Oxazolines. XX. Synthesis of Achiral and Chiral Thiiranes and Olefins by Reaction of Carbonyl Compounds with 2-(Alkylthio)-2-oxazolines

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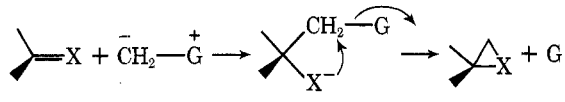
Metalation of 2-(alkylthio)-2-oxazolines (**6–12**) followed by addition of a variety of carbonyl compounds leads to thiiranes **17** in 60–70% yield. The process is also useful for the direct synthesis of alkenes and dienes by extrusion of the sulfur from thiiranes. In many cases a high degree of stereoselectivity is observed in the alkene formation. An asymmetric synthesis of chiral thiiranes has also been achieved providing these substances in 19–32% enantiomeric excess.

Thiiranes, known for over 50 years, have been the subject of several reviews[2] which have dealt mainly with their preparations and reactions. Although reaction of thiiranes with nucleophilic reagents leading to olefins is now a well-known process,[2e,3] the synthetic utility of this transformation has only recently been appreciated.[4,5] From the past literature the preferred route to thiiranes has been by conversion of epoxides and vicinally substituted ethane derivatives.[2,6] Additions of organometallics to thioketones is an interesting route[2d,e] but the availability and inherent instability of thiocarbonyls have deterred this method from further development.

In recent years, a variety of methylene transfer reagents have been cleverly employed[7,8] to convert carbonyl compounds to oxiranes (Scheme I). Thus, sulfur ylides have added

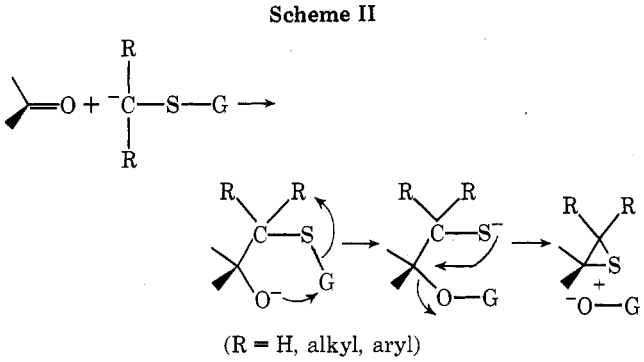
Scheme I



X = O, S, NR; G = SMe_2, $SOMe_2$, $S(NMe_2)OPh$, $S(NTsNa)OPh$

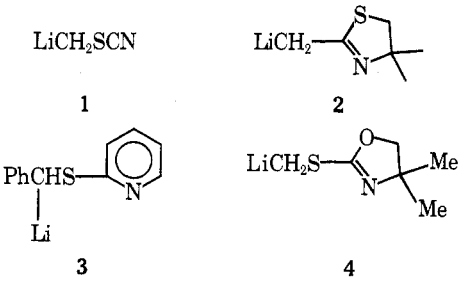
smoothly to carbonyls (X = O) affording a variety of oxiranes. This process would seem to be most attractive for reaching thiiranes if the thiocarbonyls (X = S) were a more accessible functional group. Unfortunately, as mentioned above, this is not the case. A more viable route to thiiranes using carbonyl compounds would be in hand if a thiomethylene transfer reagent ($^-CR_2SG$) were readily accessible (Scheme II). Such a

Scheme II



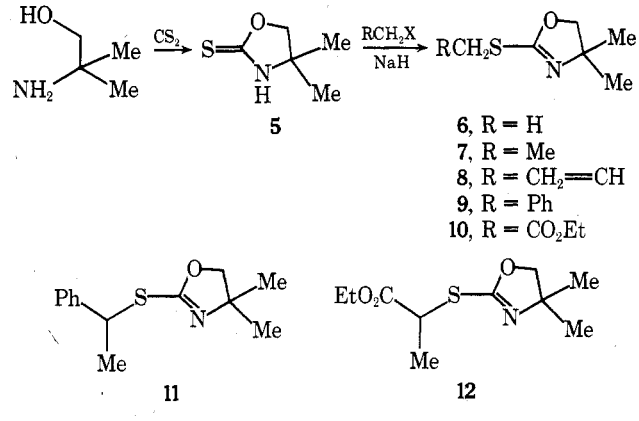
(R = H, alkyl, aryl)

reagent would require a group G which allows ready O for S substitution while also performing as a good leaving group. Several reports have recently appeared utilizing this concept where the thiomethylene transfer group originates from sulfur-stabilized carbanions **1**,[9] **2**,[9,10] **3**,[9] and **4**.[11] The lithio thiocyanate failed to undergo reaction leading to thiiranes whereas **2**, **3**, and **4** indeed gave thiiranes in varying yields.



It is now desirable to fully describe our results using **4** and its homologues as an efficient thiomethylene transfer reagent producing a variety of thiiranes, both achiral and chiral, as well as the conversion of the latter to various olefins. In one instance a chiral olefin was prepared (vide infra). The sequence leading to the 2-(alkylthio)-2-oxazolines **6–12** is shown in Scheme III. Alkylation of oxazolidine-2-thione **5**[12] with various

Scheme III



primary alkyl halides and sodium hydride gave the thioalkyl oxazolines **6–10** whereas metalation of **9** (BuLi) and **10** (LDA) followed by addition of methyl iodide gave **11** and **12**. The yields of **6–12** ranged from 56 to 94% and they are easily prepared in multigram quantities.

Treatment of the 2-alkylthio-2-oxazolines **6**, **8**, **9**, and **11** with *n*-butyllithium (−78 °C, THF) gave the lithio derivative **13** as a yellow-orange solution after 2 h. Addition of a carbonyl compound at −78 °C and allowing the mixture to warm to ambient temperature resulted in the formation of thiiranes **17** in yields ranging from 60 to 70% (Table I). The one-pot process may be depicted as passing through the intermediates **14**, **15**, and **16** in a fashion similar to that reported by Hirai utilizing thiazolines.[13] The sequence outlined in Scheme IV therefore fulfills the general requirements set forth in Scheme II. The ejection of the lithio oxazolidinone **18** as the requisite

Table I. Thiiranes (17) and Olefins (20) from 2-(Alkylthio)-2-oxazolines[a]

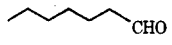
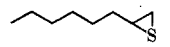
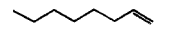
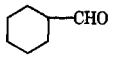
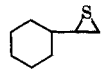
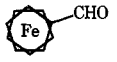
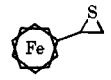
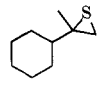
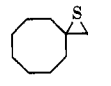
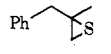
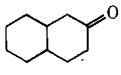
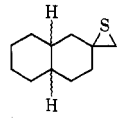
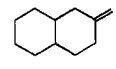
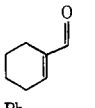
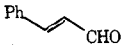
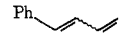
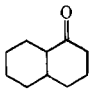
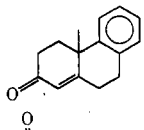
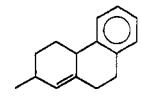
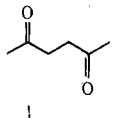
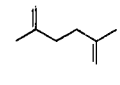
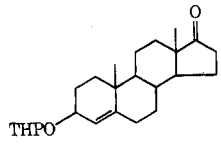
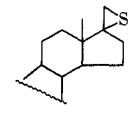
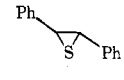
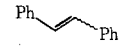
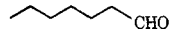
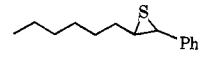
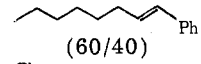
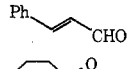
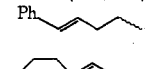
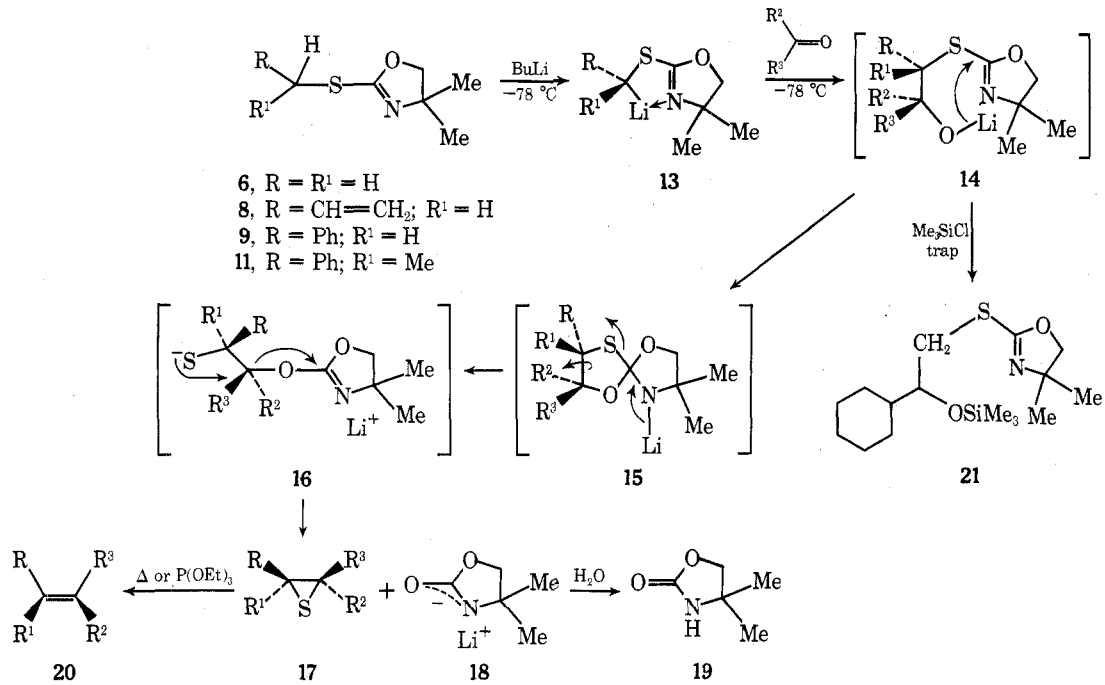
Entry	Oxazoline R	Carbonyl compd	Registry no.	Thiirane 17	Yield,[b] %	Olefin (E/Z)[c]	% yield[b] A[d]	% yield[b] B[e]
1	6 (R = H)		111-71-7		73		64	69
2	6 (R = H)		2043-61-0		78			69
3	6 (R = H)		12093-10-6		68	*f*		
4	6 (R = H)		823-76-7		66	*f*		
5	6 (R = H)		502-49-8		61		65	47
6	6 (R = H)		103-79-7		31 (62)[g]			
7	6 (R = H)		4832-17-1		61		52	
8	6 (R = H)		932-66-1	*h*				42
9	6 (R = H)		14371-10-9	*h*		 (96/4)		46
10	6 (R = H)		529-34-0	*h*				46[i]
11	6 (R = H)		6606-34-4	*h*				48[i]
12	6 (R = H)		110-13-4	*h*				40
13	6 (R = H)		583-60-8		61		56	
14	6 (R = H)		19637-35-5		70	*f*		
15	9 (R = Ph)	PhCHO	100-52-7		71[j]	 (86/14)	81	
16	9 (R = Ph)				64[k]	 (60/40)	75	
17	9 (R = Ph)			*h*		 (96/4)		70
18	9 (R = Ph)			*h*				72
19	11 (R = PhCH(Me))		119-61-9	*h*				62
20	11 (R = PhCH(Me))		712-50-5	*h*		(91/9)		51
21	8 (R = CH=CH$_2$)	PhCHO		*h*		(96/4)		62
22	8 (R = CH=CH$_2$)			*h*		(97/3)		47

Table I (*Footnotes*)

[a] Literature references for all known compounds and physical data for all new compounds are given in the Experimental Section. [b] Purified by chromatography and/or bulb-to-bulb distillation (see Experimental Section for typical procedural details). Products are >95% pure by VPC, NMR, and TLC. [c] Mixtures determined by VPC using a Hewlett-Packard 5750 instrument containing a 6 ft × 0.125 in. column packed with 10% UCW-98. [d] Obtained by desulfurization of the thiirane; yield based on thiirane. [e] Thiirane not isolated in pure form and desulfurization performed on crude thiirane; yield based on carbonyl compound. [f] Olefin not prepared. [g] Yield in parentheses based on recovered ketone. Thiirane decomposes at 125 °C. [h] Crude thiirane contained varying amounts of olefin (5–30%) and was taken directly to the olefin. [i] The NMR spectrum in benzene-d_6 was completely consistent with the exo structures shown. If the NMR spectrum is taken in deuteriochloroform, traces of HCl present in this solvent effects a slow isomerization to the endo (homoannular diene) compound. [j] Present as a mixture containing 85.5% trans and 14.5% cis isomers. [k] Present as a mixture containing 55% trans and 45% cis isomers.

Scheme IV

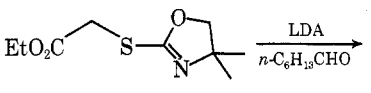


leaving group was confirmed by isolation of the oxazolidinone **19**. In many instances (Table I, entries 1–7, 13–16), the thiiranes were isolated as stable products. However, in those cases where the thiiranes contained an α-aryl or α-vinyl substituent (entries 8–11, 17–22), their thermal instability resulted in facile sulfur extrusion, producing thiiranes contaminated with varying amounts of diene or styryl systems. In this event, it was expeditious to by-pass the thiirane and transform the mixture directly to the olefinic product by heating with triphenylphosphine or triethyl phosphite. It is clear from the results in Table I that the alkylthio oxazolines are useful and efficient reagents for either the synthesis of thiiranes and/or the olefination of carbonyl compounds.

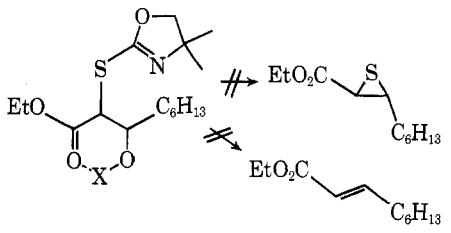
In order to assess the nature of this facile conversion of carbonyls to thiiranes, a study was performed to attempt isolation, by trapping, of the various intermediates **14**, **15**, and **16** in Scheme IV.

Oxazoline **6** (R = R′ = H) was metalated at −78 °C with *n*-butyllithium and treated with cyclohexanecarboxaldehyde. After 5 min and 1.5 h, while maintaining the temperature at −78 °C, the reaction was quenched with chlorotrimethylsilane and the only product isolated was the silyl ether **21**. Furthermore, if the initial adduct **14** was treated with chlorotrimethylsilane at −50, −25, and 0 °C the only product once again was **21** although traces (1–5%) of thiirane and **19** could be detected (TLC, NMR) from the 0 °C reaction. It is therefore concluded that the intramolecular addition of the lithium alkoxide to the C=N of the oxazoline (**14** → **15**) takes place mainly between 0 °C and room temperature. A number of attempts were made to trap the intermediate **16** prior to fragmentation but this process is apparently too rapid for interception.

Missing from Table I are thiiranes and olefins derived from 2-ethylthio- and 2-carboethoxymethylthiooxazolines **7** and **10**, respectively. In the former case, it was not possible to metalate the α-methylene group although a number of different bases and solvents were employed. It appears that the kinetic acidity of the α-methylene group is too low for proton removal unless there is present (except for CH_3S–) an activating group such as phenyl, vinyl, carbomethoxy, cyano, etc. This behavior has also been noted by others.[9,13] In the case of the carboethoxymethylthiooxazoline **10**, the α proton was readily removed by lithium diisopropylamide (−78 °C) and then treated with *n*-heptaldehyde. Workup after the reaction mixture reached room temperature gave no thiirane or evidence of the α,β-unsaturated ester, but only **22** (X = H) in 81%

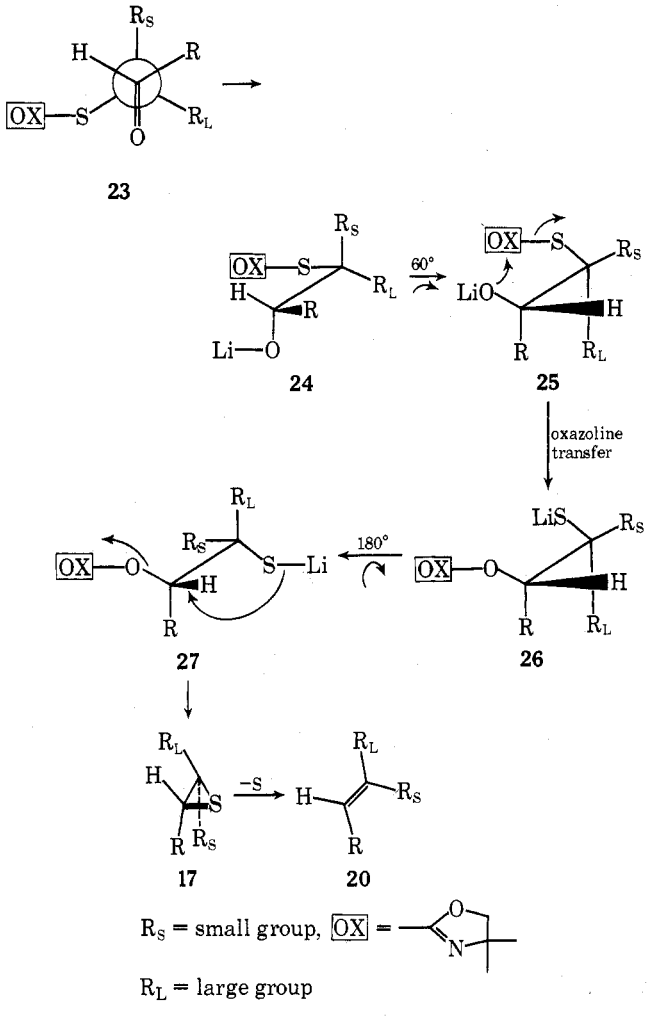


10



22 (X = Li, Na, H)

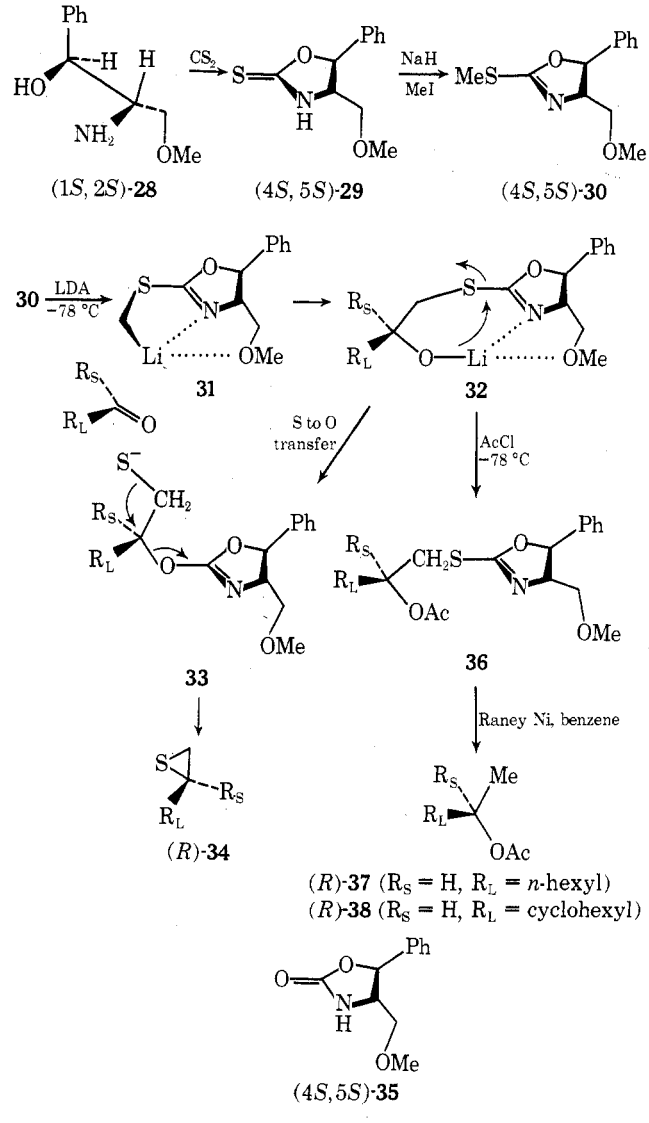
Scheme V



yield. Prolonged heating of the intermediate alkoxide (X = Li or Na) in THF or benzene at reflux returned mainly starting unreacted adduct **22** and some decomposition products. It is therefore apparent that the intermediate lithio adduct **22** is simply too stable in its chelated form to undergo rearrangement and fragmentation to the thiirane.

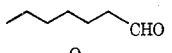
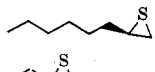
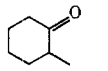
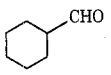
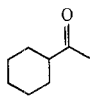
When 2-alkylthio-2-oxazolines **8**, **9**, and **11** are metalated and treated with carbonyl compounds, the resulting olefinic products were mixtures of *E*/*Z* isomers (Table I, entries 9, 15–17, 20–22). Except for 1-phenyl-1-octene (entry 16), which gave a 1.5:1 mixture of *E*/*Z* isomers, all the others were heavily in favor of the *E* isomer. This high degree of stereoselectivity can be readily understood by the formulations in Scheme V which show that carbonyl approach to the lithio thioalkyl oxazoline will occur to minimize nonbonded interactions (**23**). The resulting adduct **24** upon rotation to **25** now is properly aligned to allow S to O oxazoline transfer furnishing **26**. By 180° rotation the sulfide is now in a position to displace the oxazolidinone anion (**27**) producing the thiirane **17**. The latter is desulfurized via the stereospecific extrusion process[3b] providing the olefins **20**. That the olefin *E*, *Z* composition is, in fact, directly related to the geometric composition of the thiiranes was demonstrated in two instances. The thiiranes in entries 15 and 16 (Table I) were examined by NMR after purification by preparative layer chromatography. The NMR spectrum for 1,2-diphenylthiirane exhibited singlets at δ 7.37 (s, 10) and 3.97 (s, 2) for the trans isomer and δ 7.13 (s, 10) and 4.39 (s, 2) for the cis isomer in agreement with results previously obtained by Ketchum.[14] The integrated ratio for these signals indicated an 86:14 mixture of the trans to cis thiiranes. In a similar fashion, 1-phenyl-2-(*n*-hexyl)thiirane (entry 16, Table I) showed benzyl proton signals at δ 4.13 (q) and 3.58 (d) in a ratio of 55:45 suggesting that this thiirane had formed as an approximately equal mixture of isomers. Desulfurization of these thiiranes gave olefins in essentially the same isomeric ratio (Table I, entries 15, 16) thus confirming that the olefins produced in this study possess stereochemical compositions virtually identical with those for the thiirane precursors. The alkene and diene *E*, *Z* ratios reported in Table I were all determined by gas chromatography. Assignment of the *E* isomer in entry **20** as the major product was performed by ultraviolet spectroscopy since the compound had not been previously reported. The olefin exhibited an ultraviolet maxima at 217 and 247 nm as compared to 218 and 240 nm for the known (*E*)-2,3-diphenyl-2-butene.[15]

Chiral Thiiranes and Alkenes. Owing to the successful implementation of chiral oxazolines in asymmetric syntheses of various chiral carboxylic acids,[16] it was of interest to determine whether chiral thiiranes could be generated utilizing a chiral oxazoline. Toward this end, the chiral 2-thiomethyl oxazoline **30** was prepared starting from the methoxy amino alcohol **28**[16] and treatment with carbon disulfide which gave the thione **29**. Methylation of the latter using sodium hydride



furnished the desired chiral oxazoline. Treatment of **30** with lithium diisopropylamide gave the lithio salt **31** which on addition of various carbonyl compounds at −95 °C furnished, after aqueous quenching, the chiral thiiranes **34** in 48–70% yield and in enantiomeric purities of 19–32% (Table II). Since

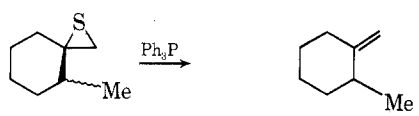
Table II. Chiral Thiiranes 34 from (4S,5S)-2-Thiomethyloxazolines

Entry	Carbonyl compd	Thiirane	Registry no.	% yield[a]	$[\alpha]^{25}_{589}$	% ee (confign)
1			58396-31-9	53	−3.45 (*c* 13.3, hexane)	21 (*R*)[c]
2			58396-32-0	67	−0.42 (*c* 7.1, hexane)	*d*
3			58396-33-1	64	+8.50 (*c* 14.5, PhH)	32 ± 6 (*R*)[c]
4	PhCHO		33877-15-5	48	−8.2 (*c* 2.2, heptane)	19 (*R*)[b]
5			58396-34-2	70	+4.95 (*c* 9.1, PhH)	(*R*)[c]

[a] Yields are of distilled or chromatographed products of >96% purity (VPC). [b] Based on literature value; see ref 17. [c] Configurations based on the corresponding acetates (see text). [d] Product was a diastereomeric mixture which was not separated but taken to the chiral olefin **39**.

among the examples studied only phenylthiirane **34** (R_L = Ph; R_S = H) had been reported[17] and chiral shift reagents failed to provide enantiomeric compositions, an alternative route was investigated. As mentioned earlier, the rearrangement–fragmentation (**32** to **33** to **34**) occurs mainly above 0 °C and thus it appeared possible to trap **32** as its acetate **36**. Reductive cleavage using Raney nickel furnished the chiral acetates **37** and **38**. This scheme provided a measure of the asymmetric induction using the assumptions that (a) nucleophilic displacement by sulfide in **33** proceeds purely by inversion and (b) Raney nickel desulfurization of **36** affords the acetates **37** and **38** without racemization. If these conditions are met, then the acetates **37** and **38** possess enantiomeric purities and absolute configurations equal to that of the corresponding thiiranes **34** (R_L = *n*-hexyl, R_S = H; R_L = cyclohexyl, R_S = H). Thus, the chiral thiiranes in Table II (entries 1 and 3) are assigned the *R* configuration and their percent enantiomeric excess is based upon the known rotation for (*R*)-(−)-2-octyl acetate (**37**)[18] and the enantiomeric purity of 1-cyclohexyl-1-acetoxyethane (**38**). The latter was determined by use of a chiral shift reagent, Eu Optishift II, and its configuration has been previously assigned as *R*.[19]

The mechanism, as currently depicted for this asymmetric synthesis of thiiranes, indicates that the carbonyl group approaches the lithio alkylthio oxazoline **31** from the underside, such that the carbonyl oxygen may be complexed to the chelated lithium cation. The chelation as shown in **31** is in direct analogy with other chiral oxazolines which have been reported to alkylate in a similar manner.[16] In order to account for the configuration of the thiiranes, it is necessary to assume that the carbonyl group aligns itself under **31** in such a manner that the larger group (R_L) in the carbonyl component is as far away from the sulfur atom (*si* face) as possible since the reverse orientation (*ri* face) results in serious nonbonded interactions with the sulfur atom. This interaction is supported by examination of space filling models (Ealing). A similar orientation for carbonyl alkylation has already been discussed earlier with respect to the racemic thiiranes. If this mechanism is correct, then all the chiral thiiranes prepared in this study should be configurationally related, namely *R*. In a single instance, the chiral thiirane derived from 2-methylcyclohexane (Table II, entry 2) was heated with triphenylphosphine and provided a 69% yield of the chiral olefin **39**. The enantiomeric purity was found to be 30 ± 5% as determined by adding silver trifluoroacetate to the sample which contained Eu Optishift II.[20] The absolute configuration of **39** is unknown.



39, $[\alpha]_{576}$ −0.45° (*c* 11, hexane)

Experimental Section

2-(Methylthio)-4,4-dimethyl-2-oxazoline (6). A solution of 26.2 g (200 mmol) of 4,4-dimethyloxazoline-2-thione (**5**)[12] in 250 ml of dry THF was added dropwise, with stirring (N_2) to 10.6 g (220 mmol) of 50% sodium hydride–mineral oil which had been previously washed with hexane (2 × 25 ml) to remove the mineral oil. Hydrogen evolution was complete after 2 h at room temperature. The resulting white suspension was then treated with 37.0 g (260 mmol) of methyl iodide in 20 ml of dry THF at ice bath temperature. The reaction mixture was warmed after 1 h at 0 °C to room temperature and partitioned between ether (100 ml) and saturated brine (150 ml). The aqueous phase was further extracted with ether (2 × 100 ml), the combined ethereal solutions were dried ($MgSO_4$) and concentrated, and the residue was distilled to give 25.0 g of a clear oil (86%), bp 82–84 °C (44 mm).[21]

2-(Ethylthio)-4,4-dimethyl-2-oxazoline (7). In a similar manner to that described above, using ethyl iodide, the product was formed in 85% yield: bp 132–134 °C (82 mm); ir (film) 1610 cm^{-1}; NMR ($CDCl_3$) δ 4.0 (s, 2), 2.97 (q, 2), 1.20–1.53 (s superimposed on t, 9).

Anal. Calcd for $C_7H_{13}NOS$: C, 52.83; H, 8.18. Found: C, 52.71; H, 8.11.

2-(Allylthio)-4,4-dimethyl-2-oxazoline (8) was prepared from allyl bromide, **5**, and sodium hydride furnishing 16.1 g (94%) of **8**: bp 55 °C (0.25 mm); ir (film) 1610, 1640, 3080 cm^{-1}; NMR ($CDCl_3$) δ 5.67–6.30 (m, 1), 5.00–5.46 (m, 2), 4.00 (s, 2), 3.65 (d, 2, *J* = 6 Hz), 1.31 (s, 6).

Anal. Calcd for $C_8H_{13}NOS$: C, 56.10; H, 7.65. Found: C, 56.10; H, 7.77.

2-(Benzylthio)-4,4-dimethyl-2-oxazoline (9) was prepared from 2.0 equiv of benzyl chloride and **5**: 79% yield; bp 123 °C (0.3 mm); ir (film) 1610, 1500, 1440 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5), 4.26 (s, 2), 4.02 (s, 2), 1.32 (s, 6).

Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83. Found: C, 65.37, H, 6.99.

2-(Carboethoxymethylthio)-4,4-dimethyl-2-oxazoline (10) was prepared from ethyl α-bromoacetate, **5**, and sodium hydride: 56% yield; bp 79–81 °C (0.1 mm); ir (film) 1610, 1740 cm^{-1}; NMR ($CDCl_3$) δ 4.21 (q, 2), 4.04 (s, 2), 3.80 (s, 2), 1.25 (t, 9).

Anal. Calcd for $C_9H_{15}NO_3S$: C, 49.77; H, 6.91. Found: C, 49.88; H, 6.88.

2-(α-Phenethylthio)-4,4-dimethyl-2-oxazoline (11). A solution of 5.5 g (25 mmol) of 2-(benzylthio)-4,4-dimethyloxazoline (**9**) in 175 ml of dry THF was cooled (N_2) to −78 °C and treated with 11.5 ml of 2.3 M *n*-butyllithium in hexane (26.5 mmol). The resulting red-orange solution was stirred for 2 h at −78 °C and treated with 3.90 g (27 mmol) of methyl iodide. The reaction mixture was slowly allowed to

Table III. Physical Data for Thiiranes 17

Registry no.	Thiirane entry (from Table I)	NMR ($CDCl_3$), δ	Mp, °C
58437-20-0	1	2.70–3.17 (m, 1), 2.50 (d, 1, J = 6 Hz), 2.17 (d, 1, J = 6 Hz), 0.6–2.00 (m, 13)	*a*
58437-21-1	2	2.52–2.97 (m, 1), 2.50 (d, 1, J = 6 Hz), 2.20 (d, 1, J = 6 Hz), 0.73–2.13 (m, 11)	*b*
58462-45-6	3	4.30–4.66 (m, 9), 3.30–4.30 (m, 3)	>200 dec
58437-22-2	4	2.36–2.46 (m, 2), 1.00–2.10 (m, 8) 1.50 (s, 3)	*c*
58396-35-3	5	2.43 (s, 2), 1.16–2.40 (m, 14)	*b*
58396-36-4	6	7.26 (s, 5), 3.03 (q, AB, J = 2, 14 Hz, 2) (d, J = 6 Hz, 2), 1.50 (s, 3)	*c*
58396-37-5	7	2.34 (br d, J = 8 Hz, 2), 0.80–2.40 (m, 16)	*b*
	13	2.35 (br d, J = 5 Hz, 2), 1.15–2.20 (m, 9), 1.01 (d, J = 7 Hz, 3)	*b*
58396-38-6	14	5.23–5.46 (m, 1), 4.60–4.86 (m, 1), 3.20–4.17 (m, 2), 0.6–2.80 (m, 33) includes Me at 0.90 (s, 3), 1.00 (s, 3), 2.46 (br d, J = 8 Hz, 2)	138–140[c]
57694-36-7	15	trans 7.37 (s, 10), 3.97 (s, 2)	52–54[d]
3372-81-4		cis 7.13 (s, 10), 4.39 (s, 2)	
58396-39-7	16	7.30–7.35 (br s, 5), 4.13 (q, 0.5), 3.58 (d, J = 5 Hz, 0.5)	*b*

[a] C. G. Moore and M. Porter, *J. Chem. Soc.*, 2062 (1958). [b] Since these thiiranes were transformed into olefins, the latter were characterized (cf. Table IV). [c] Analysis performed and gave ±0.4% of calculated values. [d] R. Ketchum and V. P. Shah, *J. Org. Chem.*, 28, 229 (1963).

Table IV. Trimethylsilyl Chloride Trapping of Alkoxide 14. Formation of 21

Temp of aliquot,[a] °C	TLC, R_f (benzene)	Ir, cm^{-1} (film)	NMR ($CDCl_3$), δ	Products
−78 (5 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	**21**
−78 (90 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	**21**
−50 (90 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	**21**
−25 (90 min)	0.55	1610	4.00 (s, 2), 3.50–3.87 (m, 1), 3.00–3.20 (dd, 2), 0.66–2.00 (m, 17), 0.13 (s, 9)	**21**
0 (90 min)	0.55, 0.90 (faint)	1610	Same as above plus small peak at 0.37	**21** + **19**[b]
25 (30 min)	0.9, 0.15, 0.55 (faint)	1740 (s) 1610 (w)	Weak signals for **21**, 3.93 (s), 1.37 (s), 0.37 (s), 2.20 (d, J = 6 Hz), 2.50 (d, J = 6 Hz), 2.52–2.97 (m)	**17**,[c] **19**[b]

[a] Elapsed time after addition of cyclohexanecarboxaldehyde in parentheses. [b] Product is **19** as its *N*-trimethylsilyl ether. [c] Product is 2-cyclohexylthiirane.

warm to room temperature (~3 h) and the reaction mixture partitioned between ether and saturated brine. The aqueous layer was extracted once with ether and the combined ethereal extracts were dried ($MgSO_4$) and concentrated. Distillation gave 5.2 g (89%) of pure material (by VPC): bp 116–117 °C (0.1 mm); ir (film) 3030, 1605 cm^{-1}; NMR ($CDCl_3$) δ 7.33 (s, 5), 4.78 (q, 1), 3.95 (s, 2), 1.75 (d, 3), 1.3 (s, 6). Product was homogeneous by VPC.

Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28. Found: C, 66.26; H, 7.39.

Ethyl α-(4,4-Dimethyloxazolinethio)propionate (12). A solution of 2.17 g (10 mmol) **10** in 50 ml of dry THF was cooled to −78 °C (N_2) and treated with lithium diisopropylamide (10 mmol in 10 ml of dry THF). Stirring was continued for 3 h, 0.7 ml (1.56 g, 11 mmol) of methyl iodide added, and the solution allowed to warm to room temperature. Aqueous quenching followed by ether extraction and concentration gave 1.9 g (82%): bp 83.5 °C (0.06 mm); ir (film) 1610, 1735 cm^{-1}; NMR ($CDCl_3$) δ 4.35–4.06 (m, 3), 4.06 (s, 2), 1.63 (d, 3), 1.13–1.50 (s superimposed on t, 9). Product was homogeneous by VPC.

Anal. Calcd for $C_{10}H_{17}NO_3S$: C, 51.95; H, 7.36. Found: C, 51.99; H, 7.28.

The formation of **12** was also achieved by utilizing the sodium salt of **5** (100 mmol) and 16.2 g (100 mmol) of ethyl α-bromopropionate according to the procedure given for **6**. This provided 20.0 g of **12**, homogeneous by VPC, in 82% yield.

General Procedure for Thiiranes (17). Method A (Table I). A solution of 10 mmol of 2-(alkylthio)-4,4-dimethyl-2-oxazolines **6**, **8**, **9**, and **11** in 50 ml of dry THF (0.2 M) under nitrogen at −78 °C was treated with 10 mmol of *n*-butyllithium (hexane). After 2 h at −78 °C, 10 mmol of the carbonyl compound was introduced dropwise via syringe either neat (if liquid) or in 10 ml of THF if solid and the reaction mixture stirred for 30 min at −78 °C. After warming to room temperature (1–2 h) the reaction mixture was quenched in saturated brine (100 ml) and extracted with 50 ml of ether (twice). The ethereal extracts were dried ($MgSO_4$) and concentrated to give the crude thiiranes along with the oxazolidinone **19**. Chromatography (benzene, silica gel) gave the pure thiiranes (TLC R_f 0.85–0.95) listed in Table I. Further elution of the silica gel column (benzene–ether, 5:1) provided pure **19**, mp 55–56 °C (lit.[22] 55.6–56.4 °C). Physical data and literature references for the thiiranes prepared in this manner are given in Table III.

Alkoxide-Trapped Trimethylsilyl Ether 21. A solution of 2-(methylthio)-4,4-dimethyloxazoline (**6**, 1.45 g, 10 mmol) in 30 ml of dry THF was cooled to −78 °C (N_2) and treated with 4.5 ml of 2.3 M *n*-butyllithium in hexane. After 2.5 h at −78 °C, a solution of 1.12 g (10 mmol) of cyclohexanecarboxaldehyde in 5 ml of THF was added via a syringe. After 5 and 90 min, aliquots were removed (8 ml) and quenched in 5 ml of THF containing 0.3 ml (1.1 equiv) of trimethylchlorosilane. Similarly, aliquots were taken at −50, −25, 0, and 25 °C and quenched in the trimethylchlorosilane–THF solution. In all cases, the quenching solution was at the same temperature as the aliquot removed from the reaction mixture. Workup of each aliquot by ether extraction, drying, and concentration gave the results summarized in Table IV.

General Procedure for Conversion of Carbonyl Compounds Directly to Alkenes 20. Method B (Table I). The general procedure for alkylation of the lithio alkylthio oxazolines with carbonyl compounds was followed as for thiiranes **17** up to the purification stage using column chromatography. Instead of column purification, the crude thiirane **17** contaminated with the oxazolidinone **19** was treated either with 1.15 equiv of neat triphenylphosphine at 90 °C for 2 h or with 1.5 equiv of triethyl phosphite at 90 °C for 2 h. When triphenyl phosphine was used, the reaction mixture was allowed to cool, the reflux condenser was replaced by a short path distillation head, and the olefinic products were distilled. When triethyl phosphite was used

Table V. Physical Data for Olefins 20

Registry no.	Olefin entry (from Table I)	Desulfurization reagents	Ir, cm^{-1} (film)	NMR ($CDCl_3$), δ	Lit. bp, °C
111-66-0	1	Ph_3P	1640, 3078		118–120[a]
695-12-5	2	Ph_3P	1638, 3080		125–127[b]
3618-18-6	5	Ph_3P	1635, 3080	4.80 (br s, 2), 1.30–2.26 (m, 14)	154–156[c]
58396-40-0	7	Ph_3P	1650, 3080	4.46–4.70 (br s, 2), 0.70–2.40 (m, 16)	200–201[d]
13511-13-2	8	Ph_3P	1600, 1660, 3080	5.90 (m, 1), 4.93 (br d, 2), 1.90 (s, 3), 1.50–2.50 (m, 11)	49–50 (7 mm)[e]
16939-57-4	9	$(EtO)_3P$	1610, 1640	7.03–7.53 (m, 5), 6.10–6.80 (m, 3), 5.00–5.43 (m, 2)	86 (11 mm)[e,f]
25108-63-8	10	$(EtO)_3P$	1635, 3080	7.53–7.83 (m, 1), 7.03–7.46 (m, 3), 5.50 (br s, 1), 4.96 (br s, 1), 1.60–3.00 (m, 6)[g]	103 (14 mm)[h]
57662-71-2	11	$(EtO)_3P$	1610, 1650, 3080	7.00–7.50 (m, 4), 6.03 (br s, 1), 4.77 (br s, 2), 1.47 (s, 3), 1.13–3.10 (m, 11)[g]	Oil[i]
627-58-7	12	Ph_3P	1645, 3080	4.70 (br s, 4), 2.17 (s, 4), 1.73 (t, J = 2 Hz, 6)	110–112[j]
58396-41-1	13	Ph_3P	1642, 3075	4.60 (br s, 2), 0.77–2.57 (m, 12)	145[k]
103-30-0 645-49-8	15	$(EtO)_3P$	*E, Z* mixture		113–116[n]
28665-60-3 42036-72-6	16	$(EtO)_3P$	*E, Z* mixture		144 (10 mm)[l]
538-81-8 5808-05-9	17	$(EtO)_3P$	*E, Z* mixture		(mp 141–144)[m]
58396-42-2	18	$(EtO)_3P$	1600, 1575	7.26 (m, 5), 6.30 (br s, 1), 2.06–2.60 (m, 4), 1.3–2.00 (m, 10)	Oil[o]
3677-70-1	19	$(EtO)_3P$	1600, 3020	7.33 (s, 5), 7.16 (s, 5), 6.97 (br s, 5), 2.16 (s, 3)	Oil
58396-43-3	20	$(EtO)_3P$	1600, 3020	*E, Z* mixture	Oil[p]
58396-44-4	21	$(EtO)_3P$	Identical with entry 9		
58396-45-5	22	$(EtO)_3P$	1650, 1600, 3090, 1010	4.85–6.70 (m, 4), 1.80–2.46 (m, 2), 0.50–1.80 (m, 11)	168–170[q]

[a] Huntress and Mulliken, "Identification of Pure Organic Compounds", Order 1, Wiley, New York, N.Y., 1941, p 586. [b] L. F. Slaugh and E. F. Magoon, *J. Org. Chem.*, **27**, 1037 (1962). [c] W. T. Brady and A. D. Patel, *Synthesis*, 565 (1972). [d] M. Mousseron and R. Granger, *C. R. Acad. Sci.*, **217**, 483 (1943), mixture of cis–trans isomers. [e] P. S. Wharton and B. T. Au, *J. Org. Chem.*, **31**, 3787 (1966). [f] O. Grummitt and E. I. Becker, *J. Am. Chem. Soc.*, **70**, 149 (1948). [g] Spectrum taken in CCl_4 or benzene-d_6; see footnote *i*, Table I. [h] G. Schroeder, *Ber.*, **58B**, 713 (1925). [i] Pure sample from silica gel chromatography (benzene). Anal. Calcd for $C_{16}H_{18}$: C, 91.40; H, 8.57. Found: C, 91.19; H, 8.40. [j] E. Muller and G. Roscheisen, *Ber.*, **90**, 543 (1957). [k] B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 967 (1954). [l] R. Y. Mixer and W. G. Young, *J. Am. Chem. Soc.*, **78**, 3379 (1956). [m] B. B. Corson, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 229; mp for pure trans,trans is 152.5–153.5 °C. [n] W. Schlenk and E. Bergman, *Justus Liebigs Ann. Chem.*, **463**, 98 (128). [o] Pure sample from silica gel (benzene). Anal. Calcd for $C_{15}H_{20}$: C, 90.00; H, 10.00. Found: C, 89.89; H, 9.78. [p] Pure sample from silica gel (benzene). Anal. Calcd for $C_{21}H_{24}$: C, 91.25; H, 8.75. Found: C, 90.96; H, 8.80. [q] H. Fournier, *Bull. Soc. Chim. Fr.*, **13**, 884 (1918).

as the desulfurization agent, the mixture was applied to a column (silica gel) and eluted with benzene. Physical data for the olefins prepared are presented in Table V.

(1*S*,2*S*)-(+)-1-Phenyl-2-amino-3-methoxy-1-propanol (28). To a solution of 20.5 g (100 mmol) of (4*S*,5*S*)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline[16,23] in 400 ml of ethanol was added 100 ml of 12 M aqueous hydrochloric acid (1.2 mol, 12-fold excess). The resulting solution was heated under reflux for 8 h, cooled to room temperature, and the ethanol removed under reduced pressure. Slow, cautious addition to the aqueous residue (ice bath) of KOH pellets and ether extraction provided 17.3 g after removal of the ether. Crystallization from ether (−78 °C) gave 15.5 g (86%) of **28**, mp 48–50 °C, $[\alpha]_{589}^{25}$ +25.8° (*c* 8.55, $CHCl_3$) [lit.[16] mp 48–50 °C, $[\alpha]_{589}^{25}$ +24.4° (*c* 10.6, $CHCl_3$)].

(4*S*,5*S*)-(−)-4-Methoxy-5-phenyl-2-oxazolidine-2-thione (29). To a solution of 18.1 g (100 mmol) of (+)-**28** in 250 ml of dry DMF at ice bath temperature was added 6.4 ml (107 mmol) of carbon disulfide, and the resulting yellow-orange solution stirred (0 °C) for 1 h. The solution was heated in an oil bath (80 °C, 2 h), cooled to room temperature, and the residual hydrogen sulfide removed in vacuo in a hood overnight. The DMF was evaporated in vacuo and the residue partitioned between ether and saturated brine. The ether layer was washed with 1 M sodium bicarbonate, followed by 1 M HCl, and finally with water, dried ($MgSO_4$), and concentrated. The residue was recrystallized from carbon tetrachloride yielding 15 g (67%) of **29**: mp 88–89 °C; $[\alpha]_{589}^{25}$ −14.4° (*c* 6.05, $CHCl_3$); ir ($CHCl_3$) 3400, 3200, 1550–1460 cm^{-1}; NMR ($CDCl_3$) δ 8.17 (br s, 1), 7.43 (s, 5), 5.72 (d, J = 6 Hz, 1), 3.93–4.30 (m, 1), 3.43–3.73 (m, 5). Elemental analyses performed on the 2-thiomethyl derivative **30** given below.

(4*S*,5*S*)-(−)-2-Methylthio-4-methoxymethyl-5-phenyloxazoline (30). A solution of 11.15 g (50 mmol) of (−)-**29** in 125 ml of dry THF was added dropwise (N_2) to 2.7 g (55 mmol) of a 50% sodium hydride suspension (previously washed twice with 20-ml portions of hexane). Gas evolution was complete after 1.5 h. The resulting mixture was treated with 9.3 g (65 mmol) of methyl iodide in 15 ml of dry THF at 0 °C and after 1 h allowed to warm to 25 °C. The mixture was partitioned between ether (100 ml) and saturated brine (150 ml). The aqueous phase was extracted (2 × 75 ml) and the ethereal solutions combined, dried ($MgSO_4$), and concentrated. The residue was distilled, bp 140–142 °C (0.25 mm), to give 9.1 g (80%) of **30**: $[\alpha]_{589}^{25}$ −42.4° (*c* 10.3, $CHCl_3$); ir (film) 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.35 (s, 5), 5.45 (d, J = 6 Hz, 1), 3.97–4.33 (m, 1), 3.33–3.80 (m, 2), 3.43 (s, 3), 2.53 (s, 3).

Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.73. Found: C, 60.82; H, 6.55.

General Procedure for Chiral Thiiranes 34. A solution of 1.2 g (5 mmol) of **30** in 25 ml of dry THF (0.25 M) was cooled to −78 °C (N_2) and treated with 1.05 equiv of lithium diisopropylamide. After 4 h at −78 °C, the mixture was cooled to −95 °C and the carbonyl compound (1.0 equiv) was added dropwise in 5 ml of THF. The reaction was maintained at −95 °C for 1 h and then allowed to warm to 25 °C. The mixture was quenched in saturated brine solution and extracted several times with ether, then dried ($MgSO_4$) and concentrated. The pure thiiranes were obtained by passing through a silica gel column using benzene as the eluent. Further elution using ether gave the chiral oxazolidinone **35**: ir 3300, 1760 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5), 5.3 (d, J = 6 Hz, 1), 4.10–3.73 (q, 1), 3.63–3.40 (m, 2), 3.40 (s, 3).

The chiral thiiranes prepared in this manner are presented in Table II. No spectral data are presented for **34** since they were found to be identical with their racemic counterparts (**17**) given in Table III.

Alkoxide Trapped Acetates 36. General Procedure. The procedure above (for **34**) was followed up to the reaction of the carbonyl compound with the lithio thiomethyloxazoline **31** at −95 °C for 1 h. At the end of this period, the mixture was warmed to −78 °C for 2 h and then treated with 0.37 g (5.25 mmol) of freshly distilled acetyl chloride. After a further 2 h at −78 °C, the reaction mixture was allowed to warm slowly to 25 °C and quenched in saturated brine solution. Ether extraction followed by drying ($MgSO_4$) and concentration gave the acetates **36** (85–95% purity via NMR). The major impurity was 5–10% of starting oxazoline **30**. Physical data for **36** follow.

36 (R_S = H; R_L = *n*-hexyl): 76% yield; ir (film) 1750, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5), 5.45 (d, J = 6 Hz, 1), 2.93–4.37 (m, 9), 2.07 (s, 3), 0.67–1.93 (m, 13).

36 (R_S = H; R_L = cyclohexyl): 75% yield; ir (film) 1740, 1610 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5), 5.30–5.60 (m, 1), 3.03–4.43 (m, 9), 0.67–2.26 (m, 11).

These materials were not purified further and were used as obtained for the desulfurization to **37**.

Chiral Acetates 37 and 38. The Raney nickel reagent for the desulfurization was prepared by removal of the ethanol from a tenfold weight excess of W-4 Raney nickel as the benzene–ethanol azeotrope. Sufficient benzene was included so that the volume of solvent present after removal of the azeotrope was approximately 50 ml. A solution of the acetates **36** (4 mmol in 10 ml of dry benzene) was added to the suspension and the resulting mixture heated for 3 h at reflux. Cooling, filtration, and fractional distillation of the benzene gave the crude acetates **37**. Pure samples were obtained by preparative gas chromatography. Physical data follow.

37 (R_S = H; R_L = *n*-hexyl): $[\alpha]_{589}^{25}$ −1.36° (*c* 2.21, EtOH), reported[18] $[\alpha]_{589}^{25}$ −6.5° (*c* 5, EtOH); absolute configuration designated as *R*.

38 (R_S = H; R_L = cyclohexyl): $[\alpha]_{589}^{25}$ −1.6° (*c* 1.1, CCl_4); optical purity determined by Eu Optishift II [tris(heptafluoropropylhydroxymethylene-*d*-camphorato)europium(III)]. Absolute configuration of the (−) alcohol and (−) acetate is known.[19]

(−)-Methylene(2-methyl)cyclohexane (39). A mixture of 586 mg (4 mmol) of the chiral thiirane **34** (Table II, entry 2) and 1.2 g (4.6 mmol) of triphenylphosphine was heated to 90 °C for 2 h. The mixture was cooled to room temperature and the reflux condenser replaced with a short-path distillation head. Distillation gave 303 mg (69%) of **39**. The observed optical rotation at 589 nm was <0.01° and thus too low to permit a reliable [α] value; these rotations were, therefore, taken (Jasco DIP-180 automatic polarimeter) at 576 nm, which gave an observed rotation of −0.05° or $[\alpha]_{576}^{25}$ −0.45° (*c* 11, hexane). The spectral characteristics (ir, NMR) were identical with those of the racemic compound (entry 13, Tables I, V). The enantiomeric purity of **39** was determined as follows, which represents a modification of the method of Evans.[20]

A solution of 29 mg (0.26 mmol) of **39** was dissolved in 0.66 ml of CCl_4, containing 1% Me_4Si, to give approximately a 0.4 M solution. Addition of 0.13 mmol of both silver trifluoroacetate and Eu Optishift II [in place of Eu($[^2H_9]$fod)$_3$ used in the reported[20] procedure] was followed by shaking the solution until all the solid had dissolved. Examination of the 60-MHz spectrum gave partial resolution of the terminal vinyl protons. Integration and peak height comparison indicated that the enantiomeric purity was 30 ± 5%.

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