

with *N*-iodosuccinimide<sup>19</sup> cleaved the bisdithiane **24** smoothly to the diketone **25** (mp 117.5–118.5 °C,  $[\alpha]_D +13.88^\circ$  (*c* 0.5, CHCl<sub>3</sub>)) in 90% yield. The 2-oxopropyl side chains were then restored by trans ketalization with boron trifluoride etherate in acetone, furnishing, after recrystallization from acetic acid, pure (–)-vermiculine (**1**) (mp 177–178 °C,  $[\alpha]_D -10.6^\circ$  (*c* 0.2, CHCl<sub>3</sub>)) as colorless prisms in 90% yield, identical in all respects with the natural product.<sup>20</sup>

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## References and Notes

- J. Fuska, P. Nemeč, and I. Kuhr, *J. Antibiot.*, **25**, 208–211 (1972).
- P. Sedmera, J. Vokoun, M. Podojil, and Z. Vaněk, *Tetrahedron Lett.*, 1347–1348 (1973).
- R. K. Boeckman, Jr., J. Fayos, and J. Clardy, *J. Am. Chem. Soc.*, **96**, 5954–5956 (1974).
- E. J. Corey, K. C. Nicolaou, and T. Toru, *J. Am. Chem. Soc.*, **97**, 2287–2288 (1975); Y. Fukuyama, C. L. Kirkemo, and J. D. White, *ibid.*, **99**, 646–647 (1977).
- D. Seebach, B. Seuring, H. O. Kalinowski, W. Lubosch, and B. Renger, *Angew. Chem., Int. Ed. Engl.*, **16**, 264–265 (1977).
- W. S. Wadsworth, Jr., *Org. React.*, **25**, 73–253 (1977).
- K. E. Wilson, Ph.D. Thesis, University of Alberta, 1973 (see also S. Masamune, G. S. Bates, and J. W. Corcoran, *Angew. Chem.*, **89**, 608 (1977)).
- A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Am. Chem. Soc.*, **89**, 431–434 (1967).
- A. I. Meyers and R. C. Strickland, *J. Org. Chem.*, **37**, 2579–2583 (1972).
- T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.*, **82**, 5339–5342 (1960).
- The relative configuration of **5a** was deduced later by X-ray of the derivative **26**.
- A. I. Meyers, G. Knaus, and P. M. Kendall, *Tetrahedron Lett.*, 3495–3498 (1974).
- R. Greenhalgh, R. M. Heggie, and M. A. Weinberger, *Can. J. Chem.*, **41**, 1662–1670 (1963); A. I. Meyers and D. L. Temple, *J. Am. Chem. Soc.*, **92**, 6646–6647 (1970).
- K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957–962 (1976).
- Best results were obtained at substrate concentrations of 0.25%, in THF, using 1 equiv of NaH or NaOEt as a base. At  $\geq 1\%$  concentration, cyclic oligomers larger than **15** (e.g., a "trimer" was isolated) predominate in the resulting mixture.
- The CSA salt of **5b** (mp 178–179 °C,  $[\alpha]_D +24.16^\circ$  (*c* 2, MeOH)), obtained in 66% recovery by addition of 0.5 equiv of CSA to a CH<sub>3</sub>CN solution of **5a** followed by one recrystallization from CH<sub>3</sub>CN–MeOH, was of sufficient optical purity for the ensuing transformations.
- E. J. Corey and K. Achiva, *J. Am. Chem. Soc.*, **91**, 1429–1432 (1969).
- E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 1718–1722 (1976).
- The best conditions were found to be 12 equiv of NIS (6 min, –7 °C) in acetone–H<sub>2</sub>O (19:1), followed by quenching with aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution.
- We thank Professor J. D. White for providing us with an authentic sample of natural vermiculine for comparison of the CD and ORD spectra.
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## Poly(cinchona alkaloid-co-acrylonitrile)s. New Polymer Catalysts for Asymmetric Synthesis<sup>1</sup>

Sir:

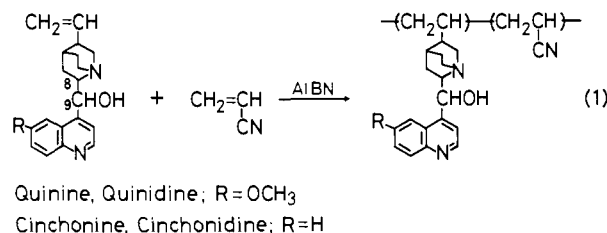
The catalytic activities of cinchona alkaloids in asymmetric organic reactions have been extensively studied.<sup>2</sup> The principal drawback in the use of the alkaloid catalyst is the relative difficulty of separating the product from the catalyst. One way to overcome this drawback would be to fix the alkaloid on a

**Table I.** Copolymerization of Quinine with Acrylonitrile<sup>a</sup>

| entry | quinine/<br>acrylonitrile | polymer  |                   |                                 |   |
|-------|---------------------------|----------|-------------------|---------------------------------|---|
|       |                           | yield, % | $\eta_{inh}^b$    | $[\alpha]_D$ , deg <sup>c</sup> | quinine<br>content,<br>mol % <sup>d</sup> |
| 1     | 1:20                      | 51.4     | 0.23              | –15.7                           | 3.2                                       |
| 2     | 1:15                      | 42.0     | 0.20              | –19.4                           | 4.2                                       |
| 3     | 1:9                       | 28.8     | 0.20              | –24.8                           | 5.8                                       |
| 4     | 1:4                       | 17.9     | 0.16 <sup>e</sup> | –37.0                           | 9.9                                       |
| 5     | 1:3                       | 11.4     | 0.13              | –41.8                           | 12.0                                      |

<sup>a</sup> Reaction conditions: acrylonitrile, 1.59 g (30 mmol); AIBN, 0.04 g (0.24 mmol); chloroform, 10 mL; refluxing for 44 h with stirring under argon. <sup>b</sup> Measured in DMF at 30 °C. <sup>c</sup> Measured in DMF at 28 °C. <sup>d</sup> Calculated from the analytical data. <sup>e</sup>  $M_n$  3800.

solid support in a way that retains the stereoselectivity of the alkaloid (eq 1).



In designing such a polymeric alkaloid, it has to be taken into account that the amino alcohol part of the alkaloid, N(1)–C(8)–C(9)–OH, generally plays an crucial role in asymmetric reactions: the configurations at C(8) and C(9) in the alkaloid are of fundamental importance in determining the configuration of products; in addition, modification of the hydroxyl or amino group affects significantly the extent of stereoselectivity, usually in the direction of lowering optical yields.<sup>3,4</sup> In this respect the previously known polymeric cinchona alkaloids, in which the alkaloid moiety is anchored in either O-acylated form<sup>5</sup> or N-alkylated form,<sup>6</sup> seem to have limited potential as catalysts for asymmetric synthesis.

Accordingly, we investigated the utilization of the vinyl group of the alkaloids as the connecting site to polymers.<sup>7</sup> We report herein a remarkably general procedure for the synthesis of new polymeric cinchona alkaloids, in which the amino alcohol part can be free or protected, and demonstrate their potential as asymmetric catalysts. Our procedure is based on the radical copolymerization of cinchona alkaloids with vinyl monomers. This is the first report of vinyl polymerization of cinchona alkaloids.<sup>8</sup>

Of the various vinyl monomers examined, acrylonitrile showed the highest copolymerizability with the alkaloids.<sup>9</sup> Copolymerization of cinchona alkaloid with acrylonitrile was carried out using azobisisobutyronitrile (AIBN) as an initiator under an inert gas atmosphere. A typical experimental procedure follows. A solution of quinine (7.5 mmol), acrylonitrile (30 mmol), and AIBN (0.24 mmol) in chloroform (10 mL) was stirred magnetically for 44 h with refluxing. The precipitated polymer was filtered, washed with methanol, reprecipitated from DMF into methanol, and dried at 70 °C under a vacuum. Table I summarizes the representative results of quinine-acrylonitrile copolymerization.

All the polymers had negative rotations. The IR spectra (KBr) showed bands at 1620, 1590, 1245, and 1230 cm<sup>–1</sup> characteristic of quinine, and a band at 2250 cm<sup>–1</sup> due to nitrile groups. The polymer gave <sup>1</sup>H NMR spectra (Me<sub>2</sub>SO-*d*<sub>6</sub>, 100 MHz,  $\delta$ ) without signals due to allylic protons: in the 4.8–6.1 region only two signals due to H–O (~5.2) and H–C(9) (~5.6) were observed. Since quinine is resistant to homopolymerization under the conditions employed, it was

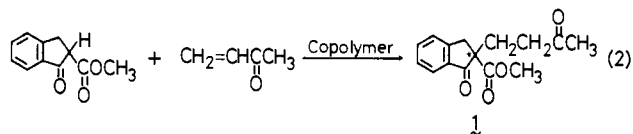
concluded, on the basis of above observations, that quinine moiety is incorporated in the polymers through its vinyl group. The average number of quinine units per molecule was calculated as 3.2 for the 1:4 copolymer (entry 4) from the molecular weight and the analytical data.

As can be seen from Table I, the yield and inherent viscosity decrease with increasing the mole fraction of quinine in feed. This behavior is rationalized in terms of the allylic structure of quinine.<sup>10</sup> When benzoyl peroxide (BPO) was used as the initiator in place of AIBN, polymerization did not take place.<sup>11</sup> A variety of solvents can be used in the copolymerization, including acetone, acetonitrile, benzene, THF, and DMF. For a large-scale synthesis, DMF is the solvent of choice because the copolymerization proceeds homogeneously in that solvent.

This procedure is applicable to a wide range of cinchona alkaloids and their derivatives. Quinidine, cinchonidine, quinine hydrochloride, and 9-*O*-ethoxycarbonylquinine were copolymerized successfully with acrylonitrile in a similar manner. The copolymerization of cinchonine was somewhat difficult on account of its poor solubility, but was accomplished by conducting the reaction in DMF at 80 °C at a small ratio of cinchonine to acrylonitrile (1:19). Also synthesized in DMF were copolymers of quinine dihydrochloride-acrylonitrile and 1-benzylquininium chloride-acrylonitrile.

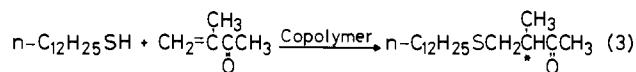
The copolymers are thermally stable,<sup>12</sup> light yellow powders. They are soluble in polar aprotic solvents, such as DMF and Me<sub>2</sub>SO, and insoluble in common organic solvents. Because of these solubility characteristics, not only purification and characterization of the copolymers but also their use as insoluble catalysts for asymmetric reactions is possible.

Preliminary experiments revealed that the cinchona alkaloid-acrylonitrile copolymers are efficient catalysts for some asymmetric reactions.<sup>13</sup> A mixture of methyl indan-1-one-2-carboxylate (5 mmol), methyl vinyl ketone (10 mmol), and a quinidine-acrylonitrile copolymer (quinidine residue 0.25 mmol) in toluene (30 mL) was stirred at room temperature for 48 h. Workup of the reaction mixture and elution of the crude product on silica gel/hexane-ethyl acetate (1:1) gave a 92% chemical yield of the Michael adduct **1** (eq 2),  $[\alpha]^{25}_D +33.7^\circ$



(*c* 1.50, benzene), 42% ee.<sup>14,15</sup> With a quinine-acrylonitrile copolymer the (–) enantiomer was formed in 30% excess (chemical yield 98%) under the same conditions. These optical yields are more than three times those obtained recently in the same reaction catalyzed by quinine anchored to cross-linked polystyrene in *O*-acylated forms (6–11% ee).<sup>16</sup>

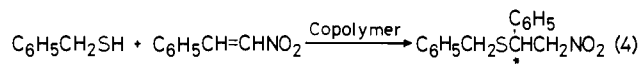
The reaction of dodecanethiol (25 mmol) with isopropenyl methyl ketone (37 mmol) in the presence of a quinidine-acrylonitrile copolymer (quinidine residue 0.6 mmol) in toluene (30 mL) at room temperature under nitrogen for 7 days afforded **2** (76% conversion) (eq 3),  $[\alpha]^{25}_D +9.90^\circ$  (*c* 1.50,



methanol), 57% ee.<sup>15,17</sup> This is the highest value ever achieved in the asymmetric reactions catalyzed by synthetic organic polymers.<sup>18</sup> Monomeric quinidine as catalyst also gave (+) enantiomer in excess but the selectivity was somewhat lower (51% ee).

More distinct polymer effect was observed in the reaction of benzyl mercaptane with 2-nitrostyrene.<sup>19</sup> A quinine-acrylonitrile copolymer and a quinidine-acrylonitrile copolymer

gave product **3** (eq 4) with  $[\alpha]^{25}_D$  (toluene) +18.7° (*c* 2.73)



and +36.3° (*c* 2.41), respectively, while monomeric quinine and quinidine gave **3** with  $[\alpha]^{25}_D$  (toluene) –6.0° (*c* 2.48) and +3.9° (*c* 2.77), respectively.<sup>15,20</sup> Although the enantiomeric excess of the product **3** has not yet been determined, it is to be noted that the stereoselectivities of the present polymer catalysts exceed those of their monomeric counterparts by factors of 3–9.

In all of above reactions the polymer catalysts were recovered from the reaction mixture with retention of their stereoselectivities by a mere filtration.

While much work remains to be done on the evaluation of polymerization variables and the characterization of copolymers, the potential applications of the copolymers should be obvious and the catalytic properties of these materials are currently under study.

## References and Notes

- Functional Polymers. 1. Presented in part at the 37th Annual Meeting of the Chemical Society of Japan, April 1–4, 1978, Tokyo.
- J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N.J., 1971.
- (a) V. Prelog and M. Wilhelm, *Helv. Chim. Acta*, **37**, 1634–1660 (1954); (b) G. Berti and A. Marsili, *Tetrahedron*, **22**, 2977–2988 (1966); (c) Y. Ohgo, S. Takeuchi, Y. Natori, and J. Yoshimura, *Chem. Lett.*, 33–36 (1974); (d) L. Meurling, *Chem. Scr.*, **7**, 90–96 (1975); (e) H. Pracejus, F.-W. Wilcke, and K. Hanemann, *J. Prakt. Chem.*, **319**, 219–229 (1977).
- In some special cases acetylated or N(1)-quaternized cinchona alkaloids exhibit high stereoselectivities. See S. Winter and H. Pracejus, *Chem. Ber.*, **99**, 151–159 (1966), and references cited therein; R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett.*, 1831–1834 (1976); J. C. Hummelen and H. Wynberg, *ibid.*, 1089–1092 (1978).
- (a) N. Grubhofer and L. Schleith, *Naturwissenschaften*, **40**, 508 (1953); (b) K. Yamauchi, M. Kinoshita, and M. Imoto, *Bull. Chem. Soc. Jpn.*, **44**, 3186–3187 (1971); (c) T. Yamashita, H. Yasueda, and N. Nakamura, *Chem. Lett.*, 585–586 (1974); (d) T. Yamashita, H. Yasueda, Y. Miyauchi, and N. Nakamura, *Bull. Chem. Soc. Jpn.*, **50**, 1532–1534 (1977); (e) C. P. Pinazzi, A. Menil, J. C. Rabadeux, and A. Pleurdeau, *J. Polym. Sci., Polym. Symp.*, **No. 52**, 1–7 (1975).
- H. Suda and R. Oda, *Kanazawa Dalgaku Kogakubu Kiyō*, **2**, 215–217 (1960).
- Previous studies concerning the reactions involving the vinyl group of cinchona alkaloids: (a) R. B. Turner and R. B. Woodward in "The Alkaloids", Vol. 3, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N.Y., 1953, Chapter 16; (b) A. Lempka, *Wycza Szk. Ekon. Poznaniu, Zesz. Nauk., Ser. 1*, **53**, 145–149 (1974) (*Chem. Abstr.*, **81**, 120841u (1974)).
- Insoluble polymer formation in the radical polymerization of 9-*O*-methacryloylquinine has been assumed to be caused by cross-linking through the participation of the vinyl group of quinine.<sup>5b</sup>
- Methacrylonitrile, *N*-vinylcarbazole, and acrylamide also copolymerized with cinchona alkaloids but to a lesser extent.
- T. Alfrey and J. G. Harrison, Jr., *J. Am. Chem. Soc.*, **68**, 299–301 (1946).
- Quinine also inhibited the polymerization of styrene initiated by BPO.
- The decomposition points range from 230 to 280 °C as determined by TGA.
- For the special purpose of using copolymers as asymmetric catalysts, copolymers were synthesized in DMF on 0.3 mol scale (with respect to acrylonitrile) and purified by triplicated reprecipitations from DMF into methanol followed by Soxhlet extraction with methanol for 3 h.
- The  $[\alpha]^{25}_D$  of optically pure **1** was calculated as  $80.5 \pm 1.5^\circ$  by the least-squares method from the % ee– $[\alpha]_D$  relationship determined for chemically pure samples by <sup>1</sup>H NMR spectroscopy with the aid of Eu(TFC)<sub>3</sub>. The  $[\alpha]^{RT}_{578}$  of optically pure **1** has been calculated as  $77.0^\circ$ ; see H. Wynberg and R. Helder, *Tetrahedron Lett.*, 4057–4060 (1975).
- The absolute configuration is unknown.
- K. Hermann and H. Wynberg, *Helv. Chim. Acta*, **60**, 2208–2212 (1977).
- Based on  $[\alpha]_D$  17.5 ± 1° (methanol) reported in ref 18.
- Y. Ueyanagi and S. Inoue, *Makromol. Chem.*, **178**, 235–239 (1977).
- The conditions are 11 mmol of benzyl mercaptane, 10 mmol of 2-nitrostyrene, 0.25 mmol of catalyst, 30 mL of toluene, room temperature, nitrogen atmosphere, and 17 h.
- Pracejus and co-workers conducted the same reaction at 0 °C. The  $[\alpha]_D$  (toluene) values reported are –7.4° (quinine catalyst) and +7.2° (quinidine catalyst).<sup>3e</sup>

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