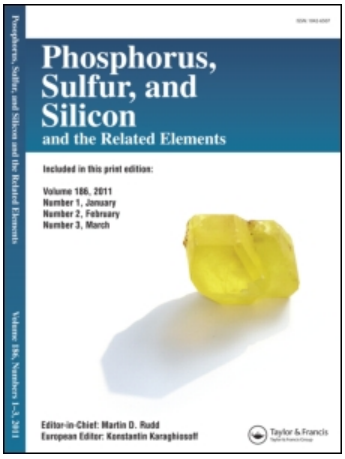

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Kinetic Resolutions in Anti Aldol Reactions: Asymmetric Synthesis of Heterocycles with Phenylthio Migration

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To cite this Article Chibale, Kelly and Warren, Stuart(1993) 'Kinetic Resolutions in Anti Aldol Reactions: Asymmetric Synthesis of Heterocycles with Phenylthio Migration', Phosphorus, Sulfur, and Silicon and the Related Elements, 74: 1, 401 — 402
To link to this Article: DOI: 10.1080/10426509308038135
URL: http://dx.doi.org/10.1080/10426509308038135

Phosphorus, Sulfur, and Silicon, 1993, Vol. 74, pp. 401–402
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KINETIC RESOLUTIONS IN ANTI ALDOL REACTIONS: ASYMMETRIC SYNTHESIS OF HETEROCYCLES WITH PHENYLTHIO MIGRATION

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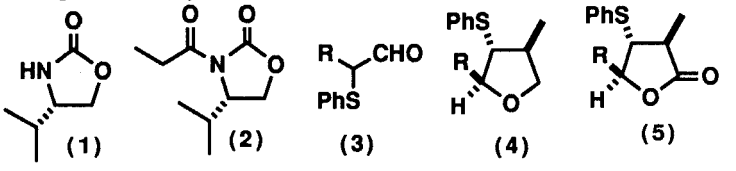
Abstract Kinetic resolutions in Lewis acid catalysed asymmetric *anti* aldol reactions of the boron enolate of imide (**2**) with racemic 2-phenylthio aldehydes (**3**) give good yields of Felkin anti,anti aldols (**6**). The synthesis of homochiral cyclic ethers (**4**) and a simple novel route to homochiral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

INTRODUCTION

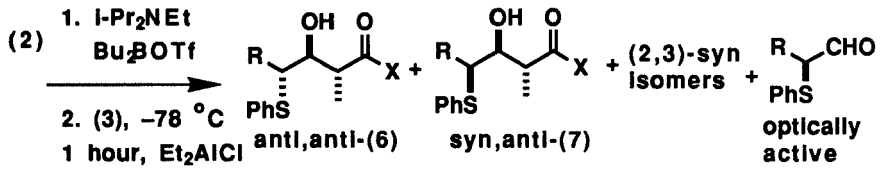
In continuing with the development of coupled stereocontrolled asymmetric aldol reactions and stereospecific phenylthio migrations via asymmetric episulphonium ions in the synthesis of optically active heterocyclic compounds, we report the extension of our method[1] to the synthesis of homochiral cyclic ethers (**4**) and lactones (**5**). The homochiral starting materials are derived from open chain 2-phenylthio aldehydes (**3**) by kinetic resolution during the Lewis acid-catalysed asymmetric *anti* aldol reaction of the Evans imide (**2**) pioneered by Heathcock.[2]



(1) (2) (3) (4) (5)

Condensation of the boron enolate of the Evans imide (**2**) from the valine-derived chiral auxiliary (**1**) with the racemic 2-phenylthio aldehydes (**3**) in the presence of Et_2AlCl gave predominantly the Felkin anti,anti aldol (**6**) and the non-Felkin syn,anti aldol (**7**) depending on the amount of aldehyde and Et_2AlCl used, as expected from Heathock's work, scheme 1.

Scheme 1: Kinetic Resolution in the *anti* Aldol Reaction (X = Chiral auxiliary)

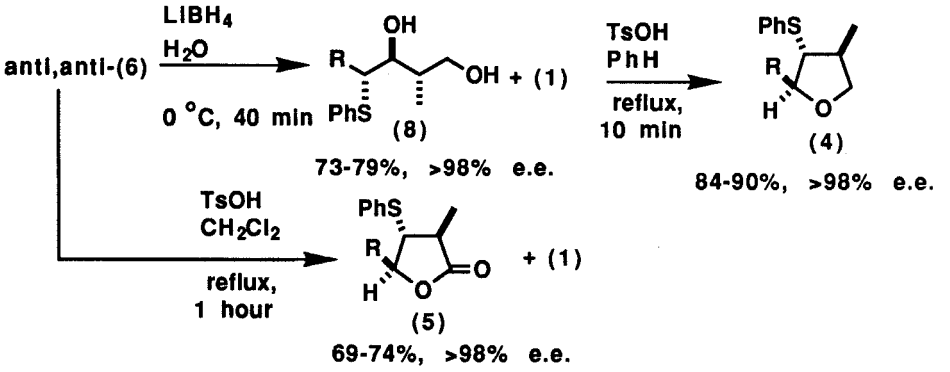


(3), 1.5 equiv; Et_2AlCl (3.0 equiv):
anti*:*syn 81:19 (R = i-Pr) to 89:11 (R = Et)
(6):(7) 58:31 (R = Et, 54% yield of (6)) to 66:22 (R = n-Pr, 52% yield of (6))

(3), 2.0 equiv; Et_2AlCl (4.0 equiv):
anti*:*syn 96:4 (R = i-Pr) to >97:3 (R = Et)
(6):(7) 75:25 (R = Et, 63% of (6)) to 85.4:14.0 (R = n-Pr, 75% yield of (6))

The (2,3) *anti/syn* and the Felkin (3,4-*anti*) ratios improve with increases in the amount of aldehyde and Et_2AlCl. The *anti* aldol product (**6**) was easily separable by column chromatography and used in the transformations depicted in scheme 2. Reduction to the diols (**8**) and subsquent stereospecific cyclisation via an asymmetric episulphonium ion under our usual conditions[1] gave cyclic ethers (**4**) in high yields and excellent e.e.s, along with the recovered chiral auxiliary (**1**). By simply refluxing the aldol products (**6**), lactones (**5**) were obtained in good yields and excellent e.e.s. The chiral auxiliary (**1**) is recovered under these non-destructive conditions and is reusable.

Scheme 2: Synthesis of Cyclic Ethers and Lactones



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2. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.*, **1991**, *56*, 5747-5750.