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Kinetic Resolutions in *Anti* Aldol Reactions with Racemic 2-Phenylthio Aldehydes: Asymmetric Synthesis of Cyclic Ethers and Lactones with Phenylthio Migration

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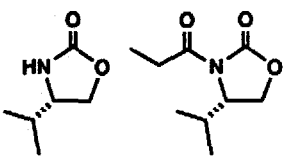
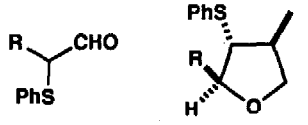
Abstract: *Kinetic resolutions in Lewis acid catalysed asymmetric* anti *aldol reactions of the boron enolate of imide* (2) *with racemic 2-phenylthio aldehydes (3a) - (3c) give good yields of* anti,anti *aldols (7). Synthesis of homochiral cyclic ethers (4a) - (4c) and (5a) - (5c), and a simple novel route to homochiral lactones (6a) - (6c) are described.*

Many natural products such as polyether antibiotics[1] and pheromones[2] contain cyclic ether or lactone sub-units. Stereo-controlled asymmetric synthesis of these heterocycles has attracted a great deal of research effort in recent years.[3,4] As part of our continuing programme of developing coupled stereo-controlled asymmetric aldol reactions and phenylthio migration,[5] we report the extension of our method to the synthesis of homochiral cyclic ethers (**4a**)-(**5c**) and lactones (**6a**)-(**6c**). These are derived from open chain 2-phenylthio aldehydes by kinetic resolution during the Lewis acid-catalysed asymmetric *anti* aldol reaction of imide (2) pioneered by Heathcock.[6]

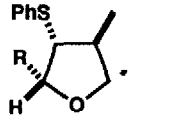


(1) (2)

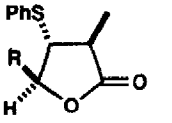


R = Et, (3a)
R = n-Pr, (3b)
R = i-Pr, (3c)

R = Et, (4a)
R = n-Pr, (4b)
R = i-Pr, (4c)



R = Et, (5a)
R = n-Pr, (5b)
R = i-Pr, (5c)



R = Et, (6a)
R = n-Pr, (6b)
R = i-Pr, (6c)

There were few general routes to asymmetric *anti* aldols until methods based on familiar chiral auxiliaries used in unfamiliar ways began to emerge in recent years.[7] Heathcock's Lewis acid-catalysed reactions of boron enolates from imide (**2**) of Evans's valine-derived chiral auxiliary (**1**) looked particularly promising as his initial studies on 3-arylthiopropenals revealed that the sulphur atom and the aromatic ring played a role in the developing stereoselectivities,[8] and both features are present in the 2-phenylthio aldehydes (**3a**)-(**3c**) we wished to use. Work on racemic compounds suggested[9] that aldol reactions on aldehydes (**3**) would lead mainly to products with the PhS and OH groups *anti* by Felkin control regardless of the stereochemistry of the aldol process itself (Me and OH *syn* or *anti*). In the event, condensation of the boron enolate of the Evans imide (**2**)[10] with racemic 2-phenylthio aldehydes[11] (**3a**) - (**3c**) in the presence of Et_2AlCl gave *anti* aldols (**7**) and (**8**) with good *anti* stereoselectivity depending on the amount of aldehyde and Et_2AlCl used, as expected from Heathcock's work,[6] scheme 1 and table 1. The major *anti* aldol products were easily separable by column chromatography except for entries 3 and 6. The absolute configuration at the 3-hydroxy position is assumed from previous work.[6,10]

Scheme 1: Kinetic Resolution in the *anti* Aldol Reaction

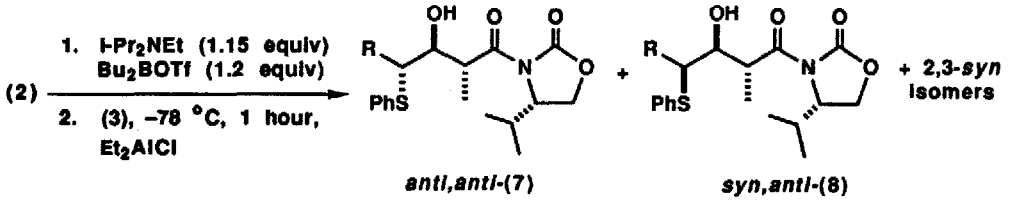


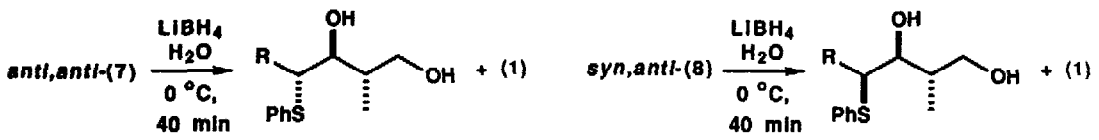
Table 1: *Anti* Aldol Reactions of (2) with 2-phenylthio aldehydes (3)

Entry	R	Equivalents (3)	Equivalents Et_2AlCl	Aldol Ratio[a] *anti*[b]:*syn*	Felkin Ratio[a] (7):(8)	Yield[c] (7) %	Yield[c] (8) %
1	Et	1.5	3.0	89:11	58:31	54	15
2	n-Pr	1.5	3.0	88:12	66:22	52	19
3	i-Pr	1.5	3.0	81:19	62:19	d	d
4	Et	2.0	4.0	>97:3	75:25	63	16
5	n-Pr	2.0	4.0	99.4:0.6	85.4:14.0	75	6
6	i-Pr	2.0	4.0	96:4	89:7	d	d

[a]Ratios determined by HPLC. [b]Total (7) + (8). [c]Yield of purified aldol product. [d]*Anti/syn* aldols inseparable, yield not determined

The high reactivity of 2-phenylthio aldehydes (3a) - (3c) in the aldol reactions of scheme 1 is notable: the reactions were normally complete after 1h at –78 °C. Increasing the amount of aldehyde and Et_2AlCl gave improved *anti/syn* aldol (2,3) ratios and the bonus of improved Felkin (3,4-*anti*) ratios. This kinetic resolution presumably means that the faster reacting enantiomer of the 2-phenylthio aldehydes (3a) - (3c) fits better with the enolate in the Felkin transition state (PhS *anti* to OH) for the aldol reaction.[9] We determined the enantiomeric excess of recovered aldehyde (3c) (20% e.e.) with the chiral lanthanide shift reagent, $Eu(hfc)_3$. Our attempts to prepare optically active 2-phenylthio aldehydes had revealed the sensitivity of (3a) and (3b) to racemisation under basic conditions, so the less reactive enantiomer of (3) may be racemising under the reaction conditions. The 2,3-*anti* relative stereochemistry of aldol products (7) and (8) was confirmed by successful cyclisations to the ethers (4a) - (5c) and the lactones (6a) - (6c), schemes 3 and 4, as secondary to secondary phenylthio migration takes place only from 2,3-*anti* aldols.[12] The 3,4 relative stereochemistry was confirmed by clean reduction to the diols (9) and (10) (scheme 2) and by NMR comparison with the known (R = Et) racemic diols.[9]

Scheme 2: Reduction of Aldols



(9a); R = Et, 79%, >98% e.e.
(9b); R = n-Pr, 73%, >98% e.e.
(9c); R = i-Pr,[13a] >98% e.e.

(10a); R = Et, 74%,[13b]
(10b); R = n-Pr, 69%,[13b]
(10c); R = i-Pr,[13a] >98% e.e.

The enantiomeric excesses of the diols (9) and (10c) were determined by ^1H (250 MHz) and ^{19}F (235 MHz) NMR analysis of Mosher esters[14] prepared from both racemic[15] and homochiral diols. Stereospecific

cyclisation of diols (**9a**) - (**10c**) via the episulphonium ion under our usual conditions[9] gave cyclic ethers (**4a**) - (**5c**) in good yields and enantiomeric excesses with inversion of configuration at both the migration origin and terminus (scheme 3 and table 2).

Scheme 3: Synthesis of Cyclic Ethers

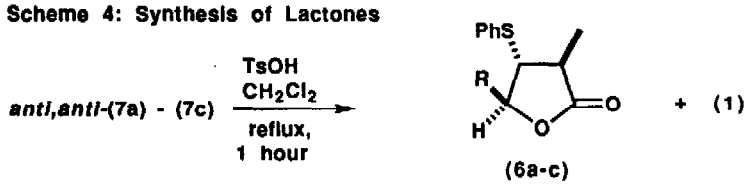
Table 2: Cyclisation of Homochiral Diols (**9a**)-(**10c**) to Cyclic Ethers (**4a**)-(**5c**)

		Cyclic Ether			
Entry	Diol	Compound	Yield (%)	e.e.[a] (%)	$[\alpha]_D^{20}$
1	(**9a**)	(**4a**)	85	>98	–12.3° ($CHCl_3$, c = 0.97)
2	(**9b**)	(**4b**)	90	>98	–1.3° ($CHCl_3$, c = 1.1)
3	(**9c**)	(**4c**)	84	>98	–275° ($CHCl_3$, c = 0.20)
4	(**10a**)	(**5a**)	91	b	+95° ($CHCl_3$, c = 0.63)
5	(**10b**)	(**5b**)	84	b	+13.9° ($CHCl_3$, c = 1.1)
6	(**10c**)	(**5c**)	86	>98	+42° ($CHCl_3$, c = 1.2)

[a]Determined by ^1H NMR (250 MHz) using the chiral lanthanide shift reagent,[16] Eu(hfc)3, on both racemic[17] and homochiral cyclic ethers. [b]Not determined but assumed to be >98 %.

γ-Lactones (**6a**) - (**6c**) were made in moderate to good yields with excellent enantiomeric excesses by simply refluxing the aldol products with TsOH (5.0 equiv) in dichloromethane. Previous attempts to cyclise aldol products directly have usually given allyl sulphides as the major products,[18] but here the lactones are formed in high yields and the chiral auxiliary (**1**) is recovered in good yield under these non-destructive conditions and is reusable.

Scheme 4: Synthesis of Lactones



(6a); R = Et, 69%, >98% e.e., $[\alpha]_D^{20}$ –46.6° ($CHCl_3$, c = 0.1)
(6b); R = n-Pr, 74%, >98% e.e., $[\alpha]_D^{20}$ –23.5° ($CHCl_3$, c = 1.0)
(6c); R = i-Pr,[13a] >98% e.e., $[\alpha]_D^{20}$ –7.8° ($CHCl_3$, c = 0.6)

The enantiomeric excesses of the γ-lactones (**6a**) - (**6c**) were determined by ^1H NMR (250 MHz) using Pirkle's reagent, (S)-2,2,2-trifluoromethyl-1-(9-anthryl)ethanol[19] on both racemic[20] and homochiral γ-lactones.

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11. The racemic 2-phenylthio aldehydes were prepared in good yields from silyl enol ethers by sulphenylation.
12. This is because the phenylthio group then develops an *anti* relationship with the methyl group as it migrates. No cyclisation is observed if the phenylthio group is forced to migrate *syn* to the methyl group: see ref. 9.
13. (a) Yields not determined. Diols (**9c**) and (**10c**) were easily separable by column chromatography although minor diol (**10c**) was contaminated with the 2,3-*syn* diols (b) e.e. not determined, probably >98%.
14. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.*, **1969**, *34*, 2543-2549.
15. The racemic diols were prepared by reduction of the major racemic *anti* aldol products from the aldol reaction of the lithium enolate of Heathcock's 2,6-dimethylphenyl propionate ester with 2-phenylthio aldehydes (**3a**)-(**3c**), ref. 9.
16. Unlike the spirocyclic compounds, which gave useful signal splittings from the racemic spirocyclic ethers, thus enabling e.e. determinations with Pirkle's chiral solvating alcohols (5 molar excess) (ref. 5), no signal splittings were observed with racemic cyclic ethers in this study even with a 20 molar excess of Pirkle's alcohol. $Eu(hfc)_3$ Gave very useful signal splittings without any serious broadening.
17. The racemic cyclic ethers were prepared by cyclisation of racemic diols (note 15).
18. Aggarwal, V. K.; Coldham, I.; McIntyre, S.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 451-460.
19. Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.*, **1977**, 42, 384-387.
20. Racemic γ-lactones were prepared from racemic aldol products (note 15).

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