Diastereoselective Radical Hydrogenation of α-(1-Hydroxyalkyl)vinyl Sulfoxides and Sulfones Controlled by Intramolecular Hydrogen Bonding

Nobuyuki Mase,[†,‡] Yoshihiko Watanabe,[†] Takeshi Toru,*[,†] Terumitsu Kakumoto,[§] and Tsuneo Hagiwara[||]

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan, Osaka Gas Co., Ltd., 17 Chuodori-minami-machi, Shimogyou-ku, Kyoto 600-8813, Japan, and Teijinseiki Co., Ltd., 3-2-1 Sakato, Takatsu-ku, Kaswasaki 213-0012, Japan

toru@ach.nitech.ac.jp

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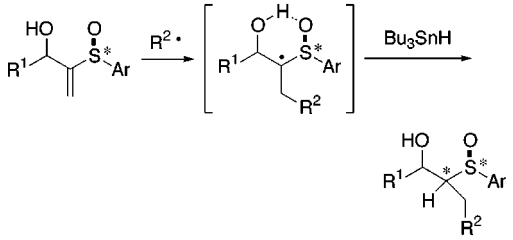
The reaction of (*S*)-α-(1-hydroxyalkyl)vinyl sulfoxides (*S*)-**5** with alkyl radicals and tributyltin hydride gave the addition−hydrogenation products with high diastereoselectivity, whereas the reaction with (*R*)-α-(1-hydroxyalkyl)vinyl sulfoxides (*R*)-**5** resulted in complete recovery of the starting sulfoxides. Stereoselective intramolecular hydrogen bonding between the hydroxy group and the diastereotopic sulfonyl oxygen led to high diastereoselectivity in the radical reaction of α-(1-hydroxyethyl)vinyl sulfone **12**. An important role of intramolecular hydrogen bonding on the diastereoselectivity as well as the reactivity toward alkyl radicals is discussed.

Introduction

There are a number of reports of stereochemical studies on the radical-mediated allylation, hydrogenation, cyclization, and addition reactions.[1] Intramolecular hydrogen bonding is known to effectively stabilize the preferred conformation of the intermediate radical in the reaction of *β*-hydroxy-radicals α to the carbonyl group, and to induce high stereoselectivity.[1,2] The 1,2- and 1,3-asymmetric inductions[3,4,5] effected by the sulfinyl group, where intramolecular hydrogen bonding does not effectively work to stabilize the conformation of *β*-hydroxy-α-sulfinyl radicals.[3d] On the other hand, we recently communicated an excellent stereocontrol achieved in the radical reaction of α-(1-hydroxyalkyl)vinyl sulfoxides, in which we showed the significant role of intramolecular hydrogen bonding between the hydroxy group and the sulfinyl oxygen in reactivity as well as in diastereoselectivity (eq 1).[6]



(eq 1)

The sulfonyl group is a synthetically useful functional group.[7] We preliminarily reported a new version of the function of the sulfonyl group as a stereo-inducer.[8,9] Stereoselective hydrogen bonding to one of the diastereotopic sulfonyl oxygens would newly form a chiral

* To whom correspondence should be addressed. Phone: +81-52-735-5217. Fax: +81-52-735-5217.

† Nagoya Institute of Technology.

‡ Present address: Department of Molecular Science, Faculty of Engineering, Shizuoka University, 3-5-1 Johoku, Hamamatsu 432-8561, Japan.

§ Osaka Gas Co., Ltd.

|| Teijinseiki Co., Ltd.

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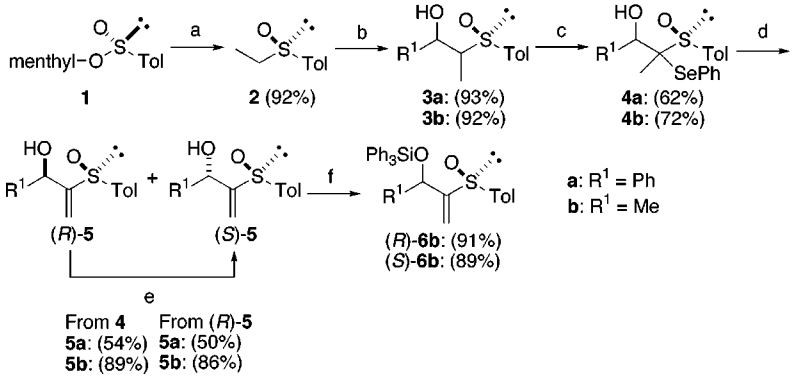
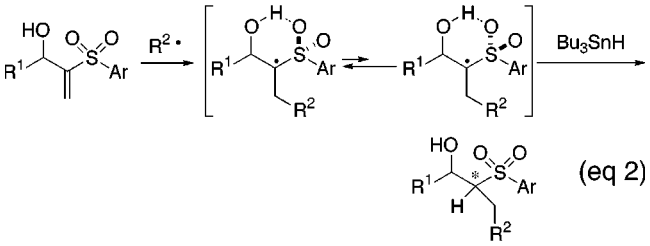
Scheme 1. Preparation of the α-(1-Hydroxyalkyl)vinyl Sulfoxides[a]



[a] Key: (a) EtMgI, Et_2O/THF, 0 °C; (b) LDA, R^1CHO, THF, −78 °C; (c) MeLi, $(PhSe)_2$, THF, 0 °C; (d) (i) *m*-CPBA, CH_2Cl_2, 0 °C; (ii) flash column chromatography; (e) (i) Ph_3P, PhCOOH, diethyl azodicarboxylate, THF, rt; (ii) MeONa, MeOH, rt; (f) Ph_3SiCl, pyridine, rt.

sulfur center which affects the diastereoselectivity in the reaction of β-hydroxy-radicals α to the sulfonyl group (eq 2). We now report in detail a stereoselective radical hydrogenation of β-hydroxy-radicals α to the sulfinyl and sulfonyl groups.



Results and Discussion

Reaction of α-(1-Hydroxyalkyl)vinyl Sulfoxides. Optically pure (S_S)-1-phenyl-2-(*p*-tolylsulfinyl)-2-propen-1-ol (**5a**) and (S_S)-3-(*p*-tolylsulfinyl)-3-buten-2-ol (**5b**) were prepared in four steps as shown in Scheme 1.[10,11] Optically pure (*R*)-ethyl *p*-tolyl sulfoxide[12] (**2**), prepared from (S_S)-*l*-menthyl *p*-toluenesulfinate[13] (**1**), was treated with 1.2 equiv of LDA at −78 °C and subsequently with aldehyde to afford the β-hydroxy sulfoxide **3**. The β-hydroxy sulfoxide **3** was treated with 3 equiv of methyllithium at 0 °C, and the resulting anion was reacted with diphenyl diselenide to give the selenide **4**.[14] Selective oxidation[15] gave a diastereomeric mixture of the α-(1-hydroxyalkyl)vinyl sulfoxides (*R*)-**5** and (*S*)-**5**, which were separable by flash column chromatography.[10b] A single crystal of the less polar diastereomer-**5b** ((*R*)-**5b**) was subjected to X-ray crystallographic analysis (Figure 1). The absolute configuration of the less polar diastereomer (*R*)-**5b** was determined to be (S_S,2*R*), and the hydroxy group was found to form hydrogen bonding intermolecularly with a sulfinyl oxygen of the neighboring molecule. The Mitsunobu reaction of (*R*)-**5** gave (*S*)-**5**. The absolute configuration of **5a** was deduced from ^1H NMR analyses as mentioned below. The hydroxy group, when required, was silylated with triphenylsilyl chloride in pyridine.[16]

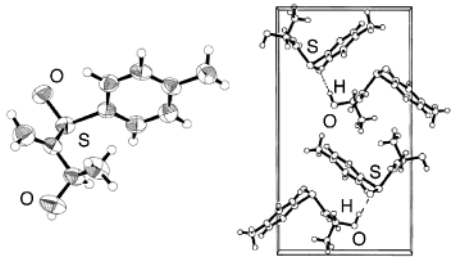


Figure 1. View (ORTEP) of the (S_S,2*R*)-3-(*p*-tolylsulfinyl)-3-buten-2-ol ((*R*)-**5b**).

Radical addition−hydrogenation reactions were carried out as follows. A solution of the α-(1-hydroxyalkyl)vinyl sulfoxide **5** in CH_2Cl_2 (0.01 mol/L) was reacted with an alkyl iodide (3 equiv), tributyltin hydride (3 equiv), and triethylborane (3 equiv) as a radical initiator[17] at −78 °C. For the reaction in the presence of a Lewis acid, a mixture of **5** and a Lewis acid (1.1 equiv) was stirred for 30 min before addition of other reagents. The results are shown in Table 1. The reaction of (S_S,1*S*)-1-phenyl-2-(*p*-tolylsulfinyl)-2-propen-1-ol ((*S*)-**5a**) with *tert*-butyl radical gave the addition-hydrogenation product **7a** in 98% yield but with low diastereoselectivity (entry 1). On the other hand, the reaction of (S_S,1*R*)-1-phenyl-2-(*p*-tolylsulfinyl)-2-propen-1-ol ((*R*)-**5a**) resulted in recovery of the starting (*R*)-**5a** after 24 h, and no formation of the addition−hydrogenation product was observed (entry 2). Diastereoselectivity dramatically changed in the reaction of (*S*)-

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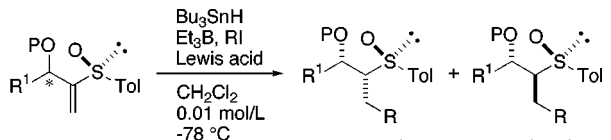
Table 1. Radical Hydrogenation of α-Sulfinyl Radical Generated from Addition of Alkyl Radicals to α-(1-Hydroxyalkyl)vinyl Sulfoxide[a]



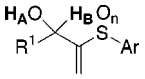
(*S*)-**5a**: P = H , R^1 = Ph
(*R*)-**5a**: P = H , R^1 = Ph
(*S*)-**5b**: P = H , R^1 = Me
(*R*)-**5b**: P = H , R^1 = Me
(*S*)-**6b**: P = $SiPh_3$, R^1 = Me
(*R*)-**6b**: P = $SiPh_3$, R^1 = Me

entry	sub-strate	R	Lewis acid[b]	time (h)	product	yield (%)	syn/anti
1	(*S*)-**5a**	*t*-Bu	none	3	**7a**	98	60:40
2	(*R*)-**5a**	*t*-Bu	none	24	no reaction		
3	(*S*)-**5b**	*t*-Bu	none	3	**7b**	89	>98:<2
4[c,d]	(*S*)-**5b**	*t*-Bu	none	24	**7b**	81	>98:<2
5[e,d]	(*S*)-**5b**	*t*-Bu	none	24	**7b**	trace	
6	(*S*)-**5b**	*c*-Hex	none	12	**8b**	66[f]	93:7
7	(*S*)-**5b**	*i*-Pr	none	12	**9b**	72[f]	93:7
8	(*S*)-**5b**	Et	none	12	**10b**	38[f]	79:21
9	(*S*)-**5b**	*t*-Bu	$EtAlCl_2$	3	**7b**	75	>98:<2
10[d]	(*S*)-**5b**	*t*-Bu	$EtAlCl_2$[g]	24	**7b**	19[f]	>98:<2
11	(*S*)-**5b**	*t*-Bu	Et_2AlCl	6	**7b**	68	>98:<2
12	(*S*)-**5b**	*t*-Bu	Et_3Al	6	**7b**	70	>98:<2
13[d]	(*R*)-**5b**	*t*-Bu	none	72	no reaction		
14[d]	(*R*)-**5b**	*t*-Bu	$EtAlCl_2$	24	no reaction		
15[d]	(*R*)-**5b**	*t*-Bu	$EtAlCl_2$[g]	24	no reaction		
16	**5b**[h]	*t*-Bu	none	3	**7b**	48 (94)[i,j]	>98:<2
17[d]	(*S*)-**6b**	*t*-Bu	none	24	no reaction		
18[d]	(*R*)-**6b**	*t*-Bu	none	24	no reaction		

[a] The reaction was carried out using Bu_3SnH (3.0 equiv), RI (3.0 equiv), and Et_3B (3.0 equiv) in a 0.01 mol/L CH_2Cl_2 solution at −78 °C unless otherwise noted. [b] 1.1 equiv of Lewis acid was used unless otherwise noted. [c] The reaction was carried out in toluene. [d] The reaction was carried out at −78 °C → rt. [e] The reaction was carried out in THF. [f] (*S*)-**5b** was recovered in 24% (entry 6), 22% (entry 7), 55% (entry 8), and 76% (entry 10). [g] 2.0 equiv of $EtAlCl_2$ was used. [h] A diastereomeric mixture of **5b** in a ratio of (*S*)-**5b**: (*R*)-**5b** = 51:49 was used. [i] Yield in parentheses is the one based on the (*S*)-**5b** isomer. [j] The starting material (*R*)-**5b** was recovered in 43% yield (88% yield based on the (*R*)-**5b** isomer).

5b, in which the reaction in a solvent such as dichloromethane or toluene gave the addition-hydrogenation product **7b** in a syn/anti ratio of >98:<2 (entries 3 and 4). The reaction in THF resulted in recovery of the starting (*S*)-**5b** together with the formation of a trace amount of **7b** (entry 5). Cyclohexyl, isopropyl, and ethyl radicals could also add to (*S*)-**5b** to give a mixture of syn and anti isomers in moderate yields (entries 6−8). The addition−hydrogenation product *syn*-**7b** was also obtained in good yield and with high diastereoselectivity when the reaction was carried out in the presence of 1.1 equiv of a Lewis acid such as $EtAlCl_2$, Et_2AlCl, or Et_3Al (entries 9, 11, and 12), but only in 19% yield with 2 equiv of $EtAlCl_2$ (entry 10). In contrast to the results of (*S*)-**5b**, no addition products were obtained even after 72 h in the reaction of (*R*)-**5b**, where the starting (*R*)-**5b** was quantitatively recovered (entry 13). The addition of $EtAlCl_2$ did not improve the reactivity of (*R*)-**5b** for the addition of *tert*-butyl radical (entries 14 and 15). Obviously from these results, reactivity toward *tert*-butyl radical is quite different between (*S*)-**5b** and (*R*)-**5b**. This difference in reactivity was further confirmed by the following results. The reaction of a 51/49 diastereomeric mixture of (*S*)-**5b** and (*R*)-**5b** afforded *syn*-**7b** derived only from (*S*)-**5b** in 48% yield (94% yield based on (*S*)-**5b**), and recovered the starting **5b** composed of only (*R*)-**5b** in 43% yield (88% yield based on (*R*)-**5b**) (entry 16). Therefore, these diastereomers **5b**, which were rather difficult to separate by chromatography, could be kinetically separated in the radical reaction. Furthermore, the recovered (*R*)-**5b** could be easily converted to (*S*)-**5b** by the Mitsunobu reaction in 86% yield (Scheme 1). Since (*S*)-**5b** thus obtained can be converted to *syn*-**7b** as mentioned above, the present diastereomer-differentiating radical reaction efficiently gives enantiomerically pure *syn*-**7b**. Neither (*S*)-**6b** nor (*R*)-**6b**, the hydroxy group of which was protected with a triphenylsilyl group, afforded the addition-hydrogenation product (entries 17 and 18).

Table 2. Chemical Shifts of the Hydroxy Proton and Coupling Constants J_{AB} of the α-(1-Hydroxyalkyl)vinyl Sulfoxides 5 and Sulfones 12 and the *β*-Hydroxy-α-(phenylselenenyl) Sulfones 22 in $CDCl_3$



compd	chemical shift (δ) 0.1 M	0.05 M	0.01 M	J_{AB}[a] (Hz)
(*S*)-**5a**	3.83	3.80	3.77	2.4
(*R*)-**5a**	3.01	2.73	2.42	*b*
(*S*)-**5b**	3.33	3.24	3.20	2.5
(*R*)-**5b**	2.35	2.08	1.83	5.6
12a	3.13	3.02	3.00	3.2
12b	2.66	2.61	2.58	3.3
anti-**22**	3.50	3.49	3.49	5.2
syn-**22**	4.19	4.19	4.19	1.8

[a] Measured in 0.01 mol/L solution. [b] The hydroxy proton in (*R*)-**5a** is overlapped with methyl protons of the *p*-tolyl group.

The above results show that the reactivity of the α-(1-hydroxyalkyl)vinyl sulfoxides **5** toward radicals largely depends on intramolecular hydrogen bonding which significantly enhances the reactivity of **5**. In addition, hydrogen bonding also plays an important role for increasing diastereoselectivity. Compounds (*S*)-**5a** and (*S*)-**5b** showed intramolecular hydrogen bonding in their ^1H NMR spectra, in which only a small upfield shift for the hydroxy proton was observed upon dilution (Table 2). Furthermore, the values of J_{AB} (2.4 Hz for (*S*)-**5a**, 2.5 Hz for (*S*)-**5b**) were in good accord with intramolecular hydrogen bonding.[18] The infrared spectra also showed a band (3500−3200 cm^{-1}) for hydrogen bonding in a dilute solution. On the other hand, the ^1H NMR study of (*R*)-**5a** and (*R*)-**5b** supported no intramolecular hydrogen bonding in solution; upfield shift for the hydroxy proton is observed upon dilution. The value of J_{AB} (5.6 Hz for (*R*)-**5b**) was bigger than that for (*S*)-**5b** and were in good accord with the anticipated value given by the Karplus equation. In addition, analysis of the infrared spectra showed the existence of a free hydroxy group (3605 cm^{-1}).

Nucleophilic radicals such as *tert*-butyl radical more easily add to an olefin with lower LUMO energy.[1b] Table 3 shows LUMO energy and heat of formation of the α-(1-hydroxyalkyl)vinyl sulfoxides **5** calculated by MOPAC 93/

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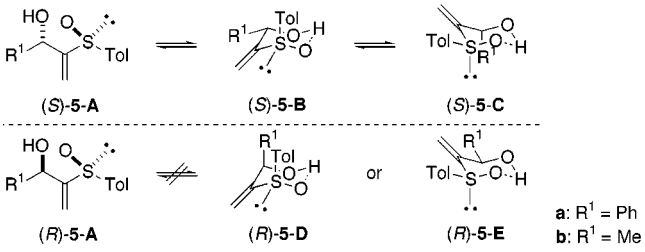
Table 3. Calculation of the Distance between the Hydroxy Proton and the Sulfinyl Oxygen, the Relative LUMO Energy, Heat of Formation, and Total Energy for the α-(1-Hydroxyalkyl)vinyl Sulfoxides 5



	OH···O═S (Å)		ΔLUMO[a] (eV)		Δ*E*[b] (kcal/mol)	
conformer	PM3	HF/3-21G	PM3	HF/3-21G	PM3[c]	HF/3-21G[d]
(*S*)-**5a-A**	5.23	*e*	0.000	*e*	0.000	*e*
(*S*)-**5a-B**	1.81	*e*	−0.264	*e*	+0.562	*e*
(*S*)-**5a-C**	1.81	*e*	−0.233	*e*	−1.272	*e*
(*R*)-**5a-A**	4.86	*e*	0.000	*e*	0.000	*e*
(*R*)-**5a-D**	1.81	*e*	−0.216	*e*	+0.039	*e*
(*R*)-**5a-E**	1.80	*e*	−0.243	*e*	+1.656	*e*
(*S*)-**5b-A**	4.89	4.83	0.000	0.000	0.000	0.000
(*S*)-**5b-B**	1.82	1.77	−0.205	−0.400	−1.106	−3.889
(*S*)-**5b-C**	1.82	1.80	−0.173	−0.210	−3.095	−4.065
(*R*)-**5b-A**	4.94	4.57	0.000	0.000	0.000	0.000
(*R*)-**5b-D**	1.82	1.72	−0.174	−0.359	+0.280	−0.073
(*R*)-**5b-E**	1.80	1.75	−0.138	−0.271	+2.217	+0.011

[a] ΔLUMO = LUMO (**5-B**, **5-C**, **5-D**, or **5-E**) − LUMO (**5-A**). [b] Δ*E* = *E*(**5-B**, **5-C**, **5-D**, or **5-E**) − *E*(**5-A**). [c] Difference in heat of formation. [d] Difference in total energy. [e] Not optimized.

PM3[19] and GAUSSIAN 94/HF/3-21G.[20] The distance between the hydroxy proton and the sulfinyl oxygen is approximately 1.8 Å in the optimized structures (*S*)-**5a-B**,**C** and (*S*)-**5b-B**,**C**, showing the existence of intramolecular hydrogen bonding in these optimized conformers. LUMO energies of conformers (*S*)-**5a-B**,**C** and (*S*)-**5b-B**,**C** with intramolecular hydrogen bonding are lower than those of the corresponding conformers (*S*)-**5-A** without intramolecular hydrogen bonding in the **5a** and **5b** series. Therefore, (*S*)-**5a** and (*S*)-**5b** which form a large extent of intramolecular hydrogen bonding, can easily react with an alkyl radical. In addition, the results of the energy differences (Δ*E*) show that cyclic conformers (*S*)-**5a-C**, (*S*)-**5b-B**, and (*S*)-**5b-C** are more stable than the acyclic (*S*)-**5a-A** and (*S*)-**5b-A**, respectively; especially, the most stable conformers are (*S*)-**5a-C** and (*S*)-**5b-C**. (*R*)-**5a-D**,**E** and (*R*)-**5b-D**,**E** also show 1.8 Å for the distance between the hydroxy proton and the sulfinyl oxygen, and lower LUMO energies than the corresponding acyclic (*R*)-**5a-A** and (*R*)-**5b-A**. In (*R*)-**5a** and (*R*)-**5b**, however, the most stable conformers are (*R*)-**5a-A** and (*R*)-**5b-A** both of which hardly form intramolecular hydrogen bonding, and thus (*R*)-**5a** and (*R*)-**5b** without intramolecular hydrogen bonding cannot be good substrates toward alkyl radicals (Table 1). These calculation data are in good accord with the observation of their ^{1}H NMR and IR spectra (Table 2).

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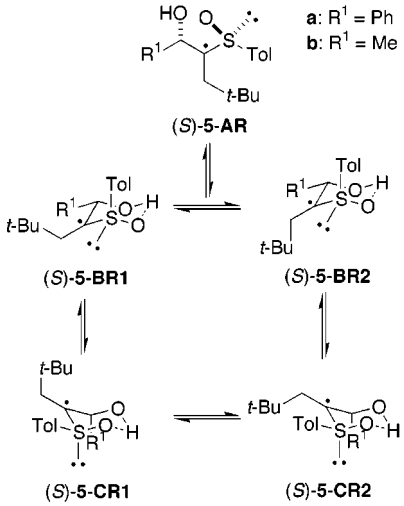
Table 4. Calculation of the Distance between the Hydroxy Proton and the Sulfinyl Oxygen, the Relative Heat of Formation, and Total Energy for the Radical Intermediates 5R Derived from 5



	OH···O═S (Å)		Δ*E*[a] (kcal/mol)	
conformer	PM3	HF/3-21G	PM3[b]	HF/3-21G[c]
(*S*)-**5a-AR**	5.17	*d*	0.000	*d*
(*S*)-**5a-BR1**	1.81	*d*	+0.248	*d*
(*S*)-**5a-BR2**	1.81	*d*	−0.502	*d*
(*S*)-**5a-CR1**	1.81	*d*	−5.000	*d*
(*S*)-**5a-CR2**	1.82	*d*	−2.571	*d*
(*S*)-**5b-AR**	5.20	5.45	0.000	0.000
(*S*)-**5b-BR1**	1.82	1.84	−0.268	−5.068
(*S*)-**5b-BR2**	1.81	1.81	−1.268	−9.136
(*S*)-**5b-CR1**	1.80	1.84	−1.897	−5.625
(*S*)-**5b-CR2**	1.83	1.75	−3.721	−9.912

[a] Δ*E* = *E*(**5-BR** or **5-CR**) − *E*(**5-AR**). [b] Difference in heat of formation. [c] Difference in total energy. [d] Not optimized.

Next, we calculated heat of formation and the distance of the hydrogen bonding for the intermediate radicals derived from the reactive vinyl sulfoxide (*S*)-**5** and the results are shown in Table 4. The cyclic radical intermediates (*S*)-**5a-** and (*S*)-**5b-BR1**, **-BR2**, **-CR1**, **-CR2** were found to be more stable than the noncyclic intermediates (*S*)-**5a-** and (*S*)-**5b-AR** except (*S*)-**5a-BR1**. The distance between the hydroxy proton and the sulfinyl oxygen was approximately 1.8 Å in optimized structures **5-BR** and **5-CR**. The conformer (*S*)-**5a-CR1** was the most stable conformer derived from (*S*)-**5a**. In (*S*)-**5a-CR1**, both radical faces are shielded to some extent by the *tert*-butyl, *p*-tolyl, and phenyl groups, and hydrogenation with tributyltin hydride resulted in low diastereoselectivity (Table 1, entry 1). On the other hand, (*S*)-**5b-CR2** was the most stable among conformers derived from (*S*)-**5b**. The lower face is shielded so efficiently by both the methyl and *tert*-butyl groups in (*S*)-**5b-CR2** that tributyltin hydride attacks predominantly from the upper face to give *syn*-**7b** with high diastereoselectivity (Figure 2, Table 1, entry 3).

Reaction of α-(1-Hydroxyalkyl)vinyl Sulfones. Intramolecular hydrogen bonding was demonstrated to enhance the radical addition−hydrogenation reaction of the α-(1-hydroxyalkyl)vinyl sulfoxides **5** and fix the conformation of the radical intermediates to allow the reaction to proceed with high stereoselectivity. These results encouraged us to examine the sulfonyl group as a new stereo-inducer in the radical reaction, even though the sulfonyl group had been recognized as an inefficient

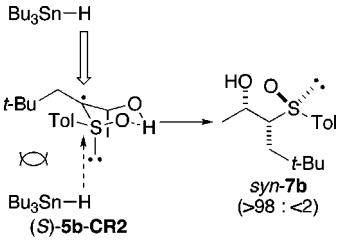
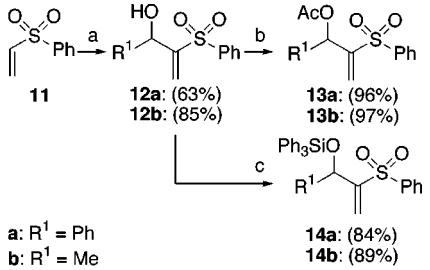


Figure 2. Proposed model for hydrogenation of the α-sulfinyl radical with tributyltin hydride.

Scheme 2. Preparation of the α-(1-Hydroxyalkyl)vinyl Sulfones[a]

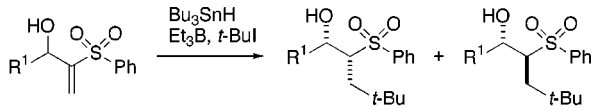


[a] Key: (a) R^1CHO, DABCO; (b) Ac_2O, $BF_3{\cdot}OEt_2$; (c) Ph_3SiCl, pyridine.

1,2-stereo-inducer in the hydrogenation of the *β*-oxy-α-sulfonyl radicals.[21] Since the stereochemistry of the α-(1-hydroxyalkyl)vinyl sulfoxides **5** had considerable influence on the formation of an intramolecular hydrogen bonding, intramolecular hydrogen bonding was expected to be formed stereoselectively between the hydroxy proton and the specific diastereotopic sulfonyl oxygen in the α-(1-hydroxyalkyl)vinyl sulfones **12** (eq 2). The vinyl sulfones **12a**,**b** were prepared by the reaction of phenyl vinyl sulfone[22] **11** with benzaldehyde and acetaldehyde, respectively, in the presence of a catalytic amount of 1,4-diazabicyclo[2.2.2]octane (DABCO) as shown in Scheme 2.[23] The acetoxy- and triphenylsilyl-protected derivatives were also prepared.

Radical reaction of the α-(1-hydroxyalkyl)vinyl sulfones **12** was carried out in a manner similar to the reaction of the α-(1-hydroxyalkyl)vinyl sulfoxides **5**. The results are shown in Table 5. Treatment of 1-phenyl-2-(phenylsulfonyl)-2-propen-1-ol (**12a**) with *tert*-butyl iodide, tributyltin hydride, and triethylborane furnished the expected products **15** in high yields, with diastereoselectivity variously changed by the reaction conditions used. The reaction of **12a** in 0.01 mol/L CH_2Cl_2 solution gave the addition-hydrogenation product **15a** with slightly better diastereoselectivity than that in the reaction performed in 0.1 and 0.05 mol/L solutions (entries 1−3). Higher diastereoselectivity was obtained when the reaction was carried out at lower temperature (entries 5 and 6). The reaction of **12b** proceeded with higher diastereoselectivity, favoring the *syn*-isomer **15b**, than in the reaction of **12a**. A polar solvent such as THF lowered the diastereoselectivity in both cases (entries 7 and 12). Notably, the reaction of **12b** in 0.01 mol/L CH_2Cl_2 solution at −78 °C gave the addition-hydrogenation product **15b** in a syn/anti ratio of 98:2 (entry 11).

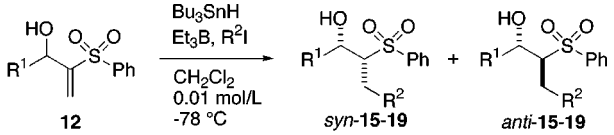
Table 5. Hydrogenation of the α-Sulfonyl Radical Generated from the Addition of *tert*-Butyl Radical to the α-(1-Hydroxyalkyl)vinyl Sulfones 12[a]



entry	substrate	*T* (°C)	solvent	time (h)	yield (%)	syn/anti
1[b]	**12a**	rt	CH_2Cl_2	1	98	63:37
2[c]	**12a**	rt	CH_2Cl_2	1	98	63:37
3	**12a**	rt	CH_2Cl_2	1	91	69:31
4[d]	**12a**	80	PhH	0.5	95	66:34
5	**12a**	0	CH_2Cl_2	1	88	70:30
6	**12a**	−78	CH_2Cl_2	2	94	80:20
7	**12a**	−78	THF	2	94	68:32
8[b]	**12b**	rt	CH_2Cl_2	1	95	86:14
9	**12b**	rt	CH_2Cl_2	2	98	87:13
10[d]	**12b**	80	PhH	0.5	93	74:26
11	**12b**	−78	CH_2Cl_2	2	91	98:2
12	**12b**	−78	THF	2	84	81:19

[a] The reaction was carried out in 0.01 mol/L solution unless otherwise noted. [b] The reaction was carried out in 0.1 mol/L solution. [c] The reaction was carried out in 0.05 mol/L solution. [d] AIBN was used as a radical initiator.

Table 6. Hydrogenation of the α-Sulfonyl Radical Generated from the Addition of Various Alkyl Radicals to the α-(1-Hydroxyalkyl)vinyl Sulfones 12



entry	substrate	R^2	time (h)	product	yield (%)	syn/anti
1	**12a**	*t*-Bu	2	**15a**	94	80:20
2	**12a**	*c*-Hex	1	**16a**	94	79:21
3	**12a**	*i*-Pr	1	**17a**	96	81:19
4	**12a**	Et	3	**19a**	91	80:20
5	**12b**	*t*-Bu	2	**15b**	91	98:2
6	**12b**	*c*-Hex	1	**16b**	93	76:24
7	**12b**	*i*-Pr	1	**17b**	91	69:31
8[a]	**12b**	Bu	3	**18b**	88	62:38
9[a]	**12b**	Et	8	**19b**	95	60:40
10[a]	**12b**	Me	24	no reaction		

[a] The reaction was carried out at −78 °C → rt.

The reaction with various alkyl radicals was also examined. The results are shown in Table 6. Cyclohexyl, isopropyl, and ethyl radicals successfully added to **12a** and **12b**. It should be noted that no steric influence of alkyl radicals on the diastereoselectivity was observed in the reaction of **12a**, the syn/anti ratio being always approximately 80:20 (entries 1−4). On the other hand, the stereoselection was lowered in the reaction of **12b**, as the size of alkyl radicals was sterically smaller (entries 5−9).

Results in the reaction of **12** in the presence of Lewis acids are shown in Table 7. Addition of a Lewis acid such as Et_2Zn, Me_3Al, and Et_2AlCl did not improve the diastereoselectivity (entries 2−4), whereas $EtAlCl_2$ increased the diastereoselectivity in reactions of both **12a** and **12b** (entries 5 and 10). Especially, the reaction of **12b** proceeded with high diastereoselectivity in a ratio

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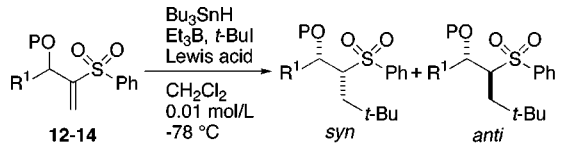
(22) Paquette, L. A.; Carr, R. V. C. *Org. Synth.* **1986**, *64*, 157.
(23) (a) Weichert, A.; Martin, H.; Hoffmann, R. *J. Org. Chem.* **1991**, *56*, 4098. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095.

Table 7. Hydrogenation of the α-Sulfonyl Radical Generated from the Addition of *tert*-Butyl Radical to the α-(1-Hydroxyalkyl)vinyl Sulfones 12−14 in the Presence of Lewis Acids



12-14

12a: P = H, R^1 = Ph **13a**: P = Ac, R^1 = Ph **14a**: P = $SiPh_3$, R^1 = Ph
12b: P = H, R^1 = Me **13b**: P = Ac, R^1 = Me **14b**: P = $SiPh_3$, R^1 = Me

entry	substrate	P	Lewis acid	time (h)	product	yield (%)	syn/anti
1	**12a**	H	none	2	**15a**	94	80:20
2	**12a**	H	Et_2Zn	2	**15a**	94	81:19
3[a]	**12a**	H	Me_3Al	10	**15a**	81	79:21
4	**12a**	H	Et_2AlCl	3	**15a**	83	81:19
5	**12a**	H	$EtAlCl_2$	3	**15a**	94	85:15
6	**12a**	H	MAD	24	**15a**	98	68:32
7	**12a**	H	MAD[b]	4	**15a**	92	58:42
8[c]	**12a**	H	none	4	**15a**	98	80:20
9	**12b**	H	none	2	**15b**	91	98:2
10	**12b**	H	$EtAlCl_2$	5	**15b**	64	99:1
11[d]	**12b**	H	$EtAlCl_2$	2	**15b**	76	99:1
12[a]	**12b**	H	MAD	24	**15b**	93	88:12
13	**12b**	H	MAD[b]	7	**15b**	93	68:32
14[c]	**12b**	H	none	5	**15b**	91	99:1
15	**13a**	Ac	none	2	**20a**	87	77:23
16	**13a**	Ac	$EtAlCl_2$	1	**20a**	99	79:21
17	**13b**	Ac	none	2	**20b**	92	90:10
18	**13b**	Ac	$EtAlCl_2$	1	**20b**	97	92:8
19	**14a**	$SiPh_3$	none	2	**21a**	88	31:69
20	**14b**	$SiPh_3$	none	2	**21b**	99	67:33

[a] The reaction was carried out at −78 °C → rt. [b] MAD (5 equiv) was used. [c] Ph_3SnH was used instead of Bu_3SnH. [d] The reaction was carried out at room temperature.

of 99:1 even at room temperature, favoring the same *syn*-isomer **15b** as that obtained in the reaction without a Lewis acid (entry 11). These results show that high diastereoselectivity obtained with $EtAlCl_2$ can be ascribed to the formation of the rigid chelated structure in the intermediate radical derived from the addition of *tert*-butyl radical to **12**. The diastereoselectivity decreased in the presence of the bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD), probably due to formation of the nonchelated intermediate (entries 6−7, 12−13). The diastereoselectivity increased when triphenyltin hydride was used as a hydrogen donor in the reaction of **12b** (entry 14). The acetyl or triphenylsilyl protection of the hydroxy group decreased the diastereoselectivity (entries 15−20).

According to the results of the reaction of the vinyl sulfones **12** shown in Tables 5-7, intramolecular hydrogen bonding seems to be strongly related to the stereochemical outcome as in the reaction of α-(1-hydroxyalkyl)vinyl sulfoxide **5**. Actually, significant intramolecular hydrogen bonding was shown to exist in both of **12a** and **12b**, since only a small upfield shift of the chemical shift of the hydroxy proton was observed upon dilution and the values of J_{AB} (3.2 Hz for **12a**, 3.3 Hz for **12b**) were in good accord with those of the conformer having an intramolecular hydrogen bonding (Table 2). The infrared spectra also support the existence of intramolecular hydrogen bonding (3575−3400 cm^{-1}).

We performed the calculation of the LUMO energy and heat of formation of the α-(1-hydroxyalkyl)vinyl sulfones **12** by MOPAC 93/PM3 and GAUSSIAN 94/HF/3-21G. The distance between the hydroxy proton and the sulfonyl oxygen is approximately 1.8 Å in cyclic optimized structures **12a-B**,**C**,**D**,**E** and **12b-B**,**C**,**E** except for **12b-D**, showing that intramolecular hydrogen bonding is formed in these conformers (Figure 3). Calculation by PM3 showed that LUMO energies of cyclic conformers **12a-** and **12b-B**,**C**,**D**,**E** with intramolecular hydrogen bonding are lower than those of **12a-A** and **12b-A** without intramolecular hydrogen bonding. Although the LUMO difference (ΔLUMO) of these cyclic conformers relative to the respective acyclic conformers **12a-A** and **12b-A**, does not remarkably decrease in comparison with that of the α-(1-hydroxyalkyl)vinyl sulfoxides **5** (Table 3), the α-(1-hydroxyalkyl)vinyl sulfones **12** can easily react with nucleophilic alkyl radicals, since the value of LUMO of the sulfone **12** is lower than that of the sulfoxide **5** (for example, ΔLUMO = LUMO (**12b-A**) − LUMO ((*S*)-**5b-A**) = −0.787 (eV) obtained by HF/3-21G calculation).

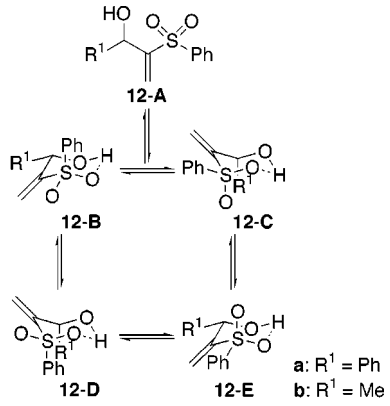


Figure 3. Optimized conformers for the α-(1-hydroxyalkyl)-vinyl sulfones **12** (see the Supporting Information for the calculation data).

Diastereoselectivity in hydrogenation of the radical α to the sulfonyl group is possibly ascribed to conformationally and configurationally different radical intermediates. We performed the calculation of the hydrogen bonding length and the relative LUMO energy, heat of formation and total energy for the cyclic radical intermediates relative to the acyclic intermediates **12-AR** (Figure 4). In the case of **12a**, the radical intermediate **12a-CR2** was found to be the most stable conformer and the hydrogen bonding length was 2.51 Å, indicating that considerably weak intramolecular hydrogen bonding exists between the hydroxy group and the *anti*-sulfonyl oxygen. It would be ascribed to this loosely bound radical intermediate **12a-CR2** that **12a** gave the products **15a**, **16a**, **17a**, and **19a** with moderate diastereoselectivity (syn/anti = 80:20) irrespective of the bulkiness of the alkyl radicals (Table 6, entries 1−4). On the other hand, the most stable conformer among the radical intermediates **12b-R** was **12b-CR2** in which strong intramolecular hydrogen bonding exists between the hydroxy group and the *anti*-sulfonyl oxygen. The structure of **12b-CR2** fully corresponds with that of the most stable α-sulfinyl radical intermediate (*S*)-**5b-CR2** in Table 4. The upper face is more widely open in **12b-CR2** to the attack of tributyltin hydride, and the hydride approaches from the upper face opposite to the methyl and *tert*-butyl groups, leading to the addition-hydrogenation product with syn stereochemistry (Figure 5). As the alkyl radical is sterically bulkier, the lower face is more shielded by the newly formed alkyl group to cause higher diastereoselectivity (Table 6,

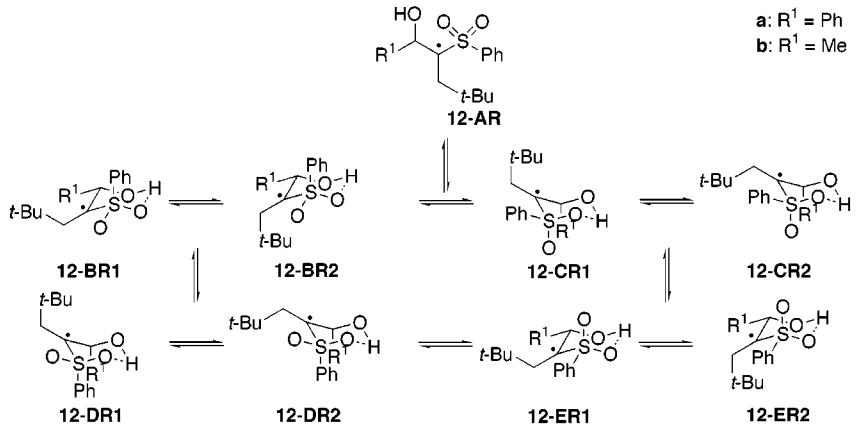


Figure 4. Conformers of the radical intermediates derived from **12** (see the Supporting Information for the calculation data).

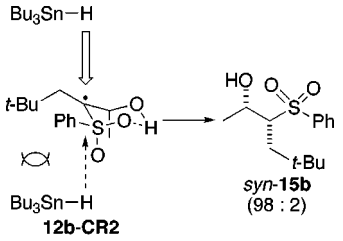
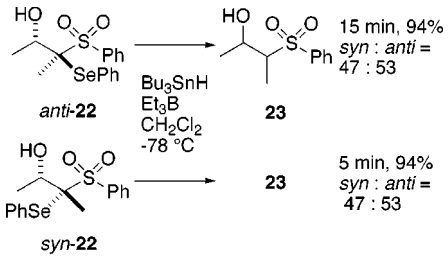


Figure 5. Proposed model for hydrogenation of the α-sulfonyl radical with tributyltin hydride.

Scheme 3. Radical Hydrogenation of *β*-Hydroxy-α-(phenylselenenyl) Sulfones 22



entries 5−9). These results were quite different from those reported in the radical reaction of the *β*-hydroxy α,*β*-unsaturated esters[24] or *β*-amino α,*β*-unsaturated esters,[25] in which the diastereoselectivity decreases as the alkyl radicals become sterically bulkier. The substituents on the ester have little influence on the stereoselectivity due to the trigonal planar structure of the ester, whereas the substituents on the sulfonyl group in the present reaction have significant influence on the stereoselectivity definitely due to the tetrahedral sulfur structure of the sulfone.

The planar radical intermediates have been assumed through the above discussion. To confirm the planarity of the carbon radical α to the sulfonyl group, the stereochemical outcome in the radical reduction of the *β*-hydroxy-α-(phenylselenenyl) sulfones *anti*- and *syn*-**22** was studied (Scheme 3). The radical precursors *syn*- and *anti*-**22** were prepared by aldol reaction of the carbanion derived from the corresponding α-(phenylselenenyl) sulfone with acetaldehyde. Both precursors showed a small upfield shift upon dilution in the ^{1}H NMR spectra, suggesting the existence of intramolecular hydrogen bonding (see, Table 2). However, from the coupling constant (J_{AB} = 5.2 Hz) in the ^{1}H NMR spectrum *anti*-**22** appears not to form an intramolecular hydrogen bonding. Precursors *anti*- and *syn*-**22** were reduced separately with tributyltin hydride in the presence of Et_3B at −78 °C to give the reduction product **23** with the same diastereoselectivity in a ratio of 47:53, indicating that both radical reductions of *anti*- and *syn*-**22** proceeded via conformationally the same radical intermediates, i.e., a rapidly equilibrated or sp^2 carbon radical intermediate was formed.

In conclusion, we have shown an important role of intramolecular hydrogen bonding in diastereoselectivity at the carbon α to the sulfinyl and sulfonyl groups as well as in reactivity toward alkyl radicals in the reaction of α-(1-hydroxyalkyl)vinyl sulfoxides and sulfones. In this reaction, a diastereotopic sulfonyl oxygen was successfully discriminated by stereoselective intramolecular hydrogen bonding or by chelating coordination with a Lewis acid to a specific sulfonyl oxygen which corresponded to the hydrogen-bonded sulfinyl oxygen in the radical intermediate. This new version of the use of a sulfonyl group as a stereo-inducer would open a way to various useful stereoselective reactions.

Experimental Section

General Procedure for the Radical Reaction of the α-(1-Hydroxyalkyl)vinyl Sulfoxides 5 and the α-(1-Hydroxyalkyl)vinyl Sulfones 12. To a degassed solution of **5** or **12** in CH_2Cl_2 (0.01 mol/L) were added an alkyl iodide (3 equiv), tributyltin hydride (3 equiv), and triethylborane (3 equiv). For the reaction using a Lewis acid, the Lewis acid (1.1 equiv) was added to a CH_2Cl_2 solution of **5** or **12** and the mixture was stirred for 30 min before the addition of other reagents. After the mixture was stirred for the appropriate time, the mixture was poured into saturated NaH_2PO_4, and extracted with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography to give the addition−hydrogenation products.

(*S*$_S$,1*S*,2*R*)-4,4-Dimethyl-2-(*p*-tolylsulfinyl)-1-hexanol (*syn*-7a): R_f = 0.33 (hexane/ethyl acetate = 50/50); ^{1}H NMR δ 0.69 (s, 3H), 1.86 (dd, J = 1.7, 15.9 Hz, 1H), 2.10 (dd, J = 7.8, 15.9 Hz, 1H), 2.38−2.47 (m, 1H), 2.49 (s, 3H), 4.71 (s, 1H), 5.30 (s, 1H), 6.81−7.30 (m, 5H), 7.45 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H); IR (neat) 3120−3600, 2970, 1470, 1010, 730 cm^{-1}; MS (EI) *m*/*e* 330 (M$^+$, 2), 315 (5), 92 (100). Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93. Found: C, 72.94; H, 8.16.

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(*S*$_S$,1*S*,2*S*)-4,4-Dimethyl-2-(*p*-tolylsulfinyl)-1-hexanol (*anti*-7a): R_f = 0.53 (hexane/ethyl acetate = 50/50); ^{1}H NMR δ 0.60 (s, 9H), 1.22−1.38 (m, 2H), 2.32−2.42 (m, 1H), 2.44 (s, 3H), 4.96 (dd, J = 2.3, 6.8 Hz, 1H), 5.44−5.51 (m, 1H), 6.97−7.67 (m, 9H); IR (neat) 3600−3100, 2970, 1470, 1030 cm^{-1}; MS (EI) *m/e* 330 (M$^+$, 1), 140 (100). Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93. Found: C, 72.71; H, 8.22.

(*S*$_S$,2*S*,3*R*)-5,5-Dimethyl-3-(*p*-tolylsulfinyl)-2-hexanol (*syn*-7b): R_f = 0.61(hexane/ethyl acetate = 30/70); $[\alpha]^{26}_D$ = +213 (*c* 0.137, $CHCl_3$); ^{1}H NMR δ 0.97 (s, 9H), 1.09 (d, J = 7.2 Hz, 3H), 1.87 (dd, J = 3.1, 15.9 Hz, 1H), 1.98 (dd, J = 6.5, 15.9 Hz, 1H), 2.29 (ddd, J = 1.2, 3.1, 6.5 Hz, 1H), 2.44 (s, 3H), 4.25−4.50 (m, 1H), 4.36 (s, 1H), 7.37 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 20.6, 21.4, 29.6, 30.6, 36.5, 63.1, 66.3, 124.6, 130.0, 138.2, 141.7; IR (neat) 3600−3200, 2950, 1470, 1040, 810 cm^{-1}; MS (EI) *m/e* 268 (M$^+$, 1), 252 (11), 151 (45), 140(100). Anal. Calcd for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01. Found: C, 67.36; H, 9.24.

***syn*-4,4-Dimethyl-1-phenyl-2-(phenylsulfonyl)-1-pentanol (*syn*-15a):** R_f = 0.61 (hexane/ethyl acetate = 60/40); ^{1}H NMR δ 0.44 (s, 9H), 1.93 (d, J = 3.6 Hz, 2H), 3.08 (dt, J = 0.9, 3.6 Hz, 1H), 3.80 (s, 1H), 5.24 (s, 1H), 7.10−7.35 (m, 5H), 7.60−7.80 (m, 3H), 7.98−8.09 (m, 2H); IR (neat) 3600−3300, 2950, 1450, 1295, 1245, 1140, 740 cm^{-1}; MS (EI) *m/e* 332 (M$^+$, 6), 275 (20), 226 (16), 190 (18), 169 (100). Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28. Found: C, 68.86; H, 7.35.

***anti*-4,4-Dimethyl-1-phenyl-2-(phenylsulfonyl)-1-pentanol (*anti*-15a):** R_f = 0.56 (hexane/ethyl acetate = 60/40); ^{1}H NMR δ 0.68 (s, 9H), 1.71 (dd, J = 4.6, 15.5 Hz, 1H), 2.15 (dd, J = 3.6, 15.5 Hz, 1H), 3.46 (ddd, J = 3.6, 4.6, 6.0 Hz, 1H), 4.36 (d, J = 6.3 Hz, 1H), 4.99 (dd, J = 6.0, 6.3 Hz, 1H), 7.15−7.35 (m, 5H), 7.37−7.60 (m, 3H), 7.65−7.73 (m, 2H); IR (neat) 3600−3200, 2960, 1475, 1450, 1300, 1140 cm^{-1}; MS (EI) *m/e* 332 (M$^+$, 6), 275 (23), 226 (19), 190 (25), 169 (100).

***syn*-5,5-Dimethyl-3-(phenylsulfonyl)-2-hexanol (*syn*-15b):** R_f = 0.60 (hexane/ethyl acetate = 60/40); ^{1}H NMR δ 0.82 (s, 9H), 1.29 (d, J = 6.3 Hz, 3H), 1.73 (dd, J = 4.3, 15.8 Hz, 1H), 1.91 (dd, J = 3.6, 15.8 Hz, 1H), 3.00 (ddd, J = 1.5, 3.6, 4.3 Hz, 1H), 3.57 (d, J = 4.9 Hz, 1H), 4.16 (ddq, J = 1.5, 4.9, 6.3 Hz, 1H), 7.52−7.75 (m, 3H), 7.88−8.00 (m, 2H); ^{13}C NMR δ 20.0, 29.4, 30.2, 34.2, 66.2, 66.3, 128.6, 129.3, 133.9, 138.3; IR (KBr) 3650−3150, 2970, 1480, 1450, 1420, 1375, 1280, 1150, 750, 690 cm^{-1}; MS (EI) *m/e* 255 (M$^+$-15, 4), 226 (28), 169 (99), 143 (54), 129 (100). Anal. Calcd for $C_{14}H_{22}O_3S$: C, 62.19; H, 8.20. Found: C, 62.38; H, 8.45.

***anti*-5,5-Dimethyl-3-(phenylsulfonyl)-2-hexanol (*anti*-15b):** R_f = 0.60 (hexane/ethyl acetate = 60/40); ^{1}H NMR δ 0.78 (s, 9H), 1.39 (d, J = 6.6 Hz, 3H), 1.63 (dd, J = 5.2, 15.5 Hz, 1H), 1.87 (dd, J = 3.1, 15.5 Hz, 1H), 3.09 (ddd, J = 3.1, 5.2, 5.6 Hz, 1H), 3.31 (d, J = 6.2 Hz, 1H), 4.14 (ddq, J = 5.6, 6.2, 6.6 Hz, 1H), 7.48−7.75 (m, 3H), 7.82−7.97 (m, 2H); IR (neat) 3600−3200, 2965, 1480, 1450, 1410, 1375, 1280, 1145, 740 cm^{-1}; MS (EI) *m/e* 270 (M$^+$, 0.9), 255 (9), 226 (22), 169 (96), 143 (52), 129 (100).

Radical Hydrogenation of the *β*-Hydroxy-α-(phenylselenenyl) Sulfone 22. To a solution of **22** in CH_2Cl_2 (0.01 mol/L) were added tributyltin hydride (2 equiv) and triethylborane (1 equiv) at −78 °C. The mixture was concentrated to give the crude product, which was purified by column chromatography (silica gel, hexane/ethyl acetate = 85/15) to give the reduction product **23**.

3-(Phenylsulfonyl)-2-butanol (23): R_f = 0.10 (hexane/ethyl acetate = 70/30); ^{1}H NMR δ 1.14 (d, J = 7.1 Hz, 3H, anti-isomer) and 1.21 (d, J = 6.5 Hz, 3H, syn-isomer), 1.25 (d, J = 6.4 Hz, 3H, anti-isomer) and 1.34 (d, J = 7.2 Hz, 3H, syn-isomer), 3.01 (dq, J = 1.3, 7.2 Hz, 1H, syn-isomer) and 3.14 (dq, J = 7.1, 8.2 Hz, 1H, anti-isomer), 2.99 (s, 1H, anti-isomer) and 3.93 (s, 1H, syn-isomer), 4.15−4.25 (m, 1H, anti-isomer) and 4.40−4.55 (m, 1H, syn-isomer), 7.45−7.80 (m, 3H), 7.80−8.05 (m, 2H); IR (neat) 3600−3300, 2980, 2930, 1445, 1300, 1140, 1080 cm^{-1}.

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Supporting Information Available: Spectroscopic data and experimental details of **3**−**6**, **8**−**10**, **12**−**14**, and **16**−**22**. Determination of the absolute configuration of the addition product **7b**. Determination of the relative configuration of the addition products **15**−**19** and **23**. Calculations data for **12** and radical intermediates **12R** derived from **12**. This material is available via the Internet at http://pubs.acs.org.

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