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LIGAND EFFECTS IN ENANTIOFACE DIFFERENTIATING 1,4 ADDITION TO 1,3 DIPHENYL-2 PROPEN-1 ONE

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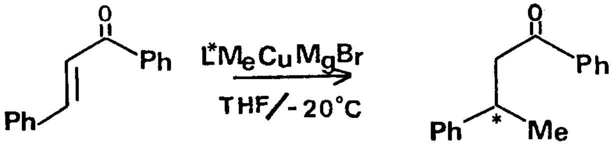
Abstract: *The extent of enantiomeric excess in the β-methylation of chalcone by chiral cuprates is shown to depend strongly on small structural modifications of the ligands, all of which are derived from the basic carbon framework of L-prolinol. Enantiomeric excesses up to 88% have been realised.*

Because of the numerous applications of organo-cuprates in organic synthesis, they have been the focus of a number of studies aimed at the asymmetric synthesis[1]. Very high diastereomeric excesses have been realised either by copper catalysed addition of Grignard reagents on enantiomerically pure enones sulfoxydes[2] or by conjugative transfer of chiral ligands from chiral cuprates to prochiral enones[3]. But the enantioselective β-addition of an achiral R_t group from chiral mixed cuprates $R^*_rR_tCuZ$ still remains a difficult task. The highest optical and chemical yields have so far been recorded on acyclic enones with N-methylprolinol and prolinol as chiral auxiliaries[4]. In the course of our studies concerned with the reaction outlined in Eq. 1, we first observed a strong increase of the ee's upon dilution as depicted in Fig.I. This effect, reminiscent of that reported for the alkaloïd catalysed



Eq 1

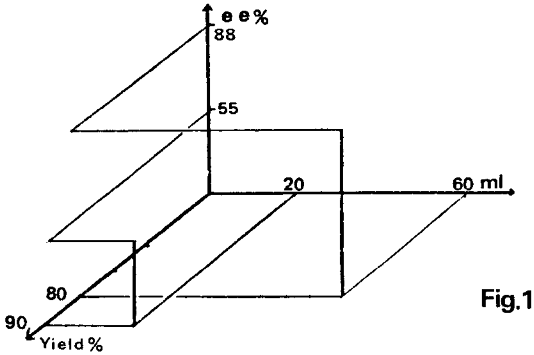


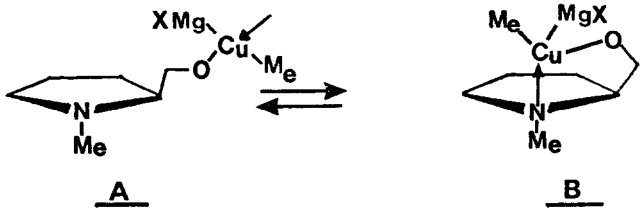
Fig.1

Reagents/Substrate Ratios (10^{-3} mole)

Enone	/ CuBr	/ MeMgBr/	L*
1 :	4 :	8.8 :	5.6

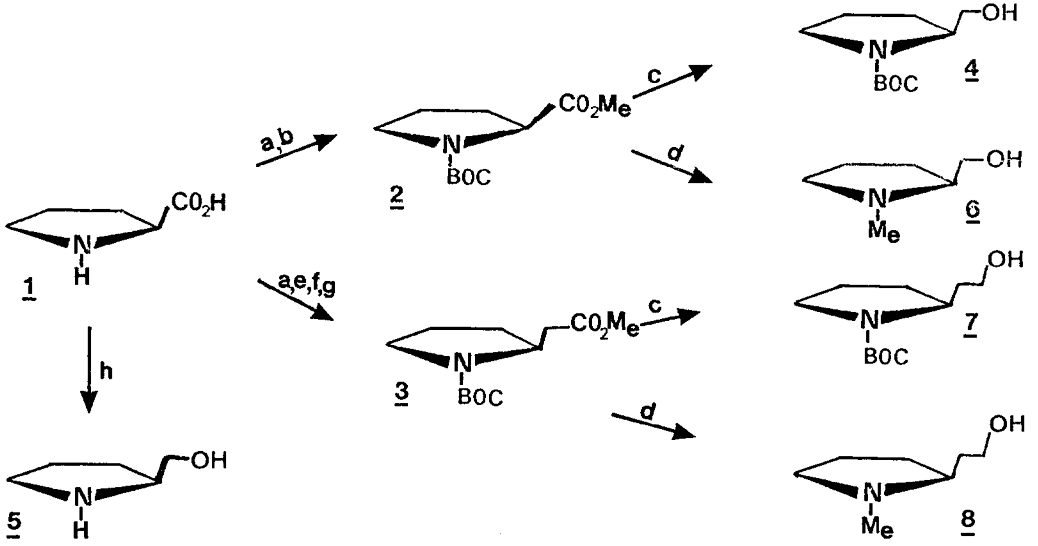
(L* = N-methylprolinol)

Michael addition of aromatic thiols to 2-cyclohexen-1-one[5], could be tentatively ascribed to the existence of two reacting species in equilibrium, which are respectively the acyclic form A and the bicyclic "structure"[6] B obtained via intramolecular nitrogen chelation.



The chelated form B was assumed to possess higher enantiodifferentiating ability than the form A as a result of (i) its bicyclic C_5/C_5 structure[7] (ii) the metal center directly connected to the so generated chiral nitrogen atom[8].

In order to assess this hypothesis the ligands 4 to 8 have been synthesised[13].



a) Di-^{t}Butyl dicarbonate/H_2O, 94% b) CH_2N_2/Et_2O, 95% c) 0.55 eq. $LiAlH_4/Et_2O$, 95% d) 3 eq. $LiAlH_4/Et_2O$, 90% e) $(COCl)_2/DMF-CH_2Cl_2$ f) CH_2N_2/Et_2O g) $MeOH/PhCO_2Ag$,60% h) Réf. 11.

The methylprolinate 2, readily obtained from L-proline by standard methods[9], was reduced either partially to N-^{t}Butoxycarbonylprolinol 4 or completely to N-methylprolinol 6. This applied equally well to the reduction of ester 3, derived from L-proline by Wolff rearrangement according to the procedure earlier reported to proceed without racemization[10].

The chiral methyl cuprates prepared from these aminoalcohols according to Eq. 2

$$\mathrm{Me_2CuMgBr} \xrightarrow{\mathrm{L^*/THF/-25^\circ}} \overset{\nearrow}{\mathrm{CH_4}} + \mathrm{MeL^*CuMgBr} \qquad \text{Eq 2}$$

were reacted with chalcone and led to the results given in Table I.

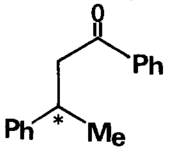


Table I

Ligands	Isolated Yields %	e.e.%	Configuration
4	55	6,5	S
5	70	15	S
6	80	88	S
7	86	2	R
8	94	0	-

- Enantiomeric excesses were determined by optical measurements : R-(6)-1,3-diphenylbutane-1-one α_D = -14°6 (CCl_4, C = 10)[12]

These results deserve the following comments :

- going from ligands 4 to 6 one observes an increase of the ee's from 6.5 to 88%. This trend, which is the reverse of that one might expect on the sole basis of steric bulk of the substituent at the nitrogen atom, parallels the increasing basicity and therefore chelating ability of this center. This is convergent with the conclusions drawn from the dilution experiments.
- ligands 7 and 8 are the higher homologues of ligands 4 and 5 by one methylene in the side chain. The corresponding B form of the former would involve a six-membered metallocycle, less favoured than the five-membered ones of the latter. Therefore we predicted a decrease of the asymmetric induction in the order 6 > 8 > 7. This is experimentally confirmed, but to a much higher extent than expected.

Finally, any structural modification which would favour the intramolecular chelation i.e. which would convert the prolinol ligand from an unidentate ligand into a bidentate ligand, should contribute to higher optical yields. Attempts along such lines will be the matter of the following communication.

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    4 $|\alpha|_D = -24.9°$ (C = 1, Bz); 5 $\alpha_D = +32°$ (C = 1, Bz)
    6 $|\alpha|_D = +2.4°$ (C = 2,Bz); 7 $\alpha_D = -57°6$ (C = 1, Bz)
    8 $|\alpha|_D = -117°$ (C = 1, Bz).

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