Pergamon

Tetrahedron, Vol. 52, No. 32, pp. 10799-10810, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00601-1

Copper-mediated Regio- and Enantio-selective Cross-coupling of Heterocyclic Allyl Sulphides with Organomagnesium Compounds: A Case of 1,7-Relative Stereogenesis†

Vincenzo Caló,* Angelo Nacci and Vito Fiandanese

CNR Centro di Studio sulle Metodologie Innovative di Sintesi Organiche, Dipartimento di Chimica, Università di Bari, via Orabona 4-70126 Bari, (Italy)

Abstract: Optically active heterocyclic allyl sulphides **1-7** react with organomagnesium compounds in the presence of CuBr to afford optically active alkenes in good yields and very high γ-selectivity. The regioselectivity depends on the solvent as well on the CuBr: allylic sulphide ratio. The heterocyclic nucleus imparts asymmetric induction in the range of 50-98% ee. The regio- and enantio-selectivity of these reactions would be related to the coordination exerted by the heterocyclic nitrogen toward the copper organyl. Copyright © 1996 Elsevier Science Ltd

Introduction

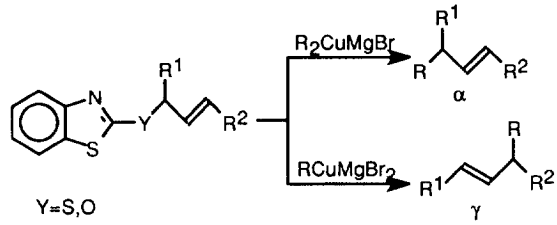
The creation of central chirality by the γ-substitution of an allylic substrate with an organocopper or an organocuprate reagent constitutes an important process in organic synthesis.[1-4] Whereas the asymmetric induction in such reactions by chirality residing in the allylic moiety has been investigated intensively, the one caused by chirality contained in the nucleofuge has received less attention. However, studies of the reaction of chiral nucleofuge-containing allylic acetals, carbamates, pyrrolidines, sulfoximines, acetates and sulphides by Alexakis et al.,[5] Denmark et al.,[6] Tamura et al.,[7] Gais et al.,[8] Bäckvall, van Koten et al.[9] and by us[10] respectively revealed fair to good asymmetric inductions.

Over the last fifteen years, our research group has uncovered[11] a number of highly regio- and stereo-selective cross-coupling reactions of oganocopper reagents with allylic electrophiles containing nitrogenous heterocycles as leaving groups. For these substrates the observed selectivity is probably dictated by a preliminary chelation of the organometallic reagent to the nucleofuge. The allylic substrates of choice were allylic sulphides[12,13,14] or ethers[15,16,17] of benzothiazole, benzimidazole,[14] oxazolines and thiazolines.[10,14] (Scheme 1).

---

†Dedicated to Professor Giorgio Modena on the occasion of his 70th birthday.

Scheme 1



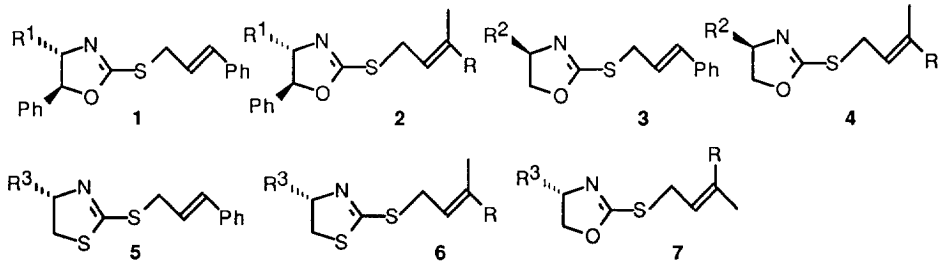
We observed that heteroleptic cuprates of $RCuMgBr_2$-type, prepared by addition of Grignard reagent to an excess of CuBr, gave exclusively products arising from a S_N2' process whereas homoleptic magnesium cuprates of $R_2CuMgBr$-type afforded α-susbstituted products (S_N2). In these reactions the α:γ ratio depends strictly on the CuBr: Grignard reagent ratio. For example a 4:1 molar ratio which would favours the formation of a heteroleptic cuprate, leads to γ-subtituted products whereas lower ratios, which would favour the formation of homoleptic cuprates, afford almost exclusively α-substituted products. Since the reaction of organomagnesium compounds in the presence of an excess of copper salt proved to be almost γ-selective to afford alkenes having a stereogenic carbon, we report our attempts to control both the regio- and enantio-selectivity of this C-C coupling reaction by using optically active oxazolin- and thiazolin-2-yl allyl thiothers as useful substrates for the synthesis of optically active alkenes bearing a ternary or quaternary carbon stereocentre.

Results

1.1 *Regioselectivity of the cross-coupling process.*

The acyclic substrates chosen for the present study are oxazolin- and thiazolin-2-yl allyl thiothers **1-7** (figure 1). These compounds were easily prepared by reaction of the corresponding 2-thioxo-oxazolidine and -thiazolidine with (E) or (Z) allylic alcohols, triphenyl phosphine and diethyl azodicarboxylate (DEAD) in anhydrous toluene.[10,18]

Figure 1

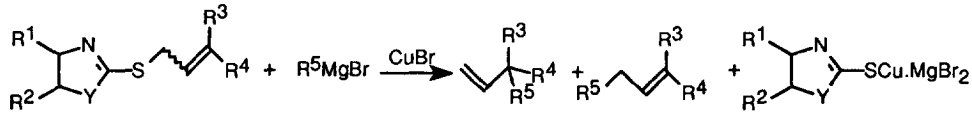


R= $CH_2CH_2CH{=}C(CH_3)_2$; R^1= CH_2Opivaloyl; R^2= CH(Opivaloyl)phenyl; R^3= i-propyl.

These compounds react in diethyl ether or THF (scheme 2) at -30 °C with orgamagnesium compounds in the presence of variable CuBr concentrations to give alkenes. As found for allylic sulphides of benzothiazole,[13] for substrates **1-7** the α:γ ratio depends on the reaction medium and CuBr concentration with diethyl ether favouring the S_N2' pathway, whereas THF encourages S_N2 delivery. Contrary to that found by Bäckvall et al.[19,20] the rate

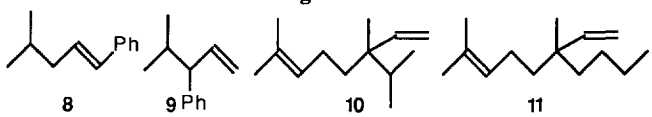
of the Grignard reagent addition does not influences the regioselectivity. Moreover, these displacements appear to be independent of steric demands of the substituent on the allylic framework.

Scheme 2



Thus, compounds **1** and **5** (entries 1,7) react in THF with i-propylmagnesium bromide in the presence of an excess of CuBr (CuBr: Grignard reagent 4:1.5) to afford a mixture of α– and γ- substituted products **8** and **9** (figure 2) whereas in ether compound **9** is the reaction product. The change of the CuBr: Grignard reagent ratio to 0.2: 1.5 (entry 9) or by using the copper salt of 2-thioxo-thiazolidine leads (entry 10) preferentially to **8.** Reactions of compounds **2, 4, 6, 7** afford only **10** by reaction with i-propylmagnesium bromide whereas **6** gives **11** by reaction with the n-butyl Grignard reagent.

Figure 2



Almost paragonable results are observed by using CuCl or CuI as copper salts but Cu salt of 2-thioxothiazolidine favors the α-substitution product (entry 9). Table 1 reports some relevant results.

Table 1. Solvent effect on cross-coupling of **1-7** with isopropyl Grignard reagent and CuBr.

Entry	Substrate	Solvent	Products[a]	α:γ[b]	Yield(%)[c]
1	**1**	THF	**8+9**	7:93	62
2	**1**	Et_2O	**9**	>99	78
3	**2**	THF	**10**	>99	75
4[d]	**2**	THF	**11**	>99	55
5	**3**	Et_2O	**9**	>99	80
6	**4**	Et_2O	**10**	>99	83
7	**5**	THF	**8+9**	50:50	68
8	**5**	Et_2O	**9**	>99	82
9[e]	**5**	THF	**8+9**	97:3	74
10[f]	**5**	THF	**8+9**	83:17	53
11	**6**	THF	**10**	2:98	70
12	**6**	Et_2O	**10**	>99	74
13	**7**	Et_2O	**10**	>99	78

[a] The reaction was performed by dropwise addition of the Grignard reagent to the substrate and CuBr at -30 °C during 15 min. Substrate: CuBr: Grignard ratio 1:4:1.5. [b] Evaluated by GC. [c] Isolated yields on reacted substrates. [d] n-BuMgBr was used. [e]Substrate: CuBr: Grignard ratio 1:0.2:1.5. [f] Cu salt of 2-thioxothiazolidine: substrate: Grignard ratio 1:1.5:2.

Beside the dependence of regioselectivity on the solvent, worthy of note is the dependence of the reaction rates on the CuBr: Grignard reagent ratio. In fact, experiments performed with a low ratio (entry 8) or by using the Cu salt of 2-thioxothiazolidine (entry 9), not only do the allyl sulphide react more slowly, but in addition the ratio **8:9** changes in favour of the S_N2 substitution product **8**

1.2 *Enantioselectivity of the cross-coupling process.*

Since the reactions of allylic electrophiles **1-7** with organomagnesium compounds in the presence of an excess of CuBr in ether are γ-selective to give C-C coupling products having a stereogenic carbon, it would be possible, by using these compounds, to obtain optically active alkenes and this process can be employed as a means for a enantioselective construction of tertiary and quaternary carbon centres. Thus compounds **1-7** react with with i-propyl and n-butyl magnesium bromide, under the conditions which favour the formation of γ-substituted products, to give alkenes **9-11** with fair to good enantioselectivity (table 2). Among these **9** is an important intermediate for the synthesis of optically active fenvalerate insecticides.[21] It appears that steric congestion on the heterocyclic carbon α to the nitrogen and on the γ-carbon substituent in the allylic framework controls the extent of the enantioselectivity in the C-C coupling process. In fact compounds **3** and **4**, whose α-carbon is more sterically congested than compounds **1**, **2**, **5-7**, react with a better enantioselectivity (entries 2-4) than **6** and **7** which give comparable values. The (E)-compound **6** and the (Z)-isomer **7** afford the (+) and (-) enantiomers respectively.

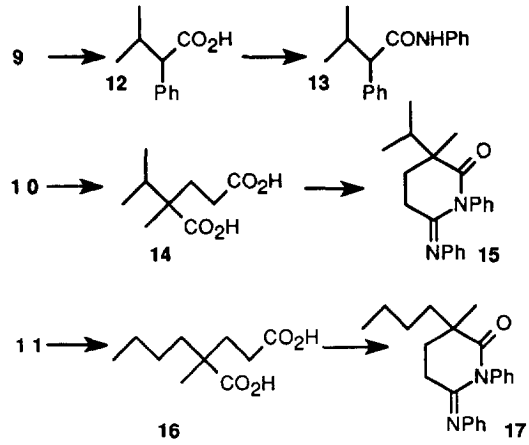
Table 2. Enantioselective cross-coupling reaction of Grignard reagents with **1-7** in diethyl ether.[a]

Entry	Substrate	RMgBr	Product	E.e. (Abs. conf.)	$[\alpha]_D$[b]
1	**1**	i-prop.	**9**	58(S)	+71.3
2	**2**	"	**10**	73(n.d.)	+17.4
3	**3**	"	**9**	78(R)	-95.5
4	**4**	"	**10**	98(n.d.)	-24.3
5	**5**	"	**9**	50(S)	+61.5
6	**6**	"	**10**	83(n.d.)	+19.8
7	**6**	n-but.	**11**	67(n.d.)	+8.2
8	**7**	i-prop.	**10**	77(n.d.)	-18.3

[a] The reaction was performed by adding dropwise the Grignard reagent to the substrate and CuBr at -30 °C during 15 min. CuBr:substrate: organomagnesium ratio 4:1:1.5. [b] Values measured at at 25 °C in $CHCl_3$

The determination of the enantiomeric excess of alkenes **9-11** proved to be difficult either by HPLC equipped with different chiral columns or by ^1H NMR in the presence of chiral shift reagents. Therefore (Scheme 3) we oxidized compound **9** to 2-phenyl-3-methyl-butanoic acid **12** and **10** and**11** to the bicarboxylic acids **14** and **16** respectively. **12**, By reaction with aniline gave the anilide **13** whose e.e. was determined easily by HPLC, whereas **14** and **16**, afforded compounds **15** and **17** respectively whose e.e. values were determined by ^1H NMR in the presence of $Eu(hfc)_3$ as shift reagent.

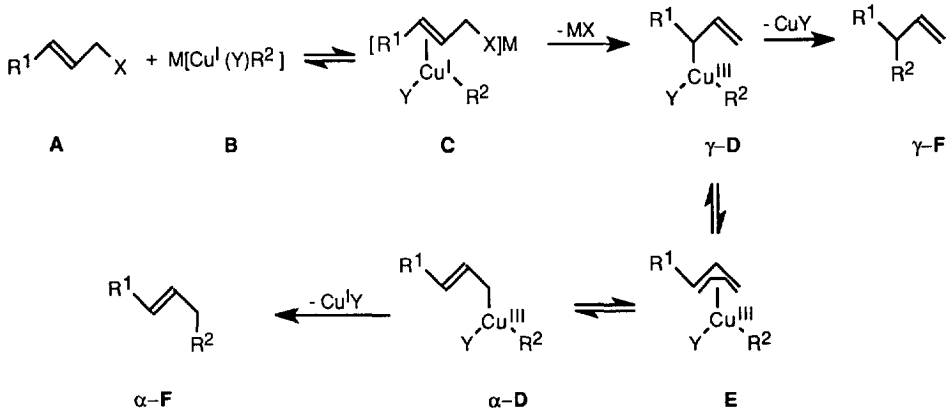
Scheme 3



Discussion

The mechanistic scheme put forward by Rudler et al.,[22] Goering et al.,[23] Bäckvall et al.,[19] for the reaction of primary allylic substrates with copper organyls is based on homoleptic cuprates **B** (Y=R^2) and heteroleptic cuprates **B** (Y=Hal) and features the following steps (Scheme 4): (1) reaction of substrate **A** with cuprate **B** with formation of π-alkene complex **C**, (2) conversion of **C** through an oxidative addition-substitution to σ-allyl complex **D**, and (3) reductive elimination of **D** to substitution product **F**. In the case of γ-**D** (Y=R^2), reductive elimination is thought to be relatively slow because of the two C-bonded organic ligands, thus allowing for an equilibrium via π-allyl complex **E** (Y=R^2) to isomeric α-**D**, followed by reductive elimination of the latter to α-**F**.

Scheme 4



X= Hal, OR', OCOR', SO_2R', $PO(OR')_2$, SR', SeR', SOR'. Y= R^2, Hal.

Reductive elimination of **α-D** is anticipated to be faster than that of **γ-D** perhaps because of steric reasons. In the case of **γ-D** (Y=Hal), reductive elimination is assumed to be faster than its isomerization to **α–D** (Y=Hal) because of the electronegative and thus **γ–F** would be formed preferentially. Thus, lithium or organomagnesium cuprates, prepared, the first by addition of 2 equiv of RLi to a copper salt, commonly written as $R_2CuLi{\cdot}LiX$, display a greater reactivity than the corresponding organocopper reagent, $RCu{\cdot}LiX$, prepared by using a 1:1 ratio of RLi and CuX.[1,3,24,25] The existence and structures of homoleptic cuprates ($Y=R^2$) has been demonstrated beyond any doubt by chemical and spectroscopic means as well as by X-ray analysis [26,27] and there is now sufficient information on the structure of some heteroleptic cuprates.[28,29] Although the above mechanistic scheme correlates many experimental observations with the various copper organyls and allylic substrates, one must recognize that the experimental evidence for the proposed intermediates **C-E** is very scarce.[1,19,22,23,26,27,30,31] The regio- and stereochemical results reported in this paper, cannot be entirely explained with the above scheme because of: **(i)**, contrary to that generally observed,[1-4] the heterocuprates, which are formed by using high ratios CuBr: magnesium organyls, display a greater reactivity than the corresponding homocuprates (table 1, entries 9,10); **(ii)** the extent of asymmetric induction observed in spite of the distance between the prochiral olefinic carbon and the stereocentre on the heterocycle. Since different allylic sulphides react with copper oganyls without regioselectivity,[32] our data could be explained with the chelation exerted toward the copper organyl(s) by the heterocyclic nucleus. It is known that on mixing a Grignard reagent with a copper(I) halide the equilibria in equations (1) and (2) operate. The predominance of either one of the two equilibria is dictated by the CuX concentration. In the presence of an excess of organomagnesium compound the equilibrium in equation (2) predominates over that in equation (1) to give mainly a homoleptic cuprate, whereas with an excess of CuX the main product in a heteroleptic cuprate.

$$RMgX + CuX \rightleftharpoons RCu{\cdot}MgX_2 \quad (1)$$

$$RCu{\cdot}MgX_2 + RMgX \rightleftharpoons R_2CuMgX{\cdot}MgX_2 \quad (2)$$

These two reagents, which would show different degree of chelation toward donor ligands, could react with our allyl sulphides with different regioselectivities. Of these reagents $RCu{\cdot}MgX_2$ would be the most "electrophilic", and therefore more susceptible to chelation by the allyl sulphide. Thus preliminary coordination of $RCu{\cdot}MgX_2$ by the allyl sulphide could give an intermediate complexe which, by bringing reacting centres into close proximity, would influence the positional selectivity of the nucleophile. This intermediate would react with a S_N2' fashion with delivery of R exclusively on the γ-carbon. On the other hand, in the reaction with cuprates $R_2CuMgX{\cdot}MgX_2$, whose formation is favoured by low or catalytic copper salt concentration, the metal would be

less susceptible to coordination by the allyl sulphide than $RCu{\cdot}MgX_2$ and therefore the nucleophile would attack the less hindered α-position, leading to a S_N2 product. Proofs in favour of the an intermediate complex comes from the following observations: **a**) the isolation[33] of a stable CuBr π–complex with allyl ethers of benzothiazole in which the metal is coordinated between the azomethine and the C-C double bond of the allylic framework; **b**) placement of a carboalkoxy group on the double bond, as in a γ-(benzothiazol-2-yl-thio)-substituted α,β-enoates, does not direct $RCu{\cdot}MgBr_2$ toward 1,4 addition, this pathway being completely overridden by 1,3-displacement mode;[34] **c**) the influences on the treaction rate, being the reaction of the heteroleptic cuprate faster than that of the homoleptic cuprate. This probably occurs because of the coordination of the organocopper reagent which, by increasing the electron withdrawing properties of the azomethine group, increases the nucleofugicity of the leaving group. More difficult to explain is the solvent effect. Two hypotheses can be proposed: the solvent influences the formation equilibria of the copper organyls and hence the regioselectivity of the C-C coupling process or/and, as well as solvating properties, the solvent could influence to different extents the reaction rates of the copper organyls with the allyl sulphide.

In conclusion, although there are some evidences on the chelation effect, nothing can be said on the intermediate complex or the stereochemistry (syn or anti) of the C-C coupling process and this is now actively pursued. However, it appears that by using these allylic sulphides, the regio-, chemo-[10] and enantio-selectivity in certain allylic substitutions can be made into a synthetic method of great potential.

Experimental Section

General methods. The regiochemical purity of the reaction products was tested by GLC recorded on HP 5890A capillary GC (SE 30; 30m; 0.25 mm. i.d.). GC-MS (EI, 70 eV) analyses were performed on a HP 5970 instrument. IR spectra were recorded on a Perkin Elmer 681 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 500 spectrometer and chemical shifts were in parts per million (δ), solvent $CDCl_3$. Optical rotations were measured on a Perkin Elmer polarimeter at 25 °C, solvent $CHCl_3$. E. e. were evaluated either by ^1H NMR in the presence of [Eu(hfc)3] as chiral shift reagent or by HPLC (Chiralcell OD; hexane: isopropanol 95:5). (*S*)-valinol, (*1S,2S*)-(+)-2-amino-1-phenyl-1,3-propanediol, CuBr, CuI, geraniol, nerol and cinnamyl alcohol were purchased from Fluka and used as received. Diethyl ether, THF and toluene were dried and distilled under nitrogen from sodium benzophenone ketyl immediately prior to use. (S)-4-Isopropyl-2-thioxooxazolidine and (S)-4-isopropyl-2-thioxothiazolidine were prepared as previously reported.[10] (4S,5S)-4-[(Trimethylacetoxy)methyl]-5-phenyl-2-thioxooxazolidine and (4S)-4-[(S)-Trimethylacetoxy)phenylmethyl]-2-thioxooxazolidine were prepared as a mixture by reaction of (*1S,2S*)-(+)-2-amino-1-phenyl-1,3-propanediol with carbon disulphide and KOH under standard conditions.[10]

General Procedure for the Synthesis of Allyl Substrates (1-7):

To 2.2 mmol of 2-thioxo-oxazolidine or thiazolidine, the allyl alcohol (2.2 mmol) and triphenyl phosphine (4.6 mmol) dissolved in 20 ml of anhydrous toluene, was added, dropwise at 0 °C and under strirring, diethyl azodicarboxylate (DEAD) (4.62 mmol) dissolved in 10 ml of toluene. Stirring was kept on until the disappearance of the oxazolidine or thiazolidine (TLC, petroleum ether-ethyl acetate 5:1). Evaporation of the solvent followed by silica gel chromatography with the above eluent gave compounds **1-7** in a 60-85% yield.

2-[(E)-(2-Propen-3-phenyl-1-yl)thio]-(4S,5S)-4-trimethylacetoxymethyl-5-phenyloxazoline (1).
Pale yellow oil (80% Yield), prepared from cinnamyl alcohol. $[\alpha]_D$ =-30.4 (*c* =7 in $CHCl_3$); ^1H NMR: δ =1.14 (s, 9H), 3.77 (ddd, *J* = 13.6, 7.3, 0.9 Hz, 1H, CH_2S), 3.88 (ddd, *J* = 13.6, 7.4, 0.7 Hz, CH_2S), 4.20-4.33 (m, 3H), 5.35 (d, *J* = 5.8 Hz, 1H, CHPh), 6.31 (dt, *J* = 15.7, 7.3 Hz, 1H, CH=CHPh), 6.60 (d, *J* = 15.7 Hz, 1H, CH=CHPh), 7.17-7.38 (m, 10H, Ph); ^{13}C NMR: 27.1, 34.3, 38.8, 65.9, 73.7, 85.1, 123.9, 125.6, 126.4, 127.8, 128.5, 128.6, 128.8, 133.7, 136.3, 139.5, 165.9, 178.1; IR (liquid film): ν = 2935, 1732, 1606, 1480, 1238, 1153, 734 cm^{-1}.

2-[(2E)-(3,7-Dimethyl-2,6-octadien-1yl)thio)]-4-trimethylacetoxymethyl-5-phenyl oxazoline (2).
Obtained by reaction of geraniol and (4S,5S)-4-[(Trimethylacetoxy)methyl]-5-phenyl-2-thioxooxazolidine in a 76% yield as pale yellow oil. $[\alpha]_D$ = -24.8 (*c* =4.5 in $CHCl_3$); ^1H NMR: δ =1.19 (s, 9H), 1.58 (s, 3H, Me), 1.66 (s, 3H, Me), 1.67 (s, 3H, Me), 1.98-2.11 (m, 4H, CH_2), 3.69 (dd, *J* = 12.9, 7.9 Hz, 1H, CH_2S), 3.72 (dd, *J* = 12.9, 7.9 Hz, 1H, CH_2S), 4.19-4.33 (m, 3H), 5.02-5.08 (m, 1H), 5.29-5.36 (m, 2H), 7.24-7.40 (m, 5H, Ph); ^{13}C NMR: 16.2, 17.7, 25.6, 26.3, 27.1, 30.1, 39.5, 65.1, 73.7, 85.0, 117.8, 123.7, 125.6, 128.5, 128.8, 131.8, 139.7, 141.4, 166.7, 178.1; MS (70 eV, EI) *m/z* (%): 429 (M^+, 1), 360 (25), 293 (11), 258 (13), 191 (13), 178 (13), 130 (25), 118 (20), 93 (40), 91 (29), 85 (28), 69 (53), 57 (100), 41 (64).

2-[(E)-(2-Propen-3-phenyl-1-yl)thio]-(4S)-4-trimethylacetoxymethylphenyl oxazoline (3).
Prepared by reaction of (4S)-4-(trimethylacetoxyphenylmethyl)-2-thioxooxazolidine and cinnamyl alcohol. M.p. 113-115 °C; $[\alpha]_D$ = +108.3 (*c* =2 in $CHCl_3$); ^1H NMR: δ =1.20 (s, 9H), 3.73 (ddd, *J* = 13.7, 6.3, 1.1 Hz, 1H, CH_2S), 3.87 (ddd, *J* = 13.7, 7.2, 1.1 Hz, 1H, CH_2S), 4.16 (dd, *J* = 8.7, 6.3 Hz, 1H), 4.26 (t, *J* = 8.7 Hz, 1H), 4.53 (ddd, *J* = 9.5, 6.3, 5.0, 1H, CHN), 5.82 (d, *J* = 5.0 Hz, 1H, CHPh), 6.31 (dt, *J* = 15.7, 7.3 Hz, 1H, CH=CHPh), 6.58 (d, *J* = 15.7 Hz, 1H, CH=CHPh), 7.21-7.45 (m, 10H, Ph); ^{13}C NMR: 27.1, 34.5, 38.9, 70.3,70.7, 75.8, 124.4, 126.4, 127.0, 127.8, 128.2, 128.3, 128.5, 133,4, 136.5, 137.1, 166.8, 177.4; MS (70 eV, EI) *m/z* (%): 324 (4), 307 (6), 218 (13), 147 (8), 117 (100), 85 (18), 57 (45).

2-[(2E)-(3,7-Dimethyl-2,6-octadien-1yl)thio)]-(4S)-4-trimethylacetoxymethylphenyl oxazoline (4).
Prepared by reaction of (4S)-4-(trimethylacetoxyphenylmethyl)-2-thioxooxazolidine and geraniol. Yellow oil (64% yield). $[\alpha]_D$= +53.5 (*c* =1.2 in $CHCl_3$); ^1H NMR: δ = 1.22 (s, 9H), 1.59 (s, 3H, Me), 1.68 (s, 3H, Me), 1.99-2.12 (m, 4H), 3.64 (dd, *J* = 13.0, 8.0 Hz, 1H, CH_2S), 3.69 (dd, *J* = 13.0, 7.6 Hz, 1H, CH_2S), 4.15 (dd, *J* = 8.6, 6.2 Hz, 1H, heter.), 4.22 (t, *J* = 9.4 Hz, 1H, heter.), 4.50 (ddd, *J* = 9.4, 6.2, 5.0 Hz, CHN), 5.03-5.11 (m, 1H), 5.30-5.38 (m, 1H), 5.78 (d, *J* = 5.0 Hz, 1H, CHPh), 7.25-7.40 (m, 5H, Ph). ^{13}C NMR: 16.1, 17.6, 25.6, 26.3, 27.0, 30.0, 38.8, 39.4, 70.1, 70.4, 75.8, 118.1, 123.7, 126.9, 128.1, 128.2, 131.6, 137.0, 140.9, 167.3, 177.2.

2-[(E)-(2-Propen-3-phenyl-1-yl)thio]-(4S)-4-isopropyl thiazoline (5).
Obtained by reaction of cinnamyl alcohol and (S)-4-isopropyl-2-thioxo thiazolidine as pale yellow oil (69% yield). $[\alpha]_D$ = -66.4 (*c* = 5.4 in $CHCl_3$); ^1H NMR: δ = 0.98 (d, *J* = 6.7 Hz, 3H, Me), 1.08 (d, *J* = 6.7 Hz, 3H, Me), 1.97 (octet, *J* = 6.7 Hz, 1H, $CH(Me)_2$), 3.12 (dd, *J* = 10.7, 9.1 Hz, 1H), 3.37 (dd, *J* = 10.7, 8.2 Hz, 1H), 3.88 (ddd, *J* = 13.5, 7.3, 1.2 Hz, 1H, CH_2S), 3.96 (ddd, *J* = 13.5, 7.4, 1.2 Hz, 1H, CH_2S), 4.19 (ddd,

J = 9.1, 8.2, 6.7 Hz, 1H), 6.30 (dt, *J* = 15.7, 7.3 Hz, 1H, CH=CHPh), 6.60 (d, *J* = 15.7 Hz, 1H, CH=CHPh), 7.20-7.26 (m, 1H, Ph), 7.28-7.39 (m, 2H, Ph), 7.33-7.37 (m, 2H Ph); ^{13}C NMR 19.1, 19.7, 33.1, 35.1, 37.4, 83.2, 124.3, 126.3, 127.6, 128.4, 133.3, 136.6, 162.2; MS (70 eV, EI) *m/z* (%): 277 (M^+,41), 224 (10), 186 (5), 176 (16), 117 (100), 115 (60), 91 (25), 41 (17), 39 (15).

2-[(2E)-(3,7-Dimethyl-2,6-octadien-1yl)thio)]-(4S)-4-isopropyl thiazoline (6).

Obtained by reaction of geraniol with (**4**) in a 70% yield as pale yellow oil. $[\alpha]_D$ = -42.5 (*c* =6.5 in $CHCl_3$); ^{1}H NMR: δ =0.94 (d, *J* = 6.7 Hz, 3H, Me), 1.03 (d, *J* = 6.7 Hz, 3H, Me), 1.57 (s, 3H, Me), 1.66 (s, 3H, Me), 1.68 (s, 3H, Me), 1.90-1.97 (m, 1H), 1.98-2.09 (m, 4H, CH_2), 3.09 (dd, *J* = 10.4, 9.1 Hz, 1H, CH_2 heter.), 3.35 (dd, *J* = 10.4, 8.2 Hz, 1H, CH_2 heter.), 3.69-3.80 (m, 2H, CH_2S), 4.11-4.19 (m, 1H, CHN), 5.05 (t, *J* = 6.9 Hz, 1H), 5.31 (t, *J* = 7.8 Hz, 1H); ^{13}C NMR: 16.2, 17.7, 19.0, 19.8, 25.7, 26.3, 30.9, 33.1, 37.3, 39.5, 83.3, 118.3, 123.8, 131.7, 140.8, 163.5; MS (70 eV, EI) *m/z* (%): 297 (M^+, 2), 229 (14), 228 (93), 194 (3), 162 (31), 118 (24), 93 (13), 81 (18), 69 (83), 55 (19), 41 (100).

2-[(2Z)-(3,7-Dimethyl-2,6-octadien-1yl)thio)]-(4S)-4-isopropyl oxazoline (7).

Pale yellow oil obtained by reaction of (S)-4-isopropyl-2-thioxo oxazolidine with nerol (73% yield). $[\alpha]_D$ = -51.0 (*c* =7.4 in $CHCl_3$); ^{1}H NMR: δ = 0.85 (d, *J* = 6.8 Hz, 3H, Me), 0.94 (d, *J* = 6.8 Hz, 3H, Me), 1.58 (s, 3H, Me), 1.67 (s, 3H, Me), 1.71 (s, 3H, Me), 1.72-1.78 (m, 1H), 2.02-2.13 (m, 4H, CH_2), 3.59-3.70 (m, 2H, CH_2S), 3.87-3.94 (m, 1H, CHN), 4.02 (t, *J* = 7.7 Hz, 1H, CH_2O), 4.29 (dd, *J* = 9.3, 8.2 Hz, 1H, CH_2O), 5.05-5.12 (m, 1H), 5.32 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR: 17.7, 18.0, 18.7, 23.4, 25.7, 26.5, 29.9, 31.9, 32.8, 71.5, 72.5, 119.0, 123.8, 132.1, 140.9, 164.8; MS (70 eV, EI) *m/z* (%): 281 (M^+, 2), 212 (78), 146 (72), 136 (17), 121 (23), 101 (32), 93 (59), 81 (35), 77 (17), 69 (74), 55 (24), 43 (30), 41 (100), 39 (25).

Reaction of sulphides 1-7 with organocopper reagents. General procedure:

To substrate (4.6 mmol) and CuBr (18.4 mmol) in 25 ml of dry THF or diethyl ether at -30 °C was added dropwise during 15 min, under nitrogen atmosphere and stirring, the Grignard reagent (0.5 M, 6.9 mmol) in ether or THF. After the addition was complete, the reaction mixture was stirred at the same temperature for 1h and then allowed to slowly warm to room temperature. Silica gel column chromatography (eluent petroleum ether-ethyl acetate 10:1) gives the pure alkenes (**8-11**) as colorless oils.

(E)-1-Phenyl-4-methyl-1-Pentene (8).

B.p. (11 mmHg) 107-109 °C; MS (70 eV, EI) *m/z* (%): 160 (M^+, 21), 118 (12), 117 (100), 115 (40), 104 (31), 91 (17), 77 (4), 65 (5); IR (neat): ν = 3020, 1680, 1580, 960 cm^{-1}.

3-Phenyl-4-methyl-1-pentene (9).

^{1}H NMR: δ = 0.82 (d, *J* = 6.7 Hz, 3H, Me), 1.02 (d, *J* = 6.7 Hz, 3H, Me), 1.90-2.10 (m, 1H, CH), 2.93 (t, *J* = 8.9 Hz, 1H, CHPh), 5.0-5.15 (m, 2H, CH_2=CH), 6.04 (ddd, *J* = 19.6, 10.6, 8.9 Hz, 1H, CH_2=CH), 7.20-7.35 (m, 5H, Ph); MS (70 eV, EI) *m/z* (%): 160 (M^+, 8), 118 (20), 117 (100), 115 (41), 104 (10), 91 (18), 77 (4), 65 (6). From the reactions of sulphides **1, 3** and **5** with isopropyl magnesium bromide, (**9**) had the following optical rotations: $[\alpha]_D$ = +71.3, - 95.5, +61.5 (*c* =1.5 in $CHCl_3$) respectively.

3-Isopropyl-3,7-Dimethylocta-1,6-diene (10).[13] B.p. 49 °C(0.7mm). ^{1}H NMR: δ = 0.79-0.89 (m, 9H, Me), 1.25-1.57 (m, 3H, CH_2), 1.58 (s, *J* = 3H, MeC=C), 1.68 (d, *J* = 1.0 Hz, 3H, MeC=C), 1.79-1.88 (m, 2H, CH_2C=C), 4.83-5.09 (m, 2H, $C\underline{H}_2$=CH), 5.05-5.12 (m, 1H, CH=C(Me)$_2$), 5.69 (dd, *J* = 17.5, 10.9 Hz, 1H, CH_2=C$\underline{H}$); MS (70 eV, EI) *m/z* (%): 180 (M^+, 3), 165 (1), 137 (15), 109 (22), 95 (17), 81 (40), 69 (100), 55 (51), 41 (80). From the reactions of sulphides **2, 4, 6** and **7** isopropyl magnesium bromide, (**10**) had the following optical rotations: $[\alpha]_D$= +17.4, -24.3, +19.8, -18.3 (*c* =7.2 in $CHCl_3$) respectively. $C_{13}H_{24}$ calcd C 86.66, H 13.33; found C 86.60, H 13.28.

2,6-Dimethyl-6-vinyl-2-decene (11).[15]
Prepared by reaction of (**7**) with n-butyl magnesium bromide in 78% yield. [a]$_D$= + 8.2.

Enantiomeric excess determination of alkene (**9-11**).

a) Conversion of alkene (9) into the anilide (13).
To (**9**) (1.12 g., 7.0 mmol) dissolved in 80 ml of tert-butanol were added, under stirring at r.t., K_2CO_3 (2.90 g. 21.0 mmol) in 80 ml of water followed by $NaIO_4$ (11.98 g. 56.0 mmol) and $KMnO_4$ (1.42 g. 9.0 mmol) in 100 ml of water. After 2h the solution, acidified at pH 2 with conc. HCl and treated with bisulphite solution to reduce the excess of oxidants, was extracted with ether (3x30 ml). Solvent evaporation followed by preparative TLC (hexane-ether 1:1) afforded 2-phenyl-3-methyl butanoic acid (40%). This acid (0.5 g. 2.8 mmol), aniline (0.26 g. 2.8 mmol) and dimethylamino pyridine (DMAP) (0.12 g. 1.0 mmol) were dissolved in 15 ml of anhydrous toluene and under stirring was added dicyclohexyl carbodiimmide (DCC) (0.62 g. 3.0 mmol). The solution was heated at 80 °C for 2h, cooled, washed with diluted HCl and then with $NaHCO_3$. Solvent evaporation and silica gel chromatography (petroleum ether-ethyl ether 1:1) afforded the anilide (**13**) as colorless solid (56%). M.p.138-140 °C; ^{1}H NMR: δ = 0.74 (d, *J* = 6.7 Hz, 3H, Me), 1.14 (d, *J* = 6.5 Hz, 3H, Me), 2.49-2.60 (m, 1H, CH), 3.11 (d, *J* = 10.3 Hz, 1H, CHPh), 7.02-7.07 (m, 1H, Ph), 7.19-7.32 (m, 5H, Ph), 7.38-7.43 (m, 2H, Ph), 7.47-7.52 (m, 2H, Ph), 7.90 (br s, 1H, N$\underline{H}$); IR (KBr): ν = 3288, 3259, 3202, 3142, 3072, 2963, 1660, 1602, 1549, 1445, 1372, 737, 699 cm^{-1}; MS (70 eV, EI) *m/z* (%): 253 (M^+, 22), 211 (20), 182 (6), 160 (38), 145 (8), 133 (26), 117 (16), 93 (39), 91 (100), 77 (17), 65 (13), 55 (13), 39 (13); $C_{17}H_{19}NO$: calcd C 80.60, H 7.56, N 5.52; found C 80.50, H 7.48, N 5.40. The two enantiomers of (**13**) are well separated by HPLC.

b) Absolute configuration assignment of the alkene (9). The alkene obtained from the reaction of the substrate (**3**) (table 2, entry 3) was oxidized to the acid (**12**) $[\alpha]_D$ = -34 (c=1.6 in $CHCl_3$) whose absolute configuration it is known[35] to be (*R*). Therefore to dextrorotatory (**9**) was attributed the (*S*) configuration.

c) Conversion of alkenes (10,11). By the above oxidation procedure followed by reaction with aniline, (**10**) gave (**15**) and (**11**) (**17**) respectively, whose enantiomeric excess was determined by ^{1}H NMR with [Eu(hfc)3] as the shift reagent. Such analyses were based upon the splitting of the signal due to the methyl bound to the stereocenter.

3-Methyl-3-isopropyl-6-phenylimino-N-phenyl-2-piperidinone (15). Yellow oil. ^{1}H NMR: δ = 0.95 (d, *J* = 6.9 Hz, Me), 0.96 (d, *J* = 6.8 Hz, 3H, Me), 1.26 (s, 3H, Me), 1.58-1.67 (m, 1H), 1.90-1.98 (m, 1H,), 2.28 (heptet, *J* = 6.9 Hz, 1H, CH isopr.), 2.53 (ddd, *J* = 14.9, 9.6, 5.2 Hz, 1H), 2.71 (ddd, *J* = 12.2, 7.1, 5.2 Hz, 1H), 6.63-6.68 (m, 2H, Ph), 6.96-7.01 (m, 1H, Ph), 7.12-7.16 (m, 2H, Ph), 7.20-7.26 (m, 2H, Ph), 7.29-7.34 (m, 1H, Ph), 7.40-7.45 (m, 2H, Ph); ^{13}C NMR: 16.6, 17.6, 20.8, 22.9, 25.3, 32.9, 45.1, 120.2, 122.9, 127.6, 128.8, 128.9, 129.0, 138.4, 149.1, 157.3, 177.1; MS (70 eV, EI) *m/z* (%): 320 (M^+, 11), 319 (34), 279 (15), 235 (11), 207 (62), 167 (49), 149 (100), 113 (11), 77 (9), 57 (21), 43 (18); $C_{21}H_{24}N_2O$: calcd C 78.71, H 7.55, N, 8.74; found C 78.65, H 7.60, N 8.72.

3-Methyl-3-n-butyl-5-phenylimino-N-phenyl-2-piperidinone (17). Yellow oil. $[\alpha]_D$= -22.6 (*c* =1 in $CHCl_3$); ^{1}H NMR: δ = 0.95 (t, *J* = 7.1 Hz, 3H, Me), 1.28-1.40 (m, 4H, CH_2), 1.30 (s, 3H, Me), 1.57-1.80 (m, 3H), 1.89-1.98 (m, 1H, heter.), 2.56-2.72 (m, 2H, CH_2 heter.), 6.62-6.66 (m, 2H, Ph), 6.94-6.99 (m, 1H, Ph), 7.12-7.16 (m, 2H, Ph), 7.19-7.26 (m, 2H, Ph), 7.29-7.34 (m, 1H, Ph), 7.40-7.45 (m, 2H, Ph); MS (70 eV, EI) *m/z* (%): 334 (M^+, 33), 333 (100), 305 (14), 277 (14), 235 (21), 207 (10), 145 (8), 130 (18), 117 (21), 77 (23), 41 (7); $C_{22}H_{26}N_2O$: calcd C 79.00, H 7.83, N 8.38; found: C 78.95, H 7.88, N 8.35.

Acknowledgement. This work was supported by the Italian Ministry of University and Scientific Research (40 and 60%).

References

1. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, 41, 135-631.
2. Lipshutz, B. H.; in *Organometallic in Synthesis*; Schlosser, M.; Ed.; Wiley: New York, 1994; p 283.
3. Yamamoto, Y. *Angew. Chem.* **1986**, 98, 945; *Angew. Chem. Int. Ed. Engl.*. **1986**, 26, 947-959.
4. Ibuka, T.; Yamamoto, Y. *Synlett.*. **1992**, 769-777.
5. Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, I.; Sedrani, R.; Guir, C.; Normant, J. F. *J. Pure Appl. Chem.* **1988**, 60, 49-56.
6. Denmark, S. E.; Marble, L. K. *J. Org Chem.*, **1990**, 55, 1984-1986.
7. Tamura, R.; Watabe, K. I.; Ono, N.; Yamamoto, Y. *J. Org. Chem.*, **1992**, 57, 4895-4903.
8. Gais, H-J.; Müller, H.; Bund, J.; Scommoda, M.; Brandt, J.; Raabe, G. *J. Am. Chem. Soc.* **1995**, 117, 2453-2466.
9. van Klaveren, M.; Persson, E. S. M.; Grove, M. D.; Bäckvall, J. E.; van Koten, G. *Tetrahedron Lett.*, **1995**, 36, 3059-3062.
10. Calò, V.; Fiandanese, V.; Nacci, A.; Scilimati, A. *Tetrahedron*, **1994**, 50, 7283-7292.
11. Calò, V.; Fiandanese, V.; Nacci, A.*Trends in Org. Chem.*, **1993**, 4, 479-491.
12. Barsanti, P.; Caló, V.; Lopez, L.; Marchese, G.; Naso, F.; Pesce, G. *J. Chem. Soc. Chem. Commun.*, **1978**, 1085-1086.
13. Caló,V; Lopez, L.; Carlucci, W. *J. Chem. Soc., Perkin Trans.* I, **1983**, 2953-2956.
14. Caló, V.; De Nitti, C.; Lopez, L.; Scilimati, A. *Tetrahedron*, **1992**, 48, 6051-6058.
15. Caló, V.; Lopez,L.; Pesce,G.; Calianno A.*J.Org. Chem.* **1982**, 47, 4482-4485.
16. Caló, V.; Lopez, L.; Pesce, G.*J. Chem. Soc., Chem. Commun.*, **1986**, 1252-1253.

17. Caló, V.; Lopez, L.; Pesce, G. *J. Chem. Soc., Perkin Trans.* I, **1988**, 1301-1304.
18. Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A.*Tetrahedron*, **1992**, 48, 2143-2156.
19. Bäckvall, J. E.; Sellén, M.; Grant, M. *J. Am. Chem. Soc.*, **1990**, 112, 6615-6621.
20. Bäckvall, J. E.; Persson, E. S. M.; Bombrun, A. J *J. Org. Chem.* **1994**, 59, 4126-4130.
21. Bowers, W. S. in *Recent Advances in the Chemistry of Insect Control*, Janes, N. F.; Ed., R.S.C., London, **1985**, Vol. 1, p. 276.
22. Levisalles, J.; Rudler-Chauvin, M.; Rudler, H. *J. Organomet.Chem.*, **1977**, 136, 103-110.
23. Goering, H. L.; Kantner, S. S. *J. Org. Chem.*, **1981**, 46, 2144-2148.
24. Posner, G. H. *Org. React.*, **1975**, 22, 253-400.
25. Taylor, R. J. K. *Synthesis*, **1985**, 364-392.
26. Power, P. P. *Prog. Inorg. Chem.*, **1991**, 39, 75.
27. van Koten, G.; Noltes, J. G. in *Comprensive Organometallic Chemistry*, Barton, D.; Ollis, W. D. Ed.; Pergamon Press: Oxford, 1979, Vol. 1, p 223.
28. Stemmler T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Böhme M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, 117, 12489-12497.
29. Bertz, S. H.; Miao, G.; Eriksson, M. J. *J. Chem. Soc., Chem. Commun.*, **1996**, 815-816.
30. Willert-Porada, M. A.; Burton, D. J.; Baenzinger, N. C. *J. Chem. Soc., Chem. Commun..*, **1989**, 1633-1634.
31. de la Pradilla, R. F.; Rubio, N. B.; Marino, G. P.; Viso, A. *Tetrahedron Lett.* **1992**, 33, 4985-4988.
32. Okamura, H.; Takei, H. *Tetrahedron Lett.*, **1979**, 36, 3425-3428.
33. Caló, V.; Lopez, L.; Pesce, G. *J. Organomet. Chem.* **1982**, 231, 179-183.
34. Caló, V.; Lopez, L.; Pesce, G. *J. Chem. Soc., Chem. Commun..* **1986**, 1252-1253.
35. Ahmar, M.; Girard, C.; Bloch, R. *Tetrahedron Lett.*, **1989**, 30, 7053-7056.

(*Received in UK* 22 *May* 1996; *accepted* 26 *June* 1996)