RAFT and click chemistry: A versatile approach to well-defined block copolymers†

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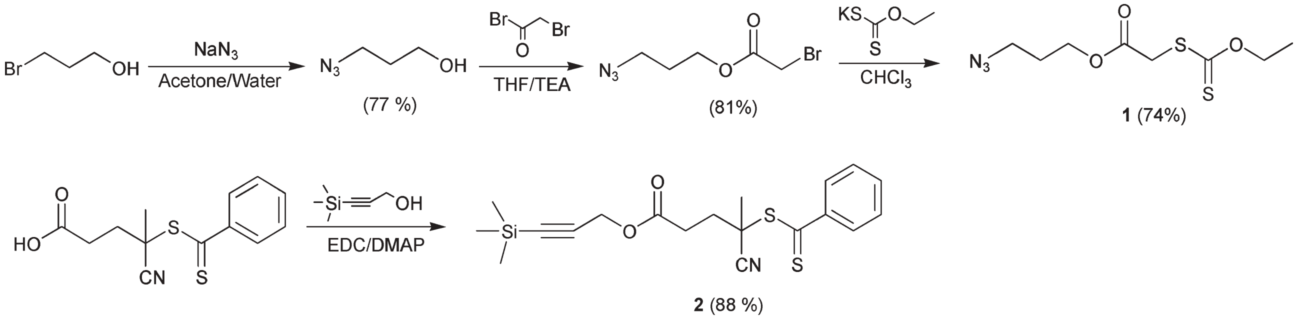
The combination of reversible chain transfer chemistry with highly orthogonal [2 + 3] cycloadditions ('click chemistry') allows for the synthesis of well-defined block copolymers of monomers with extremely disparate reactivities.

Block copolymers, in their diversities (selective solubilities, charge repartition, molar mass balance, …), form part of essential building blocks of "smart materials". Most of the new materials with well-defined nano- and/or micro-structures[1] can be employed as powerful macromolecular engineering tools due to their excellent ability to self-assemble.

Several routes can be considered to synthesize block copolymers. The most convenient consists in the successive polymerization of two or more monomers[2] without purification steps of intermediate compounds. However, this method is strongly limited to a few monomers, usually with the same chemical and physical properties (*i.e.* similar radical reactivity), which make them often inadequate for the material synthesis by self-assembly. An alternative route is the so-called macroinitiator method:[3] a polymer chain is chemically modified to be end-functionalized by an initiator molecule in order to trigger the polymerization of the second monomer. Although this method is applicable to a large variety of monomers, the presence of residual homopolymers potentially hidden by an increase of the molar mass distribution is difficult to avoid, due to partial functionalization of the starting polymer and an incomplete initiation of the second monomer's polymerization.

Recently, a novel method has been successfully applied to block copolymer synthesis, combining pericyclic [2 + 3] "click chemistry" and atom transfer radical polymerization (ATRP). Coupling of two polymers is usually thermodynamically unfavorable. The steric hindrance of the polymer chains acts as a shield preventing the molecular reaction between polymer end groups. However, the coupling reaction was found to be achievable using "click reactions"[4] such as copper-catalysed alkyne and azide 1,3-dipolar cycloaddition (CuAAC) or the Diels Alder reactions (DA). The term "click chemistry" was coined by Sharpless *et al.*[5] to encompass all reactions of high yields, modularity and stereospecificity. This method was first applied by van Hest *et al.*[6] in 2005 for the synthesis of different block copolymers from PS, PMMA and PEG homopolymers. PS and PMMA were both prepared by ATRP. The "clickable" functions were subsequently obtained by chemical reactions onto the chain end groups. In 2006, Hizal *et al.*[7] synthesized block copolymers from PS, PMMA, PEG and PtBA using the same strategy. All polymers, except the PEG, were prepared by ATRP and chain end groups were subsequently modified to introduce an anthracene and a maleimide functions in order to perform DA reactions.

Here we propose an alternative strategy by using mediating agents (compounds **1** and **2**, Scheme 1) carrying azide or acetylene functions for the subsequent click reactions, avoiding the use of any post-polymerization reactions. Moreover, polymerizations are performed by reversible addition fragmentation chain transfer (RAFT) instead of ATRP. RAFT polymerization[8] is extremely versatile as most of the vinylic monomers can be polymerized under controlled/living conditions. For example, vinyl acetate is easily polymerized with excellent control *via* RAFT using xanthate (*i.e.* MADIX) agents, while the polymerization fails with ATRP. However, RAFT agents must be chosen carefully according to the monomer, which represents a severe limitation in block copolymer synthesis. For example, vinyl acetate RAFT polymerization can only be mediated by a xanthate agent,[9] whereas styrene is polymerized in the presence of dithiobenzoate compounds.[10] The only potential expectation to the above dilemma is the use of universal RAFT agents such as F-RAFT, which hold great



Scheme 1 Synthesis of the "clickable" RAFT agents; see ESI† for details on the synthetic procedure.

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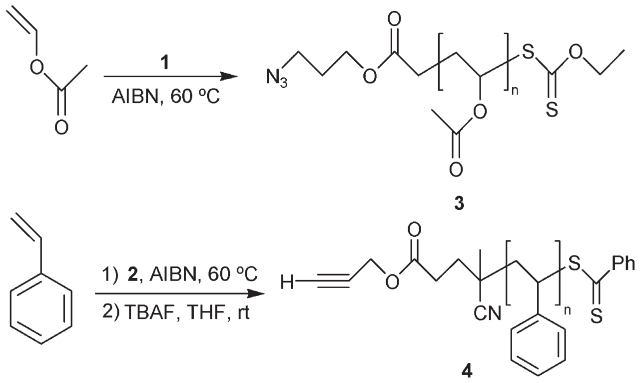


Scheme 2 RAFT polymerization of vinyl acetate and styrene controlled by the mediating agents **1** and **2**.

promise for sequential block copolymer formation of monomers with disparate reactivities, such as styrene and vinyl acetate.[11] Click chemistry can enable us to circumvent the problems posed by conventional RAFT agents by synthesizing first a collection of homopolymers by RAFT polymerization, and then by clicking them together without further modification. In this contribution, we illustrate this strategy *via* the synthesis of poly(styrene)-*b*-poly(vinyl acetate). To the best of our knowledge, this work represents the first example of the combination of RAFT polymerization and highly orthogonal click chemistry to prepare block copolymers. Furthermore, this is the first example of a synthetic route to very narrow polydispersity poly(styrene)-*b*-poly(vinyl acetate) copolymers.

Two RAFT agents were specifically designed to entail the functionality required for the click chemistry. Xanthate derivative **1** (Scheme 1) was prepared in three steps by conventional substitution reactions, from the commercially available 3-bromo-1-propanol. Dithiobenzoate derivative **2** (Scheme 1) was prepared in one step using a carboxidiimide coupling reaction. A trimethyl silyl group was used to protect the acetylene function, as the terminal alkyne hydrogen may interfere with the radical polymerization.

RAFT polymerizations of vinyl acetate and styrene were subsequently carried out in bulk at 60 °C in the presence of mediating agents **1** and **2** (Scheme 2). Both mediating agents **1** and **2** effect a good control of the polymerization, up to relatively high conversions. In both cases, the molecular weight increases linearly with conversion (Fig. 1), leading to homopolymers with molecular weight close to that expected and low PDI (polydispersity index).

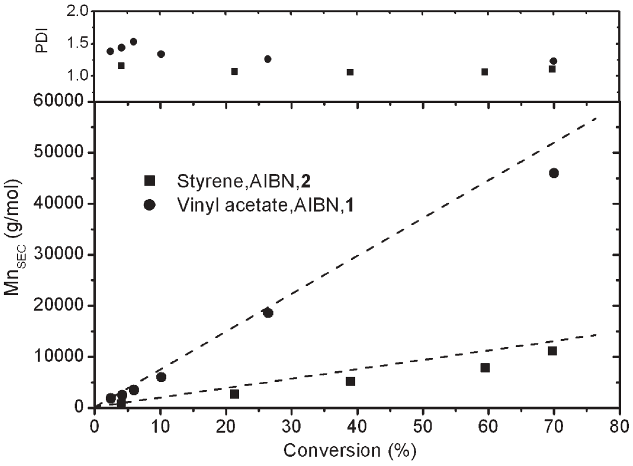
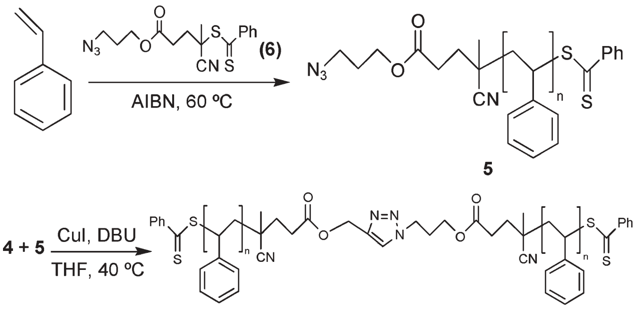


Fig. 1 Evolution of the number-average molecular weight with monomer conversion. The dashed lines illustrate the theoretical number-average molecular weight (calculated from GPC analyses).

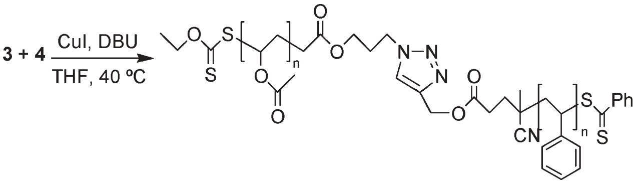


Scheme 3 Model CuAAC between PS homopolymers.

Table 1 Selected examples of "click" coupling of RAFT-made homopolymers of PS and PVAc by CuAAC

	Polymer-C≡CH			Polymer-N$_3$			Block copolymer	
		$M_{n,exp}$[a]/ kg mol^{-1}	PDI[b]		$M_{n,exp}$[a]/ kg mol^{-1}	PDI[b]	$M_{n,SEC}$[c]/ kg mol^{-1}	PDI[b]
1	PS	7.51	1.09	PS	3.18	1.11	10.60	1.14
2	PS	8.22	1.12	PS	11.07	1.13	19.41	1.14
3	PS	7.51	1.09	PVAc	6.83	1.16	15.24	1.18
4	PS	8.22	1.12	PVAc	35.19	1.18	45.26	1.24
5	PS	7.51	1.09	PVAc	3.71	1.17	12.15	1.17

[a] Measured by gel permeation chromatography (GPC) in *N,N*-dimethylacetamide (DMAC) with RI detector (calibration with PS standards) and confirmed by NMR calculation. [b] Measured by GPC in DMAC with RI detector (calibration with PS standards). [c] Apparent molecular weight measured according to linear PS standards.



Scheme 4 CuAAC between N$_3$-PVAC (**3**) and ≡PS (**4**).

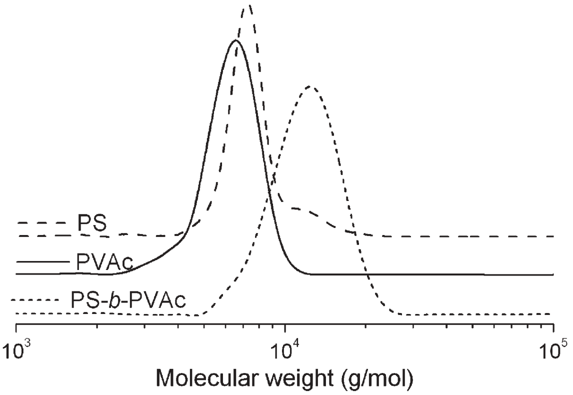


Fig. 2 SEC curves of PS≡, PVAC-N$_3$, and its coupling product (entry 3, Table 1).

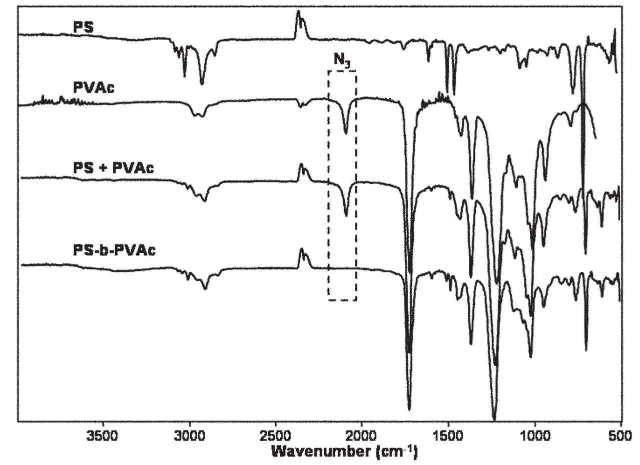


Fig. 3 IR spectra of PS$\equiv$, PVAC-N_3 and its mixture before and after "click" coupling (entry 3, Table 1).

A model reaction of CuAAC was first carried out involving the coupling of two PS homopolymers. In that way, the corresponding block copolymer PS-*b*-PS is easily recovered (same solubility of the two parts) and the true molecular weight is determined *via* SEC *via* the use of a direct calibration with linear polystyrene standards. To set up this experiment, an other dithiobenzoate RAFT agent carying an azide group (**6**, Scheme 3) was prepared according to the methodology described above. The same control of the polymerization of styrene was observed, leading to homopolystyrene (**5**, Scheme 3) end-functionalized by an azide group. CuAACs between N_3-PS and $\equiv$-PS were then performed. After surveying the efficiency of reaction with a variety of Cu^I sources (CuBr, CuI, $CuSO_4$/sodium acsorbate,), ligands (DBU, PMEDTA, DIEA), and solvents (DMF/H_2O, THF), we found that the catalyst system CuI/DBU/THF gives the best results with a reaction yield close to completion. SEC analysis shows a clear molecular weight shift, and the experimental molecular weight perfectly matches with the expected one (Table 1, entry 1 and 2). Moreover, FT-IR experiments show the complete disappearance at 2100 cm^{-1} of the azide signal.

These conditions were kept for the subsequent CuAACs of N_3-PVAC (**3**) and $\equiv$-PS (**4**) (Scheme 4). Various PS-*b*-PVAc block copolymers of different molecular weights were prepared with success (Table 1).

Copolymers were all characterized by SEC in order to observe the molecular weight distribution (Fig. 2). The comparison between the starting homopolymers and the copolymer clearly shows a molecular weight shift according to the "click" coupling. However, a slight increase of the polydispersity index was detected after the reaction, which could be due to the presence of remaining homopolymers. This result can be explained by the difficulty to work at the perfect stoichiometry 1 : 1 with polymers.[12]

Further confirmation of the "click" coupling can be taken from FT-IR spectroscopy. In Fig. 3, the IR spectra of PS and PVAc homopolymers are compared to the spectra of the mixture before and after the click reaction. The strong signal at 2100 cm^{-1} assigned to the azide group disappeared completely in the copolymer, proving the efficiency of the "click" reaction.

In conclusion, well-defined block copolymers PS-*b*-PVAc were obtained by combining for the first time RAFT polymerization and click chemistry. In a first part, new "clickable" RAFT agents were designed and used to produce under control/living conditions homopolymers of PS and PVAc. In a second part, "click" coupling reactions were performed, based on the conditions determined *via* a model reaction. Experimental data (SEC, FT-IR) demonstrate the formation of various block copolymers with variable block ratios. In ongoing studies we intend to employ this strategy for the preparation of more complex macromolecular architectures such as star or dendrimer-like entities.

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Notes and references

1 E. R. Gillies and J. M. J. Fréchet, *Chem. Commun.*, 2003, 1640–1641; J. Yang, D. Levy, W. Deng, P. Keller and M.-H. Li, *Chem. Commun.*, 2005, 4345–4347; S. A. Jenekhe and X. L. Chen, *Science*, 1999, **283**, 372–375; S. Jain and F. S. Bates, *Science*, 2003, **300**, 460–464.
2 R. Matmour, A. S. More, P. P. Wadgaonkar and Y. Gnanou, *J. Am. Chem. Soc.*, 2006, **128**, 8158–8159.
3 K. V. D. Wetering, C. Brochon, C. Ngov and G. Hadziioannou, *Macromolecules*, 2006, **39**, 4289–4297.
4 Selected recent articles about "click" reactions in polymer science: V. Ladmiral, G. Mantovani, G. J. Clarkson, S. Cauet, J. L. Irwin and D. M. Haddleton, *J. Am. Chem. Soc.*, 2006, **128**, 4823–4830; G. Mantovani, V. Ladmiral, L. Tao and D. M. Haddleton, *Chem. Commun.*, 2005, 2089–2091; J. A. Johnson, D. R. Lewis, D. D. Dıaz, M. G. Finn, J. T. Koberstein and N. J. Turro, *J. Am. Chem. Soc.*, 2006, **128**, 6564–6565; R. Luxenhofer and R. Jordan, *Macromolecules*, 2006, **39**, 3509–3516; T. Liebert, C. Hänsch and T. Heinze, *Macromol. Rapid Commun.*, 2006, **27**, 208–213; D. A. Ossipov and J. Hilborn, *Macromolecules*, 2006, **39**, 1709–1718.
5 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.
6 J. A. Opsteen and J. C. M. v. Hest, *Chem. Commun.*, 2005, **57**, 57–59.
7 H. Durmaz, B. Colakoglu, U. Tunca and G. Hizal, *J. Polym. Sci., Part A: Polym. Chem.*, 2006, **44**, 1667–1675.
8 T. P. T. Le, G. Moad, E. Rizzardo and S. H. Thang, *PCT Int. Appl., WO 9801478 A1 980115*, 1998 (*Chem. Abstr.*, 1998, **128**, 115390); D. Charmot, P. Corpart, D. Michelet, S. Z. Zard and T. Biadatti, *PCT Int. Appl., WO 9858974*, 1998 (Chem. Abstr., 1999, **130**, 82018); G. Moad, E. Rizzardo and S. H. Thang, *Aust. J. Chem.*, 2005, **58**, 379; C. Barner-Kowollik, T. P. Davis, J. P. A. Heuts, M. H. Stenzel, P. Vana and M. Whittaker, *J. Polym. Sci. Polym. Chem.*, 2003, **41**, 365.
9 M. Stenzel, L. Cummins, G. E. Roberts, T. P. Davis, P. Vana and C. Barner-Kowollik, *Macromol. Chem. Phys.*, 2003, **204**, 1160–1168.
10 C. Barner-Kowollik, J. F. Quinn, D. R. Morsley and T. P. Davis, *J. Polym. Sci., Part A: Polym. Chem.*, 2001, **39**, 1353–1365.
11 M. L. Coote, E. I. Izgorodina, G. E. Cavigliasso, M. Roth, M. Busch and C. Barner-Kowollik, *Macromolecules*, 2006, **39**, 4584–4591; A. Theis, M. H. Stenzel, T. P. Davis, M. L. Coote and C. Barner-Kowollik, *Aust. J. Chem.*, 2005, **58**, 437–441.
12 H. Gao and K. Matyjaszewski, *Macromolecules*, 2006, **39**, 4960–4965.