Synthesis of Amino Acids and Peptides Using Chromium Carbene Complex Photochemistry

LOUIS S. HEGEDUS

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

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Introduction

Amino acids are a biologically significant class of compounds, since they are the basic building blocks for peptides and proteins, the biopolymers responsible for both the structure and function of most living things. From the standpoint of organic synthesis, however, they have a number of unfortunate features. They are chiral molecules, and usually only one enantiomer is of interest, so efficient asymmetric synthesis is essential. Because they contain mutually reactive functional groups, they are usually prepared and handled in some protected form, which is often prone to racemization. In the free state they bear little resemblance to "normal" organic compounds. They exist as zwitterions, soluble in water, insoluble in most organic solvents, and purified by aqueous ion exchange chromatography, all quite foreign features to synthetic organic chemists.

In spite of these drawbacks, amino acids have been the subject of intense study and interest by synthetic chemists over the past decade. The driving force for much of this activity is the synthesis of *unnatural*, nonproteinogenic amino acids, for preparing new synthetic enzymes, immunostimulants, hormones, and other peptide drugs having unusual biological properties. Many different and efficient approaches to this class of compounds have been developed (Figure 1).[1] A wide range of chiral glycine enolate equivalents which undergo reaction with electrophiles to produce α-amino acids has been developed (path a). These include Schollkopf's bis-lactim ethers[2] and Seebach's cyclic aminals,[3] as well as many others.[1] Nucleophilic alkylation of chiral glycine *cation* equivalents (path b) is less common, with the Williams oxazinone[4] approach the most extensively developed. Asymmetric *electrophilic* amination of ester enolates[1b] (path c) is a relatively uncommon approach to amino acids because of the paucity of electrophilic sources of nitrogen. Evans,[1] Oppolzer,[1] and others[1] have contributed in this area. Asymmetric nucleophilic amination of α-substituted acids (path d) is also relatively undeveloped. In contrast, following the seminal early studies of Kagan and Knowles, the asymmetric hydrogenation of dehydroamino acids (path e) has been extensively developed and utilized,[5] even for the industrial production of optically active amino acids. Finally, asymmetric versions of the classic Strecker

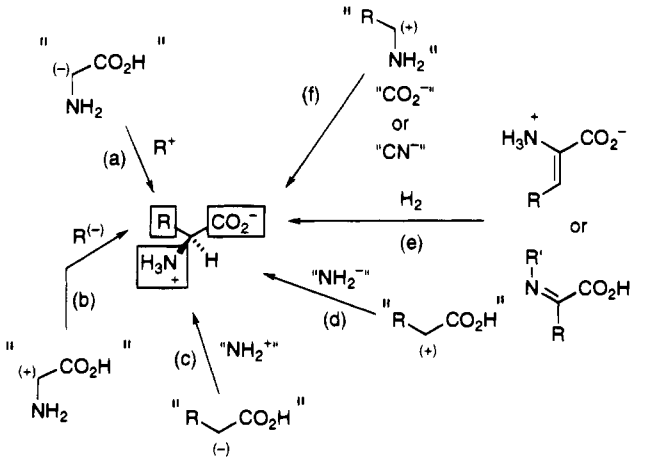
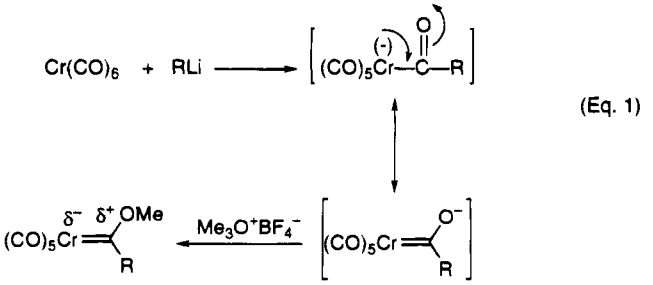


Figure 1. Asymmetric syntheses of α-amino acids.

synthesis (path f) usually involving the addition of cyanide to an optically active imine, have recently been developed.[1]

However varied these approaches are, they all involve the use of "classic" organic reactions involving conventional organic intermediates. Research in our laboratories has centered on the development of unconventional transition metal organometallic complexes for the synthesis of biologically active compounds. Much of our recent work has centered on the photochemical reactions of chromium carbene complexes, easily prepared from commercially available chromium hexacarbonyl, a white, air-stable solid, and organolithium reagents (eq 1).[6] The resulting carbene



(Eq. 1)

complexes are air-stable yellow to red solids, purified by column chromatography, and handled like any normal, stable organic compound. The $Cr(CO)_5$ group is strongly electron withdrawing, making the carbene

Lou Hegedus was born in 1943 in Cleveland, OH, but grew up in rural Ohio, away from big city temptations. He did his undergraduate studies at Pennsylvania State University, where he studied aqueous chromium redox chemistry with Professor Albert Haim. After Ph.D. studies at Harvard on nickel carbonyl chemistry with E. J. Corey (1970) and a postdoctoral year at Stanford with J. P. Collman studying polymer-supported homogeneous catalysis, he moved to Colorado State University, where he remains today as professor of chemistry. His research interests center on the use of transition metals in organic synthesis.

(1) (a) For an exhaustive review of recent activity in the area, see: Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*; Organic Chemistry Series; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, U.K., 1989; Vol. 7. (b) For an updated review on the stereoselective synthesis of α-amino acids, see: Duthaler, R. O. *Tetrahedron* **1994,** *50,* 1539.

(2) Schöllkopf, U. *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer: Berlin, 1983; Vol. 109, pp 65–85.

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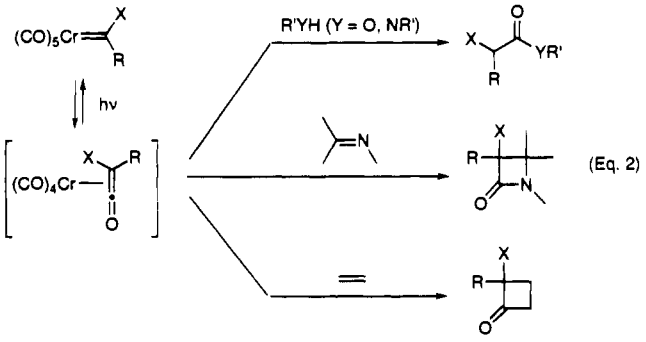
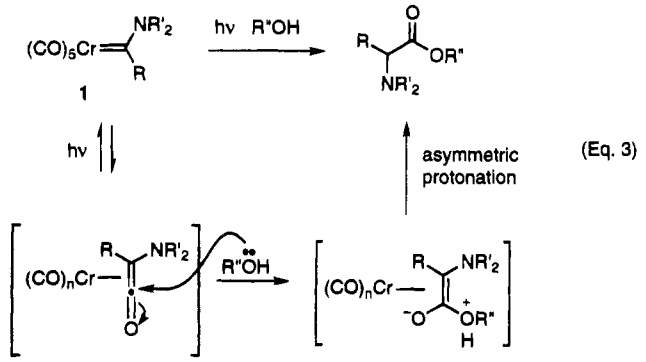
carbon quite electrophilic, and protons on an α-carbon quite acidic.

Irradiation of these complexes with visible light through Pyrex (into the absorption band responsible for their color) photochemically drives a reversible insertion of one of the four *cis* CO groups into the metal–carbon double bond to produce species with ketene-like reactivity (eq 2),[7] producing cyclobu-



tanones from olefins,[8] β-lactams from imines,[9] and carboxylic acid derivatives from alcohols or amines. To utilize this chemistry to produce optically active α-amino acids requires the use of an *amino* carbene complex, as well as some way to control the absolute configuration of the new stereogenic center, presumably generated by asymmetric protonation of the ketene-derived zwitterion (eq 3). Previous studies[9f,h]



of the synthesis of optically active α-amino β-lactams had shown that efficient asymmetric induction in *this* process could be achieved by using chromium aminocarbene complexes having a chiral auxiliary on nitrogen, with the oxazolidine group being most effective. Asymmetric amino acid synthesis studies began with this class of complex.

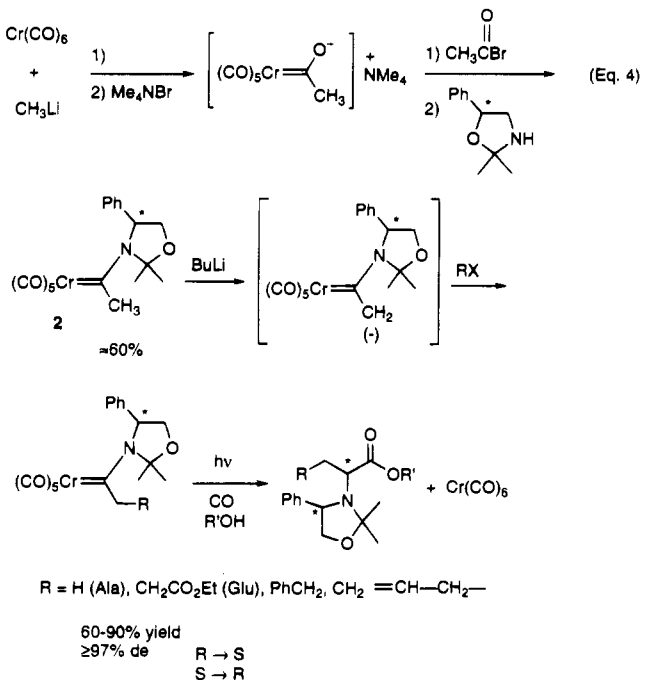
Asymmetric Synthesis of α-Amino Acids

The simplest optically active α-amino acid is α-deuterioglycine, a molecule of some interest for the study of biochemical reactions and the subject of several recent asymmetric syntheses.[10] The synthesis of this "chiral glycine" should provide a stringent test for the asymmetric amino acid synthesis shown in eq 3 (R = H) since the prochiral center of this zwitterionic intermediate should be less sterically biased than those of more elaborate substrates. The requisite carbene complex (**5**, eq 8) was easily synthesized in very high yield[11] from $K_2Cr(CO)_5$ and the formamide of the oxazolidine. Photolysis in the presence of methanol-*d* produced protected α-deuterioglycine in excellent chemical yield (93%) and with very good diastereoselectivity (86% de). Although not *stereospecific*, this approach exhibited stereoselectivity comparable to that obtained by other routes.[10] When the reaction was carried out under a slight pressure of carbon monoxide, chromium hexacarbonyl could be recovered and reused.[12]

The reaction became even more diastereoselective when an alkyl group was on the carbene carbon. The parent carbene complex **2** was synthesized by a different route, involving the reaction of chromium hexacarbonyl with methyllithium to produce an anionic acylate complex. O-Acylation followed by displacement of acetate by the optically active oxazolidine produced complex **2** in reasonable yield. Taking advantage of the acidity of the α-protons, treatment with butyllithium followed by reactive halides permitted homologation of this position. Photolysis of the crude alkylation product produced α-amino acids in fair yield with virtually complete control of stereochemistry (eq 4).[13] Since the absolute configuration of the amino acid produced was opposite that of the oxazolidine (derived from phenylglycine) used, both natural (L) and unnatural (D) amino acids could be prepared with equal facility. In addition, amino acids with a range of alkyl side chains could be synthesized by this procedure. Again, chromium hexacarbonyl could be recovered in good yield.

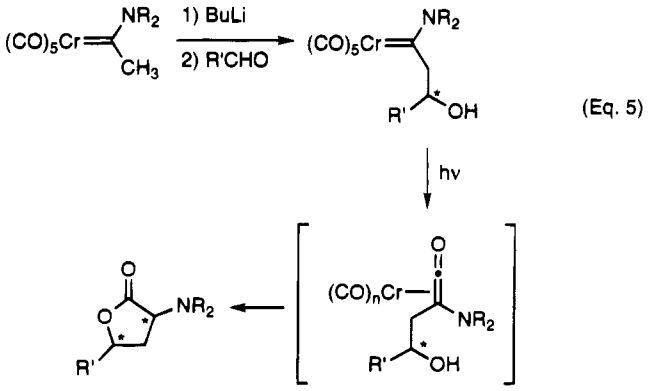
Isotopically labeled amino acids are useful for studying peptide conformations, biosynthesis, and metabolism, and chromium carbene methodology offers an efficient route to multiply labeled amino acids. Carbon-13-labeled chromium hexacarbonyl is readily prepared by the exchange of ^{13}CO with $Cr(CO)_3$-

(3) Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; **1986**, *4*, 128.
(4) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11.
(5) For recent reviews, see: Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p 1. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.
(6) For a recent summary of the use of chromium carbene complexes in organic synthesis, see: Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994; Chapter 6.
(7) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.
(8) (a) Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779. (b) Söderberg, B. C.; Hegedus, L. S. *J. Org. Chem.* **1991**, *56*, 2209. (c) Hegedus, L. S.; Bates, R. W.; Söderberg, B. C. *J. Am. Chem. Soc.* **1991**, *113*, 923. (d) Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364. (e) Sierra, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1989**, *111*, 2335.
(9) (a) Ronan, B.; Hegedus, L. S. *Tetrahedron Symposium-in-Print* **1993**, *49*, 5549. (b) Narukawa, Y.; Juneau, K. N.; Snustad, D.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453. (c) Betschart, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 5010. (d) Thompson, D. K.; Suzuki, N.; Hegedus, L. S.; Satoh, Y. *J. Org. Chem.* **1992**, *57*, 1461. (e) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784. (f) Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109. (g) Hegedus, L. S.; D'Andrea, S. *J. Org. Chem.* **1988**, *53*, 3113. (h) Borel, C.; Hegedus, L. S.; Krebs, J.; Satoh, Y. *J. Am. Chem. Soc.* **1987**, *109*, 1101. (i) Hegedus, L. S.; Schultze, L. M.; Toro, J.; Yijun, C. *Tetrahedron* **1985**, *41*, 5833. (j) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680. (k) McGuire, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1982**, *104*, 5538.
(10) (a) Hamon, D. P. G.; Razzino, P.; Massy-Westropp, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 332. (b) Ramalingam, K.; Nanjappan, P.; Kalvin, D. M.; Woodard, R. W. *Tetrahedron* **1988**, *44*, 5597. (c) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021.
(11) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814.
(12) Hegedus, L. S.; Lastra, E.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1992**, *114*, 2991.
(13) Hegedus, L. S.; Schwindt, M. A.; De Lombaert, S.; Imwinkelried, R. *J. Am. Chem. Soc.* **1990**, *112*, 2264.

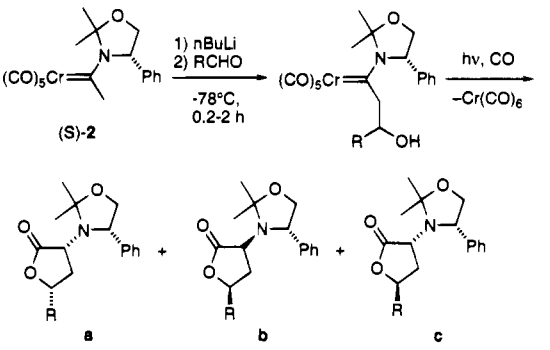


$(NH_3)_3$.[14] Using labeled material to prepare the requisite aminocarbene complexes resulted in the carbene carbon being labeled. Photolysis then inserted a labeled CO to produce a 1,2-bis-^{13}C-labeled ketene, the trapping of which with methanol-*d* provided 1,2-$^{13}C_2$-2D-amino acids in excellent yield.[15] When the reaction was carried out in acetonitrile, the labeled $Cr(CO)_4$ fragment was recovered as the bis-acetonitrile adduct, which could be reconverted to labeled $Cr(^{13}CO)_6$ by exposure to ^{13}CO, thereby minimizing the loss of the unused labeled carbon monoxide in the photoreaction.

γ-Hydroxy-α-amino acids (homoserines) and their related α-amino butyrolactones are found in a number of biologically active peptides. A carbene complex approach to this class of α-amino acids is available by an aldol reaction of an aminocarbene complex with an aldehyde, followed by photolysis of the resulting β-hydroxy aminocarbene complex (eq 5). To be of any



synthetic use, both the aldol step and the photochemical cyclization step must proceed with reasonable diastereoselectivity. Treatment of (*S*) carbene complex **2** with butyllithium followed by an aldehyde produced the aldol product; photolysis of the crude reaction mixture produced the desired amino butyrolactones in fair to good yield (eq 6).[16] This reaction had several



R	yield (%)	a	b	c
C_6H_5	78	92	8	---
$(p\text{-OMe})C_4H_6$	39	100	---	---
2-furyl	44	100	---	---
$C(CH_3)_3$	32(50)	100	---	---
Me	61	22	67	11
$CH(CH_3)_2$	59	22	68	10
$CH{=}CH_2$	37	41	41	18

unusual features. With aromatic aldehydes and pivaldehyde, the diastereoselectivity in the aldol step and the photochemical step was very high and resulted in almost exclusive production of 2*R*,4*R*-diastereoisomer. In contrast, with other aliphatic aldehydes and acrolein, the process was less diastereoselective, giving easily separated mixtures of diastereoisomers and favoring formation of the *opposite cis* amino lactone. Most remarkable was the observation that it was the absolute configuration of the *aldol* center which determined the stereochemical outcome of the photoreaction, completely overriding the normal dominance of the oxazolidine group adjacent to the center being formed in that step. Removal of the chiral auxiliary followed by hydrolysis produced the γ-hydroxy-α-amino acids in good yield. Again, the enantiomers to these amino acids were available simply by starting with enantiomeric **2**. Using this procedure, (+)-bulgecenine ((2*R*,4*R*,5*S*)-4-hydroxy-5-(hydroxymethyl)-proline) was synthesized.

Arylglycines are another class of nonproteinogenic amino acids found widely in biologically active compounds including the vancomyins[17] and amoxicillins.[18] Their synthesis is complicated by the higher lability of the α-position leading to partial racemization, and a variety of approaches to these compounds have been developed.[19] Unfortunately they cannot be made by the chromium carbene chemistry in eq 4 because we are unable to make the required arylcarbene complexes bearing the optically active oxazolidine auxiliary required for efficient asymmetric induction. However, we have developed a related route, which is a broadly general process and offers an efficient approach to many of these compounds, despite the

(14) Darensbourg, D. J.; Darensbourg, M. Y.; Walker, N. *Inorg. Chem.* **1981**, *20*, 1918.
(15) Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 87.
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(18) Meyer, E. M.; Boesten, W. H.; Schoemaker, H. E.; van Balken, J. A. M. In *Biocatalysts in Organic Synthesis*; Tramper, J., van der Plas, H. C., Linko, P., Eds.; Elsevier: Amsterdam, 1985; p 135.
(19) For a survey of synthetic approaches to arylglycines, see: Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723; *Chem. Rev.* **1992**, *92*, 889 and extensive references therein.

modest diastereoselectivity (eq 7).[20] Aromatic chromium acylate complexes are available from either the reaction of aryllithiums with chromium hexacarbonyl or the reaction of aroyl chlorides with chromium pentacarbonyl dianion. O-Acylation followed by displacement of acetate by the optically active diphenyl amino alcohol gave aminocarbene complexes **3** in good yield. Photolysis resulted in intramolecular trapping of the ketene, giving oxazinones **4** in good chemical yield. The diastereoselectivity for this process was surprisingly modest, 60–76% de. However, the diastereoisomers of **4** were very easy to separate, and the facile hydrogenolytic cleavage of the oxazinone made a wide range of optically pure aryl glycines available in reasonable overall yield. Again, the enantiomeric arylglycines were readily available merely by using the antipode of the diphenyl amino alcohol. Oxazinones **4** are closely related to the key intermediates in the Williams synthesis of arylglycines,[19] differing primarily in the relative stereochemistry of the introduced aryl group (*syn* in our case, *anti* in his) resulting in the greater ease of heterogeneous catalytic hydrogenolysis of **4** to the free amino acids. While the intrinsic diastereoselectivity of the Williams arylglycine synthesis is higher, the isolated yields of enantiomerically pure amino acids are comparable and the two approaches are complementary.

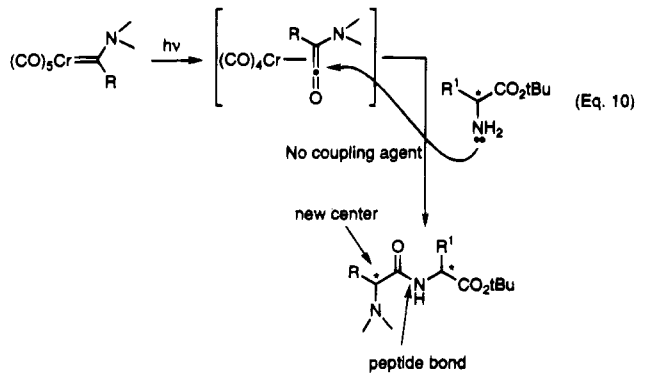
α-Alkyl-α-amino acids are another important class of nonproteinogenic amino acid, used to increase conformational restrictions in peptides and thereby change their biological stability and activity. These, too, have attracted a great deal of synthetic interest recently, and a number of interesting approaches have been developed.[21] This class of amino acid is also unavailable *directly* from chromium carbene chemistry since the α-center is set in an asymmetric protonation. However, by combining an efficient β-lactam synthesis developed in our laboratories[9f] with α-alkylation chemistry developed by Ojima,[22] an efficient approach to α-alkyl-α-amino acids has been developed.[23]

Photolysis of (*R*)-carbene complex **5** with a simple oxazole gave the bicyclic β-lactam **6** in excellent yield and diastereoselectivity. Conversion of the oxazolidine to the oxazolidinone gave a system which underwent Ojima's alkylation with complete retention of configuration, generating the key quaternary center found in α-alkyl-α-amino acids (eq 8). Hydrolysis of the bicyclic system of the methyl derivative gave the key precursor aldehyde **7**, the synthetic source for all of the α-methyl-α-amino acids shown in eq 9. The yields shown are for the overall multistep conversion of the carbene complex **5** to the ultimate product and are equal to or better than the overall yields of alternate approaches, most of which start with the desired α-amino acid (serine, alanine, etc.) and α-methylate it. Again, both enantiomers are equally accessible by this route.

(20) Vernier, J.-M.; Hegedus, L. S.; Miller, D. B. *J. Org. Chem.* **1992**, *57*, 6914.

Synthesis of Peptides

The major impetus for all of this recent synthetic activity is to provide nonproteinogenic α-amino acids to incorporate into peptides to alter their chemistry and their biology. However the peptides are synthesized, intact, protected amino acids are required as starting materials. In contrast, the chromium carbene complex methodology described above offers a potentially unique approach to the incorporation of unusual amino acid fragments into peptides. If photolysis of aminocarbene complexes does indeed produce an amino ketene, then trapping that ketene with an α-amino acid should form both the peptide bond *and* the stereogenic center on the new amino acid residue in a single step, without the intervention of the free amino acid itself (eq 10). To test the validity of this,

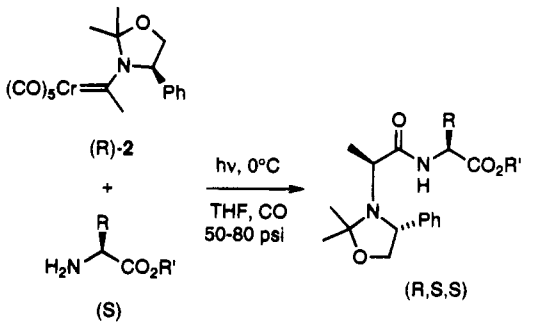


(Eq. 10)

the achiral dibenzylamino chromium carbene complex **1**, R = Me, R′ = Bn, was photolyzed in the presence of alanine *tert*-butyl ester. Although the yield of the dipeptide was excellent, the diastereoselectivity was exceedingly poor, making the process of no use.

Previous experience suggested that a chiral auxiliary on the carbene complex might correct this deficiency, and that was indeed the case. Photolysis of (*R*)-carbene complex **2** in the presence of a wide range of α-amino acid esters produced dipeptides in good yield and with high diastereoselectivity (eq 11).[24] Functionalized amino acids such as serine, tyrosine and threonine (OH), cysteine (SH) and methionine (SMe), and tryptophan (indole) underwent clean dipeptide coupling at the α-amino position without requiring protection of the remote functional group. *Free* amino groups were not tolerated, and free acid groups (glutamic, aspartic) were esterified for solubility purposes. α-Alkylated carbene complexes and ^{13}C-labeled carbene complexes also formed dipeptides under these conditions.

The introduction of α-alkyl-α-amino acids into peptides is often problematic because the steric hindrance about the amino group in concert with the steric bulk of most acid-activating groups greatly reduces the reactivity of these coupling partners. However, the "activated ester" in these chromium carbene dipeptide coupling processes is the sp carbon of a ketene, with

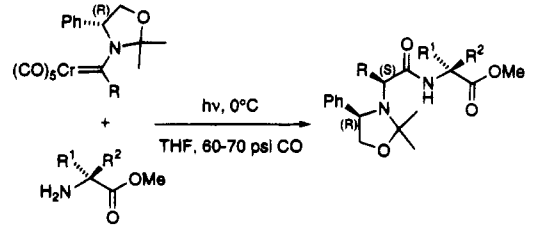


(Eq. 11)

	Ratio	Yield
R = Me (Ala)	98:2	88%
R = H (Gly)	94:6	68%
R = $PhCH_2$ (Phe)	97:3	72%
R = Ph (Phenylgly)	98:2	86%
R = $(CH_3)_2CH$ (Val)	86:14	65%
R = $CH_3CH(OH)$ (Thr)	95:5	56%
R = 3-indoyl (Trp)	90:10	60%
R = CH_2OH (Ser)	98:2	61%
R = CH_2SH (Cys)	92:8	32%
R = $(CH_2)_2CO_2Me$ (Glu)	98:2	75%
R = p-$HOPhCH_2$ (Tyr)	94:6	64%
R = CH_2CO_2Me (Asp)	95:5	64%
R = $CH_2CH_2SCH_3$ (Met)	95:5	68%

Note: Cannot tolerate free NH_2, NH

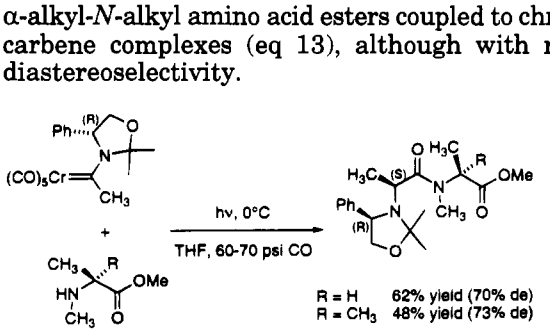
very little intrinsic steric hindrance. As anticipated, α-alkyl-α-amino acid esters coupled efficiently to chromium carbene complexes, making these congested dipeptide fragments readily available (eq 12).[24b] When



(Eq. 12)

	Yield	
R = R^1 = R^2 = CH_3	78%	≥95% de
R = CH_3, R^1 = R^2 = Ph	82%	≥95% de
R = $(CH_3)_2CHCH_2$, R^1 = R^2 = CH_3	76%	≥95% de
R = R^1 = CH_3, R^2 = $PhCH_2$	84%	95% de
R = CH_3, R^1 = $CH_3CH_2CH_2$, R^2 = $PhCH_2$	68%	84% de
R = R^1 = CH_3, R^2 = $CH_3CH_2CH_2$	67%	94% de
R = R^1 = CH_3, R^2 = CH_2OH	68%	86% de

the corresponding (*S*)-carbene complex was used, slightly lower diastereoselectivity was observed, indicating that this corresponds to the "mismatched" combination for double diastereoselection. Even α-alkyl-*N*-alkyl amino acid esters coupled to chromium carbene complexes (eq 13), although with reduced diastereoselectivity.



(Eq. 13)

The amino terminus of small di- or tripeptides also participated in this coupling reaction, and either (*R*) or (*S*) amino acid fragments could be incorporated by

(21) For a recent review, see: Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238. For an extensive list of references, see: Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276.

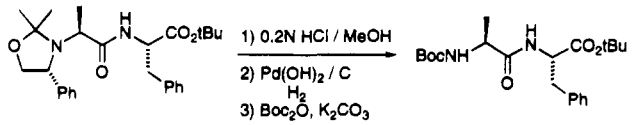
(22) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770 and references therein.

(23) Colson, P.-J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.

(24) (a) Miller, J. R.; Pulley, S. R.; Hegedus, L. S.; DeLombaert, S. *J. Am. Chem. Soc.* **1992**, *114*, 5602. (b) Dubuisson, C.; Fukumoto, Y.; Hegedus, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3697.

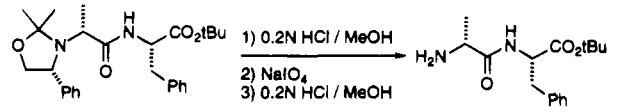
this methodology.[23] The chiral auxiliary was easily removed under either reductive or oxidative conditions to free the amino terminus of the peptide for further coupling (eq 14).[25]

I. Reductive Methods:



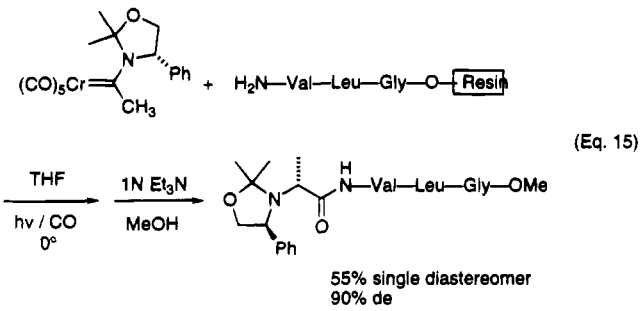
(Eq. 14)

II. Oxidative Methods:



Perhaps the most common way to synthesize peptides is on a solid support, since this process has been effectively automated. This procedure takes advantage of having the growing peptide immobilized on a solid, insoluble support (usually polystyrene) while the incoming amino acid residues and the coupling reagents are in solution[26] and must diffuse in and out of the polymer support for reaction to occur. This raises a potential problem for incorporating chromium carbene complex peptide coupling methodology into solid phase peptide synthesis methodology, since the reactive ketene fragment is photogenerated in very low concentration and has a very short persistence. To be effective in solid phase coupling, the carbene complex would have to diffuse into the support in close proximity to a free amino terminus, and light would have to penetrate the support sufficiently to effect the photoactivation. Although this is asking for a great deal, it works.

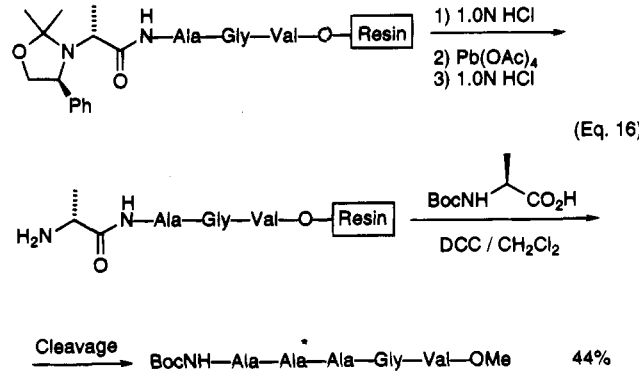
Photolysis of Merrifield-resin-bound amino acids with either (*R*)- or (*S*)-carbene complex **2** (1.3 equiv) followed by cleavage from the resin gave modest yields of dipeptides with good diastereoselectivity. With polymer-supported tripeptides the process was slightly more efficient (eq 15). The lower yields in comparison



(Eq. 15)

to solution coupling reactions are, at least in part, due to mechanical losses of the polymer while the required experimental manipulations are being carried out, since it sticks to everything making quantitative transfer from flask to filter to flask difficult. However, the heterogeneous coupling procedures were indeed less efficient than those carried out in solution.

Removal of the chiral auxiliary from the polymer-supported tetrapeptide, to generate a free amino terminus for further coupling, required a new procedure, since hydrogenolysis would cleave the entire peptide from the resin, and the hydrophobic nature of the polystyrene support precluded the use of the aqueous periodate oxidative method used in homogeneous solution (eq 14). However, hydrolysis of the acetonide followed by oxidation with lead tetraacetate generated the requisite free amino terminus (eq 16).



(Eq. 16)

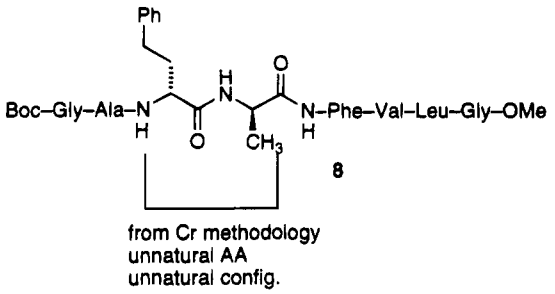
Classic coupling to another alanine followed by cleavage from the resin gave the pentapeptide containing the chromium carbene derived alanine residue in 44% overall purified yield for the entire process starting with the polymer-supported tripeptide.

Although successful, the combination of solid phase peptide synthesis with chromium carbene complex photochemistry was cumbersome, and iterative introduction of several amino acid residues into a solid phase supported peptide by this process was inefficient. The ideal use for this methodology appeared to be in segment condensation syntheses of polypeptides, using the chromium carbene complex methodology to synthesize small, unusual peptide fragments in solution, where the chemistry is efficient and the reactions are easy to carry out, and to then incorporate these unusual polypeptide fragments into solid phase peptide synthesis. To demonstrate the feasibility of this segment condensation approach, a tripeptide containing (*R*)-alanine and (*R*)-homophenylalanine, two unnatural amino acids, was synthesized in solution using chromium carbene complex photochemistry. This tripeptide was then coupled to a polymer-supported tripeptide using conventional Merrifield synthesis methodology, to give the solid phase supported hexapeptide. Sequential incorporation of two more amino acid residues by conventional methodology, followed by cleavage from the support, gave the octapeptide **8** having two unnatural, chromium carbene complex derived amino acid residues at positions 5 and 6 from the carboxy terminus.

Concluding Remarks

From the discovery that photolysis of chromium carbene complexes produced short-lived species having ketene-like reactivity over 10 years ago to the present time, this process has developed into useful methodol-

(25) Pulley, S. R.; Hegedus, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 9037.
(26) For a practical treatment of solid phase peptide synthesis, see: Bodanszky, M. *Peptide Chemistry*; Springer-Verlag: New York, 1993.



ogy for the synthesis of a wide range of interesting organic compounds: β-lactams, cyclobutanones, allenes, amino acids, and peptides. In the latter context, it offers not only the ability to synthesize a wide range of optically active natural and unnatural amino acids but also the ability to directly incorporate them into small peptides. This methodology will complement existing methodology and should find most use in the solution synthesis of small peptide fragments containing (*R*)-amino acid residues, multiply labeled amino acid residues, or very sterically hindered amino acid residues, such as those which are α-alkylated and/or N-alkylated, for incorporation into larger peptides by conventional means. Although it is possible to directly couple to solid phase supported peptides, iterative use in this regard is probably too cumbersome to be practical. Ongoing studies are directed toward increasing the complexity of the amino acid fragments available by this methodology, which is, in essence, the development of new approaches to chromium amino carbene complexes, and toward devising ways of using this chemistry to synthesize cyclic peptides.

The fundamental discovery that made this work possible was made by Dr. Michael McGuire in the early 1980s, and he and the outstanding collaborators cited in the references are responsible for the success of this area. Support from the National Science Foundation for the fundamental studies which led to the discovery of chromium carbene photochemistry, as well as from the National Institutes of General Medical Sciences (Public Health Service), GM26178, for the development of all the chemistry discussed herein is gratefully acknowledged.

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