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 organocupper 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 organocupper complexes were prepared from different copper(I) salts, such as CuCl, CuBr, CuI and CuCN, and their reactivity both in Et₂O and THF were studied. In THF, monobutylcuprates gave the γ-substituted product whereas the dibutylcuprates afforded the z-substituted product. In Et₂O, cuprates formed from CuCN and CuI gave γ-selective reactions whereas those from CuCl and CuBr resulted in z-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 Et₂O resulted in formation of the γ-product (S₉₂γ) while THF yielded the z-product (S₉₂z).¹ In THF it was possible to direct the nucleophile in the cross-coupling reactions regioselectively to either the z- or γ-position by careful choice of reaction conditions [eqn. (1)].¹ Reaction conditions which favored formation of a dialkylcupper intermediate ‘RCu(X)MgBr’ (fast addition of the Grignard reagent, low temperature, low concentration of the catalyst) gave the z-product, whereas reaction conditions favoring the formation of a monoalkylcupper intermediate ‘RCu(X)MgBr’ (slow addition of the Grignard reagent, increased temperature, increased concentration of the catalyst) led to γ-substitution.¹

The mechanism for the copper-catalyzed cross-coupling reaction has been studied and discussed in a number of reports.¹ It has been proposed that a (σ-allyl)cupper(III) intermediate A is initially formed by oxidative addition of the allylic substrate to the cuprate in an anti S₉₂ γ fashion (Scheme 1). 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 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 z-product.

The mechanisms (Scheme 1) suggests that a monocupper salt [RCuX]⁻ gives the γ-product while a dicupper salt [RCu₂]⁻ forms the z-product.¹ We have now studied the reaction between preformed mono- and di-butylcuprates and primary allylic acetates in both Et₂O 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.

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allowed to react with a preformed mono- or dibutyl-cuprate, 1 or 2, in Et₂O 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)].

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-

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

A. CuCN, different organometallic reagents (Table 1, Table 2)

BuMgBr. In Et₂O, both ‘BuCu(CN)MgBr’ 1 and ‘Bu₂Cu(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 reactivities 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 BF₃·OEt₂ (1–4 equiv.) did not increase the reactivity, rather the reaction rate went down and no product could be detected after 120 min. 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 Et₂O, 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 Et₂O.

The allylic acetate 7 showed similar reactivity and regioselectivity to 8 towards cuprates 1 and 2 in both Et₂O and THF [eqn. (3), Table 2]. In Et₂O both cuprates 1
Table 1. The stoichiometric cross coupling of 8 with preformed mono- and di-butyl cuprates.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Product distribution (%)</th>
<th>Conversion (%)</th>
<th>9 + 10:11</th>
<th>9:10</th>
<th>9 + 10 + 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BuCu(CN)MgBr</td>
<td>Et(_2)O</td>
<td>100: 0</td>
<td>&lt; 1: &gt; 99</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bu(_2)Cu(CN)MgBr(_2)</td>
<td>Et(_2)O</td>
<td>100: 0</td>
<td>&lt; 1: &gt; 99</td>
<td>100(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>BuCu(CN)MgI</td>
<td>Et(_2)O</td>
<td>100: 0</td>
<td>6:94</td>
<td>100(^d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Bu(_2)Cu(CN)(Mgl)(_2)</td>
<td>Et(_2)O</td>
<td>100: 0</td>
<td>3:97</td>
<td>100(^e)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>BuCu(CNI)Li</td>
<td>Et(_2)O</td>
<td>100: 0</td>
<td>50:50</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Bu(_2)Cu(CNI)Li(_2)</td>
<td>Et(_2)O</td>
<td>50:50</td>
<td>38:62</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>BuCu(CN)MgBr</td>
<td>THF</td>
<td>100: 0</td>
<td>&lt; 1: &gt; 99</td>
<td>&lt;2(^f)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Bu(_2)Cu(CN)MgBr(_2)</td>
<td>THF</td>
<td>65:35</td>
<td>99:1</td>
<td>61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>BuCu(CN)MgI</td>
<td>THF</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Bu(_2)Cu(CN)(Mgl)(_2)</td>
<td>THF</td>
<td>37:63</td>
<td>88:12</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>BuCu(CNI)Li</td>
<td>THF</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Bu(_2)Cu(CNI)Li(_2)</td>
<td>THF</td>
<td>33:67</td>
<td>100:0</td>
<td>80</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The Grignard reagent was added to a slurry of CuCN in Et\(_2\)O of THF at \(-30^\circ\)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 \(^1\)H 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.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Product distribution (%)</th>
<th>Conversion (%)</th>
<th>12 + 13:6</th>
<th>12:13</th>
<th>12 + 13 + 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BuCu(CN)MgBr</td>
<td>Et(_2)O</td>
<td>100:0</td>
<td>&lt; 1: &gt; 99</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Bu(_2)Cu(CN)MgBr(_2)</td>
<td>Et(_2)O</td>
<td>100:0</td>
<td>2:98</td>
<td>100(^0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>BuCu(CN)MgI</td>
<td>THF</td>
<td>—</td>
<td>—</td>
<td>0(^0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Bu(_2)Cu(CN)(Mgl)(_2)</td>
<td>THF</td>
<td>81:19</td>
<td>98:2</td>
<td>97</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The Grignard reagent was added to a slurry of CuCN in Et\(_2\)O or THF at \(-30^\circ\)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 \(^1\)H 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).

![Image of the reaction](image.png)

BuMgI. The cross-coupling reaction of geranyl acetate (8) in Et\(_2\)O with both 'BuCu(CN)MgI' 1 and 'Bu\(_2\)Cu(CN)(Mgl)\(_2\)' 2 resulted in \(\gamma\)-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 'Bu\(_2\)Cu(CN)(Mgl)\(_2\)' 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 \(\alpha\)- and \(\gamma\)-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 'Bu\(_2\)Cu(CN)(MgBr)\(_2\)' (entry 8).

BuLi. Cuprates 'BuCu(CNI)Li' 1 and 'Bu\(_2\)Cu(CNI)Li\(_2\)' 2 in Et\(_2\)O were less selective in the coupling with 8 than those obtained from the Grignard reagent and gave 1:1 and 2:1 mixtures of \(\alpha\)- and \(\gamma\)-products, respectively (Table 1, entries 5 and 6). Lowering the temperature to \(-60^\circ\)C did not increase the selectivity. The lower regioselectivity for lithium cuprates in Et\(_2\)O has been observed previously in the stoichiometric cross-coupling of allylic acetates.\(^{44}\) 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 monobutylcupperate 1 was completely unreactive whereas the dibutylcupperate 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

Monobutylcupperate in THF. All the monobutylcuprates ‘Bu-Cu(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.

Dibutylcupperate 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. Cu-CN and two equiv. Bu-MgBr 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).

Monobutylcupperate in Et₂O. (Table 4) The corresponding monobutylcupperates 1 formed from Cu-CN and Cu-I with n-Bu-Mg-Br 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 monobutylcupperate 1 formed from Cu-Cl or Cu-Br were unreactive and no product formation could be detected (entries 2 and 3).

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

<table>
<thead>
<tr>
<th>Cu-salt</th>
<th>Product distribution (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu-CN</td>
<td>1:1:99</td>
<td>72</td>
</tr>
<tr>
<td>Cu-Cl</td>
<td>1:1:1</td>
<td>0</td>
</tr>
<tr>
<td>Cu-Br</td>
<td>1:1:1</td>
<td>0</td>
</tr>
<tr>
<td>Cu-I</td>
<td>1:1:1</td>
<td>30</td>
</tr>
</tbody>
</table>

* n-Bu-MgBr 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. Determined by 1H NMR spectroscopy. 9 91% isolated yield.

Table 4. Different Cu(I) salts; the cross-coupling reaction of preformed dibutyl cuprates ‘Bu₂Cu(X)(MgBr)₂’ with 8 in Et₂O.

<table>
<thead>
<tr>
<th>Cu-salt</th>
<th>Product distribution (%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu-CN</td>
<td>100:0</td>
<td>1:1:99</td>
</tr>
<tr>
<td>Cu-Cl</td>
<td>100:0</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>Cu-Br</td>
<td>25:75</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>Cu-I</td>
<td>90:10</td>
<td>6:94</td>
</tr>
</tbody>
</table>

* n-Bu-MgBr 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. Determined by 1H NMR spectroscopy. 8 87% isolated yield.

Dibutylcupperate 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 Cu-CN resulted in a γ-selective cross coupling (entry 1) whereas the cuprate from Cu-Cl afforded an α-selective reaction (entry 2). The cuprate 2 (M = MgBr) from Cu-Br 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 Cu-I gave a γ-selective coupling (94% γ) together with a small amount of geraniol (entry 4). Cuprate formation from Cu-I 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 (I.O, two coordinate, R₂CuM) and higher order (HO, three coordinate, R₂CuM₂)12,13 organocuprates can exist in the solid state.12 Knowledge about the structure of organocuprates in so-
The dialkylocuprates in THF, formed from copper(I) halides, give preferentially the $\alpha$-substituted product [eqn. (5)]. The formation of geraniol, when CuCN was used as

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

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

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 monobutylocyanocuprate would react with an allylic acetate to give the $\gamma$-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 $\alpha$-substituted product is obtained.

$$\text{CuCN} + 2 \text{BuMgBr} \xrightarrow{\ \text{THF}\ } [\ \text{Bu}_2\text{Cu(CN)MgBr}] + \text{BuMgBr}
$$

$$\xrightarrow{\ \alpha\text{-product}\ } [\ \text{Bu}_2\text{Cu(CN)MgBr} + \text{Mg(CN)Br}\ ]
$$

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 $\pi$-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 $\alpha$-product [eqn. (7)].

$$\text{CuCN} + 2 \text{BuMgBr} \xrightarrow{\ \text{THF}\ } [\ \text{Bu}_2\text{Cu(CN)MgBr}] + \text{BuMgBr}
$$

$$\xrightarrow{\ \alpha\text{-product}\ } 16$$

$$\text{CuCN} + 2 \text{BuMgBr} \xrightarrow{\ \text{THF}\ } [\ \text{Bu}_2\text{Cu(CN)MgBr}] + \text{BuMgBr}
$$

$$\xrightarrow{\ \text{alcohol}\ } 17$$

In Et$_2$O both the mono- and the di-butylocuprates formed from CuCN and BuMgX, give the $\gamma$-substituted product. Cuprate 1, a LO cyanocuprate 'BuCu(CN)-MgBr', gives the $\gamma$-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

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Fig. 1. Structural representation of the LO dimer of R$_2$CuLi 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 13 of the simple Gilman cuprate R$_2$CuLi, as an LO dimer (14, Fig. 1) has been confirmed by molecular weight determinations, 13b NMR spectroscopy, 16 and X-ray crystallography. 12c,f-g Despite intensive studies, the structure of the HO cyanocuprate copper reagents are less established. In 1981, the concept 'higher order, mixed' copper reagents R$_2$Cu(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, 16-20 The structure of the HO cyanocuprate in THF, represented by the formula R$_2$Cu(CN)Li$_2$, 18 has been shown by NMR 14 and EXAFS 17 spectroscopic studies to be better represented by the formula R$_2$CuLi-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, 18d the structure of the HO cyanocuprate was revised and it was proposed that the nitrile ligand probably is incorporated in the cuprate cluster: $\sigma$-bond to Li$^+$ and $\pi$-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 $\gamma$-substituted product with the allylic acetates [eqn. (4), cf. Scheme 1]. The reason for the low reactivity of the monobutylocuprates in THF is not clear.

$$
\begin{align*}
\text{CuX} + \text{BuMgBr} & \xrightarrow{\ \text{THF}\ } [\ \text{Bu}_2\text{Cu(X)MgBr}] \\
X & = \text{CN, Cl, Br, I} \\
& \downarrow \text{slow} \\
& \gamma\text{-product}
\end{align*}
$$

---

903
$n$-BuMgBr is added to CuCN in Et$_2$O, a HO cyanocuprate $\text{Bu}_3\text{Cu}(\text{CN})(\text{MgBr})_2$ might be formed. In this cuprate the electron-withdrawing group is still bonded to copper, or at least incorporated into the copper cluster. In this case the cuprate reacts in the same way as the LO cyanocuprate, i.e., fast reductive elimination from the initially formed (s-allyl)cupper(III) intermediate A (Scheme 1).

The cuprates formed from copper(I) halides and one equivalent of the Grignard reagent in Et$_2$O 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 $\gamma$-selectivity observed in Et$_2$O 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 $\alpha$-selectivity, presumably via a Gilman-type cuprate [R,Cu]. A possible explanation for the $\gamma$-selectivity obtained with 2 BuMgBr CuI is the formation of a cuprate complex in which the iodide is still incorporated ($\text{Bu}_3\text{Cu}(\text{MgBr})_2$ or $\text{Bu}_2\text{Cu}(\text{I})(\text{MgBr})_2^+$ 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 [R,Cu(I)] species. This explains the slightly variable cuprate formation and hence the formation of geraniol (11) (10%). Also the latter monoalkycuprate would react to give the $\gamma$-substituted product.

The change in regioselectivity with solvent (Et$_2$O or THF) observed in the CuCN-catalyzed cross-coupling reaction can be explained by the formation of different organocuprates in Et$_2$O and THF. The $\gamma$-selectivity observed in Et$_2$O 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-butycuprate give the $\gamma$-product preferentially. In THF, on the other hand, the monobutylenecyanocuprate reacts slowly to give $\gamma$-substituted product whereas the dibutycuprate reacts quickly to give the $\alpha$-substituted product. Thus, in the catalytic reaction, the first-formed monobutycopper species (responsible for $\gamma$-substitution) reacts with another equivalent of the organometallic reagent to form a dibutycuprate, which will give the $\alpha$-product. In the CuCN-catalyzed reaction, slow addition of the Grignard reagent will depress formation of the dialkycuprate and hence favor formation of the $\gamma$-product.

The formation of different organocupper species in Et$_2$O and THF is presumably due to the different coordinating ability of the solvents. 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 CDCl$_3$ solutions, $^1$H and $^{13}$C NMR at 400 and 100.6 MHz, respectively using a Varian 400 spectrometer. The chemical shifts are reported with CDCl$_3$ as internal reference. Merck silica gel (130-400 mesh) was used for flash chromatography. Concentrations of the Grignard and lithium reagents were determined by titration. All reactions were carried out in flame-dried glassware under an atmosphere of nitrogen. Et$_2$O and THF were distilled from sodium benzenophenone ketyl solution while CH$_2$Cl$_2$ and pyridine were distilled from CaH$_2$, triethyl phosphonoacetate (98%), cyclohexanecarbaldehyde (98%), DIBAL-H (1.0 M in CH$_2$Cl$_2$), 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 CuSO$_4$ and CuI was purified by a procedure from Kaufman and Fang.

**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 Et$_2$O (4 × 50 ml) and the combined organic layers were washed with brine, dried (MgSO$_4$) 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−Et$_2$O 90:10) to give 12.9 g (91%) of the $E$-isomer as a colorless oil. $^1$H NMR: $\delta$ 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). $^{13}$C NMR: $\delta$ 167.0, 154.1, 118.8, 60.0, 40.3, 31.6, 25.9, 25.7, 14.2. IR (neat, KBr) 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 C$_{11}$H$_{16}$O$_2$: 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. $^1$H NMR: $\delta$ 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). $^{13}$C NMR: $\delta$ 166.4, 155.6, 117.7, 59.7, 37.4, 32.4, 25.9, 25.5, 14.3. IR
(2E)-3-Cyclohexylprop-2-enol (6). The ester 4 (7.07 g, 38.8 mmol) in CH₂Cl₂ (40 ml) was added dropwise to a solution of DIBAL·H in CH₂Cl₂ (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 x 50 ml) and the combined acidic aqueous layers were back-extracted with CH₂Cl₂ (50 ml). The combined organic layers were dried (MgSO₄). 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: 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, 2 H, 1 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). ¹³C 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 CH₂Cl₂ (25 ml) at 0°C. After the reaction mixture had been stirred for 3.5 h at r.t., CH₂Cl₂ (25 ml) and 2 M HCl (25 ml) were added. The organic layer was washed with 2 M HCl (3 x 25 ml),aq. saturated KHCO₃ (2 x 25 ml) and water (25 ml). The acetic and basic aqueous layers were back-extracted with CH₂Cl₂ (25 ml). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Flash chromatography (silica gel; pentane-Et₂O = 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 (ddt, J = 15.0, 6.5, 1.5 Hz, 1 H), 4.48 (dd, 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). ¹³C 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 C₁₁H₁₆O₂: 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 Et₂O 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 Et₂O 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.

References


3. It has previously been observed, in the stoichiometric coupling of CuBr 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.


7. The addition of BF₃·OEt₂ to a mono-organocuprate has previously been shown to give a copper complex which results in highly α-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 Et₂O, 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 Et₂O left, which would explain the slightly lower α-selectivity compared with that obtained with n-BuMgBr.


10. Reproducible cuprate formation from Cul in Et₂O 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-cyclohexeneone, see Ref. 9.


23. It has been discovered that the phenyl Gilman reagent contains Li incorporated into the cuprate cluster and should be represented as Ph₂CuLi·LiI or Ph₂CuLi·Li₂. Bertz, S. H. and Dabbagh, G. J. Am. Chem. Soc. 110 (1988) 3668. See also, Lipshutz, B. H., Kays, F. and Siegmund, K. Tetrahedron Lett. 34 (1993) 6693.


