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Studies on Novel and Chiral 1,4-Dihydropyridines. III.[1] Asymmetric Reduction of Some Ketones with Novel NADH Model Compounds, (S_S)-3-(*p*-Tolylsulfinyl)-1,4-dihydropyridines[2]

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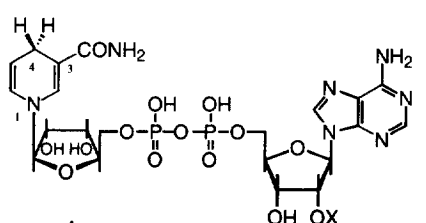
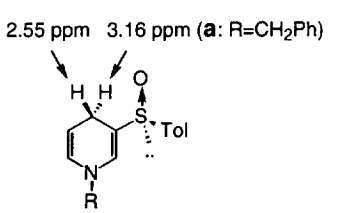
Abstract: The reactions of the novel NADH model compounds **2** with methyl benzoylformate and some other ketonic compounds were studied. The 3-(*p*-tolylsulfinyl) derivatives **2** successfully reduced methyl benzoylformate to give methyl (*R*)-mandelate in good chemical and optical yields. Some other ketones were also found to be reduced with the compound **2b**. A possible transition state model is discussed. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The important role of NAD(P)H (**1**) to work as a coenzyme in the biological redox transformation has stimulated a great deal of interest in the field of bioorganic chemistry. The development of artificial systems which mimic enzymatic reactions in the living systems is a fascinating challenge to organic chemists. A number of NADH model compounds have been developed[3] since Ohno and co-workers reported the first example of asymmetric reduction with such a model compound.[4] In previous papers,[1] we reported the syntheses of a novel type of potent NADH model compounds **2**, in which we introduced a chiral *p*-tolylsulfinyl group at the C-3 position of the 1,4-dihydropyridine nucleus in place of an amido group in NADH from the viewpoint of the



1: X=H (NADH)
X=OPO_2H_2 (NADPH)



2 **a**:R=CH_2Ph
b:R=*n*-Pr
c:R=Me
d:R=H

Fig. 1. The Structures of NADH (NADPH) and Our Model Compounds

following aspects: A sulfinyl group is known to have a moderate electron-withdrawing character similar to that of the amido group, and has been proved to work as an excellent chiral auxiliary for many kinds of asymmetric synthesis.[5] As shown in Fig. 1, the ^1H NMR spectra of **2** indicated that the prochiral 4-hydrogens were significantly differentiated by the sulfinyl group, suggesting their potential effectiveness as a chiral NADH mimic.[1a] In this paper, we wish to describe in detail the successful asymmetric reduction of methyl benzoylformate (**3**) and some other ketones **6-12** with the NADH model compounds **2** and also discuss a possible transition state model for the reduction.

RESULTS AND DISCUSSION

First of all, the reduction of methyl benzoylformate (**3**) with NADH model compound **2b** was tried under the typical reaction conditions previously reported [in acetonitrile (MeCN), **2b**/Mg^{2+}/**3** = 1/1/1, at 30°C, in the dark].[4] After reduction for two weeks, methyl (*R*)-(-)-mandelate (**4**) was obtained in 75% chemical yield with 97% e.e. Next, we examined the effects of the metal salt and its molar ratio on the reaction and the results are summarized in Tables 1 and 2. Magnesium perchlorate and zinc perchlorate were effective for the reaction. Although the highest optical yield was obtained in the presence of zinc perchlorate, the chemical yield was relatively low probably due to the effect of the water included in its crystals. This is supported by the fact that the addition of water to the reaction with magnesium perchlorate decreased both chemical and optical yields of **4**. From Table 2, it is obvious that the chemical and optical yields also depend on the molar ratio of the metal salt. The chemical yield was at a maximum when 1 equivalent of magnesium perchlorate was used and was lowered with either an increased or decreased amount of the metal salt.

Scheme 1

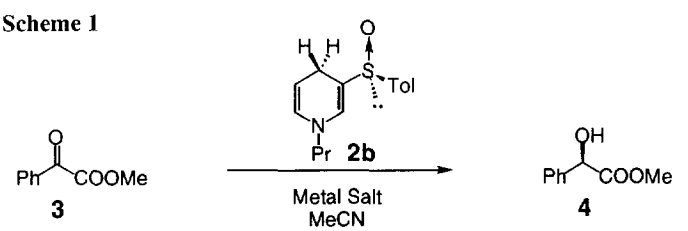


Table 1. Effects of the Metal Salts on the Asymmetric Reduction of **3** with **2b**.[a]

Metal Salts	Chemical Yield (%)[b]	$[\alpha]_D$[c]	Optical Yield (%)[d]
$Mg(ClO_4)_2$	75	-138.9°	97
$Zn(ClO_4)_2 \cdot 6H_2O$	47	-139.8°	97
$Mg(ClO_4)_2+H_2O$ (1 eq.)	65	-136.2°	95
$Mg(ClO_4)_2+H_2O$ (5 eq.)	16	-36.9°	26
$Mg(ClO_4)_2+H_2O$ (20 eq.)	0	-	-
$CoCl_2$	5	-21.6°	15
$ZnCl_2$	0	-	-

a. See Experimental. *b*. Isolated Yield. *c*. In MeOH at 25 °C. *d*. Based on the specific rotation of pure methyl (*R*)-mandelate (ref. 6), $[\alpha]_D$ -144.0° (*c* 1.0 in MeOH).

Table 2. Effects of the Stoichiometry of the Asymmetric Reduction of **3** with **2b**.[a]

$Mg(ClO_4)_2$ equivalent	Chemical Yield (%)[b]	$[\alpha]_D$[c]	Optical Yield (%)[d]
0.5	25	-132.0°	92
1.0	75	-138.9°	97
1.5	33	-124.7°	87
2.0	36	-123.4°	86

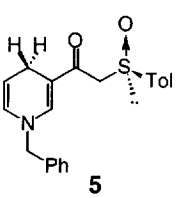
a. See Experimental. *b*. Isolated Yield. *c*. In MeOH at 25 °C. *d*. Based on the specific rotation of pure methyl (*R*)-mandelate, $[\alpha]_D$ -144.0° (*c* 1.0 in MeOH).

In the asymmetric reduction of ketones with **2**, the addition of water markedly decreased both chemical and optical yields (Table 1). Furthermore, in consideration of the influence of the ratio of the metal salt on the chemical yield, the stoichiometry of NADH model/metal ion/substrate in the transition state would be 1/1/1 and this ratio is apparently crucial for this reaction (Table 2). These results strongly suggest that the ternary complex of **2** with a metal ion and a substrate is certainly formed through this reaction process.

The role of the nitrogen substituent (**2a-d**) and the effectiveness of the sulfinyl group at the C-3 position (**2** and **5**) are evident from the results shown in Table 3. Apparently, the optical yields were little affected by the nitrogen substituents, but the stability of the model compounds is highly dependent on the nitrogen substituents. The lower chemical yields for **2c** and **2d** seem to be attributable to the lability of these compounds which might be partially decomposed before the reaction takes place. On the other hand, the reduction product was not obtained at all by using the (*p*-tolylsulfinyl)acetyl derivative **5**[1a] under the same conditions. This means that this compound **5** is too stable to reduce methyl benzoylformate, probably due to the strong electron-withdrawing property of the (*p*-tolylsulfinyl)acetyl group.

Table 3. Effects of the *N*- and 3-Substituents on the Asymmetric Reduction of **3** with **2** and **5**.[a]

Reagent	$Mg(ClO_4)_2$ (1eq.)		$Zn(ClO_4)_2 \cdot 6H_2O$ (1eq.)	
	Chemical Yield (%)[b]	Optical Yield (%)[c]	Chemical Yield (%)[b]	Optical Yield (%)[c]
2a (R=CH_2Ph)	77	94	43	96
2b (R=*n*-Pr)	75	97	47	97
2c (R=Me)	49	95	30	95
2d (R=H)	28	95	13	97
5	0	-	0	-

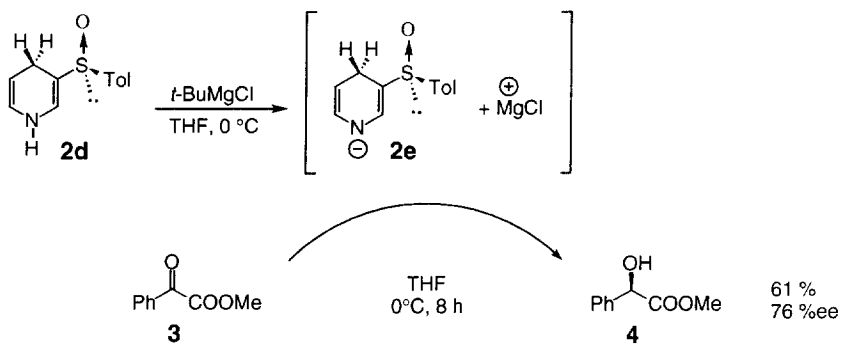


5

a. See Experimental. *b*. Isolated Yield. *c*. Based on the specific rotation of pure methyl (*R*)-mandelate, $[\alpha]_D$ -144.0° (*c* 1.0 in MeOH).

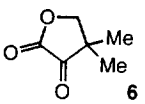
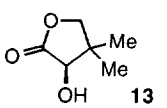
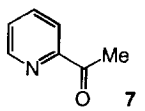
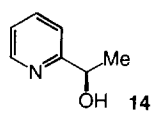
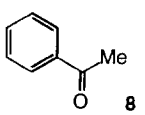
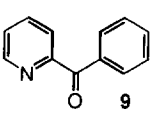
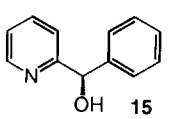
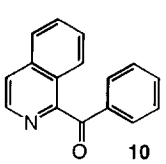
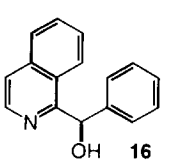
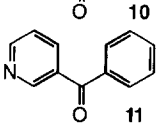
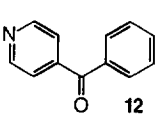
Generally, the reactivity of NADH models is thought to be largely dependent on the electron density of the 1,4-dihydropyridine nucleus.[7] Therefore, the reactivity of the anionic compound **2e** was expected to be much higher than those of the 1-alkyl derivatives. Taking into account the fact that a magnesium ion is essential for this reaction, we employed a Grignard reagent as an additive which was expected to work not only as the magnesium ion source but also as a base to abstract the N-1 hydrogen of **2d**. As illustrated in Scheme 2, the reaction of **3** with **2d** in the presence of *t*-BuMgCl gave **4** in a good chemical yield (61%) with a moderate optical yield (76 % e.e.). Although, as expected, the reactivity of **2d** was greatly increased by this procedure compared with the reaction by using $Mg(ClO_4)_2$ or $Zn(ClO_4)_2$, the enantioselectivity was unfortunately somewhat decreased. This is probably attributable to the nonspecific hydride transfer from the highly reactive anionic compound **2e**.

Scheme 2



Next, we examined the reductions of the other carbonyl compounds **6**-**12** with **2b** under the same conditions described above (in acetonitrile, **2b**/metal salt/substrate = 1/1/1, at 30 °C, in the dark). As shown in Table 4, ketopantolactone (**6**), 2-acetylpyridine (**7**), 2-benzoylpyridine (**9**) and 1-isoquinolyl phenyl ketone (**10**) were reduced into the corresponding alcohols **13**, **14**, **15** and **16** in good optical yields, while acetophenone (**8**), 3-benzoylpyridine (**11**) and 4-benzoylpyridine (**12**) were not. In the former compounds, the α-carbon of the reducible carbonyl group has a nitrogen or oxygen atom with a sp^2 hybridized orbital, which is essential for this asymmetric reduction. From these results, it is obvious that the coordination properties with Mg^{2+} or Zn^{2+} is required for this reaction rather than the electron-withdrawing properties which can activate the neighboring ketone.

Table 4. Asymmetric Reduction of Unsaturated Compounds **6-12** with **2b**.[a]

Substrate	Metal Salt	Time /day	Product	Chemical Yield (%)[b]	Optical Yield (%)[c]	Configuration
 **6**	$Mg(ClO_4)_2$	3	 **13**	38	84	*R*
	$Zn(ClO_4)_2{\cdot}6H_2O$	4		trace	-	-
 **7**	$Mg(ClO_4)_2$	3	 **14**	37	86	*R*
	$Zn(ClO_4)_2{\cdot}6H_2O$	3		45	73	*R*
 **8**	$Mg(ClO_4)_2$	6	-	0	-	-
	$Zn(ClO_4)_2{\cdot}6H_2O$	5	-	0	-	-
 **9**	$Mg(ClO_4)_2$	2	 **15**	84	86	*R*
	$Zn(ClO_4)_2{\cdot}6H_2O$	2		65	96	*R*
 **10**	$Mg(ClO_4)_2$	3	 **16**	43	92	*R*[d]
	$Zn(ClO_4)_2{\cdot}6H_2O$	2		46	90	*R*[d]
 **11**	$Mg(ClO_4)_2$	6	-	0	-	-
 **12**	$Mg(ClO_4)_2$	6	-	0	-	-

a. See Experimental. *b*. Isolated Yield. *c*. Determined by ^{19}F-NMR analysis of the corresponding MTPA esters. *d*. After derivatization to the corresponding (1*S*)-camphanate ester, the absolute configuration was determined by the X-ray analysis (ref. 8).

As described above, some experimental results support the formation of the ternary complex as a crucial step. Concerning the transition state of the NADH reduction, the following have been already found: i) from calculations of the transition structure of the simple hydride transfer, a *syn* arrangement of the carbonyl group and the π-system of the dihydropyridine ring is more favorable than an *anti* arrangement;[9] ii) hydride transfer is assisted by the amide dipole and the easier transfer of hydride occurs on the same face of the carbonyl group;[10]

iii) the role of the metal ion is not to act as a Lewis acid by activating the carbonyl group of the substrate but to form a ternary complex with the substrate and NADH;[11,12] iv) from calculations of the conformation of NADH, there is boat-like puckering of the 1,4-dihydropyridine ring and the transfer of the *pseudo-axial* hydrogen is preferred.[13] Based on these studies, some possible structures of the ternary complex of NADH model compound with a metal ion and a substrate have been proposed.[11,14-17]

Recently, Kakinuma and co-workers reported, from the results of MO calculations, that the carbonyl oxygen of an amido group is responsible for coordination with Mg^{2+}.[18] In our model compound **2**, the sulfinyl oxygen is naturally thought to be a possible candidate for this coordination in place of an amido oxygen. In our previous papers, we have already elucidated the conformation of **2**,[1a] which is represented as shown in Fig. 2 and is explainable in terms of the allylic 1,3-strain[19] of the *p*-tolylsulfinyl group, by means of ^{1}H NMR and X-ray crystallographic analyses, and also clarified that the only *pro-S* hydrogen which is *syn* arrangement with respect to the S-O bond of the *p*-tolylsulfinyl group was employed in the asymmetric reduction.[20] Taking into account these results and the results obtained in this study, the transition state as shown in Fig. 2 seems to be the most plausible.[21] This ternary complex model completely satisfies the results shown in Table 4. The only ketones having a nitrogen or oxygen atom on the α-carbon of the carbonyl can form the ternary complex as shown and are reduced to the corresponding (*R*)-alcohols by the formal hydride transfer from the *si*-face of the ketones.

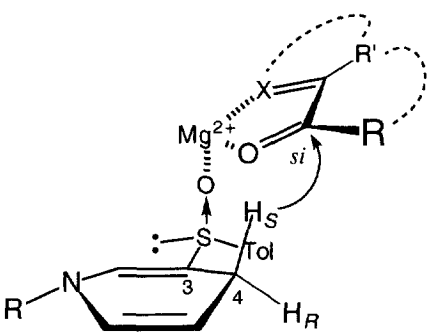


Fig. 2. Proposed Structure of Ternary Complex

In conclusion, we showed that in spite of the simple and small molecules of **2**, model compounds **2** have high abilities to reduce and to recognize the prochiral face of a substrate. This is thought to be attributable to the effectiveness of the *p*-tolylsulfinyl group as a chiral auxiliary and, moreover, the structural feature of **2**, namely, that the chiral center is close to the C-4 position. The structural requirements to work as a substrate for this asymmetric reduction were also revealed, which would provide suggestive and useful information for synthetic use and for the mechanistic study. The details of the reaction mechanism will be reported in due course.

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. ^1H and ^{19}F NMR spectra were taken on a Varian VXR-200 (200 and 188 MHz, respectively) spectrometer and tetramethylsilane and hexafluorobenzene (0.0 ppm) was used as an internal standard. Optical rotations were recorded on a JASCO DIP-370 instrument. Dihydropyridines, **2** and **5**, were prepared according to the procedure described in the previous paper.[1] Anhydrous acetonitrile was obtained by twice distillation over CaH_2 under a nitrogen atmosphere after reflux with CaH_2. Metal salts [$Mg(ClO_4)_2$, $Zn(ClO_4)_2 \cdot 6H_2O$, $CoCl_2$, and $ZnCl_2$] and *t*-BuMgCl were purchased from Wako Pure Chemical Industries, Ltd., Nacalai Tesque, Inc. or Kanto Chemical Co., Inc. and used without further purification. Methyl benzoylformate (**3**), ketopantolactone (**6**), 2-benzoylpyridine (**7**), 1-isoquinolyl phenyl ketone (**8**), 2-acetylpyridine (**9**), 3-benzoylpyridine (**10**), 4-benzoylpyridine (**11**), and acetophenone (**12**) were purchased from Aldrich Chemical Company, Inc. or Tokyo Kasei Kogyo Co., Ltd. and used without further purification. (*S*)-(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) is commercially available from Aldrich Chemical Company, Inc. and was converted to the acid chloride (MTPA-Cl) according to Moscher's procedure.[22] For column chromatography, Merck Kieselgel 60 (0.063-0.200 μm) was used.

General Procedure for Asymmetric Reduction of Ketones with 2. Under an argon atmosphere, a solution of **2** (0.30 mmol) in anhydrous MeCN was added to a stirred solution of a ketone (0.30 mmol) and a metal salt (0.30 mmol) in anhydrous MeCN (6 ml) at room temperature. The whole mixture was stirred at 30 °C under dark for 14 days. After dilution with H_2O (2 ml) and CH_2Cl_2 (20 ml), the organic layer was separated, washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to afford an alcohol. The products **4**, **13**, **14**, **15**, and **16** were identified by comparison of their spectroscopic data with those described in the cited references and gave satisfactory physical data. The spectroscopic data obtained from the reduction with **2b** in the presence of $Mg(ClO_4)_2$ are shown below.

4: Colorless needles, mp 52-54 °C. $[\alpha]_D^{25}$ -139.8 ° (*c* 1.05 in MeOH). ^1H NMR ($CDCl_3$) δ 3.47 (1H, d, *J* = 5 Hz), 3.76 (3H, s), 5.18 (1H, d, *J* = 5 Hz), 7.33-7.43 (5H, m). [lit.,[6] mp 56-58 °C. $[\alpha]_D^{21}$ -144.0 ° (*c* 1.00 in MeOH).]

13: Colorless needles, mp 64-66 °C. $[\alpha]_D^{25}$ -41.3 ° (*c* 0.25 in H_2O). ^1H NMR ($CDCl_3$) δ: 1.09 (3H, s), 1.24 (3H, s), 3.33 (1H, br s), 3.96, 4.03 (2H, AB, *J* = 9 Hz), 4.15 (1H, s). [lit.,[23] mp 89-90 °C. $[\alpha]_D^{25}$ -50.7 ° (*c* 2.05 in H_2O).]

14: A colorless oil, $[\alpha]_D^{20}$ +62.4 ° (*c* 0.67 in EtOH). ^1H NMR ($CDCl_3$) δ: 1.51 (3H, d, *J* = 6 Hz), 4.30 (1H, br s), 4.90 (1H, q, *J* = 6 Hz), 7.17-7.30 (2H, m), 7.65-7.73 (1H, m), 8.54 (1H, d, *J* = 5 Hz). [lit.,[24] $[\alpha]_D^{25}$ -56.7 ° (*c* 3.88 in EtOH) for the enantiomer of **14**.]

15: Colorless plates, mp 65-66 °C. $[\alpha]_D^{21}$ -140.3 ° (*c* 1.00 in $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 5.28 (1H, br s), 5.81 (1H, s), 7.22-7.39 (7H, m), 7.71-7.75 (1H, m), 8.55 (1H, d, *J* = 4 Hz). [lit.,[25] mp 64-65 °C for the enantiomer of **15**. lit.,[26] $[\alpha]_D^{25}$ -114.6 ° (*c* 2.81 in $CHCl_3$) for 93% e.e. of **15**.]

16: Colorless plates, mp 110-112 °C. $[\alpha]_D^{20}$ -15.6 ° (*c* 1.03 in $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 6.36 (1H, s), 7.20-8.00 (10H, m), 8.54 (1H, d, *J* = 5 Hz). (lit.,[27] mp 108-110 °C for the racemate of **16**.)

Asymmetric Reduction of 3 with the Anion of 2d. Under an argon atmosphere, *t*-BuMgCl (1.13 M in THF, 0.27 ml, 0.30 mmol) was added to a stirred solution of **2d** (66 mg, 0.30 mmol) in dry THF (10 ml) at 0 °C. The stirring was continued at 0 °C under dark for 10 min, then **3** (49 mg, 0.30 mmol) was added dropwise and the stirring was continued for 8 h. After dilution with saturated NH_4Cl (2 ml) and CH_2Cl_2 (20 ml), the organic layer was separated, washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to afford **4** (30 mg, 0.18 mmol, 61%) as a white solid.

Determination of Enantiomeric Excess for Alcohols 4 and 13-16.

a) From the specific rotation. The enantiomeric excess of alcohol **4** was determined from the specific rotation by comparison with that of pure methyl (*R*)-mandelate ($[\alpha]_D$ -144.0 ° (*c* 1.0 in MeOH).[6]

b) From MTPA ester derivatives.[22] To alcohol **15** (5 mg, 0.027 mmol) in pyridine (0.1 ml) was directly added (*S*)-(-)-MTPA-Cl (34 mg, 0.14 mmol) and *N,N*-dimethylaminopyridine (1 mg, 0.008 mmol). Usual workup was followed by ^{19}F NMR analysis of the resulting MTPA ester. ^{19}F NMR spectrum of the MTPA ester showed two singlets for CF_3 at δ 90.23 (7% for *S*-isomer) and 90.36 (93% for *R*-isomer). Enantiomeric excess of other alcohols were determined by a similar method and the ^{19}F NMR spectral data are as follows: **13**: δ 89.32 (92% for *R*-isomer) and 89.95 (8% for *S*-isomer); **14**: δ 90.06 (7% for *S*-isomer) and 90.23 (93% for *R*-isomer); **16**: δ 89.87 (96% for *R*-isomer) and 90.32 (4% for *S*-isomer).

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