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Chelation-Controlled Chemo-, Regio- and Enantio-Selective Synthesis of Homoallylic Alcohols

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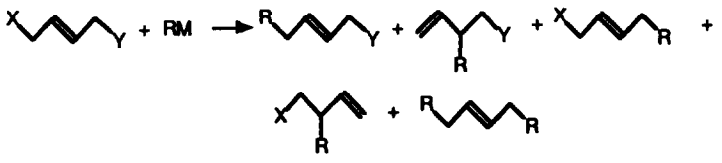
Abstract: Optically active allylic sulphides **10-13**, bearing two different leaving groups, react with organocopper reagents by selective substitution of the heterocyclic moiety leading to optically active homoallylic pivalates with chemo-, regio- and enantio-control. This selectivity seems to be related to the coordination exerted by the heterocyclic nucleus towards the organometal.

Introduction

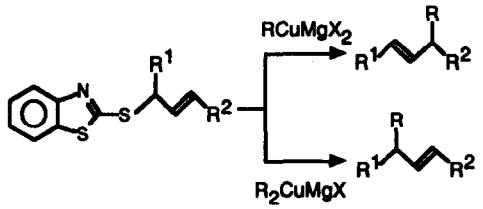
The regiocontrol in the reactions of organocopper reagents with allylic electrophiles which contain two different leaving groups has been little studied.[1-3] The control of the selectivity in these nucleophilic substitutions is difficult to achieve since many regio-(S_N2 or S_N2'), chemo-, and stereo-selective reactions occur together (Scheme I).

Scheme I



Over the last fifteen years, our research group has uncovered[4-6] a number of highly selective reactions of organocopper reagents with allylic electrophiles containing a heterocyclic moiety as leaving group. For these substrates the regioselectivity of the C-C coupling process is dictated by the preliminary coordination of the organometallic reagent to the leaving group of the allylic moiety. We observed that organocopper reagents of RCu type[4] gave exclusively γ-substituted products whereas magnesium cuprates afforded α-substituted products (Scheme II). The allylic substrates of choice were sulphides or ethers of benzothiazole whose heterocyclic nitrogen has coordinating properties towards organocopper reagents.

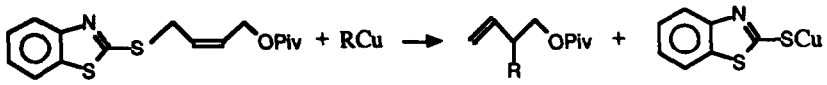
Scheme II



R^1=H or alkyl ; R^2= H, alkyl , aryl or CO_2R

In a previous paper[7] we showed that the chemoselectivity control in the organocopper reactions with allylic derivatives bearing two leaving groups displaying different reactivity can be achieved if one of the leaving groups is a sulphide of benzothiazole **1**, being selectively replaced[8] by reaction with organocopper reagents by a S_N2' mechanism to afford homoallylic pivalates exclusively (Scheme III).

Scheme III

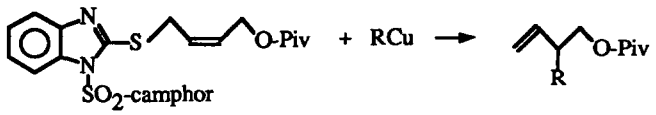


(Z)-**1** **2** Piv = $COC(CH_3)_3$

This selectivity is probably due to the coordination exerted by the heterocyclic azomethine group towards the organometallic reagent.[4] The same chemoselectivity was observed also by using sulphides of benzimidazole as leaving group[7].

Beside the chemoselectivity of this reaction, having a stereogenic carbon in the homoallylic pivalates **2** we also attempted to prepare optically active homoallylic esters[7] by using chiral benzimidazole sulphides **3** as leaving group. Although a chemoselective substitution was again obtained (Scheme IV), the enantiomeric excess measured, however, were disappointingly low.

Scheme IV



(Z)-**3** **2**

Since the chemoselectivity is probably due to an intermediate complex between the allylic system and organometallic reagent which brings together the azomethine and the prochiral olefinic carbon, the low asymmetric induction found for the reactions of **3** could be ascribed to the considerable distance between the

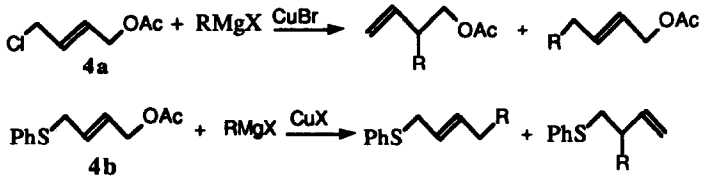
chiral group and the olefinic prochiral carbon. So, we expected that by reducing such a distance a better stereoselectivity might be obtained.

This paper reports the achievements about the control of the enantioselectivity (as well as the chemo- and regio-selectivity) towards the synthesis of homoallylic pivalates by using different chiral nitrogenous heterocycles as the leaving groups, in which the stereocenter is closer to the stereogenic center.

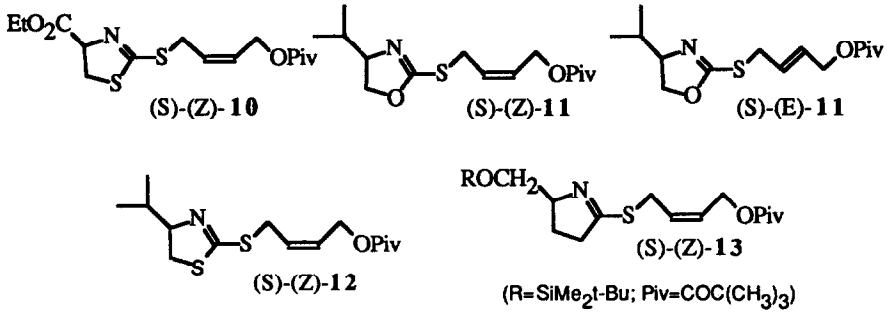
RESULTS AND DISCUSSION

The reactions of both allylic sulphides **1** and **3** with organocopper reagents show that the presence of the azomethine group is essential in dictating the regioselectivity of the C-C coupling process. In fact **4a** and **4b** reacted with organocopper reagents affording chloride (**4a**) and acetoxy (**4b**) substitution, respectively, with no regioselectivity at all[2] (Scheme V).

Scheme V

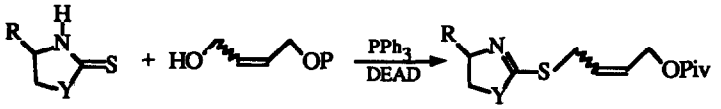


On the other hand, since the regioselectivity for the reactions of both **1** and **3** appears to be dictated by the coordination exerted by the azomethine moiety, it might be possible to obtain optically active homoallylic pivalates by using optically active nitrogenous heterocycles in which the stereocenter is in α-position to the coordinating nitrogen. The substrates of choice were the sulphides **10-13**.



Compounds **10-13** were easily synthesized by reaction of the heterocycles (S)-**5-8**, prepared by known procedures,[9,10] with (*Z*)- or (*E*)-2-butene-1,4-diol mono pivalate **9** as reported in the scheme VI.

Scheme VI



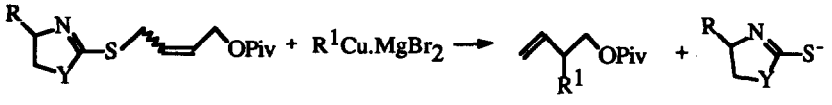
(S)-**5-8** **9**

5: R=CO_2Et, Y=S
6: R=$CH(CH_3)_2$, Y=O
7: R=$CH(CH_3)_2$, Y=S
8: R=CH_2OSiMe_2t-Bu, Y=CH_2

(S)-(Z)-**10**, R=CO_2Et, Y=S
(S)-(Z)-**11**, R=$CH(CH_3)_2$, Y=O
(S)-(E)-**11**, R=$CH(CH_3)_2$, Y=O
(S)-(Z)-**12**, R=$CH(CH_3)_2$, Y=S
(S)-(Z)-**13**, R=CH_2OSiMe_2t-Bu, Y=CH_2

These compounds reacted with organomagnesium derivatives, in the presence of CuBr, to give C-C coupling products arising again from both chemo- and regioselective substitution of the heterocyclic sulphide by a S_N2' mechanism (γ-substitution) affording homoallylic pivalates **14-16** in high yields (Scheme VII).

Scheme VII



(S)-**10 - 13** **14 - 16**

The regioselectivity of this process depends strictly on the CuBr:Grignard reagent ratio. For example, a 4:1 molar ratio which favours the formation of RCu-type reagents,[11] leading to homoallylic pivalates **14-16** cleanly. This selectivity was completely lost when conditions which promote the formation of magnesium cuprates were used (e.g. a 0.5:1 molar ratio or catalytic amounts of CuBr). In the latter case products arising from substitution of the susulphide or pivalate groups or both are observed (see scheme I).

As can be seen in the table, reactions of both (S)-(Z)-**11-13** and (S)-(E)-**11** with organomagnesium compounds in the presence of excess of CuBr, afford homoallylic pivalates with very high enantiomeric excess whereas the low values obtained from the reactions of the substrate (S)-(Z)-**10** (entries 1 and 2) are due to the partial racemization of the heterocyclic stereocenter under basic reaction conditions since unreacted (S)-(Z)-**10**, isolated at low conversion value, proved to be partially racemized.

So, beside the chemo- and regio-selectivity, high enantioselectivity of this C-C coupling process was observed, and this appears to be related to the steric hindrance of the R-group alpha to nitrogen in the heterocycle.

On the other hand, it seems from the selected data reported in the table, that the absolute configuration outcome depends on both the double bond configuration and the group bonded to the stereocenter of the oxazoline (S)-(Z)- and (S)-(E)-**11**, thiazoline (S)-(Z)-**12** and pyrroline (S)-(Z)-**13**.

Table. Cross-coupling[a] of sulphides **10-13** with Grignard reagents and CuBr.

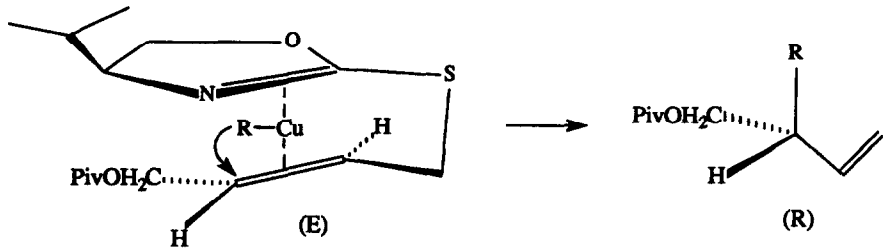
Entry	Substrate	Product R^1		Yield[b]%	E.e[c]%	Abs. Conf.
1	(Z)-**10**	i-C_3H_7	(**14**)	78	36	-
2	(Z)-**10**	n-C_8H_{17}	(**15**)	80	60	-
3	(Z)-**11**	n-C_4H_9	(**16**)	90	>98	(S)
4	(Z)-**11**[d]	"	(**16**)	82	80	(S)
5	(E)-**11**	n-C_4H_9	(**16**)	85	>98	(R)
6	(Z)-**12**	n-C_4H_9	(**16**)	93	90	(S)
7	(Z)-**13**	"	(**16**)	94	91	(R)
8	(Z)-**13**	n-C_8H_{17}	(**15**)	90	93	-

[a]Conditions: To CuBr (18.7 mmol) and substrate (4.6 mmol) in dry THF (25 ml) at -50 °C was added dropwise, under nitrogen atmosphere and stirring, the Grignard reagent (0.5 M, 6.9 mmol) in THF. [b]Isolated yields. [c]Evaluated by ^{1}H NMR in the presence of the [Eu(hfc)$_3$] as chiral shift reagent. [d]Containing a 10% of the trans isomer.

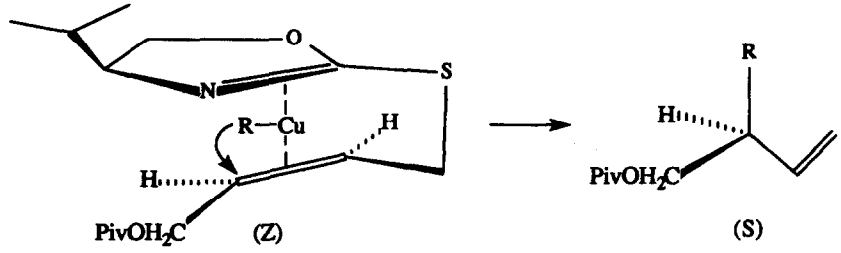
Further, another important feature of this process is the control on the e.e. exerted by the geometry of the olefinic double bond in the starting sulphide since the (Z)-sulphide **11** gives the (S)-enantiomer (entry 3) whereas the reaction of the trans isomer affords the (R)-enantiomer (entry 5). In all cases the presence of the azomethine group is again indispensable to obtain a high degree of selectivity whereas the nature of Y group in the heterocyclic moiety (entries 3, 6 and 7) has not influence.

These highly selective organometallic reactions would be explained reasonably by a preliminary chelation of the organometallic specie RCu by the heterocyclic azomethine group and the double bond of the allylic moiety and this, by bringing reacting centers into close proximity, dictates the selectivity of the C-C coupling process. Beside the enantioselectivity, the chelation of the azomethinic moiety by increasing the electron withdrawing proprties of this group, makes the heterocyclic sulphide a better leaving group than the pivalate and this explains the observed chemoselectivity. On the other hand in the reaction with dialkyl cuprates, the metal would be less susceptible to the coordination by the heterocycle than RCu and therefore the nucleophile attacks randomly both the leaving groups. Proofs in favour of chelation exerted by these heterocyclic leaving groups towards copper compounds were from the isolation of stable π-complexes of these with copper(I) halides[12] in which the CuX is inserted probably between the two double bonds. In addition, the propensity of copper ions to give complexes with nitrogenous heterocycles is well documented.[10,13]

An inspection of a molecular model of compound (S)-(E)-**11** shows that the allylic moiety should lie, for steric reasons, on the opposite side of the isopropyl group of the heterocycle and the observed selectivity could be explained by the formation of a transition state, as depicted below, in which the organocopper reagent would be coordinated by the heterocyclic nitrogen and the allylic double bond:



A similar structure for the (S)-(Z)-**11** can be represented as follows:



Work is in progress to apply this procedure to the synthesis of biological active products.

EXPERIMENTAL SECTION

General methods. The regiochemical purity of the reaction products was tested by GLC recorded on HP 5890A capillary gas-chromatograph (SE 30; 30m; 0.25 mm. i.d.). GC-MS analyses were performed on an HP 5970 instrument, and microanalyses on a mod. 1106 Carlo Erba Elemental Analyzer. IR spectra were recorded on a Perkin Elmer 681 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 500 and Varian XL 200 spectrometers; chemical shifts are reported in parts per million (δ), solvent $CDCl_3$. Optical rotations were measured on Perkin Elmer 241 polarimeter at 24 °C. Enantiomeric excess was evaluated by ^{1}H NMR in the presence of [Eu(hfc)3] as chiral shift reagent. Such analyses were based upon the splitting of the vinyl signal CH_2=CH. L-Cysteine ethyl ester hydrochloride, L-Valinol and (S)-5-(hydroxymethyl)-2-pyrrolidinone were purchased from Fluka. Solvents were dried and distilled under nitrogen immediately prior to use.

(S)-4-Carboxyethyl-2-thioxothiazolidine (5). To L-cysteine ethyl ester hydrochloride (5g, 0.44 mole) suspended in 60 ml of anhydrous THF were added triethylamine (7.8 ml, 0.92 mole) and carbon disulfide (3.4 ml, 0.94 mole). The resulting suspension was refluxed for 7 h to give a yellow-orange solution, which after evaporation of the solvent was poured in water and acidified at pH 5. After extraction of the reaction mixture with ethyl acetate (3x20 ml), the organic layer dried and and evaporated affords a crude product which was

chromatographed on silica gel (eluent hexane-ethyl acetate 2:1) to give 4.5 g of **5** as an orange solid (88% yield). Mp 44-46 °C. $[\alpha]_D$= - 22° (c=9 in $CHCl_3$). ^1H NMR: 1.28 (3H, t, J= 7.1 Hz, CH_3); 3.72 (1H, dd, J= 11.5 Hz, 6.4 Hz, CH_2-S); 3.78 (1H, dd, J= 11.5 Hz, 8.6 Hz, CH_2-S); 4.22-4.27 (2H, 2q, J= 7.1 Hz, CH_2, ethyl); 4.79 (1H, dd, J= 8.6 Hz, 6.4 Hz, CH-NH); 8.45-8.52 (1H, bs, N-H). GC-MS (70 eV) m/z (%) 191 (M^+, 100), 118 (96), 59 (27).

(S)-4-Isopropyl-2-thioxothiazolidine (7) and (S)-4-Isopropyl-2-thioxooxazolidine (6) These compounds were obtained in a 2: 1 ratio by the following procedure. To L-valinol (2g, 0.69 mole) dissolved in a mixture of water (10 ml) and ethanol (18 ml) was added carbon disulfide (5.8 ml, 3.4 mole). To this stirred solution, cooled in a ice bath, was added dropwise a solution of potassium hydroxide (5.43 g, 3.4 mole) in 10 ml of water and 18 ml of ethanol. This mixture was heated at 70 °C for 6 h. After the solvents had been evaporated the residue was poured in water and acidified at pH=5. After extraction with ether (3x20 ml), and evaporation of the solvent, the residue was chromatographed on silica gel (eluent hexane-ethyl acetate 3:1) to give 1.22 g of (S)-4-isopropyl-2-thioxooxazolidine (**6**) and 0.7 g of (S)-4-isopropyl-2-thioxothiazolidine (**7**) (total yield 87%).

(S)-4-Isopropyl-2-thioxooxazolidine (6). Mp 45-46°C; $[\alpha]_D$=-22.7° (c=0.40 in $CHCl_3$). (lit.[9] m.p. 45-46 °C, $[\alpha]_D$ =-22.5° (c=0.41 in $CHCl_3$).

(S)-4-Isopropyl-2-thioxothiazolidine (7). Colourless needles, mp 70-73 °C, $[\alpha]_D$ =-13.1° (c=8 in $CHCl_3$). ^1H NMR: 0.92 (3H, d, J= 6.8 Hz, CH_3, isopropyl); 0.95 (3H, d, J= 6.8 Hz, CH_3, isopropyl); 1.89-1.96 (1H, m, CH, isopropyl); 3.24 (1H, dd, J=11.2 Hz, 8.1 Hz, CH_2-S); 3.44 (1H, dd, J= 11.2Hz, 8.4Hz, CH_2-S); 4.00-4.04 (1H, m, CH-NH); 8.50-8.60 (1H, bs, N-H). GC-MS (70 eV) m/z (%) 161 (M^+, 75), 118 (100), 91 (5), 59 (37), 41 (28).

(S)-(Z)-1-Trimethylacetoxy-4-(2-thio-4-carboxyethylthiazoline)-2-butene (10). To a solution of (S)-(-)-4-carboxyethyl-2-thioxothiazolidine (**5**) (2 g, 0.17 mole), cis-2-butene-1,4-diol monopivalate (**9**) (1.64 g, 0.17 mole) and triphenyl phosphine (3 g, 0.34 mole) in 60 ml of anhydrous toluene, cooled in an ice bath, was added dropwise under stirring 1.54 g (0.37 mole) of diethyl azodicarboxylate (DEAD) dissolved in 20 ml of the same solvent. Stirring was kept on until the disappearance of (**5**) (TLC, petroleum ether-ethyl acetate 1:1). Chromatography on silica gel with the above eluent gave 2 g of (**10**) in a 50% yield as pale yellow oil. $[\alpha]_D$=+ 6.7° (c=7.5 in $CHCl_3$). ^1H NMR: 1.12 (9H, s, *t*-butyl); 1.24 (3H, t, J= 7.1 Hz, CH_3, ethyl); 3.53 (1H, dd, J= 11.0 Hz, 8.9 Hz, CH_2, heterocyclic proton); 3.60 (1H, dd, J= 11.0 Hz, 8.1 Hz, CH_2, heterocyclic proton); 3.79 (2H, d, J= 7.9 Hz, CH_2-S); 4.17 (2H, q, J= 7.1 Hz, CH_2, ethyl), 4.58-4.66 (2H, m, CH_2-O); 4.95 (1H, dd, J= 8.9 Hz, 8.1 Hz, CH-N); 5.59 (1H, six t, J= 10.8 Hz, 6.7 Hz, 1.1 Hz , vinyl proton); 5.71 (1H, six t, J= 10.8 Hz, 7.9 Hz, 1.4 Hz, vinyl proton). ^{13}C NMR (δ): 13.9, 26.9, 29.6, 37.2, 38.4, 59.7, 61.5, 127.4, 128.1, 167.7, 170.2. GC-MS (70eV) m/z (%) 345 (M^+,1), 244 (80), 216 (11), 170 (17), 143 (23), 85 (26), 57 (100).

(S)-(Z)-1-Trimethylacetoxy-4-(2-thio-4-isopropyloxazoline)-2-butene (11). To the ice bath cooled (*Z*)-pivalate (**9**) (1.85, 0.27mole) containing a 13% of the (*E*)-isomer, triphenyl phosphine (3.4 g, 0.32 mole) and (**6**) (1.7 g, 0.19 mole) dissolved in 40 ml of anhydrous toluene, under stirring 2.04 g of DEAD (0.30 mole) was added. After work-up and chromatography as above reported, 2.1 g of (*Z*)-(**11**) and 0.25 of (*E*)-(**11**) (67% yield) as pale yellow oils were obtained. (**11**)-(*Z*): $[\alpha]_D$= -61.4° (c=7 in $CHCl_3$). ^1H NMR: 0.84 (3H, d, J= 6.7 Hz, CH_3, isopropyl); 0.92 (3H, d, J= 6.7 Hz, CH_3, isopropyl); 1.17 (9H, s, *t*-butyl); 1.67-1.77 (1H, m, CH, isopropyl); 3.67-3.69 (2H, m, CH_2-S); 3.86 (1H, qd, J= 9.4 Hz, 7.6 Hz, 6.4 Hz, CH-N); 3.99-4.02 (1H, m, CH_2-CH-N); 4.27-4.34 (1H, m, CH_2-CH-N); 4.66-4.68 (2H, m, CH_2-OCO); 5.63 (1H, six t, J= 10.8 Hz, 6.7 Hz, 1.1 Hz, vinyl proton); 5.74 (1H, six t, J= 10.8 Hz, 7.9 Hz, 1.4 Hz, vinyl proton). ^{13}C NMR (δ) : 18.0, 18.6, 27.1, 28.7, 32.7, 38.6, 59.9, 71.8, 72.6, 127.2, 128.9, 163.8. GC-MS (70 eV) m/z (%) 198 (85), 155 (32), 57 (100).

(S)-(E)-1-Trimethylacetoxy-4-(2-thio-4-isopropyloxazoline)-2-butene (11). Pale yellow oil synthesized as by product from reaction of (**6**) with (**9**). ^1H NMR: 0.84 (3H, d, J= 6.7 Hz, CH_3, isopropyl); 0.92 (3H, d, J= 6.7 Hz, CH_3, isopropyl); 1.17 (9H, s, t-butyl); 1.67-1.77 (1H, m, CH, isopropyl); 3.64-3.75 (2H, m, CH_2-S); 3.86 (1H, qd, J= 9.4 Hz, 7.6 Hz, 6.4 Hz, CH-N); 3.99-4.02 (1H, m, CH_2-CH-N); 4.27-4.34 (1H, m, CH_2-CH-N); 4.63-4.66 (2H, m, CH_2-OCO); 5.60-5.66 (1H, m, vinyl proton); 5.68-5.72 (1H, m, vinyl proton). GC-MS (70 eV) m/z (%) 299 (M^+, 1), 256 (4), 198 (100), 155 (26), 85 (27), 57 (83).

(S)-(Z)-1-Trimethylacetoxy-4-(2-thio-4-isopropylthiazoline)-2-butene (12). To (**7**) (2 g, 0.31 mole), triphenyl phosphine (6.5 g, 0.62 mole) and 2.13 g, (0.31 mole) of pure (*Z*)-(**9**) dissolved in 40 ml of anhydrous toluene, cooled in an ice bath DEAD (4.3 g, 0.62 mole) was added under stirring. After work-up and chromatography as above reported, 2.8 g of (**12**), (71% yield) as pale pink oil were isolated. $[\alpha]_D$= -20.3° (c=7 in $CHCl_3$). ^1H NMR: 0.92 (3H, d, J= 6.7 Hz, CH_3, isopropyl); 1.00 (3H, d, J= 6.7 Hz, CH_3, isopropyl); 1.16 (9H, s, *t*-butyl); 1.88-1.95 (1H, m, CH, isopropyl); 3.08 (1H, dd, J= 10.7 Hz, 9.3 Hz, CH_2, heterocyclic proton); 3.34 (1H, dd, J= 10.7 Hz, 8.2 Hz, CH_2, heterocyclic proton); 3.73-3.82 (2H, m, CH_2-S); 4.12 (1H, qd, J= 9.3 Hz, 8.2 Hz, 6.5 Hz, CH-N); 4.65 (2H, d, J=6.8 Hz, CH_2-O); 5.61 (1H, six t, J= 10.8 Hz, 6.7 Hz, 1.1 Hz, vinyl proton); 5.73 (1H, six t, J= 10.8 Hz, 7.8 Hz, 1.4 Hz, vinyl proton). ^{13}C NMR (δ): 19.0, 19.6, 27.1, 29.4, 33.0, 37.5, 38.6, 59.9, 83.2, 127.1, 129.0, 178.1. GC-MS (70 eV) m/z (%) 315 (M^+,3), 272 (2), 214 (95), 170 (30), 118 (11), 85 (21), 57 (100).

(S)-(Z)-1-Trimethylacetoxy-4-(5-[(*t*-butyl)dimethylsilyloxymethyl]-2-thio-pyrroline)-2-butene (13). To a stirred and cooled (in an ice bath) mixture of (S)-5-[(*t*-butyl)dimethylsilyloxymethyl]-2-thioxo-pyrrolidine[10] (**8**) (1 g, 0.10 mole), (**9**) (0.95 g, 0.14 mole) and triphenyl phosphine (2.14 g, 0.20 mole) dissolved in 40 ml of anhydrous toluene, DEAD (1.44 g, 0.20 mole) was added. After work-up and chromatography, as above reported, (**13**) was isolated (as pale yellow oil) in 81% yield. $[\alpha]_D$=-4.2° (c=2.6 in $CHCl_3$). ^1H NMR: 0.01 (3H, s, $SiCH_3$); 0.02 (3H, s, $SiCH_3$); 0.85 (9H, s, Si-*t*-butyl); 1.17 (9H, s, O-*t*-butyl); 1.85-1.89 (1H, m, CH_2, heterocyclic proton); 1.98-2.03 (1H, m, CH_2, heterocyclic proton); 2.49-2.53 (1H, m, CH_2, heterocyclic proton); 2.57-2.61 (1H, m, CH_2, heterocyclic proton); 3.59 (1H, dd, J= 10.1 Hz, 5.3 Hz, CH_2-O-Si); 3.73 (2H, m, CH_2-S); 3.76 (1H, dd, J= 10.1 Hz, 3.9 Hz, CH_2-O-Si); 4.10-4.11 (1H, m, CH-NH); 4.63-4.66 (2H, m, CH_2-O); 5.59 (1H, six t, J= 10.8 Hz, 6.8 Hz, 1.2 Hz, vinyl proton); 5.75 (1H,

six t, J= 10.8 Hz, 7.9 Hz, 1.4 Hz, vinyl proton). GC-MS (70 eV) m/z (%) 384 (M^+-15, 1), 342 (25), 298 (15), 155 (52), 57 (100).

Reactions of sulphides 10-13 with organocopper reagent RCu: general procedure.
To substrate (4.6 mmol) and CuBr (18.7 mmol) in 25 ml of dry THF at -50 °C was added dropwise, under nitrogen atmosphere and stirring, the Grignard reagent (0.5 M, 6.9 mmol). After the addition was complete, the reaction mixture was stirred at the same temperature an extra 1h and then allowed to slowly warm to room temperature. Silica gel was added to the reaction mixture and the resulting suspension, evaporated to dryness, was placed on the top of a column filled with silica gel and chromatographed (eluent petroleum ether-ethyl acetate 10:1) to give the pure homoallylic pivalate. According to this procedure, the esters reported in table 1 were synthesized.

2-Vinyl-3-methyl-1-butanol trimethylacetate (14). This compound was obtained (78% yield), as colourless oil, by reaction of (**10**) with isopropyl magnesium bromide. IR (neat): 1736 and 1645 cm^{-1}. ^1H NMR: 0.90 (d, 6H, J=6.5 Hz); 1.16 (s, 9H); 1.70 (heptet,1H, J= 6.5Hz); 2.14 (m, 1H); 4.04 (d, 2H, J=6.6 Hz); 4.96-5.10 (m, 2H, $\underline{CH_2}$=CH); 5.60 (ddd, 1H, J=16.9, 10.5 and 9.0 Hz, CH_2=$\underline{CH}$). $[\alpha]_D$ = +7.64° (c=0.1 in $CHCl_3$); e.e. 36% . (Found: C, 72.68; H, 11.20. $C_{12}H_{22}O_2$ requires: C, 72.68; H, 11.18%)

(+)-2-Vinyl-1-decanol trimethylacetate (15). It was obtained by reaction of (*Z*)-(**10**) and (*Z*)-(**13**) with n-octyl magnesium bromide as colourless oil. IR (neat): 1734 and 1645 cm^{-1}. ^1H NMR (200 MHz): 0.83 (t, 3H, J=6.3 Hz); 1.14 (s, 9H); 1.18-1.46 (m, 14H); 2.25-2.37 (m, 1H); 3.94 (d, 2H, J=6.5 Hz); 4.95-5.05 (m, 2H, $\underline{CH_2}$=CH); 5.47-5.65 (ddd, 1H, J=17.2, 10.2 and 7.44 Hz, CH_2=$\underline{CH}$). $[\alpha]_D$ =+3.8°(c=25 in $CHCl_3$); (Found: C, 76.10; H, 12.01. $C_{17}H_{32}O_2$ requires: C, 76.06; H, 12.02%).

(S)-(-)-2-Vinyl-1-hexanol trimethylacetate (16). This compound was obtained, as colourless oil, by reaction of both (*Z*)-**11** and (*Z*)-**12** with *n*-butyl magnesium bromide. Yields and e.e are reported in table. IR (neat): 1734 and 1645 cm^{-1}. ^1H NMR (200 MHz): 0.78 (t, 3H, J=6.5 Hz); 1.07 (s, 9H); 1.11-1.39 (m, 6H); 2.19-2.29 (m, 1H); 3.87 (d, 2H, J=6.2 Hz); 4.89-4.98 (m, 2H, $\underline{CH_2}$=CH); 5.41 5.59 (ddd, 1H, J=17.2, 10.2 and 8.5 Hz, CH_2=$\underline{CH}$). $[\alpha]_D$ = -9.8° (c=15.8, $CHCl_3$) by reaction of pure (*Z*)-(**11**). (Found: C, 73.49; H, 11.40. $C_{13}H_{24}O_2$ requires: C, 73.54; H, 11.39%).

(R)-(+)-(**16**). Obtained by reaction of both (*E*)-(**11**) and (*Z*)-(**13**) with n-butyl magnesium bromide. $[\alpha]_D$=+ 6.2° (c=10 in $CHCl_3$). Elemental analyses and spectroscopic data were identical to those reported for the (S) isomer.

Absolute configuration assignment of the reaction products.

As an example, the assignment of the absolute configuration of (-)-(**16**) is reported. The suspension of (**16**) (0.1 g, 0.47 mmole) in 10 ml of methanol and 5% rhodium on alumina (15 mg) was hydrogenated for 15h. Then the catalyst was removed by filtration on celite pad, the solvent evaporated and the so obtained crude

product cromatographed on silica gel (eluent, pentane) affording 2-ethyl-1-hexanol trimethylacetate. $[\alpha]_D$ = +1.55° (c=2 in $CHCl_3$). ^1H NMR: 0.86 (6H, 2t almost quite overlapped, J= 7.5 Hz, CH_3); 1.17 (9H, s, *t*-butyl); 1.21-1.36 (8H, m, CH_2); 1.52-1.57 (1H, m, CH); 3.93-3.95 (2H, m, CH_2-O). ^{13}C NMR (δ) 11.0, 13.9, 22.9, 23.9, 27.2, 28.9, 30.5, 38.8, 38.9, 66.6, 178.6. GC-MS (70 eV) m/z (%) 157 (M^+-57, 1), 112 (17), 85 (17), 70 (44), 57 (100). At this point, the absolute configuration of (-)-(**16**) was established to be (S) by comparison the sign of the optical rotation of the 2-ethyl-1-hexanol trimethylacetate, prepared as just above described, with that of the same ester obtained by reacting optically pure (S)-2-ethyl-1-hexanol[14] and pivaloyl chloride which had a $[\alpha]_D$ = -1.59, (c=2 in $CHCl_3$) and identical ^1H NMR and GC-MS data of (**16**).

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