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AN INVESTIGATION OF THE ELECTRON TRANSFER PROPERTIES OF MODIFIED ORGANOCOPPER REAGENTS AND HIGHER-ORDER CUPRATES

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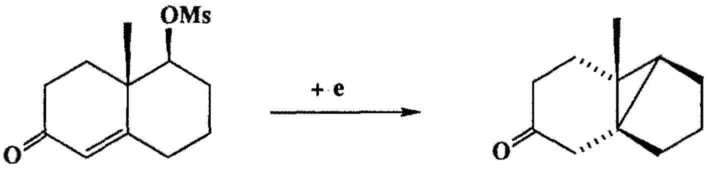
Abstract - The electron transfer properties of organocopper reagents are attenuated on introduction of BF_3OEt_2 or Me_3SiCl. The results are interpreted in concordance with current mechanistic proposals. Higher-order CuCN-based cuprates show significant electron transfer ability, in contrast to the related lower-order cuprates.

Carbon-carbon bond formation via the conjugate addition to α,β-unsaturated carbonyl compounds using organocopper reagents has developed into a widely used synthetic procedure.[1] Despite the many examples available which illustrate the great utility of these reactions, the mechanism of a typical reaction i.e. the conjugate addition of organocuprates (Gilman reagents) with an α,β-enone has not been fully resolved.[2] Currently, evidence is available which clearly demonstrates reversible π-complexation of organocuprates with α,β-enones followed by the formation of copper(III)-β-adducts.[2,3,4] We have previously shown that organocuprates are capable of electron transfer processes by observing that the conversion of 1* to 2 can be achieved by reaction with cuprates[5] or electrochemically[6] and that the internal displacement of the mesylate leaving group to create the tricyclic skeleton can take place after the addition of one electron:



1 2

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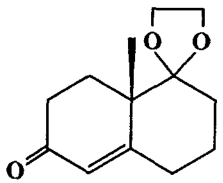
* Racemic compounds were used in this work. For clarity diagrams representing only one enantiomer have been presented.

However, it has not been established if electron transfer is necessary for conjugate addition or is only one of several possible mechanistic pathways available for these reactions. Notwithstanding these uncertainties, the available mechanistic information has promoted the rational development of some significant synthetic methodology particularly in the area of diastereoselective[7] and enantioselective[8] conjugate additions. An area of greater current activity is the alteration of the organocopper reagent reactivity using complex unsymmetrical organocopper reagents[1b] or suitable activators, particularly boron trifluoride etherate[9] ($BF_3.OEt_2$) and chlorotrimethylsilane[10] (Me_3SiCl).

With regard to certain polycyclic synthetic objectives we had reason to examine the conjugate addition of various organocopper reagents with rigid, bicyclic, δ-oxy-α,β-unsaturated ketones (e.g. 3,4) and noticed considerable variation of reactivity. Our response to these observations was to consider the possible reactivity pathways of these recent, modified organocopper reagents and herein we report the results of these studies.



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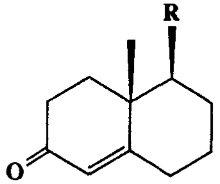


4 R = OCH_2OMe

5 R = H

Various organocopper reagents were examined for electron transfer potential by reaction with 1 and the results are presented in the Table. All organocopper reagents are listed with empirical formulae as the exact molecular composition is unknown in many instances and can vary with solvent.[11] The reactions were carried out in diethylether (Et_2O) or tetrahydrofuran (THF) for suitable literature comparison. We have previously noted[12] that polar solvents such as THF severely restrict electron transfer from organocuprates and inhibition of conjugate addition by polar solvents is also well established.[13] In order to provide maximum possible reactivity, butyl-based cuprates were generally used in preference to the corresponding methyl reagents, unless direct literature comparison was required.

$BF_3.OEt_2$ is reported to promote the reactivity of 1:1 organocopper species (RCu)[9] and also various organocuprate reagents.[14,15] $BuCu.BF_3$ was found to be completely unreactive towards 1 and also 5. In contrast, the corresponding BF_3 modified cuprate did show electron transfer properties (entries 1,2) albeit less than the simple cuprate reagent (Bu_2CuLi) which gave only 2 in high yield.[12] Some product variation dependent on the copper source was also noted (cf. entries 1 and 2). A significant observation with these modified cuprates was that appreciable amounts of the 1,2 addition product 6 were obtained which generally increased at the expense of 2. The modified higher-order cuprate also showed appreciable electron transfer properties (entry 3) but again, in comparison with the unmodified reagent (entry 4), the effect of the addition of $BF_3.OEt_2$ was to inhibit electron transfer and to promote 1,2 addition. In concert with this observation the unmodified higher-order cuprate, $Bu_2Cu(CN)Li_2$, gave good yields (65%) of conjugate addition product on reaction with 5.[16] The symmetrical higher-order cuprate "Me_3CuLi_2" has been shown[17] to consist of lower-order cuprate and organolithium (Me_2CuLi + MeLi) so it was not surprising to find evidence of considerable electron transfer (entry 5) comparing favourably with Me_2CuLi (97%).[12] Comparable reactivity of Me_2CuLi/MeLi and Me_2CuLi could not be extended to 5 however, as reaction with Me_2CuLi/MeLi in Et_2O gave only the 1,2 addition product 7. As before, the addition of $BF_3{\cdot}OEt_2$ to the organocopper (entry 6) served to reduce the amount of electron transfer product although 1,2 addition was not observed in this case.

TABLE

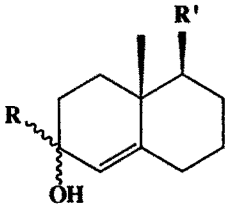
Reaction[a] of Organocopper Reagents with 1

Entry	Reagent (equiv) (Cu source)	Solvent	Additive (equiv)	Product Ratio[b] 1 : 2 : 6 (9)	Isolated Yield of Major Product (%)
1	Bu_2CuLi (3) (CuI)	Et_2O	$BF_3.OEt_2$ (3)	- : 4 : 1	
2	Bu_2CuLi (3) ($CuBr.Me_2S$)	Et_2O	$BF_3.OEt_2$ (3)	- : 1 : 2	
3	$Bu_2Cu(CN)Li_2$ (3)	Et_2O	$BF_3.OEt_2$ (3)	- : 1 : 1	
4	$Bu_2Cu(CN)Li_2$ (3)	Et_2O	-	- : 1 : -	64
5	$Me_2CuLi/MeLi$ (3)	Et_2O	-	1 :20 : -[c]	84
6	$Me_2CuLi/MeLi$ (3)	Et_2O	$BF_3.OEt_2$ (3)	1 : 8 : -[c]	67
7	Me_2CuLi (1.5)	THF	Me_3SiCl (7.5)	10 : - : 7[c]	
8	Me_2CuLi (1.5)	Et_2O	Me_3SiCl (7.5)	14 :11 : -[c]	
9	Bu_2CuLi (3) (CuI)	THF	Me_3SiCl (3) DMAP (3)	1 : - : 9	
10	Bu_2CuLi (3) ($CuBr.Me_2S$)	THF	Me_3SiCl (3) DMAP (3)	3 : - : 17	
11	BuCu (3) (CuI)	THF	Me_3SiCl (3) DMAP (3)	5 : - : 2	
12	BuCu (3) ($CuBr.Me_2S$)	THF	Me_3SiCl (3) DMAP (3)	2 : - : 1	
13	BuCu (3)	Et_2O	Me_3SiCl (3) DMAP (3)	1 : - : -	
14	BuCu (2) (CuI)	Et_2O	BF_3OEt_2 (2) Me_3SiCl (3)	1 : - : -	74
15	BuCu(CN)Li (3)	Et_2O	-	1 : - : -	80
16	BuCu(CN)Li (3)	Et_2O	BF_3OEt_2 (3)	1 : - : -	58
17	BuCu(CN)Li (3)	Et_2O	Me_3SiCl (4.5)	1 : - : -	74

[a] General reaction conditions are given in the Experimental.

[b] Ratio determined by gas chromatography unless otherwise stated.

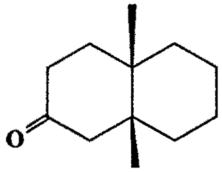
[c] Ratio determined by ^1H NMR.



6 R = Bu , R' = OMs

7 R = Me , R' = H

9 R = Me , R' = OMs



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The process by which $BF_3.OEt_2$ uniquely facilitates some conjugate addition reactions, particularly in comparison to many other Lewis acids[15] has not yet been uncovered. Activation of the carbonyl group by coordination with BF_3 has been proposed.[9] $BF_3.OEt_2$ has been found to alter the amount of 1,2 addition in the reaction of organocuprates with polysubstituted α,β-enones.[9] The addition of $RCu.BF_3$ to high reduction potential saturated ketones has also been reported.[9] The results of this study are in concert with a mechanism involving nucleophilic attack[18] of the organocopper reagent on a BF_3-activated substrate. The presence of $BF_3.OEt_2$ in the reaction of 1 with organocuprates could inhibit the electron transfer process in favour of a nucleophilic mechanistic pathway which is susceptible to steric hindrance with β,β-disubstituted-α,β-enones and hence gives 1,2 product 6. Alternatively, an enone-BF_3 complex could be produced in which appreciable negative charge does not accumulate at the β-carbon, upon electron transfer and hence intramolecular displacement of the mesylate is precluded.

Me_3SiCl has also been shown to facilitate the conjugate addition of organocopper reagents to some α,β-enones.[10] In contrast to the $BF_3.OEt_2$ mediated reactions, considerable mechanistic information is available which indicates that the silane activation is not a result of coordination with the carbonyl group but rather it facilitates an irreversible collapse of the initially formed π-complex to a β-copper(III) adduct and thence by reductive elimination to the β-alkylated product.[3] This mode of rate increase is expected to be more pronounced in THF than in Et_2O as organocuprate conjugate additions are usually slower in the former solvent. A striking example of the possibilities of using this acceleration effect in THF is shown by reaction of the electronically and sterically demanding substrate 5 with Me_2CuLi/Me_3SiCl to give 8, albeit accompanied by substantial amounts of the 1,2 addition product 7.[10b] It is possible that the products from 1,2 and conjugate addition could arise from a common π-intermediate.[19] The Me_3SiCl-induced collapse to the β-carbon in 5 is sterically restricted and thus collapse to the carbonyl carbon could possibly compete. Reaction of 5 with Me_2CuLi/Me_3SiCl in Et_2O at -30° gave 8 in 85% yield and was approximately twice as fast as the corresponding reaction (Me_2CuLi, -30°) without silane. As noted previously,[10c] isolation of the conjugate addition product as the derived trimethylsilylenol ether required the addition of an appropriate base (Et_3N) prior to or after the addition of 5 to the organometallic reagent.

Reaction of 1 with Me_2CuLi/Me_3SiCl in THF (entry 7) did not produce any 2 but instead substantial amounts of the 1,2 addition product 9. This result contrasts to the same reaction carried out in Et_2O (entry 8) where appreciable quantities of 2 but not 9 were obtained. These results clearly demonstrate that the electron transfer process is being inhibited by Me_3SiCl. In terms of the proposed mechanism, in THF the Me_3SiCl-induced acceleration is forcing the collapse of the π-complex which, because of steric hindrance at the β-position preferentially gives 9. In Et_2O, the Me_3SiCl effect is not as pronounced and enhanced collapse to 9 is not observed, allowing formation of moderate amounts of the electron transfer product 2. At this stage it is not possible to determine if electron transfer precedes π-complex formation or if these are steps on two separate mechanistic pathways.

Several amine-complexed organocopper reagents have been reported recently for conjugate additions[19,20] which have the attributes of increased convenience and efficient use of the organic ligands. Examination of a typical example, the 4-dimethylaminopyridine (DMAP) modified organocopper reagents[19], showed that Me_3SiCl again precluded organocuprate electron transfer at the expense of 1,2 addition (entries 9 and 10) irrespective of the source of copper(I). Amine-modified BuCu also failed to show any electron transfer ability (entries 11, 12 and 13) irrespective of solvent, and no cooperative reactivity effect between $BF_3.OEt_2$ and Me_3SiCl was observed (entry 14).

Reactions of 1 with mixed lower-order cuprates having non-transferable ligands such as 1-alkynyl have shown these reagents have considerable electron transfer ability.[12] Mixed organocuprates containing the cyano ligand have been promoted as useful reagents because of the ease of purification and storage of CuCN and the high reproducibility of reactions with some α,β-enones.[21] The mixed organocuprate BuCu(CN)Li in Et_2O was found to be unreactive towards 1 (entry 15) and also 5. Addition of $BF_3.OEt_2$ (entry 16) or Me_3SiCl (entry 17) did not induce any observable reaction. The cyano ligand therefore appears to stabilize the cuprates by reducing their oxidation potential which is presumably related to the electron withdrawing ability of the attached cyanide group.

For general synthetic purposes the results from these studies indicate that if the α,β-enone under examination has a low reduction potential and is relatively unencumbered at the β-position then enhancement of reactivity by the addition of Me_3SiCl or $BF_3.OEt_2$ should be a serious consideration. On the other hand, conjugate additions to highly substituted, high reduction potential α,β-enones will probably be most favoured with R_2CuLi reagents in nonpolar solvents.

EXPERIMENTAL

A general description of the experimental procedures has been given previously.[12] ^1H nuclear magnetic resonance (NMR) spectra were recorded on Varian VXR-300 and EM-390 spectrometers in $CDCl_3$ with tetramethylsilane as internal reference. Infrared spectra were obtained on a Nicolet MX-5 spectrophotometer. Gas chromatographic analyses were carried out with a Perkin Elmer 8420 gas chromatograph, fitted with a flame ionization detector, on a 12.5mx0.25mm OV-1 fused silica column, using helium carrier gas (10 psi). The samples were introduced in THF at a column oven temperature of 80° and the column was then heated to 300° at 20° min^{-1}. Retention times under these conditions were 8.86, 4.44, 5.80 and 6.00 min for 1, 2 and 6 respectively. The data was analysed by the in-built data processor using relative peak areas. Unidentified compounds in the product mixtures amounted to <10% of the total material.

CuI[22], $CuBr.Me_2S$[23] and CuCN[24] were prepared and purified according to literature methods. $BF_3.OEt_2$ and Me_3SiCl were redistilled before use.

Cis-5-mesyloxy-10-methyl-1(9)-octal-2-one 1, 6-methyltricyclo[4.4.0.$0^{1,5}$]decan-9-one 2, 10-methyl-1(9)-octal-2-one 5, *cis*-9,10-dimethyloctal-2-one 8 and 2,10-dimethyl-1(9)-octal-2-ol 7 were available from previous studies.[12] 10-Methyl-1(9)-octalin-2,5-dione-5-ethylene ketal 3[25] and *cis*-5-(methoxymethyl)oxy-10-methyl-1(9)-octal-2-one 4[26] were prepared from Wieland Miescher ketone and *cis*-5-hydroxy-10-methyl-1(9)-octal-2-one respectively. Samples of the 1,2 addition products 6 and 9 were obtained by reaction of 1 with BuLi or MeLi. These compounds were labile materials and characterized spectroscopically.

Compound 6: IR ν_{max} 3470 (OH), 1714 (C=C), 1334, 1194 (SO_2) cm^{-1}. ^1H NMR δ 5.28 (broad s, 1H, C=CH), 4.43 (m, 1H, H-5), 3.00 (s, 3H, OSO_2CH_3), 1.23 (s, 3H, CH_3), 0.90 (distorted t, 3H, J = 6Hz, butyl CH_3).

Compound 9: IR ν_{max} 3480 (OH), 1712 (C=C), 1336, 1188 (SO_2) cm^{-1}. ^1H NMR δ 5.23 (broad s, 1H, C=CH), 4.43 (m, 1H, H-5), 3.00 (s, 3H, OSO_2CH_3), 1.23 (s, 3H, CH_3), 1.01 (s, 3H, CH_3).

The methyl organocopper reagents were prepared by adding ethereal methyllithium-lithium bromide complex to copper iodide in the specified solvent at 0° followed by stirring for 15 min. The solution was then cooled to -78° and any additional reagents were added, followed 15 min later, by a solution of 1. The reaction mixtures were worked up after stirring a further 1 hr at -78°. For reactions involving $BF_3.OEt_2$ low halide methyllithium was used.

The butyl organocopper reagents were prepared by adding butyllithium to the copper salt in the specified solvent at -78°. The mixture was warmed to -40° for 15 min then cooled to -78° and any additional reagents were then added, followed 15 min later, by a solution of 1. The reaction mixtures were worked up after stirring 45 min at -78°.

Reactions were routinely run with 0.100g of 1 (0.39 mmole) which was introduced as a solution in dichloromethane (2 ml) or THF if this was the reaction solvent. Recovery of 1 from reactions where electron transfer or 1,2 addition did not occur was generally >75% except in systems containing $BF_3.OEt_2$ where the recovery of 1 was reduced to ca. 60%. Percentage yields quoted in the discussion and the Table refer to isolated materials.

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