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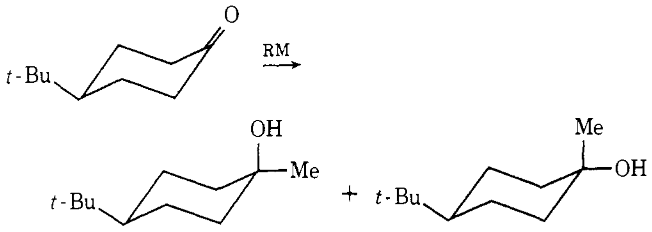
Organocuprates. A Stereoselective Synthesis of Axial Alcohols

Sir:

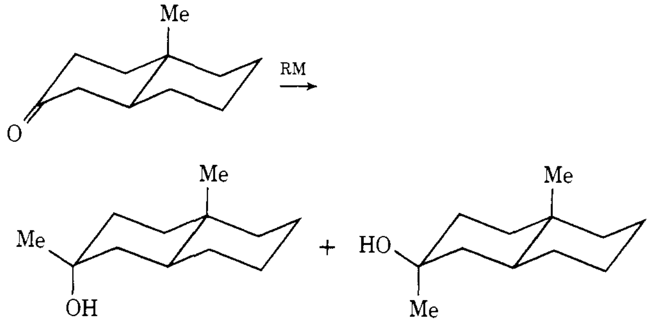
The addition of nucleophiles to ketones is an important method for the introduction of stereochemistry into organic molecules. In contrast to the numerous highly stereoselective reducing agents which have been developed,[1] the availability of reagents for the addition of unhindered alkyl nucleophiles to ketones with high stereoselectivity is limited.[2] We wish to report here that the reagent prepared by mixing lithium dimethylcuprate[3] with methyllithium reacts with cyclohexanones to produce axial alcohols with high stereoselectivity and in high yield.

The addition of a primary organolithium or Grignard reagent to an unhindered cyclohexanone generally results in a mixture of epimeric products. For example, 4-*tert*-butylcyclohexanone reacts with methyl magnesium iodide, methyllithium, or dimethylmagnesium to give only 51-70% axial alcohol.[4] In an effort to improve the stereoselectivity of this reaction, a new approach to the problem was considered. We reasoned that if an organocuprate could be induced to react with a saturated ketone,[5] those factors which give high stereoselectivity to the reaction of cuprates with enones[6] might allow a stereospecific synthesis of substituted alcohols. While a variety of methods for effecting this transformation may be envisioned, we have examined an organocuprate-mediated addition of methyllithium to a number of cyclohexanones at low temperature.[7] When 4-*tert*-butylcyclohexanone was treated with a 3:2 mixture[8] of lithium dimethylcuprate and methyllithium, a crystalline product was isolated in 91% sublimed yield. This material contained no starting ketone and consisted of a mixture of epimeric methyl carbinols, 94% of which was the expected *trans*-4-*tert*-butyl-1-methylcyclohexanol.[9] This result compares with other organometallic methylations as shown below.



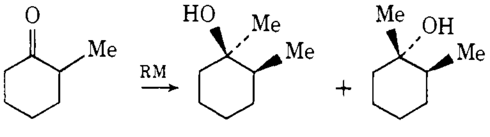
RM = MeMgI (5°)[4a]	51%	49%
= Me_2Mg[4b]	70%	30%
= MeLi (5°)[4]	65%	35%
= MeLi (−78°)	79%	21%
= MeLi-Me_2CuLi (−70°)	94%	6%

We have also observed a similar improvement in stereochemical control for the methylation of 4a-methyl-*trans*-2-decalone[10]



RM = MeLi (−78°)	76%	24%
= MeLi-Me_2CuLi (−70°)	90%	10%

and 2-methylcylohexanone



RM = MeMgI (0°)[11]	84%	16%
= MeLi (−78°)	92%	8%
= MeLi-Me_2CuLi (−70°)	97%	3%

Interestingly, MeLi-Me_2CuLi provides no stereochemical improvement over methyllithium in its reaction with 2-methylcyclopentanone. Both reagents give approximately 70% attack trans to the methyl substituent at −70°.

In each case, the epimeric methyl carbinols were the only products detected at greater than 95% conversion of starting ketone. Thus, MeLi-Me_2CuLi offers a distinct stereochemical advantage over conventional methylating reagents and appears to be the reagent of choice for the high yield equatorial methylation of unhindered cyclohexanones. Alternatively it should be noted that improved stereoselectivity in ethereal methyllithium additions may be obtained by conducting the reaction with ketones at low temperature.[12]

The detailed structure of this new reagent remains obscure. However, neither dimethylcuprate nor methyllithium alone can account for our results since 4-*tert*-butylcyclohexanone is recovered unchanged from treatment with the former reagent at low temperature and gives different stereochemical results with the latter compound. We feel that the most reasonable explanation is that lithium dimethylcuprate and methyllithium react to form low concentrations of a bulky, highly reactive cuprate having the stoichiometry Me_3CuLi_2 or Me_4CuLi_3.[13] The formation of such higher ate complexes has been supported by NMR studies[5a] and by isolation of the corresponding acetylide complexes, $(RC{\equiv}C)_3CuK_2$.[14] In addition, a reagent having the stoichiometry Ph_3CuLi_2 appears to be more reactive than Ph_2CuLi in metal-halogen exchange reactions and coupling with aryl bromides.[15] The reaction of a ketone with a dianionic trialkylcuprate (or a related higher ate complex) should be facilitated since the increased charge on copper should enhance either an oxidative addition-reductive elimination sequence[16] or an electron transfer process.[17] Whatever the mechanism, it must be fast relative to carbonyl attack by methyllithium since the same high stereoselectivity is obtained by the slow addition of methyllithium to a mixture of the ketone and lithium dimethylcuprate at −70°.

The experimental procedure is straightforward and is detailed here for 4-*tert*-butylcyclohexanone. Cuprous iodide (5.70 g, 30 mmol) was suspended in 100 ml of anhydrous ether at 0° under nitrogen. Ethereal (80 mmol) methyllithium (approximately 2 *M*) was added and the light tan solution was stirred for 10 min before cooling to −70°.[18] 4-*tert*-Butylcyclohexanone (1.54 g, 10 mmol) in 25 ml of anhydrous ether was then added over a 5-min period with stirring. The solution was maintained at −70° for 30 min and was poured into saturated ammonium chloride solution. The aqueous layer was separated and extracted with fresh ether. The organic phases were combined, dried over magnesium sulfate, and stripped at reduced pressure to a crystalline solid, 1.80 g. This material was purified by sublimation (60°, 1 mm) to yield 1.55 g (91%) of 4-*tert*-butyl-1-methylcyclohexanol, mp 62-65° (lit.[19] 70.5-71° for the pure axial alcohol).

In conclusion, MeLi-Me_2CuLi is a highly effective reagent for the equatorial methylation of unhindered, conformationally biased cyclohexanones. Further work will include studies of this reagent with other substrates and the stereochemical behavior of a variety of mixed cuprates and other transition metal ate complexes.

Acknowledgment. We wish to thank Professors David J. Goldsmith, Gilbert Stork, and Herbert O. House for a number of fruitful discussions and comments. We also wish to acknowledge NIH GMO5147-18 for support.

References and Notes

(1) Examples include the reagents of: H. B. Henbest and T. R. B. Mitchell, *J. Chem. Soc. C*, 785 (1970); H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972); and J. Hooz et al., *ibid.*, **96**, 274 (1974).

(2) To the best of our knowledge, the most stereoselective addition of an organometallic methylating agent to 4-*tert*-butylcyclohexanone utilizes trimethylaluminum and gives 90% axial attack: (a) E. C. Ashby, S. H. Yu, and P. V. Roling, *J. Org. Chem.*, **37**, 1918 (1972); (b) T. Suzuki, T. Kobayashi, Y. Takegami, and Y. Kawasaki, *Bull. Chem. Soc. Jpn*, **47**, 1971 (1974). The previous record for equatorial methylation is 86% with *n*-propyloxydimethylaluminum at 10% conversion and was recently reported by E. C. Ashby and J. T. Laemmle, *J. Org. Chem.*, **40**, 1469 (1975). An alternate approach to this type of conversion involves stereospecific epoxidation followed by reduction: E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965); C. R. Johnson, C. W. Schroeck, and J. R. Shanklin, *ibid.*, **95**, 7424 (1973).

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(5) The addition of dialkylcuprates to saturated ketones appears to be a very slow process based on starting material recovery ((a) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); (b) G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Am. Chem. Soc.*, **94**, 5106 (1972); (c) L. T. Scott and W. D. Cotton, *J. Chem. Soc., Chem. Commun.*, 320 (1973); and (d) H. O. House, C.-Y. Chu, J. M. Wilkins, and M. J. Umen, *J. Org. Chem.*, **40**, 1460 (1975)), although a fast, reversible oxidative addition to yield an alkoxy copper(III) species cannot be ruled out. In contrast, D. J. Goldsmith and I. Sakano (*Tetrahedron Lett.*, 2857 (1974)) have reported one example of lithium dimethylcuprate addition to a saturated ketone at low temperature.

(6) The reaction of lithium dimethylcuprate with a conformationally fixed acylalkylidine cyclohexane proceeds by greater than 95% equatorial attack: ref 5a; S. Wolff and W. C. Agosta, *J. Org. Chem.*, **38**, 1694 (1973); H. O. House, J. Lubinkowski, and J. J. Good, *ibid.*, **40**, 86 (1975).

(7) The reaction of a saturated ketone with MeLi-Me_2CuLi has been previously reported by House et al. (ref 5a).

(8) The effect of exact stoichiometry has not been thoroughly investigated, but a full equivalent of Me_2CuLi and MeLi seems to be required.

(9) Proportions of the epimeric methyl carbinols were determined by VPC (6-ft Carbowax 20M column) and were confirmed by integration of the appropriate methyl signals in the NMR. In the case of the products from 4-*tert*-butylcyclohexanone, $Eu(fod)_3$ in carbon tetrachloride was used to resolve the epimers.

(10) For comparison, cholestanone gives 57% equatorial attack with methyl magnesium iodide at 0°: D. H. R. Barton, A. S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

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(12) A similar temperature dependence with a methylaluminate complex was recently reported by Ashby et al. (ref 4b).

(13) The latter reagent could arise via equilibration among the dimeric species Me_4Cu_3Li, $Me_4Cu_2Li_2$, and Me_4CuLi_3 and was suggested by Professor H. O. House.

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(15) H. O. House, D. G. Koepsell, and W. J. Campbell, *J. Org. Chem.*, **37**, 1003 (1972).

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(17) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972).

(18) Further cooling frequently causes precipitation of the reagent. This occurence must be avoided since addition of the ketone to this suspension results in recovered starting material.

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Benzamide Oxygen Exchange Concurrent with Acid Hydrolysis

Sir:

Although it is generally accepted that bimolecular acid-catalyzed amide hydrolysis proceeds via a tetrahedral addition intermediate probably formed from the O-protonated amide,[1] a number of workers recently have found it difficult to rule out the alternate route in which water directly displaces an amine molecule from the N-protonated amide.[2] At the basis of this controversy is the fact that, to date, the occurrence of carbonyl oxygen exchange concurrent with the hydrolysis has not been demonstrated.[2a,b,3] Such exchange is observed during base hydrolysis,[3,4] as well as with carboxylate esters in both acid and base solutions,[1a,5] and is usually taken to imply the presence of tetrahedral intermediates.[1a] We report here that accompanying the acid-catalyzed hydrolysis of benzamide there is a small, but detectable, amount of exchange.

This study was carried out using a sample of the amide enriched with ca. 90% ^{18}O.[6] This was hydrolyzed in 5.9% H_2SO_4 at 85°, and the unreacted amide was recovered[7] at various times and subjected to direct mass spectrometric analysis (Table I). A small, but definite, increase with time is seen in the ratio of the intensities of the peaks at *m/e* 121 and 123 (molecular ions), indicative of exchange of the benzamide oxygen with solvent oxygen. Conversion[8] of these ratios to per cent ^{18}O shows that there is a decrease of about 0.2% ^{18}O for each half-life of hydrolysis. From the data can be calculated a rate of exchange of 1.28×10^{-5} min^{-1}, $\frac{1}{320}$ the rate of hydrolysis. In control experiments (i) the analysis procedure was shown to be capable of reproducing the small differences in ^{18}O content very accurately (Table II), and (ii) it was demonstrated that the observed decrease in ^{18}O content on hydrolysis cannot have arisen either through the work-up procedure or because of reversibility of the hydrolysis reaction.[9]

The very small amount of exchange found here shows why this was not detected in previous investigations, where a much smaller ^{18}O enrichment was used. For example, in that study with the greatest enrichment (3%),[2a] our result shows that there was a decrease in ^{18}O content of only 0.02% (over three half-lives of hydrolysis), not outside the limit of experimental error. Interestingly Bender and Ginger,[3c] on the basis of the error in their data, placed a lower limit on k_H/k_E of 374 (for benzamide under slightly different acidic conditions).

The observation here of the exchange process establishes that a tetrahedral intermediate is formed during the acid-catalyzed hydrolysis of benzamide. Although this species is not necessarily on the hydrolysis pathway, it is difficult to imagine that this is not the case. In particular the small amount of return to amide relative to break-up to products (a factor of 160 assuming rapid proton transfer) is precisely what is expected for such a tetrahedral intermediate formed under acid conditions.[1] In such solutions it will exist pre-