Memory of Chirality in the Enantioselective Synthesis of β-Lactams Derived from Amino Acids. Influence of the Reaction Conditions

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Abstract: The asymmetric induction observed during cyclisation of *N*-benzyl-*N*-chloroacetyl-L-Phe derivatives to the corresponding *S*-enriched 2-azetidinones, ascribed to chirality memory, can be controlled by the appropriate choice of the base and solvent. Using the organic base BTPP, the ee values obtained in different solvents showed a good correlation with the AN solvent parameter, except for NMP. It seems that a combination of the solvent properties, rather than individual parameters, and the presence of enolate aggregates are decisive for final enantiomer distribution.

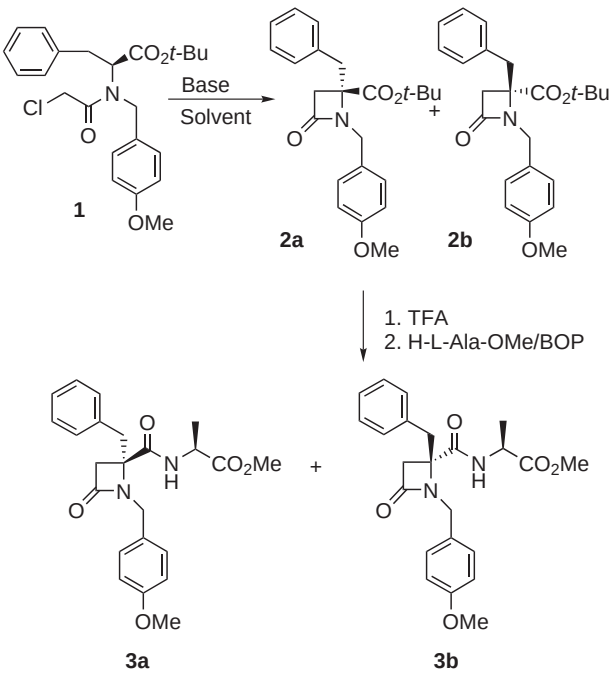
Key words: amino acids, memory of chirality, β-lactams, enantioselectivity, AN solvent-depedency

Nowadays a new stereoinduction principle, known as 'memory of chirality', is emerging as an alternative to other more classical methods in stereoselective synthesis. Memory of chirality describes a phenomenon in which the reactive intermediate is imprinted with the stereochemical memory of the starting substrate, even though the original stereogenic center is destroyed.[1] This means that the stereochemical outcome of the reaction can be controlled without using any external chiral source. Carbanions,[2] carbenium cations,[3] and different types of radicals[4] can be found among the reactive intermediates that are able to preserve the information of chirality. In the chemistry of amino acids, the memorized chirality has made an important contribution to the stereochemical course of some α-C-substitution reactions[2] and different photocyclisation processes.[4] Thus, the asymmetric alkylation of *N*-methyl- or *N*-Mom-*N*-Boc-L-amino acids and the intramolecular stereoselective aldol cyclisation of 1-(3-oxobutyryl) derivatives of Pro, and their 4-oxa and 4-thia analogues, are assumed to proceed via chiral nonracemic enolate intermediates.[2b–g]

In this context, we have recently reported that the base-promoted cyclisation of *N*-benzyl-*N*-chloroacetyl derivatives of L-Phe affords the corresponding 4-benzyl-4-alkoxycarbonyl-2-azetidinones with modest selectivity towards the preferential formation of the 4-(*S*) enantiomer.[5] In this preliminary study, in which the ee of the formed β-lactams were indirectly determined by measuring the diastereoisomeric ratio (RP-HPLC) of dipeptide derivatives (as in Scheme 1, compounds **3**), we found that the selectivity of the enolate-mediated cyclization is base and solvent dependent.

To better understand the elements governing the phenomenon of the memory of chirality in the β-lactam ring formation, we decided to initiate a detailed study on the influence of several reaction variables (base, solvent, temperature and concentration) on the selectivity of the intramolecular cyclization. For such purpose, the L-Phe-*O*-*t*-Bu derivative **1** has been selected as a model substrate, following the synthetic protocol depicted in Scheme 1. Now, to determine the enantioselectivity of the reaction, additionally to the preparation of the diastereoisomeric dipeptides **3**, the HPLC separation of the enantiomeric azetidinones **2a**,**b** has been achieved by means of a non-commercial chiral stationary phase, consisting of mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose covalently bonded to allylsilica gel.[6,7]

From the data shown in Table 1, it can be observed that the ratio of enantiomers **2a**:**2b**, directly measured by chiral HPLC, is very similar to the ratio of diastereoiso-



Scheme 1

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mers **3a**:**3b (**RP-HPLC), obtained after derivatization of compounds **2**. In general, the ratio of the major isomers was slightly higher in the dipeptide series (1–5%). The small differences in selectivity found between direct and indirect methods could be attributed to the existence of some kinetic resolution (2.5% on average) during dipeptide derivatives formation.

To study the influence of the base on the selectivity,[8] and in addition to Cs_2CO_3 and NaH,[5] different types of bases were selected, namely a lithium amide (LHMDS), three alkaline hydroxides (NaOH, KOH, CsOH) and three organic bases with different strength and nucleophilic character (DMAP, BTPP, BEMP).[9,10] After a preliminary exploration, DMAP and LHMDS were discarded since they did not lead to the formation of the expected β-lactam.[11,12] In contrast, the cyclization to the 2-azetidinone ring can be promoted by aqueous or solid hydroxides, under phase-transfer conditions, and by the soluble non-nucleophile phosphazene bases. Using toluene as solvent, low to moderate yields were obtained, due to the high degree of O-alkylation.[5] Under these conditions, the best selectivity was found for the organic base BTPP, followed by solid CsOH, while slightly lower ee were found for aqueous NaOH and KOH (Table 1). Compared to previous results, the selectivity found for BTPP/toluene was similar to that obtained with NaH/MeCN and lower than that originated by Cs_2CO_3/MeCN.[5] For ease of synthesis and workup, BTPP was selected to gain further insight into the significance of the solvent on the selectivity. Using this base, the reaction was readily accomplished in a variety of solvents, including low dielectric media as well as highly polarized solvents, with the best yield obtained for the reaction in MeCN (Table 1). Concerning the selectivity, it is interesting to note that quite different solvents, such as dichloromethane (CH_2Cl_2) and MeCN gave rather similar enantioselectivities.[13] On the other hand, solvents with very close dielectric constants as *N*-methyl-2-pyrrolidinone (NMP) and MeCN or DMF resulted in very different asymmetric inductions. A similar behaviour was observed for the reactions carried out with BEMP as base (compare entries 5, 8 and 9 with 11, 12 and 13, respectively). Clearly, lower ee values were found for the reactions carried out in NMP. Moreover, while a combination of BEMP with NMP resulted in almost racemic compounds, in the reaction with BTPP/NMP the sense of the asymmetric induction was reversed. Considering not only the selectivity, but also the rate of alkylation and the yield in the β-lactam, CH_2Cl_2 and MeCN were the solvents of choice. From these results it is clear that the properties intrinsic to the solvent medium are decisive for affecting the enantioselectivity, although a good correlation of the enantiomeric excesses and individual solvent parameters (ε, α, π*)[14] could not be found. However, setting NMP and butanone aside,[15] the solvent-dependent selectivity correlated excellently with the Gutmann's acceptor number (AN),[16] a solvent parameter that takes into account a combination of solvent properties like polarity, polarizability, and hydrogen bonding properties (Figure 1). The rationale for the particular behavior of NMP could be found in the polar coordinating nature of this solvent that could break up possible intermediate aggregates.[17,18] To clarify this point, we studied the influence of different alkaline iodides on the selectivity of the cyclisation in NMP (Table 2). It is known that alkaline halides can form mixed enolate aggregates, and they are often employed for increasing the degree of asymmetric induction in alkylation reactions.[19] Under BTPP/NMP conditions, the use of LiI as additive restored the preferential formation of the *S*-enriched product, probably through coordination of the Li-atom to the enolate intermediate (up to 40% increase in the *S*-selectivity). The choice of the cation of the additive also proved to be important. Thus, NaI gave similar selectivity as LiI while KI and CsI were less effective. In the

Table 1 Influence of the Base and Solvent on the Selectivity of the Cyclization of L-Phe-*O*-*t*-Bu Chloroacetyl Derivative **1**

Entry	Base	Solvent	Yield (%)[a]	**2a**:**2b**[b] (ee)	**3a**:**3b**[c] (de)
1	25% NaOH	Toluene[d]	59	64:36 (28)	67:33 (34)
2	25% KOH	Toluene[d]	37	62:38 (24)	66:34 (32)
3	$CsOH·H_2O$	Toluene[d]	35	66:34 (32)	69:31 (38)
4	BTPP	Toluene	28	68:32 (36)	73:27 (46)
5	BTPP	DCM	59	74:26 (48)	74:26 (48)
6	BTPP	THF	28	69:31 (38)	–
7	BTPP	Butanone	46	68:32 (36)	72:28 (42)
8	BTPP	NMP	56	43:57 (14)[e]	42:58 (16)[e]
9	BTPP	MeCN	73	76:24 (52)	79:21 (58)
10	BTPP	DMF	49	73:27 (46)	–
11	BEMP	DCM	65	75:25 (50)	75:25 (50)
12	BEMP	NMP	52	51:49 (2)	52:48 (4)
13	BEMP	MeCN	81	76:24 (52)	79:21 (58)

[a] Isolated compounds.
[b] Measured by chiral HPLC.
[c] Measured by RP-HPLC after transformation into dipeptide derivatives **3**.
[d] Tetrabutylamoniun bromide (10%) was used as phase transfer catalyst.
[e] Major isomer has *R*-configuration.

BEMP/NMP reaction, the addition of LiI led to a selectivity degree analogous to that obtained in BEMP/MeCN (compare Table 1, entry 13, and Table 2, entry 7). In contrast, addition of LiI to the BTPP/MeCN reaction lowered to some extent the selectivity, probably as a consequence of a change in the initial enolate structure. At the same time, in this latter case the addition of LiI had a detrimental effect on the β-lactam yield.

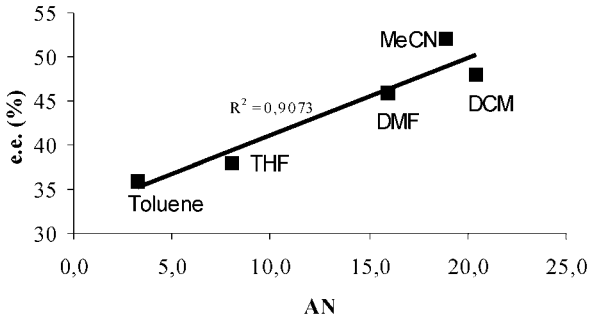

Figure 1 Plot of the stereoselectivity from the cyclisation of compound **1** in different solvents versus the 'solvent aceptor numbers' (AN) taken from ref.[16b]

Table 2 Influence of Additives on the Selectivity of the Cyclization of L-Phe-*O*-*t*-Bu Chloroacetyl Derivative **1**

Entry	Base	Solvent	Additive	Yield (%)[a]	**2a:2b**[b]	ee
1	BTPP	NMP	–	56	43:57	14[c]
2	BTPP	NMP	LiI	70	63:37	26
3	BTPP	NMP	NaI	31	62:38	24
4	BTPP	NMP	KI	31	57:43	14
5	BTPP	NMP	CsI	37	53:47	6
6	BEMP	NMP	–	52	51:49	2
7	BEMP	NMP	LiI	52	75:25	50
8	BTPP	MeCN	–	73	76:24	52
9	BTPP	MeCN	LiI	18	73:27	46

[a] Isolated compounds.
[b] Measured by chiral HPLC.
[c] *R*-Enriched product.

Taking into account that concentration is another variable that could influence the aggregation stage, we next investigated the selectivity of the cyclization at different concentrations. As shown in Table 3, the slight increase and decrease in the asymmetric induction observed for a double and a half concentrated reactions, respectively, could be attributed to high and low ordered transition-states. Autocatalysis by the optically active starting material, through formation of mixed aggregates with the enolate, could be another possible rationale for these minor differences.

While configurational stability of enolates generated from *N*-methyl- or *N*-Mom-*N*-Boc-L-amino acids was shown to be markedly labile to temperature,[2e] the effect of this variable was negligible in the cyclization to the β-lactam ring, indicating a different behavior between inter- and intramolecular alkylation processes that occur with memory of chirality.

Table 3 Influence of the Temperature and Concentration on the Selectivity of the Cyclization of L-Phe-*O*-*t*-Bu Chloroacetyl Derivative **1** (BTPP, MeCN)

Entry	Temp (°C)	Concentration (mM)	Yield (%)[a]	**2a**:**2b**[b]	ee
1	25	0.28	73	76:24	52
2	25	0.56	77	78:22	56
3	25	0.14	80	75:25	50
4	0[c]	0.28	65	76:24	52
5	60	0.28	65	74:26	48

[a] Isolated compounds.
[b] Measured by chiral HPLC.
[c] Below this temperature the reaction did not appreciably proceed.

We have shown that the memory of chirality observed during cyclization of *N*-chloroacetyl L-Phe derivatives to 2-azetidinones is highly dependent on the base and solvent used, while temperature and concentration have negligible effects.[20] The ee values were determined by two alternative methods with seemingly minor deviations between them, a direct measure of enantiomer ratios using chiral HPLC (non-commercial column) or in an indirect manner, after derivatisation to the corresponding dipeptide analogues. The superior levels of reaction efficiency and selectivity observed in BTPP(BEMP)/MeCN, BTPP(BEMP)/CH_2Cl_2 and BTPP/NMP/LiI prompted us to select these reaction conditions, along with the previously reported Cs_2CO_3/MeCN, for further exploration about the importance of the amino acid substituents on the memory of chirality phenomenon. Work in this direction is ongoing in our laboratory.

Acknowledgment

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(7) Column OL-389. Eluent: hexane/acetone (96:4). Flow rate: 1.5 mL/min. UV detection at 220 nm. Isomer **2a**: t_R = 7.77 min. Isomer **2b**: t_R = 9.07 min.

(8) A general procedure was as follows: Compound **1** (83 mg, 0.19 mmol) was dissolved in the corresponding solvent (0.7 mL) and treated, at r.t. and under Ar atmosphere, with the appropriate base (0.28 mmol). The reaction was monitored by TLC until complete disappearance of the starting material. The solution was evaporated, redissolved in EtOAc, washed with H_2O, and dried over Na_2SO_4. After evaporation, the resulting residue was purified on a silica gel column using a gradient from 20 to 30% of EtOAc in hexane. The obtained compound **2ab** was directly evaluated by chiral HPLC, or transformed into dipeptide derivatives **3a** and **3b** as described (ref.[5]). For the phase transfer reactions, 3 equiv of NaOH and KOH, and 10 equiv of CsOH were respectively used.

(9) BTPP: *tert*-Butylimino-tri(pyrrolidino)phosphorane. BEMP: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro1,3,2-diazaphosphorine.

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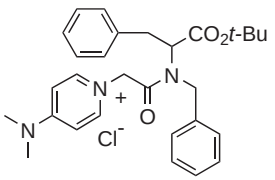

4

Figure 2

Selected data for compound **4**: HPLC: t_R = 10.74 min [50:50, H_2O/MeCN (0.05%TFA)]. ^{1}H NMR (300 MHz, $CDCl_3$): major rotamer δ = 8.09 (d, 2 H, *J* = 7.8 Hz, pyridine), 7.32–7.12 (m, 10 H, Ph), 6.68 (d, 2 H, *J* = 7.8 Hz, pyridine), 5.46 (d, 1 H, *J* = 16.8 Hz, CH_2N^+), 5.33 (d, 1 H, *J* = 16.8 Hz, CH_2N^+), 4.72 (d, 1 H, *J* = 17.2 Hz, N-CH_2), 4.39 (dd, 1 H, *J* = 8.8, 6.2 Hz, α-H), 4.25 (d, 1 H, *J* = 17.2 Hz, N-CH_2), 3.25 (dd, 1 H, *J* = 14.9, 6.2 Hz, β-H), 3.17 (s, 6 H, NMe_2), 3.07 (dd, 1 H, *J* = 14.9, 8.8 Hz, β-H), 1.31 (s, 9 H, *t*-Bu). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer δ = 168.29 (COO), 166.07 (CON), 156.34 (4-C, pyridine), 143.68 (2-C, 6-C, pyridine), 137.35, 135.32, 129.29, 128.91, 128.86, 127.91, 127.59, 126,79 (Ph), 107.14 (3-C, 4-C, pyridine), 82.22 (C, *t*-Bu), 63.09 (α-C), 58.71 (CH_2N^+), 51.41 (N-CH_2), 40.48 (CH_3N), 35.53 (β-C), 27.92 (CH_3, *t*-Bu). MS (ES, positive mode): 475.6 (M^+ + 1).

(12) Reaction of chloroacetyl derivative **1** with LHMDS afforded pyrrolidinone **5**, which was characterized as its methoxy derivative **6** after treatment with diazomethane. The formation of compound **5** could be attributed to the initial generation of the amide enolate and a Dieckmann-type condensation of this enolate with the ester group, followed by enolisation of the resulting ketone (Figure 3).

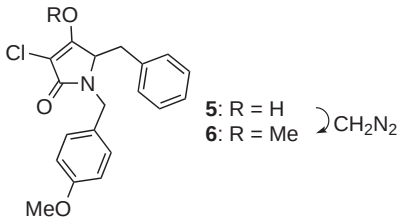

Figure 3

Selected data for compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (m, 3 H, Ph), 7.05 (m, 2 H, Ph), 7.00 (d, 2 H, *J* = 8.6 Hz, Pmb), 6.80 (d, 2 H, *J* = 8.6 Hz, Pmb), 5.18 (d, 1 H, *J* = 15.1 Hz, 1-CH_2), 4.16 (s, 3 H, OMe), 3.93 (dd, 1 H, *J* = 5.4, 4.1 Hz, 5-H), 3.83 (d, 1 H, *J* = 15.1 Hz, 1-CH_2), 3.78 (s, 3 H, OMe), 3.13 (dd, 1 H, *J* = 14.3, 4.1 Hz, 5-CH_2), 2.89 (dd, 1 H, *J* = 14.3, 5.4 Hz, 5-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.4 (2-C), 164.22 (4-C), 159.07, 134.95, 130.05, 129.45, 129.04, 128.74, 127.32, 114.03 (Ar), 97.91 (3-C), 59.05 (OMe), 58.65 (5-C), 55.21 (OMe), 43.88 (5-CH_2), 35.47 (1-CH_2). MS (ES, positive mode): 358.2 (M^+ + 1).

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