The Effect of Solvent and Copper(I) Precursor on the Regioselectivity in the Cross-Coupling Reaction of Primary Allylic Acetates with Preformed Mono- and Dibutylcuprates

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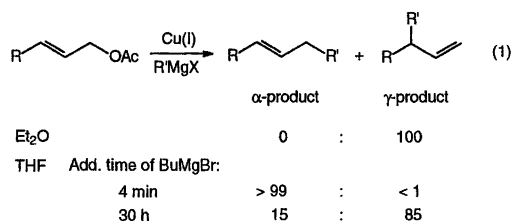
The reactions between preformed organocopper compounds and primary allylic acetates show that the solvent and the copper(I) precursor are important parameters in determining the regioselectivity of the reaction. The organocopper complexes were prepared from different copper(I) salts, such as CuCl, CuBr, CuI and CuCN, and their reactivity both in Et_2O and THF were studied. In THF, monobutylcuprates gave the γ-substituted product whereas the dibutylcuprates afforded the α-substituted product. In Et_2O, cuprates formed from CuCN and CuI gave γ-selective reactions whereas those from CuCl and CuBr resulted in α-selective reactions.

In previous studies,[1] it has been observed that the solvent and temperature as well as the addition rate of a Grignard reagent have a strong influence on the regioselectivity of the copper(I)-catalyzed cross coupling of allylic substrates with Grignard reagents. The regioselectivity in the cross coupling of primary allylic acetates with BuMgBr in the presence of catalytic amounts of CuCN is easily controlled by changing the solvent: use of Et_2O resulted in formation of the γ-product (S_N2') while THF yielded the α-product (S_N2).[1a,c,d,2] In THF it was possible to direct the nucleophile in the cross-coupling reactions regioselectively to either the α- or γ-position by careful choice of reaction conditions [eqn. (1)].[1a] Reaction conditions which favored formation of a dialkylcopper intermediate 'R$_2$CuMgBr' (fast addition of the Grignard reagent, low temperature, low concentration of the catalyst) gave the α-product, whereas reaction conditions favoring the formation of a monoalkylcopper intermedi-

Et₂O / THF table:

	α-product		γ-product
Et_2O	0	:	100
THF	Add. time of BuMgBr:		
	4 min	> 99 :	< 1
	30 h	15 :	85

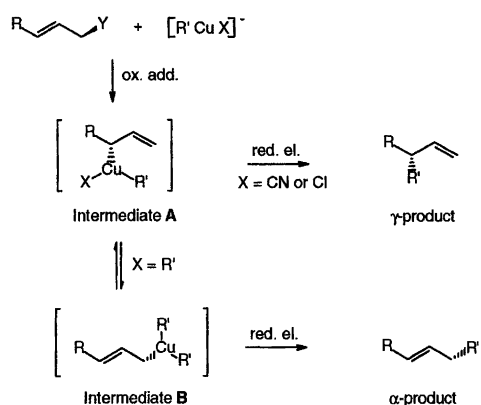† To whom correspondence should be addressed.

ate 'RCu(X)MgBr' (slow addition of the Grignard reagent, increased temperature, increased concentration of the catalyst) led to γ-substitution.[1a,3]

The mechanism for the copper-catalyzed cross-coupling reaction has been studied and discussed in a number of reports.[1–5] It has been proposed that a (σ-allyl)-copper(III) intermediate A is initially formed by oxidative addition of the allylic substrate to the cuprate in an anti S_N2' fashion (Scheme 1).[4] This intermediate can undergo reductive elimination or isomerize to intermediate B. The nature of the ligand X has a profound influence on the rate of reductive elimination and hence on the regiochemical outcome of the reaction. If the non-transferable group X is electron-withdrawing, such as CN^- or Cl^-, reductive elimination will be fast[1a,b,6] and regioselective γ-substitution is observed. On the other hand, if X is alkyl, the initially formed intermediate A isomerizes to intermediate B, presumably via a π-allyl intermediate. Subsequent reductive elimination from B affords the α-product.

The mechanisms (Scheme 1) suggests that a mono-organocuprate [RCuX]$^-$ gives the γ-product while a di-organocuprate [R$_2$Cu]$^-$ forms the α-product.[1a] We have now studied the reaction between preformed mono- and di-butylcuprates and primary allylic acetates in both Et_2O and THF. The results obtained are in accordance with the previously suggested mechanism and also show that the solvent and copper(I) precursor are important factors in determining the regioselectivity.
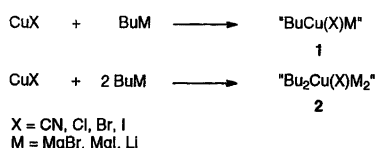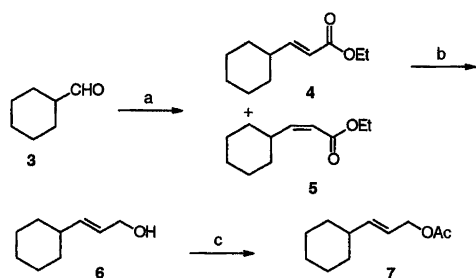
Scheme 1.

Results

The required cuprates **1** and **2** were prepared by mixing a copper(I) salt with various organometallic reagents, RM (Scheme 2).

Scheme 2.

(2E)-3-Cyclohexylpropenyl (**7**) and geranyl acetate (**8**) were chosen as model substrates. The allylic acetate **7** was prepared in three steps from cyclohexanecarbaldehyde (Scheme 3). The Horner–Wadsworth–Emmons re-


Scheme 3. (a) i: n-BuLi, THF, −78 °C, (EtO)$_2$P(O)CH$_2$CO$_2$Et. ii: 0 °C, add **3**, **4**:**5**=92:8, **4** (91%) and **5** (7%). (b) DIBAL-H, CH$_2$Cl$_2$, 0 °C. (c) Acetic anhydride, 10 mol% DMAP, pyridine, CH$_2$Cl$_2$, 0 °C (87% from **4**).

action of cyclohexanecarbaldehyde employing triethyl phosphonoacetate resulted in a mixture of E- and Z-isomers (**4** and **5**) in a ratio of 92:8. The isomers were readily separated by flash chromatography. The α,β-unsaturated ester **4**, isolated in 91% yield, was reduced with DIBAL-H to the allylic alcohol **6**. Subsequent esterification afforded the allylic ester **7**.

In the model reaction, the allylic acetate **7** or **8** was

allowed to react with a preformed mono- or dibutyl-cuprate, **1** or **2**, in Et$_2$O or THF at 0 °C. All cross-coupling reactions were performed employing the same reaction times (120 min) in order to compare the reactivity of the different cuprates. The three possible products formed in the reaction between allylic acetate **8** and **1** or **2** are, cross-coupling products **9** and **10** together with geraniol (**11**); the latter being formed by direct attack of free BuM on the carbonyl carbon [eqn.(2)].
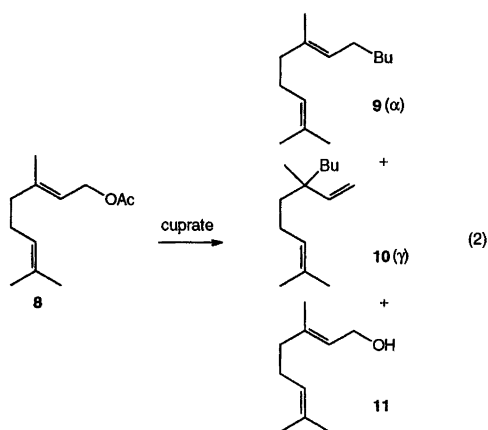
A. CuCN, different organometallic reagents (Table 1, Table 2)

BuMgBr. In Et$_2$O, both 'BuCu(CN)MgBr' **1** and 'Bu$_2$Cu(CN)(MgBr)$_2$' **2** resulted in a γ-selective copper-catalyzed cross-coupling reaction with geranyl acetate (**8**) to give **10** (Table 1, entries 1 and 2). However, the re-activities of the two cuprates were different; **1** reacted more slowly with only 72% conversion in 120 min whereas **2** gave full conversion after the same reaction time with an isolated yield of 87%.

In THF, the reactivity difference between the two cuprates was more accentuated. 'BuCu(CN)MgBr' **1** showed low reactivity towards the allylic acetate **8**, <2% conversion was observed after 120 min, with the only detectable product being γ-substituted **10** (entry 7). If the same reaction was left for 24 h at 0 °C, the conversion increased to 15% but still only the product **10** was formed. Addition of BF$_3$·OEt$_2$ (1–4 equiv.) did not increase the reactivity, rather the reaction rate went down and no product could be detected after 120 min.[7] On the other hand, cuprate **2** was more reactive towards **8** (61% conversion). Furthermore, the reaction gave the α-substituted product **9** regioselectively (α:γ = 99:1) together with geraniol (**11**) (entry 8). The formation of geraniol suggests that free BuMgBr was present in the reaction mixture. In Et$_2$O, no free Grignard reagent appeared to be present since no formation of geraniol was observed. The rate of the reaction with both **1** and **2** was decreased in THF compared with that in Et$_2$O.

The allylic acetate **7** showed similar reactivity and regioselectivity to **8** towards cuprates **1** and **2** in both Et$_2$O and THF [(eqn. (3), Table 2]. In Et$_2$O both cuprates **1**

Table 1. The stoichiometric cross coupling of **8** with preformed mono- and di-butyl cuprates.[a]

| Entry	Reagent	Solvent	Product distribution[b] (%)		Conversion (%)[b]
			9+10:11	**9:10**	**9+10+11**
1	BuCu(CN)MgBr	Et₂O	100: 0	<1:>99	72
2	Bu₂Cu(CN)(MgBr)₂	Et₂O	100: 0	<1:>99	100[c]
3	BuCu(CN)MgI	Et₂O	100: 0	6:94	100[d]
4	Bu₂Cu(CN)(MgI)₂	Et₂O	100: 0	3:97	100[e]
5	BuCu(CN)Li	Et₂O	100: 0	50:50	44
6	Bu₂Cu(CN)Li₂	Et₂O	50:50	68:32	94
7	BuCu(CN)MgBr	THF	100: 0	<1:>99	<2[f]
8	Bu₂Cu(CN)(MgBr)₂	THF	65:35	99:1	61
9	BuCu(CN)MgI	THF	—	—	0
10	Bu₂Cu(CN)(MgI)₂	THF	37:63	88:12	50
11	BuCu(CN)Li	THF	—	—	0
12	Bu₂Cu(CN)Li₂	THF	33:67	100:0	80

[a] The Grignard reagent was added to a slurry of CuCN in Et₂O of THF at −30°C. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0°C and then **8** was added. [b] Determined by ¹H NMR spectroscopy. [c] 87% isolated yield. [d] 85% isolated yield. [e] 87% isolated yield. [f] 24 h reaction time gave 15% conversion into **10**.

Table 2. Solvent effect of the stoichiometric cross coupling of **7** with cuprates **1** and **2** derived from CuCN and BuMgBr.[a]

Entry	Reagent	Solvent	Product distribution[b] (%)		Conversion (%)[b]
			12+13:6	**12:13**	**12+13+16**
1	BuCu(CN)MgBr	Et₂O	100:0	<1:>99	35
2	Bu₂Cu(CN)(MgBr)₂	Et₂O	100:0	2:98	100[c]
3	BuCu(CN)MgBr	THF	—	—	0[d]
4	Bu₂Cu(CN)(MgBr)₂	THF	81:19	98:2	97

[a] The Grignard reagent was added to a slurry of CuCN in Et₂O or THF at −30°C. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0°C and then **7** was added. [b] Determined by ¹H NMR spectroscopy. [c] 92% isolated yield. [d] 24 h reaction time gave 30% conversion **12:13**=9:91.

and **2** reacted with **7** to give **13** regioselectively with 35 and 100% conversion, respectively (entries 1 and 2).
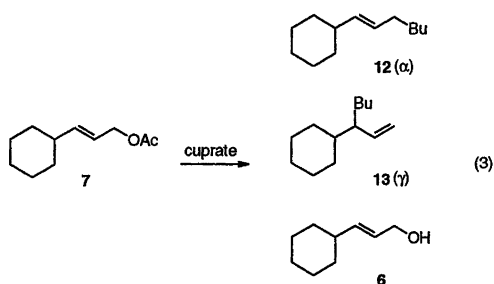
In THF, **1** was unreactive towards **7** and no reaction was observed within 120 min (entry 3). When the reaction time was prolonged to 24 h, **12** and **13** were obtained in a combined yield of 30% in a ratio of 9:91 (**12:13**). On the other hand, reaction with **2** in THF resulted predominantly in the α-substituted product **12** (α:γ = 98:2) together with formation of alcohol **6** (Table 2, entry 4). Again, attack by free Grignard on the ester competes with allylic substitution.

BuMgI. The cross-coupling reaction of geranyl acetate (**8**) in Et₂O with both 'BuCu(CN)MgI' **1** and 'Bu₂Cu(CN)(MgI)₂' **2** resulted in γ-selective substitution reactions to give **10** (Table 1, entries 3 and 4). Full conversion was observed in each case and the isolated yields were 85–87%.

In THF both 'BuCu(CN)MgI' **1** and 'Bu₂Cu(CN)(MgI)₂' **2** derived from *n*-BuMgI were less reactive than those from BuMgBr. Cuprate **1** was completely unreactive and no products could be detected (entry 9). Reaction of **9** in THF afforded α- and γ-products **9** and **10** in a ratio of 88:12 together with a large amount of geraniol (**11**) (entry 10). The conversion was 50% which is slightly lower than that obtained with 'Bu₂Cu(CN)(MgBr)₂' (entry 8).[8]

BuLi. Cuprates 'BuCu(CN)Li' **1** and 'Bu₂Cu(CN)Li₂' **2** in Et₂O were less selective in the coupling with **8** than those obtained from the Grignard reagent and gave 1:1 and 2:1 mixtures of α- and γ-products, respectively (Table 1, entries 5 and 6). Lowering the temperature to −60°C did not increase the selectivity. The lower regioselectivity for lithium cuprates in Et₂O has been observed previously in the stoichiometric cross-coupling of allylic acetates.[4a] In

THF similar reactivity and regioselectivity were observed for both the mono- and di-butylcuprates as observed for the corresponding cuprates formed from the Grignard reagent. The monobutylcuprate 1 was completely unreactive whereas the dibutylcuprate 2 resulted in an α-selective cross-coupling to give 9 together with geraniol (11) (entries 11 and 12).

B. *Different copper(I) precursors. (BuMgBr).* The reactivity and selectivity of cuprates obtained from different copper(I) precursors have previously been investigated in the 1,4-addition reaction to 2-cyclohexenone.[9]

Monobutylcuprate in THF. All the monobutylcuprates 'BuCu(X)MgBr' 1 (X = CN, Cl, Br, and I) formed in THF showed low reactivity in the cross-coupling reaction with geranyl acetate (8) (<2% conversion after 2 h). The reaction of 'BuCu(CN)MgBr' and 'BuCu(Cl)MgBr' with 8, over 24 h, resulted in a slow but γ-selective reaction with 15% conversion in both cases.

Dibutylcuprate in THF. (Table 3) All the dibutylcuprates 'Bu₂Cu(X)(MgBr)₂' 2 (X = CN, Cl, Br, I) gave α-selective cross-coupling reactions with geranyl acetate (8). However, the cyanocuprate 'Bu₂Cu(CN)(MgBr)₂' formed from reaction of one equiv. CuCN and two equiv. BuMgBr afforded, in addition to the α-product 9, geraniol (11), the ratio 9:11 being 65:35 (entry 1). No formation of geraniol (11) was observed with any of the other cuprates formed from the copper(I) halides (X = Cl, Br, I) (entries 2–5).

Monobutylcuprate in Et₂O. (Table 4) The corresponding monobutylcuprates 1 formed from CuCN and CuI with n-BuMgBr in Et₂O were highly γ-selective with a conversion of 72 and 30%, respectively (entries 1 and 4). No geraniol (11) was detected in these reactions. The monobutylcuprates 1 formed from CuCl or CuBr were unreactive and no product formation could be detected (entries 2 and 3).

Table 3. Different Cu(I) salts in the cross-coupling reaction of preformed dibutyl cuprates 'Bu₂Cu(X)(MgBr)₂' with 8 in THF.[a]

Entry	Cu-salt CuX	Product distribution (%)[b]		Conversion (%)
		9+10:11	9:10	
1	CuCN	65:35	99:1	61
2	CuCl · 2LiCl	100:0	>99:<1	100[c]
3	CuCl	100:0	>99:<1	38
4	CuBr	100:0	>99:<1	71
5	CuI	100:0	96:4	80

[a] n-BuMgBr was added to a slurry of CuX in THF at −30°C. The reaction mixture was stirred for 2 h while temperature was allowed to rise to 0°C and then 8 was added. The reaction mixture was stirred for another 2 h. [b] Determined by ¹H NMR spectroscopy. [c] 91% isolated yield.

Table 4. Different Cu(I) salts; the cross-coupling reaction of preformed monobutyl cuprates 'BuCu(X)MgBr' with 8 in Et₂O.[a]

Entry	Cu-salt CuX	Product distribution (%)[b] 9:10	Conversion (%)
1	CuCN	<1:>99	72
2	CuCl	—	0
3	CuBr	—	0
4	CuI	<1:>99	30

[a] n-BuMgBr was added to a slurry of CuX in Et₂O at −30°C. The reaction mixture was stirred for 2 h while temperature was allowed to rise to 0°C and then 8 was added. The reaction mixture was stirred for another 2 h. [b] Determined by ¹H NMR spectroscopy.

Table 5. Different Cu(I) salts; the cross-coupling reaction of preformed dibutyl cuprates 'Bu₂Cu(X)(MgBr)₂' with 8 in Et₂O.[a]

Entry	Cu-salt CuX	Product distribution (%)[b]		Conversion (%)
		9+10+11	9:10	
1	CuCN	100:0	<1:>99	100[c]
2	CuCl	100:0	>99:<1	56
3	CuBr	25:75	>99:<1	52
4	CuI	90:10	6:94	70

[a] n-BuMgBr was added to a slurry of CuX in THF at −30°C. The reaction mixture was stirred for 2 h while temperature was allowed to rise to 0°C and then 8 was added. The reaction mixture was stirred for another 2 h. [b] Determined by ¹H NMR spectroscopy. [c] 87% isolated yield.

Dibutylcuprate in Et₂O. (Table 5) The regioselectivity obtained in the cross-coupling reaction using dibutylcuprates 2 (M = MgBr) in Et₂O is strongly affected by the choice of copper(I) precursor. The cuprate formed from CuCN resulted in a γ-selective cross coupling (entry 1) whereas the cuprate from CuCl afforded an α-selective reaction (entry 2). The cuprate 2 (M = MgBr) from CuBr was also highly α-selective (entry 3) but in this case the major product was geraniol (11) (9:11 = 25:75) which may be due to incomplete cuprate formation. The use of a CuBr·SMe₂ complex gave similar results. Surprisingly, the corresponding cuprate formed from CuI gave a γ-selective coupling (94% γ) together with a small amount of geraniol (entry 4). Cuprate formation from CuI was variable; the γ-selectivity was in the range of 90–100% and formation of geraniol (11) was in the range 0–14%.[10]

Discussion

Several important crystal structure determinations of organocopper compounds have been reported,[11] which show that both lower order (LO, two coordinate, R₂CuM) and higher order (HO, three coordinate, R₃CuM₂)[12e,f] organocuprates can exist in the solid state.[12] Knowledge about the structure of organocuprates in so-
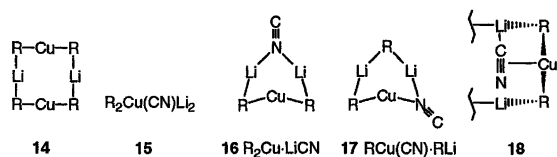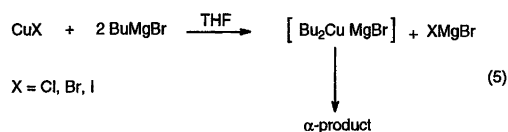
Fig. 1. Structural representation of the LO dimer of R_2CuLi **14**, the HO cyanocuprate **15**, the LO aggregates of organocopper and organolithium reagents, **16** and **17** and the revised structure of the HO cyanocuprate in which the nitrile ligand is incorporated into the cuprate cluster **18**.

lution, on the other hand, still remains unclear. NMR investigations of the cuprate structure in solution have revealed the presence of complex equilibria.[13,14] The early proposal[15] of the simple Gilman cuprate R_2CuLi, as an LO dimer (**14**, Fig. 1) has been confirmed by molecular weight determinations,[13b] NMR spectroscopy[16] and X-ray crystallography.[12c,f–h] Despite intensive studies, the structure of the HO cyanosubstituted copper reagents are less established. In 1981, the concept 'higher order, mixed' copper reagents $R_2Cu(CN)Li_2$ **15** was introduced.[17] These species were shown to display remarkably different chemical (and spectroscopic) properties compared with the Gilman reagents. Over the last four years there has been a discussion in the literature about the actual existence of these HO cyanocuprates.[14,18–20] The structure of the HO cyanocuprate in THF, represented by the formula $R_2Cu(CN)Li_2$[18] has been shown by NMR[14] and EXAFS[19] spectroscopic studies to be better represented by the formula $R_2CuLi \cdot LiCN$ **15**. A molecular orbital study[20] of these cuprates suggests that the compounds are best described as LO Gilman cuprates, complexed by ring formation with 1 mol of either RLi or CNLi rather than as 'HO' cyanocuprates. Two of the proposed structures **16** and **17** are shown in Fig. 1. In a recent paper,[18a] the structure of the HO cyanocuprates was revised and it was proposed that the nitrile ligand probably is incorporated in the cuprate cluster: σ-bond to Li^+ and π-bound to copper (Fig. 1, **18**).

An equimolar mixture of the Grignard reagent and copper(I) halide has traditionally been regarded as the species 'RCu·MgX$_2$'.[21] However, work on the role of salts in cuprate activation makes it reasonable to view these species as halocuprates 'RCu(X)MgX'.[22] Direct cuprate formation is also anticipated in the case of CuCN, owing to the strength of the Cu–CN bond. The formation of a halocuprate in THF, in which the non-transferable group X is electron-withdrawing, explains the formation of the γ-substituted product with the allylic acetates [eqn. (4), cf. Scheme 1]. The reason for the low reactivity of the monobutylcuprates in THF is not clear.
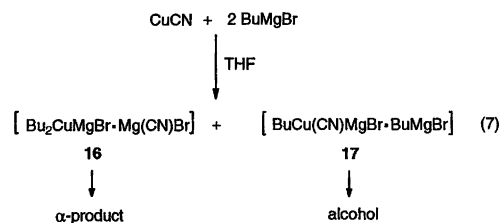
$$CuX + BuMgBr \xrightarrow{\text{THF}} [\text{BuCu(X) MgBr}]$$

$$X = CN, Cl, Br, I \qquad \downarrow \text{slow} \qquad (4)$$
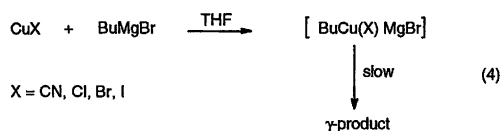
$$\gamma\text{-product}$$

The dialkylcuprates in THF, formed from copper(I) halides, give preferentially the α-substituted product [eqn. (5)]. The formation of geraniol, when CuCN was used as

$$CuX + 2\,BuMgBr \xrightarrow{\text{THF}} [\text{Bu}_2\text{Cu MgBr}] + XMgBr$$

$$X = Cl, Br, I \qquad \downarrow \qquad (5)$$

$$\alpha\text{-product}$$

the copper(I) precursor suggests that free Grignard reagent is present in the reaction mixture. An equilibrium between a LO Gilman-type cuprate and a LO cyanocuprate would explain the presence of free Grignard reagent [eqn. (6)]. The strength of the Cu–CN linkage presumably accounts for the existence of both cuprates. The monobutylcyanocuprate would react with an allylic acetate to give the γ-substituted product. However, since it was shown that equimolar amount of n-BuMgBr and CuCN give a cuprate which shows low reactivity towards allylic acetates (*vide supra*), the dibutylcuprate becomes the reactive species and hence the α-substituted product is obtained.

$$CuCN \xrightleftharpoons{2\,BuMgBr} [\text{BuCu(CN)MgBr}] + BuMgBr$$

$$\updownarrow \qquad (6)$$
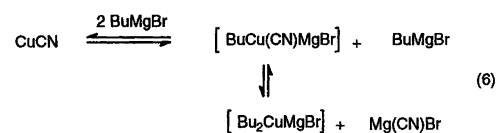
$$[\text{Bu}_2\text{CuMgBr}] + Mg(CN)Br$$

Alternatively, these cuprates may be represented as LO aggregates of organocopper and organomagnesium compounds which has been proposed for the lithium derivatives, i.e., 'Bu$_2$CuMgBr·Mg(CN)Br' **19** or 'BuCu(CN)-MgBr-n-BuMgBr' **20** (cf., **16** and **17**, Fig. 1).[14,19,20] If the cuprate is represented by **20**,[20] one of the two n-Bu moieties is *not* bonded to copper but complexed between the two magnesiums and can thus be regarded as a free Grignard reagent giving rise to alcohol formation. The reagent **19** represents a LO dibutylcuprate and will lead to formation of the α-product [eqn. (7)].

$$CuCN + 2\,BuMgBr$$

$$\downarrow \text{THF}$$

$$[\text{Bu}_2\text{CuMgBr·Mg(CN)Br}] + [\text{BuCu(CN)MgBr·BuMgBr}] \qquad (7)$$

$$\textbf{16} \qquad\qquad\qquad \textbf{17}$$

$$\downarrow \qquad\qquad\qquad \downarrow$$

$$\alpha\text{-product} \qquad\qquad \text{alcohol}$$

In Et_2O both the mono- and the di-butylcuprates formed from CuCN and BuMgX, give the γ-substituted product. Cuprate **1**, a LO cyanocuprate 'BuCu(CN)-MgBr', gives the γ-product via oxidative addition of the allylic acetate to the cuprate followed by fast reductive elimination, owing to the electron-withdrawing group on copper (X = CN, see Scheme 1). When two equiv. of

n-BuMgBr is added to CuCN in Et₂O, a HO cyanocuprate 'Bu₂Cu(CN)(MgBr)₂' might be formed. In this cuprate the electron-withdrawing group is still bonded to copper, or at least incorporated into the copper cluster.[18a,23] In this case the cuprate reacts in the same way as the LO cyanocuprate, i.e., fast reductive elimination from the initially formed (σ-allyl)copper(III) intermediate **A** (Scheme 1).

The cuprates formed from copper(I) halides and *one* equivalent of the Grignard reagent in Et₂O showed variable reactivity. Copper chloride and bromide gave an unreactive species which presumably is polymeric BuCu. The reaction observed with CuI can be explained by the stronger bond between the soft Cu(I) and the soft anion I⁻ which would prevent formation of insoluble BuCu. In the latter case the reactive species is thought to be [BuCu(I)]⁻.

The high γ-selectivity observed in Et₂O when CuI and *two* equivalents of BuMgBr was employed may at first glance look contradictory since the corresponding CuCl and CuBr cases gave a high α-selectivity, presumably via a Gilman-type cuprate [R₂Cu]⁻. A possible explanation for the γ-selectivity obtained with 2 BuMgBr/CuI is the formation of a cuprate complex in which the iodide is still incorporated ('Bu₂CuMgBr·Mg(I)Br' or 'Bu₂Cu(I)(MgBr)₂')[23] and hence can affect the regiochemical outcome of the reaction. However, the strong bond between the soft Cu(I) and soft I⁻ may depress the addition of a second equivalent of *n*-BuMgBr to the initially formed [RCu(I)]⁻ species. This explains the slightly variable cuprate formation and hence the formation of geraniol (**11**) (10%). Also the latter monoalkylcuprate would react to give the γ-substituted product.

The change in regioselectivity with solvent (Et₂O or THF) observed in the CuCN-catalyzed cross-coupling reaction[1a] can be explained by the formation of different organocuprates in Et₂O and THF. The γ-selectivity observed in Et₂O can be explained by the formation of an LO and an HO cyanocuprate from one and two equivalents of *n*-BuMgBr, respectively, in which the cyanide is still coordinated to copper. Therefore, as indicated earlier (Scheme 1 for X = CN), in this solvent both the mono- and di-butylcuprate give the γ-product preferentially. In THF, on the other hand, the monobutylcyanocuprate reacts slowly to give γ-substituted product whereas the dibutylcuprate reacts quickly to give the α-substituted product. Thus, in the catalytic reaction, the first-formed monobutylcopper species (responsible for γ-substitution) reacts with another equivalent of the organometallic reagent to form a dibutylcuprate, which will give the α-product. In the CuCN-catalyzed reaction, slow addition of the Grignard reagent will depress formation of the dialkylcuprate and hence favor formation of the γ-product.

The formation of different organocopper species in Et₂O and THF is presumably due to the different coordinating ability of the solvents.[1c,d] Further studies of the solvent effect are required to clarify the structures responsible for the regioselectivity obtained in the copper-catalyzed cross-coupling reaction in different solvents.

Experimental

General. NMR spectra were recorded for CDCl₃ solutions, ¹H and ¹³C NMR at 400 and 100.6 MHz, respectively using a Varian 400 spectrometer. The chemical shifts are reported with CDCl₃ as internal reference. Merck silica gel (130–400 mesh) was used for flash chromatography. Concentrations of the Grignard[24] and lithium reagents[27] were determined by titration. All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Et₂O and THF were distilled from sodium benzophenone ketyl solution while CH₂Cl₂ and pyridine were distilled from CaH₂. Triethyl phosphonoacetate (99%), cyclohexanecarbaldehyde (98%), DIBAL-H (1.0 M in CH₂Cl₂), geraniol (98%) and acetic anhydride (99%) were purchased from Aldrich and used without further purification. CuCN (99%) purchased from Aldrich was dried at 100°C *in vacuo* for 72 h prior to use. CuCl and CuBr were prepared from CuSO₄,[26] and CuI was purified by a procedure from Kauffman and Fang.[27]

Preparation of starting material
Ethyl (3-cyclohexyl-2-propenoate (4 and 5). BuLi (52 ml, 1.44 M, 75.5 mmol) was added dropwise to a solution of triethyl phosphonoacetate (15.3 ml, 77.0 mmol) in THF (250 ml) at −78°C. After complete addition the temperature was raised to 0°C and cyclohexanecarbaldehyde **3** (9.0 ml, 73.3 mmol) was added dropwise. The reaction mixture was stirred for 2.5 h at 0°C and then quenched with water (200 ml). The aqueous phase was extracted with Et₂O (4 × 50 ml) and the combined organic layers were washed with brine, dried (MgSO₄) and concentrated *in vacuo*. The crude esters, a mixture of *E*- and *Z*-isomers in a ratio of 92:8 (*E:Z*), were separated and purified by flash chromatography (silica gel; pentane–Et₂O = 90:10) to give 12.9 g (91%) of the *E*-isomer as a colorless oil. ¹H NMR: δ 6.88 (dd, *J* = 15.5, 6.5 Hz, 1 H), 5.73 (dd, *J* = 15.5, 1.5 Hz, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 2.15–2.05 (m, 1 H), 1.77–1.69 (m, 4 H), 1.68–1.60 (m, 1 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.33–1.18 (m, 2 H), 1.18–1.05 (m, 3 H). ¹³C NMR: δ 167.0, 154.1, 118.8, 60.0, 40.3, 31.6, 25.9, 25.7, 14.2. IR (neat) 2931, 2853, 1719, 1650, 1449, 1368, 1274, 1171, 1046, 983. MS *m/z* (rel. intensity) 182 (*M*⁺, 15%), 154 (3), 137 (20), 107 (23), 79 (56), 55 (100). Anal. Calcd. for C₁₁H₁₈O₂: C, 72.49; H, 9.95. Found: C, 72.39, H, 9.82.

From the minor fraction 0.9 g (7%) of the *Z*-isomer **5** was obtained as a colorless oil.[28] ¹H NMR: δ 6.02 (dd, *J* = 11.5, 9.5 Hz, 1 H), 5.64 (dd, *J* = 11.5, 1.0 Hz, 1 H), 4.16 (q, *J* = 7.0 Hz, 2 H), 3.34–3.24 (m, 1 H), 1.76–1.68 (m, 4 H), 1.68–1.64 (m, 1 H), 1.40–1.26 (m, 2 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 1.25–1.02 (m, 3 H). ¹³C NMR: δ 166.4, 155.6, 117.7, 59.7, 37.4, 32.4, 25.9, 25.5, 14.3. IR

(neat) 2926, 1645, 1448, 1417, 1221, 1182, 1134, 1032. MS m/z (rel. intensity) 182 (M^+, 5%), 154 (2), 137 (4), 107 (16), 79 (61), 53 (100).

(2E)-3-Cyclohexylprop-2-enol (6). The ester **4** (7.07 g, 38.8 mmol) in CH_2Cl_2 (40 ml) was added dropwise to a solution of DIBAL-H in CH_2Cl_2 (81.5 ml, 1.0 M, 81.5 mmol) at 0°C. The reaction mixture was stirred for 2 h at 0°C and then poured into ice-cooled 2 M HCl (100 ml). The organic layer was washed with 2 M HCl (3 × 50 ml) and the combined acidic aqueous layers were back-extracted with CH_2Cl_2 (50 ml). The combined organic layers were dried ($MgSO_4$). Evaporation of the solvent afforded 5.4 g (100%) of the crude alcohol **6** as a colorless oil which was used in the esterification without further purification. ^1H NMR:[29] δ 5.59 (dd, $J = 16.0$, 5.5 Hz, 1 H), 5.52 (dt, $J = 16.0$, 5.5 Hz, 1 H), 4.0 (d, $J = 5.5$ Hz, 2 H), 2.45–2.23 (br m, 1 H), 1.97–1.87 (m, 1 H), 1.72–1.64 (m, 4 H), 1.64–1.58 (m, 1 H), 1.29–0.98 (m, 5 H). ^{13}C NMR: δ 138.7, 126.3, 63.6, 40.2, 32.7, 26.1, 25.9.

(2E)-Cyclohexylprop-2-enyl acetate (7). Acetic anhydride (5.5 ml, 58.0 mmol) was added slowly to a stirred solution of the allylic alcohol **6** (5.4 g, 38.8 mmol), DMAP (0.48 g, 3.9 mmol), and pyridine (5.4 ml, 66.0 mmol) in CH_2Cl_2 (25 ml) at 0°C. After the reaction mixture had been stirred for 3.5 h at r.t., CH_2Cl_2 (25 ml) and 2 M HCl (25 ml) were added. The organic layer was washed with 2 M HCl (3 × 25 ml), aq. saturated $KHCO_3$ (2 × 25 ml) and water (25 ml). The acidic and basic aqueous layers were back-extracted with CH_2Cl_2 (25 ml). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Flash chromatography (silica gel; pentane–$Et_2O = 90:10$) of the residue afforded 6.15 g (87% in two steps) of the pure allylic acetate **7** as a colorless oil. ^1H NMR: δ 5.69 (ddt, $J = 15.0$, 5.0, 1.5 Hz, 1 H), 5.48 (dtd, $J = 15.0$, 6.5, 1.5 Hz, 1 H), 4.48 (d, $J = 6.5$ Hz, 2 H), 2.03 (s, 3 H), 2.01–1.90 (m, 1 H), 1.74–1.66 (m, 4 H), 1.66–1.59 (m, 1 H), 1.30–0.98 (m, 5 H). ^{13}C NMR: δ 170.7, 142.0, 121.2, 65.4, 40.2, 32.5, 26.1, 25.9, 21.0. IR (neat) 2925, 2852, 1744, 1669, 1449, 1366, 1228, 1025, 970. MS m/z (rel. intensity) 182 (M^+, 0.2%), 141 (2), 122 (65), 107 (40), 93 (36), 81 (100), 67 (68), 55 (46). Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.35; H, 9.79.

Geranyl acetate (8). This was prepared from geraniol by a standard method (see the preparation of acetate **7**).

Preparation of monobutylcuprates **1**. BuMgBr (0.96 ml, 0.6 M, 0.58 mmol) prepared in THF or Et_2O was added dropwise to a slurry of the copper salt (0.6 mmol) in the same solvent as the Grignard reagent at − 30°C. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0°C.

Preparation of dibutylcuprates **2**. BuMgBr (1.92 ml, 0.6 M, 1.15 mmol) prepared in THF or Et_2O was added drop-

wise to a slurry of the copper salt (0.6 mmol) in the same solvent as the Grignard reagent at − 30°C. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0°C.

General procedure for the reaction of allylic substrates (7 and 8) with preformed cuprates. The allylic acetate **7** or **8** (0.5 mmol) dissolved in the same solvent as the preformed cuprate (THF or Et_2O) was added to the cuprate at 0°C. The reaction mixture was stirred for 2 h and then quenched with NH_4Cl (5 ml) ad NH_4OH (3 ml). After 30 min of vigorous stirring the two layers were separated and the aqueous layer extracted with Et_2O (3 × 5 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo.* The product distribution was determined by ^1H NMR spectroscopy. Spectral data of the products are given below.

(6E)-2,6-Dimethyl-2,6-dodecadiene (9).[1a] ^1H NMR: δ 5.17–5.06 (m, 2 H), 2.10–1.92 (m, 6 H), 1.70 (s, 3 H), 1.61 (s, 6 H), 1.40–1.25 (m, 6 H), 0.90 (br t, $J = 6.8$ Hz, 3 H). ^{13}C NMR: δ 134.7, 131.2, 124.9, 124.4, 39.8, 31.6, 29.6, 27.9, 26.7, 25.7, 22.7, 17.7, 15.9, 14.1.

2,6-Dimethyl-6-vinyl-2-decene (10).[1a] ^1H NMR: δ 5.71 (dd, $J = 11.0$, 17.4 Hz, 1 H), 5.11 (m, 1 H), 4.99 (dd, $J = 1.4$, 11.0 Hz, 1 H), 4.90 (dd, $J = 11.0$, 17.4 Hz, 1 H), 1.94–1.81 (m, 2 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.54–1.17 (m, 8 H), 0.97 (s, 3 H), 0.90 (br t, $J = 6.8$ Hz, 3 H). ^{13}C NMR: δ 147.5, 130.7, 125.2, 111.3, 40.8, 40.6, 39.4, 26.3, 25.7, 23.6, 22.6, 22.5, 17.5, 14.1.

(E)-1-Cyclohexylhept-1-ene (12). ^1H NMR: δ 5.36–5.33 (m, 2 H), 1.99–1.93 (m, 2 H), 1.93–1.84 (m, 1 H), 1.74–1.60 (m, 5 H), 1.38–1.20 (m, 8 H), 1.20–1.11 (m, 1 H), 1.11–0.98 (m, 2 H), 0.88 (br t, $J = 7.0$ Hz, 3 H). ^{13}C NMR: δ 136.4, 127.8, 40.7, 33.3, 32.6, 31.4, 29.4, 26.7, 26.2, 22.6, 14.1. IR (neat) 2958, 2926, 2853, 1449, 971, 908. MS m/z 180 (M^+, 49), 109 (63), 96 (100), 81 (84), 67 (98), 55 (49).

3-Cyclohexylhept-1-ene (13).[29] ^1H NMR: δ 5.56 (ddd, $J = 17.0$, 10.0, 9.0 Hz, 1 H), 4.98 (ddd, $J = 10.0$, 2.5, 0.5 Hz, 1 H), 4.90 (ddd, 17.0, 2.5, 1.0 Hz, 1 H), 1.80–1.70 (m, 4 H), 1.76–1.62 (m, 2 H), 1.47–1.39 (m, 1 H), 1.36–1.09 (m, 9 H), 1.06–0.88 (m, 2 H), 0.89 (br t, $J = 7$ Hz, 3 H). ^{13}C NMR: δ 141.8, 114.6, 50.1, 41.8, 31.4, 31.2, 29.8, 29.7, 26.80, 26.77, 26.74, 22.9, 14.1. IR (neat) 2923, 2853, 1638, 1449, 997, 909. MS m/z 180 (M^+, 2), 152 (22), 98 (22), 96 (21), 83 (61), 82 (44), 81 (28), 67 (40), 55 (100).

References

1. (a) Bäckvall, J. E., Séllen, M. and Grant, B. *J. Am. Chem. Soc. 112* (1990) 6615; (b) Bäckvall, J. E., Persson, E. S. M. and Bombrun, A. *J. Org. Chem. 59* (1994) 4126; (c) van Klaveren, M., Persson, E. S. M., Grove, D. M., Bäckvall, J. E. and van Koten, G. *Tetrahedron Lett. 35* (1994) 5931;

(d) Persson, E. S. M., van Klaveren, M., Grove, D. M., Bäckvall, J. E. and van Koten, G. *Chemistry – A European Journal 1* (1995). *In press.*

2. The effect of solvent has previously been observed in the stoichiometric cross-coupling of allylic sulfides of benzothiazole-2-thiol using CuI; see Barsanti, P., Calò, V., Lopez, L., Marchese, G., Naso, F. and Pesce, G. *J. Chem. Soc., Chem. Commun.* (1978) 1085.

3. It has previously been observed, in the stoichiometric copper(I)-promoted cross-coupling of 2-allylbenzothiazoles with BuMgBr in THF, that the ratio of the α- and γ-products changes with the ratio between the Grignard reagent and the catalyst (CuBr); see, Calò, V., Lopez, L. and Carlucci, W. F. *J. Chem. Soc., Perkin Trans. 1* (1983) 2953.

4. (a) Tseng, C. C., Paisley, S. D. and Goering, H. L. *J. Org. Chem. 51* (1986) 2884; (b) Goering, H. L., Kantner, S. S. and Seitz, E. P. Jr. *J. Org. Chem. 50* (1985) 5485; (c) Goering, H. L. and Kantner, S. S. *J. Org. Chem. 49* (1984) 422; (d) Goering, H. L. and Singleton, V. D. Jr. *J. Org. Chem. 48* (1983) 1531.

5. (a) Fouquet, G. and Schlosser, M. *Angew. Chem., Int. Ed. Engl. 13* (1974) 82; (b) Commerçon, A., Bourgain, M., Delaumeny, M., Normant, J. F. and Villieras, J. *Tetrahedron Lett.* (1975) 3837; (c) Levisalles, J., Rudler-Chauvin, M. and Rudler, H. *J. Organomet. Chem. 136* (1977) 103; (d) Magid, R. M. *Tetrahedron 36* (1980) 1901; (e) Julia, M., Righini-Tapie, A. and Verpeaux, J. N. *Tetrahedron 39* (1983) 3283; (f) Curran, D. P., Chen, M. H., Leszczweski, D., Elliott, R. L. and Rakiewicz, D. M. *J. Org. Chem. 51* (1986) 1612; (g) Marshall, J. A. *Chem. Rev. 89* (1989) 1503; (h) Yanagisawa, A., Noritake, Y., Nomura, N. and Yamamoto, H. *Synlett* (1991) 251; (i) Yanagisawa, A., Nomura, N. and Yamamoto, H. *Synlett* (1993) 251; (j) Lipshutz, B. H. and Sengupta, S. *Org. React. 41* (1992) 135.

6. It is known that electron-withdrawing ligands accelerate reductive elimination: (a) Yamamoto, T., Yamamoto, A. and Ikeda, S. *J. Am. Chem. Soc. 93* (1971) 3350, 3360; (b) Kurosawa, H., Emoto, M., Ohnishi, H., Miki, K., Tatsumi, K. and Nakamura, A. *J. Am. Chem. Soc. 109* (1987) 6333; (c) See also: Collman, J. P., Hegedus, L. S., Norton, J. R. and Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books, Mill Valley, CA 1987.

7. The addition of $BF_3 \cdot OEt_2$ to a mono-organocuprate has previously been shown to give a copper complex which results in highly γ-selective reactions with allylic chlorides: Maruyama, K. and Yamamoto, Y. *J. Am. Chem. Soc. 99* (1977) 8086.

8. One problem in performing the reaction with n-BuMgI is that this Grignard reagent is not soluble in THF. If n-BuMgI is prepared in THF, a precipitate forms and the mixture is impossible to titrate. A solution to this problem was to prepare the Grignard reagent in Et_2O, titrate it, evaporate the solvent and then add THF to the Grignard reagent. Even though the solvent was changed several times one cannot exclude the possibility that there are traces of Et_2O left, which would explain the slightly lower α-selectivity compared with that obtained with n-BuMgBr.

9. Bertz, S. H., Gibson, C. P. and Dabbagh, G. *Tetrahedron Lett. 28* (1987) 4251.

10. Irreproducible cuprate formation from CuI in Et_2O has been observed previously in a study on the preparation of lithium organocuprates from various copper(I) salts which were used in reaction with 2-cyclohexenone, see Ref. 9.

11. For a review of organocuprate structures, see: Power, P. P. *Prog. Inorg. Chem. 39* (1991) 75.

12. (a) Leoni, P., Pasquali, M. and Ghilardi, C. A. *J. Chem. Soc., Chem. Commun.* (1980) 240; (b) Hope, H., Oram, D. and Power, P. P. *J. Am. Chem. Soc. 106* (1984) 1149;

(c) van Koten, G., Jastrzebski, T. B. H., Muller, F. and Stam, C. H. *J. Am. Chem. Soc. 107* (1985) 697; (d) Hope, H., Olmstead, M. M., Power, P. P., Sandell, J. and Xu, X. *J. Am. Chem. Soc. 107* (1985) 4337; (e) Olmstead, M. M. and Power, P. P. *J. Am. Chem. Soc. 111* (1989) 4135; (f) Olmstead, M. M. and Power, P. P. *J. Am. Chem. Soc. 112* (1990) 8008; (g) Olmstead, M. M. and Power, P. P. *Organometallics 9* (1990) 1720; (h) Lorenzen, N. P. and Weiss, E. *Angew. Chem., Int. Ed. Engl. 29* (1990) 300.

13. (a) Ashby, E. C. and Watkins, J. J. *J. Chem. Soc., Chem. Commun.* (1976) 784; (b) Ashby, E. C. and Watkins, J.J. *J. Chem. Soc. 99* (1977) 5312; (c) Lipshutz, B. H., Kozlowski, J. A. and Wilhelm, R. S. *J. Org. Chem. 49* (1984) 3943: (d) Lipshutz, B. H., Kozlowski, J. A. and Breneman, C. M. *J. Am. Chem. Soc. 107* (1985) 3197; (e) Bertz, S. H. and Dabbagh, G. *J. Am. Chem. Soc. 110* (1988) 3668; (f) Sharma, S. and Oehlschlager, A. C. *Tetrahedron 45* (1989) 557; (g) Hutzinger, M. W., Singer, R. D. and Oehlschlager, A. C. *J. Am. Chem. Soc. 112* (1990) 9397; (h) Singer, R. D. and Oehlschlager, A. C. *J. Org. Chem. 56* (1991) 3510; (i) Singer, R. D., Hutzinger, M. W. and Oehlschlager, A. C. *J. Org. Chem. 56* (1991) 4933.

14. (a) Bertz, S. H. *J. Am. Chem. Soc. 112* (1990) 4032; (b) Bertz, S. H. *J. Am. Chem. Soc. 113* (1991) 5470.

15. Pearson, R. G. and Gregory, C. D. *J. Am. Chem. Soc. 98* (1976) 4098.

16. van Koten, G. and Noltes, J. G. *J. Am. Chem. Soc. 101* (1979) 6593.

17. Lipshutz, B. H., Wilhelm, R. S. and Floyd, D. M. *J. Am. Chem. Soc. 103* (1981) 7672.

18. (a) Lipshutz, B. H. and James, B. *J. Org. Chem. 59* (1994) 7585; (b) Lipshutz, B. H., Sharma, S. and Ellsworth, E. L. *J. Am. Chem. Soc. 112* (1990) 4032; (c) Lipshutz, B. H., Wilhelm, R. S. and Kozlowski, J. A. *J. Org. Chem. 49* (1984) 3928, 3938, 3943.

19. Stemmler, T., Penner-Hahn, J. .E. and Knochel, P. *J. Am. Chem. Soc. 115* (1993) 348.

20. Snyder, J. P., Spangler, D. P., Behling, J. R. and Rossiter, B. E. *J. Org. Chem. 59* (1994) 2665.

21. Alexakis, A., Commerçon, A., Coulentianos, C. and Normant, J. F. *Pure Appl. Chem. 55* (1983) 1759.

22. (a) Lipshutz, B. H., Ellsworth, E. L. and Dimock, S. H. *J. Am. Chem. Soc. 112* (1990) 5869. See also (b) Lipshutz, B. H. and Hackmann, C. *J. Org. Chem. 59* (1994) 7437; (c) House, H. O. and Fischer, W. F. *J. Org. Chem. 33* (1968) 949.

23. It has been discovered that the phenyl Gilman reagent contains LiI incorporated into the cuprate cluster and should be represented as $Ph_2CuLi \cdot LiI$ or $Ph_2Cu(I)Li_2$. Bertz, S. H. and Dabbagh, G. *J. Am. Chem. Soc. 110* (1988) 3668. See also, Lipshutz, B. H., Kayser, F. and Siegmann, K. *Tetrahedron Lett. 34* (1993) 6693.

24. Bergbreiter, D. E. and Pendergrass, E. *J. Org. Chem. 46* (1981) 219.

25. Winkle, M. R., Lansinger, J. M. and Ronald, R. C. *J. Chem. Soc., Chem. Commun.* (1980) 87.

26. Furniss, B. S., Hannford, A. J., Smith, P. W. G. and Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Wiley, New York 1989; pp. 428–429.

27. Kauffman, G. B. and Fang, L. Y. *Inorg. Synth. 22* (1983) 101.

28. Vedejs, E. and Fleck, T. J. *J. Am. Chem. Soc. 111* (1989) 5861.

29. (a) Marble, L. K. Ph. D. Thesis, University of Illinois at Urbana 1991; (b) Denmark, S. E. and Marble, L. K. *J. Org. Chem. 55* (1990) 1984.