

Modular synthesis of block copolymers *via* cycloaddition of terminal azide and alkyne functionalized polymers†

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Polymeric building blocks containing terminal azide and alkyne functionalities are prepared *via* atom transfer radical polymerization (ATRP) and used to modularly synthesize block copolymers *via* 1,3-dipolar cycloaddition reactions, which are quantitative according to SEC measurements.

Recently, Sharpless *et al.* have optimized Huisgen's 1,3-dipolar cycloaddition of azides and terminal alkynes *via* copper(I) catalysis.¹ This type of "click" reaction can be characterized as highly efficient and specific, with the starting materials being very stable to other functional groups.²

This "click" chemistry has nowadays also been introduced in dendrimer and polymer synthesis³ and utilized to cross-link block copolymer vesicles.⁴ The great potential of this coupling procedure for the construction of well defined (functional) polymer architectures has been quickly recognized, and is the subject of intensive research. One of the until now still unexplored possibilities is to use this method to modularly synthesize block copolymers.

Nowadays, a wide range of "living" or controlled polymerization techniques is available to prepare block copolymers of various architectures, solubility and functionality, *via* consecutive polymerization of different monomers. These polymerization techniques comprise "living" ionic⁵ and "living" radical polymerizations.^{6–8} Various techniques can also be combined to synthesize a myriad of block copolymer structures.⁹ The disadvantages of this so-called macroinitiation approach are that complete formation of block copolymers is hard to assess and characterization of the individual blocks is very difficult.

These problems can be circumvented by applying a modular approach for the synthesis of block copolymers. Polymeric blocks bearing functional end groups are prepared separately and are linked covalently *via* their end groups. This approach enables full analysis (*e.g.* molecular weight distribution) of the separate blocks prior to coupling. A major disadvantage however of this method is that in order to have a high yield coupling reaction, reactive end groups have to be used that therefore are prone to undergo side reactions, which limits the scope of the modular approach.

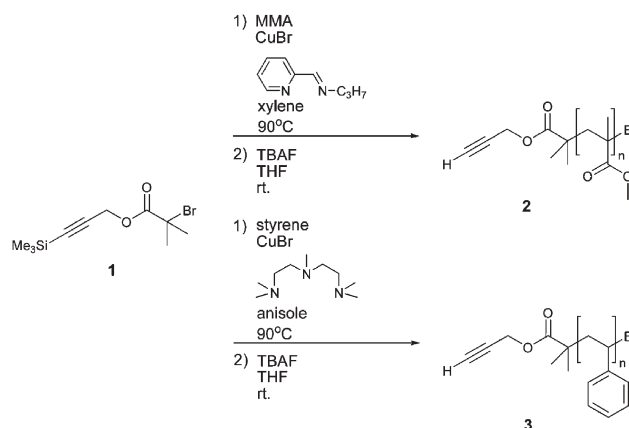
Here we report a novel modular strategy for the preparation of block copolymers by applying stable alkyne and azide end groups that are activated during the coupling process, circumventing the problem of loss of functionality. Additionally, in ATRP, end

group functionality can be introduced either by utilizing functionalized initiators¹⁰ or a post-polymerization end group modification.¹¹ The first procedure ensures complete functionalization of all polymer chains. In the latter case there is a chance of incomplete functionalization due to the presence of dead chain ends, which can however be suppressed in controlled polymerizations, such as atom transfer radical polymerization (ATRP).

Alkyne functionality was introduced in a series of poly(methyl methacrylate) (PMMA) **2a–c** with different molecular weights and polystyrene (PS) **3** *via* ATRP, utilizing functionalized initiator **1**, as depicted in Scheme 1. The alkyne functionality of this initiator was protected with a trimethylsilyl group in order to circumvent complexation with the copper catalyst during polymerization. This protective group was removed quantitatively according to ¹H NMR using tetrabutylammonium fluoride (TBAF) (Scheme 1). All polymerizations proceeded *via* first order kinetics, indicating good control over the polymerization process, and, as a consequence, polydispersity indices (PDI's) were low (Table 1).

As aforementioned, functionality can also be introduced by post-polymerization end group modification. This method was used for the preparation of azide mono- and bifunctionalized PS (Scheme 2). The bromide end groups which were present after performing ATRP were replaced by azides using azidotrimethylsilane and tetrabutylammonium fluoride (TBAF).¹² Completion of these substitution reactions was confirmed by a shift of the methine protons adjacent to the end groups in ¹H NMR spectra (δ 4.48–3.91 ppm) and the appearance of azide signals in FTIR-ATR spectra (2090 cm⁻¹).

As a third polymer, commercially available poly(ethylene glycol) methyl ether (PEG) was used. The hydroxyl group was



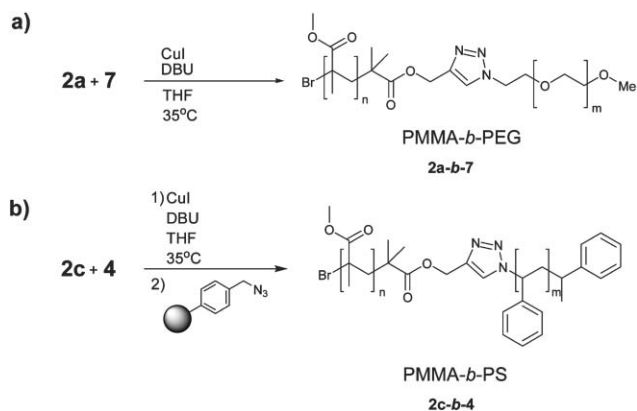
Scheme 1 Introduction of terminal alkyne functionality in polymers utilizing functionalized ATRP initiator **1**.

† Electronic supplementary information (ESI) available: Experimental procedures and details. Semilogarithmic plots of all performed polymerizations. SEC traces of all performed cycloaddition reactions. See <http://www.rsc.org/suppdata/cc/b412930j>; j.vanhest@science.ru.nl

Table 1 Results of the polymerizations and subsequent cycloaddition reactions

Polymer	$M_{n,th}^{a/}$ kg mol ⁻¹	$M_{n,SEC}^{b/}$ kg mol ⁻¹	PDI
a PMMA= [2a]	7.08	7.85	1.14
b PMMA= [2b]	18.14	21.28	1.13
c PMMA= [2c]	15.41	13.49	1.16
d PS= [3]	5.17	4.82	1.23
e PS-N ₃ [4]	4.15	3.52	1.15
f N ₃ -PS-N ₃ [5]	12.85	11.69	1.14
g PEG= [6]	2.08	2.72	1.04
h PEG-N ₃ [7]	2.02	3.18	1.04
i PMMA- <i>b</i> -PEG [2a- <i>b</i> -7]	9.10	11.77	1.12
j PMMA- <i>b</i> -PEG [2b- <i>b</i> -7]	20.16	25.32	1.08
k PS- <i>b</i> -PEG [3- <i>b</i> -7]	7.19	7.53	1.17
l PEG- <i>b</i> -PS- <i>b</i> -PEG [6- <i>b</i> -5- <i>b</i> -6]	17.01	17.69	1.13
m PMMA- <i>b</i> -PS [2c- <i>b</i> -4]	19.56	17.78	1.13

^a Theoretical M_n based on conversion measured by GC. ^b SEC measurements were conducted in THF. PMMA and PS standards were used for calibration.



Scheme 4 Two examples of the modular formation of block copolymers via a 1,3-dipolar cycloaddition of azide and alkyne functionalized polymers. (a) PMMA-*b*-PEG **2a-*b*-7**. (b) PMMA-*b*-PS **2c-*b*-4** using an azidomethyl polystyrene resin to scavenge the excess of alkyne functionalized PMMA.

end groups using CuI and 1,8-diaza[5.4.0]bicycloundec-7-ene (DBU),¹³ hence forming block copolymers (Scheme 4), as summarized in Table 1. In the case of block copolymers containing PEG blocks, a slight excess of PEG was used (1.2 equivalents) in order to drive the click reactions to completion. This excess of PEG was easily removed after the reaction *via* a washing step with methanol. In the case of PMMA-*b*-PS, an excess of alkyne functionalized PMMA was used (1.2 equivalents). Because in this case the small excess could not be removed by washing, the excess of alkyne functionalized PMMA was successfully scavenged by a click reaction onto azide functionalized polystyrene resin (Scheme 4).¹⁴ In all cases no residual starting material was observed in SEC traces of the block copolymers (Fig. 1)

Completion of the reaction was determined by the disappearance of the azide signals in FTIR spectra. Furthermore, for all performed click reactions a shift in the SEC trace was observed towards higher molecular weight, indicating block copolymer formation (Fig. 1). Moreover, no increase of the PDI was observed upon block copolymer formation which implies that the coupling reactions went to completion.

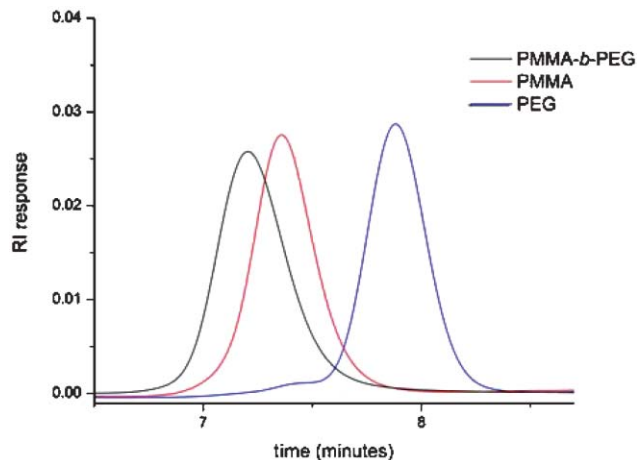
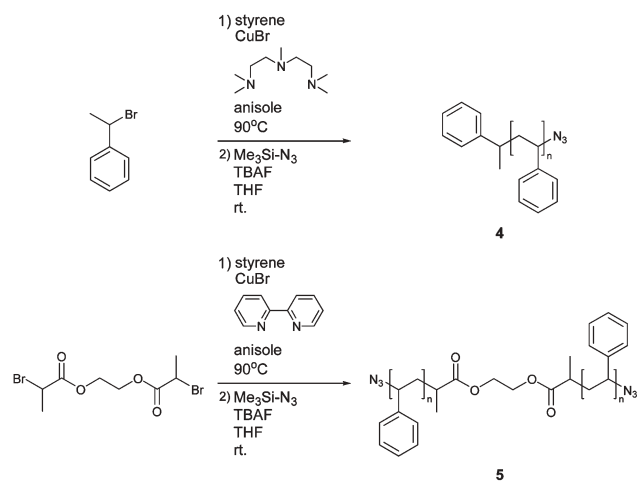


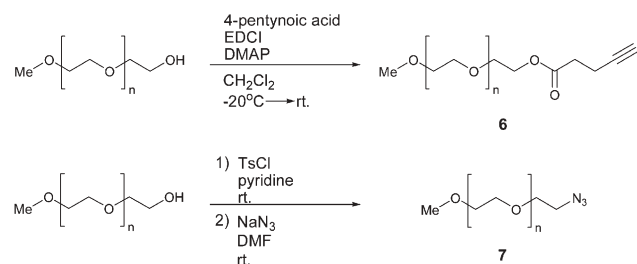
Fig. 1 SEC traces of alkyne functionalized PMMA **2a**, azide functionalized PEG **7** and the coupled diblock copolymer **2a-*b*-7**.



Scheme 2 Incorporation of azide end groups in polystyrene *via* an end group modification procedure.

quantitatively converted into an azide or alkyne functionality according to ¹H NMR, as depicted in Scheme 3. The azide end group was introduced by tosylation of the hydroxyl functionality and subsequent substitution with sodium azide. Terminal alkynes were introduced directly *via* a carbodiimide mediated coupling of 4-pentynoic acid.

The thus obtained polymer building blocks were coupled *via* 1,3-dipolar cycloaddition reactions between the azide and alkyne



Scheme 3 Preparation of azide and alkyne functionalized poly(ethylene glycol).

In conclusion, we have demonstrated a modular approach for the synthesis of block copolymers *via* a Huisgen 1,3-dipolar cycloaddition of terminal alkynes and azides. Terminal alkyne and azide functionalities were conveniently introduced *via* ATRP using functionalized initiators, or *via* a post-polymerization end group modification. SEC measurements of the subsequent cycloaddition reactions demonstrated that block copolymers were formed quantitatively and that residual polymer precursors could be removed successfully from the reaction mixture. We are currently extending this procedure to bio-related block copolymers.

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