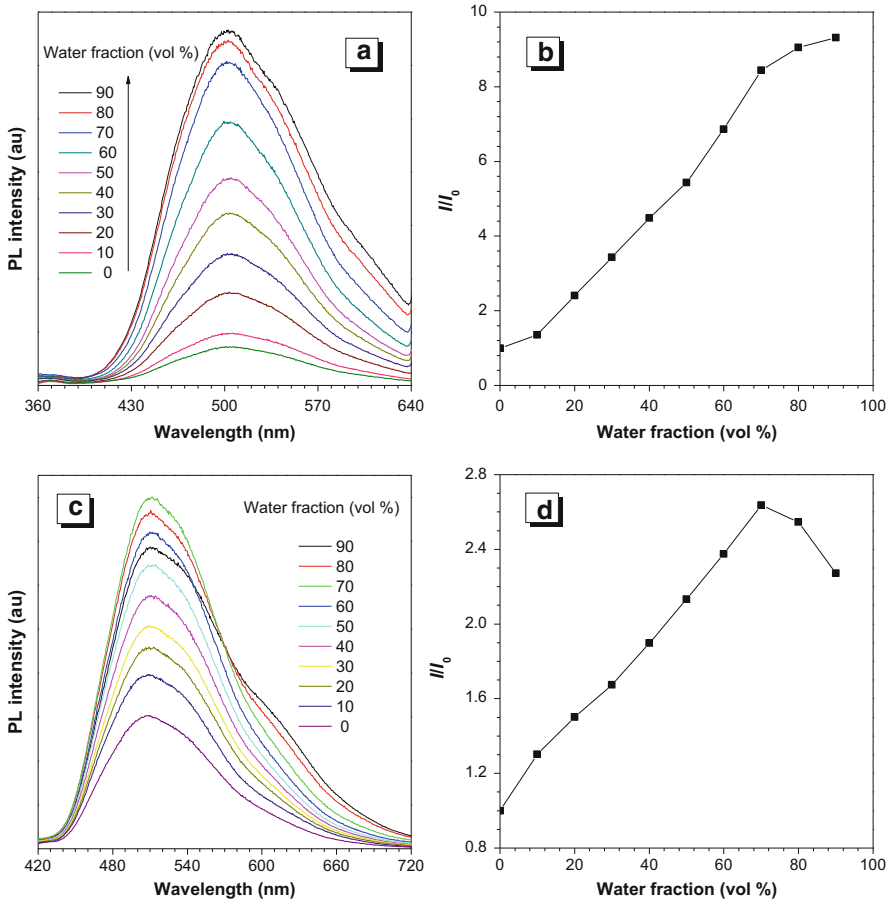
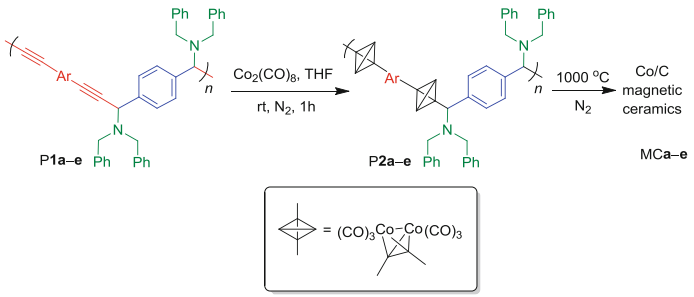


Fig. 2 PL spectra of (**a**) P**1c** and (**c**) P**1e** in THF and THF/H_2O mixtures with different water fractions. Plots of relative PL intensity (I/I_0) values versus the water fraction of the aqueous mixtures of (**b**) P**1c** and (**d**) P**1e**. Concentration 10^{-5} M; excitation wavelength 335 nm (P**1c**) and 380 nm (P**1e**)

reaction only proceeds efficiently at a high temperature of 140°C and a long reaction time of 20 h. In 2012, Uhlig and Li reported the copper-catalyzed A3-coupling reaction of alkyne, amino acid, and aldehyde under ambient aqueous conditions, generating dipropargylated products in high yields [33]. This reaction shows great superiority in terms of its mild reaction conditions and no requirement for costly catalyst or additive and has therefore been developed into an efficient polycoupling of diynes, amines, and aldehydes [34].

As shown in Scheme 3, diyne monomers **5a–f** were designed to react with a series of commercially available amines and aldehydes. The polymerization of diyne **5a**, L-phenylalanine methyl ester hydrochloride **6**, and formaldehyde **7** was first investigated and the effects of solvent, temperature, time, concentration,



Scheme 2 Complexation with cobalt carbonyls and ceramization to produce magnetic ceramics MC**a–e**

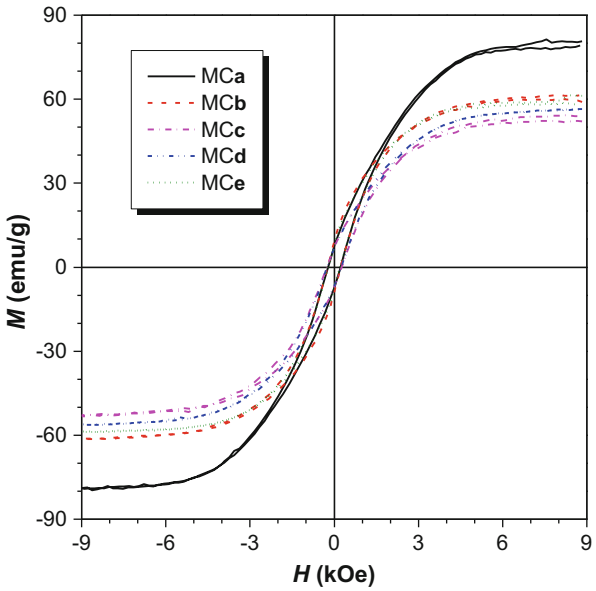
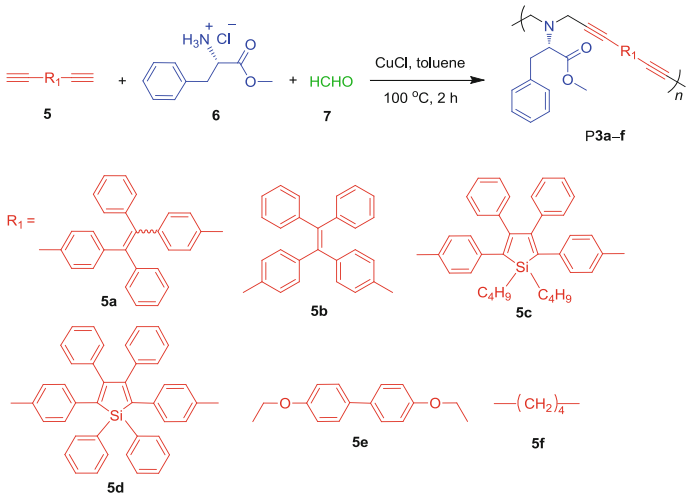


Fig. 3 Plots of magnetization (M) versus applied magnetic field (H) at 298 K for magnetic ceramics MC**a–e**

copper catalysts, and monomer structures on the MCP were evaluated. It is worth mentioning that the polymerization is moisture-tolerant and that **7** is utilized as an aqueous solution. Similarly to the indium-catalyzed MCP, this polymerization was strongly influenced by the solvent. Of the tested organic solvents, such as toluene, dimethylformamide, dioxane, methanol, ethanol, and THF, toluene provided the best polymerization result, affording P**3a** with a high M_w of 24,800 g/mol and a polydispersity index of 2.2. The temperature and time effects of this MCP were also studied. Both yield and M_w were enhanced when polymerization temperature was raised from 80°C to 100°C; however, further heating led to poor polymerization with a low M_w product. Reaction time did not have a significant effect on the M_w of



Scheme 3 Copper(I)-catalyzed polycoupling of diynes **5a–f**, amine **6**, and formaldehyde **7**

the polymer product, and time course studies suggested that 2 h of polymerization was enough to afford polymer with high M_w of 26,900 g/mol. Higher monomer concentration also improved the MCP, with better results in terms of both yield and M_w of the polymer product as a result of more efficient intermolecular collision between monomers. In addition, an array of copper salts were tested for their efficiency in catalyzing the A3-coupling polymerization. CuCl was the most efficient catalyst, probably as a result of the higher ionic character of CuCl than other copper salts such as CuI and $Cu(OAc)_2$ [35]. Last but not least, various monomer combinations of diynes, amines, and aldehydes were tested under optimized polymerization conditions and the MCPs generally proceeded smoothly. A few conclusions can be drawn regarding the monomer structures: (1) sterically more crowded diynes (**5b** and **5d**) normally generate lower M_w polymers than the less bulky monomers; (2) aromatic diynes show a higher polymerizability than their aliphatic counterparts (**5e** and **5f**); and (3) amines with a carboxylate group and phenyl group next to the amino group tend to be better monomers than the other amines.

To assist structural characterization of the resultant polymers, a model compound **8** was prepared (Fig. 4). In the IR spectra, the absorption bands stemmed from the ≡C–H and C≡C stretching vibration of **5a** and the amino functionalities of **6** were absent in the spectra of both **8** and P**3a**. Meanwhile, new bands representing C=O and C≡C stretching vibration appeared at 1,746 and 2,247 cm^{-1}, respectively, revealing the occurrence of the polymerization. Figure 4 depicts the ^1H NMR spectra comparison of monomers **5a** and **6**, model compound **8**, and polymer P**3a**. The acetylene proton of **5a** resonated at δ 3.04, but disappeared in the spectra of **8** and P**3a**. Instead, a new peak corresponding to the resonance of the methylene protons next to the triple bond functional group emerged at δ 3.88, confirming the desired product structure of the three-component reaction.

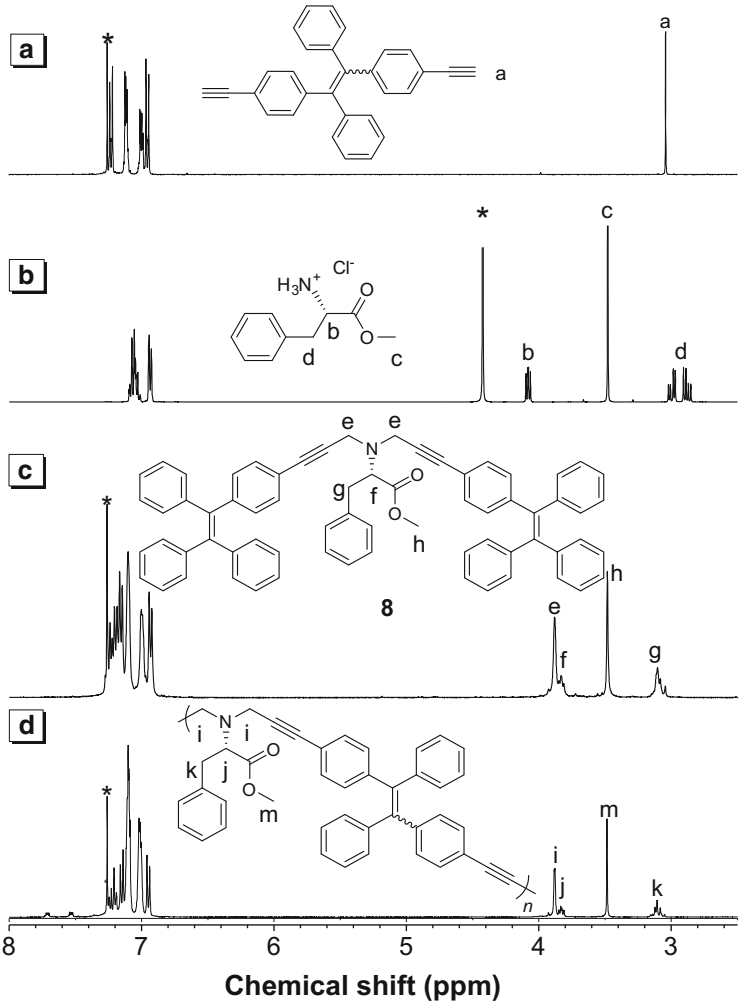


Fig. 4 ^{1}H NMR spectra of (**a**) **5a**, (**b**) **6**, (**c**) model compound **8**, and (**d**) P**3a** in $CDCl_3$ (**a**, **c**, and **d**) and D_2O (**b**). The solvent peaks are marked with asterisks

The TPE/silole-containing polymers P**3a–c** shared similar photophysical properties with the above-discussed polymers P**1c** and P**1e**. In dilute THF solution, the absorption spectra of P**3a–c** peaked at 350–395 nm. Polymers containing silole moieties displayed redder absorption maximum. When their THF solutions were photo-excited, P**3a–c** emitted green light at 505–527 nm, generally bathochromically shifted compared with P**1c** and P**1e**. Fluorescence photos of P**3a** in THF/water mixtures with different water contents suggest that P**3a** is AIE-active (Fig. 5a). The PL intensities of P**3a** and P**3c** became progressively stronger when more than 50% of water was added (Fig. 5b–d).

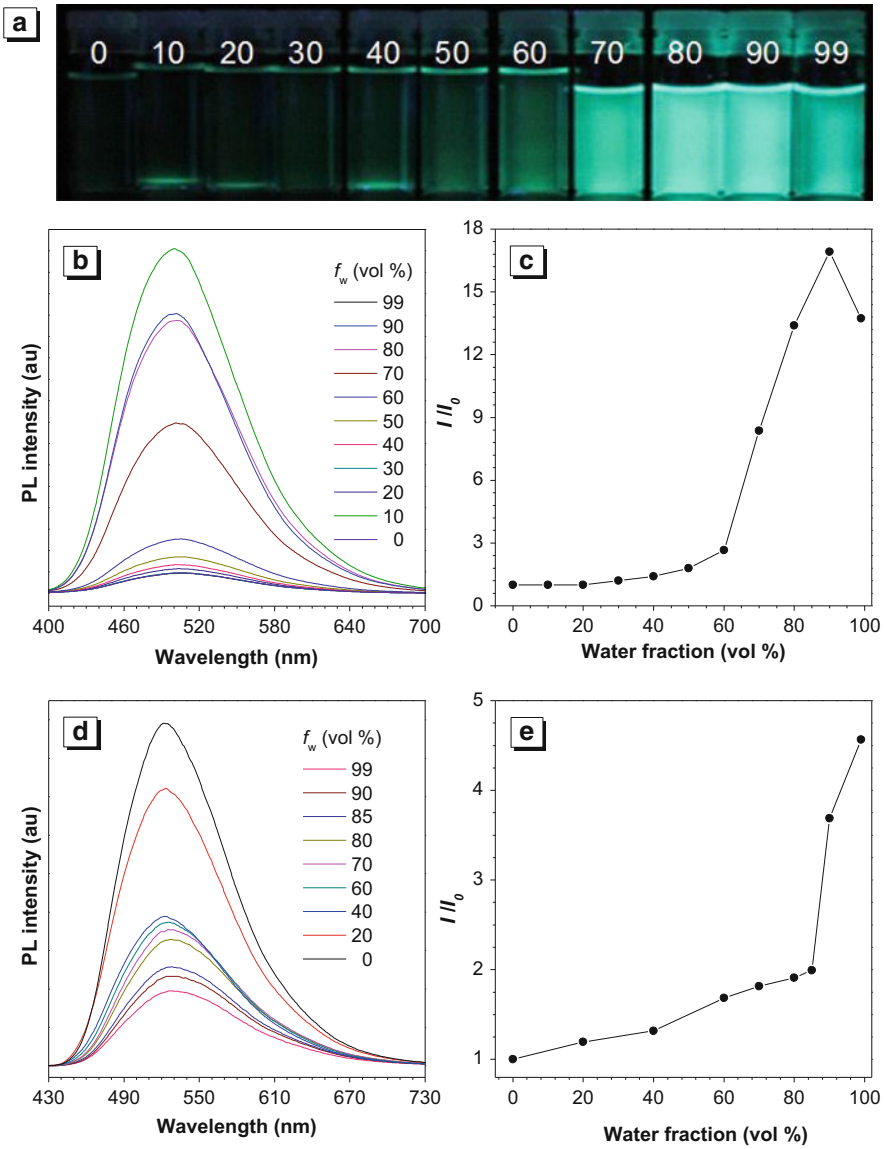


Fig. 5 (**a**) Fluorescence photos of THF/H_2O mixtures of P**3a** with different water fractions (f_w) taken under 365 nm UV irradiation. PL spectra of (**b**) P**3a** and (**d**) P**3c** in THF and THF/H_2O mixtures with different water fractions. Plot of relative PL intensity (I/I_0) values versus the water fraction of the aqueous mixtures of (**c**) P**3a** and (**e**) P**3c**. Concentration 10 μM; excitation wavelength 371 nm (P**3a**) and 395 nm (P**3c**)

Aqueous mixtures of P**3a** and P**3c** were visually transparent, suggesting that the polymer aggregates were of nanoscale size. Particle size analysis showed that the nanoparticles formed in THF/water mixtures of P**3c** possessed effective diameters ranging from 481 to 243 nm. When the water fraction was progressively increased, the particle size decreased accordingly. Most polymer chains aggregated quickly in the presence of a large amount of water, which condensed the nanoaggregates and produces nanoparticles of smaller size.

P**3a–d** could be fabricated into thin films by a facile spin-coating method. For polymers with aromatic rings, internal acetylene groups, and heteroatoms in the backbone, their thin films generally exhibited high refractivities with RI values of up to 1.8322−1.7458 in a wide wavelength region of 400–1,000 nm. Their low optical dispersion, combined with high refractivity, enables them to be used in an array of photonic applications such as coating materials and high-performance CMOS (complementary metal oxide semiconductor) image sensors [36]. Furthermore, taking advantage of the good film-forming ability, strong emission in the solid state, and photosensitivity of P**3a**, a well-resolved fluorescent pattern could be generated on a silicon wafer through UV irradiation behind a copper photomask. The exposed part of the film was photobleached and the unexposed part remained emissive under UV irradiation.

Fluorescent polymers with high emission in the aggregated state can also function as fluorescent chemosensors for sensitive detection of explosives. The emissive nanoaggregates of P**3b** in THF/water mixtures with 90 vol% water content were investigated as an example. The nanoaggregates possess many cavities to interact with explosive analytes and provide additional interchain diffusion pathways for excitons to migrate along. The detections of picric acid (PA), 2,4-dinitrotoluene (DNT), and 4-nitrobenzoyl chloride (NBC) were investigated through the fluorescence quenching of the nanoaggregates of P**3b** (Fig. 6). Excellent selectivity was obtained with the quenching constants of PA, DNT, and NBC, determined from the linear region of the Stern–Volmer plots to be 268,500, 100,800, and 9,300 L/mol, respectively. Of the three tested explosives, PA has the highest nitro group content (which should exert the strongest electron-withdrawing effect) and hence showed higher quenching efficiency than DNT and NBC.

The A3-coupling MCPs of alkynes, amines, and aldehydes represent a new programmable polymerization route for the synthesis of functional macromolecules. Such MCPs are efficient and widely applicable to a series of different monomer structures, generating polymers with high yields and good to excellent molecular weights.

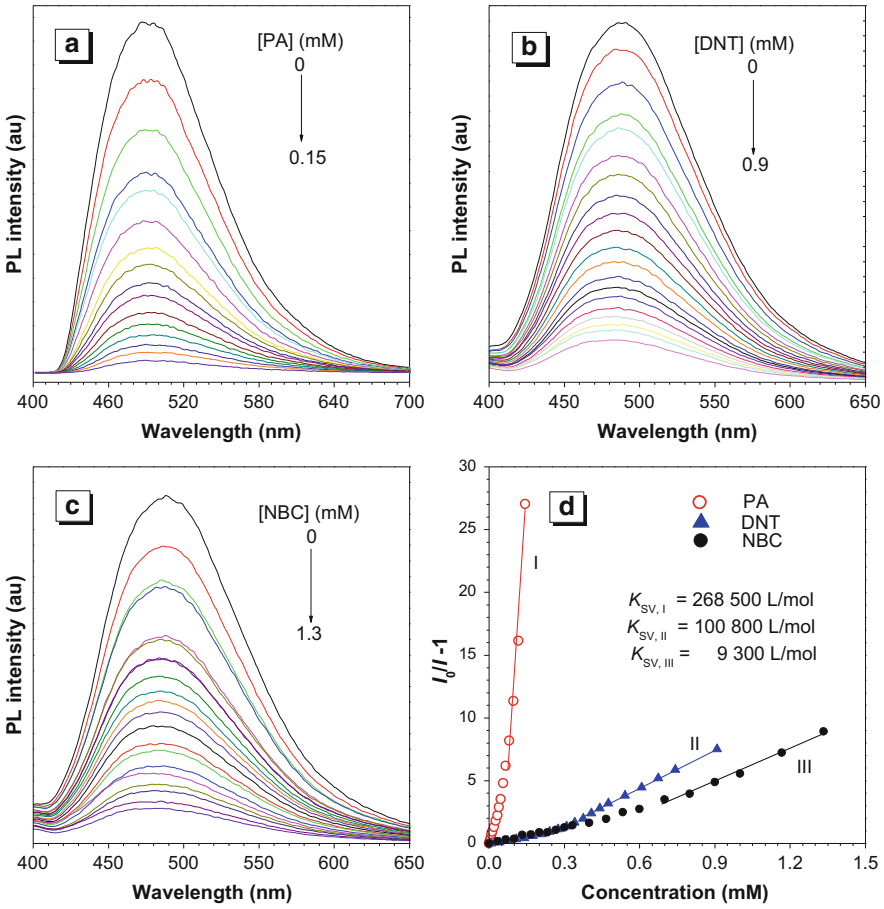


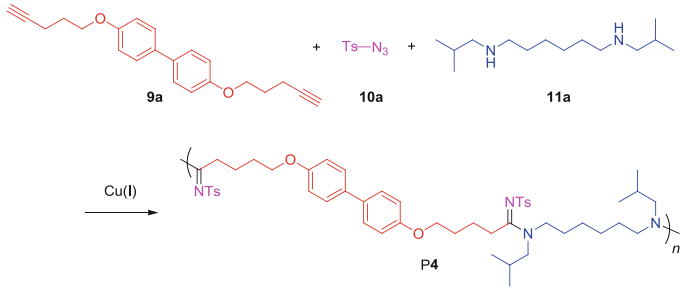
Fig. 6 PL spectra of P**3b** in THF/H_2O mixture (1/9 v/v) containing different amounts of (**a**) PA, (**b**) DNT, and (**c**) NBC. (**d**) Stern–Volmer plots of relative intensity ($I_0/I - 1$) versus the concentration of explosive. I_0 indicates the PL intensity in the absence of explosives

3 Multicomponent Polymerization of Alkynes, Azides, and Amines/Alcohols

With the rich chemical properties of alkyne monomers, polymers with rare and complicated structures can be designed and synthesized via alkyne-based polymerizations. For instance, polyamidines are a series of important polymers with potential roles as biomaterials, metallic conductors, and photosensitive semiconductors; their syntheses are limited to two-component, step-growth polymerization reactions [37, 38]. An efficient Cu-catalyzed MCR of alkynes, sulfonyl azides, and amines was recently reported by Chang and coworkers to afford a library of small-molecule amidines [3, 5]. The reaction undergoes a Cu-catalyzed azide–alkyne

cycloaddition, a successive ring-opening process followed by nucleophilic attack of the amine to produce amidines with high selectivity. This reaction was then developed by Choi and coworkers into MCP as a promising synthetic strategy for producing various polyamidine structures [39]. This versatile Cu-catalyzed MCP enables the synthesis of high M_w, defect-free poly(*N*-sulfonylamidines) from diynes, sulfonyl azides, and diamines.

Utilizing the optimal conditions reported for the small-molecule reaction, a model polymerization of diyne **9a**, *p*-toluenesulfonyl azide **10a**, and *N*,*N*′-diisobutyl-1,6-hexanediamine **11a** was carried out in THF solution at room temperature (Scheme 4). The solvent for the MCP was first screened at high temperatures. It was found that DMF was a better solvent than chloroform, 1,2-dichloroethane, and 1,4-dioxanes, although it is generally considered to be a poor solvent for MCRs of small molecules, probably as a result of high solubility of the polar poly(*N*-sulfonylamidines) in DMF [40]. Using the optimized high monomer concentration of 1.0 M, the stoichiometric balance between the diyne and the diamine was important for the polymerization. Excess *p*-toluenesulfonyl azide could be used to enhance the conversion of diyne **9a** without limiting the M_w of the polyamidine P**4**. Cu(I) catalysts and additives were then screened. Of all the tested copper catalysts, which generally show good activity, CuCl provided the best results. Organic amine additives such as tris(benzyltriazolylmethyl)amine, diisopropylethylamine, 2,6-lutidine, and triethylamine were tested. Triethylamine offered the best polymerization result with the highest M_w of 30,300 g/mol and a polydispersity index of 2.81. The addition of excess triethylamine was also found to be crucial in ensuring efficient MCP, for two possible reasons. First, protons are generated in each coupling reaction and the diamine monomers are protonated to form ammonium salts in the absence of an external base; these are poor nucleophiles that do not facilitate conversion. Excess amine reagent can circumvent this problem without interfering with the polymerization. Second, excess triethylamine can accelerate the formation of Cu-acetylide complex from the Cu(I) catalyst and a terminal alkyne, which is a key step in the polymerization. A possible side reaction is the conventional click reaction between the diyne and the monofunctionalized sulfonyl azide, which would produce chain end-capping groups and, hence,

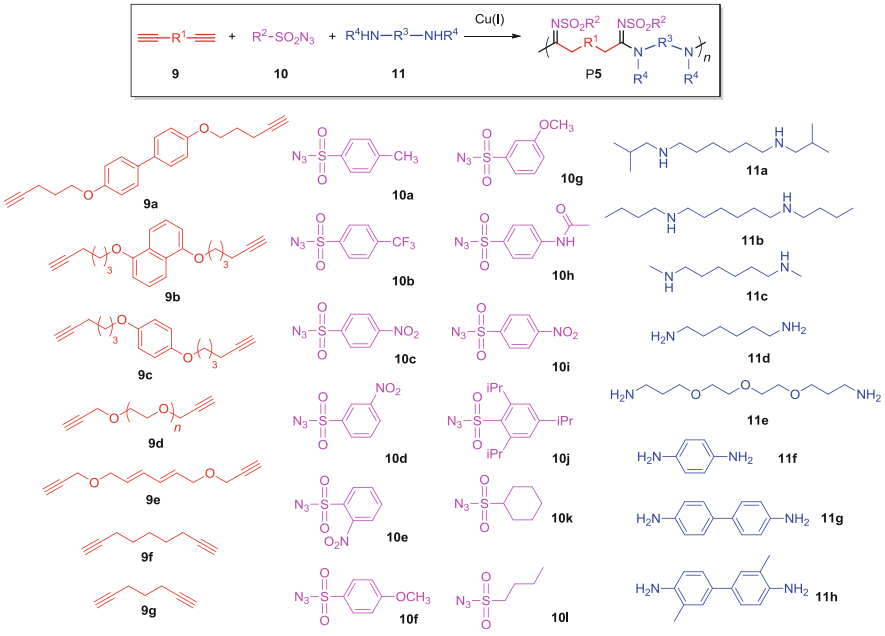


Scheme 4 Copper(I)-catalyzed multicomponent polymerization of diyne **9a**, p-toluenesulfonyl azide **10a**, and diamine **11a**

terminate the polymerization. ^{1}H and ^{13}C NMR analysis of the polymer structure confirmed that the MCP is highly selective for the MCR reaction over the conventional click reaction to generate P**4** with high M_w.

To expand the monomer scope of this MCP, a number of monomers were investigated under the optimal polymerization conditions (Scheme 5). Various diynes **9b–g** containing aromatic groups, ethylene glycol, diene, and alkyl groups were used instead of **9a** in the MCP and they all produced polyamidines with absolute molecular weights ranging from 22,400 to 63,900 g/mol, as determined by multiangle laser light scattering. Flexible diynes generally generated polymers with relatively low molecular weights and cyclic dimers/oligomers as contaminants. To suppress the possible cyclization side reactions, less flexible diyne (**9e**) or diyne with long spacer (**9d**) could be adopted. Furthermore, MCP from diynes containing highly rigid moieties such as biphenyl (**9a**), naphthyl (**9b**), and phenyl (**9c**) produced polyamidines with higher M_w and significantly smaller amounts of cyclic byproducts. By changing the rigidity or length of the diyne monomer, polyamidines with high M_w can be obtained.

Sulfonyl azides **10a–l**, including alkylsulfonyl azides and various phenylsulfonyl azides containing electron-donating/withdrawing groups or sterically hindered groups at different positions of the benzene ring, were also studied to examine the feasibility of this MCP. Polyamidines with high molecular weights were obtained, regardless of the substitution position, electronic nature, or steric hindrance of the substitutents on the phenylsulfonyl/alkylsulfonyl azides. Through



Scheme 5 Synthesis of various poly(N-sulfonylamidines)

this MCP, sulfonyl azides with diverse functional groups can be successfully introduced into the polyamidine structures.

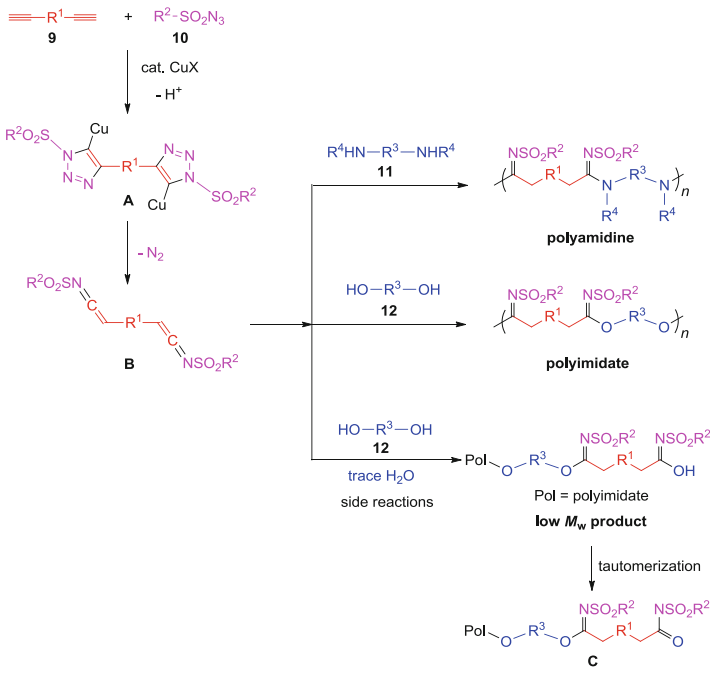
A variety of diamines to enrich the combination of monomers were also examined. Polymerization using primary dialkylamines (**11d–e**) and sterically demanding secondary dialkylamines (**11a–c**) successfully yielded polyamidines with absolute molecular weight of up to 67,200 g/mol. Surprisingly, diarylamines (**11f–h**) with much weaker nucleophilic ability than alkylamines also served as excellent monomers for this MCP, and the rigid monomer structure suppressed cyclization side-reactions.

The Cu(I)-catalyzed MCP facilitates the efficient synthesis of highly diverse polyamidines with high M_w from electronically and sterically varied diynes, sulfonyl azides, and diamines. Utilizing readily available or accessible monomers that are stable under the reaction conditions employed, this MCP can incorporate diverse moieties into the polymer backbone and overcome common limitations of MCPs such as low conversion and narrow substrate scope. One main advantage of this MCP is its high selectivity for the three-component reaction over the two-component click reaction, leading to defect-free polymer microstructures. Under optimal polymerization conditions, 26 well-defined polyamidines with high molecular weight were prepared from different monomer combinations, demonstrating the broad substrate scope of this methodology.

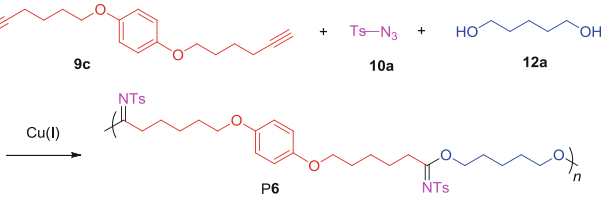
In this polymerization, the click reaction of diyne **9** and sulfonyl azide **10** first takes place to form triazole intermediate **A**. The highly reactive ketenimine species **B** is then formed via ring opening of the triazole **A**, followed by nucleophilic attack of diamine **11** to afford polyamidines (Scheme 6). The nucleophilic attack readily occurs regardless of the electronic and steric nature of the diamines, which provides a great opportunity for other nucleophiles such as diols to react. If diols are used as alternative nucleophiles instead of diamines in this MCP, polyimidates are formed instead of polyamidines.

Polyimidates are another interesting type of polymer because of their particular heat resistance and usage in resin materials [41]. However, only a few examples of polyimidates have been reported so far because the formation of imidate is quite challenging [42]. Traditionally, imidates are synthesized via two-component, step-growth polymerizations using diols and moisture-sensitive imidoyl chlorides [41]. Inspired by the successful preparation of a library of poly(*N*-sulfonylamidines) from diynes, sulfonyl azides, and diamines through Cu(I)-catalyzed MCP, Kim and Choi extended the MCP from diamines to diols and reported a versatile method for the preparation of poly(*N*-sulfonylimidates) by Cu(I)-catalyzed MCP from various diynes, sulfonyl azides, and diols [43]. Although diols are less nucleophilic than diamines, a number of polyimidates with diverse structures and high M_w can still be obtained.

The nucleophile diol **12a** was first polymerized with diyne **9c** and sulfonyl azide **10a** using the optimized conditions for the preparation of polyamidines. Nevertheless, the resulting poly(*N*-sulfonylimidates) did not have such high molecular weights as polyamidines obtained under the same conditions with DMF as solvent. The moisture-tolerance of the MCP with diols is not as good as that of the MCP

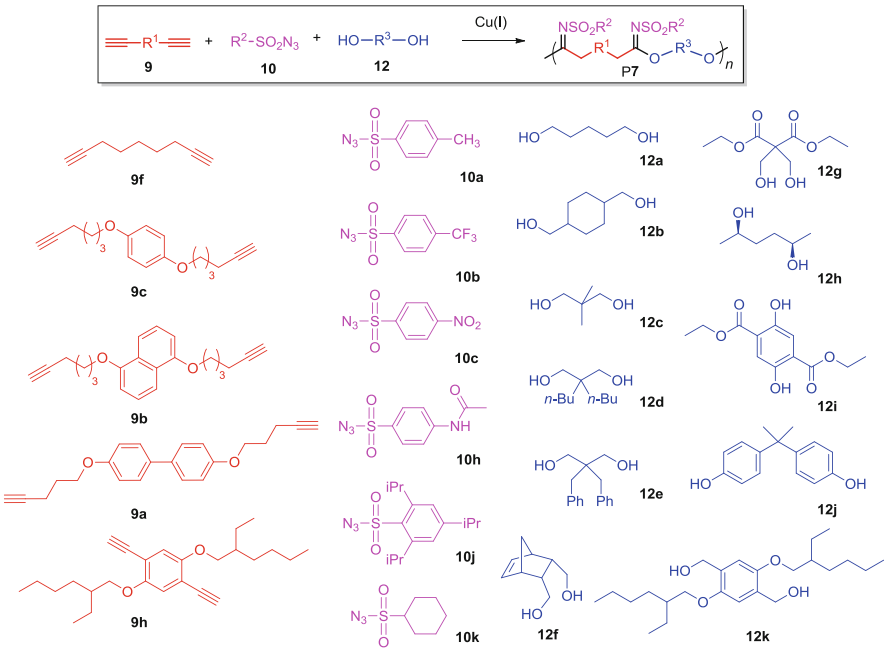


Scheme 6 Reaction pathways of copper(I)-catalyzed multicomponent polymerization of diynes **9**, sulfonyl azides **10**, and diamines **11** or diols **12**; **A** triazole intermediate, **B** ketenimine species, **C** N-sulfonyl amide



Scheme 7 Copper (I)-catalyzed multicomponent polymerization of diyne **9c**, sulfonyl azide **10a**, and diol **12a**

with diamines. The small amount of water in the hygroscopic polar aprotic solvent competes with the diols and terminates the polycondensations by forming *N*-sulfonyl amide **C** (Scheme 6). Dry solvent is necessary in this MCP to minimize the termination reaction. Solvent screening showed that chlorinated solvents, such as chloroform and dichloromethane, were the best solvents for polyimidate synthesis. The optimized polymerization was carried out using 10 mol% CuCl as catalyst in dichloromethane at room temperature in the presence of triethylamine as additive. Polyimidate with a M_w of 16,600 g/mol and a polydispersity index of 2.37 was successfully obtained although it took 2 days to complete (Scheme 7). ^{1}H and ^{13}C



Scheme 8 Synthesis of various poly(N-sulfonylimidates)

NMR spectra analysis suggested that the triazole byproduct, formed by click side reaction and terminating the polymerization, was not present. The triazole ring underwent a highly selective ring-opening reaction to produce the reactive ketenimine and eventually form polyimidates.

A large variety of diynes, sulfonyl azides, and diols were tested for this MCP and the monomer structures affected the polymerization in a similar way as in the above-discussed MCP with diamines (Scheme 8). Generally, rigid diynes or diols afforded polyimidates with higher molecular weight than those with flexible linkers, probably as a result of suppression of intramolecular cyclizations. However, the MCP of an even more rigid and reactive aromatic diyne (**9h**) was not able to afford polymer product with a high M_w, presumably because of severe steric hindrance. The structures of the arylsulfonyl azides did not have a significant effect on this MCP, and various polyimidates with moderate to high M_w of up to 33,500 g/mol could be obtained. Diol monomers **12a–k** containing primary alcohols; cyclic, bicyclic, and aromatic diols; and even secondary diols **12h** and phenolic monomers **12i–j** with weak nucleophilicity were suitable monomers for the polymerization, suggesting the excellent functional group tolerance and general applicability of this MCP. The resulting polyimidates generally had high thermal stability with decomposition temperatures ranging from 233°C to 307°C.

This polymerization has been used to achieve the facile and efficient synthesis of polyimidates. Compared with the above-discussed MCP with diamines, this MCP is inevitably limited by even a small amount of water contamination and its long reaction

time. The polymerization proceeds under mild condition and can be applied to a diversity of monomer structures, affording 24 different poly(*N*-sulfonylimidates) from various monomers.

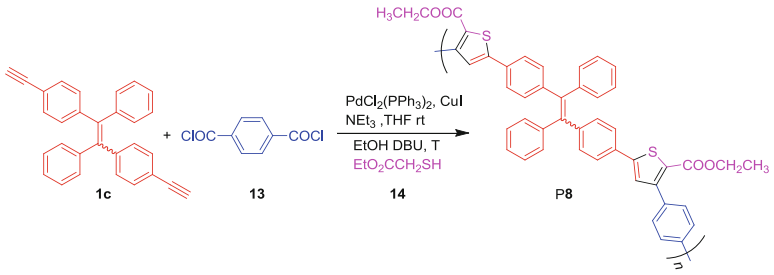
4 Multicomponent Tandem Polymerization of Alkynes, Carbonyl Chloride, and Thiols

In MCPs, which generally react in a one-step manner, all the monomers and catalysts are added together and react in one reaction system. Therefore, interference between components must be strictly avoided to reduce side reactions. Efficient MCP systems are thus quite rare because of the narrow monomer scope and limited reaction choices.

To expand the general applicability of MCRs, tandem reactions have been developed with unique advantages such as high efficiency, functional group tolerance, atom economy, and step economy [44]. In contrast to common MCRs, tandem reactions combine multiple steps in a specific order into one synthetic operation, avoiding isolation of reactive intermediates. Intermediates directly undergo further reaction in situ to selectively afford complicated structures. Tandem reactions provide a direct and efficient approach to access a diversity of complicated molecular structures from simple precursors and procedures, which is difficult to achieve by other synthetic methods.

Some pioneering works have been reported regarding tandem polymerization for the synthesis of nonconjugated polymers. Ueda and coworkers reported the preparation of ordered poly(amide-thioether) through tandem-type polymerization of 2,4-dichlorophenyl acrylate, 4,4′-thiobis(benznenthiol), and 4,4′-oxidianiline [45]. Later, an efficient approach for surface modification of silica nanoparticles through tandem reversible addition−fragmentation chain transfer polymerization and click chemistry was reported by Ranjan and Brittain [46]. A tandem ring-opening/ring-closing metathesis polymerization of various cycloalkenes and terminal alkyne-containing monomers to afford nonconjugated polymers was reported by Choi and colleagues [47, 48]. Moreover, a tandem phosphine-mediated thiol-ene/radical-mediated thiol-yne sequence was reported by Hoyle and Lowe for the preparation of multifunctional thioethers [49]. However, so far little effort has been invested in the preparation of conjugated polymers with unique electronic and photophysical properties through these convenient and efficient tandem polymerizations. Such new synthetic methodologies are in great demand for the synthesis of conjugated polymers with maximization of structure diversity, reaction efficiency, atom- and step-economy, etc.

In 2012, Teiber and Müller reported an efficient one-pot, three-component, consecutive Sonogashira–Fiesselmann cyclocondensation tandem reaction of alkyne, benzoyl chloride, and ethyl 2-mercaptoacetate to afford 2,4-disubstituted thiophenes [50]. We then developed this promising tandem reaction into the first



Scheme 9 Synthesis of thiophene-containing polymer P**8** via three-component tandem polymerization of diyne **1c**, dicarbonyl chloride **13**, and ethyl 2-mercaptoacetate **14**

tandem polymerization for the synthesis of conjugated polymers. Through the three-component tandem reaction of dialkyne **1c**, diaroyl chloride **13**, and ethyl 2-mercaptoacetate **14**, efficient polymerization for the preparation of multisubstituted thiophene-containing conjugated polymers with good processability and advanced functionality was achieved (Scheme 9) [51].

The typical one-pot, three-component, coupling–addition–condensation polymerization proceeded in THF under nitrogen in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and Et_3N. The synthetic operation was carried out in a two-step manner. In the first step, diyne **1c** was reacted with dicarbonyl chloride **13** at room temperature for 3 h. Monomer **14** was then added with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and ethanol to complete the sequential addition and cyclocondensation reactions and form the new thiophene rings in polymer P**8**. The polymerization conditions regarding temperature, time, concentration, and monomer feed ratio were investigated. Polymerization carried out at 0°C afforded the best polymerization results. Satisfactory results could also be obtained at room temperature; hence, further optimization was conducted at room temperature to conserve energy and simplify procedures. Generally, increasing the reaction time of the second step played a positive role in the polymerization, furnishing polymers with high M_w and high yield. Besides the mild reaction conditions, this multicomponent tandem polymerization can also proceed without strict stoichiometric control of the monomers. With the optimized monomer concentration range of 0.02–0.10 M, when the monomer feed ratio was stoichiometrically imbalanced, the yield was barely affected and the M_w remained high. The sole coupling polymerization between monomer **1c** and **13** could also generate conjugated linear polymer but with poor solubility. The second step of tandem polymerization, on the other hand, promoted the polymerization by endowing P**8** with enhanced solubility and thus furnished soluble polymers with high M_w of up to 156,000 g/mol. Compared with the above-discussed polymers, the polydispersity index of P**8** was generally higher, which was probably a result of the relatively poor solubility of the intermediate obtained from the first coupling reaction step.

To assist analysis of the polymer structure, model compound **15** was synthesized through similar procedures and the single-crystal structure of **15** was obtained. The IR and NMR spectra of monomers **1c**, **13**, and **14**, model compound **15**, and

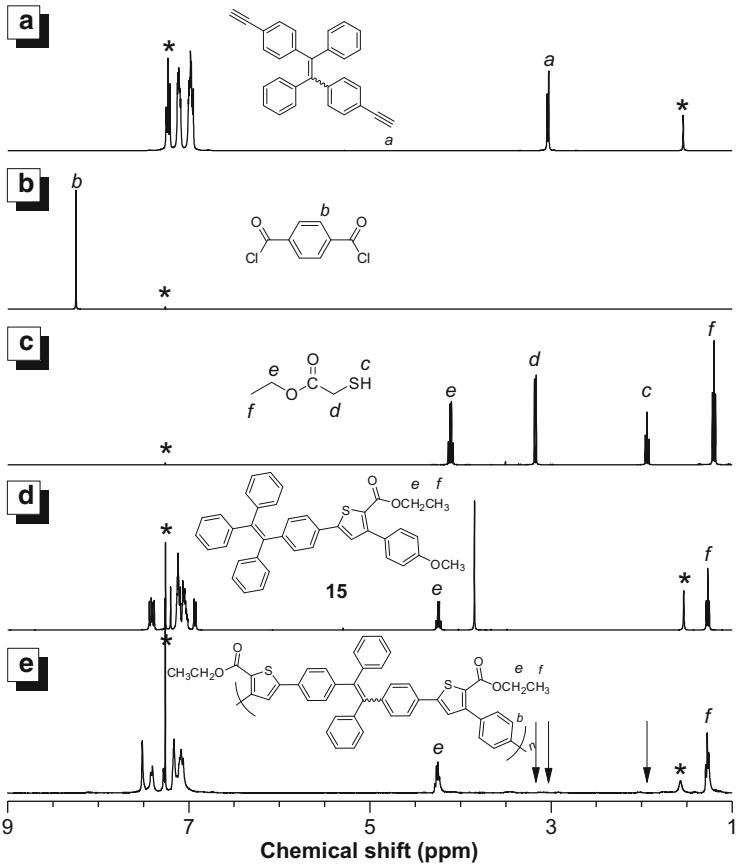


Fig. 7 ^{1}H NMR spectra of (**a**) **1c**, (**b**) **13**, (**c**) **14**, (**d**) **15**, and (**e**) P**8** in deuterated chloroform. The solvent peaks are marked with asterisks

polymer P**8** were compared, revealing their structures (Fig. 7). In the IR spectra of model compound **15** and P**8**, the absorption bands associated with the ≡C–H, C≡C, and S–H stretching vibrations from the monomers at 3,275, 2,106, and 2,571 cm^{-1}, respectively, were absent, confirming total consumption of the terminal triple bond and S–H bonds. Similarly, in the ^{1}H NMR spectra, the resonances of the typical terminal alkyne proton of **1c** at δ 3.03, the SH proton of **14** at δ 1.94, and the CH_2 protons next to SH group at δ 3.17, were all absent from the spectra of both **15** and P**8**. Meanwhile, the aromatic protons of **13** appeared at δ 8.25, which shifted to a higher field after reaction. The newly formed thiophene rings were indicated by the new peak at δ 7.28, suggesting formation of the expected polymer structure and complete conversion from alkynoyl intermediate to thiophene rings.

As mentioned before, steric hindrance from the twisted and bulky TPE moiety can result in large intermolecular distances and free volume to accommodate solvent molecules. P**8** thus possesses good solubility in common organic solvents,

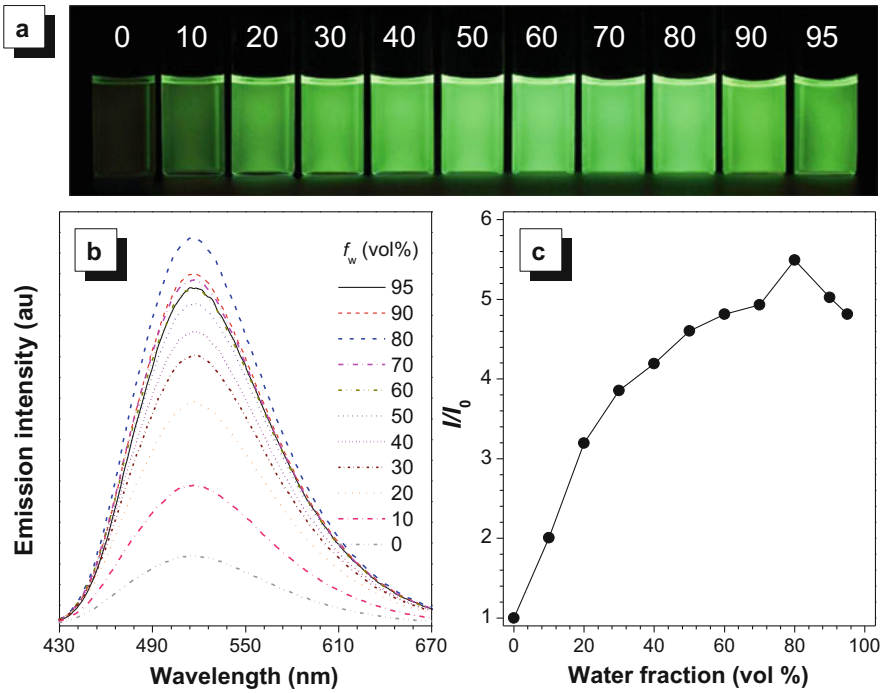


Fig. 8 (**a**) Fluorescence photos of P**8** in THF/water mixtures with different water fractions (f_w) taken under 365 nm UV irradiation from a hand-held UV lamp. (**b**) Emission spectra of P**8** in THF/water mixtures with different water fractions. (**c**) Plot of relative emission intensity (I/I_0) versus the water fraction of the aqueous mixtures of P**8**. Solution concentration 10 μM; excitation wavelength 370 nm

despite the conjugated aromatic backbone. It can also be facilely fabricated into tough thin film by spin-coating or drop-casting methods.

Unlike the polymers discussed above, P**8** is a fully conjugated polymer with thiophene and benzene rings in the polymer backbone. The absorption spectrum of THF solution of P**8** was located at 370 nm, which is bathochromically shifted about 20 nm compared with that of model compound **15**, indicating better conjugation. The typical AIE-active TPE moieties embedded in the polymer skeleton endowed P**8** with both good solubility and potential AEE characteristics. The fluorophores in P**8** are covalently linked in the polymer backbone and partially restrict rotation of the phenyl rings, even in solution. Hence, the THF solution of P**8** was faintly emissive. Addition of water, a poor solvent of P**8**, induced the polymer chains to aggregate and swiftly increased the emission (Fig. 8). In THF, the emission maximum of P**8** was located at 517 nm. Addition of water to the THF solution gradually enhanced its emission without noticeable change in the emission maximum or the spectral profile. The highest emission intensity was observed in 80 vol % aqueous mixture and its intensity was enhanced about 5.5-fold compared with that of its THF solution.

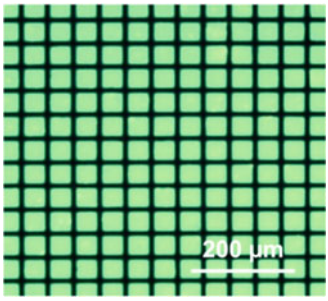


Fig. 9 Two-dimensional fluorescent photopattern generated by UV irradiation of P**8**. The photograph was taken under UV illumination (330–385 nm)

With its many polarizable aromatic rings, ester groups, and heteroatoms (well-known contributors to high refractivity), the spin-coated thin film of P**8** possessed high RI values of 1.9461−1.6668 in a wide spectral region of 400–1,000 nm. Moreover, photo-oxidation took place when UV irradiation was applied to the photosensitive thin film of P**8**, which changed the chemical structure as well as the refractive index. By controlling the irradiation time, the RI value of the polymer film can be easily modulated. The good film-forming ability, high film emission efficiency, and photosensitivity endow P**8** with potential application in generating luminescent photopatterns via photolithography. A spin-coated emissive thin film of P**8** was irradiated by UV light in air for 20 min through a copper photomask. As shown in Fig. 9, the fluorescence of the exposed regions was quenched as a result of the photo-oxidation reaction, whereas the unexposed regions remained emissive, affording a two-dimensional fluorescent photopattern with high resolution and sharp edges.

With the heterocyclic chelating groups and AEE characteristics of P**8**, it can be used as metal ion sensor, in particular, as a fluorescent chemosensor for Ru^{3+} ions. Nanoaggregates of P**8** in THF/water mixture with 90 vol% water content were used for the test. As shown in Fig. 10, gradual addition of Ru^{3+} to the nanoaggregate suspension of P**8** significantly quenched the emission. The Stern–Volmer plot of $(I_0/I - 1)$ values versus the Ru^{3+} concentration was an upward bending curve rather than a straight line, demonstrating a superamplified quenching effect. Besides the high sensitivity, other metal ions such as Ca^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, Mg^{2+}, Hg^{2+}, Ni^{2+}, Ag^{+}, and Zn^{2+} all exerted little effect on the PL of P**8**, indicating high selectivity of the fluorescent sensor towards Ru^{3+}, possibly as a result of the relatively higher standard reduction potential of the Ru(III)/Ru(0) couple (Fig. 11).

This work presents the first example of one-pot, multicomponent tandem polymerization for the preparation of heterocyclic-containing conjugated polymers. The process exhibits excellent efficiency, complete conversion, and good tolerance of stoichiometric imbalance, generating polymers with large M_w, good solubility, and multiple functionalities.

With the success of this three-component tandem polymerization, we further explored such polymerization by changing the third component monomer from ethyl 2-mercaptoacetate **14** to a normal thiol **16**. We aimed to extend the scope of the one-pot, two-step, three-component coupling–addition tandem polymerization

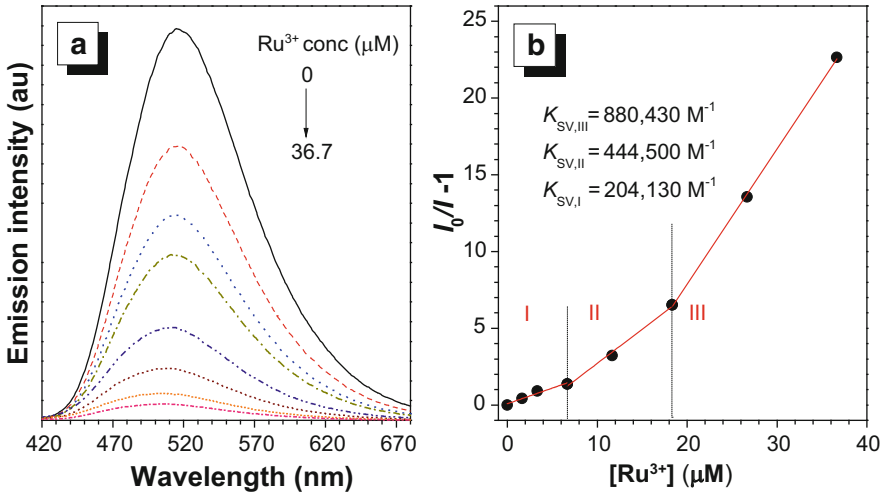


Fig. 10 (**a**) Emission spectra of P**8** in THF/H_2O mixtures (1/9 v/v; concentration 10 μM) with different Ru^{3+} concentrations. (**b**) Plots of $(I_0/I - 1)$ values versus Ru^{3+} concentration in 90% aqueous mixtures of P**8**. I_0 indicates the PL intensity in the absence of Ru^{3+}

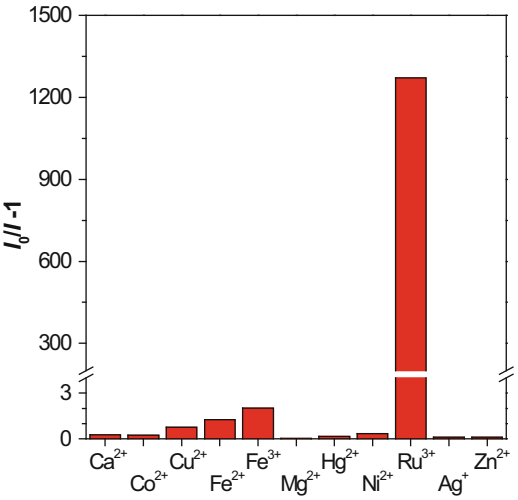
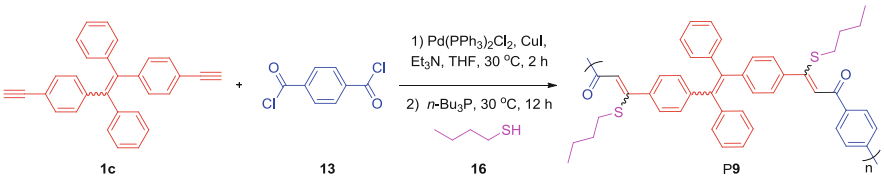


Fig. 11 Changes in relative emission intensities $(I_0/I - 1)$ of P**8** in THF/H_2O mixtures (1/9 v/v; concentration 10 μM) with various metal ions (2 mM). I_0 indicates the intensity in the absence of metal ions

and make it applicable to general thiol monomers. The diyne monomer **1c** and dicarbonyl chloride monomer **13** were first reacted at room temperature for 2 h to form the alkynone intermediate. Butanethiol **16** and tributylphosphine were then added to react with the intermediate in situ to form polymer P**9** with complete conversion and high efficiency (Scheme 10).



Scheme 10 Synthesis of polymer P**9** through three-component tandem polymerization of diyne **1c**, terephthaloyl chloride **13**, and butanethiol **16**

5 Conclusion

Multicomponent polymerization of alkynes, including tandem polymerization, provides an efficient approach for the synthesis of functional polymer materials with unique structures that are difficult to obtain using other synthetic methods. The MCPs based on alkyne monomers are still quite limited. Three types of reported MCPs of alkynes are reviewed: MCPs of alkynes, aldehydes, and amines; MCPs of alkynes, azides, and amines/alcohols; and tandem polymerization of alkynes, carbonyl chloride, and thiols. These MCPs have overcome the limitations of MCPs such as strict stoichiometric balance, poor polymer solubility, and low M_w of the products. This field is still in its infant stage and more comprehensive work is an urgent demand. Through such pioneering work, we hope to inspire research enthusiasm and accelerate the pace of development of efficient polymerization approaches for synthesis of various polymer structures, and pave the way to novel functional polymer materials.

Acknowledgements This work was partially supported by the National Basic Research Program of China (973 Program; 2013CB834701), the National Science Foundation of China (21404041), the Research Grants Council of Hong Kong (16305014, 604913, 602212, and 604711). B.Z.T. thanks the support of the Guangdong Innovative Research Team Program (201101C0105067115).

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Adv Polym Sci (2015) 269: 43–60
DOI: 10.1007/12_2014_301

Published online: 8 February 2015

Biginelli Multicomponent Reactions in Polymer Science

Lei Tao, Chongyu Zhu, Yen Wei, and Yuan Zhao

Abstract The Biginelli reaction, a three-component cyclocondensation reaction, is an important member of the multicomponent reaction (MCR) family. The Biginelli reaction is so efficient and shares many similar properties as the recent click reactions. In this chapter, we summarised the current applications of the Biginelli reaction in polymer chemistry including polymer coupling, post polymer modification, and new functional polymer synthesis. We expect this 'old' reaction (>120 years) can draw attention from polymer chemists and play new roles in the polymer science.

Keywords Biginelli reaction · Click reaction · MCR · Polymer synthesis and modification · PPM

Contents

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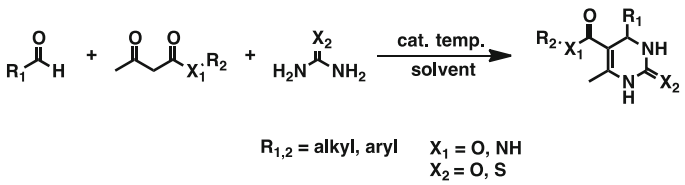


Scheme 1 The three components of the Biginelli reaction

1 The Biginelli Reaction and Its Chemistry

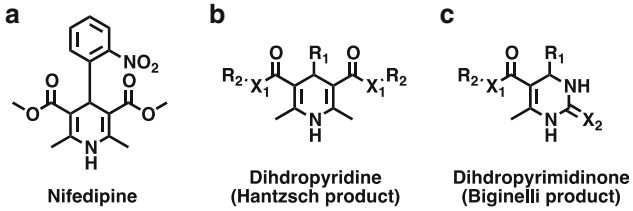
1.1 Background of the Biginelli Reaction

The Biginelli reaction is a member of the multicomponent reaction (MCR) family. It is a three-component cyclocondensation reaction using aldehyde, 1,3-dione, and urea as building blocks and is particularly useful for synthesis of 3,4-dihydro-2(*H*)-pyrimidinone (DHPM) compounds in one pot (Scheme 1).

Although discovered over 100 years ago [1], the Biginelli reaction is still attracting attention because of its potential applications in organic synthesis [2–5] as well as in the pharmaceutical field (especially in drug discovery) [6, 7]. Like other multicomponent reactions, the Biginelli reaction is a powerful tool for synthesis of a large number of compounds because of its easy operation, high efficiency, scalable manufacture, and low cost [4, 5, 8–11]. This robust three-component reaction can produce a complex structure bearing diverse functional groups through a one-pot strategy, with abundant choice of substrates.

Continuing studies of the Biginelli reaction are mainly focused on the synthesis of DHPM compounds and their related pharmaceutical properties [6]. Thanks to its high efficiency, the Biginelli reaction has been applied in the pharmaceutical field to synthesize a library of compounds [12–16]. On the other hand, because the DHPM product contains a heteroaromatic ring structure, it can be used as an aza-analog for other aromatic structures. For example, a derivative of the Biginelli product can be used as an alternative for nifedipine [17, 18], a clinical compound containing a dihydropyridine structure synthesized via the Hantzsch reaction (Scheme 2).

After finding the DHPM structure in some native anti-HIV products (batzelladine A and B) [7, 19], the Biginelli reaction has become popular in drug discovery and drug synthesis. Up to now, the derivatives generated from the Biginelli reaction have shown the potential to treat many diseases [7, 20], such as hypertension [21–23], epilepsy [24], tuberculosis [25], and malaria [26]. Some derivatives were also found to be calcium channel antagonists [6, 18, 21, 23]. Recent data even indicate that Biginelli products and derivatives have activity against viruses [27], bacteria [28, 29], and tumors [30, 31].



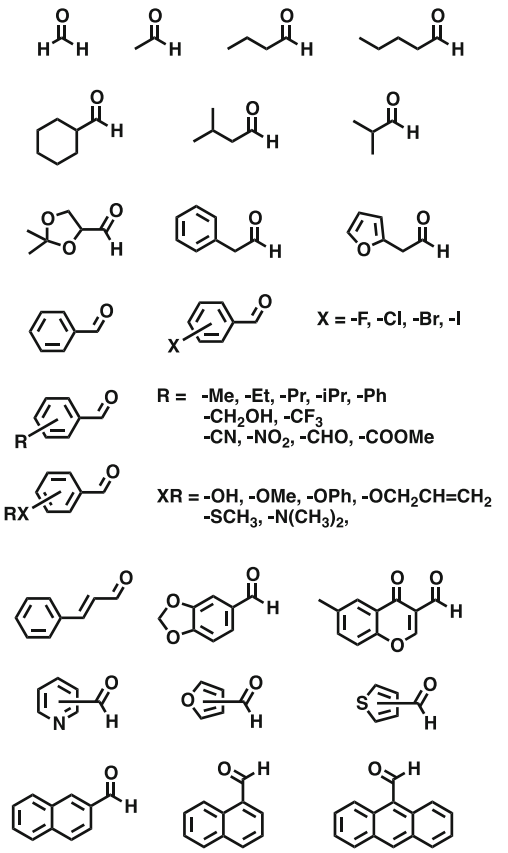
Scheme 2 The commercial drug nifedipine (**a**) and a comparison between the Hantzsch product (**b**) and the Biginelli product (**c**)

1.2 Chemistry of Biginelli Components

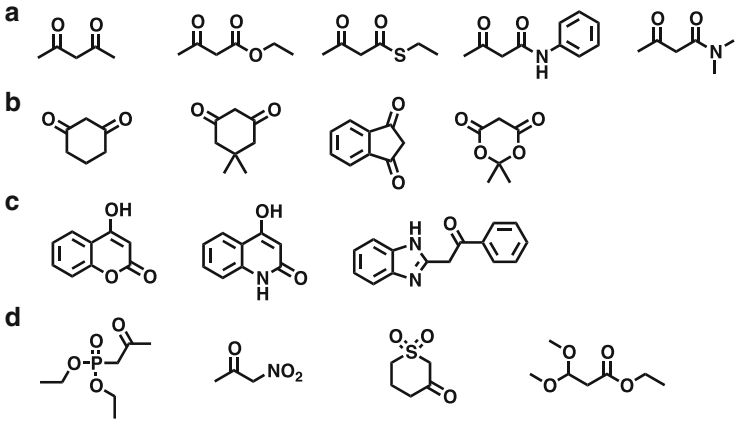
The aldehyde component of the Biginelli reaction can be highly diverse. Both aliphatic and aromatic aldehydes can act as suitable Biginelli components. Apart from the synthetic aldehydes, most of the commercially available aldehyde resources generated from nature (including benzaldehyde [9, 32], cinnamaldehyde [32, 33], and furfural [20, 32]) are proven to be suitable substrates for the Biginelli reaction. A typical library of good aldehyde candidates for the Biginelli reaction is shown in Scheme 3. In addition, the aldehyde group can be easily introduced into some compounds that contain no aldehyde groups through traditional chemistry reactions so that they can be used for the subsequent Biginelli reaction [34].

The rate of the Biginelli reaction can be varied by using different aldehyde substrates. Typically, the reaction rate can be slowed down by a bulky aldehyde under normal conditions [35]. Meanwhile, the functional group on aromatic aldehydes seems to have little effect on the activity of the aldehyde, although an electron-rich aromatic aldehyde might slightly accelerate the reaction rate and increase the yield [36]. Although influenced by various conditions (substrate, catalyst, solvent, and temperature), in general, aromatic aldehydes usually provide a faster reaction rate and a better yield than aliphatic aldehydes [32, 37].

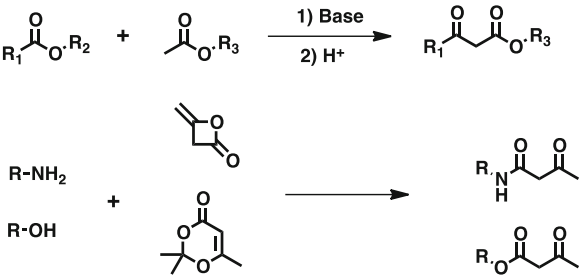
Many compounds can act as the 1,3-dione component of the Biginelli reaction (Scheme 4). Commercially available products such as acetylacetone and ethyl acetoacetate are common 1,3-dione Biginelli components (Scheme 4a). Cyclic 1,3-dione can also participate in the Biginelli reaction. Common examples include 1,3-cyclohexanedione [38], dimedone (5,5-dimethyl-1,3-cyclohexanedione) [39], Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) [40], and 1,3-indanedione [11] (Scheme 4b). Other compounds such as 4-hydroxycoumarin and 4-hydroxyquinolin-2(1*H*)-one can also act as a Biginelli component because they can transform into a 1,3-dione form through keto–enol tautomerization (Scheme 4c) [41, 42]. Apart from normal 1,3-dione compounds and their enol forms, some compounds such as nitroacetone and other ketones with an electron-withdrawing group substituted on the β-position can also perform the Biginelli reaction with high yield (Scheme 4d) [43–46]. Furthermore, the 1,3-dione component can be generated from Claisen condensation or derived from hydroxyl/amine groups by diketene or its alternative acetone adduct, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (Scheme 5).



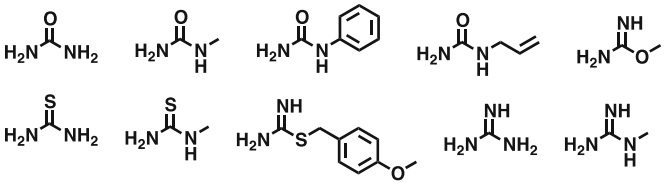
Scheme 3 Typical aldehydes that are suitable for the Biginelli reactions



Scheme 4 Suitable 1,3-dione candidates for the Biginelli reaction. (**a**) Linear forms; (**b**) cyclic forms; (**c**) enol forms; and (**d**) ketones with electron-withdrawing group on the β-position



Scheme 5 Reactions that produce the 1,3-dione unit for the Biginelli reaction



Scheme 6 Some examples of the urea component for the Biginelli reaction

The choice of the third component is, however, limited in terms of functional variety. In most cases, only urea and thiourea are used as the third component. However, some derivatives, usually monosubstituted, of urea, isourea, and thiourea can also react well in the Biginelli reaction even though they usually require a longer reaction time to provide similar yields [3, 7, 10]. There are some reports that the guanidine group could also be used as reactant to form the Biginelli product under basic conditions [47]. Some urea components used for the Biginelli reaction (urea, isourea, thiourea, guanidine, and their derivatives) are shown in Scheme 6.

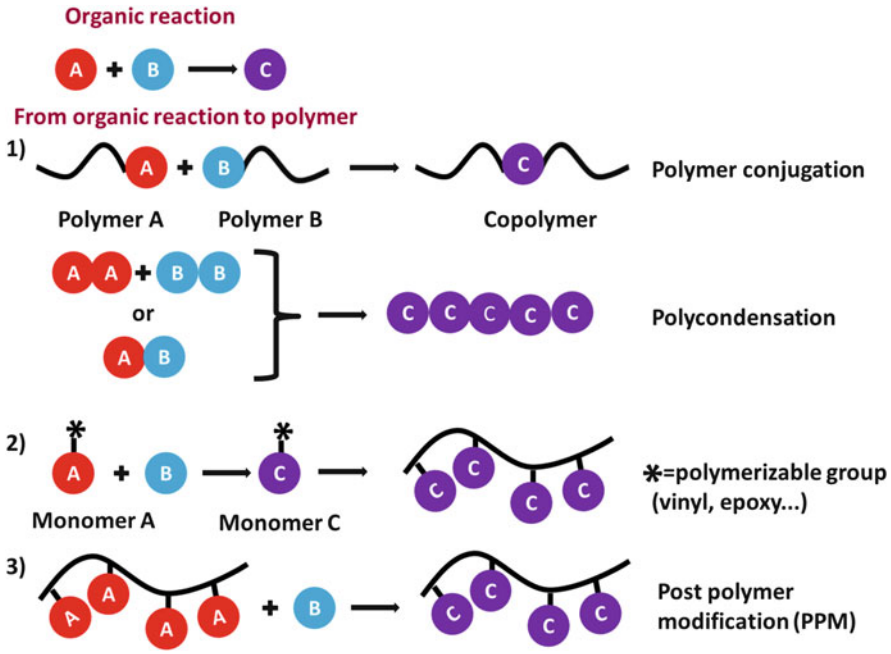
Conditions for the Biginelli reaction have been well studied and developed over the last century [10, 45, 48]. The reaction temperature can be as low as room temperature [49, 50] or as high as heating to reflux [37, 51]. Most solvents, including water [9], ionic liquids [52–54], and low molecular weight polyethylene glycol (PEG) [55], are suitable for the Biginelli reaction. A solvent-free condition is also feasible and can provide higher yield in some circumstances [56–58]. A wide range of organic and inorganic catalysts can catalyze the Biginelli reaction [10]. Other conditions such as ultrasound [59, 60], microwaves [61, 62], or grinding [63, 64] have also been applied to improve this reaction. Recent effort has been focused on the development of more economic and efficient conditions for the Biginelli reaction. With improved conditions (temperature, solvents, catalysts, etc.), a 'greener' Biginelli product can be achieved under environmentally friendly conditions with a high yield [5, 9, 10, 37, 38, 51, 52, 57, 62, 63]. This allows it to work under more biocompatible conditions. A recent report has showed its potential use in biological systems. Under physiological conditions, the Biginelli reaction can smoothly anchor a fluorescence probe onto the cell membrane, indicating the possible application of the Biginelli reaction for cell imaging [34].

Polymer-based catalysts and resins are widely used in many MCRs due to their recyclable and reusable properties. Particularly, use of polymer-supported resins is a powerful tool for organic synthesis because small organic compounds are easily separated from polymers. Therefore, the polymer-support strategy has been widely applied in MCR synthesis, multistep synthesis, and combinatorial synthesis for related pharmaceutical libraries [16, 65, 66]. As a matter of course, polymers have also been applied in the Biginelli reaction. Polymer-based catalysts and polymer-supported resins have been well studied and operated in the synthesis of Biginelli-type products [16, 67–72]. Either insoluble commercial resin (e.g., Wang resin) or soluble polymer (PEG) can act as the polymer support [67, 70]. All three components can be introduced onto the polymers or resins, although 1,3-dione-bound resins and urea-based resins are more commonly used. However, introducing the Biginelli reaction into the polymer field was rarely thought of until now. Therefore, a summary of the applications of the Biginelli reaction in polymer chemistry is given in the next section.

2 The Biginelli Reaction in Polymer Chemistry

Introducing organic reactions into polymer chemistry can greatly enrich the polymer family. Through various organic reactions, new structural functional groups can be implanted into the polymer main or side chains, resulting in whole new polymers with distinctive chemical and physical properties, i.e., new functional polymers [73–76]. Generally, there are three approaches to introduction of an organic reaction into the polymer field (Scheme 7): (1) An organic reaction can be performed as a linker. Different polymer chains can be stitched together by an organic reaction into one new polymer, termed a ‘block copolymer.’ Similarly, small molecules (monomers) can be joined together via an organic reaction into a macromolecule, also known as a ‘condensation polymer.’ (2) An organic reaction can be used to synthesize new monomers with both desired functionality and polymerizable groups (vinyl, epoxy groups, etc.). These new monomers can be subsequently polymerized to form a polymer with predesigned side groups. (3) An organic reaction can be used to directly modify the reactive groups on the polymer side chains, adding new functions for the polymer. This process is usually called ‘post-polymerization modification’ (PPM).

Based on the above-mentioned principles, almost all organic reactions could be used for polymer synthesis. However, this is not actually the case. As prerequisites for applicable polymer synthesis (low cost, large scale manufacture, etc.), the chosen organic reactions should have easily available starting materials and high efficiency, with negligible side reactions or side-products, in producing the target functional polymers. Several click reactions such as the thiol–ene/yne reaction, Michael addition, copper-catalyzed azide–alkyne cycloaddition (CuAAC), (hetero) Diels–Alder reaction, and hydroxyl/amine/thiol–isocyanate coupling as well as some enzyme-catalyzed organic reactions such as enzymatic transesterification



Scheme 7 Three common approaches (*1–3*) for applying an organic reaction in the polymer field

have proved to be powerful tools in the polymer field due to their high efficiency, atom economy, and rapid reaction rate [77–83]. Meanwhile, some MCRs such as the Passerini reaction [84–87], Ugi reaction [88–90], Mannich reaction [91, 92], and Kabachnik–Fields reaction [93–96] have also been introduced into polymer chemistry for synthesis of new functional polymers, demonstrating their potential application in current polymer chemistry.

Of all the MCRs, the Biginelli reaction has been overlooked in the polymer field for a long time. Until now, only a few reports have described this reaction for synthesizing or modifying polymers. As mentioned above, the Biginelli reaction is a highly efficient reaction under mild conditions, with versatile structures and substrates similar to those used in the click reactions, implying that this 'old' reaction could be a useful tool in the polymer field. The high efficiency and yield of the Biginelli reaction can guarantee the quality of the polymer modification. The three components of the Biginelli reaction can be easily introduced and tuned by varying the substrates, offering different choices of modification strategy and product variety. Furthermore, the Biginelli reaction is robust to many other functional groups such as hydroxyl [53], carboxyl [58], alkene [97], alkyne [98, 99], and azide groups [15, 99]. Thus, the Biginelli reaction has the potential to bear with or even cooperate with other reactions to build a one-pot system. In addition, the wide range of reaction temperature and the multiple choices of solvents and catalysts provide an excellent platform to meet the different requirements for polymer

modification and synthesis under various conditions. Some applications of the Biginelli reaction in polymer chemistry are listed as below.

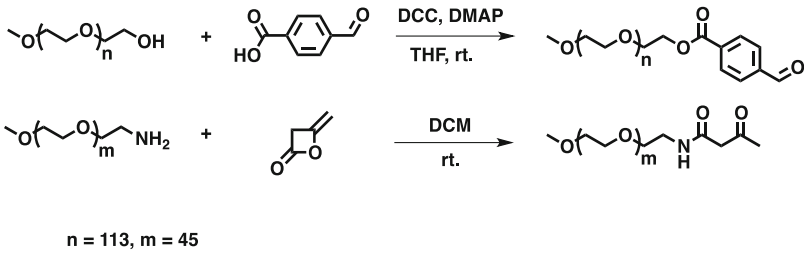
2.1 Coupling Reaction

Block copolymers combine different physical or/and chemical properties in one polymer. Hence, some new properties (e.g., amphiphilicity) can be achieved for this type of polymer. Because of their unique properties, copolymers are used everywhere in everyday life. For example, poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) block copolymers (PEO–PPO–PEO, commercially known as Pluronics) are widely used as nonionic surfactants in daily care products. One commercial thermoplastic elastomer is made from styrene–butadiene–styrene (SBS) triblock copolymers.

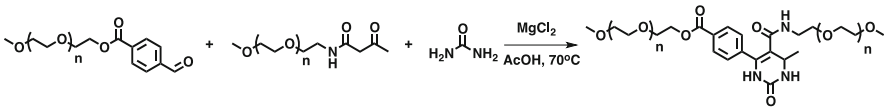
The most straightforward way to make a block copolymer is coupling two different polymers directly through a linkage. However, the direct coupling of different polymer chains is rarely conducted because the reaction often ends up with a mixture of products and unreacted starting polymers. The painful and costly separation of the mixture is usually unavoidable. Therefore, a highly efficient coupling reaction is crucial for successfully stitching different polymers together. The popular click reactions seem to provide a solution [74, 81, 100–102]. Because the Biginelli reaction shows very similar properties to current click reactions, especially under concentrated conditions, it might be able to smoothly conjugate two polymers.

To demonstrate the effective coupling capability of the Biginelli reaction, the linkage of two methyl polyethylene glycol (mPEG) chains via the Biginelli reaction was conducted. Derivatization of the Biginelli units can be easily obtained from either hydroxyl groups or amine groups through traditional reactions. Using commercially available compounds, 4-formylbenzoic acid and diketene, the two Biginelli components aldehyde and 1,3-dione, respectively, were first introduced onto two mPEGs, (Scheme 8).

Afterwards, the two mPEG chains were linked by a coupling agent (in this case, urea) to test the coupling efficiency (Scheme 9). To push the coupling process,



Scheme 8 Modification of mPEG using a traditional esterification process



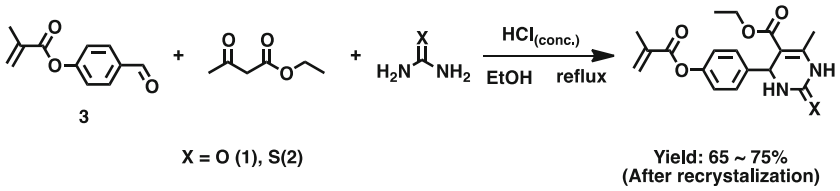
Scheme 9 Coupling reaction between two mPEG chains

excess urea was used. $MgCl_2$ was chosen as the catalyst and acetic acid (AcOH) was used as the solvent to accomplish the Biginelli reaction according to the literature [37]. The temperature was set at 70°C.

The coupling reaction proceeded smoothly under relatively mild conditions with the aldehyde/1,3-dione ratio near to 1:1. The reaction was monitored by gel permeation chromatography (GPC) and found to be completed within 3 h [33]. As reported in the literature, to produce a similar copolymer from two polymer chains via accepted click reactions (CuAAC, thiol-maleimide, etc.) typically takes from 4 h to 2 days, depending on various conditions such as room temperature [74, 102], heating [81, 100], or photomediation [101]. Thus, the Biginelli reaction can stitch polymer chains together as efficiently as traditional click reactions.

2.2 Biginelli Side-Group Polymers

Biomacromolecules like proteins are the fundamental functional material in nature. Although most proteins share similar backbones, they can act in multiple roles in nature, for example, as catalysts (enzymes), building blocks (collagen), and signal proteins, as a result of differences in the side groups (residues) and in their sequence. Sometimes a small change in a side group on the active site can dramatically change the activity of a protein [103, 104], alter function [105], or cause disorder [106]. Furthermore, the structure of each protein is also affected by the residues on the protein [107]. It can be said that the function of a biomacromolecule is mainly determined by its side groups. This principle is also applicable to synthetic polymers. Functional polymers with different side groups have proved to be useful materials, such as responsive materials [108, 109] and gene delivery materials [110, 111]. Therefore, the easy and effective synthesis of a functional side-chain polymer is a challenging task. So far, the two most widely used approaches are functional monomer polymerization and PPM. Functional monomer polymerization is a two-step approach that requires synthesis of the monomer with predesigned functional group and subsequent polymerization of the monomers. This two-step approach usually provides high functionality for the polymer side chains. PPM, on the other hand, is a one-step approach that can directly modify the side chains of the polymer precursor.



Scheme 10 Synthesis from pre-monomer (**3**) of two Biginelli monomers, with atom X being oxygen (**1**) or sulfur (**2**)

2.2.1 Polymerization of the Biginelli Monomer

Polymerization of synthesized monomers with new functionality is a widely used strategy. The desired functional groups can be introduced accurately and efficiently by the monomers onto the polymer side chains. The Biginelli product DHPM has been well studied in the last few decades and shows some unique properties [6]. Therefore, DHPM polymers were synthesized to obtain a better understanding of the functions of the DHPM structures on the polymer side groups [112]. Two DHPM monomers (**1** and **2** in Scheme 10) were synthesized via the Biginelli reaction, being further polymerized to obtain a polymer with DHPM side groups.

First, a homemade 'pre-monomer', 4-formylphenyl methacrylate **3**, was synthesized to introduce the aldehyde component for conducting the Biginelli reaction. The monomers **1** and **2** were then obtained through reacting the pre-monomers **3** with ethyl acetoacetate and either urea or thiourea, respectively. With the help of a catalytic amount of concentrated hydrochloride (HCl), the two monomers were successfully synthesized in refluxed ethanol at moderate yields by recrystallization.

The DHPM monomers were then polymerized into polymers via conventional radical polymerization initiated by AIBN under argon atmosphere. Both DHPM monomers were successfully polymerized to generate the Biginelli side-group polymers, indicating that the DHPM unit did not interfere with formation of the radicals and had no negative effect on the polymerization process.

The Biginelli side-group polymers, interestingly, showed a pH-dependent color change property. The polymers were white at neutral pH (pH 7) but turned pale yellow at a strongly acidic pH (pH 1) and became yellow in strongly basic conditions (pH 12). The reason for the color change at basic pH is mainly attributed to deprotonation of the NH groups on the DHPM structure. The acid-induced color change, on the other hand, is a result of the formation of hydrogen bonds between the side chains. Because both color changes are reversible, the DHPM polymers could be potential pH detectors or biosensors.

2.2.2 Post-polymerization Modification

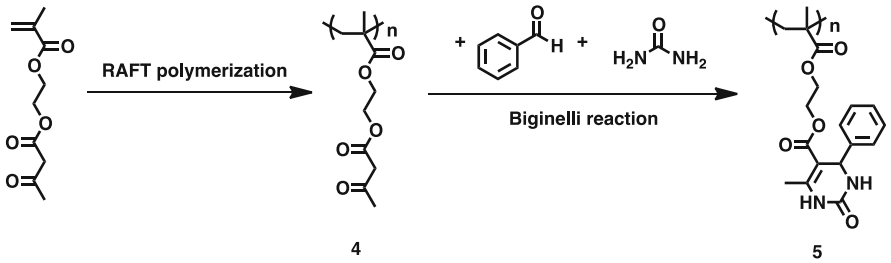
As well as the polymerization of functional monomers, PPM of a readily available polymer is also a well-applied approach. For example, the commercially available polymer poly(vinyl alcohol) (PVA) was synthesized by hydrolysis of the side

chains of synthetic poly(vinyl acetate). Another example is the biomacromolecule derivative chitosan, which is produced by the deacetylation of chitin.

Limited by the bulky size of the polymer and the viscous system caused by the existence of the polymer, PPM using traditional reactions (esterification, oxidation, reduction, etc.) usually ends up with significant unreacted residues, leading to less functionality than obtained by the functional monomer polymerization approach. However, because of its universality, PPM is still a very useful tool, especially for industrial manufacture, for obtaining functionalized polymers or biomacromolecules. PPM can be applied for most polymers, although some functional monomers cannot be directly polymerized to form functional side-group polymers because they act as inhibitors during polymerization. In addition, even if the functional monomers can be polymerized, the final polymer chain length is sometimes limited and cannot be controlled because of hindrance from the size of the monomer or poor solubility of the polymer. However, similar desired functional side-group polymers of a certain length can be achieved through PPM. The chain length of the polymer is sometimes essential for properties such as mechanical properties [113], LCST behavior [114, 115], and bioclearance/degradable lifetime [116, 117].

Recently, scientists have been looking for a better modification motif to improve the functionality of polymer. Modern efficient reactions, such as click reactions, have been chosen and applied to achieve efficient PPM [118]. Because the Biginelli reaction has proved to be a powerful tool for easily achieving complex DHPM structures with high yield, this efficient reaction can also be a potential tool for polymer modification.

A polymer with 1,3-dione side groups was synthesized as the model polymer precursor [34]. The polymer was first synthesized from the commercially available monomer, 2-(acetoacetoxy)ethyl methacrylate (AEMA) through reversible addition–fragmentation chain transfer (RAFT) polymerization. A relatively high molecular weight poly(AEMA) polymer **4** with a degree of polymerization of around 102 was obtained (number-average molecular weight as measured by NMR, $M_{\mathrm{nNMR}} \sim 21{,}900$; as measured by GPC, $M_{\mathrm{nGPC}} \sim 44{,}900$; polydispersity index, PDI ~ 1.18) for the next PPM. To evaluate the efficiency of PPM via the Biginelli reaction, benzaldehyde and urea were chosen as the other two Biginelli components to react with the 1,3-dione side-group polymer (Scheme 11). Slight



Scheme 11 Sequential synthesis of poly(AEMA) (**4**) and the final Biginelli side-group polymer (**5**)

excess (1.5 equivalents) of these two components were used to accelerate the reaction process and push to completion.

With the help of $MgCl_2$/AcOH catalyst–solvent system, the Biginelli reaction proceeded smoothly on the polymer side groups at 70°C. ^{1}H NMR was used to monitor the reaction. The characteristic peaks of the Biginelli structure, two CONH peaks (7.73 and 9.27 ppm), CH (5.16 ppm) on the heteroaromatic ring, and the protons of the benzene ring (7.00–7.40 ppm), formed gradually while the methylene peak of the 1,3-dione group (3.62 ppm) from the polymer precursor disappeared accordingly. Performed similarly to the click reactions, PPM via the Biginelli reaction was nearly complete (>99%) with almost no 1,3-dione left on the side groups after 5 h of reaction. The 1,3-dione groups were transformed successfully into the DHPM Biginelli structures with no visible side reactions. After a simple wash step, the final pure modified polymer **5** was obtained with increased molecular weight and narrow polydispersity (M_{nGPC} ~ 55,300, PDI ~ 1.15), indicating that the backbone of the polymer survived during PPM.

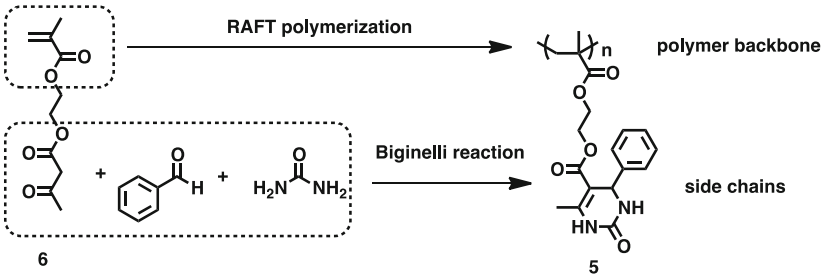
2.2.3 One-Pot Polymerization

As well as functional monomer polymerization and PPM, one-pot polymerization has also been used to obtain a highly functionalized polymer. One-pot polymerization combines polymerization with other compatible reactions to achieve the target new polymer in the same reactor. In contrast to functional monomer polymerization, one-pot polymerization can form the functional monomer in situ and thus avoid the purification step necessary with functional monomer synthesis. This approach also avoids hindrance from the polymer backbone, leading to a higher modification yield compared with the normal PPM approach. With less time and cost, the desired polymer can be achieved and functionalized with a high yield in one pot. Some reactions such as the CuAAC click reaction and enzymatic transesterification have been used for construction of a one-pot polymerization system with controlled/living radical polymerization approaches to achieve new functional polymers [119–125].

One-pot polymerization requires the collaborating reactions to proceed smoothly under the polymerization conditions while having negligible or no interference with the polymerization process. In other words, tolerance between the functional groups of each component of the polymerization is essential for this strategy. Therefore, choosing a suitable reaction to cooperate with the polymerization is very important.

The variety of substrate choices for the Biginelli reaction and its good tolerance to many functional groups offers the opportunity to use it in cooperation with other reactions in one pot. In addition, the wide choices of reaction temperature, catalysts, and solvents for the Biginelli reaction are also helpful in matching with the polymerization process.

To demonstrate the advantages of the Biginelli reaction, the RAFT polymerization was again chosen for one-pot polymerization. In this case, thanks to the



Scheme 12 One-pot polymerization of AEMA monomer (**6**) to form a Biginelli side-group polymer (**5**)

diversity of the Biginelli components, a widely used commercially available monomer, AEMA **6**, was found to be an ideal candidate. The vinyl group of AEMA can be polymerized to form the polymer backbone via RAFT polymerization, and the 1,3-dione can be converted into the DHPM structure through the Biginelli reaction (Scheme 12).

The $MgCl_2$/AcOH catalyst–solvent system was used for the Biginelli reaction because it has proved to be suitable for the Biginelli reaction and harmless to the RAFT polymerization. The temperature was set at 70°C to match the polymerization process while still allows the Biginelli reaction to occur. The Biginelli reaction under these conditions can still proceed rapidly. In the first hour, benzaldehyde and urea reacted with the AEMA monomer, converting most of the AEMA monomers into Biginelli-type monomers; the total polymerization yield of both monomers was below 20%. The subsequent polymerization can be seen as homopolymerization of the newly formed Biginelli-type monomers. The kinetic plot showed that the RAFT polymerization proceeded smoothly and was well controlled with narrow dispersity (PDI ~ 1.13), suggesting that the DHPM structure has no negative effect on the formation or growth of the radical species [33]. In other words, the Biginelli reaction and its product do not inhibit or interrupt the polymerization process.

The purified polymer **5** showed side chains with almost only Biginelli-type structures, suggesting that the AEMA monomers polymerized into the polymer chain during the first hour can still be converted into Biginelli-type structures, as well as the free AEMA in solution.

3 Conclusion and Perspective

The Biginelli reaction, as an efficient and green reaction, is ideal for both polymer modification and synthesis. It can serve as a linker to join two polymers together with high yield. PPM using this ‘old’ reaction is also successful, indicating its clickable properties. The Biginelli reaction can even cooperate with the sensitive radical polymerization in one-pot, displaying rapid reaction rate and good

compatibility. All these properties of the Biginelli reaction indicate a similarity to recent click reactions. Furthermore, the Biginelli reaction is a three-component reaction, which could provide an even more complex and functionalized product. The Biginelli reaction could also be useful in synthesizing other functional polymers such as condensation polymers, hyperbranched polymers, and dendrimers. Furthermore, the similarity between the structure of Biginelli product DHPM and nucleobases such as cytosine and thymine could deliver features like self-assembly or biomimicry to the polymers. We believe that with more and more synthesized Biginelli-type polymers, this old reaction will display new vitality in polymer science.

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Adv Polym Sci (2015) 269: 61–86
DOI: 10.1007/12_2014_298

Published online: 8 February 2015

Passerini and Ugi Multicomponent Reactions in Polymer Science

Ansgar Sehlinger and Michael A.R. Meier

Abstract Multicomponent reactions (MCRs) include more than two starting materials and are characterized by highly atom-efficient and straightforward practical procedures. Some of the most important MCRs in organic chemistry are the isocyanide-based MCRs, namely the Passerini three-component and Ugi four-component reaction. These reactions are, for example, often applied in combinatorial and medicinal chemistry due to their easy access to diversity or for the creation of complex structural motifs in the total synthesis of natural products.

Only recently, they also gained great interest in macromolecular chemistry, since the variation of the single components displays an easy tool to adjust the properties of the polymers and facile introduction of functional groups is enabled. Hereby, tailor-made high-performance and smart materials can be obtained, which are currently highly requested for many applications. In order to attain this objective, several strategies are followed: the MCRs are used to synthesize structurally diverse monomers for subsequent polymerization, or by the use of bifunctional components, these reactions are directly utilized as polymerization method. Moreover, the Passerini and Ugi reaction are applied in macromolecular engineering as conjugation method of two kinds of polymers, or as tool for grafting reactions as well as in the creation of defined primary structures. Finally, these valuable reactions are also used in the convergent and divergent synthesis of dendritic architectures.

Keywords Biocompatible hydrogels · Complex architectures · Functionalized vinyl monomers · Janus-type dendrimers · Modular nature · Passerini three-component reaction · PEGylation of proteins · Photo-responsive polymers · Sequence-defined structures · Tailor-made materials · Ugi four-component reaction

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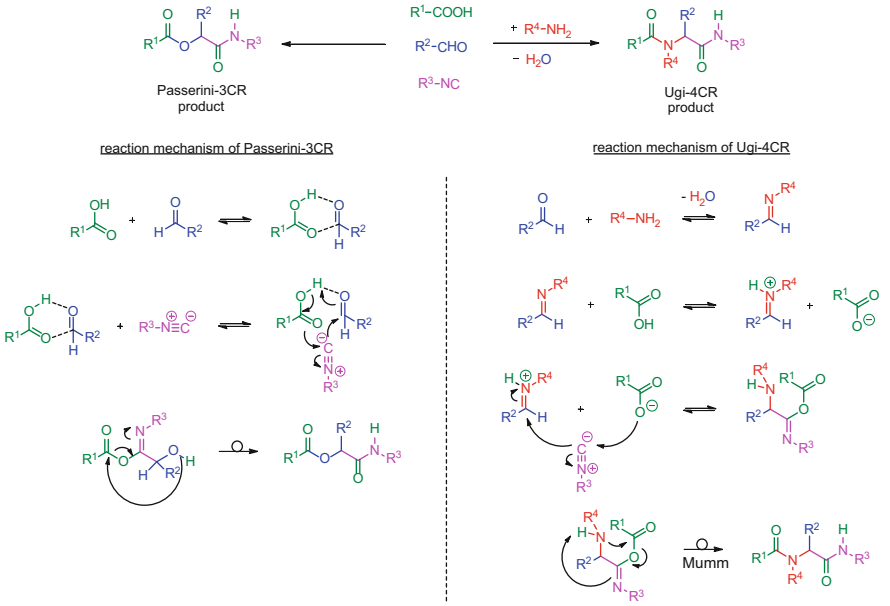
Contents

1 Introduction

The best known and most well-established isocyanide-based multicomponent reactions (IMCRs) are the Passerini three-component reaction (Passerini-3CR) and the Ugi four-component reaction (Ugi-4CR) [1–3]. They allow the synthesis of diversely substituted ester- and/or amide-containing (macro)molecules in a highly straightforward and efficient manner [4]. The Passerini-3CR combines a carboxylic acid, an oxo-component (aldehyde or ketone), and an isocyanide, leading to α-acyloxycarboxamides (Scheme 1, left). The commonly accepted mechanism starts with activation of the carbonyl component by forming a loose hydrogen-bonded adduct with the carboxylic acid. Then, in the so-called α-addition, the activated oxo-component is attacked by the isocyanide carbon in a nucleophilic fashion, whereas the same carbon acts as electrophile when it reacts with the carboxylic acid. Subsequently, the resulting intermediate rearranges in an intramolecular acyl transfer to the Passerini product. In contrast, the Ugi-4CR involves an additional primary amine as fourth component and leads to α-aminoacylamides under release of water (Scheme 1, right). Here, first an imine is formed from the aldehyde and amine component; the imine is then protonated by the carboxylic acid. Analogously to the Passerini-3CR, the isocyanide reacts in the α-addition with the activated (protonated) imine and carboxylate to form the corresponding imidate. Subsequent Mumm rearrangement yields the final Ugi product [5]. Interestingly, the additional amine component significantly increases the number of accessible compounds (i.e., molecular diversity), which is especially beneficial in the field of combinatorial and medicinal chemistry [6–8]. Furthermore, both reactions are established and valuable tools in organic chemistry for forming complex structural motifs, which are, for instance, required for the total synthesis of natural products [9–11].

Recently, multicomponent reactions (MCRs) also gained attention in polymer science and are now rapidly evolving into an independent area of research [12–14]. This extraordinary approach benefits, on the one hand, from the inherent



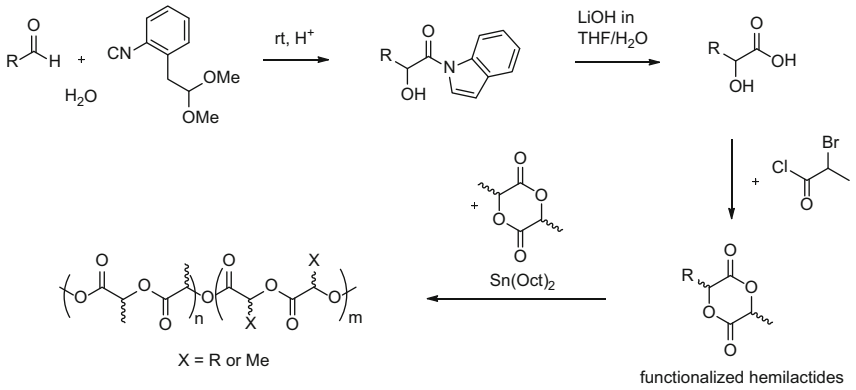
Scheme 1 The Passerini-3CR involving carboxylic acid, aldehyde, and isocyanide (*left*) and the Ugi-4CR with additional primary amine (*right*). The respective reaction mechanisms are depicted below

advantages of MCRs (straightforward procedures and high atom economy as well as molecular diversity); on the other hand, the increasing demand for high-performance and smart materials can be addressed using MCRs. In this way, the symbiosis of MCRs and polymer science provides a unique opportunity for the design of tailor-made polymeric materials. Here, especially the Passerini and Ugi reactions serve as useful tools for polymer design because simple and readily available starting materials can be used. Furthermore, reactions run at room temperature without the need for catalysts. The possibility of obtaining structurally diverse and "tuned" (i.e., in terms of properties and molecular structure) macromolecules in a straightforward fashion clearly demonstrates the mostly unexplored potential of MCRs in polymer science.

2 Passerini-3CR in Polymer Science

2.1 Monomer Synthesis

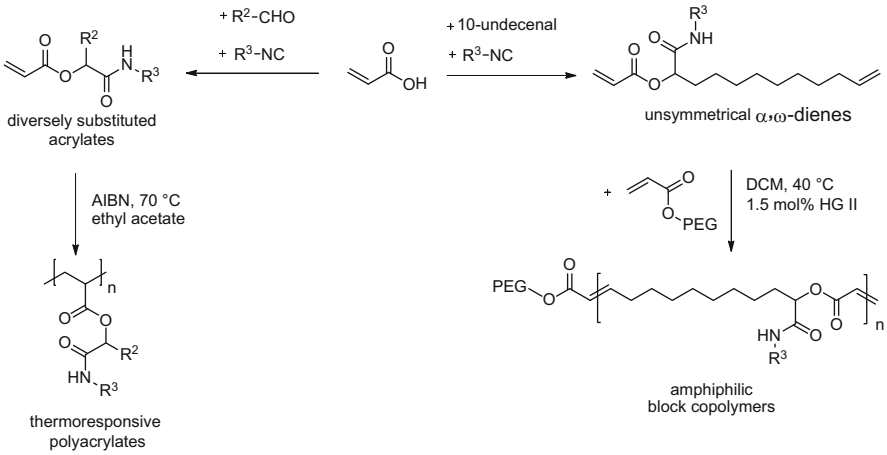
In 2010, the Passerini-3CR was used in the context of polymer science for the first time as a synthetic tool for the formation of monomers. Here, a Passerini-type condensation reaction of water, 2-(2,2-dimethoxyethyl)phenyl isocyanide



Scheme 2 Synthesis route for the formation of functionalized hemilactides via Passerini-type condensation reaction and their subsequent copolymerization with D,L-lactide [15]

(a convertible isocyanide), and various aldehydes in acidic medium was applied, leading to highly reactive α-hydroxy *N*-acylindoles [15]. Subsequent treatment of the convertible indolyl amide moiety with lithium hydroxide in a tetrahydrofuran (THF)/water mixture afforded the corresponding α-hydroxy acids, which served as precursors for the synthesis of novel hemilactides by reaction with 2-bromopropionyl chloride (Scheme 2). The introduced procedure provides access to functionalized hemilactides containing aldehyde-derived side chains. Copolymerization with D,L-lactide utilizing tin(II) 2-ethylhexanoate as catalyst resulted in side chain functionalized poly(α-hydroxy acid) copolymers, combining both biodegradability and tunable properties.

In 2011, we reported a highly efficient strategy for the synthesis of ADMET (acyclic diene metathesis) monomers via Passerini-3CR in a one-step procedure [16–19]. The combination of ricinoleic acid-derived platform chemicals (10-undecenoic acid and 10-undecenal) and various isocyanides resulted in amide-substituted α,ω-dienes in a straightforward fashion [20]. These partially renewable compounds were polymerized via ADMET polymerization employing the Hoveyda–Grubbs second generation catalyst. The resulting α-amide-substituted polyesters reached number average molecular weights (M_n) of up to 22 kDa. Furthermore, the Passerini-3CR was used for grafting-onto reactions utilizing a *tert*-butyl isocyanoacetate-derived polymer. Hydrolysis of the *tert*-butyl ester and subsequent reaction with heptaldehyde and cyclohexylisocyanide led to full conversion of the carboxylic acid moiety on the polymer backbone. In a different study, another Passerini grafting-onto reaction was demonstrated on pendant carboxylic acids of a renewable polyester [21]. Thus, the Passerini-3CR manifested its valuable applicability in post-polymerization modifications. Most interestingly, in the former report we also showed for the first time that the Passerini-3CR can be used for step-growth polymerizations using a dicarboxylic acid, a dialdehyde, and two equivalents of isocyanide, leading to high molecular weight polymers (see Sect. 2.2 for details) [16].



Scheme 3 Acrylic acid as key component in the Passerini-3CR for synthesis of diversely substituted acrylate monomers (*left*) [23]. Formation of unsymmetric α,ω-dienes and subsequent ADMET polymerization with PEG acrylate to yield amphiphilic block copolymers in a one-pot reaction (*right*) [24]

A related example was recently reported applying the convertible 2-(2,2-dimethoxyethyl)phenyl isocyanide, 10-undecenal, and 10-undecenoic acid as starting materials [22]. The resulting Passerini-3CR monomer exhibits two terminal double bonds and a functionalized side chain, which can be easily used for further modification. Similarly to the above-mentioned procedure, the corresponding ADMET polymer was synthesized, which offered manifold opportunities for grafting-onto reactions due to the convertible moiety in every repeat unit. Conversion of the indolyl amide side chain to esters, thioesters, and carboxylic acids with subsequent grafting-onto reaction using the Passerini-3CR was shown. In this way, the polymer properties and functionality can easily be tuned.

The use of acrylic acid instead of 10-undecenoic acid allowed the synthesis of unsymmetric α,ω-diene monomers, which contain an acrylate and a terminal olefin (Scheme 3) [24]. Such compounds are well known to feature high cross-metathesis selectivity and, therefore, ADMET polymerization only showed head-to-tail monomer addition [25–27]. The addition of monofunctional PEG_{480} acrylate during the polymerization led to amphiphilic block copolymers exhibiting a hydrophilic PEG block and a hydrophobic ADMET block. As shown in a previous study [25], the length of the ADMET block is determined by the ratio of the monomer to chain-transfer agent. Thus, the synthesis of defined ADMET blocks of 10 and 20 units using the above mentioned Passerini-3CR derived monomers was possible. Dynamic light scattering in water of these amphiphilic block copolymers showed the formation of well-defined nanosized particles.

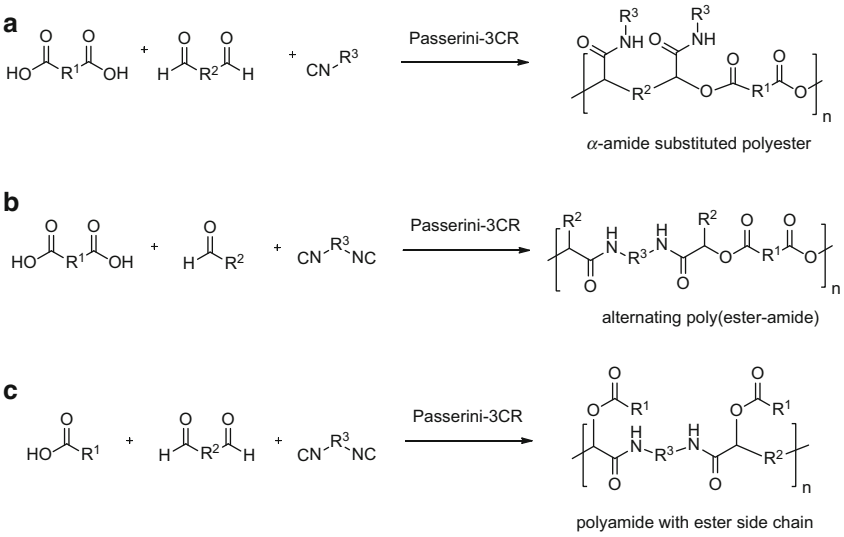
In a different approach, acrylic acid was employed in a Passerini-3CR for the formation of a set of diversely substituted acrylate monomers (Scheme 3) [23]. Here, the reaction was performed in dichloromethane (DCM) or water as

solvent [28]. The different Passerini products were polymerized via free radical polymerization using AIBN as radical initiator, reaching M_n values of up to 98 kDa. As a result of their various side chains, the polymers varied in their glass transition temperatures (T_g) in the range from 30°C to 123°C. Moreover, because hydrogen bond donors and acceptors are available in these polyacrylates, they showed thermoresponsive behavior (upper critical solution temperature) in protic solvents (alcohols). The lowest cloud point was measured at −37°C and the highest at an elevated temperature of 74°C, demonstrating that the material properties can easily be tuned using a muticomponent approach.

Analogously, Passerini-derived vinyl monomers (acrylic, methacrylic, and styrenic) were synthesized by Roth and coworkers [29]. The novel methacrylic and styrenic monomers were generated by the use of methacrylic acid or 3-vinylbenzaldehyde as key substrates. Regarding structural diversity, the latter derivatives are of great benefit because styrenic monomers often lack modification possibilities. The novel monomers were polymerized in a controlled manner via reversible addition fragmentation chain transfer (RAFT) polymerization (polydispersity index, $Đ \leq 1.29$). Moreover, not only homopolymers were formed, but also statistic copolymers as well as defined block copolymers with methyl methacrylate (MMA), styrene, or poly(ethylene glycol) methyl ether methacrylate (PEGMA) as co-monomers. Additionally, this approach facilitates simple introduction of different functionalities into the monomer units, which can be used for post-modifications, as shown with dienes, double bonds, protected triple bonds, and pentafluorophenyl or acetate moieties. Exemplarily for a post-polymerization modification, the polystyrene homopolymer with pendant acetate groups was saponified and reacted with Methyl Red in a Steglich esterification. Additionally, successful thiol-*para*-fluoro substitution of several polyacrylates and polymethacrylates bearing pentafluorophenyl moieties was demonstrated using a set of thiols in the presence of tertiary amines [30]. When copolymerized with thermoresponsive poly(ethylene glycol) methyl ether acrylate (PEGA), thiol-*para*-fluoro substitution resulted in a slight shift of the cloud point, allowing fine-tuning of the thermoresponsive behavior of the respective polymers. Furthermore, copolymers with pentafluorophenyl acrylate instead of PEGA were prepared, providing two dissimilar reactive sites in the side chain. While the pentafluorophenyl ester selectively underwent acyl-substitution with amines, sequential thiol-*para*-fluoro substitution of the Passerini-derived moieties was enabled.

2.2 *Passerini Addition Polymerization*

The use of bifunctional components (i.e., AA + BB, or AB-type monomers) in a Passerini-3CR either leads to ring or polymer formation [31]. Directed synthesis is mainly determined by the concentration of the reaction mixture, as typical for step-growth processes. Ring formation is more likely to take place in high dilution, whereas polymer formation only occurs at high concentrations or in bulk. For



Scheme 4 Possible combinations of two bifunctional components (AA + BB) and one monofunctional component in a Passerini-3CR, resulting in different repeat units: (**a**) alpha-amide substituted polyesters, (**b**) alternating poly(ester-amide)s and (**c**) polyamides with ester side chains

polymer formation, three possibilities of combining two different bifunctional components with one monofunctional component exist: the combination of a dicarboxylic acid and a dialdehyde; a dicarboxylic acid and a diisocyanide; or a dialdehyde and a diisocyanide (Scheme 4). In this way, polyesters or polyamides with functional side chains are formed, depending on the combination.

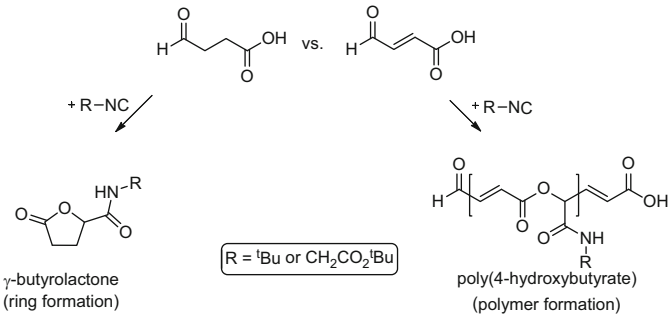
Meier et al. reported the first Passerini addition polymerization using a dicarboxylic acid and a dialdehyde in combination with various isocyanides (Scheme 4a), as already mentioned above [16]. The resulting α-amide-substituted polyesters were obtained with M_n of up to 56 kDa, highly depending on the concentration of the reactants. It was shown that high monomer concentrations favor the polymerization process. The Passerini addition polymerization of a dicarboxylic acid and a diisocyanide with different aldehydes was subsequently investigated by Li and coworkers [32]. For this purpose, the reaction of adipic acid, 1,6-diisocyanohexane, and phenylacetaldehyde was screened using different solvents (1M solution in water, methanol, THF, toluene, chloroform, and dichloromethane), revealing that toluene gave the highest molecular weights in this step-growth polymerization. Nevertheless, reactions performed in dichloromethane also resulted in M_n values above 15 kDa along with excellent yields. Moreover, detailed kinetic studies of the polymerization process confirmed the step-growth mechanism of the Passerini polyaddition reaction. Interestingly, with this combination of starting materials, the resulting polymers exhibit an alternating poly(ester-amide) backbone, having side chains derived from the aldehyde component (Scheme 4b). Using 10-undecenal as monofunctional component, double bonds were introduced to these side chains, which were further used for successful post-polymerization

modification via thiol-ene addition reactions. In a recent study, Li and coworkers extended the presented Passerini polymerization approach by using alcohols instead of aldehydes [33]. Here, the aldehyde component was generated by in situ oxidation of the alcohol with 2-iodoxybenzoic acid (IBX), as already reported for small molecules [34]. In this way, a broader scope of possible side chains is accessible and the incorporation of otherwise unstable aldehydes is possible, as shown for glycidol. On the other hand, this new procedure restrained the Passerini polymerization since only moderate molecular weights were obtained.

Furthermore, a dialdehyde, a diisocyanide, and a carboxylic acid were applied in the Passerini one-pot polymerization (Scheme 4c). For this combination of reactants, Li et al. used adipaldehyde, 1,6-diisocyanohexane, and undecanoic acid, resulting in polyamides with functional side groups [35]. Optimization of the reaction conditions revealed that a 1M chloroform solution of bifunctional components and a 2.2-fold excess of the carboxylic acid at 40°C gave the best results, yielding polymers with M_n of up to 16.6 kDa in a yield of 90%. Here, ω-alkene- or ω-alkyne-functionalized carboxylic acids were used as monomers in order to allow post-polymerization modifications via thiol-ene addition or copper-catalyzed azide-alkyne click chemistry (CuAAC).

Taking into account that AB-type monomers are also conceivable in a Passerini polyaddition, more than the three mentioned options are possible. In this regard, Meier et al. found that the combination of a carboxylic acid and an aldehyde as an AB-type monomer was the most convenient approach, because isocyanides are mostly introduced by a two-step procedure that results in a more complex synthesis route [36, 37]. Moreover, isocyanides exhibit a low acid stability, making the combination of an isocyanide and a carboxylic acid unreasonable [38]. The one-step synthesis followed by Meier and coworkers took advantage of the atom-economic and efficient thiol-ene addition of 3-mercaptopropionic acid to 10-undecenal. The resulting AB-type monomer was polymerized with various isocyanides via the Passerini reaction, simplifying the procedure to a two-component three-center reaction. Interestingly, the synthesized polymers bore a sulfur atom in every repeat unit of the backbone, which was oxidized to the corresponding sulfone with 3-chloroperbenzoic acid (mCPBA), thus increasing their glass transition temperatures by ~30°C after oxidation.

The same route was followed by Li et al., employing 4-oxobutyric acid as AB-type monomer [39]. In this case, however, the Passerini reaction mainly led to the corresponding γ-butyrolactone instead of the desired poly(4-hydroxybutyrate) as a result of the favored formation of a five-membered ring (Scheme 5). To prevent the internal cyclization, the corresponding *trans*-α,-β-unsaturated analog was used instead, yielding polymers with M_n of up to 8.8 kDa. Subsequent hydrogenation resulted in the originally targeted polymer. Moreover, the acidic degradation of the functional polyester backbone was investigated in detail, revealing a dominant cascade intramolecular cyclization mechanism resulting in nontoxic γ-lactone degradation products. Therefore, these diversely functionalized poly(4-hydroxybutyrate)s were suggested as self-immolative polymers that could be used in surgical treatments.

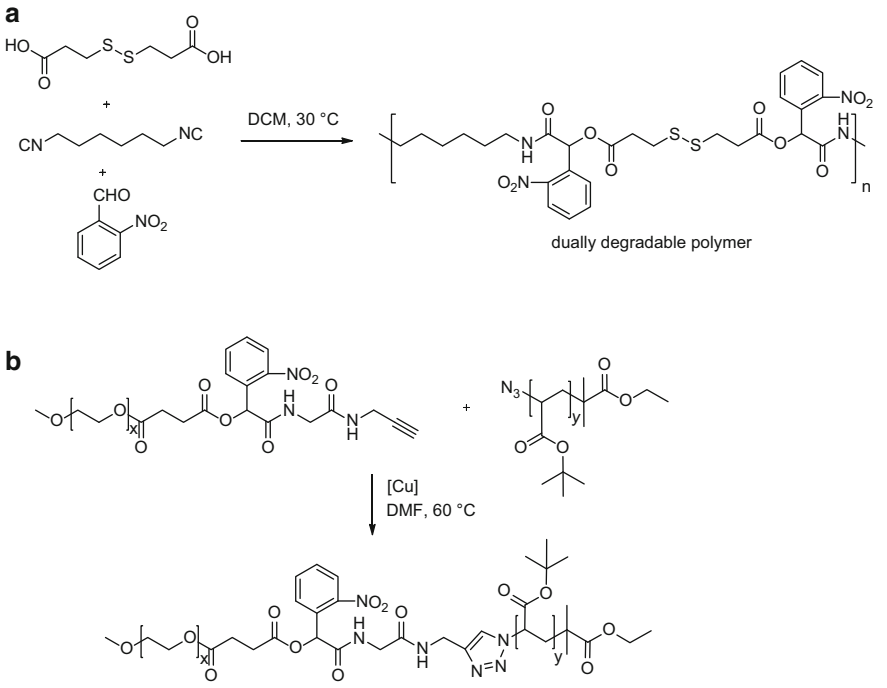


Scheme 5 Selective ring formation employing 4-oxobutyric acid (*left*) or selective polymer formation employing the *trans*-α,β-unsaturated analog in the Passerini reaction (*right*) [39]

Moreover, the application of three bifunctional components was reported by Li et al. in order to obtain highly branched polymers, exhibiting a high degree of functionalization [40]. Thus, adipic acid (A), hexane-1,6-dial (B), and 1,6-diisocyanohexane (C) served as components in the Passerini-3CR. Using different *ratios* of the dicarboxylic acid component (A:B:C = x:1.0:1.0) led to highly branched polymers having end-functionalized aldehyde and isocyanide branches. Interestingly, fine-tuning of the molar ratio was of crucial importance, since only if $x = 0.41$ was a hyperbranched polymer of $M_n = 3.5$ kDa obtained. Otherwise, only oligomers were formed ($x = 0.40$) or gelation occurred ($x = 0.42$). Higher molecular weights were achieved by applying 10-undecenoic acid and adipic acid simultaneously in the Passerini-3CR, consequently lowering the degree of crosslinking while increasing the degree of additional functionalization. The adjustment of the proper molar ratio was also crucial in this case. Theoretical calculation of the critical gelation line via the Carothers equation gave only rough agreement with experimental data.

Furthermore, the crosslinking of polymers via IMCRs was demonstrated by Crescenzi and coworkers, employing polysaccharides as multifunctional carboxylic acid [i.e., (carboxymethyl)cellulose] along with glutaraldehyde and cyclohexyl isocyanide [41, 42]. The obtained hydrogels showed good swelling properties and complete transparency. Nevertheless, their chemical stability in aqueous media was low as a result of the hydrolysis of ester linkages. Crosslinking via Ugi-4CR was more suitable because the respective polymers exhibited only amide linkages, being more stable towards hydrolysis (details on Ugi polycondensation are given in Sect. 3.2).

Another attractive field of research in combination with muticomponent polymerizations is that of photochemical reactions. The modular nature of MCRs allows the simple introduction of photoresponsive moieties, offering novel and extremely versatile reaction or modification possibilities. For instance, the Passerini addition polymerization of adipic acid, 1,6-diisocyanohexane, and photosensitive 2-nitrobenzaldehyde led to poly(ester-amide)s with photolabile linkages in the backbone (Scheme 6) [43]. UV-irradiation ($\lambda = 365$ nm) of the polymer solution



Scheme 6 Two routes for the synthesis of photodegradable polymers using 2-nitrobenzaldehyde in the Passerini reaction [43]: (**a**) incorporation of the photolabile group in every repeat unit, and (**b**) incorporation of 2-nitrobenzaldehyde as linkage between two polymers

for 20 min resulted in full degradation of the polymer backbone as a result of cleavage of the 2-nitrosobenzyl moiety, allowing controlled decomposition of the polymer. Moreover, 3,3′-dithiodipropionic acid was used as the dicarboxylic acid in the Passerini-3CR, enabling redox-initiated degradation of the polymer (Scheme 6a). Orthogonal degradation via UV irradiation or redox initiation using dithiothreitol was also demonstrated. In addition, a monofunctional PEG acid was reacted with propargyl isocyanoacetamide and 2-nitrobenzaldehyde in a Passerini-3CR. The resulting macromolecular alkyne was used in a CuAAC with an azide-terminated poly(*tert*-butyl acrylate) to obtain block copolymers (Scheme 6b). Similarly to the aforementioned procedure, subsequent irradiation with UV light cleaved the blocks at the Passerini-derived ester linkage, yielding the two starting polymers. Thus, this method offers the opportunity to synthesize photodegradable polymers in a straightforward fashion.

In another study, the photodegradable Passerini polymer was used as a reactive photoresist [44]. Additional functionalization of 5-hydroxy-2-nitrobenzaldehyde with three different reactants (i.e., allyl bromide, propargyl bromide, or epichlorohydrin) led to four different polymers bearing either an alkene, alkyne, or epoxide moiety, or all of them. The latter polymer, having three different kinds of reactive sites, was spin-coated onto a silica wafer from a THF-mixture, including

diethylenetriamine as crosslinker. Subsequent amine-epoxy curing at elevated temperature hardened the photoresist, still exhibiting alkyne and alkene moieties. Irradiation of the polymer film with UV light by the use of a photomask generated a regular polymeric grid after development of the wafer. Post-polymerization modification of the pendant alkyne and alkene groups via sequential CuAAC and thiol-ene reaction was used to introduce fluorescein and rhodamine B molecules, respectively. Fluorescence microscopy of the functional polymeric grids proved the successful conversion of the peripheral groups, implementing a powerful procedure for adjustable photoresists.

The synthesis of a heterogeneous macromolecular photocatalyst via Passerini-3CR was carried out by the research group of Jing [45]. Here, the concept of the ABC-type Passerini reaction, presented by Li et al. [40] was used to synthesize crosslinked polymers by employing sebacic acid, 1,6-diisocyanohexane, terephthalaldehyde, and $[(bpy)_2Ru(fmbpy)](PF_6)_2$ as photocatalyst. In this way, an insoluble crosslinked polymer was formed, exhibiting immobilized ruthenium complexes (loading of 3.9 wt%). Its catalytic activity was demonstrated in the photo-oxidation of benzylamine and various sulfides. Most advantageous was the full recovery of the crosslinked polymer by simple filtration from the reaction mixture and its reuse for further catalytic reactions. Remarkably, the prepared photocatalyst was recovered up to three times without observing a decrease in catalytic activity of the incorporated ruthenium complexes.

Moreover, the Passerini addition polymerization allows the simple introduction of photoswitchable components such as diarylethenes, spiropyranes, or azobenzenes. For instance, Song and coworkers introduced an azobenzene-substituted carboxylic acid into the polymer by applying the Passerini reaction [46]. Interestingly, the synthesized polyamides having azobenzene side chains showed self-assembly in THF. Spherical nanostructures were observed by several microscopy techniques (AFM, SEM, and TEM) and showed sizes of hundreds of nanometers to a few micrometers. Moreover, the size of the nanoparticles could be controlled in aqueous solution by the stirring rate, the size ranging from 164 nm (no stirring) to 74 nm (1,500 rpm). Exposure of these nanospheres to UV light ($\lambda = 365$ nm) induced isomerization of the azobenzene moieties, triggering deformation of the particles and agglomeration to larger aggregates. Surprisingly, the *cis–trans* isomerization upon irradiation occurred reversibly, whereas deformation did not.

2.3 Macromolecular Engineering

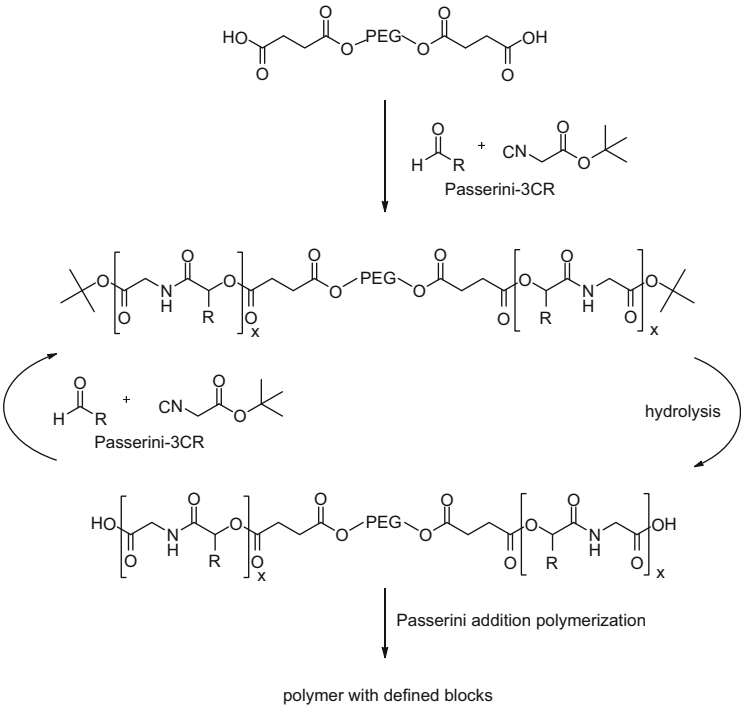
The design of highly defined polymer architectures remains a challenging issue in macromolecular chemistry. MCRs are certainly an inherently powerful tool in macromolecular chemistry as a result of their modular nature. A striking approach demonstrating the advantages of using the Passerini-3CR has been reported by Li and coworkers [47]. The reaction of a monofunctional PEG aldehyde, 2-bromo-2-

methylpropionic acid, and propargyl isocyanoacetamide led to a double α-end-functionalized PEG macroinitiator, bearing both an atom transfer radical polymerization (ATRP) initiator and an alkyne moiety. Consecutive ATRP with *N*-isopropylacrylamide (NIPAM) as monomer, and subsequent CuAAC of the azide-terminated polystyrene, resulted in a miktoarm star terpolymer. The simultaneous approach of ATRP and CuAAC was also demonstrated, making the procedure more attractive in view of simplicity and efficiency.

Furthermore, the synthesis of Passerini-derived graft copolymers was shown in a straightforward fashion [48]. The use of adipaldehyde, 1,6-diisocyanohexane, and 2-bromoisobutyric acid in a Passerini addition polymerization led to a polyamide backbone with pendant ATRP initiators. Subsequent ATRP grafting from the polymer backbone, employing NIPAM or MMA as monomers, gave PA-*g*-PNIPAM or PA-*g*-PMMA architectures. This simple two-step procedure was also performed in a one-pot manner. Moreover, because the grafts were only linked by ester groups, easy detachment of the graft-polymers was feasible in order to study the living character of the ATRP polymerization. Alternatively, 11-hydroxyundecanoic acid was used as acid component in the Passerini reaction to install pendant hydroxyl side groups, which initiated the ring-opening polymerization of *ε*-caprolactone.

Furthermore, not only complex polymer architectures can be obtained by the Passerini-3CR, but also sequence-defined primary structures. So far, only a few techniques allow the preparation of sequence-controlled macromolecules, for example, the stepwise peptide synthesis procedure first established by Merrifield in 1963 [49, 50]. Other routes utilize DNA template-based techniques or make use of the high crosspropagation reactivity of styrene and maleimides or maleic anhydride in chain-growth polymerizations [51, 52]. Another innovative approach using MCRs was highlighted by Li et al. [53]. First, a PEG 1000 polymer was reacted with succinic anhydride to obtain a double acid end-functionalized building block. This component was further reacted with *tert*-butyl isocyanoacetate and 10-undecenal via Passerini-3CR. Simple purification by precipitation and subsequent hydrolysis of the *tert*-butyl ester with formic acid gave the corresponding extended polymeric diacid (Scheme 7). Repetitive application of the Passerini reaction using two different aldehydes and iterative hydrolysis of the *tert*-butyl ester induced a defined primary structure. Interestingly, the synthesized ABA block copolymers with a sequence-defined A block were further processed as macromonomers in a Passerini addition polymerization with phenylacetaldehyde and 1,6-diisocyanohexane to obtain multiblock copolymers with an ordered side chain sequence of three different compounds.

A similar approach was followed by Meier and coworkers, which allowed variation of the isocyanide component [54]. In this case, stearic acid served as onset for the chain elongation via Passerini-3CR along with 10-undecenal and various isocyanides. 10-Undecenal, because of its terminal double bond, enabled the subsequent thiol-ene addition of 3-mercaptopropionic acid with 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photoinitiator. The newly introduced carboxylic acid provided reactivity for further sequences of Passerini-3CRs and thiol-ene

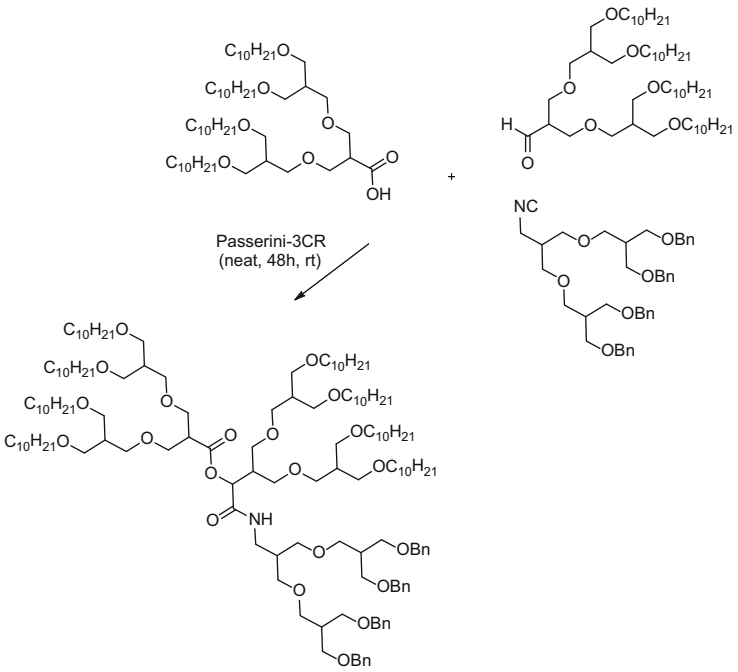


Scheme 7 Synthesis of polymers having sequence-defined side groups via iterative use of Passerini-3CRs (using *tert*-butyl isocyanoacetate and different aldehydes) and hydrolysis of the *tert*-butyl esters [53]

reactions. The iterative strategy was utilized for the synthesis of a tetramer having four different side chains. Finally, the protocol was transferred to a monofunctional PEG acid, which simplified the purification. Thus, the desired block copolymer having five defined unique sequences was obtained in high purity. In this way, sequence control was realized without the need for any protecting group or activating agents.

2.4 Dendritic Architectures

Dendrimers are an important class of monodisperse macromolecules that provide a large surface for manifold advanced technologies [55]. For their synthesis, two main approaches are used: the convergent and divergent approaches. Recently, both routes were successfully used employing MCRs. Rudick et al. reported a convergent approach using the Passerini-3CR for the first time [56]. Starting with β-methallyl chloride, a second generation dendron was built bearing an alcohol at the center. This alcohol was further converted to the three components needed for



Scheme 8 Convergent approach for the synthesis of dendrimers via Passerini-3CR [56]

the Passerini reaction by stepwise oxidation to the corresponding aldehyde and carboxylic acid. The corresponding isocyanide was synthesized by transformation into the amine and subsequent application of the standard two-step procedure to yield isocyanides [36, 37]. Finally, these functionalized precursor dendrons were combined via Passerini-3CR in an isolated yield of 60% (Scheme 8).

Regarding the divergent approach, Wessjohann et al. performed pioneering work in this field of research [57, 58]. The Passerini-3CR of Cbz-monoprotected bifunctional components (isocyanide, aldehyde, and carboxylic acid) led to a three-arm core unit (yield of 80%) having terminal benzyl esters. These peripheral protecting groups were subsequently cleaved by hydrogenation with palladium hydroxide on carbon to afford the corresponding carboxylic acids. Iteration of this synthesis protocol (Passerini-3CR and hydrogenation) resulted in a dendrimer of the third generation. This concept was extended using more building blocks for IMCRs and is presented in the section on Ugi-4CR (Sect. 3.4).

Another divergent approach was demonstrated by the use of castor oil-derived platform chemicals. Here, 10-undecenal, 10-undecenoic acid, and 10-isocyanodec-1-ene served as components for the formation of the core unit via Passerini-3CR [59]. The resulting product, having three terminal olefins, was subsequently reacted with an excess of *tert*-butyl acrylate in a cross-metathesis reaction, followed by hydrogenation of the newly formed double bonds. The introduced *tert*-butyl esters were cleaved with trifluoroacetic acid; thus, three carboxylic acid groups were

installed in the periphery, allowing further Passerini-3CRs for the synthesis of the first generation dendrimer. Repetitive application of this synthesis sequence allowed the formation of a third generation dendrimer.

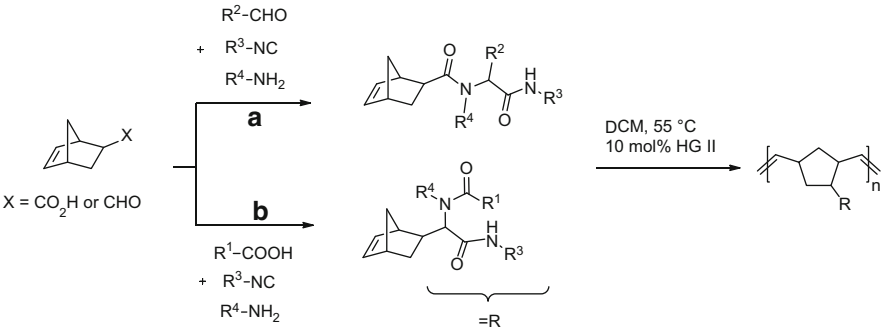
This concept was refined by the research group of Li, who employed the thiol-yne reaction instead of the olefin cross-metathesis reaction as key step [60]. In this case, the carboxylic acid component served as anchor, whereby terminal alkynes were introduced by the remaining components (5-hexyn-1-al and propargyl isocyanoacetamide). Interestingly, thiol-yne addition of 3-mercaptopropionic acid to the pendant alkynes enabled not only the incorporation of further carboxylic acids, but also resulted in additional branching. Therefore, the second generation dendrimer, synthesized in three steps, exhibited 16 peripheral triple bonds. Moreover, this concept offers the opportunity to introduce structural diversity into the dendrimer architecture because the use of only one alkyne-functionalized compound in the Passerini-3CR still results in branching due to the thiol-yne reaction. Here, a structural sequence of employed phenylacetaldehyde and 2-nitrobenzaldehyde was demonstrated.

3 Ugi-4CR in Polymer Science

3.1 Monomer Synthesis

Although the Passerini-3CR found its way into polymer chemistry only recently, a few examples of Ugi-4CRs in polymer science were reported as early as 1999 for the crosslinking of polysaccharides, and in 2003 for the synthesis of monomers [42, 61]. Afterwards, for about 10 years no significant contributions of Ugi-4CRs to polymer science are found in the literature until it was rediscovered as an essential tool for the synthesis of peptoidic structure motifs [12, 13]. This "long sleep" might be because of the solvent usually used in Ugi reactions, namely methanol, which dissolves polymers poorly and is applied for their precipitation rather than for their synthesis. Thus, the synthesis of monomers by the Ugi-4CR seemed to be more attractive in the early stages.

It was Wright et al. who first introduced the Ugi-4CR for the synthesis of norbornenyl monomers (Scheme 9) [61]. Here, the synthesis of four different monomers, either starting from a norbornenyl acid or aldehyde component, was demonstrated. Successful polymer formation was shown via ring-opening metathesis polymerization (ROMP) using the Grubbs second generation catalyst with a loading of 10 mol%. In this way, molecular weights of up to 50 kDa were reached. Further efforts were made to employ enantiomerically pure reactants in the Ugi-4CR to finally obtain chiral materials. Therefore, a chiral norbornenyl aldehyde, benzoic acid, benzylamine, and *tert*-butyl isocyanide were used in an Ugi-4CR to yield the complementary diastereomer as monomer. However, the diastereoselectivity of the reaction was only 1.7:1 and chromatographic separation



Scheme 9 Monomer synthesis using norbornenyl-derived acid (*a*) or aldehyde (*b*) in an Ugi-4CR and subsequent ROMP [61]

of the diastereomers was necessary. Finally, with these chiral monomers in hand, ROMP gave the corresponding macromolecules bearing chiral peptide-structures as side chains. Interestingly, such materials have found application as asymmetric catalysts or for the separation of racemic mixtures in chiral chromatography.

Further applications have been demonstrated by Meier and coworkers. Analogously to the monomer synthesis via Passerini-3CR [16], 10-undecenal and 10-undecenoic acid in combination with various amines and isocyanides were used as reactants in the Ugi-4CR to yield a small library of α,ω-diene monomers [62]. The reaction involved aliphatic and aromatic substituents, as well as ester and alcohol functional groups. For the polymerization of these diversely substituted monomers via ADMET, the Umicore $M5_1$ catalyst showed the best functional group tolerance. In this way, M_n of up to 28.8 kDa were reached. Furthermore, by the addition of methyl 10-undecenoate as chain-transfer agent (5.0–30 mol%), control over the molecular weight was demonstrated. The end groups of the obtained telechelics were used to determine an absolute degree of polymerization by NMR analysis. Additionally, thiol-ene addition polymerizations of selected monomers were successfully performed employing 1,4-butanedithiol as co-monomer. A highlight of this study was the use of 2-nitrobenzylamine in the Ugi-4CR to introduce a photo-labile group to the polymer. After cleavage of the 2-nitrosobenzyl derivative by sunlight, a monosubstituted amide was generated, allowing hydrogen bonding. In this way, a dramatic change in the thermal properties of the polymers was achieved ($\Delta T \sim 300°C$) by simple light irradiation, offering potential applications as photoresponsive coatings or resists.

Moreover, the use of the convertible 2-(2,2-dimethoxyethyl)phenyl isocyanide in the Ugi-4CR enabled interesting post-polymerization modification opportunities [22]. Similarly to the use of Passerini monomers, many grafting-onto reactions could be realized using primary and secondary amines or lithium hydroxide to afford the corresponding amide- or carboxylic acid-functionalized polymers, respectively. Interestingly, the conversion into the amide was not possible via the Passerini approach as a result of the weak polyester backbone. However, because Ugi-4CR-derived polymers contain amide bonds, harsher reaction conditions are

tolerated and polymers with carboxylic acid side chains could be synthesized without affecting the polymer backbone. Subsequent Ugi-4CR of the carboxylic acid-substituted polymer using ω-unsaturated compounds offers the possibility of synthesizing dendronized polymers by iterative reaction sequences (cross-metathesis, deprotection, Ugi-4CR), comparable to the strategy presented for dendrimer syntheses in Sect. 2.4.

Another attractive monomer synthesis was demonstrated using the related Ugi five-component condensation (Ugi-5CC) [2, 63]. Compared with the Ugi-4CR, the acid component is generated in situ from carbon dioxide and an alcohol, affording carbamate products. The strategy, followed by Meier and coworkers, was focused on the synthesis of dicarbamate monomers, which were subsequently applied in step-growth polymerizations [64]. For this purpose, 1,12-diaminododecane was used as bifunctional linker along with different alcohols (methanol, allyl alcohol, and 1,4-butanediol) and the other required components (aldehyde, isocyanide, and carbon dioxide). The obtained products were diversely substituted dimethyl dicarbamates, α,ω-dienes, or α,ω-diols with molar CO_2 content of 12–14%. Subsequent polymerization of these monomers was only feasible for the two latter compounds because the dimethyl dicarbamate underwent a favored intramolecular cyclization, resulting in hydantoin derivatives [65]. In contrast, the α,ω-diene monomer was polymerized with 1,4-butanedithiol in a radically initiated thiol-ene addition polymerization. In this way, non-isocyanate-based polyurethanes were formed with M_n of up to 19.3 kDa. The polymerization of the diol monomer was performed with diphenyl carbonate as co-monomer and 5.0 mol% titanium (IV) isopropoxide as catalyst to obtain alternating polyurethane–polycarbonate structures ($M_n = 19.7$ kDa). Both kinds of polymers exhibited amorphous behavior due to their bulky side chains. This procedure broadened the structural diversity of Ugi reaction-derived polymers, while incorporating carbon dioxide as an abundant, cheap, and renewable substrate.

3.2 Ugi Polycondensation

The one-pot synthesis of polymers via Ugi-4CR can only be performed if either two bifunctional AA-type components or one AB-type component are used. Moreover, highly concentrated reaction mixtures are needed because otherwise ring formations occur, as thoroughly investigated by Wessjohann and coworkers. Here, the directed synthesis of macrocycles or cryptands under classic or pseudo high dilution conditions, or even without dilution exploiting metal template effects were demonstrated [66, 67].

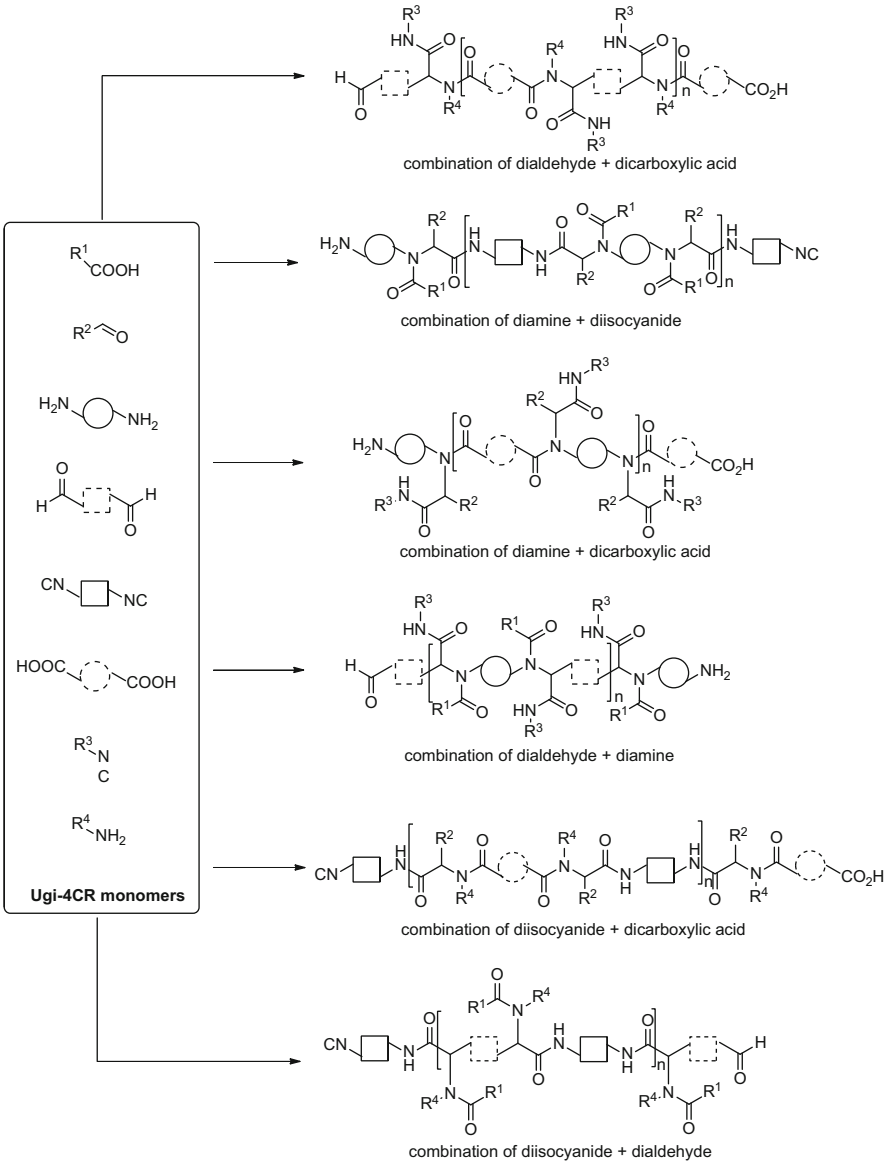
The first application relating to a polymerization process was reported by the group of Crescenzi in 1999, when the Ugi-4CR was used for the crosslinking of polysaccharides [42]. Here, (carboxymethyl) cellulose (CMC) served as multifunctional acid component and was crosslinked with 1,5-diaminopentane, formaldehyde, and cyclohexyl isocyanide in different ratios. The resulting

transparent networks, having amide linkages between the CMC chains, exhibited 5.0–10% crosslinking depending on the initial composition. Other networks were synthesized with 1-(deoxylactit-1-yl) chitosan, a multifunctional amine component, and L-tartaric acid. Both types of hydrogels showed good swelling properties. It is noteworthy that Passerini-3CR crosslinked polymers showed a better swelling behavior (about twice the water uptake) but, on the other hand, they exhibited reduced chemical stability under basic conditions as a result of the ester linkages. Moreover, other biopolymers were synthesized using hyaluronic and alginic acid [41, 68]. The former was additionally crosslinked with L-lysine ethylester, which afforded extra carboxylic acid groups after hydrolysis of the ester groups, resulting in a better swelling capacity compared with 1,5-diaminopentane as crosslinker. Interestingly, these approaches enabled the fine-tuning of hydrogels by adjusting the ratio and kind of components.

Nyström and coworkers have investigated the gelation system of alginate, formaldehyde, cyclohexyl isocyanide, and 1,5-diaminopentane in detail [69]. Here, the effects of different ratios of the single components and of increased temperatures were examined. Rheological investigations revealed that high concentrations of either polymer or crosslinking agent retarded the gelation process, whereas a higher temperature sped up the gelation. Furthermore, the transparency of the biocompatible hydrogel decreased along with gel formation, as revealed by turbidity measurements. Small-angle neutron scattering attributed this effect to large-scale heterogeneities of the gel, enhanced by high crosslinker concentration. Further studies focused on the pH dependency of the Ugi reaction mixture [70]. Interestingly, the desired hydrogel was not formed above pH 3.8. The fastest gelation was observed at pH 3.5. Moreover, cloudy hydrogels were obtained at increasing pH values, attributed to unreacted crosslinker. Summarizing, the presented approaches are highly interesting because the mechanical and optical properties of the Ugi-4CR-derived gels can be precisely adjusted to prepare tailor-made hydrogels for biomedical applications such as tissue engineering or drug release.

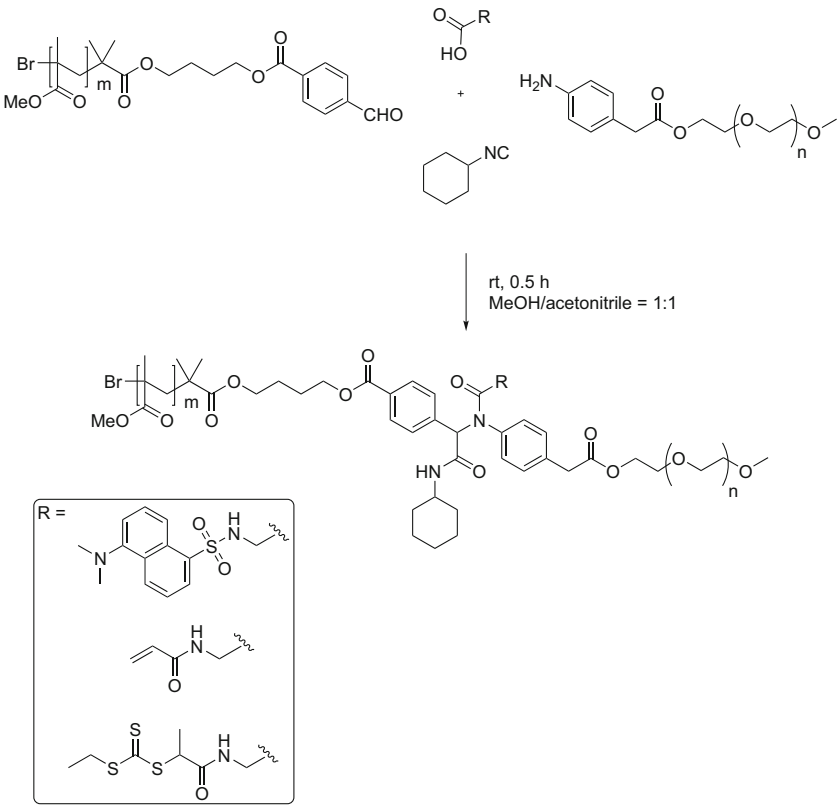
Structurally defined thermoplastics were first synthesized by Ugi polycondensations in 2014 by Meier and coworkers [71]. Here, all six possible monomer combinations of two bifunctional AA-type components and two monofunctional components were investigated, resulting in diversely substituted polyamides (Scheme 10). Their synthesis was particularly facilitated in methanol/THF mixtures, allowing high conversions and good solubility, to yield amorphous polymers with M_n above 10 kDa. Regarding the aldehyde monomer, it is noteworthy that the α-position had to be blocked to avoid side reactions (i.e., aldol condensation). To point out the versatility and functional group tolerance of this approach, 5-hexynoic acid was incorporated into the polymer, introducing alkyne moieties that served as anchors for post-polymerization modifications via CuAAC.

A similar strategy was followed when using the Ugi-5CC for the direct polymerization of two bifunctional components [72]. The application of 1,12-diaminododecane, 1,6-diisoyanohexane, isobutyraldehyde, methanol, and carbon dioxide resulted in the respective polyamide bearing methyl carbamate side chains.



Scheme 10 All possible combinations for polyamide synthesis via Ugi-4CR employing two AA-type monomers and two monofunctional components [71]

Interestingly, this kind of polymer serves as a valuable precursor for conversion into the corresponding polyhydantoin [65]. Simple basic treatment with potassium hydroxide afforded the polyhydantoin after 48 h. Thus, this protocol demonstrates the first non-isocyanate-based approach for the synthesis of polyhydantoins.



Scheme 11 Synthesis of mid-functional polymers bearing a fluorescent molecule, a terminal double bond, or a RAFT agent by the Ugi-4CR [73]

3.3 Macromolecular Engineering

For the synthesis of highly defined and complex polymer architectures, the Ugi-4CR serves as conjugation method for two kinds of polymers: benzaldehyde-terminated PMMA and aniline-terminated PEG 5000 (Scheme 11) [73]. For this purpose, the remaining components, isocyanide and carboxylic acid, were added in high excess (ten and five equivalents, respectively) to achieve full conversion of the parent polymers. Removal of the excess was accomplished via dialysis. Attractively, this approach not only combines two different polymers, but also facilitates the synthesis of mid-functionalized block copolymers by simple introduction of functional isocyanides or carboxylic acids. In this way, Tao and coworkers introduced a fluorescent molecule via the carboxylic acid (using dansylglycine) or a terminal double bond (using 2-acrylamido acetic acid) to obtain a mid-vinyl PMMA-*b*-PEG polymer. Mid-reactive polymers are known to behave differently to their end-functionalized counterparts due to the "umbrella-effect" [74]. Therefore, it was

shown that chemical agents such as captopril can easily be introduced via light-induced radical thiol-ene addition. Moreover, a RAFT agent was installed for grafting-from with NIPAM, resulting in a miktoarm star copolymer. This promising and very useful concept of stitching two molecules together was claimed as a "green click" reaction, which appears a bit too ambitious because the high excess of the isocyanide compound is certainly not green and, more generally, the use of high excess of reagents does not meet the definition of click chemistry [75, 76].

Subsequently, this concept was extended for the PEGylation of proteins, which is an important modification for improving their pharmacological and biologic activity [77]. This aim was achieved in a similar manner as described before, except that this time a protein reactive functionality was installed on the polymer backbone by introduction of pyridyldisulfide (PDS) via the carboxylic acid [78]. Finally, it was linked with bovine serum albumin as model protein, which still showed steady bioactivity after conjugation. The modular nature of the Ugi-4CR also allowed the incorporation of fluorescent molecules.

In the context of material science, Tao et al. developed a highly efficient hexacomponent system to yield carbon-based composites [79]. The system comprises four components of the Ugi reaction (pyrenecarboxaldehyde, cyclohexyl isocyanide, aniline, and a RAFT agent linked to the carboxylic acid) as well as carbon nanotubes and NIPAM. In a one-pot procedure with catalytic amounts of AIBN and heating at 65°C, the respective Ugi product was formed simultaneously with the RAFT polymerization of NIPAM and the supramolecular π–π interaction of the pyrene moiety with nanotubes. In this way, well-defined PNIPAM chains conjugated to the carbon nanotube surface (~66%) were generated, greatly enhancing the dispersion behavior in both organic and aqueous solution. For instance, the carbon-based composites showed thermoresponsiveness.

An interesting approach for sequence-controlled polymers via consecutive Ugi-4CRs was suggested by Wessjohann et al. [80, 81]. Here, the iterative application of the Ugi-4CR involving one glycine-derived building block, such as ethyl isocyanoacetate, and saponification of the introduced ethyl ester resulted in alternating peptide-peptoid structures. This concept was demonstrated for small molecules (five cycles), but also suggested for, for instance, the synthesis of sequence-defined polymers using PEG derived components. Additionally, sequences of IMCRs yielded oligomeric cycles such as pentadepsipeptoids [82].

3.4 Dendritic Architectures

Wessjohann et al. showed the divergent synthesis of peptoidic and peptidic dendrimers by multiple iterative Ugi-4CRs [57, 58]. Compared with conventional techniques, this strategy impresses through the highly flexible and structurally diverse modular design. The application of monoprotected bifunctional components (i.e., mono-methyl glutarate, methyl 5-oxopentanoate, methyl 4-aminobutyrate, and methyl 4-isocyanobutanoate) led to a core unit having four

methyl ester protected branches. Iterative alkaline hydrolysis and application of the Ugi-4CR resulted in dendrimers up to the fourth generation. This concept was demonstrated for a large range of building blocks, and many more potential monomers were suggested. Especially the use of different protecting groups (i.e., methyl ester and benzyl ester) allowed the synthesis of selectively functionalized branches. In this way, the synthesis of Janus-type dendrimers was also shown. Moreover, by using monofunctional building blocks, the degree of branching could be controlled. Finally, the high versatility of this approach was extended to the Passerini-3CR, which was shown for the formation of a third generation dendrimer (see above).

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Adv Polym Sci (2015) 269: 87–104
DOI: 10.1007/12_2014_299

Published online: 6 January 2015

Sequential Thiol-Epoxy and Esterification Reactions: A Facile Route to Bifunctional Homopolymer Sequences

Mihaiela C. Stuparu and Anzar Khan

Abstract In this chapter, a post-polymerization double-modification strategy involving sequential thiol-epoxy and esterification reactions is discussed for the preparation of bifunctionalized homopolymer sequences. For this, initially, the synthesis and stability of poly(glycidyl methacrylate), the primary reactive scaffold, are considered. Double modification of the glycidyl units through consecutive thiol-epoxy and esterification reactions is then examined along with its potential to give rise to functionalized molecular bottlebrushes. Finally, application of this strategy for the preparation of amphipathic homopolymer sequences and their application in the arena of siRNA delivery are discussed.

Keywords Amphipathic polymers · Bifunctionalized homopolymers · Dual-functional polymers · Poly(glycidyl methacrylate) · Post-polymerization modification · Sequential reactions · siRNA delivery · Thiol-epoxy reaction

Contents

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1 Introduction

Post-polymerization modification of reactive polymeric substrates is a valuable route for the preparation of functional soft materials [1–12]. The advantage of this strategy lies in the fact that one reactive scaffold can be transformed into multiple derivatives simply by changing the chemical identity of the functionalizing moiety. The functionalized polymer library generated in this manner differs in the chemical composition of the repeat unit. However, the molecular weight distribution among the members of one library remains constant. This attribute allows direct comparison to be made between the structures and properties of the library members [13]. Thus, a variety of post-polymerization modification approaches have been established and the wealth of information in this arena is commandingly covered in recent articles [1–11]. In some cases, the modification reaction can be carried out more than once. This goal can be achieved in two different ways. First, the functionalization protocols can be applied in a stepwise manner to a polymer precursor. This approach, in most cases, requires purification of the functionalized polymer after each modification step. Alternatively, a reactive polymer scaffold can be subjected to multicomponent reactions. In this approach, multiple functionalities can potentially be installed in a simultaneous fashion to a polymer precursor. In this way, a multifunctionalized polymer family can be accessed through multiple post-polymerization modification reactions on a single reactive scaffold. In this context, the discussion in the present chapter is centered on synthetic access to bifunctionalized homopolymer sequences through double modifications of each polymer repeat unit (Fig. 1). In order to understand the implications of this approach on the structure and properties of the resulting materials, one has to consider the alternative approach in which a random copolymerization process of two or more functionalizable monomers can also lead to polymers carrying multiple functionalities. The random copolymerization process, however, yields polymers with ill-defined monomer sequence that is subject to change from reaction to reaction, even if the total percentage of the two monomers remains constant. Therefore, it is difficult to assume that a direct property comparison, especially in the biomedical applications context in which pharmacokinetic

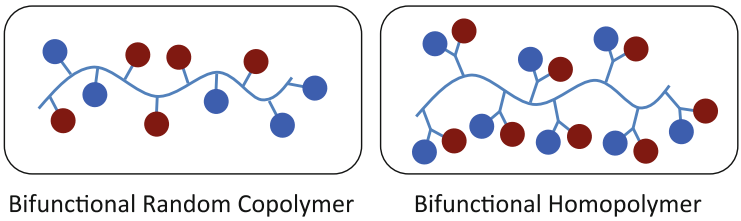


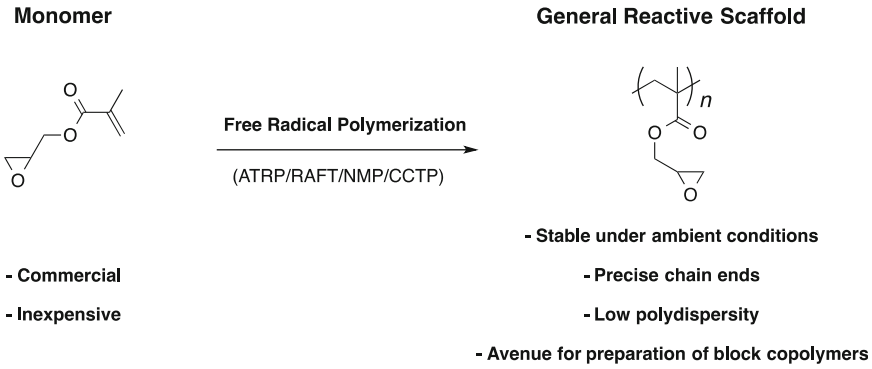
Fig. 1 Cartoon representation of a bifunctionalized random copolymer (*left*), and a homopolymer sequence in which each polymer repeat unit carries a 1:1 ratio of the active residues (*right*)

behavior is known to be sensitive to the precise molecular structure [14], can be made in a multifunctional polymer family that is prepared through a random copolymerization process. In the case of multifunctional homopolymers, however, such direct structure–property comparisons can be made due to the identical chemical structure of each polymer repeating unit involved. Moreover, a reproducible synthesis and pharmacokinetic behavior can be expected from such molecularly precise materials. The groups of Novak, Haddleton, Grubbs, Tao, Meier, and Theato have established distinctly different strategies to access such multifunctional homopolymer sequences [15–23]. We have contributed to this aspect by introducing a post-polymerization double-modification strategy involving sequential thiol-epoxy and esterification reactions on a poly(glycidyl methacrylate)-based reactive scaffold [13, 24–26]. In the following sections, we will discuss various aspects of this sequential double-functionalization synthetic scheme in detail.

2 The General Reactive Scaffold

2.1 Synthetic Approaches

Poly(glycidyl methacrylate) is a versatile reactive scaffold that has been used by various researchers in the preparation of a wide variety of functional soft materials and surface coatings (for use of poly(glycidyl methacrylate) scaffold in bio-relevant applications, please see the following selected examples: [27–34]; for an excellent review article on applications and assembly aspects of poly(glycidyl methacrylate) derivatives, please see [35]; for synthesis of well-defined polyglycidyl methacrylates, please see [36–46]). This polymer can be prepared through free radical polymerization of commercially available glycidyl methacrylate monomer (Scheme 1). If truly high molecular weights are required then a conventional free radical polymerization can be carried out using traditional free radical initiators such as azobisisobutyronitrile (AIBN) [24]. However, if controlled chain lengths, low polydispersity, and defined end groups are desired then controlled free radical polymerizations such as atom transfer radical polymerization (ATRP) [47],



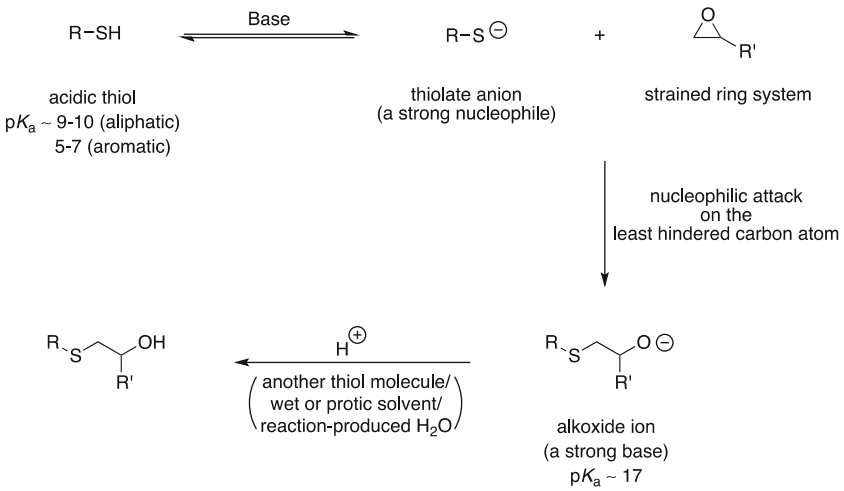
Scheme 1 Synthesis of poly(glycidyl methacrylate)

nitroxide-mediated polymerization (NMP) [48], radical addition fragmentation and chain transfer (RAFT) [49], and cobalt-catalyzed chain transfer polymerization (CCTP) can be applied [50]. These free radical polymerizations are perfectly orthogonal to the reactivity of the pendant glycidyl unit of the methacrylate monomer. It is for this reason that homopolymers can be prepared without observation of any gelation or crosslinking during the polymerization reaction. Regarding thermal properties, the glass transition temperature of poly(glycidyl methacrylate)s is in the range of 75–80°C. Therefore, under ambient conditions, these materials exist as a white powder. Furthermore, these polymers can be readily solubilized in various solvents such as dichloromethane, chloroform, tetrahydrofuran (THF), anisole, dimethylformamide (DMF), and dimethylsulfoxide (DMSO). The homopolymer of glycidyl methacrylate is entirely stable during storage under ambient conditions. However, if required, the epoxide unit of this polymer can be opened under a variety of conditions, as exemplified in this chapter through their reaction with thiols. It is noteworthy that the epoxide units can also be opened by other nucleophiles such as azides [36]. Therefore, alternative strategies for sequential multifunctionalization of poly(glycidyl methacrylate)s are available, as exemplified by the work of Gao and coworkers [51].

3 The Thiol-Epoxy Reaction

3.1 Reaction Mechanism

Epoxides are strained three-membered rings. The ring strain comes from the 60° angle between the bonds and renders the molecule susceptible to nucleophilic attacks in order to restore the ideal tetrahedral angle (109°) at all atoms. Thiols can participate in such a ring-opening reaction. However, the thiol functionality has to be transformed into an attacking thiolate anion. This can be achieved by using a

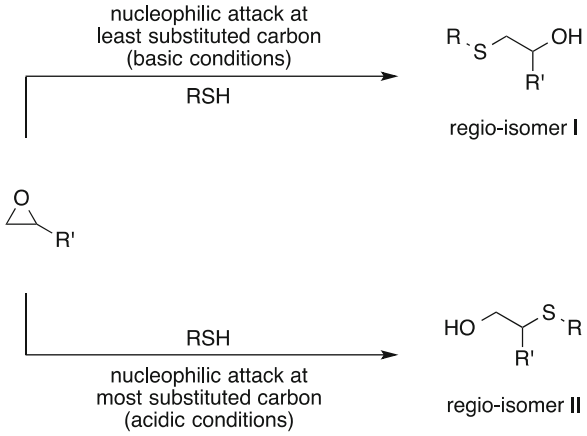


Scheme 2 Thiol-epoxy reaction under basic conditions. The reaction is most likely to proceed by an S_N^2 mechanism. Therefore, the step-wise depiction is meant only to simplify the process for better understanding

base that is strong enough to deprotonate the thiol group. In chemistry textbooks, this base is most often depicted as lithium or sodium hydroxide. The hydroxide anion can deprotonate a thiol molecule quantitatively. In terms of the attack on the epoxide ring, it should be noted that there is no competition between hydroxide and thiol because thiols are more acidic than water (pK_a of RSH is typically 5–10, pK_a of PhSH is 6.4, and pK_a of water is 15.7) [52, 53] and therefore a rapid proton transfer occurs from sulfur to oxygen. Once formed, the thiolate nucleophile attacks the less hindered site of the epoxide unit. The alkoxide unit thus formed becomes protonated, due to its high basicity ($pK_a \sim 17$) [54], by the thiol molecules present in the system (due to their acidity), by the typical wet/protic nature of the reaction medium, or by the water generated during the reaction (e.g., when using a hydroxide base) (Scheme 2). This thermodynamically driven proton transfer step is crucial in quenching the alkoxide anion and, hence, in stopping a ring-opening polymerization reaction from commencing. The end product of this reaction, therefore, is a new thioether linkage and a secondary hydroxyl group. This hydroxyl group can be used for a successive second functionalization.

3.2 Regiochemical Aspects

In a nucleophilic ring-opening reaction of asymmetric epoxides, two regio-isomers can form (Scheme 3). It is the reaction conditions that decide the structure of the formed product. In the presence of a strong thiolate anion (under basic conditions) and a poor leaving group (an alkoxide anion), an S_N^2 pathway prevails and the best



Scheme 3 Two possible regio-isomers expected from a thiol-epoxy reaction

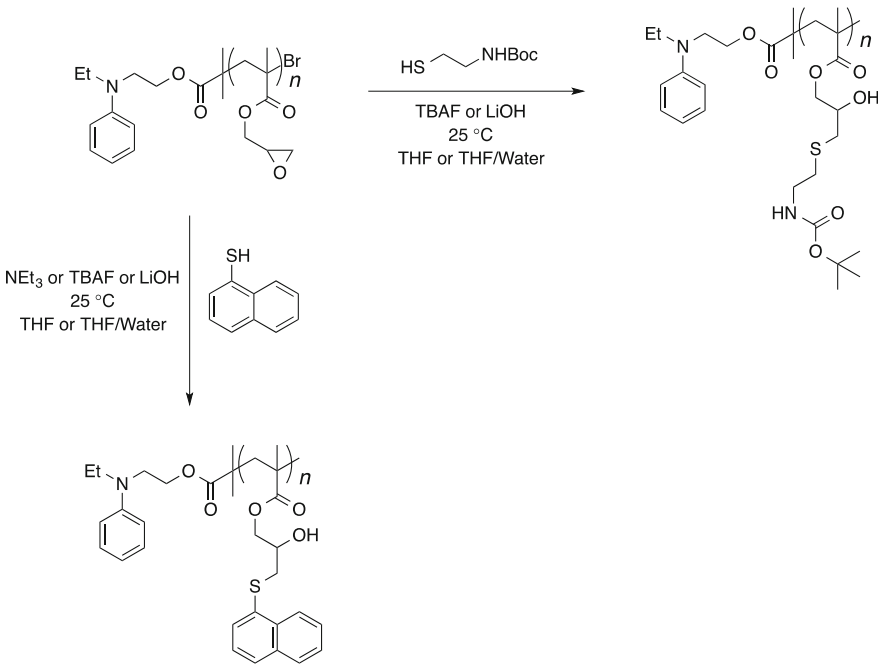
target for the nucleophile to attack is the least hindered carbon atom. Therefore, isomer I is formed under basic conditions. Under acidic conditions, however, the oxygen atom of the epoxide is protonated, creating a good leaving group and building up a positive charge on the most substituted carbon atom because this carbon atom is best suited to stabilize a positive charge. The nucleophilic attack in this case, therefore, occurs at the most substituted carbon atom because it holds a greater degree of positive charge. This results in the formation of regio-isomer II.

3.3 At the Small Molecule Level

The thiol-epoxy reaction has proved to be an important synthetic tool in the preparation of a variety of pharmaceutical and natural products [55–64]. As mentioned above, this reaction can be performed using an acid or a base as a catalyst. The acid catalysts include boron trifluoride etherate [57], lanthanide chlorides [65], lithium perchlorate [60], cobalt chloride [66], and neutral alumina [67]. The basic catalysts can be organic or inorganic and include, among others, triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), tetra-*n*-butylammonium fluoride (TBAF), and LiOH [61–64, 68, 69]. In the literature on small molecules, it is important to note that this reaction is complete in a few minutes to a few hours of reaction time, with quantitative yields and with high regioselectivity. In the case of LiOH and TBAF, quantitative conversion of the epoxide to a desired thio-ether compound is observed within minutes and with 100% regioselectivity (isomer I) [68, 69].

3.4 At the Polymer Level

It should be mentioned that this chemistry is already used as a polymerization reaction for building large polymer chains or networks from small monomers as well as for post-functionalization of copolymers, hyperbranched polymers, and end-functional polymers [51, 70–81]. Moreover, a partial functionalization strategy is also employed to access sequence-regulated polymers [82]. In this chapter, however, we will only discuss the use of this chemistry for post-polymerization modification of homopolymers [13, 24–26]. In this context, initially high molecular weight poly(glycidyl methacrylate) was employed [24]. Among other issues, quantification of functionalization remained unclear in this system. Therefore, in a subsequent system, the reactive scaffold was prepared through a well-defined aromatic initiator (Scheme 4) [26]. This initiator allowed determination of the degree of polymerization through end-group analysis. This attribute also allowed the extent of post-polymerization functionalization to be measured in a precise fashion. This study suggested that the choice and amount of catalyst had a significant impact on the outcome of the thiol-epoxy reaction. TBAF in THF, and LiOH in aqueous THF (10% water) were found to be good catalyst choices for thiol-epoxy reactions involving aliphatic and aromatic thiols. In the case of TBAF, >20 mol% catalyst loading was required to achieve quantitative conversion of the epoxy groups into the targeted thio-ethers in a reaction time of 3 h. LiOH, on the other



Scheme 4 First functionalization of the reactive scaffold through the thiol-epoxy reaction

hand, proved to be a better catalyst because quantitative conversion could be obtained at a catalyst loading of 1–4 mol% and in a reaction time of 1–3 h. Triethylamine (in THF) failed to provide any ring-opening reaction. However, it could be employed in the case of aromatic thiols. Nonetheless, high catalyst loading (>34%) and long reaction times (~12 h) were required for quantitative conversions at room temperature. Interestingly, a change of reaction medium to DMSO could lead to the ring-opening reaction while using triethylamine as base and an aliphatic thiol as reactant. In this case, however, longer reaction times, high catalyst loading, higher temperature, and higher thiol content were required to see significant epoxy group conversion (>85%). Moreover, the toxicity of DMSO does not provide much incentive to look further into this aspect. Importantly, the first functionalization reaction can be followed by ^{1}H-NMR spectroscopy because the three unique proton resonances of the epoxide unit diminish in intensity during progress of the thiol-epoxy reaction (Fig. 2).

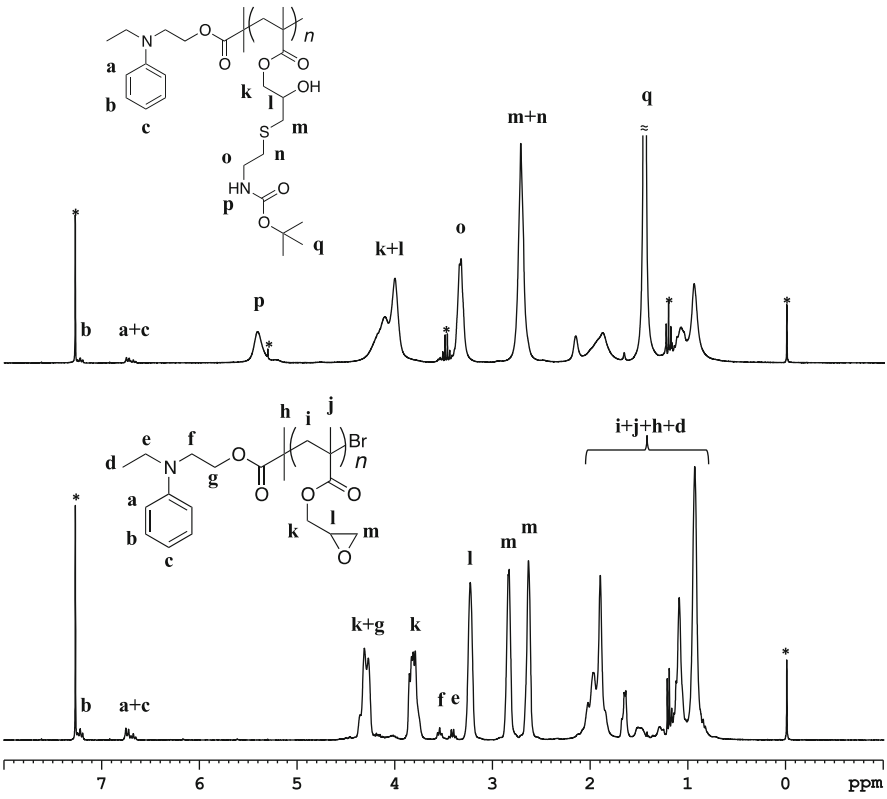
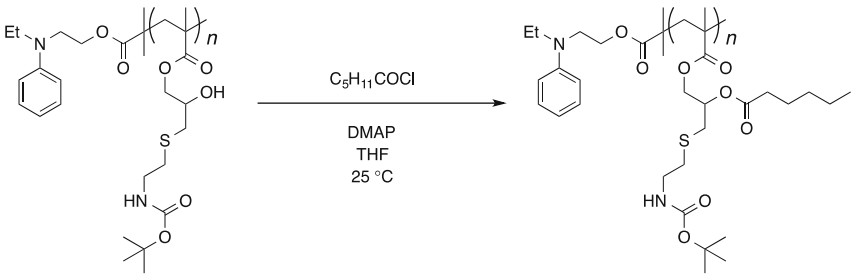


Fig. 2 ^{1}H-NMR of poly(glycidyl methacrylate) before and after functionalization. Typically, the epoxide proton resonances are seen at 2.6, 2.8, and 3.2 ppm. The ring opening reaction results in the disappearance of these proton resonances. Residual solvent signals are marked with an *asterisk*

An important feature of this study [26] was determination of the regiochemistry of the polymer repeat unit after the thiol-epoxy reaction. This was accomplished through a careful model compound study, which suggested that the attack of the thiolate anion occurs at the least hindered carbon atom of the pendant glycidyl unit of the polymer chain and that regio-isomer I (Scheme 3) forms exclusively during thiol-epoxy functionalization.

4 Esterification of the Secondary Hydroxyl Groups

As discussed above, post-polymerization modification of the glycidyl units with a thiol nucleophile results in a new thio-ether linkage and a secondary hydroxyl group. This hydroxyl group can be used for a successive second functionalization. The secondary hydroxyl group, however, is known to be less reactive than the primary hydroxyl groups (For post-polymerization modification of structurally similar hydroxyl groups, please see [83–86]). Moreover, depending on the structure of the thiol, a significant steric demand may also pose problems in complete conversion of these hydroxyl groups (Scheme 5). Therefore, it is natural to question whether the hydroxyl groups produced during the first functionalization reaction would be willing partners in the subsequent esterification reaction. This question is of high importance because it relates directly to the structural precision of the prepared final materials and therefore bears heavily on their description as 'bifunctional homopolymers.' In the aforementioned study [26], ^{1}H-NMR spectroscopy demonstrated that these hydroxyl groups can be quantitatively converted into an ester group by using an excess of the activated acid groups. The success of the second functionalization reaction can be evaluated simply by ^{1}H-NMR spectroscopy, in which a new signal appears at 5.2 ppm belonging to the proton located adjacent to the newly formed ester moiety (Fig. 3).



Scheme 5 Second functionalization of the mono-functionalized homopolymer sequence

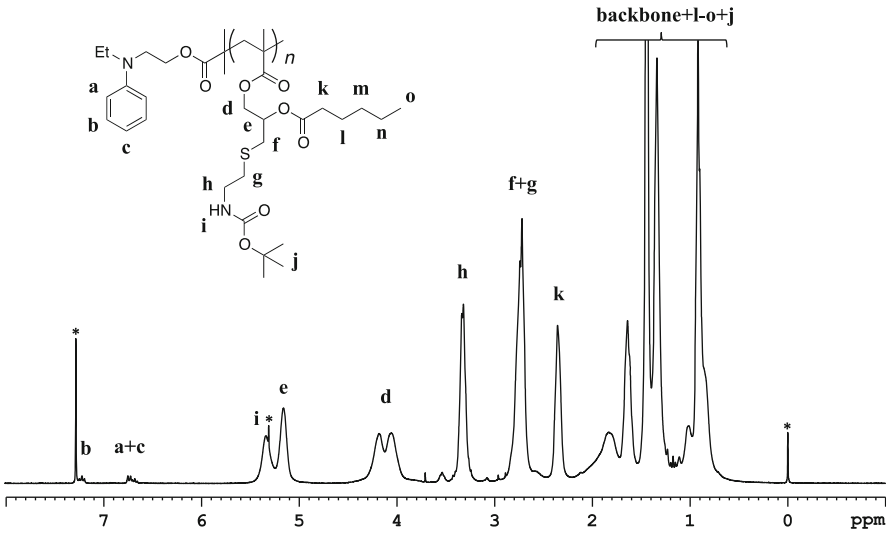


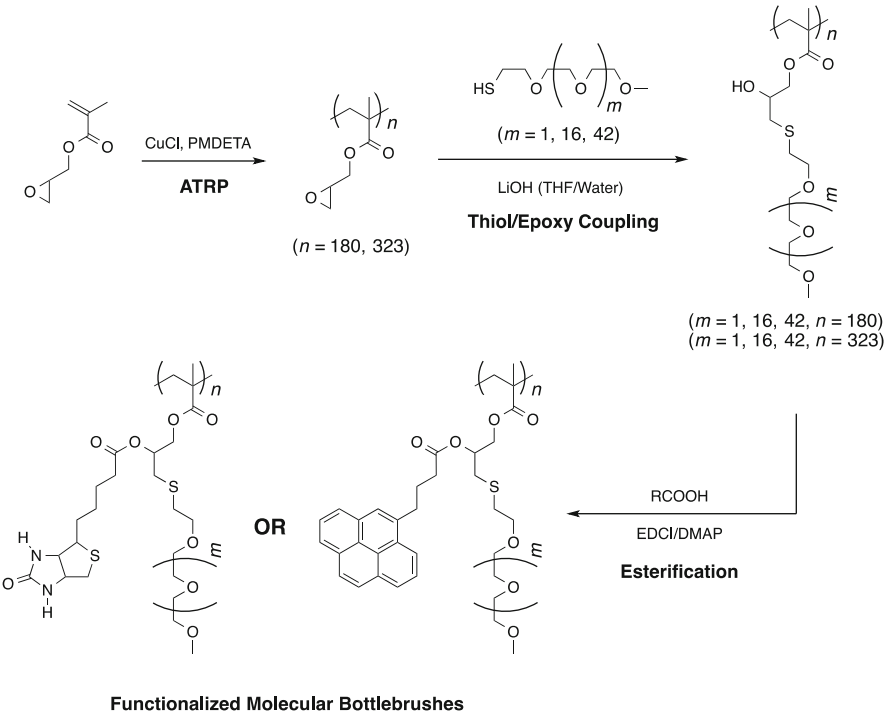
Fig. 3 ^{1}H-NMR of the bifunctionalized homopolymers. The proton resonance at 5.2 ppm belongs to the proton located at the tertiary carbon atom adjacent to the newly formed ester group. Residual solvent signals are marked with an *asterisk*

5 Increasing Steric Demand of the Substituents

5.1 Synthetic Access to Functionalized Molecular Bottlebrushes

The efficient nature of thiol-epoxy coupling chemistry encouraged us to employ it for the attachment of thiol-terminated poly(ethylene glycol) (PEG) polymers (0.18, 0.8, and 2 kDa) to the poly(glycidyl methacrylate) backbone (25 and 46 kDa) (Scheme 6) [25]. This polymer–polymer coupling reaction resulted in the formation of water-soluble bottlebrush copolymers with molecular weights ranging from 50 to 426 kDa. When low molecular weight PEG polymers with relatively little steric demand were used as the side-chain precursor, high grafting densities were observed irrespective of the length of the poly(glycidyl methacrylate) backbone (96–97%). The grafting density, however, decreased with an increase in the length and steric demand of the PEG side-chain (88–95%). In gel permeation chromatography (GPC), a clear shift in the retention time of the polymers was observed. Polymers substituted with low molecular weight PEG exhibited high retention time as a result of their lower hydrodynamic volume, and polymers substituted with long PEG displayed low retention time as a result of their higher hydrodynamic volume (Fig. 4).

The hydroxyl groups of the prepared bottlebrush copolymers, although screened by the polymeric side chain, could be functionalized with pyrene (a fluorescent probe) or biotin (a biological ligand) molecules through an esterification reaction.



Scheme 6 Use of sterically demanding substituents to prepare water-soluble and functionalized bottlebrush copolymers through sequential thiol-epoxy and esterification reactions

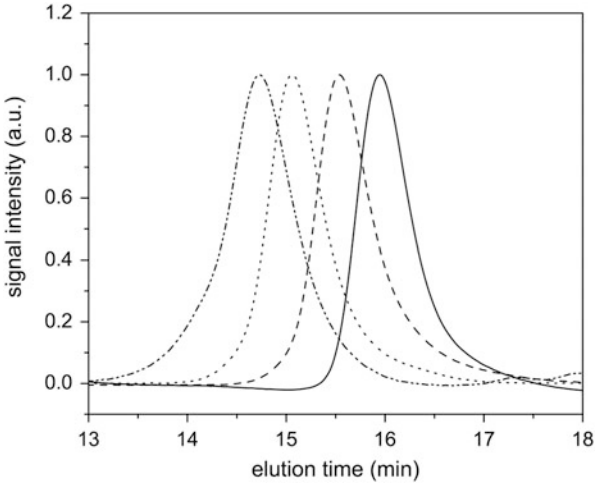


Fig. 4 GPC traces of the reactive poly(glycidyl methacrylate) scaffold ($n = 180$, $M_n = 25{,}700$) (*solid line*), and after substitution with poly(ethylene glycol) ($m = 1$, $M_n = 50{,}900$) (*dashed line*), ($m = 16$, $M_n = 133{,}400$) (*dotted line*), and ($m = 42$, $M_n = 266{,}300$) (*dashed and dotted line*) (n and m are as defined in Scheme 6)

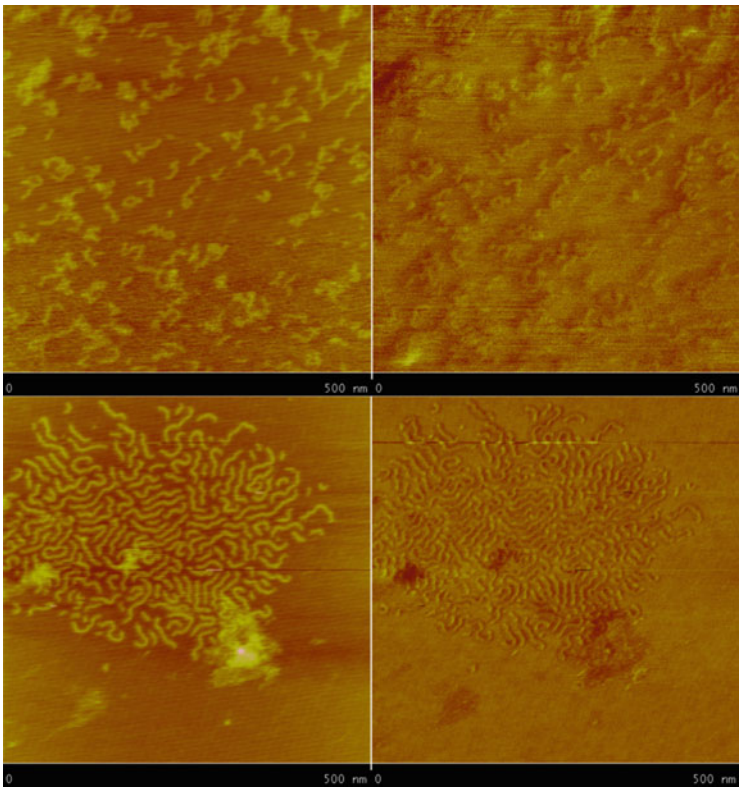


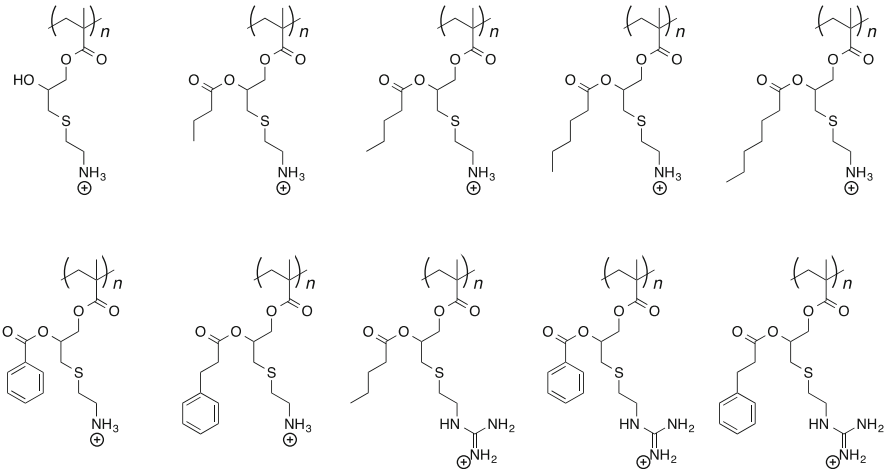
Fig. 5 AFM height (*left*) and phase (*right*) images of polymer with a short (*top*) and a long (*bottom*) poly(ethylene glycol) side chain

In this case, again, the extent of esterification reaction decreased with an increase in the length of the already attached PEG side chain. The prepared polymers displayed structure-dependent thermal and optical properties. Because of their bottlebrush nature, the polymers could also be visualized at a single molecule level on mica substrate using atomic force microscopy (AFM). Polymers having the shortest side chain length appeared coiled (Fig. 5, top), whereas polymers having longer side chain length appeared cylindrical in shape as a result of the steric congestion offered by the long and densely populated PEG side chains (Fig. 5, bottom).

6 Applications

6.1 Synthetic Access to Amphipathic Homopolymers

Polymers carrying a positively charged site and a lipophile may display antibacterial and cell penetration properties [87–93]. The present synthetic design



Scheme 7 Chemical structures of the amphipathic polymer family investigated for their siRNA delivering properties

allows accessing such bifunctional materials. This is demonstrated by preparing amphipathic structures carrying either an ammonium or a guanidinium cation as the polar group and an alkyl or aromatic group as the nonpolar moiety (Scheme 7). These polymers are found to be soluble in water and the presence of the cation can be confirmed by the variable-solvent experiments in the ^{1}H-NMR analysis.

6.2 *Applications in the Gene Delivery Arena*

The aforementioned bifunctional polymers could form electrostatic complexes with siRNA and deliver it to human colon carcinoma cells (HT-29-luc) [13]. In general, cell viability and transfection efficiency were observed to be higher for ammonium-containing polymers than for guanidinium-carrying polymers. In vitro transfection studies with polymers containing ammonium groups and aliphatic carbon chains showed that silencing efficiency increased with an increase in the length of the lipophilic moiety. A polymer carrying pentyl carbon chains and ammonium groups showed the best gene silencing effect, even though its intracellular uptake efficiency was lower in comparison with the other polymers. In addition, this polymer exhibited lower cytotoxicity and higher transfection efficiency than branched-polyethylenimine (B-PEI) and linear-polyethylenimine (L-PEI). Unlike PEI, however, the system did not seem to rely on the 'proton sponge' effect for siRNA delivery. The success of amphipathic polymer-mediated siRNA delivery can be attributed to the long aliphatic chains in the polymer structure, facilitating endosomal escape by interaction with endosomal membrane lipids as well as the release of free siRNA in the cytosol. This study underlines the importance of the

amphipathic structure in the design of cationic siRNA delivery vectors that do not rely on the proton sponge effect.

7 Summary and Outlook

To summarize, polymers carrying a 1:1 ratio of the active residues at each polymer repeat unit can be prepared by post-polymerization double-modification of a poly (glycidyl methacrylate) scaffold through sequential thiol-epoxy and esterification reactions. Such polymers can be referred to as bifunctional homopolymers. The general reactive scaffold, poly(glycidyl methacrylate), can be prepared from its commercially available monomer by a variety of controlled free radical polymerization methods. The resulting homopolymer shows remarkable stability at ambient conditions. The glycidyl groups of this polymer can be opened with a thiol molecule under basic conditions. This reaction produces a thio-ether linkage and a hydroxyl group. This hydroxyl unit can be used as an anchor point to install a second functionality at the polymer repeat unit through an ester linkage. These sequential reactions can be performed even under high steric demand and allow the preparation of functionalized bottlebrush copolymers. Furthermore, application of this synthetic strategy can give access to amphipathic homopolymers that mimic cell-penetrating peptides. These polymers are capable of complexing with siRNA and delivering it to human colon carcinoma cells (HT-29-luc). Remarkably, such polymers do not rely on the 'proton-sponge' effect for successful siRNA delivery. To further enhance their applicability in the biomedical arena, a future synthetic target would be preparation of block copolymers carrying a PEG segment. This would reduce the unfavorable interactions of the cationic polymers with proteins and lead to enhancement of their bioactivity under serum conditions. To further improve their structural sophistication, one can envisage employing a controlled free radical polymerization initiator carrying an imaging/contrast agent. This would enable localization and monitoring of polymer activity during in vitro and in vivo investigations. To further reduce their cytotoxicity, structural elements could be introduced to enhance the biodegradability of the bifunctionalized polymers. For this purpose, it would be possible to depart from the acrylate-based polymer backbones and use biodegradable scaffolds. In essence, the post-polymerization double-modification strategy involving sequential thiol-epoxy and esterification reactions leads to the formation of a unique family of bifunctionalized homopolymers. The properties of these polymers are just beginning to be examined. Based on the initial results, these polymers appear to be promising candidates for sophisticated biomedical applications.

Acknowledgements M.C.S. gratefully acknowledges Nanyang Technological University (Singapore) for financial support. A.K. thanks A. D. Schlüter (ETH-Z) for support.

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Adv Polym Sci (2015) 269: 105–132
DOI: 10.1007/12_2014_304

Published online: 11 March 2015

One-Pot Double Modification of Polymers Based on Thiolactone Chemistry

Pieter Espeel and Filip E. Du Prez

Abstract One-pot multistep reactions based on thiolactone chemistry have emerged as a powerful tool for modifying thiolactone-containing polymers in one-pot and in an elegant manner. In general, thiolactones can be opened by a wide variety of functional amines and the released thiol can react with thiol 'scavengers' of choice. This overview highlights the most important features of this approach, illustrated by the versatile and site-specific double post-polymerization modification of various reactive systems.

Keywords Aminolysis • One-pot conjugation process • Site-specific double post-polymerization modification • Thiolactone chemistry • Thiol-click reaction

Contents

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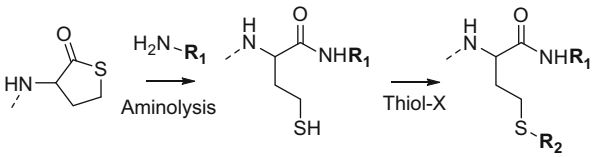
1 Introduction

The decoration of polymers with reactive functional handles followed by post-polymerization modification (PPM) [1–3] via 'click' chemistry [4–11] has recently become a popular approach in macromolecular research as it provides an efficient pathway to a large variety of synthetic materials that have potential applications in different areas (bioconjugation [12–16], electronics [17–19], medicine [20–23], and labeling [24–28]). The synergy between functionality and modularity [29] is indeed an appealing feature for potential users.

An important driver for the sustained development of conjugation chemistries for PPM purposes is the desire for simplification of reaction protocols and associated experiments. An increasing number of complex macromolecular designs are the result of a combination of different (and consecutive) reactions. The orthogonality [30] of 'click' reactions is especially relevant when targeting multistep processes in a one-pot fashion. These reactions can occur in parallel or in sequential order, leading to one-pot accelerated protocols for the preparation of advanced polymer materials [31–33]. The one-pot application of multiple orthogonal click reactions [33–35] is obviously attractive as it simplifies the experimental set-up and reduces the efforts of reaction work-up and product isolation. In some cases, a one-pot approach can also circumvent issues related to reactant stability or availability. The latter was the main argument for our initial exploration of the scope of thiolactone-based chemistry in polymer science. Despite the fact that click reactions involving thiols [36–43] are valuable metal-free alternatives to the copper-assisted azide–alkyne cycloaddition (CuAAC) reaction [44–47], thiol-related issues (smell, shelf life, and synthetic availability) prevent their widespread use. Hence, the reactivity of a γ-thiolactone (a five-membered cyclic thioester) as a latent thiol functionality has recently been investigated by us [48–58] and others [59–66]. Synthetic concepts based on thiolactone chemistry generally share a common feature: a thiol is released by nucleophilic ring opening (aminolysis) and subsequently reacts with a thiol 'scavenger' (Scheme 1).

The current interest in thiolactone chemistry in synthetic polymer science, disseminated in at least 15 original peer-reviewed papers since 2011, is an indication that it entails more than the solving of some thiol-related problems. It has indeed been recognized that this concept holds two particular advantages compared



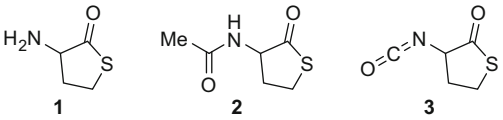
Scheme 1 γ-Thiolactone entity as a reactive thiol precursor: the thiol is released by aminolysis and a subsequent thiol-click occurs, incorporating $\mathbf{R}_1$ and $\mathbf{R}_2$ residues

with other chemistries employed in polymer synthesis and PPM. First, thiolactone-based reactions are 100% atom-efficient conjugations because no atoms are wasted. For example, popular activated-ester chemistries, such as pentafluorophenyl esters [67–71], have the intrinsic disadvantage of releasing the corresponding alcohol derivative as a side product. Second, compared with azlactone-based reactions [72–76], another atom-efficient methodology, thiolactone chemistry enables double modification of polymer scaffolds. Both introduced residues have a different origin: the first residue, $\mathbf{R}_1$, originates from the (primary) amine employed in the aminolysis and the second residue, $\mathbf{R}_2$, can be incorporated through the subsequent thiol-X reaction (Scheme 1). In addition to these advantages, it is important to note that in some cases this double modification can be performed in a one-pot fashion (vide infra), leading to simplified experimental set-ups and, thus, accelerated synthetic protocols. As the latter is particularly relevant for double PPM, an overview of the possibilities and limitations of thiolactone-based chemistry in polymer modification is given by means of literature examples, after having discussed some specific aspects related to accelerated (one-pot) synthetic protocols involving thiolactones.

2 Reactivity and Synthetic Use of Homocysteine-γ-thiolactone and Derivatives

The most commonly used γ-thiolactone derivative is homocysteine-γ-thiolactone **1**, a five-membered cyclic thioester of homocysteine (Scheme 2). Large-scale preparation of **1** requires an acid-catalyzed intramolecular condensation of methionine [77] or homocysteine [78], both bioresource compounds. The hydrochloric acid salt of the racemate **1** is a white solid that displays long-term stability at room temperature and is readily available as a bulk chemical at low cost.

Homocysteine-γ-thiolactone **1** is a valuable synthetic building block; however, its implementation in polymer science as a versatile functional handle requires some special attention. In order to take part in a PPM, thiolactone **1** needs to be transformed into monomers and/or initiators and subsequently used in a (controlled) polymerization, while maintaining the integrity of the thioester ring. Because the intrinsic instability of the neutral homocysteine-γ-thiolactone **1** leads to the formation of the corresponding diketopiperazine adduct [79], an efficient



Scheme 2 Chemical structure of homocysteine-γ-thiolactone **1** and synthetically valuable derivatives

reaction between the amino group in the α-position and an electrophile is mandatory, eventually leading to the targeted monomer or initiator. Amidation reactions are most frequently used: conjugation with acid halides [80–83], (in situ) activated carboxylic acids [83–89], and anhydrides [90] enables the synthesis of homocysteine-γ-thiolactone derivatives. A carbamate linkage is formed by treatment with chloroformates [91].

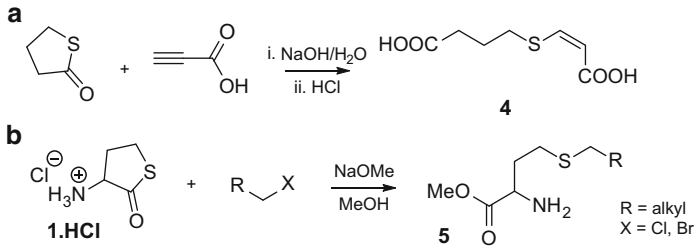
An important homocysteine-γ-thiolactone derivative is *N*-acetylhomocysteinethiolactone or citiolone **2** (Scheme 2), a commercial compound that was introduced as a thiolating agent for proteins. This thiolation consists of aminolysis of the water-soluble *N*-acetylhomocysteinethiolactone **2** by the ε-NH_2 groups of lysine residues [92–94]. Thiolation of a large variety of macromolecular biochemical systems has been reported [80, 94–106].

In contrast to the reactivity of **2**, which fully relies on its acylating capacity, other noteworthy derivatives of homocysteine thiolactone **1** enable the incorporation of thiolactones into (macro)molecules as an alternative to the previously mentioned approach. Requirements are conversion of the α-amino group of **1** into a functional handle and, most importantly, its conjugation to the reactive system of interest. Both steps should proceed while maintaining the integrity of the thiolactone ring. For example, in the presence of alcohols, amines, or hydrazines, the isocyanate **3** is converted to the corresponding carbamates, urea, and semicarbazides [107].

Once installed, the nucleophilic ring opening is the most important reactivity-related property of incorporated thiolactone units. In general, the stability of the ring towards lysis increases with increasing number of substituents as a result of steric hindrance of the nucleophilic attack [79]. Water, alcohols, and amines (vide infra) are the most common nucleophilic agents able to perform the ring opening. Hydrolysis and alcoholysis are only significant in basic medium, and aminolysis requires no additives. Aminolysis can thus be performed in aqueous medium, although hydrolysis is an important side reaction [92, 108, 109]. No reports of thiolysis of γ-thiolactones have been found so far, whereas thiolactones, having smaller and larger ring sizes, are susceptible to nucleophilic attack by a thiolate anion [108, 110–112].

3 One-Pot Multistep Reactions Based on Thiolactones

As mentioned in Sect. 1, the search for a solution to some thiol-related issues was a driver and initial argument for an evaluation of thiolactone chemistry. Indeed, in addition to the fact that the commercial availability of thiols as starting materials is rather limited, thiols usually have an unpleasant smell and often have a poor shelf life due to oxidation reactions, generating the corresponding disulfides. Therefore, thiolactones are considered to be valuable thiol precursors. First of all, and most importantly, thiolactone ring opening, resulting in the release of a free sulfhydryl group, can be achieved by means of a wide variety of nucleophiles. Moreover,



Scheme 3 Two literature precedents of thiolactone-based two-step one-pot sequences: (**a**) treatment of γ-thiobutyrolactone with propiolic acid in basic aqueous medium generates the acrylic acid **4** and (**b**) methanolysis and S-alkylation of **1.HCl** enables the synthesis of *S*-alkylhomocysteine **5**

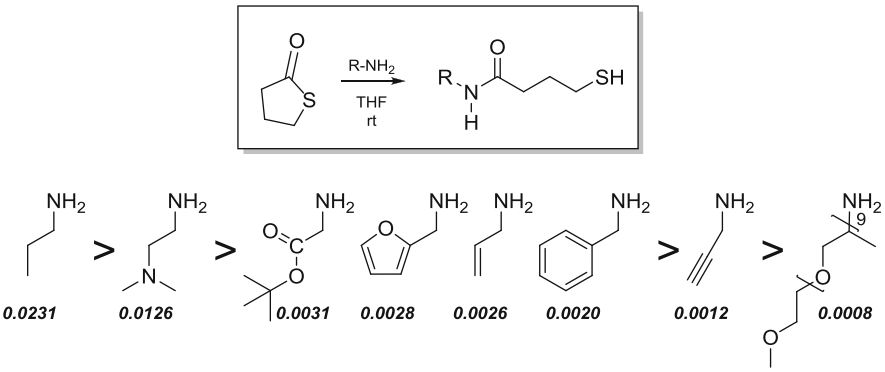
thiolactone substrates can be subjected to one-pot two-step reaction sequences. In fact, a rather large variety of potential combinations between (i) the nucleophile chosen for ring opening and (ii) the selected thiol-click [38, 42] follow-up reaction can be explored. A prerequisite for a successful one-pot accelerated thiolactone-based protocol is the orthogonality of both steps, entailing complete chemoselective discrimination between the involved nucleophilic species (nucleophile for lysis versus generated thiol).

Prior to our endeavors, this approach had been evaluated mainly by combining hydrolysis (or alcoholysis) and *S*-alkylation for the preparation of low molecular weight adducts (Scheme 3).

A first literature precedent describes the reaction of γ-thiobutyrolactone with propiolic acid under basic hydrolysis conditions, generating the corresponding acrylic acid **4** (Scheme 3a) [113]. As an alternative to this sequential hydrolysis and conjugate addition (thio-Michael addition), the lysis of thiolactones under basic conditions is often carried out in the presence of an alkylating agent. Because of the high nucleophilic character of the liberated thiol, *S*-alkylated compounds are the final products of these reactions [108]. Methanolysis of homocysteine-γ-thiolactone hydrochloride **1.HCl** and subsequent alkylation by treatment with an alkyl halide in a one-pot fashion has been reported as a simple method for the synthesis of *S*-alkylhomocysteines **5** (Scheme 3b) [114, 115].

Compared with both hydrolysis and alcoholysis, aminolysis as the start of a multistep reaction sequence based on thiolactones is advantageous because it does not require any additives for it to occur. Although the related one-pot process proceeds in an unassisted way, it is not straightforward because, in many cases, orthogonality issues can arise as a result of the reactive nature of amines. On the other hand, it provides the opportunity to introduce a functional group into the reaction product via the amine (Scheme 1), which is very relevant for double modification purposes (vide infra).

We consider the aminolysis reaction to be rate-determining for the corresponding two-step process and (in most cases) independent of the thiol-click follow-up reaction. Hence, the influence of the nature of the primary amine in the

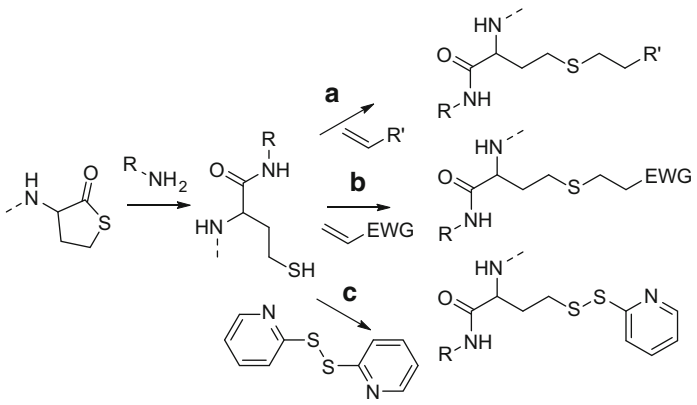


Scheme 4 Rate constants (in L mol^{-1} s^{-1}, pseudo-first order kinetics) of the aminolysis of γ-thiobutyrolactone in the presence of different primary amines

ring opening of thiolactones was studied. Kinetic screening of the lysis of γ-thiobutyrolactone in the presence of different (functional) primary amines was performed (Scheme 4) [51]. Generally, the aminolysis of thiolactones can be described by second-order kinetics [116]. Stereo-electronic properties of the primary amines are the basis for the relative rate differences: aliphatic nonfunctional amines react faster than amines containing an inductive-withdrawing group. The steric constraints resulting from α-branching in Jeffamine M-600 greatly decrease the reaction rate (Scheme 4).

In addition to the kinetic screening of aminolysis, a study on the chemoselectivity of the ring opening was performed. Using the same reaction conditions, i.e., 50-fold excess of the nucleophile (pseudo-first order conditions) and neutral pH (no added base), other nucleophiles such as water, alcohols, thiols, and anilines were not able to open the thiolactone ring. This result indicates that primary amines are the preferred reaction partners in the lysis of a thiolactone, even in the presence of other nucleophilic species. Another important observation during this study was the fact that, at high amine concentrations, thiolactones opened to yield the corresponding thiol, which readily dimerized through disulfide formation. It is crucially important that this side-reaction is carefully monitored during thiolactone-based synthetic endeavors, especially in the framework of double modification. If the side reaction occurs during double PPM, it can compromise the introduction of the second functional residue (Scheme 1) and even lead to ill-defined and sometimes crosslinked adducts. However, when the extent of disulfide formation can be mastered, it can be a useful transformation in selected cases (vide infra).

After obtaining some useful insights regarding the ring opening of a γ-thiolactone through model reactions, several modular reactions were considered as thiol-click follow-up reactions. The combination of thiolactone aminolysis with conjugation of the generated thiol in a one-pot fashion is a simple and versatile linking process, holding many attractive features. However, prior to its



Scheme 5 One-pot thiolactone-based conjugation: aminolysis of a thiolactone, followed by thiol-click conjugation. The in situ generated thiol can react according to three distinct reaction pathways: (*a*) radical (UV-initiated) or (*b*) nucleophilic (thiol-Michael) addition of a thiol to a double bond (thiol-ene), and (*c*) thiol–disulfide exchange

implementation in synthetic polymer science, model studies should explore its possibilities and limitations. It should be stressed that the following discussion, describing some recent method developments, is devoted to the execution of thiolactone-based two-step sequences in a one-pot manner. Hence, we focus on conjugation without intermediate purification of the thiol and without addition of chemicals during the process (everything present from the start). Of course, this process can be also performed as two separate batch processes, with the preparation and isolation of the corresponding (poly)thiol [117] as an intermediate, facilitating every possible thiol-click conjugation [38, 42] as the subsequent reaction. This two-step batch approach is described in the next section, illustrated by two literature examples [49, 54].

Scheme 5 depicts the thiolactone-based one-pot conjugation, displaying three distinct reaction pathways according to the nature of the reaction partner of the generated thiol. It is clear that the choice of reaction partner greatly influences the set-up, potential side-reactions, and outcome of the reaction (vide infra). The feasibility of the proposed reactions was assessed through carefully monitored model reactions (reaction pathways a and b in Scheme 5), using low molecular weight compounds to guarantee compatibility between aminolysis and the subsequent thiol-click conjugation reaction of the in situ generated thiol. To the best of our knowledge, there are no reports on the systematic study, through model reactions, of the reaction pathway involving thiolactone aminolysis and thiol–disulfide exchange. Nevertheless, it has been used for double PPM purposes [63, 64] and is therefore discussed in the next section 4.5.

3.1 Radical Amine-thiol-ene Conjugation

The combination of thiolactone aminolysis and the radical thiol-ene process, so-called radical amine-thiol-ene conjugation (Scheme 5, pathway a), was performed on a mixture of benzylamine, *N*-acetylhomocysteinethiolactone **2**, and norbornene as low molecular weight model compounds in order to master the reaction conditions [48]. The solution was irradiated by an external UV light source, and 2,2-dimethoxy-2-phenyl acetophenone (DMPA) was selected as an efficient photoinitiator for thiol-ene conjugation [118]. Furthermore, thorough analysis of the reaction mixture obtained after the two-step reaction revealed the formation of side products originating from the reaction between benzylamine and radical fragments of DMPA. However, using optimal conditions (no photoinitiator) and after a straightforward chromatographic purification, the model reaction yielded the conjugation compound with an isolated yield of 80% [48].

Encouraged by the successful model reaction, implementation of the radical amine-thiol-ene conjugation in synthetic polymer science was envisaged. Consequently, several AB′-type monomers containing both a double bond and a thiolactone unit were prepared. Upon aminolysis, these monomers form a reactive thiol-ene, which is consumed in the same medium in a stepwise polyaddition. It is clear that the nature of the introduced double bond and chemical linkage (amide, urethane, etc.) connecting the thiolactone and double bond determine both the reaction conditions and outcome of the two-step process, as well as the final properties of the synthesized polymers.

Two different AB′ monomers, susceptible to radical amine-thiol-ene conjugation, were synthesized and successfully used in a photopolymerization, yielding linear polymers with either a polythioether/polyurethane [48] or a polythioether/polyamide backbone [48, 55].

However, conceptual issues directly related to the radical reaction in the one-pot process partially impede extension of the scope of the radical amine-thiol-ene conjugation. First, some functional groups (e.g., furan [119–123], double and triple bond) introduced via the amine are incompatible with this radical environment. Additionally, UV curing takes place upon decomposition of a photoinitiator (e.g., DMPA), but model studies revealed that some amines (e.g., benzylamine) react with the formed radical fragments, thus limiting the use of a photoinitiator [48].

3.2 Nucleophilic Amine-thiol-ene Conjugation

In addition to the radical amine-thiol-ene conjugation, the one-pot combination of aminolysis of a thiolactone unit and a nucleophilic thiol-ene conjugation (Michael addition) (Scheme 5, pathway b) was explored. The Michael addition between a nucleophile (e.g., thiol, amine, or stabilized carbanion) and an activated double bond (e.g., imidazole, acrylate, vinyl sulfone) is often the key step in polymer

synthesis and conjugation, especially when complex macromolecular architectures are targeted [124]. In this case, the feasibility of the proposed nucleophilic amine-thiol-ene conjugation between an amine, a thiolactone entity, and a Michael acceptor entirely relies on the selectivity of the conjugate addition. Therefore, selection of the reaction partners in this fundamentally challenging two-step reaction sequence is crucially important. Although maleimides react with both amines and thiols as Michael donor [124], acrylates are less reactive; at room temperature and without a catalyst, only secondary amines readily react with acrylates [125]. Hence, a reaction mixture of a primary amine, a thiolactone, and an acrylate in the absence of any catalyst results in the formation of the targeted conjugation product. The anticipated chemoselective discrimination between both heteroatomic nucleophiles (primary amine and the in situ generated thiol) is based upon different reaction rates. The slow aza-Michael addition allows aminolysis of the thiolactone to proceed, whereas the subsequent thiol-Michael addition is known to be relatively fast [38].

The kinetic profile and outcome of the nucleophilic amine-thiol-ene conjugation through a series of model reactions involving *n*-propylamine, γ-thiobutyrolactone, and *n*-butyl acrylate has also been investigated [51]. The major conclusion from this model study was that, as anticipated, aminolysis is the rate-determining step. The acrylate functions were consumed as fast as the thiolactones. With 1.1 equivalents of *n*-propylamine and an equimolar mixture of thiolactone and acrylate, it took 9 h to reach 70% conversion. Using these conditions, only a minor fraction of disulfide was detected. Although the overall rate could be increased by adding more amine, disulfide formation was more prominent at higher amine concentration, indicating that the excess of amine should be limited. Occurrence of the other suspected side-reaction, the aza-Michael addition between the primary amine and the acrylate, depends on the nature of the solvent. Trace amounts of the aza-Michael adduct were detected when performing the two-step reaction in $CHCl_3$ or THF, whereas this reaction was more prominent in DMF.

In order to evaluate the nucleophilic amine-thiol-ene conjugation regarding the versatile synthesis of diversely functionalized linear polymers, another stable AB′ monomer, containing an acrylate (A) and a thiolactone unit (B′), has to be devised and synthesized on a large scale. Upon aminolysis, this monomer forms a reactive thiol-acrylate (AB monomer), which is consumed in the same medium by a conjugate addition [51]. This strategy offers an easy-to-perform, one-pot method for the synthesis of functionalized polyaddition polymers. Mixing the two ingredients (AB′ monomer and the selected amine) at room temperature without any additive or external trigger gives access to a polymer library displaying a large variety of functional side chain residues. In addition to the additive-free aspect of the nucleophilic amine-thiol-ene conjugation, another advantage over its radical counterpart is the improved tolerance towards functional amines as a result of the mild reaction conditions and the complete absence of radical species. These benefits will be particularly useful when attempting double PPM of thiolactone-containing polymer (vide infra).

4 Site-Specific Double PPM of Thiolactone-Containing Polymers

4.1 Site-Specific Double PPM

Double PPM of linear polymers generally entails that two distinct functional handles, positioned along the polymer backbone, are subjected to chemoselective transformation, leading to doubly modified species [33–35]. These functional handles can be randomly distributed or localized in a more structured way, and both functional handles in the polymer are not usually present in equal amounts. The user has the option of performing the double modification in a two-step batch process or in one-pot. Additionally, it should be stressed that these double PPMs are considered to be relevant when offering the possibility of incorporating (at least) two functional residues (as shown in Scheme 1), generating certain functions or properties in the final material. Although the aminolysis [126, 127] of a trithiocarbonate end group of a reversible-addition fragmentation transfer (RAFT) [128–132] polymer, followed by a thiol-click reaction of choice (e.g., thiol-bromo [133] and thiol-ene [134–136] conjugation), is a one-pot double modification, it only allows introduction of a single functional residue, originating from the second reaction.

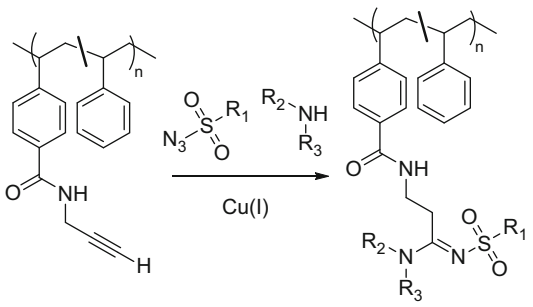
Very few PPM chemistries provide the opportunity of incorporating two residues at the same site in a polymer. When established, the site-specific double PPM not only offers the possibility of introducing both residues, closely positioned at the molecular level, but also virtually guarantees introduction of the residues in equal amounts, provided both reactions reach full conversion. Therefore, the unique character of the thiolactone-based site-specific (one-pot) double modification approach is highlighted in the discussion below. Interestingly, three distinct chemical platforms allowing for site-specific double PPM have been very recently developed by Theato and coworkers [137–139].

In a first study [137], the Cu-catalyzed three-component reaction between a terminal alkyne, a sulfonyl azide, and a secondary amine for double PPM purposes was established. Hence, alkyne-containing random copolymers based on polystyrene (PS) have been prepared and modified (Scheme 6).

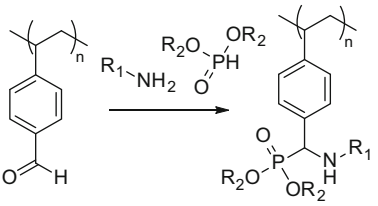
Alternatively, the Kabachnik–Fields reaction is a metal-free approach, enabling PPM of poly(4-vinylbenzaldehyde) in the presence of primary amines and phosphites (Scheme 7).

A very versatile polymeric scaffold for site-specific double PPM is poly(1-aceto-1-pentafluorophenoxycarbonyl-2-vinylcyclopropane) [poly(APVCP)] (see Scheme 8) [139]. In this case, the two-step modification is performed in a sequential batch process. Following aminolysis by treatment with various primary amines, the ketone can be converted in the presence of hydrazide or hydroxylamine derivatives. Furthermore, the ketone can be reduced to the secondary alcohol, which is subsequently converted into the ester or carbamate through the use of different acyl halides and isocyanates.

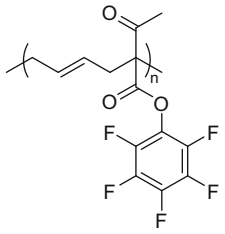
Scheme 6 Cu-catalyzed three-component reaction between a terminal alkyne, a sulfonyl azide, and a secondary amine for double PPM purposes



Scheme 7 Kabachnik–Fields PPM of poly (4-vinylbenzaldehyde)

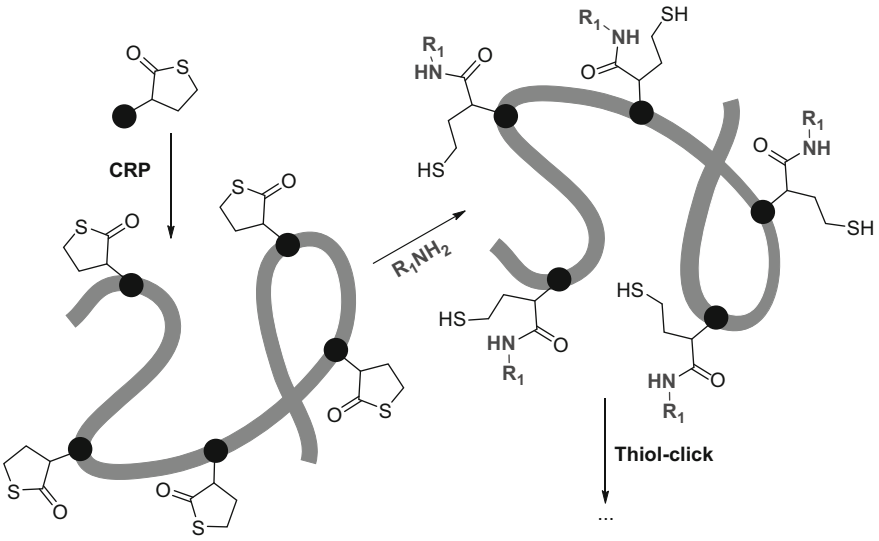


Scheme 8 Structure of poly(APVCP), a homopolymer susceptible to site-specific double PPM



4.2 Polythiolactones as Versatile Precursors for Polythiols and Derived Structures

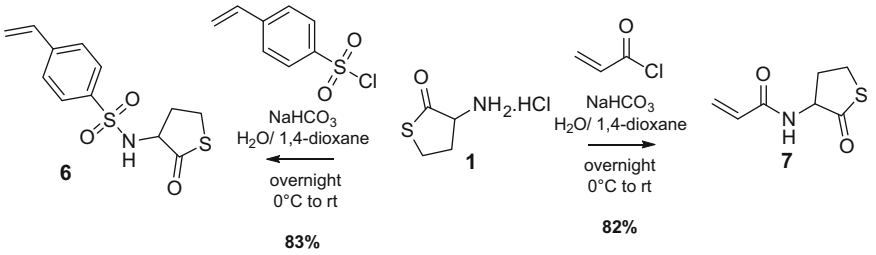
One of the most versatile functional handles for PPM is a thiol functionality. Although the latter can be easily introduced at the polymer chain end through aminolysis of a RAFT polymer [126, 127], the preparation of polythiols as polymeric scaffolds generally includes protecting-group chemistry and crosslinking because oxidative disulfide formation is a major concern. Additionally, the reactive nature of thiols renders direct incorporation into polymer systems very challenging. The interference of free thiols in most polymerization processes is a major issue, especially for controlled/living polymerization reactions [140–145], which suffer from thiol-induced side reactions. Thiols can react with (vinylic) monomers through radical or Michael additions and also induce chain transfer reactions with propagating radicals [146]. Consequently, reported synthetic routes towards polythiols [117] require a protection/deprotection strategy, which is a detrimental approach in terms of atom efficiency and overall yield. Nevertheless, once



Scheme 9 Site-specific double PPM of pendant thiolactone moieties. After CRP of a stable vinylicthiolactone monomer, aminolysis of the linear poly(thiolactone) yields a linear polythiol, i.e., a reactive polymer scaffold for follow-up thiol-click modification

successfully prepared and conserved, these polythiols are indeed extremely versatile click precursors, potentially employable in both radical and nucleophilic PPM reactions [36–43]. As introduced, thiolactones as functional handles along the backbone of a variety of linear polymers are sites where a double modification/functionalization, a prime example of site-specific PPM, can occur. First, a wide variety of amines can be employed for the aminolysis, followed by a thiol-click reaction of choice (Scheme 9). These polythiolactones can thus serve as precursors for polythiols, thereby solving issues involving the preparation and long-term storage of polythiols.

The two main requirements enabling implementation of thiolactone chemistry for the purpose of PPM of linear narrow-dispersity polymers are straightforward preparation of reactive vinylic thiolactone-containing monomers and subsequent controlled radical polymerization (CRP), ensuring clean incorporation of the thiolactone unit along the backbone. First, we devised and synthesized two different types of vinylic monomers on a large scale, styrenic [*N*-(4-vinylbenzenesulfonyl) homocysteine-γ-thiolactone, **6**] [49] and acrylic [*N*-(acryloyl) homocysteine-γ-thiolactone, **7**] [52] (Scheme 10). The synthesis of both thiolactone-containing monomers started from homocysteine-γ-thiolactone **1**. The most straightforward synthesis of a styrenic analogue **6** is the reaction between **1** and 4-vinylbenzenesulfonyl chloride, the corresponding sulfonyl chloride of styrene sulfonic acid. The corresponding acrylamide **7** is obtained through treatment with acryloyl chloride, using the same procedure. In both cases, a stable linkage



Scheme 10 Synthesis of two different types of vinylic thiolactone-containing monomers: *N*-(4-vinylbenzenesulfonyl) homocysteine-γ-thiolactone **6** and *N*-(acryloyl) homocysteine-γ-thiolactone **7**

(a sulfonamide in **6** and an amide in **7**) avoids unwanted detachment of the thiolactone unit during PPM.

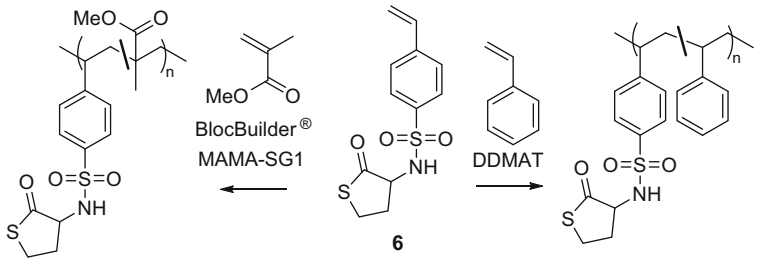
Following the large-scale preparation of the vinylicthiolactone monomers **6** and **7**, the CRP was targeted. As there were no literature precedents on the compatibility of thiolactone in the presence of carbon-centered propagating radical systems, we adapted polymerization conditions guaranteeing the integrity of the thiolactone moiety. We deliberately avoided the use of metal-mediated CRP in order to completely exclude transition metal residues throughout the processes of monomer synthesis, CRP, and PPM. Hence, RAFT [128–132] and nitroxide-mediated polymerization (NMP) [147] were the preferred polymerization techniques.

A first important observation was the lack of control and/or low conversions when attempting to homopolymerize either monomer **6** or **7**, as a result of solubility issues during the polymerization. Consequently, random copolymerizations of both monomers were performed.

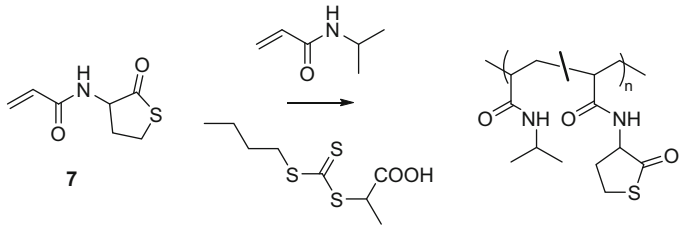
Successful copolymerization of monomer **6** with styrene or methyl methacrylate (MMA), via RAFT or NMP, yielded linear polymers with tunable thiolactone content (4–25%) and controlled molecular weight ($M_n = 6.0$–18.0 kDa), although dispersities were relatively high ($Đ \sim 1.5$) in the case of PMMA synthesized by NMP (Scheme 11) [49].

In an analogous manner, copolymers were produced by RAFT polymerization using monomer **7** as comonomer with *N*-isopropylacrylamide (NIPAAM) (Scheme 12). Thiolactone contents of the final polymers were determined via ^{1}H-NMR spectroscopy and elemental analysis. The polymers used for the PPM exhibited thiolactone contents between 23 and 32 mol%, with molar masses in the range of 10–20 kDa and low dispersities ($Đ = 1.2$–1.3) [52].

Although only narrow-disperse thiolactone-containing copolymers could be obtained, it has been demonstrated that thiolactones are compatible with radical polymerization conditions, using two different techniques (RAFT and NMP). Consequently, these poly(thiolactones) can be subjected to site-specific double PPM (vide infra).



Scheme 11 RAFT of styrene and monomer **6**, and the NMP of MMA and monomer **6** yielding the respective random copolymers

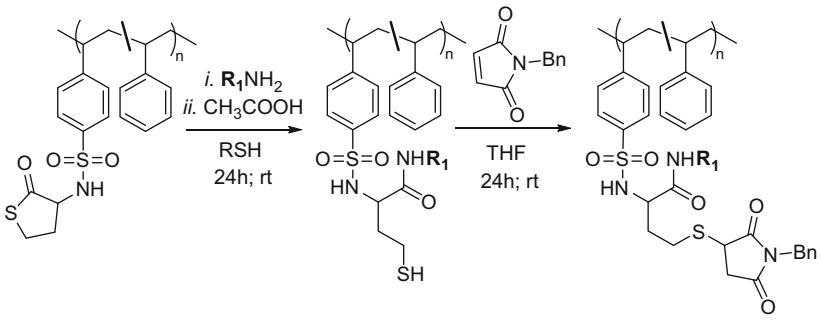


Scheme 12 RAFT copolymerization of NIPAAM and thiolactone-containing monomer **7**

4.3 Double PPM of Polythiolactones: Two-Step Batch Process

There are two approaches for the transformation of linear polythiolactones. On the one hand, the PPM consists of two separate batch processes (aminolysis and thiol-click), with isolation of the polythiol. On the other hand, the double PPM can be conducted in a one-pot manner, thus avoiding any intermediate purification. Both approaches were investigated and the respective advantages and disadvantages evaluated.

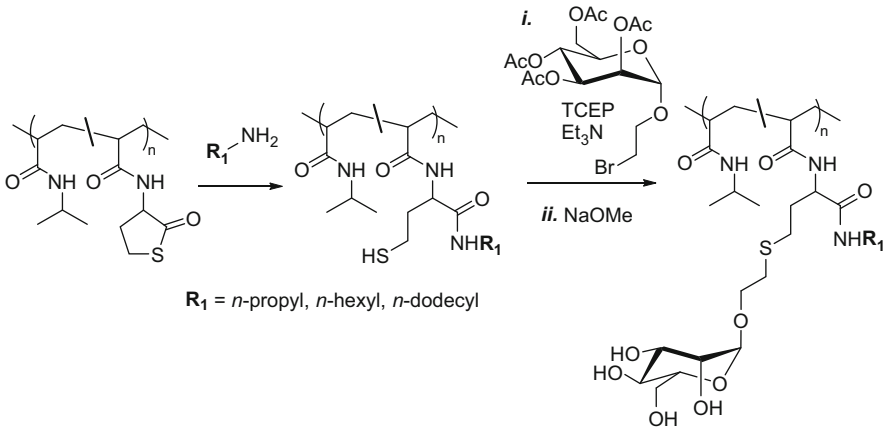
The first PPM approach was examined using styrene-based polythiolactones (Scheme 13). In the first step, aminolysis with a series of amines ($\mathbf{R}_1NH_2$: benzylamine, *n*-propylamine, ethanolamine, and Jeffamine M-1000) generates thiols as pendant groups on the polymer chain [49]. Disulfide formation could be suppressed using an excess amount of low molecular weight thiol (ethanethiol or octanethiol) as reducing agent. Acidic work-up before precipitation guaranteed the formation of a series of polythiols. After isolation of these polythiols, conjugate addition (thiol-Michael reaction) with *N*-benzylmaleimide yielded the double-modified polymers. This result demonstrates that the thiols introduced on the polymer backbone can serve as functional handles for subsequent thiol-click reactions, permitting a double modification of the polymer (Scheme 13). The reaction conditions were adapted during all stages of the process to completely suppress undesired disulfide formation. The low and constant dispersity of all linear



Scheme 13 Double PPM of thiolactone-containing linear polymers in a two-step approach. Nucleophilic ring opening of pendant thiolactone moieties with an amine, generating polythiols. After intermediate purification, further modification with *N*-benzylmaleimide via a Michael addition reaction was performed

polymers, as indicated by size-exclusion chromatography (SEC) analysis, is proof of the success of this two-step batch approach. Similar results were obtained when the double modification sequence was started with thiolactone-containing PMMA [49]. The main disadvantage of this two-step approach is the laborious work-up procedure enabling isolation of the polythiol without the formation of disulfide crosslinks. However, these polythiols, once purified, can be stored in the dried state for long periods (several months). The obtained polythiols are versatile scaffolds for further modification using a variety of established conjugation reactions. Moreover, this approach is particularly advantageous over one-pot double PPM when exploring thiol-X reactions that are not compatible with the aminolysis process, like the demonstrated thiol-maleimide conjugation.

In some cases, it is not necessary to isolate the polythiol by intermediate purification and subsequent reactions can thus be performed in the same pot. In this study, the copolymer (50% thiolactone content) from NIPAAM and *N*-homocysteine thiolactone acrylamide **7** (Scheme 12) was reacted with various amines bearing alkyl residues of increasing length ($\mathbf{R}_1NH_2$: *n*-propylamine, *n*-hexylamine, and *n*-dodecylamine) to liberate the corresponding thiol, which was subsequently reacted in situ with 2-bromoethyl-2′,3′,4′,6′- tetra-*O*-acetyl-α-D-mannopyranoside (Scheme 14). The reactions proceeded with high efficiency, leading to site-specific double PPM of the poly(thiolactone) in a near-quantitative manner. Undesirable crosslinking between polymer chains as a result of disulfide formation was eliminated by working in a one-pot fashion prior to final purification. After cleavage of the acetyl protecting groups, the reaction mixture in solution was dialyzed directly against water, resulting in stable aqueous solutions of glycopolymer-based nanoparticles by self-assembly. A trend in particle size was observed with increasing length of the amine side chains. The size of the amine residue did not only control the particle size, but also the morphology of the particles. Whereas the *n*-propylamine-derived amphiphiles mainly led to micelles (30 nm), the *n*-hexylamine



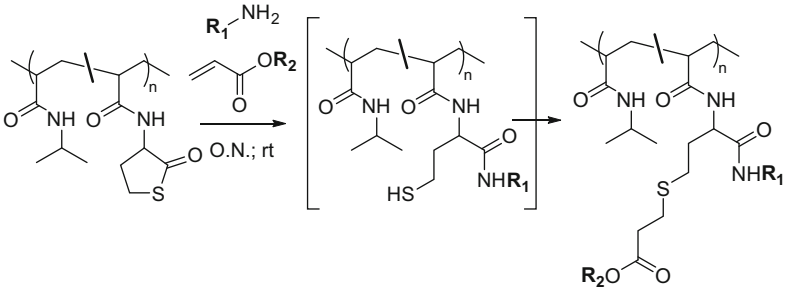
Scheme 14 One-pot reaction pathway (two-step batch process) to glycopolymers, employing a double modification (aminolysis and nucleophilic substitution) of thiolactone-containing copolymers

adducts gave rise to larger vesicles (200–600 nm). Longer alkyl amines resulted in the formation of large compound micelles.

Nanoparticles obtained from amines with shorter chain length were more uniform in size and also displayed higher bioactivity by interaction with the selected lectin (Concanavalin A). In contrast, larger amine-adducts led to nanoparticles of various shape and size, and the lectin interaction was severely reduced [54]. This last example nicely illustrates the power of thiolactone chemistry in site-specific double PPM, providing straightforward access to various adducts (e.g., by selecting different amines in the first step) and enabling the incorporation of functional residues (e.g., the sugar unit). The resulting libraries of glycopolymer-based nanoparticles can be screened for bioactivity, eventually establishing relevant structure–property and structure–activity relationships.

4.4 Double PPM of Polythiolactones: One-Pot Process Through Nucleophilic Amine-thiol-ene Conjugation

The second approach for site-specific double PPM was performed using the polythiolactones prepared by random RAFT copolymerization of NIPAAM and thiolactone acrylamide monomer **7** (Scheme 12) [52]. The respective copolymers were subjected to additive-free nucleophilic amine-thiol-ene conjugation. A chloroform solution of the polythiolactone at a concentration of 10 wt% was treated with the desired acrylate, followed by addition of the primary amine. Both reagents were used in a fivefold excess with respect to the number of thiolactone units (Scheme 15).



Scheme 15 Double PPM of thiolactone-containing linear polymers in a one-pot approach using nucleophilic amine-thiol-ene conjugation

Table 1 SEC data for polymers obtained through double PPM of thiolactone-containing linear polymers in a one-pot approach using nucleophilic amine-thiol-ene conjugation

Entry[a]	Amine/acrylate combination	M_n (kDa) (Đispersity)[b]	
		Before PPM	After PPM
1	Benzylamine/methyl acrylate	6.4 (1.23)	7.0 (1.23)
2	4-Fluorobenzylamine/2,2,2-trifluorethyl acrylate	6.4 (1.23)	8.3 (1.18)
3	Ethanolamine/2-hydroxyethyl acrylate	6.4 (1.23)	8.9 (1.21)
4	*n*-Octylamine/isobornyl acrylate	6.4 (1.23)	8.3 (1.20)
5	Ethanolamine/isobornyl acrylate	6.4 (1.23)	8.4 (1.22)
6	*n*-Octylamine/2-hydroxyethyl acrylate	6.4 (1.23)	8.0 (1.21)
7	Benzylamine/2-(2-ethoxyethoxy) ethyl acrylate	6.4 (1.23)	7.3 (1.22)
8	*N,N*-Dimethyl-ethylenediamine/1-ethoxyethyl acrylate	6.4 (1.23)	4.7 (1.23)
9	*n*-Propylamine/benzyl acrylate	6.4 (1.23)	7.7 (1.22)
10	Furfurylamine/benzyl acrylate	6.4 (1.23)	7.8 (1.22)
11	3-Morpholino-propylamine/methyl acrylate	10.9 (1.27)	12.5 (1.25)
12	*N,N*-Dimethyl-ethylenediamine/benzyl acrylate	10.9 (1.27)	6.0 (1.35)
13	*N,N*-Dimethyl-ethylenediamine/2-(2-ethoxyethoxy) ethyl acrylate	10.9 (1.27)	9.0 (1.27)

[a]Thiolactone content in the copolymer was 25% for entries *1–10* and 32% for entries *11–13*
[b]Number-average molecular weight (M_n) and dispersity was obtained from size-exclusion chromatography measurements. Figures in brackets indicate the polydispersity index

In all cases, a clear molecular weight shift was observed while a low dispersity was maintained, which shows that side reactions such as disulfide formation were negligible (Table 1). In other words, the released thiol groups were immediately trapped by the acrylate present in the solution. In addition to the performed SEC analysis, in-depth structural investigations of a selection of the modified polymers using ^{19}F-NMR (Table 1, entry 2) and 2D-NMR (entry 10) confirmed the near-quantitative double PPM. Furthermore, successful functionalization was also

achieved by combining reagents of different hydrophilicity and hydrophobicity (entries 3–6).

Another important observation was the changed solubility properties of the modified copolymers, especially when a hydrophilic (entry 3) or a hydrophobic (entry 4) amine/acrylate pair was used. Furfurylamine (entry 10), 3-morpholinopropylamine (entry 11), and *N*,*N*-dimethylethylenediamine (entries 8, 12, 13) were tested as functional amines, giving pNIPAAm a multiresponsive character or providing the opportunity for further functionalization. 1-Ethoxyethyl acrylate (entry 8) was tested as a protected carboxylic acid derivative [148, 149] and 2-(2-ethoxyethoxy)ethyl acrylate (entries 7 and 13) introduced short ethylene glycol side chains to the polymer [52].

Encouraged by successful application of the nucleophilic amine-thiol-ene conjugation in a one-pot double PPM approach, we additionally demonstrated that the degree of functionalization can be controlled through different substoichiometric amounts of the ring-opening amine. This proved to be particularly interesting for tuning the lower critical solution temperature (LCST) of the respective polymer. Indeed, in the selected case of double PPM with *N*,*N*-dimethylethylenediamine/2-(2-ethoxy ethoxy)ethyl acrylate (Table 1, entry 13), the modification degree could be tuned using different amounts of amine per batch. The tertiary amine residues can, upon protonation at a sufficiently low pH, cause increased hydrophilicity of the polymer. Because attachment of the acrylate to the polymer backbone depends on prior aminolysis, the final polymers also bear varying amounts of 2-(2-ethoxy ethoxy)ethyl side chains. Consequently, a series of water-soluble polymers showing an LCST depending on the pH and the degree of functionalization was obtained. Starting from a precursor polymer with a thiolactone content of 32 mol%, an increase in the degree of functionalization from 40% to 95% led to a cloud point shift from 27°C to 66°C at pH 7. Additionally, the polymer with the highest degree of functionalization (95%) exhibited a transition temperature of 35°C at pH 9 although it was still water-soluble at 75°C in acidic medium (pH 5) [52].

The simplicity of the approach in terms of experimental set-up, together with the mild reaction conditions and the almost endless choice of amine/acrylate combinations, render the nucleophilic amine-thiol-ene conjugation a powerful and versatile PPM tool for site-specific double modification. The possibility for simultaneous introduction of chemical functionalities and solubility modulators provides paths to multifunctional tailor-made materials.

4.5 Double PPM of Thiolactone-Containing Polymers Combined with Disulfide Chemistry

A disulfide bond is a relatively stable, yet reversible, linkage that is able to (inter) connect a whole range of different substrates [150–156]. This inherent reversibility means that it can be (re)formed or broken on the users' demand, generally under

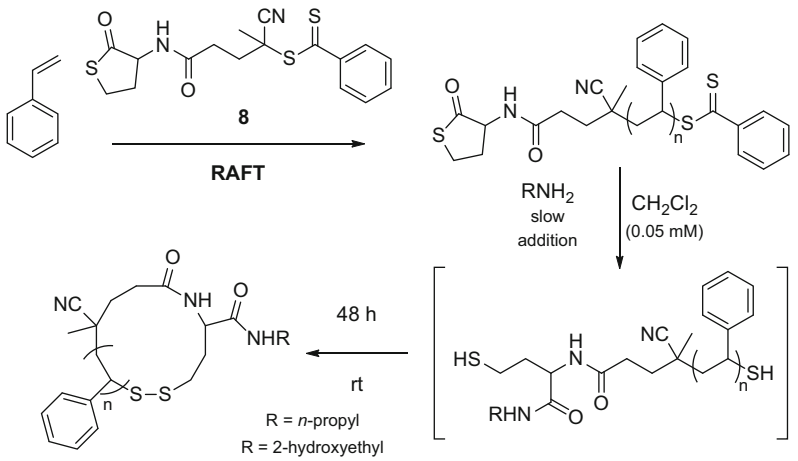
relatively mild conditions. Hence, it has been included in the dynamic covalent chemistry (DCC) toolbox [157–161] and it is essential in some covalent adaptable networks (CANs) [162–164] with self-healing capabilities [165–168].

However, undesired disulfide formation during thiol-click reactions and/or long-term storage of thiol-containing substrates is of particular concern and was one of the initial reasons for starting our thiolactone research (vide supra). Although this unwanted secondary reaction can be avoided when employing one-pot thiolactone-based reactions, such as nucleophilic amine-thiol-ene conjugation, it still requires careful monitoring. Sometimes the corresponding disulfide is the major adduct of a ring opening of the thiolactone precursor, especially in the absence of a thiol scavenger and in the presence of a larger excess of primary amine during aminolysis [51]. At present, we still do not fully understand the parameters that influence the extent of disulfide formation during aminolysis of a thiolactone, compromising the prevention, prediction, and control of this event. However, we observed that (a) amine concentration during ring opening correlated with the extent of disulfide formation, (b) disulfide formation was independent of the nature of the primary amine, and (c) additional oxidizing agents were not required for disulfide formation to occur.

Based on these experimental observations, we explored the scope of the concomitant disulfide formation during the aminolysis of thiolactones as a useful synthetic method for the preparation of cyclic polymers [53]. First, we envisaged the synthesis of linear α,ω-heterotelechelic precursor via RAFT. The initial design of a thiolactone-containing chain transfer agent (CTA) was therefore mandatory, providing direct access to a thiol group at both the α- and ω-termini of the polymer upon treatment with an amine [126, 127]. Then, the in situ produced thiol-telechelics can engage through disulfide bonding in an intramolecular fashion to yield cyclic polymers, under high dilution and ambient conditions (open air, room temperature, without need for a catalyst or any additive).

Following the synthesis of the thiolactone-containing dithiobenzoate **8** as CTA and RAFT polymerization of styrene, the aminolysis reaction of this heterotelechelic precursor by slow addition of a primary amine (*n*-propylamine or ethanolamine) in dilute solution (0.05 mM in CH_2Cl_2), which acts as a nucleophile for both the thiolactone and dithiobenzoate units, generated the α,ω-telechelic-dithiol under ambient conditions without the need for any catalyst or other additive (Scheme 16). Moreover, a controlled ring opening via either disulfide reduction or thiol–disulfide exchange enables easy and clean topology transformation, re-establishing the corresponding linear polymer and confirming the ring closure mechanism through disulfide formation [53].

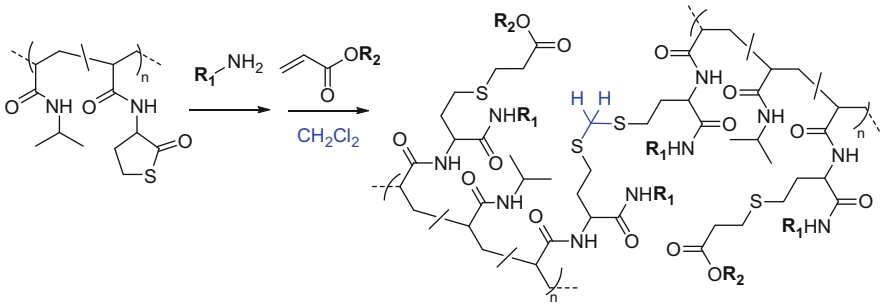
The next case is a good illustration of the complex nature of disulfide formation following thiolactone aminolysis [56]. In an attempt to make degradable multifunctionalized hydrogels, the polythiolactones, prepared according to Scheme 12, were treated with an excess of primary amines, anticipating gelation via disulfide formation. To our surprise, performing the reaction in various solvents (DMSO, THF, MeOH, and EtOH) with increasing amounts of different amines did not result in the expected gelation. A crucial observation was the fact that crosslinking only



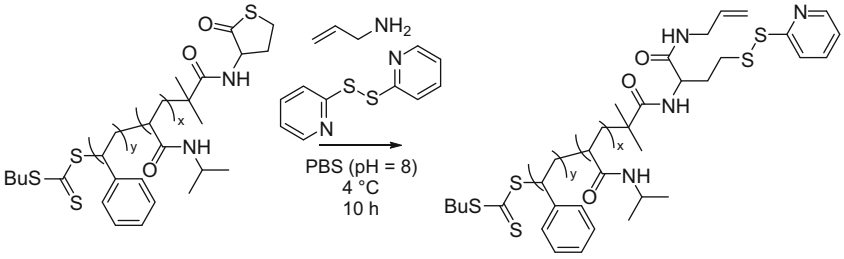
Scheme 16 Cyclization approach for the preparation of cyclic polystyrene using RAFT and thiolactone/disulfide chemistry

occurred when dichloromethane (DCM) was present in the starting formulation. Moreover, the obtained chemical networks were not degradable, excluding the option of (reversible) disulfide formation as the only crosslinking reaction. After thorough analysis of model reactions, investigating the outcome of thiolactone aminolysis and the effect of DCM as potential crosslinker, we confirmed a gelation mechanism involving the nucleophilic substitution of the chlorine atoms in DCM by the in situ generated thiols [56]. Hence, the newly discovered crosslinking chemistry was combined with nucleophilic amine-thiol-ene conjugation to prepare multifunctionalized hydrogels with tunable swelling degrees and response features (Scheme 17). Functional residues originated from the employed primary amine and acrylate, while DCM fulfilled a dual role as solvent and crosslinking agent. More importantly, the residues induced responsive properties in the final gel, such as CO_2 sensitivity and optical response, in addition to the thermoresponsive character of the PNIPAAM-based gel matrix.

An alternative route to disulfide formation is a thiol–disulfide exchange reaction [160, 167, 168] in the presence of a 2,2′-dipyridyl disulfide(or derivative) as a reactive disulfide. Two very recent studies revealed that the thiol–disulfide exchange reaction (pathway c in Scheme 5) offers better selectivity and control over the disulfide formation process. Moreover, the obtained mixed disulfide remains reactive towards thiols for further modification. In contrast to the above-described amine-thiol-ene conjugation, this approach is not 100% atom-efficient because 2-mercaptopyridine (or a derived structure) is released in the reaction medium. Monteiro and coworkers synthesized multifunctional nanostructures (worms and rods) with multiple chemical functionalities directly in water using a one-step RAFT-dispersion polymerization. The introduced functional handles originate from their presence in the R group on the CTA. In the case of thiolactone worms and rods, aminolysis with allylamine and subsequent one-pot scavenging of



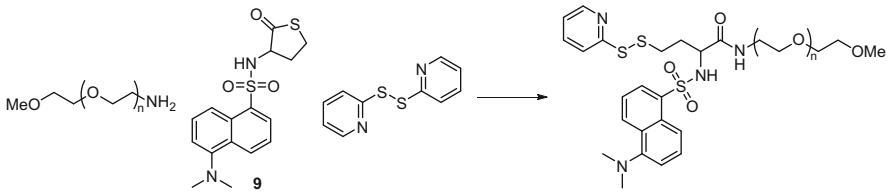
Scheme 17 Preparation of (multi)functionalized hydrogels in a one-pot procedure using DCM as crosslinking agent, starting from thermosensitive polythiolactones



Scheme 18 One-pot double modification of thiolactone functional nanostructures with allylamine and 2,2′-dipyridyldisulfide through aminolysis and disulfide exchange

the released thiol using 2,2′-dipyridyl disulfide (thiol–disulfide exchange) in buffered aqueous solution results in the formation of the corresponding pyridyl disulfide and alkene functional nanostructures, allowing further orthogonal reactions (Scheme 18). It is remarkable that this double modification involving thiolactone aminolysis has been successfully performed in water and that the trithiocarbonate is shielded from aminolysis by the nanostructure morphology [63].

The same transformation has been employed by Lei Tao and coworkers for the preparation of a fluorescent protein-reactive poly(ethylene glycol) (PEG) [64]. Synthesis of the latter consists of the aminolysis of dansylthiolactone **9** using commercial monofunctional PEG-NH_2 (~5 kDa) as a nucleophile in the presence of 2,2′-dipyridyl disulfide (Scheme 19). Once prepared, this PEGylation agent can subsequently react with bovine serum albumin (BSA) as a model therapeutic protein to form a fluorescent PEGylated protein as a model of sophisticated theranostic combination, with almost complete preservation of structural integrity and thus bioactivity of the protein.



Scheme 19 One-pot synthesis of the fluorescent protein-reactive PEG derivative

5 Conclusion and Outlook

In summary, several thiolactone-based synthetic approaches for the site-specific double modification of a variety of thiolactone-containing polymers have been established. Thiolactones are sensitive towards ring opening in the presence of amines and generally serve as thiol precursors under these conditions. The 100% atom-efficient aminolysis can be followed by thiol-click conjugation, offering the possible introduction of two residues: the first ($\mathbf{R}_1$) originating from the ring-opening amine and the second ($\mathbf{R}_2$) from the thiol-X reaction. Extensive method development through dedicated model studies, focusing on the one-pot aminolysis of thiolactone units and subsequent thiol-click conjugation, resulted in elaboration of the amine-thiol-ene conjugation.

Both variants of this one-pot two-step reaction sequence, following either the radical or nucleophilic pathways, are applicable, although the radical version has some limitations because of orthogonality issues when using functionalized amines. The nucleophilic amine-thiol-ene conjugation is particularly attractive because this 100% atom-efficient polymerization is a very mild process, occurring at ambient conditions without any additive or external trigger.

Next, the site-specific double PPM of narrow-disperse thiolactone-containing linear polymers was discussed. First, two vinylic monomers (styrenic and acrylic), derived from homocysteine-γ-thiolactone **1**, were copolymerized using RAFT and NMP. At this stage, the compatibility of thiolactone units with radical polymerization conditions was demonstrated. Following successful CRP, the resulting polythiolactones, with varying thiolactone content and molecular weight, were subjected to double modification using two distinct approaches. On the one hand, the PPM can consist of two separate batch processes (aminolysis and thiol-click), with isolation of the polythiol. On the other hand, the double PPM can be conducted in a one-pot manner, using a reactive mixture of a primary amine, an acrylate and a polythiolactone, thus avoiding any intermediate purification. Both approaches offer the possibility for double PPM of narrow-disperse polythiolactones, although the first approach requires more laborious work-up to isolate the polythiol without disulfide formation; however, it offers the user more options for the thiol-click used in the second modification step. At this point, we want to highlight again the scope of the nucleophilic amine-thiol-ene conjugation for double PPM because it has proven to be a very straightforward and versatile method.

While developing these thiolactone-based synthetic methods, we recognized the general importance of disulfide formation as a side reaction during aminolysis of a thiolactone ring, especially in the absence of a thiol scavenger. Although not fully mastered, we can influence the degree of disulfide formation to some extent, making it a useful and clean transformation. This knowledge was used to prepare cyclic polymers. CRP of styrene, mediated by a designed thiolactone-containing CTA, resulted in the synthesis of narrow-disperse heterotelechelic polystyrene, having both reactive thiolactone and dithiobenzoate end groups. Upon aminolysis in a dilute medium, the linear precursor was transformed into an α,ω-dithiol, which cyclized through disulfide formation. Topology transformation, from cyclic to linear, via scission of the disulfide bond offered further support for the proposed thiolactone/disulfide cyclization chemistry. In an attempt to prepare (multi) functionalized hydrogels through disulfide formation, we discovered an important side reaction when thiolactone aminolysis is executed in dichloromethane as a solvent. An alternative approach for disulfide formation is the thiol–disulfide exchange reaction, involving a primary amine, a thiolactone unit, and 2,2′-dipyridyl disulfide or derived structure as reactive disulfide.

As a general conclusion and outlook, it can be stated that, because of its versatility, the thiolactone approach in polymer science can be regarded as a breakthrough development of the modern functionalization toolbox. Therefore, it will undoubtedly lead to many more applications. In material science, the unique properties of the thiolactone functional handle, such as double modification, one-pot strategies, and mild conjugation protocols involving biomolecules, will attract the efforts of many more research groups worldwide.

Acknowledgements Both authors are thankful to Ghent University, the Belgian program on Interuniversity Attraction Poles initiated by the Belgian State, the Prime Minister's office (P7/05), and the European Science Foundation Precision Polymer Materials (P2M) program for financial support.

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Published online: 6 May 2015

Sequential Reactions for Post-polymerization Modifications

Fenja Moldenhauer and Patrick Theato

Abstract In this chapter, selected examples of sequential post-polymerization modifications are highlighted. Initially, we focus on side chain and chain end modifications in solution and at surface bounded polymers. Afterwards, the usage of this modifications as powerful tools in the synthesis of polymer structures such as graft and star polymers are discussed.

Keywords Chain end · Sequential reactions · Side chain · Star shaped polymers · Surface modification

Contents

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1 Introduction

Since their discovery by Strecker in 1850, multicomponent reactions (MCRs) have become increasingly important [1]. From the first, organic chemists realized the huge advantages of this type of reaction class. Many years later, the concept also became interesting for macromolecular chemists [2, 3]. Among other reactions, MCRs enable efficient post-polymerization modification of either chain ends or side chains with more than one functional group at the same time. As a result of the mechanism of MCRs, singly modified polymers can be avoided, which simplifies the purification enormously. Thus, MCRs have become a favorite tool, allowing construction of defined polymers such as branched and star-shaped polymers. Several chapters in this volume cover various MCRs that find use in polymer synthesis. However, the MCR approach also has some disadvantages. First of all, the number of known MCRs is still limited; furthermore, MCRs require suitable reaction conditions for all components involved, and, last, but not least, one must beware of the reactive side groups, which can cause side reactions.

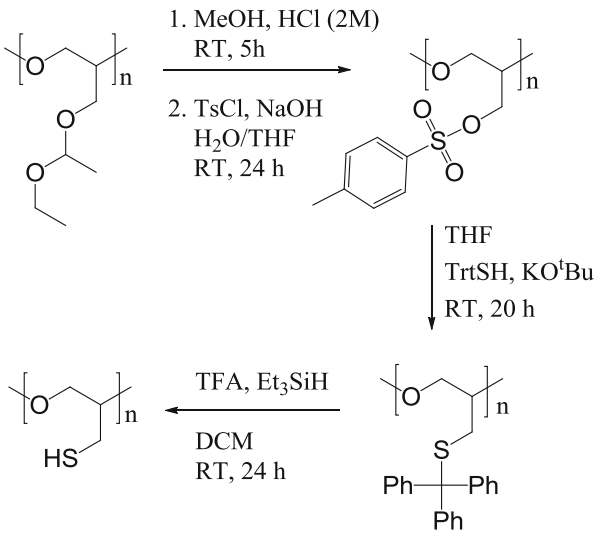
As an alternative to MCRs, a cascade of reactions can be used as a solution to the above-mentioned problems. Here, functional groups can be modified in a sequence of reactions, and different reaction variations can be distinguished. If a reaction of a functional group generates another functional group or reactive intermediate that can react in further steps, it is called a cascade reaction (also called tandem reaction or domino reaction). The isolation of (reactive) intermediates is mostly impossible. In other words, in a tandem reaction several bonds are formed in sequence without isolating intermediates, changing reaction conditions, or adding other reagents. If it is necessary to change reaction conditions between the steps, the reaction is called consecutive. The addition of further reagents also falls into this category. However, in this case, the isolation of intermediates is in principle possible. A third possibility is the use of sequential reactions, which are conducted successively. After each step, purification and isolation of intermediate compounds is possible (and sometimes necessary). The latter in particular enables planning of a synthetic route that avoids possible side reactions, but allows a broad variation in functional groups. Similarly to MCRs, sequential reactions can be used to construct advanced polymer structures. The modification of polymer side chains and chain ends, as well as the modification of polymer-coated surfaces and the synthesis of grafted and star-shaped polymers, are discussed in this review. This chapter also discusses selected examples that employ sequential reactions in the context of post-polymerization modification. We do not claim to give exhaustive coverage of the topic.

2 Functionalization of Polymer Side Chains

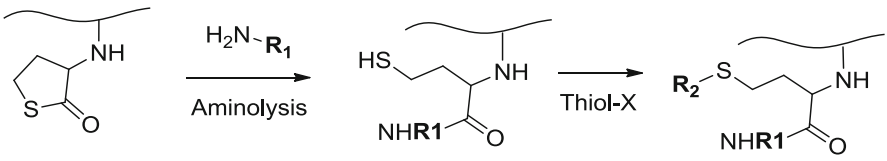
Sequential reactions can be used for post-polymerization modifications. In this case, two general approaches are commonly used: the polymer chain ends can be modified or the modification can take place at each repeating unit. We first focus on side chain modifications. Some of these reactions, which can be subdivided according to their functional groups, are discussed next.

As a first example, polyethers, such as glycidol-bearing poly(ethylene glycol)s (PEGs), are discussed. The group of Tovar demonstrated the possibility of converting the protected glycidol units into thiol groups in a three-step reaction (Scheme 1) [4]. After deprotection and tosylation, a triphenylmethyl-protected thiol was introduced, which was deprotected in the final step, yielding the thiol in an overall yield of 87%. The resulting poly(glycidylthiol) could be crosslinked with PEG diacrylate to result in hydrogels that supported the adhesion and proliferation of human fibroblasts. Using subsequent inkjet printing of these compounds onto acrylated glass slides, spatially well-defined and surface-attached gel structures were obtained, making this chemistry highly interesting for various applications. The crosslink density could be adjusted by varying the monomer ratio for copolymers of PEG and poly(1-ethoxyethyl glycidyl ether).

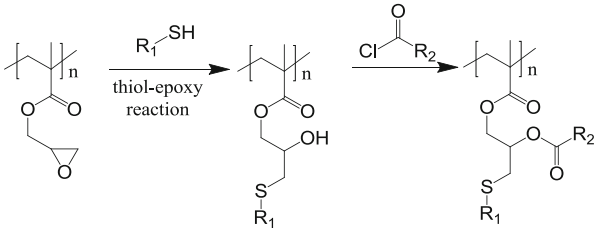
Another possibility for the introduction of thiols at the polymer side chains, as well as their further modification, is described in the chapter on thiolcatones by Espeel and Du Prez in this book [5]. In their approach, polymers with γ-thiolactone side groups were used as starting materials. The thiolactones were ring-opened by aminolysis in a first step, yielding thiol moieties (Scheme 2). The introduction of another residue can be enabled by a subsequent thiol–X reaction, for example the



Scheme 1 Synthetic route to mercaptomethyl side chain-functionalized PEG-based polymer



Scheme 2 Formation of thiol moieties at polymer side chains by aminolysis of γ-thiolactones and subsequent thiol–X reaction, enabling the introduction of two new residues

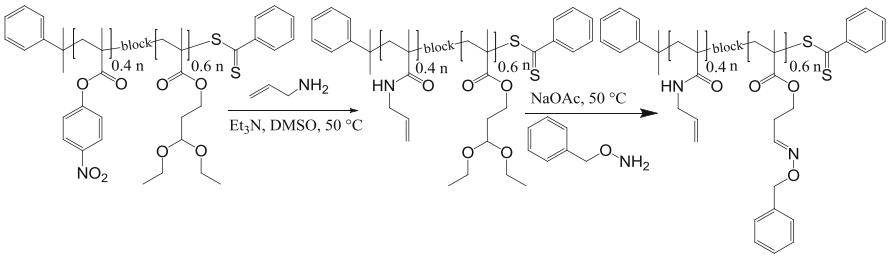


Scheme 3 Post-polymerization modification of epoxy side groups by thiol–epoxy reactions and subsequent esterification

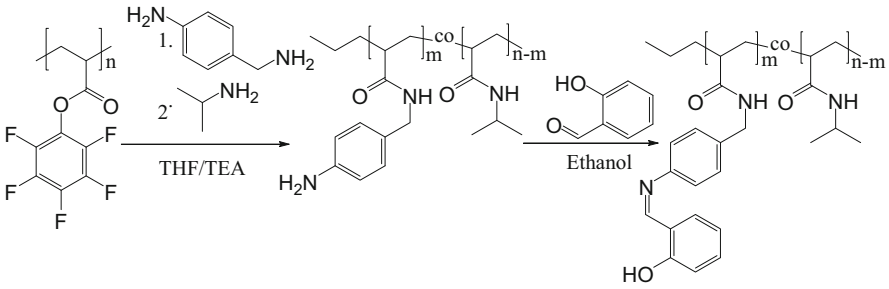
thiol–ene reaction. This synthetic pathway enables a double functionalization of each repeating unit.

Alternatively, thioethers can also be synthesized using epoxide-containing polymers and their reaction with free thiols. As described in detail by Stuparu and Khan in another chapter in this volume [6], the epoxide side groups could easily be introduced by polymerizing glycidylmethacrylates. Ring-opening of the epoxides by thiols (thiol–epoxy reaction) led simultaneously to thioether and hydroxy functionalities (Scheme 3). Subsequently, the latter hydroxyl group could be quantitatively converted into an ester. As in the previous example, this synthetic route enabled the double modification of all repeating units.

Other researchers directly focused on the use of copolymers as starting materials for their sequential modifications and aimed at the subsequent modification of two differing functional blocks. For example, Li et al. demonstrated a stepwise post-polymerization modification of poly(*p*-nitrophenylmethacrylate)-*block*-poly (diethoxypropyl methacrylate) block copolymers (PNPMA-*b*-PDEPMA) (Scheme 4) [7]. In this case, the polymer was synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization to obtain a well-defined starting material (number average molecular weight, $M_n = 12{,}000$ g/mol; polydispersity index, PDI = 1.24). Afterwards, allylamine was used for PNPMA modification, followed by modification of the PDEPMA block with *O*-benzylhydroxylamine hydrochloride. This stepwise, selective, and easy modification of orthogonal groups enabled the synthesis of block copolymers with amide and imine functionalities originating from activated ester and protected aldehyde side chains. The group of Theato reported a similar orthogonal functionalization approach [8]. They took advantage of the reactivity difference between



Scheme 4 Double functionalization of PNPMA-*b*-PDEPMA

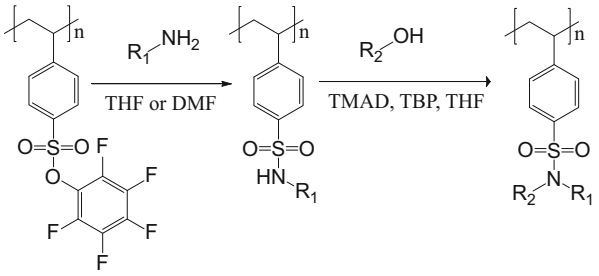


Scheme 5 Sequential modification of PFPA via amidation followed by imidation

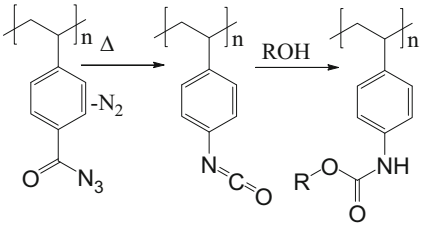
pentafluorophenyl (PFP) esters of methacrylate and 4-vinylbenzoate-derived block copolymers [9, 10]. A sequential conversion of the esters was achieved by varying the amines in the amidation step.

In 2009, Theato and Jochum proposed a concept for modifying poly (pentafluorophenyl acrylate) (PPFPA) sequentially in a two-step reaction [11]. As shown in Scheme 5, the activated PFP-ester was treated with two different primary amines to first obtain a statistical copolymer. Using 4-(aminomethyl) aniline in this step enabled formation of an imide by adding 2-hydroxybenzaldehyde in a subsequent step. This approach facilitated the synthesis of doubly functionalized polymers from simple starting materials. Furthermore, the assignment of different amine ratios appeared to be an easy tool for adjusting the lower critical solution temperature (LCST) properties of the resulting polymers.

In both cases described above, the newly formed amides stayed untouched; but, in a more recent study Kakuchi and Theato demonstrated synthetic routes for the insertion of further functionalities at an amide position when switching to the synthesis of polymeric sulfonamides [12]. Therefore, the starting polymer poly (pentafluorophenyl-4-vinylbenzene sulfonate) was aminolyzed to obtain the corresponding sulfonamide. A subsequent Mitsunobu reaction led to doubly functionalized side chains (Scheme 6). This succession enabled the double functionalization of each repeating unit with a huge library of different amines and alcohols in almost quantitative yields.



Scheme 6 Sequential post-polymerization modification process comprising sulfonamidation and Mitsunobu reaction

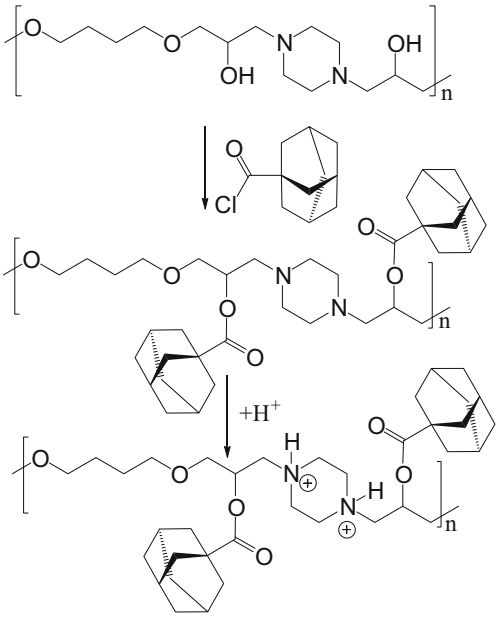


Scheme 7 Two-step reactions towards polymers with carbamate side chains

The insertion of alcohols plays an important role in post-polymerization modification, because of their high variability, stability, and commercial availability. In addition to the Mitsunobu reaction, the introduction of alcohols can take place in different modes. Klinger et al. established a two-step synthesis towards carbamates, starting from poly(4-vinylbenzoyl azide) [13]. As illustrated in Scheme 7, the acyl azide side groups underwent a Curtius rearrangement by heating and generated in situ isocyanato groups. At this point, different alcohols could be used to convert the isocyanato group into carbamates, resulting in quantitative yields.

Up to this point, solely low molecular weight alcohols were used; nevertheless, polymeric hydroxyl side chains can also be successfully modified. Khan and coworkers used a hydroxyl-containing polycondensate, which was derived from piperazine and 2,2′-[butane-1,4-diylbi(oxymethanediyl)]dioxirane, as starting polymer (Scheme 8) [14]. Tricyclo[3.3.1.1]decane-1-carbolyl chloride could be attached onto these poly(β-hydroxy amines). By acidic treatment, the backbone amine units were protonated and transformed the main chain into a cationic polymer system. The introduced monoadamantyl moiety could then be selectively linked to β-cyclodextrin units to create graft polymers.

The group of Lei Tao has reported several approaches that realize a polymerization and sequential post-modification in one pot. For example, simultaneous copper(I)-catalyzed azide–alkyne cycloaddition, enzymatic transesterification, and atom transfer radical polymerization (ATRP) were successfully conducted [15].

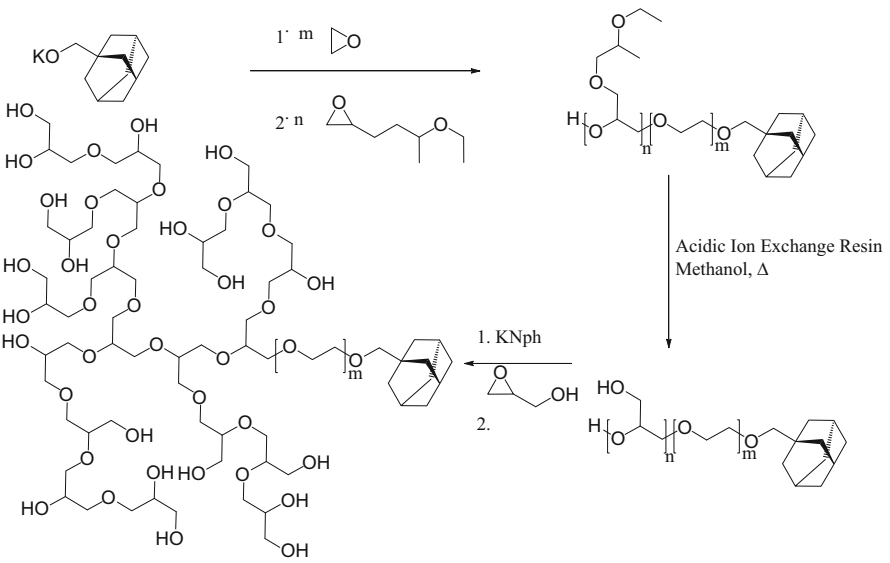


Scheme 8 Attachment of tricyclo[3.3.1.1]decane-1-carbolyl chloride onto a poly(β-hydroxy amine) followed by main chain cationization

3 Synthesis of Graft Polymers

To synthesize graft polymers, chemists differentiate between two synthetic routes: direct polymerization of macromonomers and attachment of chain end modified polymers to existing polymers as side chain functionalities. In an example using monoadamantyl and β-cyclodextrin as linkers for supramolecular connections, Moers et al. used an orthogonal approach [16]. First, hyperbranched arms were synthesized in an anionic ring-opening polymerization (ROP) using monoadamantyl alcoholate as the initiator. Here, oxiran was used to install a PEG spacer before 2-(3-ethoxybutyl)oxirane was polymerized to form the hyperbranched structure. Deprotection of the masked hydroxyl side chain in the second block and use of this unmasked hydroxyl group as a ROP initiator opened a way to obtain a hyperbranched structure (Scheme 9).

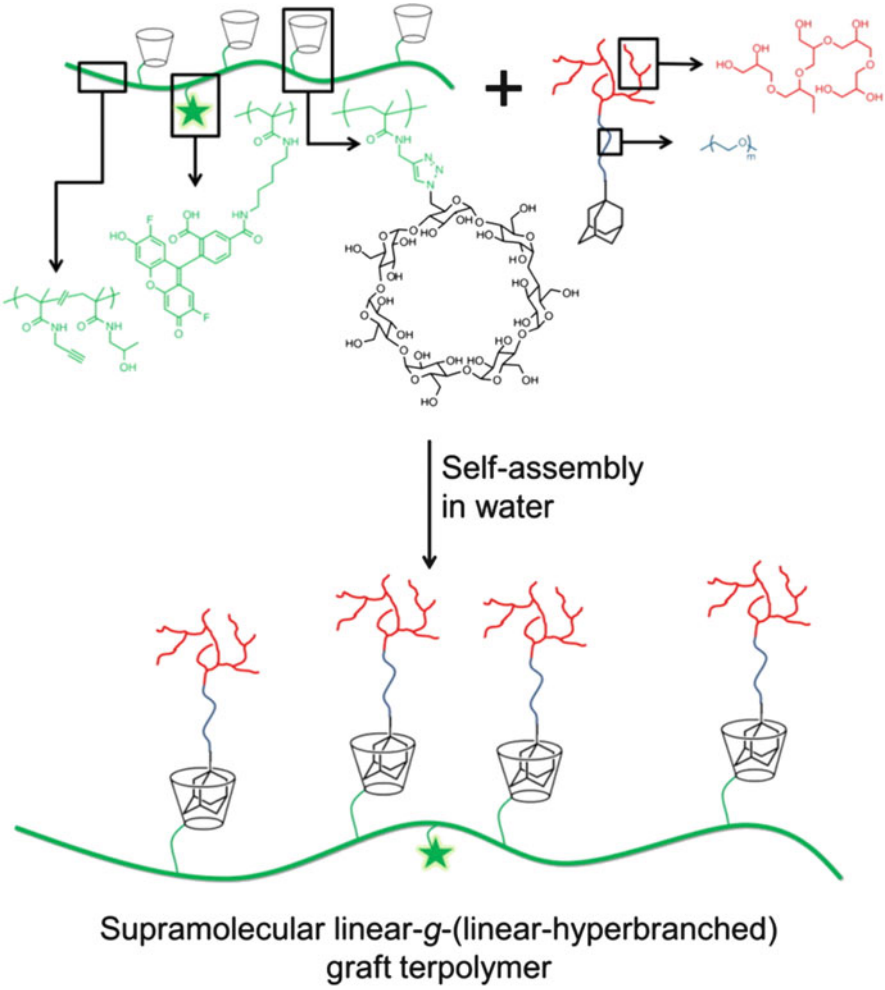
Preparation of the future main chain occurred via activated PFP-ester chemistry, as discussed in Sect. 2. For this, PFPA was used as monomer in a RAFT polymerization. After removal of the thioester chain end by treatment with excess AIBN, the aminolysis using monoamine-functionalized fluorescent dye (Oregon Green Cadaverine) and prop-2-yn-1-amine and 1-aminopropan-2-ol was conducted. Via an azide–alkyne 1,3-dipolar cycloaddition, an azide-capped cyclodextrin was attached onto the alkyne units along the main chain. As demonstrated in Scheme 10, the cyclodextrin moiety works as a supramolecular binding site for adamantyl residues. This supramolecular binding concept resulted ultimately in linear-*g*-(linear-hyperbranched) graft terpolymers.



Scheme 9 Synthesis of hyperbranched monoadamantyl-capped polymers via ring-opening polymerization

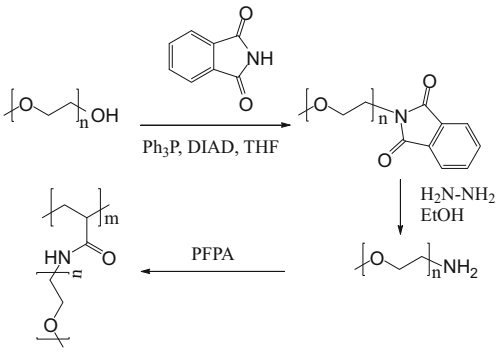
Although, in this specific case, attachment of the arms is reversible, activated esters can also be used for covalently bound graft polymer arms. Therefore, amine-capped polymers are required as arms. Lowe and coworkers decided to use amino-PEG, which could be prepared in a two-step reaction [17]. In the first step, commercially available methoxy-PEG was capped with phthalimide; subsequent cleavage with hydrazine yielded the amino-PEG (Scheme 11). The resulting primary amine was used to aminolyze the activated PFP-ester of the PFPA main chain to result in linear-*g*-linear graft-copolymers.

In addition to the activated ester approach, alkyl-halide reactions are frequently used in the synthesis of graft polymers. Because of their easy availability, active anionic polymers are commonly used as arms. This requires the introduction of halides to the polymer main chain, in order to allow substitution with, for example, active anionic polymers. Ito et al. prepared such main chains by living anionic polymerization of (3-*tert*-butyl-dimethylsilyloxymethylstyrene)s and subsequent quantitative transformation into the corresponding benzyl bromide. Yang's group resorted to the direct polymerization of *p*-chloromethylstyrene [18, 19]. In both cases, anionic polymerized monomers could be used to obtain polymers with high grafting densities. Brush polymers and graft polymers with Y-shaped arms are also accessible via this synthetic pathway. An overview of possible structures is shown in Scheme 12.

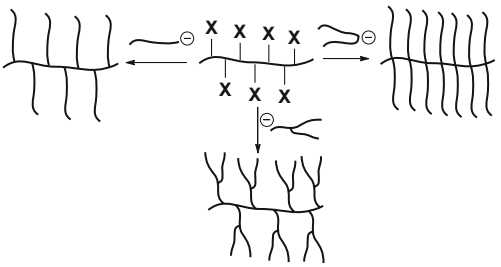


Scheme 10 Representation of the formation of supramolecular linear-*g*-(linear-hyperbranched) graft terpolymer (Reproduced with permission from Ref. [16])

Scheme 11 Synthesis of amino-PEG and its use in the formation of methacrylamide-PEG graft copolymers



Scheme 12 Obtainable structures via the substitution of halide-containing polymer chains with anionic polymer chains

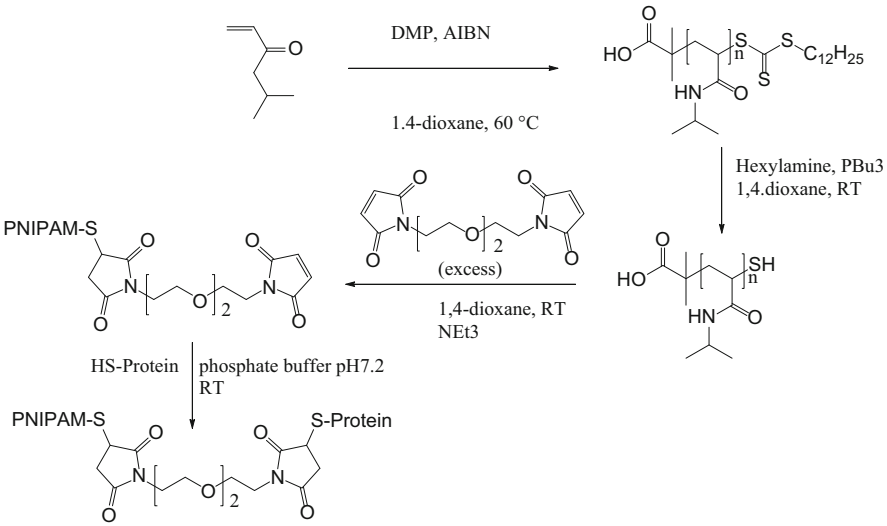


4 Chain End Modifications

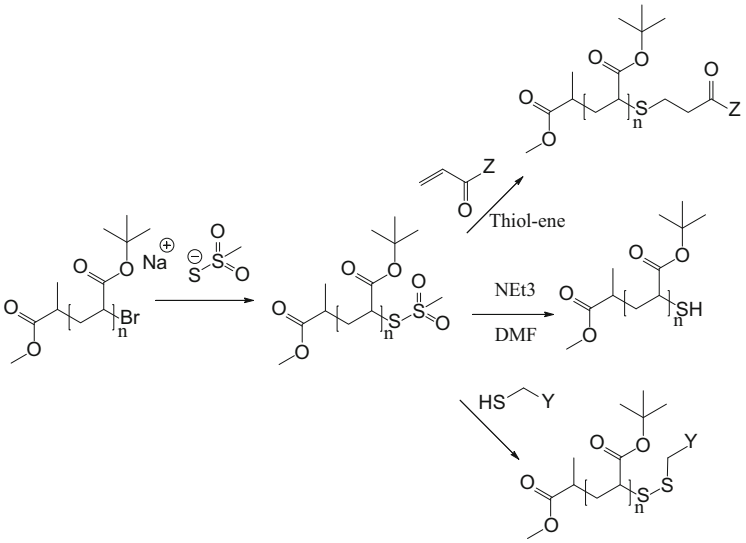
As summarized in Sect. 3, the synthesis of grafted polymers requires side chain functionalities on the main chain as well as chain end functionalities on the polymers forming the arms. Besides, chain end modified polymers themselves exhibit highly interesting properties. To obtain chain end modifications, well-defined chain ends are a primary requirement and can be obtained via controlled polymerization techniques and subsequent chain end modification. For example, Sumerlin and coworkers reduced the thioester of poly(*N*-isopropylacrylamide) (PNIPAM; prepared by RAFT polymerization) using 1-hexylamine in the presence of tributylphosphine to yield a thiol-terminated polymer (Scheme 13). Subsequently, a bismaleimide was used to connect the PNIPAM and other thiols. Thereby, small organic molecules could be used as well as other polymers or thiol-containing proteins [20, 21].

Similarly, post-polymerization modifications of RAFT end groups in sequential steps are well described in several publications and have been reviewed intensively [22, 23]. They are therefore not discussed further in this article.

Polymers synthesized via ATRP can be easily modified, generally by substitution of the bromide end group [24]. For example, substitution with an azide opens the route for copper-catalyzed azide–alkyne cycloaddition to yield a functional triazole or reduction to yield an amine that is amenable to further modification. As a recent example, Boyer et al. presented a straightforward method for the

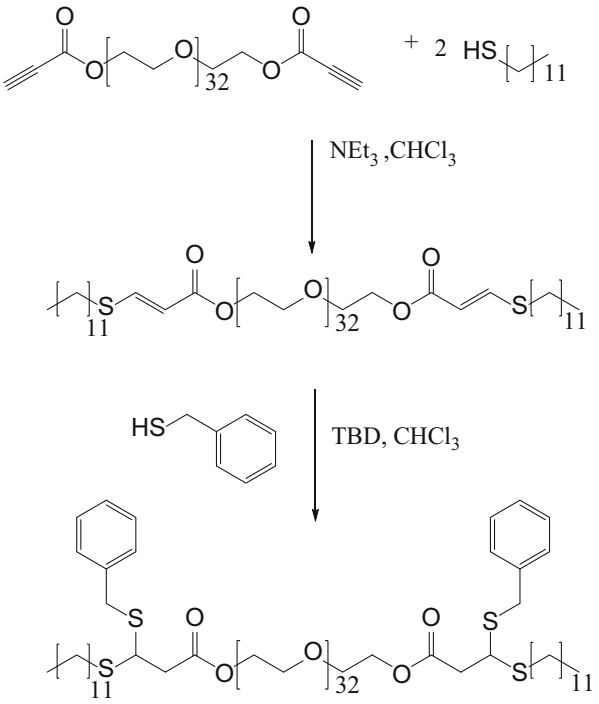


Scheme 13 General route for the synthesis of PNIPAM–protein bioconjugates



Scheme 14 Modifications of bromide end groups using sodium methanethiosulfonate

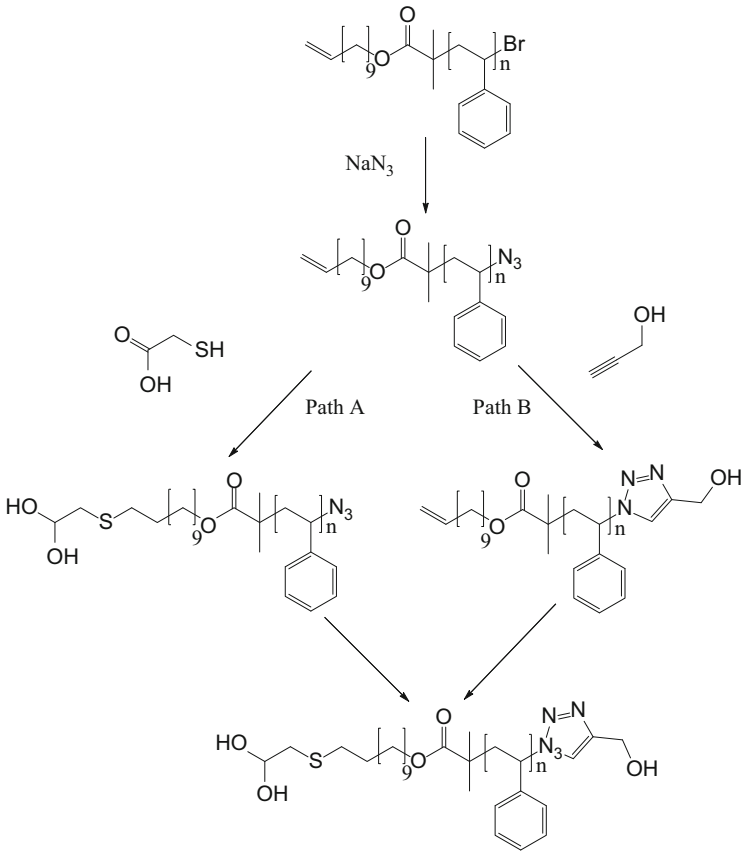
transformation of the bromide end groups into disulfides using methanethiosulfonate (Scheme 14) [25]. These activated disulfides were utilized for further reactions with different thiols, for hydrolyzation to thiols in the presence of water under basic conditions, and in thiol–ene reactions, which makes this route a very versatile choice for the synthesis of end-functionalized polymers.



Scheme 15 Sequential addition of thiols to PEG-bispropiolates

Both low and high molecular weight thiols can be used in alkyne hydrothiolations. Thereby, a thiol reacts with an alkyne to form an alkenyl sulfide. Dove and Truong utilized this chemistry for the trimethylamine-catalyzed conjunction of PEG_{32}-bispropiolate and dodecylane-1-thiol, which took less than 10 min (Scheme 15) [26]. In a subsequent step, the authors showed the attachment of a second thiol onto the main chain double bonds. With this approach, H-shaped polymers could be obtained when high molecular weight thiols were used.

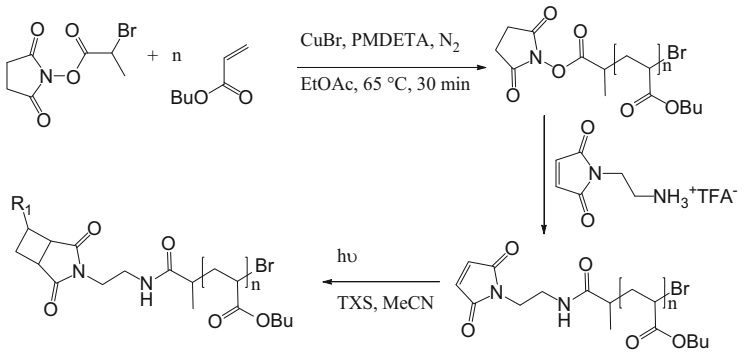
Thiol–ene reactions are also useful tools for avoiding side reactions with other functional groups. Campos et al. took advantage of this fact to modify an ATRP-synthesized polystyrene [27]. First, the bromide end group was substituted with sodium azide, yielding an ω-azide and an α-ene-capped polymer (Scheme 16). This method opened two subsequent synthetic pathways (Paths A and B in Scheme 16). Path A uses an initial thiol–ene coupling reaction followed by a copper-catalyzed azide–alkyne Huisgen cycloaddition. Path B shows the reverse strategy, whereby the cycloaddition is followed by thiol–ene coupling. By using thermal thiol–ene reactions the efficiency of both steps was almost 100%, and both routes led to similar products. Utilizing, thiol–yne reactions by substitution of the α-ene chain end with an α-yne chain end (described earlier in this section) would cause side reactions in the form of polycondensations when following path B.



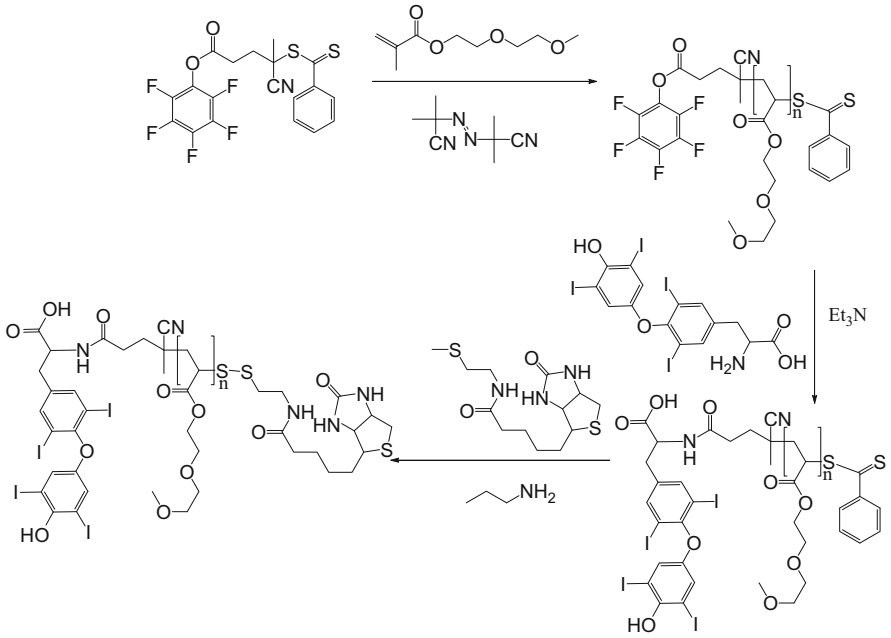
Scheme 16 Strategies (*A* and *B*) for combined thiol–ene and azide–alkyne modification of end-functionalized polystyrene

The transformation of bromides into azides and subsequent azide–alkyne Huisgen cycloaddition, as shown in the previous example, has become a common powerful modification technique. These sequential modifications are described in detail in the chapter by Kakuchi in this book [28] and were used to introduce a whole variety of functional groups, such as triple bonds, alcohols, carboxylic acids, esters or other polymer chains [29–31].

Retrospectively, we showed the modification of functional groups, which were in many cases directly introduced by the initiators of the polymerization. In the same way, activated esters could be inserted. Using this strategy, Junker and Conradi synthesized poly(butyl acrylates) bearing *N*-hydroxysuccinimide at the α-chain end [32]. The activated ester was substituted with 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl) ethanaminiumtrifluoroacetate (Scheme 17). This additional step was necessary to avoid the copolymerization of maleimide and butyl



Scheme 17 Synthesis and modification of a *N*-hydroxysuccinimide-bearing PBA



Scheme 18 RAFT polymerization with a PFP-bearing chain transfer agent and successive α- and ω-chain end functionalization

acrylate which would, consequently, result in crosslinking. However, this detour allowed the double bond to be accessible for [2 + 2] UV cycloadditions.

Similarly, chain transfer agents (CTAs) featuring an active ester were used successfully in RAFT polymerizations. Theato and coworkers designed a dithioester CTA that featured an activated PFP-ester (Scheme 18) [33]. After polymerizing diethylene glycol monomethylester methacrylate, the α-chain end can be

aminolyzed by one equivalent of, for example, thyroxin. It is very important to maintain the exact ratio of amine and polymer because both chain end functionalities are reactive to amines. The reason for the selective aminolysis is the higher reactivity of the PFP-ester compared with the dithio ester, which enables subsequent aminolysis of the dithioester in the presence of a biotinylated methane thiosulfonate. Both steps were conducted in quantitative yields at room temperature and facilitated easy access to heterotelechelic (bio)functionalized polymers.

Furthermore, the same group demonstrated the ability to transform the dithioesters of the CTAs into PFP-esters using bis(pentafluorophenyl)azobis (4-cyanovalerate). They used this method to synthesize thermo- and light-responsive polymers by adding *N*-(2-aminoethyl)-4-(2-phenyldiazeyl)benzamide [34] or other telechelic polymers with the help of 4-nitro-7-piperazin-1-yl-2,1,3-benzoxadiazole [35]. The additional use of PFP-bearing CTAs enabled the modification of both chain ends and, thus, a doubling of the functional density.

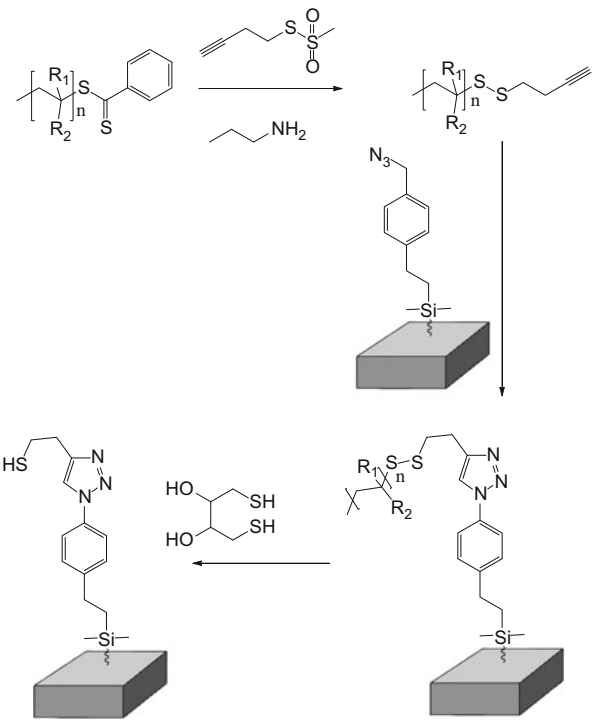
The orthogonal modification of α-alkyne, ω-azido heterotelechelic polystyrene via sequential nitrile oxide–alkyne and azide–alkyne Huisgen cycloadditions was reported by the group of Lutz [36]. Alternatively, Su et al. reported a sequential triple "click" modification of polyhedral oligomeric silsesquioxanes (POSS), involving strain-promoted azide–alkyne cycloaddition (SPAAC), copper-catalyzed azide–alkyne cycloaddition (CuAAC), and thiol–ene click coupling (TECC) [37].

5 Sequential Surface Modifications

The wide variety of sequential reactions also includes surface modifications. For example, orthogonal photosensitive protecting groups allow sequential chemical lithography [38]. But, sequential reactions can also be used to immobilize premodified polymers by creating polymer brushes. For this grafting-to method, the dithioester end group of a polymer synthesized by RAFT can be treated with but-3-ynyl methane thiosulfonate to obtain alkyne-terminated polymers. Roth et al. clicked those resulting polymers onto a glass surface, which was modified with 4-(azidomethyl)-phenylethyl-(dimethyl)-chlorosilane methanethiosulfonate (Scheme 19) [39]. This modification is associated with a change in contact angle. Note that the polymer chain could be "unclicked" by cleavage of the disulfide with dithiothreitol, which is a well-established method in biochemistry for cleaving disulfides.

Furthermore, the modified chain ends can also be directly bonded onto the surfaces, an approach that was followed by Liu et al. [40]. The synthesis started with an anionic polymerized polystyrene that was reacted with (3-chloropropyl) trimethoxysilane (Scheme 20). The obtained silane end groups enabled the attachment onto silica nanoparticles, to achieve inorganic SiO_2 nanoparticles in organic polystyrene matrices.

Multifunctional surfaces can be prepared by a sequential functionalization of orthogonal reactive groups that are immobilized on a surface. For example, the

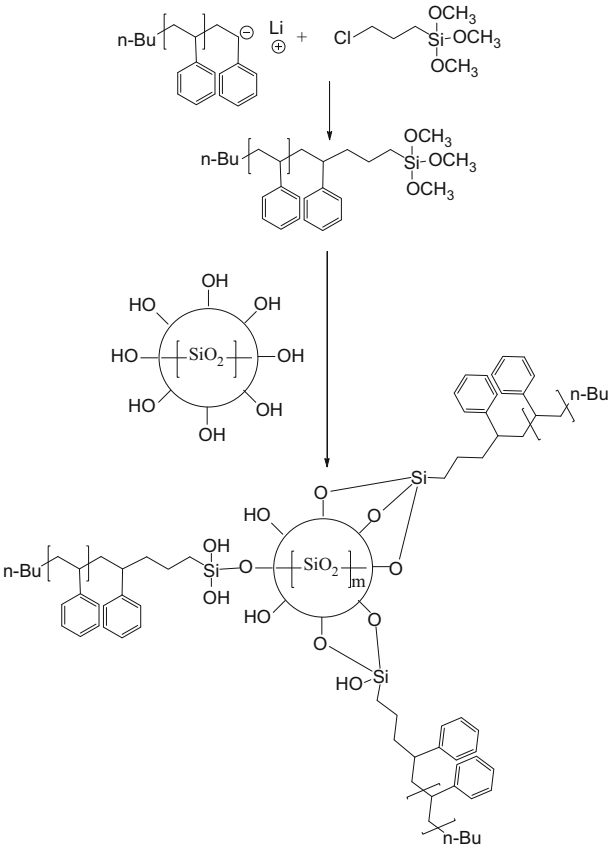


Scheme 19 Synthesis of alkyne-capped polymers, their immobilization on glass surfaces, and ultimate cleavage

group of Theato reported poly(methylsilsesquioxane)-based hybrid polymers carrying orthogonally reactive moieties to create multiresponsive surfaces via an effective modular modification approach [41].

Another possibility is the modification of surface-attached polymers. For example Park and Yousaf utilized the high affinity of gold surfaces for disulfides to bind 4,5-dimethoxy-2-nitrobenzyl-11-(decyldisulfanyl)-undecyloxycarbamate [42]. The nitrobenzyl group was cleaved by UV irradiation, leaving a surface-attached amine oxide. In a subsequent reaction, an aldehyde was added to form an oxide (Scheme 21). This reaction was used to immobilize two different fluorescent dyes in patterns simply by using templates for the UV irradiation.

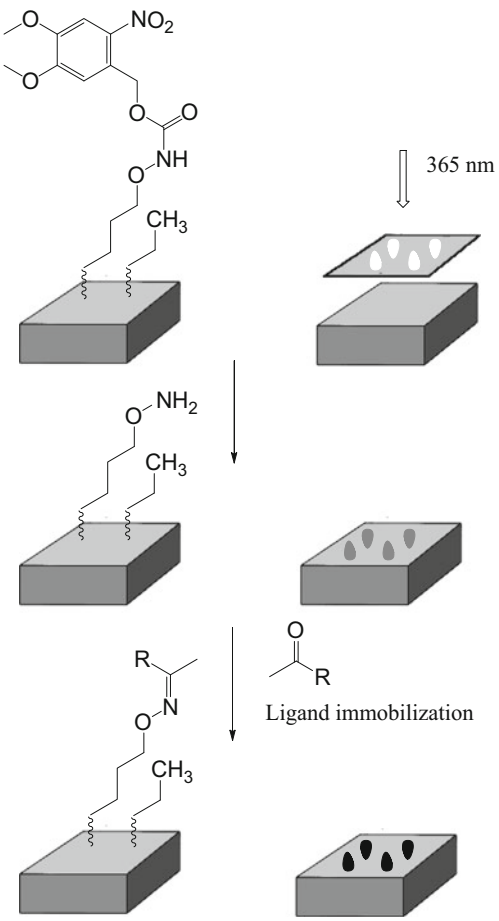
The same chemistry was used by Maynard and coworkers in a reverse way to immobilize biomolecules on antifouling PEG surfaces [43]. In their approach, acetal-protected aldehydes as chain ends of surface-bonded poly(3,3′-diethoxypropyl methacrylate) were partially deprotected by irradiation with UV light (Scheme 22). Subsequently, the free aldehydes reacted with *N*-(aminooxyacetyl)-*N*′-(D-biotinoyl) hydrazine (ARP). Afterwards, the sample was irradiated again to deprotect further aldehydes. These free aldehydes were then used for the addition of aminooxy-terminated PEG, which is well-known for its antifouling properties. In the same step, dye-labeled streptavidin was attached onto ARP. Afterwards, the streptavidin could be used to immobilize any biotinylated proteins.



Scheme 20 Synthesis of polystyrene-coated silica nanoparticles

In recent years, activated esters have become increasingly important in polymer chemistry; therefore, it is not surprising that they are also represented in the field of surface modification. In one example, Lin et al. used silica oxide-coated Fe_3O_4, where amine functionalities could be attached simply by adding 3-aminopropyltrimethoxysilane (Scheme 23) [44]. The amine was introduced by a disuccinimide, whereby one succinimide reacted with the surface-bonded amine and the other remained accessible for subsequent reaction with 3-azidopropane amine. As described before, the introduced azide could then be used for copper-catalyzed azide–alkyne Huisgen cycloaddition to obtain sugar-coated iron nanoparticles.

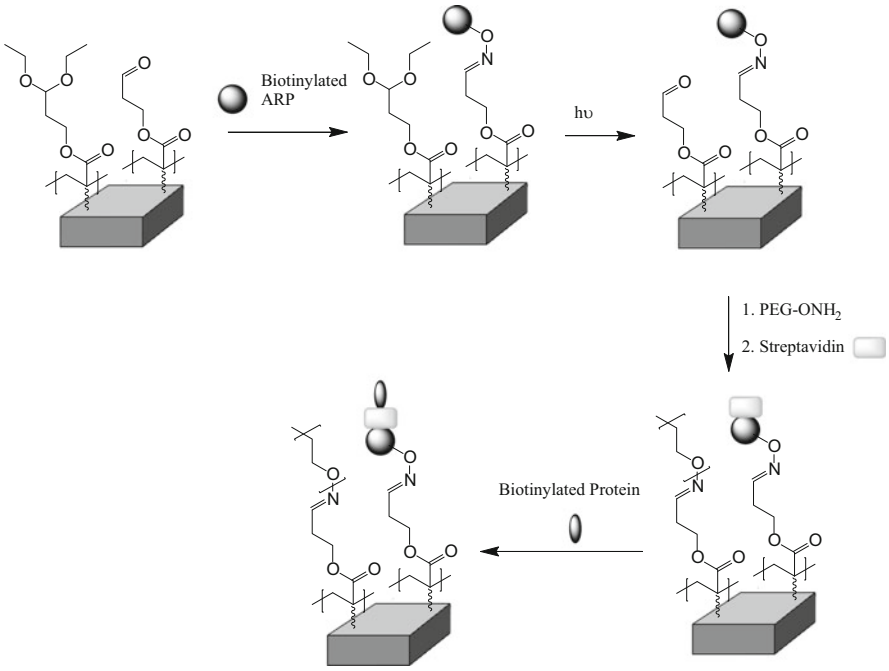
In a second noteworthy example, vertically aligned carbon nanofibers (VACNF) were used as a surface by Baker et al. [45]. Freshly prepared VACNFs are known to bind alkenes, which were used to attach *tert*-butyloxycarbonyl (BOC)-protected 10-aminodec-1-ene onto the surface (Scheme 24). After deprotection, the amino



Scheme 21 Immobilization of aldehydes on gold surfaces in patterns

groups reacted with sulfosuccinimidyl-4-(*N*-maleimidomethyl)-cyclohexane-1-carboxylate, which acted as a linker between the surface and thiol-terminated DNA via thiol–ene chemistry.

To complete this subsection, sequential modifications on the side chains of surface-bonded polymers also have to be mentioned. Hensarling et al. chose a grafting-from approach to obtain trimethylsilane-protected poly(propagyl-methacrylate)s on silicon surfaces [46]. After deprotection of the TMS group, a thiol–yne reaction, directly followed by a thiol–ene reaction, was conducted to yield dithioether linkages (Scheme 25). This step was used to introduce, for example, carboxylic acids on surfaces. By changing the pH, the hydrophilicity can be tuned, as evidenced by contact angle changes of up to 60°. Side chain modifications have a huge advantage here, because of the high density of functional groups that can be achieved.



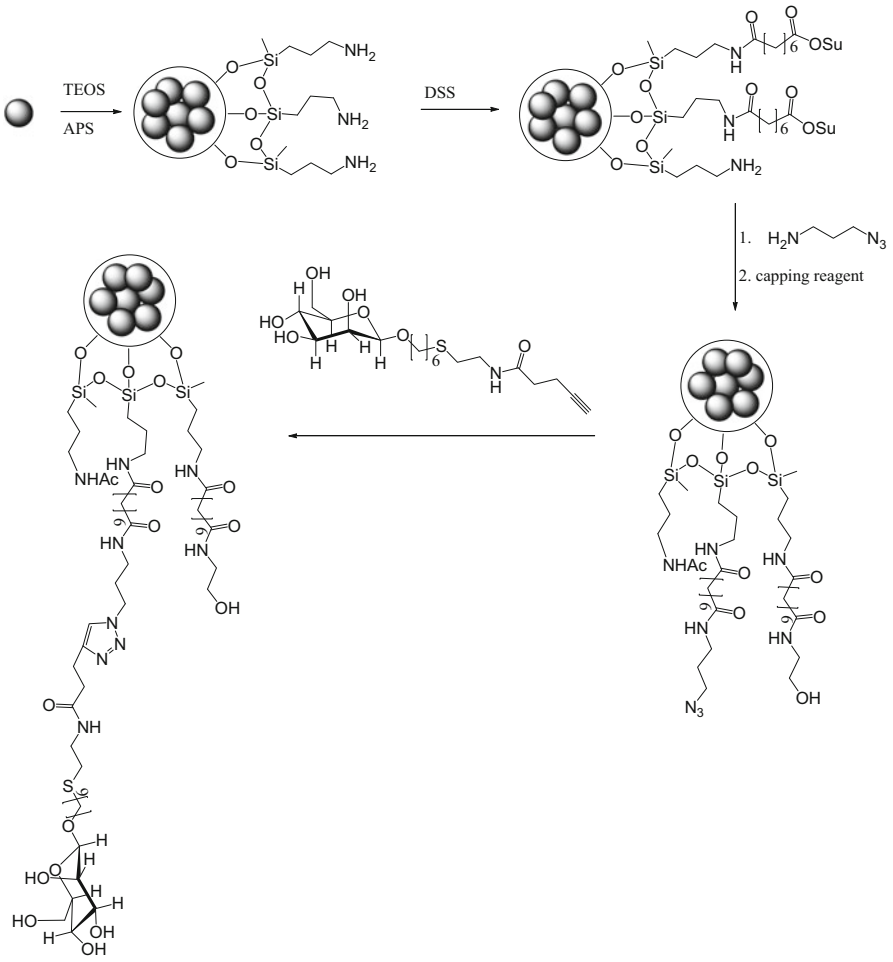
Scheme 22 Attachment of proteins onto antifouling-coated surfaces

When choosing the right orthogonal reactive groups for a surface functionalization, self-sorting conditions of click reactions can be achieved [47].

6 Synthesis of Star-Shaped Polymers

So far, we have focused on modifications with small organic molecules. In this section, we focus on macromolecules that can be joined in sequential reactions to construct star-shaped polymers. Generally, all arm-first approaches, which require prior chain end modification, can be considered as sequential reactions. Therefore, we highlight some selected examples and recommend that the interested reader looks at the reviews of Hirao et al. [48], Matsuo and coworkers [49], and Lowe [50] for further information.

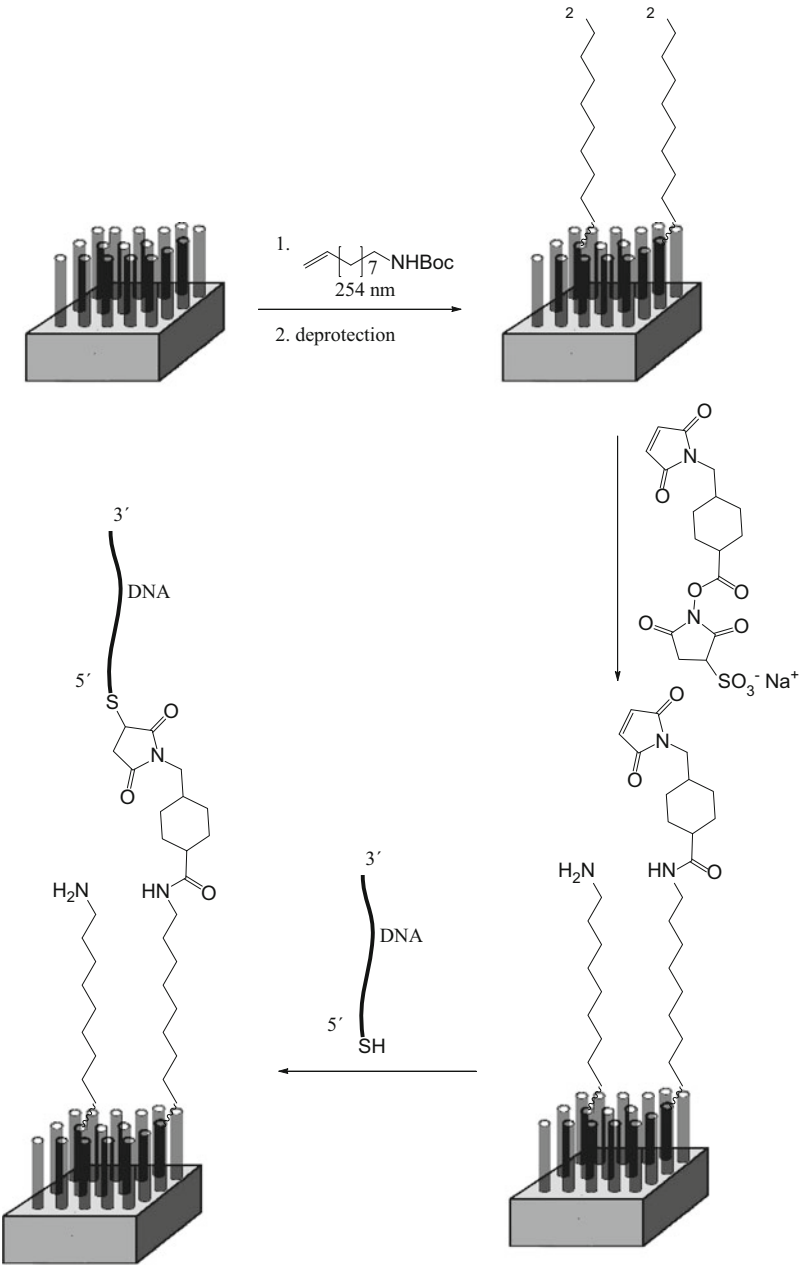
In many cases, the well-defined end groups of polymers can be obtained by any of the numerous controlled polymerization techniques and they can be directly used in a star synthesis. A common example is the use of living anionic polymers (Scheme 26). Thereby, the negatively charged polymer chain end reacts with the olefinic double bond of 1,1-diphenylethylene (DPE) to give a more stabilized anion. This resulting 1,1-diphenylalkyl anion can be subsequently reacted with a halide-modified DPE derivative to introduce a new DPE functionality. To introduce



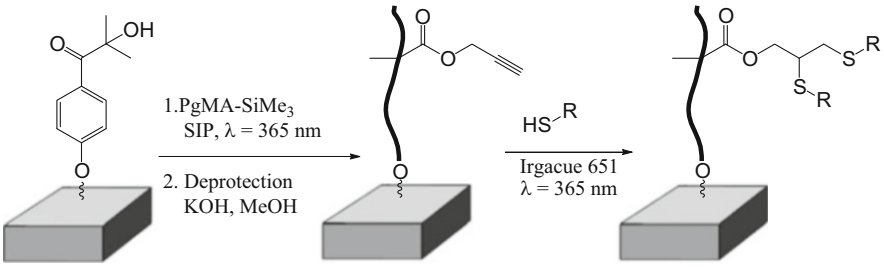
Scheme 23 Fabrication of azido- and alkynyl iron nanoparticles and their subsequent azide–alkyne cycloaddition

further arms, these reactions can be repeated. The use of this method enables the synthesis of well-defined star polymers with up to 64 arms. [51] Furthermore, the simple introduction of different polymers can lead to multifunctional stars [51–58].

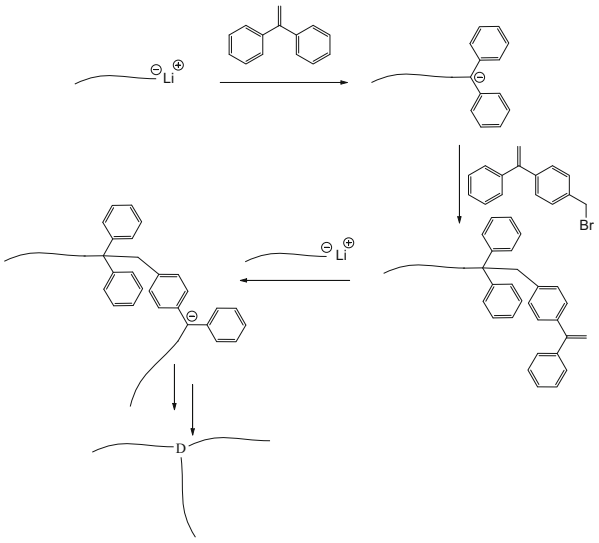
RAFT end groups can also be used in arm-first approaches. Here, presynthesized arms were simply combined with bis(2-methacryloyl)oxyethyl disulfide as a crosslinker [59–63]. The advantages of this synthesis are the huge versatility of this method and the possibility to cleave the arms by adding tributylphosphine (Scheme 27). But, this comes hand-in-hand with a huge disadvantage: The number of arms and their compilation is not unitary.



Scheme 24 Coating of vertically aligned carbon nanofibers with DNA by using a linker



Scheme 25 Introduction of two new functionalities by thiol reactions to create pH-responding surfaces

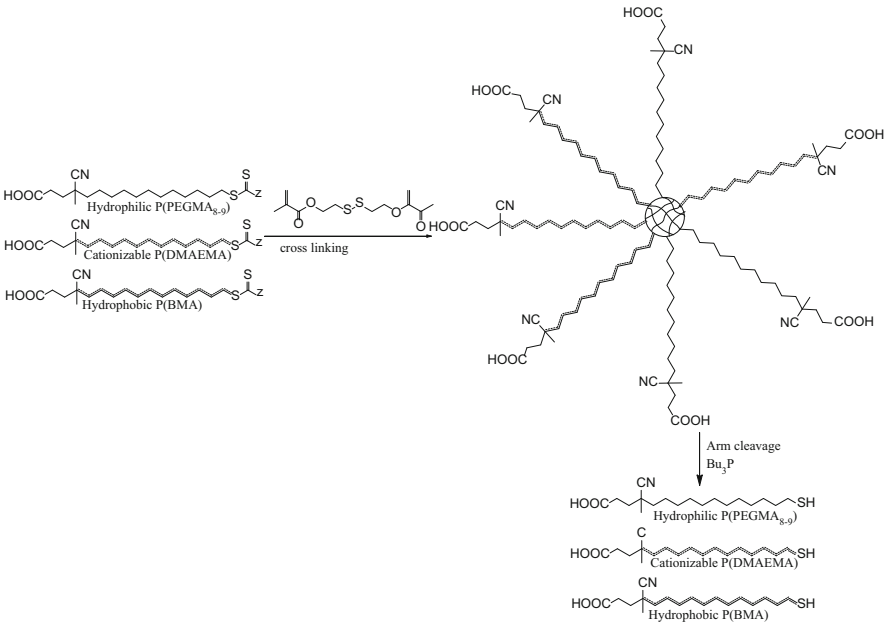


Scheme 26 Synthesis of star polymers using anionic polymers and DPE

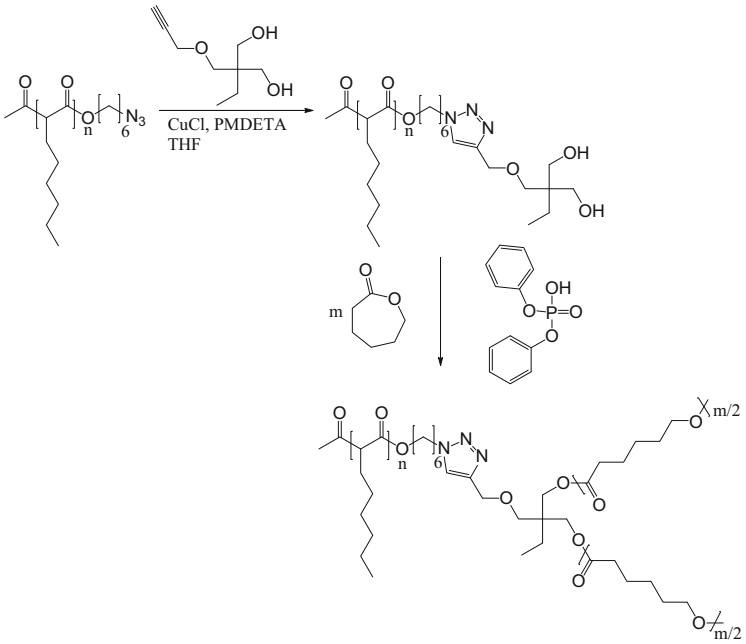
To prepare uniform star polymers, click reactions have become increasingly important. The focus in this section is on star polymers made with the help of the copper-catalyzed azide–alkyne Huisgen cycloaddition, which is one of the most commonly used click reactions in polymer science. Satoh et al. used this reaction to attach 2-ethyl-2-[(prop-2-yn-1-yloxy)methyl]propane-1,3-diol onto the ω-chain end of a poly(*n*-hexylisocyanate)-PEG block copolymer [64]. For the formation of three-arm star polymers, the introduced hydroxy groups were used as initiators for the ROP of ε-caprolactones (Scheme 28).

Furthermore, the same technique could be used to synthesize four-arm star polymers simply by using 2-(hydroxymethyl)-2-[(prop-2-yn-1-yloxy)methyl]propane-1,3-diol for the cycloaddition.

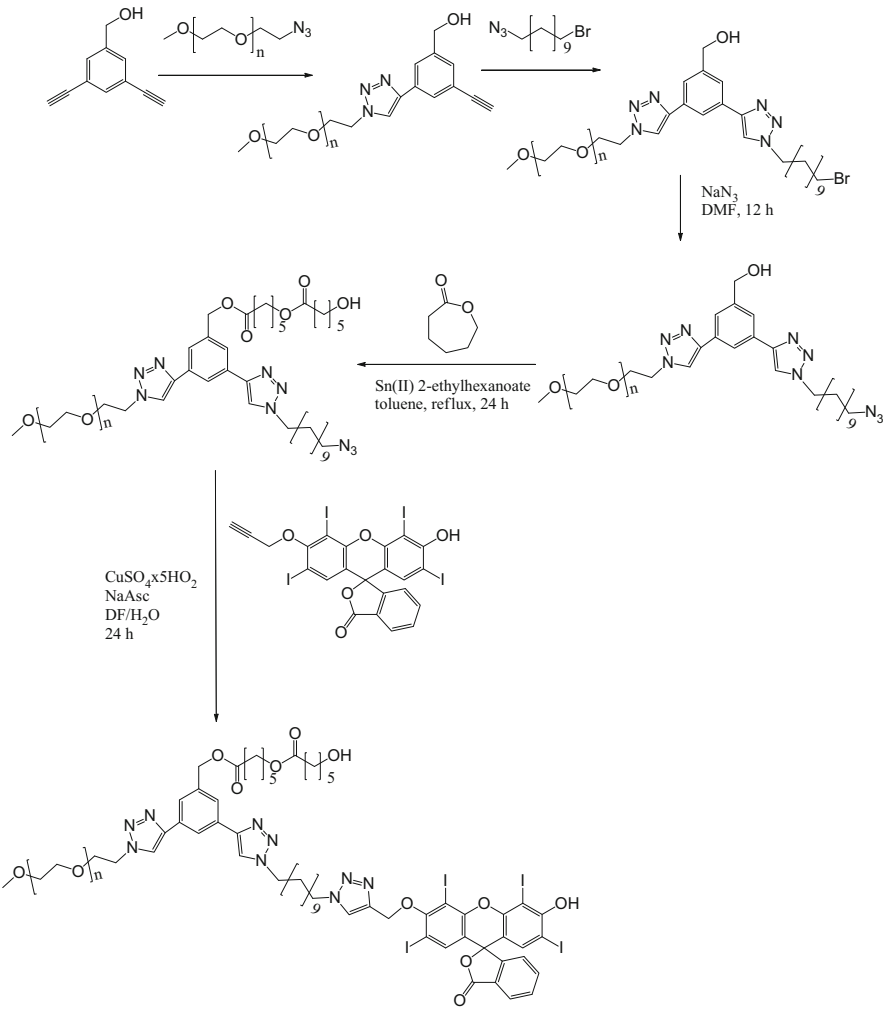
The same idea was used by Soliman to create a star polymer with three different arms. In their first step, azide-capped PEG was clicked onto one triple bond of (3,5-diethynylphenyl)methanol (Scheme 29) [65]. The other triple bond was used to



Scheme 27 Synthesis of star polymers using crosslinking RAFT end groups



Scheme 28 Synthesis of three-arm star polymers by introducing a ROP-enabled initiator via azide–alkyne cycloaddition



Scheme 29 Synthesis of star polymers with three different arms using azide–alkyne cycloadditions

attach a polyethylene containing an azide moiety and one bromide chain end. To avoid side reactions in the form of crosslinking, the bromide was transferred into an azide directly after this step instead of using a diazide. After the synthesis of the third arm, by using the hydroxyl group as initiator to polymerize ε-caprolactones, the free azide was used to attach a fluorescein-based marker.

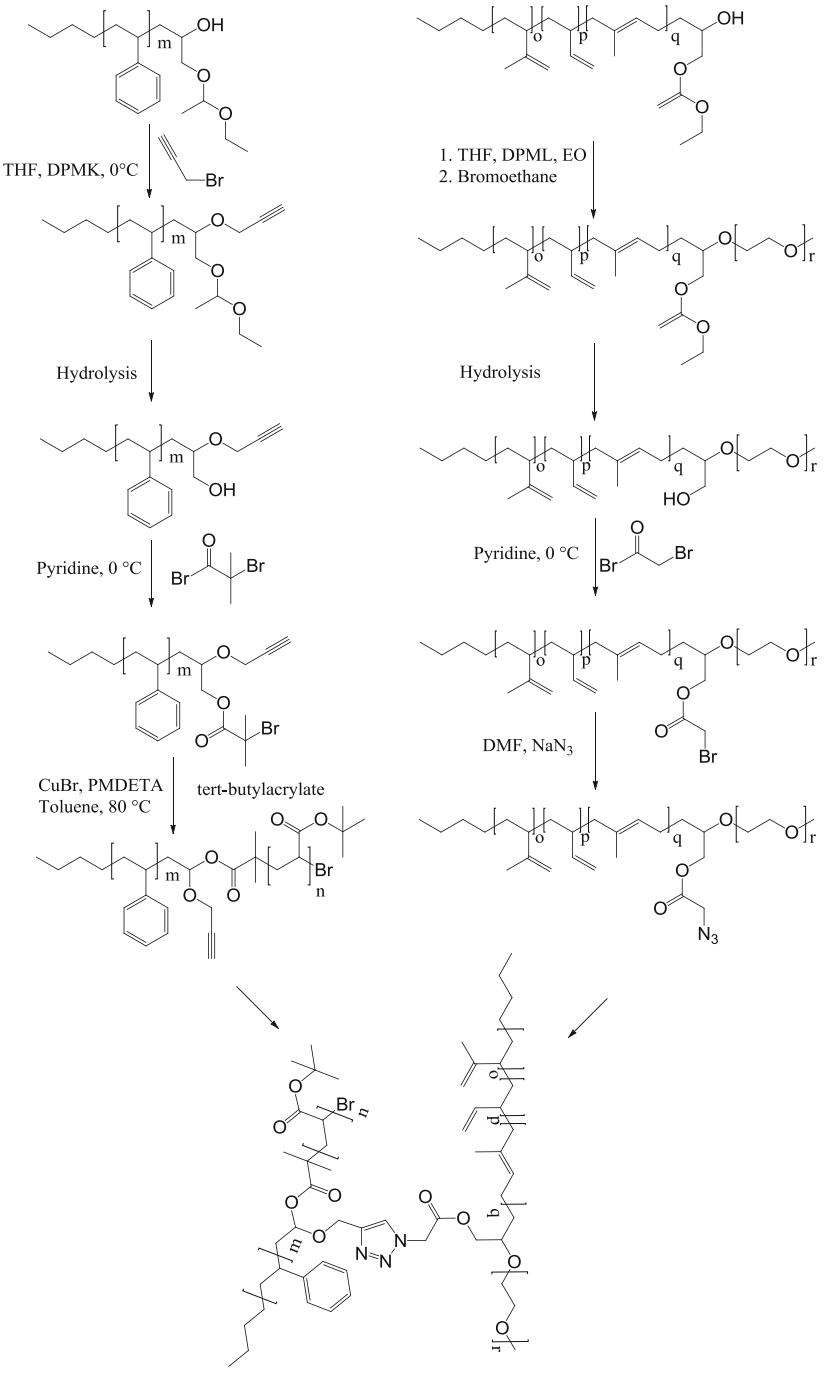
Wang et al. used linear block copolymers with azide or other alkyne functionalities at the junction points of the blocks polymers to synthesize star polymers with four different arms. These could simply be clicked together [66]. To introduce the alkyne functionality, the hydroxyl end group of an anionic polymerized polystyrene

was treated with 3-bromopropyne. Afterwards, the other 2-ethoxyethoxy-protected hydroxyl group was deprotected and esterified with 2-bromo-2-methylpropanoyl bromide. The new bromide was subsequently used as an ATRP initiator to polymerize *tert*-butyl acrylate. The azide-carrying block copolymer was synthesized in a similar way. First, the free hydroxyl end group of an anionic polymerized polyisoprene was used for ROP of ethylene oxide. Afterwards, the protected hydroxyl group, which was now in the middle of the chain, was deprotected and esterified with bromoacetyl bromide. The resulting bromide was treated with sodium azide to obtain the required product. In the last step, both block copolymers were clicked together by an azide–alkyne cycloaddition to result in a well-defined ABCD four-arm star-shaped quaterpolymer (Scheme 30).

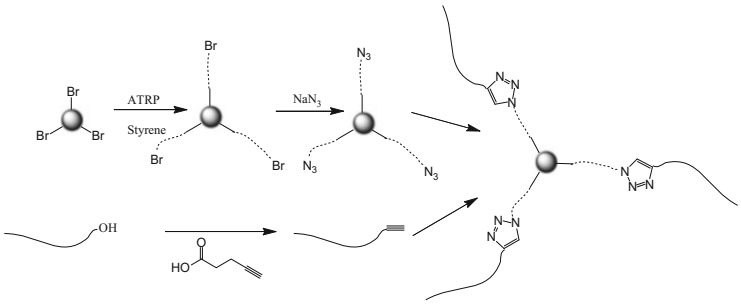
Whereas in the previous examples partial grafting-from approaches were employed, Matyjaszewski and coworkers used a core-first and coupling-onto method [67]. As shown in Scheme 31, they used trifunctional cores to obtain three-arm polystyrene stars with bromide end groups, which could easily be transformed into azides. Next, the hydroxyl end group of a methoxy-PEG was esterified with pent-4-ynoic acid to introduce an alkyne functionality. In the last step, cycloaddition created three-arm star polymers with polystyrene-PEG block copolymer arms.

Also, by using a coupling-onto approach, Fleischmann et al. created four-arm star polymers with physically bonded arms [68]. The arms were based on methoxy-PEG. In the first step, the terminal hydroxyl group was treated with 3-bromopropyne to introduce an alkyne group, which could be clicked with an azide-functionalized phenolphthalein derivative in the second step (Scheme 32). The core preparation was based on dipentaerythrol, whose hydroxyl groups were transformed into alkynes using an alkyne-carrying acid bromide, as described in the literature [66, 69]. This triple bond was necessary to attach azide-modified cyclodextrin onto the core. When both compounds were mixed, the phenolphthalein units and the cyclodextrin moieties showed strong supramolecular interaction, which resulted in the reversible formation of six-arm star-shaped polymers. In contrast to the previous star polymers, the arms could be cleaved by simple heating.

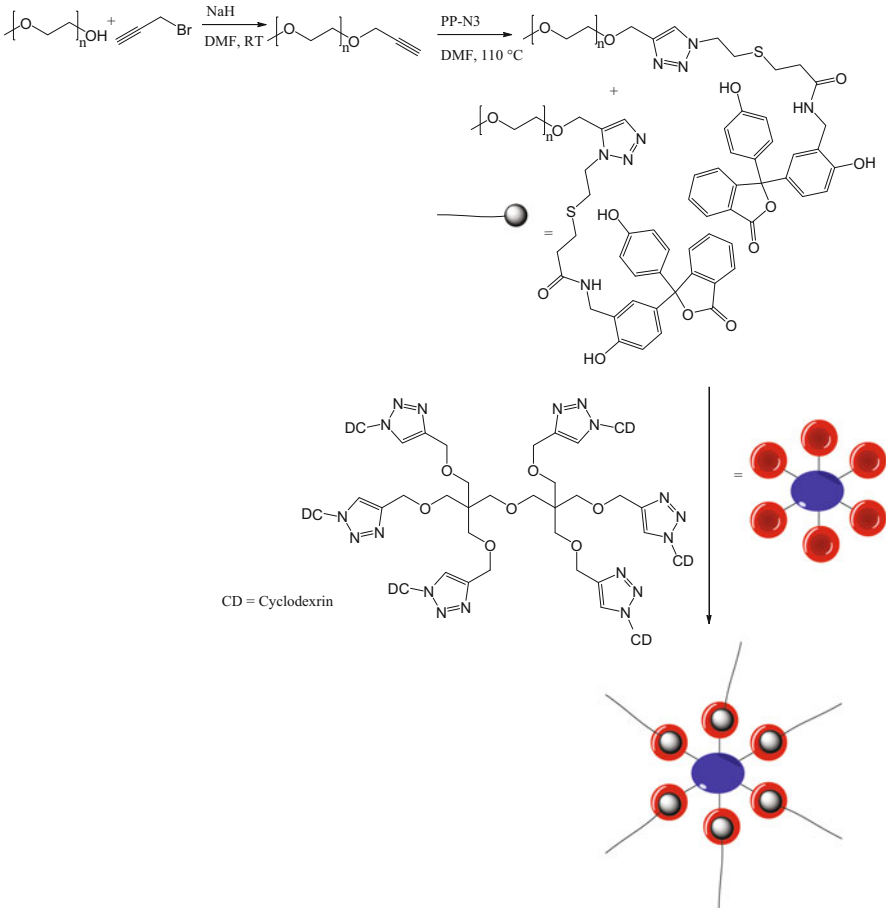
A completely new approach to the creation of star-shaped polymers is the use of activated esters. Our group found that it was possible to introduce single PFP-bearing maleimide units into polystyrenes synthesized via nitroxide-mediated polymerization (NMP) [70]. As described in Sect. 2, PFP-ester of sulfonic acids could be aminolyzed and subsequently modified with alcohols in a Mitsunobu reaction. Consequently, the attachment of polymers as side chains led to well-defined four-arm star polymers. Although the hydroxyl functionality was introduced via the ATRP initiator, the required amine was synthesized in a two-step reaction (Scheme 33). First, the bromide of a polystyrene prepared by ATRP was treated with sodium azide. The obtained polystyrene-azide was reduced in a Staudinger reduction to yield the amine. These two polymer arms could then be attached to a PFP-ester of a single sulfonic acid unit, which was placed in the middle of a polystyrene chain, taking advantage of the controlled installation of a



Scheme 30 Synthesis of four-arm star polymers by clicking two block copolymers together

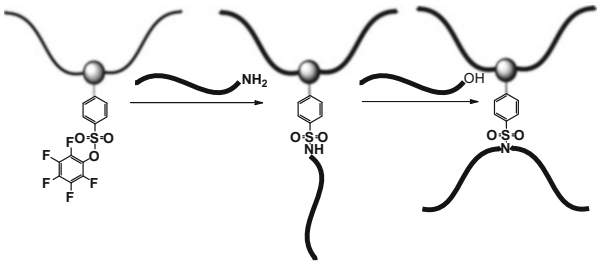


Scheme 31 Synthesis of three-arm star polymers by a coupling-onto approach



Scheme 32 Synthesis of six-arm star polymers in which the arms are bound physically

Scheme 33 Synthesis of four-arm star polymers by amidation and subsequent Mitsunobu reaction



single functional maleimide unit using a synthetic route developed by Lutz and colleagues [71–73].

7 Summary

In summary, selected examples of sequential post-polymerization modifications have been highlighted to provide an insight into the possibilities of this method. First, we focused on side chain modifications and discussed the multiple functionalization of equal repeating units as well as the sequential functionalization of different blocks. The use of chain end modified polymers for side chain modifications leads to graft copolymers. Although the use of activated esters enables easy access to standard graft polymers, the formation of brush polymers, graft polymers with Y-shaped arms, and polymers with physically bonded arms were also discussed. For most approaches, premodified polymers were used as arms. The synthesis of such chain end modified polymers was also discussed. By using different chemistries, such as activated esters, thiol–ene, and thiol–yne reactions, the modification of one or both chain ends was described. The attachment of one chain end onto a surface enables surface modifications. We have presented methods for the creation of light-, temperature-, and pH-switchable surfaces. Further, the immobilization of biomolecules, such as DNA and proteins, onto surfaces was enabled by using sequential post-polymerization modifications. The synthesis of star-shaped polymers by combining multiple chain end functionalized polymers was shown, with a focus on controlled polymerized starting materials. Although polymers prepared anionically or via RAFT can be used directly, the bromide end group of polymers prepared by ATRP was first transformed into azide groups to enable subsequent usage in azide–alkyne cycloadditions. Finally, we showed a new approach, whereby a single sulfonic acid PFP-ester unit was used in a two-step reaction for the synthesis of star polymers. Overall, sequential reactions have proved to be powerful tools in the field of post-polymerization modification and are highly promising for future applications.

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Adv Polym Sci (2015) 269: 163–202
DOI: 10.1007/12_2015_309

Published online: 6 May 2015

Sequential Post-modifications of Polybutadiene for Industrial Applications

Jan-Philipp Dilcher, Hannes Jürgens, and Gerrit A. Luinstra

Abstract Polybutadiene is a versatile starting material for polymer-analogous reactions because of the high content of easily accessed double bonds. It is a large scale polymeric product with relatively low costs. Polybutadiene may be tuned in its properties by consecutive chemical functionalizations to expand its range of applications. The polarity decreases content double bond hydrogenation and may be increased by the addition of heteroatoms to the olefinic entities. The functionalized of double bonds (e.g. to epoxides, aldehydes, carboxylates, hydroxyls or amines) opens the option of subsequent reactions in particular with nucleophilic reagents. This article focuses on post-modifications of polybutadiene homo-polymers by such sequential reactions and shows their relevance to applications.

Keywords Epoxide · Hydrogenation · Multi-step functionalization · Oxidation · Polybutadiene · Polymer-analogous reactions · Post-modification · Subsequent reactions

Contents

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1 Introduction

Cracker products such as ethylene, propylene, and butadiene fulfill the prerequisites of being cheap and abundant starting materials for large-scale polymerization processes giving access to low cost materials. Large-scale products should have useful properties for large-scale applications and/or the possibility of tuning the properties, thus giving the option of modification to serve several markets with smaller volumes. Production of polybutadiene, its derivatives, and analogs fall within these constraints. Additionally, the material property profile of these products, with a low glass transition temperature (T_g), puts them in a class of their own. They are precursors for large-volume elastomers such as styrene-butadiene-rubber (SBR), butadiene-rubber (BR), acrylonitrile-butadiene-rubber (NBR), chloroprene-rubber (CR), ethylene-propylene-diene-monomer (-rubber; EPDM), polyisoprene-rubber (IR), and, less distinctly, butyl rubber (IIR), which consists mainly of isobutylene and some isoprene. The market for these products is expected to reach 56 billion US$ in 2020 [1].

This chapter covers a selection of the chemistry that can be performed on the parent derivative polybutadiene (PBD). Radical crosslinking reactions or vulcanizations are not the topic of this chapter; the focus is instead on nucleophilic chemistry that results, after preceding oxidation reactions, in a double bond. These functionalization reactions can also be applicable to the olefinic elastomers listed above. The reactions relate to the reactive double bonds that are the prominent feature of the backbone of these polymers. PBD differs in this aspect from commodity products such as polyethylenes, polypropylenes, polystyrene, poly(ethylene terephthalate), or poly(butylene terephthalate). Functionalization of the latter polymers is certainly possible, but not at every monomer unit as is the case for PBD, and generally requires harsh conditions that can alter the polymer in several ways (e.g., deterioration of the molecular weight, crosslinking). The higher reactivity of PBD and its chemical derivatives can also lead to decomposition and crosslinked products that have inferior properties, so the reaction conditions need to be carefully optimized. Interactions with compounds of the average atmosphere or with sunlight can also limit the application of (non-confectioned) PBD-based products.

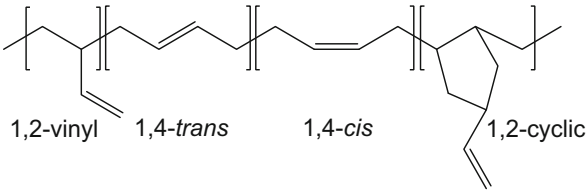


Fig. 1 Typical microstructures of polybutadienes

PBD is the rough designation for a family of polymers derived from butadiene. The polymerization of butadiene can be effected using radical and ionic species (preferentially anionic) and results in products of varying microstructure, depending on temperature, solvent, initiator, catalysts, etc.. Typical microstructures are depicted in Fig. 1.

The physical properties of the various types of PBD are very much dependent on the microstructure and also on the molecular weight. Tables 1 and 2 list a selection of commercially available products with their producers and properties. Although the double bonds in the polymer are quite reactive in general, they can differ in reactivity depending on the 1,4-*cis*, 1,4-*trans*, or monosubstituted 1,2-vinyl entities, and also on their relative position in the chain. The relative reactivity of the entities is also dependent on the type of reaction that is performed (i.e., the outcome of a hydrogenation can differ from that of a bromination reaction). In addition, double bonds in close vicinity to each other and the effects of neighboring groups can influence the outcome of the transformation. This is particularly prominent in the hydrogenation of PBD.

Some end-functionalized PBDs are also commercially available. Anionic living polymerization of butadiene gives anionic chain ends that are reactive and easily transformed into hydroxyl or carboxyl end groups, giving hydroxyl- or carbonyl-terminated polybutadiene (HTPB or CTPB), respectively. If the polymerization is initiated by a dianion, telechelic PBDs are formed. In contrast to radical butadiene polymerization, anionic polymerization yields HTPBs with very narrow dispersities and about two hydroxyl groups per molecule. The reactive living chain ends can be capped by reaction with ethylene oxide or propylene oxide to give HTPBs with primary or secondary hydroxyl groups, respectively. HTPBs are described as good binders for solid rocket propellants and can be cured with isocyanates to obtain elastic resins. CTPBs can be prepared from HTPBs by reaction with a twofold molar excess of a carboxylic anhydride such as succinic anhydride or maleic anhydride [2] or with an excess of dicarboxylic acids [3]. The living chain ends of an anionic polymerization of PBD can also be terminated with carbon dioxide. This procedure was developed by Phillips Petroleum Company and yields a CTPB after treatment of the carboxylic salt with hydrogen chloride [4]. CTPB can also be used as binder [5]. Control over the microstructure of PBD in an anionic polymerization can be obtained by control of the solvent used for the polymerization and the temperature. A review on chemical modification and applications of HTPBs was published recently and gives a good summary of various chemical modifications related to the hydroxyl groups and the unsaturated polymer chain [6]. Radical

Table 1 Commercial sources and properties of low molecular weight polybutadienes

Company	Product name	Molecular weight	1,2-Units (%)	1,4-Units (%)	Viscosity	Functionalization
Cray Valley	Ricon 130	2,500	28	N/A	0.75 Pa s	
Cray Valley	Ricon 131	4,500	28	N/A	2.8 Pa s	
Cray Valley	Ricon 152	2,900	80	N/A	20 Pa s (45°C)	
Cray Valley	Ricon 154	5,200	90	N/A	250 Pa s (45°C)	
Cray Valley	Krasol LBH P2000	2,000	65	35	13 Pa s	Hydroxyl-terminated
Cray Valley	Krasol LBH 2000	2,000	65	35	13 Pa s	Hydroxyl-terminated
Cray Valley	Krasol LBH P3000	3,000	65	35	20 Pa s	Hydroxyl-terminated
Cray Valley	Krasol LBH 3000	3,000	65	35	20 Pa s	Hydroxyl-terminated
Cray Valley	Poly bd R-45HTLO	2,800	20	80	5 Pa s (30°C)	Hydroxyl-terminated
Cray Valley	Poly bd R-20LM	1,200	20	80	1.4 Pa s (30°C)	Hydroxyl-terminated
Synthomer	Lithene *ultra* AH	1,800	45–55	45–55	400–700 dPa s	
Synthomer	Lithene *ultra* AL	750	40–55	45–60	30–55 dPa s	
Synthomer	Lithene *ultra* N4-5000	5,000	10–20	80–90	30–50 dPa s	
Synthomer	Lithene *ultra* N4-9000	9,000	10–20	80–90	120–160 dPa s	
Synthomer	Lithene *ultra* P4-150P	3,200	17–20	80–83	120–180 dPa s	
Synthomer	Lithene *ultra* P4-25P	2,600	15–25	75–85	20–30 dPa s	
Synthomer	Lithene *ultra* PH	2,600	35–50	50–65	65–90 dPa s	
Synthomer	Lithene *ultra* PM4	1,500	15–25	75–85	7–9.5 dPa s	
Nippon Soda	Nisso-PB B-1000	1,100	Min. 85	Max. 15	10 P (45°C)	
Nippon Soda	Nisso-PB B-2000	2,100	Min. 90	Max. 10	62 P (45°C)	
Nippon Soda	Nisso-PB B-3000	3,200	Min. 90	Max. 10	210 P (45°C)	
Nippon Soda	Nisso-PB G-1000	1,400	Min. 85	Max. 15	75 P (45°C)	Hydroxyl-terminated
Nippon Soda	Nisso-PB G-2000	2,000	Min. 90	Max. 10	135 P (45°C)	Hydroxyl-terminated
Nippon Soda	Nisso-PB G-3000	3,000	Min. 90	Max. 10	310 P (45°C)	Hydroxyl-terminated

Table 2 Commercial sources and properties of high molecular weight polybutadienes

Company	Product name	1,2-Units (%)	1,4-Units (%)	*cis*:*trans* ratio	Viscosity	Catalyst
Styron	SE PB-5800 – Schkopau	12	88	37:51	51 MU (Mooney)	Lithium
Styron	SE PB-3501 – Schkopau	10	90	39:51	45 MU (Mooney)	Lithium
Styron	BUNA *cis* 132 – Schkopau	5	95		45 MU (Mooney)	Nickel
Sabic	BR 4010	2	98		40+/−5 MU (Mooney)	Nickel
Sabic	BR 4610	2	98		46+/−5 MU (Mooney)	Nickel
Sabic	BR 5510	2	98		55+/−5 MU (Mooney)	Nickel
Firestone Polymers	Diene 35NF	10	90	40:50	38 ML/4 100°C	Lithium
Firestone Polymers	Diene 40NF	10	90	40:50	40 ML/4 100°C	Lithium
Firestone Polymers	Diene 45NF	10	90	40:50	45 ML/4 100°C	Lithium
Firestone Polymers	Diene 55NF	10	90	40:50	52 ML/4 100°C	Lithium
Firestone Polymers	Diene 645	0	100	96:4	45 ML/4 100°C	Nickel
Firestone Polymers	Diene 140ND	0	100	96:4	40 ML/4 100°C	Neodymium
Sibur	BR-1234 Nd	Max 3	Min 97	Min 97:3	44+/−5 ML/1 + 4 100°C	Neodymium
Sibur	BR-1203 Ti	Max 10	Min 90	Min 90:10	45+/−4 ML/1 + 4 100°C	Titanium
Lanxess	Buna CB 21	Max 4	Min 96	Min 96:4	73 MU (mooney)	Neodymium
Lanxess	Buna CB 22	Max 4	Min 96	Min 96:4	63 MU (mooney)	Neodymium
Lanxess	Buna CB 23	Max 4	Min 96	Min 96:4	51 MU (Mooney)	Neodymium
Lanxess	Buna CB 24	Max 4	Min 96	Min 96:4	44 MU (mooney)	Neodymium
Lanxess	Buna CB 55 NF	11	89	38:51	55 MU (mooney)	Lithium
Lanxess	Buna CB 45	ca. 11	ca. 89	Min 38:51	45 MU (mooney)	Lithium
Lanxess	Buna CB 55 H	11	89	36:53	54 MU (mooney)	Lithium
Lanxess	Buna CB 55 L	11	89	36:53	51 MU (mooney)	Lithium
Lanxess	Buna CB 70	11	89	36:53	70 MU (mooney)	Lithium
Lanxess	Buna CB 1220	Max 4	Min 96	Min 96:4	40 MU (mooney)	Cobalt
Lanxess	Buna CB 1221	Max 4	Min 96	Min 96:4	53 MU (mooney)	Cobalt

(continued)

Table 2 (continued)

Company	Product name	1,2-Units (%)	1,4-Units (%)	*cis*:*trans* ratio	Viscosity	Catalyst
Lanxess	Buna CB 1203	Max 4	Min 96	Min 96:4	43 MU (mooney)	Cobalt
Goodyear Chemicals	Budene 1207	Max 3	Min 97	Min 97:3	55 ML/1 + 4 100°C	Nickel
Goodyear Chemicals	Budene 1208	Max 3	Min 97	Min 97:3	46 ML/1 + 4 100°C	Nickel
Goodyear Chemicals	Budene 1280	Max 3	Min 97	Min 97:3	40 ML/1 + 4 100°C	Nickel
Goodyear Chemicals	Budene 1209			Low	54+/−4 ML/4 100°C	Lithium
Goodyear Chemicals	Budene 1235			Low	71+/−4 ML/1 + 4 100°C	Lithium
Goodyear Chemicals	Budene 1222	Max 4	Min 96	Min 96:4	63 ML/1 + 4 100°C	Neodymium
Goodyear Chemicals	Budene 1223	Max 4	Min 96	Min 96:4	55 ML/1 + 4 100°C	Neodymium
Goodyear Chemicals	Budene 1224	Max 4	Min 96	Min 96:4	44 ML/1 + 4 100°C	Neodymium
Kumho Petrochemical	KBR 01	Max 4	Min 96	Min 96:4	45 ML/1 + 4 100°C	Ziegler Natta
Kumho Petrochemical	KBR 01 L	Max 5	Min 95	Min 95:5	30 ML/1 + 4 100°C	Ziegler Natta
Kumho Petrochemical	KBR 01 N	Max 5	Min 95	Min 95:5	35 ML/1 + 4 100°C	Ziegler Natta
Kumho Petrochemical	KBR 710S	14.5	85.5	34.5:51	50 ML/1 + 4 100°C	Lithium
Kumho Petrochemical	KBR 710H	14.5	85.5	34.5:51	68 ML/1 + 4 100°C	Lithium
Kumho Petrochemical	NdBR 40	Max 3	Min 97	Min 97:3	43 ML/1 + 4 100°C	Neodymium
Kumho Petrochemical	NdBR 60	Max 3	Min 97	Min 97:3	63 ML/1 + 4 100°C	Neodymium
Nizhnekamskneftekhim	PBD-Nd				50–59 ML/1 + 4 100°C	Neodymium
Nizhnekamskneftekhim	PBD-Li	11–16	84–89		46–60 ML/1 + 4 100°C	Lithium
Nizhnekamskneftekhim	PBD-Li Grade R	60–64	34–40		40–60 ML/1 + 4 100°C	Lithium
UBE Industries LTD.	UBEPOL BR-150	Max 2	Min 98	Min 98:2	43 ML/1 + 4 100°C	Cobalt
UBE Industries LTD.	UBEPOL BR-130B	Max 4	Min 96	Min 96:4	29 ML/1 + 4 100°C	Cobalt
UBE Industries LTD.	UBEPOL BR-360 L	Max 2	Min 98	Min 98:2	51 ML/1 + 4 100°C	Cobalt
UBE Industries LTD.	UBEPOL BR-230	Max 2	Min 98	Min 98:2	38 ML/1 + 4 100°C	Cobalt
UBE Industries LTD.	UBEPOL BR-710	Max 2	Min 98	Min 98:2	44 ML/1 + 4 100°C	Cobalt
JSR	JSR BR01	Max 5	Min 95	Min 95:5	45 ML/1 + 4 100°C	
JSR	JSR T700	Max 5	Min 95	Min 95:5	42 ML/1 + 4 100°C	

JSR	JSR BR51	Max 5	Min 95	Min 95:5	38 ML/1 + 4 100°C	
JSR	JSR BR730	Max 5	Min 95	Min 95:5	55 ML/1 + 4 100°C	
Karbochem	Neodene 40	Max. 3	Min 97	Min 97:3	35–45 ML/1 + 4 100°C	Neodymium
Karbochem	Neodene 45	Max. 3	Min 97	Min 97:3	40–50 ML/1 + 4 100°C	Neodymium
Karbochem	Afdene 45	Max. 63	Min 37	Min 37:63	41–49 ML/1 + 4 100°C	Lithium
Karbochem	Afdene 50	Max. 63	Min 37	Min 37:63	45–55 ML/1 + 4 100°C	Lithium
Eni	Europrene Neocis BR 40	Max. 2	Min 98	Min 98:2	43 ML/1 + 4 100°C	Neodymium
Eni	Europrene Neocis BR 60	Max. 2	Min 98	Min 98:2	63 ML/1 + 4 100°C	Neodymium
Eni	Indene 50	Max. 62	Min 38	Min 38:62	48 ML/1 + 4 100°C	Lithium
Eni	Indene C 30 AF	Max. 62	Min 38	Min 38:62	40 ML/1 + 4 100°C	Lithium

polymerization of PBD with hydrogen peroxide as radical initiator, performed in alcohols such as methanol, ethanol, or isopropanol, also gives access to HTPB. This product has properties that depend on the microstructure and the molecular weight which, in turn, depend on the solvent used for the polymerization. The average content of hydroxyl groups ranges from 2.1 to 2.4 per chain. HTPBs are a widely used substrate for functionalization with low molecular weight PBD. The terminal hydroxyl group undergoes further reactions with carboxylic acids, anhydrides, isocyanates, or epoxides, reactions that are orthogonal to the reactivity of the remaining double bonds. An advanced example is the tosylation of primary hydroxyl groups on hydrogenated PBD. The reaction gave a product with good leaving groups for grafting with living lithium-terminated PBDs [7].

The large-scale application of PBD in tire manufacturing and as impact modifier in (styrene-based) plastics has turned it into a commodity with worldwide availability and with concomitantly favorable pricing. PBDs per se are rather hydrophobic, which leads to a certain incompatibility with inorganic substrates and water, common materials of everyday life. Functionalization at the double bond is chemically simple and can increase the polarity to the extent that the product becomes water soluble. Perhaps this combination of availability, low price, and simple tuning of properties has led to the ongoing interest in PBD post-polymerization chemistry.

2 Functionalization Reactions

This section addresses some aspects of PBD functionalization that are characteristic for a polymer with many reactive sites of different reactivities. It focuses on some typical reactions such as reduction, isomerization, and oxidation. The functionalization reactions in this review have been selected with the aim of making it possible to perform them on a larger (commercially relevant) scale, and with the option to prepare products that have a cost of production that is within the (commercially) common range for PBD applications. Such transformations include hydrogenation and epoxidation and have the promise of exceeding a purely academic interest.

Functionalization of double bonds in PBDs can lead to more stable products, which is important in long(er)-term applications, or can generate reactive intermediates that are susceptible to nucleophilic reactions. The latter leads to multistep functionalization at the backbone, which is discussed further in Sect. 3.

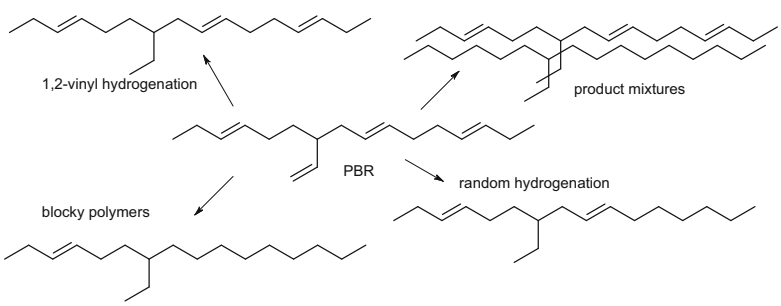
2.1 Hydrogenation

Hydrogenation of (residual) double bonds is the method of choice for inherently stabilizing PBD derivatives and maintaining most of their (elastomeric) properties

[8]. It is also an important reaction because it transforms PBDs into polyethylene derivatives. The polymerization of butadiene and consecutive hydrogenation of the products has been used to obtain polyethylene derivatives [9]. Hydrogenation of tailored PBDs can, thus, be the most convenient route to a specific polyethylene microstructure [10]. Hydrogenation is generally the last step in the functionalization of PBD.

Hydrogenation of synthetic rubber dates back to the early twentieth century [11]. The polymeric nature of rubbers and the stability of the "hydrorubbers" was substantiated by Staudinger. A study was initiated several years later in 1953 to obtain a deeper understanding of the hydrogenation process and the properties of hydrogenated rubbers [8]. Other catalytic systems such as nickel on "kieselgur" were also found to be active in hydrogenation at lower temperatures. Organometallic catalysts in the form of Ziegler-like chromium- and cobalt-based compounds were effectively used for the hydrogenation of rubbers. Hydrogenation of butadiene rubbers in benzene with the homogeneous Wilkinson's catalyst [12] proceeds at ambient temperatures and 1 bar of hydrogen pressure [13]. Bulk hydrogenation of PBDs is also possible with Wilkinson's catalyst. It has low reaction rates but reaches high conversions (>90%) at moderate temperatures and pressures, which is important for a cost-efficient process [14]. Anionic PBD (60% 1,2-inserted units in PBD) was hydrogenated twice as fast as radically prepared PBD (20% 1,2-units) in solution at 100°C and 50 bar, because Wilkinson's catalyst has a selectivity for the hydrogenation of 1,2-units over 1,4-units [15, 16]. It was also noticed that some of the hydroxide functionalities (if present) can be lost during the hydrogenation process [17].

The hydrogenation was found to be first order for the concentration of double bonds, catalyst concentration, and hydrogen concentration at low hydrogen pressure. Double bonds in 1,4-*cis* inserted butadiene units are hydrogenated faster than those in 1,4-*trans* butadienes [18, 19]. A dynamic model of the hydrogenation of diene polymers was established, comprising the usual reaction steps and a mass transfer [20]. In the kinetic model for Wilkinson's catalyst, the coordination of double bonds to the metal is the rate-controlling step. This is an important point; as a consequence, the statistical hydrogenation of the double bonds is expected. To increase productivity, an increase in double bond loading would be useful as long as the mass transfer performance is sufficient. Also, hydrogenation of PBD in an ionic liquid using a sulfonated analog of Wilkinson's catalyst has been reported, with a clear preference for the conversion of 1,2-vinyl units [21–23]. Cyclopropanated 1,2-PBD can also be hydrogenated using Wilkinson's catalyst without opening the cyclopropane rings; thus, a two-step post-polymerization procedure was found to produce atypical polyethylenes [24]. Many more homogeneous and heterogeneous catalysts were identified and studied [25, 26] over the course of time, some with remarkable selectivities [27–40]. The selective hydrogenation of 1,4-PBD can, thus, be achieved in the presence of 1,4-polyisoprene using different cobalt-based alkylaluminium and organo-lithium catalysts. Polybutadiene was converted quantitatively within 1 h at 50°C and 3.5 bar, with the polyisoprene block remaining unchanged [41, 42].

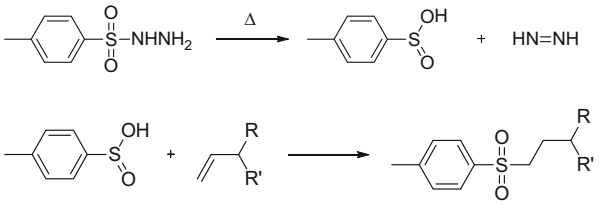


Scheme 1 Outcome of catalytic PBD hydrogenation with dihydrogen

A (partial) hydrogenation reaction can lead to several products and gives the typical situation for post-polymerization functionalization of PBD (Scheme 1) [43]. Hydrogenation of (the majority of double bonds in) one chain can also lead to mixtures of "polyethylene" and PBD, with T_g reminiscent of chains with the respective structures [44]. Evidence for a decreasing local reactivity by in situ crystallization of intermediates was found in the hydrogenation by palladium on calcium carbonate [45, 46]. Another interpretation for the same catalyst system is that after coordination of a chain to the catalyst surface it becomes extensively hydrogenated (85% of the double bonds), whereas other chains keep their composition [47]. In contrast, homogeneous hydrogenation seems to proceed randomly in the sample and on the chains [48].

Hydrogenation can be performed with the preservation of hydroxyl groups. End-functionalized PBDs can be hydrogenated without losing the hydroxyl end groups [49–51]. A high content of ethyl side chains, resulting from 1,2-vinyl entities in PBD, gave polyethylenes with relatively low melting points. The hydrogenation of 1,4-PBDs gave linear, polyethylene-like, end-functionalized polymers. It was further reported that the hydrogenation of low molecular mass OH-telechelic PBDs with $Ni(acac)_2$ or $Ni(2\text{-ethyl-hexanoate})_2$ and lithium-diene adducts leads to the most active catalyst system that does not affect the OH-functionality [43]. End-functionalized polyolefins with controlled molecular weight distribution were obtained from the same type of precursors by hydrogenation in the presence of colloidal nickel [51]. The T_g and viscosity of various partially and fully hydrogenated (9–100%) HTPBs with molecular masses between 1,700 and 4,350 were strongly dependent on the microstructure of the PBDs. The melt viscosity was not influenced by the hydrogen bonding between hydroxyl groups, in contrast to the glass transition [52].

Hydrogenation of PBD with hydrazides (toluenesulfinyl hydrazide) as hydrogen source has also become common practice [53–55]. PBDs showed 30% hydrogenation after 2 h, and isomerization of the remaining double bonds with a preference for the *trans* configuration (*cis*/*trans* = 1:2.5) [56]. The formation of *p*-tolylsulfinic acid can induce side reactions such as the addition of *p*-tolylsulfone to the double bonds and bond cleavage (Scheme 2) [57, 58]. Addition of amine base (tri-*n*-propyl amine) is useful to prevent this [59]. The *cis–trans* isomerization of



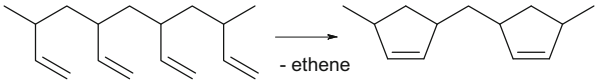
Scheme 2 Decomposition of toluenesulfenyl hydrazine and reaction with PBD

cis-PBD during diimide hydrogenation has also been observed, leading to the presumption that the hydrogenation of *trans* units is slower [60]. The hydrazine hydrogenation was also combined with a metal-catalyzed hydrogen addition. This route almost completely avoided side production of tolylsulfenic hydrazine and was comparable with the results using a proton scavenger [59]. The PBD in that case was first hydrogenated up to 95% using the Ziegler–Natta system of nickel acetylacetonate and trimethyl aluminum at 40°C and 19 bar of hydrogen pressure for 30 min [61].

Silanes as pseudo-hydrogens can also reduce the double bonds of PBD [62]. SiH_4 addition to PBD in the presence of $Pt(PPh_3)_4$ as catalyst gives a modified polymer with about 3% silicium (stable in air; no gain in mass was found to accompany hydrolysis). Gaseous Me_3SiH or $EtMe_2SiH$ react with PBD to give trialkyl silane groups bound to the surface after UV irradiation of the surface. This functionalization lowers the surface tension. The process is very sensitive to the presence of oxygen, but is a technical option [63]. Silanation is also used to increase the free volume in membranes with butadiene or isoprene blocks, a reaction that is also catalyzed by Wilkinson's rhodium(I) catalyst [64].

2.2 *Isomerization and π-Bond Metathetical Reactions*

Whereas hydrogenation chemically stabilizes PBD, isomerization and metathesis of the double bonds leave the system in a reactive form. PBD is a polymer suitable for olefin metathesis reactions because of the large amount and variety of double bonds it contains [65]. Metathesis with 1-olefins has, in addition, been used to mildly cleave PBD into small fragments that are more easily analyzed by gas chromatography/mass spectrometry (GC/MS) and enable elucidation of the microstructure after functionalization [44, 48, 50, 66, 67]. For example, partially hydrogenated PBD was reacted with 4-octene in the presence of WCl_6-Bu_4Sn to yield internal dienes with butyl groups [68]. A similar study concluded that homogeneous hydrogenation is a statistical process [48]. Bromination of double bonds is a reaction that goes to completion. The bromination of 1,4-*trans* PBD is likely to proceed in a random manner. This was concluded from the length of halogenated segments obtained after metathesis of partly chlorinated or brominated PBD [69].



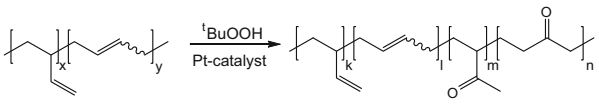
Scheme 3 Metathesis of 1,2-vinyl PBD with Grubbs-type metathesis catalyst

The metathesis reaction can also be used to isomerize *cis*-1,4-PBD to *trans* derivatives [70]. An in situ metathesis catalyst built from tungsten hexachloride and two equivalents of diethylaluminum chloride or tungsten hexachloride and tetramethyl tin was effective for the latter transformation. The rate of isomerization was found to be dependent on the presence of *trans*-4-octene, and seems to result from steric interactions on the catalyst [71]. ADMET (acyclic diene metathesis) can be used to prepare PBD with specific end groups. Vinyl-terminated PBDs and even 1,5-hexadiene were obtained by reaction of PBD with ethylene under the action of a Grubbs-type catalyst, $RuCl_2(=CHPh)(PCy_3)_2$ [72]. The metathesis between PBD and unsaturated polyester (*cis*-2-butendiol and adipoyl chloride), thus, leads to multiblock copolymers, where the block length is dependent on the reaction time [73, 74]. Structural changes can also be obtained using metathesis; for example, metathesis of 1,2-PBD yields a ladder polymer (Scheme 3) [75]. The metathesis of 1,4-PBD with a Grubbs-type catalyst leads to the extensive formation of *trans*, *trans*,*trans*-1,5,9-cyclododecatriene (CDT), which is a thermodynamically stable compound. The metathesis catalyst can be sensitive to 1,4-*cis* or 1,4-*trans* units, but the rates of their conversion may differ [76].

2.3 Oxidation Reactions to Form Oxo Derivatives of PBD

Halogenation and oxidation (addition of oxygen) of the double bonds of PBD render it susceptive to nucleophilic substitution reactions. Radical or electrophilic reactions dominate the chemistry of parent PBD and catalysts are necessary to break the symmetry of the π-system for the addition of hydrogen, whereas common substitution reactions are feasible for preparation of derivatives.

The oxidation of double bonds to carbonyl species is a convenient way of introducing polar functionalities into molecules. Polybutadiene can be oxidized with *tert*-butyl hydroperoxide under the action of a homogeneous platinum complex to give PBDs with keto groups (Scheme 4). Oxidation with hydrogen peroxide using the same catalyst yields an epoxidized PBD. This selectivity of the catalyst is believed to result from the steric properties of the *tert*-butyl group of the peroxide in the coordination sphere of the platinum ligand. A β-hydrogen abstraction leads to an α-peroxyalkyl structure that decays to a ketone [77]. The resulting polyketones are interesting because they are photolabile and have a reactive carbonyl group, the functionality that is probably the most versatile for subsequent reaction. The oxidation of PBD with the homogenous platinum catalyst and *tert*-butyl hydroperoxide was found to yield methyl ketones from pendent 1,2-vinyl groups as the



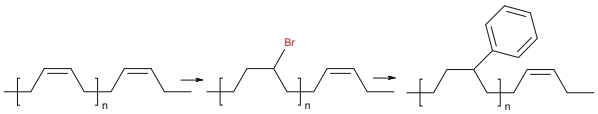
Scheme 4 Oxidation of PBD to unsaturated polyketones

major product. Methyl ketones are obtained, together with ketones from the 1,4-*trans* unsaturated and 1,4-*cis* entities. The latter show the lowest reactivity in the oxidation to polyketones [78, 79].

The Wacker oxidation of olefins was successfully applied to 1,2-vinyl PBD to convert pendent 1,2-vinyl groups into methyl ketones by using oxygen at a pressure of 20 bar as oxidizing agent. The catalytic system comprising palladium chloride, copper chloride, and traces of water is effective in dimethoxyethane as solvent. A complete conversion of PBD into polyketones is attained under specific conditions [80]. The hydroacylation of PBD gives access to acyl-functionalized PBD. Transition metal catalysts allow the addition of acyl, aldimine, aldehyde, or primary alcohols to the backbone. Thus, rhodium(I) complexes can be used to introduce 2-acylphenyl groups to PBD with a high 1,4-content. Polybutadienes with 1,2-vinyl groups are less reactive in that sense, possibly for steric reasons [81]. Reference is made here to a review dealing with this type of chemistry [82]. A corresponding reaction of PBD with diols gives access to a polyhydroxy polymer. Addition of the hydroxyl entity to the double bonds is again possible through the action of a rhodium(I) catalyst [83].

Photo-oxidation of PBD films leads to α,β-unsaturated carbonyl compounds. This usually undesired aging process is suppressed by potential UV-stabilizers, which can be identified from their triplet energy [84]. Thermal oxidation of PBD has also been described [85–87]. The build-up of peroxide radicals and polymer decomposition gives ketones. High radical concentrations during the aging process decrease the content of unsaturated bonds by crosslinking [88]. In general, thermal and photo-oxidation of PBD are important for understanding degradation processes and are not systematically used in the preparation of functionalized PBDs.

Bromination proceeds readily in a statistical manner [69]. Halogens can also be introduced into PBD by reaction with dichlorocarbene generated by the reaction of chloroform with an aqueous base in the presence of a phase-transfer catalyst. The product containing cyclopropane rings has a higher T_g [89]. Vulcanization of the remaining double bonds gives a membrane with a lower permeability for gases (dinitrogen) as a result of stiffer chains. Allylic groups in PBD can be brominated with bromosuccinimide. Consecutive reactions with aromatic Grignard reagents gave aryl entities with methoxy and thiophenyl substituents on the PBD [90]. Phenyl groups were added to the backbone by reaction of hydrobrominated PBD with phenyl magnesium chloride (Scheme 5) [91]. The hydrobromination was catalyzed by aluminum tribromide [92]. Hydrochlorination of PBD catalyzed by $SnCl_4$ is a slow reaction; it proceeds over hours to give chlorinated polyethylene with chlorides randomly distributed over the chain [93]. Halogenation of PBD with chlorine



Scheme 5 Post polymerization functionalization addition of HBr and reaction with phenyl Grignard

or bromine proceeds readily. Some reports use these derivatives as starting materials for further functionalization. For example, brominated PBD reacts with 2-methyl-2-oxazoline, with formation of a carbon–nitrogen bond [94].

2.4 Epoxidation

Epoxidation is an easy and extensively used method for creating reactive intermediates and is the focus of this section. The versatile reactivity of epoxy groups makes epoxidation of PBD a preferred first step for subsequent nucleophilic addition reactions. The epoxidation procedure used most frequently relies on percarboxylic acids, which are added as reagent or are prepared in situ. Epoxidations are also carried out with transition metal oxides as well as organic precursors such as dimethyl dioxirane.

Epoxidized PBDs have found many applications (vide infra). Unsaturated polyesters can be mixed with epoxidized PBD and a peroxide initiator to prepare resins. Several crosslinking reactions are imaginable in such a system, including esterification and transesterification parallel to radical reactions of the different double bonds [95]. Epoxidized PBDs are potential stabilizers for aromatic polyesters. Most common stabilizers for aromatic polyesters are effective at service temperatures and, therefore, below the melting temperature but not above it. To prevent those esters from undergoing thermal decomposition during processing, epoxidized fatty acids or epoxidized PBDs can be added [96]. Epoxidized PBDs are also used without the need for subsequent reactions to promote the adhesion of PVC coatings, especially on metal surfaces [97].

The addition of an electrophilic oxygen atom is significantly faster at the electron-rich disubstituted double bonds of 1,4-inserted butadiene units of PBD. Differences in the reactivity of 1,4-*cis* and 1,4-*trans* configured double bonds are much smaller and can vary with the type of PBD being epoxidized [98, 99]. A full chemoselective epoxidation of either *cis*- or *trans*-1,4-units in PBD has not yet been reported. The attempt to exclusively epoxidize 1,2-vinyl moieties was undertaken using hydrogen peroxide and a platinum complex known to be selective in the epoxidation of terminal alkenes. No epoxidation of the PBD was observed with this system, revealing that post-functionalization of polymers can be more challenging than that of low molecular weight compounds [78].

Performic and peracetic acid are not capable of epoxidizing terminal 1,2-vinyl groups in anionically prepared PBDs [98]. Successful epoxidation of the pendent 1,2-double bonds of PBD was reported with *meta*-chloroperoxybenzoic acid (m-CPBA) and after almost all of the 1,4-moieties were epoxidized [100]. The influence of the secondary structure of PBDs on the epoxidation was found to be important at low epoxidation levels because the supramolecular structure is significantly influenced by the introduction of epoxides [101]. The reactivity of the various microstructures of PBD and the microstructure of partly epoxidized PBD have been addressed in a number of reports. The epoxidation was carried out using a formic acid/hydrogen peroxide system. The outcome showed a higher rate for epoxidation of *cis*-1,4-PBD over equibinary *cis*-1,4/1,2-PBD over 1,2-PBD, and a random distribution of olefinic and epoxy moieties [102, 103].

Larger scale epoxidations are frequently performed in aromatic solvents such as toluene [104] even though it is known that the π-donor aromatic system of toluene competes with the olefin for coordination to the positively charged carbonyl carbon [105]. The epoxidation reaction is generally faster in more polar solvents, Laboratory scale epoxidations of PBD with peracids can be performed in chlorinated solvents such as dichloromethane or chloroform. Ethers such as dioxane are known to decrease the reactivity of peroxides in the epoxidation of PBD because their oxygen atoms can interact with the percarboxylic acid, thereby decreasing the reactivity (Fig. 2) [106]. Epoxidations in cyclohexane show lower conversion than epoxidations in toluene [107].

Percarboxylic acids are conveniently prepared in situ from hydrogen peroxide and the corresponding carboxylic acid. The epoxidation of PBD in such a system is performed in a two-phase system. PBD is insoluble in water and is, therefore, dissolved in hydrocarbons or chlorinated solvents that are immiscible with the aqueous media containing the acid and hydrogen peroxide. Surfactants or phase-transfer agents can be used to accelerate the reaction [108]. Generally, peracids are more soluble in the organic phase, whereas the PBD is dissolved as the parent acid. This approach takes advantage of a shift in the chemical equilibrium of Scheme 6, and allows use of catalytic amounts of acids (Scheme 7). The lower concentration of acid is favorable for product selectivity. Epoxidation of about 70% of the double bonds in PBDs has been realized without any notable side reactions or gelation of the polymer [109]. Aqueous solutions of hydrogen peroxide can induce epoxide opening to form vicinal diols [105].

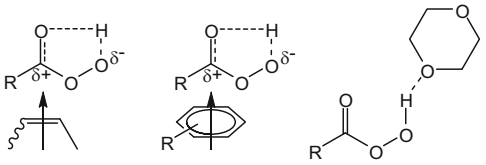
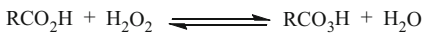
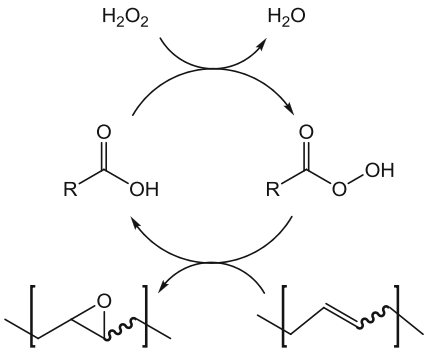


Fig. 2 Coordination of polybutadiene to aliphatic peracids (*left*) and π-donor stabilized peracids by coordination to aromatic solvents (*center*) and ether-coordinated peracids (*right*)



Scheme 6 Equilibrium of aliphatic acids and hydrogen peroxide in water



Scheme 7 Two-phase PBD epoxidation with hydrogen peroxide and aliphatic acids

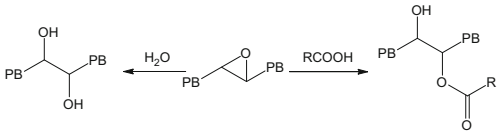
Formic acid is a carboxylic acid that is able to autocatalyze its peracid formation from hydrogen peroxide. The in situ epoxidation of PBD is, therefore, frequently performed with formic acid systems [104, 108–114]. HTPBs can also be epoxidized by in situ-generated performic acid at room temperature, without epoxide opening by the hydroxyl groups [115].

Higher carboxylic acids such as acetic acid and propionic acid have also been used to epoxidize PBD [100]. Acetic acid is known not to react below 40°C with hydrogen peroxide to form a peracid; therefore, a strong protonic acid is added to catalyze peroxide formation [116]. Mineral acids such as sulfuric acid [117, 118] or phosphoric acid [118] are effective for this. Trichloroacetic acid was found to induce epoxide opening faster than the epoxidation [118].

Acidic resins can be used as heterogeneous catalysts for in situ peracid formation. Protonic ion-exchange resins based on sulfonated polystyrene were used for epoxidations [119]. Acetic acid was, thus, used successfully as epoxidation catalyst in combination with resins such as Dowex 50W-X8 [104, 120, 121], Dowex 50X-12 [95], or Amberlite IR-120 [118, 122] to epoxidize PBD. The formation of products from side reactions of the epoxides are to be expected and in some cases have been reported [122]. A more advanced approach uses the immobilized enzyme Novozym 435 to catalyze the in situ formation of peracetic acid from acetic acid and hydrogen peroxide [123].

The degree of epoxidation can be controlled by the stoichiometric addition of percarboxylic acids [124–126]. When aiming for high epoxidation levels in the polymer, the quantity of peracid needs to be increased over a 1:1 molar ratio. The concomitant high concentration of carboxylic acids in the reaction media leads to side reactions [99, 118, 124]: an acid-catalyzed ring opening of epoxides by water or the carboxylic acid can occur. The resulting PBD contains vicinal hydroxyl

Scheme 8 Side reactions under typical conditions of aliphatic peracid epoxidation



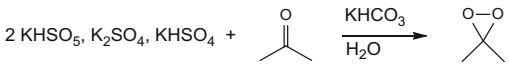
groups and hydroxyl esters (Scheme 8). Acid concentration as well as reaction temperature affect the degree of side reactions [118]. To reduce side reactions, the pH value can be adjusted by adding a base such as anacetate [104]. Hydroxyl groups from side reactions can, on the other hand, also be favorable for further functionalization [124].

A phase-transfer catalyst such as tetra-*n*-butyl ammonium bromide has been used to chemoselectively epoxidize 1,4-units rather than 1,2-units in PBD [127] or HTPB [128] in a biphasic system. The degree of conversion accessible with peracids was up to 90% before the epoxidation of 1,2-vinyl groups was possible. Side reactions such as epoxide opening or oxidation of terminal hydroxyl groups have not been observed [128]. Modified clays (e.g., Closite 30B, a montmorillonite modified with ammonium salts) were also found to be favorable for epoxidation of *cis*-1,4-PBD because no phase-transfer agents need to be separated and phase transfer was not the rate-determining step [129, 130].

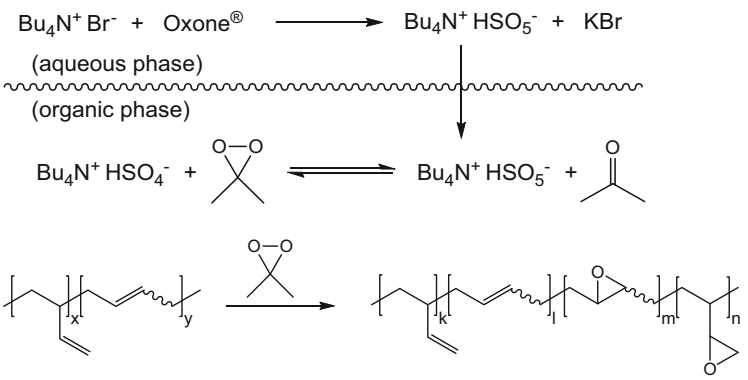
Perbenzoic acid was one of the first peracids used to epoxidize PBD [118, 131]. Internal double bonds are epoxidized quantitatively by perbenzoic acid in the presence of the double bonds of 1,2-inserted butadienes [132]. This one-phase reaction can be used analytically to determine the content of 1,4-inserted units in PBD [131]. The commercial availability of m-CPBA makes it the preferred peroxide for epoxidation [100, 133–139]. m-CPBA epoxidizes double bonds quantitatively, although the 1,4-inserted butadiene units react faster [100]. The final epoxide content of the PBD can, thus, be controlled by the amount of m-CPBA added [138]. Despite its chemical benefits, m-CPBA is not used in large-scale epoxidation because of its high cost and the cost of disposal of *meta*-chlorobenzoic acid residue. Epoxidations of PBDs are described with monoperphthalic acid using reactive mixing techniques [140]. The preparation of perphthalic acid from phthalic acid anhydride and hydrogen peroxide in solution was found to be convenient for the preparation of epoxidized polyenes, without notable side reactions [107, 141–143].

The epoxidation of PBD with dimethyl dioxirane (DMD) as the oxidizing species shows that the epoxidation proceeds as expected with high stereoselectivity: *cis* double bonds give *cis*-epoxides. The latter was confirmed by NMR spectroscopic analysis. DMD can be prepared by conversion of acetone with Oxone, a potassium monopersulfate compound (Scheme 9). Prepared in situ or purified by distillation, DMD is an efficient oxidizing species for polydienes (Scheme 10) [127, 130].

Transition metals have also been used to epoxidize PBDs (using the Helcon process [144]). The epoxidation of low molecular weight *cis*-PBD with a bis-(acetylacetonate)dioxomolybdenium catalyst, thus, yielded up to 23 wt% epoxy groups at a high conversion of *tert*-butyl hydroperoxide [145]. Molybdenum-based catalysts have the same preference for epoxidation of 1,4-inserted butadiene units; the



Scheme 9 Dimethyl dioxirane prepared from Oxone® and acetone



Scheme 10 Epoxidation of PBD with dimethyl dioxirane in a two-phase system [128]

chemoselective epoxidation of 1,4-double bonds proceeds in the presence of 1,2-vinyl entities [146]. The epoxidation of 1,4-*trans*-PBD using a dichlorodioxomolybdenum complex with *tert*-butyl hydroperoxide gave a completely epoxidized polymer. The reaction appears to be sensitive to water and hydrogen chloride liberated from the catalyst precursor, which leads to ring opening and crosslinking [79, 147]. Removal of the acid and addition of molecular sieves to bind water during the reaction gave conversions of over 95% with no side products. The epoxidation of PBD as well as HTPB was successfully performed with tungstic acid as catalyst in combination with phosphoric acid, ammonia salts, and hydrogen peroxide in the presence of ammonium alkyl phase-transfer catalyst [144]. An ammonium tungstate hydrate was described as catalyst in combination with the quaternary ammonium salt Aliquat 336 as phase-transfer catalyst [107]. A process for the epoxidation of PBD was patented using hydrogen peroxide in the presence of $Ce(SO_4)_2$ and various types of glycerols to obtain an epoxidized product in a clean reaction [148]. Several manganese porphyrins were successfully screened for epoxidation of *cis*-1,4-PBDs using iodosobenzene as preferred oxygen source [149–152].

High conversion of double bonds in a 1,4-*cis*-PBD has been achieved using several transition metal catalysts (Ti, V, Cd, Ni, Zn, Mn, and Cu metals ion) and with Oxone/acetone as oxygen source [153]. A full conversion was obtained in the case of $CuSO_4$ or Cu-DABTZ (2,2′-diamino-4,4′-bithiazole) [154]. Methyltrioxorhenium (MTO) was found to be an efficient catalyst in a biphasic system with hydrogen peroxide. Because all of the peroxide adds to double bonds of PBD, the epoxide content can be controlled by the quantity of hydrogen peroxide added [155].

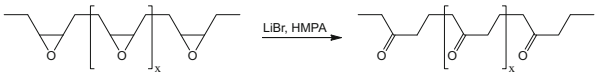
Introduction of polar epoxide entities into PBD causes a linear increase in T_g with the epoxide content [108]. Melts of epoxidized PBD show higher molecular friction and have longer relaxation times, indicative of the stiffer chain [109]. The T_g increases by about 0.6–1.0°C per mol% of epoxide groups on PBD, depending on the position of epoxide in the chain. Epoxidation of 1,2-vinyl groups affects the T_g less than 1,4-epoxidation: reducing the chain flexibility is much more effective by stiffening of the backbone [108]. MALDI-TOF analysis of epoxidized PBD, especially in combination with size-exclusion chromatography, can give detailed information on epoxide content, side reactions, and even the polymerization process of the parent PBD substrate [139].

3 Polybutadiene Multistep Functionalization

The aim of multistep PBD functionalization is to reach or adjust material properties in a scalable, controlled, and economically viable way. The products generally carry heteroatoms and, in consequence, range from being polar to soluble in water, which is found for sulfonic or phosphonic acid derivatives. PBD with residual reactive double bonds and/or functional PBD with good leaving groups have the option of radically forming crosslinks, which leads to thermoset resins. This can be a desired process or a reaction to prevent, depending on the target. A multistep functionalization procedure can have the advantage of offering higher control over the outcome (yield, regio- and stereochemistry, molecular mass, etc.) and can be carried out in a more cost-efficient way with respect to reactor time, necessary infrastructure, reagents and their handling, and so on.

As an example, we consider the preparation of phosphorous acid derivatives. Phosphonate groups can be directly added to the 1,2-double bonds of PBD by a presumably radical reaction with $HPO(OEt)_2$. However, this reaction is accompanied by gelation, which takes place at low conversions (>6%) and is not really an option for the preparation of phosphonic acid derivatives [156]. Phosphorous acid derivatives are also accessible through multistep reactions. Trichloromethylphosphonyl dichloride adds to the double bonds of 1,2-PBD through the action of a catalyst in the form of tris(triphenylphosphine)ruthenium(II) dichloride, $CuCl_2$-Et_3N.HCl, or $FeCl_3$-Et_3N.HCl-benzoin mixtures [157]. Subsequent hydrolysis in air gives a polyacidic surface in two simple steps. In addition, phosphorus tribromide can be added photochemically to PBD. Reaction with methanol results in a PBD with phosphonic acid groups on the surface. The latter procedure can even be used to achieve patterning on PBD coatings on metal surfaces. Phosphonic ester functionalization of polymer surfaces is a route toward formation of biocompatible surfaces [158].

The single-step simultaneous sulfonation and phosphorylation of 1,4-*cis* PBD was successful with SO_3 and triethoxy phosphorous oxide to yield a water-soluble polymer with a $SO_3/(EtO)_3PO$ molar ratio of 3:1. This polymer is, for example, applied in the dehydration of drilling muds [159]. Sulfonated PBD products are



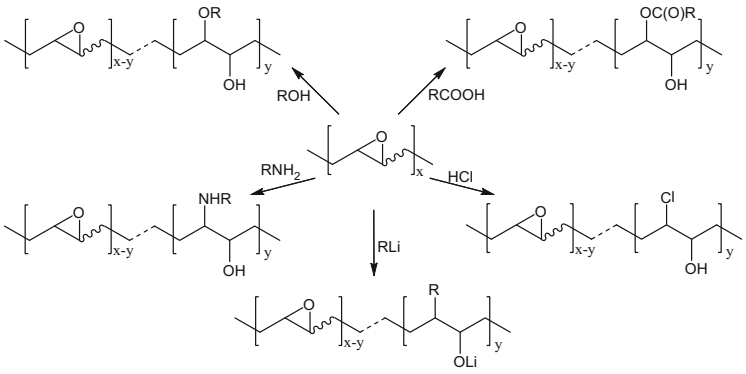
Scheme 11 Rearrangement of epoxidized PBD to give polyketones

obtained by addition of bisulfite directly to PBD derivatives in air [112, 160, 161], or to a surface containing PBDs with predominantly 1,2-vinyl groups after oxidation with HNO_3 and exposure to fuming H_2SO_4 [162]. A two-step post-polymerization functionalization in a single reactor leads to a SO_3H ion-exchange polymer under milder conditions. The consecutive free radical addition of thiol acetic acid to the double bonds of 1,4-PBD and oxidation of the intermediate thioacetylated polymer gave the sulfonated product [163]. Photochemically generated thiyl radicals also add effectively to the double bonds of 1,2-PBD. Very high degrees of substitution are reached, showing that this reaction can precede an oxidation reaction to yield polysulfonates [164]. The sulfenyl chloride BuSCl can likewise be added to the double bonds in PBD [165]. It could be shown that a neighboring group effect here gives blocky polymers.

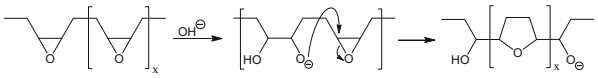
Photodegradable polymers such as polyketones are accessible either via direct oxidation of PBD [78, 79] or in a facile two-step reaction sequence from a lithium bromide-catalyzed rearrangement of epoxidized PBD. Polyketones readily undergo aldol-like reactions, leading to an insoluble crosslinked resin as the major product. The lithium bromide-induced rearrangement of the epoxides on the PBD backbone in tetrahydrofuran (THF) solution (or when using other organic solvents in the presence of a solubilizing agent such as hexamethylphosphoramide or dimethyl imidazolidinone) form isolable polyketones (Scheme 11) [147].

3.1 Reactions of Epoxidized PBD

The epoxidation of PBD gives access to reactive intermediates that can be functionalized under mild conditions in a further step. Radical crosslinking can generally be avoided under the conditions of nucleophilic substitutions. The ring opening leads to alkoxide intermediates that in some cases react as a chain-located nucleophile with other PBD epoxide units to yield crosslinked materials (intermolecular) or polyether structures (intramolecular; vide infra). Terminal epoxides in that context are more reactive than internal epoxides. PBD having internal epoxide groups on the polymer backbone require, as a consequence, harsher reaction conditions for further functionalization, and, at the same time, are less apt to undergo crosslinking reactions [79]. The reactivity of substituted epoxides in PBD is generally a function of the microstructure [166, 167]. Reactions with functional groups having active hydrogen atoms are possible, as well as ring expansions, carboxylation, or nitration [168, 169] (Scheme 12).



Scheme 12 Typical ring-opening reactions of epoxidized PBD



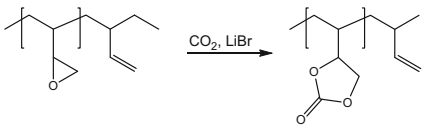
Scheme 13 Ring expansion in epoxidized PBD

PBDs having a high epoxide content, and highly diluted polymers, react predominantly intramolecularly with neighboring epoxides under ring expansion (Scheme 13) [170]. This ring expansion can occur with any ring-opening reagent (e.g., during solvolysis in alcohols or in aqueous hydrogen chloride). The base-catalyzed intramolecular reaction of multiply epoxidized PBD gives epoxide openings with an inversion of the configuration. In the case of epoxidized 1,4-*cis* PBD, ring-expanded polyethers with high cation-complexing properties similar to those of crown ethers are obtained [171, 172].

The reactivity of the epoxides towards certain nucleophiles, and optionally in combination with electrophilic catalysis [173], is also used to characterize epoxidized PBDs. The epoxide content in PBDs is usually determined by titration methods using acids that add to epoxides. Hydrogen bromide [174], perchloric acid [175], and hydrochloric acid [166, 176] are typical examples; they can expand the accuracy of measurement in combination with spectroscopic techniques [177]. The polymeric products are hydrins.

Epoxidized PBDs react with carbon dioxide to form cyclic carbonates. The reaction is catalyzed by Lewis acidic metal-complexes, especially effectively by tetrabutyl ammonium cations and lithium salts to give carboxylated products at ambient pressure in a carbon dioxide atmosphere. The resulting material showed interactions with lithium ions, making it suitable for preparing lithium-conducting membranes (Scheme 14) [178].

Scheme 14 Formation of carbonate-substituted PBDs from 1,2-vinyl PBD

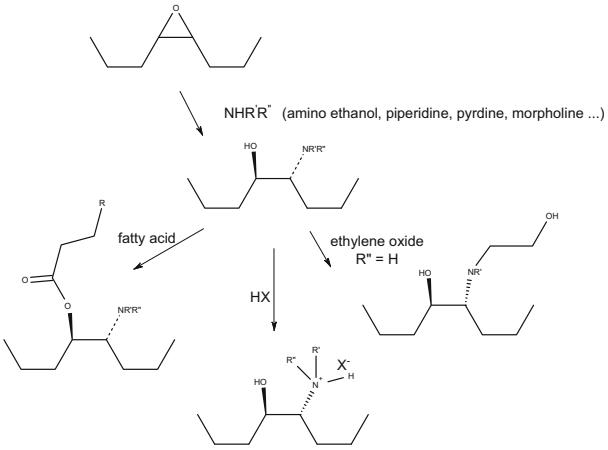


3.2 Amine Modification of Epoxidized Polybutadiene

Polymers with amine moieties are generally not easily accessible in one step (the chemical modification of 1,2-vinyl PBD with amines in the presence of sodium tetrachloroaluminate yielding amino-functionalized PBD is one exception [164]). PBD epoxides are effectively aminolyzed to polymers with amine groups on the backbone. The introduction of amino groups has a large impact on the polarity and leads to polymers with improved compatibility with water. Amino-functionalized PBDs can, thus, be used in aqueous coating dispersions and other products of industrial interest. They have the possibility of becoming polycations after quaternization. Reacting epoxidized PBD with molecular weights of about 1.0 MDa with tertiary amines gives quaternary ammonium derivatives that are useful as flocculation agents in water treatment operations [179]. Amine-containing reaction products of epoxidized PBD can be protonated by mineral acids (e.g., hydrochloric acid) to yield water-soluble cationic polymers. The ammonium hydrochloride salt of polyamine PBD is, for example, used as a static dissipator additive in shampoo and hair cosmetic products [180]. In one other case, the hydroxyl group of amine ring-opened epoxy PBD was esterified with unsaturated fatty acids to obtain water-based adhesive dispersions after drying in air [181].

Epoxide entities of low molecular weight PBD react with primary–tertiary or secondary–tertiary diamines [182] or amino ethanol [183] to give polymers with amino groups (Scheme 15) [184]. Those amino groups can be reacted with epoxides such as ethylene oxide or propylene oxide to give water-soluble PBD binder (useful for, e.g., wood preservation). Epoxidized PBD also reacts with derivatives of piperidine to give amino-functionalized polymeric materials with low migration, and has been used as a non-volatile compound for the stabilization of hot melt adhesives [185, 186]. Reaction with morpholine or other secondary amines gives functionalized PBD, which is applied as binder for inorganic powders in ceramic moldings [187].

Study of the reaction of *cis*-1,4-PBD with a low percentage of epoxides and morpholine showed that nucleophilic attack of the secondary amine opens the ring. The initial product was protonated by lactic acid, which was also present. The competing electrophilic ring opening by lactic acid was only a minor reaction. The resulting low-functionalized polymer was not soluble in water [188]. A comparable study of (in situ) generated epoxidized *cis*-1,4-PBD with pyridine as nucleophile gave cationic polymers (lactate as anion) that were soluble in water [189].



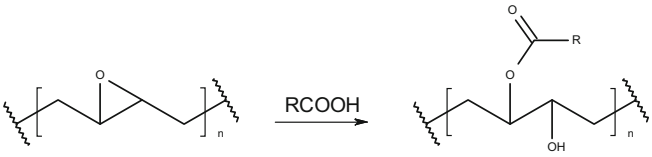
Scheme 15 Aminolysis of epoxidized PBD and secondary reactions

3.3 Carboxylic Acid Modification of Epoxidized Polybutadienes

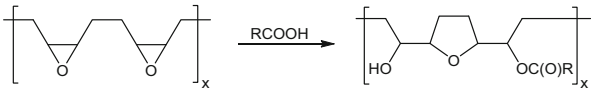
Reaction of epoxidized PBD with carboxylic acids gives access to hydroxy esters. The reaction can occur during the epoxidation of PBD with carboxylic peracids (vide infra). The reaction is acid-catalyzed and it should be no surprise that the reaction with acetic acid gives the hydroxyl ester if catalytic amounts of sulfuric acid are present (Scheme 16) [80].

It is challenging to obtain defined products from the reaction of PBD epoxides with carboxylic acids. Transesterfication accompanies the epoxide ring opening by a carboxylic acid and leads to 1,2-dihydroxy and other motives on the backbone. The exclusive formation of polyalcohols has been reported during the reaction of PBD epoxide with oxalic acid [150]. The epoxide opening with benzoic acid was intensively investigated and the ester formation was found to be limited by side reactions such as the formation of diols and intramolecular epoxide opening by a neighboring hydroxyl group to give five-membered cyclic ethers (Scheme 17). The hydroxyl ester could be obtained kinetically in good yield with an excess of carboxylic acid over epoxide groups on PBD [190].

The ring opening of epoxidized PBD with carboxylic acids is also useful for introduction of further functionalities to the polymer. Reaction with pyridine carboxylic acids, especially nicotinic acid, again leads to amine-containing polymers. These are applied as additives in lubricants to suppress corrosion and improve viscosity [191]. In a further example, fatty acids were added to the epoxide functionality in PBD, resulting in alkyl side chains. An organo-tin catalyst [192] or trifluoroacetic acid [141] was necessary in the process. The resulting liquid polymers are used as additives for reducing the viscosity of mineral oils.



Scheme 16 Ring opening of epoxidized PBD with acids



Scheme 17 Side reactions in an epoxidized PBD chain after acid ring opening

Another approach for obtaining carboxyl-functionalized PBDs by a post-polymerization technique from PBD is the reaction of olefinic double bonds with thioglycolic acid. Addition of the thiol functionality to the double bonds results in a carboxylic PBD, which reacts with epoxy compounds to form thermoset resins [193].

Acrylic acid, methacrylic acid, or maleic acid ring opening of epoxidized PBD give access to hydroxyl esters with an α,β-unsaturated double bond next to a carbonyl group. The acrylic derivatives are much more reactive in radical polymerizations than the double bonds of PBD. Peroxide-initiated copolymerization of PBD with acrylic esters and styrene proceeds readily to give hard and tough resins [194]. The approach was also reduced to a one-pot reaction of epoxidized PBD, acrylic acid, and styrene with a peroxide initiator and zinc stearate as accelerator [195]. The system can be extended through ring opening of the epoxide by reaction with an amine (amino alcohol) prior to attaching acrylic acid by esterification. The resulting resins are useful for cathode-depositing coatings [196–198].

3.4 Hydroxyl Groups on Polybutadienes

The reaction of epoxidized PBD with protonic nucleophiles such as water and alcohols (or amines and acids) yields polyhydroxides. Showing considerably low reactivity to alcohols even at elevated temperatures, acidic catalysts are necessary to convert epoxidized PBD to poly-α-hydroxyl ethers. Epoxidized PBD was, thus, ring-opened with 1-octanol using triflouroacetic acid at 130°C. Reaction is slow, reaching only 30% conversion after 8 h [141]. Sulfuric acid is capable of catalyzing the epoxide opening with benzyl alcohol, but is accompanied by strong coloration, which is indicative of polymer degradation [79]. Hydrolysis of PBD epoxides in THF solutions with sulfuric acid as catalyst gives quantitative conversions to the corresponding diols without coloration [178]. The stronger triflic acid was used to prepare vicinal diols from epoxidized PBD in THF/water mixtures [199].

PBD epoxides can also be opened by organo-lithium reagents to obtain alcohols or allyl alcohols, but the reaction is accompanied by the formation of vicinal diols from the remaining epoxides during the final hydrolysis of lithium alkoxide [80]. Base-catalyzed epoxide opening with potassium hydroxide is described for the addition of fatty alcohols. An alternative route to such derivatives first generates a PBD triol, which can be esterified with fatty acids through reaction of epoxidized PBD with trimethylolpropane. The resulting PBDs with alkyl side chains are useful as drag reducers in mineral oils [194]. Such grafted derivatives of epoxidized PBD are useful additives in lubrication oils because of their ability to improve the viscosity, lower the flow point, act as detergent, and lower the shear resistance. These derivatives generally include the reaction products of epoxidized PBD amines, alcohols, phenols, and carboxylic acids [141].

Polybutadiene-based polyols can also be reached by consecutive reaction of 1,2-vinyl PBD with 9-borabicyclo[3.3.1]nonane (9-BBN), leading to hydroboration, and oxidation with H_2O_2/NaOH [141]. Direct bishydroxylation with osmium tetroxide or using permanganate as catalyst has been reported as unsuccessful [200].

3.5 Graft Copolymers from Epoxidized Polybutadienes

Epoxidized PBD is a convenient basis for various graft copolymers. Reaction with hydrogen chloride gives polychlorohydrins, which can be cured with (poly)isocyanates to give rubbery to hard castings [201]. Chlorohydrins of PBDs were also reacted with *p*-toluenesulfonyl isocyanate to introduce pendent sulfonylurethane groups that form hydrogen bonds, giving a thermoreversible crosslinked rubber [202]. Living polyTHF cations were grafted onto chlorohydrin PBD to give copolymers with a crystallizing block. The products are thermoplastic elastomers having physical crosslinks of crystallized polyTHF blocks [134, 203]. As the "grafting-to" procedure gave unsatisfactory results, epoxidized PBDs were also grafted with polyTHF chains, using a "grafting-from" THF polymerization with an excess of BF_3 over the initiating epoxy groups [204]. Reducing the formation of polyTHF homopolymers to 4% demonstrates that an efficient grafting technique was found.

High molecular weight polyurethanes were formed from epoxidized HTPB with methylene diphenyl diisocyanate (4,4′-MDI) and diethylene glycol as chain extender. Polyethylene glycol side chains were subsequently grafted to the PBD polyol by reacting it with amino-terminated polyethylene glycol, thus giving a polar and hydrophilic copolymer with suppressed interaction with blood components [205].

Epoxidized PBD is also useful for grafting PBDs onto inorganic surfaces such as silica, alumina, and ferric oxide [206–210]. These PBD-modified materials exhibit, for example, good separation properties as the stationary phase in liquid chromatography [211]. Subsequent treatment with neat PBD or in the presence of silica with hydrochloric acid allows crosslinking of the remaining epoxide entities in PBD and formation of diether or α-hydroxyl ether entities [212, 213]. Also, amine-terminated

polyaniline was grafted onto epoxidized PBD to obtain elastomeric conducting materials. Polyaniline needs protonation to reach electrical conductivity (at about $10^{-5}\Omega^{-1}\,cm^{-1}$). The addition of hydrochloric acid to the graft polymer resulted in a resin with presumably ether-type crosslinks, because not all epoxide groups had reacted with polyaniline [138].

The addition of organo-lithium groups to epoxidized PBD opens the possibility of adding carbon side chains to the backbone. Anionic polymerization of butadiene with butyl lithium leads to lithium-terminated PBDs of various architectures. Subsequent addition to epoxidized PBD gives comb-like grafted PBDs with reduced or even suppressed cold flow and better processing properties [213, 214]. The reaction of epoxidized PBD with lithium-terminated PBD anions can be monitored if a compound such as an ether, thioether, or tertiary amine is added that colors the solution while living carbanions are present [215]. Complex architectures are easily reached. A dendrigraft star-comb structure has been synthesized starting from a four-armed PBD obtained from living lithium-terminated PBD anions and silicium tetrachloride. Subsequent epoxidation of the PBD and coupling of epoxides with more living PBD anions gave a four-generation highly branched PBD with narrow molecular weight distribution [216]. Other PBD dendrimers and combs were also prepared from terminal lithium polybutadienyls in combination with chlorosilanes [217, 218]. Hydrogenation of such products leads to defined polyethylenes with long and short branches [219].

3.6 PBD Epoxide Thermosets

Epoxidized PBDs have a major use as precursors of epoxy resins. The low T_g of PBD toughens rigid epoxide resins, and epoxidized PBD can form a substantial part of rubber-toughened resins. The curing of these epoxy resins can be reached with amines, carboxylic acids, anhydrides, or Lewis acids such as BF_3 complexes using the reactions discussed above [220]. Curing through ring opening with cationic initiators such as iodonium salts is described for flexible microelectronic adhesive resins with high filler content of silver, aluminum, or aluminum oxide [221]. Curing of epoxidized PBDs with amines to form amino alcohol resins is a common practice, whereas hydrazines were originally used as curing amines [122]. The lower reactivity of disubstituted epoxide groups on the PBD backbone allows the preparation of slowly curing epoxy resins with polyamines, giving a long shelf life to a one-component system of such formulation [222]. Resin compositions with a very long pot life consist of mixtures of epoxidized PBD, *para*-aminobenzoic acid, and resorcinol. Complete formulations can be stored for up to 3 months without crosslinking before curing is induced at 80–150°C [223]. Epoxy resins can contain the epoxidized PBDs alone or as a component together with reactive dilution components such as the diglycidyl ether of bisphenol A. The compatibility of PBD polyols with aromatic epoxide resins is enhanced by introduction of epoxy

groups into the PBD, and the secondary hydroxyl groups formed after opening were found to participate in the curing process [224].

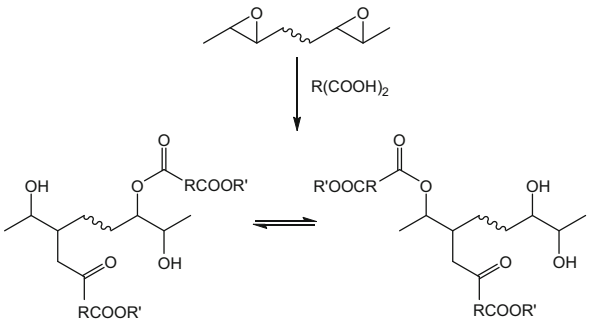
Primary amines react with more than one epoxide, thus generating crosslinks in epoxidized PBD. The former react at elevated temperatures of 80–200°C, and addition of a catalyst is advantageous. Trialkyl stannous halogenides are efficient but toxic. Tertiary amines are suitable alternatives [225]. Curing of epoxidized PBD with amine complexes of BF_3 gave adhesives especially useful for application on metal surfaces [226]. Crosslinking of epoxidized PBDs with diamines was also performed in formulations with PBD and silica. Epoxidized PBDs bind covalent to inorganic materials and the intermediate is further crosslinked by action of the diamines [227]. The hydroxyl group formed next to the amino group is also capable of reacting with epoxides in spite of its smaller nucleophility [220]. Epoxy resins from mixtures of epoxidized PBD and diglycidyl ether of bisphenol A cured with amino-functional polyamide [A211] or methylene dianiline [228] show phase separation during the reaction. The specific reaction conditions (temperature, initial composition) give control over the chemical architecture, morphology, and mechanical properties of this system and can give an interpenetrating network [209].

Polybutadiene derivatives dispersible in water are obtained from epoxide opening with primary or secondary polyamines [209, 229–231] or amino alcohols [232, 233] such as methyl ethanol amine. The amino groups can be quarternized by reaction with epoxides, such as those based on bisphenol A and epichlorohydrin. The resulting functional PBDs can be crosslinked with blocked isocyanates. The uncured mixtures are dispersible in water and can be used for cathodic deposition for preparing coatings on metal surfaces (vide supra). The coatings exhibit good resistance to solvents and corrosion, in addition to good elasticity. The addition of hydrazides such as β-(diethyl amino)-propanoic acid hydrazide to epoxidized PBD gives a resin that can be crosslinked with sulfur in combination with accelerators at a lower curing temperature of 120°C relative to 180°C of the former system [229].

Hydroxyl group-containing epoxidized PBDs can be used to generate resins directly. The reaction conditions for PBD epoxidation by peracids from hydrogen peroxide are favorable for ring opening (vide supra) under hydroxyl group formation, particularly when strong mineral acids are used to enhance the rate of epoxidation. In the 1960s, the first commercially available types of epoxidized PBD were sold as Oxiron and had such hydroxyl groups [233]. Resin formation directly from Oxiron is possible, but is usually enhanced by the addition of alcohols. Ink formulations for printing on glass surfaces were made from these Oxirons alone or by reaction with the monomethyl ether of tripropylene glycol with BF_3-based catalysts [234]. Epoxidized PBD cured with glycidol, an epoxy alcohol itself, gives hard resins in formulations with methyl nadic anhydride (methyl norbornene 2,3-dicarboxylic acid anhydride) for chain extension and a tertiary amine as catalyst [235].

Oxazolidones result from the reaction of epoxides with isocyanates. Oxazolidones have a high thermal stability. A one-component foam system was developed, based on the formation of urethane and oxazolidone from an isocyanate. Mixing an excess of crude 4,4′-MDI with an aliphatic polyester polyol and an

Scheme 18 Transesterification in dicarboxylic acid-cured epoxy resins



epoxidized PBD polyol gives this isocyanate compound. Combined with a polyol component in a spray can, it is useful as a one-component construction foam [236].

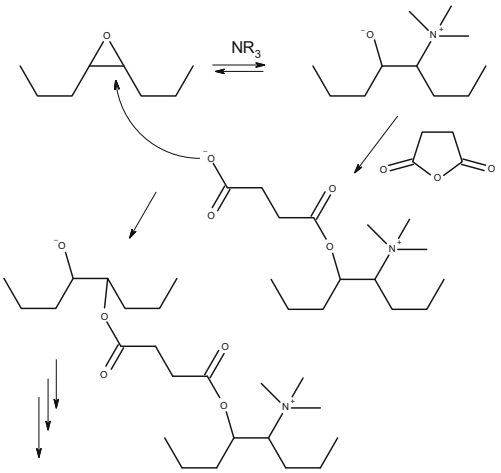
Commercial PBDs are available (e.g., from Sartomer) that bear epoxy entities on the polymer backbone and also have terminal hydroxyl groups The hydroxyl groups can cure a formulation containing reactive monomers such as cycloaliphatic or siloxane epoxides, or the epoxidized PBD itself [237]. Bisphenol epoxy resins show an increased impact strength when the formulation contains less than 10 wt% of an epoxidized HTPB. Higher contents of HTPBD result in a resin that is softer and has a lower T_g and generally unfavorable mechanical properties [115].

Curing of epoxidized PBD with dicarboxylic acids proceeds by formation of intermediate hydroxyl esters that open further epoxides (Scheme 16). Transesterification reactions can redistribute the ester bonds, and gel fractions are formed simultaneously, even with difunctional monomers used in a stoichiometric ratio (Scheme 18) [220]. Curing with carboxylic anhydrides is believed to proceed via a zwitterion that is generated by activation of the epoxide with an amine catalyst to give an alkoxide. The latter is an initiator for anionic copolymerization of epoxides and anhydrides (Scheme 19).

PBDs with end groups such as carboxylic acids in combination with epoxidized PBD can yield resins. CTPBs have been commercially available since the 1960s and have become a substrate for consecutive reactions, especially reactions with alcohols and epoxides. Telomerization of butadiene with dithiodibutyric acid as regulator and a carboxyl-functional azo initiator gives CTPB [238]. Radical polymerization initiated by peroxides of a dicarboxylic acid (e.g., glutaric acid peroxide) allows control over molecular weight by adjusting the initiator to monomer ratio and varying the reaction temperature [239].

PBDs with a high content of epoxides can form a densely crosslinked hard resin in response to the action of a carboxylic acid. Anhydrides are not suitable as curing agents for this type of epoxidized PBD because the number of alkoxy groups generated is usually too low to sufficiently initiate the copolymerization reaction. The addition of low molecular weight alcohols allows curing of such formulations, typically at temperatures of 100°C or higher within 1–2 h, to give resins that are particularly useful as coatings [124, 240]. Curing with acids and anhydrides at room temperature takes much longer. A tack-free film is obtained only after several hours

Scheme 19 Curing of epoxidized PBD/anhydride formulations with amines



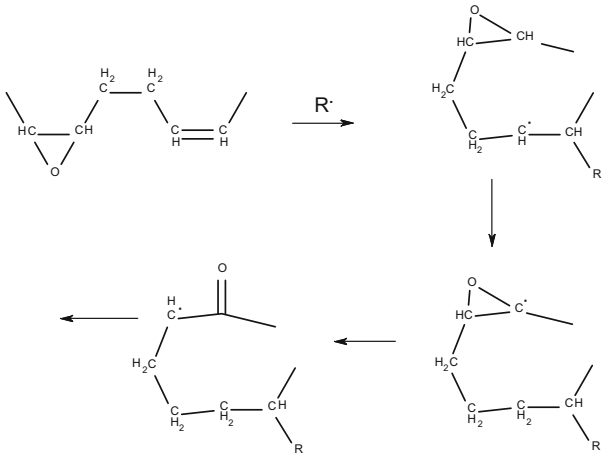
and complete curing takes several days. Fillers such as talc and coal tar can be added to such resin formulations, which can then be sprayed onto concrete surfaces and cured overnight to form tack-free films [241]. Conversion of epoxidized PBD bound to a stationary phase such as silica or alumina with ethylene diamine gives a crosslinked resin with weak anion-exchange phases. Ion-exchange capacity can be controlled by changing the thickness of the polymer on the supporting material [242].

3.7 Functional PBDs in Applications

The curing of epoxidized PBD with radical initiators such as dicumyl peroxide causes rearrangements of the epoxy rings and leads to crosslinking via α-disubstituted ketones or oxygen-bridged vinyl ethers (Scheme 20). These rearrangements are typical for internal epoxide groups and an atom radical from 1,4-double bonds, and they are exclusively observed in 1,4-PBDs. The 1,2-double bonds do not give intermediate radicals that are stable enough for such rearrangements [167].

Epoxidized PBD and PBD were radically crosslinked by dicumyl peroxide to investigate the influence of epoxidation on crosslinking. The heat of crosslinking was measured by DSC and the crosslinking efficiency determined as the amount of heat of reaction in relation to one repeating unit of PBD and per molecule of dicumyl peroxide. The crosslinking efficiency was four times lower for 1,4-inserted butadienes (over vinyl units). Epoxidized PBD samples generally showed a lower crosslinking efficiency. Infrared and chemical analyses indicated a loss of epoxide groups of 11%, which was attributed to radical side reactions such as the formation of carbonyl groups and ether bridges [167].

Scheme 20 Rearrangements during radical curing of partly epoxidized 1,4-PBD



Lithographic resists for chromium and aluminum surfaces curable by electron beam and consisting of epoxidized PBD are much more sensitive than the parent PBDs [125]. The curing of such resists was found to obey Charlesby's theory on gel formation [243]. Compared with other materials, epoxidized PBD demonstrated the best contrast at low voltages [244]. Other sensitive photo- and radical-curable resins of epoxidized PBD modified with esters of carboxylic acids (e.g., acrylic acid or methacrylic acid) have also been reported [194, 195, 245–247]. UV-initiated curing to prepare coating materials from mixtures of epoxidized HTPB and cycloaliphatic diepoxides gave higher conversions in any mixture than with each of the epoxide materials alone (curing time lower than 1 min). The curing proceeds via a cationic onium species (e.g., arylsulfonium) as photoinitiator, which decomposes to give a strong Brönstedt acid [248]. UV irradiation of PBD in the presence of mercaptopropyltriethoxysilane gives a resin with alkoxysilane groups. Subsequent reaction with water yields a crosslinked product [249]. The reaction of PBD with dithioglycolate directly yields a crosslinked product upon irradiation.

The double bonds in PBD resins can be functionalized on the surface, which is an important method for making PBD adhere to polymers or inorganic substrates [250]. Supercritical carbon dioxide swells PBD and allows reagents to contact the polymer. The bulk shape of the material is, to a large extent, not altered by the procedure. The surface was accordingly successfully functionalized with vinyl derivatives such as vinyl benzoic acid or crotonic acid [251]. The surface of a PBD/polycarbonate membrane for O_2/N_2 separation was edged with an ethylenediamine plasma, with the result that the nitrogen content at the surface increased and the permeability and selectivity increased [252]. The epoxidation of PBD-containing polyurethane membranes was performed with in situ-generated formic acid to increase the water absorption of these membranes as well as the surface energy [253, 254]. Epoxidized PBD membranes showed a lower gas permeability, which can be interpreted in terms of decreased chain mobility as a result of ring formation (vide infra). A phase-separated porous copolymer of

1,2-vinyl PBD was treated at the internal surface to photochemically add bromo-isobutyrate, as a typical ATRP initiator, to the double bonds. Grafting of acrylates yielded a hydrophilic nanoporous structure. Azide groups were attached to the nanoporous material and, after a click reaction, methoxy polyethylene glycol was added in the vicinity of the polar substrate.

4 Concluding Remarks

Some chemistry of polybutadienes has been compiled in this review. PBDs are readily prepared by radical and anionic polymerization. The low-cost, reactive polymers are readily crosslinked by radical reactions. Post-polymerization reactions can stabilize the polymer by hydrogenation. Full catalytic hydrogenation leads to derivatives of polyethylene. Partial hydrogenation shows how functionalization is dependent on the reactivity of the different microstructures, solubility, and/or neighboring group effects. Isomerization of the double bonds and olefin metathetical redistributions can be used to alter the structure of a parent PBD. Oxidation reactions introduce heteroatoms to the backbone and give the possibility for nucleophilic substitutions. Epoxidation is particularly useful in that regard because intermediates with a high chemical potential are formed. Addition reactions with common reagents such as alcohols, amines, and acids give hydroxy compounds. Grafted copolymers and resins are easily formed by such nucleophilic reactions. Curing reactions can proceed via nucleophilic as well as radical processes that can be induced at different temperatures. The properties are tunable over a broad range and the products are used in many general and high technology applications. The development will certainly continue, particularly in view of the current need for new materials (e.g., in the energy sector).

Acknowledgments Research on polybutadiene functionalization at the University of Hamburg was supported by LEXI "Key Technologies for Sustainable Energy Systems in Smart Grids".

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