Tetrahedron Vol. 45, No. 24, pp. 7643–7677, 1989
Printed in Great Britain.

0040–4020/89 \$5.00+.00

TETRAHEDRON REPORT NUMBER 266

SYNTHETIC USES OF THE 1,3-DITHIANE GROUPING FROM 1977 TO 1988

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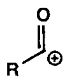
(*Received* 29 *November* 1988)

CONTENTS

1. INTRODUCTION

Synthetic organic chemists are concerned with the formation of arrangements of carbon–carbon bonds and functional groups. Amongst the most commonly encountered reactive sites for carbon–carbon bond formation are carbonyl groups; their normal pattern of reactivity is such that they provide acyl cation (**1**) and enolate anion (**2**) equivalents.

The methodology of synthetic organic chemistry has been greatly enriched by the development of functional group equivalents which provide an umpolung of the normal pattern of reactivity, and among these, reagents which act as equivalents of acyl anions (**3**) and enolate cations (**4**) are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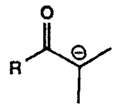
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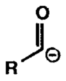
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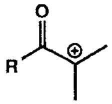
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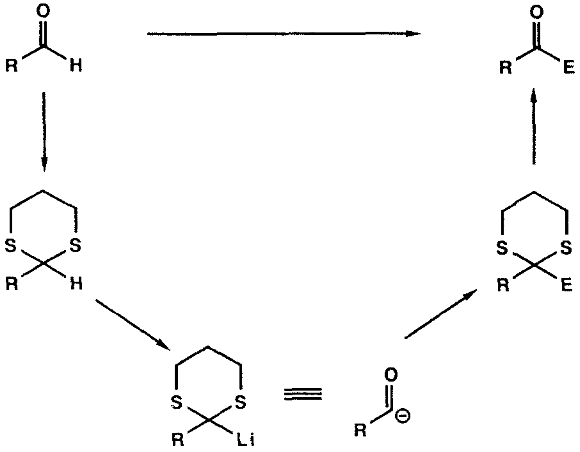

(5) (3)

Scheme 1.

particularly valuable. In 1965 Corey and Seebach suggested that certain sulphur stabilised anions could be suitable for use as masked nucleophilic acylating agents.[1] Their pioneering work over a number of years has led to the widespread use of several reagents of this type. The most successful sulphur stabilised acyl anion equivalents that have been studied to date, in terms of availability, ease of preparation and general suitability, are the cyclic 2-lithio-1,3-dithiane derivatives (**5**).

As indicated in Scheme 1, the sulphur stabilised anion (**5**) directly reverses the normal pattern of reactivity of the carbonyl group and is thus an equivalent of an acyl anion (**3**). After reaction with an electrophile the dithioacetal moiety may be hydrolysed to provide the corresponding ketone. The term umpolung was coined by Corey and Seebach to describe this *temporary* reversal of the characteristic pattern of reactivity of a functional group. The term has since been widely adopted.

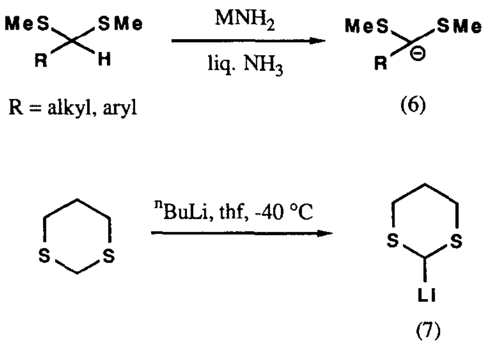
Since the introduction of 2-lithio-1,3-dithiane, its use has become ubiquitous in the chemical literature. A number of very thorough reviews on the use of 1,3-dithianes in organic synthesis have been published;[2] however, none has appeared for more than a decade, and during that time the use of 1,3-dithiane moieties has spiralled enormously.

This survey will attempt to bridge the gap by providing an insight into the more interesting 1,3-dithiane chemistry that has appeared in the literature over the last 10 years, together with recent examples of standard types of reactions. Coverage must necessarily be selective due to the vast quantity of relevant publications.

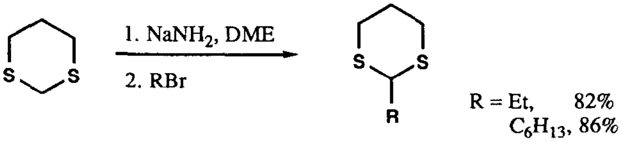
2. CARBANIONS ADJACENT TO SULPHUR ATOMS

2.1. *Generation*

Carbanions of thioacetals and orthothioformates were generated using alkali metal amides in liquid ammonia as early as 1962.[3]



Scheme 2.



Scheme 3.

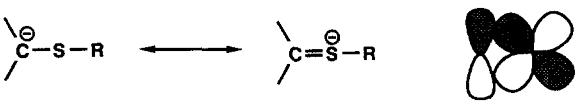
However, the metallated derivative (**6**) lacked general synthetic applicability since its alkylation only took place using a large excess of alkyl halide and no reaction was observed on treatment of (**6**) with ketones.

2-Lithio-1,3-dithiane (**7**) is now normally generated from commercially available 1,3-dithiane by the addition of one equivalent of *n*-butyl lithium (Scheme 2).[1] These cyclic acyl anion equivalents are easily prepared, and are relatively stable and usefully reactive. A few methods have been developed which introduce counterions other than lithium. For example, a recent publication outlines the preparation of the anion of 1,3-dithiane using sodamide in dimethoxyethane (DME) at room temperature.[4] Addition of electrophiles gave alkylated products in yields which were comparable to literature procedures using a lithium counterion (Scheme 3).[2d]

Very little use appears to have been made of 1,3-dithiane anions with other counterions such as potassium,[2d] magnesium, or copper.

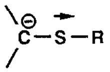
2.2. *The nature of carbanion stabilisation by sulphur*

Abundant evidence based on qualitative metallation and quantitative acidity studies shows that sulphur has a marked stabilising effect on adjacent carbanions.[5] Detailed quantitative investigations illustrating the increased carbanion stabilisation in the series $CH_2 < O < S < Se$ have been published by Lehn.[6] The common explanation for this anion stabilising effect of sulphur involves the idea of back-donation of electrons into vacant sulphur *d*-orbitals.[7] Two representations of the d_π–p_π bonding involving the orbitals C-2p_z–S-3d_{xy} or C-2p_y–S-3d_{yz} are shown in Scheme 4.



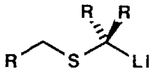
Scheme 4.

Streitweiser[8a] has shown that the acidity of 2-substituted-1,3-dithianes is almost independent of the nature of the substituent. This suggests that the carbanion is highly localised. Streitweiser[8b] has also performed primitive *ab initio* calculations on the α-thio carbanion which suggest that the principal mechanism of carbanion stabilisation by adjacent sulphur atoms involves polarisation. The effect of the induced dipole of polarisable sulphur electrons is symbolised in (**8**).



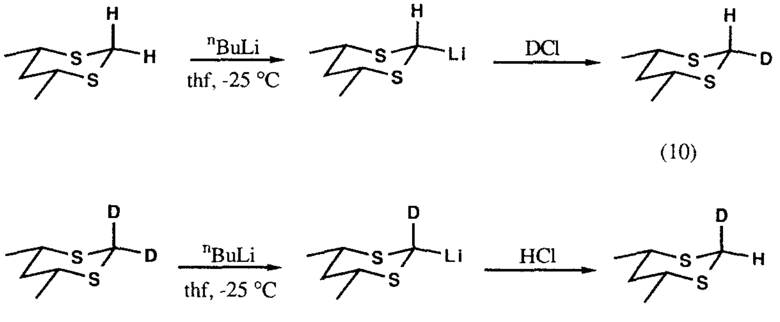
(8)

Wolfe[9a] has performed *ab initio* calculations on α-thio carbanions which indicate that the same energy minimum resulted both with and without the inclusion of *d*-type functions in the calculation. He concluded that the stabilisation is highest when the number of gauche interactions between adjacent electron pairs and/or polar bonds is maximised [e.g. (**9**)]. This explains the greater acidity of equatorial over axial protons in 1,3-dithiane. *Ab initio* calculation techniques have improved since the early work of Wolfe[9a] and Streitweiser,[8b] and more recently *d*-orbitals have been found to be significant in describing the bonding in α-thio carbanions.[9b,c]

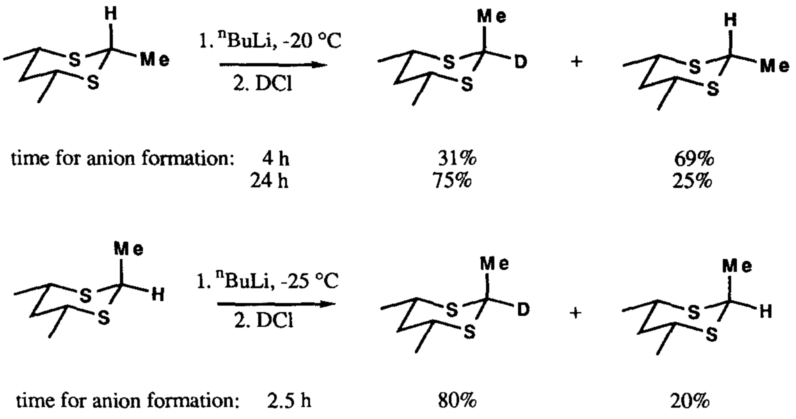


(9)

Eliel[10] has described the selective abstraction of the equatorial proton in conformationally locked 1,3-dithianes, and polarisation theory helps to explain his findings. Treatment of *cis*-4,6-dimethyl-1,3-dithiane with *n*-butyl lithium followed by D_2O–DCl quenching gave, rather surprisingly, exclusively the equatorially deuteriated compound (**10**) (Scheme 5). The high stereoselectivity of lithiation and protonation was found to be independent of the solvent. Eliel suggests that this observation is the result of a carbanion or an ion pair rather than a covalent lithium compound. Steric factors alone cannot account for such a highly stereoselective, non-enzymatic, H–D exchange, because similar factors would be found to operate in cyclohexyllithium.

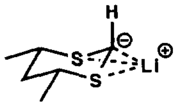


Scheme 5.



Scheme 6.

Eliel attempts to rationalise his results by suggesting that the equatorial preference may be caused by stereoelectronically favourable *p–d* overlap, the gauche effect, or simply a preference for the lithium atom to lie equatorially:



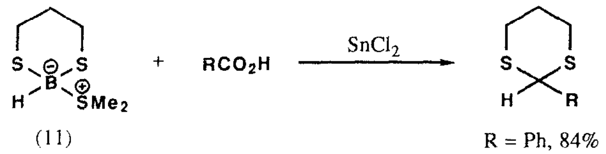
Other similar experiments by Eliel showed that the equatorial proton of 2-methyl-1,3-dithiane is readily metallated, but that the metallation proceeds poorly with the axial counterpart and leads to equatorially deuteriated products (Scheme 6). This suggests that the axial anions are not configurationally stable and allows the synthesis of the less stable axial 2-alkyl-1,3-dithianes. This 'contrathermodynamic' process has been estimated to require *ca* 6 kcal/mole by Eliel,[10a] who also used acid-catalysed equilibration to investigate conformational preferences.

3. METHODS FOR THE INTRODUCTION OF THE 1,3-DITHIANE MOIETY

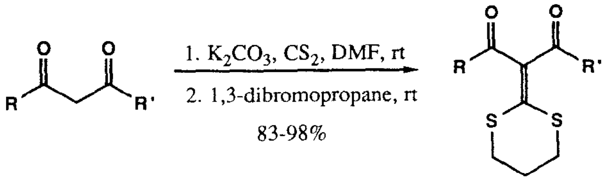
There are two general approaches to the introduction of the 1,3-dithiane ring. By far the most commonly used method involves the reaction of the anion of 1,3-dithiane, with or without further substitution around the ring, with any one of a wide range of functional groups. The great scope of this type of reaction is illustrated throughout the majority of this review.

The 1,3-dithiane ring may also be introduced by thioacetalisation of a carbonyl group, using Lewis acid or acid catalysis,[11] or of a 1,1-dihalide, using transition metal catalysis.[12] Being stable to acidic and basic conditions, the dithioacetal group is most suitable for the protection of carbonyl groups. Although zinc chloride and boron trifluoride etherate have long been employed as condensing agents for thioacetal synthesis, aluminium chloride was not fully investigated until recently.[13] It was found to be particularly useful for less reactive aromatic ketones and generally gave fast and efficient thioacetalisation of carbonyl compounds under mild reaction conditions.

An unusual conversion of carboxylic acids into the corresponding 1,3-dithiane derivatives using 1,3-dithia-2-borinane (**11**) and stannous chloride has been published[14] (Scheme 7). Good to excellent yields of the product were reported with a diverse array of carboxylic acid derivatives. Propane-1,3-dithiol di-*para*-toluene sulphonate,[15a,b] and also 1,3-dibromopropane in combination with carbon



Scheme 7.

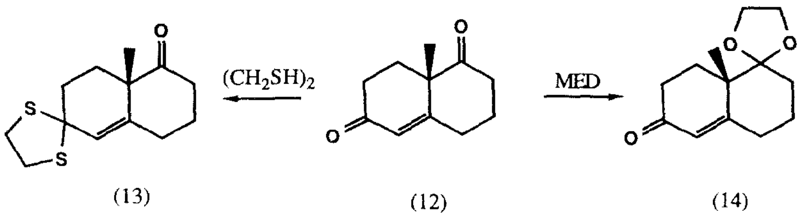


Scheme 8.

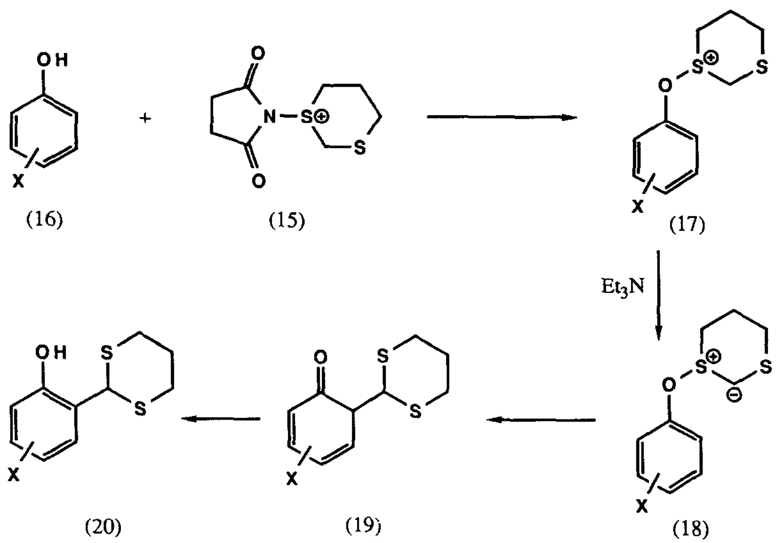
disulphide[15c] (Scheme 8), have been used for the synthesis of the dithiane ring by reaction with enolates or enols.

Thionyl chloride supported on silica-gel has recently been reported as a new catalyst for thioacetalisation reactions.[16] Treatment of ketones or aldehydes with propanedithiol in the presence of this catalyst gave excellent yields of the corresponding dithianes under mild reaction conditions. The reaction was also found to be chemoselective, aldehydes being preferentially protected ; the authors suggested that hindered catalytic centres located in cavities on the silica-gel surface favoured protection of the less hindered aldehydes. Similarly, deprotection could be achieved using thionyl chloride and wet silica-gel to catalyse the reaction.

Chemodifferentiation between a non-conjugated ketone and an α,β-unsaturated ketone can be especially difficult. One recently developed and particularly useful method has been described by Meinwald[17] and others.[17b,c] Wieland-Miescher ketone (**12**) was selectively protected at the enone carbonyl group with ethanedithiol to give (**13**) in almost quantitative yield. Complementary to this, the non-conjugated ketone could be selectively protected via transacetalisation with methyl ethyl dioxolane (MED) to give a 95% yield of monoacetal (**14**) (Scheme 9). Only 2% of the diacetal was obtained, representing a marked improvement over the results obtained by conventional acid-catalysed treatment with ethylene glycol. Interestingly, the problems encountered with ethylene glycol and *para*-toluenesulphonic acid as catalyst in the controlled acetalisation of α,β-unsaturated ketones in the presence of saturated carbonyl groups could readily be overcome by using 2,4,6-collidinium *para*-toluenesulphonate (CPTS) as catalyst.[18] The corresponding 2,6-lutidinium salt (LPTS) was found to be almost as effective, although the selectivity of neither catalyst gave such satisfactory results as the method of Meinwald.



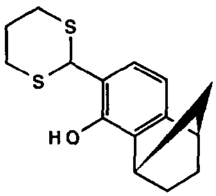
Scheme 9.



Scheme 10.

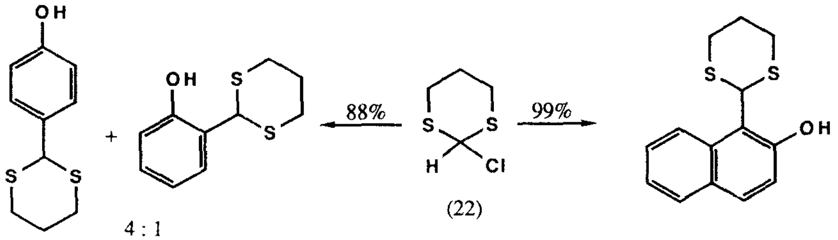
The formylation of aromatic substrates has been known for a considerable number of years. Gassman has developed a reaction which introduces a formyl group, protected as a 1,3-dithiane, *ortho* to substituted phenols.[19] The reaction is of interest since it introduces a protected formyl group in one step, and hydrolysis to the aldehyde provides an alternative to the classic aromatic formylations such as the Vilsmeier, Gatterman and Riemer–Tiemann reactions. Reaction via the 2-lithio-1,3-dithiane derivative followed by hydrolysis also gives access to other acyl derivatives. Thus, reaction of *N*-chlorosuccinimide with 1,3-dithiane formed an azasulphonium salt (**15**). Addition of the phenol derivative (**16**) to a solution of (**15**) gave the sulphonium ion intermediate (**17**), treatment of which with base produced the zwitterion (**18**) which underwent a Sommelet–Hauser type rearrangement to give dienone (**19**). Rearomatisation provided the *ortho* substituted phenol (**20**) in 50–70% yield (Scheme 10). Although known since the mid 1970s, little use appears to have been made of this interesting reaction in the literature.

In one rare example, building block (**21**) was synthesised using the Gassman procedure, and was used in the construction of chasmanine and napelline alkaloids.[20]



(21)

A new version of the *ortho* formylation reaction was reported in 1979.[21] 2-Chloro-1,3-dithiane (**22**) on reaction with a range of phenols gave excellent yields of *ortho* substituted products (Scheme 11). The simplicity of the reaction compared to Gassman's original procedure together with the excellent yields obtained should make this a most attractive reaction.



Scheme 11.

4. HYDROLYSIS OF 1,3-DITHIANE DERIVATIVES TO GIVE CARBONYL COMPOUNDS

Since the introduction of 2-lithio-1,3-dithiane as an acyl anion equivalent, many dethioacetalisation procedures have been reported. By definition, umpolung is the *temporary* reversal of the normal pattern of reactivity of a functional group. If dithiane is to be used as an acyl anion equivalent during a synthesis, it must at some stage be hydrolysed to reveal the carbonyl group which it originally masked. The existence of many reported procedures for dethioacetalisation may be taken as evidence that deprotection has often been extremely difficult to achieve, especially for complex and sensitive derivatives. There is no single method that can be generally applied and as a consequence there still exists a need for new deprotection procedures.

Only a few genuinely novel methods of hydrolysis have been reported (Table 1) since Seebach

TABLE 1 Recent methods for thioacetal hydrolysis

Entry	Reagent / reaction conditions	Typical yields	Ref	Comments
a	Preparative scale electrolysis 1.5 V, 0.03 Acm^{-3}	35 – 77%	22	A range of solvents and electrolytes used
b	Polystyryl mercury trifluoroacetate $CHCl_3$ or CH_2Cl_2, 23–50 °C, 2-96 h	42 – 96%	23	
c	PbO_2, $BF_3.Et_2O$ thf/H_2O, rt, 30–60 min	80 – 96%	24	Perchloric acid an alternative to $BF_3.Et_2O$
d	HgO, $BF_3.Et_2O$ thf/H_2O, rt, up to 36 h	36 – 98%	25	
e	HgO, 35% HBF_4 thf/H_2O, rt, <5min	92 – 100%	25	Much superior to (d)
f	Isoamyl nitrite CH_2Cl_2, reflux, 0.5–2.5 h	65 – 93%	26	Chemoselective reagent
g	Pyridine/HBr/Br_2, $^{n}Bu_4NBr$ pyridine/CH_2Cl_2/H_2O, 0 °C then rt	74 – 91%	27	No bromination
h	$Tl(NO_3)_3$ MeOH/$CHCl_3$, 25–50 °C, 5-60 min	0 – 98%	28	
i	2 eq. $Hg(ClO_4)_2.3H_2O$ MeOH/CH_2Cl_2, rt, 5 min	75 – 96%	28	Range of solvents used Superior to (h)
j	$(CH_3)_3OBF_4$ CH_2Cl_2/H_2O, rt, 5 min	89 – 94%	29a	
k	1.1 eq. $PhOPOCl_2$,4.5 eq. NaI 1.1 eq. DMF, CH_3CN, rt, 1–17 h	71 – 94%	29b	

collated all current methods in his 1975 review.[2d] Many of the newer deprotection methods and modifications lack real generality.

One useful fact, commonly overlooked by chemists experiencing difficulties with thioacetal deprotection, is that the corresponding sulphoxides undergo hydrolysis much more readily. The sulphur moiety is then a better leaving group and there are many mild methods for the deprotection of dithiane-1-oxides; indeed, S-oxides or their derivatives are probably intermediates in some oxidative thioacetal hydrolyses.

5. REACTIONS OF 2-LITHIO-1,3-DITHIANE DERIVATIVES

5.1. *Alkyl halides*

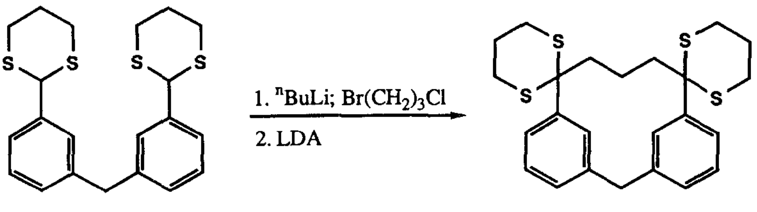
At least 30 notable examples of reactions between 2-lithio-1,3-dithiane derivatives and a wide variety of alkyl halides have appeared in the literature in the last 10 years. A selection is shown in Table 2.

Almost without exception, the reactions were used in total syntheses of natural products such as prostacyclin derivatives, including a particularly interesting intramolecular alkylation,[40] sesquiterpenoids,[32,41] insect pheromones and lichen metabolites.[43] New developments in synthetic organic chemistry are often applied to the synthesis of natural products. One measure of the power of 1,3-dithiane derivatives in organic synthesis is given by their use in a diverse range of total syntheses in the very recent literature.[44]

A wide range of C–C bond forming reactions have also taken advantage of the highly nucleophilic nature of the dithiane anion. For example, the chemistry of dithiane is well suited to a convergent synthesis of macrocycles.[45] (Scheme 12).

The anions of the 1,3-dithiane derivatives in these cases were generally readily prepared at between −40°C and −78°C using tetrahydrofuran as solvent. Only one reaction was found to require additional cosolvents.[37] It is interesting to note that all the authors added the electrophile to the anion at −78°C. Although good to excellent yields were reported for these alkylation reactions carried out via 'normal' addition procedures, major side products and poorer yields can be a major drawback.[46,85] The formation of side products can be limited by use of inverse addition procedures, which keep the concentration of the highly reactive 2-lithio-1,3-dithiane low with respect to the reacting electrophile.

Seebach has successfully reacted 2-lithio-1,3-dithiane with an enantiomerically pure chiral epoxyhalide (**23**) (Table 2, entry j) and observed regioselective attack at the bifunctionalised electrophile if appropriate reaction conditions were employed.[33,39] 2-Lithio-1,3-dithiane gave exclusive attack at the halide between −100°C and −20°C. Addition of a further equivalent of dithiane anion between −20°C and ambient temperatures then gave attack at the epoxide (Scheme 13). Addition of other reagents, such as selectride or lithium dimethyl cuprate, instead of the second equivalent of dithiane was also found to give stereocontrolled epoxide ring opening.



Scheme 12.

TABLE 2 Reactions with alkyl halides

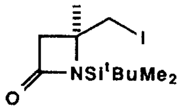
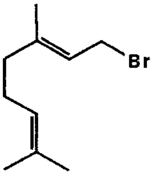
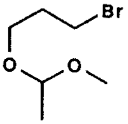
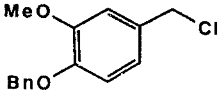
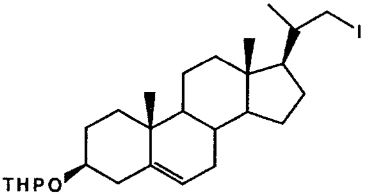
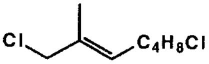
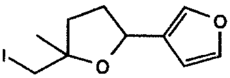
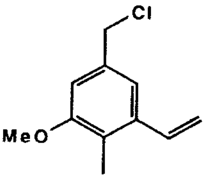
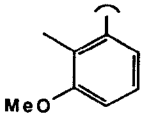
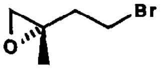
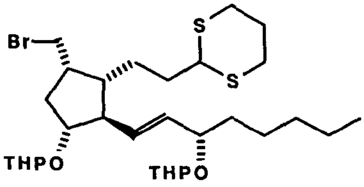
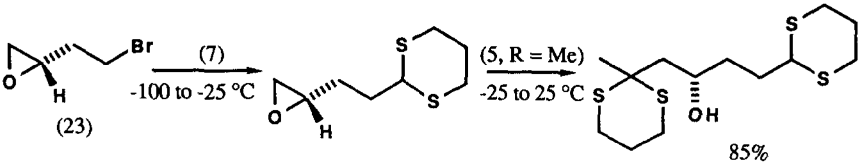
Entry	Alkyl halide	2-Substituent in (5)	Yield/%	Reference
a	$CH_3(CH_2)_{14}Br$	H	80	30
b		Me_3Si	80	31
c		H	83	32
d		H	94	33
e		H	50	34
f		H	60	35
g		H allylic halide displaced	75	36
h		H	54	37
i			58	38

TABLE 2 *Continued*

Entry	Alkyl halide	2-Substituent in (5)	Yield/%	Reference
j		H	85	39
k	 (cyclisation substrate)		100	40

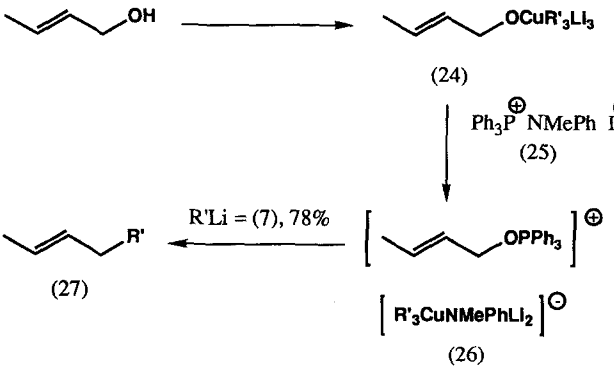


Scheme 13.

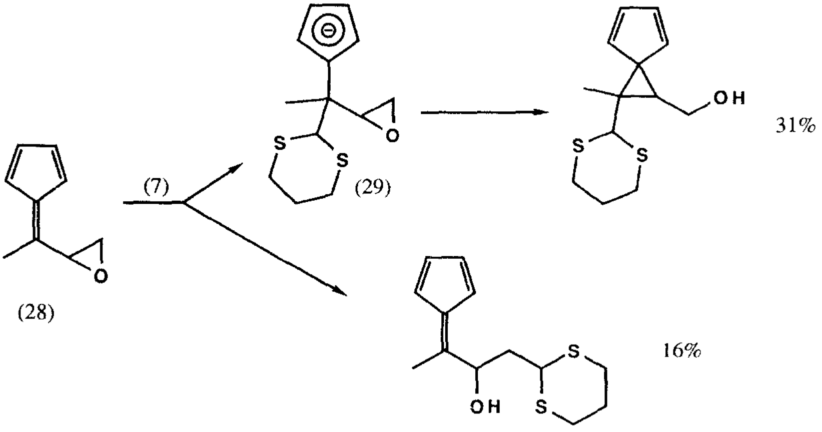
5.2. *Allylic alcohols*

In addition to substitution reactions of alkyl halides, carbon–carbon bond formation by substitution of the hydroxyl group of allylic alcohols also offers attractive synthetic potential. There are many useful methods for the synthesis of allylic alcohols, which are widely used as synthons for the allyl unit.

An efficient regio- and stereo-selective method for the synthesis of olefins from allylic alcohols via allylic displacement of the hydroxyl group has been reported.[47] An example is shown in Scheme 14. The reaction is carried out by mixing a lithium alkoxyalkylcuprate and an alkyl lithium. This is thought to form a mixed cuprate, with stoichiometry presumed to be as shown in (**24**).



Scheme 14.



Scheme 15.

Addition of *N,N*-methylphenylaminotriphenyl phosphonium iodide (**25**) then forms a complex amino cuprate (**26**). Nucleophilic attack of the alkyl anion at the alkoxy group gives the substituted olefin (**27**) in good to excellent yields. A range of examples encompassing wide structural variety was quoted by the authors including use of 2-lithio-1,3-dithiane as the nucleophile.

5.3. *Epoxides*

Chiral alcohols occur widely in nature, and a regiospecific and stereospecific ring opening of an epoxide by nucleophiles provides an attractive strategy for their synthesis. It is already well established that ring opening of epoxides by nucleophiles proceeds essentially via an S_N2 process. Further functionality located in close proximity to the epoxide may enhance regiochemical and stereochemical preferences already present in the epoxide.

A collection of some more recent examples of epoxide ring opening by derivatives of 2-lithio-1,3-dithiane is given in Table 3. The majority of examples are part of synthetic schemes directed towards the total syntheses of natural products; the reactions reported in Table 3 generally gave good regiochemical and stereochemical control.

In addition to the examples shown in Table 3 in which the epoxide is attacked directly, one unusual example has been published in which nucleophiles, including 2-lithio-1,3-dithiane, preferentially attacks at an alternative site of a fulvene derivative (**28**) to generate the cyclopentadiene intermediate (**29**) (Scheme 15).[54] The two reaction products which are observed are formed by a 3-*exo*-tet pathway and by direct attack at the epoxide. There is good precedence for *exo*-tet pathways in the ring opening of cyano-epoxides,[55a] and these reactions have been recognised by Baldwin as favoured processes.[55b] The product which was not observed in the cyano-epoxide cleavage was the 6-*endo*-tet product, corresponding with the 5-*endo*-tet product not observed in the present example. It is interesting to note that the 4-*exo*-tet product (**92b**) is also the only product which is produced from (**91b**) (Scheme 44).

5.4. *Simple carbonyl compounds*

5.4.1. *General remarks.* A very significant proportion of all reactions involving the use of 2-lithio-1,3-dithiane derivatives were carried out using aldehydes and ketones as electrophiles. A few representative examples have been collected together in Tables 4–6. Addition to carbonyl groups and conjugate addition to α,β-unsaturated ketones and aldehydes represents an important achievement of umpolung since two oxygen functional groups are introduced into molecular structures with an even number of carbon atoms separating them. This has only been achieved prior to the introduction

TABLE 3 Reactions with epoxides

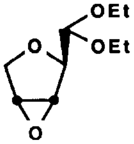
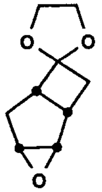
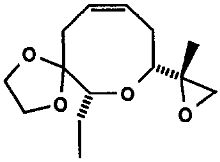
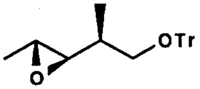
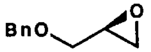
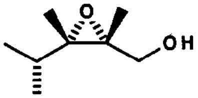
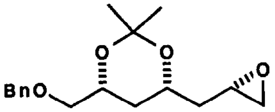
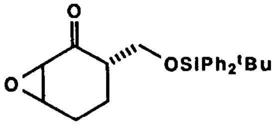
Entry	Epoxide	2-Substituent in (5)	Yield/%	Reference
a		3-furyl	95	48
b		isobutyl	66	49
c		H	88 C-4 attack	50
d		H	91 C-2 : C-3 73 : 27	51
e		H	80	52
f		H	83 C-3 : C-4 4.5 : 1	53a
g		H	87	53b
h		H	79 C-2 : C-3 12 : 1	53c
i		H	79	53c
j		CH_2O^-	83 C-2 attack	53d

TABLE 4 Reactions with ketones and aldehydes

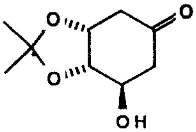
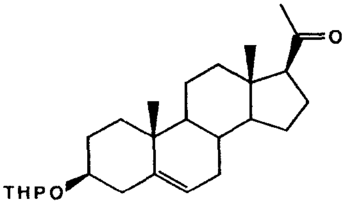
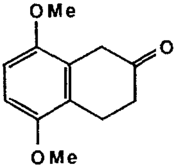
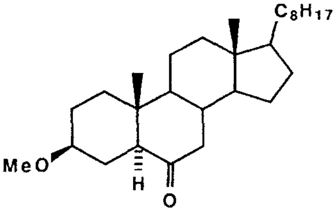
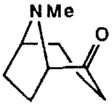
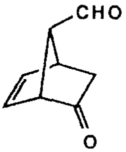
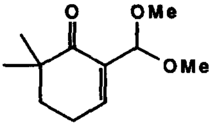
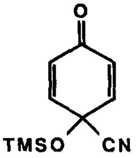
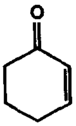
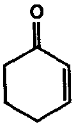
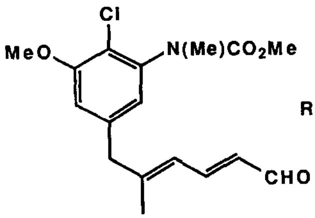
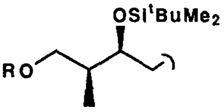
Entry	Ketone/aldehyde	2-Substituent in (5)	Yield/%	Reference
a		methyl (3 eq. anion used)	38	57
b		H	80	58
		C_5H_{11}	51	58
c		Me	59	59
d		H	78	60
e		$SiMe_3$	78	62a
f		$(MeO)_3P^+$	–	62b

TABLE 5 Reactions with α,β-unsaturated ketones and aldehydes: selected examples

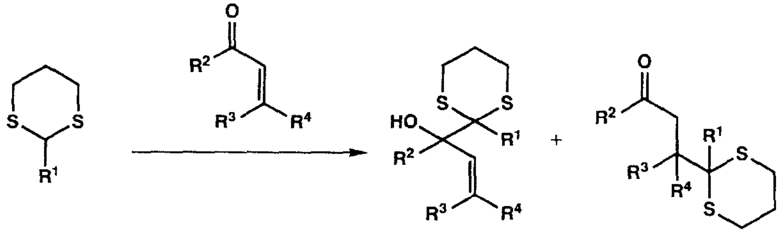
Entry	Ketone	2-Substituent in (5)	Yield/%	Reference
a		H 1,2 addition	100	63
b		H 1,2 addition	95	64
c		Me 1,2 addition	62	65
d		H 1,4 addition	73	66
e		 1,2 addition	90	61

of acyl anion equivalents via a limited number of methods including the Baeyer–Villiger rearrangement, ozonolysis, and formation of epoxides and diols from alkenes.

2-Lithio-2-trimethylsilyl-1,3-dithiane is commonly used to prepare ketene thioacetals from carbonyl compounds.[62a,117] Table 4 (entry f) shows one example of the use of an alternative phosphorus reagent for carrying out this transformation.[62b,c]

It is somewhat surprising that acyl anions such as 2-lithio-1,3-dithiane have not until recently been used for intramolecular addition reactions.[40,56] In one such report[56a] a 2-trimethylsilyl group

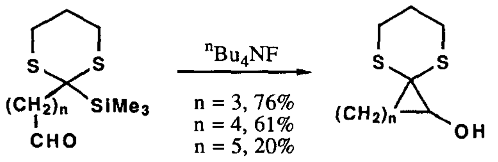
TABLE 6 Reactions with α,β-unsaturated ketones and aldehydes: 1,2 versus 1,4 addition

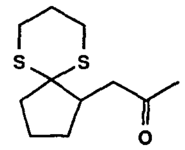


Entry	R^1	R^2	R^3	R^4	Solvent / Additive	Temp/°C	Yield/%	Ratio 1,2:1,4	Reference
a	Ph	$-(CH_2)_3-$		H	THF	-78 → -25	93	100 : 0	71
b	Ph	$-(CH_2)_3-$		H	THF	-78	100	35 : 65	71
c	Ph	$-(CH_2)_3-$		H	THF/hexane	-78	100	5 : 95	71
d	H	$-(CH_2)_3-$		H	THF	-78	90	2 : 98	72
e	H	$-(CH_2)_3-$		H	THF/2 eq.HMPA	-78	80	95 : 5	72
f	H	$-(CH_2)_3-$		H	THF/2 eq.DMPU	-78	70	82 : 18	72
g	H	$-(CH_2)_3-$		H	THF/4 eq.DMPU	-78	70	92 : 8	72
h	H	H	H	Me	THF	-70	70	0 : 100	67a
i	H	H	H	Me	THF/HMPA 1:1	-70	70	45 : 55	67a
j	Ph	H	H	Me	THF	-70	75	35 : 65	67a
k	Ph	H	H	Me	THF/HMPA 1:1	-70	80	95 : 5	67a
l	Ph	Ph	H	Ph	THF	-78	78	50 : 50	73
m	Ph	Ph	H	Ph	THF/HMPA 1:1	-78	74	5 : 95	73

was used as a protected carbanion, and was unmasked under mild conditions using fluoride ion (Scheme 16). This avoided nucleophilic attack by basic reagents at the carbonyl group. Satisfactory yields were obtained for medium sized rings and the methodology was used to prepare the masked 1,4-dicarbonyl compound (**30**) in 64% yield. One novel intramolecular addition of a 2-metallated 1,3-dithiane to a carbonyl group is shown in Scheme 17.[56b] This cyclisation formed the key step in a synthesis of the rocaglamide skeleton. A variety of bases were used because the use of *n*-butyllithium alone gave a complex mixture of products.

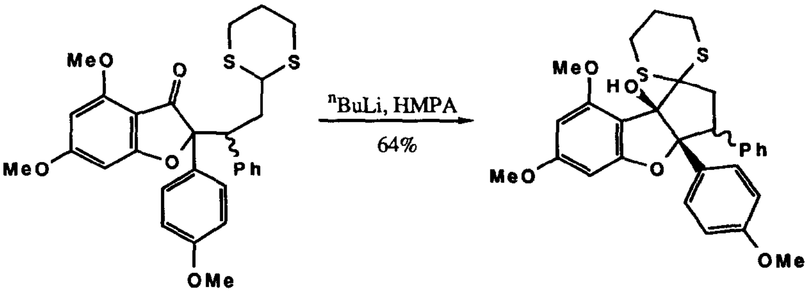
5.4.2. *Factors influencing the regioselectivity of addition to α,β-unsaturated aldehydes and ketones.* There has been considerable debate in the chemical literature concerning the factors influencing





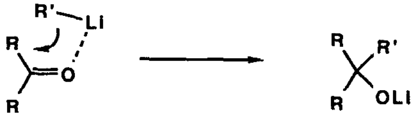
(30)

Scheme 16.



Scheme 17.

regioselectivity of addition to α,β-unsaturated aldehydes and ketones. With the exception of only a very few examples, 1,2-addition is generally favoured for organolithium compounds in which the sp^3 carbanionic centre does not bear extra stabilising groups. This is thought to be due to a favourable carbonyl group–lithium interaction[67] prior to reaction. The proximity of the nucleophile to the carbonyl group then encourages 1,2-addition:



A number of workers have noted that the presence of 1–2 equivalents of hexamethylphosphoramide (HMPA) as a cosolvent induces a major change in the course of reaction[68–70] (Table 6).

Several substitutes for the carcinogenic HMPA are now available. Seebach and others have demonstrated that the commercially available cyclic urea 1,3-dimethyl-2-oxohexahydropyrimidine (dimethylpropyleneurea, DMPU) exhibits similar effects to HMPA in a range of reactions.[72] DMPU was shown to be compatible with highly nucleophilic and basic reagents and it has been successfully used at dry ice temperatures and below. The cosolvent does not interfere with alkyl lithium reagents and may be recovered from hydrocarbon and ether solvents by washing with water followed by extraction with chlorinated solvents.

Seebach studied the addition of 2-lithio-1,3-dithiane to cyclohexenone and found that 1,2-addition was suppressed almost as effectively with DMPU as with HMPA (Table 6, entries d to g), although a somewhat larger proportion of DMPU was generally necessary.[72] A number of other reactions also clearly demonstrate that DMPU can successfully replace HMPA as a cosolvent.

Although several generalisations concerning conjugate addition can be made there are always exceptions to such rules: Kane has reported that 2-lithio-2-aryl-1,3-dithianes readily undergo 1,4-addition to α,β-unsaturated ketones in THF if reaction and work-up are carried out at 25°C (Table 6, entries a to c).[71] However, if the reaction is carried out at −78°C a mixture of the 1,2- and 1,4-addition products (65 : 35) is obtained. Kane noted that addition of hexane as a cosolvent followed by quenching at −78°C strongly favoured the formation of the 1,2-addition product. No explanation for this unusual result was given.

Another interesting anomaly has been reported by Krief.[69] His early observations reported that the presence of HMPA changed the course of reaction with enones to allow introduction of organometallic reagents predominantly or exclusively by conjugate addition.[73] However, his subsequent study of the addition of 2-lithio-1,3-dithiane and other organometallics to chalcone (Table 6, entries l and m) showed the formation of a mixture of 1,2- and 1,4-addition products in which the latter often predominated. In the presence of HMPA Krief found that 1,2-addition was favoured. No satisfactory explanation was given.

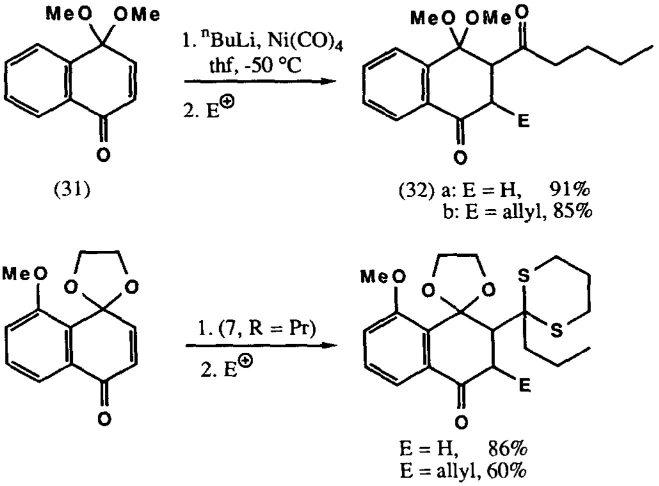
This reversal of the 'normal' pattern of regioselectivity has also been found for reactions performed at −78°C in THF in the presence of 4,7,13,16,21,24-hexaoxo-1,10-diazabicyclo[8.8.8] hexacosane (Kryptofix-2,2,2) and in dimethoxyethane (DME) under conditions that usually favour conjugate addition.[73] The reason for the change in regioselectivity caused by the addition of HMPA and other additives is not clear.[74] HMPA may make the addition process more reversible because of its cation solvating ability. It is also possible that carbonyl group activation by the counterion may become insignificant in the presence of HMPA, thus removing any proximity effect and favouring 1,4 addition. Eliel has observed that HMPA causes upfield shifts of the phenyl proton and carbon resonances in an NMR study of 2-lithio-2-phenyl-1,3-dithiane.[10c] They have suggested that the observed shifts are due to the presence of a contact ion pair in THF and a solvent separated ion pair in the presence of HMPA. This is a significant result since it implies the likelihood of electron transfer between the nucleophile and electrophile.

Complex studies using well established probes for the detection of radicals by, for example, the cyclisation of the hexenyl radical failed to indicate that the reaction occurs via single electron transfer.[75] The authors concluded that although no definite evidence was found, electron-transfer may be possible in some conjugate addition reactions to enones, especially with soft nucleophiles and in the presence of HMPA.

While there has been much discussion of the factors governing regioselectivity of addition of 2-lithio-1,3-dithiane derivatives to enones, other acyl anion equivalents also undergo conjugate addition very readily. Corey and Hegedus have reported that acylnickel carbonylate anions react with α,β-unsaturated ketones via conjugate addition of the acyl unit.[76a] Despite the wide use of other acyl anion equivalents, further use of this interesting reagent has been limited. Semmelhack has more recently used acylnickel carbonylate anions, reacting them with quinone monoacetals, for example (**31**), which gave the conjugate addition product (**32a**) in excellent yield (Scheme 18).[76b] The intermediate lithium enolate could also be trapped with a variety of electrophiles to give, for example, (**32b**). A similar reaction with 2-lithio-2-propyl-1,3-dithiane also gave a very good yield of the conjugate addition product.[76b]

Conclusions

1. 1,2-Addition is generally favoured due to carbonyl group–metal interaction.
2. 1,2-Addition is particularly favoured for α,β-unsaturated aldehydes.
3. 1,2-Addition is favoured in less polar solvents, at low temperatures for short reaction times. 1,4-Addition is favoured in polar solvents at higher temperatures for long reaction times.
4. Regioselectivity of addition reactions of α,β-unsaturated aldehydes is *not* temperature-dependent.[67a] However, regioselectivity of addition reactions of α,β-unsaturated ketones

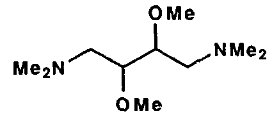


Scheme 18.

is temperature-dependent;[71] this may be explained by the higher stability of secondary over tertiary alcohols.[67b]

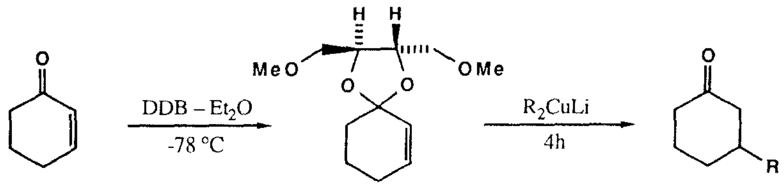
5. 1,4-Addition is difficult to achieve in THF solution. Cosolvents such as HMPA and DMPU reduce complexation of the metal ion to the carbonyl group, thereby reducing its reactivity and favouring 1,4-addition of nucleophiles.
6. Steric hindrance in the substrate or nucleophile favours 1,4-addition in THF solution.
7. The ratio of regioisomers for a given α,β-unsaturated carbonyl compound is dependent upon the natures of the carbon nucleophile (hard or soft) and the counterion, and the reaction conditions (solvent and temperature). If the reaction is reversible 1,2- and 1,4-adducts are usually the result of kinetic and thermodynamic control respectively. Reversible addition is usually observed with well stabilised and delocalised anions, and is promoted by high reaction temperatures and high solvent polarity.

5.4.3. *Chiral cosolvents*. Seebach[77] has used the chiral cosolvent 2,3-dimethoxy-1,4-bis-(dimethylamino)-butane (DDB) (**33**) in reactions which enantioselectively add achiral lithium, copper



(33)

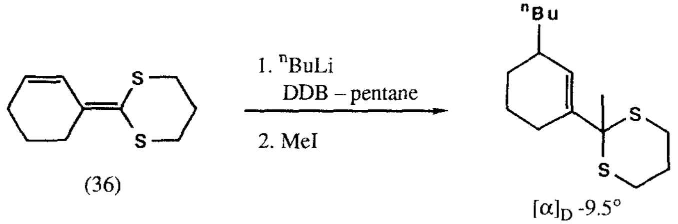
and zinc nucleophiles to the prochiral β-carbon atom of α,β-unsaturated aldehydes, ketones, lactones, and nitro compounds. Both enantiomers of DDB are readily available (Aldrich Chemical Company: (*R*,*R*)-(−)-2,3-dimethoxy-1,4-bis-(dimethylamino)-butane, £52.90/10g; (*S*,*S*)-(+)-2,3-dimethoxy-1,4-bis-(dimethylamino)-butane, £38.30/10g). A DDB to organolithium ratio of 10:1 was used at −78°C; the selectivity of reaction ranged from 55:45 to 63:27. Addition of DDB to cyclohexenone is thought to form acetal (**34**), which reacts with lithium cuprates enantioselectively to form 3-alkyl cyclohexanones (**35**) in a ratio of 57:43 (Scheme 19).



(34) (35)

Scheme 19.

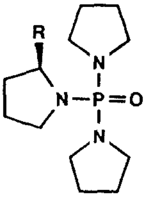
Most remarkably, even in ketene thioacetal (**36**), the enantiotopic faces of the π system could be differentiated, and some selectivity was obtained in the addition of *n*-butyllithium.



(36)

$[\alpha]_D$ -9.5°

Subsequent to this report by Seebach on the use of DDB to induce enantioselective addition of nucleophiles to enones, chiral analogues of HMPA have been synthesised.[78]



(37a), R = H
(37b), R = CO_2Me
(37c), R = CH_2OH
(37d), R = CH_2OMe

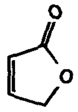
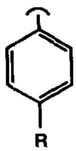
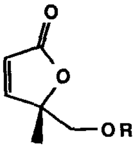
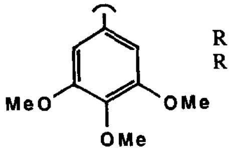
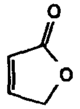
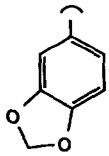
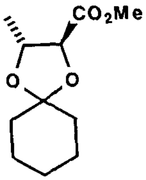
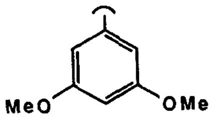
Trispyrrolidinophosphoramide (TPPA) (**37a**) is commercially available.[79] Chiral TPPA analogues would be useful as chiral ligands for enantioselective additions to carbonyl and α,β-unsaturated carbonyl compounds. Studies reported in the communication indicate that of the three analogues synthesised (**37b** to **d**), (**37d**) is a better ligand than HMPA for lithium. Under identical conditions, two equivalents of (**37d**) gave conjugate addition of 2-lithio-1,3-dithiane to cyclohexenone in 96% yield. This is slightly better than one equivalent of HMPA has achieved.[78] Studies indicated that three HMPA ligands are optimum for a lithium counterion and four for sodium or potassium.

Although the authors were reported to be studying the use of these compounds for asymmetric induction, no further publication giving any successful examples has yet appeared.

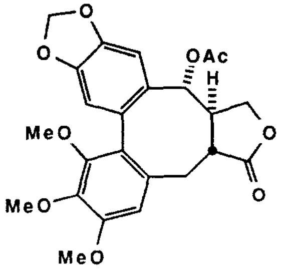
5.5. *Esters and lactones*

Addition of dithiane-2-anions to simple esters, like other acyl derivatives, gives acyl dithianes in variable yields[1,2] (e.g. Table 7, entry e).[84] Little investigation has been carried out into conjugate addition to α,β-unsaturated esters or lactones. 2-Lithio-1,3-dithiane does not add to but-2-enolide, but electron releasing groups at the 2-position of the dithiane anion facilitate the addition (e.g. Table 7, entry a). In the last decade, the addition to butenolides has been used exclusively for the total synthesis of steganin lignans, which have been shown to have significant antitumour activity *in vivo*.[81,86] (*S*)-4-Hydroxymethyl-butan-4-olide (Table 7, entry b), prepared from L-glutamic acid,

TABLE 7 Reactions with esters and α,β-unsaturated lactones

Entry	Ester/Lactone	2-Substituent in (5)	Yield/%	Reference
a			R = OMe, 88 R = H, 33	80
b			R = Bn, 56 R = CPh$_3$, 36	81
c			90	82
d			63	83
e	$C_6H_{13}CO_2Me$	H	–	84

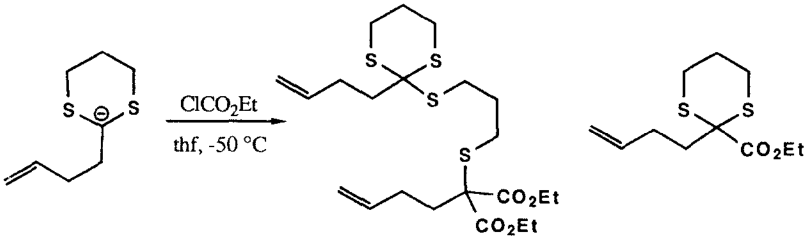
was used as a source of chirality for asymmetric induction and as part of the carbon framework in the target molecule (**38**).



(38)

Addition of the 2-lithio-1,3-dithiane derivative (Table 7, entry b) to the chiral butenolide gave an enolate anion, no 1,2-addition being observed and the addition occurring predominantly from the less hindered β-face. Quenching with piperonyl bromide gave alkylation on the α-face, opposite to the face at which the nucleophile was introduced, with a *cis* : *trans* product ratio of 2 : 98. Complete stereoselection was achieved by using a trityl ether as the acceptor, but at the expense of a drop in yield (Table 7, entry b). Ziegler has used an identical approach to synthesise a number of members of the steganin family.[86]

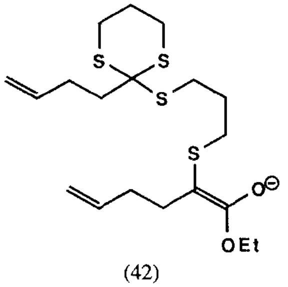
An unusual dimer (**39**) has been isolated from the reaction of the 2-lithio-1,3-dithiane derivative (**40**) with ethyl chloroformate (Scheme 20).[46] The formation of the dimer could be avoided if inverse addition procedures were used. It was suggested that under normal addition procedures anion (**40**) attacked the sulphur atom of (**41**) to generate the ester enolate (**42**). In the presence of ethyl chloroformate (**42**) was trapped to give the dimer (**39**). This is an unusual example of a nucleophile attacking at a sulphur atom in preference to a carbonyl group.[87]



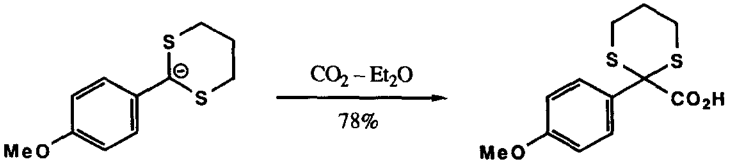
(40) (39) (41)

	(39)	(41)
Normal addition	16%	25%
Inverse addition	–	85%

Scheme 20.



(42)



(43) (44)

Scheme 21.

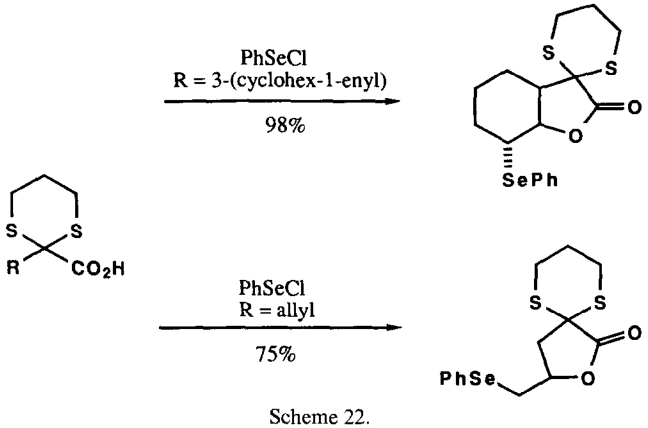
5.6. *Carbon dioxide and α,β-unsaturated carboxylic acids*

In common with the other carboxylic acid derivatives, little work has been published on the reaction of 2-lithio-1,3-dithiane with carbon dioxide or carboxylic acids.

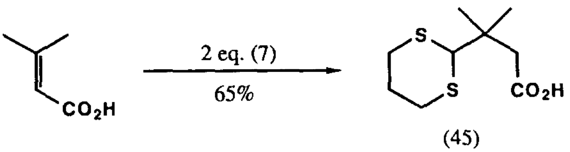
Carboxylation of the 2-lithio derivative (**43**) to give (**44**) (Scheme 21) proceeded in excellent yield, and esterification gave the ester in a good overall yield.[88,89]

Derivatives of 1,3-dithiane substituted at the 2-position with the free carboxylic acid can be useful intermediates for the synthesis of functionalised lactones, formed by phenylselenolactonisation.[89] Nicolaou has developed a synthesis of lactones using an internal lactonisation of unsaturated carboxylic acids by reaction with the electrophilic phenylselenyl chloride. The reaction proceeds under mild conditions and at low temperatures. Addition to the double bond occurs in a *trans* manner but the regiochemistry was not selective in any of the examples studied. Representative examples involving substituted 1,3-dithiane derivatives are shown below (Scheme 22).

A few examples have appeared of the reaction of 2-lithio-1,3-dithiane with α,β-unsaturated carboxylic acids.[90a] In one early report, two equivalents of 2-lithio-1,3-dithiane were required—the first being consumed by deprotonation of the free carboxylic acid. Good yields of the 1,4-adduct (**45**) were obtained (Scheme 23). Unfortunately polymerisation occurred in the reactions; a problem which could be rectified by the use of α-silylated α,β-unsaturated carboxylic acid salts.[90b] The silyl group both retards polymerisation and aids conjugate addition.

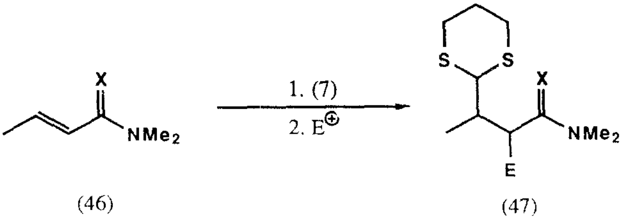


Scheme 22.



(45)

Scheme 23.



Scheme 24.

5.7. *α,β-Unsaturated amides and thioamides*

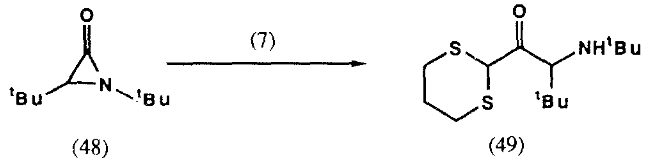
Although much work has been reported on conjugate addition reactions to unsaturated carbonyl systems, the corresponding conjugate addition of nucleophiles to unsaturated amides and thioamides has been relatively neglected.

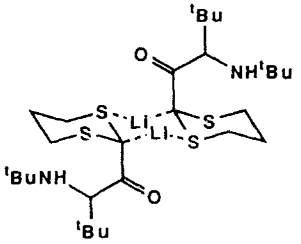
Tamark[91] and Snieckus[92,93] have demonstrated that α,β-unsaturated amides and thioamides (**46**) are also effective substrates for tandem conjugate addition-α-alkylation. This reaction, like the corresponding cuprate–enone reaction, is synthetically most useful since it allows the formation of two new carbon–carbon bonds in one step. The tolerance of the reaction to wide structural variety is also ideally suited to further structural transformations. A range of organolithium and magnesium reagents including lithiated dithianes undergo conjugate addition to tertiary crotonamides and thioamides. The resulting amide enolates may be quenched with alkyl and allyl halides and other electrophiles to give the α,β-dialkylated products (**47**) in 50–97% yield (Scheme 24).

The scope and synthetic use of this conjugate addition reaction with unsaturated amides was illustrated by Snieckus who used it to construct a lignan natural product.[93]

5.8. *Aziridinones*

2-Lithio-1,3-dithiane is reported to react with aziridinones, e.g. (**48**), at the carbonyl group to form anions by cleavage of the acyl–nitrogen bond.[94] In this case it was suggested that product (**49**) was stabilised as its bimolecular lithium salt (**50**).





(50)

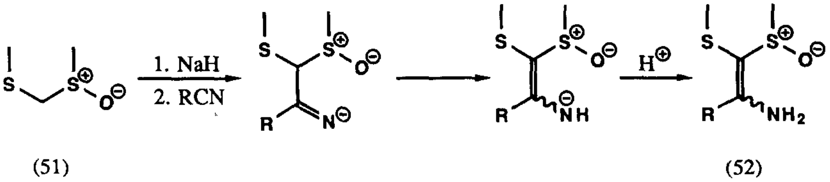
5.9. *Nitriles*

The first reports of a sulphur-stabilised anion reacting with nitriles appeared in 1974.[95,96] Addition of the carbanion derived from (**51**) to nitriles gave enamines (**52**) in *ca* 75% yield following a 1,3-proton migration (Scheme 25).[95]

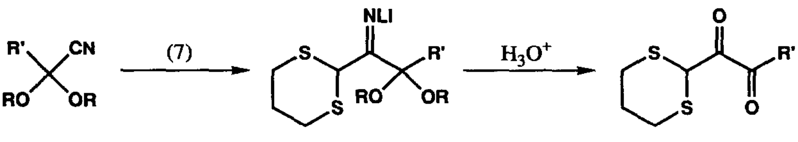
Other Japanese workers noted that addition of 2-lithio-1,3-dithiane to 2,2-dialkoxynitriles[97] gave a ketone following acidic work-up.[96] Enamine formation was presumably not observed due to hydrolysis by the acidic conditions used in the work-up (Scheme 26).

Almost 10 years after these initial reports, Fuji[98] investigated the reaction of 2-lithio-2-trimethylsilyl-1,3-oxathiane (**53**) with nitriles (Scheme 27).

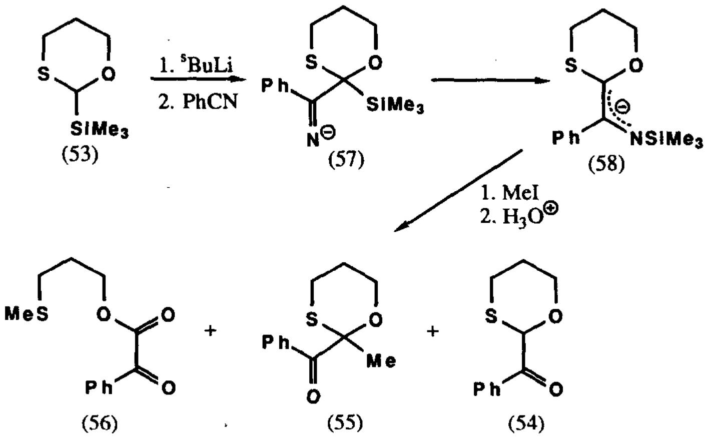
The anion (**53**) was generated using *sec*-butyllithium and added to nitriles. Subsequent addition of methyl iodide gave a mixture of (**54**), (**55**), and (**56**) in 13, 10, and 45% yield respectively. It was suggested that attack of the anion occurred at the nitrile to give (**57**). A carbon to nitrogen migration of the silicon moiety could then give delocalised anion (**58**). This could react with methyl iodide to give the carbon alkylated product which on hydrolysis of the *N*-silylated imine would give (**55**). Protonation on carbon followed by hydrolysis would similarly give (**54**). The formation of (**54**) and (**55**) is evidence that 2-lithio-2-trimethylsilyl-1,3-oxathiane can be regarded as an equivalent of an acyl dianion.



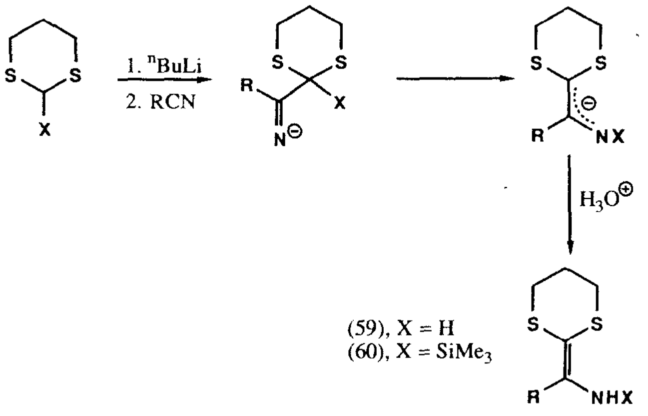
Scheme 25.



Scheme 26.



Scheme 27.



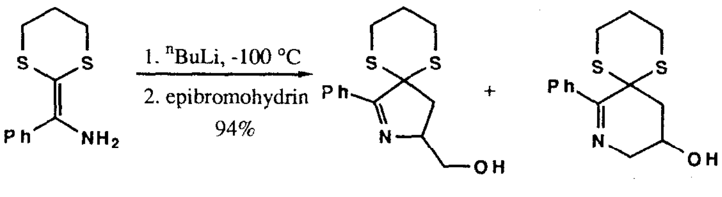
(59), X = H
(60), X = SiMe₃

Scheme 28.

More recently, the present authors have shown that addition of 2-lithio-1,3-dithiane or 2-lithio-2-trimethylsilyl-1,3-dithiane to solutions of nitriles in THF at -78°C followed by simple work-up and chromatography upon reaching room temperature gave good yields of the primary aminoketene dithioacetals (**59**).[99,100] Use of inverse addition procedures was found to give a cleaner reaction and higher yields of products. This reaction presumably proceeds via inter- or intramolecular migration of the proton or silicon moiety from carbon to nitrogen (Scheme 28).

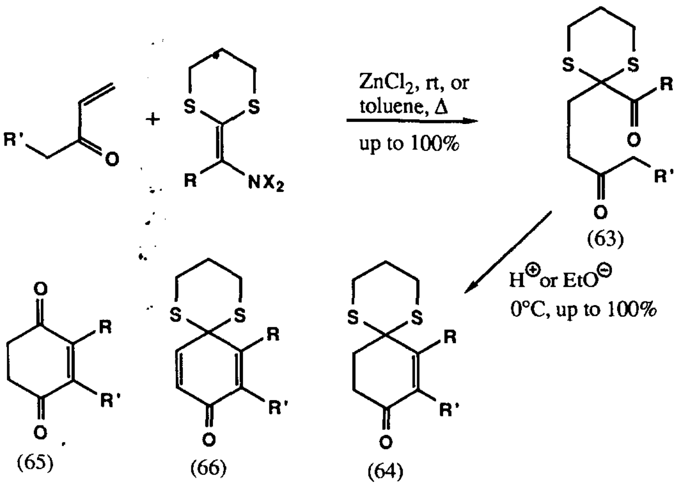
In contrast to the work of Fuji[98] only protonation on nitrogen was observed in these reactions. No 2-acyl-1,3-dithiane derivatives were observed in the product mixtures. The corresponding N-silylated amino-ketene dithioacetal (**60**) could be isolated by crystallisation from the reaction mixture if acidic conditions were avoided during the work-up procedure. The ambident nuclophilicity of aminoketene dithioacetals has been utilised in a synthesis of nitrogen heterocycles including (**61**) and (**62**) (Scheme 29).[101]

Aminoketene dithioacetals also react via a cycloaddition or conjugate addition mechanism with α,β-unsaturated ketones to give the δ-diketones (**63**).[102,103] Reaction temperatures are reduced by use of Lewis acid catalysis, up to quantitative yields then being observed.[103,104] Under acidic or basic conditions the δ-diketones (**63**) were transformed via aldol annelation into the interesting cyclohex-2-ene-1,4-dione monoacetals (**64**) in up to quantitative yields (Scheme 30).[102,103] Compounds (**64**) were shown to be useful singly-protected equivalents of cyclohex-2-ene-1,4-diones (**65**) in Diels–Alder and conjugate addition reactions, and could be converted in reasonable yields into quinone monoacetals (**66**).[102]

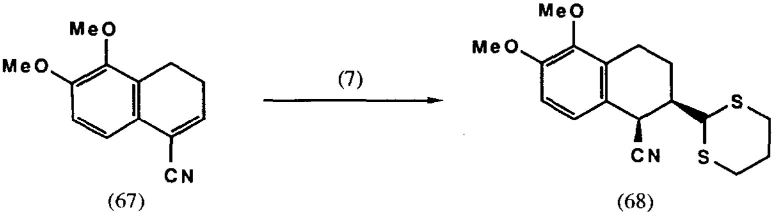


(61) 6 : 1 (62)

Scheme 29.



Scheme 30.



Scheme 31.

5.10. *α,β-Unsaturated nitriles*

To date, only one report has appeared in the literature concerning a successful reaction of 2-lithio-1,3-dithiane with α,β-unsaturated nitriles.[105] Addition of the α,β-unsaturated nitrile (**67**) to the anion derived from 1,3-dithiane resulted in an excellent yield of the 1,4-addition product (**68**). The major product was shown by NMR coupling constants to have *cis* stereochemistry (Scheme 31). This is in agreement with previous studies on the alkylation of α-cyano carbanions which undergo equatorial protonation.

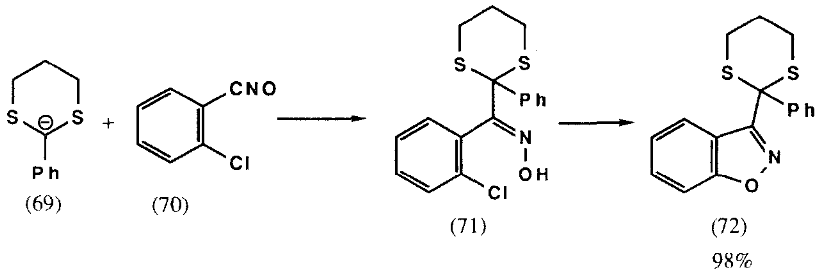
5.11. *Nitrile oxides*

Nitrile oxides are 1,3-dipoles and are known to readily undergo cycloaddition reactions. They also react with nucleophiles; however, only a few reactions have been reported with carbanions.

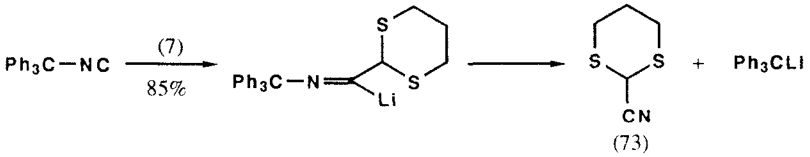
2-Lithio-2-phenyl-1,3-dithiane (**69**) reacted readily with nitrile oxide (**70**) to give the ketoxime (**71**) as the product.[106] Compound (**71**) was thermally unstable and could be converted to (**72**) in quantitative yield by heating (Scheme 32). This route provides a simple synthesis of 3-acyl-1,2-benzisoxazoles.

5.12. *Isocyanides*

Addition of alkyl lithium reagents to isocyanides has been found to result in the formation of cyanides via dissociation of the initially favoured aldimine[107] (Scheme 33). Use of 2-lithio-1,3-dithiane gave 2-cyano-1,3-dithiane (**73**) which could be alkylated at the C-2 position.



Scheme 32.



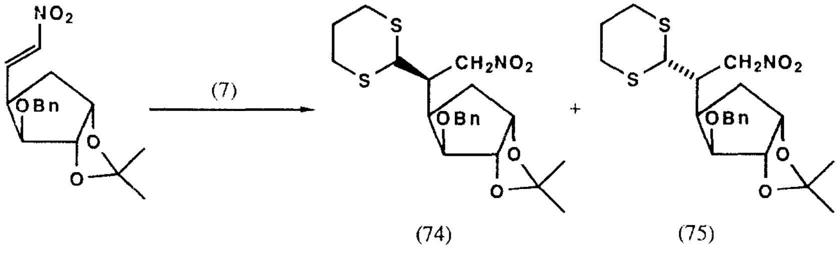
Scheme 33.

5.13. *Nitroalkenes*

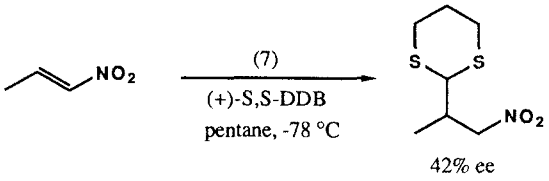
Funabashi has made use of a conjugate addition of 2-lithio-1,3-dithiane to a nitroalkene group within a sugar derivative[108] (Scheme 34). The reaction proceeded readily to give the 1,4-addition products **(74)** and **(75)** in the ratio 4 : 3.

Seebach has also studied the use of the chiral cosolvent DDB in addition reactions of 2-lithio-1,3-dithiane to nitroalkenes.[77] Good yields of the 1,4-addition product were obtained together with some differentiation between the two faces of the π-system (Scheme 35).

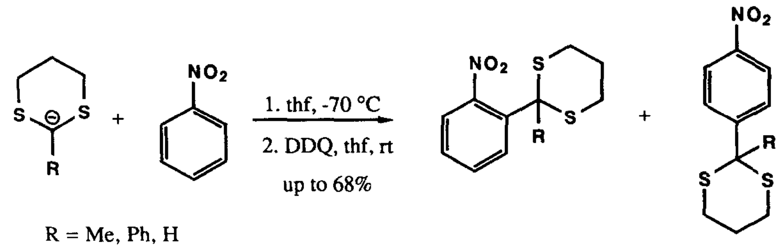
A reaction of 2-lithio-1,3-dithiane with nitroarenes has been reported. The 1,4 addition process, which requires disruption of the aromatic ring, is followed by re-aromatisation.[109] (Scheme 36).



Scheme 34.

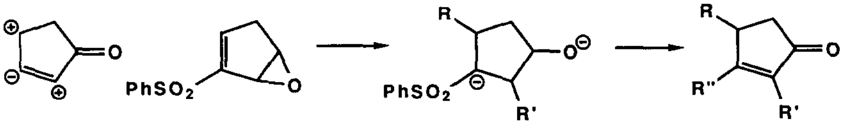


Scheme 35.



R = Me, Ph, H

Scheme 36.



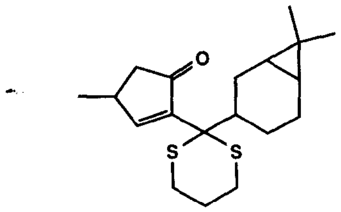
(77) (76) (78) (79)

Scheme 37.

5.14. *Vinyl sulphones*

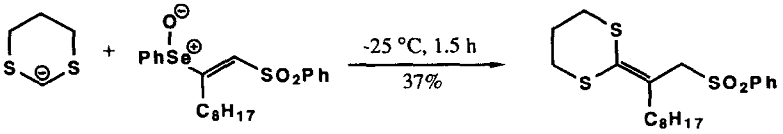
Oxygenated vinyl sulphones (**76**) have been successfully used as doubly-charged inverted enone synthons (**77**) by Fuchs.[110] A double conjugate addition of hard nucleophiles to the vinyl sulphone (**76**) gave the α-sulphonyl stabilised anion (**78**). Alkylation of the anion *in situ* followed by oxidation of the alcohol and β-elimination of phenyl-sulphenic acid generated an α,β,γ-trifunctionalised enone (**79**) (Scheme 37).

An intermediate used in diterpene synthesis was prepared using this method. Addition of methyl copper to enantiomerically pure epoxy vinyl sulphone (**76**) was found to give preferential attack at the face opposite the epoxide. Conjugate addition of a 2-lithio-1,3-dithiane derivative to the α,β-unsaturated sulphone followed by regeneration of the enone gave key intermediate (**80**), which was used to synthesise a lathrane type diterpene.



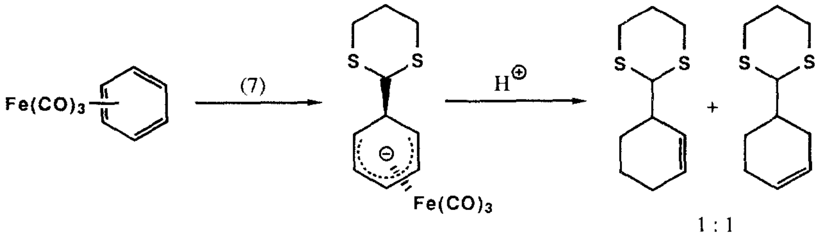
(80)

2-Lithio-1,3-dithiane has been shown to undergo a substitution reaction with a α,β-(phenylseleno)-vinyl sulphone selenoxide (Scheme 38).[111] The anion attacked the sulphone (**81**) and subsequent loss of the phenylselenyl group gave the ketene thioacetal (**82**).

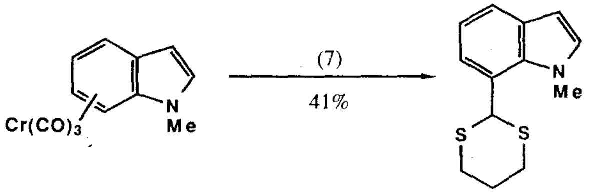


(81) (82)

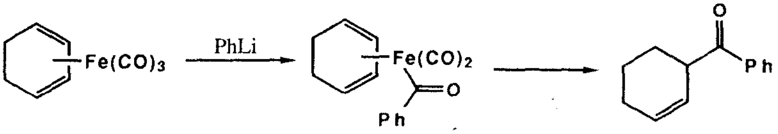
Scheme 38.



Scheme 39.



Scheme 40.



Scheme 41.

5.15. *Arene–metal complexes*

Attachment of $Cr(CO)_3$ units to dienes or arenes induces a strong polarisation of the π-bond system. This allows successful nucleophilic addition, approach occurring towards the face of the π-system opposite to that of the metal (Scheme 39).[112,113]

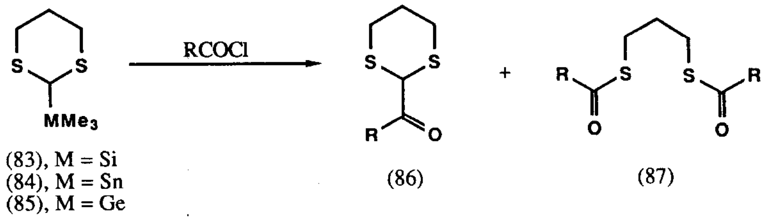
Transition metal promoted reactions are being used increasingly in organic synthesis, no doubt because of the attainable selectivity in the formation of carbon–carbon bonds. Regiochemical problems can arise because the activating group is equally bound to each of the arene ring atoms which may give no obvious directing effects (Scheme 39). Regiochemical control can be achieved with *meta*-directing substituents such as methoxy, amino and fluoro substituents (Scheme 40).[114] The formation of large quantities of side products is often a major limitation of the reaction. They are formed profusely with simple alkyl lithium reagents and originate from CO insertion (Scheme 41).[112,115,116]

6. MISCELLANEOUS REACTIONS

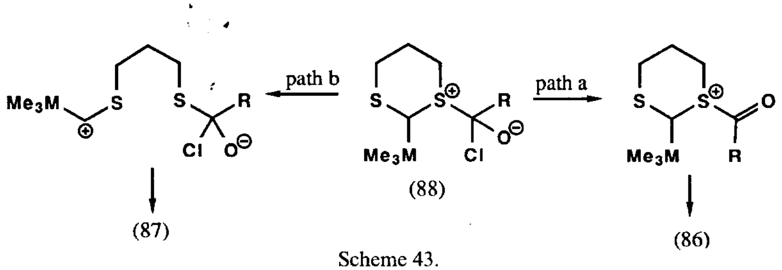
6.1. *Preparation and reactions of 2-stannyl, silyl, germyl and titanium derivatives*

The chemistry of 1,3-dithiane has not been restricted solely to the 2-lithio derivative. Considerable use has been made of the 2-lithio-2-trimethylsilyl derivative (**83**) especially with respect to the synthesis of ketene dithioacetals.[62a,117] A limited number of reports have appeared concerning the use of other such derivatives with trialkyl stannyl (**84**) and germyl (**85**) substituents.[118]

Treatment of derivatives (**83**), (**84**), and (**85**) with acid chlorides at high reaction temperatures found to result in formation of 2-acyl-1,3-dithiane derivatives (**86**) or ring opened products (**87**) heme 42). The ratio of products obtained was dependent upon the nature of the dithiane



Scheme 42.

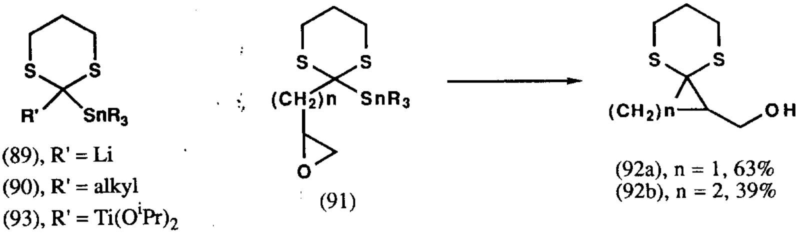


Scheme 43.

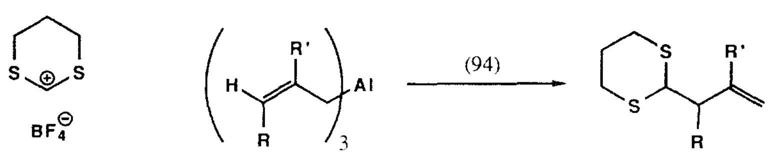
derivative and the acid chloride used. Two reaction pathways were proposed to account for these observations (Scheme 43). Elements capable of stabilising the positive charge in intermediate (**88**), such as silicon and tin, favour the formation of ring opened products (**87**), via path b. The higher electronegativity of germanium favours path a, and hence the formation of 2-acyl-1,3-dithiane derivatives.

Seebach has successfully used tin derivative (**84**) and demonstrated that it could be lithiated with LDA to give (**89**).[119] Addition to (**89**) of alkyl halides gave 60–90% yields of the corresponding 2-substituted stannyldithiane derivatives (**90**). In contrast to previous observations regarding regioselectivity of addition of 2-lithio-1,3-dithiane to α,β-unsaturated carbonyl compounds, addition of tin derivative (**89**) to cyclohexenone resulted in exclusive formation of the conjugate addition product.

Seebach has demonstrated the generation of a nucleophilic centre by fast Sn/Li exchange in the presence of a highly reactive electrophilic functional group.[120] The substituted dithianes (**91**) were prepared by alkylation of (**89**) with a variety of bromo epoxides as the bis-electrophiles. Addition of *n*-butyl lithium to (**91**) resulted in a fast Sn/Li exchange followed by rapid intramolecular cyclisation (Scheme 44); the spiro structures were obtained in yields of up to 65%. The synthetic utility of the reaction was illustrated by syntheses of the strained spiro structures (**92a**) and (**92b**) in reasonable yields.



Scheme 44.



(94) (95) (96)

Scheme 45.

The titanium analogues (**93**) were also prepared and were found to be more stable than the corresponding lithium and magnesium derivatives; the titanium analogues were isolable and less reactive, and therefore more selective.[120] For example, 2-lithio-1,3-dithiane adds to mixtures of benzaldehyde and acetophenone in a 2 : 1 ratio at −78 °C within a few minutes, whereas the lithiated titanium analogue was found to require 16 hours at room temperature to react exclusively with benzaldehyde.

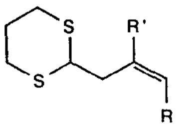
In view of the interesting chemical characteristics of these dithiane derivatives, it is rather surprising that little use has been made of them.

6.2. 1,3-*Dithienium tetrafluoroborate*

The majority of reactions described in this review have involved nucleophilic attack of a dithiane moiety onto a range of electrophiles. In contrast, very little is known about the reactivity and potential use of dithiocarbocations as electrophilic species in organic synthesis. 2-Chloro-1,3-dithiane (**22**) was the first electrophilic dithiane to be studied and a preparation of 1,3-dithienium tetrafluoroborate (**94**) was subsequently reported in the literature.[123]

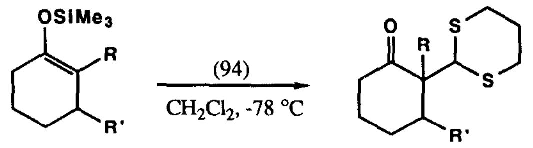
Reaction of 2-substituted-1,3-dithianes with sulphuryl chloride also generates the 1,3-dithienium cation; but with a chloride counterion.[122] This is much more sensitive to moisture and undergoes rapid hydrolysis. The chloride salt is readily converted to the more stable tetrafluoroborate salt by addition of boron trifluoride etherate.

1,3-Dithienium tetrafluoroborate is a yellow crystalline solid which is more usually prepared from 1,3-dithiane and trityl-tetrafluoroborate.[121,123] Interestingly, addition of organometallic reagents such as (**95**) to (**94**) gives good yields of 2-substituted 1,3-dithianes (**96**) via allylic rearrangement (Scheme 45).[124] 2-Chloro-1,3-dithiane also reacted readily with the aluminium reagent (**95**) to give the identical substituted dithiane (**96**) in somewhat poorer yields. The reaction is particularly valuable since the product (**96**) is not available from the reaction of 2-lithio-1,3-dithiane with substituted allylic reagents as such reactions proceed mainly to give the isomeric structure (**97**) or mixtures of products.[124]



(97)

O-Silylated enolates (**98**) are readily alkylated by 1,3-dithienium tetrafluoroborate giving regiocontrolled introduction of the 1,3-dithiane moiety at the α-position of carbonyl compounds (**99**) (Scheme 46).[125,126] A wide range of *O*-silylated enolates gave rapid and high yielding reaction under mild conditions.



(98)

(99) R = R' = H, 92%
R = Me, R' = H, 80%
R = H, R' = Me, 88%

Scheme 46.

6.3. *Conclusion*

A very large number of useful applications of 1,3-dithiane and its derivatives have been reported since its introduction as an acyl anion equivalent in 1965. The ease of preparation of 1,3-dithiane derivatives, together with their versatile chemistry, has encouraged the use of dithiane moieties as building blocks; for example, alkylation products are stable and can easily be further functionalised. Removal of the dithiane moiety may be accomplished by elimination, reduction, or hydrolysis. This review should give to the reader a flavour of the available chemistry; no doubt 1,3-dithianes will continue to prove valuable as intermediates for organic synthesis.

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