

Asymmetric Reduction with Chiral NADH Model Compounds: A Dynamic Aspect of Product Stereochemistry

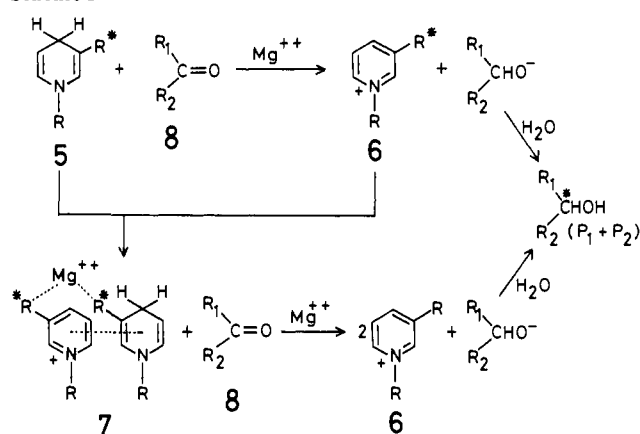
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Abstract: In the asymmetric reduction of ethyl benzoylformate with chiral NADH model compounds bearing L-prolinamide and L-prolinol, the dependence of optical yield on the reaction conversion was observed, as were the cases with other chiral NADH models reported so far. This phenomenon was studied in terms of kinetics involving the feedback effect of the oxidized form on the reductant remaining in the reaction mixture, and an a priori prediction was made from the final mathematical expression that the product stereochemistry should be dependent also on the initial concentration of the substrate. Indeed, significant increase from 46% to 76% in the optical yields with the NADH model bearing L-prolinamide and from 39% to 52% with that bearing L-prolinol was observed by increments of the initial substrate concentration.

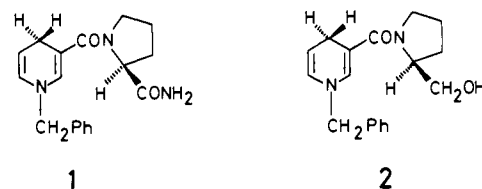
The mechanism of hydrogen transfer and catalytic activation of nicotinamide coenzyme as well as substrate has been a problem for a long time in relation to the biochemical function of dehydrogenases. Approaches to this by use of coenzyme model systems have been made extensively.¹ In addition, a number of new aspects of dihydropyridine chemistry have been presented in recent years.² In this connection, the study of asymmetric syntheses involving nonenzymic NADH model reactions is of current interest, and much attention has been paid in quest of understanding the factors that control the direction of asymmetric preference as well as the level of stereoselectivity in hydrogen transfer from chiral 1,4-dihydronicotinamide to prochiral substrates.³ For example, it is noteworthy to describe that three types of chiral NADH models have been established all of which showed nearly 100% stereoselectivity in asymmetric reduction of some prochiral substrates without the aid of enzymes.^{3,4} One of the other topics was a finding that, in asymmetric reduction of ethyl benzoylformate with some chiral NADH models, the optical yield increased as the reaction proceeds.⁵ There had been no similar example in other asymmetric synthesis so far,⁶ and it cannot be explained by a single kinetically controlled process. In relation to this observation, we wish to describe here some dynamic aspects of the stereochemistry in the asymmetric reduction by the use of different chiral NADH models. The experimental results were discussed in terms of kinetics.

Scheme I



Results

In a previous communication,⁷ we reported that an NADH model, **1**, reduced ethyl benzoylformate to (*R*)-mandelate with



the enantiomeric excess of 80% and the optical yield was affected greatly by the metal ion species employed as the catalyst. In the present study, at first, the optical yield was followed at varying reaction time (reaction conversion or chemical yield) in the same asymmetric reduction with **1**. A substrate, ethyl benzoylformate, was reduced with an equimolar amount of the model **1** in the presence of magnesium perchlorate for the reaction time of 5–10 min and the optical purity of the (*R*)-mandelate was plotted against the reaction time. As Figure 1 shows, conspicuous dependence of the optical yield on the reaction conversion was observed. The same was also the case with another NADH model, **2**, bearing L-prolinol instead of L-prolinamide (Figure 2).

As will be discussed later, to examine the possibility of dependence of the optical yield on initial concentration of the sub-

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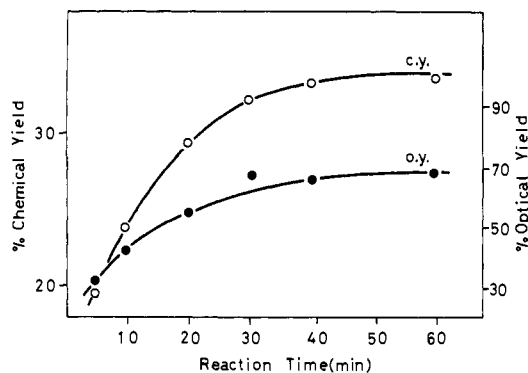


Figure 1. Dependence of optical yield on the reaction conversion in the asymmetric reduction of ethyl benzoylformate with model 1. Chemical yield: ○. Percent optical yield: ●. Reactant concentrations: model 1, 0.31 mmol/mL; $Mg(ClO_4)_2$, 0.16 mmol/10 mL. Reaction temperature, 0 °C.

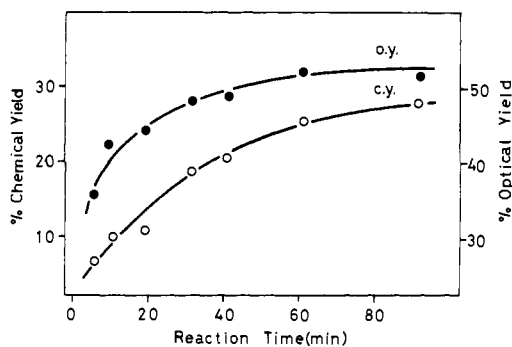


Figure 2. Dependence of optical yield on the reaction conversion in the asymmetric reduction of ethyl benzoylformate with model 2. Chemical yield: ○. Percent optical yield: ●. Reactant concentrations: model 2, 0.30 mmol/10 mL; $Mg(ClO_4)_2$, 0.24 mmol/10 mL. Reaction temperature, 0 °C.

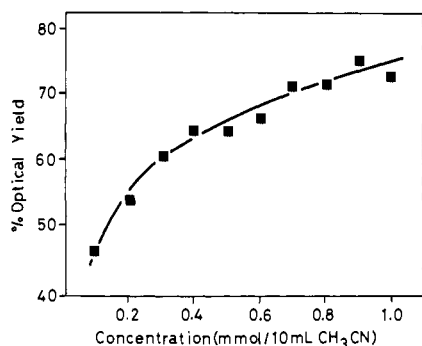
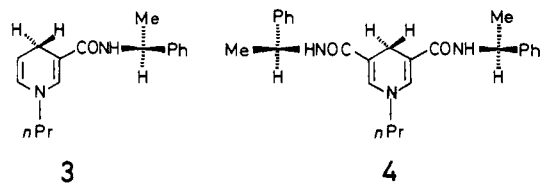


Figure 3. Dependence of optical yield on the initial concentration of ethyl benzoylformate in the asymmetric reduction with model 1. Reactant concentrations: model 1, 1.0 mmol/10 mL; $Mg(ClO_4)_2$, 0.8 mmol/10 mL. Reaction temperature, 40 °C. Reaction time, 100 min.

strate, a series of asymmetric reductions of ethyl benzoylformate by use of the NADH models 1, 2, 3, and 4 were conducted at the



concentrations of the substrate over the range of 0.1 to 1.0 mmols relative to the reductants in the presence of anhydrous magnesium perchlorate in dry acetonitrile under the specified conditions. The percent optical yields found for the resulting mandelate were plotted against the initial concentration of the substrate, and the

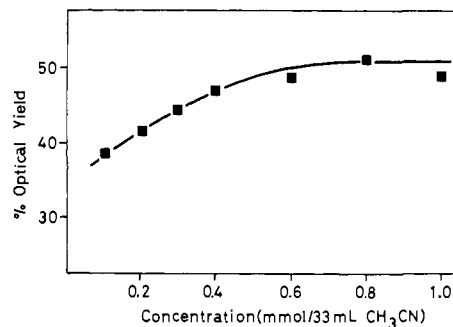


Figure 4. Dependence of optical yield on the initial concentration of ethyl benzoylformate in the asymmetric reduction with model 2. Reactant concentrations: model 2, 0.30 mmol/10 mL; $Mg(ClO_4)_2$, 0.24 mmol/10 mL. Reaction temperature, 25 °C. Reaction time, 24 h.

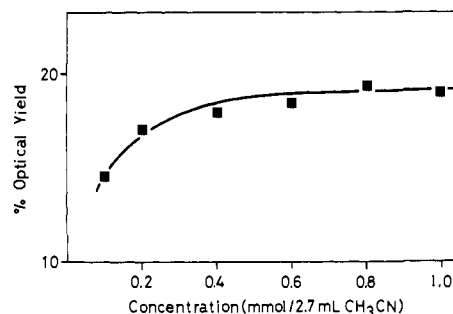


Figure 5. Dependence of optical yield on the initial concentration of ethyl benzoylformate in the asymmetric reduction with model 3. Reactant concentrations: model 3, 3.7 mmol/10 mL; $Mg(ClO_4)_2$, 3.7 mmol/10 mL. Reaction temperature, 25 °C. Reaction time, 24 h.

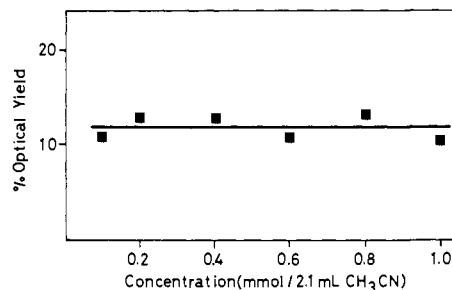


Figure 6. Dependence of optical yield on the initial concentration of ethyl benzoylformate in the asymmetric reduction with the model 4. Reactant concentrations: model 4, 4.8 mmol/10 mL; $Mg(ClO_4)_2$, 4.8 mmol/10 mL. Reaction temperature, 60 °C. Reaction time, 17 h.

results were given in Figures 3–6 for the models 1, 2, 3, and 4, respectively. As shown in the figures, significant changes of the optical yield of the product, ethyl mandelate, were observed for the NADH models except for 4.

Discussion

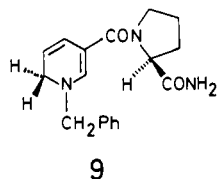
Dependence of Enantiometric Excess on the Reaction Conversion. As described in the above section, the optical yields were found to change greatly with the extent of the reaction conversion in asymmetric reductions by use of the models 1 and 2. This unusual phenomenon was first reported by Ohno^{5a} and Inouye^{5b} and has reasonably been accounted for in terms of the feedback interaction of the oxidized form, which accumulated in the mixture as the reaction proceeded.

According to Scheme 1, the oxidized form 6, a good electron acceptor, interacts with the reduced form 5 through a chelative mediation⁸ of metal ion and probably by a charge-transfer attraction.⁹ The interaction may bring about a specific blockage

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of one of the diastereotopic faces of dihydropyridine nucleus by virtue of the chirality used, permitting an easier access of the substrate carbonyl to the unhindered face and thereby contributing much toward improving the optical yield at the later stage of the reduction. Thus the overall optical yield should increase as the second component process becomes important due to the progress of the reaction. The higher enantiospecificity of such a hypothetical intermediate, **7**, formed by the feedback of the oxidized form in situ was evidenced by the initial addition of the oxidized form^{5b,10} as well as the external addition of either chiral or achiral aromatics capable of chelating and/or CT complexing.¹¹ This view, that the specific blockage of diastereotopic faces of dihydropyridine nucleus is an essential factor for higher enantioselectivity, is cogently supported by the high optical yield found for the asymmetric reduction with 4-methyl-substituted chiral dihydronicotinamide,^{4a} 1,4-dihydronicotinamide incorporated into crown ether macrocycle with L-amino acid residue,^{4b} and chiral bis-type NADH mimics with C₂ symmetry^{3a} where the transfer of hydrogen from dihydropyridine to substrate carbonyl is of necessity feasible only at the face of hydrogen available.

So far, attention has been paid to the oxidized form alone, however, there could be another possibility that the dependence of optical yield on the reaction conversion is due to some participations of the 1,6-dihydro isomer, which might be produced in situ via the process reported by Kellogg^{12a} and Minato^{12b} from the 1,4-dihydro form in the presence of its oxidized form. To check this points, pure 1,6-isomer **9** was prepared by sodium borohydride



reduction of the oxidized form, **10**, of the model **1** and submitted to the reduction of ethyl benzoylformate in the presence of magnesium perchlorate under exactly the same conditions. However, no reduction product was detected by VPC. Furthermore, addition of the 1,6-isomer to the reaction mixture depressed the optical yield by about 20%. Accordingly, the possibility of the involvement is safely excluded.

As a third possibility, magnesium ion paired with chiral mandelate anion produced in the reaction mixture, may also catalyze the latter process in parallel with the original reaction. Should this be the case, such a magnesium ion pair must likewise change the final stereochemical outcome to some extent in any asymmetric reductions with different chiral NADH models. However, as demonstrated by a recent study¹³ concerning the relation between the structure of NADH models and the product stereochemistry therewith, a C₂-symmetric model (**4**) did not show any dependence of the optical yield on the reaction conversion (Figure 7) while a strong dependence was manifested by Ohno^{5a} with the corresponding C₁-symmetric model **3** carrying the same chiral center. So that, it seems unlikely that the ion-pair catalysis, if any at all, alone is responsible for the phenomenon.

Accordingly, although the feature of the true reaction intermediate may not be so simple as we imagine, the oxidized form is at present the most probable entity based on the experimental

(9) (a) Pullman, B.; Pullman, A. *Proc. Natl. Acad. Sci. U.S.A.* **1959**, *45*, 136–144. (b) Saito, G.; Colter, A. K. *Tetrahedron Lett.* **1977**, 3325–3328. (c) Piepers, O.; Kellogg, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1154–1156.

(10) Since isolation and purification of perchlorates of the oxidized forms, **10** and **12**, were unsuccessful, the addition effects of the oxidized forms on the optical yield of the product could not be examined in our present model systems.

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(12) (a) van Bergen, T. J.; Mulder, T.; Kellogg, R. M. *J. Am. Chem. Soc.* **1976**, *98*, 1960–1962. (b) Minato, H.; Ito, T.; Kobayashi, M. *Chem. Lett.* **1977**, 13–16.

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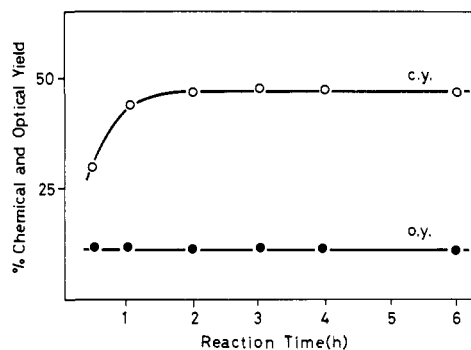
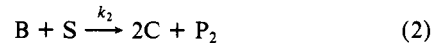
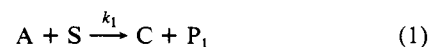


Figure 7. Dependence of optical yield on the reaction conversion in the asymmetric reduction of ethyl benzoylformate with model **4**. Chemical yield: ○. Percent optical yield: ●. Reactant concentrations: model **4**, 1.0 mmol/10 mL; Mg(ClO₄)₂, 1.0 mmol/10 mL. Reaction temperature, 60 °C.

results in addition to those reported so far.⁵

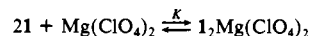
Qualitative Kinetic Consideration. We started from conventional kinetic treatment and definition of optical yield. According to Scheme I, eq 1–3 follow, where A, C, B, and S denote chiral



NADH model **5**, the oxidized form **6**, the intermediate **7**, and the substrate **8** in Scheme I, respectively.¹⁴ P₁ and P₂ are the product ethyl (R)-mandelate given by the first- and the second-component reactions (1) and (2), respectively. It was found experimentally that there was no equilibrium in the substrate reduction process from the fact that addition of an excess of substrate, at the time when the reaction apparently ceased, resulted in no measurable improvement of chemical yield. Therefore, irreversibility of eq 1 and 2 may be reasonable.¹⁵ For eq 3, there is no evidence for its nonequilibrium, however, its reverse might be little if any as compared with the forward because dihydropyridine (**5**) is an electron donor and pyridinium salt is an electron acceptor, and their mutual interaction is attractive⁹ while those between oxidized forms or reduced forms must be rather repulsive.

Then, four differential equations obtained from eq 1–3 were solved for P₁ and P₂ as functions of substrate concentration under a steady-state approximation that the concentration (B) of the

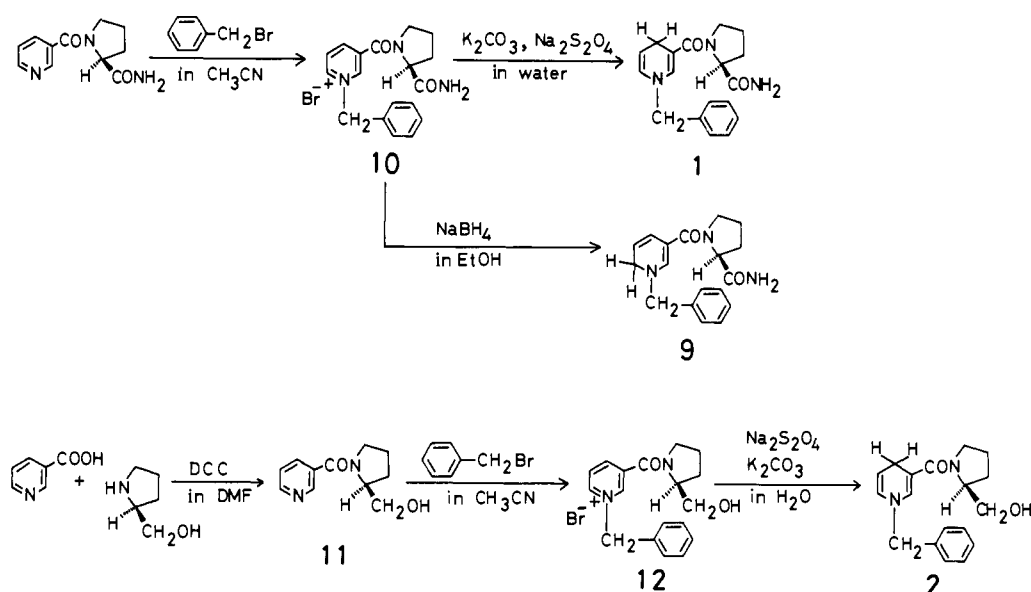
(14) UV spectra of model **1** in the presence of varying amounts of magnesium perchlorate showed a complex formation between the two components with 1:Mg(ClO₄)₂ = 2:1 molar ratio in dry acetonitrile. The stability constant was found to be 1 × 10⁸ M⁻² at 25 °C. If we assume that the operating



reaction species is the complex itself, the equilibrium equation should be considered. However, as evaluated by measuring the decreasing rate of the reactant by the addition of an excess of magnesium perchlorate and that of the complex by the addition of an excess of the substrate successively, the rate of the complex formation was found to be much faster (≈ 120 times) than that of the substrate reduction with the complex. The similar conclusions were reported by Ohno et al. This fact, in addition to the marked trend of equilibrium to the formation of the complex, suggests that the equation is not required for the total kinetic expression, or the reactant species in Scheme I can be replaced by the complex with small change (k₂/k₁ → 2k₂/k₁) in the final equations (eq 7 and 8). The change did not alter the mathematical treatment and the conclusion therefrom. Ohno, A.; Yamamoto, H.; Okamoto, T.; Oka, S.; Ohnishi, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2385–2386.

(15) The nonenzymic reverse reaction, i.e., oxidation of alcohol to carbonyl by the use of the NAD model (as an oxidizing reagent) involving pyridinium salt or oxidation–reduction equilibrium of substrate and the coenzyme model, have been attempted under strongly basic conditions. However, it has turned out to be very difficult, and no successful example has been reported. (a) Overman, L. E. *J. Org. Chem.* **1972**, *37*, 4214–4218. (b) Ohno, A.; Ushida, S.; Oka, S. *Tetrahedron Lett.* **1982**, *23*, 2487–2490 and references cited herein.

Scheme II



hypothetical intermediate 7 is constant and when $t = 0$, $S = S_0 - B$ and $A = A_0 - 2B$ are held. The solutions were as follows:

$$P_1 = S_0 - S + (k_2/k_1)B \ln [S - S_0 + A_0 + (k_2/k_1 - 1)B] \times [A_0 + (k_2/k_1 - 2)B]^{-1} \quad (4)$$

$$P_2 = (k_2/k_1)B \ln [A_0 + ((k_2/k_1) - 2)B] \times [S - S_0 + A_0 + (k_2/k_1 - 1)B]^{-1} \quad (5)$$

Where, S_0 is the initial concentration of substrate and S is that of at any reaction stage.

When we define m and n as the percent optical yield (or enantiomeric excess) of P_1 and P_2 , respectively, a relation, $n > m > 0$, should be fulfilled according to the explanation described above for the increasing in optical yield as the reaction proceeds (Scheme I). Then, the total optical yield contributed from P_1 and P_2 is expressed by eq 6 (see Appendix I), which can be compared

$$\% \text{ optical yield} = \frac{mP_1 + nP_2}{P_1 + P_2} \quad (6)$$

directly with observed percent enantiomeric excess of the product. Substitutions of P_1 and P_2 given by (4) and (5) into eq 6 and rearrangement give (7) as the final expression:

$$\% \text{ optical yield} = m + (k_2/k_1)B(n - m)(S - S_0)^{-1} \ln [(S + A_0 - S_0 + (k_2/k_1 - 1)B)(A_0 + (k_2/k_1 - 2)B)^{-1}] \quad (7)^{16}$$

Without any mathematical approximations or assumptions, this equation proved to be a monotonic increasing function of the decreasing substrate concentration, S , being in the range of $S_0 \geq S > 0$ (see Appendix II). Since the decrease in S is identical with the reaction conversion, the mathematical outcome supported the experimental findings given in Figures 1 and 2.

Furthermore, when we suppose a reaction stage at which all the substrate was transformed into the product and substitute $S = 0$ into eq 7, another equation eq (8) is obtained. Here, when

$$\% \text{ optical yield} = m + (k_2/k_1)B(n - m)S_0^{-1} \ln [(A_0 + (k_2/k_1 - 2)B)(A_0 - S_0 + (k_2/k_1 - 1)B)^{-1}] \quad (8)$$

the initial concentration of substrate, S_0 , is regarded as a variable,

(16) In principle, it should be that $k_1 = k_{1R} + k_{1S}$ and $k_2 = k_{2R} + k_{2S}$, and we can also start from $d(R_1 + R_2)/dt = k_{1R}AS + k_{2R}BS$ and $d(S_1 + S_2)/dt = k_{1S}AS + k_{2S}BS$ leading of course to the same expression (eq 7). However, this way is more complex.

A similar expression reported in a preliminary communication^{5c} was found to be incomplete. However, it was improved in a complete form here.

the right side of eq 8 becomes a function of S_0 . Mathematical treatment (Appendix III) indicated that this was a monotonic increasing function of increasing S_0 . It unequivocally predicts that the optical yield should arise by increments in the initial substrate concentration. In accord with this prediction, significant increments in optical yield from 46% to 76% for the reduction with **1** (Figure 3) and from 39% to 51% with **2** (Figure 4) were in fact found. This finding constitutes the first example in which dependence of product stereochemistry on the initial concentration of substrate was shown and received as kinetic justification. As described above, model 3 was known to show the dependence of optical yield on the reaction conversion whereas another model, **4**, with the same chiral center did not (Figure 7). Accordingly, the theoretical consideration described above predicts that model **3** should exhibit the dependence of optical yield on the initial concentration but model **4** may not. Indeed, this turned out to be true as shown unambiguously in Figures 5 and 6.

In summary, a kinetic means was applied for the hypothesis in Scheme I involving the duality in the NADH model reaction caused by the oxidized form as a most probable origin, and the agreement of the prediction therefrom with the experimental outcome cogently supports the hypothesis. The present study suggests that in other asymmetric systems⁶ as well, similar feedback effects of reaction product(s) on the product stereochemistry may operate in addition to other factors, i.e., solvent polarity, catalyst, temperature, etc. A feedback effect of this kind could be revealed simply by varying the initial concentration of substrate.¹⁷

Experimental Section

UV and ¹H NMR spectra were recorded on Hitachi 340 and Varian EM-360 spectrometers, respectively. The optical rotations were taken on a Perkin-Elmer 241 polarimeter. Shimadzu gas chromatograph GC-4CM with 5% polyethylene glycol succinate was used for VPC analyses. Elemental analyses were by Yanagimoto CHN Corder MT-3. Melting points were uncorrected.

The NADH model compounds **1**, **2**, and **9** were prepared according to Scheme II.

The asymmetric reductions were carried out by stirring a mixture of NADH model compounds (1.0 mmol), anhydrous Mg(ClO₄)₂ (0.5 or 0.8 mmol), and ethyl benzoylformate (1.0 mmol or varying amount) in dry CH₃CN under the specified conditions described in each figure. After the reaction, the mixture was worked up as usual.^{5b}

1-Benzyl-3-[(S)-(2'-carbamoylpyrrolidinyl)carbonyl]pyridinium Bromide (10). A solution of *N*-nicotinoyl-L-prolinamide¹⁸ (2.37 g, 10 mmol)

(17) The same can be done by following the reaction period, however, it is often very difficult to stop with accuracy fast reactions at an early stage in particular.

and benzyl bromide (1.71 g, 10 mmol) in dry CH₃CN (15 mL) was shaken vigorously for 4 h, and crystalline compound separated from the solution was filtered, washed with 99% EtOH, and dried over P₂O₅ in vacuo, yield, 3.4 g (83%): mp 212–214 °C; $[\alpha]_D^{25}$ –68.2° (*c* 1.765, H₂O); ¹H NMR (CF₃COOH) δ 2.0–3.0 (m, 4 H, 3', 4'-pyrrH), 6.0 (s, 2 H, CH₂Ph), 7.6 (s, 5 H, ph H), 8.2–8.4 (dd, *J* = 3, 3 Hz, 1 H, 5-py H), 8.8–9.1 (m, 2 H, 4, 6-py H), 9.4 (s, 1 H, 2-py H). Anal. Calcd for C₁₈H₂₂N₃O₃Br: C, 55.39; H, 5.68; N, 10.77. Found: C, 55.26; H, 5.16; N, 10.79.

1-Benzyl-3-[(S)-(2'-carbamoylpyrrolidinyl)carbonyl]-1,4-dihydropyridine (1). To an aqueous solution of Na₂S₂O₄ (3.8 g, 80% purity, 17.5 mmol) and anhydrous K₂CO₃ (6.6 g, 62.3 mmol) in H₂O (20 mL) was added an aqueous solution of the bromide **3** (1.72 g, 4.2 mmol) in H₂O (14 mL), and the mixture was stirred at 50–60 °C for 1.5 h under nitrogen atmosphere. Yellow oil separated from the solution was extracted with CH₂Cl₂ 3 times, washed with water, and dried over anhydrous Na₂SO₄. Complete evaporation of the solvent afforded the dihydronicotinamide **1** as light yellow powder, yield, 80%: UV (λ_{\max} , ϵ_{\max} in EtOH) 349 nm (5040); $[\alpha]_D^{25}$ +67.6° (*c* 1.235, EtOH); ¹H NMR (CDCl₃) δ 1.6–2.4 (m, 4H, 3', 4'-pyrrH), 3.1–3.3 (m, 2 H, 4, 4-py H), 3.4–3.8 (m, 3 H, 2', 5'-pyrrH), 4.3 (s, 2H, CH₂Ph), 4.4–4.9 (m, 1 H, 5-py H), 5.8 (dd, *J* = 4, 1 Hz, 6-py H), 5.9 (m, 1 H, amide proton), 6.6 (d, *J* = 1 Hz, 1 H, 2-py H), 6.8 (m, 1 H, amide proton), 7.3 (s, 5 H, ph H).

N-Nicotinoyl-L-prolinol (11). To a solution of nicotinic acid (18.5 g, 150 mmol) in DMF (450 mL) was added dicyclohexylcarbodiimide (32.0 g, 155.1 mmol), and the mixture was stirred for 1 h at –5 to 0 °C. L-Prolinol was added dropwise over 90 min at the same temperature, and the solution was stirred overnight at 25 °C. After the period, the mixture was acidified with 3 N HCl (ca. 50 mL), and 100 mL of H₂O was added. Continuous extraction (2 days) with ether was performed to remove DMF. The aqueous phase was made alkaline with KOH to pH 11, and the HCl-free chiral nicotinic acid derivative of L-prolinol was extracted continuously with ether overnight. The ether phase was concentrated, and the residue was dried by azeotropic distillation with benzene. L-Prolinol in the residue was removed by distillation under reduced pressure. The amide as brown resinous material (7.2 g) was submitted as such to the following quaternization without further purification.

1-Benzyl-3-[(S)-(2'-(hydroxymethyl)pyrrolidinyl)carbonyl]pyridinium Bromide (12). A solution of the nicotinic acid derivative of L-prolinol (**11**) (5.38 g, 26.1 mmol) and benzyl bromide (4.46 g, 26.1 mmol) in dry CH₃CN (34 mL) was refluxed for 4 h. When excess of EtOAc was added to the solution after cooling to room temperature, the bromide precipitated. The supernatant was decanted off, and the residue was left open to the air overnight. When partial crystallization occurred, the whole residue was crystallized from CH₃CN–EtOAc–EtOH and recrystallized from EtOH–EtOAc, yield, 3.7 g (37%): mp 117–122 °C; $[\alpha]_D^{25}$ –93.7° (*c* 0.63, H₂O); ¹H NMR (CF₃COOH) δ 1.8–2.5 (m, 4 H, 3', 4'-pyrrH), 3.4–4.0 (m, 2 H, 5'-pyrrH), 8.1–9.1 (m, 3 H, 4, 5, 6-py H), 9.2 (s, 1 H, 2-py H). Anal. Calcd for C₁₈H₂₁N₃BrO₂·½H₂O: C, 55.96; H, 5.74; N, 7.25. Found: C, 55.95; H, 5.75; N, 7.25.

1-Benzyl-3-[(S)-(2'-(hydroxymethoxy)pyrrolidinyl)carbonyl]-1,4-dihydropyridine (2). To an aqueous solution of Na₂S₂O₄ (3.83 g, 80% purity, 17.6 mmol) and anhydrous K₂CO₃ (6.75 g, 48.8 mmol) in H₂O (20 mL) was added an aqueous solution of the bromide **4** (1.62 g, 4.2 mmol) in H₂O (17 mL), and the mixture was stirred at 30–40 °C for 6 h under nitrogen atmosphere. The product was extracted with CH₂Cl₂ 4 times, and the combined extract was washed with NaCl-saturated H₂O and dried over anhydrous Na₂SO₄. Complete evaporation of the solvent afforded the reductant **2**, yield, 1.13 g (90%): $[\alpha]_D^{25}$ +47.0° (*c* 0.876, CH₃CN); UV (λ_{\max} , ϵ_{\max} in CH₃CN) 342 nm (4500); ¹H NMR (CDCl₃) δ 1.3–2.4 (m, 4 H, 3', 4'-pyrrH), 3.1–3.4 (m, 2 H, 4, 4-py H), 3.0–4.0 (m, 4 H, 5', 5'-pyrrH and CH₂O), 4.3 (s, 2 H, CH₂Ph), 4.5–4.8 (m, 1 H, 5-py H), 5.8 (dd, 1 H, 6-py H), 6.5 (s, 1 H, 2-py H), 7.3 (s, 5 H, ph H).

1-Benzyl-3-[(S)-(2'-carbamoylpyrrolidinyl)carbonyl]-1,6-dihydropyridine (9). This compound was prepared by reduction of bromide **10** with sodium borohydride according to the method by Wallenfels.¹⁹ An aqueous solution of bromide **10** (1.8 g, 4.4 mmol) in H₂O (90 mL) was added to an aqueous solution of Na₂CO₃ (0.4 g, 3.8 mmol) and NaHCO₃ (0.4 g, 4.8 mmol) in H₂O (39 mL), and the solution was stirred at 25 °C for 1.5 h. The organic phase was extracted with CHCl₃ 3 times. The solution was washed with H₂O and dried over anhydrous Na₂SO₄. Evaporation of the solvent gave a mixture of the 1,4- and 1,6-dihydro forms with unknown impurities. The 1,6-isomer was isolated pure by

silica gel column chromatography, eluted with EtOAc–EtOH, as yellow resinous oil, yield, 0.35 g (26%): UV (λ_{\max} , ϵ_{\max} in CHCl₃), 355 nm (4300); ¹H NMR (CDCl₃) δ 1.6–2.5 (m, 4 H, 3', 4'-pyrrH), 3.4–3.8 (m, 3 H, 2', 5'-pyrrH), 3.9 (m, 2 H, 6, 6-py H), 4.5–5.0 (m, 1 H, 5-py H), 6.0 (m, 1 H, amide proton), 6.2 (m, 1 H, 4-py H), 7.0 (br, 1 H, amide proton), 7.4 (s, 5 H, ph H).

Appendix I

Since P₁ and P₂ are the mixture of R and S enantiomers, *m* and *n*, the percent optical purities of P₁ and P₂, are expressed by each enantiomer concentrations, R₁, R₂, S₁, and S₂ as follows:

$$m = 100 \frac{|R_1 - S_1|}{R_1 + S_1} \quad n = 100 \frac{|R_2 - S_2|}{R_2 + S_2}$$

According to these definitions in addition to P₁ = R₁ + S₁ and P₂ = R₂ + S₂, the following relationship obtains:

$$\begin{aligned} \% \text{ optical yield} &= 100 \frac{R_{\text{total}} - S_{\text{total}}}{R_{\text{total}} + S_{\text{total}}} \\ &= 100 \frac{R_1 + R_2 - S_1 - S_2}{R_1 + R_2 + S_1 + S_2} \\ &= \frac{\pm mP_1 \pm nP_2}{P_1 + P_2} \end{aligned} \quad (9)$$

Here, when we define that percent optical yield has plus (rich in R) as well as minus (rich in S) signs, four cases can be drawn from the expression 9.

$$\% \text{ op} = \frac{-mP_1 - nP_2}{P_1 + P_2} \quad \text{when } S_1 > R_1 \text{ and } S_2 > R_2 \quad (\text{i})$$

$$\% \text{ op} = \frac{-mP_1 + nP_2}{P_1 + P_2} \quad \text{when } S_1 > R_1 \text{ and } S_2 < R_2 \quad (\text{ii})$$

$$\% \text{ op} = \frac{mP_1 - nP_2}{P_1 + P_2} \quad \text{when } S_1 < R_1 \text{ and } S_2 > R_2 \quad (\text{iii})$$

$$\% \text{ op} = \frac{mP_1 + nP_2}{P_1 + P_2} \quad \text{when } S_1 < R_1 \text{ and } S_2 < R_2 \quad (\text{iv})$$

As the final expression (7) can be drawn from eq iv, three similar expressions are obtained from i–iii, for which the same mathematical procedures described in the following appendices can be applied arriving at essentially the same conclusion. First, in case i, minus rotational values increase with the increase in the optical yield rich in S as the reaction proceeds. In contrast, in cases ii and iii, the rotational signs of the product change from minus (rich in S) to plus (rich in R) or plus to minus, respectively, with continuous change in their optical yields. On the other hand, in case iv, plus rotational values increase as the reaction proceeds (e.g., Figures 1 and 2).

Appendix II

Since $(k_2/k_1)B > 0$ and $n - m > 0$ in eq 7, we examine the term that contains the variable S as a function *f*(S) for simplification.

$$f(S) = (S - S_0)^{-1} [\ln(S + D) - \ln(S_0 - B + D)] \quad (10)$$

Here, a substitution, $A_0 - S_0 + (k_2/k_1 - 1)B = D(\text{constant})$, is made. Differentiation of (10) with S gives

$$f'(S) = -(S - S_0)^{-2} \left[\ln \frac{S + D}{S_0 + D - B} - \frac{S - S_0}{S + D} \right] \quad (11)$$

Since $-(S - S_0)^{-2} \leq 0$, we consider the inside part of the bracket as a function *g*(S).

$$g(S) = \ln \frac{S + D}{S_0 - B + D} - (S - S_0)(S + D)^{-1} \quad (12)$$

Differentiation of (12) by S gives (13).

$$g'(S) = -(S_0 - S)(S + D)^{-2} \leq 0 \quad (13)$$

Thus, (12) is a monotonic decreasing function of S. Taking account $g(S_0) = \ln(S_0 + D)/(S_0 + D - B) > 0$ since $0 < S +$

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$D < S_0 + D$, $g(S) > 0$ leading to $f'(S) \leq 0$. Accordingly, $f(S)$, the right side of eq 7, is found to be an increasing function of decreasing S .

Appendix III

When essential part of eq 8 as a function $h(S_0)$

$$h(S_0) = S_0^{-1}[\ln(H - B) - \ln(-S_0 + H)] \quad (14)$$

and $A_0 + (k_2/k_1 - 1)B = H (=S_0 + D) > 0$ were considered, the right side of the eq 8 was shown to be an increasing function of

increasing S_0 by the treatment similar to that of Appendix II.

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Registry No. 1, 76030-79-0; 2, 88337-07-9; 3, 58368-95-9; 4, 88337-08-0; 5, 88337-09-1; 10, 88337-10-4; 11, 88337-11-5; 12, 88337-12-6; *N*-nicotinyl-L-prolinamide, 85084-02-2; nicotinic acid, 59-67-6; L-prolinol, 23356-96-9; ethyl benzoylformate, 1603-79-8; NADH, 58-68-4.

Communications to the Editor

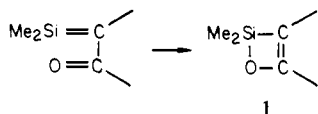
1,2-Silaoxetene

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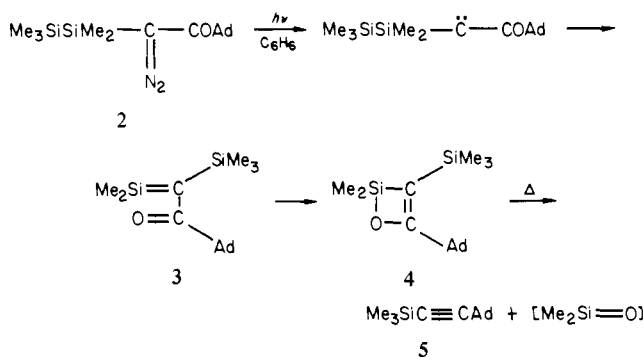
1-Oxa-2-silacyclobutenes **1** (1,2-silaoxetenes) merit special interest in view of their ring strain and their fascinating chemistry.



The silaoxetene was first postulated as a reactive intermediate in the reaction of 1,1-dimethyl-2,3-bis(trimethylsilyl)-1-silirene with dimethyl sulfoxide.¹ However, the study of these intriguing silaoxetenes has been hampered by the lack of a convenient reaction. In our recent silene formations from α -silyl carbenes,² the intramolecular [2 + 2] cyclization reaction has received much attention in the synthesis of silaoxetenes. We now report here the first successful synthesis of the 1,2-silaoxetene 2,2-dimethyl-3-(trimethylsilyl)-4-adamantyl-1-oxa-2-silacyclobutene (**4**), by the photolysis of pentamethyldisilanyl adamantyl diazo ketone **2**.³

When a benzene solution of **2** was photolyzed with a high-pressure mercury lamp for 1 h at room temperature and the photolysate was directly subjected to gas chromatography, adamantyl(trimethylsilyl)acetylene (**5**) was isolated as a sole volatile product (Scheme I). The structure of **5** was determined by the following spectroscopic characterization: ¹H NMR (C_6D_6 , δ) 0.12 (s, 9 H, SiMe₃), 1.42–2.15 (m, 15 H, adamantyl CH); ¹³C NMR (C_6D_6) δ 0.6 (SiMe), 28.4 (adamantyl CH), 30.7 (adamantyl C attached to ethynyl group), 36.6 (adamantyl CH₂), 43.3 (adamantyl CH₂), 82.4 (ethynyl C), 116.1 (ethynyl C); IR (neat) 2150

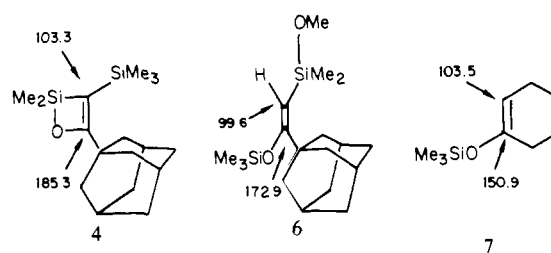
Scheme I



Ad = 1-adamantyl group

cm⁻¹ (C \equiv C); mass spectrum, m/e 232 (M⁺), 217 (M⁺ - Me). Anal. Calcd for C₁₅H₂₄Si: C, 77.50, H, 10.40; Found: C, 77.57, H, 10.44. When the photolysate was directly analyzed by NMR in benzene-*d*₆, the signals at 0.25 (s, 9 H, SiMe₃), 0.38 (s, 6 H, SiMe₂), 1.47–2.23 (m, 15 H, adamantyl CH) were observed but no signals attributed to the acetylene **5**. ¹³C NMR spectrum (C_6D_6) had peaks at δ 0.9 (SiMe), 2.6 (SiMe), 28.8 (adamantyl CH), 37.2 (adamantyl CH₂), 40.3 (adamantyl CH₂), 40.9 (adamantyl C attached to olefin), 103.3 (olefinic C), and 185.3 (olefinic C). These resonances are completely consistent with the structure of the silaoxetene **4**. Characteristic signal of the enol carbon is observed at much lower field (185.3 ppm) than those of the strain-free enol silyl ethers, 172.9 ppm for **6**⁴ and 150.9 ppm for **7**. The photolysis of **2** is extremely clean, and the

¹³C NMR spectra (in C_6D_6) of enol silyl ethers



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(3) Silyl diazo ketone **2** was prepared from lithium (pentamethyldisilanyl)diazomethane and 1-adamantanecarboxylic acid chloride in 86% yield. Sekiguchi, A.; Sato, T.; Ando, W. *Chem. Lett.* **1983**, 1083.

(4) Enol silyl ether **6** was prepared by the thermal isomerization of **11**. We tentatively assigned the structure as the trans form. ¹H NMR (CCl_4 , δ) 0.07 (s, 9 H, SiMe₃), 0.20 (s, 6 H, SiMe₂), 1.90–2.63 (m, 15 H, adamantyl CH), 3.98 (s, 3 H, OMe), 4.73 (s, 1 H, C=CH); ¹³C NMR (C_6D_6) -2.1 (SiMe), 0.5 (SiMe), 29.1 (adamantyl CH), 37.2 (adamantyl CH₂), 40.2 (adamantyl C attached to olefin), 40.7 (adamantyl CH₂), 50.0 (OMe), 99.6 (olefinic C), 172.9 (olefinic C); IR (neat) 1590 (C=C), 1065 cm⁻¹ (SiOC); mass spectrum m/e 338 (M⁺). Anal. Calcd for C₁₈H₃₄O₂Si₂: C, 63.84; H, 10.12. Found: C, 63.79, H, 10.20.