Tetrahedron Letters No. 31, pp 2659 - 2662, 1976. Pergamon Press. Printed in Great Britain.

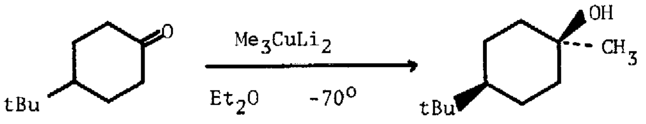
ORGANOCUPRATES. II. REACTION OF TRIALKYLCUPRATES WITH SATURATED AND UNSATURATED CARBONYL COMPOUNDS.[1]

W. Clark Still*
Department of Chemistry, Vanderbilt University, Nashville, TN. 37235

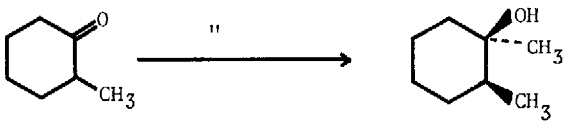
T. L. Macdonald*[2]
Department of Chemistry, Columbia University, New York, N.Y. 10027

(Received in USA 25 March 1976; received in UK for publication 15 June 1976)

We recently reported a new reagent having the stoichiometry Me_3CuLi_2 which reacts with cyclohexanones to produce high yields of axial alcohols.[1,3] For example:



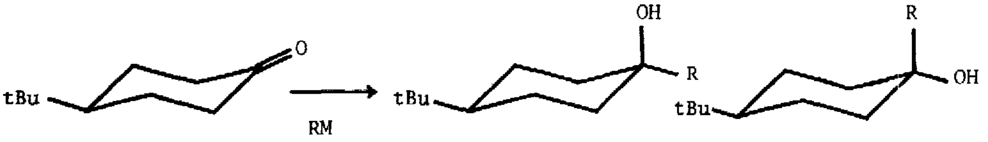
94% of Product
(91% yield)



97% of Product
(96% yield)

Since this reagent is one of the most highly stereospecific organometallic methylating agents known[4] and differs in reactivity from the related dialkylcuprates,[5] we have extended our studies in this area. Our results on the reactions of dilithium trimethylcuprate with unsaturated carbonyl compounds and on the addition of other trialkylcuprates to cyclohexanones are reported here.

To evaluate the generality of our recently described synthesis of axial cyclohexanols, we have examined the reaction of other trialkylcuprates with 4-*tert*.-butylcyclohexanone. The reagents were prepared and utilized as described previously[1] by adding three equivalents of alkyllithium[6] to one equivalent of cuprous iodide in ether at -40°, and were then reacted with 0.7 equivalents of ketone at -78°.[7] The results of this study and a comparison study with alkyllithium reagents are outlined below:[8]



RM	=	n-BuLi(5°)	73%	27%	(93% conv.)
	=	n-BuLi (-78°)	86%	14%	(98% conv.)
	=	$(n\text{-Bu})_3CuLi_2$(-78°)	97%	3%	(>99% conv.)
RM	=	s-BuLi(5°)	76%	24%	(72% conv.)
	=	s-BuLi(-78°)	83%	17%	(74% conv.)
	=	$(s\text{-Bu})_3CuLi_2$(-78°)	90%	10%	(78% conv.)

In line with our results with Me_3CuLi_2, high yields of axial cyclohexanols were obtained. Thus R_3CuLi_2 seems superior to the corresponding alkyllithium reagents both from the standpoints of stereochemical control and starting ketone conversion.[9] We have been unable, however, to extend this approach to the stereoselective introduction of a vinyl substituent. We observed approximately 55% equatorial addition to 4-*tert*.-butylcyclohexanone at 5°, at -78°, and at -78° in the presence of Cu(I).[10] These results could reflect either an unfavorable dialkyl-trialkylcuprate equilibrium or formation of a relatively unreactive trivinylcuprate.

One possible disadvantage of these reagents is the requirement of at least three equivalents of alkyllithium per equivalent of starting ketone. This requirement can in principle be circumvented either by substituting nontransferable ligands for two equivalents of alkyllithium[11] or by utilizing a process catalytic in R_3CuLi_2.[12] We have found that the catalytic approach is a viable alternative to the stoichiometric trialkylcuprate procedure and gives only slightly inferior stereochemical control. Thus, when 4-*tert*.-butylcyclohexanone was mixed with 0.25 equivalents of Me_2CuLi in ether at -78° and then 1.25 equivalents of methyllithium was slowly added, an epimeric mixture of methyl carbinols was obtained which contained 90-91% of the axial alcohol.

We have also examined the reaction of these reagents with α,β-enones. It was found that -60° solutions of both Me_2CuLi[13] and Me_3CuLi_2 deliver methyl exclusively via the 1,4 mode to 2-cyclohexenone and isophorone to give comparable yields (85-90%) of β-substituted cyclohexanones. Likewise, 2-octenal gives an 81% yield of

3-methyloctanal with Me_3CuLi_2. In view of these results, it seems likely that the success of the conjugate addition reaction of dialkylcuprates with α,β-enones may in part be due to the insensitivity of the reaction to inadvertent addition of excess alkyllithium. Competition experiments show that, like the related dialkylcuprates, Me_3CuLi_2 adds preferentially to α,β-enones in the presence of saturated ketones. Thus when 0.25 equivalents of Me_3CuLi_2 was added dropwise to a 1:1 mixture of 2-cyclohexenone and cyclohexanone at -78° and the reaction was quenched with cold methanol, 3-methylcyclohexanone and 1-methylcyclohexanol were isolated in the ratio of 15:1. The ratio of methylated to unmethylated material in the product indicates that each equivalent of Me_3CuLi_2 transfers two equivalents of methyl to the starting carbonyl compounds.

We are continuing our studies of these interesting new reagents.

ACKNOWLEDGEMENT: Acknowledgement is made to the donors of The Petroleum Research Fund, administered by the ACS, for partial support of this research. One of us (TLM) would like to thank Prof. Gilbert Stork for his support (NIH GM05147-18) of these studies.

NOTES AND REFERENCES:

[1] Paper I: T. L. Macdonald and W. C. Still, *J. Amer. Chem. Soc.*, 97, 5280 (1975).

[2] Current address for TLM: Department of Chemistry, Stanford University, Stanford Calif. 94305.

[3] Several other reports of organocuprate/ketone additions have appeared: J. P. Marino and D. M. Floyd, *Tetrahedron Lett.*, 3897 (1975); G. Palmisano and R. Pellegata, *J. Chem. Soc., Chem. Commun.*, 892 (1975).

[4] With 4-*tert.*-butylcyclohexanone, Me_3CuLi_2 gives better stereochemical control than any other organometallic methylating agent yet reported. For an excellent review of the stereochemistry of other organometallic additions to cyclic ketones, see: E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, 75, 521 (1975).

[5] Irreversible addition of lithium dialkylcuprates to saturated ketones is normally a slow process at low temperature: (a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 31, 3128 (1966); G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Amer. Chem. Soc.*, 94, 5106 (1972); (c) L. T. Scott and W. D. Cotton, *J. Chem. Soc., Chem. Comm.*, 320 (1973); (d) H. O. House, C. -Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, 40, 1460 (1975). See also: D. J. Goldsmith and I. Sakano, *Tetrahedron Lett.*, 2857 (1974).

[6] We have been unable to effect a similar transformation with methyl magnesium bromide or iodide. This failure to show enhanced stereoselectivity could, however, be simply due to the low solubility of the magnesium reagents in the solvents employed (Et_2O, THF and THF-HMPA) (*cf.* W. H. Mandeville and G. M. Whitesides, *J. Org. Chem.*, 39, 400 (1974) and references therein; H. Normant, *J. Organomet. Chem.*, 100, 189 (1975)).

[7] Unlike Me_3CuLi_2, the Bu_3CuLi_2 reagents described here were homogeneous at -78° and were utilized at the temperature.

[8] Proportions of the epimeric alcohols were determined by VPC. In each case, the axial alcohols corresponded to the more mobile spot on silica gel TLC.

[9] Factors influencing extent of conversion for the reaction of ketones and alkyllithium have been studied: J. D. Buhler, *J. Org. Chem.*, 38, 904 (1973).

[10] Both CuI and $CuBr{\cdot}Me_2S$ (Ref. 5d) were used.

[11] This strategy has been used to advantage with dialkylcuprates; *cf. inter alia:* E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, 94, 7210 (1972); G. H. Posner, C. E. Whitten and J. J. Sterling, *ibid.*, 95, 7788 (1973); H. O. House and M. J. Ummen, *J. Org. Chem.*, 38, 3893 (1973); G. H. Posner, D. J. Brunelle, and L. Sinoway, *Synthesis*, 662 (1974).

[12] This approach is closely related to the copper-catalyzed addition of Grignard reagents to enones. Review: G. H. Posner, Org. React., 19, 1 (1972).

[13] House (reference 5d) has reported that, at -78°, Me_2CuLi adds only very slowly to α,β-unsaturated ketones. Our reactions were quenched with aqueous NH_4Cl after 1 hr. at -60°.