

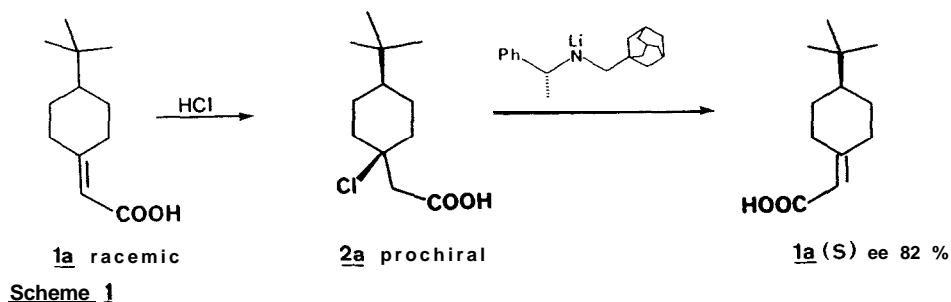
DERACEMIZATION OF AXIALLY DISSYMMETRIC COMPOUNDS BY  
ENANTIOSELECTIVE DEHYDROHALOGENATION USING CHIRAL LITHIUM AMIDES - II -

Lncette Duhamel\*, Alain Ravard and Jean-Christophe Plaquevent  
URA D 0464, UFR Sciences et Techniques, Université de Roan  
BP 118 F 76134 Mont Saint Aignan Cedex.

(Received 17 April 1990)

Abstract : New findings about deracemization of unsaturated carboxylic acids **1** by enantioselective dehydrohalogenation of prochiral species **2** by chiral lithium amides leading to axially dissymmetric compounds with 80% e.e. are reported. The role of the structure of the prochiral hydrochlorinated intermediate is discussed. An example of axial to central chirality transfer is described. (**1a**  $\rightarrow$  **3**)

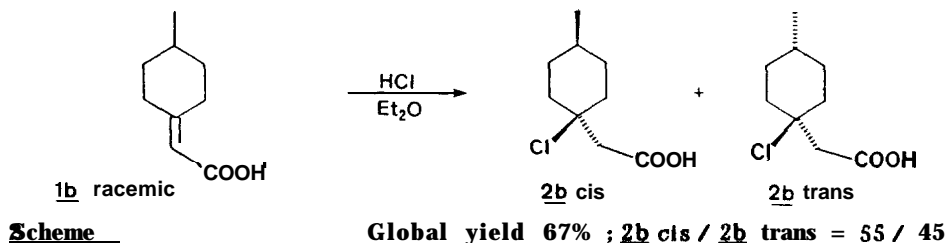
During our previous studies about the use of chiral lithium amides in asymmetric synthesis<sup>1,2</sup>, we recently reported that this class of chiral bases can exert high asymmetric induction in enantioselective dehydrohalogenation of prochiral acids **2**, leading to optically active acids **1** bearing a chiral axis<sup>1c</sup> (Scheme 1):



Our previous communication was essentially focused on the role of the structure of the chiral auxiliary on the enantioselectivity of the dehydrohalogenation step. Furthermore higher e.e.'s were generally observed for dehydrochlorination vs dehydrobromination.

In this report, we wish to describe new findings about influence of three other parameters on deracemization viz : the 4- substituent of the cyclohexyl moiety, the configuration of the prochiral hydrochlorinated intermediate and an excess of the chiral base.

In a first set of experiments, we generalized the deracemization procedure to 4-methyl cyclohexylideneacetic acid **1b**. We observed that the hydrochlorination of the racemic acid **1b** led to a mixture of the two isomeric prochiral acids **2b cis** and **2b trans** (Scheme 2):



Recrystallization of this mixture led as to the pure cis isomer (petroleum ether, RT, 3 recrystallizations, overall yield 43%) and Intermediate mixtures of various compositions. In the case of 4-tert-butyl cyclohexylideneacetic acid **1a**, only the cis hydrochlorinated acid **2a** was obtained<sup>1c</sup>. The relative configuration of these intermediate prochiral species was deduced from NOB difference data<sup>1c,3</sup>.

The hydrochlorinated compounds **2** were then submitted to dehydrohalogenation using chiral lithium amides as bases **4** (Scheme 3, Table I):

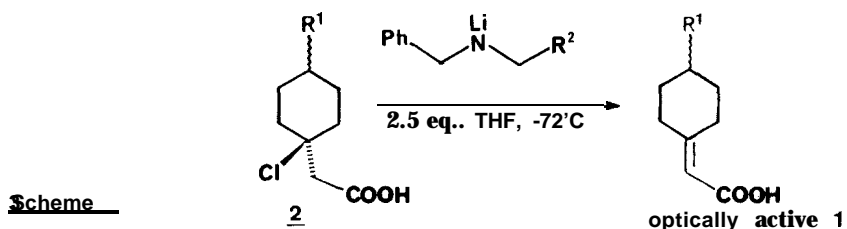


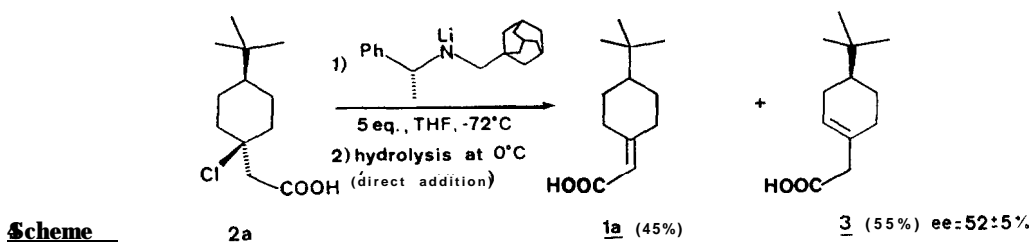
TABLE I: ENANTIOSELECTIVE DEHYDROCHLORINATION <sup>4</sup>

ENTRY	PROCHIRAL ACID <b>2</b>		BASE R <sup>2</sup>	CHIRAL ACID <b>1</b>		Yield %
	R <sup>1</sup>	cis / trans		[α] <sub>546</sub> <sup>25</sup>	o.p.%(conf.)	
1	t-Ba	100 / 0	t-Bu	+50.9° (a)	54 (S)	88 <sup>1c</sup>
2	t-Ba	100 / 0	1-adamantyl	+77.3° (a)	82 (S)	84 <sup>1c</sup>
3	Me	100 / 0	t-Bu	+49.8° (b)	52 (S)	73
4	Me	83 / 17	t-Bn	+29.1° (b)	30 (S)	64
5	Me	46 / 54	t-Bu	-13.6° (b)	14 (R)	64
6	Me	0 / 100	t-Bu		>75 <sup>c)</sup> (R)	—
7	Me	100 / 0	1-adamantyl	+76.8° (b)	80 (S)	75
8	Me	5s / 45	1-adamantyl	+9.7° (b)	10 (S)	70
9	Me	0 / 100	1-adamantyl	—	>75 <sup>c)</sup> (R)	—

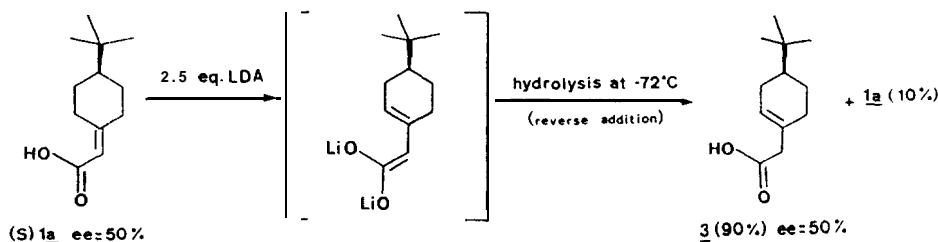
(a) EtOH, c=1 Ref. (R), [cd&- -94.87' (c=0.98, EtOH)<sup>5</sup>; (b) EtOH, c=0.9 Ref. (S) [α]<sub>546</sub><sup>25</sup>=+95.8 (c=0.87, EtOH)<sup>6</sup> (c) Since the pure **2b trans** isomer was not available, this e.e. was estimated by extrapolation of values reported in entries 3 to 5 and 7 to 8.

- These results provide us with new informations about the deracemization reaction :
- the enantioselectivity for the cis isomers is not depending on the steric hindrance of the 4 substituent on the cyclohexyl ring ( see entries 1 and 3 ; 2 and 7 ).
  - the asymmetric induction is directly related to the configuration of the prochiral hydrochlorinated acid 2b. Indeed, for a same chiral lithium amide, the sense of asymmetric induction is reversed for the two isomeric forms of 2b, and high e.e.'s can be obtained in both cases. ( see entries 3 to 6 ; 7 to 9 ). Obviously, the chiral base selects the same enantiotopic hydrogen in the two isomeric prochiral species 2b, thus leading to opposite configuration of 1b. A study of models rationalizing this observation is in progress and will be published elsewhere.
  - this last information demonstrates that the enantioselectivity of the dehydrohalogenation step is under kinetic control since a thermodynamic control would lead to the same optical activity starting from either 2b cis or 2b trans ( see also ref.1c, note 6 ).

Finally, we performed dehydrochlorination in the presence of an excess of chiral base ( 5 eq. ). The recovered material was a mixture of both isomeric acids bearing the double bond in exo or endo position. After separation by flash chromatography ( petroleum ether/Et<sub>2</sub>O=80/20)<sup>7</sup>, acid 3 turned out to be optically active<sup>8</sup>( Scheme 4 ). We assumed that the e.e. of 3 was due to the stereoselective deconjugation of optically active 1a under basic conditions, with racemization ( 52% e.e. only instead of 82% ).



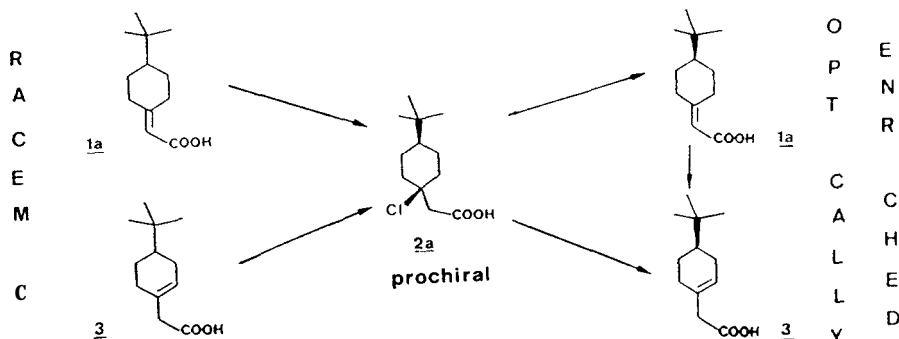
In order to decide this mechanism and to improve this deconjugation, we treated (S) 1a by 2.5 eq. of an achiral base (LDA), then added the cool reaction mixture (-72°C) to water ( instead of adding water to the reaction mixture at ca 0°C ).



### Scheme 5

This procedure allowed us to increase the 3/1a ratio to 90/10, without any loss of optical activity (Scheme 5). Obviously, the protonation step of the anionic species during the aqueous workup was more regio and stereoselective at low temperature<sup>1d,10</sup>.

This example of axial to central chirality transfer constitutes the key step of the deracemization by enantioselective dehydrohalogenation of the acid **3**, since the prochiral intermediate **2a** can be easily obtained by hydrohalogenation of racemic **3**.



**Scheme 6**

#### References and Notes

- (1) a- L. DUHAMEL and J.C. PLAQUEVENT, *Tetrahedron Letters*, **21**, 2521 (1980); b- L. DUHAMEL and J.C. PLAQUEVENT, *Bull. Soc. Chim. Pr.*, II-75 (1982); c- L. DUHAMEL, A. RAVARD, J.C. PLAQUEVENT and D. DAVOUST, *Tetrahedron Letters*, **28**, 5517 (1987); d- L. DUHAMEL, P. DUHAMEL, S. FOUQUAY, J. JAMAL EDDINE, O. PESCHARD, J.C. PLAQUEVENT, A. RAVARD, R. SOLLIARD, J.Y. VALNOT and H. VINCENS, *Tetrahedron*, **44**, 5495 (1988); e- J.C. PLAQUEVENT and A. RAVARD, *J. Organometall. Chem.*, **361**, C51 (1989)
- (2) For a recent review on chiral lithium amides in asymmetric synthesis, see N.S. Simpkins, *Chem. and Ind.*, 387 (1988); see also D. Seebach, *Ang. Chem. Int. Ed. Eng.*, **27**, 1624 (1988) chapter 4.
- (3) This determination was performed on BRUCKER 400 and 500 MHz  $^1\text{H}$  NMR spectrometers by Professor D. DAVOUST and Doctor G. PLE who are gratefully acknowledged.
- (4) For experimental procedure, see ref. 1c note 4 and A. RAVARD, *Thèse de Doctorat, Roen* 1990.
- (5) M. DURAISAMY and H.M. WALBORSKY, *J. Am. Chem. Soc.*, **105**, 3252 (1983).
- (6) a- W.H. PERKIN and W.J. POPE, *J. Chem. Soc.*, 1510 (1911); b- H. GERLACH, *Helv. Chim. Acta*, **49**, 1291 (1966); c- H. M. WALBORSKY and R.B. BANKS, *Bull. Soc. Chim. Belg.*, **89**, 849 (1980).
- (7) W.C. STILL, M. KHAN and A. MITRA, *J. Org. Chem.*, **43**, 2923 (1978).
- (8)  $[\alpha]_{\text{D}}^{25} = -57.4'$  (0.7, EtOH).  $^1\text{H}$  NMR analysis of the derived methyl ester in the presence of chiral shift reagent  $\text{Eu}(\text{hfc})_3$  shown that this compound exhibited an e.e. of  $52 \pm 5\%$ ; (-) **3** should be of S configuration according to deconjugation mechanism of  $\alpha$ -ethylenic acids demonstrated in the following references: a-K.I. NUNAMI, M. SUZUKI, N. YONEDA, *J. Chem. Soc. Perkin I*, 2224 (1978); b- F.L. HARRIS, L. WEILER, *Tetrahedron Letters*, **25**, 1333 (1984); c- F.L. HARRIS, L. WEILER, *Tetrahedron Letters*, **26**, 1939 (1985).
- (9) A solution of 280mg of (S) **1a** (ee 50%) in 2 ml of THF was added at  $-72^\circ\text{C}$  to a 3.5mmol solution of LDA in 17 ml of THF. After 18hrs at  $-72^\circ\text{C}$ , 10 ml of  $\text{Et}_2\text{O}$  were added at this temperature and this mixture was poured in 10 ml of cool water, then extracted twice by 20 ml of 0.1 N aqueous sodium hydroxide. Acidification and usual workup gave the crude product (**3**/**1a**=90/10). Acid **3** was isolated by flash chromatography (petrolcam ether /  $\text{Et}_2\text{O}$  = 80/20) (70%, see note 8).
- (10) O. PESCHARD, *Thèse de Doctorat, Roen*, 1989