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LIGAND EXCHANGE IN ASYMMETRIC REACTIONS OF LITHIUM ENOLATES : APPLICATION TO THE DERACEMIZATION OF α-AMINOACIDS

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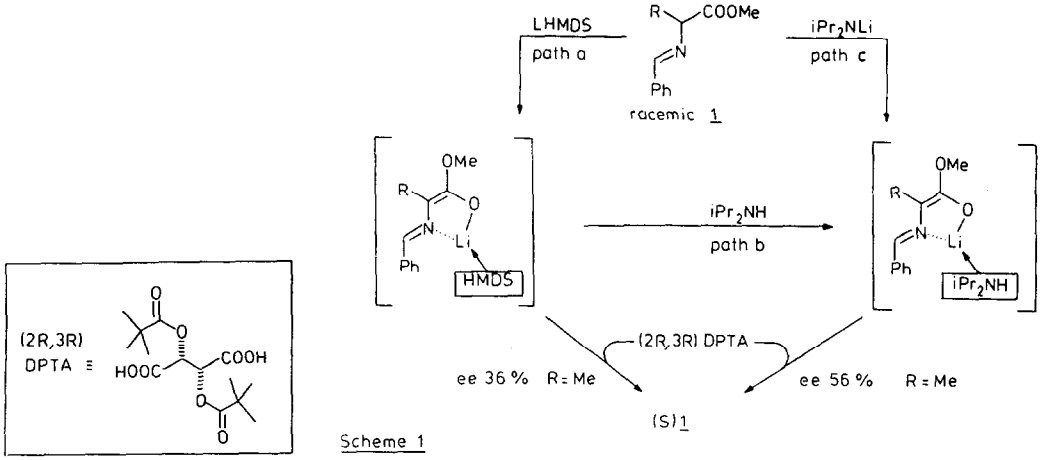
ABSTRACT : *In the search for the factors controlling the enantioselective protonation of enolates of α-aminoacid derivatives, we report a new procedure allowing the use of various ligands of lithium, involving an amine exchange after the metalation step by LHMDS and prior to the asymmetric protonation by means of a chiral acid. The stereoselectivity of this last step was affected by the ligand exchange. In some cases, a higher e.e. was observed compared to the LDA or LHMDS procedure.*

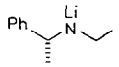
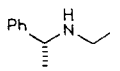
During our studies on enantioselective protonations of lithium enolates of α-aminoacid derivatives (1), the structure of the secondary lithium amide used for the metalation of the racemic starting material has been shown to affect significantly the ratio of asymmetric induction (1, 2). Here we wish to report a new procedure involving an amine exchange which opens up a route for the use of various ligands of lithium, and consequently modifies the stereoselectivity of the asymmetric step.

Thus, the deracemization (3) was carried out on N-benzylidene methyl esters of racemic aminoacids, using the lithium amide of hexamethyldisilazane (LHMDS) as base and (2R,3R) O,O-dipivaloyltartaric acid (DPTA) as chiral proton donor (4) (Scheme 1, path a) :



Scheme 1

TABLE 1 : VALIDITY OF THE HMDS-AMINE EXCHANGE PROCEDURE FOR THE DERACEMIZATION OF ALANINE, VALINE and PHENYLGLYCINE [a]

Entry	R	Lithium amide	Added amine	e.e% (S)	Yield %	Ref.
1	Me	LHMDS	-	36.5 [d]	87	-
2	Me	LDA	-	56 [d]	71	-
3	Me	LHMDS	iPr_2NH	56 [d]	85	-
4	iPr	LHMDS	-	34 [b,d]	83	-
5	iPr	LDA	-	47 [b,d]	79	-
6	iPr	LHMDS	iPr_2NH(0.25 eq)[c]	47 [b,d]	83	-
7	iPr	LHMDS	iPr_2NH(1.4 eq) [c]	46 [b,d]	83	-
8	iPr	LDA	HMDS	46 [b,d]	80	-
9	Ph	LHMDS	-	51 [d]	80	-
10	Ph	LDA	-	50 [d]	80	1,2
11	Ph	LHMDS	iPr_2NH	50 [d]	81	-
12	Ph		-	70 [d]	84	1,2
13	Ph	LHMDS		70 [b]	-	-

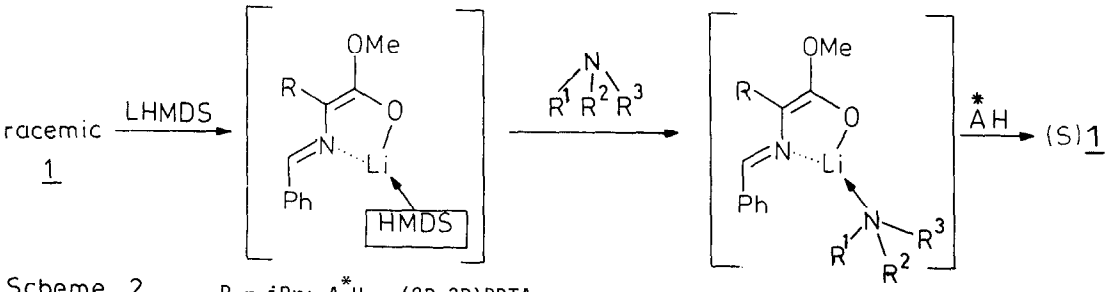
a) Protonation of the resulting enolate by means of (2R,3R) O,O-dipivaloyltartaric acid (DPTA) (3, 4); b) Determined by HPLC on chiral column (PIRKLE HPLC type CSP (R) -N- (3,5-dinitrobenzoyl)phenylglycine, hexane/dioxane = 98/2, 1.5 ml/mn; c) With respect to 1; d) Determined by polarimetry on amino ester hydrochlorides obtained by acidic hydrolysis of the deracemized Schiff bases (8).

It was observed that for alanine and valine derivatives (R = Me and R = iPr), the asymmetric induction was lower than in the classical procedure using LDA as the base (Scheme 1, path c and Table 1, entries 1 and 2; 4 and 5). In the case of phenylglycine (R = Ph), similar results were fortuitously observed with the two bases (entries 9 and 10). Moreover, an additional experiment was carried out as follows : after metalation by means of LHMDS, diisopropylamine was added before the asymmetric protonation step : the optical enrichment of the material recovered was then identical to that of the "classical" experiment with LDA as the base (Scheme 1, path b and Table 1, entries 2 and 3; 5 and 7). A reverse procedure, involving metalation by means of LDA followed by addition of HMDS also gave the same result (entry 8). Entries 12 and 13 describe a similar effect observed on phenylglycine derivative using a double asymmetric induction with a secondary chiral amine.

Among the possible explanations of the observed results (5), we consider essentially that the HMDS molecule liberated after metalation is a poor ligand of lithium because of its low basicity (6) and can thus be replaced by the added nucleophile (7). The enantioselective

protonation of the resulting new solvated prochiral lithium enolate would obviously lead to a different asymmetric induction.

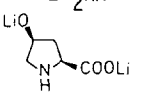
To illustrate this possibility of lithium ligand exchange, various primary, secondary and tertiary amines were added after the LHMDS metalation step (Table 2 and Scheme 2) :



Scheme 2 R = iPr; A*H = (2R,3R)DPTA

A higher deracemization ratio can be obtained with examples of each class of amines compared to the experiments without an additional ligand. In the case of ethylamines, the primary and secondary amines afforded a significant increase of stereoselectivity, whereas the triethylamine caused a dramatic decrease of asymmetric induction.

Table 2 : DERACEMIZATION OF VALINE VIA HMDS-AMINE EXCHANGE PROCEDURE [a]

Entry	Lithium amide	Added amine	e.e % (S) [b]
4	LHMDS	-	34
14	LHMDS	1,3-propanediamine	49.5
15	LHMDS	$EtNH_2$ (0.25 eq) [c]	53
16	LHMDS	$EtNH_2$ (1.4 eq) [c]	55
17	LHMDS	piperidine	50
18	LHMDS	Et_2NH	44
19	LHMDS		63.5
20	LHMDS	Et_3N	18
21	LHMDS	sparteine	51

a, b, c) as in Table 1.

It is noteworthy that this procedure avoids any addition reaction which could occur with the corresponding lithium amide. Morever, the added ligand can act almost catalytically (0.25 eq., entries 6 and 7; 15 and 16).

Studies are in progress.

ACKNOWLEDGEMENT : *We thank the National Society ELF for a grant given to one of us (S.F.).*

REFERENCES AND NOTES :

(1) For a review on asymmetric protonations, see L. Duhamel, P. Duhamel, J. C. Launay and J. C. Plaquevent, Bull. Soc. Chim. Fr. 1984, II-421.

(2) a - L. Duhamel and J. C. Plaquevent, Tetrahedron Letters 1980, 21, 2521;
b - L. Duhamel and J. C. Plaquevent, Bull. Soc. Chim. Fr. 1982, II-75.

(3) In a typical experiment, a solution of 3.5 mmol of the racemic Schiff base 1 in 6 ml of dry THF was added dropwise (10 mn) to a solution of LHMDS (5 mmol) in 10 ml of dry THF prepared at - 50°C by a standard procedure. After 30 mn at -50°C, a solution of the desired amine (5 mmol) in 5 ml of dry THF was added dropwise (10 mn). After 20 mn, the solution was cooled to - 70°C, and 10 mmol of (2R,3R) DPTA dissolved in 10 ml of dry THF was added dropwise (20 mn). The reaction mixture was allowed to stand 20 mn at this temperature, then was warmed up to room temperature, and was submitted to usual work up (see ref. 2 b).

(4) L. Duhamel and J. C. Plaquevent, Org. Prep. Proc. Int. 1982, 14, 347. Both enantiomers of DPTA are now commercially avalaible from Fluka.

(5) Another interpretation is to consider that the proton carrier could be in fact a chiral ammonium salt of DPTA (see ref. 1).

(6) R. R. Fraser and T. S. Mansour, J. Org. Chem. 1984, 49, 3443.

(7) For related studies in aldol and Michael type additions of lithium enolates, including discussions about the effect of added ligand on the degree and the type of aggregation, see D. Seebach, R. A. Welsh, Found. Proc., 1984, 93; see also S. Kiyooka, K. Kandori, R. Fujiyama and K. Suzuki, Memoirs Fac. Sci., Kochi Univ., Ser. C, 1985, 1.

(8) - (R) alanine methyl ester hydrochloride, $\{\alpha\}_D^{25}$ = - 6.5° (1, MeOH);
- (S) valine methyl ester hydrochloride, $\{\alpha\}_D^{25}$ = + 24.2° (1, MeOH);
- (R) phenylglycine methyl ester hydrochloride, $\{\alpha\}_D^{25}$ = - 132° (1, MeOH);
See for example D. S. Lingenfelter, R. C. Helgeson and D. J. Cram, J. Org. Chem. 1981, 46, 393 and references therein.

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