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

Kelly Chibale<sup>a</sup>; Stuart Warren<sup>a</sup>

<sup>a</sup> University Chemical Laboratories, Cambridge, UK

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## KINETIC RESOLUTIONS IN ANTI ALDOL REACTIONS: ASYMMETRIC SYNTHESIS OF HETEROCYCLES WITH PHENYLTHIO MIGRATION

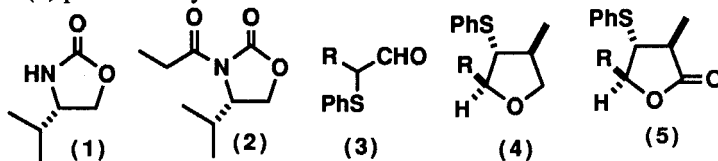
KELLY CHIBALE AND STUART WARREN

University Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW, UK.

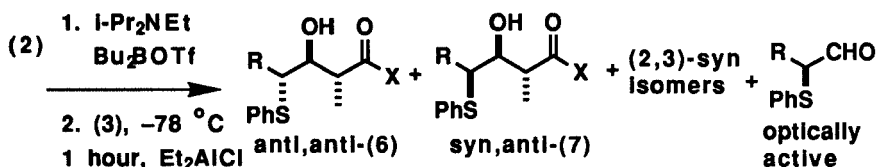
**Abstract** Kinetic resolutions in Lewis acid catalysed asymmetric *anti* aldol reactions of the boron enolate of imide (2) with racemic 2-phenylthio aldehydes (3) give good yields of Felkin anti,anti aldols (6). The synthesis of homochiral cyclic ethers (4) and a simple novel route to homochiral lactones (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<sup>1</sup> 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.<sup>2</sup>



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 Heathcock's work, scheme 1.

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

(3), 1.5 equiv; Et<sub>2</sub>AlCl (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))

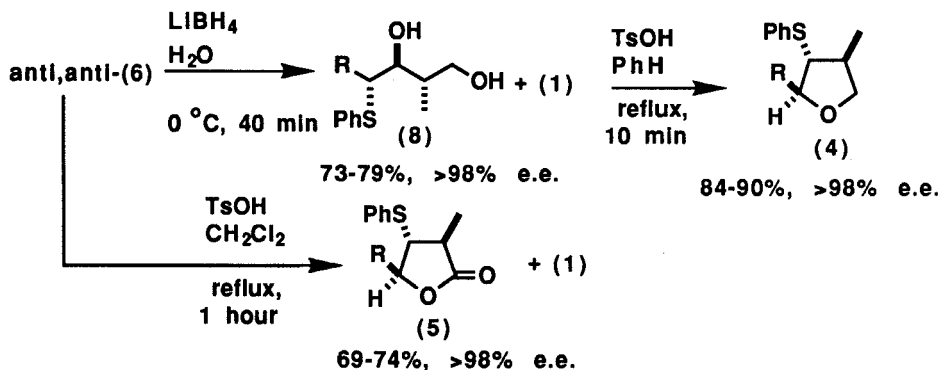
(3), 2.0 equiv; Et<sub>2</sub>AlCl (4.0 equiv):

*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<sub>2</sub>AlCl. 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 subsequent stereospecific cyclisation via an asymmetric episulphonium ion under our usual conditions<sup>1</sup> 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**

## REFERENCES

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