Experimental Evidence Supporting a Cu^{III} Intermediate in Cross-Coupling Reactions of Allylic Esters with Diallylcuprate Species

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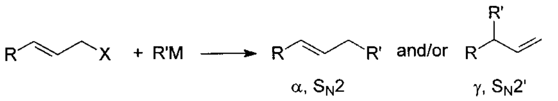
Abstract: The reaction between an allylic ester and a magnesium diallylcuprate, or an allylic Grignard reagent in combination with a catalytic amount of a copper salt, has been studied. These reactions yield a mixture of homo- and cross-coupled 1,5-diene products. The product ratios obtained are close to those expected for a reaction proceeding via a triallylcopper(III) intermediate consisting of three equivalent allyl groups bound to copper. When the reaction is performed with a stoichiometric amount of a preformed diallylcuprate, a homo-coupling/cross-coupling ratio larger than that predicted for a Cu^{III} intermediate is observed. However, on dilution this ratio decreases and becomes close to the predicted ratio. The deviation from the predicted homo-coupling/cross-coupling ratio was accounted for by an olefin-induced homo-coupling, as demonstrated in control experiments. The possibility of the allylic ligands to coordinate to the metal center in a η^3 or η^1 fashion provides an opportunity for the stabilization of the intermediate Cu^{III} species.

Keywords: copper · cuprate · C–C coupling · reaction mechanisms · organocopper(III) intermediate

Introduction

Copper-mediated reactions are of great importance in synthetic organic chemistry.[1] The conjugate addition reaction to α,β-unsaturated systems is regarded as one of the fundamental reactions in organic chemistry and has been well studied.[1] Another thoroughly studied reaction is the allylic substitution reaction between an allylic electrophile and an organocopper reagent.[1, 2] Much attention has been devoted to the control of the selectivity of this reaction [Eq. (1)], as well as to the understanding of its mechanism.[3–6]



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However, despite extensive studies of this allylic coupling, and other related copper(I)-mediated reactions, such as the conjugate addition to α,β-unsaturated carbonyl compounds, the mechanistic course is still unclear. The study of the mechanism of these reactions turned out to be rather difficult by direct methods. Intermediate π complexes with copper have been observed for α,β-unsaturated compounds;[7] however, it has not been possible to detect any other intermediate before the appearance of the final conjugate addition product. It has been suggested that an organocopper(III) intermediate is involved in Cu^{I}-mediated substitutions and conjugate additions,[6f, 8, 9] but skepticism has also been raised against such a species as a reasonable intermediate.[10] Recent calculations have shown that neutral trialkylcopper species are likely intermediates in cuprate reactions provided that they are stabilized by a donor, for example Et_2O.[11, 12]

We have previously studied the copper-catalyzed allylic substitution reaction of allylic esters with Grignard reagents.[3, 4] The mechanism of this reaction has been a matter of considerable debate and today two principal pathways (one via a Cu^{III} intermediate and one via direct displacement) have been suggested for this transformation.[1, 13, 14] We have now undertaken a mechanistic study to shed some light on this mechanistic problem. By performing reactions between allylic esters and diallylcuprates we hoped to obtain indirect information about a possible Cu^{III} intermediate from the product composition. It was argued that a triallylcopper(III) intermediate, if formed, would give a different product pattern to that of a direct displacement mechanism. In the triallylcopper pathway (path I, Scheme 1) a 2:1 ratio between cross-coupled and homo-coupled product is expected, provided that the allyl groups bound to copper behave in an equivalent manner. In the direct displacement pathway, in which copper stays as Cu^{I} (path II),[13] only cross-coupled product would be produced and no homo-coupled product should be formed.

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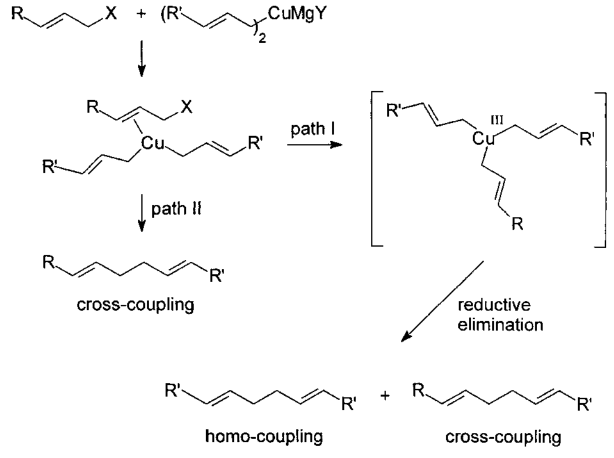
Supporting information for this contribution [Derivation of Equation (2)] is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.



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Scheme 1. Two possible mechanisms in the allylic substitution reaction, via a copper(III)-intermediate (path I) and a direct displacement mechanism (path II).

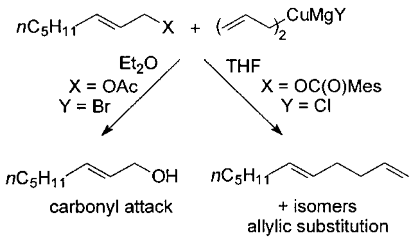
It has been argued that three R groups on a Cu^{III} center do not occupy equivalent structural positions due to the fact that the Cu^{III}-ligand environment is square planar. This would be in accordance with the observation that many substitution reactions give a very high yield of cross-coupled products. The Cu^{III} intermediate is assumed to have a square planar structure where the two groups originally present in the cuprate occupy *trans* positions. Two groups involved in a reductive elimination have to be *cis* to one another, and therefore the last incoming group would always be involved in the reductive coupling.[14b, 15] However, with a triallylcopper(III) intermediate the situation could be different as a result of the rapidly interconverting bis(σ-allyl)(π-allyl)Cu^{III}, which may make the three allyl groups equivalent.

In general, the use of allylic Cu^{I} reagents has been limited due to their difficult preparation and limited thermal stability.[1] The development of allylic “higher-order cyanocuprates” (cyano-Gilman reagents) by Lipshutz et al.,[16] and the synthesis of highly reactive allylcopper from zerovalent copper developed by Rieke and co-workers[17] have recently made this class of reagents more accessible. Allylic copper reagents derived from Grignard reagents have been successfully used in a number of reactions. Substitution reactions of dienyl triflates,[18] alkyl halides[19] and 1,1-dibromo-1-alkenes,[20] ring opening of epoxides[21] and lactones,[22] addition to imines,[23] and conjugate additions[24] have been realized either by employing a stoichiometric preformed cuprate, or a catalytic amount of a copper salt together with the allylic Grignard reagent. Some examples of allylic substitution reactions employing (allyl)copper intermediates have also appeared in the literature.[19a, 25–27]

Results

We started our investigations with simple nonsubstituted allyl Grignard reagents and γ-alkyl-substituted allylic acetates. It soon became obvious that allylic esters are very susceptible towards attack on the carbonyl function by the allyl Grignard reagents, thus producing the corresponding allylic alcohol and a tertiary alcohol. This reaction is very fast due to the involvement of a cyclic six-membered transition state. This side reaction took place even if magnesium diallylcuprates were preformed before addition of the allylic substrate.

By adjustment of the reaction conditions, the undesired reaction of the carbonyl function with the Grignard reagent can be slowed down compared with the allylic substitution. Allylic esters with a more sterically hindered leaving group, for example a mesitoate (2,4,6-trimethylbenzoate, OC(O)-Mes), are known to be less susceptible to carbonyl attack by Grignard reagents[27] and this was also the case in our system. Further improvement was achieved by a change of solvent from Et$_2$O to THF, and by use of allylMgCl instead of allylMgBr. Thus, the carbonyl attack was suppressed completely in favor for the allylic substitution reaction (Scheme 2).



Scheme 2. Carbonyl attack or allylic substitution depending on the reaction parameters.

With THF as solvent the Grignard reagent becomes less reactive towards the carbonyl group and under these conditions allylMgCl did not attack the carbonyl of the allylic acetate. The solvent effect can be explained in two ways: i) coordination of THF to Mg blocks the coordination of the carbonyl oxygen to the allyl Grignard reagent and ii) THF is a better solvent for the precursor Cu^{I} salt and the allylic copper species formed, and therefore results in a more complete cuprate formation compared with Et$_2$O as the solvent. It has recently been concluded from X-ray measurements that the structure of Me$_2$CuLi is solvent dependent, Me$_2$CuLi being present as a dimer in Et$_2$O, but as a monomeric ionic species Me$_2$Cu$^-$ and Li$^+$ in THF.[28]

With these optimized reaction conditions in hand we turned to reactions with γ-substituted allylic Grignard reagents.

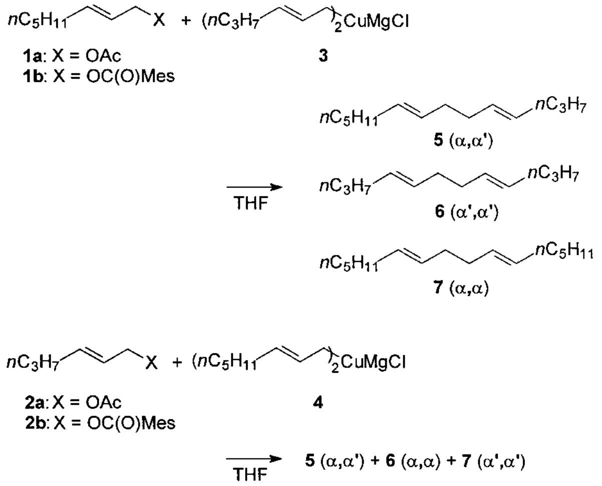
Reactions involving preformed diallylcuprates: An allylic ester and an allylic Grignard reagent containing γ-alkyl substituents of similar size were chosen for this study to minimize the influence of the substituents on the product distribution (Scheme 3, Table 1).

A diallylcuprate was generated from 2.3 equiv Grignard reagent and 1.2 equiv Cu^{I} salt in THF at -20 to $-30\,^{\circ}$C. The allylic ester (1 equiv) was subsequently added at the temperature specified in Table 1. Cross-coupling α,α' and homo-coupling α',α' predominated, but also minute amounts of α,α-homo-coupling product originating from the allylic ester was observed. A control reaction without any addition of allylic ester was always run parallel to estimate the amount of α',α'-homo-coupling products from decomposition reactions of the

Table 1. Reactions between allylic esters and preformed diallyl cuprates.[a]

Entry	Substrate	Diallyl cuprate	Cu source	T [°C]	Conversion [%]	Product distribution[b] 5	6	7
1	**1a**	**3**	$CuBr\cdot SMe_2$	–60	100	40	56 (α',α')	4 (α,α)
2	**1a**	[c]	$CuBr\cdot SMe_2$	–60	< 10	–	–	–
3	**1a**	[d]	$CuBr\cdot SMe_2$	–60	100	40	55 (α',α')	5 (α,α)
4	**1a**	**3**	$CuBr\cdot SMe_2$	–20	90	50	43 (α',α')	7 (α,α)
5[e]	**1a**	**3**	$CuBr\cdot SMe_2$	–20	95	56	38 (α',α')	6 (α,α)
6	**1a**	**3**	CuI	–60	100	44	50 (α',α')	6 (α,α)
7	**1a**	**3**	$CuCl\cdot 2LiCl$	–30	100	38	57 (α',α')	5 (α,α)
8	**1b**	**3**	$CuBr\cdot SMe_2$	–20	95	49	41 (α',α')	9 (α,α)
9[e]	**1b**	**3**	$CuBr\cdot SMe_2$	–20	90	58	37 (α',α')	5 (α,α)
10	**2a**	**4**	$CuBr\cdot SMe_2$	–60	100	39	5 (α,α)	56 (α',α')
11	**2a**	**4**	$CuBr\cdot SMe_2$	–20	100	42	5 (α,α)	53 (α',α')

[a] Unless otherwise noted, the reactions were run according with the general procedure stated in the Experimental Section. [b] Product ratios are after subtraction of the amount of α',α'-product formed in the control reaction. [c] A monoallyl copper species made from 1.3 equiv $CuBr\cdot SMe_2$ and 1.3 equiv allyl Grignard was used. [d] 3 equiv of allyl Grignard for each Cu. [e] Ten times more diluted reaction mixture. Reaction time 2 h.



Scheme 3. Reactions between allylic esters and preformed diallylcuprates.

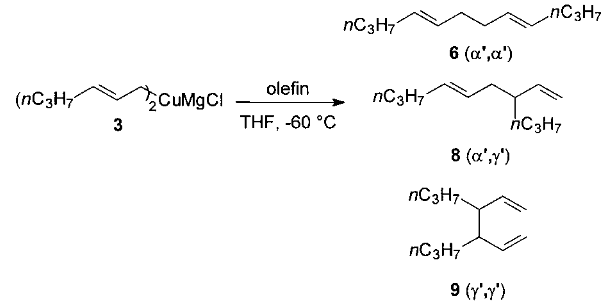
Grignard reagent or allylic copper species under the reaction conditions. The product ratio stated was determined from GC-analysis of the reaction mixture, and after subtraction of the small amount of α',α'-homo-coupling product in the control reaction in each case. It should be noted that careful preparation of the allylic Grignard reagents gives a diallylcuprate reagent free from these Wurtz-coupling-type products. However, these Grignard reagents have limited stability and decompose slowly to give coupling products (complete decomposition within a week).[29] They should therefore be used shortly after preparation.[30] From the results of the control reactions it could be concluded that the magnesium diallylcuprates did not give any significant amounts of homo-coupling products at low temperature (–60 °C) under the reaction conditions employed, but when the temperature was raised, increasing amounts of homo-coupling were observed.[31]

All copper-mediated coupling reactions studied showed high selectivity (≈95%) for the straight-chain products, as mixtures of E/Z-isomers,[32] with only minor amounts of other regioisomers being formed. A similar selectivity was noted by Linstrumelle et al.[19a] This is in contrast to the results of Yamamoto et al.[26] for the reaction between allylic substrates and prenyl Grignard reagents mediated by $CuCN\cdot 2LiCl$. The latter reaction was γ,α'-selective, with the prenyl unit reacting at the least substituted terminus and the allylic electrophile reacting in a S_N2' fashion.

The reaction of allylic acetate **1a** with diallylcuprate **3**, prepared from $CuBr\cdot SMe_2$, was studied under different conditions. At –60 °C (Table 1, entry 1) a mixture of cross-coupling product **5** and homo-coupling products **6** (α',α') and **7** (α,α) was formed in a ratio of 40:56:4. A monoallylcopper species on the other hand resulted in a very poor reaction, less than 10% conversion was achieved at –60 °C (Table 1, entry 2). Changing the stoichiometry of copper salt to Grignard reagent to 1:3 resulted in a similar ratio compared to that of the reaction with a diallylcuprate (Table 1, entry 3). Performing the reaction between **1a** and **3** at a higher temperature (–20 °C) gave a product ratio **5**:**6**:**7** of 50:43:7 (Table 1, entry 4). Apparently, a higher temperature gives a ratio between the cross-coupling and homo-coupling products slightly closer to the predicted ratio of 67:33:0 for a Cu^{III} intermediate (Scheme 1). To investigate the effect of concentration, reactions were also run under more dilute conditions (10 times more diluted, 0.01 M of **1a**). At –60 °C, the reaction was very slow under these conditions, but at –20 °C a reasonably fast reaction was achieved (more than 90% conversion after 2 h) and **1a** and **3** gave a product ratio **5**:**6**:**7** of 56:38:6 (Table 1, entry 5). This ratio is closer to the predicted ratio than that obtained at higher concentration. Changing the catalyst precursor to CuI had a minor influence on the ratio (Table 1, entry 6). $CuCl\cdot 2LiCl$ could also be used as catalyst precursor with a similar result (Table 1, entry 7). The reaction of allylic mesitoate **1b** was also investigated (Table 1, entries 8 and 9) and resulted in similar product ratios as obtained for **1a**. Also here, reaction under more dilute conditions (entry 9) gave a ratio quite close to that predicted by a Cu^{III} intermediate.

As can be noted in Table 1, in all cases the reactions give substantial amounts of α',α'-homo-coupling product and also small amounts of the α,α-product. Formation of the α',α'-homo-coupling product is expected if the reaction proceeds via a Cu^{III} intermediate with three equivalent allyl groups (Scheme 1). With the alternative direct displacement mechanism, not involving Cu^{III} (path II, Scheme 1), only the cross-coupling product α,α' would be formed. However, the Cu^{III} pathway should only result in 33% of α',α' coupling. The observation of an excess of α',α' product compared with the model compound, and the formation of α,α-homo-coupling, must be explained in a different way.

It is known that reductive elimination is favored by electron-withdrawing ligands. For example, for organopalladium and organonickel complexes it has been shown that coordination of an electron-withdrawing olefin such as maleic anhydride or allyl chloride can induce reductive elimination resulting in a coupling product and a metal–olefin complex.[33] We reasoned that the coordination of an allylic ester to the diallylcopper(I) species can result in a similar effect, and promote the α',α'-homo-coupling reaction, before the oxidative addition of the allylic ester would occur. To test this hypothesis, the electron-withdrawing olefins maleic anhydride and allyl ethyl ether were added to a diallylcuprate at −60 °C under the same conditions as for the reactions with allylic esters (Scheme 4). The amount of homo-coupling was then compared with a control reaction without the olefin. The solution of cuprate **3** turned bright red immediately upon addition of maleic anhydride at −60 °C. After 30 min at this temperature, significant formation of α',α'-product **6** was noted; about 30% was formed in the presence of maleic anhydride compared with less than 5% in the control reaction. Also 10% of the α',γ'-product **8** was formed in this reaction. Interestingly, a considerable amount of γ',γ'-product **9** was formed. Diene **9** could not be detected in the control reaction, but increased to 30% in the presence of maleic anhydride. With allyl ethyl ether a smaller, but nevertheless significant effect was observed. 10% each of the α',α'-product **6** and α',γ'-products **8** were formed together with 3% of the γ',γ'-product **9**. It should be noted that no conjugate addition to maleic anhydride, or substitution reaction of allyl ethyl ether could be detected under the reaction conditions employed for these experiments. These results clearly show that an olefin with electron-withdrawing properties can interact with a diallylcuprate to promote coupling of the allyl groups. The different regiochemistry of the coupling products in the presence of maleic anhydride and allylic esters can not be explained at the moment.

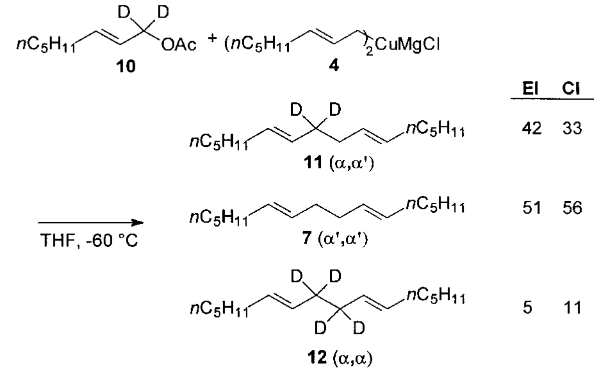


Scheme 4. Olefin-promoted homo-coupling in a diallyl cuprate.

An explanation for the observation of the homo-coupling product α,α is that there is incomplete formation of the diallylcuprate.[34] In this case free allyl Grignard reagent would be present in the solution. A reductive elimination from the Cu^{III} intermediate to give α',α'-homo-coupling then leaves an R-allyl-Cu^{I} species that can react with this free R′-allyl Grignard reagent to give a mixed diallylcuprate. The latter can then in turn react with the R-allylic ester to give rise to α,α'- and α,α-products. This is further discussed for the reactions involving a catalytic amount of Cu^{I} (see below). Similarly, any ligand-exchange processes between the remaining diallylcuprate and the allylCu released after a reaction cycle can also give rise to a mixed cuprate. Lipshutz et al. have shown that Gilman cuprates readily exchange ligands in ether solvents.[35]

To rule out that the above results are a consequence of the different chain lengths of the substituents on the allyl moieties, reactions were also performed using substrates with the opposite substitution pattern (Table 1, entries 10 and 11). Reaction of allylic acetate **2a** with diallylcuprate **4** gave results similar to those obtained for **1a** and **3**.

In addition, reactions were also run using the deuterated allylic acetate **10** and the nondeuterated diallylcuprate **4** with the same γ substituent, nC_5H_{11} (Scheme 5). The product composition was evaluated using electron impact (EI), and chemical ionization (CI) GC-MS, by comparison of the molecular ion peaks for the deuterated and nondeuterated products. The values obtained from EI and CI differ to some extent, but the product ratios are comparable to those obtained with nondeuterated substrates in Table 1.

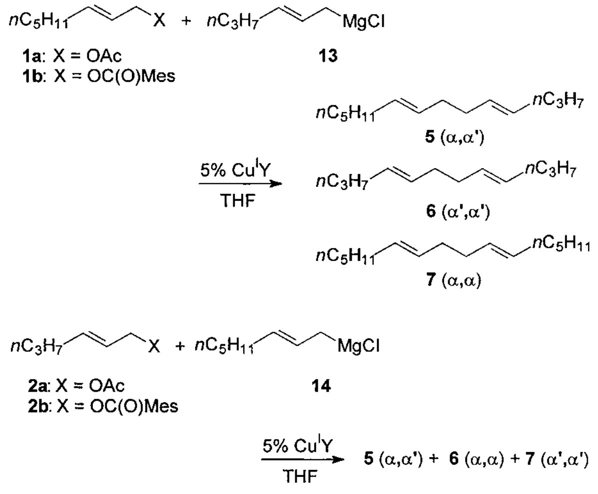


Scheme 5. Reaction of a deuterated allylic acetate with a diallyl cuprate.

Reactions with a catalytic amount of a copper(I) salt: A reaction mediated by a catalytic amount of copper is expected to give a slightly different product ratio compared with the stoichiometric reaction. The reason is that after the first cycle α',α'-homo-coupling product from (R′-allyl)$_2$(R-allyl)Cu would leave 33% of (R-allyl)Cu, in which the allyl group now originates from the allylic ester. Reaction with the Grignard reagent and subsequent oxidative addition would give (R-allyl)$_2$(R′-allyl)Cu, which now would produce ⅔ of cross-coupling (α,α') and ⅓ of α,α-homo-coupling. The cross-coupled product should still make up for ⅔ of the total product yield, but the relative amount of α',α'-product should decrease for each successive catalytic cycle and the relative amount of α,α-product should increase. The product ratio ($\alpha,\alpha':\alpha',\alpha':\alpha,\alpha$) will be determined by Equation (2) and will approach approximately ⅔:⅙:⅙ at high turnover numbers according to this statistic analysis.[36] The catalytic reaction was studied using 5 mol% of a Cu^I salt as catalyst (Scheme 6, Table 2). The predicted ratio **5**:**6**:**7** at 20 turnovers is 67:18:15 according to Equation (2).

$$(\alpha',\alpha,\ \alpha',\alpha',\ \alpha,\alpha)_n = \frac{1}{n}\left(\frac{2}{3},\ \frac{1}{3},\ 0\right) + \frac{1}{n}\sum_{n=2}^{n}\left(\frac{2}{3},\ \frac{1}{3} - \sum_{k=2}^{k=n}\frac{1}{3^{\mathrm{k}}},\ \sum_{k=2}^{k=n}\frac{1}{3^{\mathrm{k}}}\right) \tag{2}$$

The Grignard reagent in THF was added over 30 minutes by means of a syringe pump to minimize carbonyl attack by the Grignard reagent (see above). For these catalytic experiments, the temperature is critical. At low temperatures (−70 or −30 °C) with CuI as catalyst, no reaction was observed between allylic mesitoate **1b** ($R = nC_5H_{11}$) and Grignard reagent **13** ($R' = nC_3H_7$). Even if the reaction temperature is raised later, the reaction does not perform well. At −20 °C and at 0 °C the allylic substitution reaction goes to completion. At 0 °C the reaction is fast, and full conversion is achieved within one hour (Table 2, entry 1) giving the cross-coupled product **5** and homo-coupled products **6** and **7** in the ratio 62:23:15. At −20 °C the reaction is slower and full conversion is reached within 3 h (Table 2, entry 2). $CuBr \cdot SMe_2$ could also be used as catalyst and at 0 °C, and gave a similar result to that of CuI (Table 2, entry 3).



Scheme 6. Reactions between allylic esters and allylic Grignard reagents catalyzed by a copper(I)-salt.

Reactions run with allylic mesitoate **2b** ($R = nC_3H_7$) and Grignard reagent **14** ($R' = nC_5H_{11}$) gave similar results. Thus, opposite chain lengths compared with **1b** and **13**, as in the stoichiometric reaction, did not affect the outcome of the reactions (Table 2, entries 4 and 5). Allylic acetates were not suitable substrates in the catalytic reaction and carbonyl attack by the Grignard reagent was the main reaction.

The allylic mesitoate **1b** did not react with $CuCN \cdot 2\,LiCl$ as catalyst at low temperatures and the starting material was recovered. At −20 °C full conversion of **1b** was achieved, but the major reaction was carbonyl attack leading to the formation of the corresponding allylic alcohol. Only when the reaction was run at 0 °C a reasonable selectivity for the allylic substitution reaction was achieved (Table 2, entry 6), but there was still a significant amount carbonyl attack under these conditions. For this reason the ratio of homo- and cross-coupled products deviated slightly to those observed for the other catalysts studied (CuI and $CuBr \cdot SMe_2$). Again, there was high selectivity for the straight chain products **5**–**7** in all cases studied.

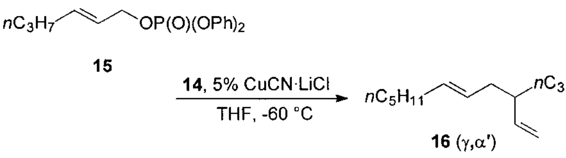
Notably the product ratios obtained under these catalytic conditions are close to the ratio predicted by Equation (2). Compared with the stoichiometric reactions, the catalytic reactions give more of the α,α-, and less of the α',α'-homo-coupling products. Especially the formation of more α,α-homo-coupling product under the catalytic conditions, is a strong indication for a Cu^{III} intermediate. It is also noteworthy that the catalytic reaction, as observed for the preformed cuprates, is highly selective for the straight chain 1,5-diene products. Yamamoto et al.[26c,d] have studied the $CuCN \cdot 2\,LiCl$ catalyzed cross-coupling between allylic Grignard reagents and allylic phosphates in THF. They found that the reaction was selective for the γ,α'-product. Only minor amounts of the straight chain α,α'-products were formed. This is in sharp contrast to our study with allylic mesitoate in THF where the straight chain cross-coupling products dominate. Also, Yamamoto et al. report high isolated yields (>89%) of the cross-coupling product without any mentioning of homo-coupling as side reaction.[26c,d] We repeated this reaction and obtained results similar to those of Yamamoto et al. Compound **16** (γ,α') was formed together with the α,α'-product **5** in a ratio of 95:5 (isolated yield 63%) from allylic phosphate **15**[26d] and Grignard reagent **14** [Eq. (3)]. Less than 2% of homo-

Table 2. Allylic substitution between allylic esters and allylMgCl catalyzed by a Cu^I salt.[a]

Entry	Cu-catalyst	Substrate/Grignard	T [°C]	Conversion [%]	t [h]	Product distribution[b] **5**	**6**	**7**
1	CuI	**1b**/**13**	0	100	1	62	23 (α',α')	15 (α,α)
2	CuI	**1b**/**13**	−20	100	3	59	25 (α',α')	16 (α,α)
3	$CuBr \cdot SMe_2$	**1b**/**13**	0	100	1	59	26 (α',α')	15 (α,α)
4	CuI	**2b**/**14**	−20	90	4	62	19 (α,α)	19 (α',α')
5	CuI	**2b**/**14**	0	100	1	58	15 (α,α)	27 (α',α')
6	$CuCN \cdot 2\,LiCl$	**1b**/**13**	0	100 [c]	1	60	30 (α',α')	10 (α,α)

[a] Unless otherwise stated, the reactions were run according with the general procedure in the Experimental Section. [b] Product ratios are after subtraction of the amount of α',α'-product formed in the control reaction. [c] Allylic substitution accompanied by carbonyl attack.

coupling products from the Grignard reagent **14** was formed and homo-coupling products from the allylic phosphate could not be detected.



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However, as mentioned above, the less reactive allylic mesitoate **1b** did not react with CuCN • 2LiCl as catalyst at low temperatures. We interpret these results in the following way: The very reactive allylic phosphate reacts with a lower-order cyanocuprate, allylCu(CN)MgCl, formed from the allylic Grignard reagent and CuCN at $-78\,^{\circ}C$. At this temperature the cyano diallylcuprate reagent[27] allyl$_2$CuMgCl • LiCN is not formed. The regioselective S_N2'-attack on the allylic phosphate and the absence of homo-coupling products supports that the active catalyst is a monoallylcopper species which would favor formation of γ product (see Scheme 7). The unreactive mesitoate **1b**, on the other hand, does not react with these lower-order species, but at $0\,^{\circ}C$, a temperature high enough for the formation of a cyano diallylcuprate, a coupling reaction takes place. The more reactive diallylcuprate reacts with **1b** via a triallyl-Cu^{III} intermediate and a mixture of homo- and cross-coupled products are formed. Diallylcuprate would favor formation of the α product. Attempts to react either **1a** or **1b** with preformed monoallyl cyanocuprate **17** or cyano diallylcuprate **18** were unsuccessful. Cuprate **17** did not react with **1a** at -40 or $-20\,^{\circ}C$ and decomposed immediately when warmed to $0\,^{\circ}C$. Cuprate **18** did react with **1b** to some extent at $0\,^{\circ}C$ before decomposition, resulting in products **5**, **6**, and **7** in a ratio of 54:43:3. Reaction of **18** with **1a** was unsuccessful, leading to carbonyl attack and recovery of the starting material.

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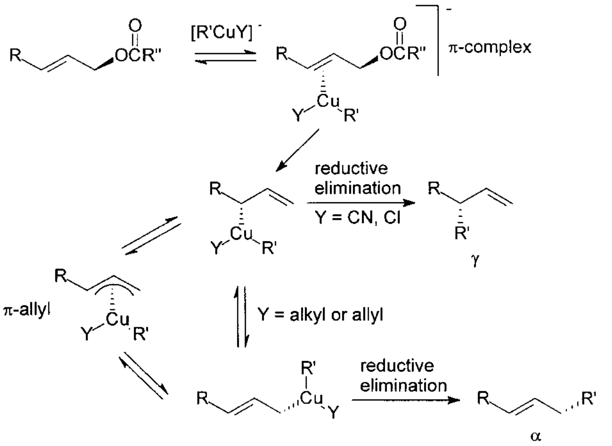
The similarities in regioselectivity and product composition in the reaction between **1b** and **13** catalyzed by CuI and CuCN • 2 LiCl further support the view[37] that the cyano group is not residing on copper in a "higher-order" cyanocuprate.

Discussion

Extensive studies by Kochi et al.[38] of the reactions of gold complexes RAu^{I}L and R$_2$Au^{I}L have revealed that they react with alkyl halides through an oxidative addition to yield an Au^{III} complex which on reductive elimination yields a cross-coupled product and an Au^{I} species. The oxidative addition of alkyl halides to R$_2$Au(L)Li gives the *trans*-product. The square planar R$_3$Au^{III}L-complex can undergo reductive elimination, through initial dissociation of L, as well as *cis*–*trans* isomerization of the ligands. The reductive elimination proceeds by loss of *cis*-alkyls from a T-shaped R$_3$Au^{III} intermediate. Scrambling of groups between different R$_3$Au^{III}L complexes has also been noted. However, Kochi et al. also investigated the corresponding reaction of dimethylcuprate with CD$_3$I without finding any exchange of alkyl groups or homo-coupled products. Only cross-coupled product (CH$_3$–CD$_3$) was observed. A mechanism via Cu^{III} with reductive elimination of *cis* groups, similar to the gold mechanism, was proposed, but a direct displacement via a four-centered transition state could not be ruled out.[38a]

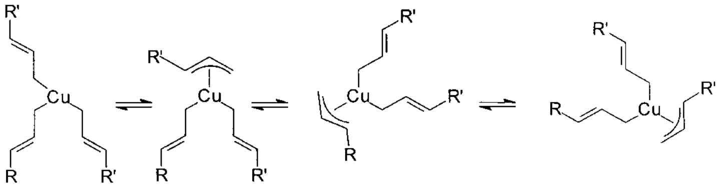
We and others have earlier proposed that the allylic substitution reaction between an allylic ester and an organocuprate proceeds through initial π complexation of Cu^{I} to the allylic double bond, followed by an S_N2'-selective oxidative addition anti to the leaving group.[3, 5g, 6a, f, 39] The (σ-allyl)-Cu^{III} complex thus formed can undergo a fast reductive elimination if one group on Cu is cyanide or halide (cf. the case of a lower-order cyano cuprate, see above). Without an electron-withdrawing group on Cu^{III} ($Y = R' =$ alkyl or allyl), the reductive elimination is delayed and an isomerization, presumably via a (π-allyl)copper(III) intermediate can take place to a terminal (σ-allyl)copper(III) species. Reductive elimination from this species would give the product of formal S_N2 attack (Scheme 7).



Scheme 7. Proposed mechanism for the copper-mediated allylic substitution reaction ($R' =$ alkyl or allyl).

The results of the present study strongly support this mechanistic proposal. The product ratios obtained from the stoichiometric reactions differ slightly from the ratio predicted by the Cu^{III} pathway (α,α'-cross-coupling and α',α'-homo-coupling in a ratio of 2:1) but our results can not be accommodated by the direct displacement mechanism. It is noteworthy that the results from the study with catalytic amounts of copper give product ratios very close to those predicted by the Cu^{III} mechanism. For the stoichiometric reactions with preformed diallylcuprates, a larger deviation from the ratio predicted is observed. The excess α',α'-homo-coupling can be partly accounted for by an olefin-promoted reductive elimination. The difference between the stoichiometric and catalytic reactions with respect to the relative amount of α',α'-homo-coupling product can also be accounted for by the different concentrations of the organocopper species. Indeed, stoichiometric reactions performed under more dilute conditions resulted in product ratios closer to those expected from a Cu^{III} intermediate (Table 1, entries 5 and 9). These results imply that aggregation or other concentration-dependent phenomena can be important for the cuprate reactivity.

The possibility of the allyl group to form both σ- and π-allyl complexes[40] provides a way for equilibration of the different allyl groups in a Cu^{III} intermediate (Scheme 8). Thus, by formation of a complex with two σ-allyl ligands and one π-allyl ligand, a 16-electron configuration is achieved. The corresponding trialkyl Cu^{III} complexes do not match this configuration, and the R$_3$Cu 14-electron complex would need stabilization from a donor ligand to give a 16-electron complex.[12] This would explain the lack of homo-coupling in the reaction between dimethylcuprate and CD$_3$I.[38a] Stabilization could also be possible by dimerization through bridging alkyl groups. In this case the three groups bound to the copper will not be equivalent and a selective cross-coupling reaction is achieved. Hutchinson and Fuchs proposed that the sometimes odd reactivity of lithium diallylcuprate, compared with dialkylcuprates, is due to that the allyl ligands can act as η^3, 4-electron ligands to Cu^I.[41]



Scheme 8. Equilibration of the ligands in a triallyl-Cu^{III} intermediate via σ-allyl–π-allyl interconversions.

Conclusion

The copper-mediated allylic substitution reaction of allylic esters with allylic Grignard reagents gives mixtures of different homo- and cross-coupled 1,5-dienes. The ratio between cross-coupling and homo-coupling product obtained rules out a direct displacement mechanism and provide strong support for a Cu^{III} intermediate with three pseudo-equivalent allyl groups. The latter intermediate would give the observed mixture of 1,5-dienes through reductive elimination. The fact that the experimental data from the copper-catalyzed coupling reactions are in good agreement with the predicted statistical distribution between the 1,5-dienes, lends strong support to a copper(III) intermediate. The possibility of the allylic group to form both σ- and π-allyl complexes provides a way for equilibration of the different allyl groups on Cu^{III}.

Experimental Section

General methods: NMR spectra were recorded for CDCl$_3$ solutions (^{1}H at 300 or 400 MHz and ^{13}C at 100.5 or 75 MHz, using residual CHCl$_3$ as internal reference ($\delta = 7.26$ in ^{1}H, $\delta = 77.0$ in ^{13}C NMR spectra). THF and Et$_2$O were distilled from Na/benzophenone under a nitrogen atmosphere. All glassware was oven-dried, or flame-dried under vacuum prior to use. Low reaction temperatures were maintained by use of a cryostat or an acetone-dry ice bath. All reactions were run under an argon atmosphere. Product compositions were evaluated by GC (with decane as internal standard), GC-MS (Electron impact (EI) or chemical ionization (CI)), and NMR-analysis.

Preparation of starting materials: (*E*)-2-Octen-1-ol[42] was prepared by DIBAL-H reduction[3d] of ethyl-*trans*-2-octenoate. Allylic chlorides (*E*)-1-chloro-2-hexene[43] and (*E*)-1-chloro-2-octene[42b] were prepared from the corresponding allylic alcohols through reaction with NCS and Me$_2$S[44] or PPh$_3$.[45] Acetylation and mesitoylation of the allylic alcohols were performed with acetic anhydride and mesitoyl chloride, respectively.[3d] Compounds **1a**[3b] and **2a**[46] had spectral data in accordance with the literature.

(*E*)-2-Octenyl-2,4,6-trimethylbenzoate (1b): ^{1}H NMR (300 MHz): $\delta = 6.83$ (s, 2H), 5.85 (m, 1H), 5.65 (m, 1H), 4.74 (dd, $J = 6.6$, 0.8 Hz, 2H), 2.28 (s, 6H), 2.27 (s, 3H), 2.06 (q, $J = 6.9$ Hz, 2H), 1.45–1.20 (m, 6H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz): $\delta = 169.8$, 139.0, 137.2, 134.9, 128.2, 123.5, 65.6, 32.3, 31.4, 28.6, 22.6, 21.2, 19.8, 14.1; IR: $\tilde{\nu} = 1725$, 1612 cm^{-1}; MS (EI): *m*/*z* (%): 274 (6) [*M*]$^+$, 176, 175, 164, 163, 147 (100), 146, 119, 91.

(*E*)-2-Hexenyl-2,4,6-trimethylbenzoate (2b): ^{1}H NMR (400 MHz): $\delta = 6.89$ (s, 2H), 5.86 (dtt, $J = 15.3$, 6.7, 1.1 Hz, 1H), 5.68 (dtt, $J = 15.3$, 6.6, 1.5 Hz, 1H), 4.75 (dq, $J = 6.6$, 0.9 Hz), 2.29 (s, 6H), 2.27 (s, 3H), 2.06 (brq, $J = 7.4$ Hz, 2H), 1.43 (sextet, $J = 7.4$ Hz, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100.5 MHz): $\delta = 169.7$, 139.0, 136.9, 134.9, 130.9, 128.2, 123.7, 65.6, 34.4, 22.2, 21.3, 19.8, 13.8; IR: $\tilde{\nu} = 1725$, 1612 cm^{-1}; MS (EI): *m*/*z* (%): 246 (18) [*M*]$^+$, 217, 203, 176, 175, 164, 163, 147, 146, 119, 91.

The deuterated allylic acetate **10** was prepared from ethyl-(*E*)-2-octenoate by reduction with diisobutylaluminium deuteride[47] followed by standard acetylation.

1,1-Dideuterio-(*E*)-2-octenol: ^{1}H NMR (400 MHz): $\delta = 5.70$ (dt, $J = 15.3$, 6.3 Hz, 1H), 5.62 (brd, $J = 15.3$ Hz, 1H), 2.04 (tdd, $J = 7.3$, 6.3, 1.0 Hz, 2H), 1.43–1.23 (m, 6H), 0.89 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100.5 MHz): $\delta = 133.9$, 128,8, 32.6, 31.8, 29.2, 22.9, 14.5; IR: $\tilde{\nu} = 3326$ (br), 2187, 2085, 1668 cm^{-1}; MS (EI): *m*/*z* (%): 128 (3) [*M*]$^+$, 113, 112, 97, 96, 84, 83, 82, 81, 80, 79, 71, 70, 69 (100), 68, 67.

1,1-Dideuterio-(*E*)-2-octenyl acetate (10): ^{1}H NMR (400 MHz): $\delta = 5.77$ (dt, $J = 15.4$, 6.8 Hz, 1H), 5.55 (brd, $J = 15.4$, 1H), 2.05 (s, 3H), 2.05 (m, 2H), 1.43–1.22 (m, 6H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100.5 MHz): $\delta = 170.7$, 136,7, 123.4, 32.3, 31.5, 28.7, 22.6, 21.2, 14.2; IR: $\tilde{\nu} = 2232$, 2164, 2105, 1742 cm^{-1}.

Preparation of allylic Grignard reagents: Magnesium turnings (121 mg, 5 mmol) were flame-dried under vacuum for a few minutes in a Schlenk tube. Vigorous stirring under argon overnight produced very active magnesium. THF (0.5 mL) was added to the magnesium. (*E*)-1-Chloro-2-hexene (119 mg, 1 mmol) was dissolved in THF (1.5 mL). A few drops of this solution were added at room temperature to start the reaction. The reaction mixture was then cooled to −15 °C by means of an ice-salt bath. The solution of allyl chloride was added dropwise during 1 h using a syringe pump. The resultant grey-brown solution was stirred for 30 min. A GC-analysis was made to ensure complete conversion. The molarity of the Grignard reagent was then estimated by titration against an 1 M solution of 2-butanol in xylene using *N*-phenyl-1-naphthylamine as indicator.[48] The reagent usually had a concentration ranging between 0.42–0.45 M, and was best used the same day as it was prepared. Storage resulted in decomposition and formation of Wurtz-type-coupling products.[29]

General procedure for reactions using preformed diallylcuprates: CuBr·SMe$_2$ (37 mg, 0.18 mmol) was placed in a Schlenk tube. The tube was evacuated and filled with argon. This procedure was repeated twice. THF (1 mL) was added. The suspension was cooled to −20 °C and allylic Grignard reagent **3** (0.45 M, 0.8 mL, 0.35 mmol) was added. The resulting dark green-brown reaction mixture was stirred at this temperature for 15 min. The temperature was then adjusted to the given reaction temperature (see Table 1). Substrate **1a** (26 mg, 0.15 mmol) and decane (21 mg, 0.15 mmol) were dissolved in THF (1 mL) and added to the reaction mixture through a cannula. GC samples were taken from the reaction mixture at regular intervals and quenched in 2 M HCl (aq). Usually the reactions were complete within 1 h. The reaction was quenched by addition of 2 M HCl (1 mL) and Et$_2$O (2 mL). Extraction of the aqueous phase with Et$_2$O followed by washing of the combined organic fractions, drying over MgSO$_4$ and evaporation of all volatiles gave a mixture of the reaction products that was analyzed by NMR and GC. A control reaction was prepared and treated in the same manner as the reaction, but excluding addition of the allylic ester.

General procedure for reactions employing a catalytic amount of copper: CuI (2 mg, 10 µmol), allylic ester **1b** (55 mg, 0.20 mmol), and decane (28 mg, 0.20 mmol) were placed in a Schlenk tube. The tube was evacuated and filled with argon; this procedure was repeated three times. THF (2 mL) was added. The suspension was cooled to the given reaction temperature (see Table 2) and the allylic Grignard reagent **3** (0.45 M, 0.67 mL, 0.30 mmol) was added over 30 min by use of a syringe pump. After complete addition, GC samples were taken at regular intervals. When the reaction was completed the same workup procedure as above was performed, except when CuCN was employed as catalyst, NH_4Cl (aq) was used to quench the reaction. A control reaction was prepared and treated in the same manner as the reaction, but excluding the allylic ester.

Data for the substitution products: 1,5-Dienes **5**–**7** were synthesized by an independent method and had the same spectral data and retention times as the products obtained in the copper-mediated coupling reactions.

(*E,E*)-6,10-Tetradecadiene (5): ^1H NMR (400 MHz): $\delta = 5.40$ (m, 4H), 2.04 (m, 4H), 1.96 (m, 4H), 1.36 (sextet, $J = 7.3$ Hz, 4H), 1.29 (m, 4H), 0.89 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (100.5 MHz): $\delta = 130.6$, 130.3, 129.8, 129.5, 34.8, 32.9, 32.7, 31.5, 29.4, 22.8, 22.7, 14.2, 13.8; MS: m/z (%): 194 (19) $[M]^+$, 193, 152, 151, 138, 137, 124, 123, 110, 109, 96, 95, 82, 81, 79, 69, 67 (100).

(*E,E*)-4,8-Dodecadiene (6):[49] ^1H NMR (400 MHz): $\delta = 5.40$ (m, 4H), 2.05 (m, 4H), 1.96 (m, 4H), 1.36 (sextet, $J = 7.3$ Hz, 4H), 0.89 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (100.5 MHz): $\delta = 130.3$, 129.8, 34.8, 32.9, 22.8, 13.8; MS: m/z (%): 166 (9) $[M]^+$, 165, 124, 123, 110, 109, 95, 82, 81, 79, 67 (100).

(*E,E*)-6,10-Hexadecadiene (7): ^1H NMR (400 MHz): $\delta = 5.40$ (m, 4H), 2.04 (m, 4H), 1.97 (m, 4H), 1.38–1.20 (m, 12H), 0.89 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (100.5 MHz): $\delta = 130.6$, 129.6, 32.9, 32.7, 31.5, 29.4, 22.7, 14.2; MS: m/z (%): 222 (28) $[M]^+$, 221, 152, 151, 138, 137, 123, 110, 109, 96, 95, 82, 81 (100), 79, 69, 68, 67.

3-Propyl-1,5-undecadiene (16): (isolated as a mixture of *E*- and *Z*-isomers, with 5% of **6** and 8% of **7**): ^1H NMR (400 MHz): $\delta = 5.58$ (m, 1H), 5.44–5.31 (m, 2H), 4.98–4.91 (m, 2H), 2.00 (m, 2H), 1.42–1.15 (m, 10H), 0.91–0.86 (m, 6H); MS: m/z (%): 194 (4) $[M]^+$, 165, 151, 137, 123, 109, 96, 95, 82, 81, 79, 69, 67 (100).

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[31] Diallylcuprate **3**, made from CuBr·SMe$_2$, when stirred at $-60\,^{\circ}$C for 30 min, forms less than 5% of homo-coupling product **6** (and regioisomers **8** and **9**). Warming of the reaction mixture to $-20\,^{\circ}$C gives after 2 h: 17% **6**, 13% **8**, 3% **9**, and after warming to $0\,^{\circ}$C and a total reaction time of 3.5 h: 28% **6**, 21% **8**, 6% **9**.

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$$\lim_{n\to\infty}\sum_{k=2}^{n}\frac{1}{3^k} = \frac{1}{6}$$

For further details concerning the derivation of Equation (2), see the Supporting Information.

[37] The term "higher-order cyanocuprate" should be avoided due to the recent spectroscopic evidence concerning the structure of the corresponding lithium reagents R$_2$CuLi·LiCN. The cyano group was found not to be bound to copper, and this class of reagents was proposed to be called cyano-Gilman reagents. See for example: a) S. H. Bertz, *J. Am. Chem. Soc.* **1990**, *112*, 4031–4032; b) S. H. Bertz, *J. Am. Chem. Soc.* **1991**, *113*, 5471–5474; c) S. H. Bertz, G. Miao, M. Eriksson, *Chem. Commun.* **1996**, 815–816; d) S. H. Bertz, K. Nilsson, Ö. Davidsson, J. P. Snyder, *Angew. Chem.* **1998**, *110*, 327–331; *Angew. Chem. Int. Ed.* **1998**, *37*, 314–317; e) C. M. P. Kronenburg, J. T. B. H. Jastrzebski, A. L. Spek, G. van Koten, *J. Am. Chem. Soc.* **1998**, *120*, 9688–9689; f) G. Boche, F. Bosold, M. Marsch, K. Harms, *Angew. Chem.* **1998**, *110*, 1779–1781; *Angew. Chem. Int. Ed.* **1998**, *37*, 1684–1686; h) see ref. [1e].

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