Anion Reactions of *trans*-1,3-Dithiolane 1,3-Dioxide with Aldehydes and Comparison with *trans*-1,3-Dithiane 1,3-Dioxide

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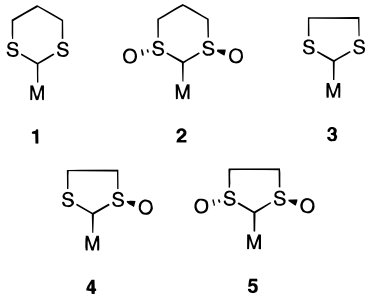
Received October 16, 1996[⊗]

The reactions of metalated *trans*-1,3-dithiolane 1,3-dioxide (**10**) with aldehydes have been studied through variations in the metal counterion, reaction temperature, and aldehyde. High yields of adducts were obtained, indicating that, in contrast to the monoxide or parent sulfide, the anion of 1,3-dithiolane 1,3-dioxide was sufficiently stable and did not decompose. High diastereoselectivities were obtained under kinetically controlled conditions, using an excess of lithium base at −78 °C. Lower selectivities were obtained under thermodynamic conditions. These results are in contrast to those obtained with 1,3-dithiane 1,3-dioxide. The origins of selectivity in both series are discussed.

Introduction

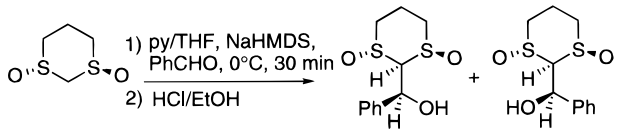
Sulfur-stabilized carbanions are key intermediates in contemporary organic synthesis.[1] Particularly noteworthy is metalated 1,3-dithiane **1**, which is a versatile acyl anion equivalent,[2] and the corresponding metalated bis-sulfoxide **2**, which we have found to be useful in asymmetric synthesis.[3]



1 **2** **3** **4** **5**

We have investigated the reactions of **2** with aromatic aldehydes and found low diastereocontrol under kinetically controlled conditions but high diastereocontrol under thermodynamic conditions (Scheme 1). Aliphatic aldehydes reacted with poor diastereocontrol under both sets of conditions. A possible rationale for low diastereoselectivity in the kinetically controlled reactions is that, while 1,3-dithiane 1,3-dioxide is C_2 symmetric on average due to ring inversion, a chair conformation is occupied at the time of reaction so that there are more than two different transition states that can lead to the two possible products. Indeed, very few C_2 symmetric

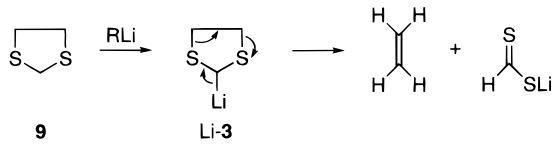
Scheme 1



6 **7** (4:96) **8**

87%

Scheme 2



9 Li-**3**

reagents are based on six-membered rings; they are mostly based on five-membered rings, probably for this reason.[4]

We therefore considered the possibility of using 1,3-dithiolane derivatives in order to improve the kinetic control in addition reactions with aldehydes. However, in contrast to 1,3-dithianes, comparatively little work has been reported on metalated 1,3-dithiolane **3**.[5−7] This is presumably due to its instability as **3** readily undergoes elimination to form ethylene and dithiocarbonate(Scheme 2).[1b,d,8−12] Cleavage can only be suppressed if suitably 4,5-substituted 1,3-dithiolanes are employed,[6−7,11] but this strategy is not generally applicable in synthesis. Similarly, attempts to alkylate metalated 1,3-dithiolane

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⊗ Abstract published in *Advance ACS Abstracts,* February 1, 1997.

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(2) For reviews see: (a) Gröbel, B. T.; Seebach, D. *Synthesis* **1977**, 357−402. (b) Page, P. C. B.; van Niet, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643−7677. (c) Hanack, M., ed. *Houben-Weyl, Methoden der Organischen Chemie;* Thieme: Stuttgart, 1993; Vol. E19d, pp 970−992.

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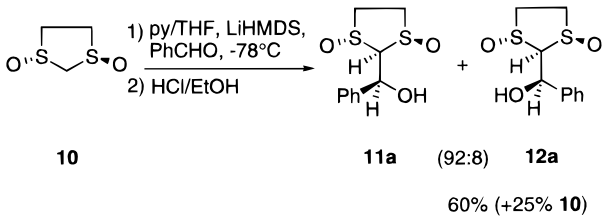
S0022-3263(96)01944-5 CCC: $14.00

Scheme 3



1-oxide **4** were unsuccessful and resulted in an elimination reaction closely related to that of **3**.[11]

We reasoned that the presence of two sulfinyl groups might provide sufficient stabilization of the anion **5** to prevent elimination. Furthermore, because the C_2 symmetry is now incorporated in a five-membered ring it should show superior levels of diastereocontrol under kinetically controlled conditions compared to the six-membered ring analogue. In this paper, we describe the metalation of 1,3-dithiolane 1,3-dioxide **5** and its subsequent reaction with aldehydes.

Results

Racemic *trans*-1,3-dithiolane 1,3-dioxide (**10**) has been prepared by H_2O_2[13a] or *m*-CPBA[13b] oxidation of 1,3-dithiolane (**9**). We have found that oxidation with *m*-CPBA in Et_2O (previous oxidation with *m*-CPBA used CH_2Cl_2[13b]) at −40 °C resulted in *precipitation of the required product*, and it was therefore isolated simply and practically, and in high yield. In all cases the oxidation is *trans* selective; none of the *cis* isomer was observed.

trans-1,3-Dithiolane 1,3-dioxide (**10**) was suspended in pyridine/THF[3a,14] and treated with lithium hexamethyldisilazide (LiHMDS) at −78 °C, followed by addition of benzaldehyde and quenched with HCl/EtOH.[3a,15] Upon workup, the benzaldehyde adduct was obtained as a mixture of diastereoisomers in moderate yield (Scheme 3). This indicated that the anion of 1,3-dithiolane 1,3-dioxide with two sulfoxide groups was sufficiently stable to undergo addition reactions with aldehydes without elimination to ethylene.

We then focused on the diastereoselectivity of the reaction and studied the influence of base, temperature, and time. In our first experiments, the dioxide **10** was metalated with 1.2 equiv of either LiHMDS or NaHMDS (Scheme 4, Table 1) at either −78 or 0 °C, and after 60 min at −78 °C, or 15 min at 0 °C, an excess of benzaldehyde was added. In order to determine the diastereoselectivity of the reaction as a function of time, an aliquot was removed from the reaction at the times indicated in Table 1. Quenching with HCl (aq)/EtOH gave the two diastereomeric adducts **11a** and **12a**, the ratios of which were determined by integration of the ^{1}H-NMR spectra of the crude reaction products.

Scheme 4

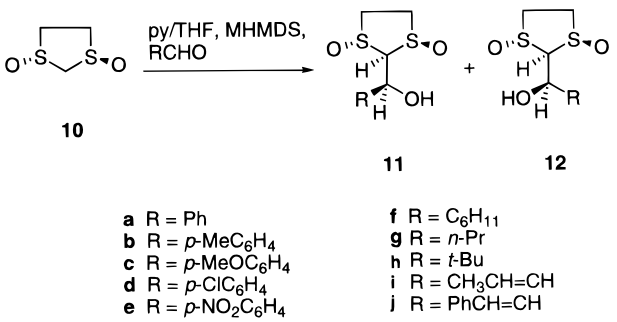
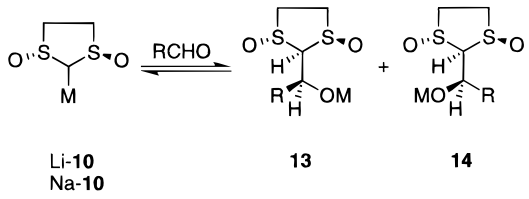


Table 1. Metalation of 10 with 1.2 Equiv of Base and Reaction with Benzaldehyde

entry	base	*T* (°C)	time[a]	ratio of products[b] **11a:12a**
1	LiHMDS	−78	15 min	90:10
2	LiHMDS		60 min	92:8
3	LiHMDS		3 h	91:9
4	LiHMDS	0	15 min	51:49
5	LiHMDS		60 min	54:46
6	LiHMDS		3 h	54:46[c]
7	NaHMDS	−78	15 min	89:11
8	NaHMDS		60 min	89:11
9	NaHMDS		3 h	84:16
10	NaHMDS	0	15 min	39:61
11	NaHMDS		60 min	41:59[d]
12	NaHMDS		3 h	e

[a] Aliquots were removed from the reaction at the times indicated. [b] Ratios determined by integration of the ^{1}H-NMR spectra of the crude reaction mixtures. [c] Low yield, presumably due to decomposition of the anion Li-**10**. [d] Low yield, presumably due to decomposition of the anion Na-**10**. [e] Alcohols **11a**/**12a** no longer observable, presumably due to complete decomposition of Na-**10**.

Scheme 5



It was found that when Li-**10** was used higher selectivity was obtained at −78 °C (Table 1, entries 1−3) compared to 0 °C (entries 4−6), and these ratios did not change with time, *suggesting* that the reactions were under kinetic control. In contrast, when the sodium anion Na-**10** was used, a small but perceptible reduction in diastereoselectivity was observed at −78 °C over time (Table 1, entries 7−9) suggesting that equilibration was beginning to occur. At 0 °C, low diastereoselectivity was observed but in favor of the opposite diastereoiosmer. Furthermore, considerable decomposition occurred over time. These two observations suggested that the reaction was now reversible and that the sodium anion Na-**10** had only limited stability at 0 °C (Scheme 5).

The highest diastereomeric ratios were obtained using the lithium base and carrying out reactions at low temperature. It was *presumed* that these conditions gave the kinetic product (*vide infra*). Reversibility of the reaction led to lower diastereocontrol, and therefore, conditions were sought that reduced or even eliminated this possibility. Another problem we encountered was the presence of significant quantities of starting material (up to 30%) at the end of the reaction. We reasoned that using excess base (e.g., 2.4 equiv) would both reduce the

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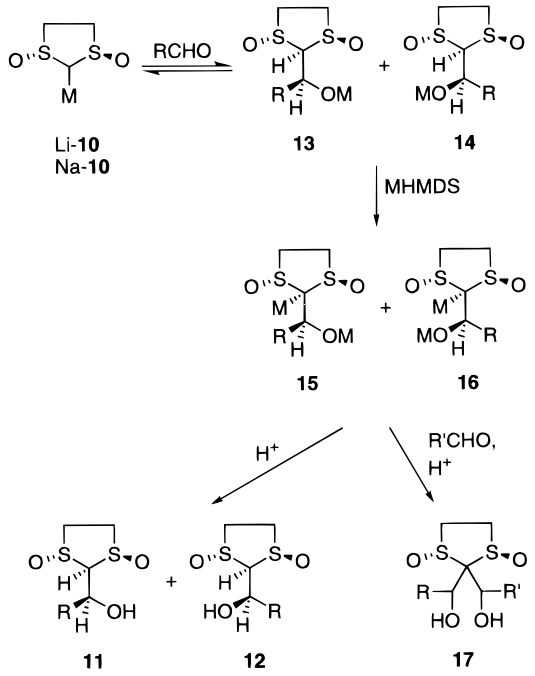
(14) Due to the poor solubility of **10** in etheral solvents, a pyridine/THF solvent system had to be used in all the reactions. Warming of **10** in this solvent mixture and subsequent cooling led to the formation of a fine suspension that was used in the following reactions. Extremely dilute reactions can be conducted in neat THF without changing the selectivity (see ref 3a).

(15) We have found previously that the nature of the quench of **2** was critical (see ref 3a). Best results were obtained in a fast quench when the reaction mixture was added to a rapidly stirring solution of HCl (aq) in EtOH. We therefore used the same methodology to quench **5**.

Scheme 6



tendency for equilibration to occur and increase conversion of starting material. We assumed that, upon formation of the intermediates **13** and **14**, the second equivalent of base would deprotonate these intermediates again in the 2-position to yield the new dimetalated intermediates **15** and **16** (Scheme 6) and thereby inhibit the reverse reaction.

Of concern was the acidity of the C-2 proton as MHMDS bases have relatively low pK_a (28). The pK_a of **10** was therefore determined[16] and found to be surprisingly low (19.1).[17] Thus, the C-2 proton in **13** and **14** should still be sufficiently acidic to be deprotonated by MHMDS and give **15** and **16** (scheme 6). In this way, equilibration could be suppressed and the high diastereoselectivity of the kinetically controlled reactions conserved. To investigate this, the metalation reactions were carried out using 2.4 equiv of the amide bases, followed by addition of an excess of benzaldehyde after 10 min at −78 °C, or after 5 min at 0 °C, respectively. As above, aliquots were taken from the reaction and quenched with HCl (aq)/EtOH. The results are summarized in Table 2.

Metalation with 2.4 equiv of LiHMDS at −78 °C gave **11a** and **12a** with slightly higher diastereoselectivity than reactions using 1.2 equiv of base, and the diastereomeric ratio **11a**:**12a** did not change with time (Table 2, entries 1−3). Complete consumption of the starting material under these conditions occurred and led to improved yields of the adducts, as expected. At 0 °C, higher ratios were obtained compared to the use of 1.2 equiv of base, and again the ratios did not change with time (Table 2, entries 4−6). It is therefore likely that the proposed intermediates Li-**15** and Li-**16** have indeed formed. Reactions using NaHMDS at −78 °C initially gave a high ratio of **11a**:**12a**, but this decreased slowly over time (Table 2, entries 7−9). This indicated that equilibration was still occurring, either because the second deprotonation was not occurring with NaHMDS or because this process was itself reversible. At 0 °C, significant decomposition occurred even at short reaction times (Table 2, entries 10−12), indicating that the Na compounds Na-**15** and Na-**16** are less stable than their Li counterparts.

(16) We thank Professor F. G. Bordwell for carrying out the pK_a measurements.

(17) This value should be compared to *trans*-1,3-dithiane 1,3-dioxide, which has a pK_a of 24.9. See ref 19.

Table 2. Metalation of 10 with 2.4 Equiv of Base and Reaction with Benzaldehyde

entry	base	*T* (°C)	time[a]	ratio of products[b] **11a**:**12a**
1	LiHMDS	−78	15 min	93:7
2	LiHMDS		60 min	92:8
3	LiHMDS		3 h	93:7
4	LiHMDS	0	15 min	69:31
5	LiHMDS		60 min	70:30
6	LiHMDS		3 h	72:28[c]
7	NaHMDS	−78	15 min	92:8
8	NaHMDS		60 min	88:12
9	NaHMDS		3 h	85:15
10	NaHMDS	0	15 min	42:58[d]
11	NaHMDS		60 min	43:57[d]
12	NaHMDS		3 h	e

[a] Aliquots were removed from the reaction at the times indicated. [b] Ratios determined by integration of the ^{1}H-NMR spectra of the crude reaction mixtures. [c] Low yield, presumably due to decomposition of the anion Li-**10**. [d] Low yield, presumably due to decomposition of the anion Na-**10**. [e] Alcohols **11a**/**12a** no longer observable, presumably due to complete decomposition of Na-**10**.

Thus, optimum conditions for yield and diastereoselectivity required the use of 2.4 equiv of LiHMDS at −78 °C, and these were used with a range of aldehydes (Table 3).

It was found that good yields of adducts could be obtained in all cases except for reaction with pivaldehyde (Table 3, entry 8). High diastereoselectivity was observed in reactions with aromatic aldehydes (Table 3, entries 1−5) and α,β-unsaturated aldehydes (Table 3, entries 9−10), but slightly lower selectivities were observed with aliphatic aldehydes (Table 3, entries 6−8).

Even though an excess of the aldehyde was used (3 equiv), in most cases *mono*addition to the dioxide **10** was observed. Only in the reaction with crotonaldehyde was a small amount of the *bis*-aldehyde addition product **17i** (8%, R = R′ = 1-propenyl) formed (Table 3, entry 9). NMR spectroscopic data indicated that **17i** was a symmetrical compound. Apparently, in most cases the second aldehyde addition is sterically and electronically disfavored.

Crotonaldehyde and cinnamaldehyde did not undergo 1,4 addition. The only reaction observed with both α,β-unsaturated aldehydes was 1,2 addition to yield the alcohols **11i**,**j** and **12i**,**j** (Table 3, entries 9 and 10), providing further evidence for the reaction occurring under kinetic control.

Separation of the alcohols **11** and **12** turned out to be difficult: they could not be separated by column chromatography. Instead, the pure major diastereomers were obtained by recrystallization of the mixtures. In some cases, partial reverse reaction occurred upon recrystallization and resulted in lower yields of adducts.

Mechanistic Studies

We wanted to determine if the reactions of lithiated 1,3-dithiolane 1,3-dioxide Li-**10** with aldehydes at −78 °C were reversible. Initially we metalated dioxide **10** with 1.2 equiv of LiHMDS to form intermediate Li-**10**. The solution was then reacted with benzaldehyde (1.5 equiv), followed after 60 min by cyclohexanecarboxalde-

Table 3. Metalation of 10 with 2.4 Equiv of LiHMDS at −78 °C and Reaction with Various Aldehydes

entry	aldehyde	isolated yield of both diastereomers **11** and **12**[a] (%)	ratio of diastereomers **11**:**12**[a]	isolated yield of major diastereomer **11**[b] (%)
1	PhCHO	90	96:4	47
2	*p*-MeC_6H_4CHO	90	92:8	45
3	*p*-$MeOC_6H_4CHO$	92	88:12	54
4	*p*-ClC_6H_4CHO	76[c]	92:8[c]	57[d]
5	*p*-$NO_2C_6H_4CHO$	81	85:15	12
6	$C_6H_{11}CHO$	92	76:24	44
7	*n*-PrCHO	94	76:24	8
8	*t*-BuCHO	53	81:19	32
9	crotonaldehyde	67[e]	95:5	34
10	*trans*-cinnamaldehyde	62	86:14	*f*

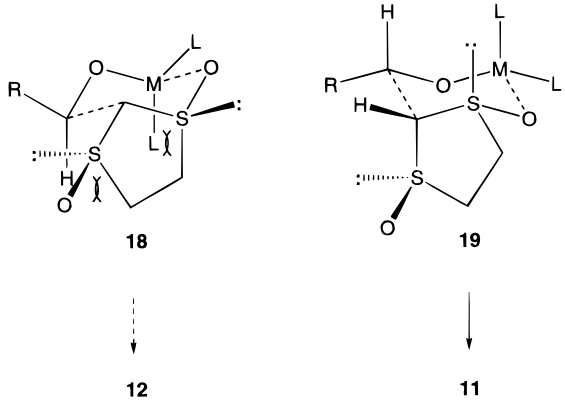
[a] After column chromatography. [b] After recrystallization. [c] 15% of pure major **11d** and 61% of a **11d**:**12d** = 92:8 mixture. [d] Total yield of **11d**; 15% after column chromatography and 42% after recrystallization. [e] Plus 8% of the bis-aldehyde adduct. [f] Diastereomers could not be separated.

hyde (1.5 equiv), and after a further 60 min quenched with HCl/EtOH. This period of time (60 min) is sufficient for complete reaction to occur with all aldehydes. Analysis of the crude reaction mixture by ^{1}H-NMR spectroscopy showed that the benzaldehyde adducts **11a** and **12a** were the main products (>90%, diastereomeric ratio 93:7). The cyclohexanecarboxaldehyde adducts **11f** and **12f** had formed in only minor amounts (<10%). In a second experiment, we reversed the order of aldehyde addition. This time, both the benzaldehyde adducts **11a** and **12a** (52%, diastereomeric ratio 93:7) and the cyclohexanecarboxaldehyde adducts **11f** and **12f** (48%, diastereomeric ratio 68:32) had formed in nearly equal amounts. Taking account the higher reactivity of benzaldehyde compared to cyclohexanecarboxaldehyde, the experiments clearly show that the reaction depicted in Scheme 5 is reversible. As a single aldehyde adduct was obtained in the first experiment (benzaldehyde is more reactive than cyclohexanecarboxaldehyde) but a mixture of adducts incorporating both aldehydes was obtained in the second experiment, this showed that the reverse reaction was slow. If the reverse reaction was rapid, the second experiment should have furnished the same single aldehyde adduct. These experiments also explain why there is little change in diastereoselectivity with time for the reaction of Li-**10** with PhCHO at −78 °C (Table 1, entries 1−3). Again, the reverse reaction must be slow, and it is also possible that at −78 °C the major kinetic product is the same as the major thermodynamic product.

We repeated these competition experiments with 2.4 equiv of the Li base. In the first experiment (benzaldehyde added first), only the benzaldehyde adducts **11a** and **12a** (diastereomeric ratio 91:9) were formed. In the second experiment (cyclohexanecarboxaldehyde added first), the only products obtained were the cyclohexanecarboxaldehyde adducts **11f** and **12f** (diastereomeric ratio approximately 70:30). These experiments clearly show that metalation of **10** with 2.4 equiv of LiHMDS and subsequent adduct formation with aldehydes at −78 °C is an irreversible process. We believe that when excess base is used the dimetalated intermediates Li-**15** and Li-**16** are formed, and these effectively block the reverse reaction (Scheme 6).

It was surprising that reactions of Li-**10** (formed from 1 equiv of base) with aldehydes were reversible even at −78 °C, as we had previously shown that reactions of lithiated *trans*-1,3-dithiane 1,3-dioxide (Li-**6**) with aldehydes were irreversible at the same temperature. The greater propensity for Li-**10** to undergo reversible reaction with aldehydes compared to Li-**6** must be due to the greater thermodynamic stability of Li-**10** (pK_a of **10** is 19.1) compared to Li-**6** (pK_a of *trans*-1,3-dithiane 1,3-dioxide **6** is 24.9).

Scheme 7



Rationalization of Stereochemistry

The stereochemistry of the major benzaldehyde adduct **11a** from the anion reaction at −78 °C was determined by X-ray crystallography.[18] We assume that the stereochemistry of the major diastereomer is the same for all aldehyde adducts **11a**−**j**. Their ^{1}H-NMR and ^{13}C-NMR spectra were very similiar, and the signal of the OH proton of the minor diastereomer **12a**−**j** always appeared at lower field to that of the major diastereomers **11a**−**j**.

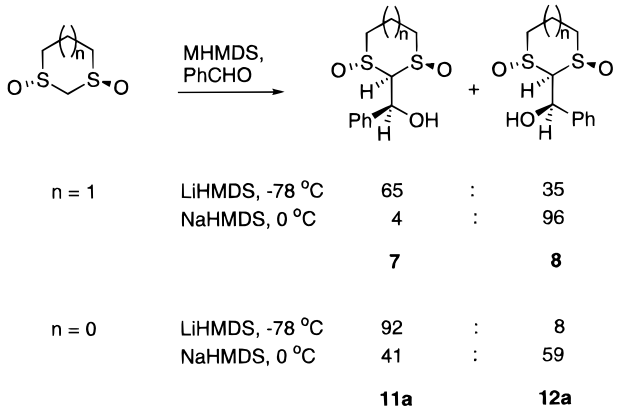
The stereochemical outcome of the reaction of Li-**10** at −78 °C can be rationalized by consideration of six-membered chair transition states analogous to the Zimmerman−Traxler transition states used to rationalize the aldol reaction. The metal can chelate to either sulfoxide, but due to C_2 symmetry these are equivalent and so chelation to only one of the sulfoxides needs to be considered. There are two possible chair forms (**18**, **19**) of the Zimmerman−Traxler transition state in which the aldehyde substituent occupies an equatorial position, and these are shown in Scheme 7.

Transition state **18** suffers from nonbonded interactions between the axial dithiolane methylene groups and both the ligand on the metal and CH of the aldehyde. Neither of these interactions are present in transition state **19**, which leads to the major diastereomer **11**.

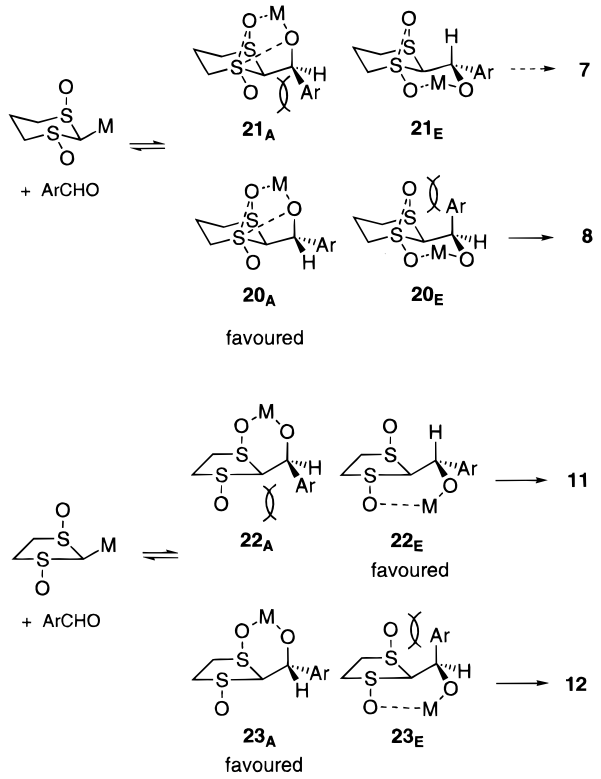
(18) The author has deposited atomic coordinates for **11a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(19) Aggarwal, V. K.; Davies, I. W.; Franklin, R.; Maddock, J.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2363−2368.

Scheme 8



Scheme 9



Comparison of Selectivity with 1,3-Dithiane 1,3-Dioxide

It is interesting to compare the difference in selectivity between 1,3-dithiolane 1,3-dioxide (**10**) and 1,3-dithiane 1,3-dioxide (**6**) under kinetic and thermodynamic conditions (Scheme 8). Under kinetically controlled conditions, higher diastereoselectivity was obtained with the dithiolane system compared to the dithiane system. This is because the two sulfinyl groups in the dithiane system are not equivalent during the course of the reaction and so two further transition states need to be considered. As the reaction can occur via additional transition states selectivity is eroded.

In contrast, under thermodynamically controlled conditions, higher diastereoselectivity was obtained with the dithiane system compared to the dithiolane system. The possible chelated metal alkoxides for the dithiane- and dithiolane-based reactions are shown in Scheme 9. In X-ray crystal structures of 1,3-dithiane 1,3-dioxide and aldehyde adducts thereof, it has been found that the oxygen of the axial sulfoxide is bent toward the sulfur of the equatorial sulfoxide due to stabilizing electrostatic interactions.[3a] These are maintained in all the chelated metal alkoxides **20** and **21**, but conformations $\mathbf{20_A}$ and $\mathbf{21_A}$ possess an additional electrostatic interaction and are therefore preferred. Of these two alkoxides, $\mathbf{21_A}$ suffers from electronic and steric repulsion of the sulfoxide with the aldehyde substituent, and $\mathbf{20_A}$ is favored. These steric/electronic interactions are greater in the six-membered ring than in the five-membered ring because the sulfoxide and aldehyde substituent are essentially parallel. In the five-membered ring, the two groups are pointing away from each other, and there is therefore reduced interaction and reduced selectivity. There is also reduced electrostatic interactions from the alkoxide to the sulfur of the equatorial sulfoxide in chelated metal alkoxides $\mathbf{22_A}$ and $\mathbf{23_A}$ due to chelation of the metal alkoxide with the *pseudoaxial* sulfoxide. The oxygen of the pseudoaxial sulfoxide is bent away from the ring and carries the chelated metal alkoxide with it, thereby increasing the distance of the alkoxide oxygen from the sulfur of the equatorial sulfoxide. Thus, the two conformations $\mathbf{22_E}$ and $\mathbf{23_A}$ are both favored and lead to the formation of **11** and **12** in nearly equal amounts.

Conclusion

We have shown that the anion of *trans*-1,3-dithiolane 1,3-dioxide can be obtained by reacting the dioxide with amide bases at −78 °C and, in contrast to the monoxide or parent sulfide, shows good stability. This anion can then be reacted with various aldehydes to give secondary alcohols in good yields and with moderate to high diastereoselectivity. We have demonstrated that use of 1.2 equiv of LiHMDS as base results in reversible aldehyde adduct formation, but use of 2.4 equiv of LiHMDS results in irreversible addition due to deprotonation of the initially formed adduct. Under these conditions, good yields and good diastereoselectivities were obtained with a range of aldehydes. Reactions at 0 °C gave poorer selectivity and caused decomposition of metalated *trans*-1,3-dithiolane 1,3-dioxide.

The relative stereochemistry of the major diastereomer of the benzaldehyde adduct was determined by X-ray crystallography, and we have proposed a model that accounts for the diastereoselectivity of the reaction on the basis of the Zimmermann−Traxler model for aldol reactions.

Experimental Section

THF was distilled from sodium immediately prior to use. Pyridine was distilled from calcium hydride and then stored over molecular sieves and under nitrogen until required. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien Kieselgel 60 F_{254} sheets containing fluorescent indicator. Purification of compounds was achieved by column chromatography using BDH 40−63 silica gel. All anion reactions were performed in flame-dried apparatus under a nitrogen atmosphere. *p*-Chlorobenzaldehyde, *p*-anisaldehyde, and cyclohexanecarboxaldehyde were used without further purification. All other aldehydes were recrystallized or distilled prior to use. *m*-CPBA was purified as described previously .[15]

Oxidation of 1,3-Dithiolane. 1,3-Dithiolane (5.00 g, 47.1 mmol) was dissolved in diethyl ether (60 mL) and the solution cooled to −40 °C. To this was added over 30 min a solution of *m*-CPBA (16.65 g, 96.5 mmol) in diethyl ether (180 mL) dropwise. Stirring was continued for 1 h at −40 °C, after which time the precipitate was filtered off and washed twice with mother liquor and with cold diethyl ether. Recrystalli-

zation from methanol yielded 5.09 g (36.8 mmol, 78%) of *trans*-1,3-dithiolane 1,3-dioxide (**10**). A second fraction (0.50 g) contained additional product as well as *m*-chlorobenzoic acid. Column chromatography using acetone as the eluent afforded more (0.32 g, 2.3 mmol, 5%) dithiolane dioxide (**10**). Total yield of **10** 5.41 g (39.1 mmol, 83%): mp 154−155 °C (lit.[12b] mp 156 °C); R_f (acetone/ethanol 9:1) 0.56; ν_{max} (KBr disk)/cm^{-1} 3433, 1025; δ_H (250 MHz; DMSO) 4.29 (2H, s), 3.84−3.69 (2H, m), 3.53−3.38 (2H, m); δ_C (63 MHz; DMSO) 77.1, 52.6; *m*/*z* 138 (M$^+$, 100), 110 (50), 108 (44). Anal. Calcd for $C_3H_6O_2S_2$: C, 26.07; H, 4.38; S, 46.40. Found: C, 26.29; H, 4.24; S, 46.26.

General Procedure for Monitoring Amide Reactions with *trans*-1,3-Dithiolane 1,3-Dioxide (10). Dithiolane dioxide (**10**) (100 mg, 0.72 mmol) was added to a pyridine (4.0 mL)−THF (2.4 mL) mixture and dissolved with warming. Subsequent cooling to −78 °C or to 0 °C under nitrogen afforded a fine white suspension. A solution of LiHMDS or NaHMDS (1.0 M in THF) was added in one portion.

In reactions with 1.2 equiv of base, 0.86 mL (0.86 mmol) was employed and the mixture was stirred for 60 min (−78 °C) and 15 min (0 °C), respectively, before an excess of benzaldehyde (0.11 mL, 1.08 mmol) was added. Aliquots (2 mL) were taken by syringe after 15 min, 60 min, and 3 h and transferred into a rapidly stirred mixture of ethanol (10 mL) and aqueous HCl (2 M, 0.82 mL) at 0 °C. In reactions with 2.4 equiv of base, 1.72 mL (1.72 mmol) was added and stirring was continued for 10 min (−78 °C) and 5 min (0 °C), respectively, followed by addition of an excess of benzaldehyde (0.22 mL, 2.16 mmol). Aliquots (2 mL) were taken by syringe after 15 min, 60 min, and 3 h and transferred into a rapidly stirred mixture of ethanol (10 mL) and aqueous HCl (2 M, 1.64 mL) at 0 °C.

The solvents were then evaporated and the residue dissolved in DMSO-d_6. Diastereomeric ratios **11a**:**12a** were determined by integration of the ^{1}H-NMR spectra (Tables 1 and 2).

General Procedure for the Metalation of *trans*-1,3-Dithiolane 1,3-Dioxide (10) and Its Subsequent Reaction with Aldehydes. Dithiolane dioxide (**10**) (100 mg, 0.72 mmol) was added to a pyridine (4.0 mL)−THF (2.4 mL) mixture and dissolved with warming before being cooled to −78 °C under nitrogen. A fine white suspension was obtained. A solution of LiHMDS (1.0 M in THF; 1.72 mL, 1.72 mmol) was added in one portion. After 10 min, an excess of the aldehyde (2.16 mmol) was added neat. Stirring was continued for 60 min at −78 °C. The reaction mixture was then transferred by syringe into a rapidly stirred mixture of ethanol (10 mL) and aqueous HCl (2 M, 1.64 mL) at 0 °C. The solvents were then evaporated, and the residue was purified by chromatography on silica gel with acetone as the eluent.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-phenyl-1,3-dithiolane-2-methanol (11a). Reaction with benzaldehyde (0.22 mL, 2.16 mmol) afforded 160 mg (0.65 mmol, 90%) of a 96:4 mixture of two diastereomers **11a** and **12a**, which were inseparable by chromatography. Recrystallization from methanol yielded 82 mg (0.34 mmol, 47%) of the major diastereomer **11a** as colorless crystals: mp 152−154 °C; R_f (acetone) 0.39; ν_{max} (KBr disk)/cm^{-1} 3394, 1028; δ_H (250 MHz; DMSO) 7.53−7.30 (5H, m), 6.30 (1H, d, J = 5.2), 4.99 (1H, dd, J = 8.9, 5.2), 4.32 (1H, d, J = 8.9), 3.83−3.60 (4H, m); δ_C (63 MHz; DMSO) 141.7, 128.4, 128.1, 126.8, 96.6, 68.4, 51.5, 51.4; *m*/*z* 244 (M$^+$, 4), 105 (36), 91 (53), 77 (100). Anal. Calcd for $C_{10}H_{12}O_3S_2$: C, 49.16; H, 4.95; S, 26.24. Found: C, 48.90; H, 4.86; S, 26.21.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-(*p*-methylphenyl)-1,3-dithiolane-2-methanol (11b). With *p*-tolualdehyde (0.26 mL, 2.16 mmol), 167 mg (0.65 mmol, 90%) of a 92:8 mixture of two diastereomers **11b** and **12b**, which were inseparable by chromatography, was obtained. Recrystallization from methanol yielded 83 mg (0.32 mmol, 45%) of the major diastereomer **11b** as a colorless solid: mp 142−143 °C; R_f (acetone) 0.33; ν_{max} (KBr disk)/cm^{-1} 3445, 1018; δ_H (250 MHz; DMSO) 7.38 (2H, d, J = 7.9), 7.20 (2H, d, J = 7.9), 6.22 (1H, d, J = 5.5), 4.94 (1H, dd, J = 9.2, 5.5), 4.29 (1H, d, J = 9.2), 3.81−3.59 (4H, m), 2.30 (3H, s); δ_C (63 MHz; DMSO) 138.7, 137.3, 128.9, 126.7, 96.8, 68.2, 51.5, 20.8; *m*/*z* 258 (M$^+$, 29%), 134 (82), 121 (49), 119 (100), 105 (81), 91 (70), 77 (36) (found M$^+$ 258.0379, $C_{11}H_{14}O_3S_2$ requires M 258.0384). Anal. Calcd for $C_{11}H_{14}O_3S_2$: C, 51.14; H, 5.46; S, 24.82. Found: C, 50.95; H, 5.38; S, 24.91.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-(*p*-methylphenyl)-1,3-dithiolane-2-methanol (11c). Reaction with *p*-anisaldehyde (0.26 mL, 2.16 mmol) yielded 180 mg (0.66 mmol, 92%) of a 88:12 mixture of two diastereomers **11c** and **12c**, which could not be separated by chromatography. Recrystallization from methanol afforded 106 mg (0.39 mmol, 54%) of the major diastereomer **11c** as a colorless solid: mp 146−147 °C; R_f (acetone) 0.37; ν_{max} (KBr disk)/cm^{-1} 3449, 1250, 1027; δ_H (250 MHz; DMSO) 7.41 (2H, d, J = 8.9), 6.95 (2H, d, J = 8.9), 6.19 (1H, d, J = 5.2), 4.92 (1H, dd, J = 9.5, 5.2), 4.29 (1H, d, J = 9.5), 3.86−3.59 (7H, m); δ_C (63 MHz; DMSO) 159.0, 133.6, 128.1, 113.7, 97.0, 68.1, 55.1, 51.4; *m*/*z* 274 (M$^+$, 13), 150 (33), 137 (32), 135 (100), 121 (31). Found: C, 47.88; H, 4.94; S, 23.38. Anal. $C_{11}H_{14}O_4S_2$ requires C, 48.16; H, 5.14; S, 23.37%.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-(*p*-chlorophenyl)-1,3-dithiolane-2-methanol (11d). Reaction with *p*-chlorobenzaldehyde (304 mg, 2.16 mmol) gave, after chromatography, 31 mg (0.11 mmol, 15%) of the major diastereomer **11d** and 121 mg (0.44 mmol, 61%) of a 92:8 mixture of two diastereomers **11d** and **12d**. Recrystallization from acetone afforded more of the major diastereomer **11d** (84 mg, 0.30 mmol, 42%) as colorless crystals. Total yield of **11d**: 115 mg (0.41 mmol, 57%): mp 175−176 °C; R_f (acetone) 0.39; ν_{max} (KBr disk)/cm^{-1} 3510, 3443, 3351, 1035, 996; δ_H (250 MHz; DMSO) 7.53 (2H, d, J = 8.9), 7.46 (2H, d, J = 8.9), 6.38 (1H, d, J = 5.5), 4.99 (1H, dd, J = 8.9, 5.5), 4.34 (1H, d, J = 8.9), 3.84−3.60 (4H, m); δ_C (63 MHz; DMSO) 140.7, 132.6, 128.8, 128.4, 96.3, 67.8, 51.5; *m*/*z* 278 (M$^+$, 24), 154 (88), 141 (80), 139 (100), 125 (45), 111 (37), 105 (59), 77 (58) (found: M$^+$ 277.9836, $C_{10}H_{11}ClO_3S_2$ requires M 277.9838). Anal. Calcd for $C_{10}H_{11}ClO_3S_2$: 43.09; H, 3.98; Cl, 12.72; S, 23.00 Found: C, 42.88; H, 3.82; Cl 12.97; S, 23.14.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-(*p*-nitrophenyl)-1,3-dithiolane-2-methanol (11e). With *p*-nitrobenzaldehyde (326 mg, 2.16 mmol), 168 mg (0.58 mmol, 81%) of a 85:15 mixture of two diastereomers **11e** and **12e** which were inseparable by chromatography, was obtained . Fractional crystallization from dichloromethane yielded 25 mg (0.09 mmol, 12%) of the major diastereomer **11e** as a colorless solid: mp 195−197 °C; R_f (acetone) 0.48; ν_{max} (KBr disk)/cm^{-1} 3452, 1513, 1349, 1009; δ_H (250 MHz; DMSO) 8.28 (2H, d, J = 8.9), 7.79 (2H, d, J = 8.9), 6.58 (1H, d, J = 5.5), 5.16 (1H, dd, J = 8.2, 5.5), 4.42 (1H, d, J = 8.2), 3.88−3.65 (4H, m); δ_C (63 MHz; DMSO) 149.2, 147.2, 128.2, 123.6, 95.5, 67.6, 51.7, 51.6; *m*/*z* 289 (M$^+$, 54), 165 (70), 152 (68), 151 (95), 150 (95), 138 (65), 105 (71), 77 (100) (found M$^+$ 289.0087, $C_{10}H_{11}NO_5S_2$ requires M 289.0079).

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-cyclohexyl-1,3-dithiolane-2-methanol (11f). Reaction with cyclohexanecarboxaldehyde (0.26 mL, 2.16 mmol) afforded 166 mg (0.66 mmol, 92%) of a 76:24 mixture of two diastereomers **11f** and **12f**, which were inseparable by chromatography. Recrystallization from methanol yielded 80 mg (0.32 mmol, 44%) of the major diastereomer **11f** as colorless crystals: mp 181−182 °C; R_f (acetone) 0.42; ν_{max} (KBr disk)/cm^{-1} 3233, 2920, 2849, 1047, 1015, 993, 980; δ_H (250 MHz; DMSO) 5.44 (1H, d, J = 6.1), 4.10 (1H, d, J = 7.6), 3.89−3.49 (5H, m), 1.84−1.56 (6H, m), 1.29−1.17 (5H, m); δ_C (63 MHz; DMSO) 92.6, 69.5, 51.5, 51.0, 42.4, 29.4, 25.9, 25.8, 25.7, 25.5; *m*/*z* 250 (M$^+$, 17), 93 (74), 83 (48), 79 (100), 77 (65), 55 (57) (found: M$^+$ 250.0694, $C_{10}H_{18}O_3S_2$ requires M 250.0697). Anal. Calcd for $C_{10}H_{18}O_3S_2$: C, 47.97; H, 7.25; S, 25.61. Found: C, 47.86; H, 7.22; S, 25.57.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-*n*-propyl-1,3-dithiolane-2-methanol (11g). With butyraldehyde (0.19 mL, 2.16 mmol), 142 mg (0.68 mmol, 94%) of a 76:24 mixture of two diastereomers **11g** and **12g**, which could not be separated by chromatography, was obtained. Recrystallization from ethyl acetate yielded 12 mg (0.06 mmol, 8%) of the major diastereomer **11g** as a colorless solid: mp 84−86 °C; R_f (acetone) 0.39; ν_{max} (KBr disk)/cm^{-1} 3374, 1039, 1006; δ_H (250 MHz; DMSO) 5.49 (1H, d, J = 6.1), 4.03−3.46 (6H, m), 1.72−1.22 (4H, m), 0.89 (3H, t, J = 7.2); δ_C (63 MHz; DMSO) 95.2, 65.6, 51.7, 50.9, 38.3, 18.1, 13.7; *m*/*z* 210 (M$^+$, 48), 110 (47), 108 (100), 77 (49), 71 (55), 55 (67) (found M$^+$ 210.0377, $C_7H_{14}O_3S_2$ requires M 210.0384).

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-*tert*-butyl-1,3-dithiolane-2-methanol (11h). Pivaldehyde (0.24 mL, 2.16 mmol) yielded 85 mg (0.38 mmol, 53%) of a 81:19 mixture of two diastereomers **11h** and **12h**, which were inseparable by chromatography. Recrystallization from acetone afforded 51 mg (0.23 mmol, 32%) of the major diastereomer **11h** as a colorless solid: mp 162−163 °C; R_f (acetone) 0.44; ν_{max} (KBr disk)/cm^{-1} 3390, 1028; δ_H (250 MHz; DMSO) 5.32 (1H, d, J = 5.8), 4.17 (1H, d, J = 2.4), 3.85−3.57 (4H, m), 3.45−3.37 (1H, m), 0.98 (9H, s); δ_C (63 MHz; DMSO) 90.2, 71.7, 51.8, 51.1, 36.0, 26.1; m/z 224 (M^+, 45), 167 (60), 108 (44), 77 (72), 57 (100) (found M^+ 224.0543, $C_8H_{16}O_3S_2$ requires M 224.0541). Anal. Calcd for $C_8H_{16}O_3S_2$: C, 42.83; H, 7.19; S, 28.58%. Found: C, 42.66; H, 7.13; S, 28.55.

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-(*trans*-1-propenyl)-1,3-dithiolane-2-methanol (11i). Reaction with crotonaldehyde (0.18 mL, 2.16 mmol) afforded, after chromatography on silica gel, 100 mg (0.48 mmol, 67%) of a 95:5 mixture of two diastereomers **11i** and **12i**, which were inseparable by chromatography. Recrystallization from acetone yielded 51 mg (0.24 mmol, 34%) of the major diastereomer **11i** as light brown crystals: mp 101−102 °C; R_f (acetone) 0.43; ν_{max} (KBr disk)/cm^{-1} 3275, 1027, 1001; δ_H (250 MHz; DMSO) 5.85−5.61 (3H, m), 4.41−4.33 (1H, m), 4.01 (1H, d, J = 9.2), 3.85−3.55 (4H, m), 1.69 (3H, d, J = 6.1); δ_C (63 MHz; DMSO) 131.2, 127.9, 95.4, 67.0, 51.4, 51.2, 17.5; m/z 208 (M^+, 51), 133 (55), 110 (56), 84 (100), 83 (63), 71 (93), 69 (72), 55 (64) (found M^+ 208.0236, $C_7H_{12}O_3S_2$ requires M 208.0228).

Elution of the column also gave 17 mg (0.06 mmol, 8%) of the bis-addition product **17i**: mp 146−147 °C; R_f (acetone) 0.61; ν_{max} (KBr disk)/cm^{-1} 3338, 1009, 983; δ_H (250 MHz; $CDCl_3$) 5.93 (2H, dq, J = 15.3, 6.1), 5.69 (2H, dd, J = 15.3, 6.7), 4.86 (2H, d, J = 2.8), 4.72 (2H, bd, J = 6.7), 3.82 (4H, s), 1.17 (6H, d, J = 6.1); δ_C (63 MHz; $CDCl_3$) 133.3, 126.2, 71.8, 54.3, 18.0, the signal for the quaternary carbon could not be found; m/z 278 (M^+, 72%), 162 (72), 136 (60), 121 (86), 93 (64), 71 (100), 69 (98) (found M^+ 278.0654, $C_{11}H_{18}O_4S_2$ requires M 278.0647).

(1*RS*,3*RS*,α*SR*)-1,3-Dioxo-α-(*trans*-2-phenylethenyl)-1,3-dithiolane-2-methanol (11j). With *trans*-cinnamaldehyde (0.27 mL, 2.16 mmol), 120 mg (0.44 mmol, 62%) of the alcohol **11j** was obtained. **11j** contained a small amount of the minor diastereomer **12j** (86:14 mixture) and could not be purified by chromatography or by recrystallization. **11j**: R_f (acetone) 0.40; ν_{max} (KBr disk)/cm^{-1} 3311, 1046, 1022, 1003; δ_H (250 MHz; DMSO) 7.48−7.24 (5H, m), 6.72 (1H, d, J = 16.2), 6.48 (1H, dd, J = 16.2, 6.6), 6.06 (1H, d, J = 5.5), 4.67−4.55 (1H, m), 4.19 (1H, d, J = 8.6), 3.88−3.56 (4H, m); δ_C (63 MHz; DMSO) 136.0, 131.3, 129.4, 128.7, 128.0, 126.5, 95.0, 67.1, 51.6, 51.3; m/z 270 (M^+, 30), 145 (30), 131 (100), 115 (34), 105 (38), 77 (35) (found M^+ 270.0389, $C_{12}H_{14}O_3S_2$ requires M 270.0384).

Metalation of *trans*-1,3-Dithiolane 1,3-Dioxide (10) with 1.2 Equiv of LiHMDS and Its Reaction with Benzaldehyde and Cyclohexanecarboxaldehyde. Dithiolane dioxide (**10**) (100 mg, 0.72 mmol) was added to a pyridine (4.0 mL)−THF (2.4 mL) mixture and dissolved with warming before being cooled to −78 °C under nitrogen. A solution of LiHMDS (1.0 M in THF; 0.86 mL, 0.86 mmol) was added, and after 10 min, benzaldehyde (0.11 mL, 1.08 mmol) was added. Stirring was continued for 60 min at −78 °C, and then cyclohexanecarboxaldehyde (0.13 mL, 1.08 mmol) was added. The reaction mixture was kept at −78 °C for a further 60 min and then transferred by syringe into a rapidly stirred mixture of ethanol (10 mL) and aqueous HCl (2 M, 0.82 mL) at 0 °C. After evaporation of the solvents, the crude reaction mixture was analyzed by ^{1}H-NMR spectroscopy. The benzaldehyde adducts **11a** and **12a** were the main products (>90%, diastereomeric ratio 93:7). The cyclohexanecarboxaldehyde adducts **11f** and **12f** had formed in trace amounts only (<10%).

Metalation of *trans*-1,3-Dithiolane 1,3-Dioxide (10) with 1.2 Equiv of LiHMDS and Its Reaction with Cyclohexanecarboxaldehyde and Benzaldehyde. The reaction was carried out as described above, but the order of aldehyde addition was reversed (i.e., cyclohexanecarboxaldehyde was added first). The crude reaction mixture was analyzed by ^{1}H-NMR spectroscopy. The benzaldehyde adducts **11a** and **12a** (52%, diastereomeric ratio 93:7) and the cyclohexanecarboxaldehyde adducts **11f** and **12f** (48%, diastereomeric ratio 68:32) had formed in nearly equal amounts.

Metalation of *trans*-1,3-Dithiolane 1,3-Dioxide (10) with 2.4 Equiv of LiHMDS and Its Reaction with Benzaldehyde and Cyclohexanecarboxaldehyde. The above experiment was repeated using 2.4 equiv of base and 3.0 equiv of each of the aldehydes, and the crude reaction mixture was analyzed by ^{1}H-NMR spectroscopy. The benzaldehyde adducts **11a** and **12a** (diastereomeric ratio 91:9) were the only products of the reaction.

Metalation of *trans*-1,3-Dithiolane 1,3-Dioxide (10) with 2.4 Equiv of LiHMDS and Its Reaction with Cyclohexanecarboxaldehyde and Benzaldehyde. The reaction was carried out as described above, but the order of aldehyde addition was reversed (i.e., cyclohexanecarboxaldehyde was added first). The crude reaction mixture was analyzed by ^{1}H-NMR spectroscopy. The only products found were the cyclohexanecarboxaldehyde adducts **11f** and **12f** (diastereomeric ratio approximately 70:30).

Acknowledgment. We thank Sheffield University for support.

Supporting Information Available: X-ray analysis including Ortep drawing of **11a** and annotated spectral data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9619443