Selectivity in Allylic Substitutions with Organometallics through Neighbouring Co-ordination. Part 2.[1] Reactions of 2-Allylthiobenzothiazoles with Organocopper Reagents [2]

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Efficient control of the regioselectivity in allylic substitutions with Grignard reagents in the presence of copper(I) bromide has been achieved by using 2-allylthiobenzothiazoles as electrophiles. The $S_N2:S_N2'$ product ratio depends on the degree of co-ordination between the allylic reagent and the organometallic species.

Organic and inorganic groups co-ordinated with metals can have reactivities which are very different from those of the free ligands. We were particularly interested in the degree of regio- and stereo-selectivity which sigma carbon–metal bonds can exhibit in their reactions with allylic derivatives bearing a co-ordination centre for the metal.[3-7] In order to investigate this we synthesized the 2-allyl substituted benzothiazoles (1a) and (1b) in which the anchimeric co-ordination would be exerted by the nitrogen in the heterocycle.

The co-ordination aptitude of the ether (1a) was clearly demonstrated by the isolation[3] of stable 1 : 1 π-complexes from its reaction with copper(I) halides, in which the metal atom is probably inserted between the C=N and C=C double bonds. Both the ethers and their copper(I) π-complexes react with organometallics to give alkenes with regio- and stereo-selectivity which depends on the co-ordination aptitude of the organometallic reagent towards the electrophile[1,3] (Scheme 1).

This paper reports the reactions of allyl sulphides of type (1b) with Grignard reagents in the presence of CuBr and the effect of co-ordination of the organometallic species on the regioselectivity of these reactions.

Results and Discussion

In a preliminary paper[8] we showed that allyl sulphides of type (1b) react with cuprates to give olefins with a regio-selectivity which depends on the reaction medium (Scheme 2).

These results are not easily explainable on only a slight change in the reaction medium. However, it was known that other allyl sulphides react with organomagnesium compounds in the presence of copper(I) or nickel to give alkenes without any regioselectivity.[9-11] At first sight the selectivity could be associated with the presence of the benzothiazole nucleus linked to the allylic system, and probably with the co-ordination effect exerted by this heterocycle. If this is true the selectivity would be influenced by the different co-ordination aptitudes 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.

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

$$RCu + RMgX \rightleftharpoons (R_2Cu)^-MgX^+ \qquad (2)$$

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 homocuprate, whereas with an excess of CuX the main product is RCu. These two reagents, which would show different degrees of co-ordination toward donor ligands, could
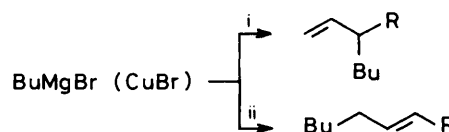

(1)

a : Y = O

b : Y = S
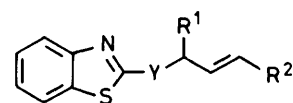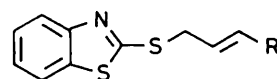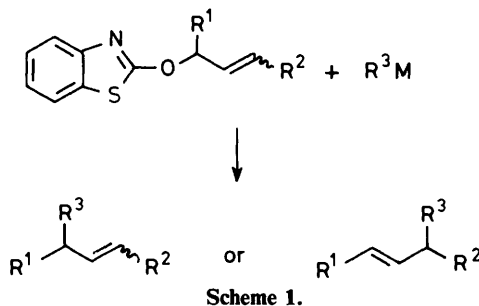
Scheme 1.

Scheme 2. *Reagents:* i, Et₂O; ii, THF

react with our allyl sulphides with different regioselectivities. In order to test this hypothesis, the reaction of the sulphides (2) with n-butylmagnesium bromide in tetrahydrofuran (THF) in the presence of various amounts of CuBr was selected as a model (Scheme 3). We found that the ratio of the reaction products (3) : (4) changed with the ratio between the organomagnesium compounds and CuBr used, the S_N2' product (4) being favoured by a low ratio of Grignard reagent : CuBr, and the S_N2 product (3) by a high one, as reported in Table 1.

Also worthy of note is the dependence of the reaction rates on the Grignard reagent : CuBr ratio. This could be associated with the low CuBr concentration (run 4) but is in contrast with
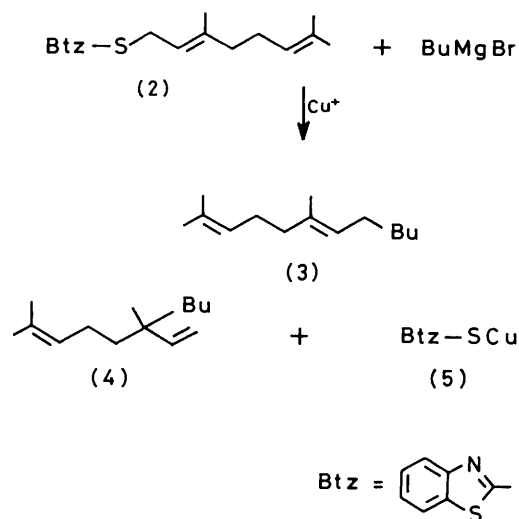
Scheme 3.

Scheme 4.

Table 1. Effect of the ratio of Grignard reagent : CuBr on the regioselectivity in the cross-coupling of the 2-octa-2,6-dienylthio-benzothiazole (2) with Bu^nMgBr

| Run	Bu^nMgBr : CuBr (equiv.)	Products (%) (3) : (4) [a]	Conversion after 15 min (%) [a]
1	1 : 3 [b]	0.5 : 99.5	98
2	1 : 2 [b]	1 : 99	89
3	1 : 1 [b]	2 : 98	71
4	1 : 0.1 [b]	50 : 50	53
5	2 : 1 [c]	70 : 30	95
6	4 : 1 [c]	99 : 1	98

[a] Determined by g.l.c. [b] Grignard reagent added to a suspension of CuBr in THF containing (2) (1 equiv.) at 0 °C. [c] Compound (2) (1 equiv.) added to a THF solution of Grignard reagent and CuBr at −30 °C.

Table 2. Regioselectivity in the cross-coupling of the 2-octa-2,6-dienylthiobenzothiazole (2) with Bu^nMgBr in the presence of copper(I) benzothiazole-2-thiolate [a]

Btz^-SCu : BuMgBr (equiv.) [b]	Products (3) : (4) (%)
1 : 1	47 : 53
1 : 2	83 : 17
1 : 4	99 : 1

[a] All the reactions were performed in THF at −30 °C by adding the allylic sulphide to a suspension of the salt (5) and the Grignard reagent. [b] Btz = benzothiazol-2-yl.

the results of runs 5 and 6 where, despite high Grignard reagent : CuBr ratios, the reactions are very fast. This can be explained by looking at Scheme 3. During the reaction, the benzothiazole-2-thiolate anion is generated as a by-product which reacts with CuBr to give (5), an insoluble orange salt. Therefore with low CuBr concentrations, at low conversion values, most of the copper ion exists as the salt (5) which in turn can react with the Grignard reagent to give a mixed cuprate of type $(RSCuR)^-MgX^+$; the reaction rate of this cuprate with (2) would be lower than that observed for BuCu (runs 1—3) or $(Bu_2Cu)^-MgBr^+$ (runs 5—6). In fact in a parallel experiment, performed with BuMgBr, and compound
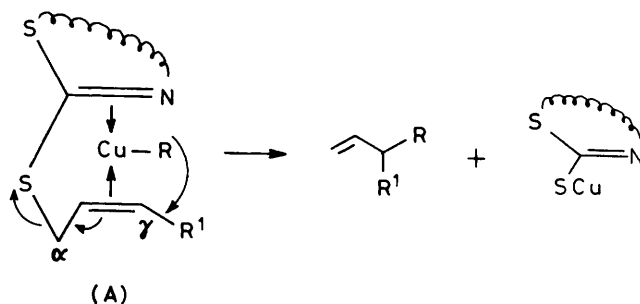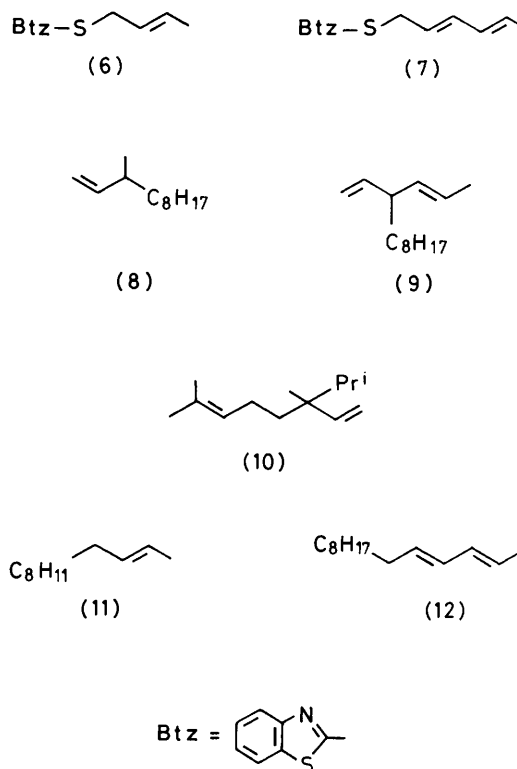
(5) in the place of CuBr, not only does the allyl sulphide react more slowly, but in addition the ratio (3) : (4) changes in favour of the S_N2 substitution product (3) (Table 2).

These data are in accord with our hypothesis that regioselectivity is dictated by co-ordination effects, and hence by the relative extent to which the two equilibria, in equations (1) and (2), occur, and can be explained as follows: in the presence of an excess of CuBr the organometallic should be mainly of the RCu type, whereas when the Grignard reagent concentration is higher than that of CuBr, $(R_2Cu)^-MgBr^+$ (Table 1, runs 5 and 6) or $(RSCuR)^-MgBr^+$ (Table 1, run 4) should be favoured. Of these reagents the organocopper one RCu would be the most ' electrophilic ', and therefore more susceptible to co-ordination by the allyl sulphide (Scheme 4).

The steric requirements of the intermediate complex (A) would influence the positional selectivity, and also suggests a lack of conformational mobility in the transition state. In this situation the nucleophilic attack of R would occur almost exclusively at the γ-carbon of the allylic system, even if this position is the more sterically hindered one. On the other hand, in the reactions with cuprates or mixed cuprates, the metal is less susceptible to co-ordination by the allyl sulphide than

Table 3. Cross-coupling of benzothiazol-2-yl allyl sulphides with organomagnesium compounds in the presence of CuBr [a]

Sulphide	Grignard reagent	Product [yield (%)] [b,c]
(6)	n-C$_8$H$_{17}$MgBr	(8) [85]
(7)	n-C$_8$H$_{17}$MgBr	(9) [80]
(2)	n-C$_4$H$_9$MgBr	(4) [90]
(2)	Pr^{i}MgBr	(10) [83]

[a] Grignard reagent (1 equiv.) added at 0 °C to the sulphide (1 equiv.) in the presence of CuBr (3 equiv.) in THF. [b] Isolated yields. [c] The amount of S_N2 product was <1%.

Table 4. Cross-coupling of benzothiazol-2-yl allyl sulphides with mixed cuprates [a]

Sulphide	Grignard reagent	Product [b] [yield (%)] [c]
(6)	C$_8$H$_{17}$MgBr	(11) [80]
(7)	C$_8$H$_{17}$MgBr	(12) [86]
(2)	n-C$_4$H$_9$MgBr	(3) [90]

[a] The sulphides were added at −30 °C to a solution of the mixed cuprate in THF formed by treating Btz–SCu (1 equiv.) with the Grignard reagent (4 equiv.). [b] The amount of S_N2' product was <1%. [c] Isolated yields.

RCu and therefore the nucleophile attacks the less hindered α-position, leading to S_N2 products.[12]

To support this hypothesis we synthesized some allyl sulphides which were subjected to reaction with various organomagnesium compounds in the presence of excess of CuBr (Table 3).

The results obtained from the sulphides (7) and (2) require some comment. The former reacts to give the unconjugated, less thermodynamically stable diene (9), whereas the latter reacts even with isopropylmagnesium bromide to give the crowded tetrasubstituted carbon in the alkene (10). These data can be reasonably explained only if RCu is forced by anchimeric co-ordination to attack the γ-carbon in the allylic moiety.

Finally, again the regioselectivity changes completely if a mixed cuprate is added to the same sulphides (Table 4).

These results help us to explain the change in regioselectivity, found previously,[8] on changing the reaction solvent. Besides the concentration, the solvating power of the reaction medium could influence the formation equilibria of the various organometallic species and hence the regioselectivity. In diethyl ether, the equilibrium in equation (1) could predominate and consequently RCu, after co-ordination by the allylic sulphide, would give S_N2'-type products. On the other hand, in THF–ether (2 : 1), owing to the better solvating power of this medium, the equilibrium could be shifted to that in equation (2), with predominant formation of (R$_2$Cu)$^-$MgX$^+$ leading to S_N2-type products. As well as solvating properties, the solvent could probably also influence to different extents the reaction rates of the two organocopper reagents with the allyl sulphide, and hence the regioselectivity.

In conclusion, it appears that anchimeric co-ordination plays a crucial role in dictating the selectivity, and this fact makes our sulphides flexible electrophilic reagents for selective C–C coupling reactions.

Experimental

General Methods.—The regiochemical purity of the reaction products was tested by g.l.c. performed on an H.P. Model

5780 (10% SP2100 on 100—120 Supelcoport) gas chromatograph. ^{1}H N.m.r. spectra were determined on Varian A-60A, HA100, and XL 200 spectometers. I.r. spectra were recorded on a Perkin-Elmer 681 spectrometer. B.p.s of the products were measured with a Kugelrohr distillation apparatus. Ether refers to diethyl ether.

Preparation of the Benzothiazol-2-yl Allyl Sulphides.—The sulphides were prepared following Overman's procedure.[13] To triphenylphosphine (0.30 mol) dissolved in dry benzene (50 ml) was added under stirring at room temperature benzothiazolyl hydrodisulphide [14] (0.30 mol). After 15 min the allylic alcohol (0.30 mol) dissolved in benzene (20 ml) was added. The stirring was continued until the phosphine disappeared (t.l.c., hexane–ether 5 : 1 v/v). After the solvent had been evaporated the residue was directly chromatographed on a short column of silica gel (hexane–ether 5 : 1 v/v) to give the allyl sulphide in 70—90% yield.

(2E)-2-(3,7-*Dimethylocta*-2,6-*dien*-1-*ylthio*)*benzothiazole* (2). This sulphide was obtained as a pale yellow liquid (75%), starting from 3,7-dimethylocta-2,6-dien-1-ol. [Attempted vacuum distillation resulted in a partial S ⟶ N Claisen rearrangement to give *N*-allylbenzothiazole-2-thione.] $v_{max.}$ (CCl$_4$) 3 020, 1 660 cm^{-1}; δ(CCl$_4$) 1.56 (s, 3 H), 1.62 (s, 3 H), 1.78 (s, 3 H), 2.02 (m, 4 H), 3.98 (d, 2 H), 4.94 (bs, 1 H), 5.35 (bs, 1 H), and 7.06—7.78 (m, 4 H, Ar) (Found: C, 67.3; H, 6.9; S, 21.0. C$_{17}$H$_{21}$NS$_2$ requires C, 67.32; H, 6.93; S, 21.12%).

(2E)-2-*But*-2-*en*-1-*ylthiobenzothiazole* (6). This *compound* (87%) was synthesized from crotyl alcohol, m.p. 43—44 °C (Found: C, 59.6; H, 4.9; S, 28.5. C$_{11}$H$_{11}$NS$_2$ requires C, 59.72; H, 4.97; S, 28.95%); δ(CCl$_4$) 1.67 (d, 3 H), 3.90 (d, 2 H), 4.40—4.80 (m, 2 H), 7.00—7.34 (m, 2 H Ar), and 7.60—7.80 (m, 2 H Ar).

2-*Hexa*-2,4-*dien*-1-*ylthiobenzothiazole* (7). This *compound* (80%) was synthesized from hexa-2,4-dien-1-ol, obtained by LiAlH$_4$ reduction of commercial (Aldrich) hexa-2,4-dienoic acid, m.p. 48—50 °C (ethanol) (Found: C, 63.1; H, 5.2; S, 25.9. C$_{13}$H$_{13}$NS$_2$ requires C, 63.15; H, 5.26; S, 25.91%); δ(CDCl$_3$) 1.65 (d, 3 H), 3.90 (d, 2 H), 5.30—6.50 (m, 4 H), 7.10—7.40 (m, 2 H Ar), and 7.50—8.00 (m, 2 H Ar).

Copper(I) *benzothiazole-2-thiolate* (5). CuBr (10 g, 1 mol equiv.) was dissolved with stirring in 32% ammonia solution (150 ml). To this solution, benzothiazole-2-thiol (5.8 g, 1 mol equiv.) was added in portions. The orange *solid* which precipitated was filtered and washed repeatedly with water until the washings were neutral and subsequently with tetrahydrofuran (THF), m.p. 240 °C (decomp.) (Found: C, 36.5; H, 1.7; Cu, 27.5; S, 27.8. C$_7$H$_4$CuSN$_2$ requires C, 36.60; H, 1.74; Cu, 27.66; S, 27.88%).

General Procedure for Production of Alkenes via an S_N2' *Process.*—CuBr (11.7 mmol) was added to a solution of the allylic sulphide (3.9 mmol) in THF (15 ml) at 0 °C under N$_2$. The Grignard reagent in THF (3.9 mmol) was then added dropwise with stirring. After 1.5 h silica gel was added and the resulting suspension was evaporated to dryness. The resulting powder was placed on the top of a column filled with silica gel and chromatographed (eluant, pentane) to give the pure alkene. According to this procedure the alkenes reported in Table 3 were synthesized.

3-Methylundec-1-ene (8), b.p. 84 °C/20 mmHg and 3-butyl-3,7-dimethylocta-1,6-diene (4), b.p. 60 °C/0.01 mmHg, had i.r. and ^{1}H n.m.r. data identical with those reported.[1]

3-*Octylhexa*-1,4-*diene* (9) (Found: C, 86.4; H, 13.5.. C$_{14}$H$_{26}$ requires C, 86.59; H, 13.41%); δ(CDCl$_3$) 5.30—5.90 (m, 3 H), 4.80—5.05 (m, 2 H), 2.50—2.70 (bm, 1 H), and 1.65 (d, 3 H); $v_{max.}$ (neat) 965, 990, and 910 cm^{-1}. This product polymerized on vacuum distillation.

3-*Isopropyl*-3,7-*dimethylocta*-1,6-*diene* (10), b.p. 49 °C/0.7 mmHg (Found: C, 86.6; H, 13.4. $C_{13}H_{24}$ requires C, 86.66; H, 13.33%). $v_{max.}$ (CCl$_4$) 3 080, 1 645, 985, and 905 cm^{-1}; δ(CDCl$_3$) 0.78—0.89 (m, 6 H), 1.32 (m, 2 H), 1.58 (s, 3 H), 1.67 (s, 3 H), 1.87 (m, 2 H), 2.04 (m, 1 H), 4.84—5.10 (m, 3 H), and 5.62—5.78 (m, 1 H).

General Procedure for Production of Alkenes via *an* S_N2 *Process*.—To a suspension of copper(I) benzothiazole-2-thiolate (3.9 mmol) in THF (15 ml) was added at −30 °C under N$_2$ with stirring the organomagnesium compound (11.7 mmol) in THF. After 30 min the allylic sulphide (3.9 mmol) dissolved in THF (15 ml) was added dropwise, and after 1.5 h the reaction mixture was treated as reported above to give the pure alkenes. According to this procedure the alkenes reported in Table 4 were synthesized.

(2*E*)-Dodec-2-ene (11) and (6*E*)-2,6-dimethyldodeca-2,6-diene (13) had i.r. and ^{1}H n.m.r. data identical with those previously reported.[1,15]

Tetradeca-2,4-*diene*, b.p. 80—85 °C/2 mmHg (Found: C, 86.5; H, 13.4. $C_{14}H_{26}$ requires C, 86.59; H, 13.41%); δ(CDCl$_3$) 5.20—6.10 (cm, 4 H), 1.98 (bd, 2 H), and 1.66 (d, 2 H).

Acknowledgements

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