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Development of a Library of *N*-Substituted Maleimides for the Local Functionalization of Linear Polymer Chains

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Abstract: A novel kinetic process was investigated for functionalizing "on-demand" local regions of well-defined linear polystyrene chains. This concept relies on the atom transfer radical copolymerization (ATRP) of functional *N*-substituted maleimides with styrene. This copolymerization is a controlled radical process, which combines two unique kinetic features: i) all the polymers chains are growing simultaneously and ii) the cross-propagation of the comonomers is highly-favored as compared to homopolymerization. Thus, discrete amounts of *N*-substituted maleimides (e.g., 1 equiv as compared to initiator) are consumed extremely fast in the copolymerization process and are therefore locally incorporated in narrow regions of the growing polystyrene chains. MALDI-TOF analysis of model copolymers indicated that this kinetic concept is efficient. Although a sequence distribution is observed, well-defined polymer chains having only one or two functional maleimide units per chain were found to be the most abundant species. Furthermore, the position of the functional groups in the polystyrene chains can be kinetically-controlled by adding the *N*-substituted maleimides at desired times during the course of the polymerization. This method is very versatile and can be applied to a wide variety of *N*-substituted maleimides. Herein, a library of 20 different maleimides bearing various functional groups (e.g., aromatic moieties, fluorinated groups, hydroxy functions, protected esters, protected amines, light-responsive moieties, fluorophores and biorelevant functions such as short poly(ethylene glycol) segments or biotin moieties) was investigated. In most cases, the functional *N*-substituted maleimides could be efficiently incorporated in the polystyrene chains.

Keywords: macromolecular engineering · polymerization · polymers

Introduction

The control of macromolecular structure is one of the main topics in polymer chemistry today.[1] Very important advances have been accomplished in this field of research over the past decades, in particular since the emergence of living-polymerization methods such as anionic polymerization and controlled radical polymerizations.[2,3] For instance, considerable progress has been made in controlling polymer topology (i.e., the shape of synthetic macromolecules). Nowadays, complex architectures, such as block copolymers, graft copolymers, stars, miktoarm stars, macrocycles and macromolecular brushes, can be routinely synthesized via a variety of synthetic routes.[4,5] On the other hand, relatively little work have been done for controlling the microstructure (i.e., tacticity and monomer sequences) of synthetic polymers, even though this aspect is of particular scientific relevance. For example, polymers with controlled microstructures play a key role in nature. Indeed, the whole complexity of the biological world relies principally on sequence-defined biopolymers such as proteins and nucleic acids. In the same way, one may think that synthetic macromolecules with tailor-made microstructures may open new avenues for the design of highly-organized nanomaterials.

Only a few experimental processes allow efficient synthesis of sequence-defined macromolecules. The most commonly used strategy is the step-by-step solid-phase synthesis introduced by Merrifield in the early 1960s.[6] In this approach, bifunctional monomers are sequentially linked one to another using successive reaction/purification cycles on a solid support. This method has been principally applied for synthesizing sequence-defined biopolymers such as oligopeptides, oligonucleotides and oligosaccharides.[7] However, this strategy can be theoretically extended to any kind of step-growth polymerizations. For instance, solid-phase synthesis

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has been explored for preparing new types of sequence-defined polymers such as peptide-nucleic acids, oligoureas, oligocarbamates, oligoesters, polyamides and polyamidoamines.[8]

Controlling monomer sequences in a chain-growth polymerization (i.e., polymerizations consisting of chain-initiation and chain-propagation steps) is, theoretically speaking, much more challenging than in a step-growth process.[9] Indeed, propagation steps rely on highly reactive transient species (e.g., radicals or ions), which are difficult to tame. Thus, chain copolymerizations are in general statistical processes leading to random microstructures.

However, in some rare cases, sequences can be controlled. One interesting exception is, for example, the radical copolymerization of styrene with cyclic monomers such as maleic anhydride or *N*-substituted maleimides. In such copolymerizations, the cross-propagation (i.e., the reaction of one comonomer with the other) is exceptionally favored as compared to homopolymerization.[10] Thus, conventional- or controlled-radical polymerizations (CRP) of these comonomer pairs typically lead to perfectly sequence-defined alternating copolymers.[11] In fact, this tendency toward alternation is so pronounced that even for comonomer feeds containing high excess of styrene, the cross-propagation still occurs in the early stages of the reaction, followed by the homopolymerization of the excess of styrene. For instance, Hawker and Russell elegantly demonstrated that, if combined with a CRP process (i.e., a living-polymerization mechanism, in which all chains grow simultaneously), this kinetic behavior could result in the formation of well-defined block copolymers composed of short copolymer sequences connected to long polystyrene segments.[12]

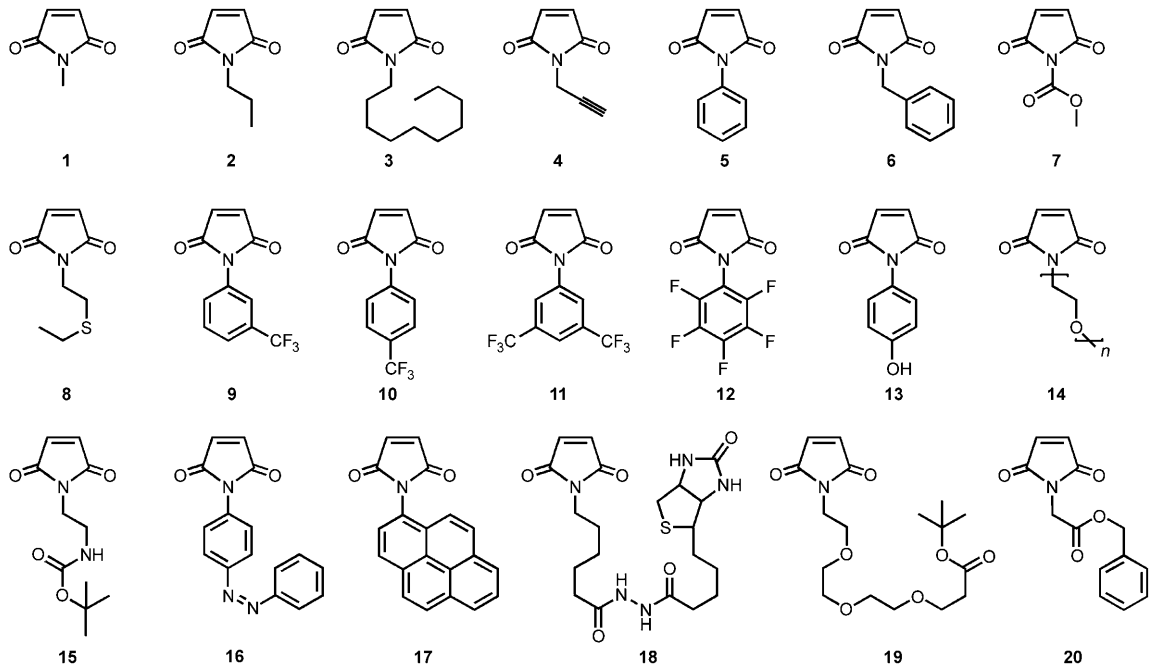
We recently pushed this concept further and reported a novel sequential copolymerization strategy for preparing macromolecules with programmed sequences of functional comonomers.[13] This concept relies on the controlled sequential addition of various functional *N*-substituted maleimides (MI) during the atom transfer radical polymerization (ATRP) of styrene (S). As a first proof of concept, four different *N*-substituted maleimides have been sequentially incorporated in growing polystyrene chains using this simple kinetic concept. Indeed, the formed copolymers are not strictly sequence-defined at the molecular level (i.e., they still exhibit a sequence distribution). However, they undoubtedly possess a pre-programmed distribution of functional side-groups along the polymer backbone.[13]

The goal of the present article is to explore further the potential of this novel kinetic strategy for preparing well-defined functional polymers. In particular, three main aspects are addressed in this manuscript: i) the possibility of adding a discrete functional group into a precise region of the polystyrene chains, ii) the shape of the resulting sequence-distribution (i.e., how many functional moieties are incorporated in average in each chain) and iii) the versatility of this approach. To demonstrate this last point, a complete library of functional *N*-substituted maleimides (Scheme 1) was developed and studied. The atom transfer radical copolymerization of these various monomers with styrene was studied in details using ^{1}H NMR, SEC and MALDI-TOF measurements.

Results and Discussion

Synthesis of *N*-substituted maleimides: The main objective of this study is to demonstrate that functional maleimides constitute a unique and versatile platform for functionalizing polystyrene chains. Thus, a wide variety of *N*-substituted maleimides were synthesized and tested in the present work (Scheme 1). Numerous synthetic strategies have been reported in the literature for synthesizing *N*-substituted maleimides. The most commonly used method is the reaction of maleic anhydride with primary amine derivatives leading to maleamic acid intermediates, which are subsequently dehydrated into the corresponding cyclic maleimides. Several variations of this main method have been described within past years. However, other straightforward routes can be utilized. Another convenient pathway involves, for example, the direct reaction of primary amine derivatives with *N*-methoxycarbonyl maleimide.[14] This straightforward method leads in one step to *N*-substituted maleimides in relatively high yields. Alternatively, an elegant Mitsunobu was reported by Walker in the mid 1990s. In this approach, alcohol derivatives are reacted with maleimide in the presence of triphenylphosphine and a dialkyl azodicarboxylate.[15] Still, most of the structures presented in Scheme 1 have been synthesized using the conventional reaction of maleic anhydride and primary amines (see Experimental Section).

Our library of *N*-substituted maleimides contains 20 model compounds, which exhibit different types of functional moieties. The simplest structures carry alkyl- or aryl- substituents. For instance, *N*-methyl maleimide (**1**), *N*-propyl maleimide (**2**), *N*-decyl maleimide (**3**), *N*-phenyl maleimide (**5**) and *N*-benzyl maleimide (**6**) were investigated in the present work. *N*-propargyl maleimide (**4**) was selected as a model for reactive moieties. Indeed, terminal acetylene functions have become lately very popular in polymer and materials science as they can easily be involved in practical reactions such as Sonogashira coupling or copper-catalyzed azide-alkyne Huisgen cycloaddition.[5,16] The structures **8**–**12** are examples of functional maleimides bearing heteroatoms (i.e., thioether, trifluoromethyl and perfluorophenyl functions). The *N*-substituted maleimides **13**, **15**, **19**, and **20** were designed for incorporating functional groups such as alcohols, amines or carboxylic acids into polystyrene backbones. Indeed, the functionalization of apolar polymer backbones with polar reactive functions is of prime importance in polymer synthesis. However, free carboxylic acids, primary amines or secondary amines are usually problematic in ATRP as they may interact with transition metal catalysts.[3] Thus, protected structures should be used in ATRP. For instance, the amine function in **13** was protected by a *t*Boc functionality, whereas the acid groups of **19** and **20** were transformed into labile esters (i.e., *tert*-butyl ester and



Scheme 1. Library of *N*-substituted maleimides investigated in the present work for functionalizing "on demand" well-defined polystyrene chains.

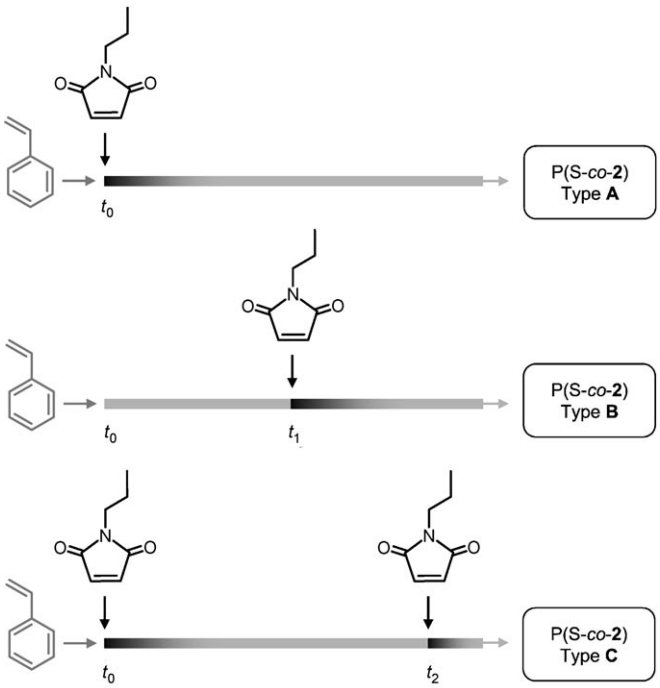
benzyl ester, respectively). The controlled radical copolymerization of functional maleimides with styrene could also be used for incorporating specific substituents (e.g., fluorescent dyes, stimuli-responsive moieties, surface anchors) at precise locations in well-defined polystyrene chains. As examples, the light-responsive monomer *N*-(4-azobenzene) maleimide (**16**) and the fluorescent monomer *N*-(1-pyrenyl) maleimide (**17**) were studied. The *N*-substituted maleimides **14** and **18** contain biorelevant moieties such as a short hydrophilic oligo(ethylene glycol) segment and a biotin moiety. The latter is a standard bio-linker, which binds with larger glycoproteins such as avidin or streptavidin.[17]

Model copolymerizations: The concept for local chain-functionalization investigated in this paper relies on the atom transfer radical copolymerization of large excess of styrene (i.e., 100 equiv) with discrete amounts of functional maleimides (i.e., 1 equiv). As styrene/maleimides comonomer pairs generally exhibit exceptionally high cross-propagation rates, this strategy theoretically allows a fast and local incorporation of the *N*-substituted maleimides in the growing polystyrene chains. In order to demonstrate the feasibility of this kinetic strategy, two model monomers *N*-propyl maleimide (**2**) and *N*-benzyl maleimide (**6**) were first examined. Both monomers exhibit a very strong tendency toward alternation with styrene. For instance, the reactivity ratios measured for the radical copolymerization of **6** and styrene were reported to be 0.013 and 0.058, respectively.[18]

At first, the kinetics of model batch copolymerizations were studied. In these cases, the functional maleimide (**2** or **6**) and styrene were added together at the beginning of the polymerization (Scheme 2, top). The atom transfer radical copolymerizations were performed at 110 °C in the presence of the initiator 1-bromoethyl benzene and the catalyst combination copper(I) bromide/4,4′-dinonyl-2,2′-bipyridine.[19] Several samples were taken during the course of the copolymerization and were analyzed by ^{1}H NMR spectroscopy.[20,21]

In all copolymerizations, it appears that, although present in very low amounts, the *N*-substituted maleimides are effectively consumed much faster than styrene. For instance, after 10 minutes of polymerization, the conversion of the maleimides was found in all cases to be above 99 %, whereas the conversion of styrene was below 10 %. After that point, the homopolymerization of styrene was solely observed. After purification and isolation, the final copolymers exhibited a controlled molecular weight and a narrow molecular weight distribution (i.e., $M_w/M_n < 1.2$). Moreover, ^{1}H NMR spectroscopy confirmed the presence of functional moieties (i.e., propyl or benzyl groups) in the purified polymer chains. For P(S-*co*-**2**) a broad signal due to the methylene protons neighboring the imide function was observed at δ 3–3.4 ppm, whereas for P(S-*co*-**6**), the same types of protons resonated at 4.1–4.6 ppm.[13]

Moreover, these kinetic data strongly suggest that the functional moieties are effectively locally incorporated close to the α-extremity of the polymer chains. Indeed, it was demonstrated in previous publications that in these particular experimental conditions: i) the initiation step takes place in less than 5 min, ii) transfer reactions are kinetically negligible and iii) experimental molecular weight increases linearly with monomer conversion.[20] Thus, all chains grow simultaneously in this copolymerization process and therefore incorporate the functional maleimides at the early stages of



Scheme 2. Synthetic strategies for preparing well-defined model copolymers P(S-*co*-**2**) with different sequence distributions: (top) direct atom transfer radical copolymerization of 100 equiv styrene and 1 equiv **2**; (middle) controlled addition of 1 equiv of **2** during the ATRP of styrene (100 equiv); (bottom) atom transfer radical copolymerization of styrene and **2** (100:1) with controlled addition of 1 equiv **2** at the end of the polymerization.

their formation. These results are in very good agreement with the data reported by Hawker and co-workers for the nitroxide mediated copolymerization of styrene and maleic anhydride.[12]

Yet, these kinetic data do not imply that all copolymer chains exhibit a single maleimide monomer unit. The copolymers are prepared via a chain-growth polymerization process and should therefore exhibit a chain-composition distribution.

The shape of the sequence distribution of models copolymers P(S-*co*-**2**) and P(S-*co*-**6**) was investigated by MALDI-TOF mass spectrometry. Both copolymers were ionized from a dithranol matrix using NaI as a cationization salt.[22] However, MALDI-TOF copolymerization spectra should be cautiously interpreted as some comonomer combinations may overlap. For example, the molar mass of four styrene units coincides with that of three units of **2**. Hence, the MALDI-TOF spectrum of P(S-*co*-**2**) did not allow a detailed characterization of the sequence-distribution. On the other hand, the spectrum of P(S-*co*-**6**) gave substantial information about the copolymerization process (Figure 1). At a first glance, the spectrum appears quite complex, but is in fact rather simple to interpret. Indeed, a single type of polymer chain was observed in this spectrum (the proposed molecular structure is shown in Figure 1). An excellent agreement between measured and calculated isotopic distributions (Figure 1, bottom-right) was observed for this particular type of macromolecules. These chains contain an initiator α-moiety, a variable amount of styrene and benzyl maleimide monomer units and an unsaturated moiety at the ω-chain end. The latter point should be briefly discussed as this terminal double bond could result from a HBr elimination step occurring either during the course of the copolymerization or during the MALDI ionization process. Although both scenarios were described in the literature,[20,23,24] in the present case the elimination mostly takes place during the ionization step. Indeed, the model copolymerizations for MALDI-TOF analysis were stopped at an early polymerization stage (i.e., conversion of styrene of approximately 25%), where elimination processes are kinetically disfavored.[20] Thus, after copolymerization and purification, the ^{1}H NMR spectra of the formed copolymers clearly exhibit a broad chain-end signal at δ 4.3–4.65 ppm, which corresponds to protons neighboring terminal bromine atoms (i.e., standard bromine-capped ATRP chains).[20,21,25] Hence, as previously described in the literature, the elimination of HBr obviously occurs upon ionization.[24]

Five main series of peaks, which correspond to polystyrene chains containing 0, 1, 2, 3 or 4 maleimide moieties, were observed in the MALDI-TOF spectrum of P(S-*co*-**6**). The intensities of these different series reflect the sequence distribution of the copolymers. For example, the zoom in Figure 1 (top-right) compares the intensity of chains possessing 20 styrene units (including initiator moiety and unsaturated end-group). It appears clearly that the nonfunctionalized chains (i.e., no maleimide in the backbone) or overfunctionalized chains (i.e., polymers containing three or more maleimides) are minor components of the sequence distribution. For instance, the peak corresponding to chains with four maleimides (m/z 2852) is barely distinguishable. Thus, copolymer chains with five maleimides or more are probably absent or only present in traces in this distribution.[26] In fact, the most intense peaks correspond to copolymer chains with 1 (i.e., the desired microstructure) or 2 functional maleimides. Chains with a single functional maleimide are predominant in the low molecular-weight part of the spectrum (i.e., $m/z < 3000$), whereas chains with two maleimides are more abundant in the high-molecular weight region. The latter is probably due to bimolecular coupling terminations.[20] Nevertheless, these MALDI-TOF data indicate a sequence-controlled copolymerization of styrene and **6** leading to a relatively narrow sequence-distribution.

Thus, this copolymerization concept can be pushed further and used for functionalizing polystyrene chains at different location of their backbones. For instance, Scheme 2 highlights different copolymerization strategies studied in the present work. The *N*-substituted maleimides can be added at the beginning of the reaction (copolymerization of type A, see above) but also at any time during the course of the ATRP of styrene (copolymerization of type B). The latter scenario should allow a precise inner-functionalization of the polystyrene chains. For example, functional maleimides could be precisely incorporated in the middle of the polymer backbones. This challenging case was studied using

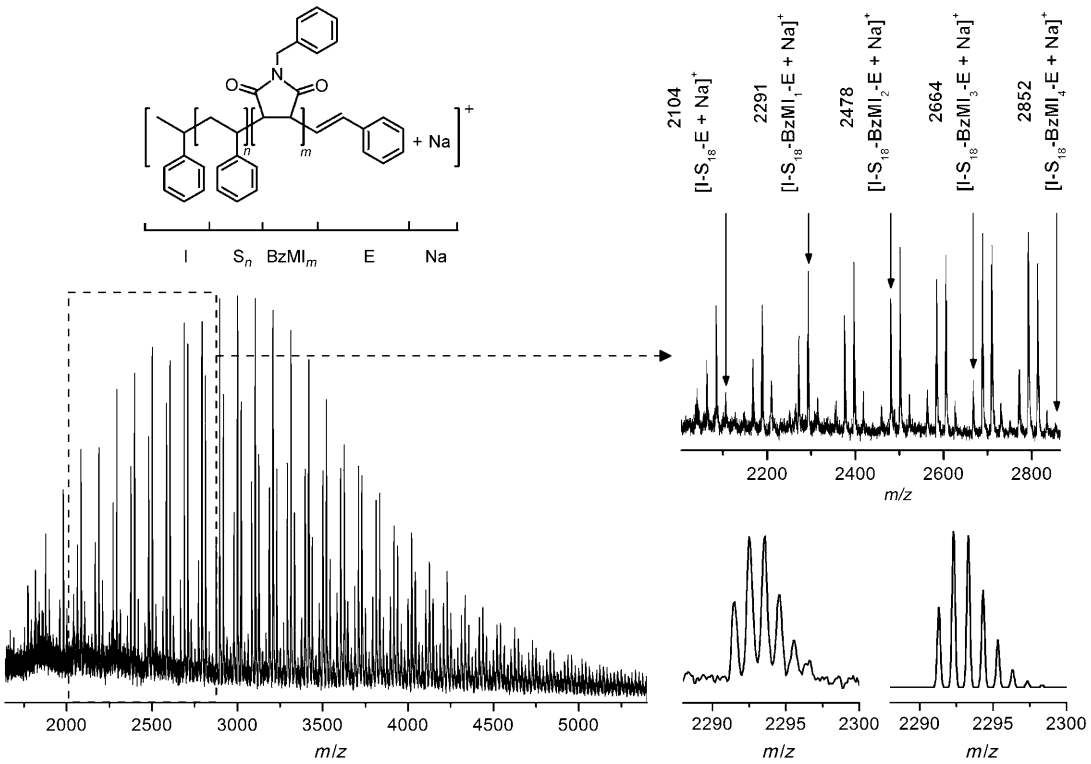


Figure 1. MALDI-TOF spectrum measured for a model copolymer P(S-*co*-**6**) prepared using ATRP. The spectrum was recorded from a dithranol matrix and in the presence of NaI as a cationization agent. The Scheme shows the probable molecular structure of the ionized polystyrene chains. The acronyms I, S, BzMI and E stand for initiating moiety, styrene, *N*-benzyl maleimide and elimination moiety, respectively. The spectrum on top-right shows a zoom of the region *m*/*z* 2005–2865. The two spectra on bottom-right compare the shape of the measured (left, zoom of the region *m*/*z* 2288–2300 of the main spectrum) and calculated (right) isotopic distribution for the copolymer structure $[I-S_{18}-BzMI_1-E+Na]^+$.

^{1}H NMR (Table 1, type B). The atom transfer radical polymerization of styrene was first started in the absence of **2**. Thus, a polystyrene homopolymer was grown up to a styrene conversion of 35%. At this stage of the reaction, 1 equiv **2** was added in the reaction mixture (most the *N*-substituted maleimides are solids and should therefore be dissolved in small amounts of degassed toluene prior to addition). The NMR monitoring of the copolymerization confirmed that the copolymerization of styrene and **2** is kinetically favored as compared to styrene homopolymerization. One hour after its addition, the conversion of **2** was found to be almost quantitative, whereas styrene conversion increased only by a few percent. After that point, styrene was homopolymerized up to 80% conversion. These kinetic data suggest that the functional maleimide were effectively incorporated in the middle of the polystyrene chains. Furthermore, the final copolymer exhibits a controlled molecular weight (experimental molecular weight was found to be 9060 g mol^{-1}, whereas theoretical molecular weight is 8660 g mol^{-1}) and a narrow molecular weight distribution ($M_w/M_n = 1.21$).

Table 1. Characterization of copolymers P(S-*co*-**2**) with different microstructures.

Type[a]	*t* [min]	$Conv._S$[b] [%]	$Conv._{MI}$[b] [%]
B	0	0	–
B	78	34.5	–
addition of 1 equiv of **2**			
B	108	39.2	75
B	138	42.1	>99
B	1380	80.2	>99
C	0	0	0
C	85	61.8	>99
addition of 1 equiv **2**			
C	300	77	>99

[a] See Scheme 1 for cartoons. Type B: controlled addition of 1 equiv **2** during the ATRP of styrene (100 equiv); Type C: atom transfer radical copolymerization of styrene and **2** (100/1) with controlled addition of 1 equiv **2** at the end of the polymerization. In all cases: 110 °C, styrene/initiator/CuBr/dNbipy = 100/1/1/2. [b] Monomer conversions measured by ^{1}H NMR.

More complex chain-functionalization scenarios may be performed via styrene/maleimide copolymerization approaches. For instance, polystyrene chains can be functionalized on both extremities. Such types of chains could be obtained by two different strategies: i) the homopolymerization of styrene is first started in the presence of a difunctional ATRP initiator and a *N*-substituted maleimide is added in the reaction medium at the end of the reaction (i.e., at high styrene conversion), ii) the ATRP of 100 equiv styrene and 1 equiv maleimide is first started and a second equivalent of the maleimide is added at the end of the reaction (Scheme 2, copolymerization of type C). The latter approach

is probably more versatile as it allows a hetero-functionalization of the polystyrene chains (i.e., two different maleimides can be used for functionalizing the chains).[13] Thus, the feasibility of this approach was studied using **2** as a model maleimide (Table 1, type C). The bulk ATRP of styrene and **2** was first started. As described above, the small amount of functional maleimide was incorporated in the chain in the early instants of the copolymerization (i.e., within the first 10 units of the polymer chains). Afterwards, styrene was allowed to homopolymerize up to a conversion of approximately 60%. At this stage, a second equivalent of **2** was added in the reaction medium and the copolymerization was pursued for several hours. The ^{1}H NMR monitoring of the copolymerization indicated that this additional equivalent of **2** was quantitatively incorporated within the last 15 monomer units of the polymer chains (Table 1). Furthermore, the resulting copolymer exhibited a well-defined molecular structure ($M_n = 8920\ g\,mol^{-1}$, $M_w/M_n = 1.14$).

"On demand" functionalization of polymer chains: It was demonstrated in the previous paragraph that model *N*-substituted maleimides allow a precise local functionalization of polystyrene chains. Thus, it was tempting to extend this straightforward concept to a wide variety of functional maleimides (Scheme 1). The bulk ATRP of styrene was investigated in the presence of various *N*-substituted maleimides (Table 2). In all cases, styrene (100 equiv) and maleimides (1 equiv) were mixed before reaction (copolymerization of type A) and atom transfer radical copolymerizations were performed at 110°C in the presence of the initiator 1-bromoethyl benzene and the catalyst combination copper(I) bromide/4,4′-dinonyl-2,2′-bipyridine.

In most cases, well-defined copolymers with a controlled molecular weight and a narrow molecular weight distribution were obtained (Table 2). Moreover, for several maleimides (e.g., **1**–**4**, **6**–**8**, **15**–**17** and **20**), the favored cross-propagation with styrene was experimentally verified. Indeed, the ^{1}H NMR analysis of reaction samples taken at the early stages of the copolymerization indicated a fast incorporation of the *N*-substituted maleimides in the growing polymer chains. In general, methylene protons neighboring the imide function, which typically resonate in the region δ 3–4 ppm, were followed by NMR. However, for maleimides **7**, **16** and **17**, methyl ester protons at 3.93 ppm, azobenzene protons at 7.9–8.05 ppm and pyrene protons at 7.8–8.3 ppm were studied, respectively. In some other cases (e.g., **5**, **9**–**12** and **13**), the kinetics of copolymerization could not be monitored by NMR as maleimide peaks lie under polystyrene signals. Nevertheless, in these particular cases, the successful incorporation of the functional maleimides in the chains was confirmed by NMR analysis of the purified copolymers. For example, ^{19}F NMR was used for characterizing copolymers containing fluorinated functions. Typical signals due to monomers **9** (−63.1 ppm), **10** (−63.2 ppm), **11** (−63.5 ppm) and **12** (−142.5, −151.6 and −161.3 ppm) were observed in the polymer spectra.[27]

Table 2. Characterization of copolymers P(S-*co*-MI) synthesized by ATRP.[a]

MI	Conv.$_{S\ 1h}$[b] [%]	Conv.$_{MI,\ 1h}$[b] [%]	Conv.$_{S,\ 5h}$[c] [%]	M_n[d] [g mol^{-1}]	M_w/M_n[d]
1	21.6	>99	50.7	5500	1.06
3	34	>99	61.6	6800	1.24
4	20.2	>99	28.2	5100	1.70
5	28.7	[f]	≈45[e]	5100	1.21
7	8.4	>99	≈20[e]	3600	1.16
8	31.6	>99	43.8	4870	1.19
9	–	[f]	75.6	8850	1.10
10	–	[f]	75.5	8800	1.13
11	–	[f]	59.8	6150	1.07
12	10	[f]	22.3	2700	1.21
13	6.8	[f]	14.7	2100	1.19
14	13	[f]	26.8	3300	1.23
15	23.2	>99	41.5	4600	1.24
16	26.9	>99	52.2	5900	1.22
17	10.2	>99	35.5	4050	1.28
18	–	–	51.1	4850	1.14
19	–	–	85.3	9700	1.14
20	32.2	>99	83.4	9400	1.13

[a] Experimental conditions: bulk, 110°C, S/MI/PEB/CuBr/dNbipy = 100/1/1/1/2. The acronyms S, MI and PEB stand for styrene, *N*-substituted-maleimide and 1-phenyl ethyl bromide (a.k.a. (1-bromoethyl) benzene), respectively. [b] Monomer conversions measured by ^{1}H NMR after 1 hour of polymerization. [c] Monomer conversions measured by ^{1}H NMR (unless noted) after 5 h of polymerization. [d] Measured by SEC in THF. [e] Determined gravimetrically. [f] No specific ^{1}H NMR peak allowing calculation of MI conversion.

For maleimide **14**, distinct signals due to the methyleneoxy (3.64 ppm) and methoxy protons (3.38 ppm) of polyethylene glycol can be seen throughout the reaction. However, these broad oligomeric signals do not allow calculation of the maleimide conversion (i.e., monomer and polymer signals are indistinguishable from another). Yet, the incorporation of this macromonomer in the growing chains was experimentally confirmed by the ^{1}H NMR spectrum of the purified copolymers (Figure 2).

A few monomers of the library were found to be problematic and obviously interfered with the polymerization

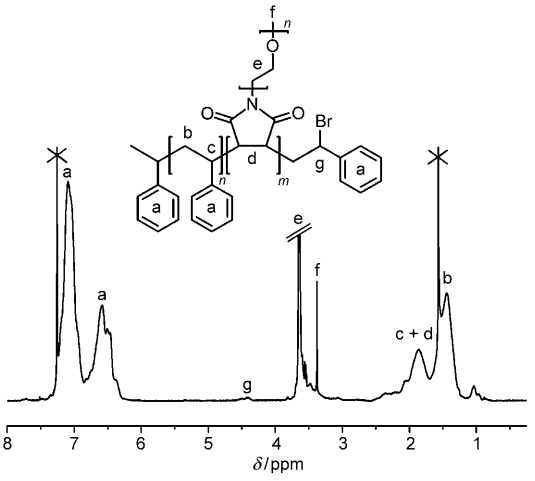


Figure 2. ^{1}H NMR spectrum of a purified well-defined copolymer P(S-*co*-**14**) (Table 2, entry 14) recorded at room temperature in $CDCl_3$.

process. For example maleimide **4** led to the formation of ill-defined copolymers with a broad molecular weight distribution (i.e., bimodal SEC traces). This behavior is probably due to coupling reactions induced by the terminal acetylene functions.[28] Some authors already reported that monomers bearing unprotected alkynes may affect radical polymerizations.[29] Yet, this problem can be easily solved by using trimethylsilyl-protected alkynes. Copolymerizations in the presence of maleimide **13** proceeded in rather low yields. This polymerization behavior is most probably due to a phenol-induced inhibition of the radical propagation. Nevertheless, as previously reported, **13** can be polymerized to some degree in a free-radical process.[30] Monomer **18** exhibited a low solubility in apolar medium. Thus, the bulk copolymerization of styrene and **18** was heterogeneous and led to very low maleimide incorporation in the polymer chains. Homogeneous copolymerizations could be performed using *N*,*N*-dimethylformamide as a cosolvent. However, in homogeneous medium, **18** obviously interfered with the ATRP catalyst (experiments turned rapidly dark green and no polymerization was observed). This problem is probably due to the hydrazide function of this commercial maleimide and could be solved by selecting other types of linkers.

Conclusion

The controlled/living radical copolymerization of styrene and *N*-substituted maleimides is a straightforward and versatile approach for functionalizing "on demand" well-defined polystyrene chains. Due to the kinetically favored cross-propagation of styrene/maleimide comonomer pairs, discrete amount of functional maleimides are rapidly incorporated in narrow regions of the growing polystyrene chains. Thus, the microstructure of the polymers can be precisely controlled by adding maleimides at different stages of the reaction. SEC, NMR and MALDI-TOF confirmed that the formed copolymers exhibit a controlled molecular weight, a narrow molecular weight distribution and a controlled sequence distribution. Moreover, a wide library of *N*-substituted maleimides can be used as functional comonomers. Hence, this simple kinetic strategy appears as a "universal" platform for functionalizing polystyrene chains.

Experimental Section

General: ^{1}H, ^{13}C and ^{19}F NMR were recorded in $CDCl_3$ with 300 and 400 MHz Bruker Avance instruments. Molecular weights and molecular weight distributions were determined by SEC performed at 25 °C in tetrahydrofuran (THF) as eluent (flow rate: 1 mL min^{-1}), using three SDV columns (Polymer Standards Service GmbH) with a particle size of 5 μ and a porosity of 10^3, 10^5 and 10^6 Å (the porosity values do not correspond to real pore diameters but to manufacturer standards). The detection was performed with a RI- (Shodex RI-71) and a UV detector (TSP UV 1000; 260 nm). For calibration, linear polystyrene standards (Polymer Standards Service GmbH) were used. MALDI-TOF measurements were performed on a Bruker Reflex II (Bruker Daltonik, Bremen, Germany) in the positive ion and reflection mode using external calibration (ACTH). Dithranol was used as a matrix (10 mg mL^{-1} in THF). Matrix, ionization agent (NaI), and polymer sample were mixed in a 10:1:1 ratio. A volume of 0.3 μL of the mixed solution was applied on the target. Copper(I) bromide (Acros, 98%), styrene (Aldrich, 99%), (1-bromoethyl) benzene (Acros, 97%), 4,4′-dinonyl-2,2′-bipyridine (dNbipy) (Aldrich, 97%), 2,2′-bipyridyl (Fluka, 98%), *N*-methyl maleimide (**1**) (Aldrich, 97%), *N*-propyl maleimide (**2**) (Aldrich, 95%), *N*-phenyl maleimide (**5**) (Fluka, 98%), *N*-benzyl maleimide (**6**) (Aldrich, 99%), *N*-methoxycarbonyl maleimide (**7**) (Fluka, 97%), α-methoxy-ω-maleimide polyethylene glycol (**14**) (M_n = 750 g mol^{-1}, Rapp Polymere GmbH), *N*-(4-azobenzene) maleimide (**16**) (Aldrich, 97%), *N*-(1-pyrenyl) maleimide (**17**) (Sigma, 99%) and *N*-biotinoyl-*N*′-(6-maleimidohexanoyl)-hydrazide (**18**) (Sigma, 95%) were used as received. *N*-Decyl maleimide (**3**), *N*-propargyl maleimide (**4**),[31] *N*-(3-trifluoromethylphenyl) maleimide (**9**),[27] *N*-(4-trifluoromethylphenyl) maleimide (**10**),[27] *N*-[3,5-bis(trifluoromethyl)phenyl] maleimide (**11**),[27] *N*-pentafluorophenyl maleimide (**12**),[27] *N*-(4-hydroxyphenyl)maleimide (**13**),[32] *N*-(2-(amino-Boc)ethylen)maleimide (**15**) [14] and benzyl *N*,*N*-maleoylglycinate (**20**)[33] were synthesized according to published procedures.

General procedure for the atom transfer radical copolymerization of styrene and *N*-substituted maleimides: Copper bromide (1 equiv) and 4,4′-dinonyl-2,2′-bipyridine (2 equiv) were added into a Schlenk tube. The tube was sealed with a septum and subsequently purged with dry argon for a few minutes. Then, degassed styrene (100 equiv) was added with a degassed syringe through the septum. The mixture turned dark brown, indicating complexation of $Cu^{I}Br$ and dNBipy. Lastly, (1-bromoethyl) benzene (1 equiv) was added with a precision syringe. The mixture was heated at 110 °C in an oil bath for several hours. The functional *N*-substituted maleimides (monomers **1**–**20**, 1 equiv) were added at different stages of the styrene polymerization, depending on the targeted microstructure. In most cases, the maleimides were present when the polymerization started (i.e., they were introduced in the flask at the same time as $Cu^{I}Br$ and dNBipy). In some other cases, they were introduced during the course of the polymerization through the septum with a degassed syringe (most of the studied *N*-substituted maleimides are solids and should therefore be dissolved in small amounts of degassed toluene prior to addition).

***N*-(2-Ethylthio ethyl)maleimide (8)**: Maleic anhydride (900 mg, 9.18 mmol), 2-ethylthio ethylamine (962 mg, 9.18 mmol), and glacial acetic acid (9 mL) were added into a dry, argon purged three neck flask with cooler and stirred first under mild reflux at 50 °C for 4 h, then overnight at RT. After reaction, acetic acid was removed by rotary evaporation. Then, the product was precipitated in water and dried. The resulting compound *N*-(2-ethylthio ethyl)maleamic acid was used without further purification and added with toluene (40 mL, water free), *p*-toluene sulfonic acid (0.26 g, 1.38 mmol), zinc acetate (0.5 mg, 0.003 mmol), and hydroquinone (1.0 mg, 0.01 mmol) into a 100 mL-round bottom flask with a water separator and cooler. The mixture was refluxed for 6 h and stirred at RT overnight. After adding *p*-toluene sulfonic acid (0.12 g) for acid treatment, the mixture was heated again to 70 °C for 1 h. The mixture was allowed to cool down to RT and filled into a separation funnel together with toluene and water. The organic phase was extracted, washed with water (5 × 50 mL) and dried over Na_2SO_4. The solvent was removed by rotary evaporation. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (s, 2H, CH=CH), 3.72 (t, 2H; C*H*$_2$-CH$_2$-S), 2.74 (t, 2H; CH$_2$-C*H*$_2$-S), 2.58 (q, 2H; C*H*$_2$-CH$_3$), 1.26 ppm (t, 3H; CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5 (2C, C=O), 134.2 (2C, CH=CH), 36.9 (1C, *C*H$_2$-CH$_2$-S), 29.5 (1C, CH$_2$-*C*H$_2$-S), 25.4 (1C, *C*H$_2$-CH$_3$), 14.5 ppm (1C, CH$_2$-*C*H$_3$); ESI-MS: *m*/*z*: calcd for $C_8H_{12}NO_2S$: 186:06; found: 186.0591 $[M+H]^+$.

***tert*-Butyl 3-[2-(2-(2-maleimidoethoxy)ethoxy)ethoxy]propionate (19)**: *tert*-Butyl 3-[2-(2-(2-aminoethoxy)ethoxy)ethoxy] propionate (1 g, 2.9 mmol) and toluene (50 mL) were added into a dry, argon purged, three-neck round bottom flask equipped with a Dean–Stark apparatus. Then, maleic anhydride (0.34 g, 3.4 mmol) was added and the mixture was heated at 70 °C for 30 minutes. Afterwards, zinc acetate (1.2 mg, 6.54 μmol) and hydroquinone (0.6 mg) were added and the mixture was heated at reflux over night. After some hours of reaction, *p*-toluenesulfonic acid monohydrate (0.05 g, 0.26 mmol) was added. After reaction,

the mixture was allowed to cool down to RT and filled into a separation funnel together with ethyl acetate (20 mL) and water (30 mL). The organic phase was extracted and washed with water (3×20 mL). The aqueous phases were combined, saturated with NaCl and extracted with diethyl ether (3×20 mL). The organic phases were combined and dried over Na_2SO_4. Solvents were removed by rotary evaporation. The crude product was purified on a silica gel column using hexane/ethyl acetate 3:7. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (s, 2H; CH=CH), 3.54–3.79 (m, 14H; CH_2-O and CH_2-N), 2.50 (t, 2H; CH_2-COO), 1.45 ppm (s, 9H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.90 (1C, COO), 170.63 (2C, CO-N), 134.15 (2C, CH=CH), 80.50 (1C, $C(CH_3)_3$), 70.1–70.6 (4C, CH_2-O), 67.83 (1C, CH_2-CH_2-N), 66.92 (1C, CH_2-CH_2-COO), 37.18 (1C, CH_2-N), 36.31 (1C, CH_2-COO), 28.12 ppm (3C, CH_3); ESI-MS: *m*/*z*: calcd for $C_{17}H_{27}NO_7Na$: 380.17; found: 380.1697 $[M+Na]^+$.

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