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Catalytic One-Handed Helix Induction and Subsequent Static Memory of Poly(biphenylylacetylene)s Assisted by a Small Amount of Carboxy Groups Introduced at the Pendants

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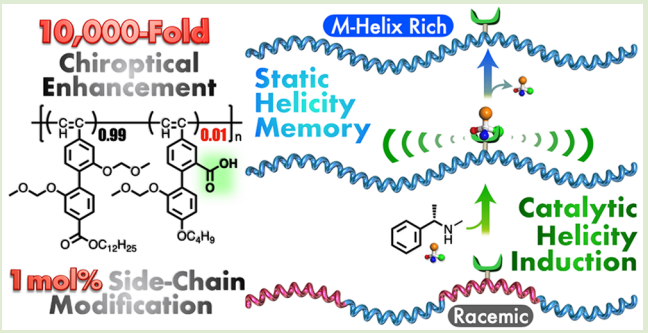
ABSTRACT: A dynamically racemic helical copolymer composed of an achiral biphenylylacetylene (BPA) bearing methoxymethoxy groups at the 2,2′-positions and 1 mol % of an achiral BPA carrying 2-carboxy-2′-methoxymethoxy groups at the biphenyl pendants was found to fold into an excess one-handed helix with significant amplification of the helicity in the presence of a small amount of optically active amines. The induced macromolecular helicity was retained ("memorized") after removal of the chiral amines. The copolymer had a significant sensitivity for detecting the chirality of chiral amines with a sensitivity more than 10000-fold higher than that of the corresponding homopolymers with no carboxy group, thus showing Cotton effects even in the presence of a 0.01 equiv of an optically active amine. The effects of the substituents at the 4′-position of the biphenyl pendants of the copolymers and the structures of the chiral amines on the macromolecular helicity induction were also investigated.



Inspired by sophisticated biological systems, in which one-handed helical DNA[1] and proteins[2] composed of homochiral repeating units and their supramolecular assemblies[3] play a vital role in their extraordinary functions, a rich variety of synthetic covalent[4−11] and supramolecular helical polymers[9,12−21] with a controlled helical handedness have been developed and applied as chiral functional materials to chiral recognition/separation,[9,22−29] asymmetric catalysis,[30−33] circularly polarized luminescence,[34−38] and drug delivery.[39]

We previously reported unique helical poly(biphenylylacetylene)s (PBPAs) with a controlled handedness. PBPAs, such as poly-**1a**[40] and poly-**1b**[41] (Figure 1a), are composed of achiral monomer units bearing methoxymethoxy (MOM) groups at the 2,2′-positions of the biphenyl pendants, which are inherently optically inactive but have dynamically racemic helical conformations. Either a right (*P*)- or left (*M*)-handed main-chain helicity as well as the axial chirality of the biphenyl units can be induced in response to the chirality of optically active guests, such as (*R*)- and (*S*)-1-phenylethanol ((*R*)- and (*S*)-PEA).[40−44] Both the macromolecular helicity and the axial chirality induced in the PBPAs are retained ("memorized") after complete removal of the chiral inducers, resulting in the one-handed helical PBPAs with a static helicity memory.[40−44] Based on this "helicity induction and its static helicity memory" approach, we have succeeded in developing a series of unique helicity-memorized PBPA-based chiral materials,[43] such as switchable chiral stationary phases[40,45] and asymmetric organocatalysts,[46,47] capable of switching the elution orders of enantiomers in HPLC and the product chirality in asymmetric reactions, respectively. However, a large excess amount of homochiral alcohols, such as (*R*)- or (*S*)-PEA ([PEA]/[polymer] > 1000), was necessary for the one-handed helix induction and subsequent static memory of the helicity in PBPAs, probably due to the relatively weak noncovalent chiral interactions between the MOM groups of PBPAs (e.g., poly-**1a** and poly-**1b**) and (*R*)- or (*S*)-PEA.[40,41,45]

Recently, we found that a one-handed helical PBPA derivative with a static helicity memory could be produced with a small amount of (*R*)- or (*S*)-1,1′-bi-2-naphthol (BINOL; 0.2 equiv) in water when amphiphilic oligo(ethylene glycol) residues instead of *n*-dodecyl chains were introduced at the pendants of poly-**1b**.[48] This is because such a water-soluble PBPA has a hydrophobic helical cavity, in which hydrophobic BINOL molecules can be efficiently encapsulated, thereby forming an excess one-handed helix in water. A poly-**1b** analogue having chiral, but racemic pendants at the 4′-position also formed a preferred-handed helix in the presence of a small amount of (*R*)- or (*S*)-BINOL (0.1 equiv) in toluene, but only at a very high concentration.[49] The MOM groups at the 2,2′-

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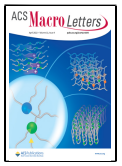

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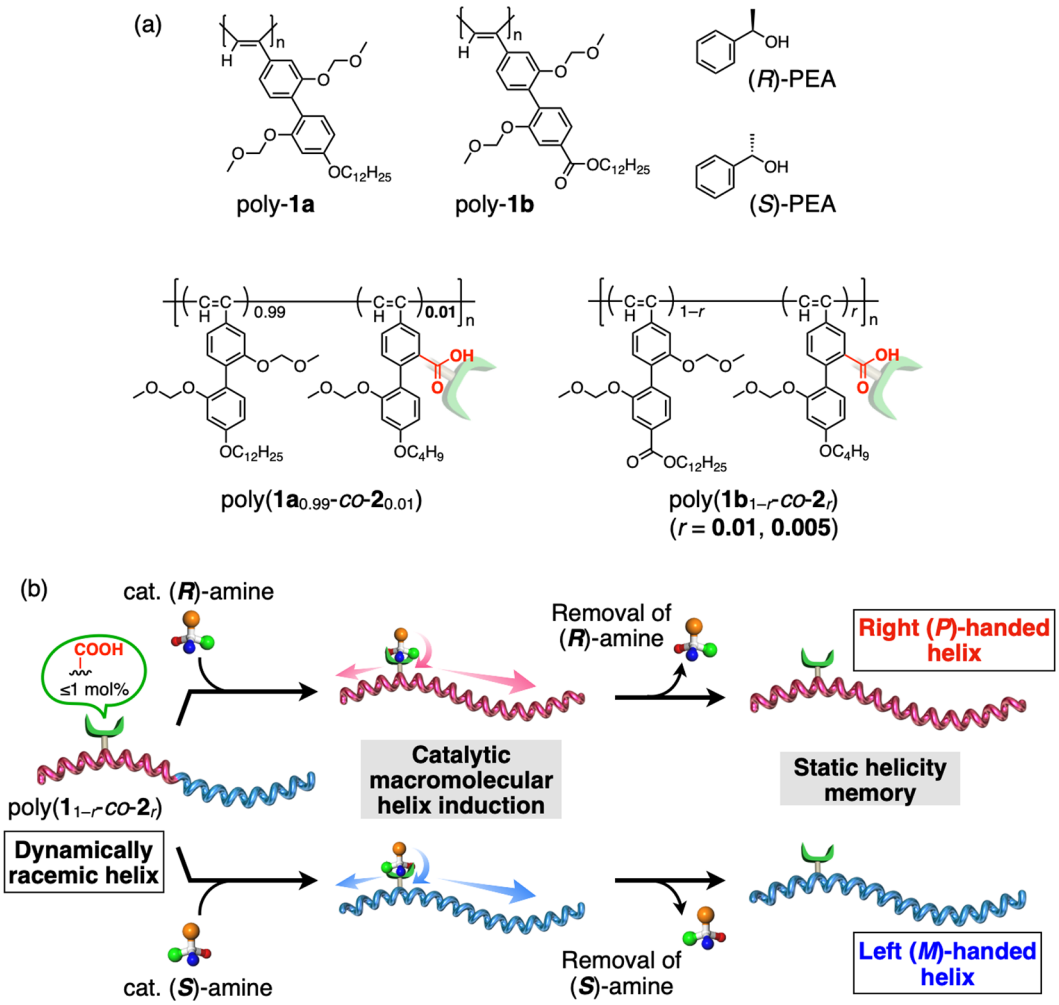

Figure 1. (a) Structures of poly(biphenylylacetylene)s (PBPAs) (poly-**1a**, poly-**1b**, poly($\mathbf{1a}_{0.99}$-*co*-$\mathbf{2}_{0.01}$), and poly($\mathbf{1b}_{1-r}$-*co*-$\mathbf{2}_r$) (r = 0.01 and 0.005)) and optically active 1-phenylethanol ((*R*)- and (*S*)-PEA). (b) Schematic illustration of catalytic macromolecular helicity induction and subsequent static helicity memory in poly($\mathbf{1}_{1-r}$-*co*-$\mathbf{2}_r$) bearing a small amount of carboxyl groups in the vicinity of the polymer backbone through noncovalent chiral interactions with optically active amines.

positions of the biphenyl pendants of poly-**1a** and poly-**1b** can be replaced with acetyloxy groups, while maintaining their static helicity memory capability after a preferred-handed helix formation induced by (*R*)- or (*S*)-PEA.[41,50] We envisaged that introducing a small amount of specific functional groups, such as a carboxy group, instead of the MOM groups, in particular, at the 2-position of the biphenyl pendants located in the vicinity of the PBPA backbone would significantly enhance the sensitivity to the chirality of the chiral amines, thus providing a powerful helical polymer-based chirality sensor of chiral amines through a catalytic one-handed helix-induction and its static helicity memory assisted by a remarkable amplification of the helical sense bias.

To this end, we designed and synthesized the biphenylylacetylene (BPA)-based copolymers, poly($\mathbf{1a}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) and poly($\mathbf{1b}_{1-r}$-*co*-$\mathbf{2}_r$) (r = 0.01 and 0.005), containing a small amount of the carboxy groups (1 or 0.5 mol %) as a functional receptor site at the 2-position of the biphenyl pendants positioned in the vicinity of the polymer backbones (Figure 1a). We showed a remarkable effect of such a small amount of the carboxy groups of the copolymers on the chirality sensing of various chiral amines when compared to the corresponding homopolymers, poly-**1a**[40] and poly-**1b**,[41] with no carboxy group using circular dichroism (CD) spectroscopy (Figure 1b).

A novel achiral BPA monomer (**2** in Scheme 1) bearing carboxy and MOM groups at the 2- and 2′-positions of the biphenyl unit, respectively, was synthesized according to Scheme S1. The monomer **2** was then copolymerized with achiral monomers (**1a**[40] and **1b**[41]) carrying the MOM groups at the 2,2′-positions and alkoxy and alkoxycarbonyl groups at the 4′-position, respectively, with feed molar ratios of [**1**]/[**2**] = 98/2 and/or 99/1 using a rhodium catalyst ($[Rh(nbd)Cl]_2$, nbd: norbornadiene) in a tetrahydrofuran (THF)/triethylamine (Et_3N) mixture according to a previously reported method (Scheme 1).[40,41] The *cis*−*transoidal* optically inactive copolymers (poly($\mathbf{1a}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) and poly($\mathbf{1b}_{1-r}$-*co*-$\mathbf{2}_r$); r = 0.01 and 0.005) composed of a small amount of the carboxy-substituted **2** (0.5−1 mol %) in the vicinity of the PBPA backbones, as estimated by ^{1}H NMR, were obtained in 37−85% yields (entries 1−3 in Table 1 and Figure S1). The number-average molar masses (M_n) and degree of polymerization of the copolymers were estimated to be approximately 2.0 × 10^5 and 350−450, respectively, by size-exclusion chromatography (SEC).[51] For comparison, *cis*−*transoidal*

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Scheme 1. Synthesis of Poly($1a_{0.99}$-*co*-$2_{0.01}$) and Poly($1b_{1-r}$-*co*-2_r) (r = 0.01 and 0.005)

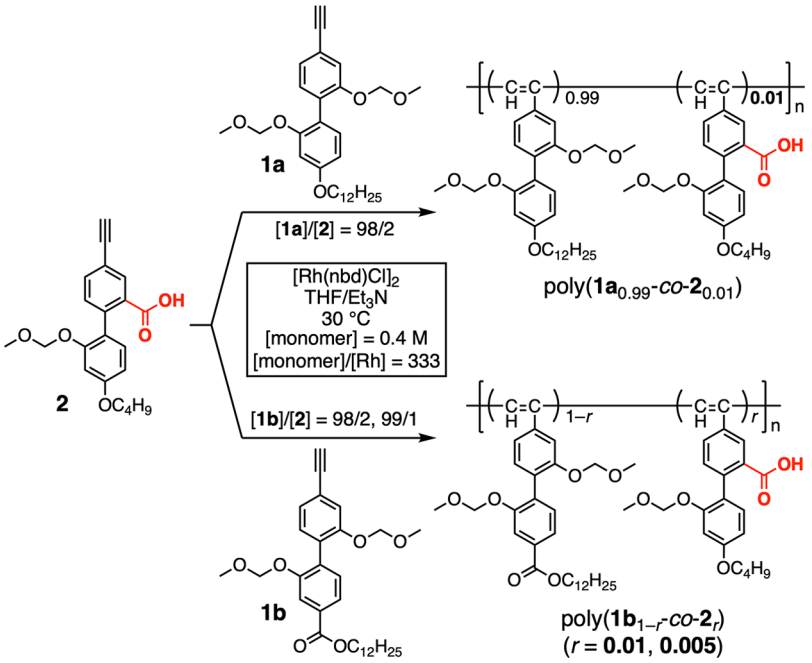

Table 1. Copolymerization Results of 1a or 1b with 2 Using $[Rh(nbd)Cl]_2$ in THF/Et_3N at 30 °C for 17 h[a]

entry	monomer in feed (mol %)		copolymer					
			sample code	yield[b] (%)	M_n (10^5)[c]	M_w/M_n[c]	DP_n[c,d]	**2** units (mol %)[e]
1	**1a** (98)	**2** (2)	poly($1a_{0.99}$-*co*-$2_{0.01}$)	37	2.11	1.67	437	1
2	**1b** (98)	**2** (2)	poly($1b_{0.99}$-*co*-$2_{0.01}$)	79	1.77	2.04	348	1
3	**1b** (99)	**2** (1)	poly($1b_{0.995}$-*co*-$2_{0.005}$)	85	2.25	2.15	441	0.5
4	**1a** (100)		poly-**1a**	94	2.19	1.92	454	
5	**1b** (100)		poly-**1b**	95	4.03	1.59	789	

[a][Monomer] = 0.4 M, $[[Rh(nbd)Cl]_2]$ = 0.6 mM, $[Et_3N]/[monomer]$ = 3. [b]Methanol insoluble part. [c]Determined by SEC (polystyrene standards) with chloroform as the eluent. [d]Number-average degree of polymerization estimated by M_n. [e]Estimated by ^1H NMR.

homopolymers with no carboxy group, poly-**1a**[40] and poly-**1b**,[41] were also prepared in the same way (entries 4 and 5).

The optically inactive poly($1a_{0.99}$-*co*-$2_{0.01}$) and poly($1b_{0.99}$-*co*-$2_{0.01}$) showed split-type Cotton effects in the absorption regions of the polyacetylene backbones in methylcyclohexane (MCH) containing a large excess amount of (*S*)-PEA as a cosolvent (20 vol%; [PEA]/[monomer units of copolymer] = ~1640; Figure S2), as observed for the poly-**1a**[40,45] and poly-**1b**[41,45] homopolymers. The induced CD (ICD) intensities of poly($1a_{0.99}$-*co*-$2_{0.01}$) and poly($1b_{0.99}$-*co*-$2_{0.01}$) at the second Cotton effect ($\Delta\varepsilon_{2nd}$) at 380 nm gradually increased with time and reached plateau values after storage at 40 °C for 0.5 h and 2 days, respectively (Figure S2a,b), affording excess (*M*)-handed[52] helical polymers, along with an excess axial twist-sense (Figure S2c,d(i)). In the presence of an equimolar amount of (*S*)-PEA in MCH ([PEA]/[monomer units of copolymer] = 1); however, CD was not induced at all in the copolymers after storage at 40 °C for 4 days (Figure S2c,d(ii)) due to extremely weak chiral interactions between the MOM groups of the copolymers and (*S*)-PEA, as anticipated from no CD induction in poly-**1a** and poly-**1b** under the same conditions (Figure S4a,b(i)).

We then measured the CD spectra of the copolymers in the presence of 1 equiv of various optically active amines in MCH (**4**–**10** in Figure 2a). As shown in Figure 2, poly($1b_{0.99}$-*co*-$2_{0.01}$) responded to most of the primary (**3** and **5**) and all the secondary (**6**–**9**) chiral amines as a result of an excess one-handed helix formation, thus showing similar ICDs, except for the less bulky aliphatic primary amine (**4**) and *N*,*N*-dimethyl tertiary amine (**10**), which exhibited very weak ICDs. Poly($1b_{0.99}$-*co*-$2_{0.01}$) showed better chiroptical responses to most of the chiral amines, except for (*S*)-**3** and (*R*,*R*)-**9**, when compared to those of poly($1a_{0.99}$-*co*-$2_{0.01}$) (Figures 2c and S3). In contrast, the corresponding homopolymers (poly-**1a**[40] and poly-**1b**[41]) with no carboxy group showed no ICD with any of the chiral amines (1 equiv) under the same conditions (Figure S4(ii–ix)). These results definitely indicated the important role of the small amount of the carboxy groups (1 mol %) introduced in the vicinity of the copolymer backbones that significantly contributed to biasing the helical handedness resulting from attractive chiral acid–base interactions. We presume that the carboxy-bound biphenyl pendants (**2**) of the copolymers are first induced into an excess twist-sense in response to a small amount of the chiral amines, which further biases the axially chiral neighboring biphenyl pendants of the **1a** and **1b** units into the same twist-sense due to close interactions between them along the polymer backbones, thereby forming a preferred-handed helical structure, because the axial chirality of the biphenyl pendants is most likely coupled mechanically to the main-chain helicity of PBPAs.[40−42,45,47] The Cotton effect signs of poly($1b_{0.99}$-*co*-$2_{0.01}$) reflect the configuration of the chiral amines except for

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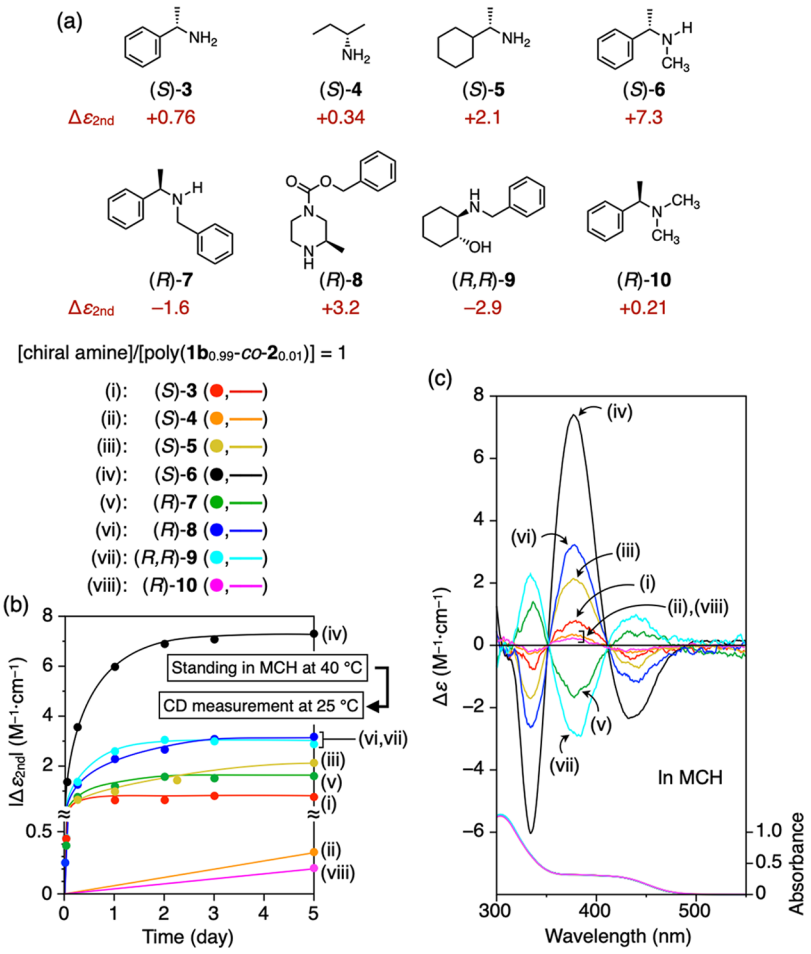

Figure 2. (a) Structures of chiral amines (**3**−**10**). The ICD intensities of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) ($\Delta\varepsilon_{2nd}$) measured in MCH at 25 °C after storage at 40 °C for 5 days ([chiral amine]/[monomer units of copolymer] = 1) are also shown. (b) Time-dependent induced CD (ICD) intensity ($|\Delta\varepsilon_{2nd}|$) changes of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) with (*S*)-**3** (i), (*S*)-**4** (ii), (*S*)-**5** (iii), (*S*)-**6** (iv), (*R*)-**7** (v), (*R*)-**8** (vi), (*R*,*R*)-**9** (vii), and (*R*)-**10** (viii) in MCH ([chiral amine]/[monomer units of copolymer] = 1) measured at 25 °C after storage at 40 °C. [Monomer units of polymer] = 1.0 mM. (c) The corresponding CD and absorption spectra measured at 25 °C after storage at 40 °C for 5 days.

(*R*)-**8** and (*R*)-**10**, and the ICD intensities tended to decrease in the following order: secondary amines > primary amines ≫ tertiary amine. This order is basically in good agreement with that of the binding constants of analogous chiral acid−base complexations in nonpolar solvent, that is, secondary amines ≥ primary amines ≫ tertiary amine.[53]

Among the tested chiral amines, the secondary amine ((*S*)-**6**) induced the most intense ICD in poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) with a helix-sense excess (*hse*) of 37%[54] after storage at 40 °C for 5 days (Figure 2b,c(iv)), probably due to its strong binding interaction as well as the appropriate steric effect. Interestingly, poly($\mathbf{1b}_{0.995}$-*co*-$\mathbf{2}_{0.005}$) composed of only 0.5 mol % of the **2** units also folded into an excess one-handed helix with 30% *hse* in the presence of 1 equiv of (*S*)-**6** (Figure S5). It is noteworthy that poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) displayed a clear Cotton effect due to the preferred-handed helix formation even in the presence of 0.1 equiv of (*S*)-**6** in MCH (Figure 3a,b(v)). The ICD intensity was greater than that of poly-**1b** measured in MCH containing a large excess of (*S*)-**6** as a cosolvent (20 vol %; [**6**]/[total monomer units of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$)] = ∼1370 equiv) (Figure 3b(vii)). As a result, by introducing a small amount (1 mol %) of the carboxy group instead of the MOM group at the 2-position of the biphenyl units, the copolymer performed a significant sensitivity for detecting the chirality of **6** with a sensitivity more than 10000-fold higher than that of the corresponding homopolymer with no carboxy group.

At a high concentration of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) in MCH (100 mM), an (*M*)-helix induction with a greater helical sense bias was possible using a catalytic amount of (*S*)- and (*R*)-**6**. The CD intensity of the copolymer induced by 0.1 equiv of (*S*)-**6** was further significantly enhanced by more than 6-fold ($\Delta\varepsilon_{2nd}$ = 12.5; *hse* = 62.5%) compared to that at 1 mM ($\Delta\varepsilon_{2nd}$ = 1.9; Figures 3b(v) and 4a,b(i)). Moreover, even in the presence of 0.01 equiv of (*S*)-**6**, which corresponds to 1.0 equiv to the carboxy groups, the copolymer predominantly formed an (*M*)-handed helix with the *hse* value of 33% at a 100 mM concentration (Figure 4a,b(ii)). When the enantiomeric (*R*)-**6** (0.01 equiv) was used, the opposite (*P*)-handed helix was induced in poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$), showing the mirror image ICD (Figure 4(iii)). Again, poly-**1b** with no carboxy group showed no CD at all under the high concentration of poly-**1b** (100 mM) even in the presence of 1 equiv of (*S*)-**6** (Figure S6). Therefore, the extraordinary high sensitivity of the copolymer toward the chiral amine (**6**) can be attributed to the small amount of the carboxy groups introduced at the pendants of the copolymer, which enables it to sense the chirality of the chiral amines in a highly efficient manner

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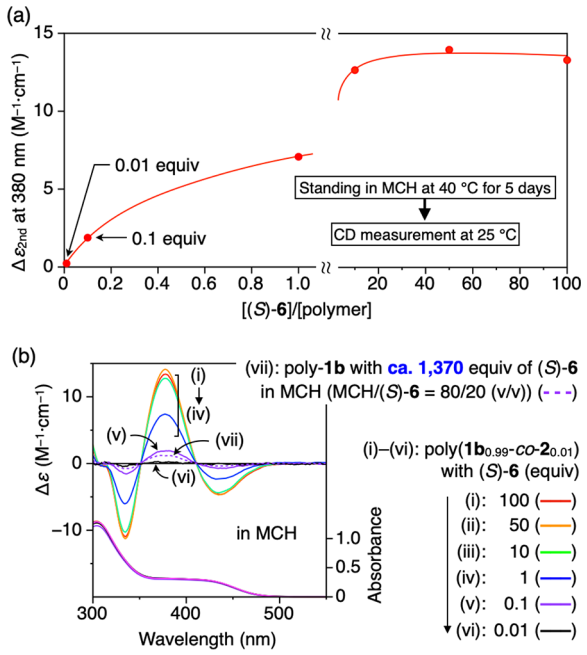

Figure 3. (a) CD titration curve ($\Delta\varepsilon_{2nd}$) of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) with (*S*)-**6** in MCH measured at 25 °C after storage at 40 °C for 5 days. The corresponding CD and absorption spectra (i–vi) and those of poly-**1b** with about 1370 equiv of (*S*)-**6** in MCH (MCH/(*S*)-**6** = 80/20 (v/v)) measured at 25 °C after storage at 40 °C for 5 days (vii) are also shown in (b). [Monomer units of polymer] = 1.0 mM.

assisted by strong chiral acid–base interactions that proceeds accompanied by noticeable amplification of the asymmetry.

As previously reported,[41,45] once one of the helices was induced in poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) with a catalytic amount of (*R*)-**6** (0.01 equiv) at a high concentration (100 mM; Figure 4(iii)), the induced one-handed helical conformations were retained after dilution[42] and further isolation due to the unique static helicity memory effect of PBPAs (Figures 4(iv) and S7). The static helicity memory of (*P*)-*h*-poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) was very stable in toluene at −10 °C and remained unchanged after 24 h (Figure S7c(i)). At 25 °C, however, the CD intensity gradually decreased with time (Figure S7c(ii)). Therefore, the chirality detection of an extremely small amount of chiral amines could be possible.[42]

In summary, we have synthesized BPA-based dynamically racemic helical copolymers containing a small amount of the carboxy groups (≤1 mol %) as a functional receptor site at the 2-position of the biphenyl pendants located in the vicinity of the polymer backbone. The alkoxycarbonyl-functionalized copolymer composed of 1 mol % of the carboxy-bound BPA units efficiently detected the chirality of optically active amines, particularly secondary amines, through a catalytic one-handed helix-induction and its static helicity memory accompanied by remarkable amplification of the macromolecular helicity that was driven by chiral acid–base interactions. The sensitivity of the copolymer toward the chiral amines was enhanced up to more than 10000-fold higher than that of the corresponding homopolymer with no carboxy group. An excess one-handed helix could be biased in the copolymer with 0.01 equiv of an optically active amine. We believe that this "catalytic macromolecular helicity induction and subsequent static helicity memory" achieved by a small side-chain modification with a receptor group provides emerging opportunities for developing versatile and practical helical polyacetylene-based switchable chiral materials for resolution of chiral molecules[40,45] and asymmetric catalysis,[46,47] whose helical handedness corresponding to their enantioselectivities can be readily switched at will with a small chiral bias. Work toward these goals is now underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmacrolett.2c00136.

Full experimental details, characterizations of monomers and polymers, and additional supporting data (PDF)

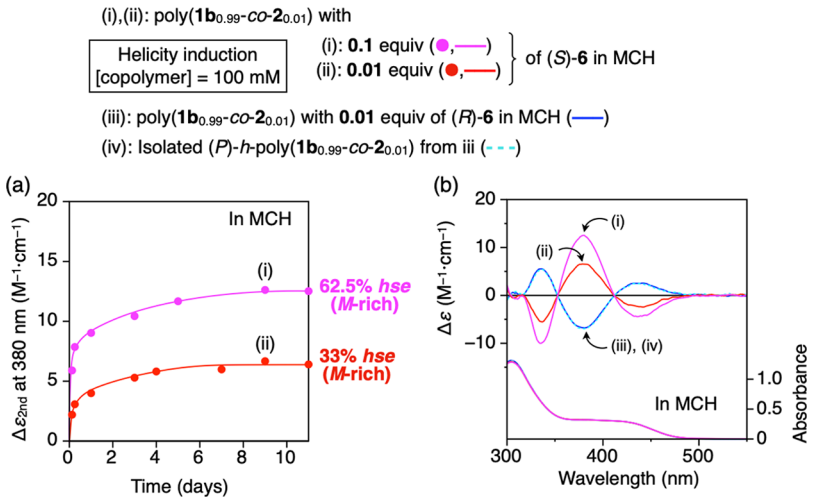

Figure 4. (a) Time-dependent ICD intensity ($|\Delta\varepsilon_{2nd}|$) changes of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) with 0.1 (i) and 0.01 (ii) equiv of (*S*)-**6** in MCH measured at −10 °C after storage at 40 °C ([monomer units of copolymer] = 100 mM). (b) CD and absorption spectra of poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) in the presence of 0.1 (i) and 0.01 (ii) equiv of (*S*)-**6** and 0.01 equiv of (*R*)-**6** (iii) in MCH measured at −10 °C after storage at 40 °C until no further increase in the ICD intensity was observed ([monomer units of copolymer] = 100 mM), and those of the isolated poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) recovered from iii (iv), measured at −10 °C. The helicity-memorized poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$) induced by (*R*)-**6** is abbreviated as (*P*)-*h*-poly($\mathbf{1b}_{0.99}$-*co*-$\mathbf{2}_{0.01}$). All the CD and absorption measurements were performed after being diluted with MCH ([monomer units of copolymer] = 1.0 mM).

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Notes

The authors declare no competing financial interest.

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