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

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Abstract: 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 ratio of the conjugate adduct and reduction product was used as a chemical scale for evaluating the electron transfer ability of the alkylcopper reagents. Consequently, the electron transfer ability of methyl and butylcopper reagents is in the following order; Me_3CuLi_2 > Me_2CuLi >> $Me_2Cu(CN)Li_2$ > MeCu > MeCu(CN)Li; Bu_2CuLi > BuCu(CN)Li ~ $Bu_2Cu(CN)Li_2$ > BuCu.

INTRODUCTION

The popularity of organocopper complexes as reagents in organic synthesis (Ref. 1) has brought forth numerous mechanistic investigations of both substitution and conjugate addition reactions (Ref. 2). Concerning conjugate addition, cuprate-olefin π-complexes have been detected by NMR spectroscopy (Refs. 2a, c, d) and it is proposed that the complexes go on to form Cu(III) intermediates (nucleophilic addition process) (Ref. 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 the second mechanism (Refs. 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 (Refs. 4, 5). 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

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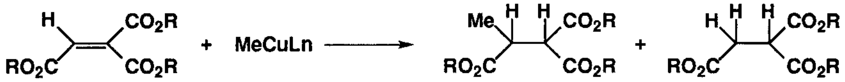
resulted in failure due to their instability (Ref. 6). However, we have found that the order of electron transfer ability for methylcopper reagents can be estimated by ratios of the conjugate adduct **2a** and reduction product **3a** in the reaction of trimethoxycarbonylethylene **1a** with methylcopper reagents Eq. 1 (Ref. 7).



1a; R = Me
b; R = Et

2a; R = Me
b; R = Et

3a; R = Me
b; R = Et

(1)

RESULTS AND DISCUSSION

Methylcopper Reagents. Product Distribution

Previously we reported that the reactions of diethyl fumarate, diethyl maleate, triethoxycarbonylethylene **1b** and tetraethoxycarbonylethylene 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 (Ref. 8). 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 in dependence on the conditions, and the intermediate ratios which would enable to discuss the order of electron transfer ability of methylcopper reagents were not obtained. Most probably, a 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 tetraethoxycarbonylethylene with any methylcopper reagents gave 1,1,2,2-tetraethoxycarbonylethane, a reduction product, in essentially quantitative yield, the reaction of 1,1-di(ethoxycarbonyl)ethylene derivatives with those methylcopper reagents afforded the corresponding 1,1-di(ethoxycarbonyl)-2-methylethane derivatives, a conjugate adduct, in essentially quantitative yields, and the reaction of triethoxycarbonylethylene **1b** with dimethylcuprate•BF_3 reagent gave the conjugate adduct **2b** exclusively (Ref. 8).

After several trials, we found that the reaction of trimethoxycarbonylethylene **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 NH_4Cl solution. In addition to the two major products, small to trace amounts of the reductive coupling product of **1a** $\{(MeO_2C)_2CH(MeO_2C)CH\}_2$ and the methoxy adduct $MeO(MeO_2C)CHCH(CO_2Me)_2$ 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; $MeCu(CN)Li{\bullet}LiBr$ > $MeCu{\bullet}LiI{\bullet}LiBr$ > $Me_2Cu(CN)Li_2{\bullet}2LiBr$ >> $Me_2CuLi{\bullet}LiI{\bullet}2LiBr$ > $Me_3CuLi_2{\bullet}LiI{\bullet}3LiBr$. The higher order reagent $Me_2Cu(CN)Li_2$ may be better represented as $Me_2CuLi{\bullet}LiCN$ (Ref. 9). 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 equivalent amount of LiBr, and therefore represented as $MeCu{\bullet}LiI{\bullet}LiBr$. The ratio was dependent also on solvent; in the reaction of $Me_3CuLi_2{\bullet}LiI{\bullet}3LiBr$ 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 on the reactions of methylcopper•additive reagents as well as the detailed results of Fig. 1 are summarized in Tab. 1.

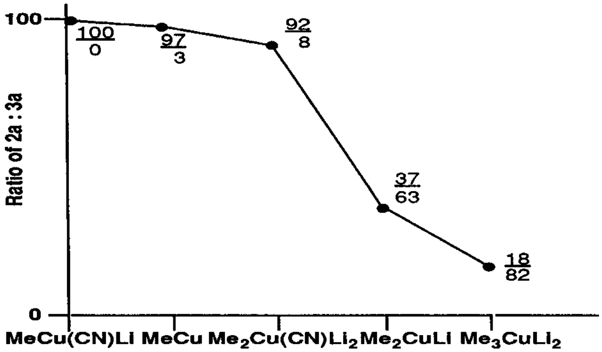


Fig. 1. MeCuLn dependence of the ratio of **2a** : **3a**

As mentioned above, no reduction product **3a** was obtained with MeCu(CN)Li (Entry 1) and in the case 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 Me_2CuLi and Me_3CuLi_2 (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 $BF_3{\bullet}OEt_2$ (Ref. 10) as an additive lead to increase of the conjugate adduct **2a** (Entry 7 *versus* 4, Entry 8 *versus* 5, and Entry 9 *versus* 6). Similar trend was observed when TMSCl was used as an additive (Entries 11, 12, and 13). Although precise reason for this effect of the additives is not clear, exclusive formation of the conjugate adduct is synthetically useful (Ref. 1). Detailed investigation revealed that the influence of LiBr upon the ratio of **2a** and **3a** was negligible, and therefore MeLi containing an equivalent amount of LiBr was used for experiments mentioned below.

Tab. 1. Reaction of **1a** with Various Methylcopper Reagents[a)]

Entry	Reagent	Product ratio **2a** : **3a**	Isolated yield of **2a** + **3a** (%)
1	MeCu(CN)Li	~100 : 0	74
2	MeLi/2CuI	99 : 1	73
3	MeCu	97 : 3	72
4	$Me_2Cu(CN)Li_2$	92 : 8	81
5	Me_2CuLi	37 : 63	91
6	Me_3CuLi_2	18 : 82	82
7	$Me_2Cu(CN)Li_2 \cdot BF_3$	~100 : 0	88
8	$Me_2CuLi \cdot BF_3$	~100 : 0	63
9	$Me_3CuLi_2 \cdot BF_3$	97 : 3	75
10	MeCu(CN)Li•TMSCl	~100 : 0	90
11	MeCu•TMSCl	~100 : 0	71
12	$Me_2Cu(CN)Li_2$•TMSCl	~100 : 0	54
13	$Me_3Cu(CN)Li_3$•TMSCl	95 : 5	99

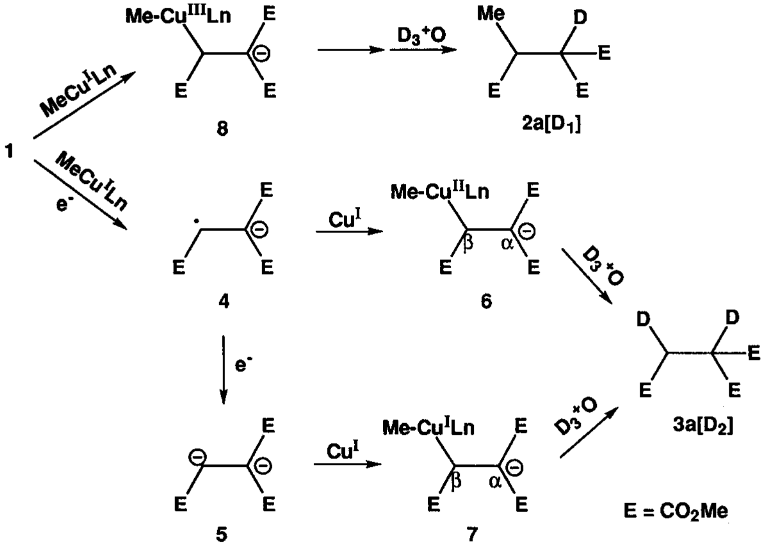
[a)] For simplicity, LiI and LiBr as compositions of the reagents are omitted.

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 (Ref. 11), 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 Cu(III) intermediate followed by reductive coupling (Refs. 4, 5). If the reduction of **1a** took place *via* 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 (MeCu(CN)Li < MeCu < $Me_2Cu(CN)Li_2$ << Me_2CuLi < Me_3CuLi_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 D_2O-DCl, instead of NH_4Cl-H_2O. The reduction product **3a[D$_2$]**, 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[D$_1$]**. The deuterium at the α-position was exchanged significantly for hydrogen during work-up procedure, but the deuterium at the β-position was not exchanged.

Scheme 1. Nucleophilic addition *versus* electron transfer process.



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 MeCu^{I}Ln to afford the Cu(II) **6** and Cu(I) **7** species, respectively. It is not clear at present whether **3a[D$_2$]** was produced *via* **6** or *via* **7**. The ratio of **2a** : **3a** and 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** ($EC^*H{=}CE_2$), is shown in Fig. 2. The intermediate was stable at 0 °C at least for 8 h, which gave **3a[D$_2$]** upon quenching with D_3^+O. A signal at δ 43.13 ppm was assigned to the β-carbon of the intermediate. The β-carbon of **3a** appeared at 32.96 ppm and that of **2a** at 39.11 ppm. If the intermediate adopts a copper enolate form $LnCuO(MeO)C{=}C^{*}HC^{-}E_2$, instead of an α-cuprio ester structure, the β-carbon (C*) should appear at much lower field, *i.e.* *ca.* 150 ppm. The α-carbon of the intermediate was not observable because of non-^{13}C-enriched carbon as well as the presence of a minus charge. The β-carbon of the precursor of a minor product **2a[D$_1$]**, $MeEC^{*}HC^{-}E_2$, was not observable in Fig. 2, the reason for which was not clear. When a diethylether solution of this intermediate was kept under O_2 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 O_2, 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.

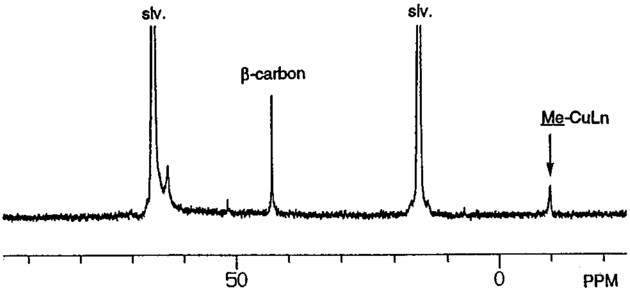
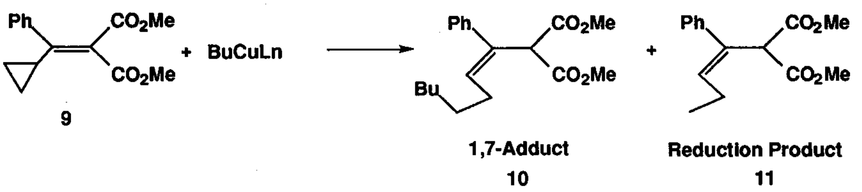


Fig. 2. ^{13}C NMR spectra of the reaction of 1a (^{13}C-enriched) with Me_3CuLi_2 in diethyl ether at 0 °C

Butylcopper Reagents

Next, we examined the reaction of **1a** with butylcopper reagents such as BuCu, BuCu(CN)Li, Bu_2CuLi, and $Bu_2Cu(CN)Li_2$, but the reduction product **3a** was obtained exclusively and none of the conjugate adduct was obtained. This observation suggested that the triester 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 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 diester substituted olefin **9** bearing phenyl and cyclopropyl group was most suitable to this study. The results of the reactions of **9** with butylcopper reagents are summarized in Tab. 2 (Eq. 2).



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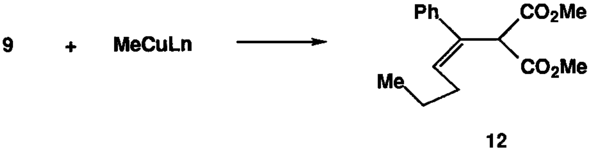

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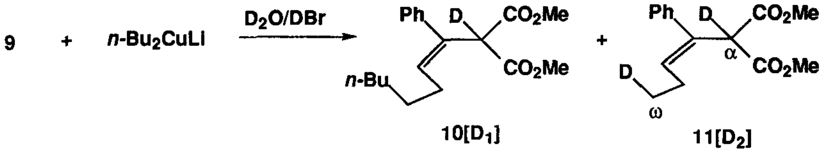
Tab. 2. Reaction of **9** with Butylcopper Reagents

Entry	Reagent	Product ratio **10** : **11**	Isolated yield of **10** + **11** (%)
1	*n*-BuCu	79 : 21	92
2	*n*-$Bu_2Cu(CN)Li_2$	53 : 47	95
3	*n*-BuCu(CN)Li	47 : 53	90
4	*n*-Bu_2CuLi	33 : 67	99

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 50:50 mixture of **10** and **11** in high yields (Entries 2 and 3). The reaction with a 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*-Bu_2CuLi > *n*-BuCu(CN)Li ~ *n*-$Bu_2Cu(CN)Li_2$ > *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 Me_3CuLi_2, Me_2CuLi, and $Me_2Cu(CN)Li_2$ 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 Bu_4NBF_4). 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.



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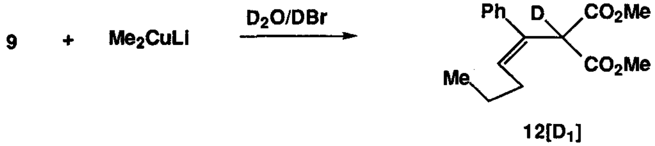

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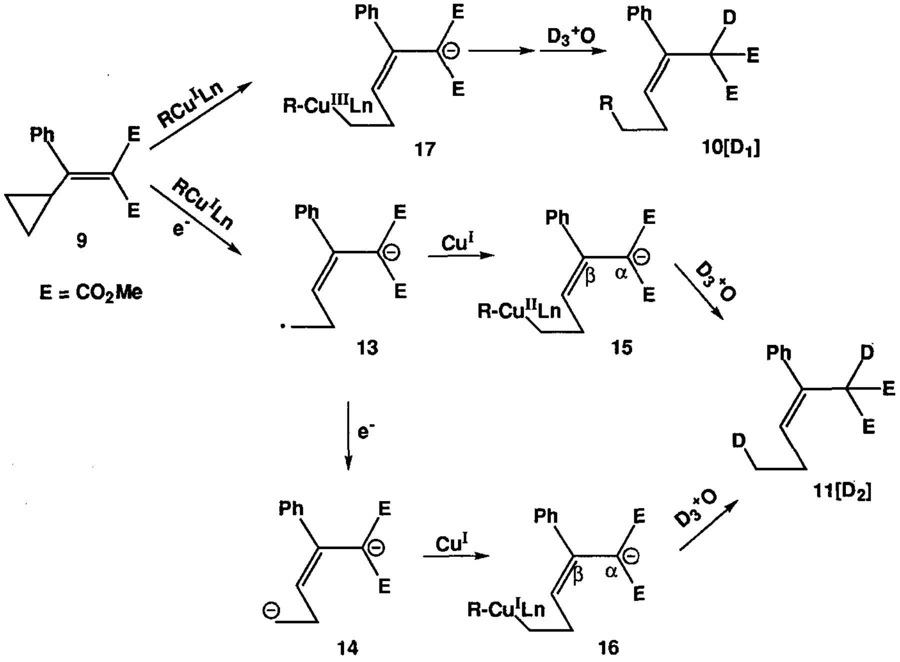
Scheme 2. Nucleophilic addition *versus* electron transfer process.



The reactions of 9 with Bu_2CuLi and Me_2CuLi were quenched with D_2O/DBr in a similar manner 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 deuterium both at the α- and ω-position 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 incorporated also one-deuterium at the α-position Eq. 5. Accordingly, it is most probable that the reaction of 9 with BuCuLn proceeds though pathways similar to those shown in Scheme 1. Plausible paths of the reaction of **9** are shown in Scheme 2. First, the copper reagent ($RCu^{I}Ln$) 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 ($RCu^{I}Ln$) to **9** would give the radical anion **13**. Further reaction of **13** with $RCu^{I}Ln$ 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 ($RCu^{I}Ln$) to the radical anion **13**, which would give the dianion **14**. The reaction of **14** with $RCu^{I}Ln$ 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 know the electron donating ability of alkylcopper reagents.

CONCLUSION

The electron transfer ability of methylcopper reagents is in the following order; $Me_3CuLi_2 > Me_2CuLi >> Me_2Cu(CN)Li_2 > MeCu > MeCu(CN)Li$. The electron transfer ability of butylcopper reagents is in the following order; $n\text{-}Bu_2CuLi > n\text{-}BuCu(CN)Li \sim n\text{-}Bu_2Cu(CN)Li_2 > n\text{-}BuCu$. 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.

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