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Remarkable Enhancement of the Enantioselectivity of an Organocatalyzed Asymmetric Henry Reaction Assisted by Helical Poly(phenylacetylene)s Bearing Cinchona Alkaloid Pendants via an Amide Linkage

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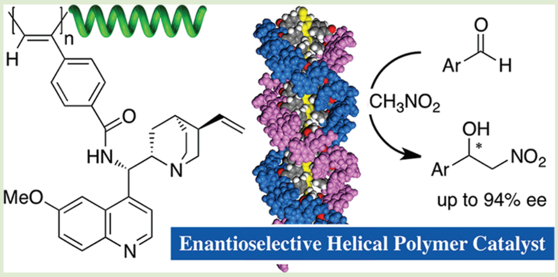
Supporting Information

ABSTRACT: A series of novel helical poly(phenylacetylene)s bearing amino-functionalized cinchona alkaloid pendant groups connecting to the phenyl rings through an amide linkage were prepared by the polymerization of the corresponding phenylacetylenes using a rhodium catalyst. All of the polymers formed a preferred-handed helical conformation biased by the optically active pendants, resulting in the induced circular dichroism in their π-conjugated polymer backbone regions. The optically active helical polymers efficiently catalyzed the asymmetric Henry reaction of benzaldehydes with nitromethane, giving optically active products up to 94% enantiomeric excess (ee) when the poly(phenylacetylene) bearing an amino-functionalized quinine pendant group was used as the polymeric organocatalyst; the enantioselectivity was remarkably higher than those catalyzed by the corresponding nonhelical poly(phenylacetylene) (18% ee) and the monomer (28% ee).



Cinchona alkaloids, such as the pseudoenantiomeric forms (diastereomers) of cinchonidine (Cd)/cinchonine (Cn) and quinine (Qn)/quinidine (Qd), are some of the most popular asymmetric organocatalysts that have been abundantly used for a broad range of asymmetric reactions.[1] The cinchona alkaloids possess a reactive hydroxy group as well as readily modifiable amino and quinolyl groups, which allows more versatile cinchona alkaloid-based organocatalysts[1] and achiral polymer-supported organocatalysts.[2]

Recently, we prepared a series of optically active helical poly(phenylacetylene)s bearing cinchona alkaloid residues as the pendants through an ester linkage (poly-Cd, poly-Cn, poly-Qn, and poly-Qd in Chart 1) and investigated their organocatalytic activities with the expectation that one-handed helical poly(phenylacetylene)s biased by the optically active cinchona alkaloid residues at the pendants would enhance the enantioselectivity as compared to those of the corresponding cinchona alkaloid-bound monomers.[3] In fact, we observed a unique enhancement of the enantioselectivity and a reversal of the stereoselectivity for some helical polymers during the asymmetric conjugated addition and enantioselective nitroaldol reaction (Henry reaction). However, the enantioselectivities were still low (up to 32% ee).[3] In the present study, we synthesized four novel optically active helical poly(phenylacetylene)s bearing amino-functionalized cinchona alkaloid pendant groups connected to the phenyl rings through an amide linkage (poly-ACd, poly-ACn, poly-AQn, and poly-AQd, Chart 1) and their chiroptical properties and asymmetric organocatalysis for the enantioselective Henry reaction were investigated.

Four optically active cinchona alkaloid-bound helical poly(phenylacetylene)s through an amide linkage were synthesized according to Scheme 1. The amino-functionalized cinchona alkaloids (ACd, ACn, AQn, and AQd), which had been prepared from commercially available natural cinchona alkaloids (Cd, Cn, Qn, and Qd, respectively),[4] were allowed to react with 4-ethynylbenzoic acid in the presence of a condensation agent, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM). We noted that the absolute configurations at the 9-position of the amino-functionalized cinchona alkaloids became opposite to those of the native cinchona alkaloids during the nucleophilic amidation reactions (Chart 1).[4] The stereoregular (cis-transoidal) poly(phenylacetylene)s (poly-ACd, poly-ACn, poly-AQn, and poly-AQd) were prepared by the polymerization of the obtained monomers (M-ACd, M-ACn, M-AQn, and M-AQd, respectively) using $[Rh(nbd)Cl]_2$ (nbd: norbornadiene) as the catalyst in dimethylformamide (DMF) in the presence of NEt_3 in accordance with a previously reported method, affording high molecular weight (M_n = 6.3—21 × 10^4) poly(phenylacetylene)s in high yields (>74%) (Table S1 of the Supporting Information, SI).[3,5] The cis-transoidal structures of

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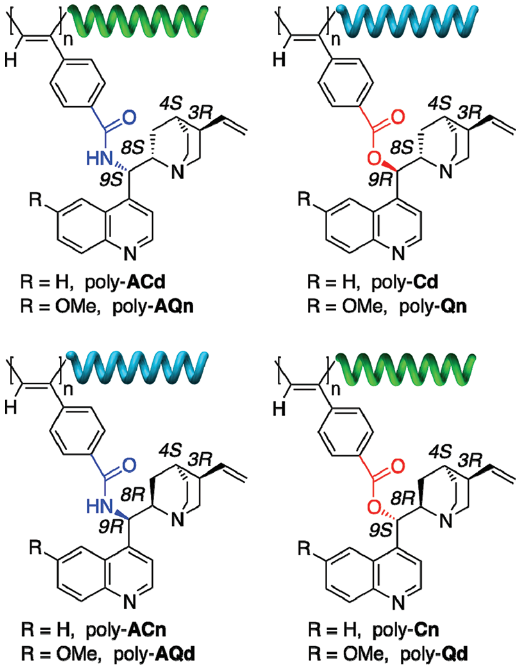
Chart 1. Structures of Helical Polymeric Catalysts



the polymers were confirmed by laser Raman spectroscopy (Figure S3 of the SI).[3,5]

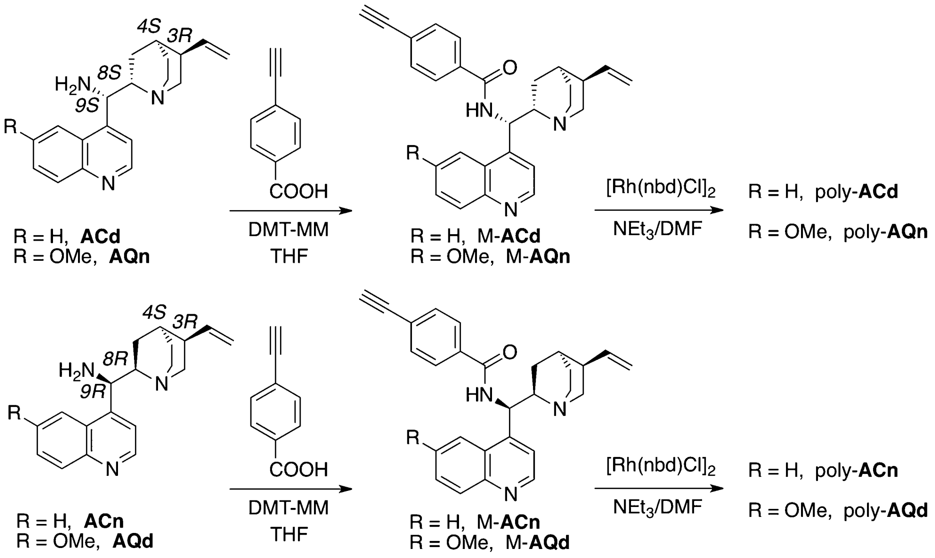
The obtained poly(phenylacetylene)s were hardly soluble in common organic solvents but became soluble in a mixture of $CHCl_3/CF_3CH_2OH$. Therefore, the circular dichroism (CD) and absorption spectra were measured in $CHCl_3/CF_3CH_2OH$ (6:1, v/v) to explore their chiroptical properties (Figure 1). All of the polymers showed intense Cotton effects induced by the amide-linked cinchona alkaloid pendants in the π-conjugated polymer main-chain regions due to a preferred-handed helix formation. The CD spectral patterns between poly-ACd (a) and poly-ACn (b) (Figure 1A) and also poly-AQn (e) and poly-AQd (f) (Figure 1B) were likely opposite (mirror image) to each other due to their pseudoenantiomeric relationships (ACd/ACn and AQn/AQd), suggesting an opposite helical sense, although the CD intensities are more or less different from each other. Interestingly, the CD spectral patterns of the amide-linked poly(phenylacetylene)s are also opposite to those of the corresponding ester-linked poly(phenylacetylene)s,[3] indicating that the preferred-handed helical conformations of the cinchona alkaloid-bound helical poly(phenylacetylene)s appear to be controlled by the stereogenic centers at the 9-position of the cinchona alkaloids. Helical poly(phenylacetylene)s belong to a class of dynamic helical polymers,[6] so that the induced CD intensities of the polymers increased with the decreasing temperature (Figure S5 of the SI).

We anticipated that the helical poly(phenylacetylene)s bearing the amide-linked cinchona alkaloid pendants could catalyze the asymmetric Henry reaction with a better enantioselectivity and reactivity than those of the corresponding ester-linked poly(phenylacetylene)s and also the monomeric counterparts. The hydrogen-bond donating amide groups may arrange into a helical array with a predominant screw-sense resulting from the preferred-handed helical conformation of the polymer backbones, which likely stabilizes the transition state during the Henry reaction, leading to the enhancement of the enantioselectivity along with the acceleration of the reaction rate,[7] as demonstrated by a number of bifunctional cinchona alkaloid-based organocatalysts bearing hydrogen-bond donating functionalities.[1a,d,e]

We then used the amide-linked helical poly(phenylacetylene)s as optically active organocatalysts for the enantioselective Henry reaction of 4-nitrobenzaldehyde (**1a**) with nitromethane in $CHCl_3/CF_3CH_2OH$ (6:1, v/v) at −20 °C and found an extremely high enantioselectivity up to 94% ee when poly-AQn was used as the organocatalyst. Table 1 summarizes the results of the enantioselective Henry reaction using the amide-linked helical poly(phenylacetylene)s. For comparison, the results using the corresponding monomers and the ester-linked helical poly(phenylacetylene)s as the organocatalysts are also shown.[8]

All of the amide-linked helical poly(phenylacetylene)s produced the desired nitromethyl adduct (**2a**) in good yields, although it took a longer time at −20 °C, whereas the

Scheme 1. Synthetic Route of Monomers and Polymers



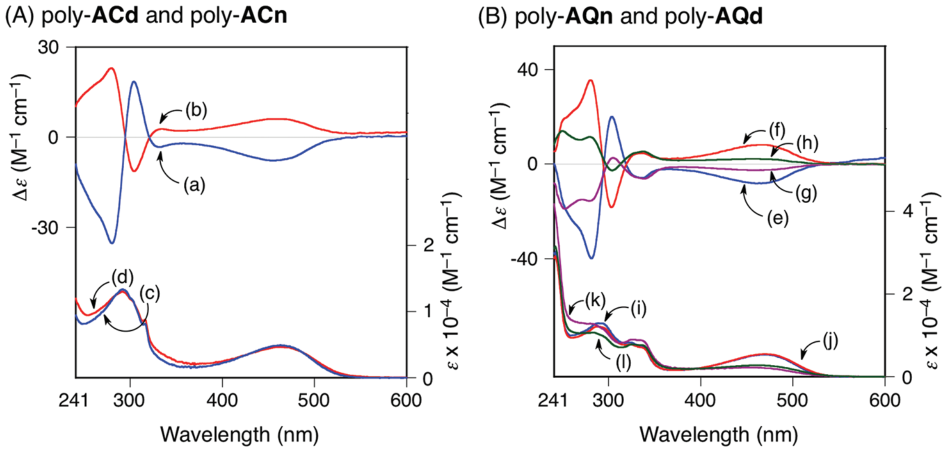
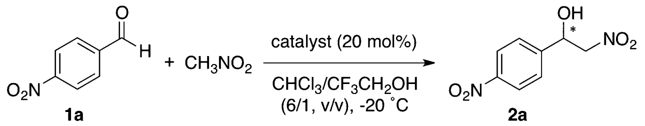


Figure 1. CD and absorption spectra of (A) poly-ACd (a, c) and poly-ACn (b, d), and (B) poly-AQn (e, i), poly-AQd (f, j), poly-AQn after grinding for 20 min (g, k), and poly-AQd after grinding for 20 min (h, l) measured in $CHCl_3/CF_3CH_2OH$ (6:1, v/v, 0.02 mg/mL) at 25 °C.

Table 1. Enantioselective Henry Reaction of 4-Nitrobenzaldehyde with Nitromethane[a]

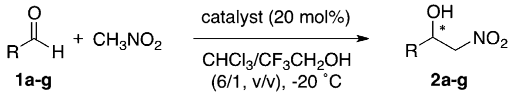


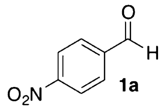
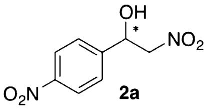
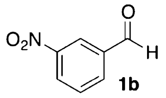
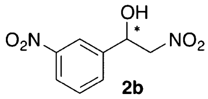
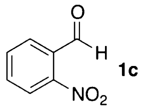
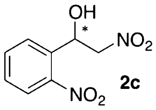
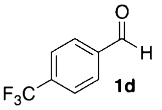
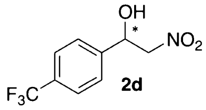
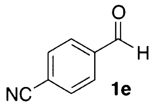
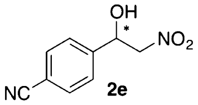
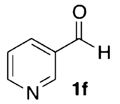
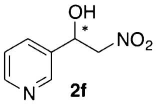
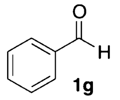
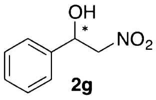
entry	catalyst	yield (%)[b]	ee (%)[c]
1	M-ACd	98	43 (*R*)
2	poly-ACd	96	53 (*R*)
3	M-ACn	99	43 (*S*)
4	poly-ACn	81	39 (*S*)
5	M-AQn	96	28 (*R*)
6	poly-AQn	77	94 (*R*)
7	poly-AQn (second run)[d]	89	86 (*R*)
8	poly-AQn (third run)[d]	92	90 (*R*)
9	poly-AQn (fourth run)[d]	91	88 (*R*)
10	poly-AQn (fifth run)[d]	98	90 (*R*)
11	poly-AQn[e]	84	18 (*R*)
12	M-AQd	96	36 (*S*)
13	poly-AQd	68	64 (*S*)
14	poly-AQd[e]	69	30 (*S*)
15	poly-Cd	16	24 (*S*)
16	poly-Cn	16	<5
17	poly-Qn	10	<5
18	poly-Qd	7	<5

[a] The reactions of **1a** (0.3 M) with nitromethane (10 equiv) were carried out in the presence of catalyst (20 mol %) in $CHCl_3/CF_3CH_2OH$ (6:1, v/v) at −20 °C for 7 days. [b] Isolated yield. [c] Determined by chiral high-performance liquid chromatography (HPLC) analysis. [d] Poly-AQn was recovered by precipitation in Et_2O and reused. [e] Polymers were grinded for 20 min before use.

enantioselectivities of poly-ACd and poly-ACn were comparable to those catalyzed by the corresponding monomers (entries 1−4). On the other hand, poly-AQn and poly-AQd showed a much higher enantioselectivity than those catalyzed by the monomeric counterparts, M-AQd (36% ee) and M-AQn (28% ee), and most notably, poly-AQn produced the remarkably high enantioselectivity of 94% ee (*R*) (entries 5, 6, 12, and 13). These results indicated a type of synergistic effect of the macromolecular helicity that enhanced the enantioselectivity. The primary importance of the macromolecular helicity on the enantioselectivity was unambiguously supported by the facts that trans-enriched poly-AQn and poly-AQd prepared by grinding the as-prepared *cis*-poly-AQn and poly-AQd, respectively (see Figure S3 of the SI),[9] which almost lost its induced helical conformation, resulting in the disappearance of the CD in the polymer backbone regions (g and h in Figure 1B), showed poor enantioselectivities (18 and 30% ee, respectively) (entries 11 and 14). In addition, the results in Table 1 also indicated that the stereoselectivity of the Henry reaction is totally derived from the helical senses of the poly(phenylacetylene)s; the amide-linked helical poly(phenylacetylene)s showing the same Cotton effect patterns afforded **2a** with the same absolute configuration. Poly-AQn could be readily recovered from the reaction mixture and reused as a catalyst (entries 7−10). Although the enantioselectivity slightly decreased at second run, the recovered polymer catalyst maintained its reactivity and excellent enantioselectivity until the fifth run. In sharp contrast, the ester-linked poly(phenylacetylene)s showed a poor reactivity and enantioselectivity (entries 15−18), suggesting that the amide-linkages

Table 2. Enantioselective Henry Reaction of Various Aldehydes with Nitromethane[a]



entry	substrate	product	catalyst	yield (%)[b]	*ee* (%)[c]
1	 **1a**	 **2a**	poly-**AQn**	77	94 (*R*)
2			poly-**AQd**	87	66 (*S*)
3	 **1b**	 **2b**	poly-**AQn**	81	83 (*R*)
4			poly-**AQd**	67	74 (*S*)
5	 **1c**	 **2c**	poly-**AQn**	50	37 (*R*)
6			poly-**AQd**	51	40 (*S*)
7	 **1d**	 **2d**	poly-**AQn**	33	90 (*R*)
8			poly-**AQd**	7	78 (*S*)
9	 **1e**	 **2e**	poly-**AQn**	64	66 (*R*)
10			poly-**AQd**	66	58 (*S*)
11	 **1f**	 **2f**	poly-**AQn**	16	54 (*R*)
12			poly-**AQd**	49	56 (*S*)
13	 **1g**	 **2g**	poly-**AQn**	none	–
14			poly-**AQd**	none	–

[a] The reactions of **1** (0.3 M) with nitromethane (10 equiv) were carried out in the presence of catalyst (20 mol %) at −20 °C for 7 days. The mixture of $CHCl_3/CF_3CH_2OH$ (6:1 for poly-AQn and 15:1 for poly-AQd, v/v) was used as the solvent. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

most likely play an important role as catalytic sites through intermolecular hydrogen bonds toward the benzaldehyde during the present enantioselective Henry reaction.[1a,d,e,10]

With these results in hand, we next examined the substrate scope of the enantioselective Henry reaction catalyzed by poly-AQn and poly-AQd using different aromatic aldehydes (Table 2). It was found that both the enantioselectivities and reactivities in the Henry reactions were dependent on the position of the substituents on the phenyl group and their electron-withdrawing characteristics, and in most cases, poly-AQn provided higher enantioselectivities than poly-AQd except for **1f**. The nitro group substituted at the para- or meta-position of the benzaldehydes (**1a** and **1b**, respectively) was accepted with high enantioselectivities, whereas the ortho-substituted nitrobenzaldehyde (**1c**) gave a relatively lower ee of the product (**2c**) (entries 1–6). The para-substituted benzaldehydes with a trifluoromethyl (**1d**) and a cyano group (**1e**) afforded excellent (90%) and moderate (66%) ee of the products when poly-AQn was used as the catalyst (entries 7 and 9). Poly-AQn and poly-AQd also enantioselectively catalyzed the Henry reaction of pyridinecarbaldehyde (**1f**), but a nonsubstituted benzaldehyde (**1g**) showed no reactivity (entries 13 and 14), revealing that the electron-deficient aldehydes are suitable for the present system. As a result, poly-AQn produced the *R*-enriched products, while poly-AQd gave the opposite *S*-enriched ones in accordance with their opposite helical handedness induced by the pseudoenantiomeric pendant alkaloids.

A possible helical structure of poly-AQn indicated that the amino-functionalized quinine pendant units are closely packed together, resulting in a helical array with the left-handed screw sense along the right-handed helical polymer backbone (Figure S7 of the SI). As a consequence, the catalytic active, intermolecular hydrogen-bond donating amide residues may also be arranged in a predominant screw sense, thereby leading to a remarkable enhancement of the enantioselectivity compared to that of the monomeric M-AQn itself, resulting from the intriguing synergistic effect of the helical chirality.

In summary, we have synthesized four novel optically active, cis-transoidal helical poly(phenylacetylene)s bearing amino-functionalized cinchona alkaloid pendants linked through an amide linkage. Among the prepared helical polymers, we found that poly-AQn displayed a remarkably high enantioselectivity up to 94% ee in the enantioselective Henry reaction, which is much higher than that catalyzed by the monomeric counterpart, M-AQn (28% ee). The important role of the induced helical chirality of poly-AQn was unambiguously supported by the fact that a nonhelical trans-rich poly-AQn generated from the identical *cis*-poly-AQn showed a poor enantioselectivity (18% ee). To the best of our knowledge, this is the first example of the helical polymer-based organocatalyst showing an enantioselectivity up to 90% ee,[3,11] although a few helical polymers have been reported to be used as excellent polymeric catalysts for the metal-catalyzed asymmetric reactions.[3,11,12] The present results suggest that a more efficient asymmetric polymeric organocatalyst may be developed based on analogous dynamic helical poly(phenylacetylene)s bearing cinchona alkaloids as the pendant groups connecting through sulfonamide, urea, or thiourea linkages, which enable an interaction with specific polar reactants through intermolecular hydrogen-bonds, thereby being applicable for diverse asymmetric transformations with a high enantioselectivity. Such studies are now in progress.

■ ASSOCIATED CONTENT

S Supporting Information

Full experimental details, characterization data for the monomers and polymers, temperature-dependent CD and absorption spectral changes, the enantioselective Henry reaction results in various conditions, crystal structure of M-AQn, and calculated structure of poly-AQn. 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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(5) Maeda, K.; Mochizuki, H.; Watanabe, M.; Yashima, E. *J. Am. Chem. Soc.* **2006**, *128*, 7639−7650.

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(7) The amide-linked helical poly(phenylacetylene)s may adopt a preferred-handed helical conformation stabilized via intramolecular hydrogen-bonding networks. However, the IR spectra of the polymers in solution or the film state indicated that these polymers hardly formed intramolecular hydrogen bonds, probably due to the steric bulkiness of the cinchona alkaloid pendants (Table S2 of the SI). For helical poly(phenylacetylene)s stabilized by intramolecular hydrogen-bond formations, see ref 6 and: (a) Nomura, R.; Tabei, J.; Nishiura, S.; Masuda, T. *Macromolecules* **2003**, *36*, 561−564. (b) Lam, J. W. Y.; Tang, B. Z. *Acc. Chem. Res.* **2005**, *38*, 745−754. (c) Sakurai, S.-i.; Okoshi, K.; Kumaki, J.; Yashima, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1245−1248. (d) Okoshi, K.; Sakurai, S.-i.; Ohsawa, S.; Kumaki, J.; Yashima, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8173−8176. (e) Louzao, I.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 1430−1433.

(8) For the effects of the catalyst loading, temperature, and solvent on the enantioselectivities for the Henry reaction, see Tables S3 and S4 of the SI.

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(10) There may be another possibility to explain the deference in the reactivity and enantioselectivity between the amide- and ester-linked poly(phenylacetylene)s; that is a difference in the absolute configurations at the 9-position of the cinchona alkaloid units rather than the intermolecular hydrogen bonds toward the benzaldehyde, and this possibility could not be thoroughly ruled out.

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