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TETRAHEDRON: *ASYMMETRY*

Stereoselective alkylation of C_2-symmetric chiral *N*-phthaloylglycinamides in the preparation of enantiopure α-amino acids[1]

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Abstract

The novel, chiral glycinamides (*S*,*S*)-**3** and (*S*,*S*)-**4** were prepared in good yields from C_2-symmetric chiral amines (*S*,*S*)-**1** and (*S*,*S*)-**2**, respectively. Enolate formation and addition to methyl iodide and benzyl bromide proceeded in good yield and high diastereoselectivity, especially in the presence of LiCl or DMPU. Removal of the phthaloyl protecting group with hydrazine, followed by hydrolysis with 6N HCl, converted the benzylated product (*S*,*S*,*S*)-**7** to enantiopure (*S*)-phenylalanine.

1. Introduction

Because of the great importance of amino acids in physiological and pharmacological events, and because biological interactions are usually stereospecific,[2] during the last two decades we have witnessed an unprecedented amount of research work directed to the enantioselective synthesis of chiral amino acids.[3]

Among the various methods available for the preparation of enantioenriched α-amino acids, those employing chiral glycine derivatives[4–15] (Fig. 1) have been particularly successful, and among these, 'open-chain' glycine substrates **I**–**L** are attractive from the point of view of simplicity and relative low cost.

Motivated in great measure by the work of Katsuki and co-workers,[13] who demonstrated the efficiency of C_2-symmetric chiral auxiliaries[16] in glycinamide **J** (Fig. 1), and encouraged by the accessibility of C_2-symmetric chiral amines (*S*,*S*)-**1**[17] and (*S*,*S*)-**2**,[18,19] we decided to explore the

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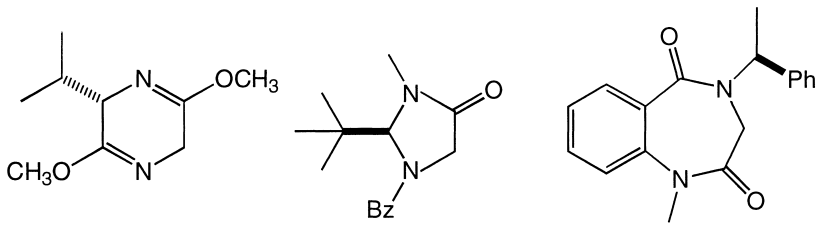
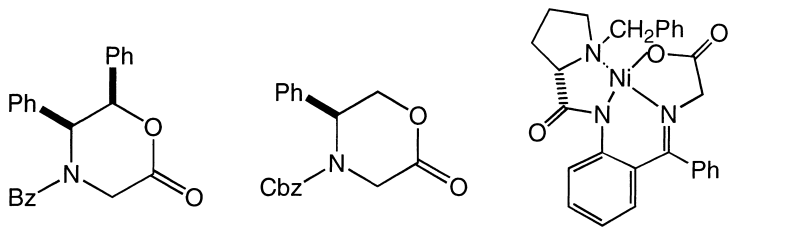
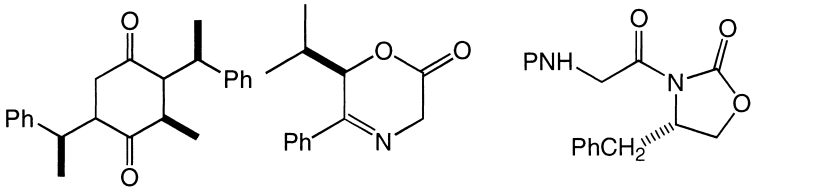


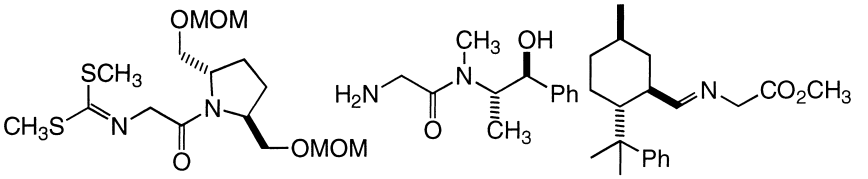
A, Schoellkopf, ref. 4 **B**, Seebach, ref. 5 **C**, Juaristi, ref. 6



D, Williams, ref. 7 **E**, Dellaria, ref. 8 **F**, Belokon, ref. 9



G, Sandri, ref. 10 **H**, Najera, ref. 11 **I**, Evans, ref. 12



J, Katsuki, ref. 13 **K**, Myers, ref. 14 **L**, Duhamel, ref. 15

[a]P, protecting group; MOM, methoxymethyl.

Figure 1.

potential of *N*-phthaloylglycinamides (*S*,*S*)-**3** and (*S*,*S*)-**4** (Fig. 2) for the enantioselective synthesis of chiral α-amino acids.

2. Stereoselectivity of alkylation of (*S*,*S*)-3

Preliminary experiments showed poor diastereoselectivity in the alkylation reaction of enolates derived from chiral glycine derivatives **M** and **N**. Nevertheless, promising results were observed with *N*-phthaloyl protected[20] glycinamide (*S*,*S*)-**3**.

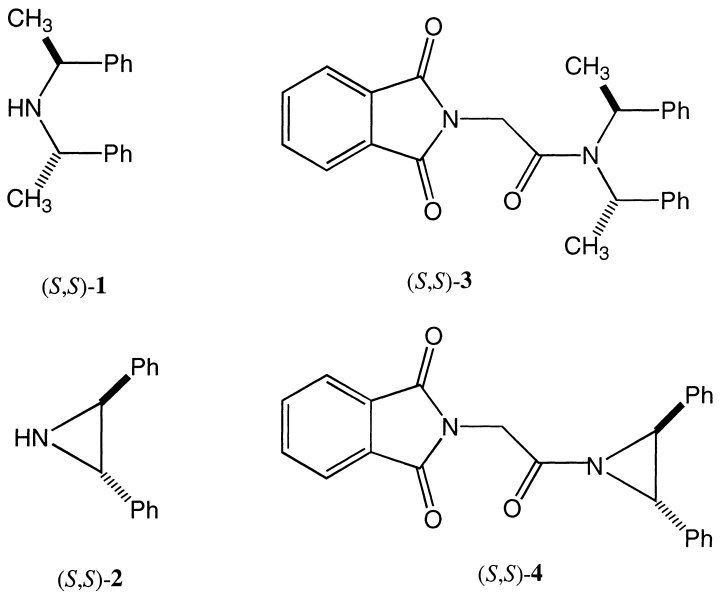
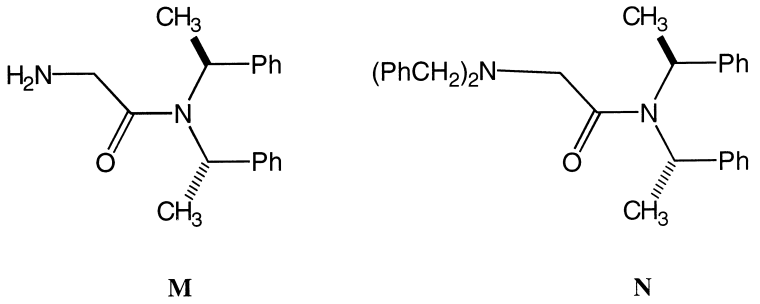


Figure 2.

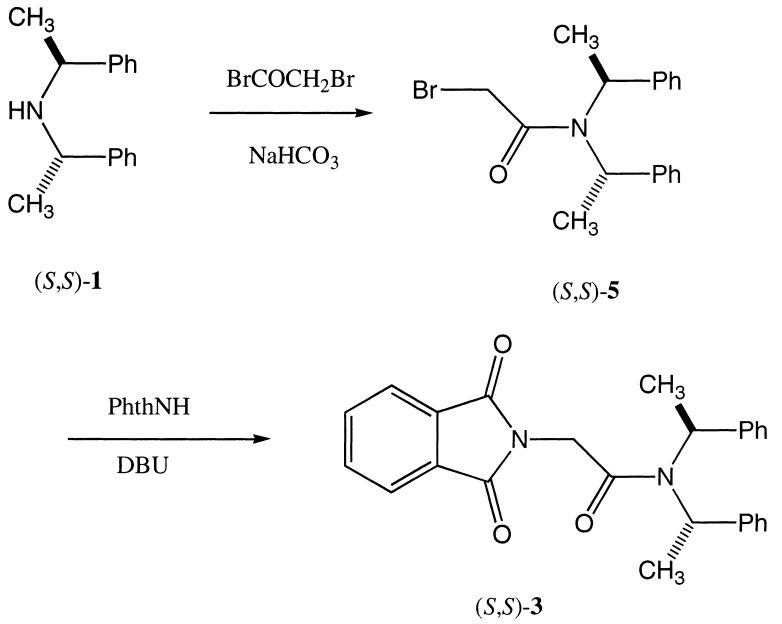


Chiral glycinamide (*S*,*S*)-**3** was obtained in 74.2% overall yield according to the synthetic route depicted in Scheme 1.

The results of alkyl halide addition (at –78°C) to enolate (*S*,*S*)-**3**-Li, generated by metallation of the corresponding glycinamide with LDA or LHMDS, are summarized in Table 1. Examination of entries 1–4 reveals that better results (higher yields and diastereoselectivities) are achieved when LDA base is used for enolate formation; indeed, methylation takes place with 81% ds and benzylation proceeds with 95% ds.

Recently,[21] addition of 'inert' salts to reaction media has been found to affect the stereoselectivity of alkylation reactions. Thus, Table 1 includes data obtained in the presence of six equivalents of lithium chloride. As can be appreciated in entries 5 and 10, diastereoselectivities do seem to improve with LiCl as additive.[22]

In this context, use of dimethylpropylene urea (DMPU) is known to activate the reaction of lithium carbanions with electrophiles.[23] In the present study, the diastereoselectivity of the benzylation reaction (entries 3 versus 11–14, Table 1) did improve in the presence of one to six equivalents of DMPU,[24] so that a single diastereomeric product was observed (ds >97%). Nevertheless, the diastereoselectivity of the methylation reaction (entries 1 versus 6–9) was erratic.



Scheme 1.

It is expected that seemingly contrasting observations such as those reported here will be understood as knowledge of structure and aggregation state of Li enolates is more advanced.[22,25]

3. Stereoselectivity of alkylation of (*S*,*S*)-4

Chiral glycinamide (*S*,*S*)-**4** was obtained in 82.3% yield according to the synthetic procedure shown in Scheme 2. Diphenylaziridine (*S*,*S*)-**2** has proven an efficient chiral auxiliary, most notably in the work of Tanner et al.[26]

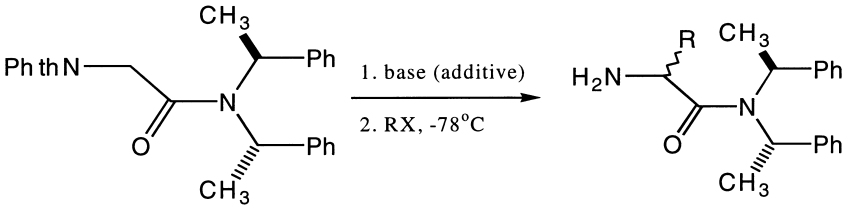
The results of alkyl halide addition (at –78°C) to enolate (*S*,*S*)-**4**-Li, generated by metallation of the corresponding glycinamide with LDA or LHMDS, are summarized in Table 2.

As was observed in the alkylation of (*S*,*S*)-**3** (see above), LDA proved a more convenient base than LHMDS (entries 1–4 in Table 2), affording higher diastereoselectivities (65% ds in the methylation reaction and 83% ds in the benzylation reaction). The moderate yields achieved in these reactions are ascribed to decomposition products whose structure could not be established.

Addition of LiCl (6 equiv.) to the reaction mixture led to decomposition products, probably via Li^+-catalyzed aziridine ring opening processes.[27] In contrast, use of DMPU as cosolvent (6 equiv.) proved quite beneficial in the case of the benzylation reaction, improving the observed diastereoselectivity from 83% in THF to higher than 97% ds in THF–DMPU (entries 4 and 8 in Table 2).

The potential of (*S*,*S*)-**4** in the preparation of α,α-disubstituted α-amino acids was then explored. Treatment of enolate **9**-Li (R = CH_3) with benzyl bromide in the presence of 6 equiv. of DMPU afforded a 67:33 diastereomeric mixture of dialkylated derivative **11** (Scheme 3). By the same token, methylation of enolate **10**-Li (R = CH_2Ph) gave a 40:60 mixture of **11** (Scheme 3). The low diastereoselectivity in the alkylation of **9** and **10** is probably due in part to the higher temperature (–20°C instead of –78°C) required for this reaction to proceed.

Table 1
Diastereoselectivity of enolate (*S*,*S*)-**3**-Li alkylations



(*S*,*S*)-**3** **6, 7**

Entry	base[a]	RX	LiCl (equiv)	DMPU [b] (equiv)	dr,[c] %	yield, %
1	LDA	CH_3I	----	----	81:19	88
2	LHMDS	CH_3I	----	----	78:22	42
3	LDA	$PhCH_2Br$	----	----	95:5	90
4	LHMDS	$PhCH_2Br$	----	----	72:28	58
5	LDA	CH_3I	6	----	83:17	71
6	LDA	CH_3I	----	1	85:15	63
7	LDA	CH_3I	----	2	78:22	66
8	LDA	CH_3I	----	4	82:18	67
9	LDA	CH_3I	- ---	6	76:24	62
10	LDA	$PhCH_2Br$	6	----	>97:3	61
11	LDA	$PhCH_2Br$	----	1	>97:3	65
12	LDA	$PhCH_2Br$	----	2	>97:3	62
13	LDA	$PhCH_2Br$	----	4	>97:3	68
14	LDA	$PhCH_2Br$	----	6	>97:3	60

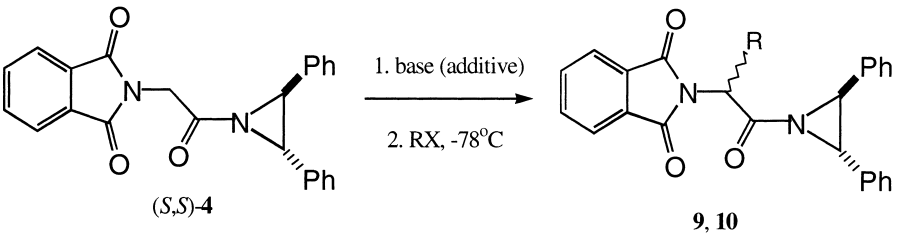
[a]LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisilazide. [b]DMPU, *N*,*N*-dimethylpropylene urea. [c]dr, diastereomeric ratio.

4. Assignment of configuration of the diastereoisomeric products 6, 7, 9 and 10

The absolute configuration of the newly created stereogenic center in the major diastereomeric product of benzylation of (*S*,*S*)-**3** was ascertained by removal of the *N*-phthaloyl protecting group,[28] followed by acid hydrolysis to the known α-amino acid (*S*)-phenylalanine, (*S*)-**13**[29] (Scheme 4).

Direct hydrolysis (6N HCl, 100°C, 18 h) of product mixtures containing (*S*,*S*,*S*)-**6** and (*S*,*S*,*S*)-**9** as the major component afforded (*S*)-alanine. Similarly, a sample enriched in the benzylated aziridine derivative (*S*,*S*,*S*)-**10** was hydrolyzed to give (*S*)-phenylalanine. Thus, enolate alkylation takes place on the *Si* face of both (*S*,*S*)-**3**-Li and (*S*,*S*)-**4**-Li.

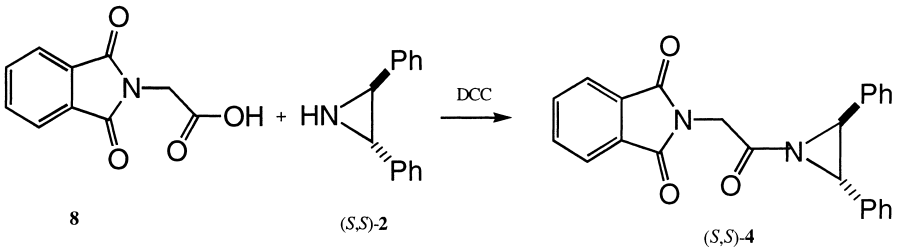
Table 2
Diastereoselectivity of enolate (*S*,*S*)-**4**-Li alkylations



(*S*,*S*)-**4** **9**, **10**

Entry	base[a]	RX	LiCl (equiv.)	DMPU[b] (equiv.)	dr[c] (%)	yield[d] (%)
1	LHMDS	CH_3I	---	---	52:48	57
2	LDA	CH_3I	---	---	65:35	57
3	LHMDS	$PhCH_2Br$	---	---	55:45	56
4	LDA	$PhCH_2Br$	---	---	83:17	59
5	LDA	CH_3I	6	---	---	NP[e]
6	LDA	CH_3I	---	6	63:37	34
7	LDA	$PhCH_2Br$	6	---	---	NP
8	LDA	$PhCH_2Br$	---	6	>97:3	46

[a]LDA, lithium diisopropylamide; LHMDS, lithium hexamethyldisyl-azide. [b]DMPU, N,N-dimethylpropylene urea. [c]dr, diastereomeric ratio. [d]Not optimized. [e]Decomposition products.

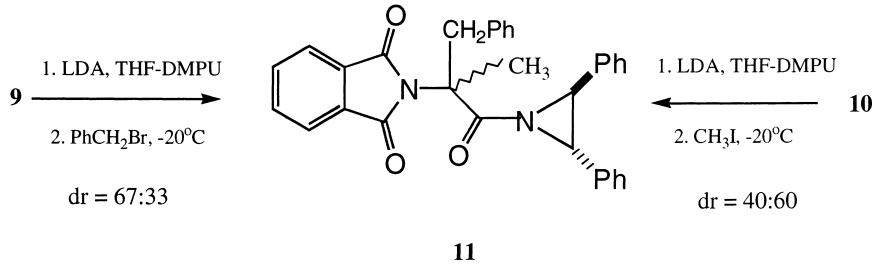


8 (*S*,*S*)-**2** (*S*,*S*)-**4**

[a]DCC, 1,3-dicyclohexylcarbodiimide.

Scheme 2.

Examination of molecular models suggests that conformer **O** in the (*Z*)-diastereoisomer of enolate (*S*,*S*)-**3**-Li should correspond to an energy minimum, which is predicted to react on the *Si* face since the bulky phenyl rings inhibit electrophile addition on the *Re* face (Fig. 3a). By the



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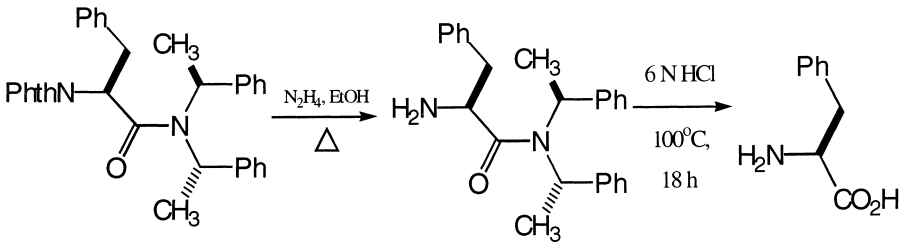
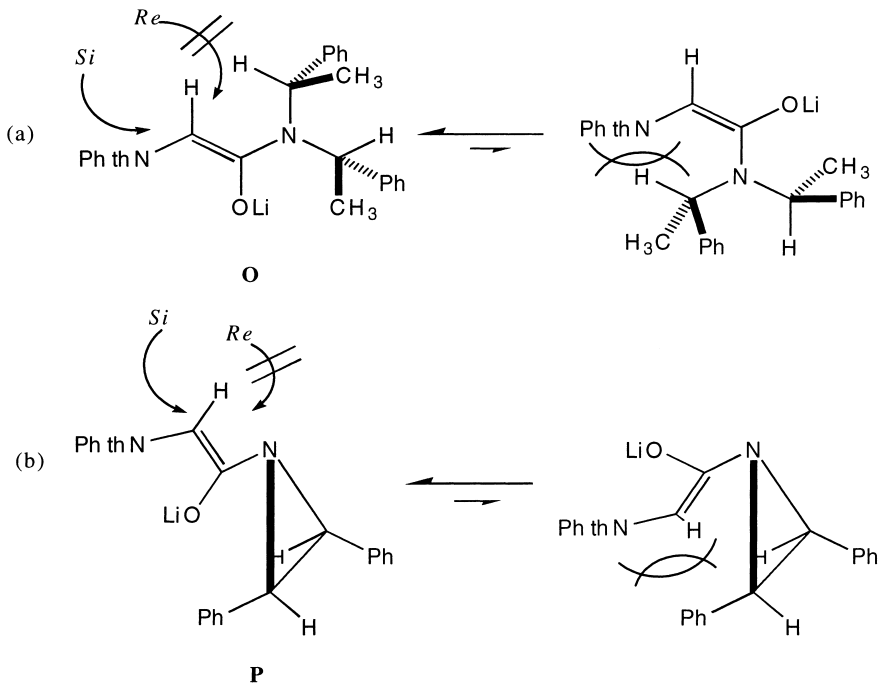
Scheme 3.



(*S*,*S*,*S*)-**7** (*S*,*S*,*S*)-**12** (*S*)-**13**

Scheme 4.



O

P

Figure 3.

same token, conformation **P** of aziridine-containing enolate (*S*,*S*)-**4**-Li should represent the energy minimum; it can be appreciated that the *Re* face of the enolate is prevented by the three-membered ring from reacting with the electrophile, so that reaction takes place on the *Si* face (Fig. 3b).

In summary, chiral *N*-phthaloylglycinamides (*S*,*S*)-**3** and (*S*,*S*)-**4** were prepared in good yields from C_2-symmetric amines (*S*,*S*)-**1** and (*S*,*S*)-**2**, respectively. Enolates (*S*,*S*)-**3**-Li and (*S*,*S*)-**4**-Li were alkylated with good to excellent diastereoselectivity, especially in the presence of LiCl or DMPU as additive or cosolvent. Hydrolysis of the main product (*S*,*S*,*S*)-**7** with 6N HCl afforded enantiopure (*S*)-phenylalanine in good yield.

5. Experimental[30]

5.1. (S,S)-N,N-*Bis*-(1-phenylethyl)amine (S,S)-*1*

This chiral amine was prepared according to the procedure described in the literature.[17] $[\alpha]_D^{28} = -205.3$ (c = 4.92, C_6H_6) {lit.[17] $[\alpha]_D$ –197.3 (c = 3.65, C_6H_6)}.

5.2. (2S,3S)-2,3-Diphenylaziridine (S,S)-*2*

This chiral amine was prepared according to the recently reported procedure.[19] $[\alpha]_D^{28} = -334.3$ (c = 1.02, $CHCl_3$) {lit.[31] $[\alpha]_D^{28} = -341.0$ (c = 0.83, $CHCl_3$)}.

5.3. (S,S)-2-Bromo-N,N-*bis*(1′-phenylethyl)acetamide (S,S)-*5*

A solution of 11.25 g (50.0 mmol) of chiral amine (*S*,*S*)-**1** in 125 mL of CH_2Cl_2 was cooled to 0°C under nitrogen atmosphere before the dropwise addition of 4.4 mL (10.1 g, 50.0 mmol) of bromoacetyl bromide. The resulting suspension was then treated with 7.6 mL (5.55 g, 55.0 mmol) of triethylamine, and stirring at 0°C was continued for 3 h. The reaction mixture was washed with 50 mL of cold water, 25 mL of aqueous 5% NaOH, and finally with two 50 mL portions of cold water. The organic phase was dried over anhyd. Na_2SO_4, filtered, and concentrated to give the crude product that was purified by flash chromatography (hexane:EtOAc, 8:2). The desired product (15.3 g, 88.6% yield) was obtained as a white solid, mp 94–95°C. $[\alpha]_D^{28} = -125.0$ (c = 3.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 60°C, 400 MHz) δ 1.78 (d, J = 7.0 Hz, 6H), 3.69 (d, J = 11.2 Hz, 1H), 3.75 (d, J = 11.2 Hz, 1H), 5.05–5.30 (br s, 2H), 7.05–7.25 (m, 10H). ^{13}C NMR ($CDCl_3$, 60°C, 100 MHz) δ 18.6, 28.6, 54.0, 127.5, 128.3, 140.4, 166.7. Anal. calcd for $C_{18}H_{20}BrNO$: C, 62.43; H, 5.82. Found: C, 62.61; H, 5.81.

5.4. (S,S)-N′,N′-*Bis*(1′-phenylethyl)-N-*phthaloylglycinamide* (S,S)-*3*

To a suspension of 4.34 g (29.5 mmol) of phthalimide in 80 mL of THF was added dropwise 4.5 mL (4.5 g, 29.5 mmol) of DBU, and the resulting mixture was stirred at ambient temperature for 0.5 h. Bromide (*S*,*S*)-**5** (10.25 g, 29.5 mmol) in 20 mL of THF was added, and the reaction mixture was stirred for an additional hour. The solvent was then removed in the rotary evaporator and the residue was suspended in 100 mL of water, to be extracted with two 50 mL portions of CH_2Cl_2. The organic extracts were dried over anhyd. Na_2SO_4 and concentrated in the

rotary evaporator. The residue was crystallized from hexane:EtOAc (1:1) to afford 7.6 g of product. An additional amount of the desired product was obtained by evaporation of the mother liquor followed by purification by flash chromatography (hexane:EtOAc, 8:2), bringing the total amount of product to 10.2 g (83.8% yield), mp 167–168°C. $[\alpha]_D^{28} = -90.1$ (c = 3.2, $CHCl_3$). ^1H NMR (DMSO-d_6, 100°C, 270 MHz) δ 1.71 (d, J = 7.1 Hz, 6H), 4.23 (d, J = 16.3 Hz, 1H), 4.52 (d, J = 16.3 Hz, 1H), 5.10 (q, J = 7.1 Hz, 2H), 7.05–7.20 (br s, 10H), 7.80–7.90 (br s, 4H). ^{13}C NMR ($CDCl_3$, 22.49 MHz) δ 18.3, 41.0, 52.7, 123.3, 127.4, 128.4, 132.1, 133.8, 140.2, 166.2, 167.9. Anal. calcd for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86. Found: C, 76.09; H, 5.92.

5.5. N-*Phthaloylglycine* **8**

A suspension of 3.7 g (25.0 mmol) of phthalic anhydride, 2.25 g (30.0 mmol) of glycine, and 5 mL of pyridine was heated to 95°C for 20 h. The reaction mixture was then allowed to cool to ambient temperature before the sequential addition of 50 mL of water and 5 mL of concd HCl. The resulting mixture was extracted with three 15 mL portions of EtOAc and the combined organic extract was dried over anhyd. Na_2SO_4, and concentrated in the rotary evaporator. The residue was crystallized from benzene to give 4.2 g (82.3% yield) of **8**, mp 194–196°C (lit.[32] mp 191–192°C). ^1H NMR ($CDCl_3$, 400 MHz) δ 4.44 (s, 2H), 7.72–7.75 (m, 2H), 7.86–7.90 (m, 2H), 10.9–11.0 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.1, 123.6, 132.1, 134.1, 167.6, 170.9.

5.6. (S,S)-(2,3-Diphenylaziridinyl)-N-*phthaloylglycinamide* (S,S)-**4**

To a solution of 4.1 g (20.0 mmol) of *N*-phthaloylglycine **8**, 4.13 g (20.0 mmol) of *N*,*N*′-1,3-dicyclohexylcarbodiimide (DCC), and 50 mL of CH_2Cl_2 was added, at 0°C, 3.9 g (20.0 mmol) of chiral aziridine (*S*,*S*)-**2** in 25 mL of CH_2Cl_2. The reaction mixture was stirred at 0°C for 3 h, the precipitate (*N*,*N*′-dicyclohexylurea) was removed by filtration, the filtrate was washed with three 25 mL portions of cold 5% AcOH and three 25 mL portions of water, dried over anhyd. Na_2SO_4, and concentrated in a rotary evaporator. The crude product was purified by flash chromatography (hexane:EtOAc, 8:2) to give 6.3 g (82.3% yield) of (*S*,*S*)-**4**, mp 127–130°C. $[\alpha]_D^{28} = -56.9$ (c = 1.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 270 MHz) δ 3.79 (s, 2H), 4.10 (d, J = 17.1 Hz, 1H), 4.53 (d, J = 17.1 Hz, 1H), 7.20–7.40 (m, 10H), 7.65–7.68 (m, 2H), 7.76–7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ = 42.1, 48.6, 123.5, 126.5, 128.6, 128.9, 132.0, 134.1, 134.6, 167.5, 174.1. MS *m*/*z* 382 (M^+), 276, 194, 160. HRMS calcd for $C_{24}H_{19}N_2O_3$ (M^++1): 383.1396. Found: 383.1388.

5.7. *General procedure for the reaction of glycinamide enolates [(S,S)-3-Li or (S,S)-4-Li] with electrophiles*

A solution of diisopropylamine (0.15 mL, 1.1 mmol) in 15 mL of dry THF and under nitrogen atmosphere was cooled to –78°C before the slow addition of 0.45 mL (1.1 mmol) of 2.4 M *n*-BuLi in hexane. The resulting solution was stirred at –78°C for 0.5 h before the dropwise addition of 1.0 mmol of the glycinamide and 1.1 mmol of the electrophile in 20 mL of dry THF (when LiCl or DMPU additives were used, they were added at this point). Stirring was continued for 7 h at –78°C, and then the reaction was quenched by the addition of 15 mL of water. The product was extracted with three 15 mL portions of CH_2Cl_2, the combined organic extracts were washed with 15 mL of brine solution, dried over anhyd. Na_2SO_4, and concentrated. Final purification was accomplished by flash chromatography.

5.8. (1′S,1′S,2S)-N′,N′-Bis-(1′-phenylethyl)-N-phthaloylalanilamide (S,S,S)-6

The general procedure was followed with 0.43 g (1.0 mmol) of (*S*,*S*)-**3**, 0.73 mL of DMPU (6.0 mmol), and 0.07 mL (0.15 g, 1.1 mmol) of methyl iodide. The isolated product (0.31 g, 71% yield) consisted of an 83:17 mixture of (*S*,*S*,*S*)-**6** and (*S*,*S*,*R*)-**6** diastereomeric products, which could not be separated by flash column chromatography, but allowed spectroscopic characterization of the major product. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.60 (d, J = 6.95 Hz, 3H), 1.76 (m, 6H), 4.30 (s, 1H), 5.10 (s, 1H), 5.37 (q, J = 6.95 Hz, 1H), 6.72–7.36 (m, 10H), 7.62–7.65 (m, 2H), 7.75–7.79 (m, 2H). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 15.0, 49.6, 53.7, 54.2, 123.2, 123.5, 127.8, 128.1, 128.6, 131.9, 133.9, 168.4, 169.9.

5.9. (1′S,1′S,2S)-N′,N′-Bis-(1′-phenylethyl)-N-phthaloylphenylalanilamide (S,S,S)-7

The general procedure was followed with 0.43 g (1.0 mmol) of (*S*,*S*)-**3** and 0.13 mL (0.19 g, 1.1 mmol) of benzyl bromide. The isolated product (0.47 g, 90% yield) consisted of a 95:5 mixture of (*S*,*S*,*S*)-**7** and (*S*,*S*,*R*)-**7** diastereomeric products, from which the major isomer was separated by flash chromatography (CH_2Cl_2:EtOAc:hexane, 10:10:1) to give 0.40 g (78.0% yield) of the major product, (*S*,*S*,*S*)-**7**, mp 84–85°C. $[\alpha]_D^{28} = -82.9$ (c = 0.41, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.75 (br, 3H), 1.85 (br, 3H), 2.95 (dd, $J^1 = 14.3$ Hz, $J^2 = 4.6$ Hz, 1H), 3.93 (dd, $J^1 = 14.3$ Hz, $J^2 = 11.6$ Hz, 1H), 5.50 (dd, $J^1 = 11.6$ Hz, $J^2 = 4.6$ Hz, 1H), 6.93–7.22 (m, 15H), 7.57–7.63 (m, 2H), 7.66–7.72 (m, 2H). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 18.7, 34.4, 54.3, 55.0, 123.3, 126.8, 127.0, 128.0, 128.5, 128.8, 129.0, 131.6, 134.0, 137.1, 139.9, 141.2, 168.4, 169.3. MS (20 eV) *m*/*z* 503 (M^++1), 397, 250, 105. HRMS calcd for $C_{33}H_{31}N_2O_3$ (M^++1): 503.2335. Found: 503.2327.

5.10. (2S,3S,2′S)- and (2S,3S,2′R)-N′-Phthaloylalanil-2,3-diphenylaziridine (S,S,S)- and (S,S,R)-9

The general procedure was followed with 0.38 g (1.0 mmol) of (*S*,*S*)-**4** and 0.07 mL (0.15 g, 1.1 mmol) of methyl iodide. The isolated product (0.22 g, 57% yield) consisted of a 65:35 mixture of (*S*,*S*,*S*)-**9** and (*S*,*S*,*R*)-**9** diastereomeric products, which proved inseparable by column chromatography, but yielded their relevant NMR spectroscopic characteristics.

(*S*,*S*,*S*)-**9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.64 (d, J = 7.3 Hz, 3H), 3.70 (s, 2H), 4.62 (q, J = 7.3 Hz, 1H), 7.13–7.36 (m, 10H), 7.70–7.74 (m, 2H), 7.78–7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 48.6, 50.4, 123.4, 126.3, 128.4, 128.7, 131.9, 134.0, 134.9, 167.3, 177.1.

(*S*,*S*,*R*)-**9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (d, J = 7.3 Hz, 3H), 3.69 (s, 2H), 4.74 (q, J = 7.3 Hz, 1H), 7.13–7.36 (m, 10H), 7.53–7.71 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 48.6, 50.0, 123.1, 126.4, 128.3, 128.6, 131.8, 133.6, 134.4, 167.3, 176.0. HRMS (for the diastereomeric mixture) calcd for $C_{25}H_{21}N_2O_3$ (M^++1): 397.1552. Found: 397.1540.

5.11. (2S,3S,2′S)- and (2S,3S,2′R)-N′-Phthaloylphenylalanil-2,3-diphenylaziridine (S,S,S)- and (S,S,R)-10

The general procedure was followed with 0.38 g (1.0 mmol) of (*S*,*S*)-**4** and 0.13 mL (0.19 g, 1.1 mmol) of benzyl bromide. The isolated product (0.28 g, 59% yield) consisted of an 83:17 mixture of (*S*,*S*,*S*)-**10** and (*S*,*S*,*R*)-**10** diastereomeric products, which could not be separated by column chromatography, but yielded the following spectroscopic data.

(*S*,*S*,*S*)-**10**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.60–3.78 (m, 2H), 3.74 (s, 2H), 4.84 (dd, $J^1 = 10.4$ Hz, $J^2 = 5.9$ Hz, 1H), 7.00–7.30 (m, 19H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.6, 48.7, 56.0, 123.0, 126.4, 126.7, 128.4, 128.5, 128.7, 131.4, 133.5, 134.3, 137.1, 167.3, 175.3.

(*S*,*S*,*R*)-**10**: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 3.4–3.8 (m, 2H), 3.71 (s, 2H), 4.80 (dd, $J^1 = 10.4$ Hz, $J^2 = 5.9$ Hz, 1H), 6.94–7.32 (m, 15H), 7.61–7.71 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.4, 48.7, 56.3, 123.3, 126.3, 126.6, 128.4, 128.8, 131.5, 133.9, 134.9, 136.9, 167.3, 176.3.

HRMS (for the diastereomeric mixture) calcd for $C_{31}H_{25}N_2O_3$ (M^++1): 473.2103. Found: 473.2103.

5.12. (2S,3S,2′S)- and (2S,3S,2′R)-2′-Methyl-N-phthaloylphenylalanil-2,3-diphenylaziridine (2S,3S,2′S)- and (2S,3S,2′R)-11

The general procedure was followed with 0.39 g (1.0 mmol) of **9** (dr = 50:50) and 0.13 mL (0.19 g, 1.1 mmol) of benzyl bromide. The reaction temperature was –20°C (7 h) and then 25°C (overnight). The isolated product (0.30 g, 61.7% yield) was shown by ^{1}H NMR to consist of a 67:33 diastereomeric mixture of the expected doubly alkylated **11** [a 40:60 mixture of these diastereomeric products was obtained in 57.6% yield (0.28 g) when 0.47 g (1.0 mmol) of **10** (dr = 50:50) was treated with 0.15 g (1.1 mmol) of methyl iodide under the same reaction conditions]. Dialkylated (*S*,*S*,*S*)- and (*S*,*S*,*R*)-**11** proved inseparable in our hands.

Diastereomer **1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (s, 3H), 3.43 (d, J = 13.8 Hz, 1H), 4.05 (d, J = 13.8 Hz, 1H), 5.09 (d, J = 9.1 Hz, 1H), 5.24 (d, J = 9.1 Hz, 1H), 7.13–7.43 (m, 15H), 7.68–7.83 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 42.3, 60.5, 79.3, 90.1, 123.1, 125.9, 126.6, 127.1, 127.3, 127.8, 128.2, 128.4, 128.8, 130.7, 131.6, 134.0, 135.9, 139.8, 141.6, 168.5, 169.3.

Diastereomer **2**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 3H), 3.47 (d, J = 13.8 Hz, 1H), 4.15 (d, J = 13.8 Hz, 1H), 5.14 (d, J = 9.4 Hz, 1H), 5.28 (d, J = 9.4 Hz, 1H), 7.13–7.43 (m, 15H), 7.68–7.83 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.6, 41.8, 60.8, 78.6, 90.8, 123.1, 125.9, 126.6, 127.1, 127.3, 127.8, 128.2, 128.5, 128.9, 130.6, 131.7, 134.0, 135.8, 139.3, 141.5, 168.6, 169.1.

5.13. (1′S,1′S,2S)-N′,N′-Bis-(1′-phenylethyl)phenylalanilamide (S,S,S)-12

A solution of 2.56 g (5.2 mmol) of (*S*,*S*,*S*)-**7** in 50 mL of abs. EtOH was treated under nitrogen atmosphere with 0.17 mL (176 mg, 5.5 mmol) of anhyd. hydrazine, and heated to reflux for 3 h. The resulting suspension was filtered and the filtrate concentrated in the rotary evaporator. The residue was dissolved in 50 mL of hot EtOAc, cooled to 4°C, and left standing overnight at this temperature. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated in the rotary evaporator to give the crude product that was purified by flash chromatography (hexane:EtOAc, 1:1) to afford 1.4 g (72.2% yield) of the desired deprotected amine product, mp 142–144°C. $[\alpha]_D^{28} = -27.3$ (c = 2.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.46 (br s, 2H), 1.68 (d, J = 6.9 Hz, 3H), 1.71 (d, J = 6.9 Hz, 3H), 2.47–2.66 (m, 2H), 3.50 (br s, 1H), 4.87 (q, J = 6.9 Hz, 1H), 5.87 (br s, 1H), 6.64 (br d, J = 5.7 Hz, 2H), 6.99 (br s, 2H), 7.13–7.34 (m, 11H). ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 17.5, 19.7, 42.2, 51.8, 52.6, 55.2, 126.2, 126.7, 127.5, 127.6, 128.4, 128.7, 129.7, 138.2, 141.0, 141.8, 176.0. Anal. calcd for $C_{25}H_{28}N_2O$: C, 80.60; H, 7.52. Found: C, 80.82; H, 7.61.

5.14. (S)-Phenylalamine (S)-13

A solution of 400 mg (1.1 mmol) of (*S*,*S*,*S*)-**12**, 5 mL of 6 N HCl, and 1 mL of 1,4-dioxane was heated in a sealed ampoule to 100°C for 18 h. The solution was then allowed to cool to ambient temperature and extracted with two 15 mL portions of CH_2Cl_2. The aqueous phase was evaporated to afford the amino acid hydrochloride, which was dissolved in 2 mL of water and adsorbed to acidic ion exchange resin Dowex 50 W×4. The resin was washed with distilled water until the washings came out neutral, and then the free amino acid was recovered with 1N aqueous NH_3. Evaporation afforded 146.2 mg (82.4% yield) of (*S*)-**13**, mp 269–273°C (decomp.) [lit.[33] mp 270–275°C (decomp.)]. $[\alpha]_D^{28} = -31.7$ (c = 2.1, H_2O) {lit.[33] $[\alpha]_D = -32.7$ (c = 2, H_2O)}.

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