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A HIGHLY EFFICIENT AND RECYCLABLE CHIRAL DIRECTOR FOR ASYMMETRIC SYNTHESIS OF SULFOXIDES

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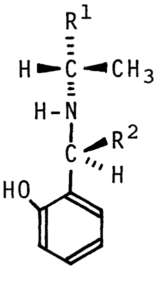
The benzoxathiazine 2-oxide derivatives (2a-f) were prepared by reaction of the aminophenols (1a-f) with thionyl chloride in good yields. Equilibrium of 2a (R^1=α-$C_{10}H_7$, R^2=CH_3) with hydrogen chloride and subsequent reaction with phenylmagnesium bromide followed by action of methyl- or butyllithium gave (S)-(-)-4a or (S)-(-)-4b with high enantiomeric excess, respectively.

In recent years much attention has been devoted to the synthesis of optically active sulfoxides and their synthetic utility in organic synthesis,[1] since Andersen[2] found a useful synthetic way to them with (-)-menthyl sulfinates. Hitherto many other strategies have been devised for the preparation of chiral sulfoxides by means of asymmetric induction with sulfinates[3] or sulfinamides,[4] asymmetric oxidation of sulfides with optically active peracids[5] or micro-organisms,[6] and optical resolution.[7] However these known methods have some limitation for general use and enantiospecificity. Therefore, a more practically useful reagent is required for the efficient preparation of optically active sulfoxides.

We wish to demonstrate herein a potential utility of an easily available optically active aminophenol for this purpose.

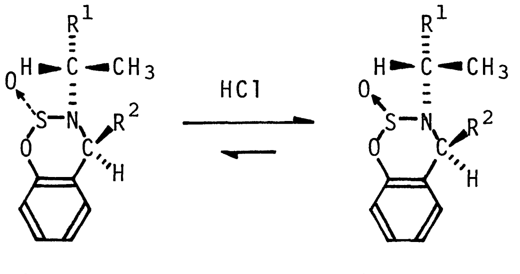
The aminophenol (S,S)-(-)-1a (R^1=α-$C_{10}H_7$, R^2=CH_3),[8] mp 141-142°, prepared without racemization by condensation of (S)-(-)-α-naphthylethylamine and *o*-hydroxyacetophenone followed by $NaBH_4$ reduction (60% yield), was reacted with thionyl chloride (1.5 equivs) in toluene at 0° for 4 h in the presence of triethylamine (5 equivs) to give 4-methyl-3-α-naphthylethyl-1,2,3-benzoxathiazine 2-oxide (2a) (R^1=α-$C_{10}H_7$, R^2=CH_3) (93% yield) in a 2 : 1 ratio of 2a-I (mp 121°) and 2a-II (mp 98-99°), respectively. These structures were confirmed by their nmr and mass spectral analyses, and the analytical data.

It is strikingly attractive that the isomer **2a**-I could easily be epimerized almost completely into **2a**-II upon treatment with 0.032N hydrogen chloride in toluene at 0° for 2 h, giving an equilibrium mixture comprised of 4% **2a**-I and 96% **2a**-II. This result indicates that the isomer **2a**-II might be thermodynamically more stable than the other one **2a**-I,[9] as depicted in the figure below.

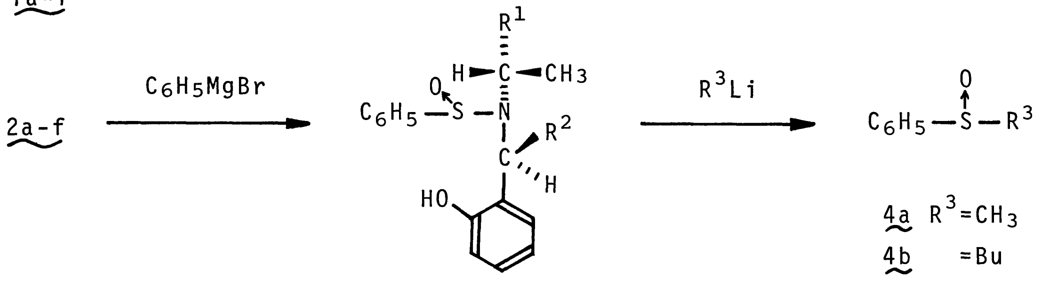


1a-f

a	$R^1=C_{10}H_7(\alpha)$,	$R^2=CH_3$
b	$=C_6H_5$,	$=H$
c	$=C_6H_5$,	$=CH_3$
d	$=C_{10}H_7(\alpha)$,	$=H$
e	$=C_{10}H_7(\alpha)$,	$=CH_2CH_3$
f	$=C_{10}H_7(\alpha)$,	$=Bu$



2a-f-I **2a-f**-II



3a-f

4a $R^3=CH_3$
4b $=Bu$

The crude product (**2a**) obtained above, containing a 2 : 1 mixture of **2a**-I and **2a**-II, was reacted with phenylmagnesium bromide at -78° for 2 h followed by addition of methyl- or butyllithium (-78°, 2 h in THF) to afford (R)-(+)-methyl phenyl sulfoxide (**4a**)[10] or (R)-(+)-butyl phenyl sulfoxide (**4b**)[11] in 42 or 41% yield from **1a** used with 33 or 32% enantiomeric excess, respectively.

However, the crude product (**2a**) was treated with 0.032N hydrogen chloride in toluene at 0° for 2 h accompanied by the same sequence (phenylmagnesium bromide, -78° 2 h and methyl- or butyllithium, -78° 2 h) to produce (S)-(-)-**4a** or (S)-(-)-**4b** in 42 or 40% yield from **1a** employed with extremely high enantiomeric excess (75 or 81%), respectively.

In the reaction of **1a** with excess thionyl chloride (3 equivs) in the presence of triethylamine (5 equivs), the direct equilibrium transformation of **2a**-I into **2a**-II could be accomplished during this reaction, presumably by the effect of hydrogen chloride generated by hydrolysis of excess thionyl chloride.

The results obtained by these sequences under various reaction conditions

Table I Asymmetric Synthesis of 4a with (S,S)-(-)-1a

Reaction Conditions for Preparation of 2a[a]				Product 4a		
$SOCl_2$ (equivs)	Et_3N (equivs)	Solvent	Yield of 4a[b] (%)	$[\alpha]_D$ (EtOH)[c] (Absolute Confign.)		Optical Yield[10] (%)
1.5	3.6-5.0	Toluene	42	+48.6°	(R)	33[d]
1.5	5.0	Toluene	42	-111.0°	(S)	75[e]
3.0	5.0	Toluene	43	-106.6°	(S)	72[d]
3.0	5.0	THF	46	-84.5°	(S)	57[d]
3.0	5.0	DME	45	-86.6°	(S)	58[d]
3.0	5.0	$CHCl_3$	36	-91.1°	(S)	61[d]
3.0	5.0	CCl_4	35	-96.0°	(S)	64[d]

a. Reacted at 0° for 4 h. b. Based on 1a used. c. Measured at 18-26°. d. Without treatment with hydrogen chloride. e. Treated with 0.032N hydrogen chloride in toluene at 0° for 2 h in the preparation of 2a.

are listed in Table I. It is definite, as shown in the Table, that the sulfoxide 4a originated from 2a formed by the reaction of 1a with thionyl chloride (3 equivs)-triethylamine (5 equivs) showed the higher optical purity than that from 1a with thionyl chloride (1.5 equivs)-triethylamine (5 equivs).

Furthermore, it should be remarked that toluene is the most effective solvent on this asymmetric synthesis among the several solvents examined for the preparation of 2a. The starting aminophenol (S,S)-(-)-1a could be recyclable in these asymmetric syntheses, since it was recovered without any racemization with high efficiency (87% recovered yield).

The results with the aminophenol derivatives (1b-f) bearing other substituents are summarized in Table II. It should be noted, on the contrary of our expectations, that the substituents R^2 in 1a, 1e, and 1f affected the asymmetric induction by the degree of their decreasing steric bulkiness.

Thus, the readily available optically active aminophenol (S,S)-(-)-1a affording consistently high enantiospecificity can serve as a highly efficient and recyclable chiral director for the asymmetric synthesis of sulfoxides.

Improvement and further development by variation of alkyl groups in sulfoxides and their use in organic synthesis are in progress.

References and Notes

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Table II Asymmetric Synthesis of 4a,b with 1b-f [a]

1	R^1	R^2	R^3	Product Yield of 4a,b [b] (%)	(S)-(-)-4a,b $[\alpha]_D$ [c]	Optical Yield[10,11] (%)
b	C_6H_5	H	CH_3	44 [d]	-26.2° [f]	18
b	C_6H_5	H	Bu	49 [d]	-24.1° [g]	15
c	C_6H_5	CH_3	CH_3	45 [d]	-24.6° [f]	17
d	α-$C_{10}H_7$	H	CH_3	44 [d]	-49.7° [f]	33
d	α-$C_{10}H_7$	H	Bu	53 [e]	-42.9° [g]	27
e	α-$C_{10}H_7$	CH_2CH_3	CH_3	48 [d]	-66.9° [f]	45
f	α-$C_{10}H_7$	Bu	CH_3	26 [d]	-35.0° [f]	23

a. The compounds 2b-f were prepared by the reaction of 1b-f with thionyl chloride (3 equivs)-triethylamine (5 equivs) at 0° for 4 h. b. Based on 1b-f used. c. Measured at 17-25°. d. Toluene was used as a solvent for the formation of 2b-f. e. THF was used as a solvent for 2b-f. f. Measured in EtOH. g. Measured in MeOH.

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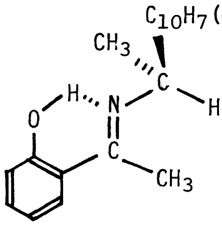

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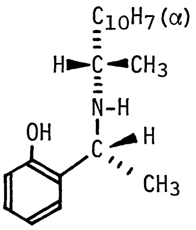

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