NMR δ 0.87–2.48 (28 H, m), 4.25 (CH_2, $J_{H,H}$ = 2.5 Hz), 4.47 (CH_2, t, $J_{H,H}$ = 2.4 Hz), 5.25 ($CHCF_3$, m), 5.72 (1 H, m), 6.37 (1 H, m), 7.09–8.45 (ArH); IR (KBr) 1725 (C=O), 1620 (C=C) cm^{-1}; high-resolution MS calcd for $C_{40}H_{47}O_7F_3$ 696.803, found 696.674.

Monomer 10d. (*R*)-(+)-4-[[[1-(Trifluoromethyl)octyl]oxy]-carbonyl]phenyl 4′-hydroxybiphenyl-4-carboxylate (**1a**; 5.0 g, 10 mmol), sodium hydride (0.26 g, 12 mmol), 12-bromoundecanyl methacrylate (6.7 g, 20 mmol), and tetrahydrofuran (30 mL) were used. Yield 78%: $[\alpha]^{23}_D$ (toluene) +15.43° (*c* 0.81); ^{19}F NMR δ −1.4 (d, $J_{F,H}$ = 7.5 Hz); ^1H NMR δ 0.89–2.91 (36 H, m), 4.23 (CH_2, $J_{H,H}$ = 2.5 Hz), 4.43 (CH_2, t, $J_{H,H}$ = 2.1 Hz) 5.23 ($CHCF_3$, m), 5.76 (1 H, m), 6.36 (1 H, m), 7.10–8.30 (ArH); IR (KBr) 1725 (C=O), 1620 (C=C) cm^{-1}; high-resolution MS calcd for $C_{44}H_{55}O_7F_3$ 752.911, found 752.750.

Ferroelectric Liquid Crystalline Polymer. Typical Procedures. (**a**) A solution of ferroelectric liquid crystalline monomer **4a** (6.0 g, 10 mmol) and azobisisobutyronitrile (0.4 g) in benzene (50 mL) was amplified under vacuum and then heated at 100 °C. After 24 h of heating at that temperature, the solvent was removed. The crude product was purified by column chromatography on silica, giving the corresponding polymer in 64% yield.

(**b**) Into a solution of ferroelectric liquid crystalline monomer **4a** (6.0 g, 10 mmol) in tetrahydrofuran (30 mL), *n*-butyllithium (0.6 mL, 1.0 mmol) in hexane was added with a syringe under an atmosphere of nitrogen at −78 °C. After 24 h of stirring at that temperature, the mixture was quenched with saturated NH_4Cl solution, and then precipitates were collected. The crude product was purified by column chromatography on silica gel, giving the corresponding polymer in a 58% yield.

Other polymerization reactions were carried out the same scale and manner.

Registry No. (*R*)-**1a**, 128054-69-3; (*S*)-**1a**, 128054-72-8; (*R*)-**1aa**, 128054-70-6; (*S*)-**1aa**, 128054-73-9; (*R*)-**1b**, 128054-75-1; (*S*)-**1b**, 128054-78-4; (*R*)-**1ba**, 128054-76-2; (*S*)-**1ba**, 128054-79-5; (*R*)-**1c**, 128054-81-9; (*S*)-**1c**, 128054-83-1; (*R*)-**1ca**, 128054-82-0; (*S*)-**1ca**, 128054-84-2; (*R*)-**1d**, 128083-46-5; (*S*)-**1d**, 128054-86-4; (*R*)-**1da**, 128083-47-6; (*S*)-**1da**, 128054-87-5; (*R*)-**2a**, 128054-89-7; (*S*)-**2a**, 128054-92-2; (*R*)-**2aa**, 128054-90-0; (*S*)-**2aa**, 128054-93-3; (*R*)-**3a**, 128054-95-5; (*S*)-**3a**, 128054-98-8; (*R*)-**3aa**, 128054-96-6; (*S*)-**3aa**, 128054-99-9; (*R*)-**4a**, 128055-01-6; (*S*)-**4a**, 128055-02-7; **4a** (homopolymer), 128055-34-5; (*R*)-**4b**, 128055-03-8; (*S*)-**4b**, 128055-04-9; **4b** (homopolymer), 128055-36-7; (*R*)-**4c**, 128055-05-0; (*S*)-**4c**, 128055-06-1; **4c** (homopolymer), 128055-38-9; (*R*)-**4d**, 128055-07-2; (*S*)-**4d**, 128055-08-3; **4d** (homopolymer), 128055-40-3; (*R*)-**5c**, 128055-09-4; **5c** (homopolymer), 128055-42-5; (*R*)-**6c**, 128055-10-7; **6c** (homopolymer), 128055-44-7; (*R*)-**7c**, 128055-11-8; **7c** (homopolymer), 128055-46-9; (*R*)-**8a**, 128055-12-9; (*S*)-**8a**, 128055-13-0; **8a** (homopolymer), 128055-48-1; (*R*)-**8b**, 128055-14-1; (*S*)-**8b**, 128055-15-2; **8b** (homopolymer), 128055-50-5; (*R*)-**8c**, 128055-16-3; (*S*)-**8c**, 128083-49-8; **8c** (homopolymer), 128055-52-7; (*R*)-**8d**, 128055-17-4; (*S*)-**8d**, 128055-18-5; **8d** (homopolymer), 128055-54-9; (*R*)-**9a**, 128055-19-6; (*S*)-**9a**, 128055-20-9; **9a** (homopolymer), 128055-56-1; (*R*)-**9b**, 128055-21-0; (*S*)-**9b**, 128055-22-1; **9b** (homopolymer), 128055-58-3; (*R*)-**9c**, 128055-23-2; (*S*)-**9c**, 128055-24-3; **9c** (homopolymer), 128055-60-7; (*R*)-**9d**, 128055-25-4; (*S*)-**9d**, 128055-26-5; **9d** (homopolymer), 128055-62-9; (*R*)-**10a**, 128083-50-1; **10a** (homopolymer), 128083-52-3; (*R*)-**10b**, 128055-27-6; **10b** (homopolymer), 128055-64-1; (*R*)-**10c**, 128055-29-8; **10c** (homopolymer), 128055-66-3; (*R*)-**10d**, 128055-31-2; **10d** (homopolymer), 128055-68-5; $PhCH_2(C_6H_4\text{-}p)CO_2H$, 128054-71-7; (*R*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_6H$, 121170-47-6; (*S*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_6H$, 128054-74-0; (*R*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_7H$, 128054-77-3; (*S*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_7H$, 128054-80-8; (*R*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_8H$, 124689-86-7; (*S*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_8H$, 128054-85-3; (*R*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_9H$, 128083-48-7; (*S*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_3)(CH_2)_9H$, 128054-88-6; (*R*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_2CF_3)(CH_2)_6H$, 128054-91-1; (*S*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CF_2CF_3)(CH_2)_6H$, 128054-94-4; (*R*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CHCF_3)(CH_2)_6H$, 128054-97-7; (*S*)-$HOC_6H_4\text{-}p\text{-}CO_2CH(CHCF_3)(CH_2)_6H$, 128055-00-5; $H_2C{=}CHCO_2(CH_2)_2Br$, 4823-47-6; $H_2C{=}CHCO_2(CH_2)_6Br$, 112231-58-0; $H_2C{=}CHCO_2(CH_2)_8Br$, 123563-83-7; $H_2C{=}CHCO_2(CH_2)_{12}Br$, 112231-59-1; $H_2C{=}C(CH_3)CO_2(CH_2)_2Br$, 4513-56-8; $H_2C{=}C(CH_3)CO_2(CH_2)_6Br$, 128055-28-7; $H_2C{=}C(CH_3)CO_2(CH_2)_8Br$, 128055-30-1; $H_2C{=}C(CH_3)CO_2(CH_2)_{12}Br$, 128055-32-3.

Regiocontrol in Copper-Catalyzed Grignard Reactions with Allylic Substrates

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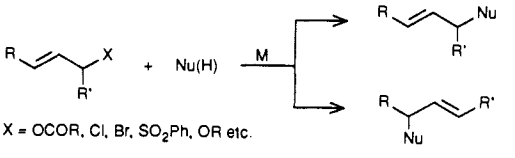
Abstract: The regiochemistry of copper-catalyzed reactions between Grignard reagents and allylic substrates has been studied. A dual regiocontrol was obtained in the Li_2CuCl_4-catalyzed Grignard reaction with primary allylic acetates. Reaction conditions that favor formation of an intermediate dialkylcuprate (fast addition of Grignard reagent, low temperature, low concentration of catalyst) gave α-substitution, whereas reaction conditions favoring formation of a monoalkylcopper intermediate (slow addition of Grignard reagent, increased temperature, increased concentration of catalyst) led to a γ-substitution. A remarkable solvent effect was observed for CuCN-catalyzed Grignard coupling with primary allylic acetates. In ether a highly γ-selective reaction took place, but in THF α-substitution predominated. Other allylic substrates such as allylic sulfones and allylic chlorides were also studied. The latter substrates showed a preference for γ-substitution, which is explained by their high reactivity.

Allylic compounds are important substrates in organic synthesis, and they have attracted a lot of mechanistic interest over the years, in particular with respect to nucleophilic displacement, i.e. S_N2 and S_N2'.[1] A number of studies dealing with the regio- and stereochemistry of nucleophilic substitution of allylic substrates have appeared.

Recently, transition metals have become popular tools for the activation of allylic substrates.[2] By coordination of the double bond to the metal, the reactivity of the allylic leaving group is considerably increased. Usually this leads to an intermediate σ- or π-allylmetal complex. A number of transition metals such as palladium,[3] nickel,[4] copper,[5] iron,[6] molybdenum,[7] and tungsten[8]

Scheme I



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are known to catalyze the reaction between an allylic substrate and a nucleophile (Scheme I). Control of the regiochemistry of these reactions is a challenging problem in organic synthesis, and several studies have dealt with this matter.[3,8-14]

The reaction of allylic substrates with dialkylcuprates,[15] or Grignard reagents in the presence of a copper catalyst,[5,12-16] is a useful and efficient method for the formation of new C–C bonds. A number of investigations have been devoted to the stereo- and regiocontrol of this reaction. By the use of different organocopper reagents and/or different leaving groups a certain degree of stereo- and regiocontrol has been obtained in the stoichiometric reactions.[11,17]

Regiocontrol in copper-catalyzed Grignard reactions of allylic substrates has also been studied but to a lesser extent.[12-14] Calo and co-workers[12a] found that a change from ether to THF–ether (2:1) reversed the regiochemistry in CuI-catalyzed butylmagnesium bromide coupling with a primary allylic benzthiazol-2-thiol from 97% γ to 95% α. High γ-selectivity in copper-catalyzed Grignard couplings with allylic pivalates was observed by Goering[13] when CuCN was employed as catalyst. We recently obtained a dual regiocontrol in copper-catalyzed Grignard reactions with primary allylic acetates when Li_2CuCl_4 was used as catalyst.[14] It was found that slow addition of the Grignard reagent and high temperature favored γ-substitution whereas fast addition and low temperature favored α-substitution. A catalytic mono- or dialkylcopper species, respectively, was inferred to account for the results. Because of the great utility of these reactions in organic synthesis we have undertaken a more thorough study of the factors governing the regiochemistry of copper-catalyzed Grignard reactions with allylic substrates.

Results

A. Copper-Catalyzed Reactions of Allylic Acetates. Allylic acetates are starting materials frequently used in copper-catalyzed Grignard couplings. It is interesting to note that the catalytic organocopper intermediate, which is present only in a low concentration, reacts faster with the allylic C–O bond than the Grignard reagent reacts with the carbonyl. Thus, in most cases ester cleavage via the latter process is only a minor side reaction.

1. Li_2CuCl_4-Catalyzed Reactions. The aim of our study has been to develop a full regiocontrol so that the reaction can be directed towards either α- or γ-substitution. From stoichiometric studies on reactions of allylic substrates with organocopper reagents it is evident that monoalkylcopper compounds favor γ-substitution.[11,18] The dialkylcopper reagents, on the other hand (cf. Gilman cuprate, R_2CuLi), show a preference for α-substitution with primary substrates,[5,11a,b,19] but often no selectivity with cyclic substrates.[15c] The approach was therefore to try to generate these different organocopper species in copper-catalyzed Grignard couplings of primary allylic acetates by variation of reaction conditions.

The catalyst Li_2CuCl_4 is commonly employed in coupling reactions between Grignard reagents and alkyl halides.[20,21] It is convenient to use since it is soluble in most solvents and is rapidly reduced to a copper(I) salt by the Grignard reagent even at −78 °C.[20a] Reaction of this Cu(I) salt with the Grignard reagent is expected to generate an organocopper complex, which may be either a mono- or dialkylcopper species. We have identified four different factors that are of importance for the nature of the catalytic species and hence the regiochemistry: (i) the addition time of the Grignard reagent, (ii) the reaction temperature, (iii) the amount of catalyst, and (iv) the reactivity of the allylic substrate.

Four different primary allylic acetates were studied. Acetate **1** was allowed to react with *n*-BuMgBr in THF at −30 °C in the

Table I. Li_2CuCl_4-Catalyzed Reaction of **1** with *n*-BuMgBr[a]

entry	addition time of *n*-BuMgBr, min	mol % of Li_2CuCl_4	product distribution,[b,c] % **2**	**3**
1	2	2	75	25
2	20	2	62	38
3	40	2	53	47
4	20	5	23	77
5	40	5	13	87

[a] The reactions were performed in THF at −30 °C by adding the Grignard reagent to a homogeneous solution of **1** and the catalyst. [b] The ratio between **2** and **3** was determined by ^1H NMR spectroscopy. The isolated yields of **2** and **3** were in the range 75–90%.

Table II. Li_2CuCl_4-Catalyzed Reaction of **4** with *n*-BuMgBr

entry	addition time of *n*-BuMgBr, min	*T*, °C	mol % of Li_2CuCl_4	product distribution,[b,c] % **5**	**6**
1	1.5	−30	2	96	4
2	40	−30	2	82	18
3	40	−30	2	75	25
4	20	0	5	44	56
5	40	0	5	38	62
6	150	0	5	14	86

[a] The reactions were performed in THF by adding the Grignard reagent to a homogeneous solution of **4** and the catalyst. [b] The ratio between **5** and **6** was determined by ^1H NMR spectroscopy. [c] The isolated yields of **5** + **6** were in the range 73–93%.

Table III. Li_2CuCl_4-Catalyzed Reaction of **7** with *n*-BuMgBr[a]

entry	addition time of *n*-BuMgBr	*T*, °C	mol % of Li_2CuCl_4	product distribution,[b,c] % **8**	**9**
1	4 min	−70	2	>99	<1
2	3 h	0	5	50	50
3	30 h	0	10	15	85

[a] The reactions were performed as in Table II. [b] The ratio of **8** and **9** was determined by ^1H NMR spectroscopy. [c] The isolated yields of **8** + **9** were in the range 75–85%.

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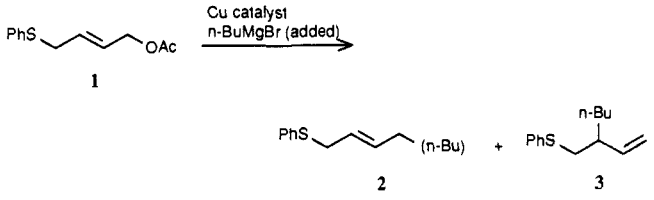
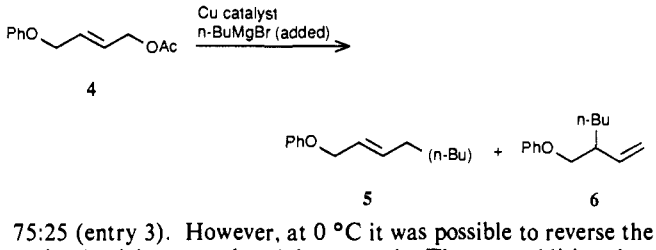
presence of catalytic amounts of Li_2CuCl_4. With an addition time of 2 min and 2 mol % of catalyst, the α-substitution product **2** predominates (Table I, entry 1). If the addition time is increased,



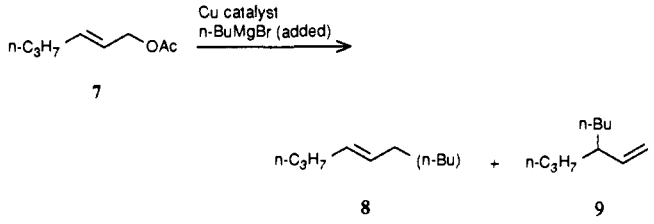
keeping the amount of catalyst constant, the γ-product **3** increases (entries 2 and 3). An increased amount of catalyst favors γ-alkylation, and with 5 mol % Li_2CuCl_2 and 40 min addition time the ratio **2**:**3** was 13:87 (entry 5).

With the less reactive substrate **4**, fast addition of the *n*-BuMgBr (1.5 min) at −30 °C, using 2 mol % of catalyst, gave essentially only α-product **5**, α:γ being 96:4 (Table II, entry 1). Increasing the addition time to 40 min and the catalyst to 5 mol %, maintaining the temperature, only changed the α:γ ratio to



75:25 (entry 3). However, at 0 °C it was possible to reverse the regioselectivity toward mainly γ-attack. Thus, an addition time of 150 min at 0 °C (5 mol % catalyst) produced **5** and **6** in a ratio of 14:86 (entry 5).

The substrates **1** and **4** have a heteroatom in the other allylic position, which may have an influence on the regioselectivity. It was therefore of interest to study an allylic acetate without this heteroatom. Reaction of **7** with *n*-BuMgBr at low temperature gave only product **8** via α-substitution (Table III, entry 1). This



regioselectivity has previously been observed for similar primary allylic acetates.[5a] For **7** the γ-substitution was less favored than for **1** and **4**, and with 3 h addition time of the Grignard reagent at 0 °C, **8** and **9** were still formed in a ratio of 1:1 (Table III). To obtain predominantly the γ-product from **7** it was necessary to use 10 mol % of Li_2CuCl_4 and an addition time of 30 h at 0 °C (entry 3). With geranyl acetate **10** it was even more difficult to reverse the α-substitution toward γ. A low temperature and short addition time afforded α-product **11**. With an addition time of 30 h at 0 °C with 10 mol % of catalyst the ratio of **11** to **12** was 40:60.

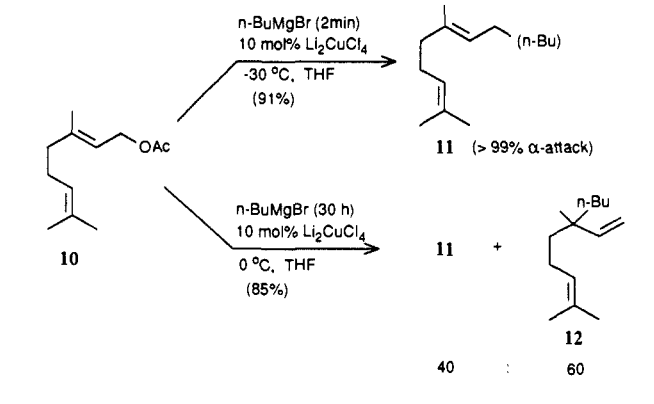


Table IV. CuCN-Catalyzed Reaction of **4** with *n*-BuMgBr[a]

entry	solvent	addition time of *n*-BuMgBr, min	*T*, °C	product distribution,[b,c] % **5**	**6**
1	THF	2	−78	100	0
2	THF	20	0	17	83
3	ether	3	20	8	92

[a] The reactions were performed in the appropriate solvent with 10 mol % of CuCN. [b] Ratio **5**:**6** determined by ^{1}H NMR. [c] Isolated yields of **5** + **6** were in the range 67–80%.

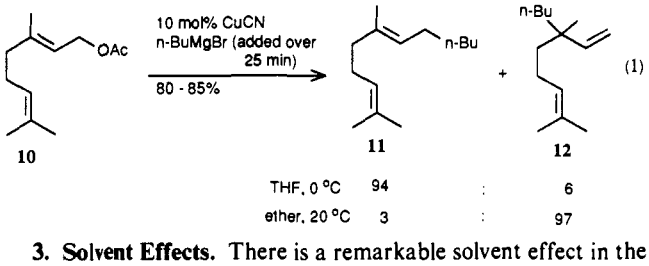
Table V. CuCN-Catalyzed Reaction of **7** with *n*-BuMgBr[a]

entry	solvent	addition time of *n*-BuMgBr	*T*, °C	product distribution,[b,c] % **8**	**9**
1	THF	25 min	0	99	1
2	THF	3 h	0	99	1
3	ether	2 min	−78	38	62
4	ether	1.5 h	0	3	97
5	ether	3.5 h	0	0	100

[a] The reactions were performed as in Table IV. [b] Ratio **8**:**9** determined by ^{1}H NMR. [c] Isolated yields of **8** + **9** were in the range 75–85%.

2. CuCN-Catalyzed Reactions. Goering found a high γ-selectivity in the reaction of allylic pivalates when copper cyanide was used as catalyst.[13a] In connection with our studies on Li_2CuCl_4-catalyzed reactions[14] we decided to study CuCN-catalyzed reactions of some primary allylic acetates. Reaction of **4** with *n*-BuMgBr in THF at −78 °C, using CuCN as the catalyst, afforded only the α-product **5** (entry 1, Table IV). When the reaction temperature was raised to 0 °C and the addition time was prolonged to 20 min, the γ-product predominated, and now **5** and **6** were formed in a ratio of 17:83 (entry 2). When the same reaction was run in ether at 20 °C (entry 3) the ratio **5**:**6** was 8:92. Thus, by variation of the addition time and reaction temperature it is possible to reverse the regioselectivity also for the CuCN-catalyzed reaction (entries 1 and 2). Previously only the highly γ-selective aspect of the CuCN-catalyzed reaction had been discussed.[13a]

With the less reactive substrate **7** it was not possible to obtain γ-substitution in THF with CuCN as catalyst. Addition of *n*-BuMgBr over 3 h at 0 °C still afforded only α-product **8** (Table V, entry 2). The same reaction in ether was more γ-selective. Reaction of **7** with *n*-BuMgBr in the presence of CuCN at −78 °C in ether gave **8** and **9** in a ratio of 38:62 (entry 3). With a longer addition time and a higher temperature (0 °C) the γ-product is exclusively formed. From Table V it is evident that also in ether the addition time and reaction temperature will affect the regiochemical outcome for the CuCN-catalyzed Grignard reaction of an allylic carboxylate. Finally, the CuCN-catalyzed reaction of **10** with *n*-BuMgBr was directed toward either α-substitution (**11**) or γ-substitution (**12**) by changing the reaction conditions (eq 1).



3. Solvent Effects. There is a remarkable solvent effect in the CuCN-catalyzed Grignard reaction with allylic acetates (Tables IV and V; eq 1). In THF, **7** gave only α-product **8** with *n*-BuMgBr, but in ether the same reaction produced only the γ-product **9** (Table V, entries 2, 4, and 5). Except for the change in solvent the reaction conditions are unchanged. Also, as shown in eq 1 a change in solvent from THF to ether completely reversed the ratio **11**:**12** from 94:6 to 3:97. A similar solvent effect was

Table VI. Copper-Catalyzed Reaction of Allylic Acetates in *n*-BuMgBr in the Presence of Additives[a]

entry	substrate	addition time of *n*-BuMgBr	*T*, °C	additive (equiv)	product[b] α	product[b] γ
1	**7**	3.5 h	0	BF_3 (0.1)	**8** (61)	**9** (39)
2	**7**	3.5 h	0	BF_3 (1.5)	**8** (39)	**9** (61)
3	**7**	3.5 h	0	BF_3 (5)	**8** (11)	**9** (89)
4	**7**	3 h	0	BEt_3 (1.5)	**8** (18)	**9** (82)
5	**7**	3 h	0	SMe_2 (0.1)	**8** (88)	**9** (12)
6	**7**	2 min	−78	SMe_2 (0.1)	**8** (100)	**9** (0)
7	**1**	5 h	0	BF_3 (0.4)	**2** (5)	**3** (95)
8[c]	**1**	2 min	−78	SMe_2 (0.1)	**2** (84)	**3** (16)

[a] Except for entry 8, 10 mol % of Li_2CuCl_4 was used as catalyst. The reactions were performed in THF by adding the Grignard reagent to a solution of the allylic acetate, the catalyst, and the additive. [b] Relative yields given in parentheses. Total yields were in the range 55–100%. [c] 10 mol % of CuCN was used.

observed by Calo and co-workers,[12a] who noticed that CuI-catalyzed reaction of primary allylic benzthiazol-2-thiol with *n*-BuMgBr gave 95% α-substitution in THF–ether (2:1) but 95–97% γ-substitution in ether. For stoichiometric cuprates it was also found that the relative amount of α-attack is higher in THF than in ether.[15b]

The solvent effect on the Li_2CuCl_4-catalyzed reactions of allylic acetates with *n*-BuMgBr was less dramatic. For example reaction of **7** with *n*-BuMgBr (added over 1.5 h) in ether catalyzed by Li_2CuCl_4 (10 mol %) afforded **8** and **9** in a ratio of 84:16. The same reaction with **1** (0 °C, 1 h addition time of *n*-BuMgBr) gave **2** and **3** in a ratio of 44:56.

4. Effects of Additives. The reactivity of cuprates can be changed by certain additives such as Lewis acids or Lewis bases.[22] Stoichiometric organocopper reactions with allylic substrates become more γ-selective in the presence of BF_3 or trialkylboranes.[11b,23,24] Thus, *n*-BuCu·BF_3 was found to give γ-substitution with both allylic chlorides and allylic alcohols.[11b,23] To our knowledge the effect of additives in the copper-catalyzed Grignard coupling with allylic substrates has not been studied. The addition of a catalytic amount of BF_3 had a minor effect on the copper-catalyzed reaction of **7** with *n*-BuMgBr (Table VI, entry 1). Increasing the amount of BF_3 increased the relative amount of γ-product, and in the presence of 5 equiv of BF_3 the ratio **8**:**9** was 11:89. This indicates that there is a weak interaction or a low reactivity between BF_3 and the catalytic intermediate. Apparently an excess of BF_3 is needed to obtain the desired organocopper–BF_3 complex. The use of 1.5 equiv of BEt_3 also gave predominantly γ-product, **8**:**9** being 18:82.

Another additive often used in organocopper reactions is Me_2S. The use of Me_2S in the copper-catalyzed cross coupling of allylic acetates with Grignard reagents favored α-substitution (Table VI, entries 5 and 7). An advantage with the use of Me_2S is that ester cleavage of the acetate by the Grignard reagent is inhibited. Thus **7** gave a quantitative yield of **8** in the presence of 0.1 equiv of Me_2S.

B. Copper-Catalyzed Reactions of Allylic Chlorides and Allylic Sulfones. Allylic chlorides are highly reactive substrates in organocopper reactions. Although there are several studies on stoichiometric organocopper reactions with allylic chlorides,[11b,23b,25] very few mechanistic studies exist for the corresponding copper-catalyzed Grignard couplings with allylic chlorides. However, the latter reaction has been used in organic synthetic transformations.[26]

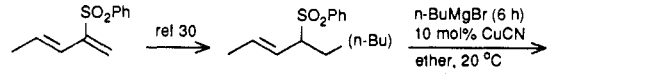
Table VII. Catalytic and Stoichiometric Copper Reactions with Allylic Chlorides[a]

entry	chloroacetate	reagent	T °C	products[b] α	products[b] γ	% yield[c]
1		Me_2CuLi	0	 **13** 83	 **14** 17	80
2		$n\text{-}Bu_2CuLi$	0	 **15** 29	**16** 71	80
3		n-BuMgBr[d]/ Li_2CuCl_4[e]	−20	**15** 22	**16** 78	85
4		$n\text{-}Bu_2CuLi$	0	 **17** 17	 **18** 83	82[f]
5		n-BuMgBr[d]/ Li_2CuCl_4[g]	−40	**17** 5	**18** 95	98[f]

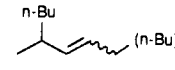
[a] All reactions were performed in THF. [b] The ratio between isomers was determined by ^1H NMR spectroscopy. [c] Isolated yield. [d] The Grignard reagent was added over 20 min. [e] 2 mol % of Li_2CuCl_4 was used. [f] Only the trans isomer could be detected in each case (>98% trans). [g] 10 mol % of Li_2CuCl_4 was used.

We studied the copper-catalyzed reactions with two 1-chloro-4-acetoxy-2-alkenes. These chloroacetates are useful building blocks readily available from the corresponding 1,3-dienes.[27] We found that it was possible to selectively displace the chloride in a copper-catalyzed Grignard reaction without touching the acetate. A few examples of organocopper reactions with chloroacetates are given in Table VII. In most cases the allylic chloride showed a preference for γ-substitution. The highly regioselective anti γ-substitution of the allylic chloride in 1-chloro-4-acetoxy-2-cycloalkenes (cf. entry 5) was recently applied to the formal total synthesis of perhydrohistrionicotoxin.[28] The anti stereochemistry in the S_N2' displacement of chloride to give **18** (entry 5) is consistent with the stereochemistry observed with other leaving groups in organocopper reactions.[1,11b,15c,d,29,30]

Allylic sulfones are known to react with Grignard reagents in the presence of a copper catalyst.[16,29] We decided to study the regiochemistry of this reaction in connection with the allylic acetates and chlorides. Reaction of allylic sulfone **19**[30] with *n*-BuMgBr in the presence of catalytic amounts of CuCN resulted



19



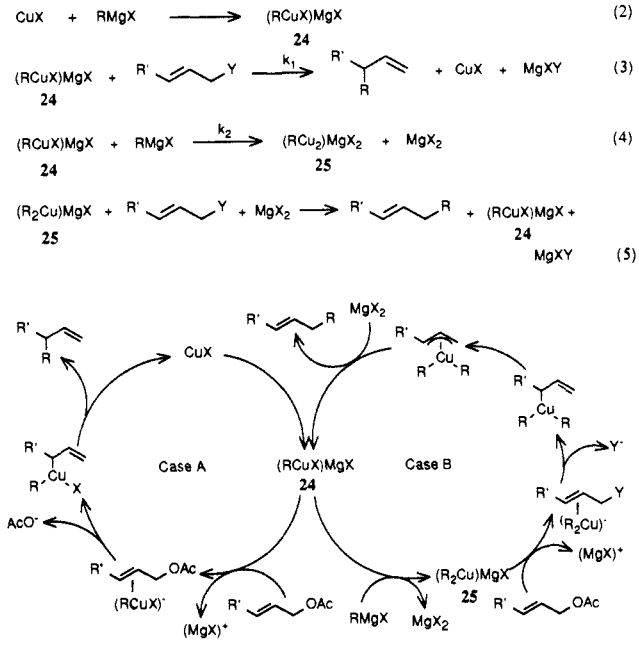
20

in a highly regioselective γ-substitution (>99% γ-selective) to give **20**. The ^1H NMR spectrum of the product olefin revealed an E/Z ratio of 60/40. A similar regioselectivity was observed by Trost in a CuCN-catalyzed Grignard coupling of a secondary allylic sulfone.[29,31]

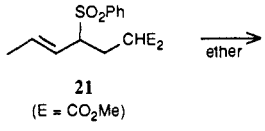
Reaction of allylic sulfone **21**[30] with *n*-BuMgBr catalyzed by CuCN afforded γ- and α-products **22** and **23** in a ratio of 86:14. A longer addition time did not change the regioselectivity significantly. A change of catalyst to Li_2CuCl_4 increased the relative amount of α-product and now a 57:43 mixture between the γ- and α-product was formed. A higher selectivity for the α-product

(22) (a) Lipshutz, B. H.; Ellsworth, B. H.; Siahaan, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 1351. (b) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.
(23) (a) Yamamoto, Y.; Maruyama, K. *J. Organomet. Chem.* **1978**, *156*, c. 59. (b) Maruyama, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1977**, *99*, 8068.
(24) Miyaura, N.; Itoh, M.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2199.
(25) Van Mourik, G. L.; Pabon, H. J. J. *Tetrahedron Lett.* **1978**, 2705.
(26) (a) Derguini-Boumechal, F.; Lorne, R.; Linstrumelle, G. *Tetrahedron Lett.* **1977**, 1181. (b) Schmid, M.; Gerber, F.; Hirth, G. *Helv. Chim. Acta* **1982**, *65*, 684. (c) Ohbe, Y.; Matsuda, T. *Tetrahedron* **1973**, *29*, 2989.
(27) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.
(28) Tanner, D.; Sellén, M.; Bäckvall, J. E. *J. Org. Chem.* **1989**, *54*, 3374.
(29) Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 5216.
(30) Bäckvall, J. E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396.
(31) In this case the authors report that only the *E*-isomer of the olefin is formed.[29]

Scheme II



(85% α) was obtained when the preformed Gilman cuprate was used.



	22		23
n-CuMgBr/CuCN(10%) 30 min/20 °C	86[a]	:	14
n-BuMgBr/CuCN(10%) 3 h/20 °C	87[b]	:	13
n-BuMgBr/Li_2CuCl_4(10%) 3 h/20 °C	57[c]	:	43
n-Bu_2CuLi, 30 min, 0 °C	15[d]	:	85

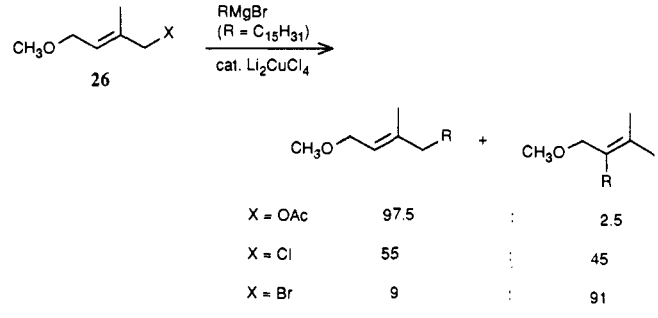
a. E/Z = 2.2/1 b. E/Z = 1.7/1 c. E/Z = 3.2/1 d. E/Z not determined

Discussion

A likely mechanism for the dual regiocontrol in the Li_2CuCl_4-catalyzed Grignard reactions with the different allylic acetates is shown in Scheme II.[32] It is well-known that Li_2CuCl_4 is rapidly reduced in situ by the Grignard reagent to give a copper(I) salt even at −78 °C.[20a] Reaction of 1 equiv of the Grignard reagent with this copper(I) salt produces the monoalkylcopper species **24** (eq 2). Now, there are two possibilities. The catalytic intermediate **24** can react with the allylic substrate (eq 3, case A) or it can react with another molecule of the Grignard reagent to give the dialkylcopper species **25** (eq 4, case B).[33] It is known in the literature that monoalkylcopper complexes preferentially give γ-alkylation of allylic substrates.[1,11,12b,13,18,24,29] whereas dialkylcuprates favor α-alkylation at least with primary allylic substrates.[1,11a,b,12b,15,19] Case A occurs when the Grignard reagent is added slowly and/or if $k_1 > k_2$. In order to keep **24** as the major catalytic species the Grignard reagent must not be added faster than the rate of the left catalytic cycle (Scheme II), i.e. the rate of eq 3. A higher temperature, more catalyst, and a substrate reacting rapidly with **24** will speed up the rate of the left catalytic cycle and hence favor the γ-substitution.

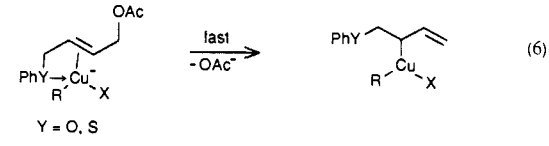
The second case (case B) will occur if the Grignard reagent is added rapidly and/or if $k_2 > k_1$. In this case, **24** is converted to the dialkylcopper complex **25** faster than it reacts with the allylic substrate. A low temperature, low concentration of copper catalyst, and low concentration of the allylic substrate will depress the reaction according to eq 3 and favor formation of **25** (eq 4).

In accordance with the mechanism depicted in Scheme II the more reactive allylic chlorides give a high degree of γ-substitution in copper-catalyzed Grignard reactions (cf. Table VII). A similar observation was reported by Schmid et al.,[26b] who found that reaction of **26** with X = OAc gave predominantly α-substitution whereas a change of X to chloride and bromide drastically increased the γ-substitution. The reactivity order of the allylic



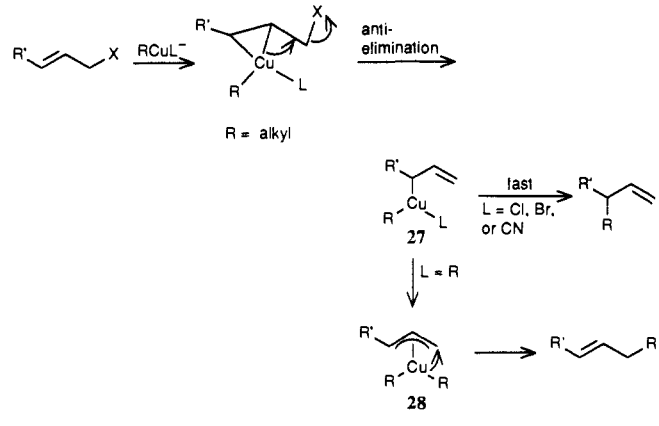
X = OAc	97.5	:	2.5
X = Cl	55	:	45
X = Br	9	:	91

acetates in our study, i.e. **1** > **4** > **7**, can be explained by coordination to the heteroatom in **1** and **4**, which would lead to a fast oxidative addition (eq 6). Rate enhancement by heteroatom-assistance has recently been observed in dialkylcuprate reactions with secondary tosylates.[34]



(6)

Another question of general interest in organocopper reactions is why a monoalkylcopper species has such a high propensity for γ-attack. Oxidative addition of the organocopper(I) complex is generally assumed[11d,13a] to give the σ-allyl intermediate **27**. Now, if L is an electron-withdrawing group such as a halide or cyanide, reductive elimination is expected to be fast.[35] On the other hand, if L is another alkyl group, reductive elimination would be slower and allow **27** to rearrange to **28**. The rearrangement of **27** to **28** would have to be fast since the *E* double bond stereochemistry



is conserved in the reactions of **1** to **2**, **4** to **5**, and **7** to **8**. Conservation of the geometry of the double bond in α-attack on both *E* and *Z* primary allylic acetates (including **10**) in organocopper

(32) The involvement of π-allyl- and σ-allylcopper complexes in these reactions has previously been discussed by Goering.[11d,13a]

(33) (a) The species **24** and **25** are only used as models for the major catalytic intermediates and higher order cuprates may ver well be formed.[33b] (b) Lipzhutz, B. H. *Tetrahedron* **1984**, *40*, 5005.

(34) Hanessian, S.; Thavonekham, B.; DeHoff, B. *J. Org. Chem.* **1989**, *54*, 5831.

(35) It is known that electron-withdrawing ligands accelerate reductive elimination: Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3350, 3360. See also: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

reactions has previously been demonstrated,[5a,11a] although it was later shown that in some cases loss of double bond stereochemistry occurs.[11e]

The dramatic effect of the solvent on regioselectivity in the CuCN-catalyzed cross-coupling reaction of allylic acetates with Grignard reagents is remarkable. A likely explanation is that in ether the predominant active catalytic species is RCu(CN)MgX whereas in THF also higher order cyanocuprates[22] operate. This could be because either the equilibria between an ordinary cyanocuprate and a higher order cyanocuprate differ in the two solvents[36] or the higher order magnesium cuprates are soluble in THF but not in ether.

Concluding Remarks

In this paper we have shown that it is possible to control the regiochemistry of copper-catalyzed cross coupling between Grignard reagents and allylic compounds. By variation of the reaction conditions different active catalytic intermediates are generated, which show different regioselectivity. The major catalytic intermediates are suggested to be monoalkyl- and dialkylcopper complexes, which give γ- and α-attack, respectively, on primary allylic compounds.

It is important to note that a common intermediate is frequently assumed in copper-catalyzed Grignard coupling reactions. In the present work we have shown that even if the same catalyst, solvent, substrate, and reagent are used, a slight variation of the reaction conditions may lead to a change of the active catalytic species.

Experimental Section

General. IR spectra were obtained on neat samples with a Perkin-Elmer 1600 (FTIR) spectrometer, and only the strongest/structurally most important peaks (ν_{max}, cm^{-1}) are reported. ^1H NMR spectra were obtained at 300 MHz (Varian 300XL) or 200 MHz (Varian 200 Gemini) with $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 75 or 50 MHz for $CDCl_3$ solutions. GLPC analyses were performed with a Varian 3400 capillary gas chromatograph with a flame ionization detector. To obtain reproducible addition times of the Grignard reagent, a syringe pump (Sage Instruments, Model 355) was used. When necessary, solvents were dried and distilled under nitrogen with use of standard procedures, while reaction flasks were oven-dried (140 °C) before use. Merck silica gel (230–400 mesh) was used for flash chromatography. (*E*)-2-Hexen-1-ol, geraniol, and 1,3-cyclohexadiene were purchased from Aldrich Chemical Co. and were used without further purification.

Preparation of Starting Materials. (*E*)-1-Acetoxy-4-(phenylthio)-2-butene (1) was prepared according to a literature procedure[37] (i.e. reaction of the corresponding chloroacetate with thiophenol, K_2CO_3, and NaI in refluxing acetone).

(*E*)-1-Acetoxy-4-(phenyloxy)-2-butene (4) was prepared in 88% yield according to the same method as above except that thiophenol was replaced by phenol. IR 2932, 1746, 1599, 1494, 1080, 969, 755 cm^{-1}; ^1H NMR δ 7.37–7.22 and 7.03–6.87 (m, 5 H, Ar), 5.97 (m, 2 H, olefinic), 4.60 (m, 2 H, allylic), 4.52 (m, 2 H, allylic), 2.09 (s, 3 H, OAc); ^{13}C NMR δ 170.79, 158.52, 129.50, 129.32, 127.18, 120.95, 114.61, 67.22, 63.90, 20.59. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.8; H, 6.7.

(*E*)-2-Hexen-1-yl acetate (7) and geranyl acetate (10) were prepared from the corresponding alcohols with use of standard conditions (acetic anhydride, pyridine).

(*E*)-1-Acetoxy-4-chloro-2-butene and 1-acetoxy-4-chloro-2-cyclohexene were prepared from 1,3-butadiene and 1,3-cyclohexadiene according to a literature procedure.[27]

Allylic sulfones **19** and **21** were prepared according to a literature procedure.[30]

General Procedure for Copper-Catalyzed Grignard Reactions with Allylic Acetates. Allylic acetate (1 mmol) and copper salt (0.02–0.1 mmol) were mixed in a dry ethereal solvent (5 mL) under an N_2 atmosphere and stirred at the temperature indicated in the tables. *n*-BuMgBr (0.4M, 1.5 mmol), in the same solvent as above, was added dropwise from a gas-tight syringe connected to a syringe pump during a time indicated (Tables I–VI). After the addition was complete the reaction was stirred an extra 0.5–1 h at the same temperature and then quenched with saturated NH_4Cl(aq) (10 mL), except when the reaction was performed at −78 °C. In the latter case, the reaction mixture was allowed to slowly warm to 0 °C and then quenched. After separation of the two layers and extraction of the water phase with ether (3 × 5 mL), the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude material obtained was eluted with ether through a short silica gel column. After removal of the solvent this afforded a clear colorless oil of alkylated product with α:γ ratios depending on the reaction conditions and yields varying between 60 and 100%. The details regarding the reaction conditions are given in the tables, and characterizations of products are given below.

Copper-Catalyzed Grignard Reaction with Allylic Chlorides. Reaction of 4-Acetoxy-1-chloro-2-cyclohexene. 4-Acetoxy-1-chloro-2-cyclohexene (87 mg, 0.5 mmol) and Li_2CuCl_4 (11 mg, 0.05 mmol) were mixed in THF (2.5 mL) under an N_2 atmosphere and stirred at −40 °C. A THF solution of *n*-BuMgBr (0.5 M, 1.1 mL) was added dropwise during 20 min from a gas-tight syringe connected to a syringe pump. After the addition was complete, the reaction was stirred an extra hour and then quenched with saturated NH_4Cl(aq) (5 mL). After separation of the two layers and extraction of the water phase with ether (3 × 5 mL), the combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude material obtained was eluted with ether through a short silica gel column. After removal of the solvent this afforded 96 mg (98%) of a clear colorless oil of the alkylated products **17** and **18**, in a 95:5 ratio. For spectral data see below.

Copper-Catalyzed Grignard Reaction of Allylic Sulfones 19 and 21. The same procedure was applied as in the reactions with allylic acetates (see above). Detailed reaction conditions for each case are given in the charts in the text. Characterization of the products are given below.

Characterization of Products. Unless otherwise specified spectral data are recorded on one pure isomer. In a few cases it was not possible to obtain one single isomer, and in those cases the spectra are recorded from a mixture of isomers (indicated in each case).

(*E*)-1-(Phenylthio)-2-octene (2):[38] ^1H NMR δ 7.37–7.11 (m, 5 H, Ar), 5.54 (dt, J = 15.5, 5.5 Hz, 1 H, H3), 5.47 (dt, J = 15.5, 5.5 Hz, 1 H, H2), 3.51 (d, J = 4.8 Hz, 2 H, H1), 1.98 (m, 2 H, H4), 1.38–1.05 (m, 6 H, three methylenes in chain), 0.85 (br t, 3 H, Me); ^{13}C NMR δ 136.41, 134.79, 129.98, 128.81, 126.16, 124.92, 36.38, 32.07, 28.68, 22.31, 13.82.

3-((Phenylthio)methyl)-1-heptene (3): ^1H NMR δ 5.64 (ddd, J = 17, 11, 8.5 Hz, 1 H, H3), 5.06 (dd, J = 9, 2 Hz, 1 H, $H4_{cis}$), 5.03 (dd, J = 17, 2 Hz, 1 H, $H4_{trans}$), 2.92 (dd, J = 6.8, 1.5 Hz, 2 H, H1), 2.30 (m, 1 H, H2), 1.42–1.11 (m, 6 H, three methylenes in chain), 0.87 (br t, 3 H, Me).

(*E*)-1-(Phenyloxy)-2-octene (5):[39] ^1H NMR δ 7.35–7.21 and 7.00–6.87 (m, 5 H, Ar), 5.83 (dt, J = 15, 6.5 Hz, 1 H, H3), 5.65 (dt, J = 15, 6.5 Hz, 1 H, H2), 4.48 (d, J = 5.5 Hz, 2 H, H1), 2.16–2.01 (m, 2 H, H4), 1.47–1.04 (m, 6 H, three methylenes in chain), 0.89 (t, J = 6.5 Hz, 3 H, Me); ^{13}C NMR δ 158.93, 135.96, 129.52, 128.84, 120.74, 114.81, 68.68, 32.17, 31.24, 28.49, 22.34, 13.84.

3-((Phenyloxy)methyl)-1-heptene (6): ^1H NMR δ 7.34–7.18 and 6.98–6.80 (m, 5 H, Ar), 5.75 (ddd, J = 16, 10, 8 Hz, 1 H, H3), 5.12 (d, J = 16 Hz, 1 H, $H4_{trans}$), 5.10 (d, J = 10 Hz, 1 H, $H4_{cis}$), 3.88 (d, J = 6.5 Hz, 2 H, H1), 2.50 (m, 1 H, H2), 1.48–1.17 (m, 6 H, three methylenes in chain), 0.90 (br t, 3 H, Me).

(*E*)-4-Decene (8) was identified by its spectral data. The *E* stereochemistry was assigned from its ^{13}C NMR spectrum.[40]

3-Propyl-1-heptene (9): ^1H NMR δ 5.51 (ddd, J = 17, 11, 9 Hz, 1 H, H2), 4.93 (dd, J = 10, 2 Hz, 1 H, $H1_{cis}$), 4.91 (dd, J = 17, 2 Hz, 1 H, $H4_{trans}$), 1.94 (m, 1 H, H3), 1.43–1.09 (m, 6 H, three methylenes in chain), 0.95 (br t, 3 H, Me).

(6*E*)-2,6-Dimethyl-2,6-dodecadiene (11):[41] ^1H NMR δ 5.12 (m, 2 H, olefinic), 2.00 (m, 6 H, allylic), 1.69 (s, 3 H, $Me_{vinylic}$), 1.60 (s, 6 H, 2 $Me_{vinylic}$), 1.40–1.20 (m, 6 H, three methylenes in the Bu chain), 0.90 (t, J = 6.6 Hz, 3 H, Me in the Bu chain).

3-Butyl-3,7-dimethyl-1,6-octadiene (12):[42] ^1H NMR δ 5.64 (dd, J = 17.5, 10.5 Hz, 1 H, H1 in ethenyl), 4.91 (dd, J = 11, 1.5 Hz, 1 H, $H2_{cis}$ in ethenyl), 4.82 (dd, J = 17.5, 1.5 Hz, 1 H, $H2_{trans}$ in ethenyl), 1.96 (m, 2 H, H4), 1.63 (s, 3 H, $Me_{vinylic}$), 1.54 (s, 3 H, $Me_{vinylic}$), 1.32–1.04 (m, 8 H, three methylenes in the chain and H5), 0.90 (s, 3 H, Me6), 0.83

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(t, J = 6.5 Hz, 3 H, Me in the chain).

(*E*)-2-Penten-1-yl acetate (13): ^{1}H NMR δ 5.84 (dt, J = 14, 5.5 Hz, 1 H, H3), 5.56 (dt, J = 14, 6 Hz, 1 H, H2), 4.52 (d, J = 6 Hz, 2 H, H1), 2.15-1.98 (m, 2 H, H4), 2.06 (s, 3 H, OAc), 1.01 (s, 3 H, Me). The product was further characterized by hydrolysis to 2-penten-1-ol.[43]

2-Methyl-3-buten-1-yl acetate (14): ^{1}H NMR δ 5.70 (m, 1 H, H3), 5.11 (d, J = 10 Hz, 1 H, $H4_{cis}$), 5.06 (d, J = 17 Hz, 1 H, $H4_{trans}$), 3.97 (d, J = 6 Hz, 2 H, H1), 2.52 (m, 1 H, H2), 2.06 (s, 3 H, OAc), 1.27 (d, J = 6 Hz, 3 H, Me2). The product was further characterized by hydrolysis to 2-methyl-3-buten-1-ol.[43]

(*E*)-2-Octen-1-yl acetate (15)[44] (from a mixture with **16**): ^{1}H NMR δ 5.78 (dt, J = 15.5, 6.5 Hz, 1 H, H3), 5.65-5.53 (m (concealed), 1 H, H2), 4.51 (d, J = 6.5 Hz, 2 H, H1), 2.36 (m, 2 H, H4), 2.06 (s, 3 H, OAc), 1.49-1.18 (m, 6 H, three methylenes in the chain), 0.90 (br t, 3 H, Me).

2-(Ethenyl)hexyl acetate (16): ^{1}H NMR δ 5.60 (m, 1 H, H1 in the ethylene chain), 5.06 (dd, J = 12, 2 Hz, 1 H, $H2_{cis}$ in the ethylene chain), 5.05 (dd, J = 17, 2 Hz, 1 H, $H2_{trans}$ in the ethenyl chain), 3.99 (d, J = 6.5, 2 H, H1), 2.35 (m, 1 H, H2), 2.04 (s, 3 H, OAc), 1.49-1.15 (m, 6 H, three methylenes in the chain), 0.88 (br t, 3 H, Me).

4-*n*-Butyl-2-cyclohexen-1-yl acetate (17) (from a mixture with **18**): ^{1}H NMR δ 5.76 (m, 2 H, olefinic), 5.31 (m, 1 H, H1), 2.12 (m, 2 H, allylic), 2.05 (s, 3 H, OAc), 1.98-1.53 (m, 4 H, H5 and H6), 1.45-1.15 (m, 6 H, three methylenes in the chain), 0.88 (br t, 3 H, Me).

2-*n*-Butyl-3-cyclohexen-1-yl acetate (18): IR 2930, 1735, 1241, 608 cm^{-1}; ^{1}H NMR δ 5.67 (ddd, J = 10, 7, 3 Hz, 1 H, H4), 5.55 (ddd, J = 10, 5, 1.5 Hz, 1 H, H3), 4.78 (ddd, J = 9, 6.7, 3 Hz, 1 H, H1), 2.19 (m, 1 H, H2), 2.11 (m, 2 H, H5), 2.06 (s, 3 H, OAc), 1.94-1.82 (m, 1 H, $H6_{eq}$), 1.77-1.59 (m, 1 H, $H6_{ax}$), 1.48-1.19 (m, 6 H, three methylenes in the chain), 0.90 (br t, 3 H, Me); ^{13}C NMR δ 170.88, 128.58, 126.22, 73.65, 40.14, 32.56, 28.55, 26.12, 23.23, 22.87, 21.40, 13.98. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.188; H, 10.11.

(*E*)-5-Methyl-6-dodecene ((*E*)-20) (from a mixture with (*Z*)-**20**): ^{1}H NMR δ 5.34 (dt, J = 15.5, 6 Hz, 1 H, H7), 5.23 (dd, J = 15.5, 7 Hz, 1 H, H6), 1.99 (m, 3 H, allylic), 1.40-1.12 (m, 12 H, six methylenes in the chains), 0.93 (d, J = 7 Hz, 3 H, Me5), 0.88 (m, 6 H, two Me). The *Z*-isomer (*Z*)-**20** is distinguishable in a mixture with (*E*)-**20** by its peaks at δ 5.10 (dd, J = 10, 10 Hz, 1 H, CHC*H*=) and 2.40.

(*E*)-(4-Methyl-2-octenyl)propanedioic acid dimethyl ester ((*E*)-22) (from a mixture with (*Z*)-**22**): ^{1}H NMR δ 5.38 (dd, J = 15, 6.5 Hz, 1 H, C*H*=), 5.29 (dt, J = 15, 6.5 Hz, 1 H, C*H*=), 3.72 (s, 6, two OMe), 3.47 (m, 1 H, $CH(COOMe)_2$), 2.70-2.52 (m, 2 H, CH_2C=), 2.02 (m, 1 H, H5), 1.36-1.08 (m, 6 H, three methylenes in the chain), 0.91 (d, J = 7 Hz, 3 H, Me), 0.87 (t, J = 5.5 Hz, 3 H, terminal Me). The *Z*-isomer (*Z*)-**22** is distinguishable in a mixture with (*E*)-**22** by its peak at δ 5.24 (m, 2 H, CH=CH).

(*E*)-(2-(1-Propenyl)hexyl)propanedioic acid dimethyl ester (23): Spectral data were in accordance with those previously reported.[30]

Acknowledgment. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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Oxidative Detoxification of Phosphonothiolates

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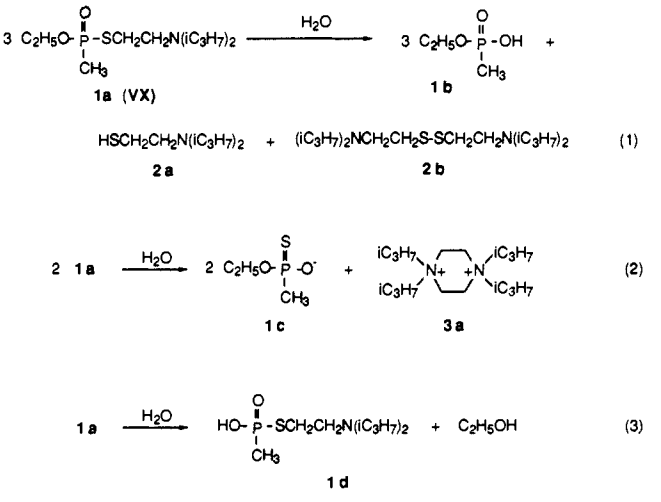
Abstract: The chemical nerve agent *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothiolate (VX) is an unusually selective oxidation substrate. Relative to the thiolo sulfur, the amino nitrogen was a more reactive oxidation site. The oxidation of VX and a phosphonothiolate derivative by a broad range of peroxygen compounds was examined in organic, polar organic, and aqueous solvents. Depending on the oxidant, VX was either unreactive or reactive via one of the following mechanisms: 1. In neutral solvents, the nitrogen was oxidized first to an *N*-oxide, which was stable in aqueous solvents but decomposed by a Cope reaction in organic solvents. 2. After the nitrogen had been oxidized or protonated in an acidic aqueous solvent, the sulfur in the *N*-oxide or the protonated VX was further oxidized to a sulfoxide intermediate, which hydrolyzed immediately. Detoxification can be accomplished by the second mechanism.

Introduction

Most of the toxic organophosphorus esters can be detoxified quickly by hydrolysis in alkaline solutions.[1,2] However, relative to the chloro- or fluorophosphonates [RP(O)(OR')X, X = Cl or F], the hydrolysis of phosphonothiolate esters (X = SR'') is much slower even at very high pH values.[3,4] The estimated half-life for the spontaneous hydrolysis of the nerve agent VX, *O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothiolate (**1a**), was 80 h at 20 °C. In addition, multiple hydrolysis pathways have been reported.[4] As shown in eqs 1-3, VX hydrolyzes via simultaneous cleavage of the P-S, S-C, and P-O bonds to form a series of products. Although both the ethyl methylphosphonic acid (**1b**) and the *O*-ethyl methylphosphonothioic acid (**1c**) are relatively nontoxic, the *S*-[2-(diisopropylamino)ethyl] methylphosphonothioic acid (**1d**) is almost as toxic as VX (see toxicity data in Table I in the Experimental Section). Contrary to the findings by Epstein et al.[4] that VX hydrolyzed via the single reaction path shown in eq 1 at pH values greater than 10, ~22% **1d** and 78% **1b** were produced from the reaction of 0.05 M VX



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