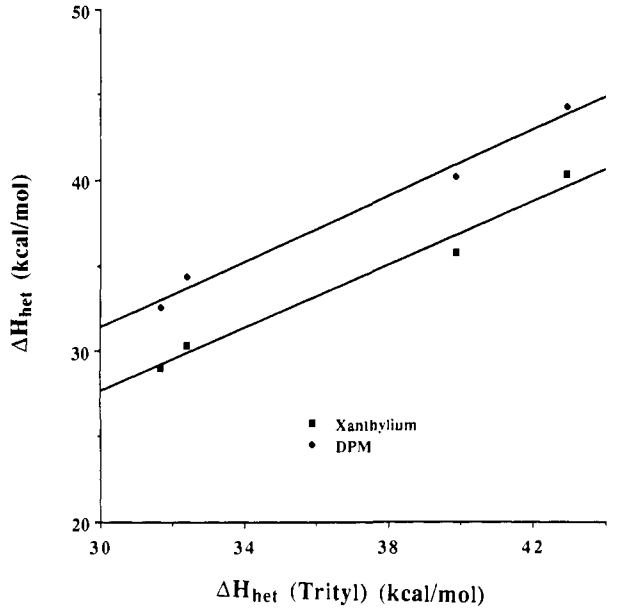

Figure 1. Plots of heats of heterolysis of nitranions with xanthylium and bis(4-methoxyphenyl)methylium ions versus those of nitranions with the triphenylmethylium ion. $\Delta H_{het}(xan^+) = 2.73 + 0.96\Delta H_{het}(trityl^+)$. $R = 0.990$. $\Delta H_{het}(DPM^+) = -0.18 + 0.93\Delta H_{het}(trityl^+)$. $R = 0.997$.

inspection of Table IV, there is a close parallel between the pK_a's of the nitrogen acids and the ΔH_{het}'s for cleavage of the carbon–nitrogen bonds formed by reaction between the anions and carbenium ions. This follows a general pattern of importance to many physical/organic interpretations; namely, the affinities of a series of anions for the proton are proportional to their affinities for a given carbenium ion.

In contrast to our previous results, there is no obvious correlation between the oxidation potentials for the nitranions ($E_{1/2}$'s) and the corresponding pK_a's, albeit a sample data set of four structurally dissimilar compounds is too small for drawing general conclusions. We have already discussed the corresponding relations between pK_{R^+}'s and reduction potentials of carbenium ions. Again, the complete lack of correlation between heterolytic ΔH_{het}'s and homolytic ΔH_{homo}'s is thoroughly precedented in our other studies where we have demonstrated the very general principle that properties which involve the gain or loss of charge correlate closely with each other.[1-5] Correspondingly, properties which do not involve any change of charge correlate well with each other, but there is no correlation between the two different sets of properties.

Finally, the same general sequence of ΔH_{het}'s is observed for the series of nitranions with each carbenium ion, and this is portrayed pictorially in Figure 1, where ΔH_{het}'s for the carbon–nitrogen bonds formed from two other carbenium ions are plotted against those for the trityl cation. Similar plots of ΔH_{het}'s of carbenium ions against ΔH_{het} for the trityl carbenium ion yield good to poor correlations (for PNA^+, $R = 0.976$; for DPA^+, $R = 0.976$; for 9-$PhXa^+$, $R = 0.963$; for TPP^+, $R = 0.960$; for $C_7H_7^+$, $R = 0.935$; for $TPCP^+$, $R = 0.882$).

Acknowledgment. We wish to express our appreciation to the Gas Research Institute for its generous support of this research and to Professor Vernon Parker for helpful criticisms. E.M.A. is also pleased to express appreciation to Loren Hepler, on the occasion of his retirement, for his patient introduction to and instruction in the science and art of calorimetry during the winter of 1962.

Registry No. $(Ph)_3C^+$, 13948-08-8; phthalimide monoanion, 28627-68-1; succinimide monoanion, 28627-67-0; 3,6-dibromocarbazole monoanion, 79990-92-4; carbazole monoanion, 23560-25-0; 9-phenyl-9-xanthylium, 20460-07-5; 9-xanthylium, 261-23-4; triphenylcyclopropenylium, 12190-17-9; tropylium, 26811-28-9; perinaphthenium, 12147-01-2; bis(4-methoxyphenyl)methylium, 13948-07-7; 2,4,6-triphenylpyrlium, 15959-35-0; 10,10-dimethyl-10-phenyl-9,10-dihydro-9-anthracenylium, 30880-10-5.

Synthesis of Dipeptides by the Photolytic Coupling of Chromium–Aminocarbene Complexes with α-Amino Acid Esters

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Abstract: Photolysis of optically active chromium–aminocarbene complexes in the presence of esters of optically active α-amino acids generates dipeptides in excellent yield and with high diastereoselectivity. In this reaction, both the peptide linkage and the stereogenic center on the carbene-complex-derived amino acid fragment are formed in the same step. The process is subject to double diastereoselection, with the (*S*)(*S*) dipeptide being the matched pair and the (*R*)(*S*) the mismatched pair. Both diastereoisomers can be made with high diastereoselectivity in this reaction.

Introduction

The volume of synthesis of natural and unnatural α-amino acids,[1] and their incorporation into peptides,[2] has experienced explosive growth in the last several years, driven primarily by major advances in the understanding of enzyme mechanisms and the concomitant development of synthetic peptide pharmaceuticals. However the requisite amino acids are synthesized, they are almost invariably incorporated into synthetic peptides by the standard array of classical peptide-coupling techniques, developed over the past 30 years,[3] and undergoing constant refinement even today. Current research in our laboratories has centered on development of photochemical reactions of chromium–aminocarbene complexes[4]

(1) For reviews see: (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E. Ed.; Pergamon Press: Oxford, U.K., 1989; Organic Chemistry Series, 7. (b) O'Donnell, M. J., Ed. Tetrahedron Symposium in Print, 33, α-Amino Acid Synthesis. *Tetrahedron* **1988**, *44*, 5253–5614.

(2) For a recent review see: (a) Hruby, V. J.; Schwyzer, R. J., Eds. Tetrahedron Symposium in Print, 31 *Tetrahedron* **1988**, *44*, 661–1006. (b) Elmore, D. T. Peptide Synthesis. In *Amino Acids Pept.* **1988**, *21*, 74; Jones, J. H., reporter.

(3) For a completely nonclassical method to introduce unnatural amino acids into *proteins* see: Noren, C. J.; Anthony-Cahill, J.; Griffith, M. C.; Schultz, P. G. *Science* **1989**, *244*, 182.

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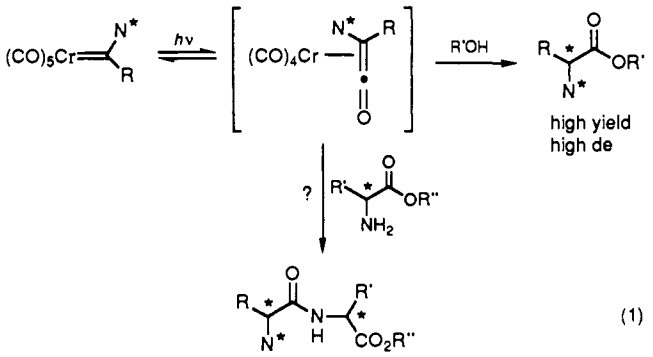
into useful processes for organic synthesis. In this area, an efficient synthesis of optically active amino acids, involving the photolysis of chromium aminocarbene complexes in alcohols, has been developed (eq 1).[5] The key step in these photochemical processes

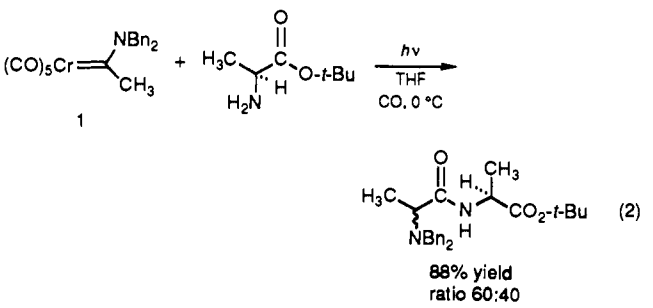


(1)

is thought to be the reversible photogeneration of a metal-bound ketene,[6] which can be trapped by external nucleophiles, in this case, alcohols. With the appropriate chiral auxiliary on the nitrogen of the carbene complex, very high (>97%) diastereoselection was observed. In principle, by using an α-amino acid ester as the nucleophile to trap the photogenerated ketene, dipeptides in which both the peptide linkage and the stereogenic center on the newly formed, carbene-complex-derived, amino acid fragment are formed in one step should be produced. Studies addressing this question are presented below.

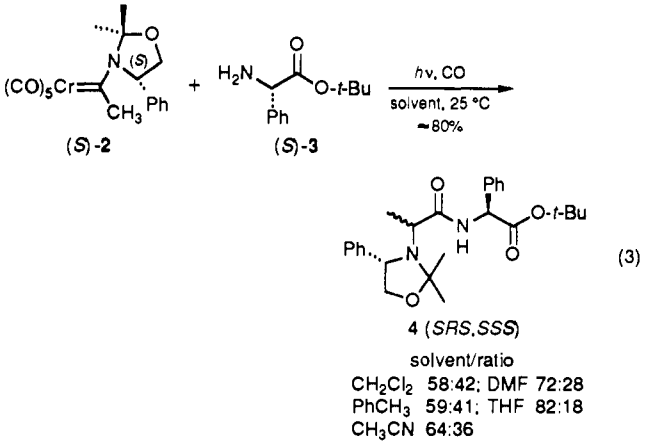
Results and Discussion

The most straightforward approach to dipeptide synthesis would be the photolysis of simple, achiral aminocarbene complexes in the presence of an optically active amino acid ester, relying on the stereogenic center in the amino acid to control the absolute stereochemistry of the newly-formed stereogenic center. This *general* process has precedent in the reaction of (alkyl)(aryl)-ketenes with optically active alcohols to produce optically active esters with high diastereoselectivity,[7] and in the reaction of (*tert*-butyl)(phthalimido)ketene with optically active amino acid esters to form dipeptides with up to 70% de.[8] In the event, photolysis of the dibenzylaminocarbene complex **1** with the *tert*-butyl ester of (*S*)-alanine provided the dipeptide in excellent yield but with very poor diastereoselectivity (eq 2).



(2)

Previous experience with the asymmetric synthesis of both amino acids[5] and β-lactams[9] from photogenerated, chromium-complexed ketenes suggested that optically active aminocarbene complexes might be necessary to achieve high asymmetric induction in this system. Initial studies using (*S*)-carbene complex **2** were both enlightening and disappointing (eq 3). The diastereoselectivity was *strongly* dependent on the solvent, varying from 58:42 in the methylene chloride to 82:18 in THF, as might be expected for a process which most likely generates the new stereogenic center by protonation of a ketene enolate.[10] (The mechanism of addition of nucleophiles to ketenes has been extensively studied;[11] this mechanism is complex, and the stereoselectivity is dependent on many factors.[12]) This system is further complicated by the possibility of "double" diastereoselection,[13] with the diastereoselectivity for the "matched" pair potentially greater than that of the mismatched pair. In the reaction of (*S*)-carbene complex **2** with alcohols, the absolute stereochemistry of the newly formed stereogenic center was (*R*),[5] opposite that of the chiral auxiliary. This same sense of stereoinduction was observed in the reactions of optically active aminocarbene complexes with alcohols to produce amino acids. To test for double diastereoselection in the peptide coupling, the reaction in eq 2 was repeated using (*R*)-**2** and (*S*)-phenylglycine. In this case, the chemical yields were comparable (80–90%) but the diastereoselectivity was substantially better, 91:9, in favor of the (*R*)(*S*)(*S*) diastereoisomers (see below). This proved to be a general phenomenon: in all cases studied in the matched pair the two amino acid stereogenic centers had the *same* absolute configuration while in the mismatched series the absolute configurations were opposite.

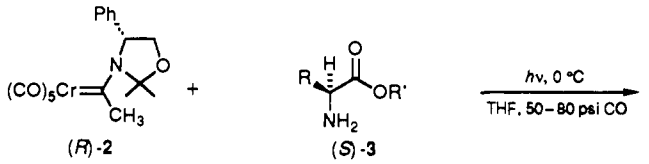


(3)

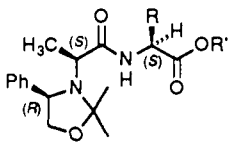
Further optimization studies led to a general procedure for forming dipeptides in good yield and with good to excellent stereoselectivity. This procedure consisted of treatment of the amino acid ester hydrochloride with 2 equiv of triethylamine in THF, followed by filtration through Celite to remove the triethylamine hydrochloride. The filtrate containing the free amino acid ester was placed in a pressure tube, along with 1 equiv of the carbene complex, and was photolyzed (Hanovia 450-W lamp, Pyrex vessels and wells) under 50–80 psi pressure of carbon monoxide at 0 °C. The results are summarized in eq 4. The ratio of diastereoisomers was calculated by integration of appropriate peaks in the ^{1}H NMR spectrum of the crude reaction product. The reported yields are purified, *isolated* yields of the single (*R*)(*S*)(*S*) diastereoisomer, separated from the minor amounts of the (*R*)(*R*)(*S*) diastereoisomer by chromatography on silica gel.

Thus, the esters of (*S*)-alanine, glycine, phenylalanine, phenylglycine, threonine, and tryptophan coupled efficiently and quite diastereoselectively to the (*S*)-alanine fragment generated from (*R*) complex **2** to form dipeptides **4a–h**. The conditions were exceptionally mild, and no coupling agent (save light) was required. Because of this, phenylglycine, an amino acid prone to racemization, coupled cleanly and without loss of stereochemistry. Pendent functional groups were also tolerated (**3e** and **3f**) without the need for protection. The only amino acid that did not undergo clean reaction was the *tert*-butyl ester of proline, the only *secondary* amino acid studied. In this case the crude mixture of

(4) For a recent review see: Schwindt, M. A.; Miller, J. R.; Hegedus, L. S. *J. Organomet. Chem.* **1991**, *413*, 143.
(5) Hegedus, L. S.; Schwindt, M. A.; DeLombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.
(6) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.
(7) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1989**, *111*, 7650.
(8) α-Phthalimidoketenes have been trapped with α-amino acid esters to form dipeptides: Winter, S.; Pracejus, H. *Chem. Ber.* **1966**, *99*, 151.
(9) Hegedus, L. S.; Imwinkelreid, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109.
(10) Hegedus, L. S.; Lastra, E.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1992**, *114*, 2991.
(11) Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2587.
(12) Tidwell, T. T. *Acc. Chem. Res.* **1990**, *23*, 273.
(13) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.



3a, R = Me, R' = *t*-Bu
3b, R = H, R' = *t*-Bu
3c, R = $PhCH_2$, R' = *t*-Bu
3d, R = Ph, R' = *t*-Bu
3e, R = $CH_3CH(OH)$, R' = Me
3f, R = 2-indolyl, R' = Me
3g, R = $(CH_2)_3$(proline), R' = *t*-Bu
3h, R = $(CH_2)_3$(proline), R' = CH_3



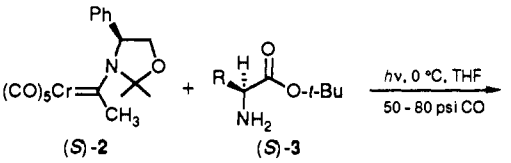
(4)

4 (*R*)(*S*)(*S*)

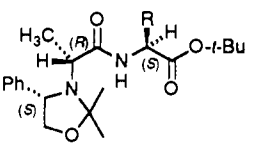
(ratio)	(isolated yield of (*R*)(*S*)(*S*))
4a 98:2	88%
4b 94:6	68%
4c 97:3	72%
4d 98:2	86%
4e 95:5	56%
4f 90:10	60%
4g –	61%
4h 74:26	60%

diastereoisomers contained a third product which had peaks in the ^1H NMR spectrum that obscured those required to assess the diastereoisomeric ratio. However, purification and separation resulted in a 60% overall yield of the (*R*)(*S*)(*S*) diastereoisomer **4g**, so the intrinsic stereoselectivity of the reaction was at least fair. When methyl prolinate was used in place of *tert*-butyl prolinate, a diastereoisomeric ratio of 74:26 was observed in the NMR spectrum of the crude reaction mixture, and the (*R*)(*S*)(*S*) diastereoisomer was again isolated in 60% yield.

One potential use for the methodology presented above is the introduction of amino acid fragments having the unnatural (*R*) absolute configuration into peptides made up of natural (*S*)-amino acids, without having to independently synthesize the unnatural amino acid. For this to be possible, efficient, stereoselective coupling in the "mismatched" manifold must be developed. Having noted the salutory effects of lowing temperatures on diastereoselectivity in eq 4, several mismatched combinations were repeated under the same conditions (eq 5). Again, an increase



3a, R = Me
3c, R = $PhCH_2$
3d, R = Ph



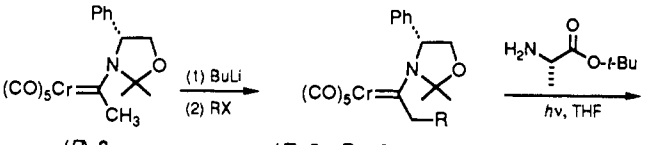
(5)

4' (*S*,*R*,*S*)

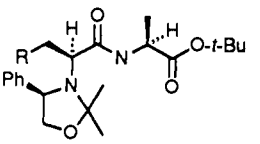
4'a 90:10	68%
4'c 92:8	65%
4'd 90:10	70%

in stereoselectivity was noted. (It is anticipated that stereoselectivity will continue to increase as the temperature decreases,[7,8,10] but photochemistry below 0 °C is experimentally cumbersome, and this has not yet been experimentally demonstrated.)

The α-protons of the methyl group of carbene complex **2** are acidic[5,14] and are easily removed by a variety of bases. The resulting carbanion undergoes facile alkylation[5] with reactive organic halides, resulting in functionalization of this position. This permits carbene complex **2** to be a source of a variety of different amino acid residues, in addition to the alanine fragment produced from the parent compound. Thus alkylation of (*R*)-**2** with *tert*-butyl bromoacetate, allyl bromide, or benzyl bromide produced carbene complexes **5a–c**. Photolysis of these carbene complexes with the *tert*-butyl ester of (*S*)-alanine produced the protected dipeptides **6a–c** containing glutamic acid, homophenylalanine, and 3-butenylglycine residues in place of alanine (eq 6).



(*R*)-**5a**, R = CH_2CO_2t-Bu
5b, R = $PhCH_2$
5c, R = CH_2=$CHCH_2$



(6)

6a	93:7	77%
6b	87:13	82%
6c	77:23	57%

The dipeptides synthesized above were characterized and stored in their protected form, since in this form they were both stable and easy to handle. Both oxidative (periodate) and reductive procedures for removal of this chiral auxiliary have previously been developed in these laboratories[5,9,10] and photochemical procedures[15] are currently being studied, so that free dipeptides will be accessible regardless of the functional groups they contain.

The absolute stereochemistry of the newly formed, carbene-complex-derived stereogenic center in these dipeptides was *assumed*, based on extensive previous studies,[5,10] to be the opposite of that in the oxazolidine chiral auxiliary. To prove this, the following studies were carried out. Authentic dipeptide *S*-ala-*S*-ala-O-*t*-Bu was synthesized by classical methods[16] (DCC coupling of *N*,*N*-dibenzyl-(*S*)-alanine with (*S*)-alanine *tert*-butyl ester, followed by debenzylation) and converted to its Mosher's amide by treatment with Mosher's acid chloride. This material had *identical* ^1H and ^{19}F NMR spectral data compared to that of the Mosher's amide of the major diastereoisomer **4a**, prepared by removal of the oxazolidine by hydrolysis/hydrogenolysis. Thus, (*R*)-carbene complex **2** combined with (*S*)-alanine *tert*-butyl ester to produce the (*S*)(*S*) dipeptide as the major diastereoisomer, as expected. As a cross check, **4a'**, prepared from (*S*)-carbene complex **2** and (*S*)-alanine *tert*-butyl ester, was converted to its Mosher's amide by the same procedure. Its ^1H and ^{19}F NMR spectra were different from those from the (*S*)(*S*) materials, confirming that the (*R*) carbene complex **2** induced the (*S*) absolute configuration, and the (*S*)-carbene complex **2** induced (*R*) absolute stereochemistry.

Summary

Photolysis of optically active chromium aminocarbene complexes in the presence of α-amino acid esters leads to the production of dipeptides in good yield and with good diastereoselectivity. This unconventional approach to dipeptides forms both the peptide bond and the stereogenic center at the same time,

(14) (a) Macomber, D. W.; Madhakur, P.; Rogers, R. D. *Organometallics* **1989**, *8*, 1275. (b) Wulff, W. D.; Anderson, B. A.; Toole, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 5485. (c) Wulff, W. D.; Anderson, B. A.; Isaacs, L. D. *Tetrahedron Lett.* **1989**, *30*, 4061.
(15) Pandey, G.; Rani, K. S. *Tetrahedron Lett.* **1988**, *29*, 4157.
(16) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788, 2024, 2034; **1973**, *106*, 3626.

permitting the introduction of both (*R*) and (*S*) amino acid fragments into peptides with equal facilty, under very mild (visible light, 0 °C, no coupling agent) conditions. The use of this methodology to incorporate a wide variety of amino acid fragments into larger peptides and into Merrifield resin supported peptides will be described in due course.

Experimental Section

Materials. Literature methods were used to prepare pentacarbonyl-[((*S* or *R*)-1-aza-2,2-dimethyl-3-oxa-5-phenylcyclopentyl)(methyl)carbene]chromium(0), **2**,[5] and the side chain, homologated carbene complexes.[5] (*S*)-*tert*-Butyl alaninate, (*S*)-*tert*-butyl phenylalaninate, (*S*)-*tert*-butyl prolinate, (*S*)-methyl threoninate, (*S*)-methyl tryptophanate, and (*S*)-*tert*-butyl glycinate were purchased from the Sigma Chemical Company, St. Louis, MO.

General Procedures for the Photolytic Coupling of Aminocarbene Complexes with Amino Acid Esters. Photolysis reactions were carried out in Pyrex pressure tubes (Ace Glass) using a Conrad Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled Pyrex immersion well. In the case of photolysis at 0 °C the pressure tube was placed in a Pyrex immersion well with ethylene glycol at 0 °C circulated as coolant. Reactions run under CO pressure were saturated with CO (3 cycles, 50–80 psi of CO) and photolyzed under 50–80 psi of CO. When the reaction was complete, oxidation of reaction mixtures was carried out by saturating a 1:1 hexane/EtOAc solution of crude product with air and exposing the resulting solution to light, in a box equipped with six 20-W Vitalite fluorescent lamps, until most of the chromium residue turned brown and precipitated. Partial recovery of the $CrCO_6$ can be achieved by filtering this solution prior to oxidation, to remove the crude $CrCO_6$ that precipitated.

The free α-amino ester was generated just prior to use. The hydrochloride salt of the α-amino ester was dissolved in 2 mL of THF and 2 equiv of Et_3N was added. After being stirred for 2 h, the solution was filtered through Celite directly into the pressure tube.

Coupling of Dibenzylaminocarbene Complex 1 with (*S*)-Alanine *tert*-butyl Ester. Photolysis (42 h) of **1** (84 mg, 0.19 mmol) in 4 mL of THF at 0 °C, containing (*S*)-alanine *tert*-butyl ester (30 mg, 0.16 mmol), gave 54 mg of a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc) (inseparable mixture of diastereomers). The crude reaction mixture consisted of a 60:40 mixture of two diastereomers (20% de), determined by integration of the *t*-Bu singlets (δ 1.49 ppm major, 1.46 ppm minor—well resolved).

^{1}H NMR (300 MHz, $CDCl_3$) (mixture) δ 1.29, 1.33, 1.36 (d's, *J* = 7.1 Hz, 6 H, CH_3CH), 1.46 (s, 3.6 H, (CH_3)$_3$Cl), 1.49 (s, 5.4 H, (CH_3)$_3$C), 3.41, 3.80, 4.42 (m's, 6 H, C*H*, CH_2N), 7.22–7.41 (m, 10 H, Ar*H*), 7.81 (d, *J* = 7.5 Hz, 0.4 H, NH), 7.97 (d, *J* = 7.5 Hz, 0.6 H, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.9, 172.1, 171.9 (C=O), 138.9, 138.7, 128.9, 128.5, 128.4, 127.3 (Ar), 81.7, 81.6 (C), 57.4 (CH), 54.4 (CH_2), 48.7 (CH), 27.9 (CH_3), 19.1, 18.6 (CH_3), 7.4, 7.3 (CH_3). IR (neat) ν 3385, 2978, 1730 (C=O), 1675 (C=O), 1153 cm^{-1}. Anal. Calcd. for $C_{24}H_{32}N_2O_3$: C, 72.75; H, 8.07; N, 7.07. Found: C, 72.80; H, 8.05; N, 6.99.

(a) Coupling of (*R*)-2 with (*S*)-Alanine *tert*-butyl Ester To Produce 4a. Photolysis (36 h) of (*R*)-**2** (202 mg, 0.51 mmol) in 4 mL of THF at 0 °C, containing 62 mg (0.43 mmol) of (*S*)-*tert*-butyl alaninate, gave 40 mg (88%) of **4a** as a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc). The crude reaction mixture consisted of a 98:2 mixture of two diastereomers (96% de), determined by integration of the methine quartets of the newly formed stereogenic center (δ 3.40 ppm major, 3.53 ppm minor—well resolved).

^{1}H NMR (270 MHz, $CDCl_3$) (major diastereomer) δ 0.84 (d, *J* = 7.1 Hz, 3 H, CH_3CH), 1.30 (s, 3 H, CH_3), 1.42 (d, *J* = 7.2 Hz, 3 H, CH_3CH), 1.43 (s, 9 H, CH_3), 1.50 (s, 3 H, CH_3), 3.40 (q, *J* = 7.2 Hz, 1 H, CH), 3.90 (dd, *J* = 13.9 Hz, 8.5 Hz, 1 H, CH_2O), 4.12 (quin, *J* = 7.4 Hz, 1 H, C*H*CH$_3$), 4.26 (m, 2 H), 7.16–7.40 (m, 5 H, ArH), 7.60 (d, *J* = 7.3 Hz, 1 H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (CH_3), 17.9 (CH_3), 21.0 (CH_3), 27.7 (CH_3), 28.0 (CH_3), 48.3, 54.9, 60.0, 72.4 (CH_2), 81.4 (C), 97.1 (C), 127.5, 128.0, 128.8, 142.9, 171.7 (C=O), 173.1 (C=O). IR (film) ν 3379 (NH), 1732 (C=O), 1671 (C=O) cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ (minor diastereomer) 1.13 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.25 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.46 (s, 9 H, CH_3), 1.48 (s, 3 H, CH_3), 3.53 (q, *J* = 7.1 Hz, 1 H, C*H*CH$_3$), 3.70 (dd, *J* = 3.3, 8.3 Hz, 1 H, CH_2O), 4.27 (m, 1 H, CH), 4.37 (t, *J* = 8.1 Hz, 1 H, CHPh), 4.53 (m, 1 H, CH_2O), 6.73 (d, *J* = 6.9 Hz, 1 H, NH), 7.20–7.41 (m, 5 H, ArH). After removal (see below) of the N protecting group, this material was identical to authentic material synthesized by the coupling of *S*-ala with *S*-ala.

(b) Coupling of (*R*)-2 with Glycine *tert*-Butyl Ester To Synthesize 4b. Photolysis (19 h) of *R*-(**2**) (200 mg, 0.50 mmol) in 4 mL of THF at 0 °C, containing (*S*)-*tert*-butyl glycinate (55 mg, 0.42 mmol) gave 103 mg (68%) of **4b** as a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc). The crude reaction mixture consisted of a 94:6 mixture of two diastereomers (88% de), determined by integration of the *tert*-butyl singlets (δ 1.47 ppm major, 1.46 ppm minor).

^{1}H NMR (270 MHz, $CDCl_3$) (major diastereomer) δ 1.32 (s, 3 H, CH_3), 1.36 (d, *J* = 7.3 Hz, 3 H, CH_3), 1.47 (s, 9 H, CH_3), 1.52 (s, 3 H, CH_3), 3.17 (dd, *J* = 18.6, 3.7 Hz, 1 H, CH_2), 3.43 (q, *J* = 7.2 Hz, 1 H, CH), 3.78 (dd, *J* = 6.4, 18.5 Hz, 1 H, CH_2), 3.91 (dd, *J* = 8.6, 9.8 Hz, 1 H), 4.28 (m, 2 H), 7.15–7.40 (m, 5 H, ArH), 7.45 (s, 1 H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 21.4, 25.4, 27.7, 27.9, 41.7, 54.5, 60.2, 67.7, 72.0, 81.0 (C), 96.7 (C), 127.4, 128.0, 128.4, 141.3, 168.5 (CO), 173.6 (CO). IR (film) ν 3388 (NH), 1739 (C=O), 1675 (C=O) cm^{-1}. Anal. Calcd (as the N-tBOC derivative, after removal of the chiral auxiliary) for $C_{14}H_{26}N_2O_5$: C, 55.61; H, 8.67; N, 9.27. Found: C, 55.78; H, 8.49; N, 9.19. ^{1}H NMR (270 MHz, $CDCl_3$) δ (minor diastereomer) 1.28 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.46 (s, 9 H, CH_3), 1.49 (s, 3 H, CH_3), 3.36 (dd, *J* = 4.2, 18.4 Hz, 1 H, CH_2), 3.52 (q, *J* = 7.0 Hz, 1 H, C*H*CH$_3$), 3.73 (dd, *J* = 4.8, 9.0 Hz, 1 H), 3.84 (dd, *J* = 5.9, 18.3 Hz, 1 H, CH_2), 4.40 (m, 2 H), 6.56 (s, 1 H, NH), 7.18–7.41 (m, 5 H, ArH).

(c) Coupling of (*R*)-2 with (*S*)-Phenylalanine *tert*-Butyl Ester To Synthesize 4c. Photolysis (16 h) of (*R*)-**2** (202 mg, 0.51 mmol) in 10 mL of THF at 0 °C, containing (*S*)-*tert*-butyl phenylalaninate (94 mg, 0.43 mmol) gave 138 mg (72%) of **4c** as a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc). The crude reaction mixture consisted of a 97:3 mixture of two diastereomers (94% de), determined by integration of the doublet of the benzyl group.

^{1}H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.27 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.34 (s, 9 H, CH_3), 1.46 (s, 3 H, CH_3), 2.55 (d, *J* = 6.6 Hz, 2 H, CH_2Ph), 3.40 (q, *J* = 7.2 Hz, 1 H, CH), 3.80 (m, 1 H, CH_2O), 4.26 (m, 2 H, CH_2O), 4.38 (q, *J* = 7.2 Hz, 1 H, PhCH_2C*H*), 6.98 (m, 2 H, ArH), 7.16–7.39 (m, 8 H, ArH), 7.55 (d, *J* = 7.2 Hz, 1 H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.3, 21.0, 27.6, 27.8 (CH_3), 38.7 (CH_2), 53.8, 55.9, 60.9, 72.3, 81.7 (C), 97.0 (C), 126.6, 127.6, 127.7, 128.2, 128.9, 129.3, 136.5, 143.0, 170.5 (CO), 173.8 (CO). IR (film) ν 3800–3300 (NH), 1728 (C=O), 1667 (C=O) cm^{-1}. Anal. Calcd (as the N-tBOC derivative, after removal of the chiral auxiliary) for $C_{21}H_{32}N_2O_5$: C, 64.26; H, 8.22; N, 7.14. Found: C, 64.41; H, 8.04; N, 7.13. ^{1}H NMR (300 MHz, $CDCl_3$) (minor diastereomer) δ 1.18 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.40 (s, 9 H, CH_3), 2.95 (dd, *J* = 2.4, 6.4 Hz, 2 H, CH_2Ph), 3.49 (q, *J* = 7.2 Hz, 1 H, CH), 3.68 (dd, *J* = 5.6, 8.4 Hz, 1 H), 4.34 (t, *J* = 8.0 Hz, 1 H, CH_2O), 4.62 (m, 2 H, CH_2O, C*H*Ph), 6.80 (d, *J* = 7.3 Hz, 1 H, NH), 7.07–7.38 (m, 10 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.4, 23.5, 27.9, 28.1, 38.0, 53.5, 56.2, 63.0, 71.0, 82.0, 96.0, 126.8, 126.9, 127.1, 128.3, 128.4, 129.4, 136.3, 144.3, 170.6 (CO), 173.9 (CO). IR (film) ν 3800–3400 (NH), 1731 (C=O), 1666 (C=O) cm^{-1}.

(d) Coupling of (*R*)-2 with (*S*)-Phenylglycine *tert*-Butyl Ester To Produce 4d. Photolysis (2 days) of (*R*)-**2** (107 mg, 0.27 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-*tert*-butyl phenylglycinate (56 mg, 0.27 mmol) gave 95 mg (81% yield) of **4d** as a clear oil. The crude reaction mixture consisted of a mixture of two diastereoisomers. The de (92%) was determined by integration of the α methine proton of the phenylglycine residue (major 5.01–minor 5.36).

^{1}H NMR (300 MHz, $CDCl_3$) (major diastereoisomer) δ 1.27 (s, 3 H, CH_3), 1.30 (d, *J* = 7.3 Hz, CH_3), 1.31 (s, 9 H, C(CH_3)$_3$), 1.50 (s, 3 H, CH_3), 3.42 (q, *J* = 7.3 Hz, 1 H, *H*C-CH_3), 3.77 (m, 1 H), 4.22 (m, 2 H), 5.01 (d, *J* = 6.8 Hz, 1 H, *H*C-Ph), 6.85–7.25 (m, 10 H, ArH), 7.98 (d, *J* = 6.8 Hz, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6 (CH_3), 20.7 (CH_3), 27.6 (CH_3), 27.8 (C(CH_3)$_3$), 55.4 (CN-Ph), 57.1 (CH), 60.5 (CH), 72.5 (O-CH_2), 82.0 (*C*(CH_3)$_3$), 97.0 (*C*(CH_3)$_2$), 127.0, 127.5, 127.8, 128.5, 128.8 (Ar), 136.8, 142.5, 169.4 (C=O), 173.7 (C=O). IR (film) ν 3380 (NH), 1733 (C=O), 1674 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.25; H, 7.76; N, 6.39. Found: C, 71.32; H, 7.54; N, 6.19.

(e) Coupling of (*R*)-2 with (*S*)-Threonine Methyl Ester To Produce 4e. Photolysis (46 h) of (*R*)-**2** (202 mg, 0.51 mmol) in 5 mL of THF, at 0 °C, containing (*S*)-methyl threoninate (57 mg, 0.43 mmol) gave 86 mg (56%) of **4e** as a white solid after chromatography on silica gel (1:1 hexanes/EtOAc). The crude reaction mixture consisted of a 95:5 mixture of two diastereomers (90% de), determined by integration of the doublets of the methyl group α to the hydroxy (δ 0.075 ppm major, 1.10 ppm minor).

^{1}H NMR (270 MHz, $CDCl_3$) (major diastereomer) δ 0.75 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.45 (d, *J* = 7.3 Hz, 3 H, CH_3), 1.55 (s, 3 H, CH_3), 3.50 (q, *J* = 7.3 Hz, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.89 (m, 1 H), 4.01 (m, 1 H), 4.33 (m, 3 H), 7.21–7.50 (m, 5 H, ArH), 7.80 (d, *J* = 8.9 Hz, 1 H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.2, 19.5, 20.7, 27.4, 52.2, 55.7, 57.6, 60.4, 68.1, 72.4, 97.3, 127.6, 127.9, 129.0, 143.6, 170.9 (CO), 175.1 (C=O). IR (film) ν 3370 (NH) (OH), 1748

(C=O), 1654 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.61; N, 7.69; H, 7.74. Found: C, 62.67; H, 7.64; N, 7.66. ^1H NMR (270 MHz, $CDCl_3$) (minor diastereomer) δ 1.10 (d, J = 6.5 Hz, 3 H, CH_3), 1.25 (d, J = 7.2 Hz, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 3.65 (q, J = 7.2 Hz, 1 H, CH), 3.77 (s, 3 H, OCH_3), 4.30 (m, 1 H), 4.41 (t, J = 8.1 Hz, 1 H), 4.49 (dd, J = 6.4, 7.4 Hz, 1 H), 4.72 (t, J = 6.6 Hz, 1 H), 7.20–7.43 (m, 5 H, ArH).

(f) Coupling of (*R*)-2 with (*S*)-Tryptophan Methyl Ester To Produce 4f. Photolysis (24 h) of (*R*)-**2** (205 mg, 0.52 mmol) in 7 mL of THF, at 0 °C, containing (*S*)-methyl tryptophanate (219 mg, 0.43 mmol) gave 116 mg (60%) of **4f** as a clear oil after chromatography on silica gel (1:1 hexanes/EtOAc). The crude reaction mixture consisted of a 90:10 mixture of two diastereomers (80% de) determined by integration of the dd's for the β-methylene of the tryptophan residue (δ 2.85 ppm major, 2.68 ppm minor).

^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.24 (d, J = 7.2 Hz, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.85 (dd, 1 H, J = 6.9, 14.8 Hz, CH_2), 2.93 (dd, J = 6.6, 14.8 Hz, 1 H, CH_2), 3.44 (q, J = 7.2 Hz, 1 H, CH), 3.58 (s, 3 H, OCH_3), 3.74 (dd, J = 5.3, 7.4 Hz, 1 H, CH_2O), 4.23 (m, 2 H), 4.53 (q, J = 6.9 Hz, 1 H, CH), 6.83–7.53 (m, 10 H, ArH), 7.63 (d, J = 7.1 Hz, 1 H, NH), 8.24 (s, 1 H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.7 (CH_3), 21.2 (CH_3), 27.7 (CH_3), 27.9 (CH_2), 52.0, 52.6, 55.5, 60.8, 72.2 (CH_2), 97.0 (C), 110.4, 111.2, 118.6, 119.5, 122.2, 122.3, 127.3, 127.6, 127.7, 128.7, 136.2, 142.0, 172.6 (CO), 174.2 (CO). IR (film) ν 3363 (NH), 1739 (C=O), 1660 (C=O) cm^{-1}. Anal. Calcd for $C_{26}H_{31}N_3O_4$: C, 69.46; H, 6.95; N, 9.35. Found: C, 69.18; H, 6.73; N, 9.44.

(g) Coupling of (*R*)-2 with (*S*)-Proline *tert*-Butyl Ester To Produce 4g. Photolysis (2 days) of (*R*)-**2** (202 mg, 0.51 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-*tert*-butyl prolinate (73 mg, 0.43 mmol) and 118 μL of Et_3N (.85 mmol) gave 105 mg (61%) of **4g** as a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc).

^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.30 (d, J = 7.3 Hz, 3 H, CH_3), 1.38 (s, 9 H, CH_3), 1.45 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.74–1.98 (m, 4 H, $(CH_2)_2$), 3.53 (m, 1 H), 3.66 (dd, J = 4.2, 7.6 Hz, 1 H), 3.73 (dd, J = 5.2, 8.6 Hz, 1 H), 3.84 (m, 2 H), 4.24 (t, 1 H, J = 8.1 Hz), 4.41 (dd, J = 5.3, 7.9 Hz, 1 H), 7.17–7.30 (m, 5 H, ArH). ^{13}C NMR (75.5 MHz $CDCl_3$) δ 13.7 (CH_3), 24.4 (CH_3), 24.7 (CH_2), 27.8 (CH_3), 28.1 (CH_3), 28.7 (CH_2), 46.2 (CH_2), 53.8, 59.6, 60.4, 71.1 (CH_2O), 80.7 (C), 96.8 (C), 126.7, 127.8, 144.1, 170.0 (CO), 171.6 (CO). IR (film) ν 1736 (C=O), 1649 (C=O) cm^{-1}. Anal. Calcd for $C_{23}H_{34}N_2O_4$: C, 68.62; H, 8.51; N, 6.96. Found: C, 68.69; H, 8.30; N, 7.08.

(h) Coupling of (*R*)-2 with (*S*)-Proline Methyl Ester To Produce 4h. Photolysis (2 days) of (*R*)-**2** (315 mg, 0.8 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-methyl prolinate (90 mg, 0.7 mmol) gave 130 mg (60%) of **4h** as a white solid after chromatography on silica gel (1:1 EtOAc/hexanes). The crude reaction mixture consisted of a 74:26 ratio of two diastereomers (48% de) determined by integration of the gem dimethyl peak (1.48 ppm) of the major and the CH_3CH doublet (1.09 ppm) of the minor.

^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.32 (d, J = 6.4 Hz, 3 H, CH_3CH), 1.48 (s, 6 H, CH_3), 1.90 (m, 4 H, $-CH_2-$), 3.58 (m, 2 H), 3.62 (s, 3 H, OCH_3), 3.74 (dd, J = 8.4, 5.1 Hz, 1 H, CHN), 3.84 (m, 2 H), 4.25 (appt, J = 8.2 Hz, 1 H, CH_2O), 4.39 (dd, J = 7.9, 5.2 Hz, 1 H, NCHPh), 7.23 (m, 5 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4 (CH_3), 24.5 (CH_3), 24.9 (CH_2), 28.1 (CH_3), 28.7 (CH_2), 46.3 (CH_2), 52.0 (NCHPh), 53.6 (CH), 58.9 (OCH_3), 60.1 (CH), 71.2 (CH_2O), 96.8 ($C(CH_3)_2$), 126.9, 127.8, 144.1, 170.2 (C=O), 173.0 (C=O). IR (neat) ν 1747 (CO), 1649 (CO) cm^{-1}.

Coupling of (*S*)-2 with (*S*)-Alanine *tert*-Butyl Ester To Produce 4a'. Photolysis (16 h) of (*S*)-**2** carbene complex (202 mg, 0.51 mmol) in 5 mL of THF, at 0 °C, containing (*S*)-*tert*-butyl alinate (62 mg, 0.43 mmol) gave 109 mg (68%) of **4a'** as a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc). The crude reaction mixture consisted of a 90:10 mixture of two diastereomers (80% de) determined by integration of the triplet and dd of the major and minor diastereomer, respectively (δ 3.83 ppm major, 3.70 ppm minor).

^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.30 (d, J = 7.2 Hz, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.50 (s, 9 H, CH_3), 1.51 (d, J = 7.2 Hz, 3 H, CH_3), 3.41 (q, J = 7.2 Hz, 1 H, CH), 3.84 (t, J = 7.8 Hz, 1 H, CH_2O), 3.99 (quin, J = 6.9 Hz, 1 H, CH), 4.23 (t, J = 7.8 Hz, 1 H), 4.31 (t, 1 H, J = 7.2 Hz), 7.24 (m, 3 H, ArH), 7.41 (m, 2 H, ArH), 7.74 (d, 1 H, J = 5.7 Hz, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) (major diastereomer) δ 14.0 (CH_3), 18.5 (CH_3), 21.6 (CH_3), 27.9 (CH_3), 48.6, 55.2, 61.1, 72.3 (CH_2), 81.6 (C), 96.7 (C), 127.6, 128.3, 128.4, 140.6, 171.8 (CO), 173.6 (C=O). IR (film) ν 3384 (NH), 1729 (C=O), 1676 (C=O) cm^{-1}.

Coupling of (*S*)-2 with (*S*)-Phenylalanine *tert*-Butyl Ester To Produce 4c'. Photolysis (19 h) of (*S*)-**2** (104 mg, 0.26 mmol) in 7 mL of THF, at 0 °C, containing (*S*)-*tert*-butyl phenylalaninate (48 mg, 0.22 mmol) gave 64 mg (65%) of **4c'** as a clear oil after chromatography on silica gel (3:1 hexanes/EtOAc). The crude reaction mixture consisted of a 92:8 mixture of two diastereomers (84% de) determined by integration of the triplets (CH_2O) (δ 4.16 ppm major, 4.00 ppm minor).

^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.26 (2, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.32 (d, J = 7.2 Hz, 3 H, CH_3), 1.42 (s, 9 H, CH_3), 3.02 (dd, J = 5.1, 13.9 Hz, 1 H, CH_2), 3.10 (dd, J = 6.6, 13.9 Hz, 1 H, CH_2), 3.35 (q, J = 7.2 Hz, 1 H, $CH(CH_3)$), 3.77 (t, J = 7.7 Hz, 1 H, CH_2O), 4.17 (t, J = 7.5 Hz, 1 H), 4.30 (m, 2 H), 7.10–7.36 (m, 10 H, ArH), 7.65 (d, J = 6.4 Hz, 1 H, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5 (CH_3), 21.6 (CH_3), 27.7 (CH_3), 27.9 (CH_3), 37.6 (CH_2), 53.7, 54.9, 60.9, 72.3 (CH_2), 82.0 (C), 96.6 (C), 126.7, 127.7, 128.2, 128.4, 128.5, 129.5, 136.5, 139.9, 170.2 (CO), 173.5 (CO). IR (film) ν 3386 (NH), 1729 (C=O), 1672 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{36}N_2O_4$: C, 71.65; H, 6.19; N, 8.02. Found: C, 71.43; H, 6.07; N, 7.99.

Coupling of (*S*)-2 with (*S*)-Phenylglycine *tert*-Butyl Ester To Give 4d'. Photolysis (2 days) of (*S*)-**2** (107 mg, 0.27 mmol) in 4 mL of dry THF, at 0 °C, containing (*S*)-*tert*-butyl phenylglycinate (56 mg, 0.27 mmol) gave 105 mg (89% yield) of **4d'** as a clear oil. The crude reaction mixture consisted of a mixture of two diastereoisomers. The de (79%) was determined by integration of the α methine of the phenylglycine residue (δ 4.88 ppm major, 5.20 ppm minor).

^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 1.24 (s, 3 H, CH_3), 1.26 (d, 3 H, J = 7.2 Hz, CH_3), 1.34 (s, 9 H, CH_3), 1.46 (s, 3 H, CH_3), 3.31 (q, J = 7.2 Hz, 1 H, H_3C-C*H*), 3.82 (t, J = 7.3 Hz, 1 H), 4.22 (m, 2 H), 4.88 (d, J = 6.2 Hz, 2 H, *H*-C-Ph), 7.15–7.38 (m, 10 H, ArH), 8.21 (d, J = 6.2 Hz, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3 (CH_3), 21.5 (CH_3), 27.8 (CH_3), 28.0 ($C(CH_3)_3$), 54.8 (*C*H-Ph), 56.9 (CH), 60.9 (CH), 72.4 (O-CH_2), 82.3 ($C(CH_3)_3$), 96.7 ($C(CH_3)_2$), 126.9, 127.7, 127.8, 128.4, 128.5 (Ar), 137.8, 140.0 (C-Ph), 169.5 (C=O), 173.2 (C=O). IR ν 3379 (NH), 1734 (C=O), 1673 cm^{-1}. Anal. Calcd for $C_{26}H_{34}N_2O_4$: C, 71.25; H, 7.76; N, 6.39. Found: C, 71.32; H, 7.54; N, 6.19.

Coupling of the Carbene Complex 5a with (*S*)-Alanine *tert*-Butyl Ester To Give 6a. Photolysis (48 h) of **5a** (46 mg, 0.09 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-alanine *tert*-butyl ester (11 mg, 0.08 mmol) gave 34 mg (77%) of a clear colorless oil after radial chromatography (20% Et_2O/hexanes). The crude reaction mixture consisted of a 93:7 ratio (86% de) of two diastereomers determined by integration of the CH_2O protons in the oxazolidine ring (δ 3.27 ppm major, 3.34 ppm minor).

^1H NMR (300 MHz, $CDCl_3$) (major) δ 0.82 (d, J = 7.1 Hz, 3 H, $CHCH_3$), 1.36 (s, 3 H, CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 1.46 (s, 9 H, $C(CH_3)_3$), 1.53 (s, 3 H, CH_3), 2.05 (m, 2 H, CH_2CH_2), 2.39 (m, 1 H, CH_2CO_2-*t*-Bu), 2.61 (m, 1 H, CH_2CO_2-*t*-Bu), 3.27 (dd, J = 8.7 Hz, 5.1 Hz, 1 H, $CHCH_2$), 3.91 (dd, J = 12.9, 8.8 Hz, 1 H, CH_2O), 4.11 (quin, J = 7.3 Hz, 1 H, $CHCH_3$), 4.30 (m, 2 H, CHPh, CH_2O), 7.29 (m, 4 H, ArH, NH), 7.43 (m, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (CH_3), 21.7 (CH_3), 25.6 (CH_2), 27.9 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$), 34.0 (CH_2), 48.2 (CHPh), 58.7 ($CHCH_3$), 60.3 ($CHCH_2$), 72.2 (CH_2O), 80.3 (OC-*t*-Bu), 81.5 (OC-*t*-Bu), 96.9 ($C(CH_3)_2$), 127.5, 127.8, 128.8, 143.4, 171.7 (CO), 172.5 (CO), 172.7 (CO). IR (neat) ν 3384 (NH), 1729 (C=O), 1670 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{42}N_2O_6$: C, 66.14; H, 8.57; N, 5.71. Found: C, 66.29; H, 8.47; N, 5.49. ^1H NMR $CDCl_3$ (300 MHz) (minor) δ 1.31 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.37 (s, 3 H, CH_3), 1.40 (s, 9 H, $(CH_3)_3$), 1.46 (s, 3 H, CH_3), 1.48 (s, 9 H, $(CH_3)_3$), 1.56 (m, 1 H, $CH_2CH_2CO_2$-*t*-Bu), 1.75 (m, 1 H, $CH_2CH_2CO_2$-*t*-Bu), 1.96 (m, 1 H, CH_2CO_2-*t*-Bu), 2.20 (m, 1 H, CH_2CO_2-*t*-Bu), 3.34 (dd, J = 8.7, 5.7 Hz, 1 H, $CHCH_2$), 3.72 (dd, J = 8.4, 4.3 Hz, 1 H, CH_2O), 4.37 (m, 2 H, $CHCH_3$), 5.06 (dd, J = 7.5, 4.2 Hz, 1 H), 6.40 (d, J = 7.5 Hz, 1 H, NH), 7.26 (m, 3 H, ArH), 7.42 (m, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (CH_3), 23.3 (CH_3), 27.5 (CH_2), 28.0 ($(CH_3)_3$), 28.1 ($(CH_3)_3$), 31.7 (CH_2), 48.4 (CHPh), 59.1 ($CHCH_3$), 61.1 ($CHCH_2$), 71.9 (CH_2O), 80.3 ($C(CH_3)_3$), 81.9 ($C(CH_3)_3$), 96.0 ($C(CH_3)_2$), 127.0, 127.1, 128.3, 145.5, 172.0 (CO), 173.0 (CO), 174.0 (CO). IR (neat) ν 3334 (NH), 1731 (C=O), 1678 (C=O) cm^{-1}

Coupling of Carbene Complex 5b with (*S*)-Alanine *tert*-Butyl Ester To Give 6b. Photolysis (48 h) of **5b** (80 mg, 0.16 mmol) in 4 mL of THF, at 0 °C, containing (*S*)-alanine *tert*-butyl ester (19 mg, 0.14 mmol) gave 53 mg (82%) of a clear colorless oil after radial chromatography (15% EtOAc/hexane). The crude reaction mixture consisted of a 84:16 (68%) ratio of two inseparable diastereomers determined by integration of the CH_3 doublet of the major isomer at 0.81 ppm and the oxazolidine CH_3 at 1.36 ppm for the minor isomer.

^1H NMR (300 MHz, $CDCl_3$) (major) δ 0.81 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.22 (s, 3 H, CH_3), 1.46 (s, 9 H, $C(CH_3)_3$), 1.51 (s, 3 H, CH_3), 1.91 (m, 1 H, CH_2CH_2Ph), 2.27 (m, 1 H, CH_2CH_2Ph), 2.76 (ddd, J = 10.2, 6.3, 3.4 Hz, 1 H, CH_2Ph), 2.97 (ddd, J = 10.5, 5.1, 4.9 Hz, 1 H, CH_2Ph), 3.30 (dd, J = 8.3, 4.6 Hz, 1 H, CH_2CH), 3.91 (dd, J = 12.1,

8.5 Hz, 1 H, CH_2O), 4.14 (quin, J = 7.4 Hz, 1 H, C*H*CH_3), 4.27 (m, 2 H, CHPh, CH_2O), 6.86 (d, J = 6.7 Hz, 1 H, NH), 7.29 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (CH_3), 21.6 (CH_3), 27.9 ($C(CH_3)_3$), 32.3 (CH_2), 34.8 (CH_2), 48.2 (CHPh), 58.7 (*C*HCH_2), 60.4 (*C*HCH_3), 72.2 (CH_2O), 81.4 ($OC(CH_3)_3$), 96.9 ($C(CH_3)_2$), 125.9, 127.5, 127.7, 128.4, 128.5, 128.8, 141.6, 143.4, 171.7 (CO), 172.9 (CO). IR (neat) ν 3383 (NH), 1732 (C=O), 1669 (C=O) cm^{-1}. Anal. Calcd for $C_{28}H_{38}N_2O_4$: C, 72.12; H, 8.15; N, 6.00. Found: C, 71.96; H, 8.29; N, 5.82. ^1H NMR (300 MHz, $CDCl_3$) (minor, only the well-resolved peaks) δ 1.28 (d, J = 7.1 Hz, 3 H, $CHCH_3$), 1.36 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.72 (m, CH_2CH_2Ph), 2.52 (m, 1 H, CH_2CH_2Ph), 3.71 (dd, J = 8.4, 4.7 Hz, 1 H, CH_2O), 4.87 (dd, J = 7.6, 4.7 Hz, 1 H, CH_2O), 6.45 (d, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3 (CH_3), 23.3 (CH_3), 33.3 (CH_2), 33.8 (CH_2), 60.5 ($CHCH_2$), 62.1 ($CHCH_3$), 71.6 (CH_2O), 81.9 ($OC(CH_3)_3$), 96.1 ($C(CH_3)_2$), 125.7, 127.0, 127.1, 128.2, 141.5, 145.2, 172.1 (C=O), 173.6 (C=O).

Coupling of Carbene Complex 5c with (*S*)-Alanine *tert*-Butyl Ester To Give 6c. Photolysis (48 h) of **5c** (50 mg, 0.11 mmol) in 4 mL of THF at 0 °C, containing (*S*)-alanine *tert*-butyl ester (14 mg, 0.09 mmol) and *N*,*N*-dimethylaminopyridine (13 mg, 0.11 mmol) gave 15 mg of a clear colorless oil after radial chromatography (30% Et_2O/hexanes). The crude reaction mixture consisted of a 77:23 ratio of two diastereomers (54% de), determined by integration of the oxazolidine geminal CH_3 groups (δ 1.35 ppm major, 1.39 ppm minor—well resolved).

^1H NMR (300 MHz, $CDCl_3$) (major) δ 0.83 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.35 (s, 3 H, CH_3), 1.46 (s, 9 H, $C(CH_3)_3$), 1.53 (s, 3 H, CH_3), 1.72 (m, 1 H, $CH_2CH_2CH{=}CH_2$), 2.00 (m, 1 H, $CH_2CH_2CH{=}CH_2$), 2.25 (m, 2 H, $CH_2CH{=}CH_2$), 3.27 (dd, J = 7.6, 5.7 Hz, 1 H, $CHCH_2$), 3.91 (dd, J = 6.8, 2.8 Hz, 1 H, CH_2O), 4.14 (quin, J = 7.3 Hz, 1 H, CH_3CH), 4.28 (m, 2 H, CHPh, CH_2O), 5.02 (m, 2 H, $CH_2CH{=}CH_2$), 5.83 (dddd, J = 16.9, 10.4, 6.5, 2.9 Hz, 1 H, $CH{=}CH_2$), 7.28 (m, 4 H, ArH, NH), 7.42 (m, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) 18.0 (CH_3), 21.9 (CH_3), 27.9 ($C(CH_3)_3$), 28.1 (CH_3), 29.5 (CH_2), 32.5 (CH_2), 48.2 (*C*HPh), 59.3 (*C*HCH_3), 60.6 (*C*HCH_2), 72.2 (CH_2O), 81.5 ($OC(CH_3)_3$), 96.9 ($C(CH_3)_2$), 115.2 ($CH{=}CH_2$), 127.5, 127.7, 128.8, 137.8 ($CH{=}CH_2$), 143.7, 171.7 (CO), 173.1 (CO). IR (neat) ν 3383 (NH), 1734 (C=O), 1670 (C=O) cm^{-1}. Anal. Calcd for $C_{24}H_{36}N_2O_4$: C, 69.25; H, 8.65; N, 6.73. Found: C, 69.05; H, 8.42; N, 6.51. ^1H NMR (300 MHz, $CDCl_3$) (minor) δ 1.30 (d, J = 7.1 Hz, 3 H, CH_3CH), 1.39 (s, 3 H, CH_3), 1.48 (m, 14 H, CH_3, $C(CH_3)_3$, $CH_2CH_2CH{=}CH_2$), 1.66 (m, 1 H, $CH_2CH_2CH{=}CH_2$), 1.94 (m, 2 H, $CH_2CH{=}CH_2$), 3.25 (dd, J = 7.71, 6.3 Hz, CH_2CH), 3.70 (dd, J = 8.4, 4.7 Hz, 1 H, CH_2O), 4.38 (m, 2 H, CH_2O, $CHCH_3$), 4.88 (m, 3 H, CH_2CHCH_2, CHPh), 5.56 (dddd, J = 17.1, 10.4, 6.8, 2.9 Hz, 1 H, $CHCH_2$), 6.41 (d, J = 8.0 Hz, 1 H, NH), 7.26 (m, ArH, 3 H), 7.43 (m, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) 18.4 (CH_3), 23.5 (CH_3), 28.0 ($C(CH_3)_3$), 28.1 (CH_3), 31.1 (CH_2), 31.3 (CH_2), 48.4 (CHPh), 60.3 (*C*HCH_3), 62.0 (*C*HCH_2), 71.7 (CH_2O), 82.0 ($OC(CH_3)_3$), 96.1 ($C(CH_3)_2$), 115.3 ($CH{=}CH_2$), 127.1, 128.3, 137.9 ($CH{=}CH_2$), 145.2, 172.2 (CO), 173.7 (CO). IR (neat) ν 3324 (NH), 1735 (C=O), 1652 (C=O) cm^{-1}.

General Procedure for Removal of the Oxazolidine Chiral Auxiliary. The oxazolidine protected dipeptide was stirred in 5 mL of a 1:4 mixture of 0.2 N HCl/MeOH for 2 h. The solvent was removed in vacuo, and 5 mL of 5% aqueous $NaHCO_3$ was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to leave the crude amino alcohol. This was dissolved in MeOH (5 mL) and added to a pressure tube containing 30 mol % $Pd(OH)_2$. The reaction was pressurized to 50 psi with hydrogen and heated to 50 °C in an oil bath. After hydrogenation was complete (2 h), the black slurry was stirred for 2 h under 50 psi of CO followed by removal of the $Pd(OH)_2$ by filtration through Celite. The filter cake was washed with MeOH and EtOAc, and the filtrate was concentrated in vacuo to give the crude amine.

Deprotection of 4a. An unoptimized procedure that did not involve heating or stirring under CO was applied to protected dipeptide **4a** (117 mg, 0.31 mmol). The crude amine product obtained after hydrogenation was complete (3–7 days), under 50–80 psi of hydrogen, was added to a solution of *tert*-butyl pyrocarbonate (203 mg, 0.93 mmol) and potassium carbonate (129 mg, 0.93 mmol) in 10 mL of 1:2 THF/H_2O with stirring for 16 h. The solution was extracted with ethyl acetate, dried with Na_2SO_4, concentrated in vacuo and chromatographed on silica gel (3:1 hexanes/EtOAc) to leave a clear oil (25 mg, 25% of the carbamate).

^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (d, 6 H, J = 7.1 Hz, CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 1.46 (s, 9 H, $C(CH_3)_3$), 4.14 (m, 1 H, CH), 4.43 (quin, 1 H, J = 7.2 Hz), 5.06 (br s, NH), 6.59 (br d, NH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.5 (CH_3), 27.9 ($C(CH_3)_3$), 28.2 ($C(CH_3)_3$), 48.6, 50.0, 80.0, 81.9, 155.3 (C=O), 171.8 (C=O), 171.9 (C=O). IR (film) ν 3311 (NH), 1734–1665 br (C=O) cm^{-1}. This material was identical in all respects to authentic N-tBOC ala·ala-*t*-Bu ester prepared by conventional methods.[16]

Deprotection of 4c. The above general procedure was applied to protected dipeptide **4c** (135 mg, 0.30 mmol). The crude amine was added to a solution of *tert*-butyl pyrocarbonate (130 mg, 0.60 mmol) and potassium carbonate (82 mg, 0.60 mmol) in 6 mL of 1:2 THF/H_2O, and the resulting mixture was stirred for 12 h. The solution was extracted with EtOAc, dried over $MgSO_4$, concentrated in vacuo, and chromatographed by radial chromatography (40% EtOAc/hexane) to leave a clear oil (108 mg, 92% of the carbamate).

^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (d, 3 H, J = 7.0 Hz, CH_3), 1.39 (s, 9 H, CH_3), 1.44 (s, 9 H, CH_3), 3.09 (d, 2 H, J = 6.1 Hz, CH_2), 4.13 (m, 1 H, CH), 4.70 (q, J = 7.0 Hz, $CHCH_3$, 1 H), 4.92 (brs, 1 H, NH), 6.51 (d, J = 7.6 Hz, 1 H, NH), 7.1–7.33 (m, 5 H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.4 (CH_3), 27.9 ($C(CH_3)_3$), 28.2 ($C(CH_3)_3$, 38.0 (CH_2), 50.1 (CH), 53.5 (*C*H), 80.0 (C), 82.3 (C), 126.9, 128.3, 129.5, 136.1 (Ar), 155.2 (CO), 170.2 (CO), 172.0 (CO). IR (film) ν 3311 (NH), 1722 (C=O), 1665 (C=O) cm^{-1}. (See **4c** above for elemental analysis.)

Oxidative Cleavage of 4c. A solution of **4c** (180 mg, 0.4 mmol) in 10 mL of 1:4 0.2 N HCl/MeOH was allowed to stir for 2 h. The MeOH was removed in vacuo and 10 mL of 5% aqueous $NaHCO_3$ was added. The aqueous layer was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to leave the crude amino alcohol. The crude amino alcohol was dissolved in 6 mL of a 10% 0.2 N HCl/CH_2Cl_2 solution followed by the addition of $NaIO_4$ (171 mg, 0.8 mmol). After being stirred at room temperature for 8 h the mixture was diluted with 5% aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL) followed by EtOAc (2 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo to leave a mixture of the amine and imine. This mixture was dissolved in 1:1 MeOH/0.2 N HCl, stirred at room temperature for 3 h, and concentrated in vacuo and then 10 mL of 5% aqueous $NaHCO_3$ was added. The aqueous layer was extracted with ethyl acetate, dried with $MgSO_4$, and concentrated in vacuo to leave the crude amine. The crude amine was added to a solution of *tert*-butyl pyrocarbonate (171 mg, 0.8 mmol) and potassium carbonate (110 mg, 0.8 mmol) in 8 mL of 1:2 THF/H_2O with stirring for 5 h. The solution was extracted with EtOAc, dried with $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (1:3 ethyl acetate/hexane) gave the carbamate (90 mg, 58%) as a clear oil. This was identical to the material obtained by hydrogenolysis.

General Procedure for the Preparation of the Mosher's Amide. The deprotected dipeptide (1.0 equiv), the Mosher's chloride (1.0 equiv), and propylene oxide (4.0 equiv) were heated at reflux in THF for 30 min. The resulting solution was filtered through Celite and concentrated in vacuo to give the desired Mosher's amide.

The dipeptide (14 mg, 0.064 mmol) formed by deprotection of the major diastereomer generated from photolysis of the (*R*) chiral carbene complex (*R*)-**2** and (*S*)-*tert*-butyl alaninate (**4a**) was derivatized according to the standard procedure and gave 16 mg (68%) of the Mosher's amide. ^1H NMR and ^{19}F NMR data were identical to that of the Mosher's amide formed from DCC, HOBt[16] coupling of (*S*)-*tert*-butyl alaninate and (*S*)-*N*,*N*-dibenzylalanine and subsequent deprotection of the amino terminus and derivatization.

^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, 3 H, J = 7.2 Hz, CH_3), 1.40 (d, 3 H, J = 7.0 Hz, CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 3.44 (s, 3 H, OCH_3), 4.43 (quin, 1 H, J = 7.2 Hz, CH), 4.55 (quin, 1 H, J = 7.2 Hz, CH), 6.48 (d, 1 H, J = 7.3 Hz, NH), 7.37–7.54 (m, 5 H, ArH). ^{19}F NMR −71.59 ppm.

The dipeptide (20 mg, 0.093 mmol) formed by deprotection of the major diastereomer generated from photolysis of the (*S*) chiral carbene complex (**2**) and (*S*)-*tert*-butyl alaninate was derivatized according to the standard procedure to give 30 mg (90%) of the Mosher's amide.

^1H NMR (270 MHz, $CDCl_3$) δ 1.29 (d, 3 H, J = 7.1 Hz, CH_3), 1.41 (d, J = 7.1 Hz, 3 H, CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 3.34 (s, 3 H, CH_3O), 4.34 (quin, 1 H, J = 7.1 Hz, CH), 4.52 (quin, 1 H, J = 7.1 Hz, CH), 6.50 (d, 1 H, J = 6.6 Hz, NH), 7.23–7.27 (m, 3 H, ArH), 7.43 (d, 1 H, J = 7.7 Hz, NH), 7.52 (m, 2 H, ArH); ^{19}F NMR −71.95 ppm (CF_3).

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