of configuration at phosphorus.

These results suggest that the mechanism for C–P bond cleavage in the protonated, aniline–CTPA Shiff base intermediate involves either a concerted displacement with an in-line arrangement of nucleophile (H_2O) and leaving group ($PhNHCH{=}CH_2$) or a dissociative process via a tightly paired metathiophosphate intermediate (Scheme II).[17] The stereochemical course of the enzyme catalyzed CTPA reaction is now being probed by use of this potentially general methodology.

Acknowledgment. Financial assistance was provided by NIH Grants GM-28688 (D.D.M.) and GM-27251 (P. S.M) and a grant from the Center of Agricultural Biotechnology at the University of Maryland. We are indebted to Dr. Joseph Ferrara (Molecular Structure Corporation) and Professor Herman Ammon (University of Maryland) for carrying out the X-ray analysis. William H. Swartz provided expert technical assistance during the course of this research.

(17) Hydrolyses of chiral thiophosphate esters occur with inversion of configuration accompanied, to varying degrees, by racemization.[18] Pressure effects on the rate of hydrolysis of 2,4-dinitrophenyl thiophosphate dianion gives evidence for a dissociation mechanism.[19]

(18) Cullis, P. M.; Misra, R.; Wilkins, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1594.

(19) Burgess, J.; Blundell, N.; Cullis, P. M.; Hubbard, C. D.; Misra, R. *J. Am. Chem. Soc.* **1988**, *110*, 7900.

Stereoselective Synthesis of α-Alkyl α-Amino Acids. Alkylation of 3-Substituted 5*H*,10b*H*-Oxazolo[3,2-*c*][1,3]benzoxazine-2(3*H*),5-diones

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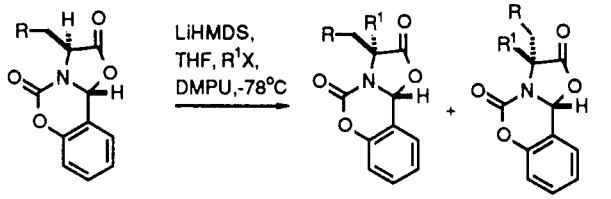
Summary: The alkylation of 3-methyl-, 3-benzyl-, or 3-isobutyl-5*H*,10b*H*-oxazolo[3,2-*c*][1,3]benzoxazine-2-(3*H*),5-dione proceeded with retention of configuration (83 to >97% ds), and the resulting products were hydrolyzed to afford α-alkyl α-amino acids.

In connection with our recent synthesis of dipeptide isosteres containing γ- or δ-lactams, we needed an expedient route to multigram quantities of optically pure (*S*)-α-allylphenylalanine 1.[3] Schollkopf reported a synthesis of 1 [90% ee (*S*)] in 1978 and to our knowledge no other synthesis has been reported.[4] Since that initial report of Schollkopf, a number of routes to α-alkyl α-amino acids have appeared in the literature.[5] However, a smaller number of these routes have addressed the synthesis of α-allylated amino acids.[6] In this paper, we report a general and efficient synthesis of α-alkyl α-amino acids which is also suitable for the preparation of α-allylated amino acids.

The starting material for our synthesis was reported in 1971 by Block and Faulkner as part of their work on peptide coupling reactions.[7] They showed that the condensation of various amino acids with salicylaldehyde and phosgene produced oxazolidinones **2a–c** in 65–70% yield (Scheme I). These compounds are tricyclic versions of the oxazolidinones that Seebach and others have used for the synthesis of α-alkyl α-amino acids.[5a–e] Block and Faulkner found that treatment of **2a** with 1 equiv of *n*-hexylamine resulted in the immediate precipitation of the corresponding carboxamide–urea **3** in 47% yield. None of the expected product **4** was isolated, and this approach to peptide synthesis was abandoned. Upon seeing this result, we reasoned that the addition of hydroxide ion to an alkylated derivative of **2a–c** should also occur and that this would directly lead to the desired amino acid (eq 1).

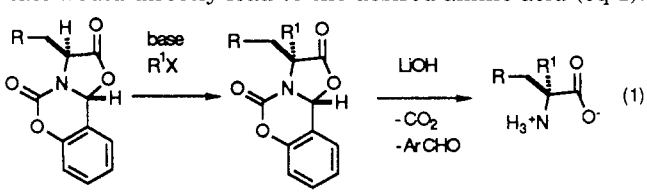
Table I. Survey of Electrophiles



2a-c **5** major **5'** minor

entry	R	R^1X	ratio[a] 5/5'	% yield[b]
1	Ph	allyl bromide	>31:1	94
2	Ph	ethyl iodide	31:1	74
3	Ph	methyl iodide	8:1	66
4	*i*-Pr	allyl bromide	>31:1	81
5	*i*-Pr	methyl iodide	5:1	82
6	H	allyl bromide	11:1	74

[a] Ratios determined by analysis of 300-MHz NMR spectrum. [b] Yield refers to single isomers except as noted in text.



(1)

(1) Cardiovascular Research Division.

(2) Analytical Research Division. Author to whom inquiries regarding the crystal structure should be sent.

(3) Zydowsky, T. M.; Dellaria, J. F.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607.

(4) Schollkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. *Angew. Chem., Intl. Ed. Engl.* **1978**, *17*(2), 117.

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(6) The oxazolidinone and imidazolidinone-based methods listed in ref 5 require strong acid or catalytic hydrogenolysis for final deprotection of alkylated intermediates. The reactivity of the allyl group under these conditions precludes their use. An oxazolidinone-based method which employs mild basic conditions for final deprotection would expand the scope of this methodology.

(7) Block, H.; Faulkner, P. J. *J. Chem. Soc. C* **1971**, 329.

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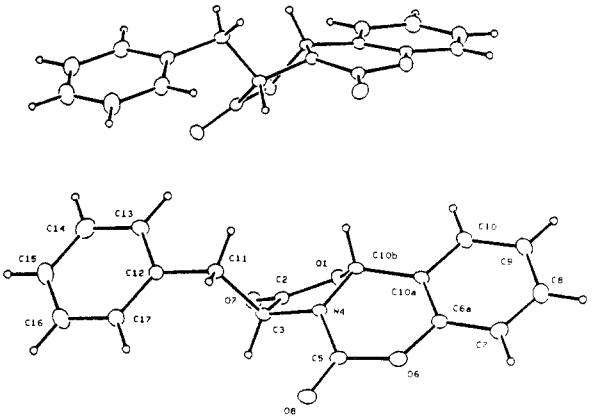
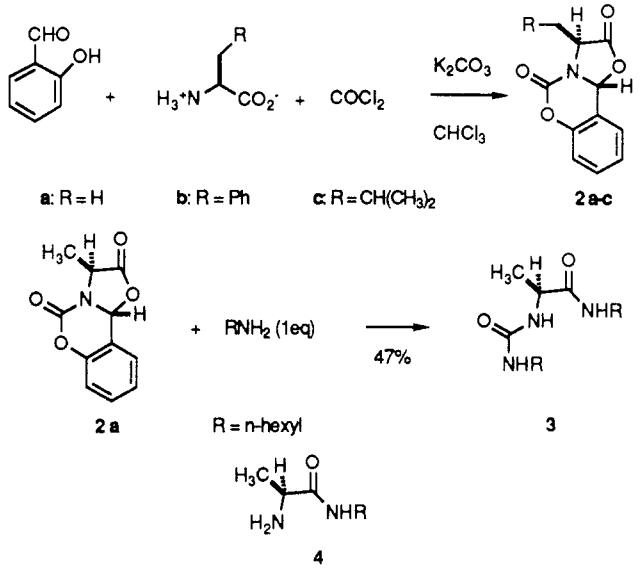


Figure 1. Molecular structure of **2b**.

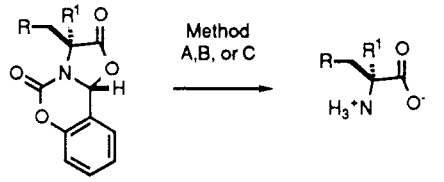
Scheme I



Block's condensation reaction was repeated using L-phenylalanine, salicylaldehyde, and triphosgene under anhydrous conditions to obtain a 48% yield of the desired product **2b**.[8] NMR analysis of the crude product clearly indicated the formation of a single isomer, and NOE studies suggested that the proton at C-10b and the benzyl side chain at C-3 had a syn relationship. A single-crystal X-ray structure determination of **2b** verified the NMR assignment (Figure 1). L-Alanine and L-leucine-derived oxazolidinones **2a** and **2c** were also prepared (45–50% yield), and NOE studies indicated that both products had the same anti stereochemistry as that in **2b**. Acidic hydrolysis of **2a–c** to the corresponding amino acids and comparison of optical rotations showed that little or no racemization had occurred during their preparation.

A general procedure for the alkylation reaction of **2a–c** is described as follows. A tetrahydrofuran solution of oxazolidinones **2b** or **2c** was treated at −78 °C with 0.98 equiv of lithium bis(trimethylsilyl)amide and 2 equiv of DMPU,[9] and after 15 min the corresponding electrophile was added.[10] For reactive electrophiles (methyl iodide and allyl bromide), the reaction was warmed to −30 °C over 2 h and then quenched at −78 °C with acetic acid. Alkylations with less reactive electrophiles (ethyl iodide) were warmed to 25 °C and then quenched. Extractive workup afforded the crude alkylated products. In the case of **2a**, a solution of the oxazolidinone was added dropwise to a precooled (−78 °C) solution of lithium bis(trimethylsilyl)amide. This inverse addition sequence prevented self-condensation reactions from occurring, and the remaining steps were performed as outlined above for **2b–c**.

Table II. Hydrolysis of Dialkylated Oxazolidinones



5 **6**

entry	R	R^1	method[a]	% yield	% ee[14]	ref
1	Ph	allyl	A	24	–	–
2	Ph	allyl	B	44	–	–
3	Ph	allyl	C	94	>98	this work
4	Ph	methyl	C	95	90	15
5	Ph	ethyl	C	92	100	5f
6[b]	*i*-Pr	methyl	C	87	66	5f
7	*i*-Pr	allyl	C	80	–	–
8	H	allyl	C	64	–	–

[a] Method A: 6 N HCl, reflux, 3 h. Method B: $FeCl_3$–SiO_2, 6 N HCl, reflux, 3 h. Method C: LiOH, aqueous dioxane, 20 min, 25 °C, then HCl to pH = 1. [b] 5:1 mixture of isomers.

As shown in Table I, the alkylation reactions of **2a–c** proceeded in good yield, and in most examples excellent diastereoselection was observed. The precursor to **1** (entry 1) was obtained as a single isomer (>97% ds) in 94% yield. The ratio of diastereomers was calculated from the NMR spectrum of the crude products by integrating the signals for the C-10b methine protons. The assignment of stereochemistry at the newly created quaternary center was based on NOE studies and/or correlation to compounds of known stereochemistry. The chemical yields for entries 1–4 refer to the purified single isomers while the yields reported in entries 5 and 6 refer to an inseparable mixture of diastereomers. In these two examples, facile epimerization at C-10b prevented isolation of the individual isomers.[11]

In every case examined, the alkylation reaction proceeded with predominant if not exclusive retention of configuration, implying that the electrophile entered from the face opposite to the proton at C-10b. This result raised the interesting possibility that the proton at C-10b directed the stereochemical course of the alkylation reaction. On the other hand, complex factors such as stereoelectronic effects, steric effects, and the aggregation state of the enolate may have played an important role in determining product distribution.

Hydrolysis of the alkylated oxazolidinones afforded the free amino acids (Table II). The best yields were obtained when the alkylated oxazolidinone (1 mmol) was added to a solution of lithium hydroxide (40 mmol) in 35% aqueous dioxane (120 mL). After 20 min the solution was acidified with 6 N HCl and then desalted on an Amberlite XAD-16 column. Strongly acidic hydrolysis conditions (6 N HCl, reflux, 3 h, or $FeCl_3$–SiO_2, 6 N HCl, reflux, 3 h)[5b] were unsatisfactory for allylated substrates (entries 1 and 2); low yields of the amino acids were obtained, and NMR and

(8) Products with lower optical purities were obtained when water was added to the condensation reaction as described in ref 7.

(9) DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

(10) Similar conditions were used in a related alkylation reaction. See: Nebel, K.; Mutter, M. *Tetrahedron* **1988**, 4793.

(11) The remaining alkylated products are reasonably stable; however, prolonged exposure to basic alumina or freshly activated silica gel sometimes catalyzed the epimerization, and whenever possible neutral alumina is used for chromatography.

TLC analysis of the reaction mixture showed a mixture of products.

A reference sample of (*S*)-1 was synthesized using Schollkopf's method, and this sample (90–92% ee) had $[\alpha]_D = +25.32°$ ($c = 0.97$, H_2O).[12] The sample of (*S*)-1 obtained by the method described in this paper had $[\alpha]_D = +27.30°$ ($c = 1$, H_2O). This result provided unequivocal evidence that the allylation of **2b** proceeded with retention of configuration. Our sample of 1 was >98% ee as determined by thin-layer chromatography on a commercially available Chiralplate.[13,14] This value was independently verified using the NMR method of Kellogg et al.[5f]

The method described in this paper provided α-alkyl α-amino acids in good overall yield and with high optical purity. The mild conditions required for the final deblocking of alkylated intermediates made this a useful method for the synthesis of amino acids containing acid sensitive side chains.

Acknowledgment. We wish to thank Drs. Merrill Nuss and Andy Zetzker, Ms. Ruth Stanaszek, and Mr. David Whittern for performing numerous NMR experiments.

Supplementary Material Available: All experimental procedures and X-ray data for **2b** (22 pages); structure factors for **2b** (6 pages). Ordering information is given on any current masthead page.

(12) The sample of (*S*)-1 prepared in ref 4 was characterized as the *N*-acetyl derivative. We repeated this synthesis and obtained the free amino acid which was used as a reference standard.

(13) Gunther, K.; Schikendanz, M.; Drauz, K.; Martens, J.; Fresenius, Z. *Anal. Chem.* **1986**, 298.

(14) Optical purity values (% ee) were calculated on the basis of specific rotation values in the literature and/or using the NMR method described in ref 5f. The optical purity of α-allylphenylalanine was determined by TLC analysis on a commercially available Chiralplate using a racemic sample of 1, which was prepared from the formaldehyde oxazolidinone. Optical rotation values for the amino acids synthesized in this work are reported in the supplementary material.

(15) Schollkopf, U.; Hausberg, H.-H.; Segel, M.; Reiter, U.; Hoppe, I.; Seanger, W.; Lindner, K. *Liebigs Ann. Chem.* **1981**, 696.

Diels–Alder Reactions of 1-Aza-1,3-butadienes: Room Temperature, Endo-Selective $LUMO_{diene}$-Controlled [4 + 2] Cycloaddition Reactions of *N*-Sulfonyl-4-(ethoxycarbonyl)-1-aza-1,3-butadienes

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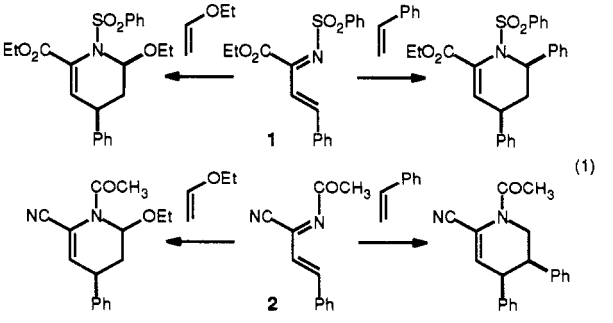
Summary: The room temperature, endo-selective $LUMO_{diene}$-controlled Diels–Alder reactions of *N*-(phenylsulfonyl)- and *N*-(methylsulfonyl)-4-(ethoxycarbonyl)-1-aza-1,3-butadiene (**3–4**) are described, and the results represent a demonstration of the [4 + 2] cycloaddition rate acceleration achievable through noncomplementary azadiene substitution.

The Diels–Alder 4π participation of simple 1-aza-1,3-butadienes, α,β-unsaturated imines, is rarely observed and typically suffers low conversions, competitive imine addition, and/or imine tautomerization precluding productive [4 + 2] cycloaddition.[1,2] However, in recent efforts we have demonstrated the general 4π participation of stable *N*-(phenylsulfonyl)-1-aza-1,3-butadienes in regiospecific and endo-specific inverse electron demand Diels–Alder reactions suitable for the diastereoselective preparation of 1,2,3,4-tetrahydropyridines and that the complementary substitution of the electron-deficient dienes with a C-3 electron-withdrawing substituent predictably accelerates their rate of participation in a $LUMO_{diene}$-controlled [4 + 2] cycloaddition reaction.[3] Extensions of these studies have illustrated that the noncomplementary C-2 addition of an electron-withdrawing substituent (CO_2Et) to the *N*-sulfonyl-1-aza-1,3-butadiene predictably accelerates the diene participation in $LUMO_{diene}$-controlled [4 + 2] cycloaddition reactions, maintains the expected cycloaddition regioselectivity, and maintains or enhances the endo diastereoselectivity (≥20:1), and that the reactions display characteristics consistent with a concerted $LUMO_{diene}$-controlled Diels–Alder reaction.[4]

Concurrent with these efforts, Fowler and Teng[5] have examined the intra- and intermolecular [4 + 2] cycloaddition reactions of *N*-acyl-2-cyano-1-aza-1,3-butadienes and have disclosed that such dienes participate in [4 + 2] cycloaddition reactions with electron-rich dienophiles with a reactivity, regioselectivity, and diastereoselectivity comparable to the *N*-sulfonyl-2-(ethoxycarbonyl)-1-aza-1,3-butadienes. However, in contrast to our disclosure of the clean observation of the 2-aryl-1,2,3,4-tetrahydropyridine cycloaddition regioisomer derived from the [4 + 2] cycloaddition of styrenes with **1**, Fowler and Teng have described the observation of mixtures of 3-aryl- and 2-aryl-1,2,3,4-tetrahydropyridines (8–1:1, respectively) with **2** (eq 1). Consequently, in efforts to define the origin of



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