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β-Lactams derived from phenylalanine and homologues: effects of the distance between the aromatic rings and the α-stereogenic reactive center on the memory of chirality

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Abstract—The enantioselectivity in the base-promoted cyclization of *N*-chloroacetyl derivatives of Phe, Phg, and Hph is dependent on the side-chain length, with the best results for Phg analogues (up to 74% ee). In contrast, shortening of the N-substituent, from a (*p*-methoxy)benzyl group to a (*p*-methoxy)phenyl moiety, led to a decrease in selectivity.

Processes occurring with memory of chirality are characterized by an initial unique stereogenic element (chiral center or chiral axis) that is destroyed during the generation of the corresponding reactive intermediates, but these intermediates are able to retain the information about the configuration of their precursors to transfer the chirality to final compounds.[1] Most of memory of chirality transformations can be found among the chemistry of α-amino acids,[2–21] with the α-alkylation reaction, initially published by Fuji's group, as the most extensively studied process.[12–21] A few years ago, we described the first intramolecular version of this procedure during the transformation of several *N*-benzyl-*N*-chloroacetyl amino acids to the corresponding 2-azetidinones.[22,23] From our previous results, we have demonstrated that the stereoselectivity, due to memory of chirality, is highly dependent on the substituents of the starting *N*-chloroacetyl derivative, with the amino acid side-chain as the principal stereodirecting element.[24] We have also determined the critical importance of the base and solvent for final enantiomer distribution,[25] and provided the first evidence for TADDOL as a memory of chirality enhancer in the case of aromatic amino acids.[26] Fuji's group has proposed a chiral non racemic enolate with restricted rotation around the C–N axis as the crucial intermediate.[1b] Similar reactive species were assumed to rationalize the observed selectivity in the amino acid-derived β-lactam synthesis. Thus, the presence of aromatic (Phe, Tyr), heteroaromatic (Trp), ramified-aliphatic (Leu, Val), and β-carboxylate-derived (Asp) side-chains favored memory of chirality in this reaction.[24]

Now, to gain further insight into the features governing the selectivity due to memory of chirality during β-lactam ring formation, in this paper we investigate the influence of the distance between the side-chain phenyl ring and the α-chiral reactive center, by comparison of the result obtained for Phe (**I**, $n = 1$) with those got for its lower and higher homologues, Phg (**I**, $n = 0$) and Hph (**I**, $n = 2$), respectively. We also explore the consequences derived from shortening the distance between the *p*-methoxyphenyl ring and the nitrogen atom (**I**, $m = 0, 1$). These two modifications should have important effects in the rotational freedom around the C–N bond in the respective enolate intermediates. In addition, the modification of selectivity by TADDOL in the cyclization of Phe homologues was also investigated, since the essential π–π interactions are supposed to be greatly influenced by the distance of the aromatic side-chain phenyl ring to the reactive center.

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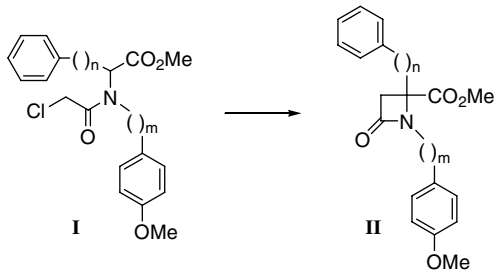
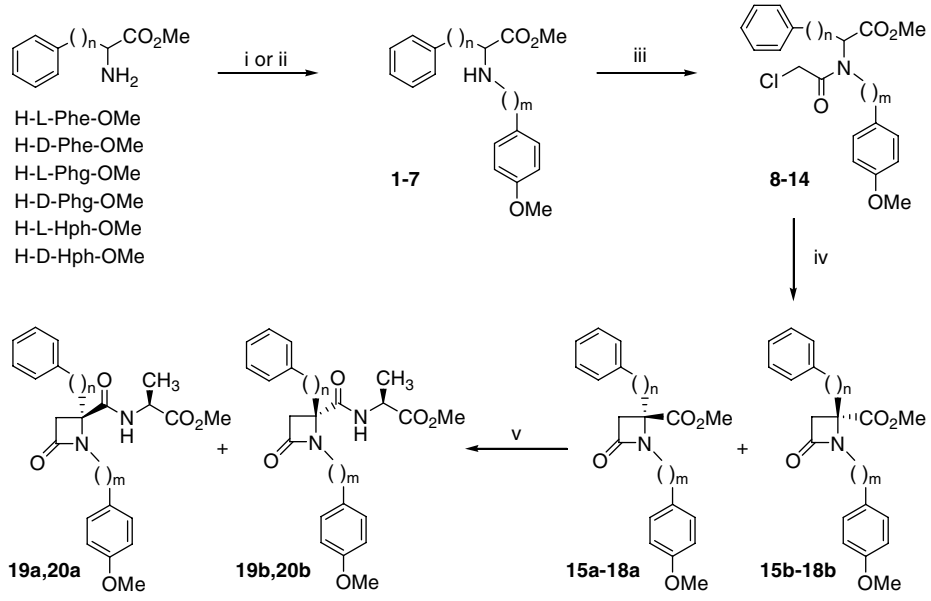


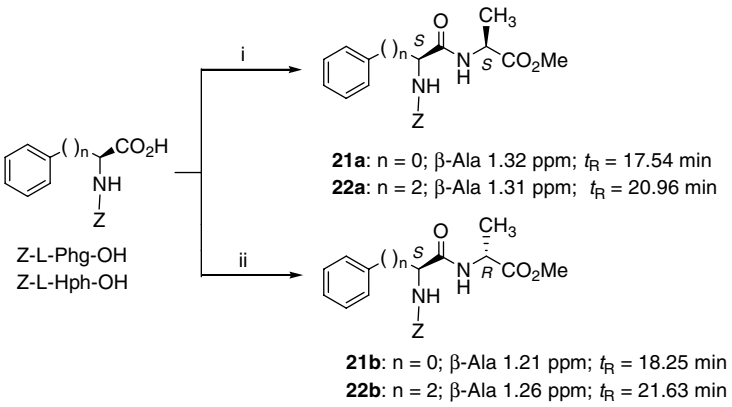
As indicated in Scheme 1, the reductive amination of commercially available α-amino esters with anisaldehyde afforded the corresponding *N*-(*p*-methoxy)benzyl-substituted analogues **1**–**6** ($m = 1$).[27] The synthesis of the optically active *N*-(*p*-methoxy)phenyl derivative **7** ($m = 0$) was achieved, although in low yield, by reaction of H–Phe–OMe with (*p*-methoxy)phenylboronic acid, catalyzed by $Cu(OAc)_2$.[28–30] The required chloroacetyl derivatives **8**–**14** were conveniently prepared by treatment of compounds **1**–**7** with chloroacetyl chloride, in the presence of propylene oxide as HCl scavenger. Cyclization of the chloroacetyl derivatives **8**–**13** to β-lactams **15**–**17** was easily achieved by treatment with BTPP as base in acetonitrile.[31–33] It is worth mentioning that a similar cyclization of the *N*-(*p*-methoxy)phenyl analogue **14** resulted in a complex mixture of reaction, from which the expected β–lactam **18** was isolated in low yield (30%).[34]

The stereoselectivity in the formation of β-lactams **15** and **18** was measured by chiral HPLC, while the efforts to determine the ees by this method in **16** and **17** were ineffective. This problem was circumvented by measuring the diastereoisomeric ratio, after derivatization to dipeptide derivatives **19** and **20**.[23,25] The configuration at C-4 position in these dipeptide derivatives was tentatively assigned on the basis of ^1H NMR chemical shifts of the β-Ala protons, which appeared at higher field in the heterochiral isomers than in the homochiral ones, as previously established for Phe-derived β-lactams.[23,35] Thus, the major isomer of **19**, coming from the D-Phg-derived azetidinone **16**, showed a signal for the β-Ala methyl protons at 1.07 ppm, while the same signal for the minor diastereoisomer appears at 0.99 ppm. Considering the change in the order of prelation of groups for Phg β-lactam derivatives, the major and minor isomers were assigned as the *S*,*S* (**19b**) and the *R*,*S* (**19a**) diaste-



Compounds	Starting amino acid	n	m
1,8,15	H-L-Phe	1	1
2,9,15	H-D-Phe	1	1
3,10,16,19	H-L-Phg	0	1
4,11,16,19	H-D-Phg	0	1
5,12,17,20	H-L-Hph	2	1
6,13,17,20	H-D-Hph	2	1
7,14,18	H-L-Phe	1	0

Scheme 1. Reagents and conditions: (i) for $m = 1$, $MeOC_6H_4CHO/NABH_4/MeOH$; (ii) for $m = 0$, $MeOC_6H_4B(OH)_2/Cu(OAc)_2/TEA/CH_2Cl_2$; (iii) $ClCH_2COCl$/propylene oxide/CH_2Cl_2; (iv) BTPP/MeCN (with or without (−)-TADDOL as additive); (v) (a) 2N NaOH/MeOH; (b) H-L-Ala-OMe × HCl/BOP/TEA/THF.



Scheme 2. Reagents and conditions: (i) H-L-Ala-OMe × HCl/BOP/DIEA/THF; (ii) H-D-Ala-OMe × HCl/BOP/DIEA/THF.

reoisomers, respectively. In contrast, in the L-Hph-derived mixture **20**, the major component was assigned as the heterochiral *R*,*S* diastereoisomer **20b** ($\delta_{CH_3} = 0.98$ ppm), and the minor as the *S*,*S*-configured isomer **20a** ($\delta_{CH_3} = 1.08$ ppm).

The dipeptide rule we have used for the configurational assignment of **19** and **20** is well established for Phe-derived dipeptides but, to the best of our knowledge, no indication about its generality to Phe homologues is described. Therefore, to be confident with the above assignements, a series of Z-L-Xaa-L-Ala-OMe and Z-L-Xaa-D-Ala-OMe dipeptide derivatives (Xaa = Phg, Hph) were prepared and analyzed by ^{1}H NMR and HPLC (Scheme 2). From the chemical shifts of the β-methyl protons and the retention times in HPLC for each diastereomeric pair, it can be concluded that Phg- and Hph-derived dipeptides follow the same general rule than Phe analogues.[36,37] As it can be seen in Scheme 2, the β-methyl protons are more shielded in the heterochiral diastereoisomers **21b** and **22b** than in their homochiral counterparts **21a** and **22a**. Also as expected,[36] the longest HPLC retention times were found for the heterochiral dipeptides of each pair.

The selectivity in the cyclization of Phe derivatives and its homologues to the corresponding β-lactams are shown in Table 1. The short distance between the phenyl ring and the α-C in L-Phg derivative **10** is expected to enhance the rigidity of the corresponding enolate intermediate with respect to the L-Phe analogue, thus increasing the selectivity (compare entries 1–5). In fact, a considerable raise in the ee value was observed when passing from L-Phe (34%) to L-Phg (70%). In both cases, isomer **a** was the major enantiomer formed, indicating similar geometries of the respective intermediates. Considering the high tendency of Phg derivatives to racemize,[38] and the strong basic reaction conditions employed, it may be possible that main isomeric β-lactam **16a** were formed after a thermodynamically favored equilibration process of the starting chloroacetyl derivative **10**. If that is the case, the cyclization of enantiomeric D-Phg derivative **11** must provide exactly the same result as its L-Phg counterpart. However, if memory of chirality applies, isomer **16b** should be the main product of the reaction. As recorded in entry 6 of Table 1, treatment of D-Phg derivative **11** with BTPP afforded β-lactam **16b** in 74% ee, corroborating that the cyclization of Phg-derived compounds is driven by the configuration of the starting amino acid derivative and therefore, memory of chirality operates.

As expected, an increase in the aromatic side-chain length, as in Hph derivatives, which should favor the flexibility of the C–N bond, is associated to a decrease in the observed selectivity (compare entries 1 and 3–8

Table 1. Results of selectivity in the BTPP-induced cyclization of Phe-, Phg-, and Hph-*N*-chloroacetyl derivatives

Entry	Starting amino acid	*N*-Chloroacetyl derivative	*n*	*m*	Additive (10%)	Final β-lactam	Yield (%)[a]	**a:b**	ee (Config.)
1	H-L-Phe-OMe	**8**	1	1	—	**15**	68	67:33[b]	34 (*S*)
2					(−)-TADDOL		87	85:15[b]	70 (*S*)
3	H-D-Phe-OMe	**9**	1	1	—	**15**	70	31:69[b]	36 (*R*)
4					(−)-TADDOL		75	86:14[b]	72 (*R*)[d]
5	H-L-Phg-OMe	**10**	0	1	—	**16**	61	85:15[c]	70 (*R*)[d]
6	H-D-Phg-OMe	**11**	0	1	—	**16**	67	13:87[c]	74 (*S*)[d]
7					(−)-TADDOL		74	19:81[c]	62 (*S*)[d]
8	H-L-Hph-OMe	**12**	2	1	—	**17**	55	40:60[c]	20 (*R*)
9	H-D-Hph-OMe	**13**	2	1	—	**17**	51	59:41[c]	18 (*S*)
10					(−)-TADDOL		69	43:57[c]	14 (*R*)
11	H-L-Phe-OMe	**14**	1	0	—	**18**	30	64:36[b]	28 (*S*)
12					(−)-TADDOL		39	56:44[b]	12 (*S*)

[a] Yield of isolated compound.
[b] Measured by chiral HPLC according to our previous work (Ref. 24).
[c] Diastereomeric excesses measured after derivatization to the corresponding dipeptide derivatives **19** or **20**.
[d] In the Phg-derived β-lactams there is a change in the prelation of groups with respect to Phe and Hph analogues.

and 9). It is worth noting that, up to date, the Hph is the only amino acid in which isomer **b** (*R*) is mainly formed from the L-chloroacetyl derivative (entry 8), while isomer **a** (*S*) was the major component of the enantiomeric mixture in the D-Hph-derived β-lactam (entry 9).

Concerning the *N*-substituent, deletion of the methylene group of the *p*-methoxybenzyl moiety in the corresponding *N*-aryl derivative led to a slight decrease in the selectivity of the cyclization ($\Delta ee = -6\%$, compare entries 1 and 11).

Attempts to improve memory of chirality in the cyclization of Phe homologues and of the *N*-(*p*-methoxy)-phenyl-Phe derivative **14** by addition of TADDOL were unsuccessful, but interesting conclusions can be drawn from the results. To explain the enhanced selectivity in Phe derivatives (entries 2 and 4) we have proposed stabilizing interactions between the starting material and the chiral additive.[26] Main contacts were characterized by a hydrogen bond between one OH of TADDOL and the CO of the chloroacetyl group and by a π–π stacking interaction between the aromatic phenyl ring of the side-chain and a phenyl group of TADDOL. Shortening the side-chain length by one methylene group not only hinders the appropriate π–π contacts with TADDOL, but leads to inappropriate interactions that results in diminished selectivity, with a 12% decrease in the ee value. For D-Hph derivative ($n = 2$), the presence of TADDOL changed the selectivity to the main formation of enantiomer **b** (entry 10), restoring the same behavior than that observed for the corresponding D-Phe derivative (entry 4). This seems to suggest that for a given configuration, Phe and Hph derivatives interact with TADDOL in the same topographical manner.

In the presence of TADDOL, cyclization of the *N*-aryl derivative **14** resulted in a marked decrease in selectivity with respect to the same reaction without additive ($\Delta ee = -16\%$, compare entries 11 to 12). The same experiment with its benzyl analogue **8** led to a big increase of the ee value ($\Delta ee = 36\%$). These results seems to indicate that the *N*-Pmb group could also be directly implicated in the interaction with TADDOL, while the shorter *N*-Pmp moiety, far to be able to reproduce the favorable interaction with TADDOL, contributes to its destabilization. Therefore, our initial model of recognition by TADDOL should be fine-tuned by considering this possible new element of interaction.

In conclusion, we have established that the selectivity of the intramolecular alkylation of Phe homologues to the corresponding β-lactams is highly dependent of the aromatic side-chain ring/α-CH distance. The best results were found for the shorter Phg homologues ($n = 0$), which reached up to 74% ee, and were associated to a lower flexibility of the corresponding enolate intermediates, with high restricted mobility around the C–N bond. Although in less extent, the existence or not of a methylene linker between the *p*-methoxyphenyl group and the nitrogen atom is also important for the control of selectivity. Finally, the ability of TADDOL to modulate memory of chirality was also greatly influenced by the above indicated distances.

Acknowledgements

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32. (*4R,S*)-*1*-(*p-Methoxy*)*benzyl-4-phenyl-4-methoxycarbonyl-2-azetidinone* (**16**). Syrup. HPLC: $t_R = 8.29$ min (A:B = 35:65). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (m, 5H, C_6H_5), 7.07 (d, 2H, $J = 8.9$, C_6H_4), 6.70 (d, 2H, $J = 8.9$, C_6H_4), 4.58 (d, 1H, $J = 15.3$, CH_2Pmb), 4.23 (d, 1H, $J = 15.3$, CH_2Pmb), 3.70 (s, 3H, OMe), 3.67 (d, 1H, $J = 14.7$, 3-H), 3.54 (s, 3H, OMe), 3.06 (d, 1H, $J = 14.7$, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.94 (COO), 166.78 (CON), 158.75 (4-C Pmb), 136.41–113.63 (11C, Ar), 65.04 (4-C), 55.16 (OMe), 52.44 (OMe), 50.68 (CH_2Pmb), 45.31 (3-C). ESI-MS: 326.2 $(M+1)^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.15, H, 5.75, N, 4.65.
33. (*4R,S*)-*1*-(*p-Methoxy*)*benzyl-4-phenethyl-4-methoxycarbonyl-2-azetidinone* (**17**). Syrup. HPLC: $t_R = 5.01$ min (A:B = 45:55). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (m, 5H, C_6H_5 and C_6H_4), 6.85 (d, 2H, $J = 6.8$, C_6H_5), 6.78 (d, 2H, $J = 8.7$, C_6H_4), 4.40 (d, 1H, $J = 15.2$, CH_2Pmb), 4.23 (d, 1H, $J = 15.2$, CH_2Pmb), 3.71 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.18 (d, 1H, $J = 14.7$, 3-H), 2.81 (d, 1H, $J = 14.7$, 3-H), 2.28 (m, 3H, γ-H, β-H), 1.86 (m, 1H β-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.73 (COO), 166.13 (CON), 159.16 (4-C Pmb), 140.26-114.02 (11C, Ar), 62.39 (4-C), 55.25 (OMe), 52.37 (OMe), 45.65 (CH_2Pmb), 44.24 (3-C), 35.40 (γ-H), 30.23 (β-H). ESI-MS: 354.2 $(M+1)^+$. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.45, H, 6.75, N, 3.65.
34. Attempt to optimize this reaction using different bases (BTPP, BEMP, Cs_2CO_3) and solvents (MeCN, CH_2Cl_2, THF) were unsuccessful. (*4R,S*)-*4-Benzyl-4-methoxycarbonyl-1*-(*p-methoxy*)*phenyl-2-azetidinone* (**18**). Syrup. HPLC: $t_R = 4.16$ min (A:B = 50:50). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, 2H, $J = 6.8$, C_6H_4), 7.04 (m, 5H, C_6H_5), 6.84 (d, 2H, $J = 6.8$, C_6H_4), 3.75 (s, 3H, OMe), 3.44 (d, 1H, $J = 12.9$, 3-H), 3.40 (d, 1H, $J = 12.9$, 3-H), 3.07 (d, 1H, $J = 14.9$, 4-CH_2), 2.90 (d, 1H, $J = 14.9$, 4-CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.14 (COO), 162.54 (CON), 156.13 (4-C Pmp), 135.24–113.92 (11C, Ar), 61.85 (4-C), 55.29 (OMe), 52.90 (OMe), 44.98 (3-C), 36.36 (4-CH_2). ESI-MS: 326.4 $(M+1)^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.45, H, 5.65, N, 4.25.
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