

A Chemical Scale for Evaluating the Electron Transfer Ability of Alkylcopper Reagents

Yukiyasu Chounan, Hiroshi Horino, Toshiro Ibuka,[†] and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-77

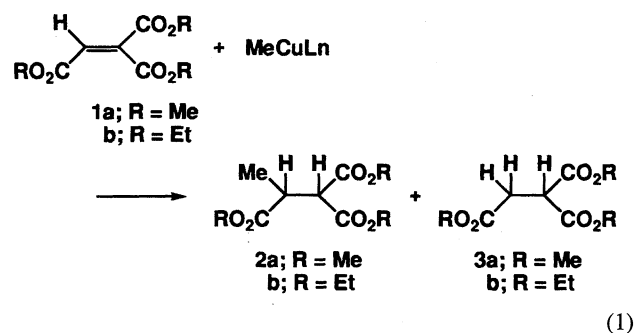
[†]Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606

(Received March 21, 1997)

In order to evaluate the electron transfer ability of organocopper reagents, the reactions of appropriate Michael acceptors with methyl- and butylcopper reagents were investigated. The reaction of trimethyl ethylene-1,1,2-tricarboxylate (**1a**) with methylcopper reagents gave a mixture of the conjugate adduct **2a** and reduction product **3a** in good to high yields. The ratio of **2a** and **3a** varied with the copper species and decreased in the following order: MeCu(CN)Li > MeCu > Me₂Cu(CN)Li₂ ≫ Me₂CuLi > Me₃CuLi₂. It was confirmed by ¹³C NMR studies and oxidation experiments of the intermediate copper species that the reduction product **3a** was produced via an electron transfer process and that the conjugate adduct **2a** was afforded through a nucleophilic attack of MeCu^ILn. Consequently, the electron transfer ability of methylcopper reagents is in the following order: Me₃CuLi₂ > Me₂CuLi ≫ Me₂Cu(CN)Li₂ > MeCu > MeCu(CN)Li. By similar experiments using 3-cyclopropyl-2-methoxycarbonyl-3-phenyl-2-propenoate (**9**) as a Michael acceptor, we concluded that the electron transfer ability of butylcopper reagents is in the order of Bu₂CuLi > BuCu(CN)Li ≈ Bu₂Cu(CN)Li₂ > BuCu, and that its ability of butylcopper reagents is higher than that of the corresponding methylcopper reagents.

The popularity of organocopper complexes as reagents in organic synthesis¹⁾ has brought forth numerous mechanistic investigations of both substitution and conjugate addition reactions.²⁾ Concerning conjugate addition, cuprate-olefin π -complexes have been detected by NMR spectroscopy^{2a,2c,2d)} and it is proposed that the complexes go on to form Cu(III) intermediates (nucleophilic addition process).³⁾ In addition to this plausible and currently more accepted mechanism, an electron-transfer process from RCuLn to unsaturated substrates has been proposed frequently as a second mechanism.^{4,5)} 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 correlation may also play an important role for controlling formation of the π -complexes in the first mechanism. The electron-accepting ability of the substrates can be elucidated from their polarographic one-electron reduction potentials.^{4–6)} Little is known, however, about the electron-donating ability of the reagents. We attempted to measure the oxidation potential of copper reagents using physicochemical methods, but all trials resulted in failure due to their instability.⁷⁾ However, we have found that the order of electron transfer ability for methylcopper reagents can be estimated by ratios of the conjugate adduct **2a** and reduction product **3a** in the reaction of trimethyl ethylene-1,1,2-tricarboxylate (**1a**) with methylcopper reagents (Eq. 1).⁸⁾ We now wish to report a fully detailed work of the previous study, together with application of this estimation method to

butylcopper reagents.



Results and Discussion

Methylcopper Reagents. Product Distribution. Previously we reported that the reactions of diethyl fumarate, diethyl maleate, triethoxycarbonyl ethylene (**1b**) and tetraethyl ethylene-1,1,2,2-carboxylate with butyl- and methylcopper reagents gave a mixture of the corresponding conjugate adducts and reduction products, and the ratios of these two major products depended upon both the reagent type and reaction conditions.⁹⁾ It occurred to us that, by a proper choice of the Michael acceptors, we might be able to evaluate the electron transfer ability of methylcopper reagents from the product ratios; in the previous reactions, either the conjugate adduct or reduction product was obtained exclusively according to the conditions, and the intermediate ratios which would enable one to discuss the order of electron transfer ability of

methylcopper reagents were not obtained. One probable reason why exclusive formation of either the reduction or conjugate addition product took place in the previous systems would be that the electron acceptability of the Michael acceptors was either too strong or too weak in comparison with the electron-donating ability of the methylcopper reagents. For example, the reaction of tetraethyl ethylene-1,1,2,2-carboxylate with any methylcopper reagents gave tetraethyl ethane-1,1,2,2-tetracarboxylate, a reduction product, in essentially quantitative yield; the reaction of diethyl ethylene-1,1-dicarboxylate derivatives with those methylcopper reagents afforded the corresponding diethyl ethylmalonate derivatives, a conjugate adduct, in essentially quantitative yields; and the reaction of triethoxycarbonyl ethylene (**1b**) with dimethylcuprate·BF₃ reagent gave the conjugate adduct **2b** exclusively.⁹⁾

After several trials, we found that the reaction of trimethyl ethylene-1,1,2-tricarboxylate (**1a**) with methylcopper reagents was a suitable system to investigate the scale of the electron-donating ability of the organocopper reagents. The reaction gave a mixture of the methyl transfer **2a** and reduction product **3a** in high yields (Eq. 1). To a diethyl ether solution of MeCuLn (2 mmol) cooled at -78 °C was added a diethyl ether solution of **1a** (1 mmol). The mixture was stirred for 5 min at -78 °C and allowed to warm to 0 °C. After stirring for 1 h at 0 °C, the reaction was quenched by adding saturated aqueous NH₄Cl solution. In addition to the two major products, small to trace amounts of the reductive coupling product of **1a** [(MeO₂C)₂CH(MeO₂C)CH]₂ and the methoxy adduct MeO(MeO₂C)CHCH(CO₂Me)₂ were produced in some cases. The **2a** : **3a** ratio-MeCuLn plots are shown in Fig. 1. The ratio of **2a** : **3a** decreased in the following order: MeCu(CN)Li·LiBr > MeCu·LiI·LiBr > Me₂Cu(CN)Li₂·2LiBr ≫ Me₂CuLi·LiI·2LiBr > Me₃CuLi₂·LiI·3LiBr. The higher order reagent Me₂Cu(CN)Li₂¹⁰⁾ may be better represented as Me₂CuLi·LiCN.¹¹⁾ We are not concerned about the exact structure, but watch the species as a reagent system. Methylcopper was prepared from CuI and MeLi, which contained an equimolar amount of LiBr,¹²⁾ and therefore is represented as MeCu·LiI·LiBr. The ratio was dependent also on solvent; in the reaction of Me₃CuLi₂·LiI·3LiBr the ratio of **2a** to **3a** was 18 : 82 in ether (Fig. 1), whereas it was 27 : 73 in THF and 37 : 63 in toluene. The results for the reactions of methylcopper-additive reagents as well as the detailed results of Fig. 1 are summarized in Table 1.

As mentioned above, no reduction product **3a** was obtained with MeCu(CN)Li (Entry 1) and in the cases of MeCu and MeLi/2CuI small amounts of **3a** were produced along with a major product **2a** (Entries 2 and 3). The yield of **3a** increased slightly with a higher order cyanocuprate reagent (Entry 4), and it increased very much with Me₂CuLi and Me₃CuLi₂ (Entries 5 and 6). The yields of the reduction product **3a** increased with increase of the molar ratio of MeLi to CuI. Very interestingly, the use of BF₃·OEt₂¹³⁾ as an additive led to an increase of the conjugate adduct **2a** (Entry 7 versus 4, Entry 8 versus 5, and Entry 9 versus 6). A similar trend was observed when TMSCl^{14,15)} was used as an additive

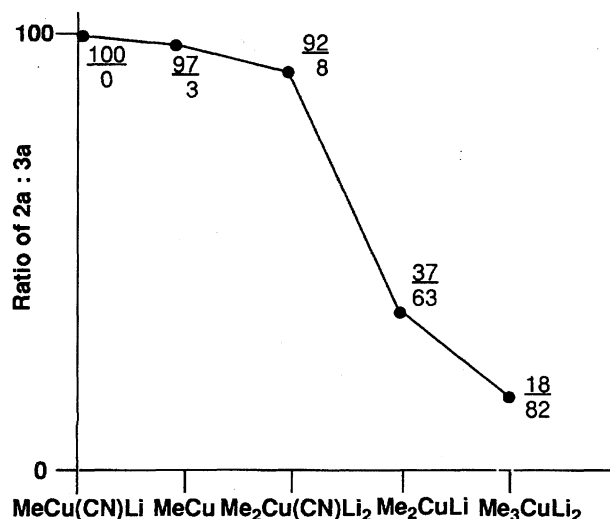


Fig. 1. MeCuLn dependence of the ratio of **2a** : **3a**.

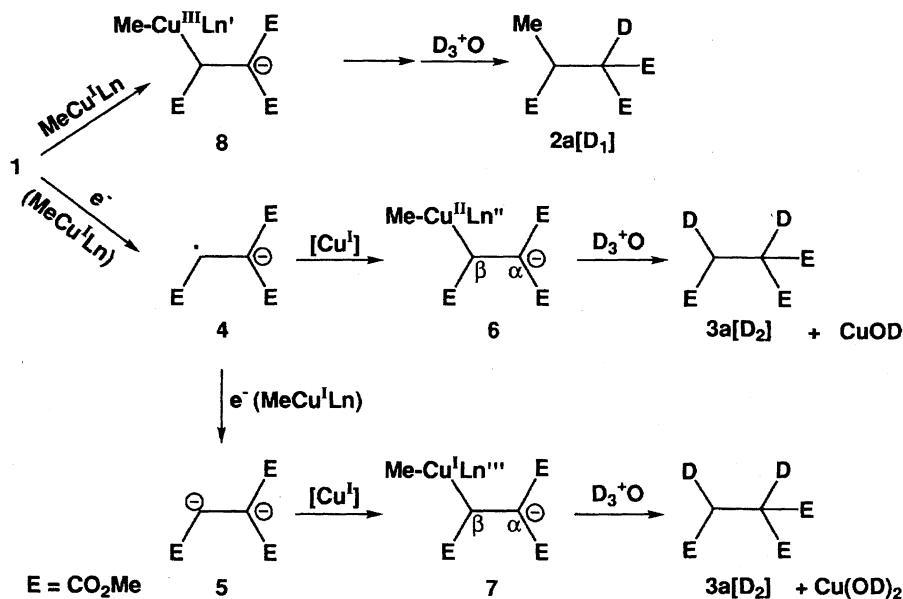
Table 1. Reaction of **1a** with Various Methylcopper Reagents^{a)}

Entry	Reagent	Product ratio ^{b)} 2a : 3a	Isolated yield of 2a + 3a (%)
1	MeCu(CN)Li	ca. 100 : 0	74
2	MeLi/2CuI	99 : 1	73
3	MeCu	97 : 3	72
4	Me ₂ Cu(CN)Li ₂	92 : 8	81
5	Me ₂ CuLi	37 : 63	91
6	Me ₃ CuLi ₂	18 : 82	82
7	Me ₂ Cu(CN)Li ₂ ·BF ₃	ca. 100 : 0	88
8	Me ₂ CuLi·BF ₃	ca. 100 : 0	63
9	Me ₃ CuLi ₂ ·BF ₃	97 : 3	75
10	MeCu(CN)Li·TMSCl	ca. 100 : 0	90
11	MeCu·TMSCl	ca. 100 : 0	71
12	Me ₂ Cu(CN)Li ₂ ·TMSCl	ca. 100 : 0	54
13	Me ₃ Cu(CN)Li ₃ ·TMSCl	95 : 5	99

a) For simplicity, LiI and LiBr as compositions of the reagents are omitted. For example, the real composition of Me₃CuLi₂ is Me₃CuLi₂·LiI·3LiBr. Me₂CuLi·BF₃ means that one equivalent BF₃·OEt₂ was added to one equivalent Me₂CuLi. b) Determined by ¹H NMR.

(Entries 11, 12, and 13). Although the precise reason for this effect of the additives is not clear, exclusive formation of the conjugate adduct is synthetically useful.¹⁾

The above investigation was carried out using MeLi which contained an equimolar amount of LiBr. Reactions of **1a** with methylcopper reagents, generated from salt-free MeLi and copper(I) cyanide (or copper(I) iodide), were studied in order to know the effect of LiBr upon the product distribution of **2a** and **3a**. The reaction of **1a** with MeCu(CN)Li, generated from MeLi (salt-free) and CuCN, gave a 98 : 2 mixture of **2a** and **3a** in 64% yield. The use of MeCu(CN)Li·LiBr afforded a ca. 100 : 0 mixture of **2a** and **3a** in 74% yield (Entry 1, Table 1). Accordingly, the influence of LiBr upon the ratio was negligible, although it exerted a significant influence on the chemical yield; the reagent involving LiBr gave higher yield than the salt-free reagent. A similar trend was observed for MeCu, Me₂CuLi, and Me₃CuLi₂. The use of MeCu·LiI



Scheme 1. Nucleophilic addition versus electron transfer process.

gave a ca. 100:0 mixture of **2a** and **3a** in 38% yield, that of $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ afforded a ca. 100:0 mixture of **2a** and **3a** in 58% yield and that of $\text{Me}_3\text{CuLi}_2 \cdot \text{LiI}$ produced a 22:78 mixture of **2a** and **3a** in 56% yield (cf. Entries 3, 4, and 6 of Table 1). Consequently, we thought that the influence of LiBr upon the ratio of **2a** and **3a** is negligible; MeLi containing an equimolar amount of LiBr was therefore used for the experiments mentioned below.

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,¹⁶⁾ and more recently it is being accepted by significant number of organocopper chemists that the conjugate addition of organocopper(I) reagents to Michael acceptors proceeds through a Cu(III) intermediate, followed by reductive coupling.^{4,5,17)} If the reduction of **1a** took place via a one electron transfer process as the initial step and the conjugate addition occurred via a nucleophilic addition of Cu(I) species to the Michael acceptor, the order of methylcopper reagents ($\text{MeCu}(\text{CN})\text{Li} < \text{MeCu} < \text{Me}_2\text{Cu}(\text{CN})\text{Li}_2 \ll \text{Me}_2\text{CuLi} < \text{Me}_3\text{CuLi}_2$), which was obtained from the ratio of **3a** and **2a**, would correspond to the order of the electron transfer ability of the reagents.

Mechanistic Study Using NMR Spectroscopy. In order to confirm the generally accepted pathways for the reduction and conjugate addition, the reactions of **1a** with MeCuLn were quenched with $\text{D}_2\text{O}-\text{DCl}$, instead of $\text{NH}_4\text{Cl}-\text{H}_2\text{O}$. The reduction product **3a[D₂]**, obtained using any MeCuLn , contained two deuteriums at the α - and β -positions, whereas one deuterium was incorporated into the α -position of the conjugate adduct **2a[D₁]**. The deuterium at the α -position was exchanged significantly for hydrogen during the work-up procedure, but the deuterium at the β -position was not exchanged.¹⁸⁾

A possible reaction mechanism, based on this observation and the generally accepted pathways, 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(II) **6** and Cu(I) **7** species, respectively. It is not clear at present whether **3a[D₂]** was produced via **6** or via **7**. The ratio of **2a**:**3a** and the deuterium content in **3a** did not depend on the reaction time, suggesting that **6** (or **7**) would be stable at 0 °C. We intended to detect the intermediate **6** (or **7**) by ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum of the stable intermediate, obtained from the addition of 2 equiv Me_3CuLi_2 to ^{13}C -enriched **1a** ($\text{EC}^*\text{H}=\text{CE}_2$),

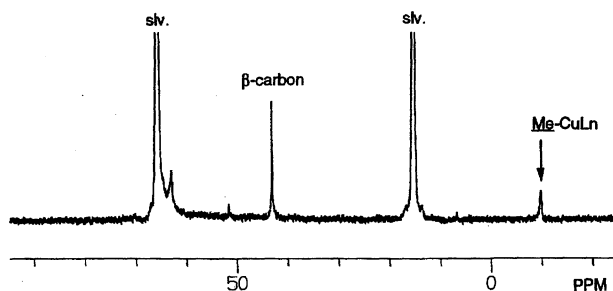


Fig. 2. ^{13}C NMR spectra of the reaction of **1a** (^{13}C -enriched) with Me_3CuLi_2 in diethyl ether at 0 °C.

Table 2. Reaction of **9** with Butylcopper Reagents^{a)}

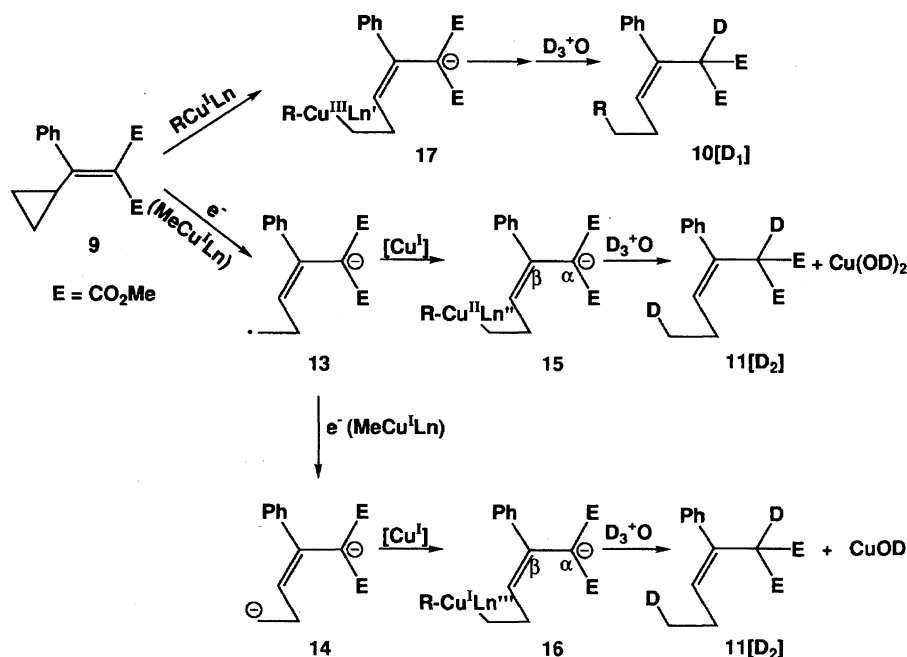
Entry	Reagent	Product ratio ^{b)} 10 : 11	Isolated yield of 10+11 (%)
1	<i>n</i> -BuCu	79 : 21	92
2	<i>n</i> -Bu ₂ Cu(CN)Li ₂	53 : 47	95
3	<i>n</i> -BuCu(CN)Li	47 : 53	90
4	<i>n</i> -Bu ₂ CuLi	33 : 67	99

a) Butylcopper reagents were prepared from CuCN (or CuI) and BuLi which contained an equimolar amount of LiBr. b) Determined by ^1H NMR.

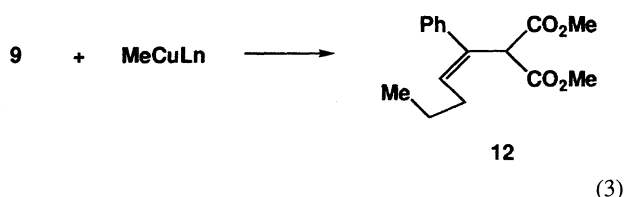
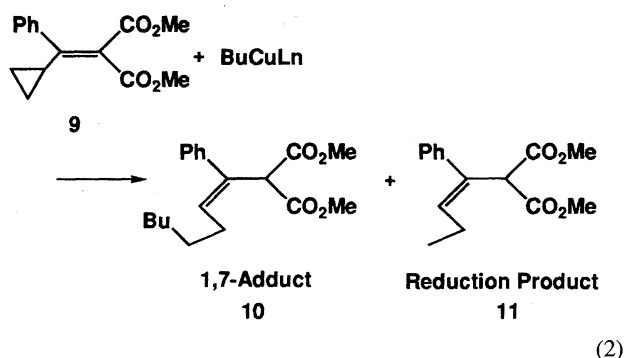
is shown in Fig. 2. The intermediate was stable at 0 °C at least for 8 h; it gave **3a**[D₂] upon quenching with D₃⁺O. A signal at $\delta=43.13$ was assigned to the β -carbon of the intermediate. The β -carbon of **3a** appeared at $\delta=32.96$ and that of **2a** at $\delta=39.11$. If the intermediate adopts a copper enolate form $\text{LnCuO}(\text{MeO})\text{C}=\text{C}^*\text{HC}^-\text{E}_2$, instead of an α -cuprio ester structure, the β -carbon (C*) should appear at much lower field, i.e. $\delta=\text{ca. } 150$ ppm. The α -carbon of the intermediate was not observable because of non-¹³C-enriched carbon as well as the presence of a minus charge. The β -carbon of the precursor of a minor product **2a**[D₁], $\text{MeEC}^*\text{HC}^-\text{E}_2$, was not observable in Fig. 2; the reason for this was not clear. When a diethyl ether solution of this intermediate was kept under O₂ atmosphere, only trace amounts of **3a** were detected and **2a** was obtained exclusively; **2a**:**3a** => 99:1, and the total yield was 85%. This clearly indicates that the intermediate (**6** or **7**) was oxidized to an unstable Cu(III) species with O₂, which instantaneously gave **2a** via reductive elimination. Taken together, the stable intermediate is either Cu(II) **6** or Cu(I) **7** species and the Cu(III) intermediate **8** is very unstable. It is now clear that the reduction product **3a** arises via an electron transfer process, whereas the adduct **2a** is produced through the nucleophilic addition.

Butylcopper Reagents. Next, we examined the reaction of **1a** with butylcopper reagents such as BuCu, BuCu(CN)Li, Bu₂CuLi, and Bu₂Cu(CN)Li₂, but the reduction product **3a** was obtained exclusively and none of the conjugate adduct was obtained. This observation suggested that the tris(alkoxy carbonyl) substituted olefins **1** would be too strong as an electron acceptor for the butylcopper reagents, and also suggested that the electron-donating ability of the butylcopper reagents would be higher than that of the corresponding methylcopper reagents. We searched for another appropriate Michael acceptor which might make it possible

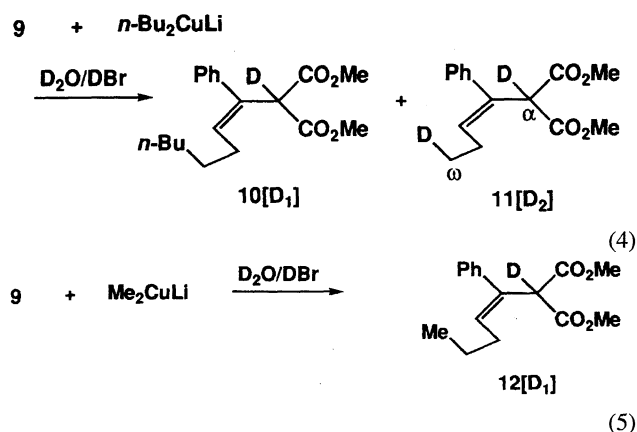
to evaluate the electron-donating ability of the butyl- and methylcopper reagents. After several attempts, we found that the bis(methoxy carbonyl) substituted olefin **9** bearing phenyl and cyclopropyl groups¹⁹⁾ was most suitable to this study. The results of the reactions of **9** with butylcopper reagents are summarized in Table 2 (Eq. 2). The reaction of **9** with *n*-BuCu·LiBr·LiI gave a 79:21 mixture of the conjugate adduct (1,7-adduct) **10** and the reduction product **11** in 92% yield (Entry 1). The reactions of **9** with lower order and higher order cyanocuprate reagents afforded nearly a 50:50 mixture of **10** and **11** in high yields (Entries 2 and 3). The reaction with Gilman cuprate gave a 33:67 mixture of **10** and **11** in 99% yield (Entry 4). Consequently, the electron transfer ability of the butylcopper reagents is in the following order; *n*-Bu₂CuLi > *n*-BuCu(CN)Li $\approx$ *n*-Bu₂Cu(CN)Li₂ > *n*-BuCu. This order is in good agreement with the order observed in the case of the methylcopper reagents. The reactions of **9** with methylcopper reagents were also investigated (Eq. 3). The reactions with Me₃CuLi₂, Me₂CuLi, and Me₂Cu(CN)Li₂ gave the 1,7-conjugate adduct **12** in high yields and no reduction product **11** was obtained. These results clearly indicate that the electron transfer ability of the butylcopper reagents is higher than that of the methylcopper reagents. The one-electron reduction potentials of the Michael acceptors **1a** and **9** were measured with cyclic voltammetry (vs. SCE in THF with 0.1 M Bu₄NBF₄). The reduction potential of **1a** was -1.06 V, whereas that of **9** was -1.21 V. Therefore, only the reduction product **3a** was obtained in the reaction of BuCuLn with **1a**, which possessed higher reduction potential, whereas a mixture of the 1,7-adduct **10** and reduction product **11** was produced in the reaction of BuCuLn with **9**, which possessed lower reduction potential.



Scheme 2. Nucleophilic addition versus electron transfer process.



The reactions of **9** with Bu_2CuLi and Me_2CuLi were quenched with $\text{D}_2\text{O}/\text{DBr}$ in a similar manner to that mentioned above. The 1,7-conjugate adduct **10**[D_1] contained one deuterium (>95%) at the α -position, whereas the reduction product **11**[D_2] contained two deuteriums both at the α - and ω -positions (Eq. 4); the content of deuterium at the ω -position was >85% although that at the α -position was >95%. These observations are in good agreement with those made in the reaction of **1a** with MeCuLn , in which the 1,4-conjugate adduct **2a** contained one deuterium at the α -position and the reduction product **3a** two deuteriums at the α - and β -position. The 1,7-conjugate adduct **12**[D_1] obtained in the reaction of **9** with Me_2CuLi also incorporated one deuterium at the α -position (Eq. 5). Accordingly, it is most probable that the reaction of **9** with BuCuLn proceeds through pathways similar to those shown in Scheme 1. Plausible paths of the reaction of **9** are shown in Scheme 2. First, the copper reagent ($\text{RCu}^{\text{I}}\text{Ln}$) would attack a cyclopropyl carbon conjugated with enoate to give Cu(III) intermediate **17**. The intermediate would undergo reductive coupling very rapidly to produce the 1,7-conjugate adduct **10**[D_1] upon hydrolysis with D_2O . On the other hand, one electron transfer from the copper reagent ($\text{RCu}^{\text{I}}\text{Ln}$) to **9** would give the radical anion **13**. Further reaction of **13** with $\text{RCu}^{\text{I}}\text{Ln}$ would produce Cu(II) intermediate **15**. The reduction product **11**[D_2] would be afforded by quenching the intermediate with D_2O . Alternatively, one electron could be transferred from the copper reagent ($\text{RCu}^{\text{I}}\text{Ln}$) to the radical anion **13**, which would give the dianion **14**. The reaction of **14** with $\text{RCu}^{\text{I}}\text{Ln}$ would produce the Cu(I) intermediate **16**, which would give **11**[D_2] upon deuterolysis. We also examined the reactions of **1** and **9** with phenylcopper reagents and vinylcopper reagents. However, a mixture of polymeric products was obtained with these organocopper reagents. Therefore, **1** and **9** can be utilized as a Michael acceptor in order to determine the electron-donating ability of alkylcopper reagents.



Conclusion

The electron transfer ability of methylcopper reagents is in the following order: $\text{Me}_3\text{CuLi}_2 > \text{Me}_2\text{CuLi} \gg \text{Me}_2\text{Cu}(\text{CN})\text{Li}_2 > \text{MeCu} > \text{MeCu}(\text{CN})\text{Li}$. The electron transfer ability of butylcopper reagents is in the following order: $n\text{-Bu}_2\text{CuLi} > n\text{-BuCu}(\text{CN})\text{Li} \approx n\text{-Bu}_2\text{Cu}(\text{CN})\text{Li}_2 > n\text{-BuCu}$. A comparison between BuCuLn and MeCuLn has been made; butylcopper reagents donate an electron to the Michael acceptors **1** and **9** more easily than methylcopper reagents. The order reported here may be useful for considering the mechanism of organocopper reactions and for designing organic synthesis via organocopper reagents.

Experimental

General Methods. Melting points were determined on either a Yamato MP-21 capillary melting point apparatus or a MRK. No. 8026. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica gel 60F₂₅₄ plates. Solvents for extraction and chromatography were reagent grade. THF and diethyl ether were distilled from benzophenone ketyl under argon immediately prior to use. Dichloromethane and carbon tetrachloride were distilled from calcium hydride under argon immediately prior to use. Butyllithium and methyllithium were obtained from the Kanto Chemical Co., Inc., and Aldrich Chemical Company, respectively, as standardized solutions. In vacuo removal of solvent refers to the use of a rotary operating aspirator and then rotary pump pressure. Column chromatography was carried out with E. Merck silica gel 60 (70–230 mesh ASTM). Flush chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM). HPLC was performed on a Hitachi L-6000 model using a Gasukuro Kogyo HPLC Packed Column Intertisil SIL (5 μm 4.6 $\times$ 250 nm). GC analysis was carried out on a Shimadzu 14A model equipped with a fused silica-capillary column (Shimadzu CPB1-M25-025). Infrared spectra were recorded on a Hitachi model 260-10. Peaks are recorded (in cm^{-1}). NMR spectra were recorded on JEOL GSX-270 and GSX-400 spectrometers. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants in (Hz), and assignments. Low-resolution mass spectra were obtained on a Hitachi M-2500S spectrometer using electron impact (EI) values obtained at 13.5 eV. High-resolution mass spectra were obtained on a JEOL JMS-HX 110. Combustion analyses were performed by the Analytical Center of the Graduate School of Science at Tohoku University.

Reactions of Alkylcopper Reagents. To a diethyl ether solution of MeCuLn (2 mmol) cooled at -78°C was added a di-

ethyl ether solution of substrate (1 mmol). The mixture was stirred for 5 min at -78°C and allowed to warm to 0°C . After stirring for 1 h at 0°C , the reaction was quenched by adding aqueous NH_4Cl solution. The usual workup gave the products, whose isomer ratios were determined by ^1H NMR. Alkylcopper reagents were prepared as follows. $\text{MeLi}/2\text{CuI}$: An ether solution of MeLi (1.0 mmol) was slowly added to a precooled ether (2 mL) suspension of CuI (380.9 mg, 2.0 mmol) at 0°C ; stirring was continued for 10 min at this temperature, and then the mixture was cooled to -78°C . MeCu : An ether solution of MeLi (2.0 mmol) was slowly added to a precooled ether (2 mL) suspension of CuI (380.9 mg, 2.0 mmol) at 0°C ; stirring was continued for 10 min at this temperature, and then the mixture was cooled to -78°C . Me_2CuLi : The procedure was similar to the above, except for the use of 2 equiv MeLi . Me_3CuLi_2 : MeLi (3 equiv) was used, and the rest of the procedure was the same as above. $\text{MeCu}(\text{CN})\text{Li}$: An ether solution of MeLi (2.0 mmol) was added slowly to a precooled ether (2 mL) suspension of CuCN (190.2 mg, 2.0 mmol) at -78°C . The mixture was allowed to warm to 0°C , and a homogeneous solution was obtained. After 10 min, the solution was cooled to -78°C . $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$: The procedure was similar to the above, except for the use of 2 equiv of MeLi . $\text{Me}_3\text{Cu}(\text{CN})\text{Li}_3$: MeLi (3 equiv) was used, and the rest of the procedure was the same as above. $\text{MeCuLn}\cdot\text{BF}_3$: $\text{BF}_3\cdot\text{OEt}_2$ (0.25 mL, 2.0 mmol) was added to each MeCuLn at -78°C , and the mixture was stirred for 5 min. $\text{MeCuLn}\cdot\text{TMSCl}$: TMSCl (2.0 mmol) was added to each MeCuLn at -78°C , and the mixture was stirred for 5 min. BuCuLn : The procedure was similar to that above, except for the use of BuLi -hexane solution instead of MeLi and for the use of -50°C instead of 0°C .

Trimethyl Ethylene-1,1,2-tricarboxylate (1a).²⁰⁾ In a 200-mL flask were placed potassium carbonate (41.5 g, 0.30 mol), dimethyl malonate (20.0 g, 0.15 mol), methyl chloroacetate (10.8 g, 0.10 mol), and acetone (100 mL), and the mixture was refluxed for 18 h. Precipitates were filtered and the solvent was evaporated. Addition of 1 M HCl , extraction three times with ether, washing with saturated NaHCO_3 aqueous solution and brine, drying with anhydrous MgSO_4 , concentration under vacuum, and purification by distillation under reduced pressure (2.0 mmHg, $102\text{--}110^{\circ}\text{C}$, 1 mmHg = 133.322 Pa) gave trimethyl ethane-1,1,2-tricarboxylate (8.23 g) in 41% yield. To a CCl_4 solution (300 mL) of trimethyl-ethane-1,1,2-tricarboxylate (41.6 g, 0.204 mol) was added dropwise bromine (11.1 mL, 0.166 mol) under the irradiation of a Hg lamp. The mixture was stirred for 8 h. After removal of bromine and CCl_4 under reduced pressure, ether (200 mL) was added. Triethylamine (30 mL, 0.215 mol) was added dropwise at 0°C , and the mixture was stirred for 2 h. Washing three times with water, extraction three times with ether, washing again with brine, drying with anhydrous MgSO_4 , concentration under vacuum, and purification by recrystallization gave **1a** in 49% yield.

^{13}C -Enriched Trimethyl Ethylene-1,1,2-tricarboxylate. ^{13}C -enriched bromoacetic acid ($\text{BrC}^*\text{H}_2\text{COOH}$), which was commercially available from Nippon Sanso, was converted to the corresponding methyl ester upon treatment with diazomethane. The rest of the procedure was the same as above.

3-Cyclopropyl-2-methoxycarbonyl-3-phenyl-2-propenoate (9). Dry THF (100 mL) was placed in a 300-mL flask kept at 0°C under Ar, and TiCl_4 (3.8 mL, 34.4 mmol) was added with a syringe to give a yellow suspension. Dimethyl malonate (17.3 mmol) and then cyclopropyl phenyl ketone (17.2 mmol) were added. The color of the solution changed from yellow to brown. Addition of pyridine (5.6 mL, 69 mmol) gave a deep red-brown solution. The mixture was stirred for 2 d at room temperature. Addition of saturated

aqueous NH_4Cl solution, extraction three times with ether, washing the organic layer with saturated aqueous NaCl solution, drying with anhydrous MgSO_4 , concentration under vacuum, and purification by silica-gel column chromatography gave **9** in 73% yield. IR (thin film) 3017, 2953, 1736, 1721, 1611, 1593, 1491, 1435, 1323, 1229, 1075, 1013, 766 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_4$: C, 69.22; H, 6.20%. Found: C, 69.16; H, 6.32%. ^1H NMR (400 MHz, CDCl_3) δ = 7.35–6.98 (m, 5H), 3.83 (s, 3H), 3.38 (s, 3H), 2.75 (ddd, J = 8.3, 5.1, 3.2 Hz, 1H), 0.88 (m, 2 H), 0.50 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ = 165.9, 165.7, 162.5, 134.6, 128.1, 127.9, 127.5, 125.1, 52.2, 51.8, 15.1, 6.9. HRMS (EI) Calcd for $\text{C}_{15}\text{H}_{16}\text{O}_4$: M, 260.1049. Found: m/z 260.1052.

Methyl 2-Methoxycarbonyl-3-phenyl-3-decenate (10). IR (thin film) 2955, 2930, 2857, 1759, 1738, 1599, 1495, 1435, 1379, 1312, 1194, 1148, 1036, 770 cm^{-1} . Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4$: C, 71.67; H, 8.23%. Found: C, 71.41; H, 8.35%. ^1H NMR (400 MHz, CDCl_3) δ = 7.42–7.13 (m, 5H), 5.91 (t, J = 7.3 Hz, 1H), 4.75 (s, 1H), 3.67 (s, 6H), 2.17 (dt, J = 7.3, 7.3 Hz, 2H), 1.50–1.20 (m, 8H), 0.89 (br t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 168.9, 141.7, 136.4, 132.5, 128.1, 127.1, 127.0, 54.1, 52.6, 31.7, 29.14, 29.05, 29.05, 22.6, 14.1. HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{26}\text{O}_4$: M, 318.1831. Found: m/z 318.1834.

Methyl 2-Methoxycarbonyl-3-phenyl-3-hexenate (11). IR (thin film) 3017, 2953, 1736, 1721, 1611, 1593, 1491, 1435, 1323, 1229, 1075, 1013, 766 cm^{-1} . Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4$: C, 68.69; H, 6.92%. Found: C, 68.60; H, 6.71%. ^1H NMR (400 MHz, CDCl_3) δ = 7.40–7.20 (m, 5H), 5.91 (t, J = 7.3 Hz, 1H), 4.76 (s, 1H), 3.68 (s, 6H), 2.16 (dt, J = 7.3, 7.3 Hz, 2H), 1.49 (tq, J = 7.3, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). HRMS (EI) Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4$: M, 262.1205. Found: m/z 262.1202.

Methyl 2-Methoxycarbonyl-3-phenyl-3-heptenate (12). IR (thin film) 2957, 2874, 1755, 1740, 1599, 1495, 1435, 1312, 1194, 1150, 1034, 901, 772 cm^{-1} . Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$: C, 69.54; H, 7.30%. Found: C, 69.26; H, 7.59%. ^1H NMR (400 MHz, CDCl_3) δ = 7.40–7.20 (m, 5H), 5.91 (t, J = 7.3 Hz, 1H), 4.76 (s, 1H), 3.68 (s, 6H), 2.16 (dt, J = 7.3, 7.3 Hz, 2H), 1.49 (tq, J = 7.3, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ = 168.9, 141.7, 136.2, 132.6, 128.1, 127.1, 127.0, 54.1, 52.6, 31.1, 22.3, 13.9. HRMS (EI) Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$: M, 276.1362. Found: m/z 276.1364.

References

- Recent review: a) N. Krause and A. Gerold, *Angew. Chem., Int. Ed. Engl.*, **36**, 186 (1997); b) N. Krause, *Kontakte*, **1993**, 3; c) B. H. Lipshutz and S. Sengupta, *Org. React.*, **41**, 135 (1992); d) T. Ibuka and Y. Yamamoto, *Synlett*, **1992**, 769; e) B. E. Rossiter and N. M. Swingle, *Chem. Rev.*, **92**, 771 (1992); f) J. A. Kozlowski, "Comprehensive Organic Synthesis," ed by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 4, p. 169; g) S. Hanessian and K. Sumi, *Synthesis*, **1991**, 1083.
- Most recent mechanistic studies with NMR: a) N. Krause, R. Wagner, and A. Gerold, *J. Am. Chem. Soc.*, **116**, 381 (1994); N. Krause, *J. Org. Chem.*, **57**, 3509 (1992) (organocuprate π -complexes); b) S. H. Bertz, G. Dabbagh, X. He, and P. P. Power, *J. Am. Chem. Soc.*, **115**, 11640 (1993) (aggregation states); c) S. H. Bertz and R. A. Smith, *J. Am. Chem. Soc.*, **111**, 8276 (1989) (cuprate-olefin π -complexes); d) B. Christenson, T. Olsson, and C. Ullenius, *Tetrahedron*, **45**, 523 (1989) (cuprate-olefin π -complexes); e) B. H. Lipshutz, S. H. Dimock, and B. James, *J. Am. Chem. Soc.*, **115**, 9283 (1993); B. H. Lipshutz and B. James, *Tetrahedron Lett.*, **34**, 6689 (1993) (cuprate- Me_3SiCl complexes); f) B. H. Lipshutz, E.

- L. Ellsworth, and S. H. Dimock, *J. Am. Chem. Soc.*, **112**, 5869 (1990) (RCu·BF₃ reagent); g) A. S. Vellekoop and R. A. Smith, *J. Am. Chem. Soc.*, **116**, 2902 (1994) (cuprate-enone complexes); h) S. H. Bertz, A. S. Vellekoop, R. A. Smith, and J. P. Snyder, *Organometallics*, **14**, 1213 (1995); i) K. Nilsson, C. Ullenius, and N. Krause, *J. Am. Chem. Soc.*, **118**, 4194 (1996).
- 3) a) E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **25**, 3063 (1984); b) E. J. Corey and N. W. Boaz, *Tetrahedron Lett.*, **26**, 6015 (1985); c) S. R. Krauss and S. G. Smith, *J. Am. Chem. Soc.*, **103**, 141 (1981); d) C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95**, 7783 (1973).
- 4) a) C. T. Wigal, *J. Org. Chem.*, **56**, 3059 (1991); b) S. H. Bertz, G. Dabbagh, J. M. Cook, and V. Honkan, *J. Org. Chem.*, **49**, 1739 (1984); c) H. O. House and K. A. J. Snoble, *J. Org. Chem.*, **41**, 3076 (1976); d) H. O. House, *Acc. Chem. Res.*, **9**, 59 (1976); e) R. A. Ruden and W. E. Litterer, *Tetrahedron Lett.*, **1975**, 2043; f) H. O. House and M. J. Umen, *J. Org. Chem.*, **38**, 3893 (1973); g) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972); h) H. O. House and W. F. Fischer, *J. Org. Chem.*, **33**, 949 (1968).
- 5) a) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, **1987**, 561; b) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, **1987**, 1572; c) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Am. Chem. Soc.*, **110**, 617 (1988).
- 6) J. P. Collman and L. S. Hegedus, "Principles and Applications of Organotransition Metal Chemistry," Univ. Sci. Books, CA (1980), p. 544.
- 7) 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.*, **114**, 7652 (1992).
- 8) Y. Chounan, T. Ibuka, and Y. Yamamoto, *J. Chem. Soc., Chem. Commun.*, **1994**, 2003.
- 9) a) T. Ibuka, T. Aoyagi, K. Kitada, F. Yoneda, and Y. Yamamoto, *J. Organomet. Chem.*, **287**, C18 (1985); b) T. Ibuka, T. Aoyagi, and Y. Yamamoto, *Chem. Pharm. Bull.*, **34**, 2417 (1986).
- 10) a) B. H. Lipshutz, *Synthesis*, **1987**, 325; b) B. H. Lipshutz, *Synlett*, **1990**, 119; c) B. H. Lipshutz, R. S. Wilhelm, and J. A. Kozlowski, *Tetrahedron*, **40**, 5005 (1984).
- 11) a) S. H. Bertz, *J. Am. Chem. Soc.*, **112**, 4031 (1990); b) B. H. Lipshutz, S. Sharma, and E. L. Ellsworth, *J. Am. Chem. Soc.*, **112**, 4032 (1990); c) S. H. Bertz, *J. Am. Chem. Soc.*, **113**, 5470 (1991); d) T. Stemmler, J. E. Penner-Hahn, and P. Knochel, *J. Am. Chem. Soc.*, **115**, 348 (1993); e) J. P. Snyder, D. P. Spangler, and J. R. Behling, *J. Org. Chem.*, **59**, 2665 (1994); f) B. H. Lipshutz and B. James, *J. Org. Chem.*, **59**, 7585 (1994); g) T. M. Barnhart, H. Huang, and J. E. Penner-Hahn, *J. Org. Chem.*, **60**, 4310 (1995); h) J. P. Snyder and S. H. Bertz, *J. Org. Chem.*, **60**, 4312 (1995).
- 12) B. H. Lipshutz, J. A. Kozlowski, and C. M. Breneman, *J. Am. Chem. Soc.*, **107**, 3197 (1985).
- 13) a) Y. Yamamoto, S. Yamamoto, H. Yatagai, and K. Maruyama, *J. Am. Chem. Soc.*, **102**, 2318 (1980); b) Y. Yamamoto, S. Yamamoto, H. Yatagai, Y. Ishihara, and K. Maruyama, *J. Org. Chem.*, **47**, 119 (1982); c) Y. Yamamoto and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, **1984**, 904; d) Y. Yamamoto, S. Nishii, and T. Ibuka, *J. Chem. Soc., Chem. Commun.*, **1987**, 464; f) B. H. Lipshutz, D. A. Parker, J. A. Kozlowski, and S. L. Nguyen, *Tetrahedron Lett.*, **25**, 5959 (1984); g) B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen, and K. E. McCarthy, *J. Organomet. Chem.*, **285**, 437 (1985).
- 14) a) A. Alexakis, J. Berlan, and Y. Besace, *Tetrahedron Lett.*, **27**, 1047 (1986); b) E. Nakamura, S. Matsuzawa, Y. Horiguchi, and I. Kuwajima, *Tetrahedron Lett.*, **27**, 4029 (1986); c) R. J. Linderman and A. Godfrey, *Tetrahedron Lett.*, **27**, 4553 (1986).
- 15) a) S. H. Bertz, G. Miao, B. E. Rossiter, and J. P. Snyder, *J. Am. Chem. Soc.*, **117**, 11023 (1995); b) J. P. Snyder, *J. Am. Chem. Soc.*, **117**, 11025 (1995).
- 16) Evidence for an electron transfer process of substitution reactions has been obtained: S. H. Bertz, G. Dabbagh, and A. M. Majsce, *J. Am. Chem. Soc.*, **113**, 631 (1991).
- 17) a) R. A. J. Smith and D. J. Hannah, *Tetrahedron*, **35**, 1183 (1979); b) D. J. Hannah, R. A. J. Smith, I. Teoh, and R. T. Weavers, *Aust. J. Chem.*, **34**, 181 (1981); c) R. A. J. Smith and D. J. Hannah, *Tetrahedron Lett.*, **1980**, 1081; d) D. J. Hannah and R. A. J. Smith, *Tetrahedron Lett.*, **1975**, 187; e) R. A. Ruden and W. E. Litterer, *Tetrahedron Lett.*, **1975**, 2043.
- 18) For the incorporation of two deuteriums, see: N. Krause and G. Handke, *Tetrahedron Lett.*, **32**, 7229 (1991).
- 19) a) L. Eberson, "Electron Transfer Reactions in Organic Chemistry," Springer-Verlag, New York (1987); b) D. Griller and U. Ingold, *Acc. Chem. Res.*, **13**, 317 (1980); c) J. M. Tanko and R. E. Drumright, *J. Am. Chem. Soc.*, **114**, 1844 (1992); d) J. M. Tanko, R. E. Drumright, N. Kamrudin Suleman, and L. E. Brammer, Jr., *J. Am. Chem. Soc.*, **116**, 1785 (1994); e) A. L. J. Beckwith and V. W. Bowry, *J. Am. Chem. Soc.*, **114**, 2710 (1994).
- 20) H. K. Hall, Jr., and P. Ykman, *J. Am. Chem. Soc.*, **97**, 800 (1975).