

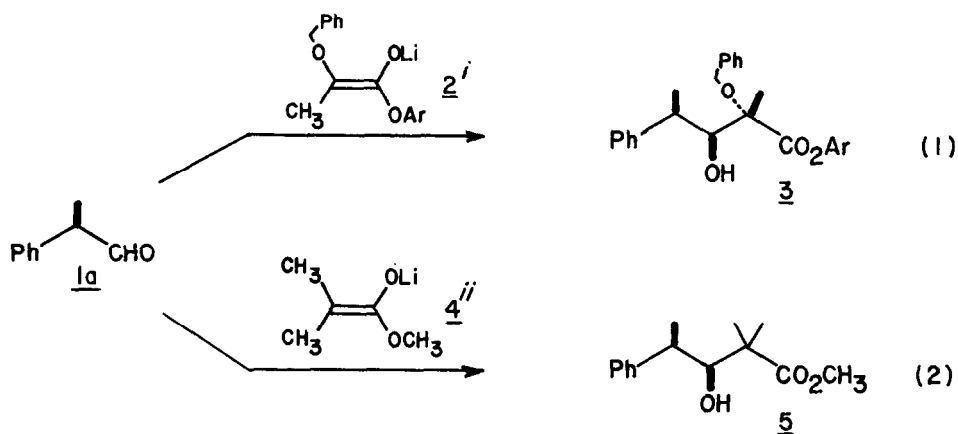
ALDOL CONDENSATIONS OF ETHYL 1,3-DITHIOLANE-2-CARBOXYLATE AND ETHYL 1,3-DITHIANE-2-CARBOXYLATE WITH CHIRAL ALDEHYDES. EXCEPTIONAL DIASTEREOFACE SELECTIVITY FROM TWO CONVENIENT ACETATE EQUIVALENTS.

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Abstract: Lithium enolates derived from the title esters show high diastereoface selectivity in their reactions with chiral aldehydes. The resulting 2,2-dithioaldols are desulfurized in good yield with $\text{Ni}_2\text{B-H}_2$ (EtOH, 20°C). With this mild desulfurization protocol, complete retention of stereochemical integrity was observed for all isolated aldols.

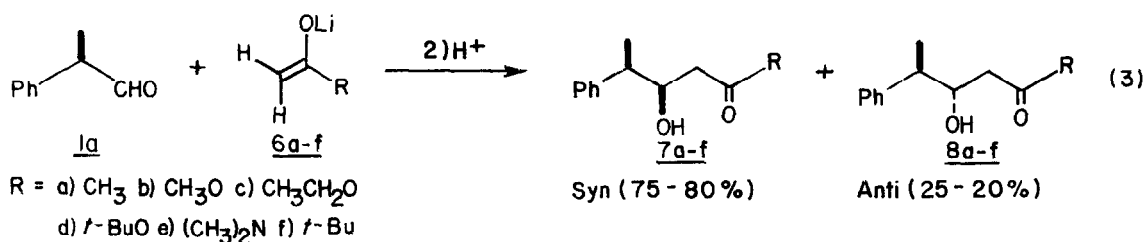
Recent reports from Heathcock's laboratory,¹ and our laboratory,² have demonstrated that the diastereoface selectivity in aldol condensations of lithium enolates with chiral aldehydes may be *significantly* enhanced by increasing the substitution at C-2 of the enolate reactant (Figure 1).



ⁱReference 1. ⁱⁱReference 2.

Figure 1.

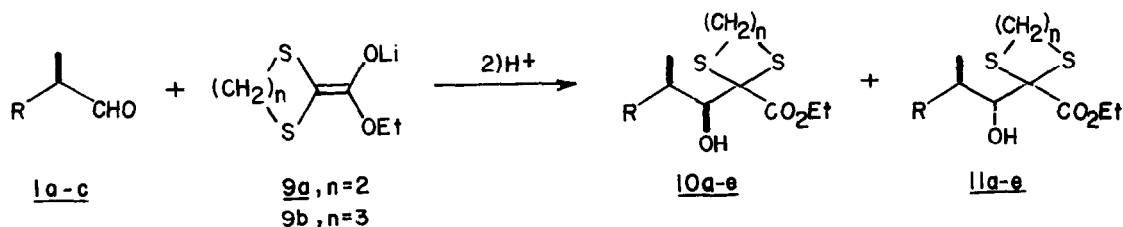
These results are in sharp contrast to the rather mediocre diastereoface selectivity usually observed in the reactions of C-2 unsubstituted,³ or monosubstituted,⁴ lithium enolates with chiral aldehydes. Thus, for example, the reactions of enolates **6 a-f** with **1a**, uniformly afford 3-4:1 mixtures of racemic *syn* and *anti* aldols, respectively (Equation 3).



While C-2 unsubstituted enolsilanes have shown promise as alternative acetate and methyl ketone equivalents in Lewis acid mediated reactions with chiral aldehydes,³ the scope of this methodology appears to be limited in comparison to aldol condensations with metal enolates.

In view of the exceptional selectivity shown by enolates 2 and 4 (vide supra), we felt that 2,2-dithio substituted enolates might be uniquely suited for exploitation as diastereoface-selective acetate equivalents in aldol syntheses.⁵ This expectation has been realized, in some cases with *outstanding* success. Selected results from our study of aldol condensations with lithium enolates 9a and 9b, prepared⁶ from ethyl 1,3-dithiolane-2-carboxylate and ethyl 1,3-dithiane-2-carboxylate, respectively, are summarized in Table 1.

TABLE I.



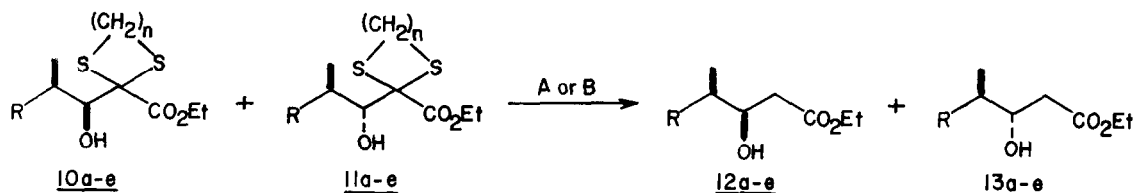
Entry ⁱ	Aldehyde	Enolate	Reaction Time	Ratio ⁱⁱ <u>10a-e</u> : <u>11a-e</u>	Total Yield ⁱⁱⁱ
1	<u>1a</u> , R = Ph	<u>9a</u>	2 min	≥99	89%
2	<u>1b</u> , R = <i>c</i> -C ₆ H ₁₁	<u>9a</u>	2 min	7	78%
3	<u>1b</u>	<u>9b</u>	3 hrs	11	61%
4	<u>1c</u> , R = C ₂ H ₅	<u>9a</u>	2min	2	75%
5	<u>1c</u>	<u>9b</u>	3hrs	3.5	77%

ⁱ Reaction conditions: Each reactant 0.5M in THF (-78°C). Reactions were quenched (-78°C) after the indicated time by addition of 2 eq glacial AcOH. An extractive work-up (Et₂O) afforded crude products of high purity. ⁱⁱ Crude product. ⁱⁱⁱ Chromatographed product (hex-EtOAc; silica).

Notably, enolate 9a reacted with +2-phenylpropanal to afford a single racemic diastereomer, 10a, in good isolated yield (Table 1, Entry 1). With less biased aldehydes (Table 1, Entries 2 and 4) the observed diastereoselection with enolate 9a was not as complete (*syn:anti* = 7:1 and 2:1, respectively, with +2-(cyclohexyl)propanal and +2-methylbutanal); these substrate aldehydes thus provided a means to critically evaluate the relative merits of enolates 9a and 9b. For example, the reactions of dithiane enolate 9b with aldehydes required 3h at -78°C for completion (as compared to 2 min for dithiolane enolate 9a) however, the quality of the diastereoselection was higher with this enolate (compare Entries 2 and 3 or Entries 4 and 5). A lithium enolate derived from ethyl-2,2-(bis)ethylthio acetate could not be induced to react to an appreciable extent with +2-methylbutanal at -78°C .

We have found $\text{Ni}_2\text{B-H}_2$ to be a highly effective reagent⁷ for desulfurization of the 2,2-dithio aldols, 10 and 11 (Table 2).

TABLE 2.



Entry	Diastereomer Mixture	Reaction Conditions ⁱ	Ratio ⁱⁱ <u>12a-e</u> : <u>13a-e</u>	Total Yield (<u>12a-e</u> + <u>13a-e</u>) ⁱⁱⁱ
1	<u>10a</u> + <u>11a</u> , $\geq 99:1$ R=Ph, n=2	A	$\geq 99:1$	94 %
2	<u>10b</u> + <u>11b</u> , 7:1 R=c-C ₆ H ₁₁ , n=2	B	7:1	94 %
3	<u>10d</u> + <u>11d</u> , 2:1 R=C ₂ H ₅ , n=2	B	2:1	88 %
4	<u>10e</u> + <u>11e</u> , 3.5:1 R=C ₂ H ₅ , n=3	B	3.5:1	61 %

ⁱ Method A: To a 0°C solution of substrate, 0.3M in 95% EtOH, was added 2.0 eq anhydrous NiCl_2 and 10 eq NaBH_4 . The reaction mixture was stirred under 1 atm H_2 for 15h (20°C), filtered through fritted glass; crude desulfurized products were isolated by extractive work-up (Et_2O). Method B: Same as above, except triple quantities of NiCl_2 and NaBH_4 ; t = 20 - 30h. ⁱⁱ Crude product. ⁱⁱⁱ Analytically pure ($\geq 95\%$ by hplc and NMR)

Dithiolane aldol 10a was smoothly desulfurized with a moderate excess of $\text{Ni}_2\text{B-H}_2$ to give aldol 12a in 94% yield, with complete retention of stereochemical integrity (Table 2, Entry 1). It is interesting to note that desulfurization of aliphatic 2,2-dithio aldols is consistently more difficult than the analogous procedure with aryl ring-containing substrates.⁸ Although

we do not have a firm rationale for this observation, it seems plausible that a π -d bonding interaction may serve to bind aromatic substrates more tightly to the Ni_2B surface than is possible for aliphatic substrates. We are continuing our examination of this question with the intent of developing cheap, efficient methodology for a general desulfurization process, however, we point out for the interim that the use of large excesses of $\text{Ni}_2\text{B-H}_2$ (Table 2, Entries 2, 3, and 4) affords desulfurized aliphatic aldols in excellent yield with no apparent detriment to the stereochemical integrity of the products.

Further experiments directed toward the development of diastereoselective, and enantioselective, 2,2-dithioenolates for use in aldol syntheses are in progress.

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References and Notes

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4. Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J. *J. Org. Chem.*, **1980**, *45*, 1066.
5. Metal enolates derived from ethyl 1,3-dithiane-2-carboxylate have been used in aldol condensations with several achiral aldehydes: Braun, M.; Esdar, M. *Chem. Ber.*, **1981**, *114*, 2924.
6. Preformed enolates were prepared as described in reference 8.
7. See Boar, R.B.; Hawkins, D.W.; McGhie, J.F.; Barton, D.H.R. *J. Chem. Soc., Perkin I*, **1973**, 654, and references therein.
8. For example, when a 7:1 mixture of 10b and 11b, respectively, was treated with 10eq of NaBH_4 and 20eq of NiCl_2 (Condition A, Table 2) desulfurization was only ~40% complete after 2 days. Qualitatively similar results were obtained with a 10c + 11c mixture and with a 10d + 11d mixture.

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