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ENANTIOSELECTIVE ELECTROPHILIC BOND CONSTRUCTION TO THE α-CARBON OF α-AMINOACIDS

Lucette Duhamel*, Pierre Duhamel, Stéphane Fouquay, Jamal Jamal Eddine, Olivier Peschard, Jean-Christophe Plaquevent, Alain Ravard, Roland Solliard, Jean-Yves Valnot and Hélène Vincens.

UA 464 CNRS and IRCOF, BP 1'8, F 76134 MONT-SAINT-AIGNAN CEDEX

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Abstract : In this report, we describe three possibilities for aminoacid synthesis using an enantioselective electrophilic process. Thus, enantioselective carboxylation, alkylation and protonation of Schiff bases yield optically active aminoacids with e.e. up to 76%.

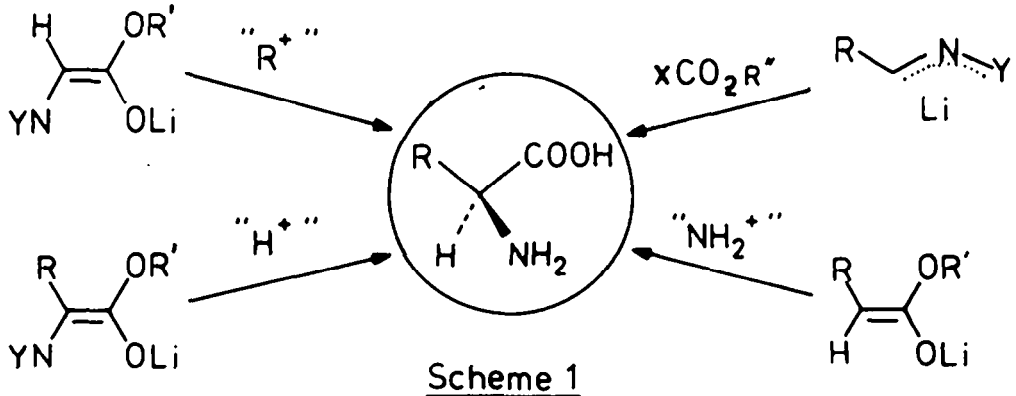
The asymmetric synthesis of natural and unnatural aminoacids is a major challenge for organic chemists. Numerous and successful works have been described in recent reviews and are still in progress.

For the asymmetric construction to the α-carbon of an α-aminoacid, one must consider the reaction of a prochiral substrate bearing three substituents on the α-carbon with a reagent bearing the fourth. Each substituent can be introduced in a neutral, nucleophilic or electrophilic manner, which can be diastereo or enantiodifferentiating.

Some successful neutral reactions have been described, such as the catalytic hydrogenation of dehydroaminoacids (1). An example of nucleophilic amination is given in a synthesis of aspartic acid (2). Nucleophilic carboxylation occurs in the asymmetric Strecker synthesis (3). Addition of organometallics on glyoxylic imines (4) and reduction of hydrazonolactones (5) represent examples of nucleophilic alkylations and reductions respectively. Diastereoselective electrophilic alkylations (6) and aminations (7) have recently been described, but enantioselective electrophilic methods have not been extensively studied (8-11). The aim of this publication is to describe our results in this field.

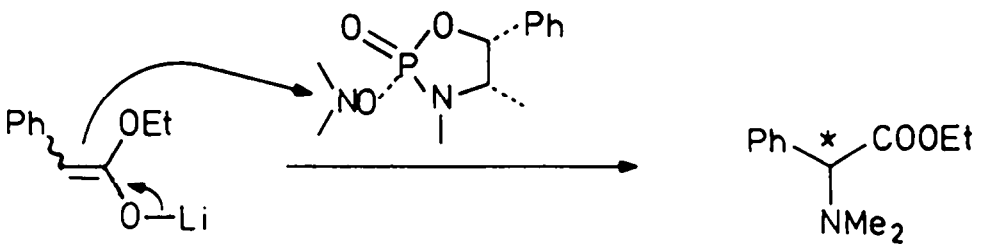
For our purposes, four possibilities were considered (Scheme 1) :

1- enantioselective electrophilic amination of a prochiral acid derivative.
2- enantioselective electrophilic carboxylation of a prochiral amine derivative.
3- enantioselective electrophilic alkylation of a prochiral aminoacid derivative.
4- enantioselective electrophilic protonation of a prochiral aminoacid derivative.



Scheme 1

During the course of our studies, an example of enantioselective electrophilic amination was described by German workers (8a) (scheme 2) :



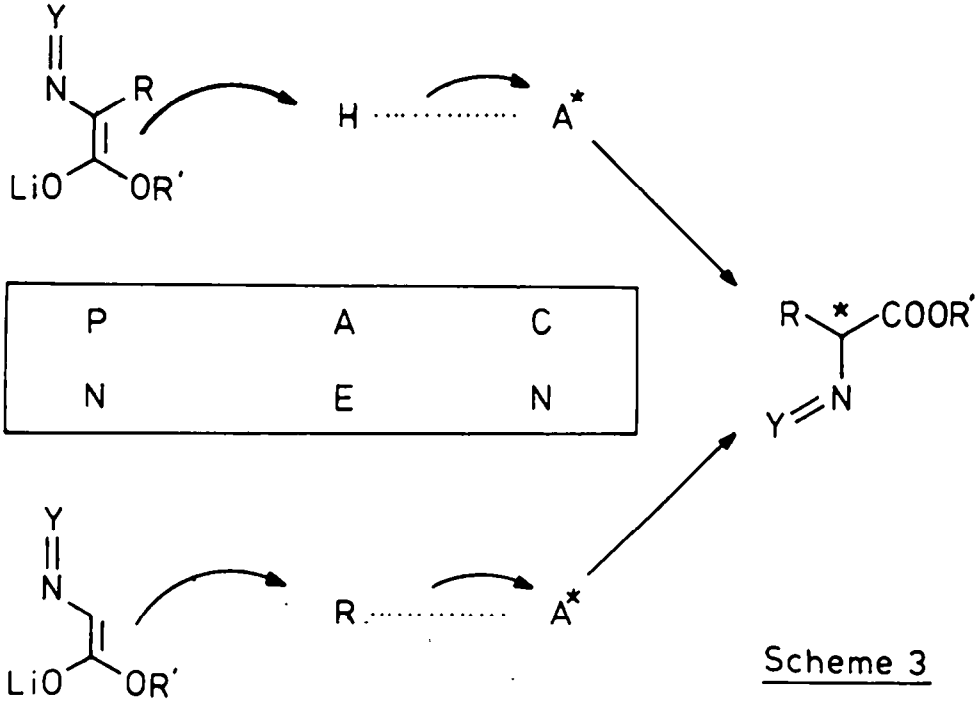
Scheme 2

The three other possibilities (enantioselective carboxylation, alkylation and protonation) have been studied in our group (9-11).

Two different methodologies were used for the enantioselective construction of the chosen bond :

1- the chirality comes from the reaction medium : this method was used for carboxylation reactions, using chiral lithium amides as chiral auxiliaries (chapter 1).

2- the chirality is brought by a reactant carrying a chiral leaving group. This kind of reagent was considered for alkylations and protonations (chapters 2 and 3). Such types of asymmetric reactions were classified as PAC/NEN (9). In such a system, a prochiral (P) nucleophilic (N) substrate is allowed to react with an achiral (A) electrophilic (E) species. This process is accompanied by the departure of a chiral (C) nucleofugal (N) moiety A* which is responsible for the asymmetric induction (schemes 2 and 3) :

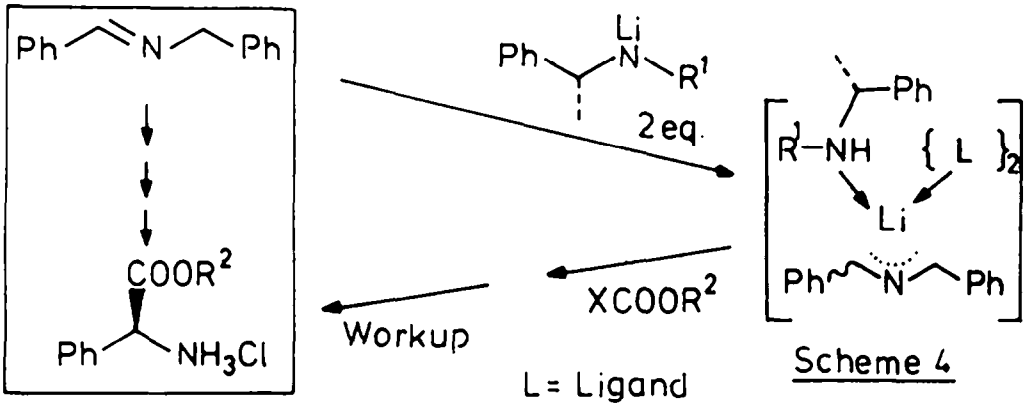


Scheme 3

1) ENANTIOSELECTIVE CARBOXYLATION :

To the best of our knowledge, this possibility for the electrophilic enantioselective synthesis of α-aminoacids has not been described previously. Although it is possible to induce asymmetry via a PAC/NEN methodology (i.e. with a chiral CO_2 carrier, by analogy with the R^* and H^* chiral carriers described in the following chapters), we exploited the potential of chiral lithium amides in asymmetric synthesis. This class of chiral auxiliaries has been recently introduced (10b, 13a) and has been used for various enantioselective reactions such as deprotonation of ketones (12), isomerization of meso epoxides (13), protonation of prochiral enolates (9b, 10b, 14), alkylations (8c, 15), addition to carbonyl compounds (16), carboxylation of a ketone (17a), dehydrohalogenation leading to axially dissymmetric compounds (17b) and Wittig type ring closure (17c).

Thus, N-benzylidene benzylamine was submitted to deprotonation by a chiral lithium amide, and the resulting azaallyllithium anion (18) was allowed to react with a carboxylating reagent. Standard workup allowed the recovery of the expected alkylphenylglycinate with e.e. as high as 40% (scheme 4, table 1) :



Scheme 4

Table 1 : Enantioselective carboxylation of N-benzylidene benzylamine under the influence of chiral lithium amides.

Chiral lithium amide		Electrophile		Optically active aminoester	
Conf.	R^1	X	R^2	Yield %	e.e. % (conf)
R	Et	MeO	Me	40	0
R	Et	Cl	Me	58	35 (S)[a]
R	Pr	Cl	Me	60	32 (S)[a]
R	Et	Cl	Et	56	41 (S)[a]
R	Pr	Cl	Et	55	34 (S)[a]
R	Et	Cl	Bu	40	40 (S)[b]

a- polarimetry. b- ^1H NMR analysis in the presence of chiral europium complex $Eu(hfc)_3$.

Methyl carbonate yielded racemic compound while chloroformates allowed a moderate asymmetric induction. The use of more hindered chiral lithium amides generally gave lower enantioselection. The results reported in table 1 were obtained when using a

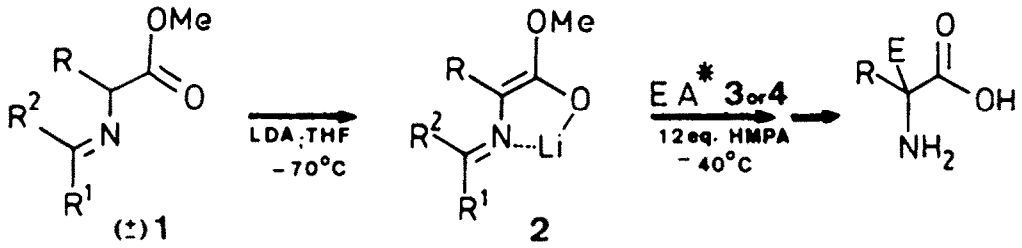
twofold excess of the chiral base with respect to the substrate. If the deprotonation step was carried out with one equivalent of the chiral lithium amide, the expected carboxylated material was recovered with a similar yield, but without any asymmetric induction. Moreover, an intermediate result (e.e. 20 %) was obtained when adding one equivalent of nBuLi to the anion (19) before the carboxylating step in an experiment carried out with two equivalents of the chiral lithium amide. These results suggest that both the secondary amine liberated after the deprotonation step and the chiral lithium amide in excess participate in the aggregate which is carboxylated (see 10b-d for related studies in protonation reactions). This necessity of two equivalents of chiral auxiliary can be related to the fact that each face of the azaallyllithium anion bears two enantiotopic centers.

Studies are in progress, to optimize and generalize this method of creating optically active aminoacids and to elucidate the mechanism of the enantioselection.

2) ENANTIOSELECTIVE ALKYLATION

Electrophilic C-alkylations in organic chemistry are usually achieved by using alkyl halides (20) and only recently have data in the literature been concerned with the use of chiral nucleofugals in asymmetric synthesis (9a, 11,21). Moreover, the biological single carbon transfer to a nucleophilic carbon center by S-adenosylmethionine (SAM) has also received considerable attention since it participates in the biosynthesis of compounds of great biological importance. For example, S A M is involved in the methylation or the methylenation of bacterial olefinic fatty acids or sterols, in the methylation of cobyrinic acid and in the biosynthesis of antibiotics (22).

In this part, we envisage the asymmetric synthesis of aminoacids via the electro - philic enantioselective alkylation of the enolates **2** derived from Schiff bases **1** of aminoesters by electrophilic reagents bearing a chiral leaving group **A*** (scheme 5).



R^1 = Ph, tBu ; R^2 = H, Ph
R = H, CH_2Ph

Scheme 5

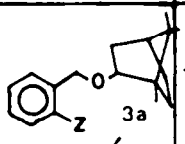
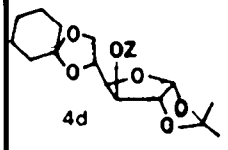
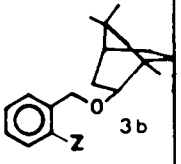
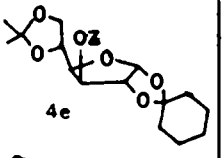
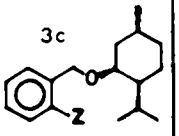
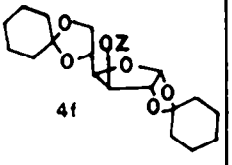
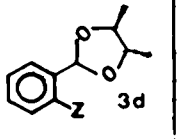
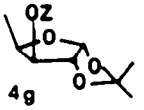
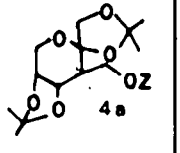
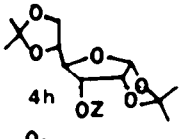
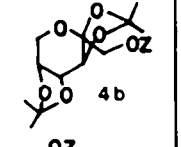
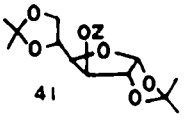
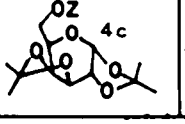
optically enriched.

The first problem was to find a chiral nucleofugal **A*** compatible with a SN_2 mechanism and having enantiodifferentiating ability. Thus, methylation of enolate **2** (R^1 =R^2 =Ph; R= H) by a series of chiral sulfonates **3** or mixed sulfates **4** (table 2) and the results communicated in a preliminary form (9a, 11) led us to some conclusive remarks.

In all cases, sulfonates **3** were poor leaving groups (twelve hours are required at -25°C for complete alkylation) and the observed stereoselectivity was low. On the contrary, everything else being equal, mixed chiral sulfates **4** required only three hours for complete alkylation at -40°C and the stereoselectivity was found to be dependent on three principal parameters:

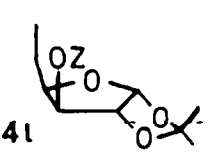
Use of the cosolvent HMPA was necessary and both the kinetic and the stereoselectivity were affected, suggesting that HMPA was present in the transition state (11a).

Table 2 Enantioselective methylation[a] of **2** (R^1= R^2= Ph; R= H) by sulfonates **3** and mixed sulfates **4**

Electrophilic reagent Z= SO_3Me	Conditions t°C	time	Yield% (transf.)	e.e.% (conf.)	Electrophilic reagent Z= SO_3Me	Conditions t°C	time	Yield (transf.)	e.e.% (conf.)
 3a	-25	4h	(78)	0[b]	 4d	-40	2h	53	30[c] (S)
 3b	-25	5h	(55)	0[b]	 4e	-40	2h	56	32[c] (S)
 3c	-25	6h	(80)	2[b] (S)	 4f	-40	3h	72	22[c] (S)
 3d	-25	5h	(71)	4[b] (S)	 4g	-40	2h	(98)	0[b]
 4a	-40	3h	(95)	0[b]	 4h	-40	2.5h	(98)	5[b] (S)
 4b	-40	3h	(100)	14[b] (R)	 4i	-40	2h	65	40[b,c,d] (S)
 4c	-40	3h	65	14[c,d] (S)					

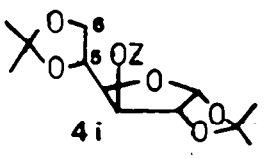
a) deprotonation, 1 eq. LDA/THF, -70°C; alkylation, THF,12eq.HMPA, -40°C; b) determination by HPLC ; c) determination by polarimetry; d) already published in ref.11a.

- From the results in table 2, it is clear that the enantioselectivity was very dependent on the structure of the chiral nucleofugal. It is noticeable that except for the sulfate **4b** derived from β-(D) fructopyranose, the major configuration of the aminoacid was always S. The best enantiomeric excesses were obtained with the sulfates derived from D(+) glucose; moreover, it was ascertained that the stereoselection was related to the solvatation of the lithium atom of the enolate and to the structure of the acetalic group linked to carbons 5 and 6 of the glucofuranose residue (11b).



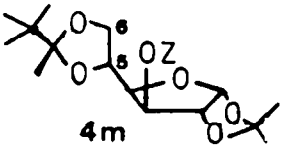
4l

Z= SO_3Me e.e. 0%



4i

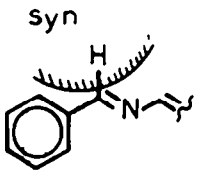
e.e. 40 %

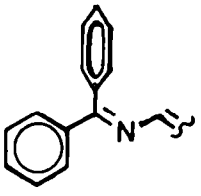


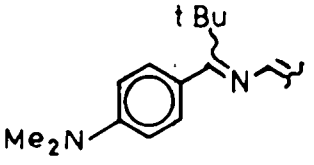
4m

e.e. 56%

During the methylation by sulfates 4i,m partioulary good results were obtained from the study of the influence of the structure of the Schiff bases derived from glycine and it was concluded that the enantioselectivity was favoured when the syn region of the imine moiety was sterically hindered (9a, 11b).







sulfate 4i : e.e. 0% e.e. 40 % e.e. 71%

4m : 56 % 76%

Thus, taking these conclusions into account, the enolates **2** (R = H, CH_2Ph) were alkylated with a series of sulfates 4i-k easily obtained from commercially available 1,2;5,6 di -O-isopropylidene -α-D glucofuranose (table 3).

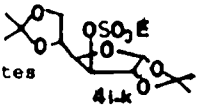
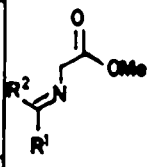
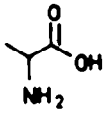
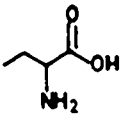
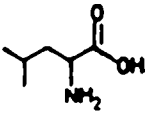
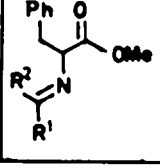
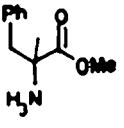


Table 3: Enantioselective alkylation[a] of enolates **2** by mixed sulfates

Entry	Starting iminoester	R^1	R^2	Conditions t °C. time	Electrophilic reagent	Isolated product	Yield%	e.e.% (conf)
1		H	Ph	1.5h	4i (E= Me)		50	0[b]
		Ph	Ph	-40 3h			70	37[b] (S)
		Ph	tBu	3h			72	61[b] (S)
2		H	Ph	5h	4j (E= Et)		64	2[b] (R)
		Ph	Ph	-15 4.5h			65	9[c] (R)
		Ph	tBu	5h			44	21[c] (S)
3		H	Ph	21h	4k (E= iBu)		22	0[c]
		Ph	Ph	0 20.5h			25	11[c] (R)
		Ph	tBu	22h			41	2[c] (R)
4		H	Ph	3h	4i (E= Me)		100	0[c]
		Ph	Ph	-40 3h			90	0[c]
		Ph	tBu	3h			d	0[c]

a) deprotonation: LDA, THF, -70°C; alkylation THF, 12 eq. HMPA ; b) by HPLC ; c) by polarimetry ; d) alkylation 60%.

Concerning the methylation (entries 1,4), the conditions were very close to those we used with dimethylsulfate or methyliodide and generally good yields of α-methylated aminoacids were obtained. The reactivity was largely dependent on the structure of the electrophilic group: in all cases, the only isolated aminoacid corresponded to the O-E cleavage, and the yields decreased from E= Me to E= iBu while the temperature of the alkylation had to be increased.

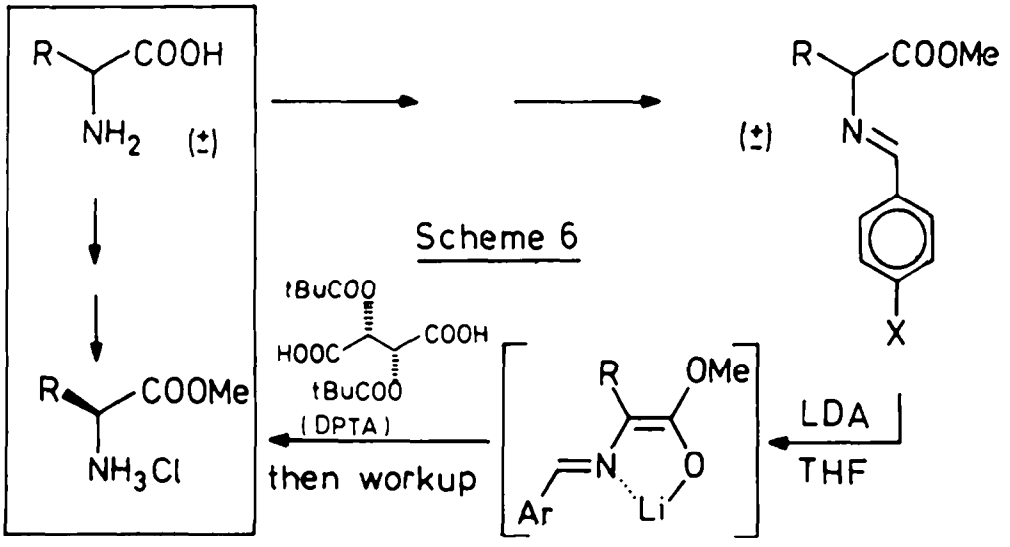
Although it is difficult to rationalize the observed stereoselectivity, we can notice that the attack of the si face of the enolate was favoured, for a given Schiff base, when the crowding of the electrophilic group decreased and, for a given electrophile, when the crowding of the syn region of the Schiff Base increased as was found previously (9a). From these last results, it was obvious that we needed more information about the mechanism of the reaction so we considered methylation again and are still currently investigating new chiral nucleofugals.

3) ENANTIOSELECTIVE PROTONATION :

Deracemization :

Deracemization by enantioselective protonation has been extensively studied in our group and enantioselectivities as high as 80% have been obtained (9b, 23). Previous studies in the aminoacid field were essentially involved with the search for the factors controlling the enantioselectivity of the protonation of prochiral derivatives of phenylglycine by various chiral acids (9b, 10) (see scheme 6). Thus it was established that the structure of the chiral proton carrier and the nature of the substituents of the prochiral substrate determined the stereoselectivity. It was also demonstrated that the base used for the deprotonation of the racemic aminoacid derivative was also involved in the asymmetric step. Thus, the use of chiral lithium amides allowed an increase in enantiodifferentiation (e.e. up to 70 %).

Results presented here summarize the experiments carried out on various aminoacids, in order to test the versatility of the method. Aldimine methyl esters were deprotonated by means of LDA, and the resulting anion was submitted to protonation by means of (2R,3R) DPTA (O,O' - dipivaloyltartaric acid) (24), thus allowing the recovery of optically active material (scheme 6 , table 4) :



Scheme 6

Table 4 : Deracemization of α-aminoacids (LDA as the base, (2R, 3R) DPTA as the chiral acid).

Initial racemic imine		Deracemized aminoester	
R	X	Yield %	e.e. % [a]
Me	H	71	56 (S)
Me	NMe_2	58	65 (S)
Et	H	78	51 (S)
iPr	H	79	47 (S)[b]
iPr	NMe_2	76	54 (S)
nBu	H	85	44 (S)
tBu	H		44 [e]
Ph	H	85	50 (S)[c]
Ph	NMe_2	75	61 (S)[c]
Ph	OMe	70	57 (S)[c]
Ph	OMe	95	70 (S)[d]
$MeSCH_2CH_2$	H	80	34 (S)
$MeSCH_2CH_2$	OMe	80	41 (S)

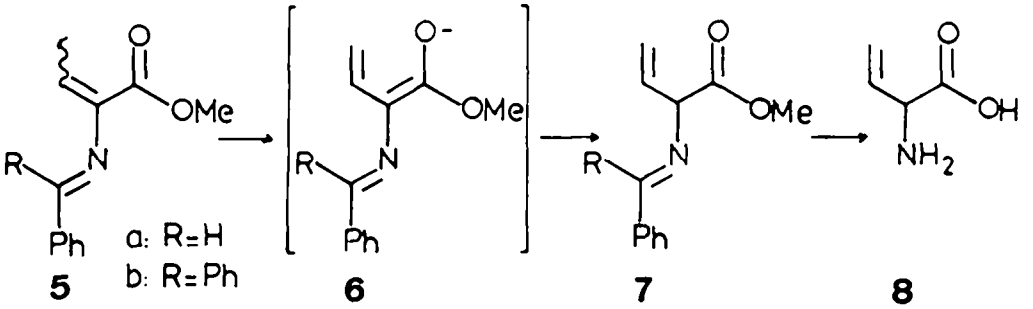
a)determined by polarimetry if not specified otherwise. b) already published in ref.10b. c) already published in ref. 10c. d) in this experiment, the protonation step was carried out at -105°C in THF/Et_2O (2/1). e) determined by HPLC.

Results indicated that the extent of the asymmetric induction was not dramatically affected by the nature of the R moiety of the aminoacid. In fact, hindering this group caused a small decrease of enantioselectivity (e.e. from 56 to 44 %, R=Me to R=tBu). Moreover, in all the studied cases, a favourable electronic effect was obtained when the imine moiety of the substrate was substituted by an electron donating group, as previously reported for phenylglycine (10c). One can also observe that the sense of the asymmetric induction was not modified, and that the final product was always of (S) configuration : this observation is consistent with the previously reported empirical rule for the prediction of the sense of asymmetric protonation, which could be used for the determination of absolute configuration of aminoacids (9b, 10c).

Finally, we observed that lowering the temperature of the protonation step increased both the yield and the enantioselectivity of the deracemization (up to e.e. 70%).

Deconjugation :

A very attractive and challenging problem was to apply enantioselective protonation to deconjugation. As a model reaction, we chose the access to vinylglycine **8** from conjugated esters **5** and describe preliminary efforts directed to the synthesis of racemic and optically enriched deconjugated esters **7** (scheme 7,table 5).



5 6 7 8

Scheme 7

Table 5 : Protonation of dienolates **6**

Entry	Starting ester E / Z	Deprotonation[a]	Protonation[b]	Results[c] 7%	5E%	5Z%	ee%[d] (conf)
1	**5a** 30/70	LHMDS (1.25 eq)[e,f]	AcOH (8 eq)[g]	35	3	42	
2	15/85	LHMDS (1.25 eq)[e]	AcOH (8 eq)	0	14	46	
3	15/85	LHMDS (1.25 eq)[e]	AcOH (8 eq)[g]	35	0	25	
4	0/100	LHMDS (1.25 eq)[e]	AcOH (8 eq)[g]	23	0	22	
5	15/85	LDA (1.25 eq)[e]	AcOH (8 eq)	0	4	66	
6	**5b** 100/0	LDA (2 eq)	H_2O[g]	0	0	100	
7	100/0	LDA (2 eq)	AcOH (9 eq)[h]	60	0	40	
8	100/0	LDA (2 eq)	AcOH (9 eq)	58	0	42	
9	100/0	LDA (2 eq)	AcOH (18 eq)	64	0	36	
10	0/100	LDA (2 eq)	AcOH (9 eq)	56	8	36	
11	**5b** 0/100	LDA (2 eq)	DPTA (4.5 eq)	22	13	65	24 (R)
12	100/0	LDA (2 eq)	DPTA (4.5 eq)	30	0	70	24 (R)
13	100/0	LDA (2 eq)[i]	DPTA (4.5 eq)	36	3	61	31 (R)
14	100/0	LDA (1 eq)[i]	DPTA (2.2 eq)	42	0	58	34 (R)
15	**7b**	LDA (2 eq)[e]	DPTA (4.5 eq)	45	0	55	36 (R)

(a) If not specified otherwise, the deprotonation temperature was -50°C. (b) If not specified otherwise, the protonation temperature was -70°C, and the protonation reagent was added to the dienolate **6** . (c) Ratio determined by ^1H NMR ; substantial amounts of autocondensation byproducts were also obtained in entries 1 to 5. (d) Determined by HPLC. (e) Reaction temperature : -70°C. (f) In this experiment, 4 eq of HMPA were added during the deprotonation step. (g) The dienolate **6** was added to the protonating solution at +20°C. (h) The dienolate **6** was added to the protonating solution at -70°C. (i) The dienolate solution was warmed to -35°C for 30 minutes before protonation.

First we investigated the non enantioselective deconjugation of esters **5a** and **5b**.This reaction had previously been experimented with ester **5a**,unsuccessfully (25). Thus, esters **5** (Z and / or E) were submitted to the deprotonation, and we treated the resulting dienolates **6** by a protonating reagent (acetic acid or water). Deconjugation of ester **5a** was only observed when the dienolate **6a** was added to the acid solution (inverse addition) ; in all cases, the deconjugated ester **7a** (35%) was accompanied by conjugated ester **5a** and autocondensation by-products (20 -50%). The deconjugation of ester **5b** occurs with a higher yield (55 - 64%) and is not affected by the addition order (entries 7 and 8) nor by the structure Z or E of the starting ester **5b** ; autocondensation by-products were not observed. After protonation, the configuration of the recovered ester **5b** was Z if the reaction proceeded from **5b** E (entries 6 to 9). The results from **5b** Z are very similar. However, a small quantity of **5b** E was also detected (entry 10).

Some protonations of dienolate **6b** by (2R, 3R) DPTA were effected. The enantioselective deconjugation of **5b** was dependent on the dienolate preparation conditions : the results were better when the dienolate **6b** prepared at -50°C was warmed to -35°C for 30 minutes prior to protonation at -70°C (compare entry 12 with entries 13 - 14) and nearly equalled those obtained by deracemization of **7b** (entry 15). All these experiments suggest that there are slight differences in the intermediate anionic species **6b** according to the starting material (**5b** or **7b**).

The separation of esters **5** and **7** is easily induced by hydrolysis : treatment by 1N HCl leads to vinylglycine methylester hydrochloride, isolated from the aqueous solution, without racemization.

(S) Vinylglycine **8** has been found in mushrooms (26). It plays a role in the enzymatic transformation of homoserine into threonine and α-ketobutyrate. Many syntheses of racemic **8** have been described (27). Optically pure vinylglycine was obtained from methionine (28) and glutamic acid (29). Some diastereoselective syntheses were also described (6c,30).

To the best of our knowledge, there have been no previous report on the enantioselective protonation of dienolates, whereas deconjugation via protonation of dienolates has been extensively studied (31) and results for enantioselective photodeconjugation have recently been published (32).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Perkin Elmer R 12 60 MHz or Bruker AW 80 80 MHz spectrometer. Chemical shifts are given in δ unit downfield from internal tetramethylsilane in $CDCl_3$ solutions. Optical rotations were measured on a Perkin Elmer micropolarimeter model 241. HPLC was performed on a chiral column Pirkle DNPG covalent bond (hexane/dioxane).

Preparation of starting Schiff bases :
All the Schiff bases used in this work have been prepared by known procedures. For the aldehyde derivatives, we used the method described in 10c, while ketimines were prepared according to M. J. O'Donnell (38).
The unsaturated Schiff bases **5a** and **5b** were prepared by dehydrohalogenation of their β-chloro precursors with DBU (25) : **5a** Z / **5a** E = 60 / 40 ; **5b** Z / **5b** E = 20 / 80.
The stereochemistry of **5a** was determined by NOE measurement experiments :
5a Z : 1.9 (3H, d, J = 7.2 Hz) ; 3.65 (3H, s) ; 6.55 (1H, q, J = 7.2 Hz) ; 8.45 (1H, s).
The signal corresponding to the imine proton was increased by 12% when irradiating the methyl protons and was not increased when irradiating the vinylic proton.
5a E : 2.05 (3H, d, J = 7.5 Hz) ; 3.80 (3H, s) ; 5.95 (1H, q, J = 7.5 Hz) ; 8.25 (1H, s).
The signal corresponding to the imine proton was increased by 29% when irradiating the vinylic proton and was not increased when irradiating the methyl protons. The opposite attribution has been proposed in the literature (25).
5b Z : 1.6 (3H, d, J = 6.9 Hz) ; 3.6 (3H, s) ; 6.1 (1H, q, J = 6.9 Hz).
5b E : 1.85 (3H, d, J = 7.6 Hz) ; 3.5 (3H, s) ; 5.5 (1H, q, J = 7.6 Hz).
The pure **5b** E was isolated by crystallization from pentane solution (m.p. 57°C). The pure **5b** Z isomer was obtained by isomerization of **5b** E in a procedure identical to deconjugation experiments using LDA as the base and water as the proton donor.

Enantioselective carboxylation. General procedure :
In a typical experiment, 2.1 mmol of chiral amine was dissolved in 8 ml of dry THF under an inert atmosphere. 1.3 ml of nBuLi (1.6 N in hexane) was added at -45°C. After 30 min at this temperature, 0.195 g (1 mmol) of N-benzylidene benzylamine in 3 ml of THF was added dropwise to give a deep purple solution. After 30 min the solution was cooled to -50°C and a solution of 3 mmol of the electrophile in 3 ml of THF was added in 6 min. The crimson coloration disapeared before the end of the addition. After 30 min, 0.11 g of triethylamine in 1 ml of THF was added, then the mixture was allowed to warm up to room temperature. After addition of Et_2O (15 ml), the reaction mixture was washed twice by 10 ml of water, then by 21 ml of aqueous 0.1 N HCl. The organic layer was treated by 5 ml of aqueous 1 N HCl for 15 min. The acidic layer was separated, water was removed by evaporation to give the aminoester hydrochloride which was purified by vegetal charcoal treatment and was dried under vacuum on P_2O_5.

Enantioselective alkylation. General procedure :
1 mmol of the Schiff Base **1** in 7 ml of dry THF was added at -72°C to a solution of lithium diisopropylamide preformed in the usual way from 1.1 mmol of diisopropylamine in 5 ml of THF and 1 mmol of nBuLi (Aldrich 1.5 N in hexane). The temperature and the time for complete deprotonation was determined in preliminary assays by ^{1}H NMR after quenching samples of the reaction medium by D_2O . Then, 1.2 mmol of the alkylating reagent in 6 ml of anhydrous THF was added in 5 min followed after 10 min at this temperature by 12 mmol of HMPA in 2 ml of THF. The resulting reaction medium was stirred 10 min at -72°C and then placed at the desired temperature. After complete alkylation (VPC or HPLC determination ; temperature and time of contact were given in table 2 and 3), the solution was diluted by 50 ml of Et_2O, washed successively with 10 ml aqueous $NaHCO_3$, 5ml water, 3x25 ml of 4 M aqueous NH_4Cl and 2x10 ml water.
For the methylation of **1** (R^1 = R^2 = Ph; R= H) the ether extracts were dried with $MgSO_4$ and the corresponding iminoester was analyzed by HPLC (solvent 1.4% dioxane in hexane). In the other cases, the ether phase was treated with 8 ml of 0.2 N HCl during 1 h and the aminoester hydrochloride was then hydrolysed under reflux after addition of 20 ml of 6 N HCl. After cooling, the solution was evaporated to dryness and the product was chromatographied on Amberlyst 15 ion-exchange resin column (elution 3.5 N NH_4OH).

Enantioselective protonations : for deracemization procedure see ref. 10c

Racemic deconjugation of 5b E (table 5, entry 7)
To a solution of lithium diisopropylamide, prepared from 4.4 mmol of nBuLi and 0.6g (5.9 mmol) of diisopropylamine in 9 ml of THF at -10°C, was added dropwise at -50°C 0.62g (2.2 mmol) of 5b E in 6 ml of THF. After 30 min, 1.2g (20 mmol) of AcOH in 6 ml of THF was rapidly added at -70°C, stirred 15 min and allowed to warm to room temperature. The mixture was diluted with 20 ml of Et_2O, washed twice with $NaHCO_3$ saturated aqueous solution, water, dried over $MgSO_4$ and evaporated in vacuo to yield 0.62g (quant. yield) of crude product: 7b / 5b Z = 60 / 40 determined by NMR.
7b ^1H NMR : 3.7 (3H, s) ; 4.65 (1H, d) ; 5-5.4 (2H,m) ; 5.9-6.5 (1H, m).
The crude product in 15 ml of Et_2O was rapidly extracted with 1 N HCl (4x5 ml), washed with Et_2O (3x10ml) and evaporated in vacuo at T° < 50°C. Then 6 N HCl (5 ml per mmol) was added and refluxed for one hour. After cooling, the solution was washed with $CHCl_3$ (3x5ml), evaporated to dryness and treated with activated charcoal (30 min). After filtration and evaporation, the product was chromatographied on Amberlyst 15 ion -exchange resin column (elution with 3.5 N NH_4OH) to yield 85.9 mg (Y= 38% from 5b E) of (+/-) vinylglycine. NMR analysis confirmed the complete disappearance of 7b in ether solutions, and the absence of α-ketobutyrate resulting from 5b Z hydrolysis.

Enantioselective deconjugation of 5b E (table 5, entry 12) :
The deconjugation procedure for 1.1 mmol of 5b was realized with 5 mmol of (2R, 3R) DPTA in 3 ml of THF at -70°C as proton donor. The crude mixture (7b / 5b Z = 30 / 70) was analyzed by HPLC (solvent : 2% dioxane in hexane) e.e.= 24%. The enantiomeric excess was confirmed by polarimetry of the aminoacid.

For polarimetric determination the measured optical rotations were compared to the following ones (589 nm) : (S) Alanine methyl ester hydrochloride : $[\alpha]_{22}$ =+6.5 ° (1.6, MeOH) (33) ; (S) Ethylglycine : $[\alpha]_{20}$ =+7.94 ° (4, water) ; (S) Valine methyl ester hydrochloride : $[\alpha]_{21}$ =+15.5 ° (2, water) (34) ; (S) norleucine methyl ester hydrochloride : $[\alpha]_{17}$ =+21.1° (0.77, EtOH) (35) ; (S) methionine methyl ester hydrochloride : $[\alpha]_{25}$ =+26.1 ° (1, water) ;(R) phenylglycine methyl ester hydrochloride : $[\alpha]_{25}$ =-132 ° (1, MeOH) (36) ; (S) Phenylglycine ethyl ester hydrochloride : $[\alpha]_{20}$ =+91°(1, water) (37); (R) Vinylglycine: $[\alpha]_{20}$ = -93.8° (1.5, water) (27a).

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