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NAD(P)$^+$–NAD(P)H Models. 84. Stereochemistry Controlled by the Electronic Effect from a Sulfinyl Group

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ABSTRACT

*2,3-Dihydro-2,2,4-trimethylthieno[3,2-b]pyridinium 1-oxide iodide (**1**) has been reacted with various inorganic and organic hydride donors. It has been found that the stereochemistry of reaction is controlled by the orientation of the sulfinyl dipole, and the relative bulkiness of substituents plays no role in determining the reaction face: a reactive hydride donor prefers to attack at the anti-face with respect to the sulfinyl dipole, whereas a less reactive hydride donor prefers to attack at the syn-face.*

The carbonyl oxygen in the carbamoyl group of NAD(P)$^+$/NAD(P)H analogs sticks out of the molecular plane, and it has been reported that H^- transfer to an NAD(P)$^+$ analog takes place predominantly from the face occupied by this carbonyl oxygen [1–3]. That is, the stereochemistry of H^- transfer is controlled by the orientation of the carbonyl dipole and is independent of steric hindrance. The mechanism of controlling stereochemistry by an electronic effect was discussed recently [4]. It is interesting to study whether a dipole other than that of a carbonyl group can play a similar role to control stereochemistry; *i.e.*, whether the mechanism proposed is universal. We studied, therefore, the stereochemistry of hydride transfer with a molecule related to an NAD(P)$^+$ analog, which is substituted by a sulfinyl group in place of a carbonyl group as the crucial dipole.

The stereochemistry of α-sulfinyl carbanion reactions has been studied extensively and subjected to discussion by many organic chemists from the viewpoints of mechanistic and synthetic organic chemistry [5–9]. We recently pointed out the importance of the counter cation as well as the solvent on the conformation of an α-sulfinyl carbanion [10–13], and we proposed that the relative bulkiness of substituents on the sulfur atom controls the stereochemistry of its reactions.

The present system is the reaction of attack by a nucleophile at the β-position of a sulfoxide, instead of by an electrophile at the α-position. In this sense, it is also interesting to compare the effects of the sulfinyl group on these different reaction systems.

EXPERIMENTAL

Instruments

^{1}H NMR spectra were recorded at 200 MHz on a Varian VXR 200 FT-NMR spectrometer. IR spectra were recorded on a Jasco FT/IR-5300 spectrometer. Elemental analyses were performed with a Yanako MT-3 elemental analyzer. Boiling and melting points were not corrected.

Materials

Deuterated NAD(P)H analogs (PNAH-4,4-d_2 [14], BNAH-4,4-d_2 [14], (4*R*)-Me$_2$PNPH-4-*d* [15], and (4*S*)-

Dedicated to Emeritus Prof. Shigeru Oae on the occasion of his seventy-fifth birthday.

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Me_2PNPH-4-*d* [15]) were prepared according to the literature methods. Acetonitrile was distilled over calcium hydride before use. The phosphate buffer and methanol were degassed before use.

Methallyl 3-Pyridyl Sulfide [16]

3-Aminopyridine (17.0 g, 0.18 mol) was placed in a 200 mL three-necked round-bottomed flask equipped with a magnetic stirrer and a thermometer and immersed in a thermostat maintained at −5°C. With stirring, 15 g of crushed ice was added, and then 15 g of concd hydrochloric acid was added slowly. The mixture was cooled to −2°C, and a cold solution of sodium nitrite (13.8 g, 0.20 mol) in 30 mL of water was slowly added dropwise. The temperature was kept below 0°C during the addition (ca. 2 hours).

Sodium ethyl xanthate (25.0 g, 0.17 mol) in 30 mL of water was placed in a 300 mL three-necked round-bottomed flask equipped with a magnetic stirrer and a thermometer. The solution was warmed to 40°C and stirred vigorously during the slow addition of the cold diazonium solution; the temperature increased to 60°C. After an additional 30 minutes at this temperature, 3-pyridyl ethyl xanthate separated as a brown oil. Organic materials in the aqueous layer were extracted with ether three times. The combined organic layer was washed with 1 M sodium hydroxide solution and brine. The ethereal solution was dried over sodium sulfate, and the ether was evaporated under reduced pressure.

Crude 3-pyridyl ethyl xanthate (28.1 g) dissolved in 200 mL of 95% ethanol was placed in a 300 mL three-necked round-bottomed flask equipped with a magnetic stirrer, a dropping funnel, a reflux condenser, and a thermometer. The solution was refluxed. After the heat source had been removed, pellets of sodium hydroxide (17.5 g, 0.42 mol) were added to this hot solution so that the solution was kept boiling. The mixture was refluxed for an additional 8 hours. To the hot reaction mixture, methallyl chloride (25 mL, 0.25 mol) was added dropwise. The temperature was kept at 70–75°C during the reaction. After an additional 30 minutes at this temperature, the reaction mixture was cooled to room temperature, and insoluble salts that had precipitated were removed by filtration. The filtrate was concentrated under reduced pressure, and, after addition of water, organic materials in the reaction mixture were extracted with hexane three times. The combined extracts were washed with brine and dried over sodium sulfate. After the hexane had been evaporated under reduced pressure, the residual oil obtained was distilled under reduced pressure to give methallyl 3-pyridyl sulfide as a yellow oil (15.9 g, 0.096 mol, bp. 70–71°C at 0.6 mm Hg) in 53% yield. Further purification was accomplished by column chromatography on silica gel with ethyl acetate/hexane (1:3) as an eluent to give a colorless oil.

^1H NMR: δ^{TMS} ($CDCl_3$) 1.85 (m, 3H, CH_3), 3.50 (m, 2H, SCH_2), 4.78 (m, 2H, $=CH_2$), 7.20 (ddd, J_{45} = 8.0, J_{56} = 4.8, J_{25} = 0.8 Hz, 1H, C5–H), 7.65 (ddd, J_{45} = 8.0, J_{24} = 2.4, J_{46} = 1.6 Hz, 1H, C4–H), 8.44 (dd, J_{56} = 4.8, J_{46} = 1.6 Hz, 1H, C6–H), and 8.57 (dd, J_{24} = 2.4, J_{25} = 0.8 Hz, 1H, C2–H). Anal. calcd for $C_9H_{11}NS$: C, 65.41; H, 6.71; N, 8.48%. Found: C, 65.40; H, 6.90; N, 8.42%.

2,3-Dihydro-2,2-dimethylthieno[3,2-b]pyridine [17,18]

The hydrochloride of methallyl 3-pyridyl sulfide (611 mg, 3.0 mmol) and 10 mL of *N,N*-dimethylaniline (DMA) were placed in a 50 mL round-bottomed flask equipped with a magnetic stirrer and a reflux condenser. The mixture was stirred and heated at 185°C for 72 hours. After removal of most of the DMA by distillation under reduced pressure, the residue was treated with 1 M sodium hydroxide solution and extracted with hexane four times. The combined extract was dried over sodium sulfate, and the hexane was evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel with ethyl acetate/hexane (1:4) as an eluent to give crude 2,3-dihydro-2,2-dimethylthieno[3,2-*b*]pyridine (419 mg, 2.5 mmol) as a red oil in 83% yield. Although the product was contaminated by a small amount of isomers and impurities derived from DMA, it was not purified further for use in the next step. Further purification was accomplished by recrystallization from chloroform/ethyl acetate as the hydrochloride. ^1H NMR: δ^{TMS} ($CDCl_3$) 1.58 (s, 6H, C2–CH_3 × 2), 3.20 (s, 2H, C3–H × 2), 6.99 (dd, J_{67} = 8.0, J_{56} = 5.0 Hz, 1H, C6–H), 7.41 (dd, J_{67} = 8.0, J_{57} = 1.4 Hz, 1H, C7–H), 8.15 (dd, J_{56} = 5.0, J_{57} = 1.4 Hz, 1H, C5–H). Anal. calcd for $C_9H_{11}NS$: C, 65.41; H, 6.71; N, 8.48%. Found: C, 65.31; H, 6.84; N, 8.40%.

2,3-Dihydro-2,2-dimethylthieno[3,2-b]pyridine 1-oxide (**2**) *[19]*

2,3-Dihydro-2,2-dimethylthieno[3,2-*b*]pyridine (323 mg, 1.95 mmol) was dissolved in 10 mL of acetic acid, and the solution was placed in a 100 mL round-bottomed flask filled with argon and equipped with a magnetic stirrer. To the solution, sodium peroxoborate (300 mg, 1.95 mmol) was added and the mixture was stirred for 20 hours. Subsequently, water was added to the reaction mixture and a part of the acetic acid was evaporated under reduced pressure. Water was added to the residue, and the organic materials were extracted with methylene chloride three times, the combined extract then being dried over sodium sulfate. After evaporation of the solvent under re-

duced pressure, the residue was subjected to column chromatography on neutral alumina and eluted with ethyl acetate/hexane (1:3) to give **2** (333 mg, 1.84 mmol) as a pale yellow oil in 94% yield.

^{1}H NMR: δ^{TMS} ($CDCl_3$) 1.36 (s, 3H, C2–CH_3), 1.56 (s, 3H, C2–CH_3), 3.14 (d, J = 16.9 Hz, 1H, C3–H), 3.65 (d, J = 16.9 Hz, 1H, C3–H), 7.33 (dd, J_{67} = 8.0, J_{56} = 4.8 Hz, 1H, C6–H), 8.13 (dd, J_{67} = 8.0, J_{57} = 1.6 Hz, 1H, C7–H), and 8.66 (dd, J_{56} = 4.8, J_{57} = 1.6 Hz, 1H, C5–H). IR (neat): 1045 cm^{-1} (ν_{S-O}). Anal. calcd for $C_9H_{11}NOS$: C, 59.64; H, 6.12; N, 7.73%. Found: C, 59.31; H, 6.17; N, 7.60%.

2,3-Dihydro-2,2,4-trimethylthieno[3,2-b]pyridinium 1-Oxide Iodide (**1**)

Into a 100 mL round-bottomed flask filled with argon and equipped with a magnetic stirrer, **2** (433 mg, 2.4 mmol) and 10 mL of acetone were placed. The flask was protected from light. To the agitated solution, 10 mL of methyl iodide was added. After 24 hours, a yellow precipitate that had formed was collected by filtration. The precipitate was washed with ethyl acetate to give **1** as a yellow powder (710 mg, 2.2 mmol) in 92% yield: mp 193–196°C (dec). ^{1}H NMR: δ^{TPS-d_4} (D_2O) 1.49 (s, 3H, C2–CH_3), 1.65 (s, 3H, C2–CH_3), 3.85 (d, J = 19.0 Hz, 1H, C3–H), 4.01 (d, J = 19.0 Hz, 1H, C3–H), 4.38 (s, 3H, N4–CH_3), 8.17 (m, 1H, C6–H), 9.01 (m, 1H, C5–H), and 9.09 (m, 1H, C7–H). IR (KBr): 1070 cm^{-1} (ν_{S-O}). Anal. calcd for $C_{10}H_{14}NIOS$: C, 37.16; H, 4.37; N, 4.33%. Found: C, 37.07; H, 4.37; N, 4.34%.

2,3-Dihydro-2,2,4-trimethylthieno[3,2-b]pyridinium Iodide (**6**)

This compound was synthesized by the same method as described earlier for 2,3-dihydro-2,2-dimethylthieno[3,2-*b*]pyridine and the succeeding *N*-methylation by methyl iodide as described for **1**. ^{1}H NMR: δ^{TPS-d_4} (D_2O) 1.68 (s, 6H, C2–CH_3 × 2), 3.67 (s, 2H, C3–H × 2), 4.21 (s, 3H, N4–CH_3), 7.67 (m, 1H, C6–H), 8.16 (m, 1H, C7–H), and 8.29 (m, 1H, C5–H). Anal. calcd for $C_{10}H_{14}NIS$: C, 39.10; H, 4.59; N, 4.56%. Found: C, 38.48; H, 4.51; N, 4.45%. Since the compound is air-sensitive, repeated elemental analyses did not give satisfactory results.

2,3-Dihydro-2,2,4-trimethylthieno[3,2-b]pyridinium 1,1-Dioxide Iodide (**7**)

The procedure employed for the preparation of **2** was used here except for the reaction conditions: 2 equivalent amounts of sodium peroxoborate were used at 70°C. The sulfone could be separated from the corresponding sulfoxide, **1**, by column chromatography on silica gel, eluted with ethyl acetate/ethanol (19:1). ^{1}H NMR: δ^{TPS-d_4} (D_2O) 1.63 (s, 6H, C2–CH_3 × 2), 3.81 (s, 2H, C3–H × 2), 4.36 (s, N4–CH_3), 8.24 (m, 1H, C6–H), 9.03 (m, 1H, C7–H), and 9.15 (m, 1H, C5–H). IR(KBr): 1310, 1169, and 1126 cm^{-1} (ν_{S-O}). Anal. calcd for $C_{10}H_{14}NIO_2S$: C, 35.41; H, 4.16; N, 4.13%. Found: C, 35.27; H, 4.12; N, 4.06%.

Reduction of **1** *with a Deuterated Reagent*

In general, all of the reductions were performed under an atmosphere of argon in the dark at 25°C. All the solvents were degassed immediately before use. The residue obtained after the reaction was purified by flash column chromatography on neutral alumina and then eluted with methylene chloride under an atmosphere of argon. The stereospecificity of the reaction was monitored by 200 MHz ^{1}H NMR spectroscopy of the product.

Two geminal protons at the C7-position of **3** are distinguishable as syn- and anti-orientations with respect to the S–O bond by ^{1}H NMR spectroscopy in $CDCl_3$: on addition of Eu(fod)$_3$ to the solution of **3**, a broad doublet at the lower field (3.35–3.5 ppm) shifts toward lower field to a greater degree than the other broad doublet at the higher field (3.2–3.35 ppm). The Eu-induced shifts of the doublets reveal that the one at the lower and the other at the higher field correspond to the syn- and anti-protons, respectively, with respect to the S–O bond (Figure 1). The stereospecificity was calculated from the ratio of integrated areas of the doublets.

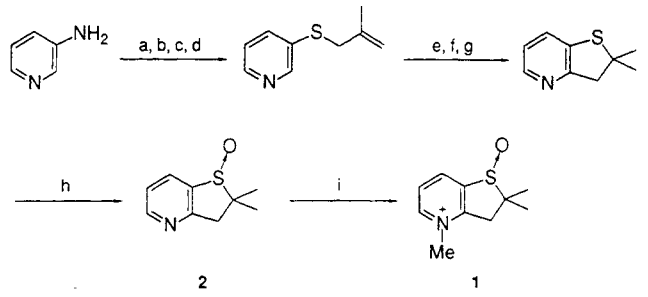
With Sodium Disulfite in D_2O. In a 30 mL round-bottomed flask equipped with a magnetic stirrer, **1** (16.3 mg, 0.05 mmol), 5 mL of *p*D 7.5 buffer (KD_2PO_4-NaOD) and 10 mL of methylene chloride were placed. To the vigorously stirred mixture, 24.9 mg of sodium disulfite dissolved in 5 mL of the buffer solution was added. After 2 hours, the organic layer was separated and the aqueous layer was extracted with methylene chloride three times. The combined organic layer was dried over sodium sulfate, and the methylene chloride was evaporated under reduced pressure to give almost pure 2,3,4,7-tetrahydro-2,2,4-trimethylthieno[3,2,-*b*]pyridine 1-oxide (**3**).

3: ^{1}H NMR: δ^{TMS} ($CDCl_3$) 1.36 (s, 3H, C2–CH_3), 1.42 (s, 3H, C2–CH_3), 2.47 (m, J = 16.2 Hz, 1H, C3–H), 2.88 (s, 3H, N4–CH_3), 2.95 (m, J = 16.2 Hz, 1H, C3–H), 3.2–3.5 (bd × 2, 2H, C7–H × 2), 4.65 (ddd, J_{56} = 8.0, J = 3.6, 3.0 Hz, 1H, C6–H), and 5.62 (ddd, J_{56} = 8.0, J = 1.8, 1.6 Hz, 1H, C5–H).

The same reduction of **7** afforded 2,3,4,7-tetrahydro-2,2,4-trimethylthieno-[3,2-*b*]pyridine 1,1-dioxide (**5**).

5: ^{1}H NMR: δ^{TMS} ($CDCl_3$) 1.48 (s, 6H, C2–CH_3 × 2), 2.56 (t, J_{37} = 1.4 Hz, 2H, C3–H × 2), 2.87 (s, 3H, N4–CH_3), 3.22 (bs, 2H, C7–H × 2), 4.74 (dt, J_{56} = 8.0, J_{67} = 3.4 Hz, 1H, C6–H), and 5.68 (dt, J_{56} = 8.0, J_{57} = 1.6 Hz, 1H, C5–H).

With $NaBD_4$. To **1** (6.8 mg, 0.02 mmol) and $NaBD_4$ (1.8 mg, 0.04 mmol) in a 20 mL round-bot-



(a) $NaNO_2$, conc.HCl, ice, 0 °C; (b) NaSCSOEt, H_2O, 40 °C; (c) NaOH, 95%EtOH, reflux; (d) methallyl chloride; (e) HCl; (f) *N,N*-dimethylaniline, 185 °C; (g) neutralization; (h) $NaBO_3 \cdot 4H_2O$, AcOH; and (i) MeI, acetone.

SCHEME 1

tomed flask equipped with a magnetic stirrer, 4 mL of methanol was added, then the mixture was stirred. After 2 hours, the methanol was evaporated under reduced pressure to give the residue.

With a Deuterated NAD(P)H Analog. In a typical run, to **1** (6.5 mg, 0.02 mmol) and BNAH-4,4-d_2 (21.5 mg, 0.1 mmol) contained in a 20 mL round-bottomed flask equipped with a magnetic stirrer, 1 mL of acetonitrile was added, and the mixture was stirred. After 6 hours, the acetonitrile was evaporated under reduced pressure to give the residue.

Here, the signals from **5** interfere with the measurement of intensities of signals from **1** in ^1H NMR spectroscopy. In this case, the ratio of signals for the dimethyl groups at the C2-positions of **3** and **5** was measured, and the total intensity of the signals at δ 3.2–3.5 was divided proportionally by the ratio.

RESULTS AND DISCUSSION

2,3-Dihydro-2,2,4-trimethylthieno[3,2-*b*]pyridinium 1-oxide iodide (**1**) was synthesized according to the processes shown in Scheme 1. Preliminary results from X-ray crystallography of **1** reveal that the sulfinyl dipole in this molecule rises above the pyridine plane at an angle of about 60° [20]. Enantiomerically pure 2,3-dihydro-2,2-dimethylthieno[3,2-*b*]pyridine 1-oxide (**2**), a precursor of **1**, was obtained by chromatographic separation of racemic **2** on an HPLC equipped with a chiral column. Thus obtained, **2** afforded enantiomerically pure **1** on *N*-methylation.

A racemic mixture of the pyridinium salt of sulfoxide, **1**, was subjected to reduction by a variety of deuterated reagents under an atmosphere of argon in the dark at 25°C. Stereospecificities of the reduction were monitored by 200 MHz ^1H NMR spectroscopy for the reduced product, 2,3,4,7-tetrahydro-2,2,4-trimethylthieno[3,2-*b*]pyridine 1-oxide (**3**). The ^1H NMR spectrum of **3** in $CDCl_3$ exhibits double doublets at δ 3.2–3.5, as demonstrated in Figure 1(a). The doublets at the lower and higher fields have been assigned to the syn- and anti-protons at the C7-position, respectively. The stereospecificity was estimated by the ratio of areas of these doublets. The results are listed in Table 1.

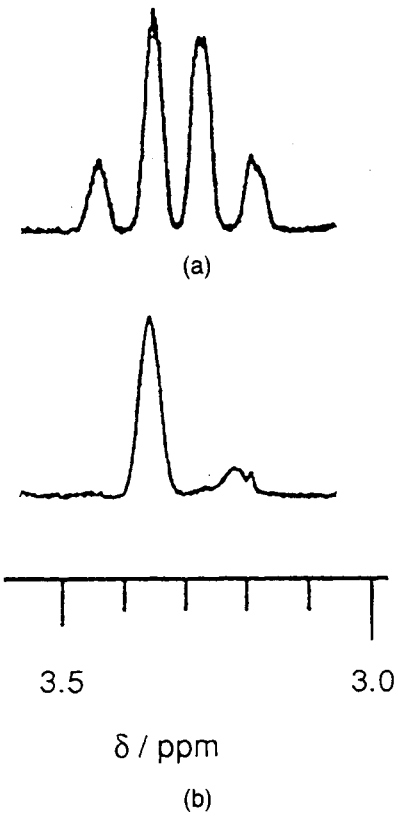


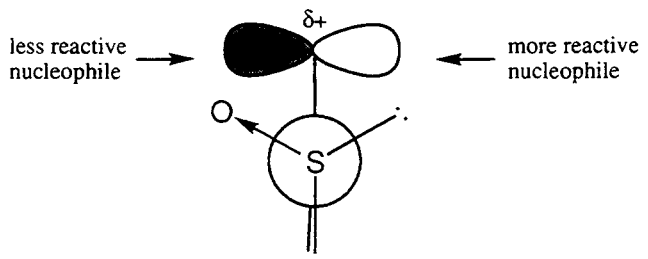
FIGURE 1 ^1H NMR spectra of geminal protons at the C7-position in (a) **1** (L = H) and (b) **1** (L = D; obtained from the reduction with $Na_2S_2O_4$ in D_2O).

Although the reduction with $NaBD_4$ affords an-

TABLE 1 Reduction of Racemic **1** with Various Reducing Agents

Reducing Agent	*Equivalent*	*Solvent*	*Product Ratio* **3**	*(syn:anti):* **4**
$Na_2S_2O_4$	2.3	D_2O(buffer)[a]/ CH_2Cl_2	96	(18:82):4
$NaBD_4$	1.4	CH_3OH	17	(21:79):83
			3	***(syn:anti):5***
PNAH-4,4-d_2	5.0	CH_3CN[b]	46	(62:38):54
BNAH-4,4-d_2	4.9	CH_3CN[b]	29	(77:23):71
(4*R*)-Me_2PNPH-4-*d*	0.4	CH_3CN[b]	71	(72:28):29
(4*S*)-Me_2PNPH-4-*d*	0.4	CH_3CN[b]	64	(72:28):36

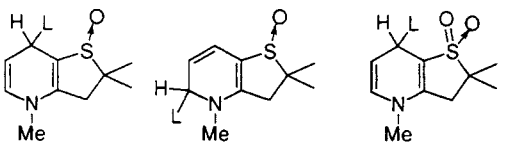
[a] KD_2PO_4/NaOD; *p*D 7.50.
[b] Distilled over CaH_2 before the use.



SCHEME 2

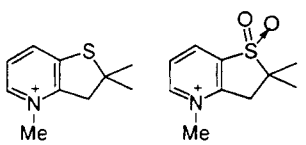
other regio-isomer, 2,3,4,5-tetrahydro-2,2,4-trimethylthieno[3,2-*b*]pyridine 1-oxide (**4**), predominantly, stereospecificity in **3** is still large enough to be recognized, as demonstrated in Figure 1(b).

It should be noted that the reductions with such inorganic, or reactive (large reduction potential), reagents as $Na_2S_2O_4$ and $NaBD_4$ afford the anti-product predominantly [21,22], whereas the reductions with organic, or less reactive (small reduction potential) and structured, reagents such as BNAH, PNAH, and Me_2PNPH lead to a preferential formation of syn-product.

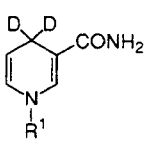


3 **4** **5**

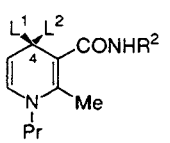
L = H or D



6 **7**



R^1 = Pr : PNAH-4,4-d_2
R^1 = Bn : BNAH-4,4-d_2



L^1 = Me, L^2 = D, R^2 = (*R*)-α-methylbenzyl: (4*R*)-Me_2PNPH-4-*d*
L^1 = D, L^2 = Me, R^2 = (*S*)-α-methylbenzyl: (4*S*)-Me_2PNPH-4-*d*

When a weak reducing agent such as BNAH was employed for the reduction, the corresponding sulfone **5** and sulfide **6** were produced as well, probably due either to disproportionation of **1**, or to an oxygen-transfer reaction between **1** and **3**, or both. With these reducing agents, the reduction from the syn-face predominates over that from the anti-face, in contrast to the reductions with inorganic reagents. It should be noted that the syn-face is sterically more hindered, if this is of any consequence, than the other. Since racemic **1** was employed for the reduction, enantiomeric isomers of Me_2PNPH yield the same result. This observation reveals that the stereochemical consequence observed herein stems from the conformation of **1** only, and it is unaffected by the conformation of the reducing agent. Thus, it has been elucidated that the orientation of the sulfinyl dipole controls the stereochemistry of the reduction, and the stereospecificity depends on the reactivity of the reagent. The result coincides with those reported previously for the influence of the carbonyl dipole in the oxidations of NAD(P)H analogs [3,23–26].

As predicted for the chemistry of the α-sulfinyl carbanion [11], it is conceivable that a sulfoxide exists as a dimeric form in an organic solvent, and its sterically hindered enantioface is different from that expected from the monomeric structure. However, in our studies reported herein, (1) there is no cationic counterpart to connect sulfinyl groups into dimeric form; (2) no ^{1}H NMR spectroscopic indication is observed for the existence of a dimeric form [11]; and, above all, (3) steric bulkiness cannot account for the change in stereochemical reaction course, depending on the reactivity of nucleophile. The evidence may support the proposal that **1** in a monomeric form reacts with a hydride donor and the stereochemistry of the reaction is controlled by the orientation of the sulfinyl group: the preference of the face depends on the reactivity of the hydride donor to give either syn- or anti-product, as illustrated in Scheme 2.

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[20] Since residuals R and R_w are not small enough (ca. 0.1) to accurately discuss regarding bond length and bond angle, we postpone the submission of detailed results from the X-ray crystallography.
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