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USE OF (2S,4R)-HYDROXYPROLINE DERIVATIVES AS LIGANDS IN CHIRAL COPPER^{I} COMPLEXES

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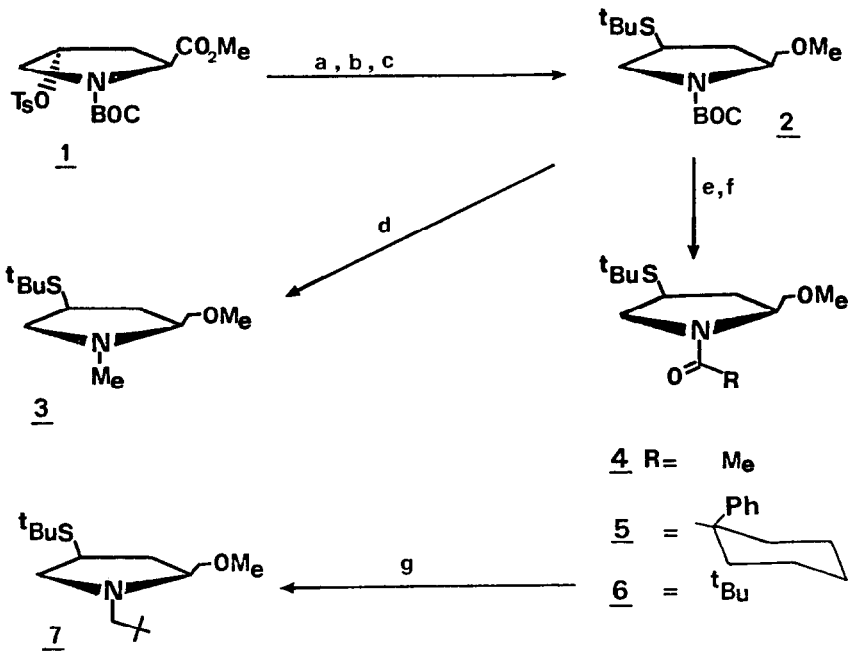
Abstract : (2S)-Methoxymethyl-(4S)-thiotertiobutoxy-N-pivaloyl pyrrolidine 6 used as ligand in chiral cuprates led up to 75% e.e. in the β-methylation of chalcone. The observed determinant role of the amide carbonyl group in the asymmetric recognition is explained in terms of lithium chelation.

In the preceeding communication[1] the effects of (i) the modulation of the basicity of the nitrogen atom and (ii) the lengthening of the side chain in L-prolinol derivatives, as ligands for chiral cuprates were highlighted in the enantioselective β-methylation of chalcone. The rationale put forward, was that the more the participating chiral auxiliary acts as a bidentate vs an unidentate ligand in the reacting copper complex, the higher is the asymmetric induction on a given substrate. Therefore, it was strongly appealing to examine similar ligands but with an additional chelating site.

The efficiency of tridentate ligands has been demonstrated in the case of the conjugate addition of butyllithium to nitroolefins[2a] and in the reduction of carbonyl compounds with a chiral aluminium hydride reagent[2b].

We wish now to report on the use of potentially tridentate ligands derived easily from (2S,4R)-hydroxyproline. The modification brought to the foregoing ligands relies on the introduction of a thiotertiobutyl group in C_4 position on the pyrrolidine ring. The sulfur heteroatom has been chosen owing to its well-known affinity towards copper.



a) ^{t}BuSNa, N-Methyl-2 pyrrolidone, overnight 96%; b) ½ eq. $LiAlH_4$, Et_2O 95%; c) NaH, DME, MeI, 80%; d) 2,5 eq. $LiAlH_4$, Et_2O, 90%; e) CF_3CO_2H; 85%; f) R–C(=O)–Cl, Py 4 83%, 5 86%, 6 93%; g) 1,5 eq. $LiAlH_4$, Et_2O, 80%.

Compound 1 was prepared in 70% overall yield by standard methods[3] ($[\alpha]_D$ = -35°1, C = 1,9 EtOH). Displacement of the tosylate by sodium thio-tertio-butoxyde, followed by controlled reduction of the ester into alcohol and methylation of the latter led to the ligand 2 (73% yield, $[\alpha]_D$ = - 60°,C=2 EtOH). This key compound was either reduced to the N-methyl derivative 3 ($[\alpha]_D$ = -9,3°C = 1,9 EtOH) or was after deprotection of the aminogroup[4] acylated with the corresponding acyl chlorides to furnish the ligands 4 ($[\alpha]_D$ = -48° C = 2 EtOH), 5 ($[\alpha]_D$ = -93,7°C = 2 EtOH) and 6 ($[\alpha]_D$ = -26,6° C = 2 EtOH). The latter was cleanly reduced into the N-neopentyl ligand 7 ($[\alpha]_D$ = -80,8° C = 2,6 EtOH).

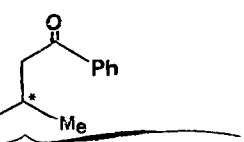
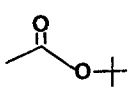
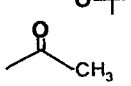
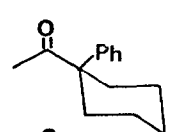
The chiral cuprates were prepared and reacted with chalcone as follows. To an etheral solution of dimethyllithiocuprate (5,5 10^{-3} mole CuBr suspended in 15 ml Et_2O anh., 11.10^{-3} mole MeLi of low lithium salts content, -20°) was added the chiral ligand L* (6.10^{-3} mole in 15 ml Et_2O).

After stirring the mixture for 30 minutes the temperature was lowered to -50° and the enone ($1{,}1\ 10^{-3}$ mole in 5 ml Et_2O anh.) was added slowly (≈ 10 minutes). The resulting deep red reaction mixture was stirred at this temperature until complete fading of the colour (≈ 5 to 6 hours). This meant always that the reaction had reached completion. After usual work-up the crude product was chromatographied over SiO_2. 1,3-diphenylbutan-1-one was eluted first (pentane/Et_2O 96:4), then the chiral ligand (pentane/Et_2O up to 70 : 30) in almost quantitative recovery (90-95%) without any detectable racemization.

The results of the asymmetric methylations are summarized in the Table. The following comments are of interest.

- in all experiments reported, the optical yields are insensitive to dilution. This is not surprising. The result of the presence of the thioalkyl group is that all the ligands behave probably as at least bidentate ligands towards the copper atom.
- in all cases, the R enantiomer is formed predominantly.
- the N-alkylated ligands 3 and 7 induced very low enantioselectivity, whereas the N-carboalkoxylated and N-acylated ligands 2, 4, 5 and 6 led to much higher optical yields. This stands in sharp contrast with the parent ligands derived from L-proline.

Table.

L*= R' in:			
7 = -CH$_2$-t-Bu	98%	2 %	R
3 -CH$_3$	97%	7 %	R
2 	95%	33%	R
4 	71%	33%	R
5 	93%	68%	R
6 	95%	75%	R
6 + TMEDA (1:1)	95%	50%	R

- the sole "introduction" of an amide carbonyl converting 7 into 6 enhanced the ee's from 2 to 75% !

Theoretical studies on the relative affinities of peptide and ester carbonyl groups for Li^+, Na^+ and K^+ ions have indicated that the intrinsic affinity of the amide carbonyl is appreciably much larger than that of the ester carbonyl[5]. Further, increased complex stability has been observed upon complete replacement of L-lactic acid residue by L-and D-proline in valinomycin[6].

In the light of these facts, our results are in agreement with the hypothesis of an increased affinity of the ligands for lithium going from the top to the bottom of the Table. As a consequence, if *coordination* of the *metal center* to the chiral ligand is a primary requirement, *simultaneous coordination* to *lithium* is at least equally important for high optical yields. The last experiment conducted in presence of TMEDA supports this statement, for which precedent is found in the literature[7]. The use of these new ligands in other strategies of asymmetric synthesis is under investigations.

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References and Notes

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