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ENANTIOSELECTIVE DEHYDROHALOGENATION VIA ASYMMETRIC DEPROTONATION BY CHIRAL LITHIUM AMIDES : DERACEMIZATION OF A COMPOUND BEARING A CHIRAL AXIS

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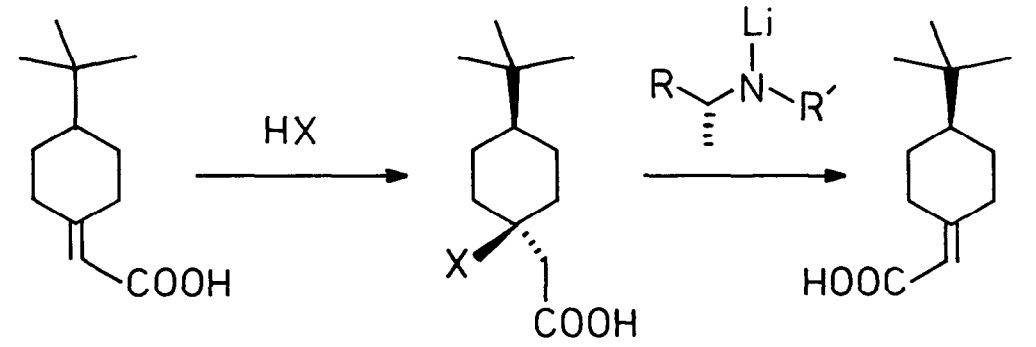
Summary : Chiral lithium amides exert asymmetric induction in dehydrohalogenation reactions leading to axially dissymmetric compounds. Thus the deracemization of 4-*tert*-butyl-cyclohexylidene acetic acid 1 via the prochiral hydrochlorinated intermediate 2 is reported with e.e. as high as 82 %.

During our studies on the deracemization by enantioselective protonation of aminoacid derivatives, we reported in 1980 (1a) that chiral lithium amides could be useful reagents in asymmetric synthesis, since they act both as bases and as chiral auxiliaries able to induce enantioselectivity in addition reactions to the prochiral anionic intermediate created by the deprotonation. This concept was applied to various asymmetric reactions, such as enantioselective alkylations (1b), additions to carbonyl compounds (1c) and carboxylation of a ketone (1d). Simultaneously, Whitesell and Felman (2a) reported the first example of enantioselective deprotonation by chiral lithium amide bases, studied in the case of the asymmetric rearrangement of epoxides to allylic alcohols. This reaction was improved by Asami (2b). Recently, enantioselective deprotonations of ketones were also described (2c).

We wish to disclose our finding that chiral lithium amides can exert asymmetric induction in dehydrohalogenation of prochiral compounds, thus yielding axially dissymmetric compounds. Enantioselective dehydrohalogenation was applied to the deracemization (1a,3) of 4-*tert*-butyl-cyclohexylidene acetic acid 1 chosen as a model compound (scheme 1) :

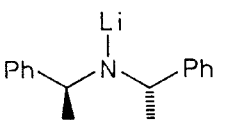


Scheme 1

Racemic **1** was obtained by Wittig-Horner condensation of 4-*tert*-butyl-cyclohexanone and triethylphosphonoacetate (NaH, DME) followed by saponification (MeOH, KOH). Hydrohalogenation (HX, Et_2O) yielded the prochiral compound **2** as a single isomer bearing the halogen in axial position cis to the *tert*-butyl moiety (10). Enantioselective dehydrohalogenation by means of chiral lithium amides gave optically active **1** with enantiomeric excess as high as 82 %.

Experiments carried out with chiral lithium amides derived from α-phenylethylamine are compiled in Table 1.

TABLE 1 : DERACEMIZATION OF **1** BY ENANTIOSELECTIVE DEHYDROHALOGENATION (4) PROMOTED BY CHIRAL LITHIUM AMIDES DERIVED FROM α-PHENYLETHYLAMINE (SCHEME 1)

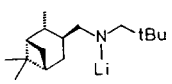
Chiral lithium amide			X	Optically active **1**			
R	R'	Conf.		Yield %	$[\alpha]_{546}^{25}$ (a)	e.e. %	(conf.)
Ph	Me	R	Br	78	-15.0 °	16	(R)
Ph	Et	R	Br	95	-33.2 °	35	(R)
Ph	Et	R	Cl	93	-21.5 °	23	(R)
Ph	Pr	R	Br	71	-30.1 °	32	(R)
Ph	*i*Pr	R	Br	78	-58.9 °	62	(R)
Ph	*i*Pr	R	Cl	85	-55.0 °	58	(R)
Ph	CH_2Ph	R	Br	80	-27.8 °	29	(R)
Ph	CH_2*i*Pr	R	Br	80	- 7.6 °	8	(R)
Ph	CH_2*t*Bu	R	Br	72	+48.6 °	51	(S)
Ph	CH_2*t*Bu	R	Cl	88	+50.9 °	54	(S)
Ph	CH_2(1-adamantyl)	R	Br	60	+66.3 °	70	(S)
Ph	CH_2(1-adamantyl)	R	Cl	84	+77.3 °	82	(S)
Ph	$(CH_2)_2$*t*Bu	R	Br	91	+17.0 °	18	(S)
		S,S	Br	74	+66.5 °	70	(S)
		S,S	Cl	96	+70.0 °	74	(S)

(a) EtOH, c=1. Ref. (R), $[\alpha]_{546}^{25}$ = -94.87 ° (c=0.98, EtOH) (5a). Enantiomeric ratios were confirmed by ^1H NMR in the presence of $Eu(hfc)_3$.

From these results, it appeared that the structure of the chiral base exerted a strong influence on the stereoselectivity (e.e. from 8 to 82 %). It is noteworthy that modification of the structure of the achiral sustituent of the nitrogen in the chiral lithium amide can reverse the enantiotopic differenciation. One can also observe that the higher selectivities were obtained for the hydrochlorinated prochiral compound. These results suggest that the preferential approach of the reagents is controlled by steric factors in a E_2 or E_{1cb} type transition state (6).

In a second series of experiments, four secondary *neo*-pentylamines were prepared from the corresponding chiral primary amines and were used in deracemization procedure in order to study the influence of the chiral moiety of the base on the stereoselectivity (Table 2).

TABLE 2 : INFLUENCE OF THE CHIRAL MOIETY OF THE LITHIUM AMIDE ON THE DERACEMIZATION OF **1**

Chiral lithium amide (Scheme 1)			X	Optically active **1**			
R	R'	Conf.		Yield %	$[\alpha]_{546}^{25}$ (a)	e.e. %	(conf.)
Ph	CH_2tBu	R	Cl	88	+50.9 °	54	(S)
1-naphtyl	CH_2tBu	R	Cl	87	+49.6 °	52	(S)
cyclohexyl	CH_2tBu	R	Cl	70	+33.9 °	36	(S)
			Cl	73	+ 0.6 °	<1	

(a) *as in Table 1.*

Naphtyl and phenylethylamine derivatives exhibited very similar results, whereas the cyclohexylethylamine and the aminomethylpinane derivatives gave dramatically lower asymmetric inductions.

To the best of our knowledge, these results represent the first example of enantioselective deprotonation leading to axially dissymmetric compounds. Moreover, deracemization by enantioselective dehydrohalogenation is a new route to optically active alkyl-cyclohexylidene derivatives, which present an interest for natural product chemistry (7c), and which were previously prepared by resolution (5), asymmetric Wittig type reactions (7), or asymmetric eliminations using chiral sulfur derivatives (8). One advantage of this method is that the secondary chiral amines necessary for the formation of the lithium amides were easily prepared from the commercial corresponding primary amines (both enantiomers available) and can be rapidly retrieved in a reusable form (11).

Studies are in progress, to search for the factors which could increase asymmetric induction, to elucidate the mechanism of the enantioselective step and to determine the scope of this reaction.

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(4) In a typical experiment, a solution of 0.52 mmol of the prochiral intermediate 2 in 1 ml of THF was added dropwise in 30 min. at -72°C to a solution of 1.30 mmol of the desired chiral lithium amide in THF/hexane (6 ml/ 1 ml) previously prepared at -45°C by standard procedure. After 18 hrs at -72°C, the mixture was warmed to 0°C, completed with Et_2O (5 ml), then extracted 3 times with 0.1 N aqueous sodium hydroxide. Acidification and usual workup gave the crude product which was purified by flash chromatography (ref. 9, eluent petroleum ether/ Et_2O = 80/20) to give optically active 1 as an oil which solidified on standing. The solid residue was dried in vacuo on P_2O_5. The secondary chiral amine was easily retrieved by standard workup with quantitative yield and without any racemization.

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(6) The possibility that the stereoselectivity could be governed by a thermodynamic process was eliminated considering the following experiment : when a sample of (R) 1 (56 % e.e.) was treated in conditions identical to that of a deracemization experiment (THF, LiBr, nBuLi, chiral amine R = Ph, R' = CH_2tBu, R configuration, -72°C, 18 hrs), the initial product was recovered without any configurational modification. If a thermodynamic equilibrium was the factor controlling the enantioselectivity, the recovered material ought to have exhibited (S) configuration (51 % e.e., see Table 1).

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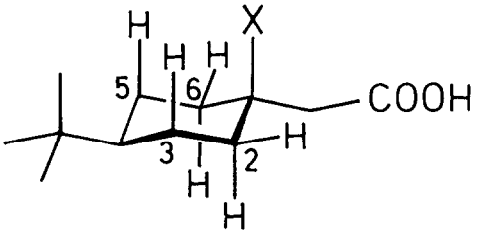
(10) Stereochemistry of compounds 2 was deduced from NOE difference data (^1H NMR 500 MHz). Saturation of 1-methylene substituent gave rise to an enhancement of the signals of both axial (2a, 6a) and equatorial (2e, 6e) protons. For an axial methylene group, enhancement would have been observed for the signals of (3a, 5a) protons.

2 =



(11) R. SOLLIARD is gratefully aknowledged for his assistance in the preparation of secondary chiral amines (unpublished results).

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