Functional Polymers. 4. Asymmetric Addition of Dodecanethiol to Isopropenyl Methyl Ketone Catalyzed by Cinchona Alkaloid–Acrylonitrile Copolymers

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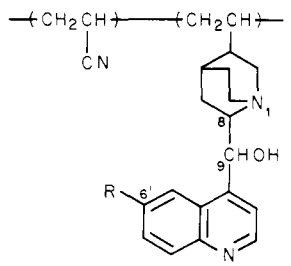
ABSTRACT: Asymmetric addition of dodecanethiol to isopropenyl methyl ketone was investigated by using cinchona alkaloid–acrylonitrile copolymers (AN–CA) as the chiral catalysts. The copolymers based on quinidine (QD) and cinchonine (CN) gave higher optical yields than the corresponding monomeric alkaloids, while the reverse was the case for the copolymers based on quinine (QN) and cinchonidine (CD). The maximum optical yield obtained was 57%, which is the highest value ever achieved in the asymmetric reactions catalyzed by synthetic organic polymers. Modification of the amino or hydroxyl group of the alkaloid moiety greatly reduced the stereoselectivity. The AN–CA catalysts were easily recovered from the reaction mixture with retention of their stereoselectivities, a decided advantage over monomeric catalysts.

In recent publications,[1,2] we described the synthesis of new polymeric alkaloids, cinchona alkaloid–acrylonitrile copolymers (AN–CA). The most characteristic features



AN–CA

CA	R	configuration C(8)	C(9)
QN	OCH_3	S	R
QD	OCH_3	R	S
CD	H	S	R
CN	H	R	S

of AN–CA are that the amino alcohol part of the alkaloid moiety, N(1)–C(8)–C(9)–OH, which generally plays an important role in asymmetric reactions,[3–7] can be kept free, and that the AN–CA are insoluble in common organic solvents. Thus, AN–CA copolymers seem to be endowed with favorable structures and properties as heterogeneous catalysts for asymmetric syntheses.

This work was undertaken to evaluate the stereoselectivities of AN–CA catalysts in asymmetric reactions. The asymmetric Michael reactions along this line have previously been reported.[8] Here we report the asymmetric addition of dodecanethiol (1) to isopropenyl methyl ketone (2) catalyzed by AN–CA. This reaction was chosen be-

$$\underset{\mathbf{1}}{C_{12}H_{25}SH} + \underset{\mathbf{2}}{CH_2{=}C(CH_3)COCH_3} \xrightarrow{\text{AN–CA}} \underset{\mathbf{3}}{C_{12}H_{25}SCH_2\overset{*}{C}(CH_3)HCOCH_3}$$

cause it had been extensively studied by Inoue and coworkers, using a variety of polymeric catalysts.[9] With poly(5-benzyl (*S*)-glutamate) as the catalyst, they achieved what was, at the time, the highest degree of asymmetric induction (47% optical yield) ever accomplished with a synthetic organic polymer catalyst.[10,11] By using AN–CA catalysts, we have obtained the sulfide **3** with a maximum optical yield of 57%. This value, therefore, constitutes a significant improvement over other existing polymer catalysts.

Experimental Section

Materials. Quinine (QN), quinidine (QD), cinchonidine (CD), cinchonine (CN), and quinine hydrochloride (QN·HCl) were commercial reagents and were used without further purification. 9-*O*-Ethoxycarbonylquinine (QNEC),[2] 1-benzylquininium chloride (QNBC),[2] dihydroquinine (DHQN),[8] dihydroquinidine (DHQD),[8] and AN–CA copolymers[2] were prepared as previously reported. Dihydrocinchonidine (DHCD) and dihydrocinchonine (DHCN) were synthesized from the corresponding alkaloids by $PdCl_2$-catalyzed hydrogenation.[12] DHCD: mp 240–240.5 °C, $[\alpha]^{15}_D$ −101.9° (*c* 2.001, EtOH) (lit.[13] mp 230 °C, $[\alpha]^{15}_D$ −98° (EtOH)). DHCN: mp 276–277 °C, $[\alpha]^{15}_D$ +204.3° (*c* 0.601, EtOH) (lit.[13] mp 268–269 °C, $[\alpha]^{14}_D$ +204° (*c* 0.6, EtOH)). Dodecanethiol (1) was distilled under N_2; bp 112 °C (3 mm). Isopropenyl methyl ketone (2) was distilled over CaH_2 under N_2; bp 96 °C. Solvents were purified by the usual methods. *dl*-**3** was synthesized by refluxing a toluene solution of **1**, **2**, and a catalytic amount of triethylamine under N_2 for 124 h; bp 138 °C (0.15 mm) (lit.[14] bp 142–143 °C (0.25 mm)).

Measurements. IR spectra were recorded on a Hitachi EPI-G3 grating infrared spectrophotometer. NMR spectra were recorded on a Varian T-60 NMR spectrometer. Optical rotations were measured in MeOH at 25 °C (*c* 1.5) with a Union PM-201 automatic digital polarimeter. Enantiomeric excess (% ee) was calculated on the basis of $[\alpha]_D$ 17.5 ± 1° for the optically pure isomer.[10]

Asymmetric Addition of 1 to 2. A typical procedure was as follows. A mixture of **1** (5.06 g, 25 mmol), **2** (3.11 g, 37 mmol), and a catalyst (0.6 mmol) in a solvent (30 mL) was stirred at room temperature for 7 days under N_2. The extent of conversion was determined by titration of the unreacted thiol in the reaction mixture with 0.1 N iodine solution. The polymer catalyst was recovered by filtration and washed with the solvent.[15] The combined filtrate and washings were concentrated by means of a rotary evaporator. The residual material was distilled two times under reduced pressure, giving spectrally pure **3**: ^1H NMR ($CDCl_3$) δ 0.6–1.7 (m, 26 H), 2.17 (s, 3 H), 2.3–3.0 (m, 5 H); IR (neat) 1715 cm^{-1} (C=O). Anal. Calcd for $C_{17}H_{34}OS$: C, 71.26; H, 11.96; S, 11.19. Found: C, 71.29; H, 11.77; S, 11.27.

When a monomeric alkaloid was used as the catalyst, the reaction mixture was extracted three times with 30-mL portions of 0.1 N HCl, washed with water until it was neutral, and then dried over anhydrous $MgSO_4$. The product **3** was isolated in a similar manner as above.

Asymmetric Addition of 1 to 2 in DMF. A solution of **1** (5.06 g, 25 mmol), **2** (3.11 g, 37 mmol), and AN–QD (9.8) (0.49 g, 0.6 mmol) in DMF (10 mL) was stirred for 19 h at room temperature under N_2. The reaction mixture was passed through a column of silica gel, using benzene as an eluent, and the eluate was

0024-9297/80/2213-0031$01.00/0

Table I
Solvent Effects on Asymmetric Addition of 1 to 2[a]

catalyst[b]	solvent	time, days	conversion, %	$[\alpha]_D$[c]	% ee
AN-QN (9.6)		7	100	−7.18	41
	toluene	7	87	−8.46	48
	chloroform	7	62	−6.91	39
	dioxane	7	51	−5.66	32
	acetonitrile	7	87	−4.75	27
	benzene	7	50	−1.90	11
	THF	7	69	−0.88	5
	DMF[d]	0.9	100	+1.82	10
	ethanol	7	100	+2.25	13
AN-QD (9.8)	toluene	7	76	+9.90	57
	DMF[d]	0.8	100	−2.16	12

[a] A mixture of 1 (25 mmol), 2 (37 mmol), and a catalyst (0.6 mmol) in 30 mL of solvent was stirred at room temperature. [b] The figures in parentheses indicate the alkaloid content of the copolymer in mol %. [c] Measured in MeOH at 25 °C. [d] Solvent, 10 mL.

concentrated under reduced pressure. Distillation of the residual liquid gave 4.92 g of **3**. Optical rotation was measured after another distillation, $[\alpha]^{25}_D$ −2.16° (*c* 1.5, MeOH) (12% ee).

Results and Discussion

Solvent Effects. The reaction of **1** with **2** was carried out in a variety of solvents, using AN–QN (9.6) and AN–QD (9.8) as the catalysts (the figures in parentheses indicate the alkaloid content of the copolymer in mol %). The results are summarized in Table I. In every case, optically active product **3** was obtained, but the direction and extent of asymmetric induction depends strongly on the solvent. Inversion of the enantiomeric composition of **3** in protic (EtOH) as opposed to aprotic solvents was observed. This reversal in stereochemistry was also observed when DMF was used as the solvent, in which polymer catalysts are soluble.[16] The highest asymmetric induction was obtained in toluene solvent. Other solvents gave lower optical yields than the system without solvent. Thus, toluene was the solvent of choice in our subsequent experiments.

With the exception of the reaction in DMF, the AN–CA catalyst was easily recovered from the reaction mixture by a mere filtration.

When racemic **3**, synthesized independently with triethylamine catalyst, was treated with AN–QN (9.6) in toluene for 7 days, the recovered sample of **3** was optically inactive. This finding ruled out the possibility of asymmetric adsorption of **3** by the catalyst under the conditions employed.

Effects of Temperature. There are wide variations in the extent of asymmetric induction with temperature. As shown in Table II, with a change in temperature from room temperature to 100 °C the asymmetric induction by AN–QD (9.8) decreased from 57 to 7%. The lowered stereoselectivity at 100 °C was not due to the decomposition of the catalyst, since both the IR spectra and $[\alpha]_D$ values of the catalyst were the same before and after the reaction. Interestingly, decreasing asymmetric bias was observed at −78 °C (2% ee) as compared to 0 °C (57% ee). This behavior is unexpected and difficult to account for but parallels those in the two-phase reduction of acetophenone[17] and AN–CA catalyzed addition of benzyl mercaptane to 2-nitrostyrene.[18]

Influence of Variation in Copolymer Structure and Composition. The asymmetric addition with various kinds of AN–CA catalysts was carried out in toluene at room temperature. The results are listed in Table III. The following observations are possible from Table III.

Table II
Effect of Temperature on the Asymmetric Addition of 1 to 2[a]

temp, °C	time, days	conversion, %	$[\alpha]_D$[b]	% ee
−78	58	6[c]	+0.3	2
0	22	37	+9.90	57
rt	7	76	+9.90	57
+60	4	58	+3.28	19
+100	1	51	+1.15	7

[a] A mixture of 1 (25 mmol), 2 (37 mmol), and AN–QD (9.8) (0.6 mmol) in 30 mL of toluene was stirred at the indicated temperature. [b] Measured in MeOH at 25 °C. [c] The product was isolated by column chromatography on silica gel.

Table III
Asymmetric Addition of 1 to 2[a]

entry no.	catalyst[b]	conversion, %	$[\alpha]_D$[c]	% ee
1	AN-QN (10.8)	78	−7.88	45
2	(9.6)	87	−8.46	48
3	(6.0)	83	−7.41	42
4	AN-QD (13.7)	79	+8.76	50
5	(9.8)	76	+9.90	57
6	(6.1)	75	+8.98	51
7	AN-CD (7.9)	64	−5.89	34
8	(6.1)	96	−6.64	38
9	(3.1)	94	−5.12	29
10	AN-CN (2.4)	88	+8.18	47
11	(2.4)[d]	84	+8.06	46
12	AN-QN·HCl (6.9)	42[e]	−3.20	18
13	AN-QNBC (3.2)	30[f]	+0.24	1
14	AN-QNEC (9.7)	69	−0.88	5

[a] A mixture of 1 (25 mmol), 2 (37 mmol), and a catalyst (0.6 mmol) in 30 mL of toluene was stirred for 7 days at room temperature. [b] See footnote *b* in Table I. [c] Measured in MeOH at 25 °C. [d] The copolymer recovered from the first reaction (entry 10) was reused. [e] Reaction time 16 days. [f] Reaction time 22 days.

(a) AN–QN and AN–CD gave the (−)-isomer, while AN–QD and AN–CN gave the (+)-isomer in excess. In view of the stereochemical relationship of cinchona alkaloids,[5,19,20] the sterochemistry of the reaction is considered to be controlled by the configurations at C(8) and C(9) in the alkaloid moiety.

(b) Optical yields were affected by the structure of the CA moiety. The following order of decreasing stereoselectivity, QD > CN, QN > CD, indicates that the methoxy group is preferred over hydrogen as the C(6′) substituent, and the combination of C(8)–(R) and C(9)–(S) is preferred over that of C(8)–(S) and C(9)–(R).

(c) In every family of copolymers, an optimum composition exists which gives the highest optical yield. The best result was obtained by using AN–QD (9.8) (entry 5). The optical yield of 57% is the highest value ever achieved in the asymmetric reactions catalyzed by synthetic organic polymers.

(d) As expected, modification of the amino group (QN·HCl, QNBC) or the hydroxyl group (QNEC) of the QN unit greatly reduced stereoselectivity (entries 12–14). AN–QNBC gave the product with low and opposite rotation. In addition, the reaction was quite sluggish with AN–QN·HCl and AN–QNBC catalysts.

(e) Comparison of entry 10 with entry 11 shows that the copolymer was recovered from the reaction mixture with retention of stereoselectivity, a decided advantage of AN–

Table IV
Asymmetric Addition of 1 to 2 Catalyzed by Monomeric Alkaloids[a]

catalyst	time, days	conversion, %	$[\alpha]_D$[b]	% ee
QN	7	82	−11.1	63
DHQN	10	82	−9.30	53
QD	7	61	+8.96	51
DHQD	5	90	+9.34	53
CD	7	30	−8.28	47
DHCD	10	58	−5.43	31
CN	7	35	+6.31	36
DHCN	10	38	+6.72	38

[a] A mixture of 1 (25 mmol), 2 (37 mmol), and a catalyst (0.6 mmol) in 30 mL of toluene was stirred at room temperature. [b] Measured in MeOH at 25 °C.

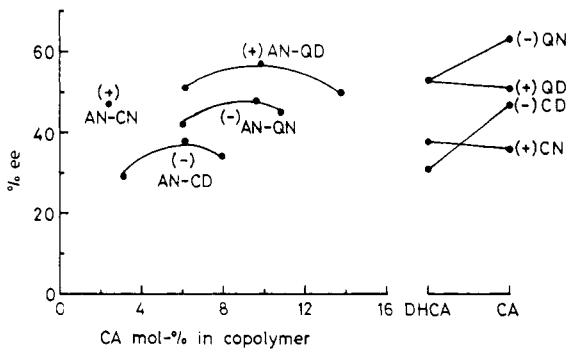


Figure 1. Effect of copolymer composition on % ee (the signs in parentheses refer to the rotation of the product 3).

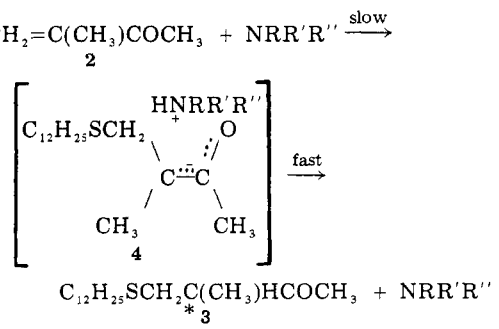
CA over monomeric catalysts.

Asymmetric Addition Catalyzed by Monomeric Alkaloids. In order to compare the catalytic behavior of AN–CA with monomeric alkaloids, we carried out the reaction using monomeric cinchona alkaloids (CA) and their dihydro derivatives (DHCA) as the catalysts under otherwise identical conditions. The results are summarized in Table IV. With both CA and DHCA catalysts, the sense of the asymmetric induction is the same as that with AN–CA catalysts; QN (DHQN) and CD (DHCD) gave the (−)-isomer, while QD (DHQD) and CN (DHCN) gave the (+)-isomer in excess. The extent of asymmetric induction, however, varied with a slight change in the catalyst structure.[21] CD and CN gave lower optical yields compared to the C(6′)–methoxy analogues, QN and QD. Changing the catalyst from QN (or CD) to DHQN (or DHCD) caused a decrease in optical yield, whereas changing it from QD (or CN) to DHQD (or DHCN) caused a slight increase. This tendency is also shown on changing the catalyst from CA to AN–CA (AN–QD and AN–CN gave higher and AN–QN and AN–CD gave lower optical yields than the corresponding CA) and is even more apparent from Figure 1.

It is interesting to note that in the CD and CN series the reaction proceeded faster with polymeric catalyst than with the low molecular weight catalyst.

When DMF was used as the solvent, reversal in stereochemistry was observed, as was the case with the polymer-catalyzed reaction (Table I); QN gave the (+)-isomer in 17% ee.[22]

Reaction Pathway. The pathway of the present reaction is considered to involve a slow formation of an ion pair, 4, within which there is rapid transfer of a proton to the incipient asymmetric center of the ketone.[23] The ammonium ion may transfer its proton to one face of the counterion giving the (*R*) enantiomer of 3 or to the opposite face giving (*S*)-3. The diminished enantioselectivity observed with the AN–QNEC catalyst indicates that the hydrogen bonding between the hydroxyl group of the alkaloid moiety and the carbonyl function plays an important role in determining the enantioface to be protonated. The CPK model study, however, did not allow us to predict the preferred enantiomer.



Conclusion

Our experiments demonstrate that AN–CA copolymers have good stereoselectivities as the catalysts for asymmetric addition of 1 to 2. Although the absoluate configuration of 3 remains to be clarified, the direction and the extent of asymmetric induction are sensitive probes for comparing AN–CA catalysis with monomeric alkaloid catalysis. From our results it is apparent that the asymmetric addition is sensitive to the change in alkaloid structure, i.e., configurations at C(8) and C(9) and substituents at C(6′) and C(3), and that the amino alcohol part should be kept free in order to achieve a high degree of asymmetric induction. Some copolymers gave higher and some copolymers gave lower optical yields than the corresponding CA catalysts, but the differences are not very large. Accordingly, AN–CA copolymers are said to have the advantage of heterogeneous catalysts (easy separation), while maintaining the activities and selectivities of monomeric catalysts.

References and Notes

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Chemical Modification of Polymers. 13.[1] Sulfonation of Polystyrene Surfaces

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Received July 31, 1979

ABSTRACT: Polystyrene surfaces are readily sulfonated by 100% sulfuric acid at room temperature. For reproducible results, the reaction must be carried out under anhydrous conditions. Controlled reaction from zero to more than 4000 monolayers is possible in times less than 1 h. Three analytical techniques for the extent of sulfonation were employed: (1) ion exchange of the films with methylene blue, a cationic dye, and subsequent visible light absorption measurement; (2) direct titration of the sulfonic acid groups; and (3) direct reaction depth measurement by interferometry. The reaction consists of two distinct processes: a rapid initial rate and a slower final rate. These are interpreted as being due to surface and "bulk" sulfonation, respectively, or alternatively the interplay of diffusion and reaction processes.

Chemical modification of polymeric surfaces is known to alter physicochemical properties [e.g., adhesion,[2] dyefastness,[3-5] wettability,[6] weatherability,[7] permeation,[8] friction,[9] electrostatic charging,[9] and biocompatibility[10]]. These modifications have generally been poorly understood due to lack of analytical procedures, kinetic data, and knowledge of the nature and distribution of the functional groups produced.

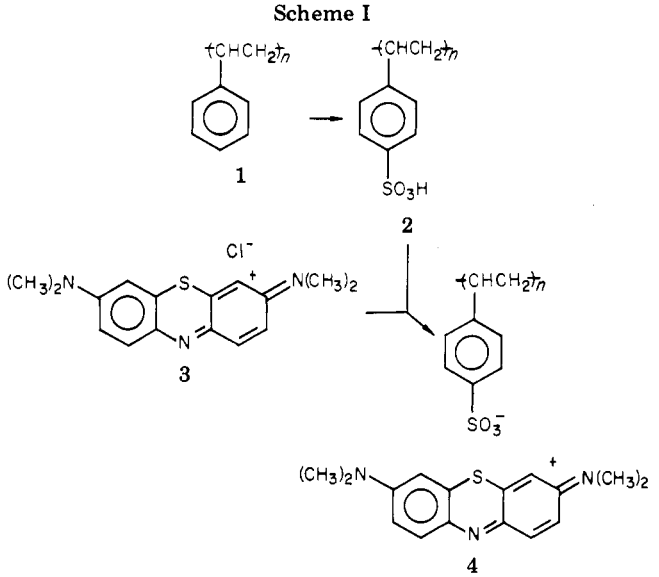
We undertook a systematic study of the sulfonation of free-standing polystyrene films as a prototypical surface modification with the following objectives: (1) establishment of techniques for quantitative analysis; (2) development of conditions for reproducible, controlled sulfonation; (3) determination of the kinetics of the reaction; and (4) analysis of the structure of the "surface" vis-à-vis the "bulk" of the resultant films. The present paper will focus upon the first three aspects.

Results and Discussion

A. Choice of Sulfonating Agent. It was desirable that the reaction be carried out at room temperature for ease of handling and that the reaction take place on a useful time scale. On the basis of these two limitations, various sulfonating agents were screened. Immersion of the polystyrene (1) films for various periods of time in the medium, followed by quenching in a suitable bath and washing with water, produced sulfonated films (2). Chlorosulfonic acid proved to be too reactive; the films were physically destroyed. Concentrated sulfuric acid was too unreactive; only very slightly sulfonated films (equivalent to a few monolayers per side) resulted from treatment with concentrated sulfuric acid at room temperature for times as long as 16 h. However, approximately 100% sulfuric acid, made from concentrated sulfuric acid and fuming sulfuric acid, is a reagent which gives reasonable sulfonation rates at room temperature.

B. Reagent Analysis. The concentrations of SO_3/H_2SO_4 and "concentrated" sulfuric acid were estimated by the determination of density.[11] From these known concentrations, solutions of known nominal SO_3 concentration in H_2SO_4 could be prepared. Each of the sulfonating mixtures was in turn analyzed by titration with standard base. In terms of weight percent sulfuric acid wherein SO_3 is analyzed as H_2SO_4 after reaction with water, the measured concentrations ranged from 99.6–100.3%.

Scheme I



C. Establishment of Analytical Techniques for the Extent of Sulfonation. Analysis of the sulfonated surfaces of the polystyrene based upon the known ability of the sulfonic acid groups to exchange cations[12] could be accomplished in one of several ways. We chose to exchange the films with methylene blue.[13] This results in exchange of the proton on the sulfonic acid group (2) for a methylene blue cation (3), leading to a film with ionically bound blue dye (4). This technique allows some judgments based on visual inspection and allows use of spectrophotometry, a rapid technique of high accuracy and precision.

1. Dyed Film Spectrophotometric Assay Reproducibility. The first objective was to determine if the spectrophotometric assay of the films was reproducible. The results for several sets of films prepared and dyed simultaneously are given in Table I. The intense absorption of these films makes measurement of the absor-

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