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Dimethyl Cuprate Undergoes C–C Bond Coupling with Methyliodide in the Gas Phase but Dimethyl Argenate Does Not

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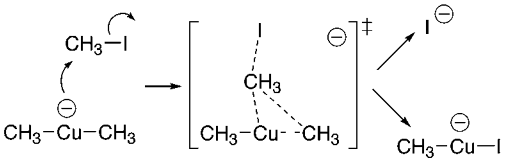
ABSTRACT



Multistage mass spectrometry experiments have been used to synthesize and study the reactions of $(CH_3)_2M^-$ (M = Cu and Ag) with methyl iodide in the gas phase. While the dimethylcuprate ion (M = Cu) reacts with CH_3I via C–C bond cross coupling, its silver congener is unreactive. The experimental results are consistent with MP2/6-31++G ab initio calculations, which reveal that the preferred mechanism for Cu involves the formation of a T-shaped Cu transition state.**

Organocopper reagents are among the most widely used organometallic reagents in organic synthesis.[1] Gilman reagents, discovered over 50 years ago and formulated as "R_2CuLi", have proved to be useful in a range of C−C bond coupling reactions,[2] including reactions with alkyl halides.[3] Unfortunately, the mechanistic aspects of their reactions remain obscure [4] largely due to two reasons: (i) the nature of the reactive species can be uncertain,[5] and (ii) there can be more than one pathway due to the potential involvement of Cu(III) intermediates.[6,7] With regard to the former point, several reactive species are possible, ranging from monomeric [8] to polymeric.[9] The latter point is nicely illustrated

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(1) For reviews and monographs on organocopper species, see: (a) *Modern Organocopper Chemistry*, Krause, N., Ed.; Wiley-VCH: Weinheim, 2002. (b) Lipshutz, B. H. *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, UK, 1994; pp 283−382. (c) *Organocopper Reagents: A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, UK, 1994.

(2) For an excellent account of Gilman's research, see: Eisch, J. J., *Organometallics* **2002**, *21*, 5439.

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(4) For an excellent review focusing on mechanistic aspects, see: Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed*. **2000**, *39*, 3751.

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(6) Cu(III) have been implicated in the cross-coupling reactions of allylic esters with diallylcuprate species: Karlstrom, A. S. E.; Backvall, J. E. *Chem. Eur. J*. **2001**, *7*, 1981.

(7) For theoretical studies on relevant Cu(III) species, see: (a) Nakamura, E.; Yamanaka, M.; Mori, S. *J. Am. Chem. Soc*. **2000**, *122*, 1826. (b) Nakamura, E.; Yamanaka, M. *J. Am. Chem. Soc*. **1999**, *121*, 8941. (c) Dorigo A. E.; Wanner J.; Schleyer, P. V. R. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 476. (d) Snyder, J. P. *J. Am. Chem. Soc*. **1995**, *117*, 11025.

(8) Structure of the simplest model system, the dimethyl cuprate ion $(CH_3)_2Cu^-$, has been determined by X-ray crystallography: (a) Hope, H.; Olmstead, M. M.; Power, P. P.; Sandell, J.; Xu, U. X. *J. Am. Chem. Soc*. **1985**, *107*, 4337. This species was reported to be unreactive towards simple electrophiles such as 1-dodecanylbromide in the condensed phase: (b) Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc*. **2000**, *122*, 7294.

(9) Negative ion ESI MS of organocuprate species are quite complex and reveal the presence of monomeric species R_2Cu^-, $RCuX^-$, CuX_2^- as well as higher clusters: (a) Lipshutz B. H., Keith J., Buzard D. J. *Organometallics* **1999**, *18*, 1571. Other spectroscopic techniques have also shown that a range of species can be present in solution: (b) Xie, X. L.; Auel, C.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc*. **2003**, *125*, 1595. (c) Gschwind, R. M.; Xie, X. L.; Rajamohanan, P. R.; Auel, C.; Boche, G. *J. Am. Chem. Soc*. **2001**, *123*, 7299. (d) John, M.; Auel, C.; Behrens, C.; Marsch, M.; Harms, K.; Bosold, F.; Gschwind, R. M.; Rajamohanan, P. R.; Boche, G. *Chem. Eur. J*. **2000**, *6*, 3060. (e) Huang, H.; Liang, C. H.; Penner-Hahn, J. E. *Angew. Chem., Int. Ed*. **1998**, *37*, 1564. (f) Gerold, A.; Jastrzebski J. T. B. H.; Kronenburg, C. M. P.; Krause, N. van Koten, G. *Angew. Chem., Int. Ed*. **1997**, *36*, 755.

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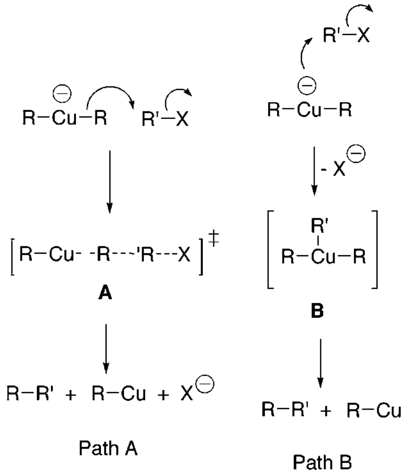
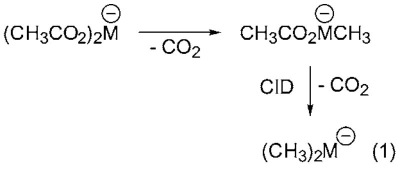
by experimental data on C−C bond coupling reactions between R_2CuLi and alkylhalides,[3,10] which are unable to distinguish between two possible mechanisms proposed over 30 years ago by Whitesides et al.[3c]: (i) a side on S_N2 mechanism (path A in Scheme 1) and (ii) a mechanism involving the formation of a Cu(III) intermediate (path B in Scheme 1). Another open question concerns the reactivity of the silver analogues of Gilman reagents toward alkyl halides.[11,12] Here we use multistage mass spectrometry[13] and ab initio calculations[14] to provide the first gas-phase data, which compares the reactivity of methyl iodide toward the simplest organocuprate, $(CH_3)_2Cu^-$ and its silver analogue, dimethylargenate.[15]

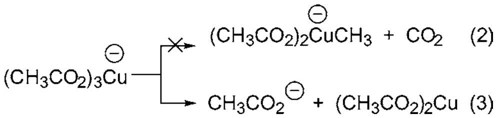
Scheme 1. Two Mechanisms for C−C Bond Coupling of Dialkycuprates with Alkyl Halides[a]



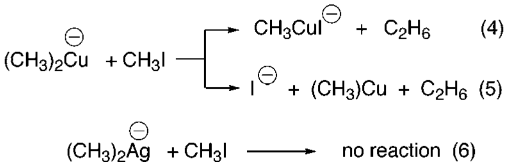
[a] Path A follows an S_N2 mechanism via the transition state A; Path B involves formation of the Cu(III) intermediate B

The organometallic ate species, $(CH_3)_2M^-$ (M = Cu and Ag), were "synthesized" in the gas phase via collision-induced dissociation (CID) in a quadrupole ion trap (QIT) mass spectrometer (eq 1).





The precursors are the metal acetate anions $(CH_3CO_2)_2M^-$,[15,16,17] which are formed via electrospray ionization (ESI). The oxidation state of the metal has a profound effect on the decarboxylation reaction. Thus, CID of the related Cu(II) system failed to form an organometallic species (eq 2),[18] undergoing acetate ligand loss instead (eq 3).



Use of the multistage mass spectrometry capabilities of the QIT allowed the organometallic ate species to be readily mass selected and subjected to gas-phase ion−molecule reactions with neutral reagents such as methyl iodide.[13] While dimethyl cuprate reacts to give two different ionic products (Supporting Information, Figure S1a): CH_3CuI^- as the minor product (eq 4) and I^- as the major product (eq 5); its silver congener is unreactive (eq 6).

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(10) Isotope labeling studies: (a) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K. *J. Am. Chem. Soc*. **1976**, *98*, 7255. (b) Guo, C. Y.; Brownawell, M. L.; San Filippo, J. *J. Am. Chem. Soc*. **1985**, *107*, 6028.

(11) Gilman was the first to show that PhAg is less reactive than PhCu: Gilman, H.; Straley, J. M., *Recl. Trav. Chim. Pay-Bas*. **1936**, *55*, 821. For other examples of organosilver species reacting more selectively than organocopper species: (b) Westmijze, H.; Kleijn, H.; Vermeer P. *J. Organomet. Chem*. **1979**, *172*, 377. (c) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer P. *J. Organomet. Chem.* **1981**, *206*, 257.

(12) The nature of metal catalysts can influence the coupling of Grignard reagents with organic halides. Silver catalysts facilitate homocoupling, while copper catalysts prefer cross coupling: Kochi, J. K. *J. Organomet. Chem*. **2002**, *653*, 11 and refs cited therein.

(13) All CID, ion−molecule reactions, and kinetic measurements were carried out on a Finnegan LCQ QIT as described previously: (a) Waters, T.; O'Hair, R. A. J.; Wedd, A. G. *J. Am. Chem. Soc.* **2003**, *125*, 3384. Metal acetates were dissolved in methanol to a final concentration of 0.1 mg mL^{-1} and introduced into the mass spectrometer via ESI with a flow rate of 3.0 μL min^{-1}, a spray voltage of 4.0−5.0 kV, a capillary temperature of 200 °C, a nitrogen sheath pressure of 40 psi, and capillary and tube lens offset voltage in the range of −30 to −20 V. The major isotope ions of Cu or Ag were mass selected (with a 1.5 Th window) and subjected to CID: activation amplitude, 0.55−0.65 V; activation (Q), 0.25 V; and activation time 30 ms. Work by Gronert has shown that the ions in a LCQ QIT are essentially at room temperature: (b) Gronert, S. *J. Am. Soc. Mass Spectrom.* **1998**, *9*, 845.

(14) Optimizations and frequency and IRC calculations were carried out at the MP2/6-31++G** level of theory, using the ECPs for Cu (SVP), Ag (SSD), and I (SSD). Data are given in Supporting Information. The MP2 level of theory has been used since it gives a closer match to experimental bond lengths than the B3LYP method: Yamanaka, M.; Inagaki, A.; Nakamura, E. *J. Comput. Chem*. **2003**, *24*, 1401. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(15) O'Hair, R. A. J *Chem. Commun*. **2002**, 20.

(16) Decarboxylation reactions have been used to synthesize organometallics in the condensed phase: (a) Deacon, G. B.; Faulks, S. J.; Pain, G. N. *Adv. Organomet. Chem*. **1986**, *25*, 237. Copper(I) salts can catalyze the decomposition of carboxylic acids, but the mechanism of these catalytic reactions are quite complex and may not involve organometallic intermediates: (b) Darensbourg, D. J.; Holtcamp, M. W.; Longridge, E. M.; Khandelwal, B.; Klausmeyer, K. K.; Reibenspies, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 318. (c) Darensbourg, D. J.; Holtcamp, M. W.; Khandelwal, B.; Klausmeyer, K. K.; Reibenspies, J. H. *Inorg. Chem.* **1995,** *34*, 2389

(17) The reverse reaction, insertion of CO_2 into organocopper species, has been described: Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P.; *Organometallics* **2004**, *23*, 1191

(18) Cu(II) organometallics have been implicated: Navon, N.; Golub G.; Cohen, H.; Meyerstein, D., *Organometallics* **1995**, *14*, 5670.

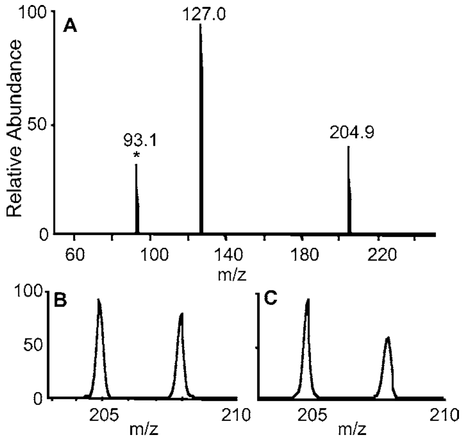

Figure 1. Ion molecule reactions of (a) $(CH_3)_2Cu^-$ with CD_3I; (b) expansion of CH_3CuI^- product region for reaction of $CH_3CuCD_3^-$ with CH_3I; (c) expansion of CH_3CuI^- product region for reaction of $CH_3CuCD_3^-$ with CD_3I.

Table 1. Rate Constants for Gas-Phase Reactions of Various Organometallic Ions Reacting with Methyl Iodide

ion	neutral	k x 10^{-11} (cm^3 $molecule^{-1}$ s^{-1})
$(CH_3)_2Cu^-$	CH_3I	3.74 ± 0.62[a]
$(CH_3)_2Cu^-$	CD_3I	4.26 ± 0.93[a]
CH_3CuI^-	CH_3I	b
$CH_3CuO_2CCH_3^-$	CH_3I	c
$(CH_3)_2Ag^-$	CH_3I	b

[a] Average of 20 measurements at a range of pressures of the neutral. [b] No reaction at 10 s for 4×10^{-6} Torr of CH_3I. [c] Minor reaction at 10 s for 4×10^{-6} Torr of CH_3I (see Supporting Information, Figure S1f).

To gain further insight into the mechanism of these reactions, we have carried out a range of labeling (Figure 1 and Supporting Information, Figure S1) and kinetic experiments (Table 1) as well as ab initio calculations (Figures 2 and 3). A key observation is that these reactions involve cross coupling since only CH_3CuI^- is observed when $(CH_3)_2Cu^-$ is allowed to react with CD_3I (Figure 1A) and CD_3CuI^- is observed when $(CD_3)_2Cu^-$ is allowed to react with CH_3I (Supporting Information, Figure S1b). These results are consistent with the condensed phase studies of Komiya *et al.*, who observed 96% CH_3CD_3 and 4% C_2H_6 in the reaction of $(CH_3)_2CuLi$ with CD_3I.[10a]

The cross coupling reaction should exhibit two isotope effects since two bonds to carbon are broken in the first step of path A, while one bond to carbon is made and another is broken in the first step of path B. The rate constant for the reaction of the parent system $(CH_3)_2Cu^- + CH_3I$ is modest ($k = 3.74 \times 10^{-11}$ cm^3 $molecule^{-1}$ s^{-1}, Table 1) and corresponds to a reaction efficiency of 3 out of every 100 collisions.[19] The rate for the corresponding reaction with CD_3I is slightly faster, showing that breaking the C−I bond involves an inverse isotope effect ($k_H/k_D = 0.88 \pm 0.40$). Interestingly, while inverse isotope effects have been observed for gas-phase S_N2 reactions,[20a] this isotope effect is different from the condensed-phase one of $k_H/k_D = 1.111 \pm 0.006$, measured for the reaction $(n\text{-}C_8H_{17})_2CuLi(P(n\text{-}Bu)_3) + CX_3I$ (X = H or D) in THF at −16 °C. An inverse β-deuterium isotope effect ($k_H/k_D = 0.82 \pm 0.05$) for the Cu−C bond was determined from a comparison of the ion abundances (integrated peak areas) of CH_3CuI^- and CD_3CuI^- in the reaction of $CD_3CuCH_3^-$ with CH_3I (Figure 1B). Interestingly, inverse β-deuterium isotope effects of similar magnitudes have been observed in the oxidative addition of CH_3I to $CX_3Ir(CO)(PPh_3)_2$ (X = H or D).[20b] That two isotope effects are operating in the cross-coupling reaction is further confirmed by the combined isotope effect of $k_H/k_D = 0.66$

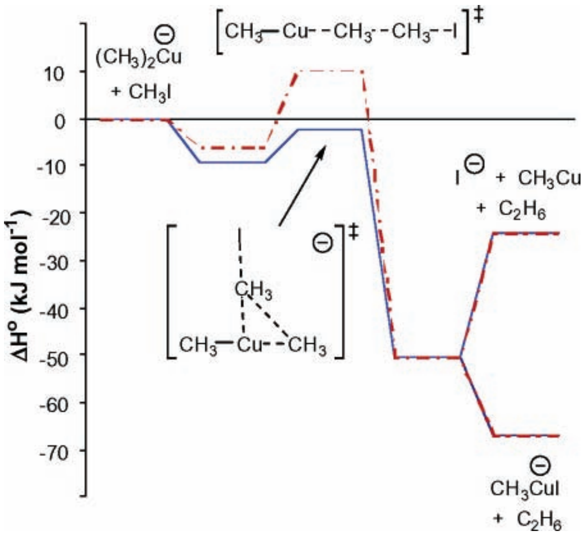

Figure 2. MP2/6-31++G** (ECP for Cu) calculated reaction energy profiles for paths A (red line) and B (blue line) of Scheme 1 for the reaction of $(CH_3)_2Cu^-$ with CH_3I. Structure of all species are given in Supporting Information, Figure S2.

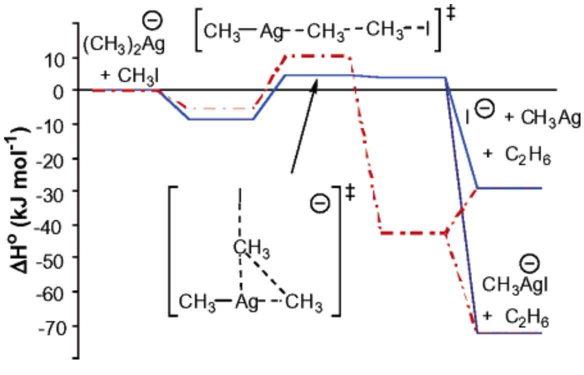

Figure 3. MP2/6-31++G** (ECP for Ag) calculated reaction energy profiles for paths A (red line) and B (blue line) of Scheme 1 for the reaction of $(CH_3)_2Ag^-$ with CH_3I. Structure of all species are given in Supporting Information, Figure S3.

± 0.05 determined from a comparison of the ion abundances of CH_3CuI^- and CD_3CuI^- in the reactions of $CD_3CuCH_3^-$ with CD_3I (Figure 1C).

To gain further insight into which mechanism is operating for these reactions, we have used ab initio calculations (Supporting Information, Figures S2 and S3 and Table S1) at the MP2/6-31++G** level of theory (with ECPs for Cu and Ag) to examine both paths shown in Scheme 1 for $(CH_3)_2Cu^-$ (Figure 2) as well as $(CH_3)_2Ag^-$ (Figure 3). The first noteworthy aspect is that the key transition states for both paths for the reaction of $(CH_3)_2Ag^-$ with CH_3I lie *above* separated reactants (Figure 3), consistent with the experimental observation that this reaction does *not* occur in the QIT at room temperature. The second noteworthy aspect is that the transition state for the "side on" reaction of $(CH_3)_2Cu^-$ (path A of Scheme 1) not only is higher in energy that the alternative pathway but also lies *above* separated reactants (Figure 2) and would thus not be expected to occur in the QIT at room temperature. More importantly, the reaction coordinate for the alternative pathway does *not* involve the formation of a stable Cu(III) intermediate.[21] Instead, a transition state is formed that has a "T shape" at the Cu center. This transition state collapses to an intermediate product complex, $[I^-(CH_3CH_3)(CH_3Cu)]$, consisting of the iodide, ethane, and methyl copper. These results are consistent with (i) the isotope effects, which indicated that C−I and Cu−C bond breaking are coupled and (ii) previous theoretical calculations on $(CH_3)_3Cu$ and $(CH_3)_3CuL$ (L = $(CH_3)_2O$, $(CH_3)_3P$, and Cl^-) systems, which demonstrated that the T-shaped $(CH_3)_3Cu$ is not a stable minimum but spontaneously undergoes reductive elimination to form CH_3CH_3 and CH_3Cu.[7a] In contrast, the ligated Cu(III) complexes $(CH_3)_3CuL$ in which Cu is four coordinate and square planar are stable minima and have significant activation energies for reductive elimination. Interestingly, although the $(CH_3)_2Ag^- + CH_3I$ reaction does not occur, the ab initio calculations reveal that the T-shaped transition state connects to a T-shaped intermediate, suggesting a slight change in mechanism from Cu to Ag. This is consistent with condensed-phase experiments, which reveal that on proceeding down group 1B, $(CH_3)_3Au$ becomes kinetically stable.[10a]

Finally, since both alkyl groups of R_2CuLi are not consumed in coupling reactions, there has been significant interest in replacing one alkyl group with a "dummy ligand".[4] An examination of Table 1 reveals that the CH_3CuL^- ions (where L = CH_3CO_2 and I) are much less reactive toward CH_3I and thus are poor "dummy ligands" as they slow C−C bond coupling.

Further studies on the gas-phase synthesis of organometallics and their mediation of C−C bond-coupling reactions are underway and will be reported in due course.

Acknowledgment. We thank the Australian Research Council for financial support and Mr. David McNaught for carrying out preliminary studies.

Supporting Information Available: Mass spectra, structures, and energies of species in Figures 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Reaction efficiencies were calculated using: Chesnavich, W. J.; Su, T.; Bowers, M. T. *J. Chem. Phys.* **1980**, *72*, 2641

(20) (a) O'Hair, R. A. J.; Davico, G. E.; Hacaloglu, J.; Dang, T. T.; DePuy, C. H.; Bierbaum, V. M., *J. Am. Chem. Soc.* **1994**, *116*, 3609. (b) Hostetler, M. J.; Bergman, R. G., *J. Am. Chem. Soc.* **1992**, *114*, 7629.

(21) Although the vector associated with the imaginary frequency shows the movement of the methyl group to the Cu centre, IRC calculations do not yield a T-shaped Cu intermediate, forming the $[I^-(CH_3CH_3)(CH_3Cu)]$ complex instead. A comprehensive manual search failed to find a T-shaped Cu intermediate without any imaginary frequencies.