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SUBSTRATE-REAGENT COMPLEXATION ABILITY IN ENANTIOSELECTIVE 1,4 ADDITION REACTIONS

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Abstract. *Hydrogen-carbonyl chelation and magnesium-arene π coordination are proposed to account for enhanced enantioselectivity in 1,4-addition reactions of chiral cuprates.*

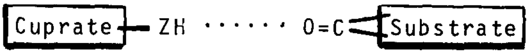
The formation of optically active compounds by asymetric induction in C-C bond formation has received much attention in the recent years (1). A common feature of many reactions reported to proceed *diastereoselectively* with good chemical and opticals yields is, inter alia, an efficient substrate-reagent complexation, as a result of properly chosen functionalities in the substrate which can interact attractively with the reagent (2).

The classical copper promoted (catalytic or stoichiometric) 1,4-addition of organometallics on α,β-unsaturated carbonyl compounds would show great promise in the *enantioselective* C-C bond formation – using chiral organocuprate species – if both high chemical and optical yields could be realised. In all attempts so far reported (3) only the work of Mukaiyama has best fulfilled this double requirement (4).

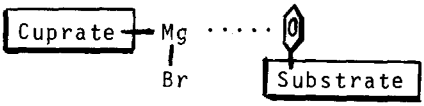
The two main handicaps of the organocuprates' 1,4 addition reaction: (i) scarcity of information regarding the structure and composition of these reagents in solution (5), (ii) uncertainty about the intimate mechanism of the reaction (6), preclude at the time any tentative representation of a transition state or primary formed intermediate of the reaction, and therefore overshadow *why* the recorded optical yields are fluctuating and *how* they can be improved.

The aim of this communication is to present some evidence that substrate-reagent complexation, and its inherently expected enantioselectivity enhancement, may be brought up in two ways :

α) by hydrogen-carbonyl chelation (7)



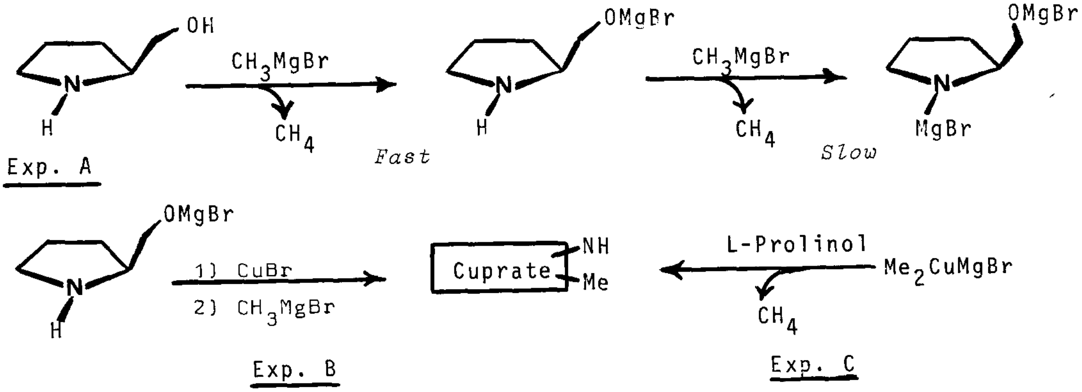
β) by magnesium-arene π coordination (8)



Chiral ligands and resulting cuprate species.

The chiral ligands used were L-prolinol and L-N-methylprolinol, keeping so an identical basic carbon framework. Both ligands should therefore lead to cuprate species of almost identical structures, except that with the former one ends up with a reagent still bearing a free $\geq$N-H group, as shown by the following experiments.

The metallation of L-prolinol by one equivalent of methylmagnesiumbromide produced immediatly a vigorous evolution of methane in almost quantitative yield, whereas the addition of a further equivalent needed at least 4 h at -20°C to liberate the second amount of gaz (Exp. A). The clear solution of monometallated prolinol in THF was added to a suspension of one equivalent of cuprous bromide, and to the resulting organocopper compound was added a second equivalent of Grignard reagent. No significant evolution of methane was observed (Exp. B). Using Mukaiyama's procedure (4), one equivalent of L-prolinol was added to one equivalent of dimethylmagnesiocuprate. Gaz evolution occured at a high rate first, and stopped when roughly one equivalent of methane was liberated (Exp. C).



Substrates.

2-cyclohexen-1-one, 4-phenyl-3-buten-2-one and 1,3-diphenyl-2-propen-1-one were selected in order to test substrates bearing an increasing number of phenyl groups. Furthermore, the corresponding β-methylated saturated ketones are known in optical pure form.

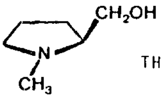
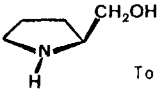
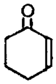
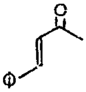
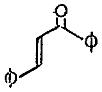
Reaction conditions and results.

For experimental conveniences, the cuprate reagents were generated according to Exp. C, i.e. by addition of the chiral ligand to a suspension of dimethylmagnesiocuprate. The reactions were run at -20°C (THF, toluene) and 0°C (benzene) with a molar ratio CuBr : RMgBr : Ligand : Enone equal to 4:8:4:1 respectively.

From the results recorded in the Table, the following observations can be made

- in all cases the optical yields are increased by at least a factor of ten when in those reactions conducted in toluene (benzene), N-methylprolinol is replaced by prolinol itself (column I vs column IV). This may reflect the substrate-reagent interaction through hydrogen-carbonyl chelation.
- the enantioselectivity is also increased when toluene (or benzene) is replaced by THF in the reactions performed with N-methylprolinol (column I vs column II). This phenomenon, particularly high in the case of 1,3-diphenyl-2-propen-1-one (II_c/I_c), may be ascribed to substrate-reagent complexation through magnesium-arene π coordination.

TABLE

	Toluene			THF			THF			Toluene		
	α_D	e.e. (Yields)	Abs. Conf.	α_D	e.e. (Yields)	Abs. Conf.	α_D	e.e. (Yields)	Abs. Conf.	α_D	e.e. (Yields)	Abs. Conf.
 a	0,12	1 (64)	R	0,72	5 (70)	R	-0,88	6 (85)	S	-3,66	26 (61)	S
 b	-2	3 (36)	R	7,1	10 (92)	S	21,8	29 (61)	S	27;7	37 (36)	S
 c	0,2	2 (32)	S	6,1	41 (81)	S	2,2	15 (70)	S	2,9	20 (42)	S
		I			II			III			IV	

- All reactions were duplicated ; Toluene was replaced by benzene in Expts I_a and IV_a.
- Optical rotations were taken in solvent and concentration conditions identical to those of the reported pure enantiomers : R(+)-3-methyl-cyclohexanone α_D= +14°4 ($CHCl_3$) (9) ; R(-)-4-phenyl pentane-2-one α_D= -74°5 (C_6H_6 c=1) (10) ; R(-)-1,3-diphenyl butane-1-one α_D= -14°6 (CCl_4 c=10) (11).

- comparison of column IV vs column III may give an idea of the relative importance of the two modes of substrate-reagent interactions. By lowering the arene π coordination and increasing the hydrogen-carbonyl chelation, the optical yields are still increased. One might therefore conceive that the latter process has a greater influence than the former. This statement finds nevertheless poor support with enone c (III_c/II_c).
- in all cases, a continuous drift to higher optical yields is observed from the left to the right of the Table, except for enone c, on which the highest induction is surprisingly realised with N-methylprolinol instead of prolinol This points to the fact that both processes of complexation outlined here do not bear the whole truth.

Further studies concerning the relationship between structure of the ligand and enantioselectivity are on line in our laboratory.

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