# Orthogonal Multifunctionalization of Random and Alternating Copolymers

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S *Supporting Information*

ABSTRACT: A series of copolymers with varying degrees of alternation are synthesized by free-radical polymerization from 2,3,4,5,6-pentafluorostyrene (PFS) and propargyl-containing styrene derivatives. The degree of alternation varied with the electronic nature of the styrene derivative: random copolymers were obtained using monomers with electron withdrawing moieties, whereas increasingly alternating copolymers were obtained by increasing the electron donating nature of the substituent. The copolymers could be functionalized in an orthogonal fashion using a nucleophilic substitution (with thiols) to functionalize PFS and the copper-catalyzed 3 + 2 cycloaddition between azides and the alkyne of the propargyl groups. This methodology allows for the facile synthesis of functional alternating copolymers.
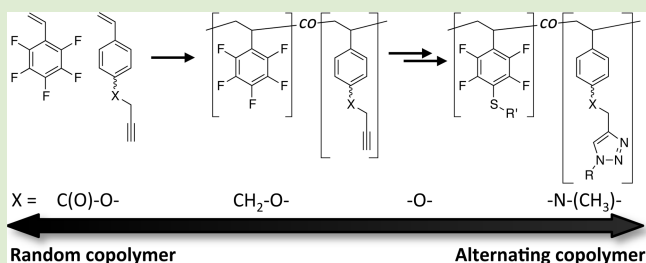
The control over monomer sequence that nature exerts on biopolymers is key toward the applications of these biomaterials.[1] A similar control over the microstructure of synthetic polymers will likely make the synthesis of very complex synthetic systems possible.[2] In chain-growth polymerizations, alternating copolymerizations have been established,[3] but they have hardly been explored for the synthesis of functional materials. Here, we introduce a facile way of preparing highly functionalized polymers with well-defined monomer sequences (varying from random to highly alternating). Our postpolymerization functionalization approach allows for the formation of well-defined sequences of functional groups with a high degree of spatial control.

Postpolymerization functionalization of polymers is an extremely useful synthetic pathway toward functional polymers.[4] The employment of click chemistries[4a−i] and orthogonal supramolecular interactions[4j] allows for modular post-polymerization functionalization as well as a high degree of functionalization. Both end-group and side-chain functionalizations of polymers have been reported.[4] Often, different coupling reactions/interactions are used in tandem in an orthogonal fashion to introduce multiple functional groups at different sites along a polymer.[4] These orthogonal post-polymerization functionalization strategies have been used with homopolymers as well as random and block copolymers.[4] In this contribution, we describe random and alternating copolymers that can be doubly functionalized using an orthogonal postpolymerization approach. Our strategy is based on the alternating copolymerization of 2,3,4,5,6-pentafluorostyrene (PFS) with propargyl styrene derivatives. It has been shown that the nucleophilic addition of amines and thiols onto PFS can be high yielding,[5] while the propargyl group of styrene derivatives can be functionalized easily via the

copper-catalyzed 3 + 2 cycloaddition of the alkynes with azides,[4a−f] giving us two high yielding click strategies for the postpolymerization functionalization step (Scheme 1A).

2,3,4,5,6-Pentafluorostyrene (PFS) and styrene (S) are known to polymerize in a highly alternating fashion due to the electron-deficient nature of PFS and the electron-rich nature of styrene.[6] Because styrene cannot be functionalized easily, we prepared six derivatives of styrene containing

Scheme 1. (A) Strategy Towards Functional Random and Alternating Copolymers Used in This Work; (B) Structures of PFS and Propargyl Containing Styrene Derivatives Used in This Work and Their Abbreviations
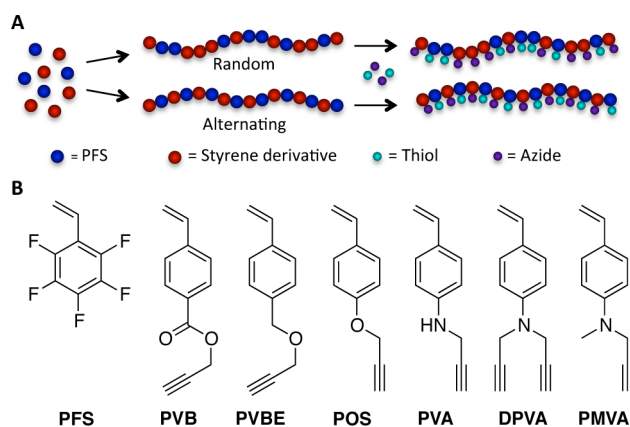
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propargyl groups in the *para*-position (propargyl 4-vinylbenzoate (PVB), propargyl 4-vinylbenzyl ether (PVBE), 4-propargyloxystyrene (POS), *N*-propargyl 4-vinylaniline (PVA), *N,N*-propargylmethyl 4-vinylaniline (PMVA), and *N,N*-dipropargyl 4-vinylaniline (DPVA), Scheme 1B).

PVB, PVBE, and POS were synthesized using adapted literature procedures.[7] PVA and DPVA were prepared by nucleophilic addition using 4-vinylaniline and propargyl bromide in the presence of potassium carbonate. The synthesis of both monomers was performed in one pot and the two monomers were separated by column chromatography. PMVA was prepared by reductive amination of PVA using formaldehyde in the presence of sulfuric acid and sodium borohydride as the reducing agent.

Initially, the copolymerization behavior of the styrene derivatives with PFS was studied. All polymerizations were performed in 1,4-dioxane solutions (30 wt % monomers) using AIBN as the radical initiator. Mixtures of PVB, PVBE, POS, PVA, DPVA, and PMVA with PFS were prepared with monomer ratios ranging from 1:5–5:1 and 0.005 equiv (to total monomer) of AIBN. After degassing the polymerization samples, the exact monomer ratios were determined by ^{1}H NMR spectroscopy. Then, the solutions were heated to 65 °C. Samples were drawn after 2 h (and, if necessary, at longer reaction times), analyzed by ^{1}H NMR spectroscopy, and the percentage of monomer consumption was determined. From the ratio of peaks corresponding to the proton on the alkyne (which are in identical positions for the monomer and the polymer so that it can be used as an internal standard) and the respective vinyl signals of the two monomers, the conversion of each monomer was determined (see Supporting Information for an example), from which the composition of the polymer was derived. We targeted monomer conversions between 20 and 30%. This information was used to determine the reactivity ratios (r_1 (= k_{11}/k_{12}) and r_2 (= k_{22}/k_{21})) of each monomer using the Fineman–Ross and Kelen–Tüdos methods (for details, see Supporting Information).[8] The values for r_1 and r_2 that were obtained are summarized in Table 1.

Table 1. Reactivity Ratios for Different Copolymerizations with PFS Obtained through the Fineman–Ross and Kelen–Tüdos Methods

M_1	M_2	Fineman–Ross			Kelen–Tüdos		
		r_1	r_2	$r_1 \cdot r_2$	r_1	r_2	$r_1 \cdot r_2$
PVB	PFS	1.66	0.59	0.99	1.39	0.49	0.68
PVBE	PFS	0.58	0.49	0.29	0.69	0.50	0.35
S	PFS	0.52	0.45	0.23	0.53	0.48	0.25
POS	PFS	0.41	0.41	0.17	0.41	0.42	0.17
DPVA	PFS	0.31	0.37	0.11	0.29	0.34	0.10
PMVA	PFS	0.20	0.09	0.02	0.20	0.09	0.02

Reactivity ratios for S and PFS have been reported in the literature for several polymerization conditions ($r_1 \cdot r_2$ = 0.17 (bulk, 70 °C, benzoyl peroxide),[6b] $r_1 \cdot r_2$ = 0.14 (toluene, 70 °C, benzoyl peroxide), and $r_1 \cdot r_2$ = 0.09 (bulk, 60 °C, AIBN)[6a]), which all indicate that the copolymerization of these two monomers is appreciably alternating.

The copolymerization of PVB and PVBE with PFS yields larger reactivity ratios than are found for the copolymerization of S and PFS (vide infra). The values indicate that PVB yields random copolymers and PVBE yields only slightly alternating copolymers.

On the other hand, with respect to POS, DPVA, and PMVA, we found very low reactivity ratios, indicating that the copolymerization of these monomers with PFS is highly alternating. The degree of alternation increases in the order POS < DPVA < PMVA. Copolymerizations with PVA did not yield any polymer, which is likely due to the very low reactivity of PVA, the same reason why 4-vinylaniline cannot be polymerized efficiently.[9] In none of the copolymerizations did we find evidence for the participation of the alkyne groups in the polymerization, which is most likely due to the much lower reactivity of the alkyne groups.[7b,10]

The differences in the degree of alternation are likely due to the electron-withdrawing/donating properties of the substituent on the aromatic ring of the styrene derivatives, because the alternating copolymerization is based on the electron-deficient nature of PFS and the electron rich nature of the styrene derivatives. The electron-withdrawing/donating influence of the substituents can qualitatively be shown using the chemical shifts of the vinyl groups of the different monomers (Table 2).

Table 2. ^{1}H NMR Spectroscopy Chemical Shifts of the Vinyl-Proton Signals (in ppm) of the Monomers

M	chemical shift (ppm)		
	1 *trans*	1 *cis*	2
PVB	5.40	5.88	6.76
PVBE	5.25	5.75	6.72
S	5.22	5.74	6.69
POS	5.15	5.63	6.66
DPVA	5.09	5.60	6.64
PMVA	5.06	5.57	6.64
PFS	5.65	6.05	6.57

The vinyl signals of PVB and PVBE are shifted downfield compared to the signals of styrene, indicating that PVB and PVBE are less electron-rich than styrene. In contrast, the signals for POS, DPVA, and PMVA are shifted upfield indicating that these systems are more electron-rich than styrene, hence, the more alternating copolymerization with PFS was observed.

Similar trends were found for the copolymerization between *para*-substituted styrene monomers with methyl methacrylate ($r_1 \cdot r_2$ S/MMA, 0.26; S-*p*-CH$_3$/MMA, 0.178; S-*p*-OCH$_3$/MMA, 0.093; S-*p*-N(CH$_3$)$_2$, 0.023).[11] We also determined the reactivity ratios of the copolymerization of S and PFS. Slightly higher $r_1 \cdot r_2$ values were found (Fineman–Ross, 0.23; Kelen–Tüdos, 0.25) than those reported in literature (vide supra).[6] This also implies that the copolymerizations of PFS with styrene derivatives too might be slightly more alternating under optimized conditions. Pugh et al. observed a dramatic improvement of the degree of alternation when the polymerization of S and PFS is conducted at room temperature (to $r_1 \cdot r_2$ = 0.048), suggesting that optimizing polymerization conditions can increase the degree of alternation.[6b]

Next, we investigated the final goal of our study, the formation of multifunctionalized alternating copolymers. The copper-catalyzed azide–alkyne [3 + 2] cycloaddition has been used extensively as an easy and high yielding method of coupling, among others, small molecules to the side chains of polymers.[4b,d,h,i] More recently, the high yielding nucleophilic addition of amines or thiols to poly(2,3,4,5,6-pentafluorostyrene) (PPFS) has been described.[5] Our random and alternating copolymers can be functionalized using these two strategies. As

a proof of principle, we functionalized PPOS-*co*-PPFS (with an ~1:1 ratio of the respective monomers) with methyl 2-azidoacetate and 6-mercapto-1-hexanol. The cycloaddition of the azide proceeded in quantitative fashion (in DMF or THF with 0.1 equiv (to alkyne groups) CuBr(PPh$_3$)$_3$, 2 equiv DIPEA, and 2 equiv methyl 2-azidoacetate at room temperature) as determined by ^{1}H NMR spectroscopy. The nucleophilic addition of 6-mercapto-1-hexanol proved to be more challenging. In THF (2 equiv DIPEA, 2 equiv thiol, reflux, 24 h) no significant functionalization was achieved. In DMF, under otherwise identical conditions, a degree of functionalization of only ~40% was achieved. When a large excess (>10 equiv) of thiol was used at 100 °C for 24 h, we not only observed the functionalization of PPFS, but also thiol-yne chemistry. Therefore, a two-step functionalization was performed, wherein the cycloaddition was performed first followed by the nucleophilic addition onto the PFS moieties. This allowed for the double and orthogonal functionalization of our copolymers in good yields (~80% functionalization of PFS).

In conclusion, we devised a synthetic strategy toward random and alternating copolymers by copolymerizing propargyl-functionalized styrene derivatives with 2,3,4,5,6-pentafluoro-styrene. Both monomers can be functionalized in a postpolymerization fashion, yielding highly functional copolymers with a predefined monomer sequence. It is possible to create functional polymers with a well-defined spacing between functional groups or with two different functionalities which are displayed in an alternating sequence. This postpolymerization methodology thus offers a novel method to create highly complex functional polymers. Such materials might find applications as biomaterials or in catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
Experimental data on monomer and polymer synthesis, determination of reactivity ratios, polymer functionalization, characterization (^{1}H NMR, ^{13}C NMR, ^{19}F NMR, SEC) of monomers and polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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