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FUNCTIONAL POLYMERS. 6. UNUSUAL CATALYSIS OF POLYMERIC CINCHONA ALKALOIDS IN ASYMMETRIC REACTION

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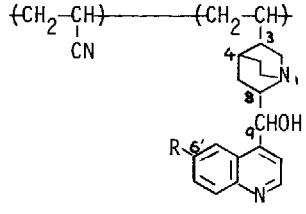
Abstract: Acrylonitrile-cinchona alkaloid copolymers catalyzed the asymmetric addition of benzyl mercaptan to 2-nitrostyrene to give always (+)-enantiomer in excess, indicating the participation of C(3)-chirality in the enantioface differentiating step.

In almost all cases so far reported, the stereochemistry of the asymmetric reactions under the influence of cinchona alkaloids or their derivatives is controlled by the configurations at C(8) and C(9) in the alkaloids;[1,2] if quinine (QN) or cinchonidine (CD) having C(8)-(*S*), C(9)-(*R*) *erythro* configurations gives (*S*)-enantiomer in excess, quinidine (QD) or cinchonine (CN) with opposite (*R*), (*S*) *erythro* arrangements will give (*R*)-enantiomer in excess (henceforth called "C(8), C(9)-control"). Since our discovery[3] that acrylonitrile copolymerizes with cinchona alkaloids, we have been exploring the catalytic behavior of the polymeric alkaloids (AN-CA) in asymmetric reactions.[2c,4,5] We now report an unusual catalysis of AN-CA which strongly indicates the participation of C(3)-chirality in the enantioface differentiating step.



AN-CA

		Config.			
Type	R	C(3)	C(4)	C(8)	C(9)
QN	OMe	*R*	*S*	*S*	*R*
QD	OMe	*R*	*S*	*R*	*S*
CD	H	*R*	*S*	*S*	*R*
CN	H	*R*	*S*	*R*	*S*

Asymmetric addition of benzyl mercaptan (1) to 2-nitrostyrene (2) was studied by using the AN-CA catalysts.[6] A mixture of 1 (11 mmol), 2 (10 mmol), and a catalyst (0.25 mmol) in toluene (30 ml) was stirred at room temperature under nitrogen. The reaction was complete within 17 hr. The catalyst was removed by filtration. Distillation of the filtrate gave chemically pure product, 3 (bp 158-160 °C(0.15 mm)). The results are summarized in the Table. The enantiomeric excess of 3 was determined by the chemical correlation with 2-benzylthio-2-phenylethylamine hydrochloride (5). Reduction of 3, $[\alpha]_D^{25}$ +15.3° (*c* 2.9, toluene), with Fe-AcOH[7] gave the corresponding amine, 4,[8] which, in turn, was treated with HCl to yield 5, $[\alpha]_D^{20}$ +15.9° (*c* 3.5, MeOH). Since optically pure 5 was reported to show $[\alpha]_D^{20}$ 205.9° (*c* 3.5, MeOH),[1i] it was

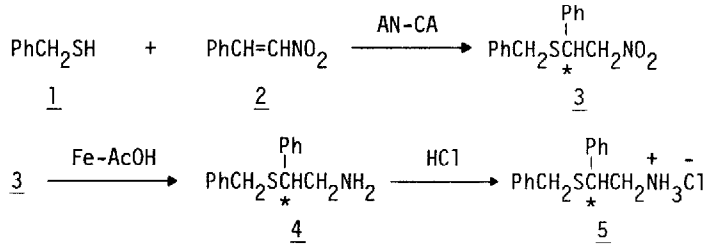


Table. Asymmetric Addition of 1 to 2

Entry	Catalyst (mac[a])	Chemical yield, %[b]	$[\alpha]_D^{25}$, deg[c]	% ee[d]
1	AN-QN (3.6)	61	+14.8	7.3
2	(6.0)	47	+18.7	9.3
3	(10.8)	51	+11.7	5.8
4	AN-QD (3.3)	51	+29.9	14.8
5	(5.4)	54	+36.3	18.0
6	(9.8)	55	+21.9	10.8
7	AN-CD (3.1)	60	+20.7	10.2
8	(6.1)	50	+25.7	12.7
9	(7.9)	48	+20.2	10.0
10	AN-CN (2.4)	50	+25.1	12.4
11	AN-QN·HCl[e](6.9)	47	+ 3.7	1.8
12	AN-QNEC[f](9.9)	44	+ 8.8	4.4

[a]Mol % alkaloid content in copolymer. [b]Calculated on the distilled sample. [c]Measured in toluene (*c* 2-3). [d]Absolute configuration is unknown. Determination of % ee: see text. [e]Acrylonitrile-quinine hydrochloride copolymer. [f]Acrylonitrile-9-*O*-ethoxycarbonylquinine copolymer.

estimated that optical rotation of the optically pure 3 was $[\alpha]_D^{25}$ 202° (toluene). The % ee data in the Table are based on this value.[9]

The Table shows that the extent of asymmetric induction was sensitive to the copolymer composition; optimum composition for the highest optical yield existed in every family of copolymers (entries 2, 5, 8). It is also shown that modification of N(1)-amino group (entry 11) or hydroxyl group (entry 12) greatly reduced the stereoselectivity.[10] The most striking aspect of the present results is that the AN-CA catalysts always gave an excess of (+)-3 irrespective of the kind of the alkaloid units incorporated. The other example of such a phenomenon could not be found in the literature.[11]

For comparison, the catalytic behavior of monomeric alkaloids (CA) and their dihydro derivatives (DHCA) were investigated. The specific rotations of 3 obtained were -6.0° (QN), +3.9° (QD), +6.3° (CD), +10.9° (CN), -13.6° (DHQN), +15.5° (DHQD), -1.7° (DHCD), and +14.7° (DHCN). The results with the CA catalysts are not simply correlated to the configurations at

C(8) and C(9),[2] but are in accord with the data of Pracejus et al.[1i] It is to be noted that the AN-CA catalysts are far more stereoselective than the CA catalysts in this particular reaction. The results with the DHCA catalysts constitute a typical example of C(8), C(9)-control. These findings show that the catalytic behavior of AN-CA is quite different from that of low molecular-weight counterparts.

In the AN-CA catalyzed reaction, some chiral factor, which is common to all the alkaloids used, must play an important role in the enantioface differentiation. Of the four asymmetric centers in the alkaloid, those at C(3) and C(4) may meet this requirement. Because, structurally, the AN-CA differs from the CA and the DHCA only in the substituent at C(3) (polymer chain, vinyl group, and ethyl group, respectively), the most probable explanation for the unusual catalysis of the AN-CA appears to be that the chiral force stemming from C(3) is greatly reinforced by a large substituent (polymer chain) to exceed the chiral force stemming from C(8) and C(9), which is otherwise stronger than that from C(3). We call this type of stereocontrol as "C(3)-control".

The reaction temperature affected the asymmetric induction in a different way depending on whether the catalyst was monomeric or polymeric (Figure). On changing the temperature from +60 ° to -78 °C, enantiomeric excess of 3 induced by QD increased almost linearly from 1.8 to 4.0%. On the other hand, with AN-QD catalyst (mol % alkaloid content (mac) = 5.4) the best result (18% ee) was obtained at room temperature, and either raising or lowering the temperature caused a decrease in optical yield. This behavior is difficult to account for,[12] but is indicative of the difference between polymer catalysis and monomer catalysis.

Work toward the understanding of the nature of C(3)-control is currently in progress.

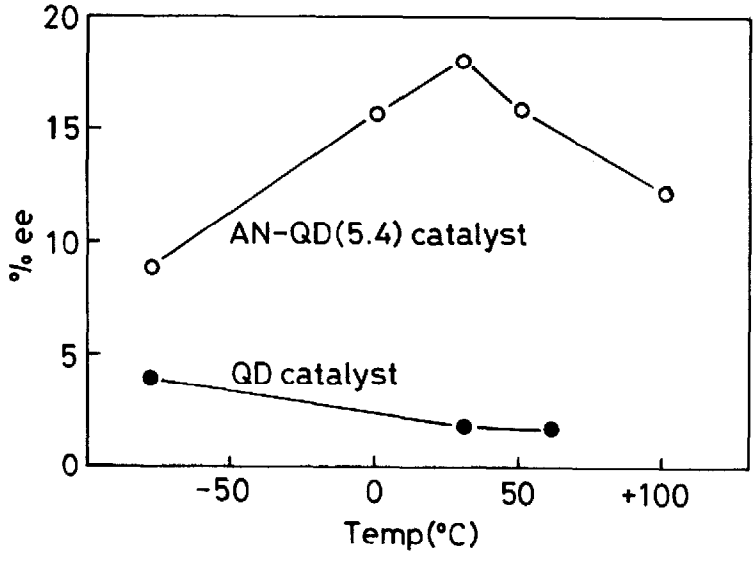


Figure. Effect of temperature on % ee.

References and Notes

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2. For reactions where this regularity was not observed: (a) V. Prelog and M. Wilhelm, Helv. Chim. Acta, 37, 1634 (1954); (b) A. Holt, A. W. P. Jarvie, and G. J. Jervis, J. Chem. Soc., Perkin II, 114 (1973); (c) N. Kobayashi and K. Iwai, J. Polym. Sci., Polym. Chem. Ed., 18, 0000 (1980).
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5. N. Kobayashi and K. Iwai, accepted for publication in J. Polym. Sci., Polym. Lett. Ed.
6. The AN-CA catalysts were prepared and purified as described earlier; see N. Kobayashi and K. Iwai, J. Polym. Sci., Polym. Chem. Ed., 18, 223 (1980).
7. N. Kornblum and L. Fishbein, J. Am. Chem. Soc., 77, 6266 (1955).
8. (+)-α-Methoxy-α-trifluoromethylphenylacetamide (J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969)) of 4 was prepared, but attempts to determine the enantiomeric composition by ^{1}H or ^{19}F nmr spectroscopy were unsuccessful.
9. A linear relationship was observed between $[\alpha]_D^{25}$ values of 3 and $[\alpha]_D^{20}$ values of 5, in contrast to the case of $LiAlH_4$ reduction.[1i] Nevertheless, the possibility of partial racemization during the course of Fe-AcOH reduction is not completely ruled out. The % ee data in the Table, therefore, are preliminary results.
10. Similar effects have been reported; see refs 1a, 1f, 1i, 2a, 2c, and 4.
11. The findings of Beamer are somewhat resembling to the present case. Hydrogenation of α-methylcinnamic acid with the catalyst prepared by depositing palladium on a silica gel, which had been pretreated with a cinchona alkaloid, gave a slight excess of (+)-2-methyl-3-phenylpropanoic acid regardless of the kind of the alkaloid used. Since all the alkaloid was leached out before hydrogenation, this phenomenon was explained in terms of imprints left on the carrier surface by the alkaloid. Obviously such a reasoning cannot be applied to our case. See P. E. Padgett and R. L. Beamer, J. Pharm. Sci., 53, 689 (1964); R. L. Beamer and W. W. Lawson, ibid., 55, 53 (1966).
12. Analogous temperature effects have been observed; see ref 4; J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N. J., 1971.

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