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ENANTIOSELECTIVE CARBOXYLATION OF A PROCHIRAL ENOLATE IN THE PRESENCE OF A CHIRAL LITHIUM AMIDE

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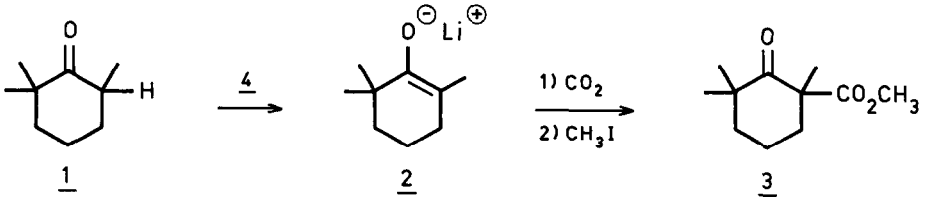
Abstract. The prochiral lithium 2,2,6-trimethylcyclohexenolate (2) was prepared from ketone 1 by deprotonation with lithium (S,S)-α,α'-dimethyldibenzylamide (4). Reaction of 2 with carbon dioxide at low temperature followed by methylation with methyl iodide yielded the corresponding ester 3 with an e.e. of 67%.

Lithium amides (e.g. LDA, LiTMP) have established an important position in organic synthesis and are widely used as strong bases with low nucleophilicity.[1-3] Their chiral analogues have come into focus more recently[4-8] as stereoselective bases and they have been applied successfully in a number of reactions.[9,10] Herewith we present preliminary results obtained in the enantioselective carboxylation[11] of a prochiral lithium enolate in the presence of a chiral lithium amide.

As model system 2,2,6-trimethylcyclohexanone (1) was deprotonated with lithium amide 4 as base; the deprotonation is known to be complete by stirring with 1 eq. of 4 for 15 minutes at 0°C. The formed lithium enolate 2 was carboxylated under various conditions (Table). To avoid concommitant decarboxylation of the product during work up, it was converted into the methylester 3 by methyliodide.[12]



1 2 3

Table: Carboxylation of enolate 2[a]

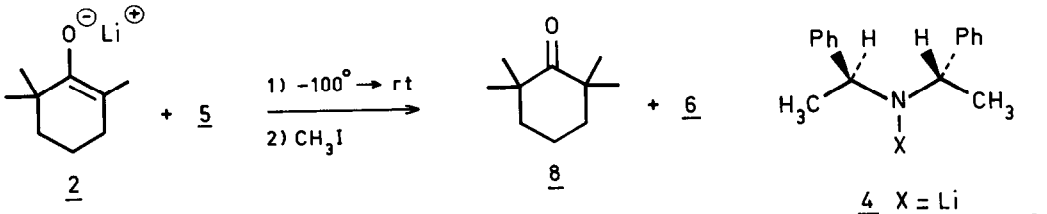
entry	solvent	eq. 4[b]	temperature of CO_2 addition	e.e. (%)[c,d,e]
1	THF	1.0	-80	0
2	THF	2.0	-80	0
3	THF	1.0	-196	0
4	THF	1.5	-196	6
5	THF	2.0	-196	13
6	THF	4.0	-196	20
7	hexane	1.0	-196	0
8	hexane	2.0	-196	3
9	hexane[f]	2.0	-196	39
10	ether	1.0	-196	7
11	ether	2.0	-196	67

a) Experiments performed at least in duplo; b) Based on the amount of ketone 1; c) Determined by chiral NMR-europium shift experiments using 0.7 eq. of $Eu(DCM)_3$; From these experiments an $[\alpha_o]^{rt}_{578} = -77.9$ (c = 1, $CHCl_3$) was calculated; d) The conversion of ketone 1 into ester 3 was higher than 95% (GLC); the yield of isolated 3 varied from 60-90%; e) Amine 7 was recovered from the reaction mixture in 90-95% yield without change in optical purity. When methyl carbamate 6 was formed in significant amounts, it was hydrolyzed and 7 recovered in 80% yield without change in optical purity; f) After deprotonation 2 eq. of ether were added.

The carboxylation of 2 in THF proceeded without asymmetric induction when carbon dioxide was bubbled through the solution at -80°C (entries 1 and 2). When carbon dioxide was condensed onto the frozen solution of 2 at -196°C followed by slowly warming to -80°C, asymmetric induction was observed in those experiments in which more than 1 eq. of 4 was used. Changing the solvent from THF to hexane (entries 7 and 8) lowered the enantiomeric excess of 3. However, addition of 2 eq. of diethylether (calculated on 2) to the hexane solution of 2 prior to carboxylation resulted in a remarkable increase in e.e. (entry 9). When ether was used as solvent the highest e.e (67%) was obtained (entry 11). This value is to the best of our knowledge the highest one reported for a non-enzymatic enantioselective carboxylation.

The mechanism of the enantioselective carboxylation remains obscure at this moment but may involve, in view of the fact that the e.e. is strongly influenced by changes in solvent, temperature, ratios of starting materials, etc., supermolecular lithium enolate complexes.[13,14] We have excluded by a control experiment a transfer mechanism in which the carboxylation of enolate 2 would have occurred via intermediately formed carbamate 5:[15] on

warming a solution of 2 and preformed 6 from -100°C to room temperature, followed by reaction with methyl iodide, compounds 6 and 8 were formed as the sole products (compound 6 is also formed on carboxylation of enolate 2 in the presence of excess 4).



4 X = Li
5 X = $CO_2^{\ominus}$ $Li^{\oplus}$
6 X = CO_2CH_3
7 X = H

The absolute configuration of ester 3 has been deduced from the CD-spectrum in EPA (-180°C to 20°C, see Figure). From the values (calculated for the optically pure compound) of the carbonyl n-π* Cottoneffect being $\Delta\varepsilon$ = -0.84 (20°C) and $\Delta\varepsilon$ = -1.95 (-180°C) and the estimated value of 0.3-0.5 for the ester group in equatorial position,[16] it is concluded that compound 3 does occur in a conformer with an axial ester group. Because there is also reason to believe that the contribution of the ester group has the usual octant sign,[16] it is indicated that ester 3 with a negative Cottoneffect has the R-configuration. Interestingly the enzymatic biotine-mediated carboxylation of propionyl-CoA to give (S)-methylmalonyl CoA with retention of configuration at carbon has recently[17] been found to occur in a stepwise process, involving an enolate anion.

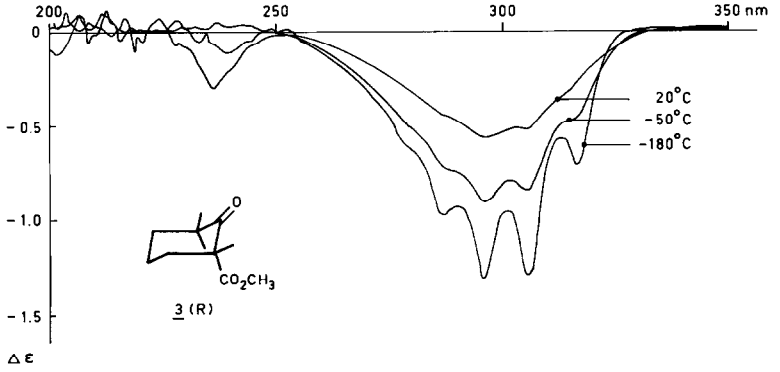
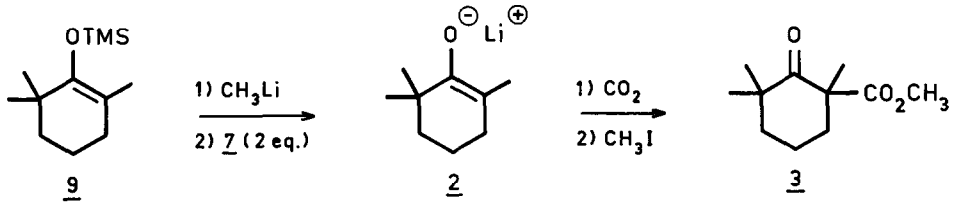


Fig. The CD-spectrum of ester 3 (e.e. 67%) at 20°C, -75°C and -180°C

Finally, it is of interest to note that ester 3 has also been obtained with an e.e. of 61% starting from the trimethylsilyl enol ether 9, 2 eq. of methyl lithium and 2 eq. of amine 7. This shows that in cases in which the sterically demanding lithium amide 4 is too



9 2 3

slow for deprotonation of the substrates to form the corresponding enolates,[18] it can still exert its function as a chiral ligand for inducing optical activity in carboxylation reactions.

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18. E.g., 2-methyl-1-tetralone and 2-methyl-1-indanone slowly deprotonate under the standard conditions and byproducts are formed.

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