Scheme III

a, R = H
b, R = CH₂CH₂NPhth

^{a} t-BuOCO₂N=C(CN)(Ph) .　^{b} $\overset{\text{NCO}_2\text{Et}}{\underset{\text{NCO}_2\text{Et}}{\|}}$, Ph₃P.　^{c} TFA.　^{d} K₂CO₃.

^{e} t-CuOCl.　^{f} $^-$OCH₃ or DBU.　^{g} t-BuNC, PhCO₂H.
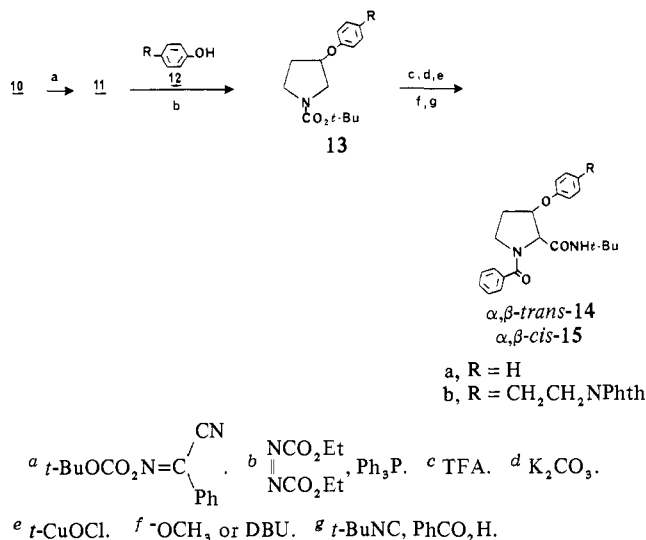
dium methoxide to afford the unstable pyrroline **8** which was trapped with *tert*-butyl isonitrile in the presence of Boc-L-valine to afford the *tert*-butylamide of Boc-valylproline (**9**) in 56% yield as a diastereomeric mixture with DL stereochemistry at proline. The product was isolated by extraction and characterized by NMR, HPLC, amino acid analysis, and high-resolution mass spectroscopy.

The synthesis of key intermediate **3** and the feasibility of using (aryloxy)pyrrolidines in the four-component condensation was first examined in a model system using phenol (**12a**) as the aryloxy group (Scheme III). Commercially available 3-hydroxy-pyrrolidine (**10**) was quantitatively converted into the corresponding *N*-butyloxycarbonyl derivative **11** by using either 2-((*tert*-butylcarbonyloxyimino))-2-phenylacetonitrile (Boc-ON)[7] or di-*tert*-butyl dicarbonate. The aryl ether **13a** was prepared in 82% yield by using equimolar ratios of **11** and **12a** and a 10% excess of both diethyl azodicarboxylate and triphenylphosphine, according to procedures developed by Mitsunobu.[8] Removal of the nitrogen blocking group by treatment with trifluoroacetic acid for a short period of time afforded the protonated phenoxy-pyrrolidine as the trifluoroacetate salt (99% yield). The free base was generated in situ by stirring an ether suspension of this compound with sodium carbonate. Subsequent treatment of the base with *tert*-butyl hypochlorite at 0 °C gave the *N*-chloro derivative, which was extracted with ether and dehydrohalogenated either with sodium methoxide or diazabicycloundecene to afford the highly unstable pyrroline derivative, which was subjected immediately to the four-component condensation conditions by rapid evaporation of the solvent and addition of methanol, benzoic acid, and *tert*-butyl isonitrile to afford two products (**14a** and **15a**). These products were readily separated by silica gel chromatography and identified as the α,β-cis and -trans isomers of benz-amido-β-phenoxyproline *tert*-butyl amide. The cis:trans isomeric ratio was 55:45. Configurational assignments were easily made from the NMR spectra of the two isomers, as the trans isomer exhibits a characteristic singlet for the α proton of the substituted proline, while the α,β-proton coupling constant of the cis isomer is 6 Hz in CD₃OD.

The total yield for the five-step reaction scheme starting with **13a** was 58%. The major side reaction that occurred during the dehydrohalogenation step was the β elimination of phenol. No condensation product derived from dehydrohalogenation in the direction of the δ carbon of the pyrrolidine derivative was observed.

Another model study incorporating a blocked tyramine derivative was also carried out as the reagents resembled more closely those that would be used in a cyclopeptide alkaloid synthesis

(Scheme III). The amino group of tyramine was blocked by the phthalimido group by using commercially available (ethoxy-carbonyl)phthalimide. Compound **12b** was obtained in 79% yield. Ether formation with Boc-β-hydroxypyrrolidine was accomplished by using 1.1 equiv of triphenylphosphine and diethyl azodi-carboxylate to afford **13b** in 75% yield. The *N*-(butyloxy)carbonyl group was removed with trifluoroacetic acid to yield the corresponding trifluoroacetate salt. Deprotonation was carried out by using potassium carbonate in tetrahydrofuran–ether, and dehy-drohalogenation was accomplished with diazabicycloundecene to give the desired pyrroline, which was dissolved in methanol and treated immediately with benzoic acid and *tert*-butyl isonitrile to afford a mixture of cis and trans isomers in a 56:44 ratio (**14b** and **15b**). The total yield for the five-step reaction sequence was 56%, with β elimination being again the major side reaction. The spectroscopic properties of **14b** and **15b** were again consistent with their assigned structures, and they showed structural features similar to the other model discussed.

Our model studies clearly show that the four-component condensation can serve as an alternate, novel, and short approach for the synthesis of substituted prolyl peptides. This methodology can also be extended to other cyclic secondary amino acids. We plan to use the four-component condenstion approach for the synthesis of cyclopeptide alkaloids of the amphibine B family. These studies represent the first application of the four-component condensation to the synthesis of cyclic secondary amino acids.

Supplementary Material Available: Experimental details, analytical data, R_f, and IR and ¹H NMR spectra for compounds **9**, **11**, **13a**, **14a**, **15a**, **12b**, **13b**, **14b**, and **15b** (2 pages). Ordering information is given on any current masthead page.

Cyclodextrin Catalysis in the Intramolecular Diels–Alder Reaction with the Furan Diene[1]

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In the course of a broad project directed toward the total syntheses of prostaglandins and tiglianes we needed to investigate the intramolecular Diels–Alder reaction with a substituted furan as the diene component. Our findings[2] indicated that for systems in which the diene (furan ring) and the dienophile were separated by a three-atom chain, substituents on carbon-2 were extremely important. For example, the reaction (eq 1) failed when R = H

(1)

1, R = H	5
2, R = CH₃	6
3, R = –S(CH₂)₃S–	7
4, R = OEt	8
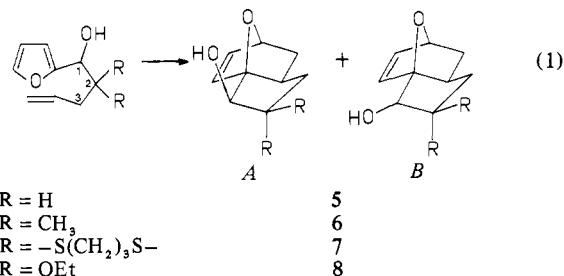
or R = CH₃[3a] (**1** and **2**); however, excellent yields were obtained

(7) Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4394.
(8) Mitsunobu, O. *Synthesis*, **1981**, 1.

(1) Portions of this work were first presented at the 183rd American Chemical Society National Meeting, Las Vegas, Mar 1982; ORGN 130.
(2) Sternbach, D. D.; Rossana, D. M. *Tetrahedron Lett.* **1982**, *23*, 303.

Table I. Comparison of Cyclization Yields of 3 with Various Catalysis

| solvent[b] (equiv)	yield[a] of epimeric products, %	
	3 h (80 °C)	6 h (89 °C)
water	≤10	20
water + α-CD (1.0)		25
water + β-CD (0.5)	45	69
water + β-CD (1.0)	55	91
water + β-CD (1.6)	71	86[c]
water + Brij-35 (1.0)		22
5:2 water/ethanol	≤10	
ethylene glycol	≤10	

[a] The yields were based on NMR integration of crude products which amounted to a material balance of >90%. In every case only starting material and products were observed. [b] All reactions were 10 mM in 3. [c] This yield is suspect since there was difficulty achieving a good material balance.

when R = -SCH$_2$CH$_2$CH$_2$S- or R = OEt (3 and 4).[3bc] The effect of substitution at this center was not altogether unexpected, since similar effects have been observed by others.[4] The yields of 7 are also remarkably solvent dependent, ranging from 45% in acetonitrile or water to 90% in ethylene glycol or ethanol/water (2:5). It is interesting to note that the hydrophobic effect[5] slows down the cyclization.

Contrasting this behavior, Breslow[6] has recently reported rate enhancements for intermolecular Diels–Alder reactions that are carried out in water (compared to the rates in organic solvents). He has also demonstrated that β-cyclodextrin will further enhance some of these reactions by simultaneously forming an inclusion complex with the diene and the dienophile. Due to the apparent effects of conformational equilibrium as well as its solvent dependence, the furan intramolecular Diels–Alder reaction appeared to be an ideal substrate to test for cyclodextrin catalysis.

When 3 is heated in water at 89 °C for 6 h, a 20% yield of Diels–Alder adducts is formed as an epimeric mixture (eq 1, 1:2 A:B).[7] While in the presence of 1 equiv of β-cyclodextrin, a 91% yield of products (epimer ratio 1:1.5) is obtained (see Table I). No significant yield enhancement was observed when either α-cyclodextrin or the nonionic detergent, Brij-35,[8] was employed. A comparison was also made with the solvents that had previously given the best yields. After 3 h these reactions yielded less than 10% products while with 1 equiv of β-cyclodextrin a 55% yield was achieved. As expected, the yields also varied depending on the amount of β-cyclodextrin present (see Table I).

It is interesting to speculate on the mechanism through which β-cyclodextrin exerts its catalytic effect.[9] Breslow[6] suggested that in the intermolecular reaction both the diene and the dienophile are simultaneously complexed within the cyclodextrin cavity. He
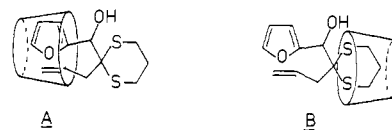

Figure 1.

also showed that a cavity too small to include both molecules (e.g., α-cyclodextrin) would not catalyze (and might even inhibit) the reaction. In our case one might imagine complexation occurring with the diene and dienophile (Figure 1A) or with the dithiane portion of the molecule (Figure 1B). Both cases would result in juxtapositioning of the two reactive ends of the molecule. The latter mode of complexation would simulate the effect of having a very large pair of geminal substituents on carbon-2.

We have evidence that initial complexation occurs fast. When equimolar amounts of β-cyclodextrin and the Diels–Alder precursor 3 are dissolved in water (brief heating is required) and the homogeneous solution is allowed to cool, a microcrystalline white solid falls out of solution. An NMR spectrum of this solid indicates the presence of both 3 and the cyclodextrin.[10] It should be mentioned that while two diastereomeric β-cyclodextrin complexes with 3 are possible, no optical activity has been observed in either the Diels–Alder products or the recovered starting material.

Compounds 2 and 4 were also subjected to cyclization conditions (1 equiv of β-cyclodextrin, 80 °C) to test the generality of catalysis by β-cyclodextrin. Compound 2 showed no tendency to cyclize while compound 4 decomposed to a number of unidentified products.

We briefly examined another furan intramolecular Diels–Alder reaction that has been shown to occur readily in nonaqueous solvents.[11] Cyclization of 9 was carried out at 80 °C in the

$$\text{9} \longrightarrow \text{10} \tag{2}$$
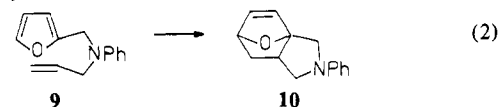
presence of α- and β-cyclodextrin. After 1 h, we obtained a 16% yield with water alone, a 9% yield with water and 1 equiv of α-cyclodextrin, and a 26% yield with water and 1 equiv of β-cyclodextrin. We hoped that if the cyclodextrin was complexing as shown in Figure 1B, then α-cyclodextrin with a known affinity for monosubstituted benzenes[12] would catalyze this reaction. If anything, α-cyclodextrin retarded the reaction to a small degree. This might mean that complexation with the furan ring is more favorable and this complexation inhibits the reaction. We did, however, observe a small but significant rate enhancement when β-cyclodextrin was used as a catalyst. The difference observed for the uncatalyzed vs. catalyzed reaction diminished as the reaction progressed (after 3 h, 53%/H$_2$O, 50%/α, 62%/β). Carrying out the reaction at 60 °C produced similar results. An examination of other substrates, in an effort to understand the nature of the complexation and to examine the potential synthetic utility, is underway.

(3) (a) We thank Katherine A. Garcia for synthesizing and carrying out the experiments on this compound. (b) We have found that 3 cyclizes to 7 in a 63% yield after 3 days in refluxing benzene while a comparable yield (61%) of 4 to 8 was achieved after only 1 day in refluxing benzene. (c) Compounds 1–4 were synthesized by either the addition of an appropriate carbanion to furfural or the addition of furyllithium to an appropriate aldehyde. The experimental details for these preparations will be reported in the full account of this work.

(4) (a) Gschwend, H. W.; Hillman, M. J.; Visis, B.; Rodenbaugh, R. K. *J. Org. Chem.* **1976**, *41*, 104. (b) Parker, K. A.; Adamchuck, M. R. *Tetrahedron Lett.* **1978**, 1689. (c) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033.

(5) Tanford, C. In "The Hydrophobic Effect: Formation of Micelles and Biological Membranes"; Wiley: New York, 1980.

(6) Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

(7) The structure of **7A** has been confirmed through an X-ray crystal structure done by Dr. Kay Onan of Northeastern University. This will be the subject of a later report.

(8) Brij-35 (polyoxyethylene(23) lauryl ether) is commercially available from Aldrich Chemical Co.

(9) To test whether the effects observed here are kinetic (i.e., true catalysis) or merely manifestations of selective complexation of the products, we heated the product mixture 7 (1:1.5 A:B) at 89 °C for 6 h in the absence of β-cyclodextrin. No starting material was observed by NMR spectroscopy, thus indicating that the reaction is essentially irreversible under these conditions.

(10) Differential scanning calorimetry experiments done on the inclusion complex showed no evidence of uncomplexed starting material, implying that this precipitate was *not* merely an intimate mixture of 3 and β-cyclodextrin. In addition uncomplexed β-cyclodextrin was completely soluble at the concentrations used in this experiment.

(11) Bilovic, D.; Stojanac, Z.; Hahn, V. *Tetrahedron Lett.* **1964**, 2071. Klepo, Z.; Jakopcic, K. *Croat. Chem. Acta* **1975**, *47*, 45.

(12) Bender, M. L.; Komiyama, M. In "Cyclodextrin Chemistry"; Springer-Verlag; New York, 1978; pp 10–14.