Optically Active 2-(Arylsulfinylmethyl)-oxazolines, Chiral Enol Acetate Equivalents in Aldol-Type Condensations

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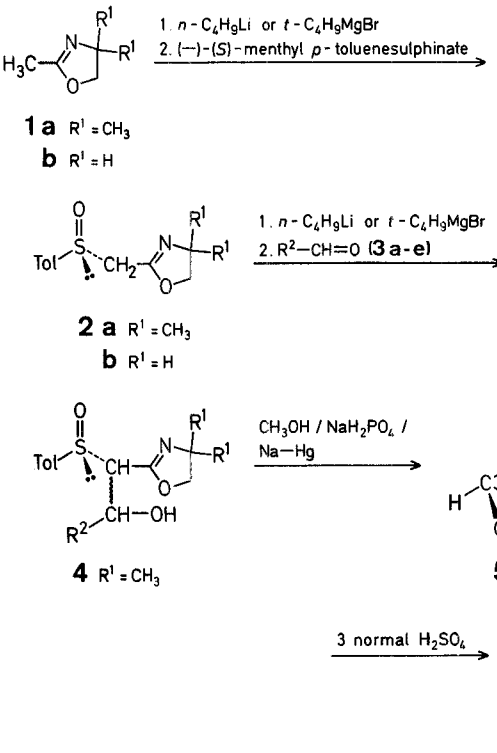
In the last few years efficient asymmetric carbon-carbon bond formations have been accomplished through a variety of chiral synthons. In the field of stereoselective alkylation, one of the more successful approaches involves the use of oxazolines[1,2]. However, these systems are only moderately effective as chiral enol acetate equivalents[3,4], unless boron enolates[5] are employed.

Optically active α-sulfinyl-hydrazones[6] and -esters[7] give good to excellent degrees of stereoselection in aldol-type reactions. We now report on the preparation of stereochemically homogeneous 2-(arylsulfinylmethyl)-oxazolines and their behaviour in asymmetric condensations with aldehydes. Reaction of metallated 2-methyloxazolines **1** with (−)-(*S*)-menthyl *p*-toluenesulfinate[7] afforded the title compounds **2a** and **2b** in 83% and 67% yields, respectively. On the basis of the reasonable assumption that this Andersen-type synthesis proceeds with inversion of chirality at the sulfinyl sulfur atom[7], the absolute configuration (*R*) can be assigned to compounds **2.** Their enantiomeric purity was shown to be ⩾97% by ^{1}H-N.M.R. analysis with the aid of the chiral shift reagent Eu(hfc)$_3$.

Metallation of compound **2a** and subsequent addition of aldehydes **3** afforded adducts **4** which were desulfurized[6] to give hydroxyalkyloxazolines **5** (Table).



3-6	a	b	c	d	e
R^2	CH_3	n-C_3H_7	i-C_4H_9	i-C_3H_7	t-C_4H_9

To confirm the extent of stereoselectivity, to demonstrate the sense of enantioface differentiation, and to widen the synthetic scope of the reaction, compounds **5** were hydrolyzed[1] to the corresponding β-hydroxy acids **6.** The optical purity and absolute configuration of the latter (as such or as methyl esters) are known in some instances[3,8].

Good enantioselectivities are generally achieved from the lithium-azaenolates deriving from (*R*)-**2a,** independently on the nature of aldehyde R^2 group, unless the latter is sterically very demanding (Table). It must be noted that lithium enolates of chiral acetate equivalents are usually rather poorly stereoselective[3,9], and only on switching to boron enolates does the chiral discrimination dramatically increase[5,8].

In our case, the use of a more chelating and bulky counterion, such as magnesium bromide, leads to a decrease of optical yields (Table)[10]. Best results are obtained by working with *n*-butyllithium at −90°C with a condensation time of 3 h. The addition of hexamethylphosphoric triamide, or the use of lithium diisopropylamide as base gave only minor variations on both chemical and enantiomeric yields.

As mentioned above, compounds **5** can be quantitatively converted by acid hydrolysis into the corresponding β-hydroxy acids **6,** thus overall yields are satisfactory (60–85% in three steps). Moreover, sulfoxides **2** can be prepared in large quantities and (−)-menthol, the real source of chirality in (−)-(*S*)-menthyl *p*-toluenesulfinate can be recovered and recycled.

Table. Optically Active Hydroxyalkyloxazolines **5** prepared by Asymmetric Synthesis

Product No.	Reaction conditions for metallation			Reaction conditions for condensation		Yield [%]	$[\alpha]_D^{25}$ [a]	e.e.[b] [%]	Absolute configuration[c]	n_D^{26}	Molecular formula[d]
	Base	time [h]	temp. [°C]	time [h]	temp. [°C]						
5a	*n*-C_4H_9Li	0.5	−90°	3	−90°	60	−14.4°	53	*R*	1.4601	$C_8H_{15}NO_2$ (157.2)
	n-C_4H_9Li	0.5	−90°	0.05	−90°	63	−14.3°	53	*R*	—	—
	n-C_4H_9Li	0.5	−78°	0.05	−78°	65	− 6.6°	24	*R*	—	—
5b	*n*-C_4H_9Li	0.5	−90°	3	−90°	76	−12.1°	36	*R*	1.4567	$C_{10}H_{19}NO_2$ (185.2)
5c	*n*-C_4H_9Li	0.5	−90°	3	−90°	68	−13.6°	48	—	1.4541	$C_{11}H_{21}NO_2$ (199.3)
5d	*n*-C_4H_9Li	0.5	−90°	3	−90°	78	−20.1°	48	*S*	1.4539	$C_{10}H_{19}NO_2$ (185.2)
	n-C_4H_9Li	0.5	−90°	0.05	−90°	85	−17.6°	42	*S*	—	—
	t-C_4H_9MgBr	1.5	−78°	3	−78°	60	−14.0°	34	*S*	—	—
	t-C_4H_9MgBr	1.5	−78°	20	−78°	62	− 9.3°	22	*S*	—	—
5e	*n*-C_4H_9Li	0.5	−90°	3	−90°	84	−13.2°	26	—	1.4522	$C_{11}H_{21}NO_2$ (199.3)
	t-C_4H_9MgBr	1.5	−78°	3	−78°	60	−10.4°	21	—	—	—

[a] *c* 1, in chloroform.
[b] Enantiomeric excess.
[c] As determined by conversion to the corresponding acid or methyl ester.
[d] Satisfactory microanalyses obtained: C, ±0.2; H, ±0.12; N, ±0.06.

2,4,4-Trimethyl-2-oxazoline **(2a)** is commercially available and 2-methyloxazoline **(2b)** is prepared according to Ref.[11]; b.p. 110–112°C (Ref.[12]; b.p. 109.5–110.5°C).

(*R*)-(4-Methylphenylsulfinylmethyl)-4,4-dimethyl-2-oxazoline 2a; Typical Procedure:

To a stirred solution of diisopropylamine (11.4 ml, 80 mmol) in dry tetrahydrofuran (150 ml) cooled at −78°C, a 1.35 normal solution of *n*-butyllithium in hexane (59 ml) is added and the temperature allowed to reach 0°C. The mixture is then cooled to −78°C and 2,4,4-trimethyl-2-oxazoline (**1a**; 9.6 ml, 85 mmol) in dry tetrahydrofuran (100 ml) is added dropwise. The solution is stirred for 1 h and then a solution of (−)-(*S*)-menthyl *p*-toluenesulfinate (11.8 g, 40 mmol) in dry tetrahydrofuran (100 ml) is added and stirring is continued at −78°C for 1.5 h. The reaction is quenched with saturated ammonium chloride solution (100 ml) and the organic phase separated. The aqueous phase is extracted with dichloromethane (2 × 50 ml). The organic extract is dried with sodium sulfate and evaporated in vacuo. The solid residue is recrystallized from 1:1 cyclohexane/diisopropyl ether to afford **2a** (6.58 g). The mother liquors are concentrated in vacuo and chromatographed on silica gel (petroleum ether/ether 70/30, then ether/methanol 95/5 as eluents), to give further quantities of **2a** (1.71 g); total yield: 8.29 g (83%); m.p. 93°C; $[\alpha]_D^{25}$: −63.7° (*c* 0.5, chloroform).

$C_{13}H_{17}NO_2S$	calc.	C 62.13	H 6.81	N 5.57
(251.3)	found	62.20	6.83	5.52

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.2$ [s, 6H, $C(CH_3)_2$]; 2.45 (s, 3H, Ar—CH_3); 3.73 (2H, AB system, CH_2—SO); 3.91 (s, 2H, CH_2—O); 7.25–7.65 ppm (m, 4H_{arom}).

Compound **2b** is prepared in an analogous manner as described above; yield: 67%; m.p. 112°C (diisopropyl ether); $[\alpha]_D^{25}$: 149.0° (*c* 0.5, chloroform).

$C_{11}H_{13}NO_2S$	calc.	C 59.18	H 5.86	N 6.28
(223.2)	found	59.09	5.91	6.22

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2.41$ (s, 3H, Ar—CH_3); 3.50–4.40 (m, 2H, CH_2—SO, CH_2—O, CH_2—N); 7.25–7.68 ppm (m, 4H_{arom}).

Hydroxyalkyloxazolines 5; General Procedure:

To a cooled, stirred solution of (−)-(*R*)-**2a** (502 mg, 2 mmol) in dry tetrahydrofuran (40 ml) a 1.35 normal solution of butyllithium in hexane (1.63 ml) is added dropwise. After 30 min stirring, the aldehyde **3** (4.4 mmol) is added and the mixture stirred for the appropriate time (see Table). The reaction is quenched with saturated ammonium chloride solution (5 ml) and the organic phase separated. The aqueous layer is extracted with dichloromethane (2 × 15 ml), the combined organic phases are dried with sodium sulfate, and concentrated in vacuo. The crude residue is taken into dry methanol (30 ml) and anhydrous sodium dihydrogen phosphate (2.4 g) is added. To the resulting slurry, cooled at −15°C, 8% sodium amalgam (3.0 g) is added in one portion. The mixture is stirred for 1 h at −15°C, then filtered, diluted with diethyl ether (20 ml) and finally saturated ammonium chloride solution (10 ml) is added. The organic solvents are evaporated in vacuo and the residue is extracted with dichloromethane (2 × 30 ml). The organic phase is dried with sodium sulfate and concentrated to give a crude product which is purified by column chromatography on silica gel (petroleum ether/ether 80/20, then 30/70 as eluents) to give pure hydroxyalkyloxazolines **5** (Table).

Hydrolysis of Hydroxyalkyloxazolines 5 to β-Hydroxy Acids 6; General Procedure:

A solution of hydroxyalkyloxazoline **5** (1 mmol) in 3 normal sulfuric acid (8 ml) is stirred at 80°C for 1.5 h. The mixture is cooled to room temperature and extracted with diethyl ether (5 × 10 ml). The combined organic phases are dried with sodium sulfate and concentrated in vacuo to give the corresponding β-hydroxy acid **6** in quantitative yield and in good purity. The known β-hydroxy acids **6** are identified by comparison of physical and spectral data with those of authentic samples.

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[1] A. I. Meyers, *Acc. Chem. Res.* **11**, 375 (1978).
[2] A. I. Meyers, E. S. Snyder, J. J. H. Ackerman, *J. Am. Chem. Soc.* **100**, 8186 (1978).
A. I. Meyers, Y. Yamamoto, E. D. Mihelich, R. A. Bell, *J. Org. Chem.* **45**, 2792 (1980).
[3] A. I. Meyers, G. Knaus, *Tetrahedron Lett.* **1974**, 1333.
[4] More efficient aldol-type condensations are obtained if oxazoline propionate equivalents are employed: A. I. Meyers, P. J. Reider, *J. Am. Chem. Soc.* **101**, 2501 (1979).
[5] A. I. Meyers, Y. Yamamoto, *J. Am. Chem. Soc.* **103**, 4278 (1981).
[6] L. Colombo et al., *J. C. S. Chem. Commun.* **1983**, 403.
[7] G. Solladié, *Synthesis* **1981**, 185, and references therein.
[8] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **103**, 2127 (1981).
[9] D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **13**, 1 (1982).
[10] For a related example in which magnesium enolates are very efficient see Ref. [7].
[11] A. I. Meyers, G. Knaus, K. Kamata, M. E. Ford, *J. Am. Chem. Soc.* **98**, 567 (1976).
[12] S. Gabriel, G. Eschenbach, *Ber. Dtsch. Chem. Ges.* **30**, 2495 (1897).