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Unusual Homocoupling in the Reaction of Diorganocuprates with an Allylic Halide

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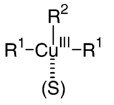
Summary: The reactions of dialkyl- and diarylcuprates (R_2CuM; M = Li, MgBr) with perfluoroallyl iodide were found to give the homocoupling products R−R as the only product of C−C bond formation. Density functional calculations revealed that the perfluoroallyl ligand, being strongly electron-withdrawing and less Lewis basic, significantly changes the electronic properties of the allylcopper(III) intermediate and acts as a spectator ligand in the reductive elimination.

Reactions of organocopper reagents with alkyl halides and tosylates and allylic substrates have been extensively used in organic synthesis as a powerful method for C−C bond formation.[1] In the early stages of organocopper chemistry, Whitesides et al. demonstrated that a reaction of a homocuprate (R^1_2CuLi) with an alkyl halide (R^2−X) exclusively gives a cross-coupling product (R^1−R^2).[2,3a] The failure to observe homocoupling products even from the reaction of $(CH_3)_2CuLi$ with CD_3I led to the assumption that the T-shaped intermediate **A** is formed.[3b]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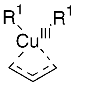
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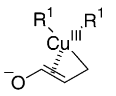
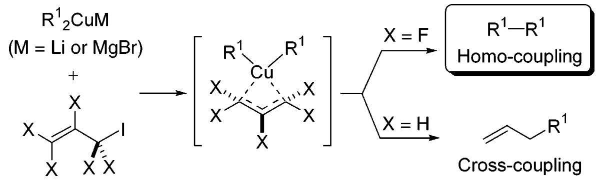

C

The formation of such a T-shaped triorganocopper(III) intermediate **A**, where the trans configuration of the two R^1 groups prevents formation of a homocoupling product (R^1−R^1), has recently been confirmed.[4]

On the other hand, homocoupling could in principle take place in reactions with allylic electrophiles and α,β-unsaturated carbonyl compounds, since the two R^1 groups are now cis to one another in the key Cu^{III} intermediates (**B** and **C**).[4c,5,6] However, to the best of our knowledge, there has been no report on the observation of such homocouplings in cuprate allylation and conjugate addition reactions except for a special case using a *diallyl*cuprate, in which several allylcopper(III) isomers are likely to be equilibrating prior to reductive elimination.[7] Previous theoretical studies have also neglected this possibility so far.[4c,5c,6f] Through theoretical and experimental studies we have now found an exception to the implicit rule of cross-coupling: perfluorination of the allyl group in **B** switched its reactivity. The significant electronic perturbation made the corresponding Cu^{III} complex decompose into the homocoupling product R^1−R^1 (Scheme 1).

Scheme 1



In light of the stability of $[Cu(CF_3)_4]^-$ as one of the few isolable copper(III) complexes,[8] we envisioned that fluorination of the allyl group in a dialkylallylcopper(III) complex would make the allyl group reluctant to participate in reductive elimination and thus result in kinetic stabilization of the complex. To evaluate this working hypothesis, we examined the reaction of perfluoroallyl iodide (**1a**) with dialkyl- or diarylcuprate (Table 1). The reaction of $(n\text{-Hex})_2CuLi$ with C_3F_5I (**1a**) in THF at −60 °C gave dodecane (**3**) as the major product without any detectable formation of cross-coupling product **2** (entry 1). A small amount (13%) of *n*-hexyl iodide (**4**, R = *n*-Hex) was also formed. In contrast, the reaction of $(n\text{-Hex})_2CuLi$ with allyl iodide (**1b**) expectedly gave only the cross-

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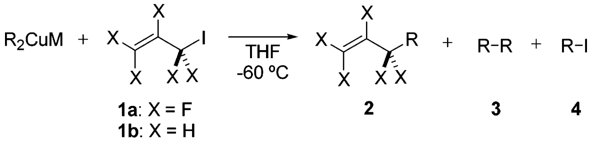
Table 1. Product Selectivity in the Reaction of R_2CuM with Allyl and Perfluoroallyl Iodide[a]



entry	R	M	X	yield of **2** + **3** + **4** (%)[b]	**2**:**3**[b]	yield of **4** (%)[a]
1	*n*-Hex	Li	F	83	0:100	13
2	*n*-Hex	Li	H	≥99	100:0	0
3	Ph	Li	F	51	0:100	6
4	Ph	Li	H	≥99	100:0	0
5	*n*-Hex	MgBr	F	87	0:100	51
6	*n*-Hex	MgBr	H	≥99	100:0	0

[a] 1.2 equiv of R_2CuM was used. [b] Determined by GC, using *n*-tridecane as internal standard.

coupling product **2** (1-nonene) in high yield (entry 2). Ph_2CuLi showed reactivity similar to that of $(n\text{-Hex})_2CuLi$, and in reactions with **1a** and **1b** it predominantly afforded biphenyl and allylbenzene, respectively (entries 3 and 4).

A change of the countercation of the cuprate from lithium to magnesium bromide in the dihexylcuprate did not change the trend in the reactions with the two allyl iodides (entries 5 and 6). Thus, reaction of $(n\text{-Hex})_2CuMgBr$ with C_3F_5I gave exclusively homocoupling (**3**) over cross-coupling (**2**) together with 51% of hexyl iodide (entry 5), whereas the corresponding reaction with allyl iodide afforded only the cross-coupling product **2** (entry 6).

To gain insight into the contrasting reactivities of C_3F_5I and C_3H_5I, we carried out density functional calculations (B3LYP) on the reaction pathways of an allylcopper(III) species as a plausible intermediate.[9–15] The π-/σ-allyl isomerization and C−C bond forming reductive elimination pathways were carefully explored, employing $Me_2(C_3X_5)Cu^{III}\cdot OMe_2$ (**5a,** X = F; **5b**, X = H) as model reactants (Scheme 2). The energy profiles for both cases are shown in Figure 1.

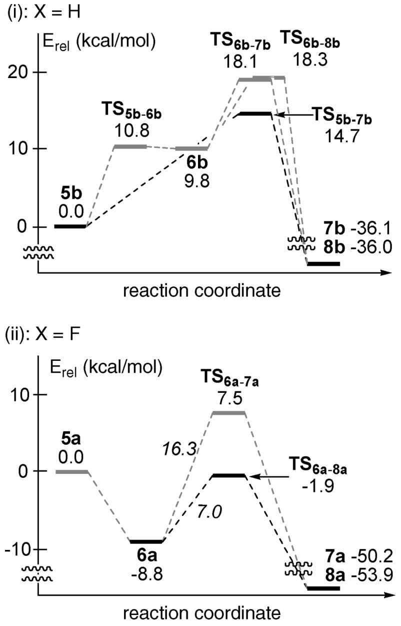
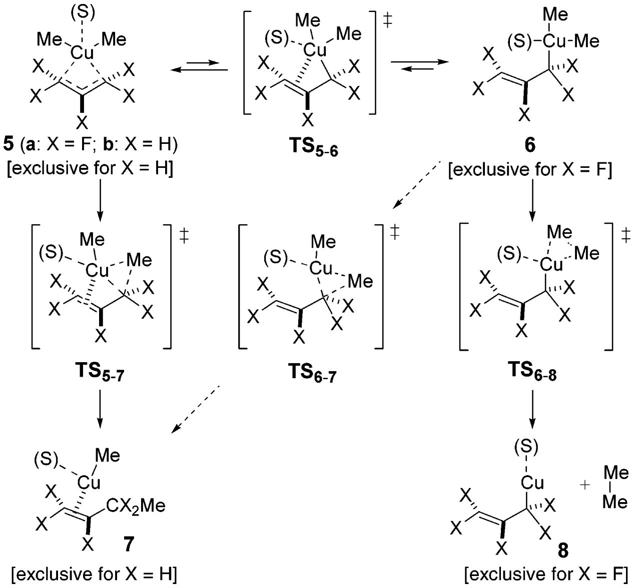


Figure 1. Potential energy profiles (kcal/mol) for reductive elimination of the allyldimethylcopper(III) complexes $Me_2(C_3X_5)Cu^{III}\cdot OMe_2$ (B3LYP/631SDD): (i) X = H; (ii) X = F. Nonproductive intermediates and transition states are indicated in gray.

Scheme 2. Cross-Coupling and Homocoupling Pathways of Allyldimethylcopper(III) Complexes (S = OMe_2)



The reaction of the parent allylcopper(III) species (X = H) is discussed first. As reported previously,[6f] the parent allylcopper(III) exists as the π complex **5b** instead of the σ complex **6b** (ca. 10 kcal/mol difference; Figure 1(i)). A seemingly straightforward path for Me−Me homocoupling starting from the π complex **5b** with retention of its C_s symmetry is symmetry-forbidden,[16a] and the homocoupling can take place from the C_1-symmetric σ complex **6b** via the transition state $\mathbf{TS_{6b-8b}}$, which is a high-energy process (18.3 kcal/mol). Allyl−methyl cross-

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(9) All calculations were carried out with a Gaussian 03 package.[10] The density functional theory method was employed using the B3LYP hybrid functional.[11] Structures were optimized with a basis set consisting of the Stuttgart effective core potential for Cu[12] and 6-31G(d) for the rest.[13] The method and basis sets used here (denoted as B3LYP/631SDD) have been applied to other cuprate reactions and are known to give reliable results. The intrinsic reaction coordinate (IRC) analysis[14] was carried out to confirm that stationary points are smoothly connected with each other. Natural charges were calculated by natural population analysis at the same level as used for geometry optimization.[15]

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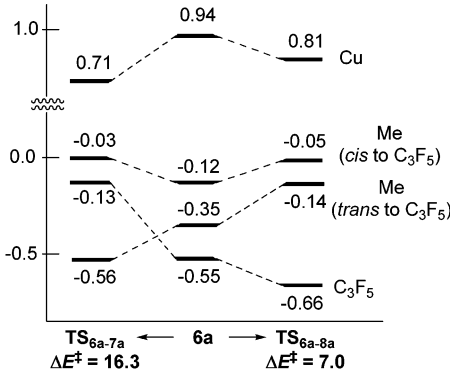

Figure 2. Natural population analysis of the decomposition of **6a** to **7a** and **8a**.

coupling, on the other hand, is a more favorable process, taking place directly from **5b** through an enyl [$\sigma + \pi$]-type TS ($\mathbf{TS_{5b-7b}}$; $\Delta E^{\ddagger} = 14.7$ kcal/mol). An alternative path via **6b** and a σ-type TS ($\mathbf{TS_{6b-7b}}$; $\Delta E^{\ddagger} = 18.1$ kcal/mol) is a high-energy process. The calculated energetics agree well with the experimental selectivity.

The perfluoroallylcopper(III) species behaves much differently (Figure 1(ii)): it exists as the σ-allyl complex **6a** instead of the π-allyl counterpart **5a** (8.8 kcal/mol less stable), because Me_2O is a much better ligand to Cu^{III} than the internal $CF_2{=}CF{-}$ moiety (vide infra).[16b] Neither σ/π isomerization nor enyl [$\sigma + \pi$] reductive elimination TSs corresponding to those in Figure 1(i) could be located after many trials. In accordance with experiments, the Me−Me coupling ($\mathbf{TS_{6a-8a}}$; $\Delta E^{\ddagger} = 7.0$ kcal/mol) is much more favorable than Me−C_3F_5 coupling ($\mathbf{TS_{6a-7a}}$; $\Delta E^{\ddagger} = 16.3$ kcal/mol). This is reasonable, in light of the population change during reductive elimination (Figure 2):[6f] the copper atom can recover its d electron (Cu^{III} to Cu^{I}) more easily from the Me ligand than from the highly electron withdrawing C_3F_5 ligand.

The electron-withdrawing property of the C_3F_5 ligand is reflected in the structures of the intermediates and TSs (Figure 3). Fluorine substitution of the (π-allyl)copper complex results in a much shorter Cu−O distance (**5a** at 2.642 Å vs **5b** at 3.260 Å), which indicates the Lewis acidity of the copper atom is much higher in **5a** than in **5b**. Note that the fluorinated π-allyl complex **5a** is slightly unsymmetrical (Cu−C1 = 2.165 Å, Cu−C3 = 2.054 Å; C1−C2 = 1.409 Å, C2−C3 = 1.441 Å), whereas the parent π-allyl complex **5b** is perfectly symmetric (Cu−C1 = Cu−C3 = 2.14 Å; C1−C2 = C2−C3 = 1.40 Å). Another structural feature is the difference in the copper−allyl bonding. Thus, in comparison with the parent complex **5b**, the copper atom in **5a** is bonded strongly to the C1 and C3 terminals (Cu−C1(C3): 2.109 Å (average) in **5a**, 2.14 Å in **5b**) but weakly to the central C2 atom (Cu−C2: 2.206 Å in **5a**, 2.117 in **5b**). This can be understood in terms of the fluorine effect on frontier orbital interactions between Me_2Cu^- and the allyl cation: having a lower level HOMO and LUMO than the parent allyl cation,[17] the fluorinated allyl cation acts as a better electron acceptor from the Cu $3d_{xz}$ orbital as well as a weaker electron donor to the Cu 4s orbital, which gives rise to the above structural feature.

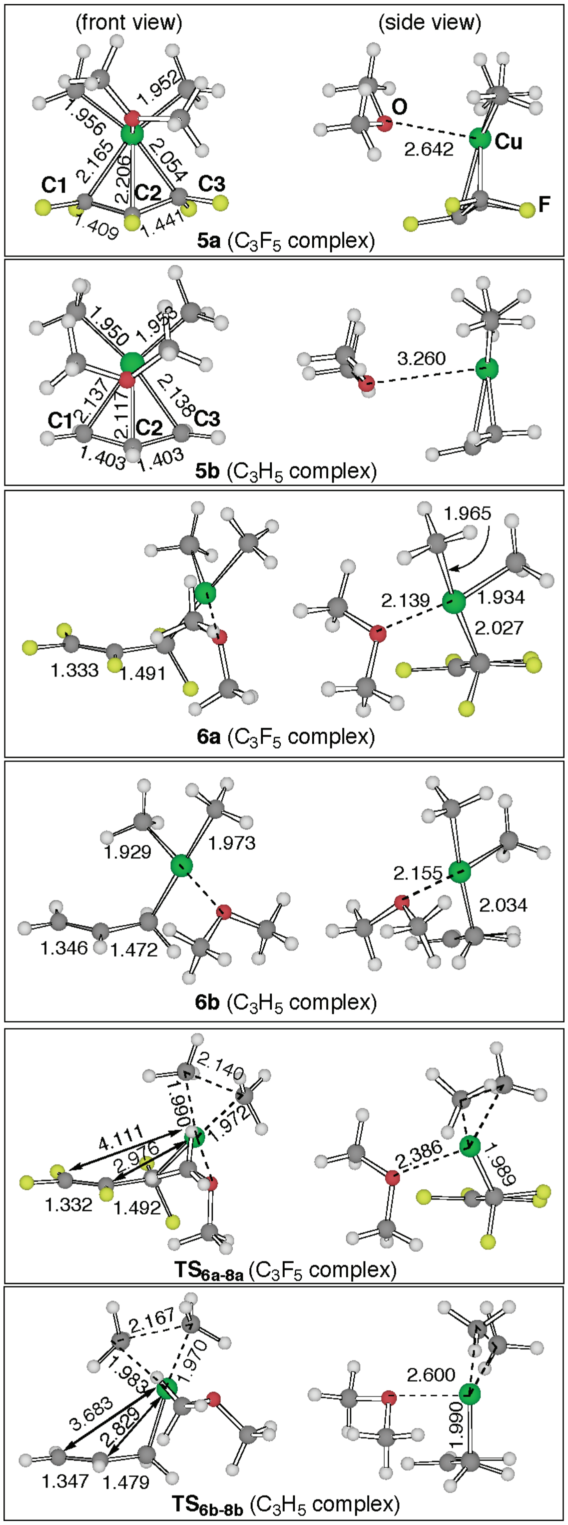

Figure 3. Structures of (π-allyl)- and (σ-allyl)copper(III) complexes (**5a**, **5b**, **6a**, and **6b**) and Me−Me coupling TSs ($\mathbf{TS_{6a-8a}}$ and $\mathbf{TS_{6b-8b}}$) optimized at the B3LYP/631SDD level. Values refer to interatomic distances (Å).

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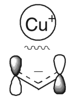
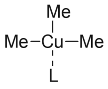
(16) (a) The direct Me−Me bond formation of **5b** gives a C_s-symmetric (π-allyl)copper(I) (structure (i) below) that is symmetry forbidden. (b) This conjecture was confirmed by a model study with $Me_3Cu^{III}{\cdot}L$ (structure (ii) below; L = C_2F_4, C_2H_4, and Me_2O). The (stabilizing) interaction energy between Me_3Cu and L is the least for the C_2F_4 ligand (C_2F_4, 5.5 kcal/mol; C_2H_4, 10.4 kcal/mol; Me_2O, 15.0 kcal/mol).

(i)



(ii)

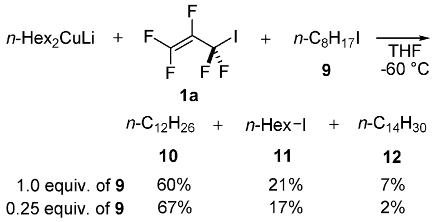


$$\begin{array}{c} \text{Me} \\ | \\ \text{Me}-\text{Cu}-\text{Me} \\ \vdots \\ \text{L} \end{array}$$

(L = C_2F_4, C_2H_4, Me_2O)

(17) Single-point calculations (HF/6-31G(d)) of the allyl fragments in the complexes **5a** and **5b** gave the following HOMO/LUMO energy levels: **5a**, HOMO −18.2 eV, LUMO −7.7 eV; **5b**, HOMO −17.4 eV, LUMO −6.1 eV.

Scheme 3. Relative Reactivities of 1a vs *n*-Octyl Iodide



There are no significant structural differences between the T-shaped (σ-allyl)copper(III) complexes **6a** and **6b** (Figure 3). In contrast to the π complexes **5a** and **5b**, the Cu−O distance is only slightly shorter for the fluorinated complex **6a** (2.139 Å) than for **6b** (2.155 Å). However, upon going to the homocoupling TSs ($\mathbf{TS_{6a-8a}}$ and $\mathbf{TS_{6b-8b}}$), where the copper atom is halfway reduced to Cu(I), Me_2O detachment is much less advanced for the fluorinated case ($\mathbf{TS_{6a-8a}}$, 2.386 Å; $\mathbf{TS_{6b-8b}}$, 2.600 Å).

In the reaction of the cuprate R_2CuM with C_3F_5I, a significant amount of RI (hexyl iodide or phenyl iodide) was formed (Table 1). This organohalide formation most likely has its origin in a copper−halogen exchange.[18,19] Because of the presence of organohalide in the reaction mixture, one may argue that the homocoupling product could have been formed from reaction of RI with the cuprate R_2CuM. For the reaction of Ph_2CuLi, this possibility was readily ruled out, because it did not react at all with PhI under reaction conditions similar to those in Table 1.

The case of (n-Hex)$_2$CuLi needed additional experimental study (Scheme 3), since this cuprate reacts quickly with hexyl iodide to give dodecane. In a control experiment, the reaction of equimolar amounts of (n-Hex)$_2$CuLi, C_3F_5I (**1a**), and octyl iodide (**9**) under the reaction conditions used in Table 1 afforded dodecane as the major product. Interestingly, only 7% of tetradecane (**12**) was formed, which shows that the reaction of the cuprate with a primary alkyl iodide is slow compared to the reaction with **1a**. The use of 0.25 equiv of **9**, which more closely mimics the actual reaction conditions, gave only 2% of tetradecane. This unambiguously shows that direct reaction of the cuprate with the alkyl halide cannot be a significant source for the homocoupling product.

Note that a perfluoroallylcopper(I) species, formed together with the homocoupling product, could have some effect on the reaction. For example, it may undergo a ligand exchange with the remaining homocuprate (R_2CuLi) to form the mixed cuprate R(C_3F_5)CuLi. Such a cuprate would be less nucleophilic than R_2CuLi due to the electron-withdrawing C_3F_5 ligand. This may account for the incomplete formation of the homocoupling product (in particular for Ph_2CuLi; see entry 3 in Table 1).

In summary, we have found experimentally that the homocoupling pathway is possible in the reaction of diorganocuprates with an allylic substrate. The calculations revealed that pentafluoroallyl (C_3F_5), being a more stabilized carbanion than allyl (C_3H_5), changes the electronic nature of allylcopper(III) species significantly enough to switch the reaction pathways in carbon−carbon bond coupling. In light of the synthetic utility of unsymmetrical biaryl coupling via cuprate oxidation,[20] the role of perfluoroallyl iodide and related compounds as two-electron oxidants deserves further investigation.

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Supporting Information Available: Text and tables giving details of experiments, energies and Cartesian coordinates of stationary points, and interaction energies between Me_3Cu^{III} and L in $Me_3Cu^{III}\cdot L$ complexes. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Reductive elimination of MeI from $[Me_2Cu^{III}(I)C_3F_5]^-$ was ruled out by theoretical calculations, which gave a barrier of 38.9 kcal/mol.

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