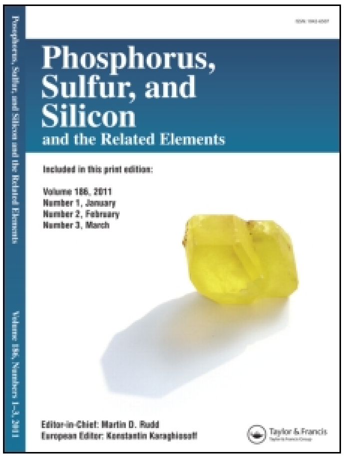

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PARTIAL KINETIC RESOLUTION OF RACEMIC SULFOXIDES BY REDUCTION WITH FORMAMIDINESULFINIC ACID/OPTICALLY ACTIVE AMINE/IODINE REAGENT[1]†

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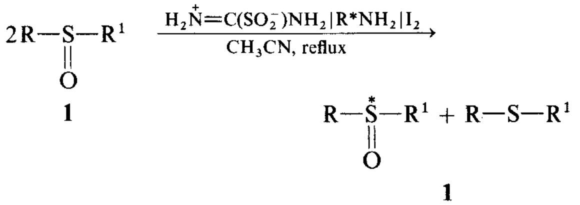
Chiral sulfoxides have been slightly enriched in one enantiomer by partial reduction of racemic mixture with formamidinesulfinic acid/optically active amine asymmetric reducing agent. The influence of steric hindrance on the optical purity of the resolved sulfoxides was observed. No configurational relationship between chirality at the sulfur atom in sulfoxide and carbon atom in optically active amine was found.

Optically active sulfoxides are important intermediates commonly applied in the synthesis and configurational correlation of other classes of chiral sulfur compounds. The majority of optically active sulfoxides of high optical purity have been prepared by means of the reaction of diastereomeric sulfinates[2] or sulfinamides[3] with organometallic reagents. Another approach is based on asymmetric synthesis reactions. These methods of synthesis of optically active sulfoxides were reviewed a few years ago by Morrison and Mosher[4] and continue to be developed.[5] In contrast to many reports on asymmetric oxidation[4,5] there are only few works published reporting an asymmetric induction accompanying the reduction of racemic sulfoxides with optically active reagents.

This approach was first used by Balenovic and Bregant[6] in 1964. The authors found that optically active sulfoxides of low optical purity were formed when racemic mixture was allowed to react with insufficient amount of optically active thiol. A similar asymmetric reaction of chiral sulfoxides with optically active phosphorus thioacids was reported by Mikołajczyk and Pała.[7] Recently an asymmetric reduction of chiral sulfoxides by lithium aluminium hydride complexes with optically active alcohols has been reported from our Laboratory.[8] Here we would like to present a new reductive method of kinetic resolution of racemic sulfoxides in which as the reducing agent an equimolar mixture of optically active amine and formamidine sulfinic acid is used with iodine serving as a catalyst.



$$2R-\underset{\underset{O}{\|}}{S}-R^1 \xrightarrow[CH_3CN,\ \text{reflux}]{H_2\overset{+}{N}=C(SO_2^-)NH_2|R^*NH_2|I_2} R-\underset{\underset{O}{\|}}{\overset{*}{S}}-R^1 + R-S-R^1$$

1 **1**

* means centre of optical activity

Knowing that formamidinesulfinic acid reduces sulfoxides to sulfides in the presence of iodine[9] and at the same time interact with optically active amine, it was conceivable that in the reaction with an excess of chiral sulfoxide should give the unreacted sulfoxide enriched in one of the enantiomers. The results which are presented below confirm this assumption. In the first set of experiments the reduction of sulfoxides **1** used in two-fold molar excess was carried out with formamidinesulfinic acid/(+) α-methylbenzylamine/reagent in the presence of iodine in boiling acetonitrile. After 10 min. the unreduced sulfoxides were isolated and purified by usual methods. The optical rotations, optical purities and absolute configuration of sulfoxides (**1**) obtained by this procedure are given in Table 1.

Inspection of the table reveals that the reduction of sulfoxides **1** was stereospecific in all cases. Although the optical purities of the recovered sulfoxides are relatively low (range between 0.3%

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† Dedicated to Professor Shigeru Oae on the occasion of his 60th birthday.

TABLE I

Asymmetric reduction of sulfoxides **1** by formamidinesulfinic acid|(+) α-methylbenzylamine|iodine reagent[a]

No.	R	R^1	Yield|%|[b]	Sulfoxide recovered $\|\alpha\|_{589}(c)$[c]	 Op.|%|[d] purity	Abs. conf.
1a	Me	n-Pr	38	+1.10 (5.06)	0.80	S
1b	Me	n-Bu	54	+4.94 (5.47)	4.50	S
1c	Me	i-Bu	21	+12.10 (5.13)	8.80	S
1d	Me	Bz[e]	75	+2.64 (5.24)	2.50	S
1e	Me	Ph	64	+4.32 (5.05)	2.90	R
1f	Et	Ph	72	+2.00 (6.25)	1.10	R
1g	i-Pr	Ph	55	+0.57 (7.01)[f]	0.30	R
1h	Me	Tol[e]	75	+2.64 (5.24)	2.50	R

[a] Boiling acetonitrile: 10 min, 1:1:2:0.3 ratio of formamidine sulfinic acid: (+)-α-methylbenzylamine: sulfoxide: iodine.

[b] Based on the weight of isolated sulfoxide.

[c] Rotations were measured in ethanol solution.

[d] Optical purity calculations were based on the following data: $|\alpha|_D = +139.02°$ (ethanol) for (S)-(1a), $|\alpha|_D = +109.9°$ (ethanol) for (S)-(1b), $|\alpha| = +138.0°$ (ethanol) for (S)-(1c) from M. Mikolajczyk, J. Drabowicz, B. Bujnicki, unpublished results; $|\alpha|_D = +106.08°$ (ethanol) for (S)-(1d) from K. Mislow, M. Green, M. Raban, J. Am. Chem. Soc., **87** 2761 (1965); $|\alpha|_D = +149.0°$ (ethanol) for (R)-(1e) from Jacobus, K. Mislow, J. Am. Chem. Soc., **89** 5228 (1967); $|\alpha|_D = +176.92°$ (ethanol) for (R)-(1f) from M. Mikolajczyk, J. Drabowicz, J. Am. Chem. Soc., **100**, 2510 (1978); $|\alpha|_D = +170°$ (acetone) for (R)-(1g) from G. Modena, U. Quintily, G. Scorrano, J. Am. Chem. Soc., **94**, 202 (1972); $|\alpha|_D = +141.0°$ (ethanol) for (R)-(1h) from K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, A. L. Ternay, J. Am. Chem. Soc., **87**, 1958 (1965).

[e] Bz = $C_6H_5CH_2$; Tol = p-$CH_3C_6H_4$.

[f] Rotation was measured in acetone solution.

to 8.8%) they are comparable or better than those obtained by any other known method involving the kinetic resolution procedure. Another advantage of the presented procedure is the use of easily available optically active amine as on asymmetric agent. The data listed in the Table I show further that there is a pronounced relation between the stereospecificity of reduction of sulfoxides and the steric bulk and nature of substituents bound to the chiral sulfur atom. Thus, dialkylsulfoxides (**1a**, **b**, **c** and **d**) recovered after reduction have S configuration whereas the chirality at sulfur in series of arylalkyl sulfoxides (**1e**, **f**, **g**, **h**) is R. It is interesting to note that in the case of sulfoxides (**1a**, **b**, **c**) the increase of the stereospecificity of reduction correlates with the increasing size of alkyl substituents at sulfur whereas in the series of arylalkylsulfoxides (**1e**, **f**, **g**) the stereospecificity is strongly depressed by branching of the alkyl chain in the sulfoxide molecule. In the next step of this study the effect of various optically active amines on the steric course of the reduction of methyl-*i*-butyl sulfoxide (**1c**) was investigated. The results which are listed in Table II indicate that the stereospecificity was the highest when (+)-α-methylbenzylamine was used as an asymmetric agent. The comparison of the absolute configuration of the optically active methyl-*i*-butyl sulfoxide **1** obtained after incomplete reduction clearly shows the complexity of the stereochemical course of the raction studied. Reduction of **1d** by formamidinesulfinic acid in the presence of (+)-α-methylbenzylamine or 1-(−)-(α-naphtyl)-ethylamine having the opposite configuration led to the enrichment of unreacted sulfoxide **1c** in the same (S)-(+)-enantiomer. On the other hand the reagent prepared from (+)-quinidine and (−)-cinchonidine having enantio meric relationship at C_8 and Cg led to the opposite configuration of **1**. Also the reagent prepared from (−)-cinchonidine and (−)-ephedrine, which possess comparable S,R "erythro" configuration at carbon centres gave the unreduced sulfoxide **1c** of the opposite optical rotation. These observations clearly shows that there is no simple way to correlate the chirality at the sulfur atom

TABLE II

Asymmetric reduction of methyl-i-butyl sulfoxide *1c* by formamidinesulfinic acid (optically active amine) iodine reagent[a]

	Sulfoxide *1c* recovered			
Optically active amine	Yield | % |[b]	$\|\alpha\|_{589}$(c)[c]	Op. %[d] purity	Abs. conf.
(+)-α-methylbenzyl	21	+12.10° (5.13)	8.80	S
(+)-N,N-dimethyl-α-methyl benzyl	30	0.0 (6.45)	—	—
1-(−)-α-naphtylethyl	28	+0.62° (4.94)	0.50	S
(−)-myrtanyl	46	+1.40°(5.51)	1.00	S
(+) quinidine	35	−1.50°(4.76)	1.00	R
(−) cinchonidine	32	+2.20° (5.15)	1.60	S
(−) ephedrine	40	+1.92° (4.93)	1.40	S

[a] Boiling acetonitrile, 10 min 1:1:2:0.3 ratio of formamidine-sufinic acid: optically active amine: sulfoxide: iodine.

[b] Based on the weight of sulfoxide isolated.

[c] Optical rotations were measured in ethanol solution.

[d] See Table 1 footnote d.

and carbon atom in the reaction under consideration. It is of interest to note that the reduction was completely nonstereospecific when (+)-N,N-dimethyl-α-methylbenzylamine was used as an asymmetric agent.

EXPERIMENTAL PART

IR spectra were recorded on Perkin-Elmer Infracord 237 Spectrometer for liquid film. ^{1}H-NMR spectra were taken on a Perkin-Elmer R-20 spectrometer in carbon tetrachloride solution with TMS as internal standard. The optical activity measurements were performed on a Perkin-Elmer 24/1 MC photopolarimeter. The following optically active amines were used.
(+)-α-methylbenzylamine $|\alpha|_{589} = +37.3°$ (neat);
(+)-N,N-dimethyl-α-methylbenzylamine $|\alpha|_{589} = +65.3°$ (neat);
(−)-cis-myrtanylamine $|\alpha|$ 589 = +30.5 (neat)
1-(−)-α-(naphtyl)ethylamine $|\alpha|_{589} = -78°$ (neat)
(+) quinidine $|\alpha|_{589} = +238°$ (3.3 ethanol);
(−) cinchonidine $|\alpha|_{589} = -103.7°$ (3.4 ethanol);
(−) ephedrine$|\alpha|_{589} = -5.02$ (7.9 ethanol).

The racemic sulfoxides *1a*-h were prepared by oxidation of the appropriate unsymmetrical sulfide with hydrogen peroxide in acetone solution in the presence of acid as catalyst. Physical properties of sulfoxides were in good agreement with literature data[8,10–12]

Asymmetric reduction of sulfoxides *1a*-h by formamidinesulfinic acid

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|optically active amines| – iodine reagent: General procedure

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A suspension of formamidinesulfinic acid[13] (0.55 g 5 mmol) and iodine (0.2 g 1.5 mmol) in acetonitrile solution (20 ml) of sulfoxide **1** (10 mmol) and optically active amine (5 mmol) was heated at 180°C for 10 min. After cooling the reaction solution was concentrated and the residue was mixed with water (50 ml). The aqueous layer was shaken with hexane to remove the sulfide and optically active amine and then extracted with chloroform (3·25 ml). The chloroform solution was washed successively with aqueous sodium thiosulfate solution, 5% hydrochloric acid solution, 5% sodium carbonate solution, water, and dried over anhydrous magnesium sulfate. Evaporation of the solvent and column chromatography of crude product |silica gel, ether-methylene chloride (1:1) as eluent |yields the pure (TLC, IR, NMR) optically active sulfoxide **1**.

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