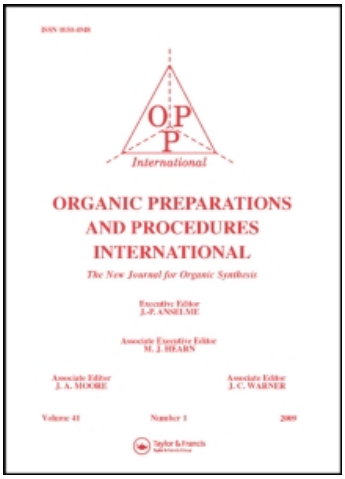

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THE DEVELOPMENT AND APPLICATION OF 1,3-DITHIANE 1-OXIDE DERIVATIVES AS CHIRAL AUXILIARIES AND ASYMMETRIC BUILDING BLOCKS FOR ORGANIC SYNTHESIS. A REVIEW

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THE DEVELOPMENT AND APPLICATION OF 1,3-DITHIANE 1-OXIDE DERIVATIVES AS CHIRAL AUXILIARIES AND ASYMMETRIC BUILDING BLOCKS FOR ORGANIC SYNTHESIS. A REVIEW

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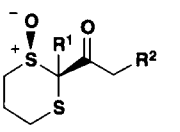
I. INTRODUCTION

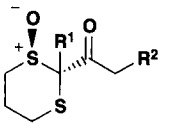
1. Outline

Since 1987 our group at Liverpool has been concerned with the design, synthesis, development, and more recently the application of dithiane 1-oxide derivatives as asymmetric building blocks for organic synthesis. This review focuses on the development of highly diastereoselective reactions, principally carried out at the acyl side chain of 2-acyl dithiane 1-oxide derivatives **1**.

In the early stages of the project, it was reasoned that the sulfoxide unit might be expected to influence the transition state geometry of the 2-acyl side chain, perhaps by chelation to a metal counter ion, and hence control the stereochemistry of a wide range of functional group transformations. Indeed, a chelation control model of the reactivity of the 2-acyl dithiane 1-oxide systems has allowed us to rationalize, and in many cases, predict the stereochemical outcome of most of the reactions studied so far. These predictions have, in many cases, been confirmed by X-ray structure determination of the relative stereochemistries within product structures.[1-4]



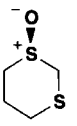
syn-**1**



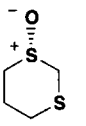
anti-**1**

2. 1,3-Dithiane 1-Oxide: Chiral Auxiliary and Asymmetric Building Block

The dithiane 1-oxide (DiTOX) moiety **2** fulfills the following criteria for an ideal chiral auxiliary:



(*R*)-**2**



(*S*)-**2**

i) DiTOX and its 2-substituted derivatives are readily prepared, generally stable and relatively inexpensive.

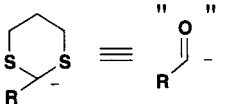
ii) No experimentally difficult chemistry is involved in their preparation.

iii) DiTOX systems are amenable to stereoselective preparation for both sulfoxide enantiomers.

iv) The DiTOX system has been shown to induce high levels of stereoselectivity for a range of reaction types based on carbonyl group reactivity.

v) The DiTOX auxiliary can be readily removed, in high yield, without loss of stereochemical integrity at the newly created asymmetric center.

Interestingly, deprotection (hydrolysis) of the heterocyclic auxiliary exposes a synthetically useful carbonyl group. This is possible in our system since the auxiliary is bonded to the carbonyl group by a carbon atom rather than a heteroatom. Such hydrolyses are well established for 1,3-dithiane derivatives as a result of their ubiquity as synthons for *umpolung* reactivity of the carbonyl group (*Fig. 1*).[5]

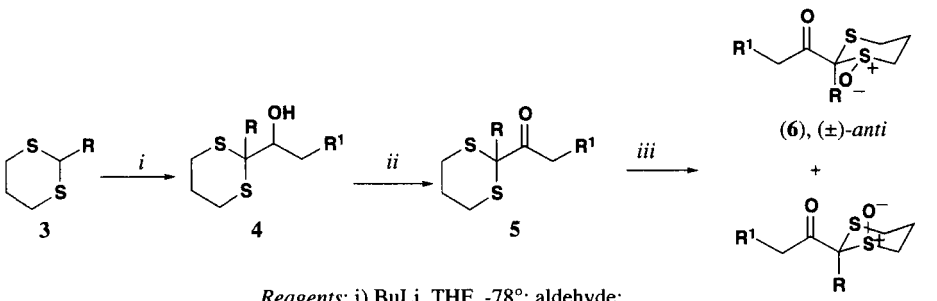


Umpolung Reactivity of 1,3-Dithane

Fig. 1

3. Preparation of Racemic 2-Acyl-2-alkyl-1,3-dithiane 1-Oxide Systems

Our early studies centered on diastereoselective transformations of racemic 2-acyl-2-alkyl-1,3-DiTOX systems, typically prepared as shown in *Scheme 1*.



Reagents: i) BuLi, THF, -78°; aldehyde;
ii) DMSO, TFAA, CH_2Cl_2, -50°; Et_3N; iii) $NaIO_4$, MeOH

(**6**), (±)-*anti* + (**7**), (±)-*syn*

Scheme 1

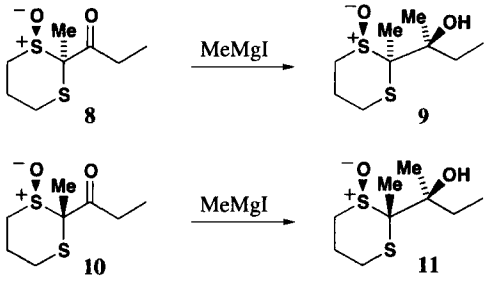
Acyl dithianes **5** may be prepared by reaction of the 2-lithio derivative of the 2-alkyl dithiane **3** with a desired aldehyde to give alcohols **4** which are oxidized using Swern conditions.[6] Racemic sulfur oxidation to yield (±)-*anti* and (±)-*syn* isomers, **6** and **7** respectively, is accomplished with aqueous sodium periodate. The *syn* and *anti* diastereoisomers are readily separated by flash column chromatography, the major isomer (*anti*) generally being the more polar. Interestingly, the *anti* isomers also display a discrete signal in their ^1H NMR spectra (ca. δ 1.7) corresponding to dithiane ring protons at C-5. This signal appears at higher field for the *syn* isomer and is sometimes masked by other resonances.

Unless otherwise stated, racemic 2-acyl-2-alkyl-DiTOX derivatives were used as substrates for the applications described in this review. The preparation of enantiomerically pure 2-acyl-2-alkyl-DiTOX systems are described in a following section.

II. DEVELOPMENT OF THE DiTOX ASYMMETRIC BUILDING BLOCK

1. Diastereoselective Control in the Addition of Grignard Reagents to Ketones[1]

The addition of organometallic reagents to ketones bearing a chiral grouping directly attached to the carbonyl group has been extensively studied by others.[7] Stereoselectivities are often not high[8] unless one of the substituents adjacent to the ketone is capable of chelation with the organometallic reagent.[9] We expected that the sulfoxide unit of the DiTOX auxiliary could influence the course of organometallic attack at the carbonyl group of a 2-acyl-1,3-dithiane 1-oxide system by chelation control. Thus, the reactions of *syn* and *anti* 2-propionyl-2-methyl-1,3-dithiane 1-oxide substrates, **8** and **10** respectively (prepared as described in *Scheme 1*), with methylmagnesium iodide was investigated (*Scheme 2*). The diastereoisomeric ratios for the product alcohols are summarized in *Table 1*. As expected, the diastereoselectivities show a dependence on temperature and solvent.[10] The major product diastereoisomers, **9** and **11** respectively, are shown in *Scheme 2*.



Scheme 2

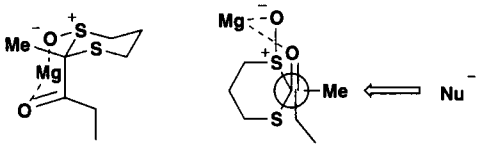
Table 1. Addition of Methylmagnesium Iodide to *syn* and *anti* 2-Propionyl-2-methyl-1,3-dithiane 1-oxide Substrates

Entry	Substrate	Solvent	Temp (°C)	Product	Yield (%)	Ratio of Isomers[a]
a	(**8**)-*syn*	THF	25	(**9**)	70	4 : 1
b	(**8**)	THF	-20	(**9**)	95	*ca.* 25 : 1
c	(**8**)	THF	-78	(**9**)	95	exclusive[b]
d	(**8**)	Et_2O	-20	(**9**)	96	1 : 1.4
e	(**8**)	Et_2O	-78	(**9**)	33	1 : 1
f	(**10**)-*anti*	THF	25	(**11**)	92	3 : 1
g	(**10**)	THF	-20	(**11**)	96	7 : 1
h	(**10**)	THF	-78	(**11**)	95	15 : 1
i	(**10**)	Et_2O	-78	(**11**)	96	3 : 1

a) Determined by 250-MHz ^{1}H NMR. b) Other isomer undetectable by hplc or NMR.

For the *syn* substrate **8**, the approach of the organometallic nucleophile is controlled by the steric bias imposed by the bulky DiTOX ring (*Fig. 2*). The nucleophile approaches the prochiral

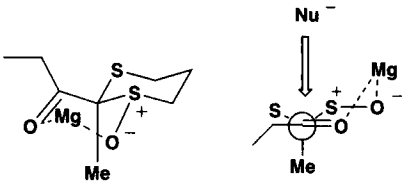
carbonyl group from the direction of the relatively small 2-methyl substituent, giving rise to excellent diastereoselectivities at low temperatures (entries b, c).



Chelated Transition State Model for *syn* Substrate

Fig. 2

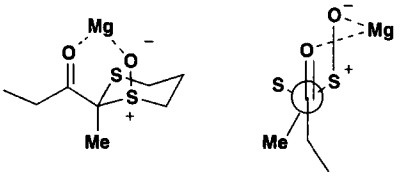
For the *anti* substrate **10**, although the chelated transition state relies solely on the 2-methyl substituent to exert any steric hindrance towards the approach of the Grignard reagent (*Fig. 3*), good stereoselectivities are achieved at low temperature (entry h).



Chelated Transition State Model for *anti* Substrate

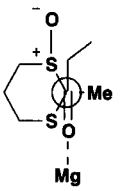
Fig. 3

Literature precedent indicated that THF was the solvent of choice for stereoselective Grignard additions.[11] Our systems were found to behave accordingly, with higher product diastereoselectivities observed in THF than in diethyl ether. Although most reactions of *syn* and *anti* substrates listed in Table 1 gave products corresponding to the Cram-type chelated transition states described above, in one instance substrate **8** gave a product ratio which violated the expected pattern (entry d). In this case an alternative chelated transition state containing an axial sulfoxide may apply (*Fig. 4*), or possibly an open transition state[7] or dipolar system (*Fig. 5*).[12]



syn Substrate-Axial Sulfoxide

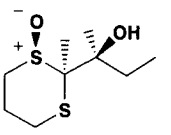
Fig. 4



syn Substrate-Dipolar Transition State

Fig. 5

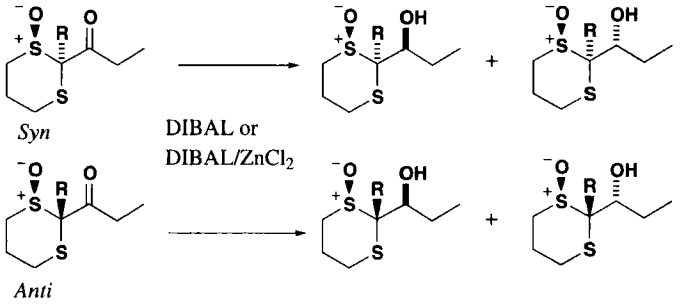
The major product diastereoisomer **12** from addition of methylmagnesium iodide to *syn* substrate **8** was isolated by recrystallization, and the structure solved by X-ray analysis. The structure was found to be in accordance with the expected chelated transition state (*Fig. 2*) and approach of the nucleophile from the least hindered face of the carbonyl group.



12

2. Highly Diastereoselective Reduction of Ketones[3]

The stereoselective reduction of ketones has been previously reported using chirally modified hydride reagents[13] and by chiral auxiliary approaches.[14] We turned our attention to this important synthetic transformation and were pleased to find that racemic 2-acyl-2-alkyl-1,3-dithiane 1-oxide



Scheme 3

Table 2. Diastereoselective Reduction of 2-Acyl-2-alkyl-1,3-dithiane 1-oxide Substrates

Entry	Substrate	R	Reagent	Yield (%)	Ratio of Isomers[a]	Comment[b]
a	*syn*	Me	DIBAL	45	exclusive	
b	*syn*	Me	DIBAL/$ZnCl_2$	75	7:1	Opposite to (a)
c	*syn*	Et	DIBAL	25	exclusive	
d	*syn*	Et	DIBAL/$ZnCl_2$	83	exclusive	Opposite to (c)
e	*syn*	Ph	DIBAL	25	exclusive	
f	*syn*	Ph	DIBAL/$ZnCl_2$	83	1.7:1	Same as (e)
g	*anti*	Me	DIBAL	40	exclusive	
h	*anti*	Me	DIBAL/$ZnCl_2$	85	exclusive	Opposite to (g)
i	*anti*	Et	DIBAL	50	10.5:1	
j	*anti*	Et	DIBAL/$ZnCl_2$	42	36:1	Same as (i)
k	*anti*	^{i}Pr	DIBAL	21	exclusive	
l	*anti*	^{i}Pr	DIBAL/$ZnCl_2$	81	exclusive	Opposite to (k)
m	*anti*	Ph	DIBAL	42	exclusive	
n	*anti*	Ph	DIBAL/$ZnCl_2$	80	6.3:1	Opposite to (m)

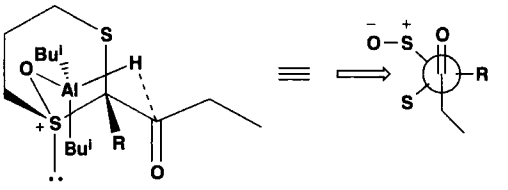
a) Determined by ^{1}H and/or ^{13}C NMR spectroscopy; exclusive diastereoselectivity indicates that minor isomer was not detected. b) Refers to "sense" of diastereoselection.

substrates underwent reduction to the corresponding secondary alcohols with extremely high levels of diastereoselectivity (*Scheme 3*, *Table 2*).[3] In our study, the reduction reactions were carried out using diisobutyl aluminum hydride (DIBAL) or DIBAL/$ZnCl_2$ mixtures in THF at low temperature (-78°). These reaction conditions and reagents were known to provide high levels of stereoselectivity in reduction of acyclic β-ketosulfoxides.[15]

Transition state models for reduction according to our usual model of chelation-controlled 2-acyl 1,3-dithiane 1-oxide reactivity, together with steric approach control were proposed to rationalize the high levels of observed stereoselectivity. Previous work by Solladié suggests that ketone reduction by the DIBAL/$ZnCl_2$ system does indeed involve such chelated transition states.[15]

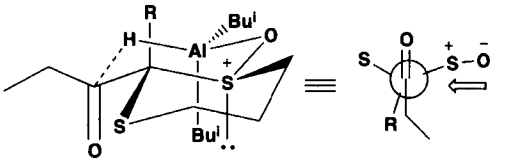
As can be seen from *Table 2*, very high stereoselectivities could be observed for both *syn* and *anti* substrates depending on the 2-alkyl substituent (R). In the absence of $ZnCl_2$, a non-chelated chair-like transition state was anticipated, following the Solladié model, with intramolecular hydride transfer. This process was expected to lead to an opposite sense of selectivity to that observed for the chelation controlled model (with DIBAL/$ZnCl_2$). This reversal in stereoselectivity was indeed observed for some substrates (See *Table 2*), however in several cases the selectivity was found to have the same sense as the chelation-controlled method. While we cannot fully explain this rather curious feature using our present rationale, the effect of the size of the R group on transition state conformation may be a factor. We should prefer not to speculate further as our simple model of acyl DiTOX reactivity does not take into account the role of solvent, electrostatic and aggregation effects. It has nonetheless remained a useful predictive working model throughout our studies.

Figure 6 [*syn* substrates, *via* major reactive conformation **13**] and *Figure 7* [*anti* substrates, *via* major reactive conformation **14**] were postulated as transition state models to explain the highly stereoselective intramolecular hydride transfer in DiTOX substrates.



13

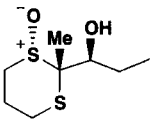
Fig. 6



14

Fig. 7

The sense of stereoselectivity expected through application of our transition state models was borne out by single crystal X-ray structure determination.



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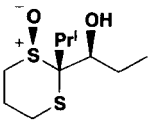
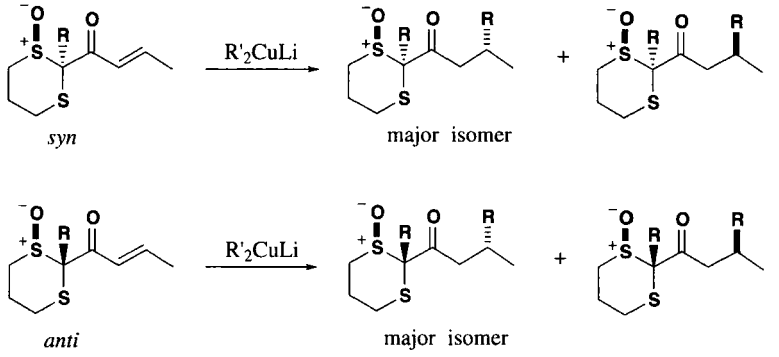


16

Structure **15** shows the product of DIBAL reduction of *syn*-2-propionyl-2-methyl-1,3-dithiane 1-oxide (entry a, *Table 2*), and **16** shows the product of DIBAL/$ZnCl_2$ reduction of *anti*-2-propionyl-2-isopropyl-DiTOX (entry l, *Table 2*).

3. Stereoselective Conjugate Addition of Lithium Organocuprate Reagents to α,β-Unsaturated 2-Acyl-2-alkyl-1,3-dithiane 1-Oxide Substrates

A number of methods for the asymmetric control of conjugate addition of organocopper reagents to α,β-unsaturated acyl derivatives have been developed.[16-18] We were able to demonstrate interesting levels of diastereoselectivity in conjugate addition of lithium organocuprate reagents to racemic 2-acyl-2-alkyl DiTOX substrates (*Scheme 4*).



syn major isomer

anti major isomer

Scheme 4

As a result of our earlier investigations, we anticipated that rapid complexation should occur between the organometallic reagent and the enone substrate involving bidentate co-ordination of the sulfoxide and carbonyl group oxygen atoms to the metal counterion. *Table 3* shows our results for *syn* and *anti* DiTOX substrates.

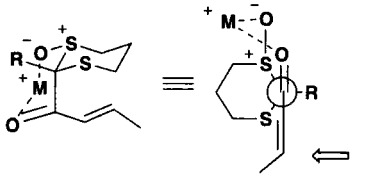
The proposed chelated transition state models are analogous to those previously presented. *Syn* substrates containing axial sulfoxide units would not be expected to show much selectivity. In the case of *anti* substrates, no chelation is possible in conformations containing axial sulfoxides.

For *syn* substrates, in the equatorial sulfoxide conformation **17**, the bulk of the dithiane ring effectively shields one face of the π-system, the other face being exposed unless a very large 2-alkyl group is present.

Table 3. Conjugate Addition to α,β-Unsaturated 2-Acyl-2-alkyl-1,3-dithiane 1-oxide Substrates

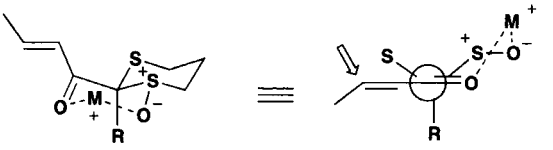
Substrate	R	Reagent	Yield (%)	Ratio of Isomers[a]
syn	Me	Bu_2CuLi	84	4.3:1
syn	Me	Ph_2CuLi	95	2.3:1
syn	Et	Bu_2CuLi	73	10.5:1
syn	Et	Ph_2CuLi	67	3.2:1
syn	Ph	Bu_2CuLi	80	6.6:1
syn	Ph	Ph_2CuLi	70	3.4:1
anti	Me	Bu_2CuLi	84	2.0:1
anti	Me	Ph_2CuLi	83	1.2:1
anti	Et	Bu_2CuLi	50	2.0:1
anti	Et	Ph_2CuLi	87	4.0:1
anti	Ph	Bu_2CuLi	75	2.0:1
anti	Ph	Ph_2CuLi	60	2.3:1

a) Determined by ^1H and/or ^{13}C NMR spectroscopy



17

For *anti* systems such as **18** in the equatorial sulfoxide conformation, only the 2-alkyl substituent is available to hinder reagent approach, and selectivity should rise as this group becomes larger.



18

While such transition state models have helped us to rationalize the patterns of selectivity observed in other reactions of 2-acyl-1,3-dithiane 1-oxide substrates, such clear trends are not found in conjugate addition reactions (*Table 3*). One simple explanation for the poorer levels of stereoselectivity may be bond rotation within the acyl substituent, allowing the enone moiety to attain other conformations to those shown in models **17** and **18**.

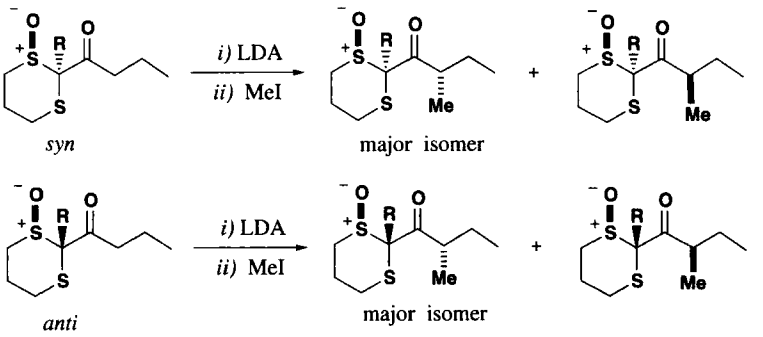
4. Stereoselective Functionalization of Enolates Derived from 2-Acyl-2-alkyl-1,3-dithiane 1-Oxides

a) Stereoselective Enolate Alkylation

There has been much interest over recent years in the enantio- and diastereocontrol of enolate alkylation.[19] Most methods which do not rely upon asymmetric alkylating agents hinge upon derivatization of the ketonic substrate with an enantiomerically pure auxiliary. Examples of such chiral auxiliaries include oxazolines[20] and oxazolidinones[21].

We reasoned that the sulfoxide unit present in our 2-acyl-2-alkyl-1,3-dithiane 1-oxide substrates might be expected to influence the transition state geometry of a ketone enolate, perhaps by chelation to a metal counterion, and hence control the stereochemistry of alkylation.

In our initial studies,[4,22] *syn* and *anti* 2-butyryl-2-alkyl-1,3-dithiane 1-oxides were prepared by our standard means and were enolized using a suitable non-nucleophilic base (LHMDS) in THF at low temperature. The resulting enolate was subjected to alkylation with iodomethane and the diastereoselectivities were determined by ^{1}H-NMR analysis of the crude product mixture. Our results are summarized in *Scheme 5* and *Table 4*.



Scheme 5

Table 4. Alkylation of Enolates of 2-Acyl-2-alkyl-1,3-dithiane 1-Oxide Substrates

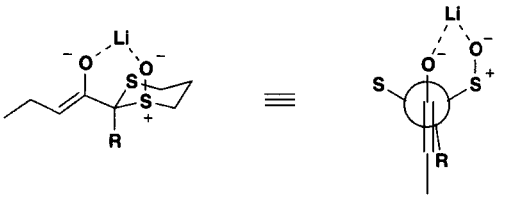
Substrate	R	Temp. (°C)	Ratio of isomers[a]
syn	Me	-78	25:1
syn	Et	-100	20:1
syn	^{i}Pr	-100	3:1
syn	Ph	-100	1:1
syn	^{t}Bu	-78	–
anti	Me	-100	2.6:1
anti	Et	-100	exclusive[b]
anti	^{i}Pr	-100	25:1
anti	Ph	-78	1:1.3
anti	^{t}Bu	-78	–

a) Determined by ^{1}H NMR spectroscopy. b) Minor isomer not detected by 250-MHz NMR spectroscopy.

Interestingly, the enolates were trapped as the corresponding silyl enol ethers, and NMR analysis revealed exclusive formation of one geometrical isomer, presumed to be the thermodynamically more favorable *Z* isomer.[23]

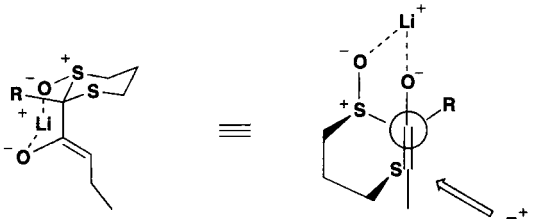
From *Table 4* it is apparent that a major controlling factor in governing the levels of product diastereoselection is the relative size of the 2-alkyl substituent (R). For *syn* substrates, the highest levels of diastereoselectivity are observed with a methyl group as the 2-substituent, whereas for *anti* substrates, ethyl gives the highest levels.

Application of our usual chelated transition state models allows us to rationalize the effect of the 2-alkyl substituent. For *syn* systems, conformations containing axial sulfoxides [e.g. **19**], which could occur for very small (axial) 2-substituents (e.g. proton), would be expected to provide only low levels of selectivity.



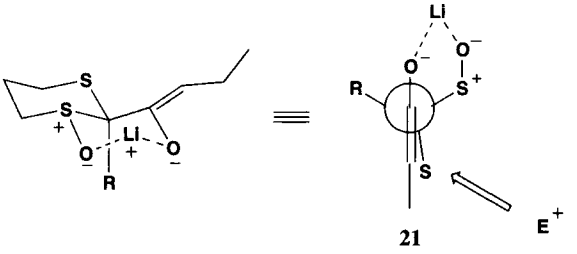
19

In the alternative, equatorial, sulfoxide conformation **20**, one face of the enolate is effectively shielded by the bulk of the dithiane ring, the other face being exposed unless a very large 2-alkyl substituent is present. Stereoselectivity is therefore expected to become poorer as the relative size of the (equatorial) 2-alkyl substituent is increased, an effect which can be observed in the results outlined in *Table 4* on moving from R = Me to R = Ph.



20

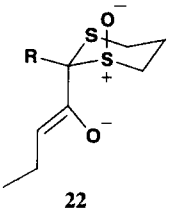
For *anti* substrates, if the 2-alkyl substituent is axial, reasonable except for very large groups (e.g. *tert*-Bu, Ph), the sulfoxide can adopt the equatorial chelated conformation **21**. Conversely to *syn* substrates however, although one face of the enolate is again partially shielded by the 2-alkyl substituent, the bulk of the dithiane ring is distant from the reacting center, and stereoselectivity is expected to be governed solely by the size of the 2-alkyl substituent. The stereoselectivity is therefore expected to improve as the relative size of the 2-alkyl substituent increases, as is indeed observed in *Table 4* on moving from 2-methyl to 2-ethyl substituents.



21

In the axial sulfoxide conformation **22**, which may occur for *anti* substrates with very bulky 2-alkyl substituents which may prefer an equatorial orientation (e.g. phenyl, *tert*-butyl), the acyl substituent is required to be axial. No chelation is possible and stereoselectivity is expected to be low. Hence a fall in diastereoselectivity is observed on moving from the 2-ethyl to 2-phenyl substituent (*Table 4*).

It is important to note that on applying the transition state models described above, the sense of stereochemical induction expected at the newly created chiral center is predicted to be the same for both *syn* and *anti* substrates for either sulfoxide conformation:



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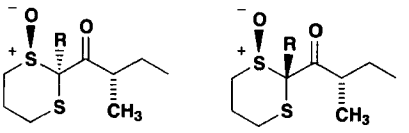


syn sulfoxide *anti* sulfoxide

This prediction was verified by X-ray structure determination of one of the major product diastereoisomers produced in the *anti* series. The structure was found to be consistent with the transition state models applied, and the intermediate formation of a chelated *Z*-enolate.

From these and other studies we have developed a rule of thumb for prediction of stereochemical induction during enolate derivatization: for both *syn* and *anti* substrates, the relative stereochemistry at the newly created asymmetric center is opposite to that of the sulfoxide moiety.

b) Asymmetric Mannich Reactions[24]

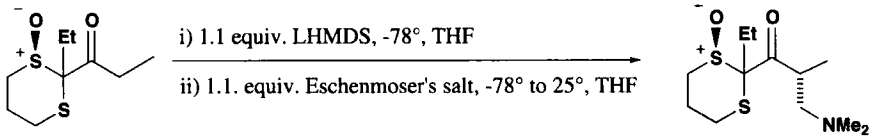
Our enolate alkylation methodology has been subsequently extended to include asymmetric Mannich reactions. The Mannich reaction can be viewed as an imino analogue of the aldol reaction and is a very common synthetic method for the preparation of β-aminoketones.

Although methods for stereocontrol of the aldol reaction are well documented, including diastereofacial selectivity in reactions of chiral enolates,[25] stereocontrol in Mannich reactions appears to have received relatively little attention.[26-30]

In our studies, we employed the 2-propionyl-2-ethyl-1,3-dithiane 1-oxide substrates, since our previous work on enolate alkylation had demonstrated optimum levels of stereocontrol with an

ethyl group as 2-substituent.[22]

Mannich reactions were first performed using commercially available Eschenmoser's salt as the aminoalkylating agent with enolates derived from *syn* and *anti* 2-propionyl-2-ethyl-1,3-dithiane 1-oxides under a variety of reaction conditions and using a range of metal counterions (*Scheme 6, Table 5*).



Scheme 6

Table 5. Mannich Reaction of Enolates of 2-Propionyl-2-ethyl DiTOX Substrates using Eschenmoser's Salt as Aminoalkylating Agent

Substrate	Metal	Temp. (°C)	Ratio of isomers[a]
syn	Li	-78	6:1
syn	Zn	-78	6:1
syn	B	-78	4:1
anti	Li	-78	1.6:1
anti	Zn	-78	1.6:1
anti	B	-78	1.4:1

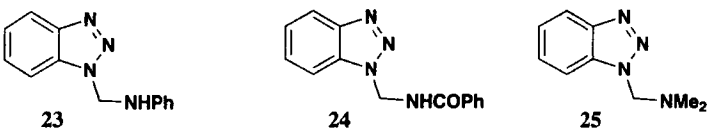
a) Determined by ^{1}H NMR spectroscopy.

Table 5 shows that no significant increase in product diastereoselectivity was observed on variation on the metal counter-ion.

Given that a larger and perhaps less reactive electrophile might distinguish between the faces of the prochiral enolate to a higher degree than does Eschenmoser's salt, and so lead to an increase in diastereoselectivity, we chose to employ the benzotriazole-based aminoalkylating agents **23 - 25** pioneered by Katritzky (*Table 6*).[31]

We were pleased to isolate the desired aminoalkylated products in good yields and, in most cases, with extremely high diastereoselectivity. The use of benzotriazole derivative **24** results in the stereoselective introduction of a primary amine equivalent.

The high levels of diastereoselectivity were rationalized through our usual transition state models for enolate derivatization. X-ray analysis of the product obtained on reaction of the *anti* enolate with benzotriazole derivative **23** confirmed that the sense of induced stereoselectivity for the major product isomer **26** was as predicted from the transition state model, and is shown below.

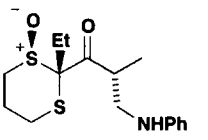


23 **24** **25**

Table 6. Mannich Reaction of Enolates of 2-Propionyl-2-ethyl-1,3-dithiane 1-oxide Substrates using Benzotriazole Derivatives as Aminoalkylating Agents

Substrate	Benzotriazole	Temp. (°C)	Yield (%)	Ratio of isomers[a]
anti	**23**	-78	72	≥48:1[b]
syn	**23**	-78	61	≥54:1[b]
anti	**24**	-78	81	36:1
syn	**24**	-78	72	≥40:1[b]
anti	**25**	-78	–	–
syn	**25**	-78	64	1:1

a) Determined by ^{1}H NMR spectroscopy. b) Minor isomer not detected by 400-MHz NMR spectroscopy.



26

From the high levels of product diastereoselectivities observed when employing benzotriazole derivatives **23** and **24**, we reasoned that addition of 1 molar equivalent of benzotriazole to a stirred solution of Eschenmoser's salt at room temperature prior to reaction with the lithium enolate might provide an increase in diastereoselectivity by forming a similar "masked" iminium ion *in situ*. Under these conditions, an increase in diastereoselectivity was indeed observed for the *anti* substrate (up to 3:1), although no improvement was seen with the *syn* isomer.

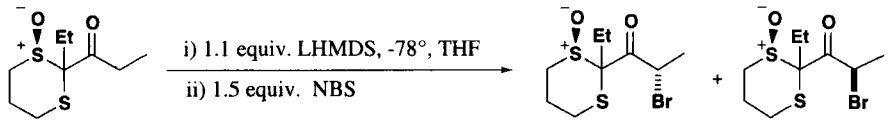
Subsequently the benzotriazole-based equivalent of Eschenmoser's salt, **25**, was prepared in our laboratory. Curiously, we found this substrate not only to be considerably less reactive than **23** or **24**, but also less reactive than the Eschenmoser's salt/benzotriazole system, suggesting that **25** is not formed *in situ* by mixing these two reagents.

One possible explanation is provided by considering the probable reactive intermediates involved: fragmentation of **25** with effective loss of a benzotriazole anion must necessarily give rise to a reactive, and therefore less selective, iminium salt; while concomitant proton loss from **23** or **24** could give rise to a less reactive neutral imine by similar, but more facile, fragmentation.

c) Stereoselective Enolate Bromination as an Approach to α-Halocarboxylic Acids and α-Aminoketones[32]

α-Haloketones are useful synthetic intermediates,[33] and may be derived from enolates by treatment with sources of electrophilic halide. This methodology has been applied by others[34,35]as a stereoselective approach to chiral α-aminoacids.

Our now favored 2-propionyl-2-ethyl-1,3-dithiane 1-oxide substrates were deprotonated using LHMDS at -78° in THF, and were treated with solid *N*-bromosuccinimide. A selection of results is presented in *Scheme 7* and *Table 7*.



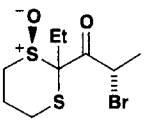
Scheme 7

Table 7. Diastereoselective Bromination of 2-Propionyl-2-ethyl-1,3-dithiane 1-Oxides

Substrate	Metal	Reagent	Yield (%)	Ratio of isomers[a]
syn	Li	NBS	59	1:2.5
anti	Li	NBS	73	1:1
syn	B	NBS	87	1.67:1
anti	B	NBS	92	5.5:1[b]

a) Determined by ^{1}H NMR spectroscopy. b) *Syn* material - see text.

The sense of induced stereoselectivity for all reactions carried out on each substrate was assessed in each series on the basis of ^{1}H NMR evidence. The structure of the minor isomer from bromination of the lithium enolate derived from the *syn* substrate was determined by X-ray crystallographic analysis. The relative stereochemistry is as shown in **27**. The changes in stereoselectivity observed upon the change in counter-ion (see *Table 7*) may result simply from the butyl groups carried on the boron atom altering the reacting conformation or the sterically-controlled approach of the electrophile.

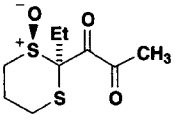


27

A particularly curious but entirely reproducible result is that obtained from the boron enolate derived from the *anti* propionyl substrate. In this case, the halogenated product isolated has the *syn* configuration around the dithiane moiety, with only a trace of *anti* material remaining. An isomerization from *anti* to *syn* has therefore taken place under the reaction conditions, perhaps the result of an equilibration process. Such *anti* to *syn* isomerization could not, however, be induced to take place under a range of conditions, including treatment with NBS,[36] with either the starting material or brominated *anti* material prepared using a lithium enolate. We have previously observed *syn* to *anti* equilibration in acyl dithiane oxides upon treatment with trifluoroacetic anhydride.[37]

α-Haloketones are themselves useful synthetic intermediates;[38] given the ready conversion of acyl dithiane oxides into the corresponding acids,[39] the 2-ethyl-2-(2-haloacyl)-1,3-dithiane 1-oxides can be regarded as protected α-halocarboxylic acids, which have found use in the synthesis of a variety of products including herbicides and pharmaceuticals.[40]

We envisaged one potential application of the 2-ethyl-2-(2-haloacyl)-1,3-dithiane 1-oxides **27** as precursors to α-aminated products, by using nitrogen-based nucleophiles. Ammonia, benzylamine and tetramethyl guanidinium azide were all unsuccessful as nucleophiles in displacement reactions, resulting either in racemization at the halogenated chiral center or protiodebromination of the substrate. Further, we were surprised to isolate in excellent yield the 1,2-diketone **28** from attempted sodium azide displacement. A transformation of α-azidoketone to diketone has however been reported in the literature.[32,41]



28

Our most successful introduction of nitrogen using a nucleophilic amination procedure was realized using potassium phthalimide in DMSO solution at 30-40° over 12-18 hours. A selection of the results is given in *Table 8*.

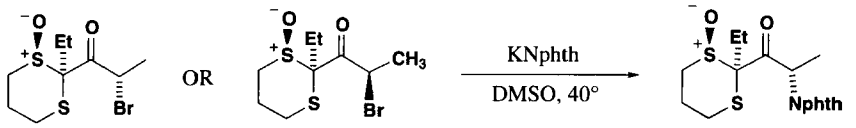


Table 8. Phthalimide Anion Displacement Reactions with 2-(2-Bromoacyl)-2-ethyl-1,3-dithiane 1-oxide Substrates

Substrate	Isomer	Yield (%)	Ratio of isomers
syn	Major	91	2:1
syn	Minor	95	2:1

It is clear that we obtain a dramatic change in stereochemistry in the isolated product mixtures. The ratio of isomers in each case has fallen to *ca.* 2:1, and the *same* isomer predominates regardless of the stereochemistry of the starting material at the brominated center. We interpret this observation as a result of equilibration of the asymmetric center through enolization resulting from deprotonation after displacement by excess phthalimide anion under the reaction conditions, or through attack by displaced bromide anion. Overall the chemistry does provide the nucleus of a high yielding approach to chiral α-aminoketones, but the reduction in stereochemical integrity following the nitrogen displacement step invariably limits the synthetic application.

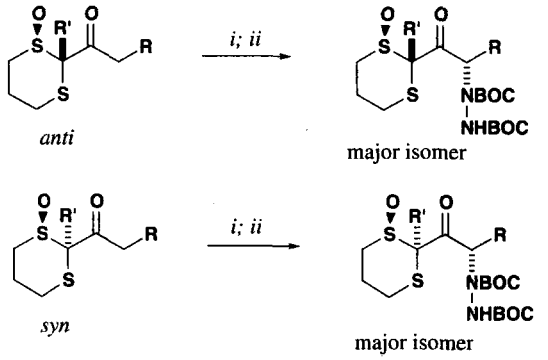
d) Diastereoselective Enolate Amination as an Approach to α-Aminoketones[42]

We have demonstrated that the Mannich reaction is successful for the highly stereoselective introduction of β-aminoketone moieties (Section 2 b)[24]). The diastereofacially selective electrophilic amination of enolates is attractive as a complementary approach to the asymmetric preparation of α-aminoketones, and is commonly used in the preparation of α-aminoacids.[43-50]

Due to the problems encountered during our nucleophilic amination as an approach to α-aminoketones, we investigated an alternative electrophilic amination procedure which would, if successful, actually provide a more direct approach to these target systems. We chose to employ di-*tert*-butyl azodicarboxylate (DBAD) as the electrophilic aminating reagent.[46-50] This reagent offers several advantages: it is a stable, crystalline solid available commercially, methods for removal of the *t*-Boc protecting groups under mild non-racemizing conditions are well documented, and they are complementary to the known methods for N-N bond cleavage.[46-50]

The corresponding lithium enolates were generated from *syn* and *anti* 2-propionyl-2-ethyl-1,3-dithiane 1-oxide substrates in dry THF solvent at -78° using LHMDS, and were added *via* cannula to pre-cooled solutions of DBAD in dry THF at -78°. Interestingly, a diastereoselectivity of only 2:1 was observed with the *anti* substrate if the reaction mixture was allowed to reach room temperature over 12 hours before quenching the reaction with saturated aqueous ammonium chloride solution. If the reaction mixture was quenched at -78° with glacial acetic acid after only 10-15 minutes of reaction time

with DBAD, the resulting diastereoselectivity was much improved to ≥99:1; only one product isomer was detected by 400-MHz ^{1}H NMR spectroscopy (*Scheme 8*). Further results are given in *Table 9*.



Reagents: i) LHMDS (1.1 equiv.), -78°, THF
ii) DBAD (1.1 equiv.), THF, -78°, 15 min; HOAc, -78°

Scheme 8

Table 9. Diastereoselectivity of Electrophilic Amination of 2-Acyl-2-alkyl-1,3-dithiane 1-oxides

Substrate	R	R'	Yield (%)	Ratio of isomers[a]
anti	Me	Me	69	2:1
anti	Me	Et	48	≥99:1
anti	Me	Ph	37	2.7:1
syn	Me	Me	76	3:1
syn	Me	Et	42	12:1

a) Determined by ^{1}H NMR spectroscopy.

It is interesting to note that the effect of the 2-alkyl substituent closely parallels the results obtained in our studies of enolate alkylation.

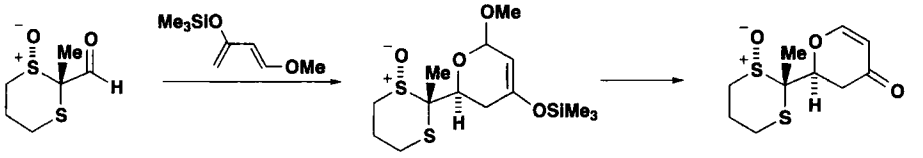
The major isomer proved to have the same relative stereochemistry from both the -78° quench and room temperature quench. The low temperature acetic acid quench may prevent loss of stereochemical integrity at the new asymmetric center, which may occur at higher temperatures. The pattern of diastereoselectivity was rationalized on the basis of our usual chelation control models.

5. Chelation Mediated Facially Selective Cycloaddition Reactions[51]

The Diels-Alder reaction is an extremely useful synthetic tool. The reaction displays excellent regio- and stereoselectivity, and these properties have been exploited in the synthesis of many natural product systems. [52]

We aimed to develop facially selective Diels Alder reactions using our DiTOX methodology. Such methodology has been the goal of many research groups, and several useful chiral auxiliaries have been developed to accomplish this aim.[53]

Syn-2-formyl-2-methyl-1,3-dithiane 1-oxide undergoes efficient cycloaddition reaction with Danishefsky's diene with excellent levels of diastereoselectivity in the presence of magnesium bromide at -78° (Scheme 9, Table 10).



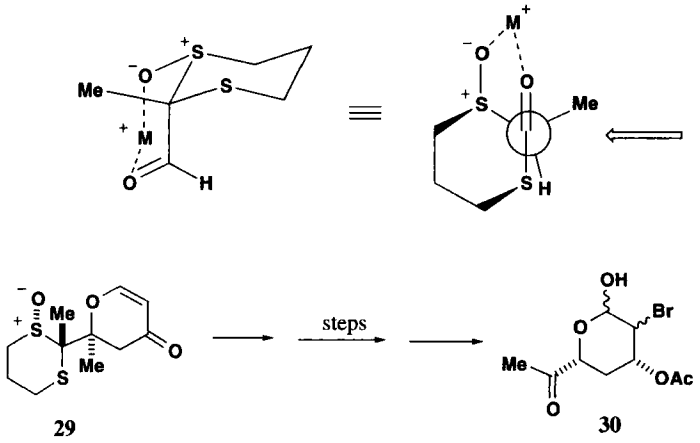
Scheme 9

Table 10. Diastereoselective Cycloaddition Reactions of Danishefsky's Diene with 2-Formyl-2-methyl-1,3-dithiane 1-Oxide

Substrate	Lewis Acid	Solvent	Yield (%)	Ratio of isomers[a]
syn	$ZnCl_2$	THF	82	2.1:1
syn	$MgBr_2$	THF	80	exclusive
syn	$MgBr_2$	toluene	15	exclusive
syn	$MgBr_2$	CH_2Cl_2	60	exclusive
anti	$ZnCl_2$	THF	53	2:1
anti	$MgBr_2$	THF	20	3.3:1

a) Determined by ^1H NMR spectroscopy

Chelation control models, which are similar to those described previously by us and others,[54] were proposed to rationalize the observed stereoselectivity. The proposed transition state model for the *syn* system is shown below. The structure of the major product diastereoisomer **29** was confirmed by X-ray single crystal analysis and conformed to the proposed model. Compound **29** was subsequently elaborated to yield a diastereoisomeric mixture of the pyranose derivative **30**.



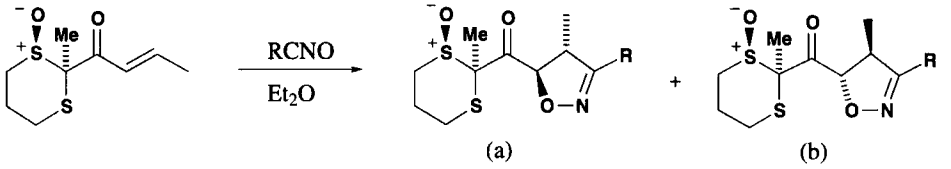
29 **30**

As is apparent from *Table 10*, yields of the cycloadducts and levels of stereoselectivity are

highly dependent upon several factors including solvent, reaction temperature and Lewis acid. One might expect solvents such as petroleum ether to favor chelated transition states by virtue of their less polar nature, but evidently the solvent effect is more complex than this. Surprisingly, only two of the Lewis acids examined gave isolable products. Yields and levels of product diastereoselectivity were generally lower for the *anti* substrate than for the *syn* isomer.

6. Regio- and Stereoselective 1,3-Dipolar Cycloaddition Reactions[55]

1,3-Dipolar cycloadditions provide a convenient and useful method for the preparation of a wide range of five-membered ring heterocycles,[56] often producing a high degree of stereocontrol as a consequence of a concerted mechanism.[57] We have recently investigated the reactions of nitrile oxides with 2-alkyl-2-crotonyl-1,3-dithiane 1-oxide substrates. The reactions proved to be remarkably regioselective, with only the 5-acyl dihydroisoxazoles being isolated, as highlighted in *Scheme 10* for the *syn*-2-methyl-2-crotyl-1,3-dithiane 1-oxide substrate.

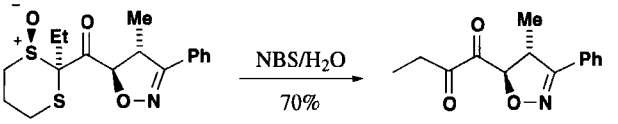


Scheme 10

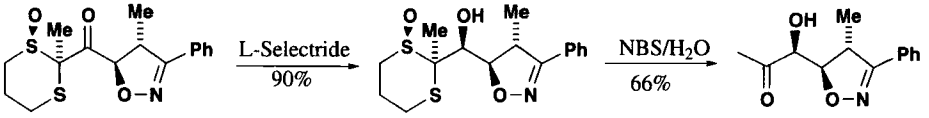
The product diastereoselectivity (a:b) was found to be relatively low for all substrates (up to 5:1), with the *syn* substrates favoring the formation of isomer (a), while the *anti* substrates tend to favor formation of isomer (b), suggesting that it is the stereochemistry at the 2-position of the dithiane unit which is exerting the greatest influence over the stereochemical course of the reactions. This observation is interesting since it contrasts directly with the pattern of stereoselectivities found in our other investigations of dithiane oxides as stereocontrol elements, where the sulfoxide is the principal controlling factor.

As with our other acyl dithiane oxide systems, the thioacetal moiety can be readily removed by hydrolysis, in this case without affecting the dihydroisoxazoline ring (*Scheme 11*).

In order to achieve chemodifferentiation of the two ketone groups, carbonyl reduction may be carried out prior to NBS-mediated hydrolysis. Reduction with L-Selectride was found to be highly efficient and stereoselective, producing only one diastereoisomer of the product alcohol (*Scheme 12*).



Scheme 11

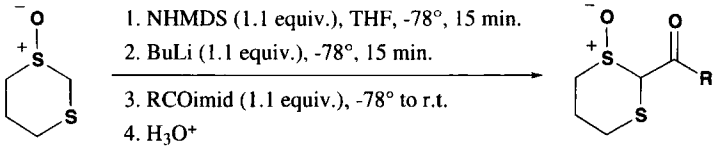


Scheme 12

III. DERIVATIZATION OF DiTOX

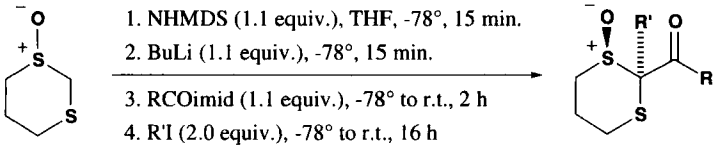
1. Acylation

In our early work, preparation of 2-acyl-1,3-dithiane 1-oxide substrates relied on a lengthy procedure from 1,3-dithiane (see Section I, 3). Lately, however, we have made considerable advances, having solved the unexpectedly difficult problem of acylation of DiTOX itself. Acylation is efficiently achieved using *N*-acyl imidazoles under mixed base conditions (sodium hexamethyl disilazide/butyllithium) to yield the desired 2-acyl-1,3-dithiane 1-oxides in good yields after protic work up (*Scheme 13*).[58]



Scheme 13

We are also now able to prepare 2-acyl-2-alkyl-1,3-dithiane 1-oxides, our most commonly used substrates, in a one-pot application of this procedure.[59] Using mixed base conditions, we were able to isolate the desired DiTOX derivatives in moderate to good yield (*Table 11*), and with excellent levels of diastereoselectivity. Interestingly, the isomer formed predominantly has the *syn* configuration. This route is therefore complementary to our earlier route involving sulfur oxidation as the final synthetic step, which provides predominantly *anti* material.

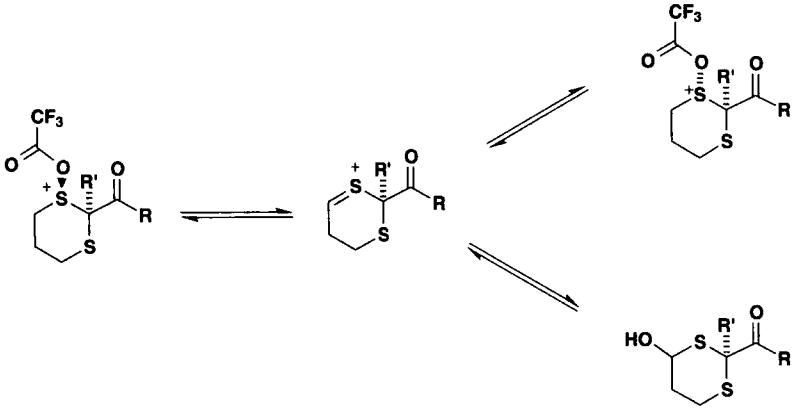


In addition, we have discovered that the *syn* isomers are cleanly converted into *anti* by low temperature treatment with trifluoroacetic anhydride. The mechanism appears to proceed through a Pummerer-type mechanism, as outlined in *Scheme 14*. Isolation of small amounts of intermediate **31** supports this hypothesis.[60]

Table 11. One-Pot Generation of 2-Acyl-2-alkyl-1,3-dithiane 1-Oxides

R	R'	Yield (%)	Selectivity (*syn/anti*)
Me	Me	65	7 : 1
Me	Et	54	exclusive[a]
Me	CH_2=$CHCH_2$	73	exclusive
Et	Me	73	exclusive
Et	CH_2=$CHCH_2$	75	15 : 1
Bu	Me	71	exclusive
Bu	CH_2=$CHCH_2$	66	4 : 1
4-*tert*-Bu-Ph	Me	67	exclusive

a) Minor isomer not detectable by 400-MHz ^{1}H NMR spectroscopy



Scheme 14 **31**

2. Perkin Ring Synthesis

Anions derived from DiTOX undergo efficient Perkin ring synthesis on treatment with dihaloalkanes to provide cycloalkane rings of up to 7 members (*Table 12*).[59]

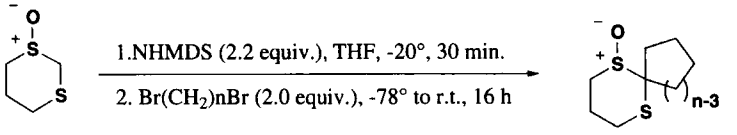


Table 12. Perkin Ring Synthesis using DiTOX

n	Yield (%)
4	75
5	79
6	81

3. One-Pot Stereocontrolled Cycloalkanone Synthesis [59]

An application of the methodology described above allows a one-pot stereocontrolled cycloalkanone synthesis. We were pleased to find that using the mixed base methodology followed by sequential treatment with *N*-acyl imidazole and a diiodoalkane led to the corresponding haloalkylated material formed exclusively with *syn* stereochemistry. Further treatment with NHMDS gave, in two cases, cyclization to carbocyclic products with sufficiently high diastereoselectivity that the minor isomer could not be detected by 400-MHz ^{1}H NMR spectroscopy (*Table 13*)

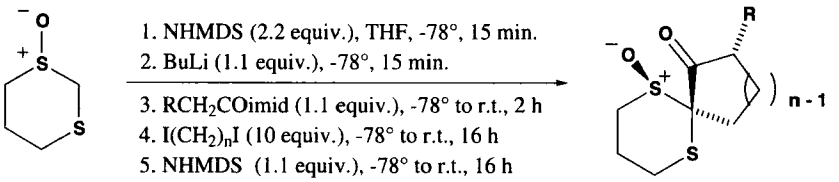


Table 13. One-Pot Stereocontrolled Cyclizations using DiTOX

R	n	Yield (%)	Selectivity (*syn/anti*)
Me	3	–[a]	–
Me	4	72	exclusive
Me	5	74	exclusive
Me	6	–[b]	–
Et	4	60	≥4 : 1
Et	5	63	exclusive

a) *syn*-2-allyl-2-propionyl-1,3-dithiane 1-oxide isolated (78%). b) uncyclized haloalkylated material isolated (64%)

Two new asymmetric centers and two new C-C bonds are therefore each formed in these one pot cyclization reactions with extremely high stereoselectivity. Curiously it is the seven and eight membered ring compounds which are most readily formed. Reaction with 1,3-diiodopropane gave preferential elimination of HI to provide only *syn*-2-allyl-2-propionyl-1,3-dithiane 1-oxide, while 1,6-diiodohexane gave the haloalkylated material but did not undergo cyclization to the nine-membered ring.

The relative stereochemistry indicated in the product structures in *Table 13* is as predicted from earlier enolate alkylation studies[4,22] and from knowledge of a favored *syn* intermediate haloalkylated species (*vide infra*). Presumably, conformations adopted by the intermediates are such that cyclization is favored only for a limited range of ring sizes.

IV. ASYMMETRIC SULFOXIDATION OF 2-ACYL-1,3-DITHIANES: *Enantioselective Synthesis of Enantiomerically Pure DiTOX Substrates*

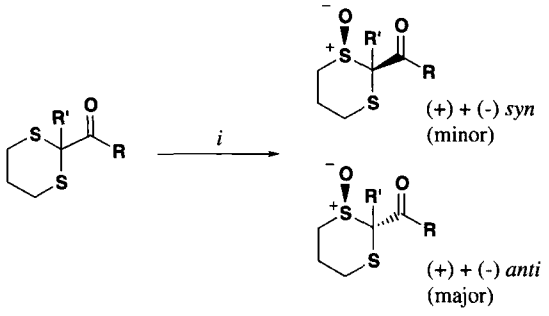
The preliminary investigations of 1,3-dithiane derivatives as asymmetric building blocks and chiral auxiliaries described in Sections II and III of this review employed the racemic DiTOX

substrates for diastereoselective transformations. To pursue syntheses of non-racemic target compounds it was necessary for us to produce DiTOX systems in the enantiomerically pure sulfoxide series.

Unfortunately, there remains a lack of general methods for the asymmetric preparation of chiral sulfoxides. The most satisfactory method would be a generally applicable enantioselective sulfoxidation reaction which would allow the preparation of sulfoxides from any prochiral sulfide with high e.e.'s and in which the sulfoxide would be amenable to enantioselective preparation in both senses.

Several approaches to the enantioselective oxidation of sulfides have been reported, including enzymatic approaches,[61] use of optically pure oxidants,[62] and several modifications of the Sharpless epoxidation procedure.[63,64] The success of these procedures is somewhat substrate dependent, for example dialkyl sulfides and more complex substrates can give unpredictable results. 1,3-Dithiane itself is oxidized with only *ca.* 20% e.e. Optically pure DiTOX has however been obtained by resolution.[65]

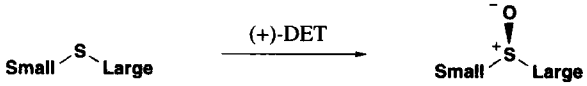
Oxidation of simple 2-substituted dithianes using modified Sharpless conditions gave poor results (*ca.* 10-20% e.e.). We subsequently recognized that, in common with the Sharpless epoxidation itself, such modifications might require the presence of a dipolar grouping within the molecule. Indeed, the enantioselective sulfoxidation of a range of β-hydroxy sulfides and derivatives has been reported in up to 80% e.e.[66] Accordingly, we examined 2-acyl dithianes as substrates and, after some adjustment of reaction conditions and work-up conditions, we were pleased to isolate acyl dithiane sulfoxides in up to 97% e.e. and in high yields, with the *anti* isomer predominating (*Scheme 15*).



Reagents: i) (+)-diethyl tartrate (2.0 equiv.), Ti $(OiPr)_4$ (1.0 equiv.), H_2O (1.0 equiv.), *tert*-butyl hydroperoxide (1.1 equiv.), CH_2Cl_2, -20°, *ca.* 1-3 days

Scheme 15

A rule of thumb for predicting the absolute configuration at sulfur in these sulfoxidation procedures has been proposed:[67] the sulfide substrate is drawn as a two dimensional representation with the sulfur lone pairs pointing upwards, the larger, or perhaps coordinating, alkyl group pointing to the right and downwards, and the smaller alkyl group pointing to the left and downwards (*Scheme 16*). Using (+)-tartrate, the oxygenation then normally occurs from the front.



Scheme 16

For 2-substituted acyldithianes this results in the *R*-configuration at sulfur. Enantiomerically pure 2-acyl-2-alkyl-1,3-dithiane 1-oxide substrates could then be obtained through recrystallization.

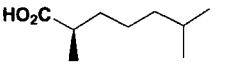
We have subsequently extended our studies to include the enantioselective synthesis of a wide range of 2-substituted-1,3-dithiane 1-oxides,[68] including 2-heterosubstituted-1,3-dithiane 1-oxides.[69]

In addition to the enantioselective preparation of 1,3-dithiane 1-oxides, our group has been concerned with the development of novel methods for the catalytic asymmetric oxidation of other prochiral sulfides. Our currently preferred system employs an enantiomerically pure sulfonylimine and commercially available hydrogen peroxide.[70]

V. APPLICATIONS OF THE DiTOX ASYMMETRIC BUILDING BLOCK

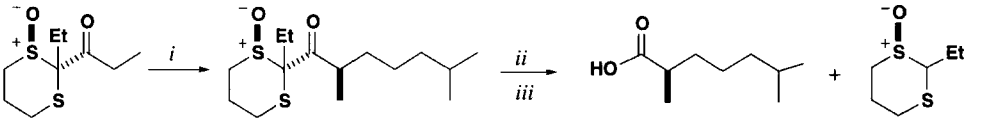
1. Enantioselective Synthesis of (R)-(-)-2,6-Dimethylheptanoic Acid.

The first application to demonstrate the use of DiTOX units as chiral auxiliaries was reported in 1994.[71] We described the two-step enantioselective synthesis of (*R*)-(-)-2,6-dimethylheptanoic acid **32**, a natural product derivative containing a carboxylic acid function substituted at the α-carbon atom, a feature common to many analgesic compounds.



32

Our synthetic route is outlined in *Scheme 17*. (1*R*, 2*R*)-(+)-*Anti*-2-propanoyl-2-ethyl-1,3-dithiane 1-oxide was prepared by enantioselective sulfur oxidation as described in Section IV of this review.



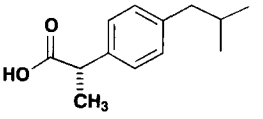
Reagents: i) LHMDS (1.1 equiv.), THF, DMPU (10 equiv.), -78°;
ii) 4-methyl iodopentane, -78° to r.t.; H_3O^+, iii) NaOH (aq.), EtOH

Scheme 17

Enolate alkylation proceeded without complication in 57% yield to give the optically pure α-alkylated product. Simple base-mediated deacylation led directly to the desired α-alkyl carboxylic acid in 39% yield, without loss of stereochemical integrity. The 2-ethyl-1,3-dithiane 1-oxide auxiliary is recoverable in optically pure form. This simple synthesis paved the way for further application of the DiTOX asymmetric building block.

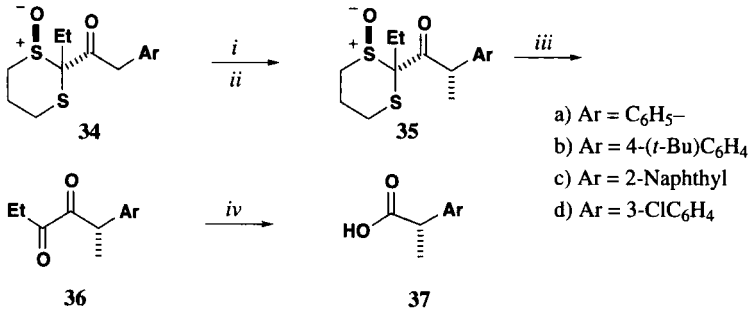
2. Enantioselective Synthesis of α-Arylpropanoic Acids.

α-Arylpropanoic acids are an important class of compounds, well known for their anti-inflammatory activity. A number of methods have been developed for the racemic and enantioselective synthesis of this class of compound.[72] Several of these compounds are successfully marketed, with perhaps the most well known example being ibuprofen **33**. The acyl dithiane oxide substrates **34a-d** used in this study were prepared by methods described in



33

this review. *Scheme 18* highlights our synthetic route to the target compounds **37a-d**. The yields and product enantioselectivities obtained are given in *Table 14*.



i), LHMDS (1.1 eq), THF, -78°; ii) MeI (1.5 equiv.);
iii) NBS (8 equiv.), acetone-water (97:3), r.t.; iv) $NaIO_4$ (2 equiv.), MeOH, 20°

Scheme 18

Table 14. Preparation of α-Arylpropanoic Acids (**37a-d**)

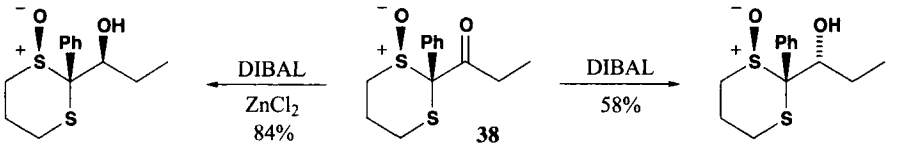
Substrate	Yield of 35 (%)	Yield of 36 (%)	Yield of 37 (%)	e.e. of 37 (%)
33a	77	96	80	93
33b	84	98	77	90
33c	80	81	68	87
33d	70	97	79	81

In this case, removal of the 1,3-dithiane 1-oxide units to unmask the carboxylic acid could not be accomplished using the base-induced cleavage employed previously,[71] but was readily achieved through a two-step procedure involving hydrolysis to furnish the α-diketones which remarkably retained their stereochemical integrity, followed by oxidative cleavage by aqueous sodium periodate in methanol.

3. Enantioselective Synthesis of α-Hydroxyketones[73]

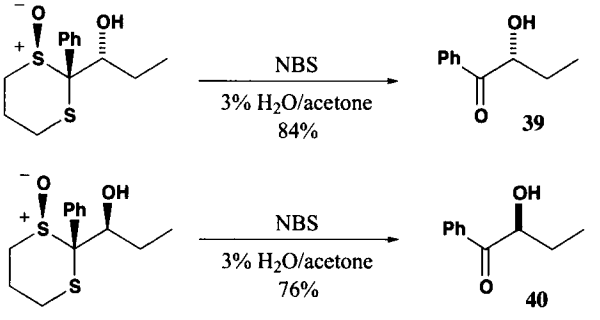
α-Hydroxyketones are an important structural feature of many biologically active molecules.[74] Compounds containing this functionality have also been reported to control the stereochemistry in several different transformations.[75]

Enantiomerically pure 1,3-dithiane 1-oxide substrates **38** was prepared by our standard methods. We have previously described the stereoselective reduction of 2-acyl-2-alkyl-1,3-dithiane 1-oxides with DIBAL,[3] and normally observe a reversal of selectivity upon addition of zinc chloride (see Section II, 2). In this case (*Scheme 19*), THF solutions of the substrates were treated at -78° with either DIBAL or DIBAL/$ZnCl_2$ reducing systems. As expected, the DIBAL and DIBAL/$ZnCl_2$ reducing systems gave products of opposite relative stereochemistry, and in most cases only one product diastereoisomer was observed.



Scheme 19

Hydrolysis of the 1,3-dithiane 1-oxide moieties of the product alcohols under our standard conditions using NBS/acetone/water gave the corresponding α-hydroxyketones **39** and **40** in excellent yields (*Scheme 20*).



Scheme 20

An excellent enantioselectivity of 93% was observed for products **39** and **40**. In the case of the 2-methyl analogues, a degree of racemization was observed, such that the corresponding α-hydroxyketone products were isolated with lower e.e.'s.

VI. CONCLUSION

In this review we have focused on the DiTOX asymmetric building block and have described its development from conception through to its general application for the enantioselective synthesis of organic functionality. Both the stereochemistry of the sulfoxide moiety and the steric bulk provided by the 2-alkyl substituent contribute to the overall level of diastereoselection which can be achieved in a given synthetic transformation. A chelation control model has allowed us to rationalize and, in many cases, predict the stereochemical outcome of a range of reaction types which have been found to be amenable to stereocontrol.

Acknowledgement.- We would like to thank all past and present members of the research group who have worked on the DiTOX project, and the many members of the industrial community who have contributed to funding the areas of research outlined in this review.

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