Asymmetric Alkylation of 8-Phenylmenthyl *N*-[Bis(methylthio)methylene]glycinate Enolates. Synthesis of D- and L-α-Amino Acids from a Single Chiral Precursor†

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The herein described studies on the enolization and subsequent alkylation of the acyclic glycine title ester evidence the involvement of the kinetics of the alkylation step on the stereochemical outcome of the overall process, apart from that of the deprotonation sequence itself. Careful choice of reaction conditions allow for the selective obtention of α-amino acids either of the L- or the D-series without the need of changing the chiral inducer: deprotonation with LDA or ^{t}BuLi followed by reaction with alkyl triflates gives rise to the 2*R* α-amino acids, whereas the 2*S* isomers can be obtained by deprotonation with KO^{t}Bu followed by reaction with alkyl halides.

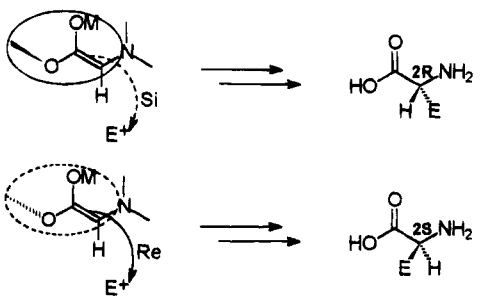
With the exception of glycine, α-amino acids bear a chiral center at carbon C2, most naturally occurring compounds belonging to the L-series (generally 2*S* configuration). Together with these, non-natural derivatives, both the L- and D-series, have shown promising biological activities[1] and have therefore been incorporated into the arsenal of therapeutic agents. Consequently, the last decade has seen the outburst of a plethora of well reviewed[2] syntheses of enantiomerically pure α-amino acids, among which the alkylations of chiral glycine enolates, in particular those derived from acyclic templates, have received special attention.

For these systems, the presence of a chiral inducer, which is to be removed after alkylation has occurred, should enforce chirality transfer by protecting one of the two diastereotopic faces of the trigonal planar enolate from attack. Steric congestion inhibits attack so that reagents approach from the less encumbered direction,[3] as depicted in Scheme 1.

Therefore, the stereochemical outcome of the alkylation, namely the obtention of either a 2*R* or 2*S* configuration on the final α-amino acid from a given enolate, will depend on the correct choice of the chiral auxiliary, enantiomerically (or even diastereomerically) related pairs of chiral inducers giving rise to opposite configurations.

However, it is well established that the stereochemistry of synthetic transformations which involve the use of chiral ester enolates, such as alkylations,[3] aldol condensations,[4] or sigmatropic rearrangements,[5] rely on the *E*- or *Z*-geometry of the C=C bond of the enolate.[6] Much effort has been therefore devoted to selectively obtain either the *E*- or the *Z*-isomers upon deprotonation of carboxylic acid derivatives[7] (Figure 1).

Scheme 1



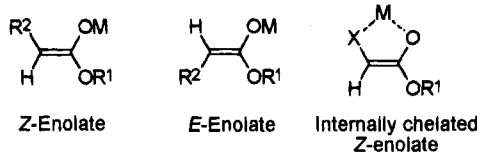


Figure 1.

Particularly, for the deprotonation of simple alicyclic esters, in the absence of chelating factors, it has been widely accepted that the most stable *Z*-isomer is the one obtained under thermodynamical control,[8] whereas the *E*-enolate prevails under pure kinetic conditions.[9] The enolization of esters containing α-heteroatoms has been

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(2) (a) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: Oxford, 1983. (b) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules using Amino Acids*; J. Wiley & Sons Inc.: New York, 1987. (c) Tetrahedron Symposia-In-Print No. 33: α-Amino Acid Synthesis, O'Donnell, M. J., Ed. *Tetrahedron* **1988**, *44*, (17). (d) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (e) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989. (f) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (g) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (h) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (i) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

(3) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon Press.: Oxford, 1991; Vol. 3, p 1.

(4) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press Inc.: New York, 1984; Vol. 3, p 111.

(5) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.

(6) The stereochemical descriptors *E* and *Z* are used in this context as recommended by Evans. See: Evans, D. A. in *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic Press Inc.: New York, 1984; Vol. 3, p 11.

(7) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Ed., Elsevier: Amsterdam, 1984; Part B, chapter 4, p 177. (c) Williard, P. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed., Pergamon Press.: Oxford, 1991; vol. 1, p 1. (d) Ganesan, K.; Brown, C. H. *J. Org. Chem.* **1994**, *59*, 2336.

(8) (a) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341. (b) Moreland, D. W.; Dauben, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2264.

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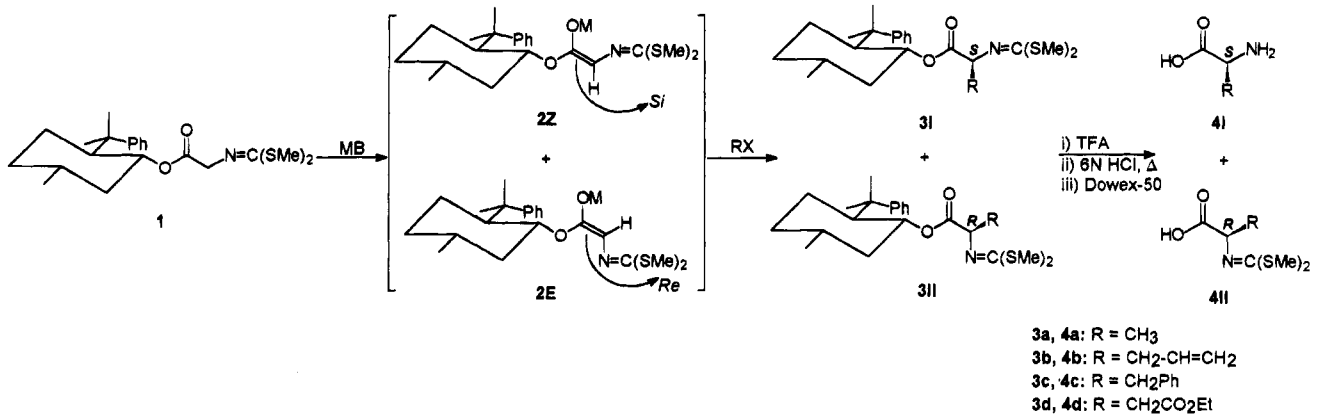
Scheme 2



comparatively less considered,[10] but a predominance of the *Z*-enolate as compared with the aforementioned cases has been noted, due to internal chelation of the metal with the lone electron pair on the heteroatom. However, the reactivity of the enolate is further complicated by the existence in solution of higher aggregated species.[11] Therefore, controlled experimental conditions both upon deprotonation and subsequent alkylation of chiral glycine-derived esters could help in providing an access to either the L- or the D-series of α-amino acids from a single optically pure alcohol as chiral inductor, provided a reliable tuning of the *E*- or *Z*-geometry of the aggregated enolates could be achieved.

We have been concerned with stereoselection on the alkylation of the less studied acyclic chiral-alcohol derived ester enolates of N-protected glycines.[12] Described herein is the study of the enolization and subsequent alkylation of the 8-phenylmenthyl ester[13,14] **1** and the transformation of the alkylation products **3** into both L- and D-α-amino acids **4** (Scheme 2).

Assignments of Configurations of Diastereomers 3(a–d)I and 3(a–d)II. The *S* configurations at carbon C2 of diastereomers **3(a–d)I** and *R* configuration at carbon C2 of diastereomers **3(a–d)II** was determined from the known configurations of the corresponding α-amino acids **4(a–d)I** and **4(a–d)II** obtained upon nonepimerizing acid hydrolysis (*vide infra*). The **I:II** ratios have been determined on the crude products using ^{1}H NMR (300 MHz) and the anisochronous SCH_3 (s) signals.

Results of Enolization and Subsequent Alkylation of Ester 1. 8-Phenylmenthyl *N*-[bis(methylthio)-methylene]glycinate (**1**) was obtained in 80% yield from 8-phenylmenthyl glycinate under PTC conditions [20 M NaOH/benzene (CS_2–MeI–TEBA)].[15] Deprotonations of **1** and alkylation of the corresponding enolates were carried out using various bases and alkylating agents under different reaction conditions, and the results are given in Table 1.

The inspection of these data reveals that methylation with MeI in THF (Table 1, entries 1–3) favored the formation of **3aII** when LDA, ^{t}BuLi, and BuLi were used as the base in the deprotonation step. This situation was reversed when $ZnCl_2$ (Table 1, entry 4) or DMPU (Table 1, entry 5) were added after enolization with LDA, which both favored isomer **3aI**. However, contrary to methylation, in the alkylations with allyl bromide, benzyl bromide, or ethyl bromoacetate after deprotonation with LDA in THF (Table I, entries 6–8) as well as in allyl bromide alkylation of the enolate generated with ^{t}BuLi in THF (Table I, entry 9), no diastereoselectivity at all was observed.

An increase of diastereoselectivity in favor of isomers **3II** was observed upon alkylation with sulfonates after deprotonation of **1** with LDA or ^{t}BuLi (Table I, entries 10–14), as compared with the corresponding halides (Table I, entries 1–9).

It has to be pointed out that, whereas alkylations with methyl iodide (Table 1, entry 2) and allyl bromide (Table 1, entry 9) of the lithium enolates generated from **1** and ^{t}BuLi gave rise to different **3I:3II** ratios, reaction with the corresponding triflates produced the same stereochemical result (Table 1, entries 12, 13). However, the same stereochemistry was obtained upon alkylation with MeI (Table 1, entry 2) and Me_2SO_4 (Table 1, entry 14) of the enolates generated using LDA as the base.

The addition of LiCl to the reaction medium either prior to (Table 1, entries 15–17) or after deprotonation (Table 1, entry 18) had a deleterious effect on the diastereoselectivity of the methylation reaction, the preference for the **3aII** isomer being diminished as compared with the results of methylation either with MeI

(9) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

(10) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099 and, references cited therein.

(11) (a) Galiano-Roth, A. S.; Kim, Y. J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. (b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624.

(12) In rigid systems it is relatively easy to predict the product. For conformationally flexible systems, however, one needs to consider the conformational population.

(13) For the use of (−)-8-phenylmenthol as chiral inducer see: (a) Comins, D. L.; Guerra-Weltzien, L.; Salvador, J. M. *Synlett* **1994**, 972 and references cited therein.

(14) The iminodithiocarbonate moiety has given better asymmetric induction levels in the alkylation of chiral amides than certain related imines. See: (a) Ikegami, S.; Uchiyama, H.; Hayama, T.; Yamaguchi, M. *Tetrahedron* **1988**, *44*, 5333. (b) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403. (c) Oppolzer, W.; Moretti, R.; Zhou, C. *Helv. Chim. Acta* **1994**, *77*, 2363.

(15) Alvarez-Ibarra, C.; Quiroga, M. L.; Martínez-Santos, E.; Toledano, E. *Org. Prep. Proc. Int.* **1991**, *23*, 611.

(16) In connection with π-facial diastereoselectivity in 8-phenylmenthyl derivatives, there is theoretical and spectroscopic evidence of a π–π stabilizing interaction of the conformer which has a *cis* relative disposition of the aromatic ring and the conjugated system of the side chain. See: (a) Maddaluno, J. F.; Gresh, N.; Giessner-Prettre, C. *J. Org. Chem.* **1994**, *59*, 793. (b) Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. *J. Org. Chem.* **1994**, *59*, 4068. (c) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859.

Table 1. Diastereoselective Alkylation of Ester 1[a]

entry	base	additive	1:additive	RX	3 (%[b])	3I:3II[c]
1	LDA	–	–	MeI	**3a** (90)	40:60
2	^{t}BuLi	–	–	MeI	**3a** (98)	30:70
3	BuLi	–	–	MeI	**3a** (98)	40:60
4	LDA	$ZnCl_2$	1.0:1.25	MeI	**3a** (50)	98:02
5	LDA	DMPU[d]	–	MeI	**3a** (75)	65:35
6	LDA	–	–	CH_2=$CHCH_2Br$	**3b** (80)	50:50
7	LDA	–	–	$PhCH_2Br$	**3c** (85)	50:50
8	LDA	–	–	EtO_2CCH_2Br	**3d** (80)	50:50
9	^{t}BuLi	–	–	CH_2=$CHCH_2Br$	**3b** (90)	50:50
10	LDA	–	–	MeOTf	**3a** (90)	25:75
11	LDA	–	–	FSO_3Me	**3a** (25)	20:80
12	^{t}BuLi	–	–	MeOTf	**3a** (98)	20:80
13	^{t}BuLi	–	–	CH_2=$CHCH_2OTf$	**3b** (80)	20:80
14	LDA	–	–	Me_2SO_4	**3a** (85)	40:60
15	LDA	LiCl	1:1.25[e]	MeI	**3a** (98)	45:55
16	LDA	LiCl	1:1.25[e]	MeOTf	**3a** (60)	40:60
17	LDA	LiCl	1:3.00[e]	MeOTf	**3a** (75)	40:60
18	LDA	LiCl	1:1.25[f]	MeOTf	**3a** (85)	30:70
19	KO^{t}Bu	–	–	MeI	**3a** (98)	90:10
20	KHMDS	–	–	MeI	**3a** (70)	90:10
21	KO^{t}Bu	–	–	CH_2=$CHCH_2Br$	**3b** (98)	95:05
22	KO^{t}Bu	–	–	$PhCH_2Br$	**3c** (98)	95:05
23	KO^{t}Bu	–	–	EtO_2CCH_2Br	**3d** (98)	95:05

[a] All reactions were carried out at −78 °C in THF with 1.25 equiv of base and 6.0 equiv of MeI. [b] Determined by integration of the ^{1}H NMR (300 MHz) of the crude products. Rest to 100% corresponds to unreacted ester 1. [c] **I:II** ratios have been determined on the crude products using ^{1}H NMR (300 MHz). [d] 30% of the total amount THF, added after enolization. [e] Added after enolization. [f] Added prior to enolization.

(Table 1, entry 1) or MeOTf (Table 1, entry 10) without added salts.

On the other hand, diastereoselectivity in favor of the **3I** isomers was high when potassium bases were used in the deprotonation of ester **1** (entries 19–23).

Discussion

In a first approach, the results of the alkylation of the lithium and potassium enolates of ester **1** with MeI can be conveniently accounted for by considering Ireland's enolization model,[9] allowing for a *cis* relative disposition between the phenyl ring of the chiral inducer and the enolate moiety.[13] Thus, deprotonation with hindered bases such as LDA or ^{t}BuLi (Table 1, entries 1, 2) under kinetic conditions[17,18] should give rise to enolate **2E** *via* transition state **A**‡ (M = Li, B = nitrogen, $L^1 = L^3 = {}^i$Pr, L^2 = none for LDA[19] and M = Li, B = carbon, $L^1 = L^2 = L^3 = CH_3$ for ^{t}BuLi[20]) devoid from the unfavorable 1,3-diaxial interaction present in transition states **B**‡. Alkylation of the *re* face, opposite to the chiral inducer, will then explain the formation of **3aII** (Scheme 3).

However, coordination of lithium with the lone electron pair on the sp^2-nitrogen of the iminodithiocarbonate moiety (transition state $\mathbf{B}^{\ddagger}_2$) should partially thermodynamically counterbalance the 1,3-diaxial interaction in $\mathbf{B}^{\ddagger}_1$, thus leading to enolate **2Z**.[21] Alkylation of the *si* face of **2Z** leads to formation of **3aI**.

In the case of BuLi[19] (Table 1, entry 3), being a less hindered base, transition states **B**‡ (M = Li, B = carbon, $L^1 = L^2 = H$, $L^3 = {}^n$Pr) will be comparatively less destabilized in comparison with those derived from ^{t}BuLi, thus leading to a decrease of the **3aI:3aII** ratio.

On the other hand, the use of KO^{t}Bu (Table 1, entry 19) should favor transition state **B**‡ (M = K, B = oxygen, $L^1 = L^2$ = none, $L^3 = {}^t$Bu) as a consequence of the $A_{1,3}$ interaction present in transition state **A**‡ and the small 1,3-diaxial interaction in **B**‡, the ^{t}Bu group being located far away from the iminodithiocarbonate moiety in a late transition state.[22] These observations also hold for the deprotonation with KHMDS[23] (Table 1, entry 20).

Transmetalation with $ZnCl_2$ of the initial *E*/*Z*- enolate mixture obtained using LDA as the base should lead to the chelation-controlled isomerization to a mixed cyclic Zn enolate,[24] from which diastereoselective formation of isomer **3aI** is expected (Scheme 4).

The low overall yield observed for this transformation (50%) could be ascribed to the lower reactivity of Zn enolates as compared with their alkaline counterparts.

In the presence of DMPU as cosolvent, an open transition state[9b] should account for the formation of **3aI** and **3aII** in nearly thermodynamic ratios. As a matter of fact, deprotonation of ester **1** with BuLi or ^{t}BuLi under thermodynamical conditions[25] gave rise to **3aI:3aII** ratios of 70:30 and 60:40, respectively. In a similar fashion, treatment of a **3aI:3aII** = 90:10 mixture with 1.25 equiv of KO^{t}Bu in ^{t}BuOH (20 °C, 48 h) gave rise to a 65:35 mixture.

However, keeping the same reaction conditions for the deprotonation step, the application of Ireland's enolization model alone does not account for the variations in stereoselectivity observed on passing from methylation with MeI of the lithium enolates of ester **1** (Table 1, entries 1–5) to their alkylation with bromides[26] (Table

(17) Enolization by addition of the ester **1** to a precooled (−78 °C) solution of the base. See ref 6.

(18) For an extension of Ireland's model to alkyllithiums see Solladié-Cavallo, A.; Csákÿ, A. G. *J. Org. Chem.* **1994**, *59*, 2585.

(19) LDA is, like BuLi, a dimer in THF solution. See: (a) Seebach, D.; Häsigg, R.; Gabriel, J. *Helv. Chim. Acta.* **1983**, *66*, 308. (b) Bauer, W.; Clark, T.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1987**, *109*, 970.

(20) ^{t}BuLi is monomeric in THF. See: Bauer, W.; Winchester, W. R.; Schleyer, P. von R. *Organometallics* **1987**, *6*, 2371.

(21) The absence of this stabilizing effect by means of chelation justifies the selective obtention of the *E*-enolates from simple alicyclic esters under these reaction conditions. See ref 9.

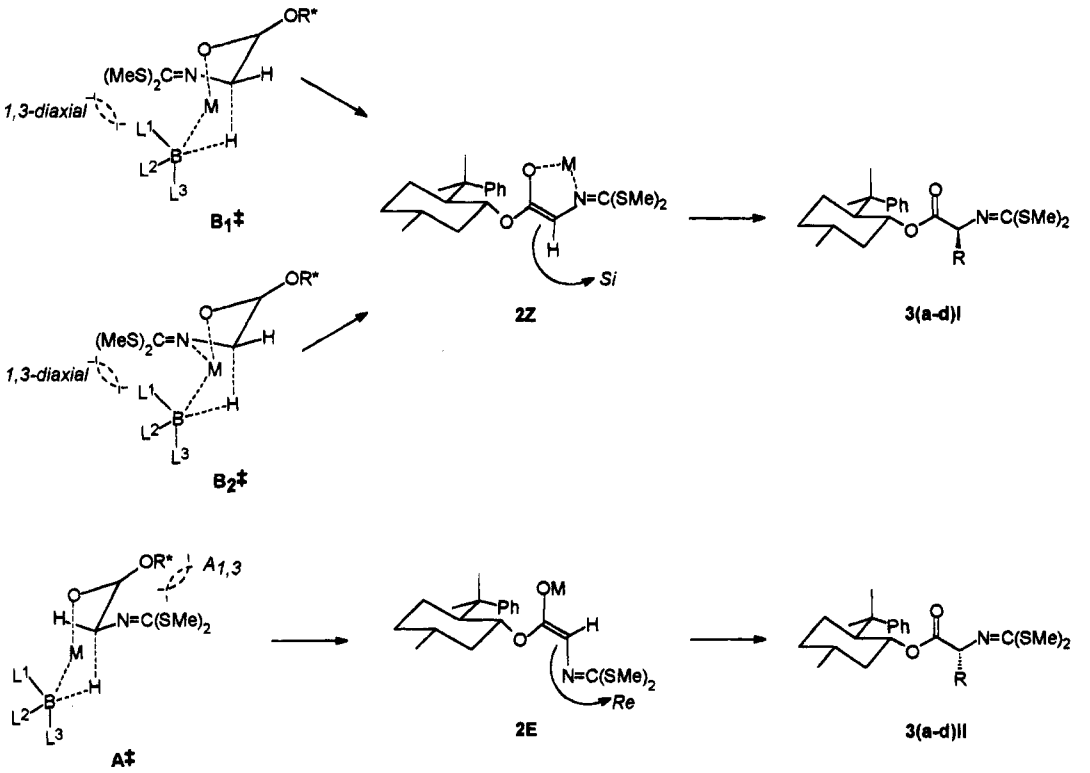
(22) Late transition states should be considered when dealing with the less basic KO^{t}Bu and KHMDS.

(23) For a deprotonation model of *tert*-butyl 2-methylpropionate with LiHMDS see Williard, P. G.; Liu, Q. Y. *J. Am. Chem. Soc.* **1992**, *114*, 348.

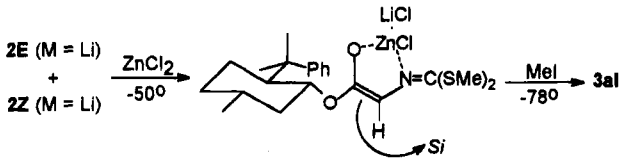
(24) van der Steen, F. H.; Boersma, J.; Spek, A. L.; van Koten, G. *Organometallics* **1991**, *10*, 2467.

(25) Enolization by slow addition of the base to a precooled (−78 °C) solution of ester **1**.

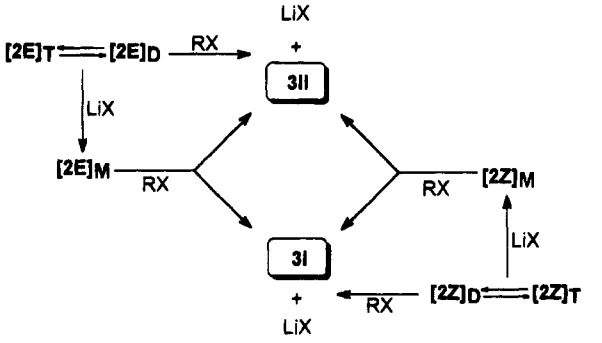
Scheme 3



Scheme 4



Scheme 5



1, entries 6–9) or sulfonates (Table 1, entries 10–14), as well as the effect of the addition of LiCl to the reaction medium (Table 1, entries 15–18). In fact, it has already been well established that metallic enolates in solution do not exist as monomers,[27] and there is increasing experimental evidence of the involvement of aggregated species in the enolate's formation and the enolate's reactivity. As pointed out by Seebach,[11b] the initially formed aggregated-enolated mixture can be modified by the formation of mixed aggregates of varied structures and stoichiometries derived whether from their reaction with added salts or with salts formed during the course of the alkylation reaction itself. Furthermore, aggregated *E*- and *Z*-enolates do not have the same reactivity,[28] and an initially formed ratio of *E*- and *Z*-enolates can be altered by kinetic resolution processes.

With these observations at hand, a diversion from the oversimplistic picture previuosly outline can be foreseen, the initially formed mixture of aggregated dimers and tetramers in equilibrium, $[\mathbf{2E}]_D \rightleftharpoons [\mathbf{2E}]_T$ and $[\mathbf{2Z}]_D \rightleftharpoons [\mathbf{2Z}]_T$, formed upon deprotonation, competitively reacting both: (a) with the corresponding electrophiles to render directly compounds **3I** and **3II** plus a salt (MX); and (b) with the salt (MX) formed in the alkylation step to give the mixed aggregates $[\mathbf{2E}]_M$ and $[\mathbf{2Z}]_M$, which should in turn react with the electrophiles, thus giving **3I** and **3II** in ratios which could differ from those directly obtained from the simply aggregated species (Scheme 5).

This competitive reaction path, namely formation of the mixed aggregates $[\mathbf{2E}]_M$ and $[\mathbf{2Z}]_M$, should be favored for the less reactive electrophiles, where slow direct alkylation of the initially formed lithium aggregates is to be presumed. Mixed-aggregate formation results in a loss of diastereoselectivity, as evidenced by the methylation experiments carried out in the presence of added LiCl (Table I, entries 15–18), which are to be compared with the corresponding essays without added LiCl (Table 1, enties 1–14). On the other hand, the highly reactive potassium enolates, as well as the cyclic-chelated Zn enolate, should be less prone to interaggregation processes than their lithium counterparts. Therefore, the best diastereoselectivities in favor of the **3II** isomers were obtained in the alkylation of the lithium enolates generated by deprotonation of ester **1** with LDA and ^{t}BuLi under kinetic conditions (mainly *E*-geometry for the

(26) A possible effect of the steric volume of the electrophile has been ruled out on the basis of the similarity of the results obtained in the alkylations of the enolates generated with LDA either with MeI or Me_2SO_4. See text.

(27) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Malgorzata, S.; Seebach, D. *Synthesis* **1993**, 1271.

(28) It has been observed that *E*-enolates are more reactive than *Z*-enolates. See: (a) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. (b) Banfi, L.; Bernardi, A.; Colombo, L.; Genari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784. See also refs 9b and 17.

Table 2. Hydrolysis of Esters 3 to the Free α-Amino Acids 4

entry	3, 4	3I:3II[a]	ee[b] (config,[b] %[c])
1	**a**	90:10	80 (2*S*, 60)
2	**b**	95:05	90 (2*S*, 60)
3	**c**	95:05	90 (2*S*, 65)
4	**d**	95:05	90 (2*S*, 65)
5	**a**	20:80	60 (2*R*, 60)
6	**b**	20:80	60 (2*R*, 60)

[a] Determined by ^{1}H NMR (300 MHz). [b] Determined by comparison of measured $[\alpha]_D$ with literature values. [c] Pure, isolated yield.

enolates) with the highly reactive triflates[29] and methyl fluorsulfonate[30] (Table 1, entries 10–13) followed by Me_2SO_4 (Table 1, entry 14) and MeI (Table 1, entries 1, 2). On the other hand, the best diastereoselectivities in favor of the **3I** isomers were obtained in the alkylations of the potassium enolates (Table 1, entries 19–23) as well as the cyclic-chelated Zn enolate (Table 1, entry 4) (mainly *Z*-geometry for the enolates), in agreement with previous observations.

Hydrolysis of Esters 3a–d to the α-amino acids 4a–d. Representative **3I:3II** mixtures obtained from the previously described alkylations of ester **1** with ^{t}BuLi and KO^{t}Bu in THF (*vide supra*, Table 1 entries 12, 13, 19, 21–23) have been subjected to hydrolysis under nonepimerizing conditions,[31] giving rise to the corresponding free α-amino acids (cf. Scheme 2, Table 2).

Conclusions

The results described above demonstrate that the diastereoselective alkylation of the acyclic glycine ester **1** is governed not only by the *E*- or *Z*-geometry of the enolate mixtures formed upon deprotonation, but also by the kinetics of the alkylation step, as a consequence of the interaggregation phenomena due to reaction of the initially generated aggregate mixture with the salts formed in this process. Combining a suitable choice of the base used for enolization, together with a careful selection of the alkylating reagent, and after nonepimerizing deprotection, the overall reaction can be selectively tuned to obtain either L- or D-α-amino acids with good yields and enantioselectivities without the need of changing the chiral inducer. Thus, L-α-amino acids (2*S*) can be selectively obtained by using potassium bases together with soft electrophiles (alkyl bromides or iodides) while *D*-α-amino acids (2*R*) can be selectively prepared by using lithium bases together with hard alkylating agents (alkyl triflates).

Experimental Section

All starting materials were commercially available research-grade chemicals and were used without further purification. THF was distilled after refluxing over Na/benzophenone. Diisopropylamine and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were dried over CaH_2 and freshly distilled under argon prior to use. All reactions were run under argon. 8-Phenylmenthyl glycinate was prepared following literature procedures.[31] Silica gel 60 F_{254} was used for TLC, and the spots detected with UV or ninhydrin solution. Flash chromatography was carried out on silica gel 60. Ion exchange chromatography was performed on Dowex-50 (H). Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with TMS as internal reference, and full assignment of ^{13}C NMR spectra has been carried out with the aid of the DEPT-135 pulse sequence.

8-Phenylmenthyl *N*-[Bis(methylthio)methylene]glycinate (1). 8-Phenylmenthyl glycinate (19.8 g, 67.0 mmol) was introduced in a round-bottomed flask provided with a magnetical stirrer, at 0 °C. Without stirring, precooled (0 °C) solutions of NaOH (40.8 g, 1.02 mol) in H_2O (46.5 mL), CS_2 (4.1 mL, 68.8 mmol) in benzene (154.5 mL), and precooled (0 °C) CH_3I (201.6 mmol) were successively added, followed by benzyltriethylammonium chloride (1.5 g, 6.4 mmol). The mixture was then vigorously stirred at 20 °C for 20 min. The benzene phase was decanted and the aqueous phase extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL) and dried on $MgSO_4$. Evaporation of the solvent under reduced pressure led to a pale yellow liquid which was purified by column chromatography (hexane:ethyl acetate, 20:80) to give a white solid (85%). Mp = 92–93 °C (hexane–ethyl acetate); $[\alpha]_D$ = +0.6 (*c* = 2, $CHCl_3$); IR ($CHCl_3$) ν 1750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.10 (5H, m), 4.88 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz), 3.71 (1H, A part of an AB, J_{AB} = 18 Hz), 3.52 (1H, B part of an AB, J_{AB} = 18 Hz), 2.55 (3H, s), 2.42 (3H, s), 2.20–0.80 (17H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6, 162.5, 156.1, 128.1, 125.5, 125.2, 74.9, 54.2, 50.5, 41.7, 39.8, 34.6, 31.4, 27.9, 26.6, 25.2, 21.9, 15.0, 14.7. Anal. Calcd for $C_{21}H_{31}NO_2S_2$: C, 64.08; H, 7.94; N, 3.56. Found: C, 64.29; H, 8.05; N, 3.79.

Alkylations Using LDA as Base. To a solution of diisopropylamine (23 μL, 0.16 mmol) in THF (0.5 mL) at −78 °C was added a 1.6 M solution of BuLi in hexane (0.1 mL, 0.16 mmol) dropwise, and the solution was stirred for 30 min at −78 °C. A solution of ester **1** (50 mg, 0.13 mmol) in THF (0.5 mL) was then slowly added, and the solution was stirred for 30 min at −78 °C. After addition of the corresponding electrophile (Table 1, entries 1–18) (0.96 mmol), stirring was maintained at −78 °C for 30 min and the temperature was then allowed to slowly rise to 0 °C. A 1 N HCl solution (2.5 mL) was then added, and the temperature was allowed to reach rt. The organic layer was decanted, and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (2 × 2.5 mL) and dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane:ethyl acetate, 90:10).

In the case of the run in the presence of $ZnCl_2$ (Table 1, entry 4) the same protocol was followed, but a solution of $ZnCl_2$ (22 mg, 0.16 mmol) in THF (2.5 mL) was added 30 min after the addition of BuLi. The temperature was allowed to slowly rise to −50 °C and stirred for 30 min. After cooling back to −78 °C, MeI (60 μL, 0.96 mmol) was added and all operations continued as above.

In the case of the run in the presence of DMPU (Table 1, entry 5) the same protocol was followed, but DMPU (0.3 mL) was added 30 min after the addition of BuLi and the mixture was stirred for 5 min, and all operations were continued as above.

In the case of the runs in the presence of LiCl (Table 1, entries 15–17) the same protocol was followed, but LiCl was added 30 min after the addition of BuLi and the mixture was stirred for 30 min, and all operations were continued as above.

In the case of the run in the presence of LiCl (Table 1, entry 18) the same protocol was followed but LiCl (6.8 mg, 0.16 mmol) was introduced prior to the addition of ester **1**.

Alkylations Using ^{t}BuLi or BuLi under Kinetic Conditions. To a 1.7 M solution of ^{t}BuLi in pentane or 1.6 M solution of BuLi in hexane (0.16 mmol) at −78 °C was added a solution of ester **1** (50 mg, 0.13 mmol) in THF (0.25 mL). After 30 min at −78 °C, the desired halide or triflate (0.96 mmol) was added and all operations were continued as above.

Alkylations Using KO^{t}Bu or KHMDS as Base. To a 0.5 M toluene solution of KHMDS (0.32 mL, 0.16 mmol) at −78

(29) MeOTf is about 10^5 times more reactive than MeI or Me_2SO_4. See: (a) Kurz, J. L.; Seif El-Nasr, M. M. *J. Am. Chem. Soc.* **1982**, *104*, 5823. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

(30) The low yield obtained in the alkylation with FSO_3Me can be attributed to competence with O-alkylation, due to the enhanced hardness of this reactant.

(31) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron* **1992**, *48*, 5163.

°C or solid KO^{t}Bu (18 mg, 0.16 mmol) in rt, THF (0.5 mL) was added and the mixture stirred for 5 min. At −78 °C, a solution of ester **1** (50 mg, 0.13 mmol) in THF (0.5 mL) was added and the mixture stirred for 30 min. The desired electrophile (Table 1, entries 19−23) (0.96 mmol) was then added, and all operations were continued as above.

Methylations Using ^{t}BuLi or BuLi under Thermodynamic Conditions. To a solution of ester **1** (50 mg, 0.13 mmol) in THF (0.25 mL) at −78 °C was added dropwise a 1.7 M solution of ^{t}BuLi in pentane or a 1.6 M solution of BuLi in hexane (0.16 mmol). After 30 min at −78 °C, MeI (0.96 mmol) was added and all operations were continued as above.

Synthesis of D-α-Amino Esters 3II (2*R*). General Procedure. To a 1.7 M solution of ^{t}BuLi in pentane (0.38 mL, 0.64 mmol) at −78 °C, a solution of ester **1** (200 mg, 0.52 mmol) in THF (1.0 mL) was added dropwise and the solution was stirred for 30 min at −78 °C. After addition of the corresponding alkyl triflate (3.84 mmol), stirring was maintained at −78 °C for 30 min and the temperature was then allowed to slowly rise to 0 °C. A 1 N HCl solution (2.5 mL) was then added, and the temperature was allowed to reach rt. The organic layer was decanted and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (2 × 2.5 mL) and dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane:ethyl acetate, 90:10).

Synthesis of L-α-Amino Esters 3II (2*S*). General Procedure. A solution of KO^{t}Bu (72 mg, 0.64 mmol) in THF (2.0 mL) was cooled to −78 °C, and a solution of ester **1** (200 mg, 0.52 mmol) in THF (2.0 mL) was slowly added. The mixture was stirred for 30 min at −78 °C. After addition of the corresponding alkyl bromide or triflate (3.84 mmol), stirring was maintained at −78 °C for 30 min and the temperature was then allowed to slowly rise to 0 °C. A 1 N HCl solution (2.5 mL) was then added, and the temperature was allowed to reach rt. The organic layer was decanted and the aqueous phase extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (2 × 2.5 mL) and dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane:ethyl acetate, 90:10).

8-Phenylmenthyl *N*-[bis(methylthio)methylene]alaninate (3a) (I/II = 40:60): colorless oil (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (5H, m, **I** + **II**), 4.80 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ac}$ = 4 Hz, **I** + **II**), 4.04 (1H, q, ^3J = 6 Hz, **I**), 4.01 (1H, q, ^3J = 6 Hz, **II**), 2.57 (3H, s, **I**), 2.54 (3H, s, **II**), 2.39 (3H, s, **I**), 2.34 (3H, s, **II**), 2.10−0.80 (17H, m, **I** + **II**). Anal. Calcd for $C_{22}H_{33}NO_2S_2$: C, 64.82; H, 8.16; N, 3.44. Found: C, 65.08; H, 8.26; N, 3.68.

8-Phenylmenthyl *N*-[bis(methylthio)methylene]alaninate (3aI): colorless oil (85% isolated from KO^{t}Bu as base); IR ($CHCl_3$) ν 1735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (5H, m), 4.80 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ac}$ = 4 Hz), 4.04 (1H, q, ^3J = 6 Hz), 2.57 (3H, s), 2.39 (3H, s), 2.10−0.80 (20H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.8, 160.6, 151.3, 128.0, 125.6, 125.2, 75.4, 60.1, 50.6, 41.6, 40.0, 34.6, 31.4, 27.1, 26.9, 26.3, 21.9, 18.3, 15.1, 14.8. Anal. Calcd for $C_{22}H_{33}NO_2S_2$: C, 64.82; H, 8.16; N, 3.44. Found: C, 64.93; H, 8.27; N, 3.65.

8-Phenylmenthyl *N*-[bis(methylthio)methylene]-2-allylglycinate (3b) (I/II = 50:50): colorless oil (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (5H, m, **I** + **II**), 5.72 (1H, m, **I** + **II**), 5.02 (2H, m, **I** + **II**), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ac}$ = 4 Hz, **I** + **II**), 4.12 (1H, t, ^3J = 6 Hz, **II**), 4.04 (1H, t, ^3J = 6 Hz, **I**), 2.58 (3H, s, **I**), 2.54 (3H, s, **II**), 2.39 (3H, s, **I**), 2.35 (3H, s, **II**), 2.34 (2H, m), 2.38−0.79 (17H, m, **I** + **II**). Anal. Calcd for $C_{24}H_{35}NO_2S_2$: C, 66.47; H, 8.13; N, 3.23. Found: C, 66.68; H, 8.25; N, 3.14.

8-Phenylmenthyl *N*-[bis(methylthio)methylene]-2-allylglycinate (3bI): colorless oil (85% isolated, from KO^{t}Bu as base); IR ($CHCl_3$) ν 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (5H, m), 5.72 (1H, m), 5.02 (2H, m), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz), 4.04 (1H, t, ^3J = 6 Hz), 2.58 (3H, s), 2.39 (3H, s), 2.35 (2H, m), 2.20−0.79 (17H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.4, 161.5, 151.5, 134.4, 128.1, 125.6, 125.2, 117.4, 75.7, 64.1, 50.6, 41.7, 39.9, 37.6, 34.7, 31.4, 27.0, 26.9, 26.4, 21.9, 15.2, 14.9. Anal. Calcd for $C_{24}H_{35}NO_2S_2$: C, 66.47; H, 8.13; N, 3.23. Found: C, 66.54; H, 8.18; N, 3.32.

8-Phenylmenthyl *N*-[bis(methylthio)methylene]phenylalaninate (3c) (I/II = 50:50): colorless oil (85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (10H, m, **I** + **II**), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz, **I** + **II**), 4.31 (1H, X part of an ABX, J_{AX} = 7 Hz, J_{BX} = 5 Hz, **II**), 4.30 (1H, X part of an ABX, J_{AX} = 7 Hz, J_{BX} = 5 Hz, **I**), 2.94 (2H, AB of an ABX, J_{AB} = 13 Hz, **I** + **II**), 2.47 (3H, s, **I**), 2.42 (3H, s, **II**), 2.38 (3H, s, **I**), 2.35 (3H, s, **II**), 2.10−0.70 (17H, m, **I** + **II**). Anal. Calcd for $C_{28}H_{37}NO_2S_2$: C, 69.52; H, 7.71; N, 2.90. Found: C, 69.43; H, 7.85; N, 3.18.

8-Phenylmenthyl *N*-[bis(methylthio)methylene]phenylalaninate (3cI): colorless oil (85% isolated, from KO^{t}Bu as base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (10H, m), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz), 4.30 (1H, X part of an ABX, J_{AX} = 7 Hz, J_{BX} = 5 Hz), 2.94 (2H, AB of an ABX, J_{AB} = 13 Hz), 2.47 (3H, s), 2.38 (3H, s), 2.10−0.70 (17H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5, 161.9, 151.4, 138.1, 129.9, 128.1, 128.0, 126.3, 125.7, 125.3, 75.8, 66.0, 50.6, 41.5, 40.0, 39.3, 34.6, 31.3, 27.3, 27.0, 26.2, 21.8, 15.3, 14.9. Anal. Calcd for $C_{28}H_{37}NO_2S_2$: C, 69.52; H, 7.71; N, 2.90. Found: C, 69.71; H, 7.57; N, 3.08.

4-Ethyl 8-phenylmenthyl *N*-[bis(methylthio)methylene]aspartate (3d) (I/II = 50:50): colorless oil (90%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (5H, m, **I** + **II**), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ac}$ = 4 Hz, **I** + **II**), 4.58 (1H, t, ^3J = 6 Hz, **II**), 4.42 (1H, t, ^3J = 6 Hz, **I**), 4.10 (2H, q, ^3J = 7 Hz, **I** + **II**), 2.58 (3H, s, **I**), 2.55 (3H, s, **II**), 2.52 (2H, m), 2.46 (3H, s, **I**), 2.32 (3H, s, **II**), 2.20−0.70 (20H, m, **I** + **II**). Anal. Calcd for $C_{25}H_{37}NO_4S_2$: C, 62.60; H, 7.77; N, 2.92. Found: C, 62.65; H, 8.03; N, 3.17.

4-Ethyl 8-phenylmenthyl *N*-[bis(methylthio)methylene]aspartate (3dI): colorless oil (85% isolated, from KO^{t}Bu as base); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (5H, m), 4.78 (1H, td, $^3J_{aa}$ = 10 Hz, $^3J_{ae}$ = 4 Hz), 4.42 (1H, t, ^3J = 6 Hz), 4.10 (2H, q, ^3J = 7 Hz), 2.58 (3H, s), 2.51 (2H, m), 2.46 (3H, s), 2.10−0.70 (20H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.8, 169.2, 163.7, 151.3, 127.9, 125.5, 125.2, 76.0, 61.2, 60.4, 50.5, 41.3, 39.9, 37.7, 34.5, 31.4, 26.9, 26.8, 26.2, 21.8, 15.2, 14.7, 14.2. Anal. Calcd for $C_{25}H_{37}NO_4S_2$: C, 62.60; H, 7.77; N, 2.92. Found: C, 62.65; H, 7.95; N, 2.72.

Isomerization of 3aI:3aII with KO^{t}Bu in ^{t}BuOH. To a solution of esters **3a** (**I/II** = 90:10, obtained from ester **1** with KO^{t}Bu in THF) (50 mg, 0.12 mmol) in ^{t}BuOH (0.5 mmol) at rt, a solution of KO^{t}Bu (17 mg, 0.15 mmol) in ^{t}BuOH (0.25 mL) was slowly added. After 48 h at rt, a 1 N HCl (2.5 mL) was added. After addition of Et_2O (5 mL), the organic layer was decanted and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (2 × 2.5 mL) and were dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (hexane:ethyl acetate, 90:10).

Hydrolyses of Esters 3a−d. To a well stirred solution of the corresponding mixture of esters **3(a−d)I:3(a−d)II** (Table 2) (0.43 mmol) in trifluoroacetic acid (0.72 mmol), a 6 N HCl solution (1.5 mL) was added and the mixture refluxed for 15 h. After cooling to rt, H_2O (3.0 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 3 mL). The aqueous phase was evaporated to dryness under reduced pressure (40 °C bath), and the resulting amorphous solid was purified on an ion exchange column (10% pyridine−water).

(2*S*)-L-Alanine (4aI): white solid (60%, from **3aI:3aII** = 90:10, ee = 80%); $[\alpha]_D$ = +11 (*c* = 5, 5N HCl), lit.[33] +14 (*c* = 5, 5 N HCl). Anal. Calcd for $C_3H_7NO_2$: C, 40.44; H, 7.92; N, 15.72. Found: C, 40.63; H, 8.14; N, 15.95.

(2*R*)-D-Alanine (4aII): white solid (60% from **3aI:3aII** = 20:80, ee = 60%); $[\alpha]_D$ = −8 (*c* = 5, 5 N HCl), lit.[33] −14 (c = 5, 5N HCl). Anal. Calcd for $C_3H_7NO_2$: C, 40.44; H, 7.92; N, 15.72. Found: C, 40.68; H, 8.11; N, 15.83.

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(2*S*)-L-2-Allylglycine (4bI): white solid (60%, from **3bI:3bII** = 95:05, ee = 90%); $[\alpha]_D = -34$ ($c = 4$, H_2O), lit.[33] −38 ($c = 4$, H_2O). Anal. Calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.23; H, 7.95; N, 12.36.

(2*R*)-D-2-Allylglycine (4bII): white solid (60%, from **3bI:3bII** = 20:80, ee = 60%); $[\alpha]_D = +23$ ($c = 4$, H_2O), lit.[34] +38 ($c = 4$, H_2O). Anal. Calcd for $C_5H_9NO_2$: C, 52.16: H, 7.88; N, 12.17. Found: C, 52.28; H, 7.76; N, 12.08.

(2*S*)-L-Phenylalanine (4cI): white solid (65%, from **3cI:3cII** = 95:05, ee = 90%); $[\alpha]_D = -31$ ($c = 2$, H_2O), lit.[35] −35 ($c = 1.6$, H_2O). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.53; H, 6.82; N, 8.67.

L-Aspartic Acid (4dI): white solid (65%, from **4dI:4dII** = 95:05, ee = 90%); $[\alpha]_D = +22$ ($c = 5$, 6 N HCl), lit.[33] +25 ($c = 5$, 6 N HCl). Anal. Calcd for $C_4H_7NO_4$: C, 36.10; H, 5.30; N, 10.52. Found: C, 36.21; H, 5.53; N, 10.41.

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