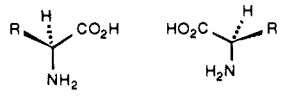
Practical Asymmetric Syntheses of α-Amino Acids through Carbon–Carbon Bond Constructions on Electrophilic Glycine Templates

Robert M. Williams,*† Peter J. Sinclair, Dongguan Zhai, and Daimo Chen

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received July 29, 1987*

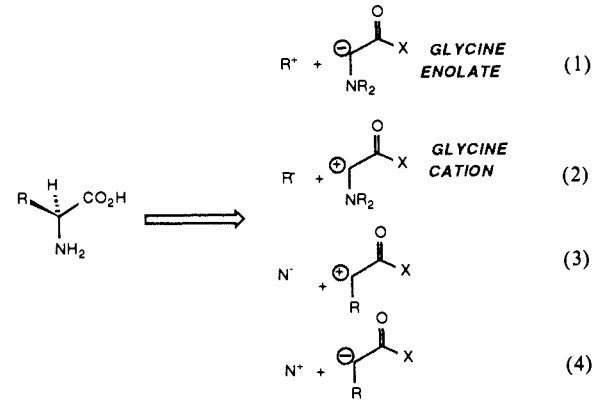
Abstract: The optically active D- and L-*erythro*-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones (**3**) and D- and L-*erythro*-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones (**3**) can be efficiently brominated to serve as electrophilic glycine templates for the asymmetric synthesis of amino acids. It was found that coupling to these templates can proceed with either net retention or net inversion of stereochemistry. The final deblocking to the amino acids is accomplished with either dissolving-metal reduction or catalytic hydrogenolysis. The syntheses of β-ethyl aspartic acid, norvaline, allylglycine, alanine, norleucine, homophenylalanine, *p*-methoxyhomophenylalanine, cyclopentylglycine, and cyclopentenylglycine and a formal synthesis of clavalanine are described. In addition, the direct asymmetric syntheses of *N*-*t*-BOC-allylglycine and *N*-*t*-BOC-cyclopentenylglycine are described.

α-Amino acids[1] serve a central role in biology and chemistry being the fundamental constituents of proteins and mediators of nitrogen metabolism and provide the raw materials from which a large number of biologically important primary and secondary metabolites are constructed.[2] In addition, the relatively abundant proteinogenic amino acids have served as useful chiral, nonracemic reagents for a variety of synthetic applications.[3] The number of naturally occurring α-amino acids currently totals at about 700;[1] many of these natural products possess important biological properties. With the advent of a variety of sophisticated spectroscopic and computational methods to elucidate the relationships between amino acid sequence, protein conformation, and physical, chemical, and biological properties, a tremendous level of interest has been generated in the de novo design and synthesis of unnatural amino acids for the purpose of imparting enzyme-inhibitory, antimetabolite, protease-resistant, and unique conformational-inducing properties to peptides and derivatives. As a consequence, the development of versatile new methodology for the preparation of proteinogenic, natural and unnatural amino acids in optically active form has emerged as an important and challenging synthetic endeavor. The diverse nature of functional groups found in the amino acid α-substituent ("R") and the obligate importance of accessing either the "L" or "D" absolute configuration require the conception and development of numerous strategic approaches to this problem.



L D

The more classical approaches involving the asymmetric hydrogenation of prochiral dehydro amino acid derivatives[4] or the highly stereoselective hydrogenation of chiral, nonracemic dehydro amino acid derivatives[5] suffer from the range of substitutions accessible on the α-R group and the variations in the percent of asymmetric synthesis (i.e., percent ee). Recent advances in this field have focused on the development of chiral, optically pure glycine derivatives that can be homologated via carbon–carbon bond constructions at the α-position through nucleophilic carbanion alkylation (eq 1),[6] or electrophilic carbocation reactions (eq 2).[7] In addition both nucleophilic[8] (eq 3) and electrophilic amination (eq 4)[9] of optically active carbonyl derivatives have very recently been developed. In this account is described the development and utility of versatile electrophilic glycine templates[7d,e] (eq 2) that



permit the construction of either D- or L-configured α-amino acids in high optical purity.

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(1) For reviews, see: (a) Barrett, G. C., Ed.; *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London 1985. (b) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816. (c) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Robert E. Krieger: FL, 1984; Vols. 1–3.

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(3) (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley-Interscience: New York, 1987. (b) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165. (c) Valentine, D.; Scott, J. W. *Synthesis* **1978**, 329. (d) Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 584.

(4) For leading references, see: Morrison, J. D., Ed. *Asymmetric Synthesis, Chiral Catalysis*; Academic: Orlando, FL, 1985; Vol. 5.

(5) (a) Vigneron, J. P.; Kagan, H.; Horeau, A. *Tetrahedron Lett.* **1968**, 5681. (b) Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476. (c) Corey, E. J.; Sachdev, H. S.; Gougoutas, J. Z.; Saenger, W. *Ibid.* **1970**, *92*, 2488.

(6) For asymmetric glycine enolates, see: (a) Fitzi, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 345. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (c) McIntosh, J. M.; Leavitt, R. K. *Tetrahedron Lett.* **1986**, *27*, 3839. (d) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403. (e) Genet, J. P.; Ferroud, S.; Juge, S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573. (f) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65 and references cited therein. (g) Seebach, D.; Imwinkelried, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4. (h) Marco, J. L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 3567. (i) Belokon, Y. N.; Zel'tzer, I. E.; Bakhmutov, V. I.; Saporovskaya, M. B.; Ryzhov, M. G.; Yanovsky, A. I.; Struchkov, Y. T.; Belikov, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2010. (j) Decorte, E.; Toso, R.; Sega, A.; Sunjic, V.; Ruzic-Toros, Z.; Kojic-Prodic, B.; Boesciani-Pahor, N.; Nardin, G.; Randaccio, L. *Helv. Chim. Acta* **1981**, *64*, 1145. (k) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (l) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (m) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (n) Kuzuhara, H.; Watanabe, N.; Ando, M. *J. Chem. Soc., Chem. Commun.* **1987**, 95.

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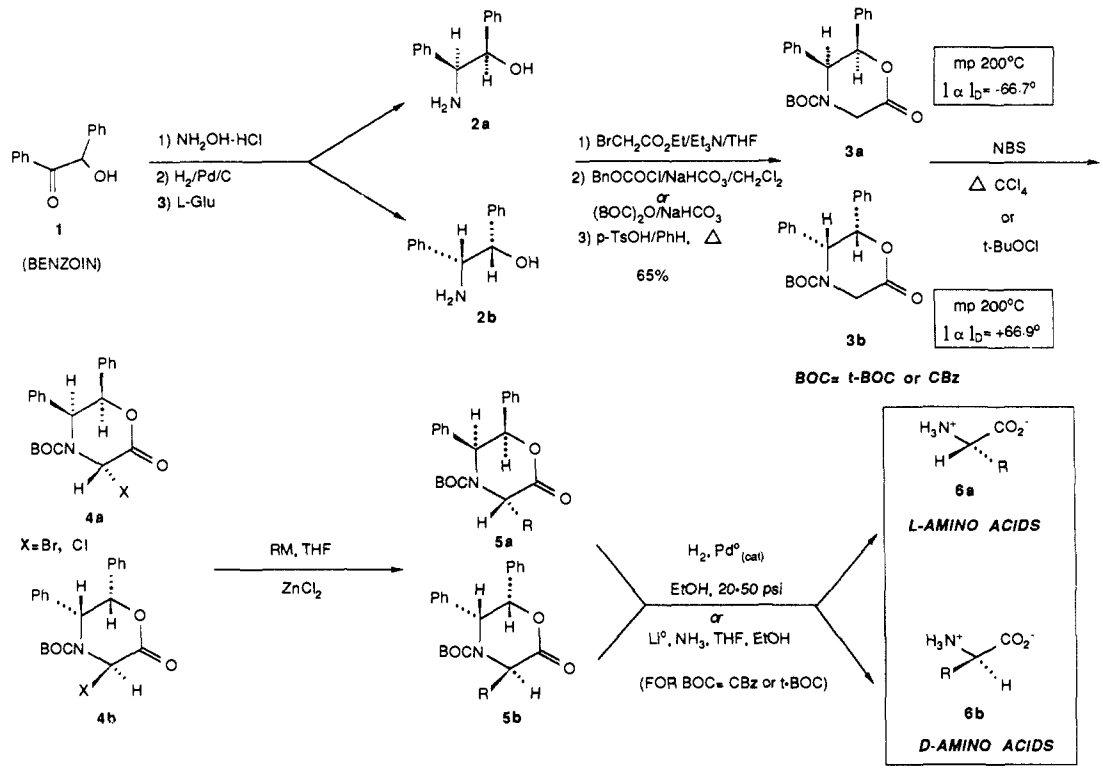
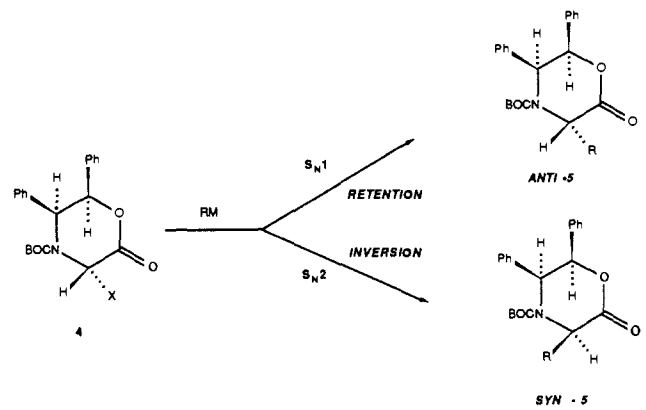
Scheme I



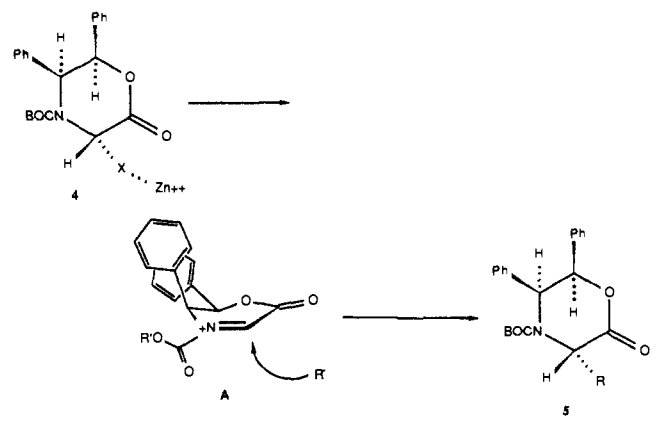
Results

Inexpensive benzoin (**1**) is converted into the corresponding oxime and stereoselectively hydrogenated to furnish the racemic *erythro*-α,β-diphenyl-β-hydroxyethylamine (**2**)[10] and resolved on large scale through the agency of the derived L-glutamic acid diastereomeric salts[10] to furnish both optically active antipodes of **2** (Scheme I). The optical purity of each amino alcohol was established at >98% ee through examination (^{1}H NMR, HPLC) of the corresponding (−)-camphanylamides (see the Experimental Section). Sequential N-alkylation with ethyl bromoacetate followed by N-acylation with either benzyl chloroformate or *tert*-butyloxycarbonyl anhydride and cyclization furnished the optically active lactones **3a,b** in 62–65% overall yield from **2**; the sequence from **1** → **3** does not require any chromatographic separations and is amenable to large scale. Both series of crystalline lactones suffer clean, stereospecific monobromination with 1 mol equiv of *N*-bromosuccinimide (NBS) in warm CCl_4 to afford, after cooling and filtration of insoluble succinimide, the bromides **4a,b** as amorphous white solids. The conversion of **3** to **4** occurs in essentially quantitative yield (crude, by ^{1}H NMR), but significant decomposition of **4** occurs upon attempted silica gel chromatography. However, the bromides **4** can be used directly for the subsequent coupling reactions and can be stored as solids in the dark at low temperature. The corresponding chloride (**4**, X = Cl) can be similarly obtained by chlorination of **3** with *tert*-butyl hypochlorite in CCl_4. Assignment of the anti relative stereochemistry to the bromides **4** is based on spectroscopic evidence as well as indirect chemical evidence as discussed below. The oxidation produces a single stereoisomeric halide as evidenced by ^{1}H NMR in $Cl_2CDCDCl_2$ at 398 K, and it has been assigned the

Scheme II



Scheme III



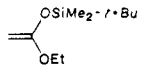
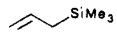
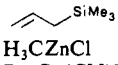
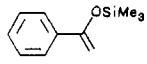
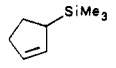
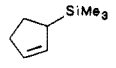
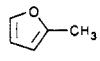
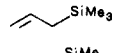
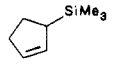
(7) Asymmetric electrophilic glycinates: (a) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *41*, 1693. (b) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131. (c) Schöllkopf, U.; Neubauer, H.-J.; Hauptreif, M. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1066. (d) Sinclair, P.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (e) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021. (f) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.*, in press.

(8) (a) Effenberger, F.; Beisswenger, T.; Isak, H. *Tetrahedron Lett.* **1985**, *26*, 4335. (b) Oppolzer, W.; Pedrosa, R.; Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831. (c) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123.

(9) (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394. (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395. (c) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397. (d) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923.

(10) Weijlard, J.; Pfister, K.; Swanezy, E. F.; Robinbson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216.

Table I

entry	nucleophile	reactn cond	5, % yield	deprotectn method	amino acid,[b] % yield	ee, %
			Amino Acids From *N*-CBz Lactones **4**[a]			
1		$ZnCl_2$/THF, 25 °C	74	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	ethyl aspartate, 85	>96
2		$ZnCl_2$/THF, 25 °C	66	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	norvaline, 93	>98
3		$ZnCl_2$/THF, 25 °C	66	Li^0/NH_3/EtOH	allylglycine, 90	>91
4	H_3CZnCl	THF, −78 °C	46	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	alanine, 100	>96
5	$Bu_2Cu(CN)Li$	THF/Et_2O, −78 °C	48	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	norleucine, 52	>99
6		$ZnCl_{2\,(cat)}$, CH_3CN, 25 °C	72	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	homophenylalanine, 91	>96
7		$ZnCl_2$/THF, 25 °C	82	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	cyclopentylglycine, 91	>96
8		$ZnCl_2$/THF, 25 °C	82	Li^0/NH_3/EtOH	cyclopentenylglycine, 94	>96
9		$ZnCl_2$/THF, 25 °C	64	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	(2-tetrahydrofuryl)glycine, 89	>96
10		$ZnCl_2$/THF, 25 °C	66	$H_2/PdCl_{2\,(cat)}$, EtOH, 20 psi	dihydrofuranomycin, 89	ND[c]
			N-*t*-BOC Amino Acids from *N*-*t*-BOC Lactones **4**			
11		$ZnCl_2$/THF, 25 °C	63	Li^0/NH_3/EtOH	*N*-*t*-BOC-allylglycine, 70	>96
12		$ZnCl_2$/THF, 25 °C	59	Li^0/NH_3/EtOH	*N*-*t*-BOC-cyclopentenylglycine, 70	>95

[a] Lactone **4a** was used for entries 1–12. [b] The absolute configuration of the amino acid obtained in each case was L with the exception of β-ethyl aspartate, which was D. [c] Not determined.

anti relative configuration. At ambient temperature, the lactones **3** and **4** as well as the subsequent homologation products (**5**) are in slow conformational exchange on the NMR time scale providing line-broadened and difficult to interpret spectra. This conformational exchange is presumably associated with rotation about the urethane moiety and/or motion of the phenyl rings relative to conformational mobility of the lactone system itself. Fortunately, at 398 K, the NMR spectra produce sharp, well-resolved signals that allow the assignment of peaks, homonuclear decoupling, NOE studies, determination of diastereomeric ratios, and relative stereochemical assignments.

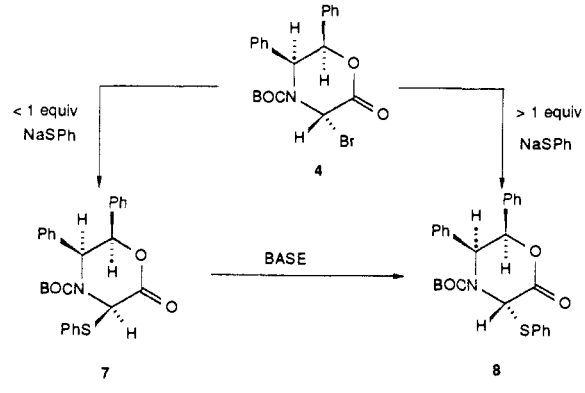
Upon condensation with organometallic reagents, the halides **4** can give rise to two diastereomeric products *anti*-**5** and *syn*-**5** (Scheme II illustrates the D-*erythro* series). The anti adducts are envisioned to arise via S_N1-type nucleophilic addition to an incipient carbocationic species A that results from Lewis acid mediated removal of the halogen atom. Attack of the organometallic reagent (R′M) is expected to occur from the less hindered β-face of A dictated by the pseudoaxially oriented[11] phenyl ring at C-5 (Scheme III).

As shown in Table I, reaction of **4** with allyltrimethylsilane in the presence of $ZnCl_2$ at room temperature for 60 h (Table I, entry 2) led to the virtually exclusive formation of the anti adduct **5** (R = $CH_2CH{=}CH_2$). The relative stereochemistry of this adduct was rigorously secured through single-crystal X-ray analysis.[7d] This determination also firmly established the absolute configurations of the optically active amino alcohols **2** and clarifies a typographical error in the original Tischler[10] resolution manuscript, which called for the use of D-glutamic acid. L-Glutamic acid furnishes the crystalline diastereomeric salt from which D-**2a** is obtained.

In marked contrast to the allyltrimethylsilane coupling, the condensation between the ketene silyl acetal of ethyl acetate and **4a** (CH_2Cl_2, 25 °C) furnished the corresponding syn lactone **5a** (R = CH_2CO_2Et) in 64% yield. This relative stereochemical

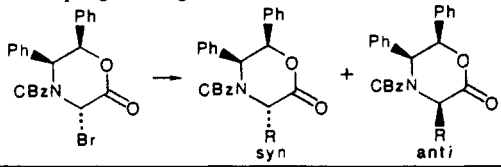
(11) See ref 7d for an X-ray stereostructure of **5** (BOC = CBz, R′ = $CH_2CH{=}CH_2$), which depicts a solid-state conformation of this compound in which the C-5 phenyl group is pseudoaxially disposed.

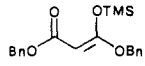
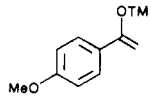
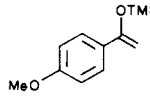
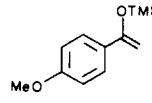
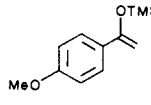
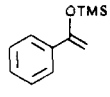
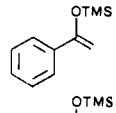
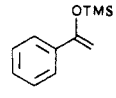
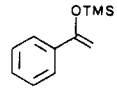
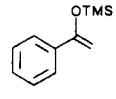
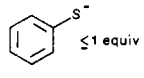
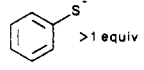
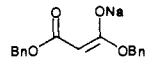
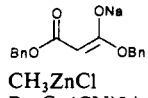
Scheme IV



assignment was firmly established by hydrogenation of the lactone to D-β-ethyl aspartic acid (>96% ee). Since these two coupling reactions must be proceeding through two distinct mechanistic pathways, several lines of evidence were collected to establish the relative stereochemistry of the bromide **4**. By assuming that **4** possesses the anti configuration, it was reasoned that powerful nucleophiles should effect a direct S_N2-type displacement of the bromide, resulting in net *inversion* of stereochemistry affording the corresponding syn isomer. Similarly, weak nucleophiles with a powerful Lewis acid should promote formation of the iminium species (A) and result in S_N1-like substitution with net *retention*. It was found that treatment of **4** with less than 1 mol equiv of sodium phenylthiolate in THF resulted in the almost exclusive formation of a single diastereomeric sulfide **7** (Scheme IV). This compound can be completely epimerized under basic conditions to the *anti*-sulfide **8**. If more than 1 mol equiv of sodium phenylthiolate is used, the anti diastereomer **8** is formed as the exclusive product. Thus, it is reasonable that the initial attack by NaSPh occurs by S_N2 displacement of the bromide to furnish *syn*-**7** which subsequently suffers base-catalyzed epimerization to the thermodynamically more stable anti adduct **8**. This hypothesis is further borne out by the observation that the *syn*-ox-

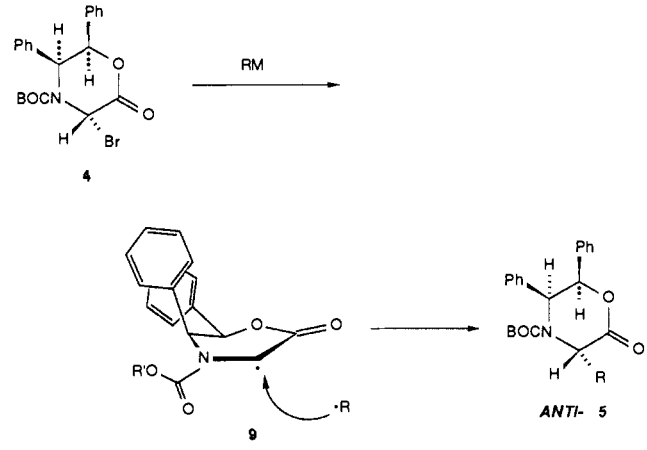
Table II. Coupling of Reagents to **4a**



entry	reagent	solvent	Lewis acid	anti:syn[a]
1		CH_2Cl_2	$ZnCl_2$	1:45
2		THF	$ZnCl_2$	1:14-45
3		THF	AgOTf	1:2
4		THF	$ZnCl_2$	5.6:1
5		CH_2Cl_2	$ZnCl_2$	1:11.2
6		THF	$ZnCl_2$	1:1.6
7		CH_3CN	$ZnCl_2$	2.9:1
8		THF	AgOTf	5.9:1
9		CH_2Cl_2	$ZnCl_2$	1:3.4
10		$CHCl_3$	$ZnCl_2$	1.4:1
11		THF	$ZnCl_2$	7:1
12		CH_3CN	$ZnCl_2$	14.5:1
13		THF	AgOTf	24.5:1
14		THF	$ZnCl_2$	≥45:1
15		THF	AgOTf	≥45:1
16		THF	$ZnCl_2$	≥45:1
17		THF		minor/major
18		THF		≥98:2
19		THF		≥98:2
20		THF		≥98:2
21	CH_3ZnCl	THF		≥98:2
22	$Bu_2Cu(CN)Li_2$	THF/Et_2O		≥98:2

[a] Ratios were determined by ^1H NMR analysis of the crude mixture in DMSO-d_6 at 393 K.

Scheme V



azinone **5a** (R = CH_2CO_2Et) will undergo partial[12] base-catalyzed epimerization while the *anti*-oxazinone **5a** (R = $CH_2CH{=}CH_2$) will not epimerize.

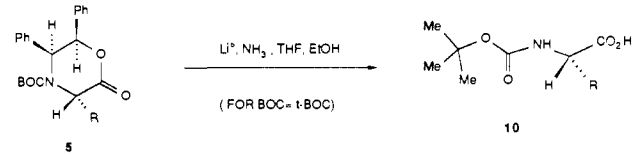
Changing the Lewis acid and solvent for the condensations also affected the overall stereoselectivity of the coupling; a sampling of results is illustrated in Table II. For example, the ketene silyl acetal of ethyl acetate gives ca. 1:45 anti to syn ratio in CH_2Cl_2 with $ZnCl_2$ as the Lewis acid. In contrast, by changing the Lewis acid to a powerful halophile AgOTf, the ratio becomes 1:2. This implies that Ag^+ is capable of promoting formation of the iminium species (A) at rates competitive with direct S_N2 displacement of the bromide by the nucleophilic ketene silyl acetal. This also implies that more electron-rich nucleophiles should show a tendency toward the inversion pathway in the presence of a mild Lewis acid than less reactive nucleophiles.

A good comparative case is the coupling of the silyl enol ethers of *p*-methoxyacetophenone and acetophenone to **4** (Table II, entries 5–13). Under the same set of conditions, the more electron-rich *p*-methoxyacetophenone derivative gives a higher proportion of syn product than acetophenone; in $CH_2Cl_2/ZnCl_2$, 1:11.2 versus 1:3.4 is obtained (entries 5 and 9). By increasing the solvent polarity to help stabilize the formation of the polar iminium species, an increase in the proportion of anti isomer was expected. As can be seen from entries 6 and 7 in Table II, a 1:1.6 ratio is observed in THF and a 2.9:1 ratio is found in acetonitrile. The use of AgOTf in THF (entry 8) brings the ratio up to 5.9:1, favoring the anti product. The fact that the acetophenone derivative gives superior anti/syn ratios (entries 11–13) when compared with the *p*-methoxy substrate indicates that the relatively electron-deficient acetophenone reacts much slower, providing additional opportunity for the iminium species to form. The iminium species is then attacked from the least hindered face, resulting in a preponderance of anti product.

The poorly nucleophilic allyltrimethylsilane derivatives (entries 14–16) give good selectivity (as expected) for the anti products. In the case of the electron-rich organometallic reagents, such as methylzinc chloride or the cuprates, virtually exclusive formation of the anti products is obtained (entries 21 and 22). However, it is believed that these couplings proceed through an electron-transfer radical/radical coupling mechanism. The fact that the bromination of **3** → **4** (a free-radical reaction) proceeds highly stereoselectively to furnish the *anti*-bromides buttresses the hypothesis that free-radical couplings to **4** should proceed stereospecifically (Scheme V). In addition, the somewhat lower yields obtained in these reactions (see Table I) are due to partial reduction of the bromide **4** to **3**, which presumably occurs by the same type of electron-transfer radical-reduction mechanism. Efforts are underway to more fully explore and utilize free-radical

(12) As noted previously, the lactones **3** and **5** dislay marked instability under basic (i.e., enolate formation, base-catalyzed H/D exchange, etc.) conditions. In this case, significant decomposition accompanied the partial epimerization and a final equilibrium ratio could not be clearly ascertained.

Scheme VI



5 10

C–C bond-forming reactions on the templates **4** to construct novel amino acids.

Two other qualitative and useful criteria could be applied to elucidate the relative stereochemistry of the adducts **5**. In virtually every case, the anti diastereomers were nicely crystalline substances, and the corresponding syn isomers were oily. This also provides a convenient means to prepare amino acids consistently in >98% ee by simply recrystallizing the *anti*-oxazinone, which, with the exceptions noted above, are usually the major stereoisomers produced. Thus, even in a marginally stereoselective coupling reaction such as the *p*-methoxyacetophenone reaction, which gave between ~3 and 6:1 anti to syn ratios, a simple crystallization of the anti isomer followed by reduction provided the corresponding amino acid in >98% ee.

Additionally, it has been found that the $\Delta\delta$ of the benzylic methine protons (C-5, C-6 DMSO-d_6 ^{1}H NMR, 270 MHz, 393 K) of syn and anti lactone isomers is characteristic: $\Delta\delta$ for anti ~0.94 to ~1.1 ppm and $\Delta\delta$ for syn ~0.6 to ~0.7 ppm (Figure 1). No explanation for these phenomena are offered, but they are nonetheless real and can serve as a reasonable indication of oxazinone relative stereochemistry. This is particularly important when a new amino acid of previously unassigned absolute stereochemistry is prepared, since the sign of optical rotation will not necessarily designate D or L absolute configuration.

It should also be noted that attempts at NOE studies on the *syn*- and *anti*-oxazinones gave interesting, albeit inconclusive, results. For example, irradiation of the methine at C-3 (δ 5.35) for the *syn*-lactone **5a** (BOC = CBZ, R = CH_2CO_2Et) afforded a difference spectrum that showed a positive enhancement of the resonance at δ 6.32 (methine at C-6) and an unexpected negative enhancement at δ 5.68 (methine at C-5). At first, the negative enhancement at δ 5.68 was thought to be due to power overflow (a partial decoupling), but the very low power used during the double irradiation experiment and the considerable chemical shift differences of the resonances make this explanation seem unlikely. According to Noggle and Schirmer,[13] a three-spin system having a geometry such that $r_{13} \gg r_{12} \sim r_{23}$ and the 1–2–3 angle is obtuse (more accurately, $r_{13} \ll r_{12} \sim r_{23}$ where r_{12} = dipole–dipole relaxation between spins 1 and 2 and is inversely proportional to r^6) will show a positive enhancement for spin 2 and a negative enhancement for spin 3 upon irradiation of spin 1. Irradiation of spin 2 will show (smaller) positive enhancements at spins 1 and 3, while irradiation of spin 3 will give a positive enhancement at spin 2 and a negative enhancement at spin 1. If the linear three-spin case applies to the oxazinone, then irradiation of spin 2 (the δ 6.32 resonance) should result in a positive enhancement for spins 1 and 3. This has been observed, but the enhancements are small. Also, any enhancements observed at δ 5.63 may be due to partial (scalar) decoupling. As expected, NOE experiments carried out on several of the *anti*-oxazinones show no enhancements at all. While not conclusive, a collection of all the properties mentioned above (crystallinity, $\Delta\delta$ shifts for H_5/H_6) and NOE experiments can provide a relatively certain measure as to the relative stereochemistry of the oxazinone and the corresponding absolute stereochemistry of the final amino acid.

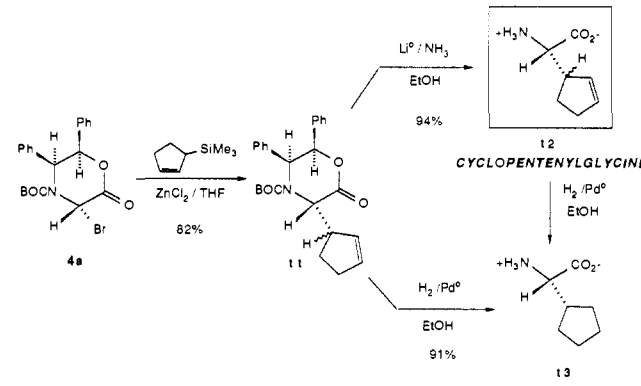
The *N*-CBz derivatives **5** can be cleanly and efficiently converted into the corresponding zwitterionic amino acids by catalytic hydrogenation over a Pd^0 catalyst in ethanol at 20–40 psi at room temperature. Operationally, the amino acids are obtained conveniently in a very pure state by simply filtering off the Pd catalyst, evaporation of the ethanol, trituration of the residue with ether to remove the bibenzyl produced, dissolution of the ether-insoluble residue in water, filtration, and evaporation. With this protocol, ion-exchange chromatography or HPLC purification of the amino acids so obtained is *not* necessary.

In the case of the amino acids containing unsaturation in the α-R group, the catalytic hydrogenolysis obviously produces the corresponding saturated amino acid. However, the oxazinone can be cleanly and efficiently removed by dissolving metal reduction (Li^0/NH_3/EtOH) to furnish the zwitterionic unsaturated amino acids (Scheme VI). The final isolation of the pure amino acid does, however, require a simple filtration of the water-soluble residue through an acidic ion-exchange resin to remove the NH_4Cl used to quench the reduction.

In the case of the *N*-*t*-BOC lactones, the dissolving-metal reduction *directly* furnishes the N-*t*-BOC-protected amino acids in high chemical and optical purity (Table I, entries 11 and 12). To our knowledge, this is the only direct asymmetric synthesis of N-*t*-BOC-protected amino acids, and it economically delivers the amino acid in a form ready for peptide coupling.

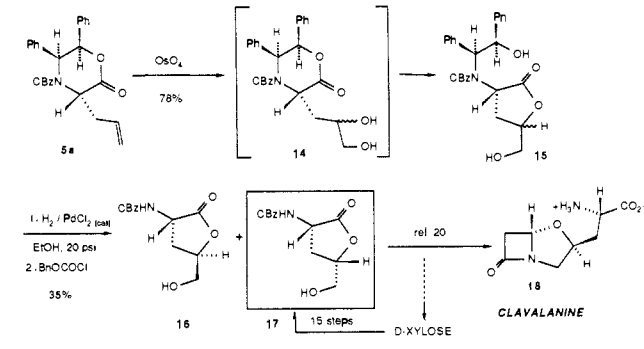
Several additional examples of the methodology possible with the electrophilic glycine template are illustrated in Schemes VII–IX.

Scheme VII



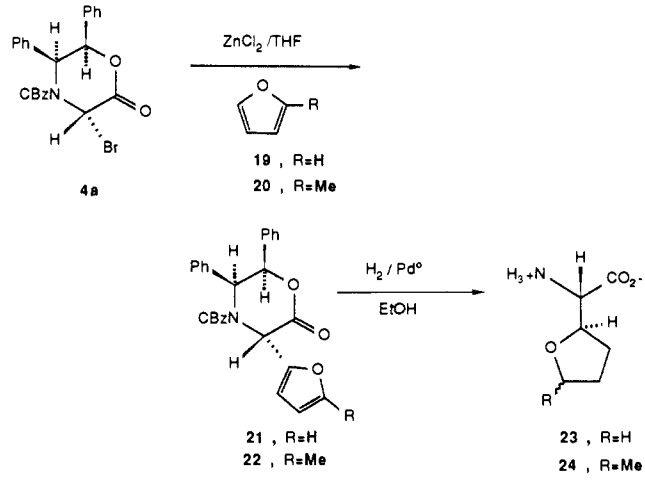
4a t1 t2 t3

Scheme VIII



5a 14 15 16 17 18

Scheme IX



4a **19**, R=H **20**, R=Me **21**, R=H **22**, R=Me **23**, R=H **24**, R=Me

(13) Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect*; Academic: New York, 1971.

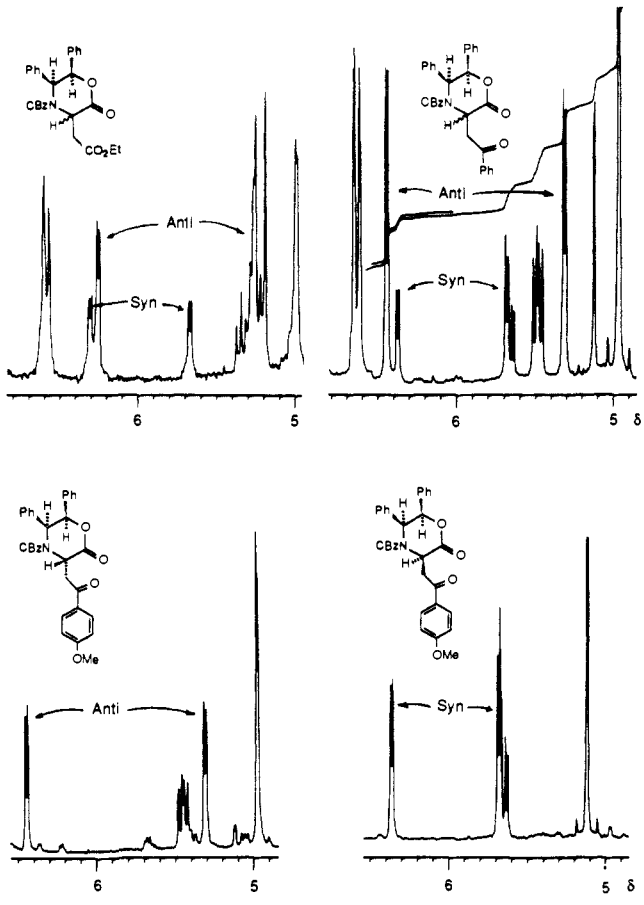


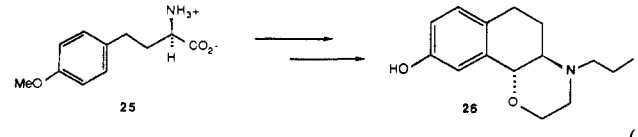
Figure 1. Relative $\Delta\delta$ of H_b and H_c for representative oxazinones. Spectra obtained at 393 K in DMSO-d_6 (200 MHz).

Cyclopentenylglycine (**12**) is a naturally occurring nonproteinogenic amino acid that has been isolated from the seeds of *Hydnocarpus anthelminthica* and the leaves of *Caloncoba echinata*.[14] Racemic cyclopentenylglycine has been shown to be a potent growth inhibitor of *Escherichia coli*[15] as well as a biogenic precursor of unusual cyclopentenyl fatty acids.[16] Cyclopentenylglycine has also been hypothesized to be a precursor of the cyanogenic glycoside deidaclin.[17] Cyclopentenylglycine has been prepared in racemic form via a Sörenson synthesis[15] but has never been synthesized in optically active form. Bromoglycinate **4a** was coupled to commercially available 3-(trimethylsilyl)-1-cyclopentene ($ZnCl_2$, THF) to furnish **11** in 82% yield as a 1:1 mixture of epimers at the cyclopentene methine. This mixture proved inseparable and was deprotected with lithium in liquid ammonia to afford **12** as a diastereomeric mixture. The stereochemistry at the amino acid α-carbon and the percent ee were determined by both direct hydrogenation of **11** to cyclopentylglycine (**13**) and hydrogenation of **12** to furnish **13**, which was determined to be >96% ee. Acylation of **13** and comparison of the specific rotation with literature values confirmed the absolute configuration as (*S*). The synthesis therefore resulted in the preparation of a mixture of diastereomers of cyclopentenylglycine having the (2*S*,2′*R*) and (2*S*,2′*S*) absolute and relative configurations. It is interesting to note that *natural* cyclopentenylglycine is isolated as the *same* diastereomeric mixture; only the (2*S*,2′*R*) isomer displays biological activity.[18] It is also worth noting that cyclopentylglycine (**13**) is itself biologically active, being a competitive inhibitor of isoleucine uptake in *E. coli*.[19]

To illustrate the potential of manipulating the α-R groups of **5** prior to reduction to the amino acid, a formal total synthesis[20] of clavalanine (Ro 22-5417, **18**) has been completed as shown in Scheme VIII. Clavalanine is a clavam antibiotic isolated from *Streptomyces clavuligerus* by a Roche group in 1983.[21] This β-lactam antibiotic is unique in that it is an antimetabolite of *O*-succinylhomoserine and intervenes in methionine biosynthesis, whereas most β-lactam antibiotics inhibit peptidoglycan biosynthesis. A total synthesis of **18** has been reported by Weigele and co-workers[20] that involved the multistep preparation of the dihydroxynorvaline derivative **17** from D-xylose. A very short synthesis of **17** was accomplished by the osmium tetroxide hydroxylation of the allyl lactone **5a**. The initially formed diol **14** undergoes a spontaneous intramolecular trans lactonization to give the γ-butyrolactone derivatives **15** in 78% yield. The OsO_4 reaction is nonstereoselective, since **15** is isolated as a 1:1 diastereomeric mixture. The mixture was hydrogenated, acylated, and separated to provide **17**, which was identical with an authentic sample kindly provided by Roche, plus the epimer **16**. Although the osmylation was nonstereoselective, the brevity of the synthesis of **17** from **5a** illustrates the potential of preparing functionalized amino acids from **5**.

In a preliminary study, electron-rich aromatics, such as furan (**19**) and 2-methylfuran (**20**), have been found to undergo facile Friedel–Crafts-type coupling to **4**. Thus, condensation of **19** and **20** with **4a** in the presence of $ZnCl_2$ in THF furnished the 2-substituted furans **21** and **22**, respectively (Scheme IX). Reduction of **21** provides a 2′-tetrahydrofurylglycine (**23**) as a 5:1 mixture of diastereomers. On the basis of a spin–spin coupling constant of 3.9 Hz for the two methine protons, the (2*S*,2′*R*) absolute and relative stereochemistry has been tentatively assigned, the other (minor) isomer being (2*S*,2′*S*). Hydrogenation of **22** results in the stereoselective production of a major diastereomer of unassigned relative configuration; the absolute stereochemistry at the amino acid α-carbon has also been assigned (*S*). Attempts to effect the partial reduction of **22** to the antibiotic furanomycin have thus far not met with success. It is important that under the mild conditions employed to effect the Friedel–Crafts-type coupling excellent stereocontrol is observed, resulting in the virtually exclusive production of the anti adducts **21** and **22**. It is also of interest that the reduction of the oxazinones **21** and **22** to the amino acids **23**/**24** does not result in the cleavage of the "benzylic" nitrogen/furan residue. The stereoselectivity observed in the reduction of the furan residues is interesting and will be pursued in greater detail.

Many potential uses of unnatural or nonproteinogenic amino acids have been forthcoming in recent years. For example, L-homophenylalanine is a structural constituent of the angiotensin-converting enzyme inhibitor Enalipril,[22] and the relatively inaccessible amino acid *p*-methoxyhomophenylalanine (**25**) has been used to prepare the potent oxazine dopamine agonist **26**.[23]



25 26

(5)

This paper serves to illustrate that the asymmetric electrophilic glycine concept and the "first generation" template **4** provide a

(14) Cramer, V.; Rehfeldt, A. G.; Spener, F. *Biochemistry* **1980**, *19*, 3074.
(15) Dennis, R. L.; Plent, W. J.; Skinner, C. G.; Sutherland, G. L.; Shire, W. *J. Am. Chem. Soc.* **1955**, *77*, 2362.
(16) Cramer, V.; Spener, F. *Eur. J. Biochem.* **1977**, *74*, 495.
(17) (a) Clapp, R. C.; Ettlinger, M. G.; Long, L. *J. Am. Chem. Soc.* **1970**, *92*, 6378. (b) Hegnaver, R. *Pharm. Acta Helv.* **1971**, *46*, 585.
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(19) Harding, W. M.; Shire, W. *J. Biol. Chem.* **1954**, *206*, 401.
(20) Debernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457.
(21) (a) Pruess, D. P.; Kellet, M. *J. Antibiot.* **1983**, *36*, 208. (b) Evans, R. H.; Ax, H.; Jacoby, A.; Williams, T. H. *Ibid.* **1983**, *36*, 213. (c) Muller, J. C.; Toome, V.; Pruess, D. L.; Blount, J. F.; Weigele, M. *Ibid.* **1983**, *36*, 217.
(22) Weller, H. N.; Gordon, E. M. *J. Org. Chem.* **1982**, *47*, 4160 and references cited therein.
(23) Jones, J. H.; Anderson, P. H.; Baldwin, J. J.; Clineschmidt, B. V.; McClure, D. E.; Lundell, G. F.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirshfield, J. M.; Smith, G.; Lumma, P. K. *J. Med. Chem.* **1984**, *27*, 1607.

practical and versatile means to prepare structurally diverse amino acids in high chemical and optical purity. The methodology nicely complements the more extensively studied enolate-based technologies and will continue to be developed in these laboratories for defining the most appropriate niche of amino acids that might best be prepared by this approach.

Experimental Section

Materials and Methods. The optically active amino alcohols (**2a**, **2b**) were prepared according to Tishler et al.[10] on a large scale. The determination of the optical purity is described below. Samples of racemic amino acids were either obtained commercially or synthesized from the racemic lactones **3** for determination of the percent ee in each case. ^{1}H NMR spectra of all lactones were recorded at high temperature (usually 393 K in DMSO-d_6) as specified to obviate the line broadening and splittings observed at ambient temperature. In all cases, the bromide **4** (X = Br) was used; the corresponding chloride gave similar results.

Determination of Optical Purity. General Procedure. The amino acid (~10 mg) was refluxed in EtOH·HCl (2 mL, 1 N), cooled, and concentrated. The residue was treated with (+)- or (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (2 equiv) in 1:1 CCl_4/pyridine (400 μL). After 8 h, the mixture was diluted with Et_2O and washed successively with 1 N HCl, saturated $NaHSO_4$, and water. The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated, and analyzed by ^{1}H and ^{19}F NMR.

Determination of Chemical Yield. The amino acids obtained crude from the hydrogenation were always recovered in greater than the theoretical amount due to a certain fraction of HCl salt resulting from the $PdCl_2$ catalyst. To ascertain the exact amount of amino acid by weight in the residue, the mixture was dissolved in H_2O with a known amount of terleucine (purity titrated against ultrapure acetamide), and ^{1}H NMR integration of a well-resolved resonance of the amino acid against the nine-proton singlet of terleucine was carried out, averaged, and calculated to give the adjusted chemical yields. The accuracy of the technique was compared (where possible) against authentic, commercially available amino acids (either racemic or optically pure) and is accurate to within ±5%. Attempted "purification" of the crude amino acids obtained from the hydrogenation procedure by HPLC or ion-exchange chromatography always resulted in materials that were less chemically pure and had suffered weight loss during the chromatography. This was verified by subjecting commercial authentic samples of pure amino acids to the same attempted purification; in every case nonquantitative recovery of the amino acid was observed. The adjusted chemical yields reported are a conservative and accurate (to within the experimental error noted) gauge of the chemical constitution of the crude residues.

An authentic sample of **17** was furnished by Dr. Manfred Weigele (Roche), and authentic ^{1}H NMR spectra of **12** were furnished by Professor F. Spener.

In cases where authentic *racemic* samples of amino acids were not obtainable from commercial sources, they were prepared from racemic **3** and used in the percent ee determinations.

(1′*S*,2′*R*)-Ethyl *N*-(1′,2-Diphenyl-2′-hydroxyethyl)glycinate. To a suspension of **2a** (51 g, 239 mmol, 1 equiv) in dry THF (1200 mL) was added ethyl bromoacetate (60 g, 359 mmol, 1.5 equiv) followed by addition of triethylamine (49 g, 485 mmol, 2 equiv). After being stirred vigorously for 18 h, the mixture was filtered to remove Et_3N·HBr. The filtrate was evaporated under vacuum to remove excess Et_3N, THF, and ethyl bromoacetate. The solid residue was washed with cold water in a large filter funnel and the product recrystallized from 250 mL of hot absolute ethanol. The crystals were collected and washed with 75 mL of cold (0 °C) absolute ethanol twice: yield 60.3 g (84.3%); ^{1}H NMR (270 MHz, $CDCl_3$, vs $(CH_3)_4Si$) δ 1.20 (3 H, t, J = 7.1 Hz), 2.2 (2 H, br s), 3.15 (1 H, $^1/_2$ AB q, J = 17.5 Hz), 3.29 (1 H, $^1/_2$ AB q, J = 17.5 Hz), 3.95 (1 H, d, J = 6.0 Hz), 4.11 (2 H, q, J = 7.1 Hz), 4.80 (1 H, d, J = 6.0 Hz), 7.17–7.32 (10 H, m); IR (NaCl, $CDCl_3$) 3840–3430, 3330, 3080, 3045, 2995, 2940, 1750, 1460, 1385, 1210, 1035, 915, 740 cm^{-1}; mp 127–128 °C; $[\alpha]^{25}_D$ − 24.3° (c 5.6, CH_2Cl_2). Anal. (recrystallized from absolute EtOH) Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.31; H, 7.16; N, 4.56.

From the antipodal amino alcohol **2b** was obtained the corresponding enantiomer: $[\alpha]^{25}_D$ +24.3° (c 5.6, CH_2Cl_2); mp 127–128 °C; yield on a 63-g scale 84.5%.

(1′*S*,2′*R*)-Ethyl *N*-(Benzyloxycarbonyl)-*N*-(1′,2′-diphenyl-2′-hydroxyethyl)glycinate. To a vigorously stirred mixture of the ethyl ester obtained above (6 g, 20 mmol, 1 equiv) in CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) was added benzyl chloroformate (3.8 g, 22 mmol, 1.1 equiv). After the mixture was stirred for 12 h, the aqueous layer was separated and extracted 3× with CH_2Cl_2, and the combined organic extracts were washed with water. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give a colorless oil, which was carried on crude: 9.6 g; ^{1}H NMR (270 MHz, $CDCl_3$, vs $(CH_3)_4Si$) δ 1.02 (3 H, t, J = 7.1 Hz), 3.7–4.0 (5 H, m), 4.98–5.18 (2 H, m), 5.42–5.53 (2 H, m), 7.1–7.5 (15 H, m); IR (NaCl, $CDCl_3$) 3450, 3060, 3035, 2980, 2900, 1755, 1700, 1500, 1455, 1400, 1190, 1120, 1025, 950, 910, 730, 695 cm^{-1}.

(5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, BOC = CBz). To a stirred solution of the crude *N*-CBz ethyl ester obtained above (9.6 g, 20 mmol, 1 equiv) in benzene (200 mL) in a 500-mL one-neck round-bottom flask equipped with a Soxhlet extractor packed with 60 g of $CaCl_2$ was added *p*-toluenesulfonic acid monohydrate (400 mg, 2.0 mmol, 0.1 equiv). The mixture was brought to reflux for 8 h. The mixture was allowed to cool, and the resultant precipitate was collected, washed with water, and recrystallized from hot absolute ethanol (250 mL) to give 6.0 g (77.9%, two steps) of **3a** as pure white crystals: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs $(CH_3)_4Si$) δ 4.60 (2 H, AB q, J = 17.6 Hz), 5.06 (2 H, AB q, J = 12.6 Hz), 5.29 (1 H, d, J = 3 Hz), 6.20 (1 H, d, J = 3 Hz), 6.66 (1 H, s), 6.70 (1 H, s), 7.0–7.3 (13 H, m); IR (NaCl, paraffin oil) 1745, 1705, 1455, 1440, 1375, 1325, 1215, 1120, 1055 cm^{-1}. Anal. (recrystallized from CH_2Cl_2) Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.61. Found: C, 73.85; H, 5.38; N, 3.5. For the D series lactone **3a**: mp 209–210 °C (recrystallized from EtOH); $[\alpha]^{25}_D$ −67.4° (c 5.5, CH_2Cl_2). For L-series lactone **3b**: mp 209–210 °C (recrystallized from EtOH); $[\alpha]^{25}_D$ +67.3° (c 5.5, CH_2Cl_2).

(1′*S*,2′*R*)-Ethyl *N*-(*tert*-Butyloxycarbonyl)-*N*-(1′,2′-diphenyl-2′-hydroxyethyl)glycinate. Di-*tert*-butyl dicarbonate (34.9 g, 160 mmol, 2 equiv), NaCl (32.8 g, 560 mmol, 7 equiv), and saturated aqueous $NaHCO_3$ solution (160 mL) were added to (1′*S*,2′*R*)-ethyl *N*-(1′,2′-diphenyl-2′-hydroxyethyl)glycinate (23.9 g, 80 mmol, 1 equiv) in $CHCl_3$ (160 mL). The resulting mixture was heated to reflux for 20 h. The reaction mixture was poured into a separatory funnel, the organic layer removed, and the aqueous layer extracted with $CHCl_3$. The combined organic layers were combined, washed twice with water, and dried over anhydrous Na_2SO_4. Filtration, evaporation, and distillation at 1–5 mm pressure removed excess di-*tert*-butyl dicarbonate (which is recovered and reused). The resulting crude *N*-*t*-BOC product was directly used for the subsequent lactonization reaction. L series: mp 60–62 °C (recrystallized from hexane/EtOAc, 3:1); $[\alpha]^{25}_D$ −20.5° (c 5.5, CH_2Cl_2); IR (NaCl, neat) 3440 br, 2970, 2920, 1800, 1730 br, 1430, 1380, 1360, 1300, 1150 br, 1110, 1050, 1020 cm^{-1}.

(5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, BOC = *t*-BOC). To a stirred solution of the crude ester obtained above (32 g) in benzene (750 mL) was added *p*-toluenesulfonic acid (1.5 g, 8 mmol, 0.1 equiv). The flask was fitted with a Soxhlet extractor packed with 75 g of $CaCl_2$, and the mixture was brought to reflux. After reflux continued for 8 h, the solvent was evaporated; the solid was dissolved in CH_2Cl_2 and washed with water to remove the *p*-TsOH; after evaporating the CH_2Cl_2, the product was recrystallized from 750 mL of hot absolute ethanol yielding 20.7 g (73.4%, two steps) of **3a** as white crystals: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 1.25 (9 H, s), 4.52 (2 H, d, J = 1.1 Hz), 5.16 (1 H, d, J = 3.0 Hz), 6.17 (1 H, d, J = 3.0 Hz), 6.63–6.68 (2 H, m), 7.0–7.3 (8 H, m); IR (NaCl, CH_2Cl_2) 3050, 2975, 1755, 1690, 1380, 1255, 1150, 1100, 1045 cm^{-1}; mass spectrum (NH_3, Cl) m/e 370.8 (M^+ + 18, 2.7), 353.8 (M^+ + 1, 0.5), 251.8 (100); mp 205–206 °C; $[\alpha]^{25}_D$ −86.0 (c 5.6, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.08; H, 6.44; N, 3.98. For L series lactone **3b**: mp 206–207 °C; $[\alpha]^{25}_D$ +86.8° (c 5.5, CH_2Cl_2).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-3-bromo-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4a, BOC = CBz). A suspension of **3** (50 mg, 0.129 mmol, 1 equiv) in CCl_4 (15 mL) was brought to reflux. Upon complete dissolution of the oxazinone, NBS (27.6 mg, 0.155 mmol, 1.2 equiv) was added, and the mixture was refluxed for an additional 45 min. The mixture was cooled to 0 °C, filtered to remove succinimide, and concentrated to yield 60 mg (100%) of **4** as a white solid: ^{1}H NMR (200 MHz, $Cl_2CDCDCl_2$, 393 K, vs $(CH_3)_4Si$) δ 5.04 (1 H, $^1/_2$ AB q, J = 12.2 Hz), 5.19 (1 H, d, J = 3.5 Hz), 5.18 (1 H, $^1/_2$ AB q, J = 12.2 Hz), 6.55 (1 H, s), 6.58 (1 H, s), 6.62 (1 H, d, J = 3.5 Hz), 6.93–7.40 (14 H, m); IR (NaCl, neat) 3035, 1760, 1725, 1455, 1390, 1350, 1280, 1265, 1160, 1110 cm^{-1}; mass spectrum (NH_3, Cl) m/e 484.7 (M^+ + 18, 0.4), 386.7 (M^+ − 80, 15.6).

(3*S*,5*S*,6*R*)-3-Bromo-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4a, BOC = *t*-BOC). To a flask containing **3a** (BOC = *t*-BOC; 50 mg, 0.142 mmol, 1 equiv) was added CCl_4 (15 mL). The mixture was brought to reflux. When dissolution was complete, NBS (28 mg, 0.156 mmol, 1.1 equiv) was added, and the mixture was heated to reflux for 1 h, then cooled, filtered to remove succinimide, and concentrated in vacuo to yield **4** as a white solid. The material was used crude.

(3*R*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(phenylthio)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7). To a stirred solution of thiophenol (17 μL, 0.16 mmol, 0.5 equiv) in THF (1 mL) at 0 °C was added NaH (8 mg, 0.16 mmol, 0.5 mg). After 10 min the resultant suspension was added to a solution of **4a** (150 mg, 0.32 mmol, 1 equiv) in THF (3 mL) at 0 °C via syringe. After 2 min the mixture was quenched, diluted with water, and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:4 EtOAc/hexanes) to afford 62.8 mg (79% based on thiophenol) of **7** as a yellowish solid: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 5.20 (2 H, AB q, J = 12.4 Hz), 5.81 (1 H, d, J = 3.6 Hz), 6.03 (1 H, s), 6.19 (1 H, d, J = 3.6 Hz), 7.0–7.5 (20 H, m); IR (KBr) 1760, 1695, 1405, 1300, 1275, 1225 cm^{-1}; mass spectrum (NH_3, Cl) m/e 512.6 (M^+ + 18, 4.5), 495.7 (M^+ + 1, 0.6), 494.8 (M^+, 0.2); mp 158–160 °C (recrystallized from EtOAc/hexanes); $[\alpha]^{25}_D$ +93.6° (c 1.04, CH_2Cl_2).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(phenylthio)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8). To a stirred suspension of NaH (37 mg, 0.78 mmol, 1.2 equiv, 50% dispersion in oil) in THF (3 mL) at 0 °C was added the thiophenol (80 mL, 0.71 mmol, 1.1 equiv) via syringe. After 5 min the resultant white suspension of sodium thiophenolate was added to a solution of **4a** (301 mg, 0.65 mmol, 1 equiv) in THF (4 mL) at 0 °C via syringe. The mixture immediately turned orange and a precipitate formed. After 1 **h** the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:4 EtOAc/hexanes) to afford, after recrystallization (EtOAc/hexanes), 146 mg (45%) of **8** as a white solid: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 5.06 (2 H, AB q, J = 12.5 Hz), 5.54 (1 H, d, J = 3 Hz), 6.06 (1 H, s), 6.22 (1 H, d, J = 3 Hz), 6.58 (1 H, s), 6.61 (1 H, s), 7.0–7.8 (18 H, m); IR (KBr) 1745, 1710, 1385, 1340, 1290, 1265, 1245, 1045 cm^{-1}; mass spectrum (NH_3, Cl) m/e 512.1 (M^+ + 17, 0.1); mp 171–172 °C (recrystallized from EtOAc/hexanes); $[\alpha]^{25}_D$ +13.0° (c 1.42, CH_2Cl_2).

(3*R*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-[(ethoxycarbonyl)methyl]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, R = CH_2CO_2Et). To a stirred solution of **4a** (226 mg, 0.48 mmol, 1 equiv in CH_2Cl_2 (11 mL) was added ethyl acetate *t*-butyldimethylsilyl ketene acetal (450 μL, 2.42 mmol, 5 equiv) followed by addition of $ZnCl_2$ (575 μL, 0.44 mmol, 0.9 equiv, 0.76 M in THF). After 4 min the reaction was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:4 EtOAc/hexanes) to afford 179 mg (78%) of **5a** as a colorless oil: ^{1}H NMR (200 MHz, DMSO-d_6, 380 K, vs $(CH_3)_4Si$) δ 1.15 (3 H, t, J = 7.0 Hz), 2.73 (2 H, d, J = 5.8 Hz), 4.04 (2 H, q, J = 7.0 Hz), 5.19 (2 H, s), 5.35 (1 H, t, J = 5.8 Hz), 5.67 (1 H, d, J = 3.0 Hz), 6.32 (1 H, d, J = 3.0 Hz), 6.88–6.93 (2 H, m), 7.16–7.32 (13 H, m); IR (NaCl, neat) 3060, 3030, 2980, 1730, 1700, 1400, 1370, 1290, 1240, 1215 cm^{-1}; mass spectrum (NH_3, Cl) m/e 491.6 (M^+ + 18, 0.7), 472.6 (M^+, 32.9); $[\alpha]^{25}_D$ +43.6° (c 0.6, CH_2Cl_2).

(*R*)-β-Ethyl Aspartate (6b, R = CH_2CO_2Et). To a solution of **5a** (R = CH_2CO_2Et; 86.5 mg, 0.18 mmol, 1 equiv) in THF (2 mL) plus absolute EtOH (2 mL) was added $PdCl_2$ (19 mg, 0.05 mmol, 0.3 equiv). The system was flushed with H_2 and hydrogenated at 20 psi for 24 h at 25 °C. The mixture was filtered through Celite to remove catalyst, concentrated, and triturated with Et_2O affording 34.2 mg (111%) of β-ethyl aspartate as a white powder: >96% ee; adjusted chemical yield 85%; ^{1}H NMR (270 MHz, D_2O, vs HOD) δ 1.11 (3 H, t, J = 7.2 Hz), 2.96 (2 H, d, J = 5.1 Hz), 4.08 (2 H, q, J = 7.2 Hz), 4.18 (1 H, t, J = 5.6 Hz); IR (KBr) 3250–2650, 1740, 1715, 1585, 1565, 1490, 1380, 1340, 1230, 1195 cm^{-1}.

(*R*)-Diethyl Aspartate Hydrochloride. To a flask containing (*R*)-β-ethyl aspartate (25 mg, 0.15 mmol, 1 equiv) was added EtOH·HCl (5 mL, 1 N). The mixture was refluxed 1.5 h, cooled, concentrated, and triturated (Et_2O, EtOAc) to afford (*R*)-diethyl aspartate·HCl as a white solid: % ee ≥96; ^{1}H NMR (270 MHz, D_2O, vs HOD) δ 1.12 (3 H, t, J = 7 Hz), 1.15 (3 H, t, J = 7 Hz), 2.90–3.13 (2 H, m), 4.08 (2 H, q, J = 7 Hz), 4.17 (2 H, q, J = 7 Hz), 4.33 (1 H, t, J = 4 Hz); $[\alpha]^{25}_D$ −7.4° (c 1, H_2O) [lit. L-diethyl aspartate·HCl +7.6° (c 1, H_2O)].

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(2′-oxo-2′-phenylethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, R = CH_2COPh) and (3*R*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(2′-oxo-2′-phenylethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, R = CH_2COPh). To a stirred solution of **4a** (300 mg, 0.65 mmol, 1 equiv) in CH_3CN (10 mL) was added the trimethylsilyl enol ether of acetophenone (265 μL, 1.29 mmol, 2 equiv) followed by addition of $ZnCl_2$ (5 mg, 0.04 mmol, 0.06 equiv). After 1.5 h all the bromide had dissolved. After an additional 45 min the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. Crystallization from the crude mixture afforded 131 mg of *anti*-**5a** (40%) as a white solid. The mother liquor was concentrated and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 104 mg as a 5.8:1 mixture of diastereomers, combined yield 72%.

(3*S*,5*S*,6*R*)-**5a** (R = CH_2COPh): ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 3.85 (1 H, dd, J_{vic} = 4.4 Hz, J_{gem} = 16.5 Hz), 4.00 (1 H, dd, J_{vic} = 7.2 Hz, J_{gem} = 16.6 Hz), 4.96 (2 H, s), 5.31 (1 H, d, J = 3.1 Hz), 5.48 (1 H, dd, J_{vic} = 4.41, 7.2 Hz), 6.44 (1 H, d, J = 3.1 Hz), 6.61 (1 H, s), 6.62 (1 H, s), 6.65–7.27 (13 H, m), 7.49–7.66 (3 H, m), 7.99 (1 H, s), 8.03 (1 H, s); IR (NaCl, $CDCl_3$) 3065, 3030, 2915, 1745, 1700, 1600, 1580, 1500, 1450, 1400, 1345, 1275, 1215, 1175 cm^{-1}; mass spectrum (NH_3, Cl) m/e 505 (M^+, 2.8), 251 (2.0); mp 200–201 °C; $[\alpha]^{25}_D$ +5.25° (c 1.2, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{32}H_{27}NO_5$: C, 76.02; H, 5.38; N, 2.77. Found: C, 75.81; H, 5.49; N, 2.88.

(3*R*,5*S*,6*R*)-**5a** (R = CH_2COPh): oil; ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 3.39 (1 H, dd, J = 3.1, 17.1 Hz), 3.64 (1 H, dd, J = 7.4, 17.1 Hz), 5.12 (2 H, s), 5.64 (1 H, d, J = 3.01 Hz), 5.68 (1 H, d, J = 3.2 Hz), 6.37 (1 H, d, J = 3.0 Hz), 6.7 (20 H, m); IR (NaCl, neat) 3050, 2880, 1750, 1700, 1345, 1450, 1205, 1110 cm^{-1}; mass spectrum (NH_3, Cl) m/e 504.8 (M^+, 0.1); $[\alpha]^{25}_D$ +46.4° (c 1.35, CH_2Cl_2).

(*S*)-Homophenylalanine (6a, R = CH_2CH_2Ph). To a solution of **5** (R = CH_2COPh) (133 mg, 0.263 mmol, 1 equiv) in 1:1 EtOH/THF (6 mL) was added $PdCl_2$ (27 mg, 0.079 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 34 h. The mixture was then purged with N_2, filtered through Celite, concentrated to dryness, and triturated with Et_2O leaving 54 mg (114%) of homophenylalanine as a pure white solid: % ee ≥96; adjusted chemical yield ~91%; IR (KBr) 2380–3300, 1735, 1600, 1495, 1450, 1210 cm^{-1}; $[\alpha]^{25}_D$ −43° (c 1, 1 N HCl); ^{1}H NMR (270 MHz, D_2O, 25 °C) δ 2.0–2.2 (2 H, m), 2.55–2.75 (2 H, m), 3.78 (1 H, m), 7.1–7.35 (5 H, m).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(2′-propenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, R = $CH_2CH{=}CH_2$). To a stirred solution of **4a** (110 mg, 0.246 mmol, 1 equiv) in dry THF (2 mL) was added allyltrimethylsilane (150 μL, 0.944 mmol, 4 equiv) followed by addition of $ZnCl_2$ (2.5 mL, 0.472 mmol, 2 equiv, 0.187 M in THF). After 60 h the mixture was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 68.3 mg (67.8%) of **5a** as a white solid. A single-crystal X-ray analysis of this compound has been reported (see ref 7d): ^{1}H NMR (200 MHz, DMSO-d_6, 396 K, vs $(CH_3)_4Si$) δ 2.9 (2 H, m), 4.92 (1 H, t, J = 7 Hz), 5.0 (2 H, AB q, J = 13.2 Hz), 5.17 (2 H, m), 5.27 (1 H, d, J = 3.1 Hz), 5.91 (1 H, m), 6.22 (1 H, d, J = 3.1 Hz), 6.59 (1 H, s), 6.63 (1 H, s), 7.0–7.35 (13 H, m); IR (NaCl, $CDCl_3$) 3095, 3075, 3045, 1760, 1700, 1500, 1450, 1400, 1345, 1310, 1295, 1280, 1240, 1210, 1185, 1115, 1080 cm^{-1}; mp 165 °C; $[\alpha]^{25}_D$ −29.2° (c 1.05, CH_2Cl_2). Anal. (racemic, recrystallized from EtOAc/hexanes) Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.27. Found: C, 75.75; H, 5.97; N, 3.31.

(*S*)-Norvaline (6a, R = *n*-Propyl). To a stirred solution of **5a** (R = $CH_2CH{=}CH_2$) (115 mg, 0.27 mmol, 1 equiv) in absolute EtOH (2 mL) plus THF (2 mL) was added $PdCl_2$ (27 mg, 0.08 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 21 h. The mixture was filtered through Celite to remove catalyst, concentrated, and triturated to give 42.4 mg (134%) of *S*-norvaline as a white powder: % ee ≥98; adjusted chemical yield 93%; ^{1}H NMR (200 MHz, 1 N DCl, D_2O, vs DSS) δ 0.95 (3 H, t, J = 7.3 Hz), 1.44 (2 H, m), 1.95 (2 H, m), 4.11 (1 H, t, J = 6.1 Hz); IR (KBr) 3620–3200, 2950, 2920, 2850, 1600 (s), 1580, 1405, 1350 cm^{-1}; $[\alpha]^{25}_D$ +15.96° (c 1.04, 10% HCl).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, R = CH_3). To a stirred solution of **4a** (301 mg, 0.643 mmol, 1 equiv) in dry THF (10 mL) at −78 °C was added MeZnCl (2.6 mL, 2.2 equiv, 0.54 M in THF) dropwise via syringe. After being stirred for 1 h at −78 °C, the mixture was poured into water and extracted 4× with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 91 mg (35%; 46% based on consumed **3**) of **5a** (R = CH_3) as a white solid and 37 mg (15%) of **3a** as a white solid. **5a** (R = CH_3): ^{1}H NMR (200 MHz, DMSO-d_6, 413 K, vs $(CH_3)_4Si$) δ 1.74 (3 H, d, J = 7.2 Hz), 4.92 (1 H, q, J = 7.2 Hz), 5.00 (2 H, AB q, J = 12.7 Hz), 5.28 (1 H, d, J = 2.9 Hz), 6.21 (1 H, d, J = 2.9 Hz), 6.56 (1 H, s), 6.59 (1 H, s), 7.03–7.24 (13 H); IR (NaCl, neat) 3060, 3030, 2950, 2930, 1760, 1705, 1500, 1455, 1400, 1350, 1285–1265, 1245, 1110, 1080 cm^{-1}; mp 186–187 °C; $[\alpha]^{25}_D$ −50° (c 1.04, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49.

Found: C, 74.52; H, 5.82; N, 3.48.

(*S*)-Alanine (6a, R = CH_3). To a stirred solution of **5a** (R = CH_3) (88 mg, 0.219 mmol, 1 equiv) in 1:1 absolute EtOH/THF (3 mL) was added $PdCl_2$ (22.3 g, 0.065 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 36 h. The mixture was purged with N_2, filtered through Celite to remove the catalyst, concentrated in vacuo, and triturated with Et_2O leaving 23 mg (117%) of (*S*)-alanine as a white powder: % ee ≥96; adjusted chemical yield 100%; ^1H NMR (200 MHz, ~1 N DCl, D_2O, vs DSS) δ 1.18 (3 H, d), 3.75 (1 H, q); IR (KBr) 3600–2200, 1605, 1570, 1435, 1395, 1345, 1285, 1090, 990 cm^{-1}; $[\alpha]^{25}_D$ +2.1° (*c* 0.37, H_2O).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-3-butyl-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, R = *n*-Butyl). To a stirred suspension of CuCN (116 mg, 1.292 mmol, 2 equiv) in dry Et_2O (10 mL) was added *n*-BuLi (1.55 mL, 2.454 mmol, 3.8 equiv) via syringe. The flask was lifted above the surface of the cooling bath for 5 min to facilitate dissolution of the CuCN. The solution of the cuprate was then cooled to −78 °C and transferred via cannula to a flask containing a solution of **4a** (301 mg, 0.6459 mmol, 1 equiv) in dry 1:1 THF/Et_2O (20 mL) stirring at −78 °C. After 50 min the reaction was quenched at −78 °C by addition of saturated aqueous NH_4Cl. The mixture was extracted 4× with CH_2Cl_2. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 82 mg (28%; 48% based on recovered **3**) of **5a** (R = *n*-butyl) as a white solid and 69 mg (28%) **3** as a white solid. **5a** (R = *n*-butyl): ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 0.90 (3 H, br t, *J* = 6.6 Hz), 1.43 (4 H, m), 2.12 (2 H, br q, *J* = 7.4 Hz), 4.80 (1 H, t, *J* = 7.3 Hz), 4.97 (2 H, m), 5.28 (1 H, d, *J* = 2.8 Hz), 6.22 (1 H, d, *J* = 2.8 Hz), 6.55 (1 H, s), 6.58 (1 H, s), 7.00–7.25 (13 H, m); IR (NaCl, $CDCl_3$) 3060, 3025, 2950, 2920, 2860, 1745, 1700, 1490, 1460, 1445, 1390, 1335, 1315, 1305, 1290, 1275, 1260, 1230, 1175, 1100, 1070, 1050 cm^{-1}; mass spectrum (NH_3, Cl) *m/e* 461.2 (M^+ + 18, 6.5), 443.3 (M^+, 8.4); mp 160 °C; $[\alpha]^{25}_D$ −46.0° (*c* 0.76, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{28}H_{29}NO_4$: C, 75.82; H, 6.59; N, 3.16. Found: C, 75.86; H, 6.63; N, 3.17.

(*S*)-Norleucine (6a, R = *n*-Butyl). To a stirred solution of **5a** (R = *n*-butyl; 82.3 mg, 0.186 mmol, 1 equiv) in 1:1 EtOH/THF (3 mL) was added 20% $Pd(OH)_2$ on carbon (39 mg, 0.0557 mmol, 0.3 equiv). The mixture was hydrogenated for 36 h at 30 psi. The mixture was then purged with N_2, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield 12.6 mg (52%) of **6a** as pure white solid: % ee ≥98; adjusted chemical yield 52%; ^1H NMR (270 MHz, D_2O, 25 °C) δ 0.75 (3 H, m), 1.15–1.4 (4 H, m), 1.7–1.9 (2 H, m), 1.85 (1 H, m); IR (KBr) HCl salt 2700–3250, 1740, 1590, 1210 cm^{-1}; $[\alpha]^{25}_D$ +16.12° (*c* 0.67, 10% HCl).

(*S*)-Allylglycine (6a, R = $CH_2CH{=}CH_2$). To a solution of Li^0 (49.2 mg, 7.092 mmol, 20 equiv) in NH_3 (25 mL, distilled from Na^0) was added a solution of **5a** (BOC = CBz, R = $CH_2CH{=}CH_2$) (150 mg, 0.355 mmol, 1 equiv) and EtOH (326 mL) in THF (5 mL) via syringe. After 1 h the blue color dissipated, and the reaction was quenched with excess NH_4Cl. The ammonia was allowed to evaporate, and the residue was diluted with water and extracted with Et_2O. The aqueous layer was loaded onto an ion-exchange column (Dowex 50W-X8, H^+ form), washed with water, and eluted with 1 N NH_4OH. The eluent was concentrated, passed through a Millipore C18 SEPPAK, and concentrated to dryness yielding 36.9 mg (90%) (*S*)-allylglycine as a pure white solid: % ee ≥96; ^1H NMR (200 MHz, D_2O + DCl, vs DSS) δ 2.64–2.84 (2 H, m), 4.20 (1 H, t, *J* = 6.5 Hz), 5.29–5.35 (2 H, m), 5.72–5.87 (1 H, m); IR (KBr) 3300–2700, 1605, 1585, 1510, 1435, 1405, 1360, 1340, 1305, 1260–1110 cm^{-1}; $[\alpha]^{25}_D$ −4.4° (*c* 0.5, 1 N HCl).

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(1′-prop-2′-enyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (5a, BOC = *t*-BOC, R = $CH_2CH{=}CH_2$). To a stirred solution of **4a** (BOC = *t*-BOC; 153 mg, 0.354 mmol, 1 equiv) in dry THF (4 mL) was added allyltrimethylsilane (225 mL, 1.416 mmol, 4 equiv) followed by addition of $ZnCl_2$ (354 mL, 0.708 mmol, 2 equiv, 2 M in THF). After 4 h the mixture was poured into water and extracted 4× with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 87.6 mg (63%) of **5a** (BOC = *t*-BOC, R = $CH_2CH{=}CH_2$) as a white solid and 15.2 mg (15%) of the product that lost the *N*-*t*-BOC moiety as a clear oil (this material could be reprotected to **5a**). **5a**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 1.20 (9 H, s br), 2.87 (2 H, m), 4.88 (1 H, t, *J* = 7 Hz), 5.15–5.29 (3 H, m), 5.84–6.05 (1 H, m), 6.20 (1 H, d, *J* = 3 Hz), 6.55 (1 H, d, *J* = 1.7 Hz), 6.59 (1 H, d, *J* = 1.2 Hz), 7.0–7.3 (8 H, m); IR (NaCl, neat) 3050, 2970, 2920, 1755, 1690, 1375, 1350, 1260, 1155, 1110 cm^{-1}; mass spectrum (NH_3, Cl) *m/e* 411 (M^+ + 18, 0.5), 393.9 (M^+ + 1, 0.5), 294 (100), 251.9 (26); mp 177–178 °C; $[\alpha]^{25}_D$ −45.8° (*c* 1.34, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{28}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 72.37; H, 6.85; N, 3.68.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)allylglycine (10, R = $CH_2CH{=}CH_2$). To a stirred solution of Li^0 (22 mg, 3.23 mmol, 13 equiv) in NH_3 (25 mL) at −33 °C was added a solution of **5a** (BOC = *t*-BOC, R = $CH_2CH{=}CH_2$) (98 mg, 0.25 mmol, 1 equiv) and EtOH (150 mL) in dry THF (5 mL) via syringe. After 15 min the blue color dissipated, and the reaction was quenched with NH_4Cl. The mixture was allowed to warm. After the NH_3 evaporated the residue was diluted with water and extracted 2× with Et_2O. The aqueous layer was carefully acidified with 1 N HCl to pH 3 while being stirred with EtOAc. The layers were separated, and the aqueous layer was extracted 3× with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, concentrated, and separated on PTLC silica gel (eluted with 5% MeOH/CH_2Cl_2) to afford 38 mg (71%) of **10** as a colorless oil: % ee ≥96; ^1H NMR (200 MHz, DMSO-d_6, 310 K, vs $(CH_3)_4Si$) δ 1.37 (9 H, s), 2.2–2.5 (2 H, m), 3.8–4.0 (1 H, m), 5.0–5.2 (2 H, m), 5.6–5.9 (1 H, m), 7.0 (1 H, d, *J* = 8 Hz), 11.65 (1 H, br); IR (NaCl, neat) 3430, 3050, 2980, 1715, 1500, 1370, 1265, 1155 cm^{-1}; mass spectrum (NH_3, Cl) *m/e* 232.9 (M^+ + 18, 1.8), 215.9 (M^+ + 1, 2.1), 214.9 (M^+, 0.3), 116.0 (62.9); $[\alpha]^{25}_D$ −3.8° (*c* 1.5, CH_2Cl_2).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-3-(2′-cyclopentenyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (11, BOC = CBz). To a stirred solution of **4a** (BOC = CBz) (301 mg, 0.646 mmol, 1 equiv) in dry THF (5 mL) was added 3-(trimethylsilyl)cyclopentene (460 μL, 2.584 mmol, 4 equiv) followed by addition of $ZnCl_2$ (646 μL, 1.292 mmol, 2 equiv, 2 M solution in THF). The mixture was stirred for 15 h, poured into water, and extracted 4× with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 240 mg (82%) of **11** as a white solid, as an approximately a 1:1 mixture of diastereomers: ^1H NMR (200 MHz, 393 K, DMSO-d_6 vs $(CH_3)_4Si$) δ 2.05–2.45 (4 H, m), 3.55 (1 H, m), 4.8–5.0 (2 H, m), 5.32 (1 H, d, *J* = 3 Hz), 5.8–6.0 (2 H, m), 6.15–6.25 (1 H, 2 d, *J* = 3 Hz), 6.5–6.6 (2 H, m), 7.0–7.4 (14 H, m); IR (NaCl, CH_2Cl_2) 3030, 1750, 1700, 1450, 1400, 1260, 110 cm^{-1}; mass spectrum (NH_3, Cl) *m/e* 471 (M^+ + 18, 11), 453.5 (M^+, 73), 251.9 (88); mp 188.5–186 °C; $[\alpha]^{25}_D$ −25.8° (*c* 0.94, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09. Found: C, 76.65; H, 6.07; N, 3.09.

Cyclopent-2-enylglycine (12). To a solution of Li^0 (52 mg, 7.549 mmol, 20 equiv) in NH_3 (25 mL, distilled from Na^0) was added a solution of **11** (171 mg, 0.377 mmol, 1 equiv) and EtOH (347 mL) in THF (5 mL) via syringe. After 1 h the blue mixture was quenched with excess NH_4Cl, and the ammonia was allowed to evaporate. The residue was diluted with water and extracted with Et_2O. The aqueous layer was loaded onto an ion-exchange resin (Dowex 50W-X8, H^+ form), washed with water, and eluted with 1 N NH_4OH. The eluent was concentrated, passed through a Millipore C18 SEPPAK, and concentrated to dryness yielding 50 mg (94%) of **12** as a white solid, as a 1:1 mixture of diastereomers. This material was identical by ^1H NMR with the ^1H NMR spectra of the natural mixture kindly provided by Professor F. Spener: ^1H NMR (200 MHz, D_2O + DCl, vs DSS) δ 1.52–1.79 (1 H, m), 1.83–21.4 (1 H, m), 2.29–2.38 (2 H, m), 3.13 (1 H, br s), 3.30–3.41 (1 H, m), 5.56–5.85 (1 H, m), 5.89–5.92 (1 H, m); IR (KBr) 3600–3300, 3050, 2940, 1610, 1585, 1510, 1420, 1340, 1415, 1140, 1120 cm^{-1}; $[\alpha]^{25}_D$ +1.4° (*c* 0.56, 1 N HCl).

(*S*)-Cyclopentylglycine (13). To a solution of **11** (150 mg, 0.33 mmol, 1 equiv) in 1:1 EtOH/THF (6 mL) was added $PdCl_2$ (33 mg, 0.1 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 28 h, then purged with N_2, filtered through Celite to remove the catalyst, concentrated in vacuo, and triturated with Et_2O several times to afford 56 mg (118%) of **13** (adjusted chemical yield 91%) as a pure white solid: % ee ≥96; ^1H NMR (200 MHz, D_2O + DC, vs DSS) δ 1.3–1.9 (8 H, m), 2.36 (1 H, q, *J* = 9 Hz), 3.99 (1 H, d, *J* = 7.4 Hz); IR (KBr) 3600–3300, 2850, 2760, 1605, 1585, 1510, 1420, 1395, 1340, 1130 cm^{-1}; $[\alpha]^{25}_D$ +11.6° (*c* 0.49, 1 N HCl).

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-3-(2′-cyclopentenyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (11, BOC = *t*-BOC). To a stirred solution of **4a** (BOC = *t*-BOC) (153 mg, 0.3541 mmol, 1 equiv) in dry THF (4 mL) was added 3-(trimethylsilyl)cyclopentene (250 μL, 1.416 mmol, 4 equiv) followed by addition of $ZnCl_2$ (350 μL, 0.708 mmol, 2 equiv, 2 M in THF). After 16 h the mixture was poured into water and extracted 4× with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 84.9 mg (58.7%) of **11** as a white solid as approximately a 2:1 mixture of diastereomers and 20 mg (18%) of the corresponding lactone that lost the *t*-BOC group as a clear oil. **11**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 1.13 (9 H, br s),

2.05–2.45 (4 H, m), 3.49 (1 H, m), 4.84 (1 H, 2 s), 5.19 (1 H, s), 5.8–6.0 (2 H, m), 6.22 (1 H, 2 d, J = 3 Hz), 6.54 (1 H, s), 6.57 (1 H, s), 7.0–7.3 (8 H, m); IR (NaCl, CH_2Cl_2) 3050, 2980, 1760, 1700, 1455, 1380, 1370, 1355, 1340, 1265, 1160, 1115 cm^{-1}; mp 183–184.5 °C. Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.56; H, 7.08; H, 3.30.

(2*S*,1′*S*)- and (2*S*,1′*R*)-*N*-(*tert*-Butyloxycarbonyl)cyclopentenylglycines (10, R = 2′-Cyclopentenyl). To a stirred solution of Li^0 (18 mg, 2.67 mmol, 13 equiv) in NH_3 (25 mL, distilled from Na^0) at −33 °C was added a solution of **11** (BOC = *t*-BOC; 86 mg, 0.21 mmol, 1 equiv) and EtOH (125 mL) in dry THF (5 mL) via syringe. After 25 min the blue color dissipated, and the reaction was quenched with excess NH_4Cl. The mixture was allowed to warm to ambient temperature. After the NH_3 evaporated the residue was diluted with water and extracted 2× with Et_2O. The aqueous layer was carefully acidified to pH 3 with 1 N HCl while being stirred with EtOAc. The layers were separated, and the aqueous layer was extracted 3× with EtOAc. The combined organic fractions were dried over anhydrous $MgSO_4$, filtered, concentrated, and passed over a silica gel plug (eluted with 10% MeOH/CH_2Cl_2) to afford 38 mg (77%) of **10** as a slightly yellow oil as an approximately 2:1 mixture of diastereomers: ^1H NMR (200 MHz, DMSO-d_6, 310 K, vs $(CH_3)_4Si$) δ 1.37 (9 H, s), 1.54–1.68 (1 H, m), 1.82–1.99 (1 H, m), 2.25 (2 H, br s), 2.93–3.0 (1 H, br m), 3.73–3.89 (1 H, 2 t, 3.77, J = 7.9 Hz, 3.85, J = 7.5 Hz), 5.5–5.65 (1 H, m), 5.76–5.83 (1 H, m), 6.84–7.03 (1 H, 2 d, 6.848 J = 8 Hz, 7.03, J = 8 Hz), 9.4–9.7 (1 H, br s); IR (NaCl, neat) 3440, 3060, 2980, 2930, 1710, 1500, 1265, 1165 cm^{-1}; mass spectrum (NH_3, CI) m/e 276 (M^+ + 35, 0.2), 258 (M^+ + 18, 0.2), 242 (M^+ + 1, 0.5), 141.9 (12.7); $[\alpha]^{25}_D$ +10.6° (c 0.31, CH_2Cl_2).

(2*S*,4*R*,1′*S*,2′*R*)-2-[(Benzyloxycarbonyl)(1′,2′-diphenyl-2′-hydroxyethyl))amino]-4-(hydroxymethyl)butyric Acid γ-Lactone and (2*S*,4*S*,1′*S*,2′*R*)-2-[(Benzyloxycarbonyl)(1′,2′-diphenyl-2′-hydroxyethyl))amino]-4-(hydroxymethyl)butyric Acid γ-Lactone (15). To a stirred solution of **5a** (BOC = CBz, R = $CH_2CH{=}CH_2$ (60.4 mg, 0.14 mmol, 1 equiv) in THF (2 mL) was added OsO_4 (910 μL, 0.14 mmol, 1 equiv, 4% solution in water). After the dark brown mixture was stirred, a solution of $NaHSO_3$ and pyridine in water (175 mg/5.5 mL/8.5 mL) was added, and the mixture was stirred an additional 2.5 h. The mixture was then thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, concentrated, and separated by radial chromatography on silica gel (eluted with 2.5% CH_3OH/CH_2Cl_2) to afford 52 mg (78%) of **15** as a 1:1 mixture of diastereomers.

(2*S*,4*R*,1′*S*,2′*R*)-15: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 2.4–2.7 (2 H, m), 3.2–3.5 (2 H, m), 4.29 (1 H, br s), 4.54 (1 H, br t, J = 9 Hz), 4.68 (1 H, br t, J = 5 Hz), 4.98 (2 H, s), 5.10–5.13 (1 H, m), 5.30–5.36 (2 H, m), 7.15–7.65 (15 H, m); IR (NaCl, neat) 3500–3300, 1755, 1695, 1420 cm^{-1}; mass spectrum (NH_3, Cl) m/e 461.8 (M^+ + 1, 0.3), 460.8 (M^+, 0.1); $[\alpha]^{25}_D$ +9.6° (c 1.5, CH_2Cl_2).

(2*S*,4*S*,1′*S*,2′*R*)-15: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 1.2–1.4 (1 H, m), 1.49 (1 H, q, J = 10.5 Hz), 3.27 (2 H, br s), 4.07–4.21 (1 H, m), 4.5–4.7 (2 H, m), 4.97 (2 H, s), 5.12–5.17 (1 H, m), 5.38 (2 H, m), 7.15–7.65 (15 H, m); IR (NaCl, neat) 3580, 3500–3300, 3050, 2950, 1760, 1695, 1450, 1415 cm^{-1}; mass spectrum (NH_3, CI) m/e 461.7 (M^+ + 1, 0.1%); $[\alpha]^{25}_D$ +59.9° (c 1.4, CH_2Cl_2).

(2*S*,4*S*)-2-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)butyric Acid γ-Lactone (17) and (2*S*,4*R*)-2-[(Benzyloxycarbonyl)amino]-4-(hydroxymethyl)butyric Acid γ-Lactone (16). To a stirred solution of **15** (mixture) (103 mg, 0.223 mmol, 1 equiv) in 1:1 THF/EtOH (4 mL) was added $PdCl_2$ (23 mg, 0.067 mmol, 0.3 equiv). The mixture was hydrogenated 48 h at 40 psi. The mixture was then purged with nitrogen, filtered through Celite, concentrated, and triturated with Et_2O leaving 38 mg (130%) of an off-white solid. The crude material was dissolved in 1 mL of dry DMF. To this stirred solution was added Et_3N (80 μL, 0.58 mmol, 2 equiv) followed by addition of benzyl chloroformate (52 μL, 0.348 mmol, 1.2 equiv). After 22 h the DMF was removed in vacuo, and the mixture was separated by PTLC on silica gel (eluted with 3:2 EtOAc/hexanes) to afford 12.3 mg (21%) of **17** and 8.8 mg (14.9%) of **16**.

17: % ee ≥89; ^1H NMR (200 MHz, DMSO-d_6, vs $(CH_3)_4Si$) δ 4.93 (1 H, q, J = 11.8 Hz), 2.28–2.42 (1 H, m), 3.40–3.65 (2 H, m), 4.41–4.63 (2 H, m), 5.05–5.12 (3 H, m), 7.36 (5 H, s), 7.81 (1 H, d, J = 8.5 Hz); IR (KBr) 3370, 3280, 1780, 1690, 1530, 1520, 1450, 1370, 1320, 1280, 1255, 1180, 1050 cm^{-1}; mp 109–110 °C (recrystallized from EtOAc/hexanes); $[\alpha]^{25}_D$ −1.0° (c 0.6, MeOH). (Authentic **17** isolated from PTLC: $[\alpha]^{25}_D$ −1.0° (c 0.6, MeOH.)

16: ^1H NMR (200 MHz, DMSO-d_6, vs DMSO) δ 2.1–2.4 (2 H, m), 3.42–3.64 (2 H, m), 4.43 (1 H, q, J = 9.7 Hz), 4.5–4.65 (1 H, m), 5.03 (2 H, s), 5.19 (1 H, t, J = 5.3 Hz), 7.35 (5 H, s), 7.78 (1 H, d, J = 8.5 Hz); mp 124 °C (recrystallized from EtOAc/hexanes); $[\alpha]^{25}_D$ −75.0° (c −0.2, MeOH).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-3-(2′-furanyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (21). To a stirred solution of **4a** (BOC = CBz) (144 mg, 0.31 mmol, 1.0 equiv) in dry THF (2 mL) was added furan (500 μL, 6.87 mmol, 22 equiv), followed by addition of $ZnCl_2$ (338 μL, 0.62 mmol, 2 equiv, 1.83 M in THF). The mixture was stirred 3.5 h at 25 °C. The mixture was partitioned between water and CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, evaporated, and separated by radial PTLC silica gel chromatography (eluted with 5:1 hexanes/EtOAc) to afford 90 mg (64%) of **21** as a white crystalline solid: mp 203–204 °C (recrystallized from EtOAc/hexanes); ^1H NMR (200 MHz, DMSO-d_6, 393 K) δ 5.00 (2 H, m), 5.47 (1 H, d, J = 3.0 Hz), 6.17 (1 H, s), 6.27 (1 H, d, J = 3.0 Hz), 6.53 (1 H, m), 6.6–7.3 (16 H, m), 7.68 (1 H, s); $[\alpha]^{25}_D$ +19.2° (c 1.26, CH_2Cl_2); IR (NaCl, neat) 1755, 1705, 1495, 1400, 1345, 1310, 1265, 1210 cm^{-1}. Anal. Calcd for $C_{28}H_{23}NO_5$: C, 74.16; H, 5.11; N, 3.09. Found: C, 73.98; H, 4.99; N, 3.12.

Tetrahydrofur-2-ylglycine (23). To a solution of **21** (100 mg, 0.27 mmol, 1 equiv) in 1:1 EtOH/THF (4 mL) was added $PdCl_2$ (22 mg, 0.07 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 30 h, purged with N_2, filtered through Celite, and concentrated to dryness. The residue was dissolved in a minimum amount of EtOH and precipitated with Et_2O, yield 35 mg (109%) of **23** (adjusted chemical yield 89%), as approximately a 5:1 mixture of diastereomers obtained as a white solid: ^1H NMR (200 MHz, D_2O + DCl, DSS) δ 1.8–2.2 (4 H, m), 3.79–3.97 (2 H, m), 4.36 (major diastereomer 1 H, d, J = 3.9 Hz), 4.40–4.46 (1 H, m); IR (KBr) 3600–3300, 3200–2800, 1620, 1590, 1550, 1515, 1400, 1350, 1315, 1055 cm^{-1}; $[\alpha]^{25}_D$ +4.4° (c 0.36, 1 N HCl).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-[2′-(5′-methylfuryl)]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (22). To a stirred solution of **4a** (BOC = CBz) (300 mg, 0.6459 mmol, 1 equiv) in dry THF (5 mL) was added 2-methylfuran (1 mL, 10.0731 mmol, 15.6 equiv) followed by addition of $ZnCl_2$ (650 μL, 1.2919 mmol, 2 equiv, 2 M in THF). After 1.5 h, the mixture was poured into water and extracted 4× with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to yield 200 mg (66%) of **22** as a white solid: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 2.29 (3 H, s), 4.99 (2 H, AB q, J = 12.6 Hz), 5.46 (1 H, d, J = 3.0 Hz), 6.10 (1 H, s), 6.13 (1 H, m), 6.30 (1 H, d, J = 3.0 Hz), 6.58 (1 H, d, J = 2.9 Hz), 6.65 (1 H, s), 6.68 (1 H, s), 6.9–7.3 (13 H, m); IR (NaCl, CH_2Cl_2) 3030, 2980, 1765, 1710, 1455, 1395, 1260, 1110, 1084, 1055, 1020 cm^{-1}; mass spectrum (NH_3, Cl) m/e 485 (M^+ + 18, 41), 467.2 (M^+, 78.3), 251.9 (18.7); mp 171–172 °C; $[\alpha]^{25}_D$ +44.7° (c 1.09, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{29}H_{25}NO_5$: C, 74.50; H, 5.20; N, 2.99. Found: C, 74.46; H, 5.26; N, 2.98.

(5-Methylfuryl)glycine (24). To a stirred solution of **22** (100 mg, 0.214 mmol, 1 equiv) in 1:1 THF/EtOH (4 mL) was added $PdCl_2$ (22 mg, 0.064 mmol, 0.3 equiv). The mixture was hydrogenated at 40 psi for 24 h. The mixture was then purged with N_2, filtered through Celite, concentrated, and triturated with Et_2O leaving 37 mg (110%) of **24** (adjusted chemical yield 89%) as an off-white solid as predominantly one diastereomer: ^1H NMR (major diastereomer) (200 MHz, D_2O·DCl, vs HOD) δ 1.12 (3 H, t, J = 6 Hz), 1.30–2.05 (4 H, m), 3.86 (1 H, d, J = 4 Hz), 3.97 (1 H, q, J = 4 Hz), 4.20–4.35 (1 H, m); $[\alpha]^{25}_D$ +4.3° (c 0.65, 1 N HCl).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-[2′-oxo-2′-(4″-methoxyphenyl)ethyl]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (*anti*-5a, BOC = CBz, R = *p*-$OCH_3PhCOCH_2$) and (3*R*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-[2′-oxo-2′-(4″-methoxyphenyl)ethyl]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (*syn*-5a, BOC = CBz, R = *p*-$OCH_3PhCOCH_2$). To a stirred suspension of **4a** (BOC = CBz) (234 mg, 0.50 mmol, 1 equiv) in dry CH_3CN (10 mL) was added $ZnCl_2$ (600 μL, 0.45 mmol, 0.9 equiv, 0.76 M in THF) followed by addition of the trimethylsilyl enol ether of 4-methoxyacetophenone (525 μL, 2.50 mmol, 5 equiv). After 4 h the solution was poured into water and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 1:5 EtOAc/hexanes) to afford 194 mg (72%) of **5a** as a 3:1 anti/syn mixture of diastereomers. The product mixture was recrystallized 2×, giving 80 mg of pure *anti*-**5a**.

anti-**5a**: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 3.77 (1 H, dd, J_{vic} = 4.5 Hz, J_{gem} = 16.5 Hz), 3.87 (3 H, s), 3.94 (1 H, dd, J_{vic} = 6.9 Hz, J_{gem} = 16.5 Hz), 4.96 (2 H, s), 5.30 (1 H, d, J = 3 Hz), 5.44 (1 H, dd, J_{vic} = 4.5, 6.9 Hz), 6.43 (1 H, d, J = 3 Hz), 6.61 (1 H, s), 6.64 (1 H, s), 6.9–7.4 (15 H, m), 8.0 (2 H, d); IR (KBr) 1750, 1710 (s), 1695, 1675, 1600, 1395, 1345, 1290, 1275, 1265, 1110 cm^{-1}; mp 178–181 °C; $[\alpha]^{25}_D$ −2.3° (c 1.12, CH_2Cl_2). Anal. (recrystallized from EtOAc/hexanes) Calcd for $C_{33}H_{29}NO_6$: C, 74.00; H, 5.46; N, 2.61. Found: C, 74.13; H, 5.57; N, 2.48.

syn-**5a**: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs DMSO) δ 3.30 (1 H, dd, J_{vic} = 3 Hz, J_{gem} = 17 Hz), 3.61 (1 H, dd, J_{vic} = 7.7 Hz, J_{gem} = 17 Hz), 3.86 (3 H, s), 5.12 (2 H, s), 5.65 (1 H, dd, J_{vic} = 7.7, 3 Hz), 5.68 (1 H, d, J = 3 Hz), 6.36 (1 H, d, J = 3 Hz), 6.9–7.9 (19 H, m); IR (NaCl, CH_2Cl_2) 1750, 1700, 1675, 1595 cm^{-1}; mass spectrum (NH_3, Cl) m/e 534.8 (M^+, 0.2), 387.3 (0.8); $[\alpha]^{25}_D$ +27.9° (c 1.02, CH_2Cl_2).

An improved ratio of anti/syn could be realized by running the reaction in THF with 1 equiv of AgOTf (25 °C) (Table II, entry 8).

(*S*)-4-Methoxyhomophenylalanine (25). To a stirred solution of **5a** (BOC = CBz, R = *p*-methoxyacetophenone; 100 mg, 0.18 mmol, 1 equiv) in THF (3 mL) and EtOH (3 mL) was added $PdCl_2$ (19 mg, 0.05 mmol, 0.3 equiv). The mixture was hydrogenated for 24 h at 40 psi H_2. The reaction mixture was then purged with N_2, filtered through Celite, concentrated, and triturated several times with Et_2O, leaving 48 mg (122%) of **25** (adjusted chemical yield 94%) as a pure white solid: % ee ≥98; ^{1}H NMR (200 MHz, D_2O + DCl, vs HOD) δ 1.9–2.1 (2 H, m), 2.4–2.6 (2 H, m), 3.61 (3 H, s), 3.87 (1 H, t, J = 6 Hz), 6.71 (2 H, d, J = 8.6 Hz), 7.06 (2 H, d, J = 8.6 Hz); $[\alpha]^{25}_D$ +34.6° (c 0.5, 1 N HCl).

(3*S*,5*S*,6*R*)-3-Chloro-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4a, X = Cl). To a stirred solution of (+)-(5*R*,6*S*)-**3** (105 mg, 0.271 mmol, 1.0 equiv) in CCl_4 (40 mL) at reflux temperature was added *tert*-butyl hypochlorite (294 mg, 2.71 mmol, 10 equiv). The reaction mixture was stirred for 2 h at reflux, cooled to room temperature, and evaporated under reduced pressure, leaving a solid white residue (120 mg; mp 182.5–185 °C dec) that was directly used without further purification: ^{1}H NMR (270 MHz, $CDCl_3$, vs $(CH_3)_4Si$) δ 4.7–5.4 (5 H, m), 6.2–7.7 (15 H, m); IR (NaCl, neat) 1770, 1730 cm^{-1}; mass spectrum (NH_3, Cl) m/e 388 (M^+ + 1 − Cl, 28), 387 (M^+ − Cl, 100).

Determination of Optical Purity of Amino Alcohols 2a and 2b. To a stirred solution of *dl-erythro*-α,β-diphenyl-β-hydroxyethylamine (**2**, racemic) (100 mg, 0.47 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added saturated $NaHCO_3$ (5 mL) and (−)-camphanic acid chloride (102 mg, 0.5 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL). The mixture was allowed to stir at room temperature for 5 h and was thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated, and separated by PTLC silica gel chromatography (eluted with 3:1 hexanes/EtOAc) to afford 118 mg (86%) of the corresponding camphanic acid amides as a 1:1 diastereomeric mixture that was used for ^{1}H NMR and HPLC comparison with those obtained individually from **2a** and **2b**.

From **2a**: yield 83%; mp 190–190.5 °C; $[\alpha]^{25}_D$ −5.88° (c 0.51, DMF); ^{1}H NMR (270 MHz, $CDCl_3$, vs $(CH_3)_4Si$) δ 0.75 (3 H, s), 1.00 (3 H, s), 1.08 (3 H, s), 1.63–1.96 (4 H, m), 2.39–2.48 (1 H, m), 2.60 (1 H, d), 5.04 (1 H, t), 5.26–5.31 (1 H, q), 7.07–7.26 (10 H, m); IR (KBr) 3500, 3320, 1770, 1665 cm^{-1}.

From **2b**: yield 83%; mp 246–247.5 °C; $[\alpha]^{25}_D$ +5.45° (c 0.44, DMF); ^{1}H NMR (270 MHz, $CDCl_3$, vs $(CH_3)_4Si$) δ 0.69 (3 H, s), 1.04 (3 H, s), 1.08 (3 H, s), 1.60–1.94 (4 H, m), 2.36–2.45 (1 H, m), 2.60 (1 H, t), 4.98 (1 H, d), 5.31–5.36 (1 H, m), 7.05–7.44 (10 H, m); IR (KBr) 3500, 3320, 1770, 1665 cm^{-1}.

Analyses of the crude samples obtained separately (above) were compared with the authentic diastereomeric mixture obtained from the racemate by ^{1}H NMR and by HPLC (silica gel, waters; eluted with 3:1 hexanes/EtOAc at 4.5 mL/min). The integration of the ^{1}H NMR absorptions of the CH_3 resonances and the HPLC peaks were taken and averaged. The amino alcohols melting at 143 °C were consistently determined to be >98% ee by this method.

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Note Added in Proof: Lactones **3a** and **3b** (both the CBz and *t*-BOC derivatives) as well as the racemic compounds are now commercially available (Aldrich). Amino alcohols **2a** and **2b** are also commercially available (Aldrich and Yamakawa Chemical Industry, Japan).

Palladium-Catalyzed Carbonylative Coupling of Aryl Triflates with Organostannanes

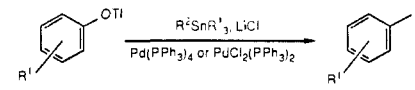
Antonio M. Echavarren† and J. K. Stille*

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received August 28, 1987*

Abstract: The palladium-catalyzed coupling reaction of aryl triflates with organostannanes in the presence of carbon monoxide and lithium chloride takes place under relatively mild conditions to give good yields of aryl ketones. Dichloro[1,1′-bis(diphenylphosphino)ferrocene]palladium(II) is unique in that it is the only one of several catalysts tried that gives consistently high yields of product. The coupling takes place even in the presence of reactive functional groups such as alcohol, aldehyde, and ester on the coupling partners. In the presence of strong electron-withdrawing groups on the tin partner, however, the coupling reaction is slow, leading primarily to decomposition of both the tin reagent and the triflate. Vinyl, acetylenic, alkyl, and aryl groups transfer to yield the corresponding ketones. Allylstannanes do not, however, give good yields of ketones; instead, direct coupling occurs without the intervention of carbon monoxide.

The palladium-catalyzed coupling reaction of aryl halides with organostannanes in the presence of carbon monoxide is a valuable synthetic procedure for the preparation of a variety of aryl ketones.[1-3] While the same ketones can be prepared by the palladium-catalyzed reaction of acid chlorides,[1] the utility of this route is limited by the availability of the corresponding carboxylic acids. Furthermore, since an acid chloride is not involved in the carbonylative cross coupling, functional groups capable of reaction with the acid chloride can be present in the aryl substrate.

We have recently reported that the palladium-catalyzed coupling of aryl triflates with organostannanes provides an efficient method for carbon–carbon bond formation on aromatic substrates[4,5] (eq 1). The cross coupling reaction proceeds under



(1)

neutral conditions with triphenylphosphine-coordinated palladium catalysts in either 1,4-dioxane or *N*,*N*-dimethylformamide. The

† Present address: Instituto de Química Orgánica, CSIC, Juan de la Cierva 3, 28006-Madrid, Spain.

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