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Tetrahedron 57 (2001) 6487–6496

# Enantioselective synthesis of β-amino acids. Part 11: Diastereoselective alkylation of chiral derivatives of β-aminopropionic acid containing the α-phenethyl group[☆]

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Received 30 January 2001; revised 23 February 2001; accepted 2 March 2001

**Abstract**—Several novel, chiral derivatives of β-aminopropionic acid were studied as potentially useful precursors of enantiopure α-substituted-β-amino acids. In particular, the diastereoselectivity of alkylation of (*R*,*R*)-**2**-Li enolate showed substantial stereoinduction by the bis[α-phenylethyl]amide auxiliary, leading to 80% ds in the methylation reaction. No appreciable effect upon diastereoselectivity was observed by the presence of additives (LiCl, HMPA, DMPU) in the reaction. On the other hand, stereoinduction by the α-phenylethylamino group in the methylation of ester enolate (*S*)-**3**-Li was lower (65% ds) under standard conditions (THF, −78°C) but improved to 81% ds in the presence of 3 equiv. of HMPA as cosolvent. 'Matched' and 'mismatched' derivatives, (*R*,*R*,*S*)-**11** and (*R*,*R*,*R*)-**11**, respectively, were methylated via their corresponding lithium enolates. Observed diastereoselectivities generally followed the anticipated tendencies based on double stereoinduction. Thus diastereoselectivity reached 89% ds in the methylation of the matched isomer, (*R*,*R*,*S*)-**11**-Li. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The great importance of amino acids in physiological and pharmacological events is well known. Furthermore, biological interactions are usually stereospecific[2] and this has led during the last two decades to an unprecedented amount of research work directed to the enantioselective synthesis of amino acids.[3,4]

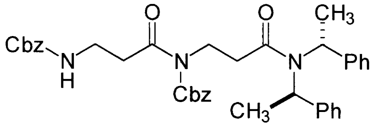
Among the various methods developed for the preparation of enantioenriched α-amino acids, those employing chiral glycine derivatives[5] (Fig. 1) have been particularly successful. In this regard, chiral glycinamide (*S*,*S*)-**1**, incorporating α-phenylethylamine as chiral auxiliary,[6] was recently used as convenient starting material for the preparation of enantiopure α-substituted α-amino acids.[7] (Scheme 1).

Our attention turned then to the potential of chiral derivatives of β-aminopropionic acid, such as (*R*,*R*)-**2** and (*S*)-**3**, as precursors for the asymmetric synthesis of α-substituted β-amino acids (Chart 1). While this work was being carried out, the groups of Lavielle[8] and Lum[9] described conceptually related studies with compounds **M** and **N** (Chart 1).[10]

## 2. Results and discussion

### 2.1. Stereoselectivity of alkylation of (*R*,*R*)-2

Chiral substrate (*R*,*R*)-**2** was obtained in 44% overall yield from β-alanine, following the synthetic route shown in Scheme 2. Protection of the amino group with benzyl chloroformate (CbzCl) was followed by treatment with thionyl chloride to afford the corresponding acid chloride, which was added to bis[(*R*)-α-phenylethyl]amine to give chiral amide (*R*,*R*)-**4**, accompanied with varying amounts of chiral dipeptide (*R*,*R*)-**5**.



(*R*,*R*)-**5**

*N*-Alkylation of (*R*,*R*)-**4** with benzyl bromide proceeded then in 81% yield to afford the desired chiral β-alanine derivative (*R*,*R*)-**2**. (Scheme 2).

Alkylation of chiral amide (*R*,*R*)-**2** was accomplished via

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[☆] For Part 10, see Ref. 1.

*Keywords*: alkylation; asymmetric induction; amino acids and derivatives; diastereoselection; enolates; solvent effects.

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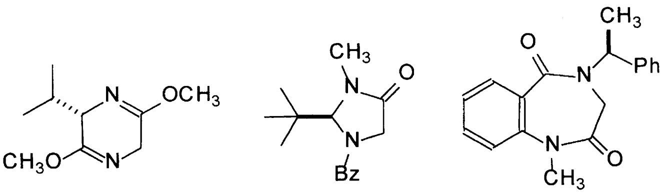
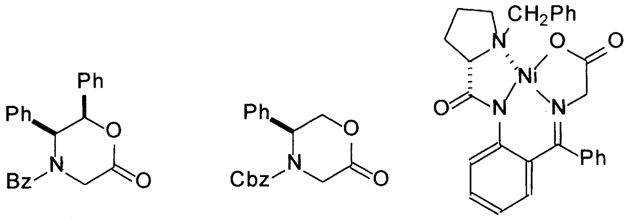
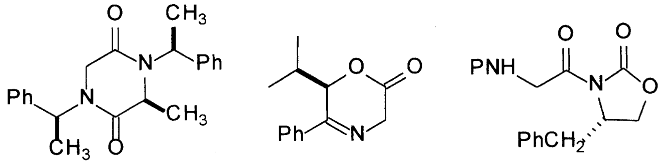
PII: S0040-4020(01)00540-3



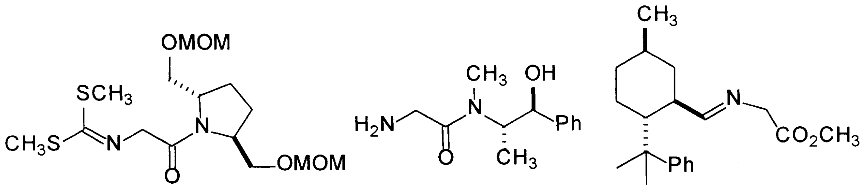
**A**, Schoellkopf, ref. 5a **B**, Seebach, ref. 5b **C**, Juaristi, ref. 5c



**D**, Williams, ref. 5d **E**, Dellaria, ref. 5e **F**, Belokon, ref. 5f

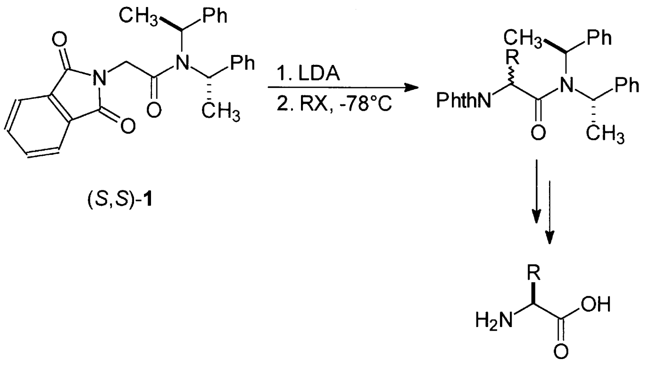


**G**, Sandri, ref. 5g **H**, Nájera, ref. 5h **I**, Evans, ref. 5i



**J**, Katsuki, ref. 5j **K**, Myers, ref. 5k **L**, Duhamel, ref. 5l

**Figure 1.** P=protecting group; MOM=methoxymethyl.

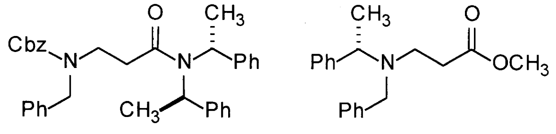


(*S*,*S*)-**1**

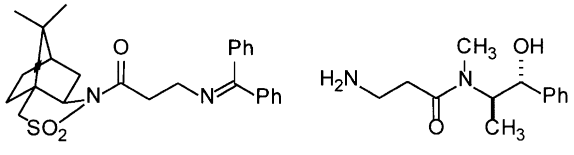
**Scheme 1.**

enolate formation with lithium hexamethyldisilylamide (LiHMDS) *in the presence* of the electrophile, in order to minimize β-elimination reaction. Results are summarized in Table 1.

Entries 1 and 5 in Table 1 show that under standard conditions (THF, −78°C) the methylation reaction proceeds with 4:1 diastereoselectivity, whereas the benzylation reaction affords a 2:1 diastereomeric ratio of the products. In contrast with alkylation reactions of chiral glycine derivative (*S*,*S*)-**1**, which are greatly influenced by the presence of



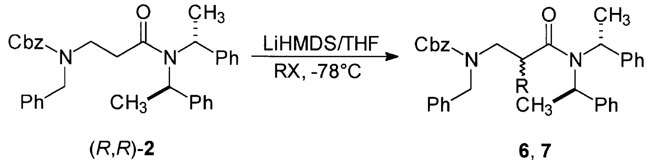
(*R*,*R*)-**2**, this work (*S*)-**3**, this work



**M**, Lavielle, ref. 8 **N** , Lum, ref. 9

**Chart 1.**

**Table 1.** Diastereoselectivity of enolate (*R*,*R*)-**2**-Li alkylations



| Entry | RX | Additive | dr[a] | Yield (%) |
|---|---|---|---|---|
| 1 | $CH_3I$ | – | 80:20 | 65 |
| 2 | $CH_3I$ | LiCl[b] | 79:21 | 60 |
| 3 | $CH_3I$ | DMPU[c] | 76:24 | 65 |
| 4 | $CH_3I$ | HMPA[d] | 80:20 | 49 |
| 5 | $PhCH_2Br$ | – | 66:34 | 50 |
| 6 | $PhCH_2Br$ | LiCl[b] | 67:33 | 28 |
| 7 | $PhCH_2Br$ | DMPU[c] | 56:44 | 50 |
| 8 | $PhCH_2Br$ | HMPA[d] | 60:40 | 43 |

[a] Diastereomeric ratio.
[b] Lithium chloride, 6 equiv.
[c] *N*,*N*-Dimethylpropylene urea, 6 equiv.
[d] Hexamethylphosphoramide, 1 equiv.

LiCl salt or DMPU as cosolvent,[6] the diastereoselectivity of the alkylation reaction of chiral β-alanine derivative (*R*,*R*)-**2** is essentially unaffected after incorporation of LiCl (entries 2 and 6 in Table 1) or polar aprotic solvents DMPU and HMPA (entries 3,4,7, and 8 in Table 1).

The absolute configuration of the newly created stereogenic center in the major diastereomeric product of methylation of (*R*,*R*)-**2**[11] was ascertained by hydrogenolytic removal of the *N*-benzyl and *N*-Cbz protecting groups, followed by acid hydrolysis to the known β-amino acid (*R*)-α-methyl-β-alanine, (*R*)-**8**[11] (Scheme 3).

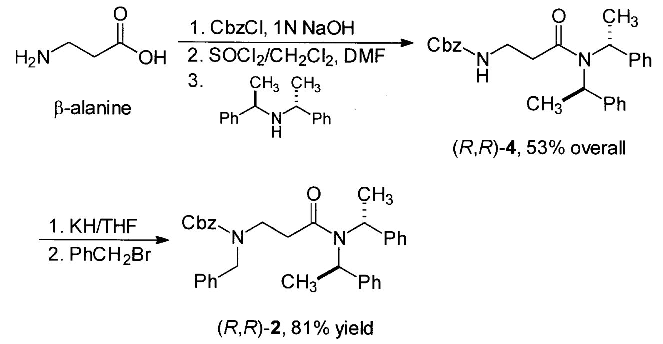
The stereochemical outcome of the alkylation reaction of (*R*,*R*)-**2** may be understood in terms of intermediate **R** in Scheme 4. The *Z*-configurated enolate is anticipated to minimize steric hindrance with the methylenic segment, and the depicted conformation of the α-phenylethyl groups should be favored by allylic $A^{1,3}$ strain considerations.[13] Therefore, the phenyl and the methyl groups at the stereogenic centers differentiate the prochiral C=C group, so that addition of electrophile from the side of the less bulky methyl groups is preferred (Scheme 4).

## 2.2. Stereoselectivity of alkylation of (*S*)-3

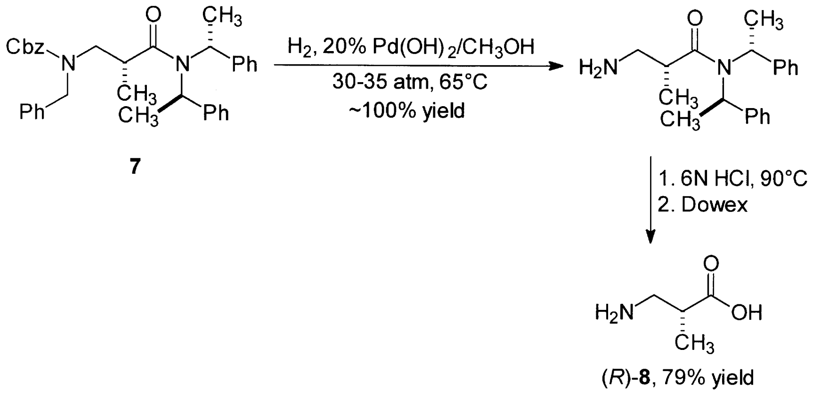
Conjugate addition of (*S*)-α-phenylethylamine to methyl acrylate proceeded in quantitative yield ($CH_3OH$, reflux, 3 h) to give chiral ester (*S*)-**9**, which was *N*-benzylated in 86% yield (Scheme 5).

Alkylation of chiral ester (*S*)-**3** was accomplished via enolate formation in THF solvent, with LiHMDS as the base. Table 2 summarizes the results observed in the methylation reaction of (*S*)-**3** with iodomethane.

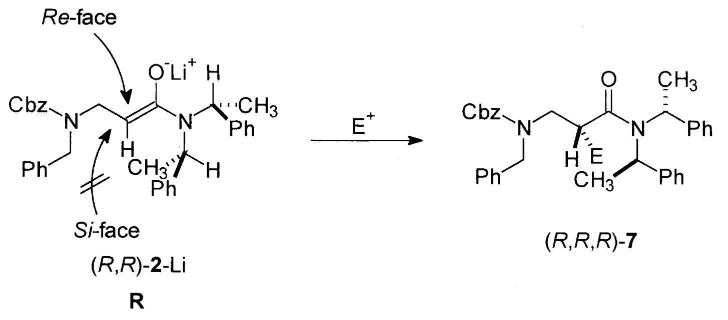
In the absence of additives (THF solvent, −78°C; entry 1 in Table 2), the methylation of enolate (*S*)-**3**-Li afforded a 2:1 mixture of the diastereomeric products **10**, in 68% yield. Nevertheless, both the diastereoselectivity and yield of the reaction improved in the presence of HMPA or DMPU as



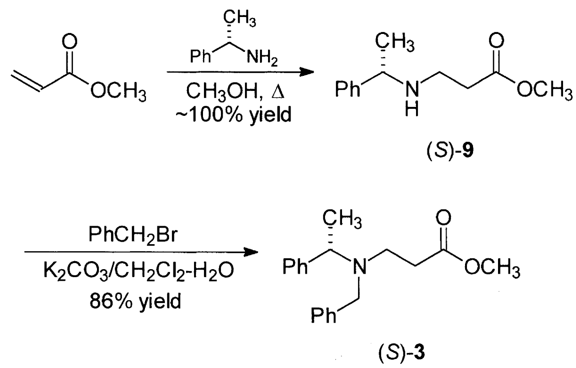
Scheme 2.



Scheme 3.

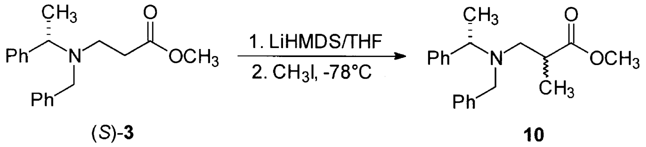


**Scheme 4.**



**Scheme 5.**

**Table 2.** Diastereoselectivity of enolate (*S*)-**3**-Li methylation with iodomethane



| Entry | Additive | dr[a] | Yield (%) |
|---|---|---|---|
| 1 | – | 65:35 | 68 |
| 2 | 1 equiv. HMPA[b] | 72:28 | 77 |
| 3 | 3 equiv. HMPA[b] | 81:19 | 87 |
| 4 | 6 equiv. HMPA[b] | 70:30 | 95 |
| 5 | 1 equiv. DMPU[c] | 71:29 | 68 |
| 6 | 3 equiv. DMPU[c] | 77:23 | 91 |
| 7 | 6 equiv. DMPU[c] | 75:25 | 95 |
| 8 | 6 equiv. LiCl | 60:40 | 64 |

[a] Diastereomeric ratio.

[b] Hexamethylphosphoramide.

[c] *N*,*N*-Dimethylpropylene urea.

cosolvent. Best results were recorded when three molar equivalents of these polar aprotic solvents were used (entries 3 and 6 in Table 2), with diastereomeric product ratios reaching 4:1, and chemical yields approaching the 90–95% range.

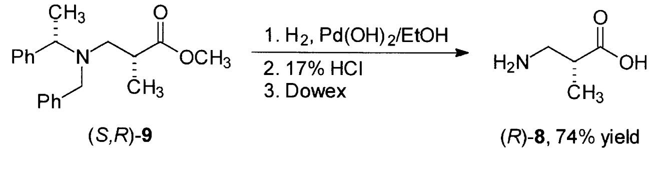
On the other hand, addition of 'inert salt' lithium chloride had a deleterious effect, both on diastereoselectivity and yield (entry 8 in Table 2). It is expected that empirical observations on additive effects such as those reported here will be understood when knowledge of structure and aggregation state of Li enolates is more advanced.[14,15]

The diastereomeric ratios reported in Table 2 were determined by integration of the $^1$H NMR spectra of crude products **10**, and the assignment of the configuration at the newly created center of chirality was established by chemical correlation with known (*R*)-**8** (Scheme 6).

In order to rationalize the observed stereoinduction by the chiral α-phenylethyl auxiliary in enolate (*S*)-**3**-Li ((*S*)-configurated auxiliary induces electrophile addition to the *Re* face of the prochiral double bond; i.e. *unlike* stereoinduction[16]), we resorted to molecular modeling studies by means of PM3 semiempirical calculations.[17] Fig. 2 presents the conformation of minimum energy calculated for enolate (*S*)-**3**-Li. Salient features are the 'parallel' orientation of the two phenyl rings, suggesting perhaps a π–π attractive interaction,[18] and the steric hindrance that should inhibit electrophilic addition on the *Si* face of the enolate. According to this model, easier addition of the electrophile will lead preferentially to the diastereomeric product of (*S*,*R*) configuration—as experimentally observed.

### 2.3. Double stereoinduction in the alkylation of (*R*,*R*,*S*)-10, a derivative of β-alanine containing two chiral auxiliaries

Considering that stereoinduction in enolate (*R*,*R*)-**2**-Li (Section 2.1) is of *like* stereoinduction (i.e. *R*-configurated auxiliary favors reaction on the *Re* face[16]), whereas stereoinduction in enolate (*S*)-**3**-Li (Section 2.2) corresponds to unlike stereoinduction (i.e. *S*-configurated auxiliary favors addition to the *Re* face[16]), we deemed it of interest to determine the diastereoselectivity of alkylation reactions in enolate (*R*,*R*,*S*)-**11**-Li (Scheme 7). According to



**Scheme 6.**

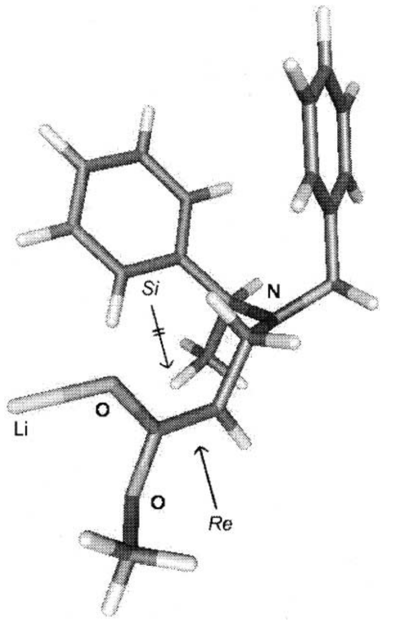
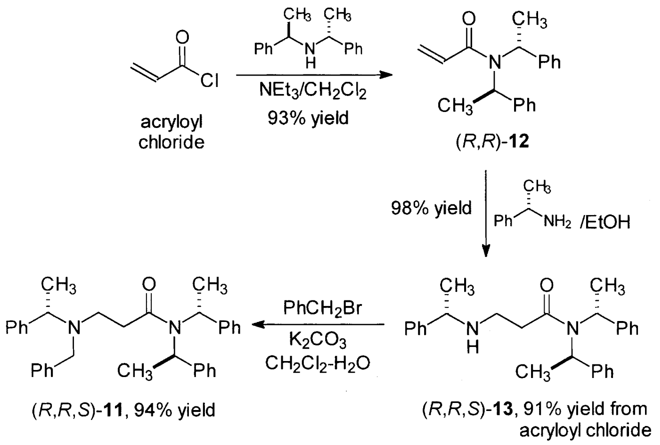


**Figure 2.** Conformation of minimum energy calculated for enolate (*S*)-**3**-Li by means of HyperChem's PM3 semiempirical program.[17]



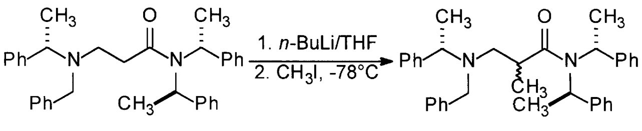
**Scheme 7.**

Masamune's theory,[19] this should be the 'matched' combination of chiral auxiliaries, whereas an all (*R*)- or (*S*)-configurated enolate would correspond to a 'mismatched' pair of auxiliaries.[20]

The preparation of (*R*,*R*,*S*)-**11** was accomplished according to the route delineated in Scheme 7. Acryloyl chloride was treated with bis[(*R*)-α-phenylethyl]amine to afford chiral acrylamide (*R*,*R*)-**12**, which was the substrate for conjugate addition of (*S*)-α-phenethylamine, providing amide (*R*,*R*,*S*)-**13** in 91% overall yield. Finally, *N*-benzylation afforded the desired substrate, (*R*,*R*,*S*)-**11** in 94% yield. (Scheme 7).

In the event, methylation of (*R*,*R*,*S*)-**11** was accomplished with *n*-BuLi as the base for enolate formation. The diastereoselectivity observed in the absence of additive was 75:25, slightly lower than that found in the methylation of (*R*,*R*)-**2**, but significantly higher than that observed in the methylation of (*S*)-**3** (compare entry 1 in Table 3 with entry 1 in Tables 1 and 2).

**Table 3.** Diastereoselectivity of enolate (*R*,*R*,*S*)-**11**-Li methylation



(*R*,*R*,*S*)-**11** **14**

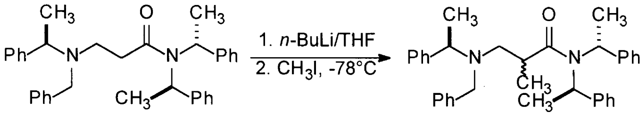
| Entry | Additive | dr[a] | Yield (%) |
|---|---|---|---|
| 1 | – | 75:25 | 73 |
| 2 | HMPA[b] | 89:11 | 73 |

[a] Diastereomeric ratio.
[b] Hexamethylphosphoramide, 3 equiv.

As anticipated from the HMPA effect described in Section 2.2 (cf. entries 1 and 3 in Table 2), the diastereoselectivity in the methylation of (*R*,*R*,*S*)-**11**-Li increased to 89:11 in the presence of 3 equiv. of HMPA. That the major diastereoisomer corresponds to the product with (*R*) configuration at the newly created center of chirality was established by chemical correlation with (*R*)-2-methyl-3-aminopropionic acid.

In the case of the methylation reaction of the mismatched combination of chiral auxiliaries in (*R*,*R*,*R*)-**11**, the observed

**Table 4.** Diastereoselectivity of enolate (*R*,*R*,*R*)-**11**-Li methylation



(*R*,*R*,*R*)-**11** **14**

| Entry | Additive | dr[a] | Yield (%) |
|---|---|---|---|
| 1 | – | 66:34 | 89 |
| 2 | HMPA[b] | 36:64 | 47 |

[a] Diastereomeric ratio.
[b] Hexamethylphosphoramide, 3 equiv.

diastereoselectivity in the absence of additives was 66:34 (see entry 1 in Table 4), which is significantly lower than the one observed in the methylation of (*R*,*R*)-**2**-Li (see entry 1 in Table 1). Interestingly, in the presence of 3 equiv. of HMPA, stereoinduction in the methylation of (*R*,*R*,*R*)-**11** is now dominated by the (*R*)-α-phenylethylamino auxiliary, so that the product of (*S*) configuration at C(2) is predominant (36:64 dr; see entry 2 in Table 4). In congruence with Masamune's principle of double stereoinduction,[19] this diastereoselectivity is lower than that encountered in the methylation of (*S*)-**3**-Li (entry 3 in Table 2).

## 3. Experimental

### 3.1. General

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organolithiums were dried for ca. 12 h at 120°C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[21] The *n*-butyllithium employed was titrated according to the method of Juaristi et al.[22]

TLC: Merck-DC-$F_{254}$ plates, detection by UV light. Flash column chromatography:[23] Merck silica gel (0.040–0.063 mm). Melting points: Mel Temp apparatus, not corrected. $^1H$ NMR spectra: Jeol Eclipse-400 (400 MHz), Bruker Ultra Shield (300 MHz), and Jeol GSX-270 (270 MHz) spectrometers. $^{13}C$ NMR spectra: Jeol Eclipse-400 (100 MHz), Bruker Ultra Shield (75 MHz), and Jeol GSX-270 (67.5 MHz). Chemical shifts ($\delta$) in ppm downfield from internal TMS reference; the coupling constants ($J$) are given in Hz. High-resolution mass spectra (HRMS) were obtained at Instituto de Química, UNAM, México.

**3.1.1. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-carbobenzyloxypropionamide [(*R*,*R*)-4].** A solution containing 10.0 g (112.0 mmol) of β-aminopropionic acid in 112.0 mL of 1N NaOH was cooled in an ice bath and treated with 17.6 mL (21.0 g, 0.12 mol) of benzylchloroformate, followed by slow addition of 112.0 mL of 1N NaOH. The resulting mixture was allowed to warm up to ambient temperature and stirred overnight. The crude product was extracted with three 100 mL portions of diethyl ether, and the aqueous phase was acidified with 6N HCl to pH<4.0. The precipitate that developed was dissolved in $CH_2Cl_2$, dried over anh. $Na_2SO_4$ and concentrated in the rotary evaporator. Recrystallization of the resulting residue from ethyl acetate–ethanol (10:1) afforded 21.5 g (86%) of the desired product (*N*-carbobenzyloxy-3-aminopropionic acid), mp 103–104°C (lit.[24] mp 103–105°C). This crystalline material (0.5 g, 2.2 mmol) was dissolved in 6.0 mL of $CH_2Cl_2$ and three drops of dimethylformamide. The resulting solution was treated with 0.65 mL (9.0 mmol) of thionyl chloride, and heated to reflux for 4 h. The solvent was removed in the rotary evaporator and the residue was washed three times with toluene, and then was redissolved in 4.0 mL of $CH_2Cl_2$, and added to a solution of 1.0 g (4.4 mmol) of (*R*,*R*)-*N*,*N*-bis-(1-phenylethyl)amine[25] in 4.0 mL of toluene, under nitrogen at 0°C. The reaction mixture was allowed to warm up and stirred at ambient temperature for 14 h. The solvent was removed in the rotary evaporator and redissolved in diethyl ether, dried over anh. $Na_2SO_4$, filtered, and concentrated to give an oil that was purified by flash chromatography (hexane–EtOAc, 9:1→7:3) to afford 0.6 g (62% yield) of (*R*,*R*)-**4**, $[\alpha]_D^{28}=+111.5$ ($c=1$, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 300 MHz, 100°C)[26] $\delta$ 1.70 (d, $J=7.1$ Hz, 3H), 1.71 (d, $J=7.1$ Hz, 3H), 2.35–2.46 (m, 1H), 2.57–2.68 (m, 1H), 3.26–3.37 (b, 2H), 5.06 (~s, 2H), 5.13 (q, $J=7.1$ Hz, 2H), 6.55–6.63 (b, 1H), 7.10–7.23 (m, 10H), 7.27–7.42 (m, 5H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 19.5, 36.2, 38.4, 54.0, 66.3, 127.5, 128.1, 128.3, 128.4, 128.6, 129.1, 138.2, 142.3, 156.8, 171.5. HRMS calcd for $C_{27}H_{30}N_2O_3$ ($M^++1$): 431.2335. Found: 431.2354.

**3.1.2. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-(*N*″-carbobenzyloxyaminopropionyl)-*N*-carbobenzyloxypropionamide [(*R*,*R*)-5].** This dipeptide was obtained as side product in the preparation of (*R*,*R*)-**4**. $[\alpha]_D^{28}=+82.6$ ($c=1$, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 400 MHz, 100°C) $\delta$ 1.65 (d, $J=7.3$ Hz, 6H), 2.46 (ddd ≈ quintet, $J^1=15.5$ Hz, $J^2=7.7$ Hz, $J^3=7.6$ Hz, 1H), 2.64 (ddd≈quintet, $J^1=15.5$ Hz, $J^2=J^3=7.6$ Hz, 1H), 3.03 (t, $J=6.8$ Hz, 2H), 3.35 (dt, $J^1=J^2=6.6$ Hz, 2H), 3.94 (dd, $J^1=J^2=7.5$ Hz, 2H), 5.01–5.18 (m, 4H), 5.21 (d, $J=12.5$ Hz, 1H), 5.25 (d, $J=12.5$ Hz, 1H), 6.78 (b, 1H), 7.06–7.55 (m, 20H). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz, 100°C) $\delta$ 19.0, 34.4, 37.4, 38.6, 41.5, 53.5, 53.5, 65.9, 68.6, 127.1, 127.8, 128.0, 128.1, 128.2, 128.2, 128.4, 128.7, 128.9, 136.0, 137.8, 141.8, 154.3, 156.5, 170.4, 173.8. MS (15 eV) *m*/*z* 636 ($M^++1$), 530, 422, 303, 259, 210, 120, 91. HRMS calcd for $C_{38}H_{42}N_3O_6$:636.3074. Found: 636.3074.

**3.1.3. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-benzyl-*N*-carbobenzyloxypropionamide [(*R*,*R*)-2].** To a suspension of 0.58 g (5.1 mmol) of 35% potassium hydride in 40 mL of dry THF under nitrogen, was added 2.0 g (4.6 mmol) of chiral amide (*R*,*R*)-**4** in 60 mL of THF, at 0°C. The resulting mixture was treated with 0.6 mL (5.1 mmol) of benzyl bromide (dropwise addition, still at 0°C), the cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 24 h. Work-up involved the addition of 15.0 mL of saturated aqueous NaCl solution, and extraction with three 20-mL portions of $CH_2Cl_2$. The combined organic extracts were dried over anh. $Na_2SO_4$, filtered, and concentrated in a rotary evaporator to give the crude product, which was purified by flash chromatography (hexane–EtOAc, 9:1). The pure product (1.96 g, 81% yield) presented $[\alpha]_D^{28}=+86.1$ ($c=1$, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 400 MHz, 100°C[26]) $\delta$ 1.65 (d, $J=7.0$ Hz, 6H), 2.38 (ddd, $J^1=14.8$ Hz, $J^2=8.2$ Hz, $J^3=6.4$ Hz, 1H), 2.60 (ddd, $J^1=14.8$ Hz, $J^2=8.2$ Hz, $J^3=6.4$ Hz, 1H), 3.46 (ddd, $J^1=14.1$ Hz, $J^2=8.2$ Hz, $J^3=6.0$ Hz, 1H), 3.56 (ddd, $J^1=14.1$ Hz, $J^2=8.2$ Hz, $J^3=6.0$ Hz, 1H), 4.39 (d, $J=15.5$ Hz, 1H), 4.48 (d, $J=15.5$ Hz, 1H), 5.03–5.13 (b, 2H), 5.14 (s, 2H), 7.06–7.36 (m, 20H). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz, 100°C) $\delta$ 19.0, 34.7, 44.4, 51.1, 53.4, 67.0, 127.2, 127.5, 127.7, 128.0, 128.2, 128.3, 128.7, 128.8, 137.5, 138.7, 141.9, 156.1, 170.8. MS (70 eV) *m*/*z* 520 ($M^+$), 415, 296, 181, 91. HRMS calcd for $C_{34}H_{36}N_2O_3$ ($M^++1$): 521.2804. Found: 521.2816.

**3.1.4. Methyl (*S*)-3-*N*-(1′-phenylethyl)amino propionate [(*S*)-9].** In a 100-mL round-bottom flask fitted with condenser and magnetic stirrer, was placed 1.0 g (11.6 mmol) of methyl acrylate, 1.4 g (11.6 mmol) of (*S*)-α-phenylethylamine and 30 mL of methanol. The reaction mixture was heated to reflux for 3 h, and then the solvent was removed in a rotary evaporator. The desired product (2.4 g, quantitative yield) was obtained as a colorless oil, $[\alpha]_D^{28}=-42.0$ ($c$=1, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.34 (d, $J$=6.6 Hz, 3H), 2.47 (t, $J$=6.6 Hz, 2H), 2.71 (m, 2H), 3.66 (s, 3H), 3.77 (q, $J$=6.6 Hz, 1H), 7.30 (b, 1H), 7.33 (m, 5H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 24.5, 34.7, 42.9, 51.5, 58.2, 126.6, 126.9, 128.4, 145.5, 173.3. HRMS calcd for $C_{12}H_{18}NO_2$: 208.1338. Found: 208.1334.

**3.1.5. Methyl (*S*)-3-[*N*-benzyl-*N*-(1′-phenylethyl)]-aminopropionate [(*S*)-3].** In a 100 mL round-bottom flask fitted with a calcium chloride trap and magnetic stirrer was placed 5.3 g (25.6 mmol) of (*S*)-**9**, 50 mL of $CH_2Cl_2$, and 3.5 g (25.6 mmol) of potassium carbonate in 20 mL of water. The flask was submerged in an ice bath before the additon of 4.4 g (25.6 mmol) of benzyl bromide, and then the reaction mixture was stirred at ambient temperature overnight. The solvents were removed at reduced pressure, the residue was suspended in 15 mL of water, and the product was extracted with three 50-mL portions of $CH_2Cl_2$. The organic phase was dried over anh. $Na_2SO_4$, filtered, and concentrated to give the crude product, which was purified by flash chromatography (hexane–EtOAc, 9:1) to provide 5.7 g (89% yield) of (*S*)-**3** as a colorless oil, $[\alpha]_D^{28}=-32.8$ ($c$=1, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 1.42 (d, $J$=6.6 Hz, 3H), 2.46 (t, $J$=7.0 Hz, 2H), 2.74 (m, 1H), 2.96 (m, 1H), 3.56 (d, $J$=13.9 Hz, 1H), 3.64 (d, $J$=13.9 Hz, 1H), 3.63 (s, 3H), 3.92 (q, $J$=6.6 Hz, 1H), 7.24–7.39 (m, 10H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) $\delta$ 15.3, 33.3, 45.5, 51.4, 54.4, 58.1, 126.8, 127.9, 128.1, 128.2, 128.6, 140.3, 143.3, 173.1. HRMS calcd for $C_{19}H_{24}NO_2$: 298.1807. Found: 298.1811.

### 3.2. General procedure for the reaction of β-alaninamide enolate [(*R*,*R*)-2-Li] with electrophiles

A solution of 0.2 g (0.38 mmol) of chiral amide (*R*,*R*)-**2**, 1.1 equiv. of alkylating agent, and the proper amount of additive (HMPA, DMPU, or LiCl; see Table 1) in 10 mL of THF was cooled to −78°C and kept under nitrogen atmosphere before the addition of 0.42 mL of 1.0 M LiHMDS (1.1 equiv.). The reaction mixture was stirred at −78°C for 3 h, and then at ambient temperature for 0.5 additional hours. The reaction was quenched by the addition of 3 mL satd. aqueous $NH_4Cl$ solution. The product was extracted with three 15-mL portions of EtOAc, the combined organic extracts were dried over anh. $Na_2SO_4$, filtered, and concentrated. Final purification and simultaneous separation of diastereomeric products was accomplished by flash chromatography (hexane–EtOAc, 11:1).

**3.2.1. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-benzyl-*N*-carbobenzyloxy-(2*R*)-2-methylpropionamide [(*R*,*R*,*R*)-6].** This corresponds to the major product of methylation of (*R*,*R*)-**2**-Li (see Section 2.1 and Table 1). $[\alpha]_D^{28}=-21.2$ ($c$=1, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 300 MHz, 100°C[26]) $\delta$ 1.06 (d, $J$=6.4 Hz, 3H), 1.66 (d, $J$=7.0 Hz, 6H), 3.10–3.25 (m, 2H), 3.37–3.50 (m, 1H), 4.13 (d, $J$=15.7 Hz, 1H), 4.48 (d, $J$=15.7 Hz, 1H), 5.00–5.10 (m, 2H), 5.11 (s, 2H), 6.98–7.35 (m, 20H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 17.0, 19.8, 37.3, 51.3, 51.7, 54.2, 67.4, 127.5, 127.8, 128.0, 128.0, 128.4, 128.6, 128.6, 129.1, 129.2, 137.8, 138.9, 142.1, 156.8, 175.4. MS (20 eV) $m/z$ 534 ($M^+$), 429, 385, 310, 181, 91. HRMS calcd for $C_{35}H_{38}N_2O_3$ ($M^++1$): 535.2961. Found: 535.2957.

**3.2.2. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-benzyl-*N*-carbobenzyloxy-(2*S*)-2-methylpropionamide [(*R*,*R*,*S*)-6].** This corresponds to the minor product of methylation of (*R*,*R*)-**2**-Li (see Section 2.1 and Table 1). $[\alpha]_D^{28}=+181.0$ ($c$=1, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 300 MHz, 100°C) $\delta$ 0.65 (d, $J$=6.6 Hz, 3H), 1.68 (d, $J$=7.1 Hz, 6H), 3.09 (ddd, $J^1$=13.5 Hz, $J^2$=6.8 Hz, $J^3$=6.8 Hz, 1H), 3.25–3.40 (m, 2H), 4.11 (d, $J$=15.7 Hz, 1H), 4.54 (d, $J$=15.7 Hz, 1H), 5.14 (d, $J^1$=12.6 Hz, 1H), 5.20 (d, $J$=12.6 Hz, 1H), 7.02–7.37 (m, 20H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 15.9, 19.3, 38.1, 51.9, 52.0, 53.7, 67.5, 127.6, 127.8, 128.0, 128.3, 128.4, 128.6, 129.1, 129.2, 137.7, 138.9, 142.2, 156.9, 175.6. MS (15 eV) $m/z$ 534 ($M^+$), 429, 385, 310, 181, 91.

**3.2.3. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-benzyl-*N*-carbobenzyloxy-(2*R*)-2-benzylpropionamide [(*R*,*R*,*R*)-7].** This corresponds to the major product of benzylation of (*R*,*R*)-**2**-Li (see Section 2.1 and Table 1). $[\alpha]_D^{28}=+19.7$ ($c$=1, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 300 MHz, 100°C[26]) $\delta$ 1.53 (b, 3H), 1.70 (b, 3H), 2.66 (dd, $J^1$=13.2 Hz, $J^2$=4.6 Hz, 1H), 2.95 (dd, $J^1$=13.2 Hz, $J^2$=9.1 Hz, 1H), 3.37 (dd, $J^1$=13.8 Hz, $J^2$=7.5 Hz, 1H), 3.54 (dd, $J^1$=13.8 Hz, $J^2$=6.4 Hz, 1H), 3.61–3.72 (m, 1H), 4.39 (d, $J$=15.6 Hz, 1H), 4.45–4.61 (b, 1H), 4.66 (d, $J$=15.6 Hz, 1H), 4.98–5.25 (m, 3H), 6.66–7.39 (m, 25H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 19.2, 19.7, 37.4, 44.8, 51.2, 52.4, 54.2, 55.7, 67.7, 126.6, 126.9, 128.0, 128.2, 128.4, 128.6, 128.7, 129.1, 129.1, 129.3, 130.0, 137.6, 138.8, 140.1, 156.9, 173.4. MS (20 eV) $m/z$ 610 ($M^+$), 505, 461, 386, 371, 91. HRMS calcd for $C_{41}H_{42}N_2O_3$ ($M^++1$): 611.3274. Found: 611.3264.

**3.2.4. (*R*,*R*)-*N*′,*N*′-Bis(1′-phenylethyl)-*N*-benzyl-*N*-carbobenzyloxy-(2*S*)-2-benzylpropionamide [(*R*,*R*,*S*)-7].** This corresponds to the minor product of benzylation of (*R*,*R*)-**2**-Li (see Section 2.1 and Table 1). $[\alpha]_D^{28}=+174.4$ ($c$=1, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 300 MHz, 100°C) $\delta$ 1.11–1.28 (b, 3H), 1.55–1.75 (b, 3H), 2.56–2.74 (m, 2H), 3.36 (dd, $J^1$=13.6 Hz, $J^2$=8.4 Hz, 1H), 3.44–3.55 (m, 1H), 3.55–3.64 (b, 1H), 3.92 (d, $J$=15.7 Hz, 1H), 4.49 (d, $J$=15.7 Hz, 1H), 4.72–4.85 (b, 1H), 4.93–5.07 (b, 1H), 5.11 (d, $J$=12.5 Hz, 1H), 6.93–7.37 (m, 25H). $^{13}C$ NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 18.8, 19.0, 38.0, 44.6, 50.8, 51.9, 54.1, 55.3, 67.6, 127.0, 127.8, 128.0, 128.5, 128.6, 128.7, 129.0, 129.1, 129.2, 130.0, 137.6, 138.8, 139.6, 141.3, 142.6, 156.8, 174.0. MS (15 eV) $m/z$ 610 ($M^+$), 505, 461, 386, 371, 91.

**3.2.5. (*R*)-2-Methyl-3-aminopropionic acid [(*R*)-8].** In a 250 mL hydrogenation flask was placed 0.46 g (0.86 mmol) of (*R*,*R*,*R*)-**6**, 0.05 g of 20% $Pd(OH)_2$ over charcoal, and 25 mL of ethanol containing five drops of acetic acid. The flask was pressurized to 33 atm of $H_2$ and heated with stirring to 65°C for 12 h. The reaction mixture was filtered over Celite and concentrated in a rotary evaporator to afford the deprotected amine in quantitative yield (0.27 g). This product was transferred to a glass ampoule and dissolved in 7.0 mL of 6N HCl and heated to 90°C for 12 h. The crude product was washed with three 20-mL portions of $CH_2Cl_2$, the aqueous phase was concentrated, and the residue was adsorbed to acidic ion exchange resin Dowex 50W X4. The resin was washed with distilled water until the washings came out neutral, and then the free amino acid was recovered with 0.1N aqueous $NH_4OH$. Evaporation afforded 0.07 g (79% yield) of the chiral β-amino acid (*R*)-**8**. $[\alpha]_D^{28}=-10.8$ ($c$=1.3, 1N HCl), lit.[12] $[\alpha]_D^{28}=-11.8$ ($c$=1, 1N HCl).

## 3.3. General procedure for the reaction of enolate (*S*)-3-Li with electrophiles

In a 50-mL round-bottom flask fitted with magnetic bar was placed 100 mg (0.34 mmol) of (*S*)-**3** and 10 mL of dry THF, under nitrogen atm. The flask was submerged in a dry ice–acetone bath (−78°C) and 1.3 equiv. of 1.0 M LiHMDS was added via syringe. The resulting solution was allowed to react for 45 min before the addition of the electrophile (dropwise addition) and the reaction mixture was stirred at −78°C for 2 h. The reaction was quenched with 3.0 mL of aq. satd. $NH_4Cl$, and the product was extracted with three 20-mL portions of diethyl ether, the combined extracts were dried over anh. $Na_2SO_4$, and concentrated. Final purification was accomplished by flash chromatography.

**3.3.1. Methyl *N*-benzyl-*N*-[(*S*)-(1′-phenylethyl)]-(2*R*)-2-methyl-3-aminopropionate [(*S*,*R*)-10].** The general procedure was followed with 0.5 g (1.7 mmol) of (*S*)-**3** in 50 mL of dry THF, 0.9 mL (5.1 mmol) of HMPA, and 0.14 mL (2.2 mmol) of methyl iodide. $^1H$ NMR analysis showed a mixture of two diastereomeric products in a 81:19 ratio. The major isomer was assigned the 2*R* configuration by chemical correlation with (*R*)-**8** (see text). The diastereomeric product mixture proved inseparable in our hands, but NMR spectroscopic analysis of the major product was feasible. $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.03 (d, $J$=7.0 Hz, 3H), 1.38 (d, $J$=7.0 Hz, 3H), 2.27 (dd, $J^1$=12.8 Hz, $J^2$=6.6 Hz, 1H), 2.66 (m, 1H), 2.94 (dd, $J^1$=12.8 Hz, $J^2$=8.4 Hz, 1H), 3.44 (d, $J$=13.9 Hz, 1H), 3.65 (d, $J$=13.9 Hz, 1H), 3.68 (s, 3H), 3.89 (q, $J$=7.0 Hz, 1H), 7.24–7.34 (m, 10H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 14.7, 15.3, 39.1, 51.4, 53.4, 54.9, 57.4, 126.8, 127.9, 128.7, 128.8, 140.6, 142.8, 176.6.

**3.3.2. (*R*,*R*)-*N*,*N*-Bis(1′-phenylethyl)acrylamide [(*R*,*R*)-12].** To a solution of 1.5 g (16.6 mmol) of acryloyl chloride in 25 mL of dry $CH_2Cl_2$ was added under nitrogen and at 0°C, 3.7 g (16.6 mmol) of (*R*,*R*)-*N*,*N*-bis(1′-phenylethyl)-amine dissolved in 5 mL of dry $CH_2Cl_2$ (dropwise addition via cannula). The resulting solution was stirred for 1 h at 0°C before the addition of 2.3 mL (16.6 mmol) of triethylamine. The reaction mixture was allowed to warm up and stirring was continued at ambient temperature overnight. Water (30 mL) was added to the resulting suspension and the mixture was extracted with three 20-mL portions of $CH_2Cl_2$, the combined organic extracts were dried over anh. $Na_2SO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (hexane–EtOAc, 8.5:1.5) to give 4.3 g (93% yield) of (*R*,*R*)-**12** as a colorless oil, $[\alpha]_D^{28}=+215.0$ ($c$=1, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz) δ 1.75 (s, 6H), 4.72–5.03 (b, 1H), 5.42 (dd, $J^1$=10.3 Hz, $J^2$=2.2 Hz, 1H), 5.83–6.08 (b, 1H), 6.12 (dd, $J^1$=16.8 Hz, $J^2$=10.3 Hz, 1H), 6.29 (dd, $J^1$=16.5 Hz, $J^2$=2.2 Hz, 1H), 6.80–7.50 (m, 10H). $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 17.6, 20.7, 52.5, 126.9, 127.3, 128.3, 130.6, 141.1, 166.8. MS (70 eV) $m/z$ 279 ($M^+$), 174, 120, 106, 77. Anal. calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.81; H, 7.81.

**3.3.3. (*R*)-*N*-(1′-Phenylelthyl)-(*R*,*R*)-*N*′,*N*′-bis(1′-phenylethyl)propionamide [(*R*,*R*,*R*)-13].** A mixture of 2.5 g (9.0 mmol) of chiral acrylamide (*R*,*R*)-**12** and 1.6 g (13.5 mmol) of (*R*)-α-phenylethylamine in 130 mL of ethanol was heated to reflux for 36 h. Solvent removal at reduced pressure and flash chromatography (hexane–EtAOc, 7:3) ($CH_2Cl_2$–$CH_3OH$–$NH_4OH$, 9:0.5:0.05) afforded 3.6 g (98% yield) of an oil identified as (*R*,*R*,*R*)-**13**, $[\alpha]_D^{28}=+135.2$ ($c$=1, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 300 MHz, 100°C[26]) δ 1.27 (d, $J$=6.5 Hz, 3H), 1.69 (d, $J$=7.0 Hz, 6H), 2.35 (ddd, $J^1$=15.1 Hz, $J^2\cong J^3$=6.8 Hz, 1H), 2.51 (ddd, $J^1$=15.2 Hz, $J^2\cong J^3$=6.7 Hz, 1H), 2.59 (b, 1H), 2.67 (dd, $J^1\cong J^2$=6.6 Hz, 2H), 3.71 (q, $J$=6.6 Hz, 1H), 5.13 (q, $J$=7.0 Hz, 2H), 7.10–7.34 (m, 15H). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz, 100°C) δ 19.5, 24.8, 36.6, 44.5, 53.9, 58.2, 127.2, 127.3, 127.4, 128.2, 128.3, 128.6, 128.9, 142.5, 147.1, 172.4. MS (20 eV) $m/z$ 401 ($M^+$+1), 295, 191, 120, 105. HRMS calcd for $C_{27}H_{33}N_2O$ ($M^+$+1): 401.2593. Found: 401.2583.

**3.3.4. (*S*)-*N*-(1′-Phenylethyl)-(*R*,*R*)-*N*′,*N*′-bis(1′-phenylethyl)propionamide [(*R*,*R*,*S*)-13].** Acrylamide (*R*,*R*)-**12** (5.7 g, 20 mmol) and 3.7 g (30.6 mmol) of (*S*)-α-phenylethylamine were handled as described above in the preparation of (*R*,*R*,*R*)-**13**. The isolated product (7.8 g, 98% yield, colorless oil) was identified as (*R*,*R*,*S*)-**13**. $[\alpha]_D^{28}=+98.5$ ($c$=1, $CHCl_3$). $^1H$ NMR (DMSO-$d_6$, 400 MHz, 100°C) δ 1.24 (d, $J$=6.7 Hz, 3H), 1.68 (d, $J$=7.0 Hz, 6H), 2.31 (ddd, $J^1$=15.1 Hz, $J^2$=$J^3$=6.7 Hz, 1H), 2.50 (ddd, $J$=15.0 Hz, $J^2$=$J^3$=6.6 Hz, 1H), 2.60 (ddd, $J^1$=11.7 Hz, $J^2$=$J^3$=6.6 Hz, 1H), 2.70 (ddd, $J^1$=11.7 Hz, $J^2$=$J^3$=6.6 Hz, 1H), 3.66 (q, $J$=6.5 Hz, 1H), 5.13 (q, $J$=7.1 Hz, 2H), 7.11–7.32 (m, 15H). $^{13}C$ NMR (DMSO-$d_6$, 100 MHz, 100°C) δ 19.2, 24.6, 36.2, 44.1, 53.4, 57.7, 126.8, 126.9, 127.1, 127.8, 128.2, 128.5, 142.1, 146.8, 172.0. MS (15 eV) $m/z$ 401 ($M^+$+1), 295, 191, 120, 105. HRMS calcd for $C_{27}H_{33}N_2O$ ($M^+$+1): 401.2593. Found: 401.2602.

**3.3.5. (*S*)-*N*-(1′-Phenylethyl)-*N*-benzyl-(*R*,*R*)-*N*′,*N*′-bis-(1′-phenylethyl)propionamide[(*R*,*R*,*S*)-11].** A solution of 3.0 g (7.5 mmol) of (*R*,*R*,*S*)-**13** in 70 mL of $CH_2Cl_2$ was cooled to 0°C and treated with 1.24 g (9.0 mmol) of $K_2CO_3$ in 45 mL of $H_2O$. The resulting suspension was stirred for 20 min before the addition of 1.1 mL (1.5 g, 9 mmol) of benzyl bromide. The reaction mixture was stirred at ambient temperature for 3 days, the organic phase was separated and the aqueous phase was extracted with three 25-mL portions of $CH_2Cl_2$. The organic extracts were combined, dried over $Na_2SO_4$, filtered, and concentrated in a rotary evaporator. The crude product was purified by flash chromatography (hexane–EtOAc, 8.5:1.5) to give 3.5 g (94% yield) of (*R*,*R*,*S*)-**11** as a colorless oil, $[\alpha]_D^{28}=+77.8$ ($c=1$, CHCl$_3$). $^1$H NMR (DMSO-$d_6$, 300 MHz, 100°C) $\delta$ 1.25 (d, $J=6.8$ Hz, 3H), 1.55 (d, $J=7.1$ Hz, 6H), 2.24 (ddd, $J^1=J^2=8.4$ Hz, $J^3=6.9$ Hz, 2H), 2.73 (dd, $J^1\cong J^2=7.4$ Hz, 2H), 3.42 (d, $J=14.3$ Hz, 1H), 3.52 (d, $J=14.3$ Hz, 1H), 3.76 (q, $J=6.8$ Hz, 1H), 5.02 (q, $J=6.9$ Hz, 2H), 6.95–7.33 (m, 20H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 16.9, 19.5, 35.2, 47.5, 53.6, 55.4, 59.8, 127.3, 127.3, 127.5, 127.7, 128.0, 128.3, 128.6, 128.7, 128.8, 129.0, 141.6, 142.5, 144.9, 172.1. HRMS calcd for $C_{34}H_{39}N_2O$ ($M^++1$): 491.3062. Found: 491.3075.

**3.3.6. (*R*)-*N*-(1′-Phenylethyl)-*N*-benzyl-(*R*,*R*)-*N*′,*N*′-bis-(1′-phenylethyl)propionamide[(*R*,*R*,*R*)-11].** According to the same procedure, 0.8 g (1.9 mmol) of (*R*,*R*,*R*)-**13** was benzylated with 0.28 mL (0.4 g, 2.3 mmol) of benzyl bromide to give 0.6 g (60% yield) of (*R*,*R*,*R*)-**11** as a colorless oil, $[\alpha]_D^{28}=+128.8$ ($c=1$, CHCl$_3$). $^1$H NMR (DMSO-$d_6$, 300 MHz, 100°C) $\delta$ 1.29 (d, $J=6.8$ Hz, 3H), 1.56 (d, $J=7.1$ Hz, 6H), 2.18 (ddd, $J^1=15.0$ Hz, $J^2=9.5$ Hz, $J^3=5.6$ Hz, 1H), 2.33 (ddd, $J^1=15.0$ Hz, $J^2=9.4$ Hz, $J^3=5.6$ Hz, 1H), 2.63 (ddd, $J^1=13.5$ Hz, $J^2=9.3$ Hz, $J^3=5.4$ Hz, 1H), 2.87 (ddd, $J^1=13.5$ Hz, $J^2=9.4$ Hz, $J^3=5.6$ Hz, 1H), 3.45 (d, $J=14.3$ Hz, 1H), 3.53 (d, $J=14.3$ Hz, 1H), 3.81 (q, $J=6.8$ Hz, 1H), 5.00 (q, $J=7.0$ Hz, 2H), 6.97–7.34 (m, 20H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 17.4, 19.5, 35.3, 47.7, 53.7, 55.5, 60.1, 127.3, 127.3, 127.5, 128.1, 128.3, 128.6, 128.7, 128.8, 129.0, 141.6, 142.5, 144.9, 172.1. HRMS calcd for $C_{34}H_{39}N_2O$ ($M^++1$): 491.3062. Found: 491.3069.

### 3.4. General procedure for the reaction of enolates (*R*,*R*,*R*)- and (*R*,*R*,*S*)-11

A solution of 0.2 g (0.4 mmol) of the chiral amide in 10 mL of dry THF was cooled to −78°C (dry ice–acetone bath) and flushed with nitrogen before the addition of 1.1 equiv. of *n*-butyllithium in hexane solution. Stirring was continued for 45 min before the addition of 1.1 equiv. of methyl iodide. The reaction mixture was stirred at −78°C for 3 h, and quenched with 3 mL of a satd. aqueous solution of NH$_4$Cl. The alkylated product was extracted with three 10-mL portions of ethyl acetate, the organic phases were combined, dried over anh. Na$_2$SO$_4$, filtered, and concentrated in the rotary evaporator. Diastereomeric ratios in the product were determined from signal integration in $^1$H NMR spectra.

**3.4.1. (*S*)-*N*-(1′-Phenylethyl)-*N*-benzyl-(*R*,*R*)-*N*′,*N*′-bis-(1′-phenylethyl)-(2*R*)-2-methylpropionamide [(*R*,*R*,*S*,*R*)-14].** $^1$H NMR (DMSO-$d_6$, 300 MHz, 100°C[26]) $\delta$ 0.93 (d, $J=6.5$ Hz, 3H), 1.22 (d, $J=6.8$ Hz, 3H), 1.68 (d, $J=7.1$ Hz, 6H), 2.42 (dd, $J^1=12.9$ Hz, $J^2=8.6$ Hz, 1H), 2.57 (dd, $J^1=12.9$ Hz, $J^2=4.6$ Hz, 1H), 2.62–2.70 (m, 1H), 3.21 (d, $J=14.1$ Hz, 1H), 3.33 (d, $J=14.1$ Hz, 1H), 3.62 (q, $J=6.8$ Hz, 1H), 5.00–5.21 (b, 2H), 7.02–7.38 (m, 20H). $^{13}$C NMR (DMSO-$d_6$, 75 MHz, 100°C) $\delta$ 13.2, 17.3, 19.9, 37.5, 53.6, 54.1, 55.5, 58.4, 127.2, 127.3, 127.5, 127.9, 128.6, 128.7, 128.8, 129.3, 141.4, 142.6, 144.4, 144.6, 176.5. HRMS calcd for $C_{35}H_{41}N_2O$ ($M^++1$): 505.3219. Found: 505.3212.

## Acknowledgements

We are indebted to Conacyt-Mexico for financial support via grant L0006-E9607. We are also grateful to Víctor M. González and María Luisa Rodríguez for their assistance in the recording of NMR spectra.

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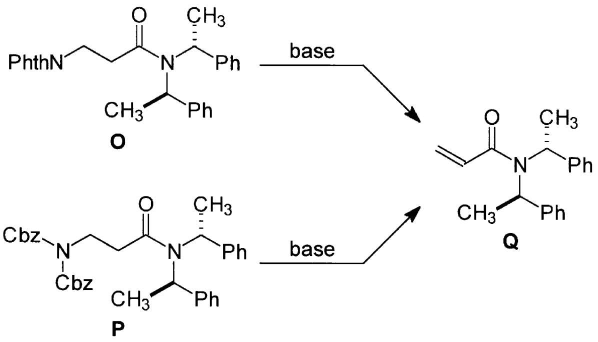

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