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ENANTIOSELECTIVE ALKYLATION OF ENOLATE DERIVED FROM GLYCINE INFLUENCE OF THE IMINE MOIETY

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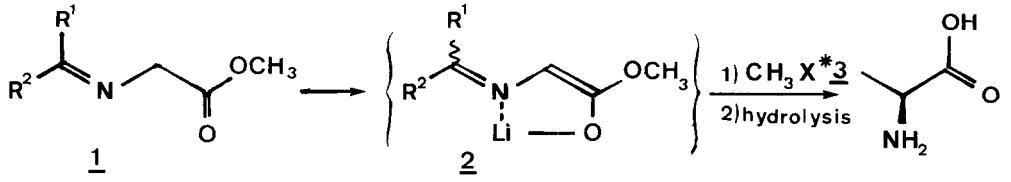
ABSTRACT : Optically active alanine was obtained by asymmetric one carbon transfer reaction. Variation of the nature of the imine moiety in the enantioselective alkylation of Schiff bases derived from glycine caused the enantiomeric excess to shift from 0 to 70 %.

During the last few years, we have been concerned with enantioselective reactions (1) and in the course of this work we have envisaged a classification (2) of these reactions connected with an apparent ionic mechanism.

For such reactions, we consider the three atoms (or group of atoms) involved in the new chiral center formation. They can be chiral **C** , achiral **A** , sp^2 or sp^3 prochiral **P** as well as electron-rich (nucleophile or nucleofugal) **N** or electron-poor (electrophile or electrofugal) **E** (3).

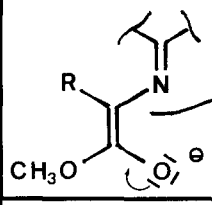
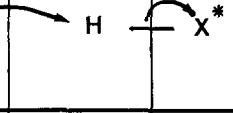
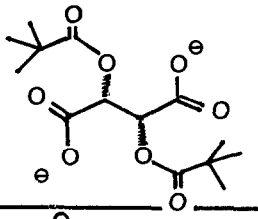
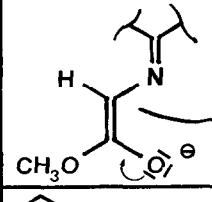
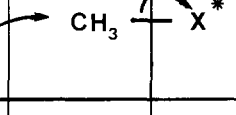
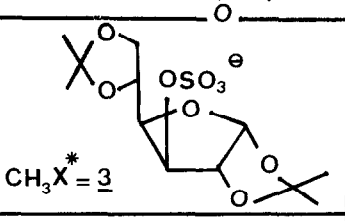
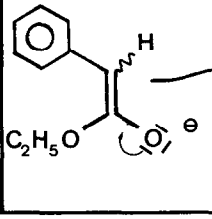
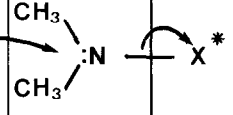
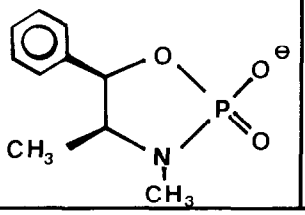
Thus, the nucleophilic substitution of a chiral **C** nucleofugal **N** by a prochiral **P** nucleophile **N** is, according to (2,3), a **PAC / NEN** scheme (4). From this scheme, three possibilities (see table 1) of synthesis of optically active α-aminoacids are possible, according as we envisage the reaction of the corresponding enolate with a proton, an alkyl group or an amino group carried by a chiral nucleofugal $X^{*\ominus}$.

In a parralel direction to path I, previously described by us (1a-g), and to path III, recently reported by G. BOCHE and W. SCHROTT (4d), the asymmetric methylation of enolate 2 by the mixed sulfate 3 derived from D(+) glucose was studied as a model for path II (1h).



1 2

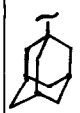
Table 1

	P N	A E	C N	Chiral Nucleofugal $X^{*\ominus}$	e.e.% (Ref.)
I					70 (1a-g)
II					71 (this work)
III					23 (4d)

Alkylation was realized by transposing the conditions of STORK (5,6). The following procedure is typical : at - 70°C, 1.5 mmol of Schiff base 1 (7) in 11 ml of THF was made to react with a stirred solution of 1.5 mmol of LDA in 7 ml of THF. After 30 mn, the temperature was raised to - 40°C and 1.6 mmol of sulfate 3 and 18 mmol of HMPA (12 eq.) in 4 ml of THF were injected; the time of contact is reported in table 2. Usual work-up led to α-aminoester hydrochloride (VPC analysis) and to α-aminoacid (polarimetric analysis) (1h).

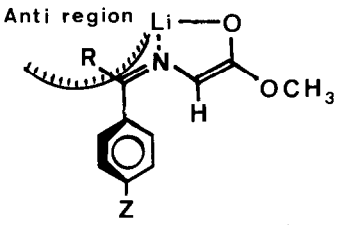
It can be seen from table 2 the dramatic effect (from 0 to 71 % e.e.) obtained by varying the nature of R^1 and R^2 in the Schiff bases. Indeed, other things being equal, enantiomeric excess shifts from 0 to 61 % when crowding by R^1 and R^2 increased (compare 1a; 1c; 1e; 1g). A much higher degree of stereoselectivity (e.e. 66 %) was observed when the phenyl group was substituted in the para position by an electron donating group. Similar results were reported for enantioselective protonations (1f). The best result (e.e. 71 %) was obtained when hindering by the adamantyl group was cumulated with an electron donating effect as in enolate 2j.

Table 2 INFLUENCE OF SUBSTITUENTS R^1 AND R^2 OF THE SCHIFF BASES **1** ON THE STEREOSELECTIVITY OF THE ALKYLATION

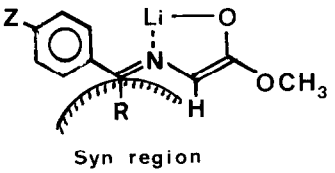
Schiff bases			Time of contact (h)	Aminoacid			e.e. %	Conf.
1	R^1	R^2		Yield % (*i*)	$[\alpha]_D^{25°}$ (C; HCl 2M)	e.e. %	VPC (*ii*)	
a	H	C_6H_5	1.5	50			0	
b	H	Mes	1.5	52	0 (0.3)	0	2.5	S
c	H	tBu	1.5	50	0 (0.1)	0	2.0	S
d	iPr	iPr	2	69	+ 4.6 (0.1)	32.5	35	S
e	C_6H_5	C_6H_5	2	60	+ 5.67 (1.24)	40	40	S
f	C_6H_5	iPr	2.25	72	+ 7.04 (1.3)	49.7	51	S
g	C_6H_5	tBu	3	72	+ 8.86 (0.35)	62.5	61	S
h	pMe_2N-C_6H_4	tBu	3.5	70	+ 9.21 (1.45)	65	66	S
i	ptBu-C_6H_4	tBu	3	63	+ 8.39 (0.87)	59.2	61.5	S
j	pMe_2N-C_6H_4		3				71 (*iii*)	S

(i) 100 % alkylation; yield is given for pure isolated alanine; (ii) N-trifluoroacetyl L-prolylamide of methylalaninate (1h); (iii) For this assay only the alkylation was 90 %.

From the molecular models of Schiff bases **1**(a, e-j)it seems that whatever was the structure of the imine part of the corresponding enolate, crowding of R^1 and R^2 results in a crowding of the syn region and it is attractive to think that enantioselectivity was favoured when the syn region was sterically hindered.



2 (Z,E)



2 (E,E)

Moreover the coordination of the pro R doublet of the oxygen linked to C-5 of the carbohydrate moiety of 3 with the lithium of the enolate 2 , provides a satisfactory model for a possible explanation of the high degree of enantioface differentiation. It can already be seen by looking at this model that hindering the syn region causes considerably more interaction with the re face than with the si face of the enolate.

References and notes

1) (a) L. Duhamel, C.R.Acad.Sci. 1976, 282C, 125; (b) L. Duhamel, J.C. Plaquevent, Tetrahedron Letters 1977, 2285; (c) L. Duhamel, J.C. Plaquevent, J.Am.Chem.Soc. 1978, 100, 7415; (d) L. Duhamel, J.C. Plaquevent, Tetrahedron Letters 1980, 2521; (d) L. Duhamel, J.C. Plaquevent, Bull.Soc.Chim.Fr. 1982, II-69; (f) L. Duhamel, J.C. Plaquevent, Bull.Soc. Chim.Fr. 1982, II-75; (g) L. Duhamel, J.C. Launay, Tetrahedron Letters 1983, 4209; (h) P. Duhamel, J.Y. Valnot, J. Jamal Eddine, Tetrahedron Letters 1982, 2863.

2) L. Duhamel, P. Duhamel, J.C. Plaquevent, J.C. Launay, Bull.Soc.Chim.Fr., in press.

3) From literature data, the most frequently reported enantioselective reactions can be specified by the eight following appellations :

PAC/NEN	APC/NEN	PCA/NEN	PPC/NEN
PAC/ENE	APC/ENE	PCA/ENE	PPC/ENE

4) Only a few reports on the PAC / NEN reactions, in which our activities are concerned, are mentionned in the literature :
(a) CH-bond : H. Matsushita, M. Noguchi, M. Saburi, S. Yoshikawa, Bull.Chem.Soc.Jap. 1975, 48, 3715; H. Matsushita, Y. Tsujino, M. Noguchi, S. Yoshikawa, Bull.Chem.Soc.Jap. 1976, 49, 3629; H. Matsushita, Y. Tsujino, M. Noguchi, M. Saburi, S. Yoshikawa, Bull.Chem.Soc.Jap. 1978, 51, 862; and ref. 1a-g and 2.
(b) C-Br bond : G. Dauphin, A. Kergomard, A. Scarset, Bull.Soc.Chim.Fr. 1976, 862.
(c) C-C bond : P. Duggan, W.S. Murphy, J.Chem.Soc.Chem.Comm. 1974, 263; S. Sakane, J. Fujiwara, K. Maruoka, H. Yamamoto, J.Am.Chem.Soc. 1983, 105, 6154; and ref. 1h.
(d) C-N bond : G. Boche, W. Schrott, Tetrahedron Letters 1982, 5403.
(e) S-N bond : A. Kjaer, O. Malver, Tetrahedron Letters 1982, 2687.

5) G. Stork, A.Y. Leong, A.M. Touzin, J.Org.Chem. 1976, 41, 3491.

6) J. Jamal Eddine, thèse de 3ème cycle, Rouen Juillet 1983.

7) Schiff bases 1 were prepared according to M.J. O'Donnel and R.L. Polt, J.Org.Chem. 1982, 47, 2663. Structures were assigned from ^1H NMR data. However, from preliminary results it seems that the structures of the corresponding enolates 2 were not obligatorily identical.

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