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ASYMMETRIC INDUCTION IN ADDITIONS OF ORGANOCUPRATES[1]

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The increasing importance of organocuprates in synthetic work[3] led us to investigate the possibility of induction of asymmetry with these versatile reagents.

Treatment of benzaldehyde (1) under the conditions mentioned previously[1] with a chiral ligand[4], *i.e.* a complex prepared with one mole each of the alcoholate of (-)-N-methylephedrine (2) with methyllithium and cuprous iodide, gave α-methylbenzyl alcohol (3a) exhibiting a specific rotation $[\alpha]_D$ +6,6°[5], *i.e.* the optical yield of this 1,2-addition reaction is 16,5%. When lithium di-n-butylcopper was used compound (3b) was obtained with a much lower optical yield (1,5%). Similarly, reaction of lithium dimethylcopper with heptylaldehyde (4) afforded 2-octanol (5) showing $[\alpha]_D$ +0,27° (*i.e.* 3% optical yield).

The chiral diamine (-)-sparteine (6) is known to cause asymmetric addition of organometallic reagents to carbonyl groups[6]. Apparently the sparteine acts as a bidentate ligand which creates a chiral environment around the metal atom ; this chirality is reflected in the stereochemistry of the addition reaction. In order to determine whether a similar effect might be operative in the cuprate conjugate 1,4-addition to α,β-unsaturated carbonyls, a methylating reagent was prepared by addition of one equivalent of sparteine (6) to one equivalent of lithium dimethylcopper. This complex was allowed to react with 2-cyclohexenone (7) in ether solution at -10°. The resulting 3-methylcyclohexanone (8a) was devoid of measurable optical activity. The corresponding n-butyl reagent, prepared in a similar manner from n-butyllithium at -40°, gave 3-n-butylcyclohexanone (8b) showing a rotation $[\alpha]_D$ +0,12°.

Since no precise information is available on the sparteine-cuprate complex, one could not rule out the possibility that the binding between these two species be weak. It was anticipated that a system in which the chiral ligand is joined to the copper atom by a metal-heteroatom bond might result in conjugate additions with higher degrees of asymmetry. Posner[7] has reported that cuprate

C_6H_5-CHO

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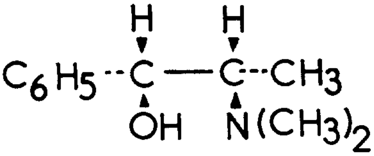
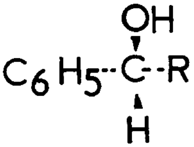


$C_6H_5-\overset{H}{\underset{OH}{C}}-\overset{H}{\underset{N(CH_3)_2}{C}}-CH_3$

2



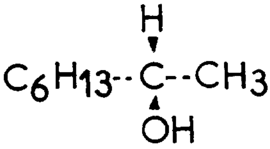
$C_6H_5-\overset{OH}{\underset{H}{C}}-R$

3 a $R=CH_3$

b R= n-Bu

$C_6H_{13}-CHO$

4



$C_6H_{13}-\overset{H}{\underset{OH}{C}}-CH_3$

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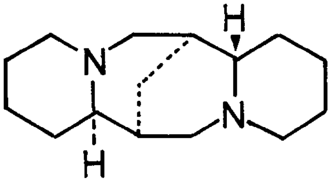

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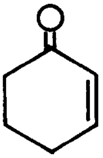

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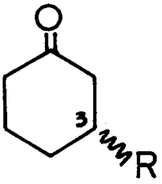
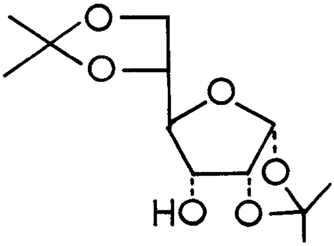


8 a $R=CH_3$

b R=n-Bu

c R=t-Bu

d $R=C_6H_5$



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reagents of the class Het(R)CuLi give selective conjugate addition of alkyl groups. It thus seemed reasonable that the use of chiral hetero species in formation of the cuprate might result in stereoselective conjugate addition. Cervinka[8] found that complexes formed between lithium aluminium hydride and a number of optically active carbinol amines give reduction of carbonyl groups with a high degree of stereoselectivity[4]. Presumably the rigid structure of the complex reducing agent, due to the bidentate ligand, greatly favours one of the two diastereomeric transition states. Such reasoning induced us to apply this approach to organocuprate reagents.

An ether solution of the alcoholate of (-)-N-methylephedrine (2) was added to a stirred suspension of cuprous iodide at 0° followed by an equivalent of methyllithium. A solution of 0,72 mole of 2-cyclohexenone (7) was then added and the reaction was allowed to proceed for two hours at 0°. The reaction was quenched with ammonium chloride and the N-methylephedrine (2) was removed by extraction with aqueous acid. The reaction product, 3-methylcyclohexanone (8a) was purified by column chromatography and found to have $[\alpha]_D$ -0,29°. The absolute rotation of this compound is known to be $[\alpha]_D$ 14,4°[9], thus the optical purity is only of the order of 2%.

Substitution of n-butyllithium for methyllithium gave good yields of 3-n-butylcyclohexanone (8b). The optical activity of this product seemed to depend upon the reaction temperature[4], since 3-n-butylcyclohexanone (8b) prepared at 0° exhibited $[\alpha]_D$ -0,56° ; at *ca.* -20°, $[\alpha]_D$ -0,45°, and at *ca.* -30° the optical rotation was $[\alpha]_D$ -0,38°. Use of t-butyllithium gave 3-t-butylcyclohexanone (8c) $[\alpha]_D$ -0,12°[9]. Use of phenyllithium gave 3-phenylcyclohexanone (8d) : $[\alpha]_D$ -0,54. No promising results were obtained with quinine or quinidine as chiral ligands[8].

The use of monosaccharide derivatives to induce stereoselectivity in lithium aluminium hydride reductions of ketones[4], in Grignard reactions[10] and Birch reduction[11] prompted the used of 1,2:5,6-di-O-isopropylidine-α-D-glycofuranose (IGF) (9)[12] as a chiral ligand in the cuprate reaction. When one equivalent of the alcoholate of IGF (9) was added to a stirred suspension of cuprous iodide in ether at 0°, followed by an equivalent of the appropriate organolithium reagent and 2-cyclohexenone (7) (0.72 mole), the saturated ketones, purified by column or preparative gas chromatography, had the following rotations : 3-methyl (8a) : $[\alpha]_D$ -0,93° ; 3-n-butyl (8b) : $[\alpha]_D$ -0,8° ; 3-phenyl (8d) : $[\alpha]_D$ +0,42°. Thus it appears that IGF (9) gives higher degrees of stereoselectivity in cuprate conjugate additions than does (-)-N-methylephedrine (2).

Further investigation on the influence of the nature of the chiral ligand in asymmetric cuprate reactions is currently underway.

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References

1. Contribution N°4 from the Laboratoire de Chimie Organique, C.E.R.M.O. For N°3, see : E. Barreiro, J.L. Luche, J. Zweig, and P. Crabbé, *Tetrahedron Letters*, previous paper.
2. a. Post-doctoral research fellow 1974-1975 ;
   b. Pre-doctoral research fellow.
3. G.H. Posner, *Organic Reactions*, *19*, 1 (1972) ; and ref. 1.
4. J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions", Prentice Hall, London (1971).
5. All compounds have been fully identified and compared with authentic samples. The rotations were taken at room temperature in chloroform solution for concentrations C=1.

H. Nozaki, T. Aratani, T. Toraya and R. Noyori, *Tetrahedron*, *27*, 905 (1971); R.A. Kretchmer, *J. Org. Chem.*, *37*, 2744 (1972) ; M. Guetté, J. Capillon and J.P. Guetté, *Tetrahedron*, *29*, 3659 (1973).

7. G.H. Posner, C.E. Whitten and J.J. Sterling, *J. Amer. Chem. Soc.*, *95*, 7788 (1973).
8. O. Cervinka, *Chimia*, *13*, 332 (1959) ; *id.*, *Coll. Czech. Chem. Comm.*, *30*, 1684 (1965) ; O. Cervinka and O. Belovsky, *ibid.*, *32*, 3897 (1967).
9. The absolute rotations and configurations of 3-methyl and 3-t-butylcyclohexanone have been reported : *8a*(R), $[\alpha]_D$ +14,4° ($CHCl_3$), see : Kretchmer, *loc. cit.* ; *8c*(R), $[\alpha]_D$ +27,5° ($CHCl_3$) ; see : G. Adolphen, E.J. Eisenbraun, G.W. Keen, P.W.K. Flanegan, *Org. Prep. Proc.*, 93 (1970).
10. T.D. Inch, G.J. Lewis, G.L. Sainsbury and D.J. Sellers, *Tetrahedron Letters*, 3657 (1969).
11. T. Kinoshita and T. Miwa, *Chem. Comm.*, 181 (1975).
12. O.T. Schmidt in "Methods in Carbohydr. Chem.", R.L. Whistler and H.L. Wolfrom (Ed.), Vol.II, 320, Academic Press, New York (1963).