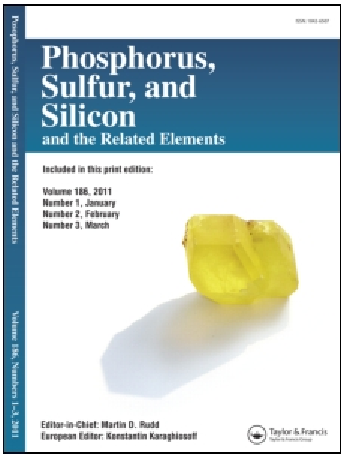

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THE PREPARATION OF OPTICALLY ACTIVE β-KETO SULFOXIDES BY THE REACTION OF α-LITHIOMETHYL p-TOLYL SULFOXIDE WITH ETHYL CARBOXYLATES IN THE PRESENCE OF (—)-SPARTEINE

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Treatment of 2 equivalents of racemic α-lithiomethyl *p*-tolyl sulfoxide (**1**) with ethyl carboxylates (**2**, $C_2H_5O—CO—R$) possessing a variety of groups R in the presence of (−)-sparteine afforded the corresponding optically active β-keto sulfoxides (**3**, p-$CH_3C_6H_4—SO—CH_2—CO—R$) together with optically active methyl *p*-tolyl sulfoxide which has the opposite configuration to **3**.

INTRODUCTION

The optically active β-keto sulfoxide has been known to be an attractive precursor in the asymmetric synthesis of optically active alcohols.[1] During the course of our research concerned with the asymmetric induction by the chiral sulfinyl group, previously, we reported that the reactions of racemic α-lithiated aryl methyl sulfoxides with the chiral electrophiles, menthyl sulfinates[2] and menthyl, bornyl, or 2-octyl carboxylates,[3] displayed the feature of an enantiomer differentiating reaction[4] affording the corresponding optically active β-disulfoxides and β-keto sulfoxides, respectively. Furthermore, as one of a current of stereochemical studies on the electrophilic substitutions of α-lithiosulfoxides, recently, Marquet *et al.*[5] and Biellmann *et al.*[6] have proposed that an electrophilic assistance (a chelation) by the lithium cation on the α-lithiosulfoxides[7] towards the electrophiles plays an important role. On the other hand, it has been reported that the reaction of achiral organometallic reagents with carbonyl compounds in chiral media affords the corresponding optically active alcohols.[8] These findings have allowed us to attempt the preparation of optically active β-keto sulfoxides by the reaction of racemic α-lithiomethyl *p*-toly sulfoxide (**1**) with ordinary ethyl carboxylates (**2**) in the presence of a chiral diamine, (−)-sparteine, which acts as a chiral bidentate ligand.[9]

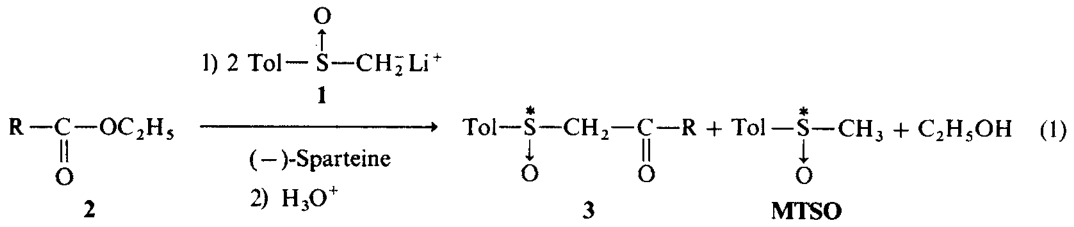
RESULTS AND DISCUSSION

As expected, on treating 2 equivalents of racemic α-lithiomethyl *p*-tolyl sulfoxide (**1**) with ethyl carboxylates (**2**).in tetrahydrofuran (THF) in the presence of (−)-sparteine one of the enantiomeric pair of **1** was found to react with **2** preferentially, affording the corresponding optically active β-keto sulfoxides (**3**) together with optically active methyl *p*-tolyl sulfoxide (**MTSO**) which has the opposite configuration to **3** (Eq. 1, where the star indicates chiral center).

In a typical reaction, when ethyl benzoate (**2g**) (1 mmol) was treated with 2 equivalents of **1** (derived from 2 mmol of racemic **MTSO** and 2 mmol of lithium diethylamide (Et_2NLi)) in the presence of 2 mmol of (−)-sparteine in THF at 0°C, dextrorotatory α-(*p*-tolylsulfinyl)acetophenone (**3g**) ($[\alpha]_D^{25}$ + 15.0° (c 1.00, acetone), 5.6% o.p., (R)-rich) and (S)-(−)-**MTSO** ($[\alpha]_D^{25}$ − 6.9°(c 0.825, acetone), 4.7% o.p.) were produced.

As generally observed, the optical purities for the β-keto sulfoxides (**3**) obtained were found to increase with the increase of the amount of (−)-sparteine added. The dependences of the optical purities for **3b**, **3e**, and **3g** on the amount of (−)-sparteine are illustrated in Table I.

Table II summarized the results of the reactions of several carboxylates (**2a–i**) possessing a variety of groups (R) with **1** using 10 equivalents of (−)-sparteine. The optical purity and the pre-



$$\underset{\mathbf{2}}{R\text{—}C(=O)\text{—}OC_2H_5} \xrightarrow[\text{(−)-Sparteine} \quad 2)\ H_3O^+]{1)\ 2\ Tol\text{—}S(\rightarrow O)\text{—}CH_2^-Li^+\ \mathbf{1}} \underset{\mathbf{3}}{Tol\text{—}\overset{*}{S}(\rightarrow O)\text{—}CH_2\text{—}C(=O)\text{—}R} + \underset{\mathbf{MTSO}}{Tol\text{—}\overset{*}{S}(\rightarrow O)\text{—}CH_3} + C_2H_5OH \quad (1)$$

Tol = p-$CH_3C_6H_4$

2 and **3**

a: R = C_2H_5
b: R = n-C_3H_7
c: R = n-C_9H_{19}
d: R = i-C_3H_7
e: R = t-C_4H_9
f: R = C_6H_{11}
g: R = C_6H_5
h: R = p-$CH_3C_6H_4$
i: R = o-$CH_3C_6H_4$

TABLE I

Reaction of α-lithiomethyl p-tolyl sulfoxide (**1**) (2 mmol)[a] with ethyl carboxylates (**2b**, **2e**, and **2g**) (1 mmol) in the presence of various amounts of (−)-sparteine[b]

(−)-Sparteine (mmol)	Yield (%)	(S)-(−)-**3b** $[\alpha]_D^{25c}$	%o.p.[d]	Yield (%)	(R)-(+)-**3e** $[\alpha]_D^{25c}$	%o.p.[d]	Yield (%)	(R)-(+)-**3g** $[\alpha]_D^{25c}$	%o.p.[d]
0.8							79	+5.5°	2.1
1.0	80	−3.4°	1.3	85	+6.6°	2.5	78	+9.0°	3.4
2.0							78	+15.0°	5.6
4.0	76	−5.7°	2.2	81	+21.5°	8.2	75	+23.2°	8.7
7.3							74	+29.5°	11.1
10.0	72	−9.4°	3.7	78	+34.0°	12.9	74	+34.4°	13.0
15.0							71	+38.0°	14.3
20.0	63	−12.0°	4.7				70	+40.3°	15.2

[a] Derived from racemic **MTSO** (2 mmol) and Et_2NLi (2 mmol).
[b] In THF at 0°C, under stirring for 1 h.
[c] Determined in acetone.
[d] Calculated on the basis of the specfic rotations for the authentic (R)-(+)-β-keto sulfoxides (see footnote **e** of Table II).

dominant configuration of the β-keto sulfoxides (**3**) obtained were confirmed by comparison with the specific rotations for the corresponding authentic (R) – (+)-β-keto sulfoxides[3] (see footnote **e** of Table II).

Table II reveals that the degree of enantioselectivity of this reaction is affected by the nature of the ester moiety R, indicating optical yields ranging from 2.1% to 15.7%. The best result has been obtained from the reaction of **1** with **2h**. The optical yields thus obtained are comparable to those of hitherto reported asymmetric syntheses using (−)-sparteine as the chiral medium.[9b–f,k] The reversal in configuration with the variation in the ester moiety R was also observed. Namely, the esters **2e** (R = t-butyl), **2g** (R = phenyl), **2h** (R = p-tolyl), and **2i** (R = o-tolyl) preferentially reacted with (R)-**1** to yield an excess of (R)-**3**, while the esters **2a** (R = ethyl), **2b** (R = propyl), **2c** (R = nonyl), **2d** (R = isopropyl), and **2f** (R = cyclohexyl) preferentially reacted with (S)-**1** affording (S)-**3** in excess.

Meanwhile, recently, we have found that some of the partially optically pure β-keto sulfoxides increase their optical purities by repeated recrystallizations.[3b] By the use of this recrystallization procedure, highly optically pure (S)-(−)-**3d** and (R)-(+)-**3c** were obtained from the partially

TABLE II

Reaction of α-lithiomethyl *p*-tolyl sulfoxide (**1**) with ethyl carboxylates (**2**) in the presence of (−)-spareine[a]

R—CO—OC$_2$H$_5$		β-Keto sulfoxides (3)			
R:	Base[b]	Yield (%)[c]	$[\alpha]_D^{25d}$	Config.	%o.p.[e]
C$_2$H$_5$ (**2a**)	Et$_2$NLi	**3a** 75	$-5.5^{\circ i}$	S	2.1
n-C$_3$H$_7$ (**2b**)	Et$_2$NLi	**3b** 72	$-9.4^{\circ i}$	S	3.7
	BuLi	68	-7.4°	S	2.9
n-C$_9$H$_{19}$ (**2c**)	Et$_2$NLi	**3c** 75	$-4.8^{\circ j}$	S	2.6
	BuLi	65	-9.1°	S	4.9
i-C$_3$H$_7$ (**2d**)	Et$_2$NLi	**3d** 73	-9.5°	S	3.7
	BuLi	69	$-13.3^{\circ f}$	S	5.2
t-C$_4$H$_9$ (**2e**)	Et$_2$NLi	**3e** 78	$+34.0^{\circ g}$	R	12.9(13.2)[k]
	BuLi	68	$+34.8^{\circ}$	R	13.2
C$_6$H$_{11}$ (**2f**)	Et$_2$NLi	**3f** 70	$-5.5^{\circ j}$	S	2.3
	BuLi	67	-6.8°	S	2.8
C$_6$H$_5$ (**2g**)	Et$_2$NLi	**3g** 74	$+34.4^{\circ h}$	R	13.0
	BuLi	70	$+39.1^{\circ}$	R	14.7
p-CH$_3$C$_6$H$_4$ (**2h**)	Et$_2$NLi	**3h** 70	$+40.5^{\circ j}$	R	15.7
o-CH$_3$C$_6$H$_4$ (**2i**)	Et$_2$NLi	**3i** 65	$+27.2^{\circ i}$	R	10.2

[a] **1** = 2 mmol, **2** = 1 mmol, (−)-sparteine = 10 mmol, in THF at 0°C for 1 h.

[b] Et$_2$NLi = (C$_2$H$_5$)$_2$NLi, BuLi = *n*-C$_4$H$_9$Li.

[c] Yields are based on the starting ethyl carboxylates.

[d] Determined in acetone.

[e] Calculated on the basis of the specific rotations for the corresponding authentic (R)-(+)-β-keto sulfoxides.[3] **3a**; $[\alpha]_D^{23}$ + 265° (c 0.194), **3b**; $[\alpha]_D^{22}$ + 256° (c 0.266), **3c**; $[\alpha]_D^{15}$ + 186.5° (c 0.222), **3d**; $[\alpha]_D^{22}$ + 258° (c 0.196), **3e**; $[\alpha]_D^{25}$ + 263° (c 0.275), **3f**; $[\alpha]_D^{14}$ + 240° (c 0.224), **3g**; $[\alpha]_D^{25}$ + 265.5° (c 0.265), **3h**; $[\alpha]_D^{25}$ + 258.5° (c 0.280), **3i**; $[\alpha]_D^{20}$ = 268° (c 0.320).

[f] The repeated recrystallizations (5 times) from ether-hexane gave a 98.8 %o.p. of (S)-(−)-**3d**, $[\alpha]_D^{25}$ − 255° (acetone), in a 3.8 % yield.

[g] The repeated recrystallizations (4 times) from ether-hexane gave a 99.2 %o.p. of (R)-(+)-**3e**, $[\alpha]_D^{25}$ + 261° (acetone), in an 11.0 % yield.

[h] The repeated recrystallizations (5 times) from ether-hexane gave an 18.5 %o.p. of (+)-**3g**, $[\alpha]_D^{25}$ + 49.0° (acetone).

[i] The optical purity decreased nearly to zero by the repeated recrystallizations from ether or ether-hexane. In this case the crystals obtained from the mother liquid exhibited a larger specific rotation than that of the starting β-keto sulfoxide.

[j] The repeated recrystallizations were not attempted.

[k] Evaluated by NMR using a chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato] europium(III) [Eu(TFC)$_3$]. For *t*-butyl protons, $\Delta\Delta\delta(\Delta\delta_S - \Delta\delta_R)$ = 5.0 Hz (**3e** = 0.1 mol/1, Eu(TFC)$_3$ = 1.0 equiv. in CCl$_4$).

optically pure (−)-**3d** and (+)-**3e** prepared here (see footnotes **f**–**j** of Table II). Therefore, the present method, in combination with the recrystallization procedure, should be applicable to the synthesis of optically active β-keto sulfoxides.

Up to now, several reports have shown that achiral organolithium reagents display an enantioface differentiating reaction[4] towards carbonyl compounds in the presence of (−)-sparteine to yield optically active alcohols through the transition state which consist of a coordinated (−)-sparteine-organolithium complex.[9b,k] In the case of the reaction of ethyl carboxylates (**2**) with α-lithiosulfoxide (**1**) which may be counted as a chiral organolithium reagent,[7] the present results indicate that an enantiomer differentiating reaction takes place in the presence of (−)-sparteine through, perhaps. the transition state including a (−)-sparteine-α-lithiosulfoxide complex. However, further study is necessary before we can obtain any clear understanding of the stereochemical course of the reaction. Additional investigations are in progress.

EXPERIMENTAL

General

The optical rotations were measured with a Jasco DIP-4 type polarimeter. The NMR spectra were determined with a Jeol PS-100 spectrometer.

Starting Materials

Racemic methyl p-tolyl sulfoxide was prepared by the periodate oxidation of methyl *p*-tolyl sulfide;[10] bp 99–100°C/1.5 mmHg, mp 43°C (lit,[11] 42–43°C). *(−)-Sparteine* used here is commercial grade (Nakarai Chemical Ltd., Kyoto), $[\alpha]_D^{30}$ −18.0° (c 5, C_2H_5OH).

Reaction of α-Lithiomethyl p-Tolyl Sulfoxide (**1**) *with Ethyl Carboxylates* (**2**) *in the Presence of* (−)*-Sparteine*

All the reactions listed in Table I and II were carried out according to the following procedure. A 50 ml round-bottomed flask containing a magnetic stirring bar was equipped with a rubber septum and a nitrogen inlet tube. After flushing with dry nitrogen, 10 ml of dry THF, a base (1.3 ml of 100 mg/ml solution of butyllithium in hexane or lithium diethylamide (Et_2NLi) derived from 1.3 ml of 100 mg/ml solution of butyllithium in hexane and 150 mg of diethylamine), a certain amount of (−)-sparteine, and 308 mg (2 mmol) of racemic methyl *p*-tolyl sulfoxide (**MTSO**) were injected successively through the septum via syringe into the flask at 0°C, and the solution was stirred vigorously for 20 minutes. A solution of an ethyl carboxylate (**2**) (1 mmol) in 2 ml of dry THF was injected via syringe, drop by drop to the solution. After 1 h stirring at 0°C, water (5 ml) was added, acidified (ca. pH 3) with 10% hydrochloric acid, and extracted with chloroform (3 × 30 ml). The combined extracts were then washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed using a preparative thin-layer chromatoplate on silica gel. Elution with diethyl ether afforded optically active **MTSO** and an optically active *β*-keto sulfoxide (**3**), and these products were subjected to the optical rotation measurement. The physical properties for all the *β*-keto sulfoxides listed in Tables I and II were found to be identical with those of the authentic *β*-keto sulfoxides prepared in our previous paper.[3b] The optical purity and the predominant configuration of the *β*-keto sulfoxides were assigned by direct comparison with the specific rotations for the corresponding authentic (R)-(+)-*β*-keto sulfoxides[3] (see footnote **e** of Table II). The optical purity of **3e** was further evaluated from the NMR spectrum using a chiral shift reagent $Eu(TFC)_3$ (see footnote **h** of Table II).

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