

Stereoselective Hydrogenation of α -Sulfinyl Radical Generated from Alkyl Radical Addition to α -(1-Hydroxyethyl)vinyl Sulfoxide

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Abstract: The reaction of (2*S*,*S*_S)- α -(1-hydroxyethyl)vinyl sulfoxide with alkyl radicals and tributyltin hydride gave the addition-hydrogenation products with high diastereoselectivity, whereas (2*R*,*S*_S)- α -(1-hydroxyethyl)vinyl sulfoxide gave no products under similar conditions. An important role of intramolecular hydrogen bonding for the diastereoselectivity as well as the reactivity toward alkyl radicals is discussed. © 1998 Elsevier Science Ltd. All rights reserved.

Recently, much effort has been devoted to the development of asymmetric radical reactions.¹ Sulfoxides have been employed in diastereoselective radical reactions,² including the diastereoselective allylation reactions of α -sulfinyl radicals in which diastereoselectivities can be improved by coordination of monodentate Lewis acids,^{2d} urea derivatives,^{2f} or hydrogen bond donating solvents with sulfoxides.^{2h} It is important to fix the conformation containing a sulfoxide moiety for achieving high diastereoselection. From this point of view, we succeeded in a highly stereoselective radical β -addition reaction of 2-(arylsulfinyl)-2-cycloalkenones by fixing the sulfoxide and the carbonyl in an antiperiplanar orientation, and demonstrated a completely reversed stereoselection by the chelation control with a bidentate Lewis acid.³ Deuteration and allylation of radicals α to the sulfinyl group derived from 2-hydroxy-1-(phenylselenenyl)alkyl sulfoxides have been reported to proceed with modest diastereoselectivities and the stereochemical outcome is rationalized by a Felkin-Anh model without intramolecular hydrogen bonding.^{2c} We now report a new stereoselective hydrogenation of the α -sulfinyl radical generated from alkyl radical addition to α -(1-hydroxyethyl)vinyl sulfoxide, the diastereoselectivity and the reactivity of which are effectively controlled by intramolecular hydrogen bonding.

Optically pure (*S*_S)- α -(1-hydroxyethyl)vinyl sulfoxide **1**⁴ was prepared by the reported procedure.⁵ (2*S*,*S*_S)- and (2*R*,*S*_S)- α -(1-Hydroxyethyl)vinyl sulfoxides (2*S*)-**1** and (2*R*)-**1** could be isolated by flash column chromatography. The hydroxy group, when required, was silylated with Ph₃SiCl in pyridine.⁶ The reaction was carried out by adding alkyl iodide (3 equiv)⁷, tributyltin hydride (3 equiv), and triethylborane (3 equiv) as a radical initiator⁸ to a 0.01 mol/L solution of (2*S*)-**1** and (2*R*)-**1**, and the mixture was stirred for an appropriate time. In the reaction in the presence of a Lewis acid, a mixture of **1** and a Lewis acid (1.1 equiv) was stirred for 30 min before addition of other reagents. The results are shown in Table. When the reaction of (2*S*)-**1** with a *tert*-butyl radical was carried out at room temperature in a 0.1 mol/L or 0.01 mol/L solution, the yield of the addition product **3** was less than 50% (entries 1 and 2). On the other hand, the reaction of (2*S*)-**1** with a *tert*-butyl radical gave a single diastereomer⁹ *syn*-**3** in high yield when carried out at low temperature (-78 °C) and at low concentration (0.01 mol/L) in a nonpolar solvent such as dichloromethane or toluene (entries 3 and 4). The reaction in THF resulted in recovery of the starting (2*S*)-**1** together with the formation of a trace amount of the addition product **3** (entry 5). Cyclohexyl, isopropyl, and ethyl radicals could also add to (2*S*)-**1** to give a mixture of *syn* and *anti* isomers (entries 6–8). The diastereoselectivity was accordingly lowered, as the size of the alkyl radical was small. The addition product *syn*-**3** was also obtained with high diastereoselectivity, when 1.1 equiv of a Lewis acid such as EtAlCl₂, Et₂AlCl, or Et₃Al was added (entries 9, 11 and 12), whereas *syn*-**3** was

obtained only in 19% yield with 2 equiv of EtAlCl_2 (entry 10). In contrast to the results of (2*S*)-1, no addition products were obtained even after 72 h in the reaction of (2*R*)-1, where the starting (2*R*)-1 was quantitatively recovered (entry 13). The addition of EtAlCl_2 did not improve the reactivity of (2*R*)-1 for the addition of a *tert*-butyl radical (entries 14–15). Neither (2*S*)-2 nor (2*R*)-2, the hydroxy group of which was protected with a triphenylsilyl group, afforded the addition product (entries 16–17).

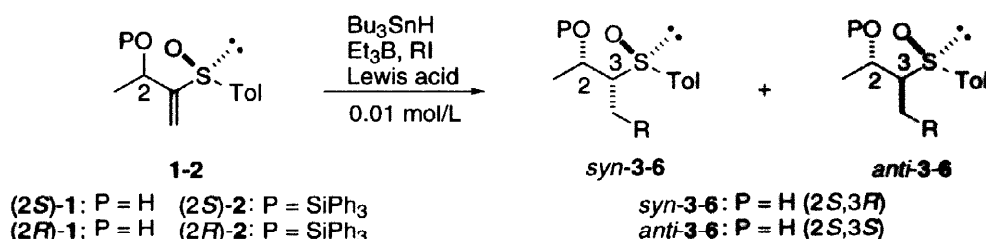


Table. Radical Addition to α -(1-Hydroxyethyl)vinyl Sulfoxides **1** Followed by Diastereoselective Trapping with Tributyltin Hydride.^a

Entry	Substrate	R	Solvent	Lewis acid ^b	Temp (°C)	Time (h)	Product	Yield (%)	syn : anti
1 ^c	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	none	rt	3	3	<40	^d
2	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	none	rt	3	3	<50	^d
3	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	none	-78	3	3	89	>98 : <2
4	(2 <i>S</i>)-1	<i>t</i> -Bu	PhMe	none	-78→rt	24	3	81	>98 : <2
5	(2 <i>S</i>)-1	<i>t</i> -Bu	THF	none	-78→rt	24	3	trace	
6	(2 <i>S</i>)-1	<i>c</i> -Hex	CH_2Cl_2	none	-78	12	4	66 ^e	93 : 7
7	(2 <i>S</i>)-1	<i>i</i> -Pr	CH_2Cl_2	none	-78	12	5	72 ^e	93 : 7
8	(2 <i>S</i>)-1	Et	CH_2Cl_2	none	-78	12	6	38 ^e	79 : 21
9	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	EtAlCl_2	-78	3	3	75	>98 : <2
10	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	EtAlCl_2 ^f	-78→rt	24	3	19 ^e	>98 : <2
11	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	Et_2AlCl	-78	6	3	68	>98 : <2
12	(2 <i>S</i>)-1	<i>t</i> -Bu	CH_2Cl_2	Et_3Al	-78	6	3	70	>98 : <2
13	(2 <i>R</i>)-1	<i>t</i> -Bu	CH_2Cl_2	none	-78→rt	72	no reaction		
14	(2 <i>R</i>)-1	<i>t</i> -Bu	CH_2Cl_2	EtAlCl_2	-78→rt	24	no reaction		
15	(2 <i>R</i>)-1	<i>t</i> -Bu	CH_2Cl_2	EtAlCl_2 ^f	-78→rt	24	no reaction		
16	(2 <i>S</i>)-2	<i>t</i> -Bu	CH_2Cl_2	none	-78→rt	24	no reaction		
17	(2 <i>R</i>)-2	<i>t</i> -Bu	CH_2Cl_2	none	-78→rt	24	no reaction		

^a The reaction was carried out in a 0.01 mol/L solution unless otherwise noted. ^b The Lewis acid (1.1 equiv) was added. ^c The reaction was carried out in a 0.1 mol/L solution. ^d Not determined. ^e (2*S*)-1 was recovered in 24% (entry 6), 22% (entry 7), 55% (entry 8), and 76% (entry 10). ^f EtAlCl_2 (2 equiv) was used.

We confirmed that a 51 : 49 diastereomeric mixture of (2*S*)-1 and (2*R*)-1 afforded the addition product *syn*-**3** derived only from (2*S*)-1 in 48% yield (93% yield based on (2*S*)-1), and thus these diastereomers, which were relatively difficult to separate by chromatography, could be kinetically separated in the radical reaction (Scheme). (2*R*)-1 recovered (87% yield based on (2*R*)-1) was easily converted to (2*S*)-1 by the Mitsunobu reaction¹⁰ in 86% yield. Thus, the present diastereomer-differentiating radical addition efficiently gives enantiomerically pure *syn*-**3** which can be a useful precursor of a chiral epoxide (Scheme).

The significant difference in reactivity between (2*S*)-1 and (2*R*)-1 can be ascribed to the effect of intramolecular hydrogen bonding in the former stereoisomer to lower the LUMO energy of the double bond, *i.e.*, to enhance the radical addition reaction. From the frontier orbital theory the nucleophilic addition of an electron-rich alkyl radical to an alkene properly reacts with an electron-deficient alkene, since the SOMO-LUMO energy

difference is smaller.¹¹ We performed semiempirical calculation of LUMO energies of α -(1-hydroxyethyl)vinyl sulfoxide **1** using the PM3 parameter set as implemented in MOPAC 93¹² (Fig. 1). Calculations of possible conformers resulted in lower LUMO energies in conformers (2*S*)-**1-B** and (2*S*)-**1-C** with intramolecular hydrogen bonding than in conformer (2*S*)-**1-A** without intramolecular hydrogen bonding. From the spectral data,¹³ (2*R*)-**1** exists mainly as the high-LUMO energy conformer (2*R*)-**1-A** without intramolecular hydrogen bonding and, therefore, gives no addition product with the nucleophilic *tert*-butyl radical.

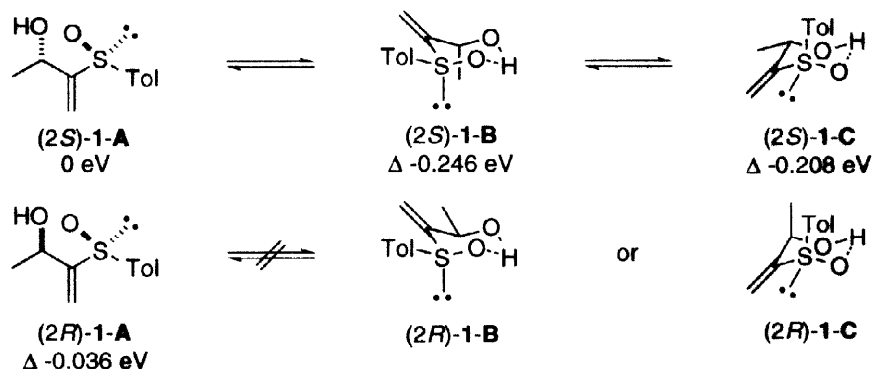
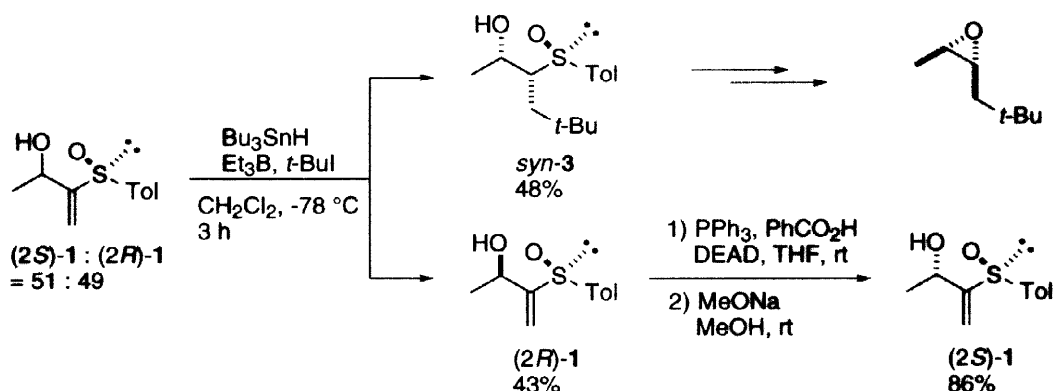


Fig. 1 LUMO energies of α -(1-hydroxyethyl)vinyl sulfoxides **1**.

The resulting high stereoselectivity in the reaction of (2*S*)-**1** is derived from the stereoselective hydrogenation of the radical intermediate with tributyltin hydride and can be rationalized by the models shown in Fig. 2. The most stable conformer was found to be (2*S*)-**1-RA** in which the *tert*-butyl group was directed downward, and the conformer (2*S*)-**1-RA** was more stable by 0.7 kcal/mol than (2*S*)-**1-RB** by PM3 calculation. In the intermediate radical (2*S*)-**1-RA** the hydrogen abstraction from tributyltin hydride occurs from the face opposite to the methyl and *tert*-butyl groups, leading to the product with 2,3-*syn* stereochemistry. That the decrease in the steric bulk of the alkyl radicals lowered the diastereoselectivity (entries 6-8) is in accord with the postulated intermediate (2*S*)-**1-RA** in which the *tert*-butyl group effectively shields one of the faces.

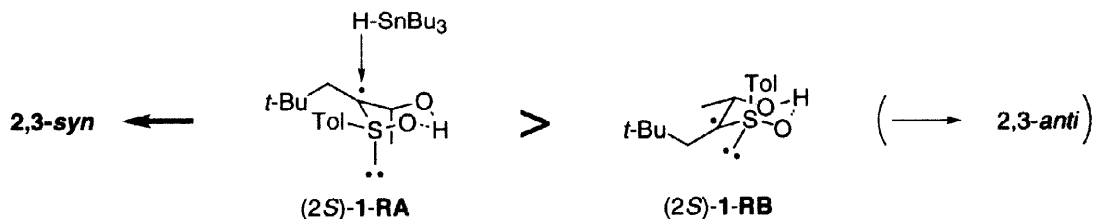


Fig. 2

