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Functional Polymers. VII. On the C(3)-Control of Stereochemistry in Asymmetric Reactions Catalyzed by Polymeric Cinchona Alkaloids*

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ABSTRACT: Asymmetric reactions of dodecanethiol with β-substituted phenyl vinyl ketones were studied using polymeric and monomeric cinchona alkaloids as chiral catalysts. The mode of stereoregulation (C(8), C(9)-control, C(3)-control) varied depending not only on the substituents at C(3) and C(6′) of the alkaloid molecule but also on the β-substituent of the unsaturated systems. The C(3)-control was observed when the steric environments of the enantioface differentiating step were sufficiently crowded (combination of polymer catalyst and bulky β-substituent).

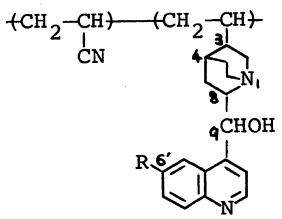
KEY WORDS Asymmetric Reaction / Polymer Catalyst / Cinchona Alkaloid / Stereochemistry / Thiol / α,β-Unsaturated Compound /

Recently, we reported on the asymmetric thiol addition to α,β-unsaturated systems catalyzed by acrylonitrile–cinchona alkaloid copolymers (AN–CA).[1-3] Two types of reactions have been studied. One is the reaction in which a chiral carbon is created at the α-position in the step of proton addition (Type I), and the other is the reaction in which an asymmetric center is induced at the β-position in the step of S–C bond formation (Type II). The stereochemistry of the Type I

Type I $RSH + CH_2=CR'X \xrightarrow{AN\text{–}CA} RSCH_2\overset{*}{C}HX$ (R′)

Type II $RSH + R'CH=CHX \xrightarrow{AN\text{–}CA} RS\overset{*}{C}HCH_2X$ (R′)

reactions, such as dodecanethiol–isopropenyl methyl ketone[1] and benzyl mercaptan–methyl α-phthalimidoacrylate,[2] was found to be controlled by the configurations at C(8) and C(9) in the alkaloid moieties of AN–CA ("C(8), C(9)-control"), as is generally observed in the asymmetric reactions under the influence of cinchona alkaloids (CA) or their derivatives.[4-12] On the other hand, the reaction of benzyl mercaptan with 2-nitrostyrene[3] (Type II) gave always an excess of (+)-enantiomer, irrespective of the kind of alkaloid residue in AN–CA. This phenomenon can be explained in terms of the chiral force stemming from C(3) being



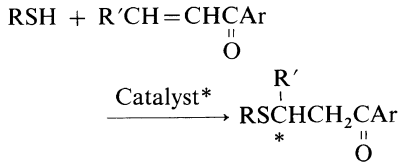
AN–CA

CA	R	Configuration 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*

* For Part VI of this series, see ref 3.

greatly reinforced by a large substituent (polymer chain) so that it exceeds the chiral force stemming from C(8) and C(9), which would otherwise be stronger than that from C(3) ("C(3)-control").

With a view to obtaining a greater understanding of the nature of the C(3)-control, we have investigated other Type II reactions. In this paper, we report on the asymmetric addition of thiols to β-substituted aryl vinyl ketones catalyzed by the polymeric and monomeric alkaloids,



EXPERIMENTAL

Materials

Quinine (QN), quinidine (QD), cinchonidine (CD), and cinchonine (CN) were commercial reagents and used without further purification. Dihydroquinine (DHQN),[12] dihydroquinidine (DHQD),[12] dihydrocinchonidine (DHCD),[1] dihydrocinchonine (DHCN),[1] and AN–CA copolymers[13] including AN–QN·HCl (acrylonitrile–quinine hydrochloride copolymer), AN–QNBC (acrylonitrile–1-benzylquininium chloride copolymer), and AN–QNEC (acrylonitrile–9-*O*-ethoxycarbonylquinine copolymer) were prepared as previously reported. Dodecanethiol (**I**) and *p*-chlorothiophenol were obtained commercially and distilled before use. Triphenylmethanethiol (Aldrich) was used as received. 2,6-Di-*t*-butyl-4-mercaptophenol was synthesized according to the method of Fujisawa and coworkers;[14] mp 87—89°C (hexane) (lit.[14] mp 87—88°C). Chalcone (**IIb**) was obtained commercially and recrystallized from petroleum ether. Crotonophenone (**IIc**) was obtained commerically and distilled. Other unsaturated ketones were synthesized by stirring an equimolar mixture of an aldehyde and an aryl methyl ketone in a diluted ethanol solution of sodium hydroxide. 2′-Methoxychalcone: bp 167—174°C (0.1 mmHg). 4′-Chlorochalcone: mp 99—100°C (EtOH) (lit.[15] mp 100°C). 4′-Nitrochalcone: mp 141—146°C (EtOH) (lit.[15] mp 146°C). β-Phenyl-2-acrylonaphthone: mp 106—108°C (EtOH) (lit.[16] mp 105—106°C). 4-Methylchalcone: mp 98—98.5°C (EtOH) (lit.[17] mp 96.5°C). 4-Methoxychalcone: mp 73.4—74°C (EtOH) (lit.[18] mp 77—78°C). 2-Methoxychalcone (**IIa**): mp 55.5—56°C (petroleum ether) (lit.[19] mp 58—59°C). 2-Nitrochalcone: mp 122—125°C (aq AcOH) (lit.[15] mp 128—130°C). The solvents were purified by the usual methods.

Measurements

Optical rotations were measured in benzene at 25°C with a Union PM-201 automatic digital polarimeter. IR spectra were recorded on a Hitachi EPI-G3 grating infrared spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra of the products were recorded on a Varian T-60 NMR spectrometer. For determining the enantiomeric excess (%ee) of **IIIa**, a Varian HA-100 NMR spectrometer was used.

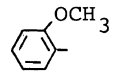
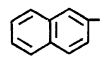
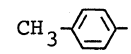
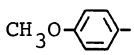
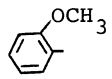
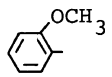
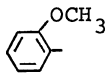
Asymmetric Reactions

The asymmetric reactions were carried out by stirring a mixture of a thiol (5.0 mmol), an α,β-unsaturated compound (6.25 mmol), and a catalyst (0.125 mmol) in a solvent (30 ml) at room temperature under N_2 for several days. The results are summarized in Tables II—VI. The physical properties and analytical data of the reaction products, γ-ketosulfides, are listed in Table I. The following sections describe typical reaction procedures. Column chromatography was carried out on silica gel with benzene.

*Asymmetric Addition of **I** to **IIa**.* A mixture of 1.01 g of **I**, 1.49 g of **IIa**, and 0.10 g of AN–QN (9.7) (acrylonitrile–QN copolymer containing 9.7 mol% of QN units) in 30 ml of toluene was stirred for 7 days at room temperature under N_2 and then filtered. The filtered catalyst was washed with toluene and dried. The recovered copolymer weighed 0.09 g. Evaporation of the combined filtrate and the toluene washings under reduced pressure followed by column chromatography of the residue afforded 0.24 g (11% yield) of **IIIa**: $[\alpha]_D$ +14.0° (*c*, 4.42 g l^{-1}) (18%ee); mp 28°C (MeOH); IR 1690 cm^{-1} ($\nu_{C=O}$); NMR ($CDCl_3$) δ 0.8—1.8 (m, 23H, $C_{11}H_{23}$), 2.46 (t, J=7 Hz, 2H, CH_2S), 3.55 (d, J=7 Hz, 2H, CH_2CO), 3.83 (s, 3H, CH_3O), 4.98 (t, J=7 Hz, 1H, CHS), 6.7—8.0 ppm (m, 9H, aromatic protons). The analytical data are listed in Table I.

When dimethylformamide (DMF) was used as the reaction medium in place of toluene, the reaction was carried out for one day. The reaction

Table I. Properties of γ-ketosulfides ($RSCHCH_2COAr$, R′ at the starred carbon)

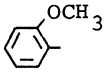
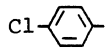
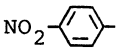
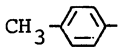
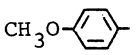
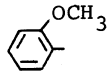
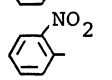
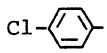
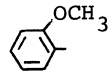
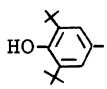
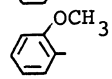
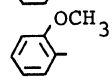
R	R′	Ar	mp (bp) °C[a]	*Anal.*, Found (Calcd)/% C	H	S
$C_{12}H_{25}$-			53.5[b]	79.05 (78.97)	9.40 (9.33)	7.65 (7.81)
			Oil	76.43 (76.31)	9.24 (9.15)	7.41 (7.27)
			67.0	72.95 (72.86)	8.40 (8.38)	7.41 (7.20)
			36.5—37.0	71.27 (71.17)	8.13 (8.18)	7.30 (7.04)
			61.5	81.11 (80.82)	8.86 (8.75)	7.08 (6.96)
			37.0	79.10 (79.19)	9.54 (9.49)	7.76 (7.55)
			40.0[c]	76.52 (76.31)	9.12 (9.15)	7.31 (7.27)
			28.0	76.40 (76.31)	9.18 (9.15)	7.16 (7.27)
			57.0—57.5	71.35 (71.17)	8.17 (8.18)	7.10 (7.04)
	CH_3-		(168—172/ 0.06 mmHg)	75.85 (75.80)	10.50 (10.41)	9.30 (9.20)
Cl-			Oil	68.86 (69.01)	5.03 (5.00)	8.38 (8.37)
HO-			133—134	75.67 (75.59)	7.54 (7.61)	6.77 (6.73)

[a] Solid products were recrystallized from MeOH.
[b] Lit.[20] mp 52°C.
[c] Lit.[20] mp 41—41.5°C.

mixture was passed through a column of silica gel and concentrated under reduced pressure. Repeated chromatography of the residue gave 1.70 g (77% yield) of **IIIa**: $[\alpha]_D$ +6.31° (*c*, 16.78 $g\,l^{-1}$) (8%ee).

When QN was used as the catalyst in place of AN–QN (9.7), the reaction was carried out for 13 days. The reaction mixture was washed with 0.1 *N* HCl, and then with water until it became neutral. The toluene solution was dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by

Table II. Asymmetric addition of thiols (RSH) to α,β-unsaturated ketones (R′CH=CHCOAr) catalyzed by AN–QN (9.7)[a]

Thiol R	Unsaturated ketone R′	Unsaturated ketone Ar	Time day	Yield %	$[\alpha]_D$ deg[b]
$C_{12}H_{25}$-			7	43	+1.88
			7	10	+2.48
			6	27	−0.40
			5	69	0.0
			6	9	−3.98
			10	22	+0.67
			12	19	+7.74
			7	11	+14.0
			10	40	−0.23
	CH_3-		4	77	+0.42
			17	82	−4.25
			10	61	+1.12
Ph_3C-			14	0	

[a] Stirring in toluene at room temperature under N_2.
[b] Measured in benzene at 25°C.

chromatography of the residue gave 2.07 g (94% yield) of **IIIa**: $[\alpha]_D$ −20.6° (*c*, 16.88 g l^{-1}) (26%ee).

Asymmetric Addition of ***I*** *to* ***IIb***. A mixture of 1.01 g of **I**, 1.30 g of **IIb**, and 0.095 g of AN–QN (10.8) in 30 ml of toluene was stirred for 10 days. The reaction mixture was worked up as above to give 0.53 g (37% yield) of **IIIb**: $[\alpha]_D$ +4.36° (*c*, 15.13 g l^{-1}); mp 53.5°C (lit.[20] mp 52°C); IR 1682 cm^{-1} ($\nu_{C=O}$); NMR ($CDCl_3$) δ 0.8—1.8 (m, 23H, $C_{11}H_{23}$), 2.33 (t, *J*=7 Hz, 2H, CH_2S), 3.51 (d, *J*=7 Hz, 2H, CH_2CO), 4.53 (t, *J*=7 Hz, 1H, CHS), 7.0—8.0 ppm (m, 10H, aromatic protons). Analytical data are listed in Table I.

Asymmetric Addition of ***I*** *to* ***IIc***. A mixture of 1.01 g of **I**, 0.91 g of **IIc**, and 0.10 g of AN–QN (9.7) in 30 ml of toluene was stirred for 4 days. The reaction mixture was worked up to give, after chromatography, 1.34 g (77% yield) of **IIIc**: $[\alpha]_D$ +0.42° (*c*, 18.99 g l^{-1}); bp 168—172°C (0.06 mmHg); IR 1695 cm^{-1} ($\nu_{C=O}$); NMR ($CDCl_3$) δ 0.7—1.7 (m, 26H, $C_{11}H_{23}+CH_3$), 2.40 (t, *J*=7 Hz, CH_2S), 2.8—3.4 (m, 3H, $SCHCH_2CO$), 7.2—7.9 ppm

(m, 5H, aromatic protons). Analytical data are listed in Table I.

Asymmetric Addition of p-Chlorothiophenol to ***IIa***. A mixture of 0.72 g of *p*-chlorothiophenol, 1.49 g of **IIa**, and 0.10 g of AN–QN (9.7) in 30 ml of toluene was stirred for 17 days. The workup of the reaction mixture and elution of the crude product on silica gel gave 1.56 g (82% yield) of 2-(4-chlorophenylthio)-2-(2-methoxyphenyl)ethyl phenyl ketone as a viscous oil: $[\alpha]_D$ $-4.25°$ (*c*, 17.40 $g l^{-1}$); IR 1693 cm^{-1} ($\nu_{C=O}$); NMR ($CDCl_3$) δ 3.61 (d, $J=7$ Hz, 2H, CH_2CO), 3.80 (s, 3H, CH_3O), 5.33 (t, $J=7$ Hz, 1H, CHS), 6.6—8.0 ppm (m, 13H, aromatic protons). The analytical data are given in Table I.

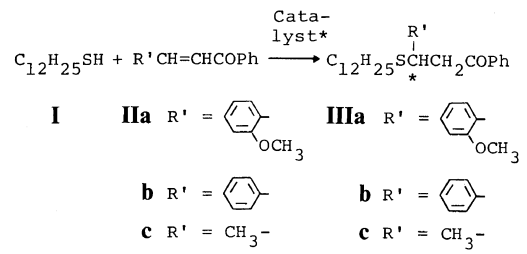
Synthesis of Racemic ***IIIa***

A solution of 4.04 g (20 mmol) of **I**, 5.95 g (25 mmol) of **IIa**, and 0.11 g (1 mmol) of triethylenediamine in 120 ml of toluene was refluxed for 41 h under N_2. The reaction mixture was extracted three times with 25 ml portions of 0.1 *N* HCl, washed with water, and then dried over anhydrous $MgSO_4$. Evaporation of the toluene under reduced pressure followed by column chromatography of the residue gave 3.28 g (37% yield) of *racemic* **IIIa** as a viscous oily material. the NMR spectrum of this material was identical with that of the optically active sample described earlier.

RESULTS AND DISCUSSION

Initially, various reactions between a thiol and an α,β-unsaturated ketone were studied in a search for suitable reactant combinations that would show the effect of the β-substituent on the stereochemistry. These reactions were carried out in toluene at room temperature using AN–QN (9.7) (the figures in parenthesis indicate the alkaloid content of the copolymer in mol%). The results are summarized in Table II. The reactions were sluggish but gave optically active products in most cases. Almost all of the products were new compounds whose structures were established by elemental analyses (Table I) and ^1H NMR and infrared (IR) spectra. The IR spectra of the products were in agreement with the proposed structures; the carbonyl stretching frequencies occurred at 1650—1673 cm^{-1} in the starting α,β-unsaturated ketones and they shifted to 1675—1695 cm^{-1} in the adducts, due to a loss in conjugation. The NMR spectra exhibited a doublet at δ 3.42—3.61 ppm (2H) owing to the methylene protons adjacent to carbonyl group and a triplet at δ 4.45—5.29 ppm (1H) due to the methine proton linked to sulfur. The only exception was the product of the dodecanethiol (**I**)–crotonophenone (**IIc**) reaction, which showed complex signals of $SCHCH_2CO$ in the region δ 2.8—3.4 ppm.

Of the thirteen runs in Table II, the combination of **I** and 2-methoxychalcone (**IIa**) gave a product with the highest optical rotation. This combination had the additional advantage that the enantiomeric excess (%ee) of the product (**IIIa**) could be determined by NMR spectroscopy (*vide infra*). Furthermore, the bulky 2-methoxyphenyl group was expected to exert a marked influence on the stereochemical course of the reaction. Accordingly, we investigated the asymmetric addition of **I** to **IIa** as fully as possible. In order to examine the steric effect of β-substituents, asymmetric reactions of **I** with chalcone (**IIb**) and **IIc** were also studied.



Asymmetric Addition of ***I*** *to* ***IIa***

The reaction of **I** to **IIa** was carried out in certain solvents other than toluene, using AN–QN (9.7) as the catalyst (Table III). In chloroform, the reaction was as sluggish as in toluene, and the extent of asymmetric induction was somewhat lower. The reaction in DMF proceeded homogeneously and quite smoothly, but gave a lower enantiomeric yield. With the protic ethanol solvent, the lowest enantiomeric yield was obtained. Thus, toluene was used as the solvent in subsequent experiments.

When *racemic* **IIIa**, synthesized independently with triethylenediamine catalyst (see EXPERIMENTAL Section), was treated with AN–QN (9.7) in toluene for 10 days, the recovered sample of **IIIa** was optically inactive. This finding ruled out the possibility of asymmetric adsorption of **IIIa** by the catalyst under the conditions employed.

Table III. Asymmetric addition of **I** to **IIa** catalyzed by AN–QN (9.7)[a]

Solvent	Time	Yield	$[\alpha]_D$	%ee
	day	%	deg[b]	
Toluene	7	11	+14.0	18
Chloroform	16	26	+13.6	17
DMF	1	77	+6.31	8
Ethanol	6	66	+4.17	5

[a] Stirring at room temperature under N_2.
[b] Measured in benzene at 25°C.

Table IV. Asymmetric addition of **I** to **IIa**[a]

Entry	Catalyst		Time	Yield	$[\alpha]_D$	%ee
	type[b]	η_{inh}[c]	day	%	deg[d]	
1	AN–QN (10.8)	0.149	12	21	+16.0	20
2	AN–QN (6.0)	0.200	7	11	+14.0	18
3	AN–QN (6.0)	0.293	9	18	+13.6	17
4	AN–QD (9.8)	0.176	9	31	+6.12	8
5	AN–CD (6.1)	0.286	11	31	+2.85	4
6	AN–CN (2.4)	0.270	9	31	+9.33	12
7	AN–QN·HCl (6.9)	0.222	12	34	+0.16	0
8	AN–QNBC (3.2)	0.236	12	22	−0.08	0
9	AN–QNEC (9.9)	0.230	11	20	+7.34	9
10	QN	13	94	−20.6	26	
11	DHQN	3	85	−21.0	27	
12	QD	13	83	+31.6	40	
13	DHQD	3	93	+34.2	44	
14	CD	6	66	−16.0	20	
15	DHCD	3	44	−12.6	16	
16	CN	6	50	+15.9	20	
17	DHCN	3	44	+23.7	30	

[a] Stirring in toluene at room temperature under N_2.
[b] The figures in parentheses indicate the alkaloid content of the copolymer in mol%.
[c] Measured in benzene at 25°C.
[d] Measured in benzene at 25°C.

The results of the asymmetric addition with various kinds of catalysts, AN–CA, cinchona alkaloid (CA), and dihydro derivatives of CA (DHCA), are listed in Table IV. The most important observation from Table IV is that the unmodified AN–CA catalysts always gave an excess of (+)-**IIIa** irrespective of the kind of the alkaloid units incorporated (entries 1—6). This is the second example of the C(3)-control. With low-molecular-weight CA and DHCA catalysts, the reaction was C(8), C(9)-control; the QN and CD series (entries 10, 11 and 14, 15) gave (−)-enantiomer in excess, while the QD and CN series (entries 12, 13 and 16, 17) gave (+)-enantiomer in excess. In this respect, this reaction is very similar to that of benzyl mercaptan with 2-nitrostyrene.[3] In the present case, however, the monomeric catalysts gave much higher enantiomeric yields than the polymeric catalysts.

The CA content in the copolymer affected the enantiomeric yield to some extent. For AN–QN copolymers, increasing the QN content tends to increase the enantiomeric yield. Modification of the amino group (QN·HCl, QNBC) or the hydroxyl group (QNEC) of the QN unit reduced the extent of asymmetric induction (entries 7—9). Especially, amino-modified copolymers gave almost optically inactive products, a fact indicating the importance of the free amino group in the asymmetric catalysis.

The enantiomeric excess of **IIIa** was determined by NMR spectroscopy. Addition of $Eu(TFC)_3$ (30 mol%) to $CDCl_3$ solution of **IIIa** gave rise to two separated singlets for the methyl group linked to

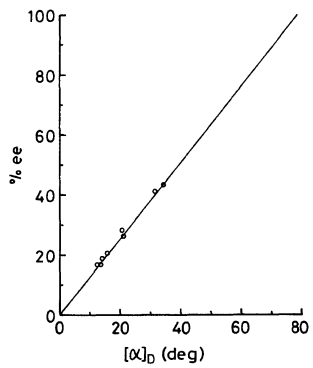


Figure 1. Percent ee–$[\alpha]_D$ relationship for **IIIa**.

oxygen. Figure 1 shows the %ee-$[\alpha]_D$ relationship. From the data the $[\alpha]_D^{25}$ (benzene) value of optically pure **IIIa** was calculated as $78.6 \pm 1.8°$ by the least-squares method. The %ee values of the reaction products listed in Tables III and IV are based on their optical rotations.

Table V. Asymmetric addition of **I** to **IIb**[a]

Catalyst[b]	Time	Yield	$[\alpha]_D$
	day	%	deg[c,d]
AN–QN (10.8)	10	37	+4.36
AN–QD (9.8)	13	26	+6.15
AN–CD (6.1)	10	41	−2.77
AN–CN (2.4)	11	44	+9.33
QN	4	78	−26.2
QD	5	86	+36.7
CD	4	42	−27.7
CN	4	62	+18.5

[a] Stirring in toluene at room temperature under N_2.
[b] The figures in parentheses indicate the alkaloid content of the copolymer in mol%.
[c] Measured in benzene at 25°C.
[d] Enantiomeric excess and absolute configuration are unknown.

Table VI. Asymmetric addition of **I** to **IIc**[a]

Catalyst[b]	Time	Yield	$[\alpha]_D$
	day	%	deg[c,d]
AN–QN (9.7)	4	77	+0.42
AN–QD (9.3)[e]	4	74	−0.82
AN–CD (7.9)[f]	4	72	+0.07
AN–CN (2.4)	4	71	−0.59
QN	1	83	+0.66
DHQN	1	77	+1.07
QD	1	79	−0.76
DHQD	1	76	−1.41
CD	1	78	+0.53
DHCD	1	76	+0.43
CN	1	75	−0.40
DHCN	1	76	−0.13

[a] Stirring in toluene at room temperature under N_2.
[b] The figures in parentheses indicate the alkaloid content of the copolymer in mol%.
[c] Measured in benzene at 25°C.
[d] Enantiomeric excess and absolute configuration are unknown.
[e] η_{inh} 0.233 (*c*, 5.0 gl^{-1}; DMF, 30°C).
[f] η_{inh} 0.352 (*c*, 5.0 gl^{-1}; DMF, 30°C).

*Asymmetic Addition of **I** to **IIb** and **IIc***

The asymmetric addition of **I** to **IIb** and **IIc** was also carried out in toluene at room temperature. Although the extent of asymmetric induction could not be determined for these reactions, the rotational signs of the products (**IIIb** and **IIIc**) are sensitive indication of the stereochemistry.

With **IIb** as the Michael acceptor, the results were somewhat complex (Table V). AN–QN and AN–QD each having a methoxy group at C(6′) gave the same enantiomer in excess, while AN–CD and AN–CN, without the C(6′)-methoxy group, gave the opposite enantiomer in excess. Here, the C(6′)-substituent is important in determining the mode of stereoregulation. Monomeric CA catalysts gave better enantiomeric yields than AN–CA, and the rotational signs reflect the configurations at C(8) and C(9).

With **IIc** as the Michael acceptor, the reaction was C(8), C(9)-control, irrespective of whether the catalyst was monomeric or polymeric (Table VI).

Relation between Steric Factors and the Mode of Stereoregulation

Table VII summarizes the stereochemical results of the asymmetric addition of **I** to **IIa**—**IIc**. With monomeric catalysts, all the reactions were C(8), C(9)-control. On the other hand, with AN–CA catalysts, the mode of stereoregulation varied, depending not only on the β-substituent (R′) but also on the C(6′)-substituent. Small R′ preferred the C(8), C(9)-control, while large R′ preferred the C(3)-control. The reaction of **I** with **IIb** was the

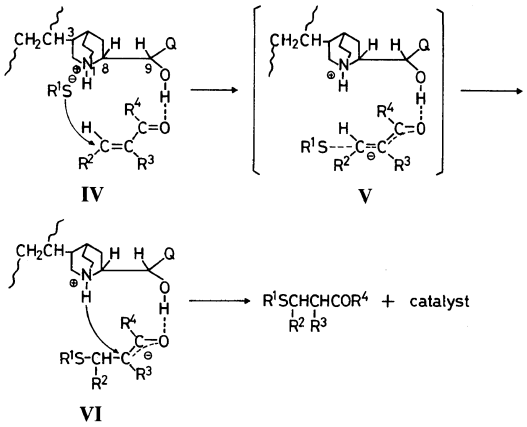
Table VII. Stereochemical results of asymmetric addition of **I** to **IIa–IIc** (R′CH=CHCOPh)

R′	Catalyst	Mode of stereoregulation
	Monomeric	C(8), C(9)-control
	AN–CA	C(3)-control
	Monomeric	C(8), C(9)-control
	AN–CA	C(3)-control [if CH_3O-C(6′)]
		C(8), C(9)-control [if H–C(6′)]
CH_3–	Monomeric	C(8), C(9)-control
	AN–CA	C(8), C(9)-control

intermediate case, where both C(8), C(9)-control and C(3)-control were observed depending on the C(6′)-substituent. These results clearly show that the C(3)-control is closely related to the steric crowdings, and becomes the predominant factor in determining the stereochemistry when the steric environments of the enantioface differentiating step are sufficiently crowded.

Reaction Pathway

The pathway of the asymmetric reactions of thiols with α,β-unsaturated systems is outlined in Scheme I, where Q represents the quinoline ring. The first



Scheme I.

step in the reaction is the proton abstraction from thiol by N(1)-nitrogen. It may be said that a hydrogen bond exists between the hydroxyl group of the catalyst and the oxygen atom of the α,β-unsaturated compound, thereby leading to a more structured state, since a lack of free hydroxyl groups in the catalyst usually results in a diminished enantiomeric yield in both Type I and Type II reactions (see Table IV and ref 1 and 3). The thiolate anion ($R^1S^{\ominus}$) attacks the β-carbon (**IV**). The stereochemistry of the Type II reactions (R^2 is not hydrogen) is determined in this step. Since three molecules (the protonated catalyst, $R^1S^{\ominus}$, and the unsaturated compound) participate in structure **IV**, the attacking direction of $R^1S^{\ominus}$ is subject to steric hindrance. Our results show that when both the C(3)-substituent and R^2 are bulky enough (combination of AN–CA catalyst and **IIa**), the direction of $R^1S^{\ominus}$ attack is more strongly controlled by the configuration at C(3) rather than by the configurations at C(8) and C(9), resulting in the formation of the same enantiomer, regardless of the kind of alkaloid moiety. If the steric bulkiness of either the C(3)-substituent or R^2 is small (monomeric catalyst or **IIc**), the chiral force stemming from C(3) does not exceed those from C(8) and C(9). The transition-state structure may be depicted as **V**. In the Type I reactions, (R^2 is hydrogen and R^3 is not), the stereochemistry is determined at the step of protonation to the α-carbon (**VI**). Only two molecules participate in this step. Furthermore, proton migration is the only action. Accordingly, this step is relatively insensitive to steric hindrance, and the direction of protonation is controlled by the configurations at the nearest chiral carbons, C(8) and C(9).

SUMMARY

The mode of stereoregulation in the AN–CA catalyzed Type II reactions varied, depending on the β-substituent of the acceptor. The C(3)-control was observed only when the steric environments of the enantioface differentiating step were sufficiently crowded. With monomeric catalysts, the reactions were always C(8), C(9)-control, regardless of the kind of β-substituent. The steric bulkiness of the thiol may also affect the stereochemistry of the AN–CA catalyzed reactions, but this point must await further study.

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