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AN EFFICIENT 1,3-ASYMMETRIC INDUCTION[1] ACCOMPANIED WITH EPIMERIZATION AT THE 2-POSITION. STEREOSELECTIVE REDUCTION OF α-SUBSTITUTED β-KETO SULFOXIDES UNDER BASIC CONDITIONS

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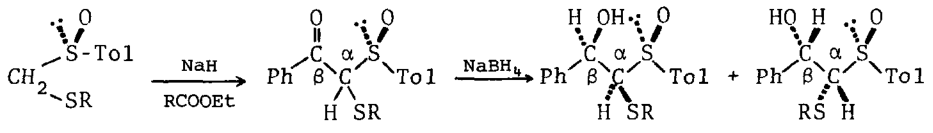
Abstract: An efficient 1,3-asymmetric induction was realized in the reduction of β-keto sulfoxides having various α-substituents with NaBH$_4$ under basic conditions and, by the application of this induction, (R)-α-acetoxyphenylacetaldehyde was synthesized.

In open-chain systems, 1,3-asymmetric induction has proven to work less effectively in comparison with 1,2-asymmetric one.[2] Now we wish to describe a novel approach to an efficient 1,3-asymmetric induction. Treatment of (S)-formaldehyde dithioacetal S-oxide (1)[3] with ethyl benzoate in the presence of NaH (2 equiv.) followed by acidification with AcOH gave the benzoylated product 2 or 3 as a diastereomeric mixture in the thermodynamically controlled ratio of 65 : 35 or 53 : 47, respectively.[4] When the diastereomeric mixture of 2[5] was reduced with NaBH$_4$ in MeOH–CH$_2$Cl$_2$ (5 : 2), among four possible stereoisomeric products (4), 4A and 4B were formed in the ratio of 68 : 32. To our surprise, one stereoisomer (4A) was given with extremely high stereoselectivity of 98% by performing the reduction in MeOH–conc NH$_3$ aq. (9 : 1 v/v). Treatment of 4A with TiCl$_3$ in MeOH gave (+)-1-phenyl-2,2-bis(p-tolylthio)ethanol, the enantiomer of which was afforded by the TiCl$_3$ reduction of 4B. Since reductive desulfurization of 4A with Raney Ni (W II) produced (S)-1-phenylethanol,[6] the β-configurations of 4A and 4B were established to be (R) and (S), respectively. Furthermore, their α-configurations were assigned as (R) for 4A and (S) for 4B from the coupling constants (4A: 3.2 Hz and 4B: 1.7 Hz) of the vicinal methine protons in their ^{1}H NMR spectra on the assumption that the conformation where phenyl and p-tolylsulfinyl groups are located in *trans* relationship is the most favorable. An analogous result was also obtained in the reduction of 3, although the stereoselectivity was somewhat lower, as shown in Table I.

In the reduction of ω-(p-tolylsulfinyl)acetophenone with NaBH$_4$ in MeOH or MeOH–Et$_3$N (1 : 1), two diastereomers of 1-phenyl-2-(p-tolylsulfinyl)ethanol were produced in the ratio of 1 : 1,

Scheme I



1a R = Tol
1b R = Me

2 R = Tol
3 R = Me

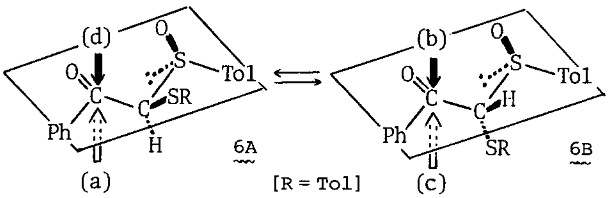
4A R = Tol
5A R = Me

4B R = Tol
5B R = Me

[Tol ≡ p-CH$_3$C$_6$H$_4$]

revealing that the chirality of the sulfinyl group has no influence on the stereochemical course of the reduction through space under the present conditions. Therefore, almost exclusive formation of 4A in the reduction of 2 under basic conditions may be explained in terms of fast equilibrium between two diastereomers (6A and 6B) of 2 and preferable attack of NaBH$_4$ from one side of the diastereotopic plane of 6A, *i. e.* from the (a) side of Scheme II.

Scheme II



In order to investigate the generality of this 1,3-asymmetric induction, we performed the reduction of β-keto sulfoxides (8) having various sizes of α-substituents (Y) with NaBH$_4$ under basic conditions. Four racemic β-keto sulfoxides (8; Y = Me, Et, i-Pr, and Ph) were prepared by oxidation of the corresponding sulfides (7) with MCPBA,[7] and the reduction of 8 was carried out with 1 mol-equiv. of NaBH$_4$ at room temperature.[5] For the sake of simplicity, only one configuration for the sulfinyl group is shown in Scheme III, although racemates were employed. As being apparent from Table I, distribution of four diastereomeric products (9) depended very much on whether a base was added or not, and one kind of diastereomer dominated over others in the reduction in a basic solvent, the tendency of which became more remarkable with the increasing bulkiness of Y. We also established the stereochemical structures of two diastereomers [9A (Y = Ph) and 9B (Y = Ph)] given from 8 (Y = Ph). Oxidation of these with MCPBA afforded the same sulfone, indicating that they had the same relationship between their α- and β-configurations. On sequential treatment of 9A with TiCl$_3$ leading to the corresponding sulfide (10),[8] S-methylation of 10 with $Me_3O^+BF_4^-$, and the subsequent ring-closure with NaOH,[9] *trans*-2,3-diphenyloxirane was obtained.[10] The major diastereomer [(R_S)-9A (Y = Ph)] was prepared in an optically active form from (R)-benzyl p-tolyl sulfoxide[11,12] and, on reductive desulfurization with Raney Ni (W II), gave (S)-1,2-diphenylethanol.[13] From these facts, the formulas 9A and 9B were unambiguously assigned to the structures of the major and minor products, respectively, in the reduction of 8 (Y = Ph). Hence, it was shown that the stereochemical course in the reduction of 8 (Y = Ph) was similar to that of 2 and the most preferable attack of NaBH$_4$ occurred from the back-side of 8A of Scheme III in a basic solvent.

Thus, an efficient 1,3-asymmetric induction accompanied with epimerization at the 2-position was realized in the reduction of α-substituted β-keto sulfoxides with NaBH$_4$ under

Scheme III

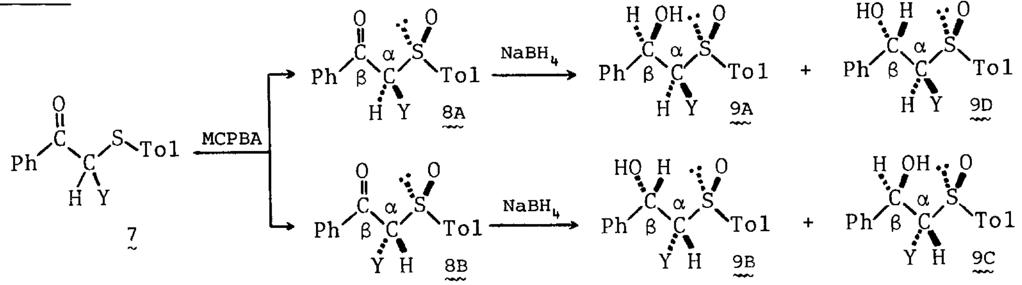


Table I. Reduction of 2, 3, and 8 with $NaBH_4$[a]

substrate[b]	solvent (v/v)	reduction product	
		% yield	A : B : C : D[c]
2 (65 : 35)[d]	$MeOH-CH_2Cl_2$ (5 : 2)	74^e	68 : 32 : 0 : 0^d
	MeOH–conc NH_3 aq. (9 : 1)	79^e	98 : 2 : 0 : 0^d
3 (53 : 47)[d]	MeOH	72^f	57 : 28 : 15 : 0^d
	MeOH–conc NH_3 aq. (9 : 1)	80^f	87 : 9 : 0 : 4^d
8; Y = Me (35 : 65)[d]	MeOH	96^g	19 : 14 : 21 : 46^h
	MeOH–conc NH_3 aq. (4 : 1)	97^g	33 : 8 : 44 : 15^h
	0.1 M NaOH/MeOH	81^g	42 : 10 : 35 : 14^h
	$MeOH-Et_3N$ (2 : 3)	97^g	55 : 7 : 30 : 9^h
8; Y = Et (~1 : 1)[d]	MeOH	72^g	33 : 0 : 24 : 43^i
	$MeOH-Et_3N$ (1 : 1)	84^g	60 : 0 : 25 : 15^i
8; Y = i-Pr (~3 : 2)[d]	MeOH	95^g	35 : 28 : 32 : 5^h
	$MeOH-Et_3N$ (1 : 3)	89^g	75 : 7 : 18 : 0^h
8; Y = Ph (7 : 3)[d]	$MeOH-CH_2Cl_2$ (3 : 2)	100^g	70 : 30 : 0 : 0^d
	$MeOH-CH_2Cl_2-Et_3N$ (1 : 1 : 1)	95^g	82 : 18 : 0 : 0^d

[a] Using 5.0 mol-equiv. of $NaBH_4$ at 0 °C for 2 and 3, or 1.0 mol-equiv. of $NaBH_4$ at room temperature for 8.

[b] The value in the parenthesis is the ratio of the diastereomers. The popuration of the diastereomer with a methine proton at a lower field was given as the first value in the parenthesis.

[c] For 9 (Y = Me, Et, and i-Pr), the stereochemical structures were tentatively assigned.

[d] Determined by a ^1H NMR analysis (60 MHz).

[e] Overall yield from 1a.

[f] Overall yield from 1b.

[g] Overall yield from 7.

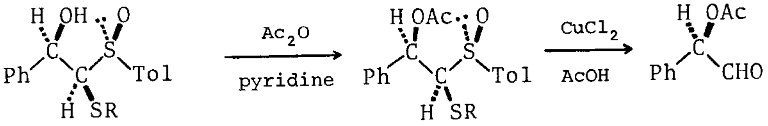
[h] Determined by a ^1H NMR analysis (100 MHz).

[i] Determined by a ^1H NMR analysis (270 MHz).

basic conditions. Since the present approach seems not to be confined to β-keto sulfoxides, we are going to study its extention to other reaction system.

Finally, we would like to describe utilization of the present 1,3-asymmetric induction for making an optically active α-acetoxyphenylacetaldehyde (12).[14] When 4A and 5A, after acetylation with pyridine-Ac_2O, was subjected to brief treatment with $CuCl_2 \cdot 2H_2O$ in AcOH, (R)-12 was obtained with a high optical purity, as summarized in Table II. It also is noteworthy that (S)-12 was produced from 4B[15] in an analogous manner. Thus, 1 has proven to be useful for asymmetric synthesis of an α-acetoxy aldehyde. The scope and limitations of this method are the subject of our on-going study.

Scheme IV



4A R = Tol
5A R = Me

11a R = Tol
11b R = Me

(R)-12

Table II. Transformation of 4 and 5 into 12

	% yield of 11	% yield of 11 → 12	12 $[\alpha]_D$[a]	12 e.e.[b]
4A	100^c	55^d	-119 (R)	99%
5A	75^e	45^f	-113 (R)	94%
4B	94^e	50^g	+118 (S)	98%

[a] In acetone.

[b] For (R)-12 derived from 5A, the enantiomer excess (e.e.) was determined by an ^1H NMR analysis using $Eu(tfc)_3$. The other values were calculated from their $[\alpha]_D$.

[c] Ac_2O-pyridine (r.t./2 h).

[d] $CuCl_2 2H_2O$ (1.2 mol-equiv) in AcOH (60 °C/1.5 h).

[e] Ac_2O-pyridine (r.t./overnight).

[f] $CuCl_2 2H_2O$ (2 mol-equiv) in AcOH (80 °C/2.5 min).

[g] $CuCl_2 2H_2O$ (2 mol-equiv) in AcOH (80 °C/7 min).

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References and Notes

1. This term was defined by Leitereg and Cram.[2a]
2. (a) T. J. Leitereg and D. J. Cram, *J. Am. Chem. Soc.*, **90**, 4011 (1968); (b) *idem.*, *ibid.*, **90**, 4019 (1968); (c) M. Brienne, C. Quannis, and J. Jacques, *Bull. Soc. Chim. Fr.*, **1968**, 1036; (d) N. Kunieda, J. Nokami, and M. Kinoshita, *Chem. Lett.*, **1974**, 369; (e) R. Annunziata, M. Cinquini, and F. Cozzi, *J. Chem. Soc. Perkin Trans. 1*, **1981**, 1109; (f) C. R. Johnson and C. J. Stark, Jr., *J. Org. Chem.*, **47**, 1196 (1982).
3. (a) L. Colombo, C. Gennari, and E. Narisano, *Tetrahedron Lett.*, **1978**, 3861; (b) K. Ogura, M. Fujita, and H. Iida, *ibid.*, **21**, 2233 (1980); (c) K. Ogura, M. Fujita, K. Takahashi, and H. Iida, *Chem. Lett.*, **1982**, 1697.
4. In THF at 50 °C for 5 h in the analogous manner to the reference: K. Ogura, S. Furukawa, and G. Tsuchihashi, *Chem. Lett.*, **1974**, 659. A diastereomeric mixture of **2** in the ratio of 38 : 62, which was obtained as a mother liquor in crystallization of **2** from diethyl ether, was converted to a 66 : 34 mixture of two diastereomers on treatment with 0.1 M aq. NaOH-CH_2Cl_2 (2 : 5) at room temperature for 5 min.
5. Since an α-substituted β-keto sulfoxide was very labile on silica gel and Florisil, it was subjected to the following reduction without purification. Cf.) P. G. Gassman and G. D. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).
6. $[\alpha]_D^{22}$ -43.3 (c = 2.43, Et_2O); lit. $[\alpha]_D$ -43.5 (neat): R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Am. Chem. Soc.*, **82**, 876 (1960).
7. With 1.01—1.06 equiv. of MCPBA in CH_2Cl_2 under ice-cooling.
8. With 20% aq. $TiCl_3$ (3 mol-equiv.) in MeOH—CH_2Cl_2 (1 : 2) under ice-cooling for 5 h. The yield based on the unrecovered sulfoxide was 89%.
9. J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, *J. Am. Chem. Soc.*, **95**, 3429 (1973).
10. The mixture of two diastereomers of 1,2-diphenyl-2-(p-tolylthio)ethanol was obtained by reduction of **7** with $NaBH_4$. When it was subjected to the same sequential treatment, a mixture of *cis*- and *trans*-2,3-diphenyloxirane was produced.
11. (R)-Benzyl p-tolyl sulfoxide (mp 165.6 °C; $[\alpha]_D^{19}$ +280 (c = 1.02, acetone) was prepared by the reaction of benzylmagnesium chloride with *l*-menthyl p-toluenesulfinate in the analogous manner to the synthesis of (R)-ethyl p-tolyl sulfoxide: K. K. Andersen, *Tetrahedron Lett.*, **1962**, 93.
12. To a suspension of KH (13.2 mmol) in THF (15 ml), was added (R)-benzyl p-tolyl sulfoxide (3.16 mmol) and the resulting mixture was stirred at room temperature for 1 h and at 50 °C for 1 h. After addition of ethyl benzoate (4.85 mmol), the mixture was stirred at 0 °C for 1 h. The usual work-up and rapid chromatography gave (R_S)-**8** (Y = Ph) in 62% yield. Reduction of (R_S)-**8** (Y = Ph) with $NaBH_4$ in MeOH—CH_2Cl_2-Et_3N (1 : 1 : 1) and chromatography on silica gel using benzene-CH_2Cl_2 (1 : 1) as an eluent gave (R_S)-**9A** (Y = Ph) in 60% yield.
13. $[\alpha]_D^{19}$ +53.0 (c = 1.02, 99% EtOH); lit. $[\alpha]_D$ +56.1 (c = 1.0, EtOH): G. Berti, F. Bottari, P. L. Ferrarini, and B. Macchia, *J. Org. Chem.*, **30**, 4091 (1965).
14. Recently, Colombo et al. reported an asymmetric synthesis of α-methoxyphenylacetaldehyde *via* the diastereomeric mixture of **4** derived by the addition of the lithiated **1a** to benzaldehyde: L. Colombo, C. Gennari, C. Scolastico, G. Guanti, and E. Narisano, *J. Chem. Soc. Perkin Trans. 1*, **1981**, 1278. See also the note (15).
15. The diastereomers of **4** were also produced by the addition of **1a** to benzaldehyde using n-BuLi as a base. The distribution (A : B : C : D) of these four diastereomers was 9 : 26 : 50 : 15, being different from the result reported by Colombo et al.[14] Here, **4C** and **4D** are identical with **9C** (Y = STol) and **9D** (Y = STol), respectively. The stereochemical structures of **4C** and **4D** were given in the similar manner to those of **4A** and **4B**. When i-Pr_2NMgBr was used as a base in the above addition, the diastereomeric ratio of **4** was 0 : 54 : 36 : 10 (92% total yield). Since **4B** was very insoluble in diethyl ether, it was easily isolated in 49% yield by once recrystallization of the reaction mixture from diethyl ether.

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