

## A Chemical Scale for Electron-transfer Ability of Methylcopper Reagents

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The ratio of methyl transfer (2) and reduction (3) products in the reaction of trimethoxycarbonyl ethylene 1 with methylcopper reagents MeCuLn varies with the copper species, and decreased in the following order: MeCu(CN)Li > MeCu > Me<sub>2</sub>Cu(CN)Li<sub>2</sub> >> Me<sub>2</sub>CuLi > Me<sub>3</sub>CuLi<sub>2</sub>.

The popularity of organocopper complexes as reagents in organic synthesis<sup>1</sup> has brought forth numerous mechanistic investigations of both substitution and conjugate addition reactions.<sup>2</sup> Concerning conjugate addition, cuprate-olefin  $\pi$ -complexes have been detected by NMR spectroscopy<sup>2a,c,d</sup> and it is proposed that the complexes go on to form Cu<sup>III</sup> intermediates (nucleophilic addition process). In addition to this plausible and currently more accepted mechanism, an electron-transfer process from RCuLn to unsaturated substrates has been proposed frequently as the second mechanism.<sup>3,4</sup> Both processes may take place competitively. In the second mechanism, there must be a correlation between the electronic requirements of the organocopper reagents and the electronic demands of the enones and enoates.† The electron-accepting ability of the substrates can be elucidated from their polarographic one-electron reduction potentials.<sup>3,4</sup> Little is known, however, about the electron-donating ability of the reagents.<sup>5</sup>

We report here the order of electron-transfer ability for methylcopper reagents. Initially we attempted to measure the oxidation potential of copper reagents using physicochemical methods, but all trials resulted in failure due to their instability.<sup>5</sup> We have found that the reaction of trimethoxycarbonyl ethylene 1<sup>6</sup> with methylcopper reagents is a suitable reaction to investigate the scale of the electron-donating ability of the organocopper reagents. The reaction gave a mixture of the methyl transfer (2) and reduction (3) products in high yields [eqn. (1)].‡ The 2:3 ratio-MeCuLn plots are shown in Fig. 1. The ratio of 2:3 decreased in the following

order; MeCu(CN)Li·LiBr > MeCu·LiI·LiBr > Me<sub>2</sub>Cu(CN)Li<sub>2</sub>·2LiBr >> Me<sub>2</sub>CuLi·LiI·2LiBr > Me<sub>3</sub>CuLi<sub>2</sub>·LiI·3LiBr.<sup>7</sup> It has been believed for a long time in organocopper chemistry, without concrete evidence, that a reduction product is produced *via* an electron-transfer process.

The reactions of 1 with MeCuLn were quenched with D<sub>2</sub>O-DCl, instead of NH<sub>4</sub>Cl-H<sub>2</sub>O.‡ The reduction product 3[<sup>2</sup>H<sub>2</sub>], obtained using any MeCuLn, contained two deuteriums at the  $\alpha$ - and  $\beta$ -positions,<sup>8</sup> whereas one deuterium was incorporated into the  $\alpha$ -position of the conjugate adduct 2[<sup>2</sup>H<sub>1</sub>]. A possible reaction mechanism is shown in Scheme 1. Transfer of one electron from MeCuLn would produce the radical anion 4, and further electron transfer would give the dianion 5. These intermediates (4 and 5) may react with MeCuLn to afford the Cu<sup>II</sup> 6 and Cu<sup>I</sup> 7 species, respectively. It is not clear at present whether 3[<sup>2</sup>H<sub>2</sub>] was produced *via* 6 or *via* 7. The ratio of 2:3 and deuterium content in 3 did not depend on the reaction time, suggesting that 6 (or 7) would be stable at 0°C.

The <sup>13</sup>C NMR spectrum of the stable intermediate, obtained from the addition of 2 equiv. Me<sub>3</sub>CuLi<sub>2</sub> (2 equiv.) to <sup>13</sup>C-enriched 1 (EC\*H=CE<sub>2</sub>), is shown in Fig. 2. The intermediate was stable at 0°C at least for 8 h, which gave 3[<sup>2</sup>H<sub>2</sub>] upon quenching with D<sub>3</sub><sup>+</sup>O. A signal at  $\delta$  43.13 was assigned to the  $\beta$ -carbon of the intermediate. The  $\beta$ -carbon of

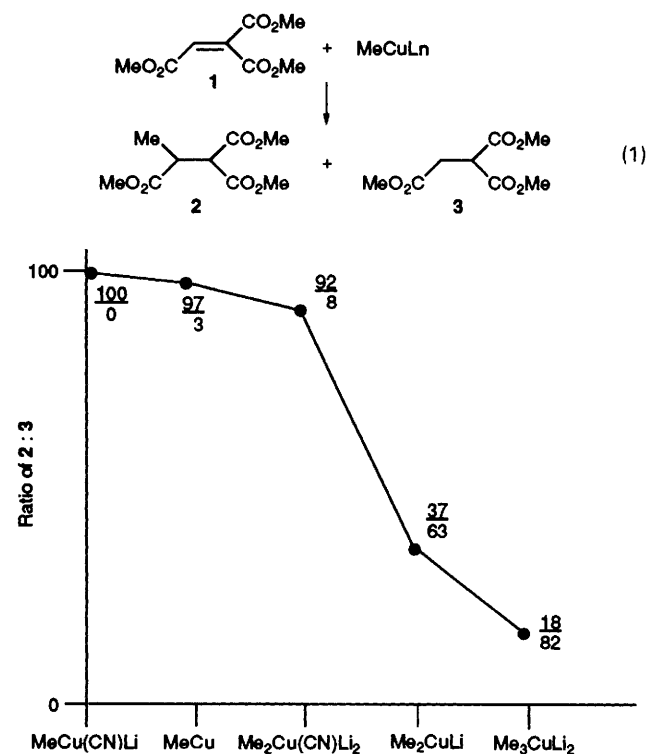
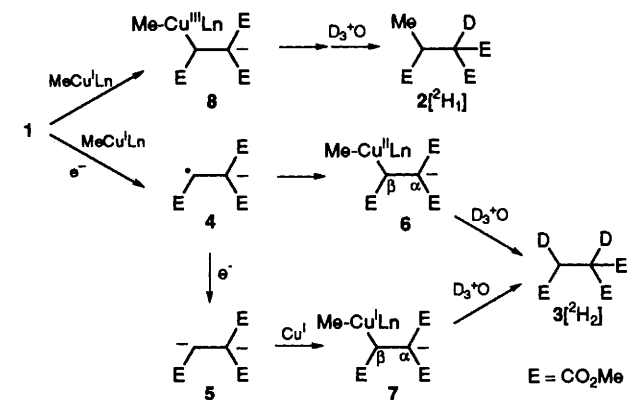


Fig. 1 MeCuLn dependence on the ratio of 2:3



Scheme 1 Nucleophilic addition vs. electron transfer process

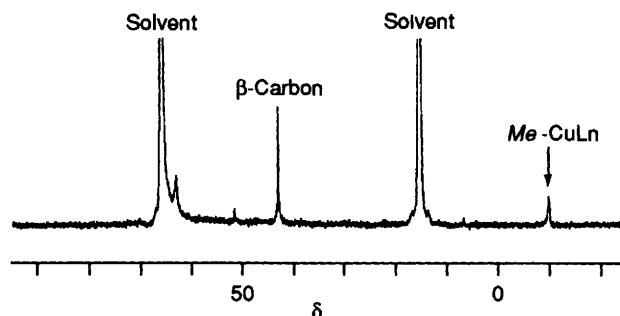


Fig. 2 <sup>13</sup>C NMR spectra of the reaction of 1 (<sup>13</sup>C-enriched) with Me<sub>3</sub>CuLi<sub>2</sub> in diethyl ether at 0°C

**3** appeared at  $\delta$  32.96 and that of **2** at  $\delta$  39.11. If the intermediate adopts a copper enolate form  $\text{LnCuO}(\text{MeO})\text{C}=\text{C}^*\text{HC}-\text{E}_2$ , instead of an  $\alpha$ -cuprio ester structure, the  $\beta$ -carbon ( $\text{C}^*$ ) should appear at much lower field, *i.e.* ca.  $\delta$  150. The  $\alpha$ -carbon of the intermediate was not observable because of non- $^{13}\text{C}$ -enriched carbon. § Furthermore, when a diethyl ether solution of this intermediate was kept under  $\text{O}_2$  atmosphere, only trace amounts of **3** were detected and **2** was obtained exclusively; **2**:**3** > 99:1, and the total yield was 85%. This clearly indicates that the intermediate was oxidized to an unstable  $\text{Cu}^{\text{III}}$  species with  $\text{O}_2$ , which instantaneously gave **2** *via* reductive elimination. Taken together, the stable intermediate is either  $\text{Cu}^{\text{II}}$  **6** or  $\text{Cu}^{\text{I}}$  **7** species and the  $\text{Cu}^{\text{III}}$  intermediate **8** is very unstable. It is now clear that the reduction product **3** arises *via* an electron-transfer process whereas the adduct **2** is produced through the nucleophilic addition.

Consequently, the electron transfer ability of methylcopper reagents is in the following order;  $\text{Me}_3\text{CuLi}_2 > \text{Me}_2\text{CuLi} >> \text{Me}_2\text{Cu}(\text{CN})\text{Li}_2 > \text{MeCu} > \text{MeCu}(\text{CN})\text{Li}$ .<sup>9</sup> This chemical scale using the reaction of **1** may be applicable to other copper reagents. The order reported here will be useful for considering the mechanism of organocopper reactions and for designing organic synthesis *via* copper reagents.

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## Footnotes

† The correlation may also play an important role for controlling formation of the  $\pi$ -complexes in the first mechanism.

‡ To a diethyl ether solution of  $\text{MeCuLn}$  (2 mmol) cooled at  $-78^\circ\text{C}$  was added a diethyl ether solution of **1** (1 mmol). The mixture was stirred for 5 min at  $-78^\circ\text{C}$  and allowed to warm to  $0^\circ\text{C}$ . After stirring for 1 h at  $0^\circ\text{C}$ , the reaction was quenched by adding  $\text{NH}_4\text{Cl}$  (aq.) solution. In addition to the two major products, small to trace amounts of the reductive coupling product of **1**  $\{(\text{MeO}_2\text{C})_2\text{CH}(\text{MeO}_2\text{C})\text{CH}_2$  and the methoxy adduct  $\text{MeO}(\text{MeO}_2\text{C})\text{CHCH}(\text{CO}_2\text{Me})_2$  were produced in some cases.

§ The  $\beta$ -carbon of the precursor of  $2[\text{H}_1]$ ,  $\text{MeEC}^*\text{HC}-\text{E}_2$ , was not observable in Fig. 2, presumably not only because it was produced as a minor product but also because a minus charge was located near the  $\beta$ -carbon.

## References

- 1 Most recent reviews: B. H. Lipshutz and S. Sengupta, *Org. React. (N.Y.)*, 1992, **41**, 135; T. Ibuka and Y. Yamamoto, *Synlett*, 1992, 769; N. Krause, *Kontakte*, 1993, 3; B. E. Rossiter and N. M. Swingle, *Chem. Rev.*, 1992, **92**, 771; S. Hanessian and K. Sumi, *Synthesis*, 1991, 1083.
- 2 Most recent mechanistic studies with NMR: (a) N. Krause, R. Wagner and A. Gerold, *J. Am. Chem. Soc.*, 1994, **116**, 381; N. Krause, *J. Org. Chem.*, 1992, **57**, 3509 (organocuprate  $\pi$ -complexes); (b) S. H. Bertz, G. Dabbagh, X. He and P. P. Power, *J. Am. Chem. Soc.*, 1993, **115**, 11 640 (aggregation states); (c) S. H. Bertz and R. A. Smith, *J. Am. Chem. Soc.*, 1989, **111**, 8276 (cuprate-olefin  $\pi$ -complexes); (d) B. Christenson, T. Olsson and C. Ullenius, *Tetrahedron*, 1989, **45**, 523 (cuprate-olefin  $\pi$ -complexes); (e) B. H. Lipshutz, S. H. Dimock and B. James, *J. Am. Chem. Soc.*, 1993, **115**, 9283; B. H. Lipshutz and B. James, *Tetrahedron Lett.*, 1993, **34**, 6689 (cuprate- $\text{Me}_3\text{SiCl}$  complexes); (f) B. H. Lipshutz, E. L. Ellsworth and S. H. Dimock, *J. Am. Chem. Soc.*, 1990, **112**, 5869 ( $\text{RCu}\cdot\text{BF}_3$  reagent); (g) A. S. Vellekoop and R. A. Smith, *J. Am. Chem. Soc.*, 1994, **116**, 2902 (cuprate-enone complexes).
- 3 H. O. House and W. F. Fischer, *J. Org. Chem.*, 1968, **33**, 949; H. O. House, *Acc. Chem. Res.*, 1976, **9**, 59.
- 4 J. P. Collman and L. S. Hegeudus, *Principles and Applications of Organotransition Metal Chemistry*; Univ. Sci. Books, CA, 1980, p. 544.
- 5 The diastereoselectivity of the conjugate addition to certain enoates depends upon, to some extent, the electron-donating ability of organocopper reagents. Y. Yamamoto, Y. Chounan, S. Nishii, T. Ibuka and H. Kitahara, *J. Am. Chem. Soc.*, 1992, **114**, 7652.
- 6 T. Ibuka, T. Aoyagi, K. Kitada, F. Yoneda and Y. Yamamoto, *J. Organomet. Chem.*, 1985, **287**, C18; T. Ibuka, T. Aoyagi and Y. Yamamoto, *Chem. Pharm. Bull.*, 1986, **34**, 2417.
- 7 For example, the higher order reagent  $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$  may be better represented as  $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$ . S. H. Bertz, *J. Am. Chem. Soc.*, 1990, **112**, 4031; B. H. Lipshutz, S. Sharma and E. L. Ellsworth, *J. Am. Chem. Soc.*, 1990, **112**, 4032; S. H. Bertz, *J. Am. Chem. Soc.*, 1991, **113**, 5470; T. Stemmler, J. E. Penner-Hahn and P. Knochel, *J. Am. Chem. Soc.*, 1993, **115**, 348. We are not concerned about the exact structure, but watch the species as a reagent system. Methylcopper was prepared from  $\text{CuI}$  and  $\text{MeLi}$  which contained an equivalent amount of  $\text{LiBr}$ .
- 8 The deuterium at the  $\alpha$ -position was exchanged significantly for hydrogen during work-up procedure, but the deuterium at the  $\beta$ -position was not exchanged. For the incorporation of two deuteriums, see N. Krause and G. Handke, *Tetrahedron Lett.*, 1991, **32**, 7229.
- 9 Although we depict the reagent, for simplification, in an ordinarily accepted formula, each reagent should be represented as its  $\text{LiX}$  including form (as shown above). Evidence for an electron-transfer process of substitution reactions has been obtained; S. H. Bertz, G. Dabbagh and A. M. Mjuscce, *J. Am. Chem. Soc.*, 1991, **113**, 631.