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Asymmetric Reduction of α-(Trimethylsilyl)methyl-*β*-ketosulfoxide with DIBAL under Basic Conditions

Shuichi Nakamura, Jun-ichi Nakayama, and Takeshi Toru*

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya, 466-8555, Japan

toru@ach.nitech.ac.jp

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Abstract: The reaction of the α-carbanion of *p*-tolyl 2-(trimethylsilyl)ethyl sulfoxide with esters followed by reduction with DIBAL gave α-(trimethylsilyl)methyl-*β*-hydroxysulfoxides with high stereoselectivity. The stereoselective reaction was demonstrated to proceed through a dynamic kinetic resolution pathway via a six-membered cyclic transition state involving Si−O interaction. These reactions provide a convenient route for the synthesis of optically pure allylic alcohols.

It is well-known that reduction of *β*-ketosulfoxides with diisobutylaluminum hydride (DIBAL) gives *β*-hydroxysulfoxides with high diastereoselectivity.[1] The DIBAL reduction of a diastereomeric mixture of α-substituted *β*-ketosulfoxides, which possibly affords four diastereomeric isomers, shows high selectivity with respect to carbonyl face selection, but the products are generally obtained as an inseparable mixture of the diastereomers.[2,3] This often becomes a disadvantage of the above type of reduction in terms of the stereoselective synthesis of *β*-hydroxysulfoxides. Highly stereocontrolled synthesis of α-substituted *β*-hydroxysulfoxides has been partly achieved: Ogura[4] and Guanti[5] with their co-workers have independently reported that reduction of α-(alkylthio)-*β*-ketosulfoxides with $NaBH_4$ or $LiAlH_4$ in the presence of tertiary amines such as triethylamine gives the products with high stereoselectivity. They have assumed that the highly diastereoselective outcome can be ascribed to the rapid equilibrium between the diastereomeric α-substituted *β*-ketosulfoxides through abstraction and addition of an α-proton as well as to the reaction rate of each diastereomer with a reducing agent (dynamic kinetic resolution). In contrast, reduction of α-alkylated *β*-ketosulfoxides under similar basic conditions shows only low stereoselectivity.[3] There is no report on the reduction of α-alkylated *β*-ketosulfoxides with DIBAL through a dynamic kinetic resolution pathway. Recently, we have reported reactions of the α-sulfinyl carbanion of *β*-(trimethylsilyl)ethyl sulfoxide as a powerful chiral inducer,[6,7] in which Si−O interaction in the transition state has been demonstrated. We now report a highly stereoselective reduction of α-(trimethylsilyl)methyl-*β*-ketosulfoxides that proceeds through a dynamic kinetic resolution pathway, involving a transition state stabilized by the Si−O interaction.

We examined the reaction of the α-sulfinyl carbanion, derived from *p*-tolyl *β*-(trimethylsilyl)ethyl sulfoxide **1**,[6a] with various esters and subsequent in situ reduction of the produced α-(trimethylsilyl)methyl-*β*-ketosulfoxides **4** with various reducing agents. We also studied a similar reaction of α-alkyl *p*-tolyl sulfoxides **2** and **3**. The results are summarized in Table 1.

A THF solution of *β*-(trimethylsilyl)ethyl sulfoxide **1** was treated with LDA (1.3 equiv)[8] at −78 °C and subsequently reacted with ethyl benzoate (1.5 equiv), forming *β*-ketosulfoxide **4a**. Without isolation of **4a**, DIBAL (1.6 equiv) was added to this solution at −78 °C. A single diastereomer **5aA** out of four possible diastereomeric *β*-hydroxysulfoxides **5a** shown in Scheme 1 was formed in 60% yield.[9] The unreduced *β*-ketosulfoxide **4a** was isolated in 38% yield in a syn/anti ratio of 79:21 (entry 1). On the other hand, the one-pot reduction of **4a** with other reducing agents such as $LiAlH_4$, L-selectride, and $NaBH_4$ gave two diastereomeric products **5aA** and **5aB** but with low stereoselectivities (entries 2−4). The reaction of **1** with other esters and subsequent reduction with DIBAL also gave *β*-hydroxysulfoxides **5bA**−**dA** as single diastereomers together with unreduced *β*-ketosulfoxides **4b**−**d** (entries 5−7). In contrast to the highly stereochemical outcome in the reduction of α-(trimethylsilyl)methyl-*β*-ketosulfoxides **4a**−**d**, reduction of α-alkyl-*β*-ketosulfoxides **4e** and **4f** with DIBAL showed low stereoselectivity on the carbon α to the sulfinyl group giving the diastereomeric products **5e** and **5f** in an **A**/**C** ratio of 74:26 and 72:28, respectively (entries 8 and 9).[11]

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

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(8) Larger amount of LDA lowered the yield of **5a**.

(9) To confirm the product distribution, four diastereomeric isomers **5aA**−**D** were separately prepared by the reaction of the α-carbanion derived from the corresponding *β*-hydroxysulfoxide with (iodomethyl)-trimethylsilane.

(10) Absolute configuration of **5c** was determined by comparison of the ^1H NMR spectral data with the reported data; see ref 3.

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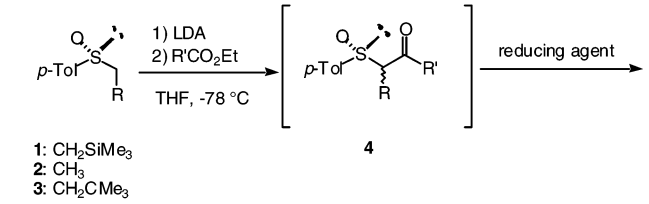
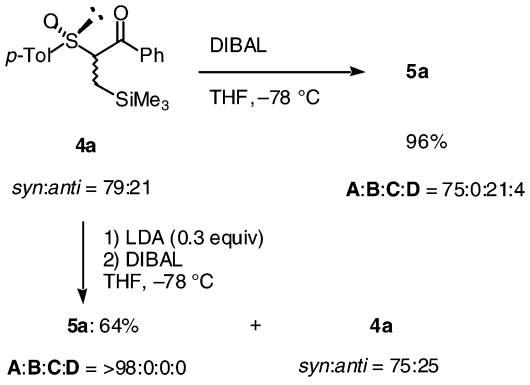
TABLE 1. Reduction of α-Substituted *β*-Ketosulfoxides 1−3 with Various Reducing Agents



entry		sulfoxide R	sulfoxide R′	reducing agent	yield (%) 4	yield (%) 5	diastereomeric ratio[a] A:B:C:D
1	**1**	CH_2SiMe_3	Ph	DIBAL	**4a**: 38[b]	**5a**: 60	>98:0:0:0
2	**1**	CH_2SiMe_3	Ph	$LiAlH_4$	**4a**: 30	**5a**: 62	65:35:0:0
3	**1**	CH_2SiMe_3	Ph	$NaBH_4$[c]	**4a**: 30	**5a**: 65	55:45:0:0
4	**1**	CH_2SiMe_3	Ph	L-Selectride	**4a**: 45	**5a**: 51	64:36:0:0
5	**1**	CH_2SiMe_3	CH_3	DIBAL	**4b**: 35[d]	**5b**: 30	>98:0:0:0
6	**1**	CH_2SiMe_3	n-C_5H_{11}	DIBAL	**4c**: 43[b]	**5c**: 52	>98:0:0:0
7	**1**	CH_2SiMe_3	$(CH_3)_2CH$	DIBAL	**4d**: 40[e]	**5d**: 55	>98:0:0:0
8	**2**	CH_3	CH_3	DIBAL	**4e**: 17[f]	**5e**: 83	74:0:26:0
9	**3**	CH_2CMe_3	Ph	DIBAL	**4f**: 47[f]	**5f**: 51[g]	72:0:28:0

[a] Diastereomeric ratio was determined by the ^{1}H NMR spectrum. [b] Syn/anti ratio was determined to be 79:21 by the ^{1}H NMR spectrum. [c] Reaction was carried out in EtOH. [d] Syn/anti ratio was 60:40. [e] Syn/anti ratio was 65:35. [f] Syn/anti ratio was 58:42. [g] Absolute configuration of **5f** has not been determined.

SCHEME 1



These results show the important role of the *β*-silyl group in the stereochemical outcome.

To obtain more information on the reaction mechanism, we performed the reduction of *β*-ketosulfoxide **4a**, which was isolated as a diastereomeric mixture in a ratio of 79:21 at the stage of the reaction of lithiated **1** with ethyl benzoate in THF at −78 °C (Scheme 1). The DIBAL reduction of **4a** in THF at −78 °C gave **5a** in 96% yield in an **A**/**B**/**C**/**D** ratio of 75:0:21:4. On the other hand, when **4a** was first treated with 0.3 equiv of LDA and then with DIBAL in THF at −78 °C, a single diastereomer **5aA** was obtained in 64% yield as in the case of in situ reduction of **4a** without isolation, together with recovered **4a** in a ratio of 75:25.

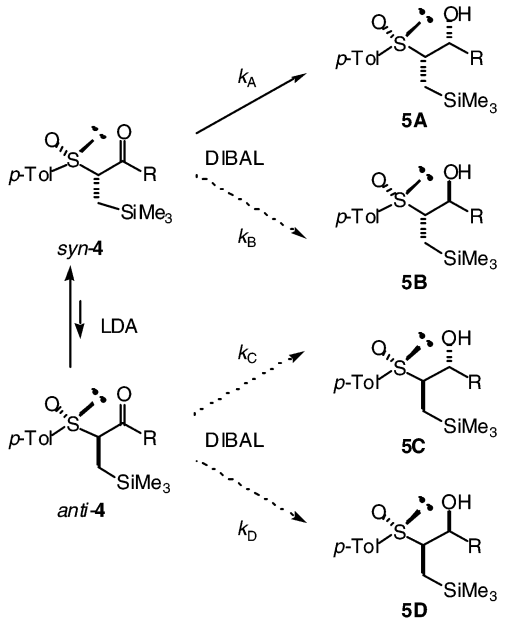


FIGURE 1. Stereoselective course to form **5A** under dynamic kinetic resolution control.

These results show that the reduction proceeds through a dynamic kinetic resolution pathway ($k_A > k_B$, k_C, k_D in Figure 1), where very rapid equilibrium between *syn*-**4a** and *anti*-**4a** occurs through formation of the enolate in the presence of LDA and *syn*-**4a** is selectively reduced to give **5aA**.[11]

(11) Another possible pathway, i.e., enolate formation with LDA selectively from *anti*-**4a** and reduction occurring only from *syn*-**4a**, can be ruled out: a solution of **4a** with a syn/anti ratio of 79:21 was treated with a smaller amount (0.1 equiv) of LDA at −78 °C and subsequently quenched with water. The syn/anti ratio of **4a** thus obtained was the same as that of the starting **4a**. The product **4a** should be composed of a higher content of *syn*-**4a** than that of the starting **4a** in the above mechanism.

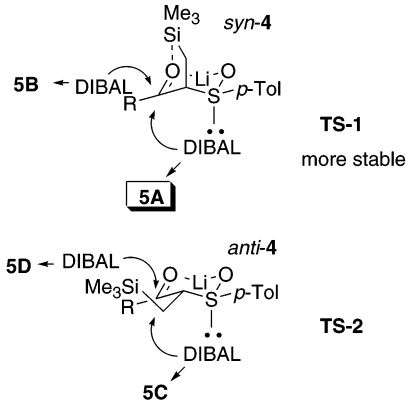
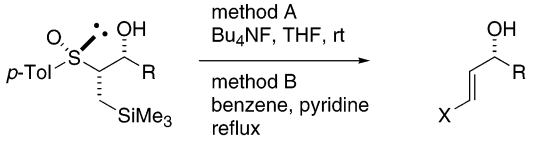


FIGURE 2. Assumed transition state in reduction of **4** with DIBAL.

SCHEME 2



5aA: R = Ph
5bA: R = CH_3
5cA: R = C_5H_{11}
5dA: R = $(CH_3)_2CH$

6: R = Ph, X = H
method A: 97% >99% ee
7: R = CH_3, X = $SiMe_3$
method B: 71% >99% ee
8: R = C_5H_{11}, X = H
method A: 91% >99% ee
9: R = C_5H_{11}, X = $SiMe_3$
method B: 80% >99% ee
10: R = $(CH_3)_2CH$, X = $SiMe_3$
method B: 70% >99% ee

Reduction of α-(silylethyl)-*β*-ketosulfoxides **4a**−**d** with DIBAL showed high stereoselectivity not only on the carbonyl face but also on the carbon α to the sulfinyl group. These results would be due to the interaction between the silicon and the carbonyl oxygen, such interaction in the transition state being demonstrated in our previous reports.[7] The in situ reduction of **4a** using other reducing agents such as $LiAlH_4$, L-selectride, and $NaBH_4$ gave **5aA** and **5aB**, which were derived from *syn*-**4a**. It is reasonable that the DIBAL reduction proceeds through a cyclic transition state, because the highly stereoselective DIBAL reduction of *β*-ketosulfoxides in the presence of a Lewis acid such as $ZnCl_2$ is well rationalized by a conformationally rigid six-membered cyclic intermediate involving chelation of a Lewis acid with the sulfinyl and the carbonyl oxygens.[1] We assumed a six-membered cyclic transition state involving the chelation with a lithium cation, possibly derived from lithium ethoxide and/or the lithium enolate formed during the reaction, where DIBAL approaches from the direction of the sulfinyl lone pair to give product **5A** (Figure 2).[12,13] The transition state **TS-1** derived from *syn*-**4** has a lower activation energy than **TS-2** from *anti*-**4**, because **TS-1** involves the Si−O interaction stabilizing the partially negative charge on the carbonyl oxygen.

The products **5a**−**d** could be converted to optically active allylic alcohols on treatment with tetrabutylammonium fluoride (TBAF, 1.1 equiv) in THF at room temperature (method A) or on heating in benzene at reflux for 30 min in the presence of pyridine (method B).[6a−c,e,7,14] The optical purities of the products **6**−**10** were determined by ^1H NMR analyses of the corresponding MTPA esters. No racemization occurred during this reaction. Thus, the chiral *p*-tolyl *β*-trimethylsilylethyl sulfoxide **1** serves as a "chiral vinyl anion equivalent".

In summary, the α-carbanion derived from *p*-tolyl 2-(trimethylsilyl)ethyl sulfoxide was reacted with esters and subsequently with DIBAL to give the single diastereomer of the *β*-hydroxysulfoxide. The reaction was demonstrated to proceed through a cyclic transition state involving the Si−O interaction. These reactions provide a convenient route for the synthesis of optically pure allylic alcohols.

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Supporting Information Available: Experimental procedures for the preparation and spectroscopic characterization of products **4a**−**f**, **5a**−**f**, and **6**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ruano and co-workers have reported that reduction of a diastereomeric mixture of **4e** with DIBAL in the presence of $ZnCl_2$ proceeds more stereoselectvely, via a six-membered cyclic transition state, than that without $ZnCl_2$ to give **5eA** and **5eC**; see ref 3. This stereochemical outcome is in good accord with that shown in entry 8 (Table 1). The DIBAL reduction of *β*-ketosulfoxides in the presence of a catalytic amount of $ZnCl_2$ also proceeds through a chelated model to give *β*-hydroxysulfoxides with high stereoselectivities; see ref 1c. These results support a six-membered cyclic transition state in the DIBAL reduction of **4** in the presence of lithium cation.

(13) Solladié and co-workers have assumed a lithium-chelated intermediate in reduction of *β*-ketosulfoxides with $LiAlH_4$; see refs 1a and 2a.

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