NEW METHODOLOGY FOR THE SYNTHESIS OF α,α-DIALKYLAMINO ACIDS USING THE "SELF-REGENERATION OF STEREOCENTERS" METHOD: α-ETHYL-α-PHENYLGLYCINE

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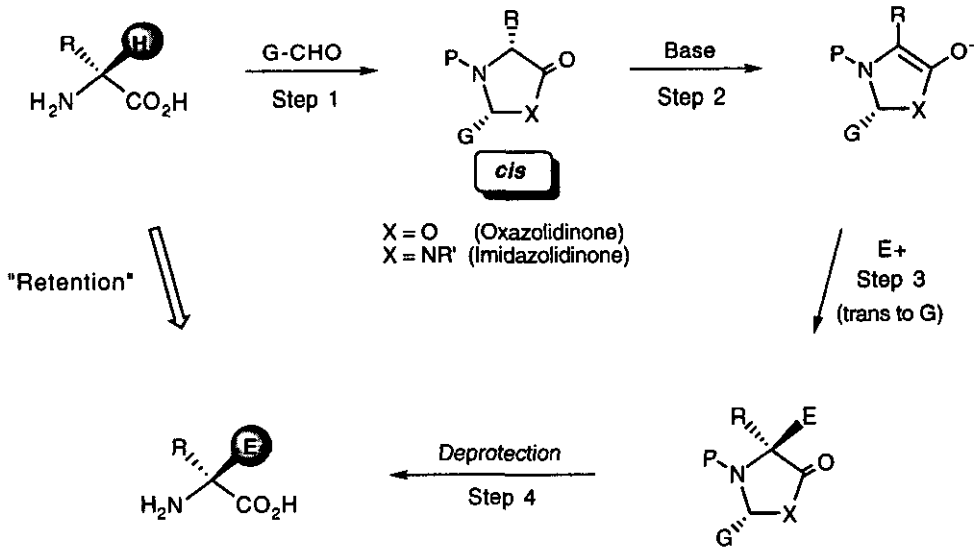
Abstract - The stereoselective room temperature ethylations of protected oxazolidinones from phenylglycine by phase-transfer catalysis or with KOtBu as base are used to prepare optically active α-ethyl-α-phenylglycine.

New and improved methodology for the asymmetric synthesis of α-amino acids is of interest because of the importance of this class of molecules in the physical and biological sciences.[1] Of particular interest are methods that can readily be adapted to the preparation of α-amino acids on an industrial scale.[2] We report results of several variations in the Seebach "Self-Regeneration of Stereocenters" Method[3-5] (see Scheme 1) for the synthesis of a particular class of α,α-disubstituted amino acids, the α-alkyl-α-arylglycines.[6-11]



Scheme 1. Seebach's "Self-Regeneration of Stereocenters" with Retention of Configuration.

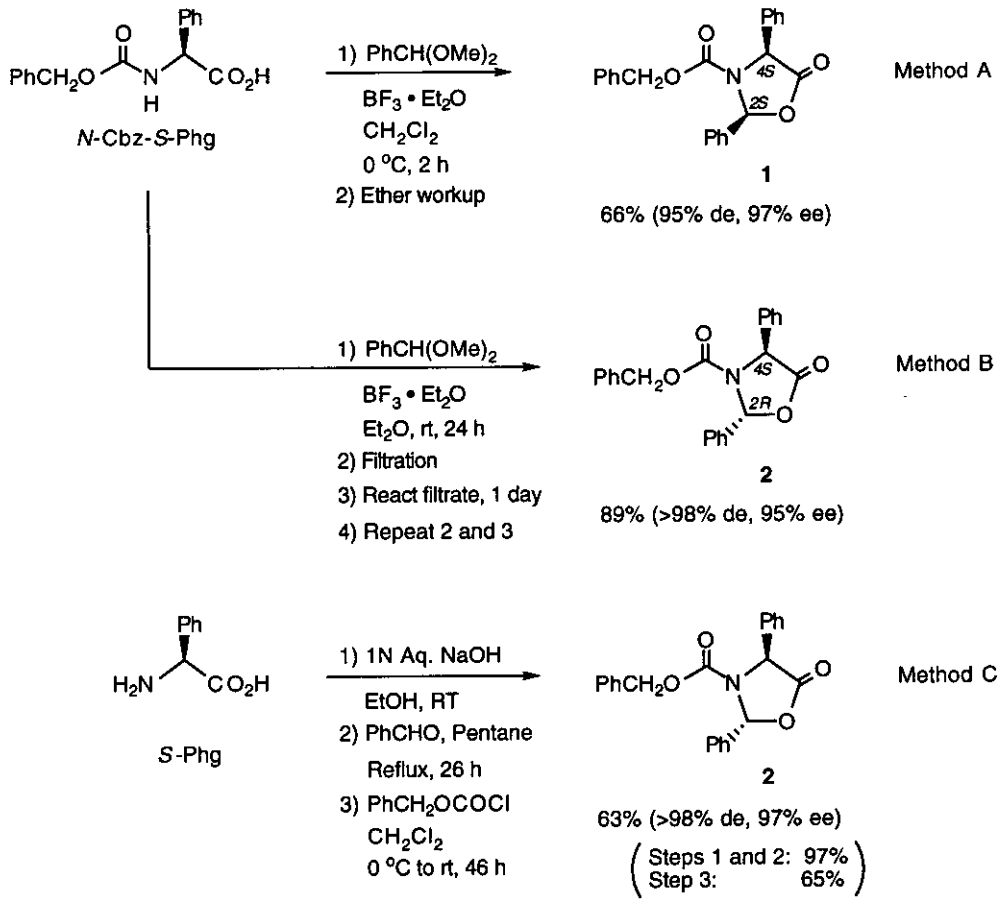
This paper is dedicated to the memory of Professor Shun-ichi Yamada

The "Self-Regeneration of Stereocenters" method in amino acid synthesis (Scheme 1) transfers the chirality of a starting homochiral amino acid to a second stereogenic center during preparation of the heterocyclic substrate (Step 1). The stereochemistry at the original α-carbon is then lost on deprotonation with base (Step 2); however, this stereochemistry is reestablished in a subsequent alkylation (Step 3), which is controlled by the newly created second stereogenic center. Finally, deprotection of the alkylated heterocycle (Step 4) leads to the product amino acid, in which the original hydrogen has been replaced with a new electrophilic group with either retention (generally from the *cis*-heterocyclic intermediates, shown in Scheme 1) or inversion (normally from the *trans*-heterocyclic intermediates).[3]

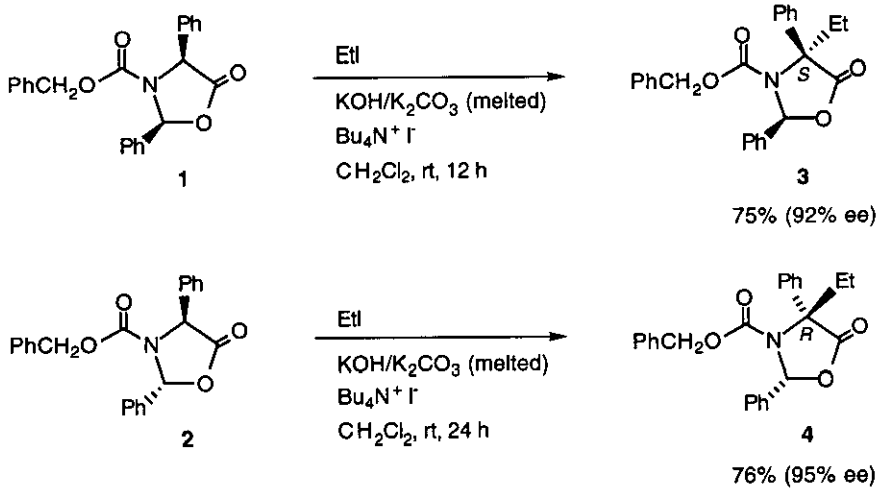
Typically the alkylation reactions described for this methodology have involved use of strongly basic, anhydrous conditions (KHMDS or $LiNEt_2$ in THF) at -78 °C.[3-5] Our own research in the use of phase-transfer catalysis (PTC)[1h] as well as other mild base systems[12] for room temperature alkylations of active methylene-type substrates prompted an in-depth study of the above described reaction. By judicious choice of the various protecting/directing groups in the substrates depicted in Scheme 1, it has now proven possible to accomplish these reactions under milder and more economical conditions for the case where R is phenyl.

Initial studies were conducted using phenylglycine as the starting amino acid since it is known from earlier studies that the phenyl group is acid-strengthening.[13] While the majority of cases using the "Self-Regeneration of Stereocenters" methodology have involved use of pivaldehyde (Scheme 1, G = tBu) to establish the second stereogenic center in the heterocycle, we chose the parent benzaldehyde as this group (G = Ph) because of a facile synthesis of the starting heterocycle based on recent results from the Bartlett group.[14] Initial studies involved use of the Cbz-protected nitrogen, although more recent research has focused on the less expensive benzoyl group. The starting heterocyclic phenylglycine substrates were prepared by three different routes (Scheme 2). The recent Bartlett methodology involves reacting Cbz-Phg[15] with benzaldehyde dimethyl acetal in methylene chloride in the presence of boron trifluoride etherate to give the phenylglycine *cis*-oxazolidinone (**1**) in good yield with excellent stereoselectivity (Method A).[16] Interestingly, the use of ether as solvent in this reaction resulted in an excellent yield of the diastereomeric phenylglycine *trans*-oxazolidinone (**2**) (Method B). The normal Seebach route involving intermediate acyclic Schiff base formation followed by heterocycle formation was also used to prepare the phenylglycine *trans*-oxazolidinone (**2**) (Method C).[4a] This latter route is attractive for large scale synthesis because it avoids the use of the Lewis acid, $BF_3 \cdot Et_2O$.

Alkylation of the heterocyclic substrates (**1** and **2**) was studied under two types of alkylation conditions: phase-transfer catalysis (Scheme 3) and KOtBu in THF (Scheme 4). The alkylating agent chosen for these initial studies, ethyl iodide, is a typical non-active alkyl halide, which leads to the protected derivatives of the important amino acid, α-ethyl-α-phenylglycine. Under PTC conditions (Scheme 3) it was necessary to use the more active base system, KOH/K_2CO_3 (melted)[17] in conjunction with the quaternary ammonium halide, Bu_4NI, in methylene chloride at room temperature.

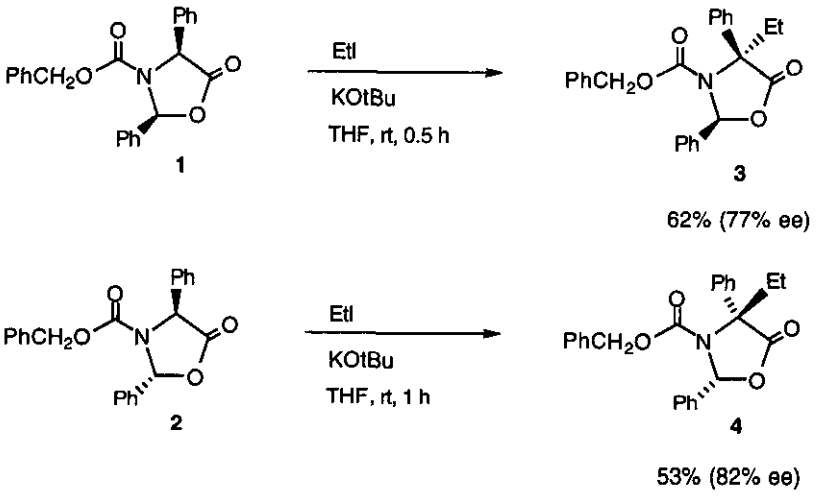


Scheme 2. Preparation of Phenylglycine *cis*- or *trans*-Oxazolidinones (**1** or **2**).



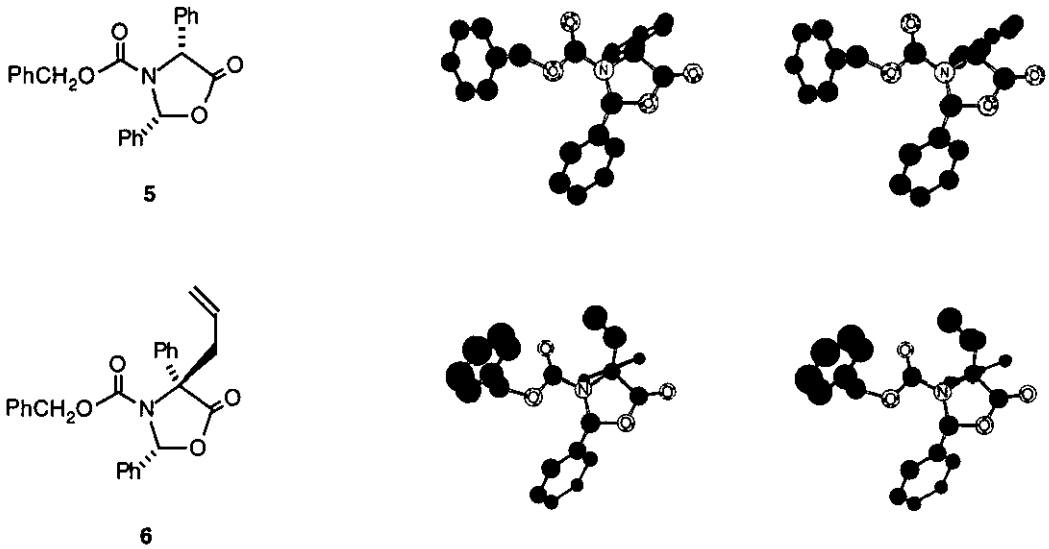
Scheme 3. Room Temperature Alkylation of Phenylglycine *cis*- or *trans*-Oxazolidinones (**1** or **2**) by PTC.

Even though it results in slightly lower levels of stereoselectivity,[16] the use of KOtBu/THF (Scheme 4) is particularly attractive since it involves short reaction times at room temperature with reasonable yields of alkylation products.



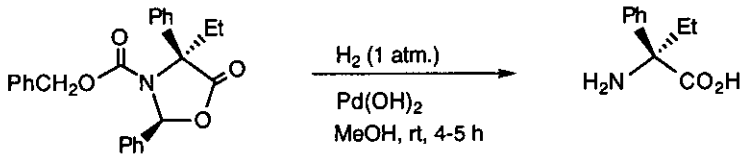
Scheme 4. Room Temperature Alkylation of Phenylglycine *cis*- or *trans*-Oxazolidinones (**1** or **2**) using KOtBu as Base.

The stereochemistry of the *cis*-selective formation of oxazolidinone (**1**) using the $PhCH(OMe)_2/BF_3{\bullet}Et_2O/CH_2Cl_2$ methodology (Scheme 1, Method A) as well as the alkylation stereochemistry of this substrate have been confirmed by crystal structures of both the starting material (**5** = enantiomer of **1**) and the α-allylated product (**6**).[18]



Scheme 5. X-Ray Crystal Structures of Starting Oxazolidinone (**5**) and Allylated Product (**6**).

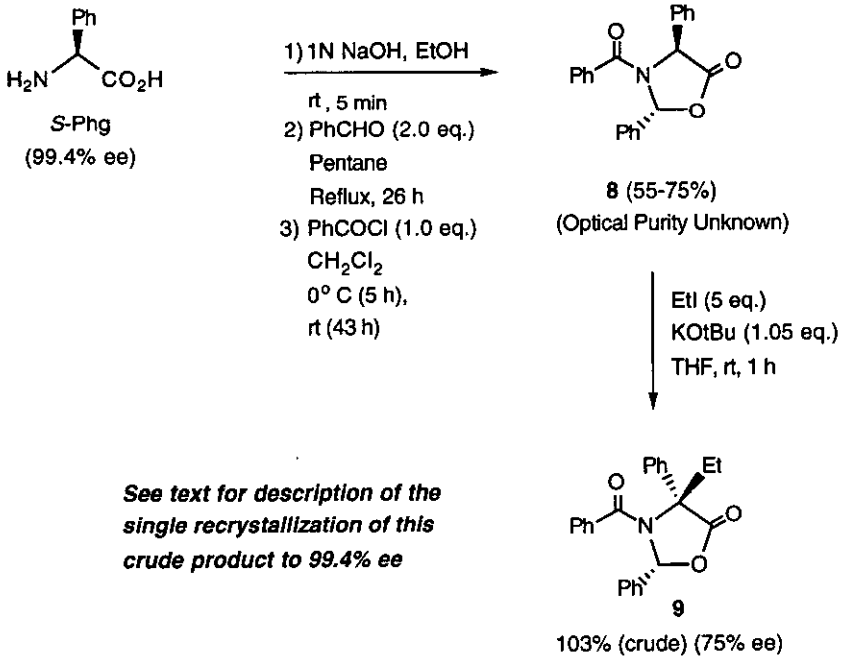
The alkylated oxazolidinone derivatives can be conveniently deprotected in 80-90% yield by simple hydrogenolysis to give α-ethyl-α-phenylglycine (**7**).



3 **7**

Scheme 6. Deprotection of Alkylated Oxazolidinone (**3**) to Amino Acid (**7**).

Recently, attention has been focused on the preparation and alkylation of the *N*-benzoyl-oxazolidinone (**8**), derived from *S*-phenylglycine, since the parent protecting group (PhCOCl) used to make this substrate is considerably less expensive than that ($PhCH_2OCOCl$ = CbzCl) used to make the *N*-Cbz-protected oxazolidinone (**2**).[19] Thus, **8** was prepared in 55-75% yield from *S*-Phg using a procedure similar to that described above for the preparation of **2** from *S*-Phg. Interestingly, it is likely that the *N*-benzoyl group in **8** causes an increase in acidity of the α-proton in **8** compared with those of **1** or **2**[20] (Jorgensen's CAMEO program[21] predicts the following pKa (DMSO) values: **1** or **2**, 19; **8**, 18). Although it has not yet been possible to accurately establish the level of stereochemical purity of **8**, alkylation of this substrate has been studied using the KOtBu/THF system described above. The alkylation of **8** is complete in one hour at room temperature under these conditions and results in a



Scheme 7. Preparation and Alkylation of *N*-Benzoyloxazolidinone (**8**).

stereoselectivity of 75%. A single recrystallization (EtOH) of this crude product resulted in a small crop of "racemic" crystals (18% ee, major **9**). Further cooling of the filtrate then yielded crystals of **9** of 99.4% stereochemical purity.

These preliminary results demonstrate the synthetic potential for the practical application of the "Self-Regeneration of Stereocenters" method in the synthesis of α-alkyl-α-arylglycines. By judicious choice of the protecting/directing groups in the substrates depicted in Scheme 1, so as to take maximal advantage of carbanion stabilizing effects, it should be possible to extend the use of these and other mild base systems combined with economically attractive protecting group strategies to realize the synthetic elaboration of α,α-dialkylamino acids from oxazolidinone-type substrates derived from alanine and other non-acid strengthening mono-substituted amino acids. Future synthetic studies will be directed toward this goal.

EXPERIMENTAL SECTION

Nuclear magnetic resonance (NMR) spectra were determined on a GE QE-300 300-MHz NMR spectrometer with $CDCl_3$ as solvent and Me_4Si (TMS) as internal standard unless otherwise specified. Chemical shifts are reported as δ values in parts per million (ppm). Proton NMR spectra are recorded in order: chemical shift, number of protons and multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br s, broad singlet; m, multiplet; J, coupling constant). Melting points were obtained directly from the samples as prepared in the described experimental procedures using a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at wavelength 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.0 mL. HPLC analyses of Schiff base ethyl ester derivatives were done on a Varian Model 9050 instrument. HPLC analyses of phenylglycines were done on a Varian Model 2050 instrument. Thin-layer chromatography (TLC) was performed on 0.25 mm thick Whatman precoated silica gel glass plates with fluorescent at 254 nm. Visualization on TLC was achieved with an ultraviolet light (model UVG-11 mineral lamp, short wave UV-254 nm, Ultra-Violet Products, Inc.) and/or heating of TLC plates submerged in a 10% solution of phosphomolybdic acid in ethanol. Flash chromatography was carried out with various columns filled with silica gel 60, 230-400 mesh, 60 Å from EM. Reagent grade chemicals were used as supplied with the following exceptions: tetrahydrofuran and ether were freshly distilled from sodium benzophenone ketyl, dry CH_2Cl_2 was obtained by distillation from CaH_2, EtI was passed through a short column of basic Al_2O_3 prior to use, Amberlite IR-120 ion-exchange resin was washed successively with 1 N NaOH, distilled water and 1 N HCl prior to use. Cbz-phenylglycine was prepared by a literature procedure.[15]

Stereochemical Analyses of Starting Oxazolidinones (1, 2, and 8): Starting material oxazolidinones were deprotected to the amino acid, phenylglycine, which was then analyzed by chiral HPLC using a CROWNPAK CR (+) column (15 cm x 0.40 cm I.D.) with pH 1.0 perchloric acid/methanol (10/1, v/v) at a flow rate of 1.0 mL/min and UV detection at 215 nm. Under these conditions, the retention times of the two enantiomers were 4.6 min (*R*) and 23.0 min (*S*).

Stereochemical Analyses of Alkylated Oxazolidinones (3, 4, and 9): Alkylated product oxazolidinones were deprotected to the amino acid, α-ethylphenylglycine, which was then converted

into the Schiff base ester for analysis by chiral HPLC. A typical experimental procedure for this two-step sequence follows. Ethanol (1 mL) was added to a 10 mL reaction tube, which was cooled in an ice bath for 10 min, and then $SOCl_2$ (20 drops, ~ 0.7 mL) was added dropwise. The solution was stirred for 5 min, product α-ethylphenylglycine (5 mg) was added, the ice bath was removed, the mixture was stirred at ambient temperature for 30 min, and then refluxed for 7 h. The reaction mixture was cooled, evaporated to dryness, ether (2 mL) was added, and the solution was evaporated again to give the ethyl ester hydrochloride salt. 4-Chlorobenzaldehyde (5 mg), $MgSO_4$ (100 mg) and CH_2Cl_2 (2 mL), followed by triethylamine (20 μl) were added to the tube containing the amino ester salt. The resulting mixture was stirred at ambient temperature for 24 h, filtered to remove solid materials, the solids were washed with CH_2Cl_2 (2 X 2 mL) and the combined solutions were evaporated. The residue was passed through a pipette containing silica gel 60 and glass wool plugs using ether as the eluent and the combined solutions were evaporated to give the Schiff base ethyl ester as a light yellow oil. This product was analyzed directly by chiral HPLC (Baker Bond Chiralcel OD Column, 600:1 hexane: isopropanol, flow rate 0.8 mL/min, UV detection 254 nm). The retention times of the two Schiff base ester enantiomers of α-ethylphenylglycine were 17.1 min (*S*) and 19.6 min (*R*).

(2*S*,4*S*)- and (2*R*,4*S*)-3-Benzyloxycarbonyl-2,4-diphenyl-1,3-oxazolidin-5-one (1 and 2, Method A): A 250 mL flask equipped with a magnetic stirring bar was charged with *N*-benzyloxycarbonyl-*S*-phenylglycine (8.96 g, 31.41 mmol). Dry CH_2Cl_2 (140 mL) was added to the flask under an argon atmosphere and the flask was cooled in an ice bath for 20 min. Benzaldehyde dimethyl acetal (3.37 mL, 22.44 mmol) and then boron trifluoride etherate (8.28 mL, 67.3 mmol) were added to the flask by syringe. After reaction at ice-bath temperature for 2 h, the reaction mixture was quenched with aq. sat. $NaHCO_3$ (70 mL). The organic layer was washed with aq. sat. $NaHCO_3$ (3 X 70 mL), dried over $MgSO_4$, filtered and evaporated to give a solid (8 g), consisting of a 3:1 mixture of **1** and **2.** Ether (120 mL) was added, the resulting mixture was stirred for 1.5 h, and then filtered. The solid was washed with ether (3 X 10 mL) to afford **2** as a white solid (1.74 g, 21%, > 98% de, 95% ee). The filtrate was evaporated to give a solid residue, which was washed with hexane (3 X 10 mL) to afford **1** as a white solid (5.5 g, 66%, ≥ 95% de, 97% ee), which was used directly in the following step. Analytical samples of **1** and **2** were prepared by chromatography of the above samples on silica gel (CH_2Cl_2).

1: mp 88-90 °C; $[\alpha]_D^{24}$=+52.9 ° (c 1.01, $CHCl_3$); ^1H NMR: δ (ppm) 5.14 (2H, s), 5.48 (1H, s), 6.81 (1H, s), 7.14-7.41 (15H, m); ^{13}C NMR: δ (ppm) 59.6, 68.1, 89.2, 126.5, 126.8, 127.9, 128.4, 128.5, 128.5, 128.6, 129.7, 134.1, 135.2, 136.6, 153.8, 170.0; Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98, H, 5.13, N, 3.75. Found: C, 73.92, H, 5.30, N, 3.66.

2: mp 193-194 °C; $[\alpha]_D^{24}$=+160.5 ° (c 1.0, $CHCl_3$); ^1H NMR: δ (ppm) 4.78 (1H, d, J=12.0 Hz), 4.96 (1H, d J=12.0 Hz), 5.43-5.49 (1H, br s), 6.70-7.44 (16H, m); ^{13}C NMR: δ (ppm) 60.3, 67.7, 90.4, 126.6, 126.7, 127.8, 128.1, 128.2, 128.9, 129.0, 129.2, 130.3, 134.9, 152.0, 169.8; Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98, H, 5.13, N, 3.75. Found: C, 73.83, H, 5.10, N, 3.80.

(2*R*,4*S*)-3-Benzyloxycarbonyl-2,4-diphenyl-1,3-oxazolidin-5-one (2, Method B): A 100 mL flask equipped with a magnetic stirring bar was charged with *N*-benzyloxycarbonyl-*S*-phenylglycine (5.70 g, 20 mmol). Dry ether was added to the flask under an argon atmosphere and the mixture was stirred for 15

min at ambient temperature. Benzaldehyde dimethyl acetal (2.14 mL, 14.2 mmol) and then boron trifluoride etherate (10.47 mL, 85.2 mmol) were added by syringe. After 24 h, the reaction mixture was filtered into a 100 mL flask equipped with a rubber septum and a magnetic stirring bar and the reaction of the filtered solution was continued. The solid in the filter was washed with ether (2 X 10 mL) to give a first batch of **2** (2.84 g, 54%). The filtered solution was allowed to react for another 24 h, and then filtration was repeated to give a second batch of **2** (1.39 g, 26%). Further reaction of the resulting filtrate for 24 h, gave a third batch of **2** (0.49 g, 9%). The three batches were combined to give **2** as a white solid (4.72 g, 89%, >98% de, 95% ee). mp: 194-195 °C; $[\alpha]_D^{24}$=+160 ° (c 1.01, $CHCl_3$); ^1H NMR and ^{13}C NMR were the same as **2** prepared as the minor product in Method A.

(2*R*,4*S*)-3-Benzyloxycarbonyl-2,4-diphenyl-1,3-oxazolidin-5-one (2, Method C): Aq. NaOH (1N, 40 mL, 40 mmol) and EtOH (20 mL) were added to *S*-phenylglycine (6.05 g, 40 mmol) in a 250 mL flask equipped with a magnetic stirring bar. The resulting mixture was stirred at ambient temperature for 5 min, then the solvent was removed *in vacuo* to give a white solid. Pentane (80 mL) and benzaldehyde (6.1 mL, 60 mmol) were added to the solid and the mixture was heated to reflux using a Dean-Stark trap to remove water. After refluxing for 26 h, the reaction mixture was filtered. The solid was washed with pentane (3 X 30 mL), dried *in vacuo* for 6 h to give the Schiff base salt [PhCH=NCH(Ph)CO_2Na] as a white solid (10.11 g, 97%), which was used directly in the following step.

Anhydrous CH_2Cl_2 (40 mL) was added to a 100 mL flask equipped with a magnetic stirring bar containing the above Schiff base salt (2.61 g, 10 mmol) under argon. The mixture was cooled with an ice bath and then benzyloxycarbonyl chloride (1.51 mL, 10 mmol) was added in one portion. The resulting mixture was stirred at 0 °C for 6 h and then at ambient temperature for 40 h. Water (20 mL) was added to the reaction mixture, the layers were separated, the organic layer was washed with 5% aq. $NaHCO_3$ (3 X 20 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. Ether (25 mL) was added to the residue, the suspension was stirred for 1.5 h, and then filtered. The solid was washed with ether (3 X 5 mL) to give **2** as a light yellow to white solid (2.42 g, 65%, >98% de, 97% ee), which was used directly in the following step. An analytical samples of **2** was prepared by chromatography of the above sample on silica gel (CH_2Cl_2). mp: 194.5-195.5 °C; $[\alpha]_D^{24}$=+160.1 ° (c 1.0, $CHCl_3$); ^1H NMR and ^{13}C NMR were the same as **2** prepared as the minor product in Method A.

General Procedure for Ethylation of 1 or 2 by PTC: To a magnetically stirred solution of **1** or **2** (prepared by Method B) (1 g, 2.68 mmol) and nBu_4NI (99 mg, 0.268 mmol) in CH_2Cl_2 (30 mL) was added EtI (1.1 mL, 13.4 mmol) and then KOH/K_2CO_3 (melted, molar ratio: 1/1, finely ground under argon using a mortar and pestle)[17] (5.21 g, 26.8 mmol) was added at once and the resulting solution was stirred vigorously at ambient temperature for 12 h for **1** or 24 h for **2**. The reaction mixture was filtered through celite to remove the solid base, the celite was washed with CH_2Cl_2 (2 X 5 mL) and the filtrate was evaporated *in vacuo*. The residue was taken up in ether (30 mL), and the organic solution was washed with water (2 X 15 mL), dried over $MgSO_4$, filtered and evaporated to give the crude product. The stereoselectivity of this reaction was determined by HPLC of the crude product. Pure product was obtained by chromatography on silica gel (first CH_2Cl_2 as eluent to give a mixture of two products, which was then subjected to a second chromatography with 5:1 hexane:ethyl acetate).

(2*S*,4*S*)-3-Benzyloxycarbonyl-2,4-diphenyl-4-ethyl-1,3-oxazolidin-5-one (3): Following the general procedure above, **1** (1 g, 2.68 mmol) gave a light yellow oil (0.98 g, 91%, 92 % ee). The oil was purified by chromatography to give **3** as a white solid (0.81 g, 75%). mp: 75.5-77.5 °C; $[\alpha]_D^{24}$=+42 ° (c 1.01, $CHCl_3$); ^1H NMR:[22] δ (ppm) 0.75-1.15 (3H, two br s), 2.35-3.05 (2H, two br s), 3.90-4.35 (2H, m), 6.55-6.75 (1H, two br s), 7.00-7.60 (15H, m); ^{13}C NMR:[22] δ (ppm) 8.6-9.0, 30.1-31.7, 67.7, 69.0-69.3, 89.5, 126.2, 127.4, 127.6, 128.1, 128.2, 128.3, 128.4, 129.8, 135.2, 136.1, 136.5, 137.9, 151.9-153.4, 172.6-173.1; Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.80, H, 5.77, N, 3.49. Found: C, 74.84, H, 5.76, N, 3.51.

(2*R*,4*R*)-3-Benzyloxycarbonyl-2,4-diphenyl-4-ethyl-1,3-oxazolidin-5-one (4): Following the general procedure above, **2** (prepared by Method B) (1 g, 2.68 mmol) gave a light yellow oil (1.01 g, 94%, >95% ee). The oil was purified by chromatography to give **4** as a white solid (0.82 g, 76%). mp: 78-79 °C; $[\alpha]_D^{24}$=-43.6 ° (c 1.0, $CHCl_3$); ^1H NMR and ^{13}C NMR were the same as **3** above.

General Procedure for Ethylation of 1 or 2 using Potassium *tert*-Butoxide as Base. To a magnetically stirred solution of **1** or **2** (prepared by Method C) (1 g, 2.68 mmol) in THF (30 mL) was added EtI (1.1 mL, 13.4 mmol) and then potassium *tert*-butoxide (2.82 mL, 2.82 mmol, 1M solution in THF) was added to the mixture dropwise via syringe at ambient temperature over 20 min. The resulting solution was stirred for 0.5 h for **1** or 1 h for **2**, diluted with ether (30 mL), quenched with saturated aq. NH_4Cl (30 mL). The layers were separated, the organic layer was washed with sat. aq. $NaHCO_3$ (2 X 30 mL), dried over $MgSO_4$, filtered and evaporated to give the crude product. The stereoselectivity of this reaction was determined by HPLC of the crude product. The pure product was obtained by chromatography as described above for the ethylation by the PTC method.

(2*S*,4*S*)-3-Benzyloxycarbonyl-2,4-diphenyl-4-ethyl-1,3-oxazolidin-5-one (3): Following the above general procedure, **1** (1 g, 2.68 mmol) gave a yellow oil (1.02 g, 95%, 77% ee). The oil was purified by chromatography to give **3** as a white solid (0.67 g, 62%). mp: 75-77 °C; $[\alpha]_D^{24}$=+36.9 ° (c 1.0, $CHCl_3$); ^1H NMR and ^{13}C NMR were the same as **3** above.

(2*R*,4*R*)-3-Benzyloxycarbonyl-2,4-diphenyl-4-ethyl-1,3-oxazolidin-5-one (4): Following the above general procedure, **2** (prepared by Method C) (1 g, 2.68 mmol) gave a light yellow oil (1.04 g, 97%, 82% ee). The oil was purified by chromatography to give **4** as a white solid (0.57 g, 53%). mp: 75-77 °C; $[\alpha]_D^{24}$=-43.5 ° (c 1.0, $CHCl_3$); ^1H NMR and ^{13}C NMR were the same as **3** above.

(2*R*,4*R*)-3-Benzyloxycarbonyl-2,4-diphenyl-4-allyl-1,3-oxazolidin-5-one (6): Anhydrous alkylation[14] of *cis*-oxazolidinone (**5**) (enantiomer of **1**, prepared from *N*-Cbz-*R*-Phg) (0.500 g, 1.34 mmol) in THF (15 mL) and HMPA (0.84 mL, 4.8 mmol), with lithium bis(trimethylsilyl)amide (1.34 mL, 1.0 M in THF, 1.34 mmol) and allyl iodide (0.14 mL, 1.5 mmol) gave crude product as a light yellow oil (0.540 g, 96%). Recrystallization with CH_2Cl_2/hexane gave pure **6** as a crystalline solid (0.398 g, 71%). mp: 85-87 °C; ^1H NMR:[22] δ (ppm) 3.05-3.75 (2 H, m), 4.95-5.35 (4H, m), 5.60-5.80 (1H, br s), 6.45-6.70 (1H, two br s), 7.05-7.70 (15 H, m); ^{13}C NMR:[22] δ (ppm) 40.3-42.0, 67.7, 68.1-68.6, 89.5, 122.1, 126.2, 127.4, 127.7, 127.9, 128.3, 128.8, 129.8, 130.0, 130.2, 130.7, 134.9, 135.2, 136.1, 136.5, 137.2, 137.4, 152.1-153.2, 172.3-172.6; Anal. Calcd for $C_{26}H_{23}NO_4$: C, 75.53, H, 5.61, N, 3.39. Found: C, 75.62, H, 5.64, N, 3.40.

***S*-(+)-α-Ethyl-α-phenylglycine (7):** Product (**3**) (prepared by alkylation of **1** using KOtBu) (0.6 g, 1.5 mmol), palladium hydroxide on carbon (Pearlman's catalyst, Pd content 20%, 105 mg, 0.75 mmol) and

MeOH (105 mL) were added to a flask. The reaction mixture was hydrogenated under an atmosphere of H_2 for 4-5 h. The mixture was filtered through celite to remove the catalyst, the filtrate was concentrated, and the resulting solid was washed with ether to give crude **7** (230 mg, 86%, 82% ee). Crude **7** (120 mg), ion-exchange resin (Amberlite IR-120, 7 g) and 1 N HCl (10 mL) were stirred overnight at ambient temperature. The resin was filtered and washed with distilled water until the aqueous washes gave a negative test for chloride ion (0.1% ethanolic $AgNO_3$). The resin was then stirred with 5 N NH_4OH (20 mL) for 4 h, filtered and washed with 5 N NH_4OH (20 mL). The filtrate was evaporated and the resulting solid was dried in a drying pistol overnight *in vacuo* to give **7** as a white solid (96 mg, 80%). $[\alpha]_D^{24}$=+48.5 ^{o} (c 1.01, 6 N HCl) [An authentic sample of (*S*)-(+)-α-ethylphenylglycine gave $[\alpha]_D^{24}$=+59.9 ^{o} (c 1.0, 6 N HCl)][23]; ^{1}H NMR (CF_3COOD): δ (ppm) 1.11 (3H, t, J=7.5 Hz), 2.60 (2H, q, J=7.5 Hz), 7.40 (5H, s); ^{13}C NMR (CF_3COOD): δ (ppm) 8.3, 29.3, 70.3, 127.2, 131.7, 132.9, 133.9, 176.5.

(2*R*,4*S*)-3-Benzoyl-2,4-diphenyl-1,3-oxazolidin-5-one (8): Anhydrous CH_2Cl_2 (50 mL) was added to a flask containing Schiff base salt prepared above in Method C (2.61 g, 10 mmol) under argon. The mixture was cooled in an ice bath and treated with benzoyl chloride (1.16 mL, 10 mmol). The resulting mixture was stirred at 0 ^{o}C for 5 h, then at ambient temperature for 43 h. Water (25 mL) was added, the layers were separated and the organic layer was washed with 5% aq. $NaHCO_3$ (3 X 25 mL), dried over $MgSO_4$, filtered, and evaporated to dryness. Ether (30 mL) was added to the residue, the suspension was stirred for 1.5 h, and then filtered. The solid was washed with ether (3 X 5 mL) to give **8** as a light yellow to white solid (2.47 g, 55-75%), which was used directly in the following step. An analytical sample of **8** was prepared by chromatography on silica gel (CH_2Cl_2). mp: 193-194 ^{o}C; $[\alpha]_D^{24}$=+271.4 ^{o} (c 1.0, $CHCl_3$); ^{1}H NMR: δ (ppm) 5.50-5.80 (1H, br s), 6.86-7.55 (16H, m); ^{13}C NMR: δ (ppm) 62.0, 91.1, 126.7, 126.8, 128.4, 128.8, 129.0, 130.1, 131.0, 135.1, 136.3, 162.0, 170.0; Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95, H, 4.99, N, 4.08. Found: C, 76.88, H, 4.95, N, 4.11.

(2*R*,4*S*)-3-Benzoyl-2,4-diphenyl-4-ethyl-1,3-oxazolidin-5-one (9): To a stirred solution of **8** (1.74 g, 5.07 mmol) in THF (55 mL) at ambient temperature was added EtI (2 mL, 25.25 mmol) and then KOtBu (5.3 mL, 1M in THF, 5.3 mmol) was added to the mixture dropwise *via* syringe over 25 min. The resulting solution was stirred for 40 min at ambient temperature, then diluted with ether (30 mL), quenched with sat. aq. NH_4Cl (40 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 X 40 mL), dried over $MgSO_4$, filtered and evaporated to give the crude product (1.94 g, 103%, 75% ee). Ethanol (15 mL) was added to the crude product (1.79 g) and the resulting mixture was heated to reflux until the crude product had totally dissolved (10 min), put aside for 24 h at ambient temperature, and then filtered to give light yellow crystals (0.32 g, 18% ee). The filtrate was refrigerated at -15 ^{o}C for 24 h, and then filtered to give **9** as white crystals. (0.7 g, 40%, 99.4% ee). mp: 133.5-134 ^{o}C; $[\alpha]_D^{24}$=-19.7 ^{o} (c 1.0, $CHCl_3$); ^{1}H NMR:[22] δ (ppm) 1.00-1.20 (3H, br s), 2.40-2.65 (2H, m), 6.75-7.60 (16H, m); ^{13}C NMR: δ (ppm) 8.9, 29.5, 70.3, 89.9, 126.7, 126.9, 127.0, 128.1, 128.4, 128.5, 129.7, 130.5, 135.6, 136.0, 171.0, 173.0; Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61, H, 5.70, N, 3.77. Found: C, 77.37, H, 5.60, N, 3.74.

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Crystal data for **6**: $C_{26}H_{23}NO_4$, space group $P2_1$, a = 11.452 (5), b = 8.587 (4), c = 22.411 (12) Å, β = 102.49 (2)°; giving D_c = 1.276 g cm^{-3} for Z = 4. A total of 5259 unique intensities were collected. Final residues were R(F) = 0.0785 and R_w(F) = 0.0727. Crystallographic details are available from http://www.iumsc.indiana.edu, entry 93248.
19. For comparative purposes, the price (Aldrich Catalog, 1996-1997, based on largest available quantity) of one mole of each reagent follows: CbzCl, $31.31; PhCOCl, $2.15.
20. The pKa's (DMSO) have been measured for the Cbz-oxazolidinones: **1**, 18.0; **2**, 18.1. We thank Professor F.G. Bordwell and Dr. X.-M. Zhang for conducting these experiments.

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