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A Chiral Oxazaborolidinone-Promoted Aldol Reaction with a Silyl Ketene Acetal from Ethyl 1,3-Dithiolane-2-carboxylate. Synthesis of Acetate Aldols in High Enantiomeric Purity

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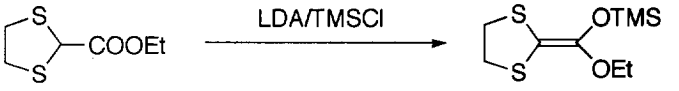
Abstract: Asymmetric synthesis of dithiolane aldols **3** was achieved in good yields by using silyl ketene acetal **1**, derived from ethyl 1,3-dithiolane-2-carboxylate, in the chiral oxazaborolidinone (**L-1** and **D-2**)-promoted aldol reaction and desulfurization of **3** resulted in production of acetate aldols **4** in high enantiomerc purity. Copyright © 1996 Elsevier Science Ltd

Through the development of a variety of chiral promoters and catalysts,[1] remarkable progress has recently been achieved in the enantioselectivity of the asymmetric Mukaiyama aldol reaction, thus meeting the level required for practical applications. However, in our approach to acetate aldols with the use of a stoichiometric amount of chiral oxazaborolidinone, a serious reduction (ca. 10-20%) of enantiomeric excess was observed in reaction with silyl ketene acetals derived from α-unsubstituted acetates, compared with the high level of enantioselectivity (>98% ee) in reaction with 1-ethoxy-2-methyl-1-(trimethylsiloxy)1-propene.[1g,2] Actually, asymmetric aldol reactions with acetate synthetic equivalents are prone to result in moderately lower enantioselectivity even with the use of chiral ester enolates, except in the cases of a few specific examples.[3] Introduction of an eliminatable substituent, e.g., a methylthio[4] or bromo substituent,[5] after aldol reaction at the α-position of chiral esters resolved this problem. We disclose herein a reliable way to acetate aldols in high enantiomeric purity by our chiral oxazaborolidinone-promoted aldol reaction.



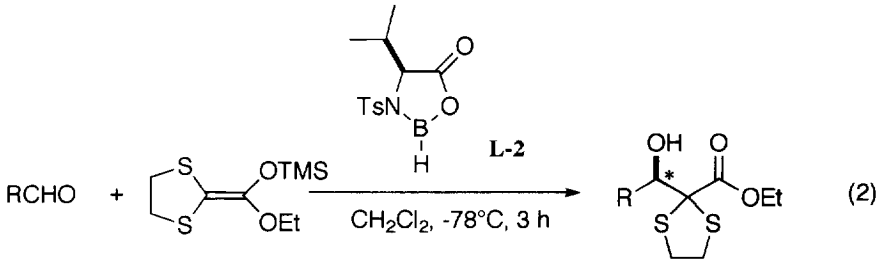
(1)

1

When we used a silyl ketene acetal derived from ethyl (methylthio)acetate in reaction with isobutyraldehyde, desulfurization of a minor syn product provided the corresponding acetate aldol in 99% ee while a major anti product gave the acetate aldol in only 13% ee. It was recognized that bulkiness at the α-position in the starting acetate is effective for enhancing the enantioselectivity in our chiral borane system. Introduction of two ethylthio substituents at the α-position of acetate, however, blocked the reaction from, presumably due to their excessive

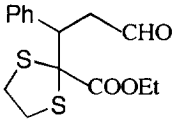
steric hindrance. We, therefore, adopted a TMS version **1** (bp 100-102°C/1mmHg) of the lithium enolate prepared from ethyl 1,3-dithiolane-2-carboxylate[6,7] as an alternative silyl ketene acetal (eq. 1).

Reaction of benzaldehyde with silyl ketene acetal **1** in the presence of a stoichiometric amount of chiral oxazaborolidinone **L-2**, derived from (*S*)-valine, (in CH_2CH_2 at -78°C for 3 h) gave aldol product **3a** in 88% yield. Treatment of **3a** with Ni_2B-H_2 (a large excess of anhydrous $NiCl_2$ and $NaBH_4$ under a hydrogen atmosphere) at rt for 16 h resulted in mild desulfurization[6] to afford acetate aldol **5a** in 85% yield. The enantiomeric purity of **5a** was determined to be 98% ee by HPLC analysis using Daicel Chiralcel OD column. Hydrolysis of **5a** gave the corresponding acid and then the absolute configuration was determined to be ***S*** by comparing its specific rotation value with the reported value.[3b,8] Therefore, the silyl ketene acetal, possessing a cyclic *S,S*-moiety, also turned out to react at *Si* face of the aldehyde coordinated to **L-2** like the other silyl ketene acetals.[1g,2]



1 **3**

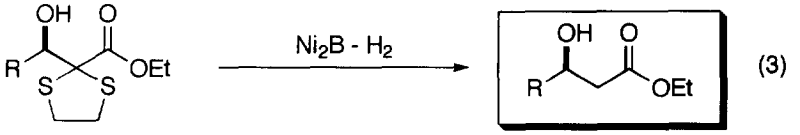
Table 1. Asymmetric Synthesis of Dithiolane Aldols **3** by Chiral Oxazaborolidinone Promoted Aldol reaction (eq. 2)

Entry	RCHO	Chiral Borane **2**[a]	Product **3**[b] (% yield)[c]		$[\alpha]^{25}_D$	($CHCl_3$)	
1	Ph	**L-2**	**3a**	(88)	-23.7	(c 0.36)	
2	Ph	**D-2**	**3a***	(85)	+24.0	(c 0.25)	
3	CH_3	**L-2**	**3b**	(73)	-2.00	(c 1.00)	83% ee[d]
4	$(CH_3)_2CH$	**L-2**	**3c**	(65)	-58.0	(c 1.00)	
5	$PhCH_2$	**L-2**	**3d**	(57)	+22.0	(c 1.00)	
6	$PhCH_2CH_2$	**L-2**	**3e**	(85)	+26.0	(c 0.40)	
7	PhCH=CH	**L-2**	**3f**	(42)	+16.8	(c 1.00)	
							
			4	(22)			
8	$CH_3(CH_2)_6$	**L-2**	**3g**	(80)	+14.1	(c 1.35)	98% ee[d]

[a] **L-2** and **D-2** represent the chiral borane catalysts derived from (*S*)- and (*R*)-valine, respectively. [b]Asterisk shows the reverse configuration. [c] Isolated yields. [d]Enantiomeric excess was determined by Daicel Chiralcel OD with the benzoyl derivative of **3b** and by Daicel Chiralcel AD with the benzoyl derivative of **3g**.

As expected, the bulkiness of the substituent was apparently advantageous for attaining the high level of acetate aldols under catalyst control.

The results on the highly enantioselective synthesis of dithiolane aldols **3** are summarized in Table 1 (eq.2). By using **D-2**, derived from (***R***)-valine, the expected aldol (**3a***) was obtained with the corresponding opposite



3 **5** (3)

Table 2 Desulfurization of Dithiolane Aldols **3** to Acetate Aldols **5** (eq. 3)

Entry	R	Dithiolane Aldol **3**	Acetate Aldol **5** (% yield)[a]	% ee[b]
1	Ph	**3a**	**5a** (85)	98 (S)
2	Ph	**3a***	**5a*** (84)	97 (R)
3	CH_3	**3b**	**5b** (87)	83 (R)
4	$(CH_3)_2CH$	**3c**	**5c** (83)	99 (S)
5	$PhCH_2$	**3d**	**5d** (86)	96 (R)
6	$PhCH_2CH_2$	**3e**	**5e** (92)	99 (R)
7	$CH_3(CH_2)_6$	**3g**	**5g** (88)	95 (R)

[a]Isolated yields and asterisk shows the reverse configuration. [b]Enantiomeric excess was determined by Daicel Chiralcel OD and OA columns with acetate aldols and their benzoyl derivatives. Absolute configurations were determined by comparing the specific rotation values of the derived acids and esters with those of literature values (lit. 3b, 8, and 11) and/or by ^{19}F-chemical shift differences for their diastereomeric MTPA derivatives (lit. 10).

configuration with a similar high enantioselectivity (entry 2). A little lowering of the enantioselectivity observed in the reaction with acetaldehyde is due to the less facial selectivity characteristic of the aldehyde (entry 3), but still having considerably high selectivity (83% ee).[9] In the case of trans-cinnamadehyde, 1,4-addition product **4** was obtained in 22% yield with normal aldol **3f** (46% yield)(entry 7). The result suggested that nucleophile **1** influenced by the sulfur substituents tends to work as a more soft reagent compared with 1-ethoxy-2-methyl-1-(trimethylsiloxy)-1-propene which gave only normal aldol with trans-cinnamaldehyde.[1g] Additionally, the enantioselectivity in reactions with **1** was not reduced so significantly at more elevated temperatures (-5 - -10°C)(>90% ee).

Table 2 shows the results of desulfurization (eq.3). Desulfurization of **3** proceeds quite easily to afford acetate aldols **5** in good yields.[11] The enantiomeric purity of **5** was determined by HPLC analysis using Daicel Chiralcel OD column. The aldols obtained were almost enantiomerically pure except the case from acetaldehyde. Then, our practical method for preparing acetate aldols in high enantiomeric purity could be realized. The utility was checked by preparing a simple aldol related to natural sources. Reaction of octanal with **1** in the presence of **L-2** gave dithiolane aldol **3g** and after benzoylation the enantioselectivity of the product was determined to be 98% ee by HPLC analysis using a Daicel Chiralcel AD column (entry 8 in Table 1). After desulfurization of **3g**, acetate aldol **5g** was converted to the methyl ester in order to compare with the reported specific

rotation value. The absolute configuration and purity of the synthetic product ($[\alpha]^{22}_{D}$ -18.4 (c 0.33, $CHCl_3$) was consistent with those from the natural (*R*)-3-hydroxydecanoic acid, a constituent degradatively obtained from a marine natural product, *didemin V*, by degradation.[12]

In conclusion, it is noted that this chiral borane-promoted aldol reaction with 1 and the following desulfurization provide a versatile and practical method for the preparation of acetate aldols in high enantiomeric purity and furthermore the dithiolane aldol intermediates seem to be available for the other conversions as a novel, chiral synthetic intermediate, which are currently under way.

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