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Regiocontrol by Anchimeric Co-ordination in the Reactions of Organocopper Reagents with Allylic Substrates Bearing Two Leaving Groups. Synthesis of Optically Active Homoallylic Alcohols

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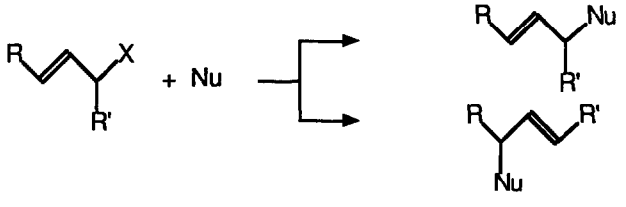
Abstract: The regiochemistry in the reactions of organocopper reagents with allylic electrophiles bearing two different leaving groups has been studied. Sulphide ester like **4** *react with organocopper reagents through regioselective substitution of the sulphide group to give esters of homoallylic alcohols. This regiocontrol is due to the anchimeric co-ordination exerted towards the organometallic reagent by the heterocyclic sulphide. By using sulphide ester* **8**, *whose heterocyclic moiety is optically active, the anchimeric co-ordination allows the synthesis of optically active esters of homoallylic alcohols. The regiocontrol is completely lost if cuprates are used as nucleophiles.*

Reaction of allylic electrophiles with dialkyl cuprates or Grignard reagents in the presence of copper catalyst is an important method for the formation of new C-C bonds and therefore a lot of investigations have been devoted to control the regio- and stereo-chemistry of this process (scheme 1).[1]

Scheme 1

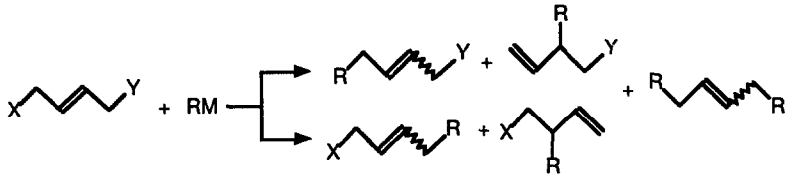


X= Cl, Br, OCOR, SO_2Ph, OR etc.; Nu= RCu, R_2CuMgX, R_2CuLi

The reactions of these organometallic reagents with allylic synthons which contain two allylic leaving groups have been studied but to a lesser extent. In this case the control of the selectivity is more difficult to achieve since

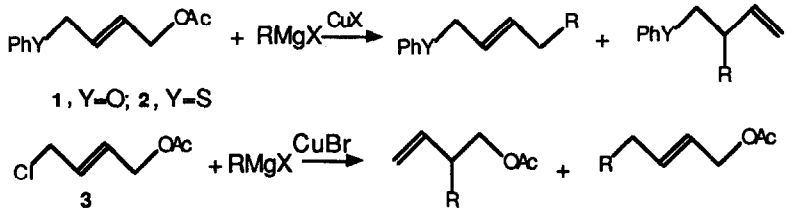
many regiochemical and stereochemical reactions occur together with the desired reaction (scheme 2).[2]

Scheme 2



Bäckvall and co-workers[1m] reported compounds **1** and **2** reacted, in the copper catalysed reactions, with Grignard reagents to give products arising exclusively from nucleophilic substitution of the acetoxy with fair to good regiocontrol, whereas chloroacetates like **3** reacted through substitution of chloride again affording a mixture of α- and γ-substitution products (scheme 3).

Scheme 3

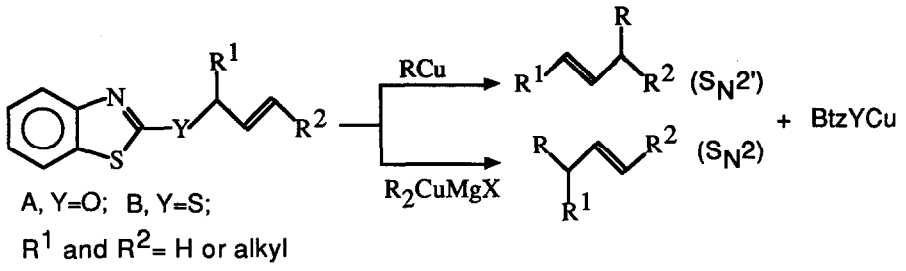


The aim of this paper has been to develop a full regio- and stereocontrol in the reactions of organocopper reagents with allylic electrophiles containing two allylic leaving groups which could be substituted in sequence by two different organocopper reagents.

Results and discussion

In a series of papers,[3] we showed that in the allylic substitutions by organocopper reagents, a full regio- and stereocontrol can be obtained by using allylic electrophiles like A or B (scheme 4) whose heterocyclic moiety behaves both as leaving group and co-ordination centre for the organometallic reagent. The regiocontrol depends on the organometallic species since monoalkylcopper reagents RCu give exclusively γ-substituted products whereas lithium or magnesium cuprates give α-substitution products (scheme 4). The S_N2' mechanism in the reaction with RCu type reagents is probably due to a strong co-ordination aptitude of the heterocyclic nitrogen towards this organocopper reagent.

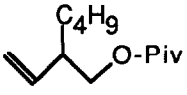
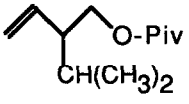
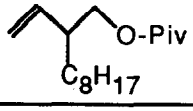
Scheme 4



Btz= Benzothiazol-2-yl

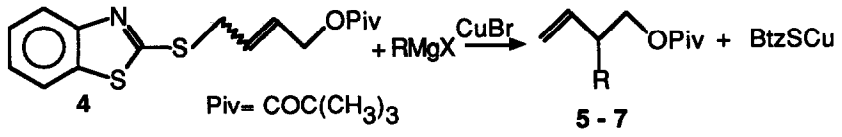
In order to study the reactions of an allylic system bearing two leaving groups with different reactivity towards organocopper reagents we synthesized as a model the compound **4** in which one of the leaving groups has coordinating properties for the organometallic reagent like a S-benzothiazolyl group and the other is the pivaloxy group. Both the geometrical isomers of compound **4** reacted with organomagnesium derivatives (scheme 5), in the presence of CuBr, to give C-C coupling products **5-7** arising from selective substitution of the heterocyclic nucleus by a S_N2' mechanism (γ-substitution) (table 1).

Table 1. Cross-coupling of **4** with Grignard reagents and CuBr.

RMgBr	Product[a]		Yield %
nC_4H_9MgBr		**5**	70
$(CH_3)_2CHMgBr$		**6**	80
$nC_8H_{17}MgBr$		**7**	87

[a]Compound **4** (1 equiv.) added at -50°C to the Grignard reagent (2.2 equiv.) and CuBr (4 equiv.) in THF.

Scheme 5

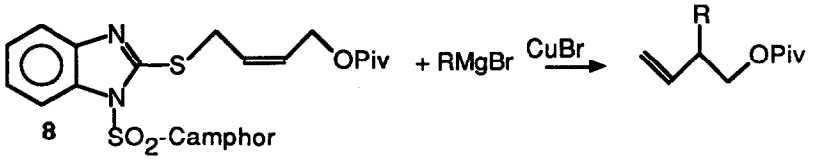


The same results where obtained by using other copper(I) halogenides but not with CuCN. With this latter salt the compoud **4** did not react at all.

The regiocontrol in these reactions depends strictly on the organocopper reagent. Reaction conditions that promote the formation of monoalkylcopper intermediate RCu (low ratio of organomagnesium to copper salt), led exclusively to homoallylic pivalates. On the contrary, higher ratios of Grignard reagents to CuBr promote the formation of magnesium dialkylcuprates affording products deriving from non regio- and non stereo-selective substitution of one or both the leaving groups as depicted in scheme 2 (Y= S-Benzothiazolyl and X= pivalate).

Since the full control of the regioselectivity in the reactions of **4** with monoalkylcopper compounds led to homoallylic esters bearing a chiral carbon, we synthesized the allylic pivalate **8** substituted in the δ-position by an optically active S-benzimidazolyl group in order to prepare optically active esters of homoallylic alcohols by regioselective substitution of the heterocyclic moiety with monoalkylcopper reagents.

Scheme 6



Compound **8** reacted as **4** by a S_N2'mechanism with a variety of RCu affording, by replacing the heterocyclic moiety containing the chiral auxiliary, optically active pivalates with fair enantiomeric excess (table 2).

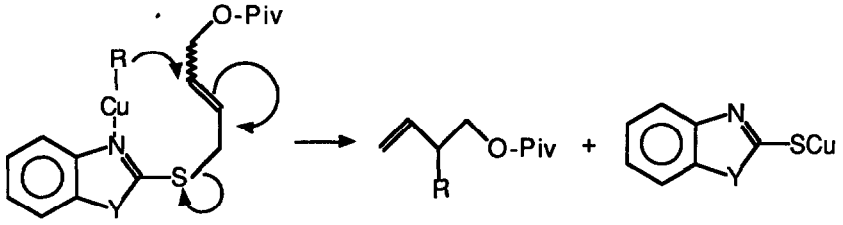
To explain these results, some considerations on the structure and composition of the organometallic reagents are necessary. At first sight the selectivity observed in the reactions with monoalkylcopper reagents could be due to the presence of the benzothiazole or benzimidazole nucleus linked to the allylic system, and probably also to co-ordination aptitude exerted by the heterocyclic nitrogen. If this is true the selectivity would be affected from different co-ordination aptitude of the allylic sulphide towards various organometallic species. It is known that on mixing a Grignard reagent with a copper(I) halide the equilibria in equations (1) and (2) operate.

$$RMgX + CuX \rightleftharpoons RCu + MgX_2 \qquad (1)$$

$$RCu + RMgX \rightleftharpoons R_2CuMgX \qquad (2)$$

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 dialkyl cuprate, whereas with an excess of CuX the main product is a monoalkylcopper reagent. These two reagents, which would show different degrees of co-ordination toward donor ligands, could react with **4** and **8** with different regioselectivity. Of these reagents the monoalkylcopper reagent would be the most 'electrophilic', and therefore more susceptible to co-ordination by the heterocyclic moiety[4] leading to a substitution of the S-benzothiazolyl or benzimidazolyl group. Since the reaction of compound **2** with organocopper reagents gives exclusively products arising from substitution of the acetoxy group and not from substitution of the PhS- group, the regiocontrol of this process can be reasonably explained only if RCu is forced, by anchimeric co-ordination due to the heterocyclic nitrogen, to attack the γ-carbon in the allylic sulphide (scheme 7).

Scheme 7

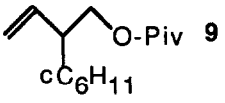


Y=S; NSO_2-camphor

On the other hand, in the reaction with dialkyl cuprates the metal would be less susceptible to the co-ordination by the heterocycle than RCu and therefore the nucleophile attacks both the leaving groups. An additional proof in support of this hypothesis comes from the non reactivity of these allylic electrophiles when CuCN is utilized as salt. Since cyanide ion is a good ligand for copper, the organocopper derived from reaction of CuCN and the Grignard reagent would be co-ordinatively saturated by cyanide ions and therefore not susceptible of co-ordination by the allylic heterocycle.

In conclusion, it appears that anchimeric co-ordination plays once more a crucial role in dictating the regioselectivity in the reactions of these substrates with organocopper reagents and this fact makes our intermediates useful allylic electrophiles for the synthesis of homoallylic alcohols. As for the application of this methodology to the synthesis of optically active homoallylic alcohols clearly an inprovement of enantiospecificity is required and work is in progress to synthesize allylic intermediates bearing different optically active nitrogen heterocycles as leaving groups.

Table 2. Yields of isolated products for cross coupling pivalate (**8**) with Grignard reagents and CuBr.

RMgBr	Product[ab]	% yield	E.e.%
n-BuMgBr	**5**	75	43
i-PrMgBr	**6**	68	30
n-C_8H_{17}MgBr	**7**	78	59
c-C_6H_{11}MgBr	 **9**	80	32

[a]The sulphide **8** (1 equiv.) was added to a suspension of CuBr (4 equiv.) and Grignard reagent (2.2 equiv.) in THF at -50°C. [b]Enantiomeric excess was evaluated by ^{1}H NMR chiral shift experiments in the presence of [Eu(hfc)$_3$].

EXPERIMENTAL

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 Elemental analyzer mod. 1106 Carlo Erba-instrumentation. IR spectra were recorded on a Perkin Elmer 681 Spectrometer. ^{1}H NMR spectra were recorded on Varian XL 200 spectrometer and chemical shifts are reported in parts per million (δ) from internal $SiMe_4$. Optical rotations were measured on Perkin-Elmer 241 polarimeter at 24°C (solvent $CHCl_3$). Solvents were dried and distilled under nitrogen immediately prior to use. (*Z*)-2-buten-1,4-diol, 2-thiobenzothiazol, 2-thiobezimidazol and (+)-10-camphorsulfonyl chloride were purchased from Fluka. Yields refer to isolated products by chromatography (Merck silica gel for flash chromatography). Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator. Flash chromatography was conducted by using silica gel with an average particle size of 60 μm, a particle size distribution 40-63 μm and 230-400 ASTM. Enantiomeric excess was evaluated by ^{1}H NMR in the presence of the [Eu(hfc)$_3$] as chiral shift reagent. Such analyses were based upon the splitting of the vinyl proton signal CH_2=CH.

(Z)-1-Trimethylacetoxy-4-(benzothiazol-2-thio)-2-butene (**4**).

To triphenylphosphine (4.27g, 0.54 mole) dissolved in dry toluene (30 ml) was added under stirring at room temperature benzothiazol disulphide[5] (5.4g, 0.54 mole). After 15 min cis 2-butene-1,4-diol mono pivalate(2.8g, 0.54 mole) dissolved in 10 ml of toluene was added. The stirring was kept on until the phosphine disappeared (TLC, petroleum ether-ethyl acetate 10:1 v/v). After the solvent had been evaporated the residue was directly chromatographed on silica gel (petroleum ether-ethyl acetate 10:1 v/v) to give 3.35g (64% yield) of the allyl sulphide-ester as pale yellow oil. IR (neat):1728, 1463, 1152 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 1.19 (s, 9H,

$C(CH_3)_3$); 4.06 (d, 2H, J=7.49 Hz, CH_2S); 4.79 (d, 2H, J=6.35 Hz, CH_2O); 5.63-5.92 (m, 2H, CH=CH); 7.21-7.42 (m, 2H Ar); 7.71 (m, 1H Ar); 7.85 (m, 1H Ar). (Found: C, 59.75; H, 6.00; N, 4.35. $C_{16}H_{19}NO_2S_2$ requires C, 59.80; H, 5.96; N, 4.36%).

(Z)-1-Trimethylacetoxy-4-(benzimidazol-1-camphorsulphonyl-2-thio)- 2-butene (**8**).

To triphenylphosphine (34.3g, 0.52 mole) dissolved in dry toluene (250 ml) was added under stirring at room temperature benzimidazol disulphide[6] (39g, 0.52 mole). After 15 min cis 2-butene-1,4-diol mono pivalate(22.5g, 0.52 mole) dissolved in 50 ml of toluene was added. The stirring was kept on until the phosphine disappeared (TLC, petroleum ether-ethyl ether 1:1 v/v). After the solvent was evaporated the residue was directly chromatographed on silica gel (petroleum ether-ethyl ether 1:1 v/v) to give as first eluted product 17.6 g of (Z)-1-trimethylacetoxy-4-(benzimidazol-2-thio)-2-butene m.p. 100-101 °C followed from 14 g of the same product contaminated by a small quantity of the (*E*)-isomer (total yield 80%). IR (CCl_4): 1731, 1267, 1156 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.21 (s, 9H, $C(CH_3)_3$); 3.97 (dd, 2H, J=7.38 and 1.22 Hz, CH_2S); 4.69 (dd, 2H, J=6.65 and 1.31Hz, CH_2O); 5.54-5.89 (m, 2H, CH=CH); 7.14-7.25 (m, 2H Ar); 7.50-7.58 (m, 2H Ar). (Found: C, 63.18; H, 6.65; N, 9.20. $C_{16}H_{20}N_2O_2S$ requires C, 63.14; H, 6.62; N, 9.20%).
To (Z)-1-trimethylacetoxy-4-(benzimidazol-2-thio)-2-butene (5g, 0.55 mole) dissolved in dry toluene (30 ml) was added under stirring at room temperature triethylamine (3.4 ml, 0.82 mole) followed by (+)-10-camphor sulphonyl chloride (4.95g, 0.65 mole). The stirring was kept on until the sulphide disappeared (TLC, petroleum ether-ethyl ether 2:1 v/v). This solution, washed three times with 10 ml of 5% HCl, twice with 10% $NaHCO_3$ dried over anhydrous Na_2SO_4 and after solvent evaporation (**8**) was quantitatively obtained as viscous oil. $[\alpha]_D$ = +7.6°(c=0.15, $CHCl_3$). IR (CCl_4): 1744, 1452, 1387, 1164, 1150 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 0.83 (s, 3H, CH_3); 1.13 (s, 3H, CH_3); 1.15 (s, 9H, $C(CH_3)_3$); 3.08 (m, 1H, CHCO); 3.64 (m, 1H, CHCO); 4.04 (d, 2H, J=7.51Hz, CH_2S); 4.63 (d,1H, J=4.89 Hz, $CHSO_2$); 4.78 (d, 2H, J=6.21, CH_2O); 4.87 (d,1H, J=4.89 Hz, $CHSO_2$); 5.61-5.85 (m, 2H, CH=CH); 7.12-7.31(m, 2H Ar); 7.58 and 783 (m, 2H Ar). (Found: C, 64.05; H, 7.20; N, 5.75. $C_{26}H_{35}N_2O_5S$ requires C, 64.04; H, 7.24; N, 5.75%).

Reactions of sulphide-esters (4) and (8) with organocopper reagent RCu: general procedure.

To CuBr (18.7 mmole) suspended in 25 ml of dry THF was added dropwise under an N_2 atmosphere and stirring the Grignard reagent (0.5M, 10 mmole) at -20 °C. After 1h the temperature was lowered to -50 °C and the sulphide ester (4.6 mmole) dissolved in 10 ml of THF was added. 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 was evaporated to dryness. The powder was placed on the top of a column filled with silica gel and chromatographed (eluent petroleum ether-ethyl acetate 10:1 v/v) to give the pure homoallylic pivalate. According to this procedure the esters reported in tables 1 and 2 were synthesized.

2-Vinyl-1-hexanol trimethylacetate (**5**). Colourless oil. IR (neat): 1734 and 1645 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 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=$\underline{CH}$). . The optical rotation value of the compound obtained from (**8**) is: $[\alpha]_D$ = +6.06°(c=0.14, $CHCl_3$). (Found: C, 73.49; H, 11.40. $C_{13}H_{24}O_2$ requires: C, 73.54; H, 11.39%).

2-Vinyl-3-methyl-1-butanol trimethylacetate (**6**). Colourless oil. 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=6.5 Hz); 2.14 (m, 1H); 4.04 (d, 2H, J=6.6 Hz); 4.96-5.10 (m, 2H, $\underline{CH_2}$=CH); 5.52-5.71 (ddd, 1H, J=16.9, 10.5 and 9.0 Hz, CH_2=$\underline{CH}$). The optical rotation value of the compound obtained from (**8**) is: $[\alpha]_D$ = +7.64°(c=0.10, $CHCl_3$). (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 (**7**). Colourless oil. IR (neat): 1734 and 1645 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 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=$\underline{CH}$). The optical rotation value of the compound obtained from (**8**) is: $[\alpha]_D$ = +3.75°(c=0.40, $CHCl_3$). (Found: C, 76.10; H, 12.01. $C_{17}H_{32}O_2$ requires: C, 76.06; H, 12.02%).

2-Cyclohexyl-3-buten-1-ol trimethylacetate (**9**). Colourless oil. IR (neat): 1734 and 1644 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 1.14 (s, 9H); 0.80-1.81 (m, 11H); 2.10-2.29(m, 1H); 4.05(d, 2H, J=5.8 Hz); 5.06(m, 2H, $\underline{CH_2}$=CH); 5.51-5.70 (ddd, 1H, J=16.9, 10.4 and 9.1Hz, CH_2=$\underline{CH}$). $[\alpha]_D$ = +2.55° (c=0.30, $CHCl_3$). (Found: C, 75.55; H, 11.99. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 10.99%).

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