Asymmetric Synthesis of Activated α-Amino Esters via Chromium Carbene Complex Photochemistry

Jiawang Zhu, Christopher Deur, and Louis S. Hegedus*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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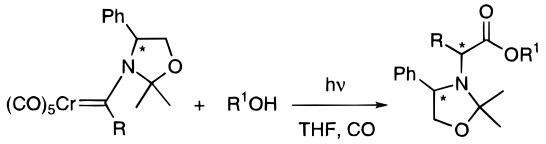
Optically active chromium aminocarbene complexes were α-alkylated and then photolyzed in the presence of 2,4,5-trichlorophenol to produce a number of optically active activated α-amino esters. These underwent coupling with amino acid esters or a soluble PEG-supported dipeptide to introduce the chromium−carbene-complex-derived amino acid residue into the peptide.

Introduction

With the growing importance of peptides, both in biology[1] and in the treatment of disease,[2] the synthesis of amino acids[3] and their incorporation into peptides[4] has undergone dramatic recent development. In addition to the synthesis of natural, unmodified peptides, the introduction of unnatural amino acid residues into peptides to increase biostability and bioavailability has become important.[5] Recently a novel procedure for the introduction of natural, unnatural, or isotopically labeled amino acid residues into peptides in solution,[6] on soluble poly(ethylene glycol) (PEG) supports,[7] or on typical Merrifield resin supports[8] has been reported from these laboratories. The process involves the photolysis of optically active chromium aminocarbene complexes in the presence of amino acid esters, and although it is highly diastereoselective (88−97% de), it is not stereospecific, and small amounts of the undesired diastereoisomeric peptide are produced.

Early studies[9] had shown that photolysis of optically active chromium aminocarbene complexes in the presence of alcohols produced α-amino esters in good yield and with high diastereoselectivity (eq 1). A class of α-amino ester of use in peptide synthesis is the "activated" ester[10]—esters having particularly good leaving groups as the alcohol component, such as *p*-nitrophenol, pentafluorophenol, trichlorophenol, or *N*-hydroxysuccinimide. Many of these esters can be purified and stored for long periods, yet couple efficiently to amino acids or peptides particularly in the presence of 1-hydroxybenzotriazole (HOBT).[11] In principle, by using one of these "activated" alcohols as the nucleophile in eq 1, activated esters could be prepared and purified to give a single diastereoisomer, permitting subsequent introduction of this optically pure amino acid residue into peptides using conventional peptide-coupling methodology. The results of studies addressing this problem are presented below.

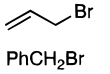
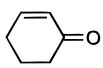
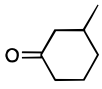
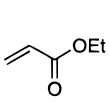
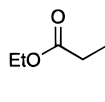


(Eq. 1)

Results and Discussion

To provide a range of amino acid activated ester precursors, it was necessary to synthesize appropriate optically active chromium aminocarbene complexes having a variety of different R groups. This was best accomplished by utilizing the acidity[12] of the α-protons of the parent methyl aminocarbene complex **1**. Treatment of carbene complex **1** with *n*-butyllithium followed by an electrophile produced alkylated chromium carbene complexes **2** (Table 1) in fair to good yield in most cases (eq 2).[13]

Table 1. Preparation of Optically Active Aminocarbene Complexes 2

RX	**2**, R, % yield (config.)
	**a**  82 (*R*)
$PhCH_2Br$	**b** $PhCH_2$, 85 (*S*)
$t\text{-}BuO_2CCH_2Br$	**c** $t\text{-}BuO_2CCH_2$, 72 (*S*)
$n\text{-}C_8H_{17}OTf$	**d** $n\text{-}C_8H_{17}$, 75 (*S*)
MeO_2CCH_2Br	**e** MeO_2CCH_2, 32 (*R*)
	**f**  75 (*R*)
$PhCH_2O_2CCl$	**g** $PhCH_2O_2C$, 45 (*R*)
	**h**  20 (*R*)

[⊗] Abstract published in *Advance ACS Abstracts,* October 1, 1997.

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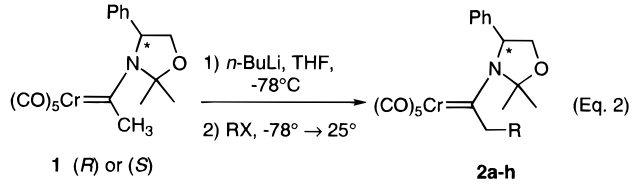
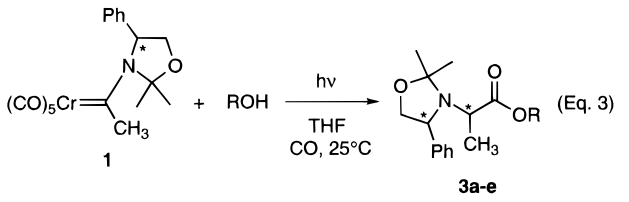


1 (*R*) or (*S*) **2a-h**

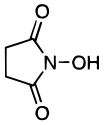
Active ester formation studies were initiated using the parent carbene complex **1** to screen a range of activated phenols as trapping agents (eq 3). Photolysis of complex



1 **3a-e**

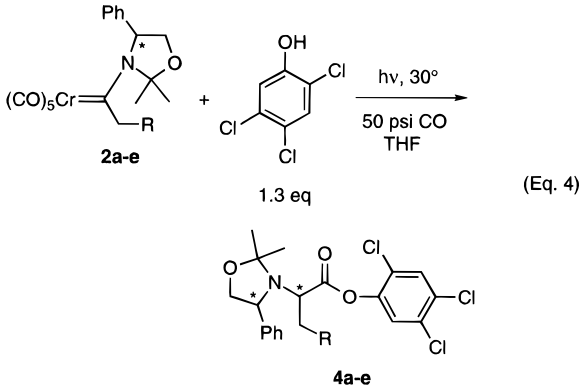
1 in the presence of 20% excess of the alcohol at room temperature under 50 psi of carbon monoxide led to the activated alanine esters in fair yield and good diastereoselectivity (Table 2). Of the alcohols screened, 2,4,5-trichlorophenol gave the best yields, and the best diastereoselectivity. In addition, this compound was relatively inexpensive and was easy to handle, leading to its choice for subsequent studies.

Table 2. Formation of Activated Esters

Carbene Complex	ROH	Product	Yield, %[a] (config)	de,[b] %
(*S*)-**1**	PhOH	**3a**	55 (*R*)	86
(*S*)-**1**	2,4,5-Cl_3PhOH	**3b**	52 (*R*)	90
(*R*)-**1**	2,4,5-Cl_3PhOH	**3c**	57 (*S*)	91
(*S*)-**1**	C_6F_5OH	**3d**	38 (*R*)	80
(*R*)-**1**		**3e**	19 (*S*)	[c]

[a] Reported yields are for isolated, pure *single* diastereoisomers. [b] Estimated from integration of relevant peaks in the ^{1}H-NMR spectra of crude material. [c] Diastereoisomeric excess could not be determined because of interferring by-products.

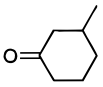
Photolysis of chromium carbene complexes **2a**−**g** in the presence of a slight excess of 2,4,5-trichlorophenol produced activated esters **4a**−**e** (eq 4, Table 3). These could



2a-e 1.3 eq **4a-e**

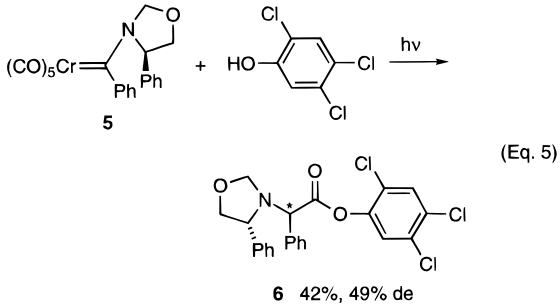
be isolated as pure diastereoisomers in modest yield, and

Table 3. Formation of Activated Esters

Carbene Complex	R	Product	Yield %[a] (config)	de[b]
(*R*)-**2a**		**4a**	60 (*R,S*)	95
(*S*)-**2b**	$PhCH_2$	**4b**	51 (*S,R*)	92
(*S*)-**2c**	*t*-BuO_2CCH_2	**4c**	48 (*S,R*)	85
(*R*)-**2d**	*n*-C_8H_{17}[c]	**4d**	40 (*R,S*)	---[d]
(*R*)-**2e**	MeO_2CCH_2	**4e**	29 (*R,S*)	86
(*R*)-**2f**		**4f**	36 (*R,S*)	---[d]

[a] Reported yields are for isolated, pure *single* diastereoisomers and are based on starting carbene complex. [b] Estimated from integration of relevant peaks in the ^{1}H NMR spectrum of crude material. [c] A two-fold excess of complex was used. [d] Diastereoisomeric excess could not be determined.

an examination of the crude reaction mixtures indicated the diastereoselectivity of the process was good. Some problems were encountered. Carbene complex **2d** was relatively unstable and decomposed both on standing and on handling. It had to be freshly prepared and used in excess in the photoreaction to get reasonable amounts of activated esters. Complexes **2g** and **2h** underwent photoreaction, but only unidentified decomposition products were obtained. The phenyl analog of complex **1**, a potential source of aryl glycine activated esters, could not be synthesized, probably because of increased steric hindrance about the carbene carbon due to α-branching. Its less-hindered analog **5** was available and was subjected to photolysis in the presence of the trichlorophenol (eq 5). Unfortunately, the reaction suffered from low diastereoselectivity, and the diastereoisomers were inseparable, making this process of no use in peptide synthesis.



5 **6** 42%, 49% de

The above methodology permits the synthesis of a range of both natural and "unnatural" (e.g. unnatural R group, *R*-configuration) activated amino acid esters for use in peptide synthesis. Since ^{13}C-labeled carbene complex **1** can be made,[14] isotopically-labeled activated amino acid esters should also be available by this process.

With activated esters **3b**, **3c**, and **4b,d,e** in hand, the coupling reactions were next examined. Under conventional peptide coupling conditions, using only a slight excess (1.1 equiv) of activated esters, dipeptides **7** were formed in fair to good yields (eq 6, Table 4).

In the photolytic coupling of chromium aminocarbene complexes with proline esters, poor diastereoselectivity (48%) was observed.[6a] In contrast, proline methyl ester coupled to activated ester **3b** in good isolated yield to give a single diastereoisomer (eq 7). Pentafluorophenol acti-

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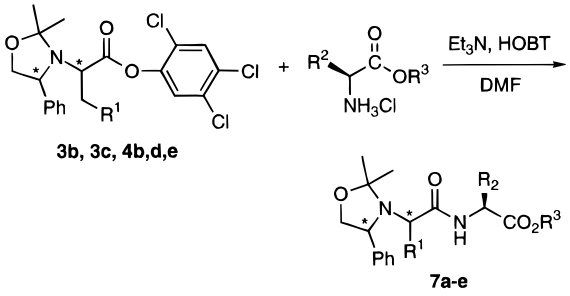
Table 4. Peptide Coupling with Activated Esters

ester (config)	R^1	R^2	R^3	peptide **7** (config)	yield, %[a]
3c (*R*,*S*)	H	Me	Me	**7a** (*R*,*S*,*S*)	86
3d (*S*,*R*)	H	iPr	t-Bu	**7b** (*S*,*R*,*S*)	90
4b (*S*,*R*)	$PhCH_2$	Me	Me	**7c** (S,R,S)	64
4d (*R*,*S*)	n-C_8H_{17}	Me	Me	**7d** (R,S,S)	63
4e (*R*,*S*)	MeO_2CCH_2	Me	Me	**7e** (R,S,S)	56

[a] Reported yields are for isolated, pure dipeptide.



(Eq. 6)

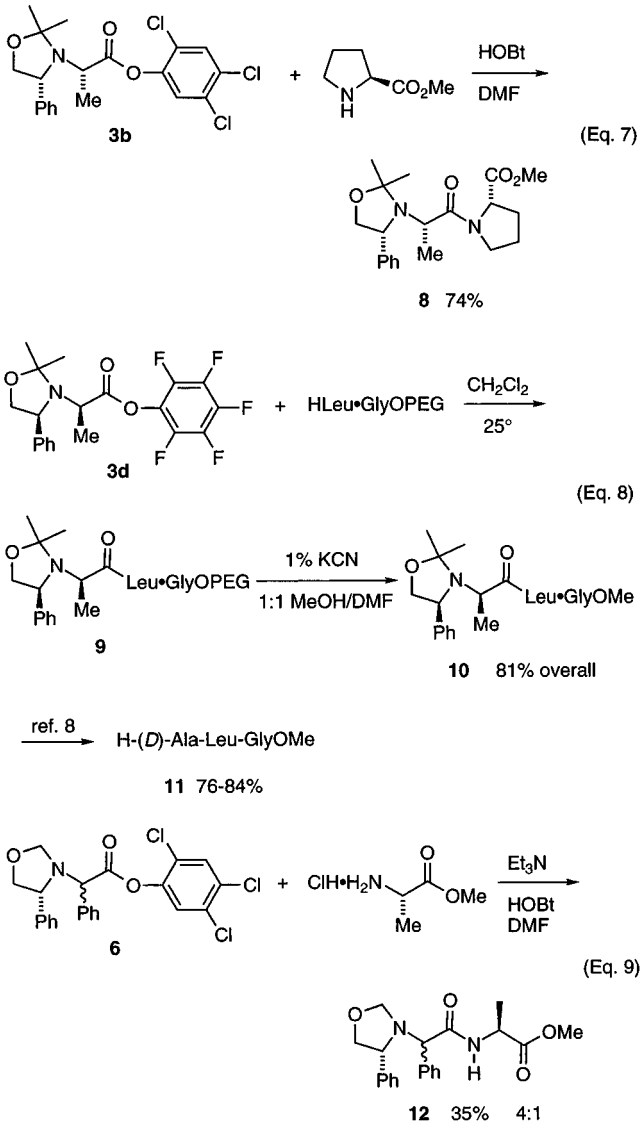
vated ester **3d** coupled efficiently to soluble poly(ethylene glycol)-bound dipeptide **9** to give good yields of the free tripeptide **10**. The oxazolidine N-protecting group could be removed under either oxidative or reductive conditions (eq 8).[8] Finally, activated ester **6** was coupled to alanine methyl ester to give a 4:1 mixture of diastereoisomers of the dipeptide (eq 9), confirming the diastereoisomeric ratio of the activated ester.

In summary, optically active chromium aminocarbene complexes could be α-alkylated and photolyzed in the presence of trichlorophenol to give a modest range of unnatural activated α-amino acid esters. These coupled to amino acid esters or a dipeptide to introduce these unnatural amino acid residues into peptides in reasonable yield.

Experimental Section

General Methods. Optical rotations were obtained on a Perkin-Elmer 24 polarimeter at a wavelength of 589 nm (sodium D line) in a 1.0-dm cell with a total volume of 1.00 mL. Specific rotation, $[\alpha]_D$, was reported in degrees per decimeter at the specified temperature, and the concentration (c) was given in grams per 100 mL in the specified solvent. The photoreactions were carried out in oven-dried pressure tubes that were charged with the carbene complex, the phenol, and glass beads while under a stream of argon. The tube was fitted with a pressure head and saturated with CO (three cycles). The reaction mixture was placed under 70−80 psi CO, and then photolysis was begun. Irradiation of the reaction mixtures was carried out in 20-mL Pyrex pressure tubes placed at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled immersion well. A Conrad-Hanovia 7830-C power supply was used. When the photoreaction was complete, the solvent was removed by rotary evaporator, and the crude reaction mixture was separated from any $Cr(CO)_6$ using the chosen chromatography solvent (hexane/ethyl acetate). Purification via standard chromatography techniques gave the desired product. ^{1}H NMR spectra were run at 300 MHz in $CDCl_3$ and referenced to Me_4Si at 0 ppm. ^{13}C NMR spectra were run at 75 MHz in $CDCl_3$ and referenced to the solvent peak at δ 77.00 ppm unless otherwise noted. Column chromatography was performed with ICN 32−63 nm, 60 Å silica gel using flash column techniques.

Preparation of Pentacarbonyl [((5*S*) or (5*R*)-1-Aza-2,2-dimethyl-3-oxa-5-phenylcyclopentyl)(methyl)carbene]-chromium(0), (*R*)- and (*S*)-1. The tetramethylammonium salt of pentacarbonyl[(oxy)(methyl)carbene]chromium (6.8 g, 21.9 mmol) was dissolved in 100 mL of degassed CH_2Cl_2 and



filtered through Celite directly into an airless flask under argon. The bright yellow solution was cooled to −78 °C, and freshly distilled acetyl bromide (2.96 g, 24.1 mmol) was added dropwise via syringe. The reaction mixture was stirred at −78 °C for 30 min to give a dark red slurry. After 30 min, a solution of 2,2-dimethyl-5-phenyl-1,3-oxazolidine (7.49 g, 43.8 mmol) in 10 mL of CH_2Cl_2 was added with a syringe. After an additional 5 min, *N*-methylmorpholine (2.6 ml, 24.1 mmol) was added, and the deep purple suspension was gradually warmed until the suspension turned bright yellow. The mixture was filtered through Celite, and the red/orange solution was absorbed onto silica gel and dried under reduced pressure. The resulting bright yellow solid was transferred to a silica gel column and eluted with 1:1 CH_2Cl_2/hexanes under argon to give a bright yellow solid 5.49 g (65%) after the solvent was removed under reduced pressure. The material was identical in all respects to previously reported results.[9] ^{1}H NMR δ 7.41−7.14 (m, 5H), 5.84 (d, J = 5.9 Hz, 1H), 4.53 (dd, J = 10.5, 6.1 Hz, 1H), 4.25 (m, 1H), 3.14 (s, 3H), 1.82 (s, 3H), 1.74 (s, 3H).

General Procedure for the α-Alkylation of Carbene Complex 1 (Table 1). Preparation of Complexes 2a−h. A THF solution (10−20 mL/mmol) of complex **1** was placed in a flame-dried airless flask containing a magnetic stir bar, degassed by evacuation/back-fill with argon (3×) and cooled to −78 °C. To this yellow solution, *n*-butyllithium (1.6 M in hexane, 1.2−1.5 equiv) was added dropwise from a syringe. The resulting orange-red solution was stirred for 0.25−0.5 h at this temperature, and the electrophile (1.2−1.5 equiv) was then added to the stirred solution dropwise through a syringe.

The reaction was stirred at −78 °C for an additional 0.5 h and then allowed to gradually warm to rt and stirred at rt for 2 h. The crude reaction mixture was adsorbed onto silica gel and subjected to flash column chromatography, by using argon as a source of pressure. Removal of the elution solvent under reduced pressure gave the pure carbene complex as a yellow solid. Although many of these could be stored for long periods without apparent decomposition, acceptable elemental analysis were difficult to obtain, and the complexes were often synthesized and utilized directly.

2a. From 0.50 g (1.27 mol) of (*R*)-complex **1**, 0.69 mL (1.38 mmol) of 2.0 M *n*-butyllithium in hexane, and 0.17 g (1.39 mmol) of allyl bromide in 3 mL of THF, (*R*)-complex **2a** (0.45 g, 1.03 mmol, 82%) was obtained as a yellow crystalline solid after chromatography (silica gel, 1:1 hexane/CH_2Cl_2). ^{1}H NMR δ 1.79 (s, 3H), 1.84 (s, 3H), 2.20 (m, 1H), 2.92 (m, 1H), 3.30 (dt, J = 6.6, 11.4 Hz, 1H), 3.44 (dt, J = 6.6, 11.4 Hz, 1H), 4.15 (d, J = 9.0 Hz, 1H), 4.60 (dd, J = 5.7, 9.3 Hz, 1H), 5.12 (d, J = 10.4, 1H), 5.21 (d, J = 14.1 Hz, 1H), 5.87 (d, J = 5.7 Hz, 1H), 5.92 (m, 1H), 7.2−7.5 (m, 5H). ^{13}C NMR δ 278.4, 221.9, 217.8, 139.5, 135.8, 128.8, 127.9, 126.3, 116.3, 101.3, 74.1, 70.1, 52.6, 34.2, 28.1, 27.0. Mass spectrum $C_{21}H_{21}O_6NCr$ M^+ 435 (parent).

2b. From 0.50 g (1.27 mmol) of (*S*) complex **1**, 0.92 mL of 2.06 M *n*-butyllithium in hexane (1.90 mmol), and 0.23 mL (1.90 mmol) of benzyl bromide was obtained complex (*S*)-**2b** (0.52 g, 1.07 mmol, 85%) as a yellow crystalline solid after column chromatography (silica gel 1:1 CH_2Cl_2/hexane). ^{1}H NMR δ 1.78 (s, 3H), 1.93 (s, 3H), 2.69 (m, 1H), 3.4−3.8 (m, 3H), 4.20 (dd, J = 1.7, 9.5 Hz, 1H), 4.60 (dd, J = 5.6, 9.3 Hz, 1H), 5.93 (d, J = 5.2 Hz, 1H), 7.2−7.5 (m, 5H). Mass spectrum $C_{25}H_{23}NO_6Cr$ M^+ 487 (parent).

2c. From 0.70 g (1.77 mmol) of (*S*) complex **1**, 1.26 mL of 1.55 M *n*-butyllithium in hexane (1.95 mmol), and 0.42 g (2.12 mmol) of *tert*-butyl bromoacetate in 6 mL of THF was obtained (*S*)-complex **2c** (0.65 g, 72%) as a yellow solid after column chromatography (1:1 CH_2Cl_2/hexane). ^{1}H NMR δ 1.49 (s, 9H), 1.82 (s, 3H), 1.88 (s, 3H), 2.49 (m, 1H), 3.03 (m, 1H), 3.54 (t, J = 9.0 Hz, 2H), 4.20 (d, J = 9.6 Hz, 1H), 4.57 (m, 1H), 5.89 (d, J = 5.4 Hz, 1H), 7.2−7.5 (m, 5H). ^{13}C NMR δ 279.2, 222.3, 217.1, 170.7, 139.4, 128.8, 127.9, 126.2, 125.6, 101.8, 81.6, 74.1, 70.1, 48.1, 35.3, 28.1, 27.8, 26.9. Mass spectrum $C_{24}H_{27}NOCr$ M^+ 509 (parent).

2d. From 0.94 g (2.38 mmol) of (*S*) complex **1**, 1.64 mL (2.62 mmol) of 1.6 M *n*-butyllithium in hexane, and 0.75 g (2.85 mmol) of *n*-octyl triflate in 50 mL of THF was obtained (*S*)-complex **2d** (0.91 g, 75%) as a dark red, unstable oil after purification by column chromatography (silica gel 9:1 hexane/EtOAc). ^{1}H NMR δ 0.89 (m, 5H), 1.30 (m, 11H), 1.80 (s, 3H), 1.84 (s, 3H), 2.13 (m, 1H), 3.31 (m, 2H), 4.16 (d, J = 9.3 Hz, 1H), 4.57 (dd, J = 5.7, 9.3 Hz, 1H), 5.88 (d, J = 5.1 Hz, 1H), 7.30 (m, 5H). This material was used without further purification since it decomposed on standing.

2e. From 0.76 g (1.92 mmol) of (*R*) complex **1**, 1.41 mL (2.04 mmol) of 1.45 M *n*-butyllithium in hexane, and 0.32 g (2.11 mmol) of methyl bromoacetate in 40 mL of THF was obtained (*R*)-complex **2e** (0.29 g, 32%) as a yellow solid, along with 0.24 g of recovered complex **1**, after column chromatography (silica gel 4:1 hexane/EtOAc). ^{1}H NMR δ 1.76 (s, 3H), 1.87 (s, 3H), 2.62 (m, 1H), 3.14 (m, 1H), 3.75 (s, 3H), 4.18 (d, J = 8.7 Hz, 1H), 4.57 (dd, J = 5.2, 9.4 Hz, 1H), 5.85 (d, J = 5.2 Hz, 1H), 7.2−7.5 (m, 5H). This material was used without further purification because of its relative instability.

2f. From 0.30 g (0.38 mmol) of (*R*) complex **1**, 0.52 mL (0.84 mmol) of 1.6 M *n*-butyllithium in hexane, and 93 μL (0.91 mmol) of cyclohexanone in 2 mL of THF was obtained (*R*)-complex **2f** (0.28 g, 75%) as a yellow solid after column chromatography (silica gel 1:1 hexane/CH_2Cl_2 followed by 1:1 hexane/EtOAc). The crude product mixture consisted of a 20:1 ratio of the diastereomers, determined by integration of the methine peaks (4.35 ppm major, 4.00 ppm minor) from the ^{1}H NMR. ^{1}H NMR δ 1.41 (m, 1H), 1.78 (s, 3H), 1.84 (m, 1H), 1.90 (s, 3H), 2.13 (m, 4H), 2.42 (m, 1H), 2.70 (m, 1H), 3.10 (m, 1H), 3.18 (m, 2H), 4.34 (dd, J = 15.3, 8.8 Hz, 1H), 4.57 (dd, J = 13.3, 4.6 Hz, 1H), 6.08 (t, J = 6.0 Hz, 1H), 7.43 (m, 5H). ^{13}C NMR δ 270.2, 217.5, 167.4, 138.7, 128.6, 128.0, 125.9, 101.8, 75.2, 69.7, 58.8, 48.6, 41.4, 41.0, 31.2, 29.7, 26.8, 24.5. Mass spectrum $C_{24}H_{25}O_7N_1Cr$: M^+ 491.

2g. From 0.30 g (0.76 mmol) of (*R*) complex **1**, 0.52 mL (0.84 mmol) of 1.6 M *n*-butyllithium in hexane, and 0.14 mL (0.91 mmol) of benzyl chloroformate in 2 mL of THF was obtained (*R*)-complex **2g** (0.18 g, 45%) as a yellow solid after column chromatography (silica gel 1:1 hexane/CH_2Cl_2). ^{1}H NMR δ 1.73 (s, 3H), 1.79 (s, 3H), 4.25 (d, J = 8.7 Hz, 1H), 4.40 (d, J = 15.9 Hz, 1H), 4.55 (m, 1H), 4.58 (d, J = 15.7 Hz, 1H), 5.20 (d, J = 12.7 Hz, 1H), 5.28 (d, J = 10.5 Hz, 1H), 5.89 (d, J = 5.1 Hz, 1H), 7.40−7.25 (m, 10H). ^{13}C NMR δ 278.4, 223.4, 216.8, 169.3, 134.8, 129.0, 128.7, 126.0, 101.8, 74.2, 70.2, 67.8, 56.8, 28.1, 27.1. Mass spectrum $C_{26}H_{23}O_8N_1Cr$: M^+ 529.

2h. From 0.15 g (0.38 mmol) of (*R*) complex **1**, 0.24 mL (0.39 mmol) of 1.6 *n*-butyllithium in hexane, and 47 μL (0.42 mmol) of ethyl acrylate in 1 mL of THF was obtained (*R*)-complex **2h** (38 mg, 20%) after column chromatography (silica gel 3:1 hexane/CH_2Cl_2). ^{1}H NMR δ 1.30 (t, J = 71 Hz, 3H), 1.81 (s, 3H), 1.93 (m, 1H), 1.97 (s, 3H), 2.38 (m, 1H), 2.61 (m, 2H), 3.30 (m, 1H), 3.44 (m, 1H), 4.17 (m, 3H), 4.57 (dd, J = 9.3, 5.9 Hz, 1H), 5.89 (d, J = 5.0 Hz, 1H), 7.42−7.15 (m, 5H). ^{13}C NMR δ 278.2, 222.9, 217.8, 172.9, 139.4, 128.8, 127.9, 126.2, 101.7, 74.2, 70.1, 60.7, 52.6, 34.1, 27.7, 27.0, 25.1, 14.2. Mass spectrum $C_{23}H_{25}O_8N_1Cr$: M^+ 495.

General Procedure for the Asymmetric Synthesis of Activated Esters (Table 2). Synthesis of Esters 3a−e. The optically active chromium aminocarbene complex **1** was dissolved in THF (or CH_2Cl_2) and was filtered through Celite into a Pyrex (Ace Glass) pressure tube that contained the nucleophile. A pressure head was attached, and the solution was degassed twice (freeze-thawing and back-filled with argon), followed by saturation of the solution with CO to about 50−60 psi. The Pyrex pressure tube was irradiated (stirred at rt, 30 h) with the apparatus described above. Partial recovery of the $Cr(CO)_6$ was achieved by filtering this solution. Oxidation of reaction mixture to remove remaining chromium residues 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 residues turned brown and precipitated. The activated esters were purified by flash chromatography over silica gel, followed by removal of the solvent.

Ester 3a. From 50 mg (0.13 mmol) of (*S*) complex **1** and 15 mg (0.16 mmol) of phenol in 1 mL of CH_2Cl_2 after irradiation and separation by flash chromatography (silica gel, 4:1:1 hexane/CH_2Cl_2/EtOAc) was obtained 23 mg (55%) of a single diastereoisomer ester **3a** as a pale yellow oil $[\alpha]^{20}_D$ = +69.5° (*c* 0.4, CH_2Cl_2). The crude reaction mixture consisted of a 93:7 ratio of two diastereomers (86%, de), determined by integration of the geminal methyl singlets (1.58 ppm major, 1.81 ppm minor) from the ^{1}H NMR spectrum. ^{1}H NMR δ 1.40 (d, J = 7.1 Hz, 3H), 1.42 (s, 3H), 1.58 (s, 3H), 3.70 (t, J = 7.5 Hz, 1H), 3.80 (q, J = 7.1 Hz, 1H), 4.21 (dd, J = 8.0, 7.1 Hz, 1H), 4.52 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 7.7 Hz, 2H), 7.33−7.14 (m, 6H), 7.44 (d, J = 8.1 Hz, 2H). ^{13}C NMR δ 172.1, 150.6, 141.2, 129.0, 128.3, 127.5, 127.4, 125.3, 121.0, 95.9, 72.1, 61.7, 53.2, 28.7, 23.0, 15.1. IR (film) ν 1755 cm^{-1}. Anal. Calcd for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12. Found: C, 73.89; H, 7.16.

Ester 3b and 3c. From 0.10 g (0.25 mmol) of (*S*) complex **1** and 0.06 g (0.30 mmol) of 2,4,5-trichlorophenol in 1 mL of CH_2Cl_2, after irradiation and purification by flash chromatography (silica gel 4:1:1 hexane/CH_2Cl_2/EtOAc) was obtained 56 mg (52%) of a single diastereoisomer of ester **3b** as a pale yellow oil after removal of the solvent: $[\alpha]^{23}_D$ = +5.2° (*c* 1.3, CH_2Cl_2). The crude reaction mixture consisted of a 95:5 ratio of two diastereomers (90%, de), determined by integration of the methine peaks (δ 4.41 ppm major, 4.69 ppm minor) from the ^{1}H NMR spectrum. ^{1}H NMR δ 1.35 (s, 1H), 1.39 (d, J = 7.1 Hz, 3H), 1.53 (s, 3H), 3.69 (dd, J = 8.2, 6.8 Hz, 1H), 3.83 (q, J = 7.1 Hz, 1H), 4.18 (dd, J = 8.1, 7.2 Hz, 1H), 4.41 (t, J = 7.0 Hz, 1H), 6.63 (s, 1H), 7.41−7.19 (m, 6H). ^{13}C NMR δ 170.6, 145.5, 141.3, 131.2, 130.9, 130.5, 129.8, 128.4, 127.7, 125.3, 124.8, 96.1, 72.7, 60.8, 52.9, 28.4, 23.0, 14.5. IR (film) ν 1769 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_3NCl_3$: C, 56.03; H, 4.70. Found: C, 55.95; H, 4.76.

Identical results were obtained starting with the (*R*) carbene complex to give **3c**.

Ester 3d. From 0.15 g (0.38 mmol) of (*S*) carbene complex **1** and 0.10 g (0.53 mmol) pentafluorophenol in 2 mL of CH_2Cl_2, after irradiation and separation by flash chromatography (silica gel 6:1 hexane/EtOAc), was obtained 56 mg (38%) of a single diastereoisomer of ester **3d** as a pale yellow oil. $[\alpha]^{24}_D = +28.1°$ (*c* 1.1, CH_2Cl_2). The crude reaction mixture consisted of a 90:10 ratio of two diastereomers (80%, de), determined by integration of the methyl doublets (δ 1.49 ppm major, 1.23 ppm minor) from the ^{1}H NMR spectrum. ^{1}H NMR δ 1.43 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H), 1.56 (s, 3H), 3.71 (t, J = 8.0 Hz, 1H), 3.95 (q, J = 7.2 Hz, 1H), 4.21 (dd, J = 8.1, 7.0 Hz, 1H), 4.49 (t, J = 7.5 Hz, 1H), 7.45−7.24 (m, 5H). ^{13}C NMR δ 169.9, 140.5, 128.5, 127.8, 127.5, 126.6, 96.0, 72.2, 62.4, 53.3, 28.8, 22.9, 15.7. IR (film) ν 1786 cm^{-1}. Mass (HR FAB): Calcd for $C_{20}H_{18}O_3NF_5$: M + H = 416.1285. Found: 416.1282 ± 0.0008 (Δ = 0.4 ppm).

Ester 3e. From 0.15 g (0.38 mmol) of (*R*) complex **1** and 0.06 g (0.50 mmol) of *N*-hydroxysuccinimide in 2 mL of CH_2Cl_2, after irradiation and separation of flash chromatography (silica gel 3:1 hexane/EtOAc), was obtained 25 mg (19%) of a single diastereiosimer of **3e** as a colorless oil. The crude reaction mixture consisted of other unidentified side products, so the diastereoselectivity was not available from the ^{1}H NMR spectrum. ^{1}H NMR δ 1.30 (d, J = 7.9 Hz, 3H), 1.34 (s, 3H), 1.47 (s, 3H), 2.68 (s, 2H), 2.74 (s, 2H), 3.57 (t, J = 8.5 Hz, 1H), 3.88 (q, J = 8.2 Hz, 1H), 4.08 (dd, J = 8.2, 7.3 Hz, 1H), 4.37 (t, J = 7.9 Hz, 1H), 7.45−7.12 (m, 5H). ^{13}C NMR δ 169.2, 169.0, 168.9, 140.1, 128.6, 127.7, 126.8, 96.0, 72.1, 62.9, 52.0, 28.9, 25.6, 23.1, 20.4, 16.0. IR (film) ν 1783, 1739 cm^{-1}. Mass (HR FAB) Calcd for $C_{18}H_{22}O_5N_2$: M + H = 347.1607. Found: 347.1603 ± 0.0014 (Δ = 0.4 ppm).

Preparation of Homologated Activated Esters (Table 3). Esters 4a−f. Ester 4a. Following the general procedure above, from 0.40 g (0.92 mmol) of (*R*) carbene complex **2a** and 0.26 g (1.30 mmol) of 2,4,5-trichlorophenol in 2 mL of THF, after irradiation and flash chromatography (silica gel 7:1 hexane/EtOAc), was obtained 0.26 g (60%) of a single diastereoisomer of ester **4a** as a pale yellow oil. $[\alpha]^{25}_D = -20.7°$ (*c* 4.5, CH_2Cl_2). The crude reaction mixture consisted of a 97.5:2.5 ratio of two diastereomers (95%, de). ^{1}H NMR δ 1.33 (s, 3H), 1.52 (s, 3H), 1.67 (m, 1H), 2.23−1.94 (m, 3H), 3.60 (dd, J = 9.9, 4.1 Hz, 1H), 3.69 (dd, J = 8.4, 6.1 Hz, 1H), 4.17 (t, J = 8.0 Hz, 1H), 4.41 (t, J = 6.6 Hz, 1H), 4.95 (m, 2H), 5.68 (m, 1H), 6.61 (s, 1H), 7.34−7.14 (m, 5H), 7.39 (s, 1H). ^{13}C NMR δ 169.5, 145.7, 141.9, 137.0, 131.1, 130.7, 128.5, 127.9, 127.7, 125.0, 116.1, 96.4, 72.3, 61.2, 57.1, 30.9, 28.7, 28.0, 23.3. IR (film) ν 1770, 1640 cm^{-1}. Mass (HR FAB) Calcd for $C_{23}H_{24}O_3NCl_3$: M + H = 470.0871. Found: 470.0844 ± 0.0017 (Δ = 2.3 ppm).

Ester 4b. From 0.15 g (0.31 mmol) of (*S*) carbene complex **2b** and 73 mg (0.37 mmol) of 2,4,5-trichlorophenol in 2 mL of THF, after irradiation and purification by flash chromatography (silica gel 7:1 hexane/EtOAc), was obtained 81 mg (51%) of a single diastereoisomer of ester **4b** as a pale yellow oil. $[\alpha]^{23}_D = +2.3°$ (*c* 1.8, CH_2Cl_2). The crude reaction mixture consisted of a 96:4 ratio of two diastereomers (92%, de), determined by integration of the geminal methyl singlets (δ 1.23 ppm major, 1.38 ppm minor) from the ^{1}H NMR spectrum. ^{1}H NMR δ 1.23 (s, 3H), 1.54 (s, 3H), 1.94 (m, 1H), 2.54 (m, 2H), 2.75 (m, 1H), 3.65 (dd, J = 9.5, 3.5 Hz, 1H), 3.76 (dd, J = 8.4, 6.1 Hz, 1H), 4.22 (dd, J = 8.2, 7.2 Hz, 1H), 4.47 (t, J = 6.8 Hz, 1H), 6.64 (s, 1H), 7.41−7.12 (m, 10H), 7.50 (s, 1H). ^{13}C NMR δ 169.4, 145.6, 141.8, 140.7, 131.0, 130.6, 129.9, 128.4, 128.1, 127.7, 127.6, 126.1, 125.4, 124.8, 96.3, 72.1, 60.9, 57.0, 32.9, 30.7, 28.4, 22.8. IR (film) ν 3086, 3026, 2975, 1769 cm^{-1}. Anal. Calcd for $C_{27}H_{26}O_3NCl_3$: C, 62.50; H, 5.05. Found: C, 62.36; H, 5.18.

Ester 4c. From 0.15 g (0.29 mmol) of (*S*) complex **2c** and 82 mg (0.42 mmol) of 2,4,5-trichlorophenol in 2 mL of THF, after irradiation and purification by flash chromatography (silica gel 4:1 hexane/EtOAc), was obtained 77 mg (48%) of a single diastereoisomer of ester **4c** as a pale yellow oil. $[\alpha]^{24}_D = +14.3°$ (*c* 0.7, $CHCl_3$). The crude reaction mixture consisted of a 92.5:7.5 ratio of two diastereomers (85%, de), determined by integration of the methylene peaks (δ 4.26 ppm major, 3.90 ppm minor) from the ^{1}H NMR spectrum. ^{1}H NMR δ 1.43 (s, 9H), 1.46 (s, 3H), 1.61 (s, 3H), 2.03 (m, 1H), 2.32 (m, 3H), 3.77 (m, 2H), 4.26 (dd, J = 8.2, 7.2 Hz, 1H), 4.52 (t, J = 6.6 Hz, 1H), 6.71 (s, 1H), 7.43−7.26 (m, 5H), 7.48 (s, 1H). ^{13}C NMR δ 172.0, 169.4, 141.7, 131.2, 130.7, 128.6, 127.9, 127.8, 125.5, 125.0, 96.3, 80.7, 72.3, 61.1, 56.8, 32.2, 28.6, 28.1, 24.1, 23.3. IR (film) ν 1770, 1726. Mass (HR FAB) Calcd for $C_{26}H_{30}O_5NCl_3$: M + H = 542.1268. Found: 542.1197 ± 0.0011 (δ = 13 ppm).

Ester 4d. From 0.46 g (0.90 mmol) of (*R*) carbene complex **2d** and 0.09 g (0.45 mmol) of 2,4,5-trichlorophenol in 6 mL of THF, after irradiation and purification by flash chromatography (silica gel 14:1 hexane/EtOAc), was obtained 0.19 g (40%) of ester **4d** as a single diastereoisomer. The diastereoselectivity of the reaction could not be assessed from the NMR spectrum of the crude material. ^{1}H NMR δ 0.88 (t, J = 6.3 Hz, 3H), 1.25 (bs, 14H), 1.42 (s, 3H), 1.60 (s, 3H), 1.63 (m, 1H), 2.11 (m, 1H), 3.64 (dd, J = 4.5, 9.9 Hz, 1H), 3.77 (dd, J = 6.0, 8.4 Hz, 1H), 4.25 (t, J = 7.5 Hz, 1H), 4.50 (t, J = 6.6 Hz, 1H), 6.67 (s, 1H), 7.39 (m, 6H). ^{13}C NMR δ 169.8, 145.8, 142.2, 131.1, 130.7, 130.0, 127.8, 127.7, 125.6, 125.0, 96.4, 72.3, 61.2, 58.3, 31.8, 29.4, 29.2, 29.0, 28.7, 27.0, 23.3, 22.6, 14.1. IR (film) ν 1770 cm^{-1}. This material was carried on to dipeptide **7d** without further characterization.

Ester 4e. From 0.12 g (0.26 mmol) of (*R*) complex **2e** and 60 mg (0.35 mmol) of 2,4,5-trichlorophenol in 3 mL of THF, after irradiation and purification by flash chromatography (silica gel, 9:1 hexane/EtOAc), was obtained 38 mg (29%) of ester **4e** as a colorless oil. $[\alpha]^{25}_D$ −8.80° (*c* 0.98, CH_2Cl_2). ^{1}H NMR δ 1.46 (s, 3H), 1.61 (s, 3H), 2.08 (m, 1H), 2.40 (m, 3H), 3.66 (s, 3H), 3.78 (m, 2H), 4.26 (t, J = 7.5 Hz, 1H), 4.54 (t, J = 6.6 Hz, 1H), 6.72 (s, 1H), 7.36 (m, 6H). ^{13}C NMR δ 173.1, 169.5, 145.6, 141.4, 131.2, 130.8, 130.2, 128.6, 128.0, 127.8, 125.5, 124.9, 96.3, 72.2, 61.4, 56.8, 51.7, 30.7, 28.7, 24.1, 23.3. IR (film) ν 1768, 1738 cm^{-1}. This material was carried on to dipeptide **7e** without further characterization.

Ester 4f. From 0.15 g (0.31 mmol) of (*R*) carbene complex **2f** and 78 mg (0.40 mmol) of 2,4,5-trichlorophenol in 2 mL of THF, after irradiation and purification by flash chromatography (silica gel 3:1 hexane/EtOAc), was obtained 59 mg (36%) of a single diastereoisomer of **4f** as a colorless oil. $[\alpha]^{25}_D = -40.1°$ (*c* 1.2, CH_2Cl_2). ^{1}H NMR δ 1.18 (m, 1H), 1.36 (s, 3H), 1.41 (m, 1H), 1.53 (s, 3H), 1.58 (m, 2H), 1.98 (m, 3H), 2.41−2.05 (m, 4H), 3.70 (m, 2H), 4.18 (t, J = 8.3 Hz, 1H), 4.49 (dd, J = 10.9, 6.3 Hz, 1H), 6.62 (s, 1H), 7.34−7.19 (m, 5H), 7.43 (s, 1H). ^{13}C NMR δ 170.0, 169.3, 145.7, 142.2, 130.8, 129.5, 128.6, 128.1, 127.8, 127.7, 125.5, 124.9, 96.2, 72.1, 61.4, 55.2, 48.1, 41.2, 36.0, 35.5, 30.6, 28.9, 24.9, 23.5. IR (film) ν 1775, 1712 cm^{-1}. Mass (HR FAB) Calcd for $C_{26}H_{28}O_4NCl_3$: M + H = 524.1162. Found: 524.1112 ± 0.0031 (Δ = 5.0 ppm).

Synthesis of Activated Ester 6. From 0.24 g (0.55 mmol) of carbene complex **5**[9] and 55 mg (0.28 mmol) of 2,4,5-trichlorophenol in 4 mL of THF, after irradiation and purification by flash chromatography (silica gel 9:1 hexane/EtOAc), was obtained 0.11 g (42%) of activated ester **6** as an inseparable 2:1 mixture of diastereoisomers. ^{1}H NMR δ 3.76 (m, 1H), 4.31 (m, 2H), 4.42 (d, J = 5.4 Hz, 1H), 4.55 (d, J = 5.4 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.83 (s, 1H), 4.85 (d, J = 4.8 Hz, 1H), 4.87 (s, 1H), 7.32 (m, 12H). This material was carried on to dipeptide **11** without further purification.

General Reaction Procedure for Synthesis of Dipeptides 7a−e and 8 (Table 4). In a round bottom flask containing ~2 mL of DMF were placed 1.0 equiv of the amino acid ester hydrochloride, 1.0 equiv of the dry amine base, 1.1 equiv of the activated ester, and 0.2 equiv of HOBT. The reaction mixture was stirred for 5−10 h unless otherwise indicated. The solvent was removed under reduced pressure, and the crude reaction mixture was taken up in EtOAc, washed twice with H_2O, and dried over $NaSO_4$. This mixture was filtered, and the solvent was removed under reduced pressure leaving the crude reaction product. This crude product was purified by column or radial layer chromatography on silica gel.

Dipeptide 7a. From 13 mg (0.10 mmol) of (*S*) alanine methyl ester hydrochloride, 13 μL (0.10 mmol) of triethyl-

amine, and 45 mg (0.11 mmol) of activated ester **3c** was obtained 28 mg (83%) of dipeptide **7a** after flash chromatography (2:1 hexane/EtOAc) as a pale yellow oil. ^{1}H NMR δ 0.89 (d, J = 7.2 Hz, 3H), 1.33 (s, 3H), 1.43 (d, J = 7.2 Hz, 3H), 1.52 (s, 3H), 3.43 (q, J = 7.2 Hz, 1H), 3.72 (s, 3H), 3.94 (m, 1H), 4.30 (m, 3H), 7.37 (m, 5H). ^{13}C NMR δ 14.2, 17.8, 21.0, 27.6, 47.5, 52.2, 54.9, 59.9, 72.4, 97.1, 127.6, 127.9, 128.8, 143.0, 173.2, 173.4. IR (film) 3377, 1744, 1671 cm^{-1}. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: 64.53; H, 7.73; N, 8.27.

Dipeptide 7b. From 45 mg (0.21 mmol) of (*S*)-valine *tert*-butyl ester hydrochloride, 0.11 g (0.26 mmol) activated ester **3d**, *N*,*N*-dimethylaminopyridine (30 mg, 0.26 mmol), and HOBT (6 mg, 0.04 mmol) in 2 mL of DMF was obtained 78 mg (90%) of dipeptide **7b** as a pale yellow oil after flash chromatography (5:1:1 hexane/CH_2Cl_2/EtOAc). ^{1}H NMR δ 0.85 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H), 1.32 (s, 3H), 1.48 (s, 9H), 1.52 (s, 3H), 2.09 (m, 1H), 3.40 (q, J = 7.2 Hz, 1H), 3.80 (t, J = 7.9 Hz, 1H), 4.10 (dd, J = 7.9, 4.2 Hz, 1H), 4.18 (t, J = 7.5 Hz, 1H), 4.31 (t, J = 7.7 Hz, 1H), 7.42−7.14 (m, 5H), 7.73 (d, J = 7.7 Hz, 1H). ^{13}C NMR δ 174.2, 170.8, 140.0, 128.8, 128.1, 97.0, 82.0, 72.9, 61.6, 57.8, 55.4, 32.1, 28.6, 28.5, 21.8, 18.9, 18.5, 13.9. IR (film) ν 1720, 1685 cm^{-1}. Anal. Calcd for $C_{23}H_{36}O_4N_2$: C, 68.29; H, 8.97. Found: C, 68.21; H, 8.76.

Dipeptide 7c. From 15 mg (0.11 mmol) of (*S*) alanine methyl ester hydrochloride, 61 mg (0.12 mmol) activated ester **4b**, 15 μL (0.11 mmol) triethylamine, and 3 mg (0.02 mmol) of HOBT in 2 mL of DMF was obtained 29 mg (64%) of dipeptide **7c** as a clear oil after flash chromatography (2:1 hexane/EtOAc). ^{1}H NMR δ 0.85 (d, J = 7.2 Hz, 3H), 1.22 (s, 3H), 1.50 (s, 3H), 1.92 (m, 1H), 2.38 (m, 1H), 2.76 (m, 1H), 2.93 (m, 1H), 3.32 (dd, J = 4.8, 8.1 Hz, 1H), 3.72 (s, 3H), 3.93 (m, 1H), 4.26 (m, 3H), 7.28 (m, 10H). ^{13}C NMR δ 17.7, 21.6, 27.9, 32.3, 34.8, 47.4, 52.2, 58.7, 60.2, 72.2, 96.9, 126.0, 127.6, 127.7, 128.4, 128.5, 128.9, 141.6, 143.6, 173.2, 173.3. IR (film) ν 1744, 1671 cm^{-1}. Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 70.73; H, 7.60; N, 6.60. Found: C, 70.28; H, 6.91; N, 6.54.

Dipeptide 7d. From 8 mg (0.06 mmol) of (*S*) alanine methyl ester hydrochloride, 34 mg (0.06 mmol) of activated ester **4d**, 8 μL (0.06 mmol) triethylamine, and 2 mg (0.01 mmol) HOBT in 2 mL of DMF was obtained 15 mg (56%) of dipeptide **7d** as a clear oil after radial layer chromatography (6:1 hexane/EtOAc). ^{1}H NMR δ 0.87 (d, J = 7.2 Hz, 3H), 1.38 (s, 3H), 1.53 (s, 3H), 1.65 (s, 1H), 2.12 (m, 2H), 2.58 (m, 1H), 2.71 (m, 1H), 3.32 (dd, J = 4.5, 9.0 Hz, 1H), 3.68 (s, 3H), 3.71 (s, 3H), 3.94 (m, 1H), 4.20 (m, 1H), 4.31 (m, 2H), 7.31 (m, 5H). ^{13}C NMR δ 17.7, 21.6, 25.4, 27.9, 32.4, 47.5, 51.6, 52.2, 58.2, 60.2, 72.2, 97.0, 127.7, 127.7, 128.9, 143.3, 172.9, 173.2, 173.6. IR (film) ν 1740, 1670 cm^{-1}. HRMS Calcd for $C_{21}H_{30}N_2O_6$: [M + H] = 407.2177. Found: [M + H] = 407.2182.

Dipeptide 7e. From 7 mg (0.05 mmol) of (*S*) alanine methyl ester hydrochloride, 19 mg (0.04 mmol) of activated ester **4e**, 7 μL of triethylamine, and 1.1 mg of HOBT was obtained 10 mg (63%) of dipeptide **7e** as a clear oil after radial layer chromatography (3:1 hexane/EtOAc). ^{1}H NMR δ 0.87 (m, 6H), 1.27 (bs, 14H), 1.34 (s, 3H), 1.52 (s, 3H), 1.66 (m, 2H), 1.89 (m, 1H), 3.25 (t, J = 6.8 Hz, 1H), 3.71 (s, 3H), 3.93 (dd, J = 3.2, 8.0 Hz, 1H), 4.27 (m, 3H), 7.32 (m, 5H). ^{13}C NMR δ 14.1, 17.8, 21.9, 22.6, 28.0, 28.6, 29.3, 29.4, 29.6, 29.8, 30.4, 31.8, 47.4, 52.1, 60.3, 72.2, 96.8, 127.5, 127.6, 128.9, 144.0, 173.2, 173.8. IR (film) ν 1745, 1673 cm^{-1}. Anal. Calcd for $C_{26}H_{42}N_2O_4$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.16; H, 9.21; N, 6.35.

Dipeptide 8. From 15 mg (0.09 mmol) of (*S*) proline methyl ester hydrochloride, 42 mg (0.10 mol) of activated ester **3b**, 15 μL of triethylamine, and 3 mg of HOBT was obtained 27 mg (74%) of dipeptide **8** as a yellow oil after flash chromatography (1:1 hexane/EtOAc). ^{1}H NMR δ 1.31 (d, J = 6.0 Hz, 3H), 1.47 (s, 6H), 1.77−1.97 (m, 4H), 3.56 (m, 2H), 3.60 (s, 3H), 3.73 (dd, J = 8.4, 5.2 Hz, 1H), 3.84 (m, 2H), 4.24 (t, J = 8.2 Hz, 1H), 4.39 (dd, J = 7.9, 5.2 Hz, 1H), 7.17−7.29 (m, 5H). ^{13}C NMR δ 173.0, 170.2, 144.0, 127.8, 126.8, 96.8, 71.2, 60.1, 58.8, 53.6, 51.9, 46.2, 28.7, 28.1, 24.9, 24.5, 13.3. IR (film) ν 1749, 1644 cm^{-1}. Anal. Calcd for $C_{20}H_{28}O_4N_2$: C, 66.65; H, 7.83. Found: C, 66.78; H, 7.59.

Preparation of PEG-Supported Tripeptide 9. To the PEG-supported H-Leu-Gly-O-PEG[7] (508 mg, 0.175 mmol) dissolved in 2.5 mL of dry CH_2Cl_2 was added the pentafluorophenyl (*R*)-alanine ester **3d** (218 mg, 0.525 mmol), and the solution was stirred at rt for 8 h. The resulting PEG-supported tripeptide **9** (485 mg) as a white powder was purified by precipitation with Et_2O, filtration, redissolution in MeOH/CH_2Cl_2 1.5:1, and reprecipitation 3× at 0 °C to give 425 mg. ^{1}H NMR δ 0.75 (d, J = 5.4 Hz, 3H), 0.84 (d, J = 5.26 Hz, 3H), 1.23 (s, 3H), 1.36 (6H), 1.47 (m, 3H), 4.03−3.30 (m), 4.35 (m, 2H), 5.78 (1H), 7.34−7.15 (m, 5H), 7.71 (1H). ^{13}C NMR δ 175.0, 171.8, 169.5, 143.0, 129.4, 128.3, 97.5, 73.0, 70.8, 68.5, 65.0, 64.5, 60.0, 55.0, 52.4, 41.2, 40.2, 28.2, 25.2, 23.8, 21.8, 21.2, 14.9. IR (film) ν 1753, 1726, 1665 cm^{-1}.

Cleavage of PEG-Supported Tripeptide 9 To Give Tripeptide 10. The PEG-supported tripeptide **9** (425 mg) dissolved in a mixture of MeOH (1.5 mL) and DMF (1.5 mL) was added to a flask containing 20 mg of KCN catalyst for the cleavage. The solution was stirred at 50 °C for 36 h. The solvent was removed under reduced pressure, and most of the polymer was isolated by precipitation with Et_2O for 4× at 0 °C (the solvent for the mixture was 1:2 of MeOH/CH_2Cl_2, at 40 °C), followed by filtration, and the filtrate was collected. Traces of PEG were removed from the cleaved tripeptide by flash chromatography on silica gel (MeOH), and the pure tripeptide **10** (51 mg, 81% overall from **9**) as a pale yellow oil was obtained by further flash chromatography on silica gel (10:9:1 hexane/EtOAc/MeOH). ^{1}H NMR δ 0.79 (d, J = 6.2 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H), 1.27 (s, 3H), 1.41 (s, 3H), 1.43 (d, J = 7.3 Hz, 3H), 1.50−1.63 (m, 3H), 3.41 (q, J = 7.2 Hz, 1H), 3.59 (dd, J = 18.1, 5.0 Hz, 1H), 3.67 (s, 3H), 3.79 (dd, J = 18.2, 5.0 Hz, 1H), 3.79 (dd, J = 18.2, 5.0 Hz, 1H), 3.85 (dd, J = 12.5, 9.2 Hz, 1H), 4.02 (m, 1H), 4.25 (m, 2H), 5.75 (t, J = 5.3 Hz, 1H), 7.13−7.35 (m, 6H). ^{13}C NMR δ 174.7, 171.4, 169.8, 142.3, 128.8, 127.8, 127.6, 96.8, 72.3, 59.7, 54.8, 51.9, 51.8, 40.7, 39.9, 27.4, 24.6, 22.8, 21.3, 20.6, 14.0. IR (film) ν 3500−3200, 1755, 1660 cm^{-1}. Mass (HR FAB) Calcd for $C_{23}H_{35}O_5N_3$: M + H = 434.2655. Found: 434.2678 ± 0.0023 (Δ = −5.6 ppm).

Oxidative Removal of the Oxazolidine Protecting Group. Synthesis of Tripeptide 11. The fully protected tripeptide **10** (0.10 g, 0.23 mmol) dissolved in 5 mL of 1:4 HCl (1 N aqueous solution)/MeOH was stirred at rt for 2.5 h. The solvents were removed in vacuo, and the residue was dissolved in an aqueous sodium bicarbonate solution (5 mL of 10% $NaHCO_3$) followed by extraction with EtOAc (3 × 6 mL) to give the crude product. The crude product dissolved in MeOH was cooled to 0 °C in an ice bath, followed by addition of Pb(OAc)$_4$ (0.13 g, 95%, 0.30 mmol), and the mixture was allowed to warm to rt and stirred for 6 h. The reaction mixture was filtered through Celite, and the Celite was washed with a 1:1 mixture solvent of MeOH/CH_2Cl_2, followed by removal of the solvent under reduced pressure. The resulting intermediate was again dissolved in a 1:4 of HCl (1 N aqueous solution)/MeOH, and the solution was stirred at room temperature for 5 h, followed by removal of the solvent in vacuo. The residue was dissolved in an aqueous sodium bicarbonate solution (5 mL of 10% $NaHCO_3$), followed by extraction with EtOAc (3 × 6 mL) to give the crude tripeptide product, which was purified by flash chromatography on silica gel (10% MeOH/CH_2Cl_2) to give **11** (48 mg, 76%) as a pale yellow oil. ^{1}H NMR δ 0.90 (d, J = 5.3 Hz, 3H), 0.94 (d, J = 5.2 Hz, 3H), 1.37 (d, J = 6.0 Hz, 3H), 1.65 (m, 3H), 3.18 (bs, 2H), 3.69 (s, 3H), 3.72 (m, 1H), 3.98 (m, 2H), 4.49 (q, J = 5.9 Hz, 1H), 7.51 (bs, 1H), 8.01 (bs, 1H). ^{13}C NMR δ 175.0, 172.7, 170.4, 52.2, 51.5, 50.2, 41.0, 40.3, 24.8, 22.8, 21.8, 20.7. IR (film) ν 1740, 1768 cm^{-1}.

Reductive Removal of the Oxazolidine Chiral Auxiliary from the Fully Protected Tripeptide 10 and Preparation of 11. The fully protected tripeptide **10** (0.10 g, 0.23 mmol) dissolved in 5 mL of 1:4 HCl (1 N aqueous solution)/MeOH was stirred at rt for 2.5 h, the solvents were removed in vacuo, and the residue was dissolved in an aqueous sodium bicarbonate solution (5 mL of 10% $NaHCO_3$) followed by extraction with EtOAc (3 × 6 mL) to give the crude product. The crude product dissolved in 5 mL of MeOH was transferred to a pressure tube containing the Pearlman's catalyst (98 mg, 20% Pd(OH)$_2$/C, 0.069 mmol). A pressure head was attached,

and the reaction mixture was flushed with argon (3×), pressurized to 50 psi of H_2, heated to 50 °C in an oil bath, and kept stirring at that temperature for 2 h. After hydrogenation was completed, the black slurry was stirred for an additional 1 h under 50 psi of CO at rt, followed by filtration of the Pd-$(OH)_2$/C through Celite, and the filter cake was washed with 3 mL of MeOH/CH_2Cl_2 (1:1 v/v). The filtrate was concentrated in vacuo. The tripeptide with a free amino group at the N-terminus **11** (53 mg, 84%) was obtained after flash chromatography on silica gel (10% MeOH/CH_2Cl_2) as a pale yellow oil. For characterization this material was N-acylated.

Tripeptide 11 (35 mg, 0.127 mmol) was dissolved in a 2 mL of Ac_2O/pyridine (1:1 v/v) and was stirred at rt under an argon atmosphere for 2.5 h. After the reaction was complete, the solvent was removed under reduced pressure, and the acetyl tripeptide (36 mg, 91%) was obtained after flash chromatography over silica gel (4:1:1 hex/EtOAc/MeOH) as a pale yellow oil. ^{1}H NMR (in MeOD-d_4 and $CDCl_3$) δ 0.92 (d, J = 6.1 Hz, 3H), 0.97 (d, J = 6.2 Hz, 3H), 1.35 (d, J = 7.1 Hz, 3H), 1.56−1.78 (m, 3H), 2.01 (s, 3H), 3.73 (s, 3H), 3.89 (d, J = 17.5 Hz, 1H), 4.04 (d, J = 17.6 Hz, 1H), 4.27 (q, J = 7.1 Hz, 1H), 4.43 (m, 1H). ^{13}C NMR (in MeOD-d_4 and $CDCl_3$) δ 174.3, 174.0, 172.4, 170.9, 52.1, 51.9, 50.0, 41.2, 40.5, 25.2, 23.1, 22.1, 21.2, 17.1. IR (film) ν 3285, 1755, 1653 cm^{-1}. Mass (HR FAB) Calcd for $C_{14}H_{25}O_5N_3$: M + H = 316.1872. Found: 316.1901 ± 0.0009 (Δ = −8.2 ppm).

Preparation of Dipeptide 12. The general procedure described above was followed using 8 mg (0.05 mmol) of (*S*)-alanine methyl ester hydrochloride, 28 mg (0.06 mmol) of activated ester **6** (a 4:1 mixture of diastereoisomers), and 8 μL (0.06 mmol) of Et_3N. The reaction mixture was stirred 15 h. The general procedure for the workup was followed, and the crude was purified by radial layer chromatography (3:1 hexane/EtOAc) giving 7 mg (35%) **12** as a clear oil and a 4:1 mixture of diastereoisomers: ^{1}H NMR δ 0.82 (d, J = 7.2 Hz, 3H), 1.35 (d, J = 6.9 Hz, 3H), 3.59 (m, 1H), 3.60 (s, 3H), 3.72 (m, 1H), 3.78 (s, 3H), 4.08 (m, 1H), 4.23 (m, 1H), 4.43 (s, 1H), 4.66 (m, 4H), 7.26 (m, 10H). ^{13}C NMR δ 17.4, 18.1, 47.3, 47.5, 52.5, 63.6, 67.1, 72.7, 73.3, 86.4, 126.3, 126.8, 127.2, 128.5, 128.5, 128.5, 128.6, 128.7, 128.8, 129.1, 136.6, 141.7, 171.0, 173.4. IR (film) ν 1743, 1674 cm^{-1}. HRMS Calcd for $C_{21}H_{24}N_2O_4$: [M + H] = 369.1822. Found: [M + H] = 369.1814.

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Supporting Information Available: ^{1}H-NMR spectra for compounds **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **3d**, **3e**, **4a**, **4c**, **4d**, **4e**, **4f**, **6**, **7d**, **10**, **11**, **12** and ^{13}C-NMR spectra for compounds **2a**, **2c**, **2f**, **2g**, **2h**, **3d**, **3e**, **4a**, **4c**, **4d**, **4e**, **4f**, **7d**, **10**, **11**, **12** (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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