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ENANTIOSELECTIVE DEPROTONATION OF TWO RACEMIC CYCLIC CARBONYL COMPOUNDS BY A CHIRAL LITHIUM AMIDE

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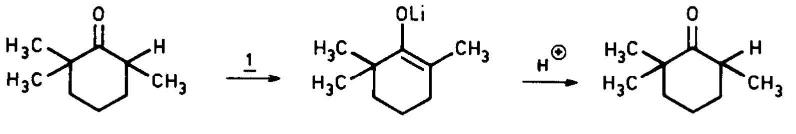
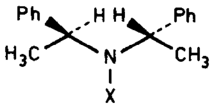
Abstract: The cyclic carbonyl compounds 2 and 8 have been obtained in optical active form (o.y. 46% and 36%, respectively) from the racemic compounds by a deprotonation/protonation sequence, using chiral lithium amide 1. The optical activity of 2 is caused by a difference in the deprotonation rates of the enantiomers.

Despite the great interest in stereoselective synthesis nowadays only a few stereoselective deprotonation/protonation reactions have been reported.[1] An isolated example of an enantioselective deprotonation is found in the reaction of cyclohexene oxide by a series of chiral lithium amides yielding enantiomerically enriched 2-cyclohexenol.[2] Hogeveen and Zwart reported the enantioselective deprotonation/protonation reaction of the strained tricyclic ketone 1,2,4,5,6-pentamethyltricyclo$[3.1.0.0^{2,6}]$ hexanone-3 using lithium (S,S')-α,α'-dimethyldibenzylamide (1) as chiral base and H_2O as proton donor.[3] It was suggested that the existence of two diastereomeric lithium enolate.chiral amine complexes would be responsible for the observed enantioselectivity. In order to gain more insight in this type of reaction we investigated it in more detail using 2,2,6-trimethylcyclohexanone (2) as model system.[4]

A THF solution of racemic 2 was added to a THF/hexane solution of 2 eqs. of 1 (prepared by addition of n-butyllithium to the amine 4) at -80°C and the reaction temperature was subsequently raised in 0.5 hours to -40°C; on recooling the solution to -80°C and addition



2 (racemic) 3 2 (opt. act.)



1 X = Li
4 X = H

of 10 eqs. of an aqueous 1N HCl solution, the ketone 2 was regained in 84% yield, but now in optical active form; $[\alpha]^{rt}_{578}$ = +11.7 (c=2, $CHCl_3$). In this reaction the amine 4 could be recovered without any epimerization or racemization (<2%) in a yield over 90%. A number of variables of this reaction were investigated: the use of 1-4 eqs. of 1, the addition of 4 eqs. of amine 4 and the use of protondonors such as water, nitromethane, the HCl-salt of 4 or (2R,3R)-O,O-dipivaloyltartaric acid did not change the enantioselectivity. However, a change in the solvent showed a great effect: when the reaction was performed, under otherwise identical conditions, in THF/HMPA (4:1, v/v) or DME as solvent, the e.e. decreased (Table I, runs 1-3); on the other hand, with diethyl ether as solvent the enantioselectivity increased strongly (e.e. 46%, run 4). It is remarkable that the change of solvent from THF to diethyl ether not only increases the e.e. but also gives enrichment of the opposite enantiomer.[11]

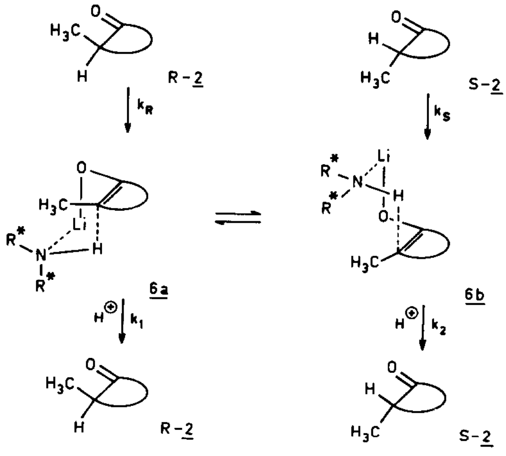
Table I: Deprotonation of 2 by 1[a], followed by quenching with 1N HCl in H_2O[b]

run	solvent	c.y.(%)[c]	e.e.(%)[5]	conf.[10]
1	THF	84	15	S
2	THF/HMPA (4:1, v/v)	77	4	R
3	DME	65	2	R
4	ether	63	46	R

[a] Temperature of deprotonation: -80°C to -40°C in 0.5 h (except run 3: -60°C to -40°C)
[b] Temperature of quenching: -80°C; [c] Yields of isolated product (not optimalized);

When the lithium enolate anion 3 in THF, prepared by deprotonation of 2 with 2 eqs. of 1, was quenched with an 1N DCl solution in D_2O, no deuterium incorporation (<5%) was observed in product 2 (e.e. 16% [S-configuration]). This indicates that protonation of the lithium enolate 3 does not occur directly by the added proton donor but that instead the amine is the immediate proton source. In the reverse experiment, starting with 2,2,6-trimethylcyclohexan-one-6-d_1 (5)[12] and quenching with 1N HCl in H_2O, only 5 and no 2 was obtained.

The general mechanistic scheme for the optical activation is shown below. Indications for the existence of diastereomeric lithium enolate.chiral amine complexes (with the



presumed structures 6a and 6b) are the following: i) the lack of deuterium incorporation when 3 is quenched with 1N DCl in D_2O; ii) the found enantioselectivities in the benzylation[13] and carboxylation[14] reaction of 3 require an interaction of 3 with a chiral auxiliary, in this case the chiral amine 4; iii) examples of carbanion.amine complexes are known in the literature.[15] Evidence for believing that the optical induction is due to a rate difference in the deprotonation of R-2 and S-2 (Scheme, $k_R \neq k_S$) is based on the following observations[16]: i) when an enantiomerically enriched sample of 2 (e.e. 15%) was used as starting material in the deprotonation/protonation sequence under otherwise identical conditions (Table I, THF), the product 2 showed an e.e. of 28%; ii) on changing the temperature of the deprotonation of racemic 2 to either 0°C (0.5 h) or to -80°C (0.5 h) no optical activity was observed in the reaction product 2. The latter results are explained by assuming that at -80°C virtually no deprotonation and at 0°C a complete deprotonation has taken place, whereas under the conditions of the standard reaction the protonation is incomplete. This was checked by silylation of the formed lithium enolate in a series of parallel experiments (Table II). The absence of a silylated product in the experiment of -80°C proves that there is no deprotonation (run 1), while at 0°C complete deprotonation of 2 has occurred (run 3). The result of run 2 shows that the deprotonation of 2 under the standard conditions is indeed an incomplete process. In summary, it is concluded that the observed enantioselectivity is exclusively due to kinetic resolution. In this model the theoretical maximum e.e. is 50%, which shows that the results in run 4 (Table I) are indeed quite impressive.

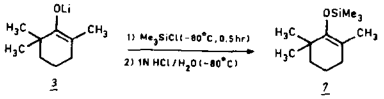


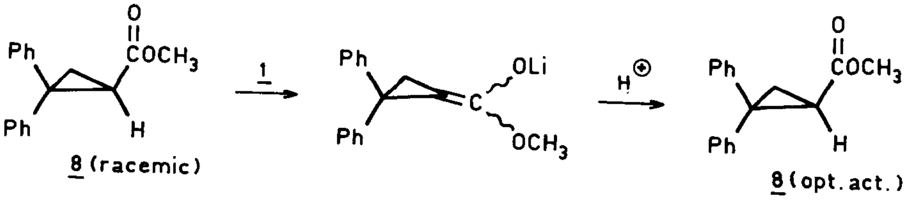
Table II: Silylation of lithium enolate 3

run	temp. of deprot. (°C)[a]	rel. amount of 7 (%)[b]	rel. amount recovered 2 (%)[b]
1	-80	0	100
2	-80 → -40	40	60
3	0	100	0

[a] Reaction time: 0.5 h; ratio 2:1 = 1:2.

[b] Relative amount of 7 and 2 measured by GLC (SE-30 column, column temperature: 120°C).

Finally we have also briefly investigated the possibility of inducing optical activity in esters by a deprotonation/protonation sequence with 2 as base and methyl-2,2-diphenylcyclopropane carboxylate (8) as substrate. When the reaction with racemic 8 as substrate was performed in a similar way as with 2 using THF as solvent, 8 was obtained in optical active



form ($[\alpha]_D^{rt}$ = -77.9) in 72% chemical yield which shows that this reaction yielded the R-enantiomer in an optical yield of 37%.[17,18]

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References and Notes

1. L. Duhamel, P. Duhamel, J.-C. Launey, J.-C. Plaquevent, Bull. Soc. Chim. Fr. 1984, II-421.
2. a) J.K. Whitesell, S.W. Felman, J. Org. Chem. 1980, **45**, 755; b) M. Asami, Chem. Lett. 1984, 829.
3. H. Hogeveen and L. Zwart, Tetrahedron Lett. 1982, 105.
4. Ketone 2 was chosen as model system because in the corresponding carbanion (3) there is no Z/E stereochemistry to deal with and on deprotonation of 2 only one prochiral center is formed.
5. The e.e. values were determined by two independent methods. First, chiral shift NMR experiments with $Eu(DCM)_3$ showed samples of 2 with $[\alpha]_{578}^{rt}$ = -36.3 (c=1.8; $CHCl_3$) and $[\alpha]_{578}^{rt}$ = +11.7 (c=1.8; $CHCl_3$) to have an e.e. of 46% and 15%, respectively. Second, by a method developed by Konig,[6] *in which compound* 2 *was converted to the corresponding* anti-oxime the enantiomeric ratio of which was determined by GLC using a chiral capillary column (XE-60-(S)-valine-(S)-α-methylbenzylamide.[7] When a sample of 2 with $[\alpha]_{578}^{rt}$ = -67.9[8] was used an e.e. of 92% was found. The observed $[\alpha]_{578}^{rt}$ and the calculated e.e. values do linearly correlate.
6. W.A. Konig, I. Benecke, K. Ernst, J. Chromat. 1982, **253**, 267.
7. The capillary fused silica column, coated with XE-60-(S)-valine-(S)-α-methylbenzylamide was obtained *from Chrompack (Middelburg, The Netherlands).*
8. The R-enantiomer of 2 has also been synthesized starting from 2,2-dimethylcyclohexanone by a method developed by Enders et al.[9] In this way compound 2 was obtained in a chemical yield of 25% (not optimalized) with an $[\alpha]_{578}^{rt}$ of -67.9.
9. D. Enders, H. Eichenauer, Angew. Chem. 1979, **91**, 425.
10. By application of the octant rule the absolute configuration was determined. A sample of 2 with $[\alpha]_{578}^{rt}$= -36.3 (run 4) is enriched in its R-enantiomer because the sample showed a negative Cotton effect in its CD-spectrum ($[\theta]_{296}$ = -2680).
11. The ethereal solvents, diisopropyl ether and t-butyl methyl ether gave irreproducible results (under apparently the same reaction conditions the e.e. changed from 0% to 48% and from 0% to 42%, respectively).
12. Compound 5 was synthesized by treatment of 2 (1.0 g) with a 20% DCl solution in D_2O (5 ml) with THF as co-solvent (15 ml) at room temperature for 16 h (91% yield; >95% D-incorporation in one cycle).
13. M.B. Eleveld, Ph.D. Thesis, University of Groningen, 1984; e.e. ≈10%.
14. H. Hogeveen and W.M.P.B. Menge, to be published; e.e. 67%.
15. a) P.L. Greger, J. Am. Chem. Soc. 1976, 92, 1396; b) T. Laube, J.D. Dunitz, D. Seebach, Helv. Chim. Acta, 1985, 68, 1373; c) C.H. Heathcock in "Asymmetric Reactions and Processes in Chemistry", E.L. Eliel and S. Otsuka (Eds.), Am. Chem. Soc., Washington, p. 69-70 (1982).
16. These observations are neither consistent with a mechanism in which a difference in the rates of protonation ($k_1 \neq k_2$) is responsible for the observed optical induction nor with one in which the equilibrium ratio 6a/6b differs from unity.[3,13]
17. a) H.M. Walborsky, L. Barash, A.E. Young, F.J. Impasto, J. Am. Chem. Soc., 1961, **83**, 2517; b) H.M. Walborsky, F.M. Hornyak, J. Am. Chem. Soc., 1955, 77, 6026.
18. When diethyl ether instead of THF was used as solvent irreproducible results were obtained (the o.y. ranged from 0% to 40% in various apparently similar experiments).

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