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CONCERNING THE UNUSUAL STEREOSELECTIVITY OBSERVED IN THE REACTION OF CH_3Li-$LiCu(CH_3)_2$ WITH 4-t-BUTYLCYCLOHEXANONE.

A REPORT OF SIMILAR RESULTS WITH CH_3Li-$LiClO_4$ AND CH_3Li-LiBr

E. C. Ashby*, J. J. Lin and John J. Watkins

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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Recently, it was reported that a mixture of CH_3Li and $LiCu(CH_3)_2$ provides unusually high stereoselectivity (94% equatorial attack) in the methylation of 4-tert-butylcyclohexanone compared to reactions of CH_3Li or $LiCu(CH_3)_2$ alone.[1] It was suggested that a "bulky, highly reactive cuprate having the stoichiometry $Li_2Cu(CH_3)_3$ or $Li_3Cu(CH_3)_4$" was formed when CH_3Li and $LiCu(CH_3)_2$ are allowed to react and that reaction of these cuprates with the ketone would explain the observed results. We wish to report here that the reaction of CH_3Li in the absence of $LiCu(CH_3)_2$, but in the presence of LiBr or LiI (which are normally present in $LiCu(CH_3)_2$) also produce enhanced stereochemistry in the 1,2-addition of 4-t-butylcyclohexanone compared to pure CH_3Li and that CH_3Li in the presence of $LiClO_4$ produces the same stereochemistry (94% equatorial attack) as observed in the CH_3Li-$LiCu(CH_3)_2$ system. Since we have shown by NMR that $LiClO_4$ does not form a complex with CH_3Li, but does form a complex with 4-t-butylcyclohexanone, the indication is that the mechanism of the reaction involves attack of CH_3Li on the ketone-lithium salt complex. This pathway accounts for both the enhanced rate and stereoselectivity observed even with those lithium salts that do not contain copper and which have been shown not to interact with CH3Li.

The CH_3Li-$LiCu(CH_3)_2$ mixture used to methylate 4-tert-butylcyclohexanone was prepared by reacting CH_3Li with CuI in an 8:3 molar ratio in diethyl ether solvent. In such a mixture at least three species are present: $LiCu(CH_3)_2$, CH_3Li and LiI. The reaction of any one of these compounds with 4-tert-butylcyclohexanone fails to produce the identical stereochemistry reported above. One can suggest four possible explanations for this stereoselectivity. (1) CH_3Li reacts with $LiCu(CH_3)_2$ to form a complex which then reacts with the ketone.[1] (2) CH_3Li reacts with LiI to form a complex (a reaction known to produce $Li_4(CH_3)_3I)$[2] which then reacts with the ketone. (3) $LiCu(CH_3)_2$ and LiI react to form a complex which then reacts with the ketone. (4) One of the species in solution reacts with the ketone to form a complex followed by reaction of CH_3Li with the complexed carbonyl compound.

Recently we reported low temperature ^1H NMR evidence for the existence of $Li_2Cu(CH_3)_3$ in a mixture of CH_3Li and $LiCu(CH_3)_2$ in dimethyl ether, tetrahydrofuran and diethyl ether solvents.[3] No evidence was found to indicate the presence of any higher order complexes, such

$$CH_3Li + LiCu(CH_3)_2 \rightleftharpoons Li_2Cu(CH_3)_3 \quad (1)$$

as $Li_3Cu(CH_3)_4$. Reaction of CH_3Li-$LiCu(CH_3)_2$ with 4-tert-butylcyclohexanone in THF did not yield any increased stereoselectivity when compared to CH_3Li alone (Table 1). Since we have determined that $Li_2Cu(CH_3)_3$ exists in both ether and THF and is monomeric in both solvents, it is doubtful that $Li_2Cu(CH_3)_3$ would react with 4-tert-butylcyclohexanone in diethyl ether to give unusual stereoselectivity while in THF no trace of unusual stereoselectivity is observed. Therefore, one is lead to question that the observed stereoselectivity in diethyl ether is due to the reaction of $Li_2Cu(CH_3)_3$ with the ketone.[4]

The stereochemical improvement in the CH_3Li-$LiCu(CH_3)_2$ reagent in diethyl ether cannot be explained by assuming that a complex between CH_3Li and LiI (formed in the reaction of CH_3Li with CuI) is reacting with the ketone. A mixture of CH_3Li and LiI or LiBr (Table 1) while giving some improvement in stereoselectivity, does not give the same selectivity observed with the CH_3Li-$LiCu(CH_3)_2$ mixture. Also a mixture of CH_3Li and LiI or LiBr in THF (Table 1) gives no improvement in stereoselectivity over CH_3Li alone. It is known that MeLi forms complexes with both LiI[8] and LiBr[9] in THF. Likewise, the stereochemical improvement cannot be explained by assuming that a complex between either $LiCu(CH_3)_2$ or $Li_2Cu(CH_3)_3$ and LiI is reacting with the ketone, since a halide free mixture of CH_3Li and $LiCu(CH_3)_2$ (Table 1) gives the same high stereoselectivity.

Table 1. Reactions of Organometallic Reagents with 4-tert-Butylcyclohexanone in Ether Solvents at -78°.

Reagent	Yield of Axial Alcohol Ether	THF
CH_3Li	69	65
$2CH_3Li + LiCu(CH_3)_2$	92	65
$2CH_3Li + LiCu(CH_3)_2$ (halide free)	93	65
$CH_3Li + LiBr$	87	65
$CH_3Li + LiI$	87	65
$CH_3Li + LiClO_4$	92	67

The only possibility remaining is that CH_3Li reacts with a complex between one of the components of the mixture and the ketone. This would explain the results in THF, since the ketone would not be expected to compete effectively with THF solvent molecules for coordination sites. This suggestion also explains the unusual rate enhancement in diethyl ether since the concentration of ketone complexed to $LiCu(CH_3)_2$, LiI, etc. would be considerably higher than in THF and certainly the complexed carbonyl compound would be much more reactive than uncomplexed.

In order to test this possibility, a system composed of CH_3Li and a lithium salt, was chosen where there would be little chance for complex formation between CH_3Li and the lithium salt but a good chance for complex formation between the lithium salt and the ketone. Such a system is CH_3Li-$LiClO_4$, since $LiClO_4$ is known to complex the carbonyl group of ketones.[10] Low temperature ^1H and ^{13}C NMR of CH_3Li-$LiClO_4$ mixtures show only signals for pure CH_3Li indicating the absence of any complex formation. ^{13}C NMR of 4-tert-butylcyclohexanone mixtures with LiBr, LiI, $LiClO_4$ and $LiCu(CH_3)_2$ in diethyl ether show a downfield shift for the carbonyl carbon of about 10 ppm, indicating the presence of a complex. However, in THF only a small downfield shift was observed with the above salts indicating the presence of very little complexed ketone. The reaction of the CH_3Li-$LiClO_4$ mixture with 4-tert-butylcyclohexanone in diethyl ether (Table 1) shows the same stereochemical improvement as was obtained with CH_3Li-$LiCu(CH_3)_2$. In THF this reaction (Table 1) showed no improvement in stereoselectivity over that obtained with CH_3Li alone.

The results shown in Table 1 indicate that CH_3Li-LiBr, CH_3Li-LiI, CH_3Li-$LiClO_4$ and CH_3Li-$LiCu(CH_3)_2$ mixtures react with 4-tert-butylcyclohexanone in diethyl ether to give higher stereoselectivity in the product methyl carbinols than were obtained with CH_3Li alone. The results suggest that the methylation reaction is proceeding by attack of CH_3Li on a ketone complex. In the particular case where a CH_3Li-$LiCu(CH_3)_2$ mixture is allowed to react with 4-tert-butylcyclohexanone, the results suggest that methylation is proceeding by CH_3Li attack on a complex between $LiCu(CH_3)_2$ and the ketone.

References and Notes

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4. Molecular weight measurements[2] indicate that $Li_2Cu(CH_3)_3$ is monomeric in diethyl ether and THF, whereas CH_3Li is tetrameric and $LiCu(CH_3)_2$ is dimeric.[6,7] Qualitative rate measurements indicate that in diethyl ether, CH_3Li-LiI mixture and a halide free CH_3Li-$LiCu(CH_3)_2$ mixture methylate 4-tert-butylcyclohexanone at least 1000 fold faster than CH_3Li alone.

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