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THE SYNTHESIS OF AMINO ACIDS BY REACTION OF AN ELECTROPHILIC GLYCINE CATION EQUIVALENT WITH NEUTRAL CARBON NUCLEOPHILES

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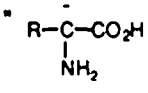
Abstract: Seven neutral carbon nucleophiles (active aromatics, allylsilanes and a silyl enol ether) were reacted with the glycine cation equivalent **12** in the presence of $TiCl_4$ to yield α-substituted amino acid derivatives in moderate yield (1 - 61.5 mmolar scale). Deprotection of the Schiff base ester products led to the corresponding amino acids.

INTRODUCTION

New routes for the synthesis of amino acids continue to present a challenge for the synthetic organic chemist.[1] Because of the key role of carbon-carbon bond formation in organic synthesis, the development of new and versatile anionic (**1**) and cationic (**2**) amino acid equivalents is an important area of research. Our attention has focused on use of the carbon-



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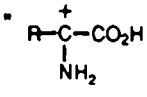

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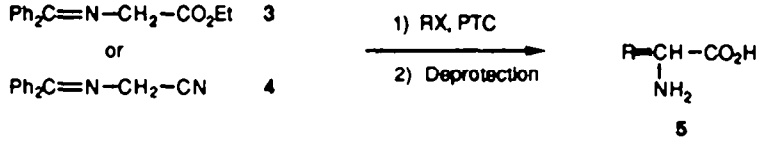
nitrogen double bond in the form of a Schiff base for protection of the primary amino group in conjunction with ester or nitrile functionality for carboxyl-group protection.

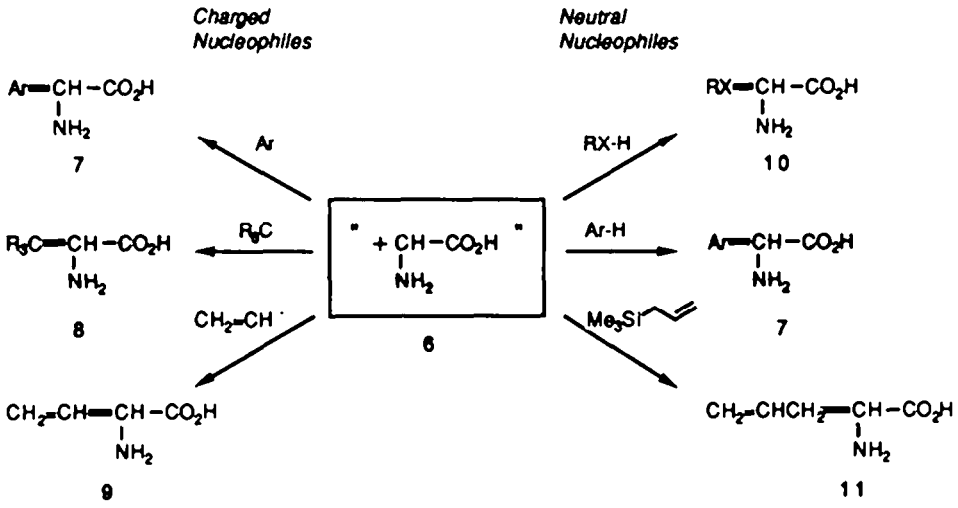
Carbon-carbon bond construction involving the reaction of anionic synthons **1** of glycine or the higher amino acids with electrophiles has been utilized by numerous groups for the preparation of amino acids.[2] We have developed a general synthesis of amino acids based on catalytic phase-transfer (PTC) alkylations of the benzophenone imine of



either glycine ethyl ester or aminoacetonitrile, (**3** or **4**, respectively).[3] In contrast to known anhydrous alkylative routes, the PTC method involves a simple reaction procedure, mild conditions, inexpensive and safe reagents and solvents as well as commercially available starting substrates.[4]

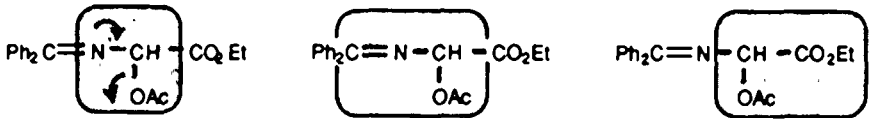
The synthesis of amino acids involving cationic amino acid equivalents **2** is not nearly as well developed as that using their anionic counterparts.[5] The α-cation equivalent of glycine **6** [**6** = **2** (R=H)] represents a polarity reversed reagent which can be reacted with nucleophiles to yield derivatives of higher amino acids. A number of interesting amino acid derivatives

Scheme 1. Reactions of Glycine Cation Equivalent (6) with Charged and Neutral Nucleophiles.

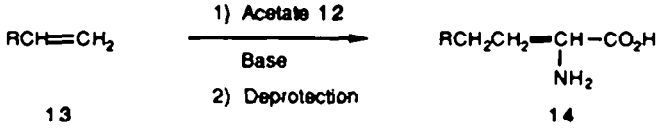


which are, in principle, accessible using this strategy are generally difficult to prepare via the anion equivalent **1**, because of the inaccessibility of the requisite electrophiles. Such products could be prepared using either charged or neutral nucleophiles as depicted in Scheme 1. Thus, aryl and β,γ-unsaturated amino acids (**7** and **9**, respectively) as well as β-quaternary substituted amino acids **8** could be prepared by reacting appropriate carbanionic species with synthon **6** while neutral nucleophiles, such as heteratom nucleophiles (alcohols, thiols, etc.), or activated aromatics could serve as precursors to derivatives **10** and **7**, respectively. Finally, various organosilicon derivatives could be used as nucleophiles to prepare derivatives such as **11**.

We have introduced the acetate derivative **12**[6-8] as a versatile cationic glycine equivalent. This multifunctional compound, which is readily prepared from Schiff base ester **3**[6] and is also commercially available,[9] contains several structural subunits of interest for bond formation to the α-carbon. Substructure **12a** contains a good leaving group (-OAc) on a carbon bearing a heteroatom which could lead to ionization as depicted to form a 2-azaallenium cationic



system. Reaction of acetate **12** with neutral heteratom nucleophiles to yield products **10** provides an example of this mode of reaction.[6] Substructure **12b** represents a pseudo allylic acetate, which has been reacted with organocopper species to form carbon-carbon bonds and lead to products of general structures **7** and **8**.[7] Finally, **12c** is a pseudo α-halo ester which has

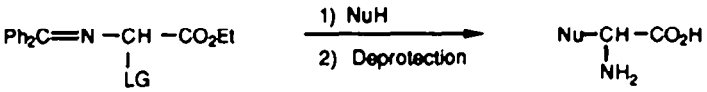


been utilized for the first general synthesis of amino acids from organoboranes.[8] This chemistry provides a convenient method for "appending" the amino acid functionality to olefins (**13** → **14**) and additionally provides access to products such as **7** and **8** from the appropriate organoboranes.[8]

In this Symposium we will present our results from the reaction of acetate **12** as well as other electrophilic glycine equivalents with neutral carbon nucleophiles as a route to higher amino acids **7** and **11**.

RESULTS AND DISCUSSION

Since the heteroatom-substituted derivatives from the benzophenone imine of glycine ethyl ester **3** are readily prepared, several different types of compounds with a leaving group (LG) on the α-carbon of a protected glycine



LG = OAc **12**
SPh **15**
NMe_2 **16**
OMe **17**

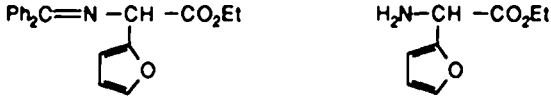
18

derivative are potential candidates as glycine cation equivalents. Thus, in addition to acetate **12**, reactions of compounds containing other sulfur-, nitrogen- or oxygen-based leaving groups (compounds **15**, **16** and **17**, respectively)[6] with nucleophiles were investigated.

Aromatic Nucleophiles

New and practical synthetic routes to the α-arylglycines are of interest because these amino acids are structural elements of several widely used penicillin and cephalosporin antibiotics.[10]

Initial studies were carried out using the acetate Schiff base ester **12** on a 1 mmolar scale (0.325 g) with furan as the nucleophile to yield arylated product **19**. Experiments were conducted to find the best conditions in terms of (a) Lewis acid, (b) solvent and (c) stoichiometry, temperature and mode of addition. Normally, the arylated Schiff base ester **19** was isolated by an aqueous $NaHCO_3$ quench of the reaction mixture followed by normal aqueous workup. Since the benzophenone imines are relatively stable in the absence of acid, it is possible to purify the reaction products by flash chromatography. In the solvent study, however, the arylated amino ester **20** was isolated because of the water solubility and consequent ease of separation of this compound from higher boiling organic solvents. A systematic study (Table 1)



19 **20**

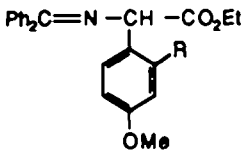
showed that titanium tetrachloride was the best Lewis acid of those tried (Table 1, part a) and that methylene chloride was the best solvent for this reaction (Table 1, part b). These results are in accord with the known affinity of $TiCl_4$ for oxygen as well as the general success of $TiCl_4/CH_2Cl_2$ as a Lewis acid system.[11] It is necessary to use one equivalent of $TiCl_4$, neither a catalytic amount nor more than one equivalent give good results (compare entries 1, 15, 17 and 18, Table 1). When more than one equivalent of $TiCl_4$ was used, a black, semi-solid polymeric product resulted, presumeably due to the polymerization of furan.[12] The reaction can conveniently be conducted at room temperature, an excess of the nucleophile furan can be used (entry 19, Table 1) and it is advantageous to add the nucleophile last (entries 1 and 16, Table 1).

Attention was next turned to the use of other active aromatic compounds with acetate Schiff base ester **12**. Using anisole under conditions similar to those which were successful with furan gave mainly benzophenone and a small amount of unreacted starting Schiff base (Table 2, entry 3).[13] Use of two equivalent of $TiCl_4$ (Table 2, entry 4) gave better results; however, additional $TiCl_4$ did not improve the yield of arylated product (Table 2, entry 5). Similar results were obtained with 1,3-dimethoxybenzene; the best yield of product was obtained when an equivalent of $TiCl_4$ was added for each oxygen in the nucleophile in addition to an additional equivalent of $TiCl_4$ for the Schiff base **12** (Table 2, entries 7-10). In all of the reactions using multiple equivalents of Lewis acid, the nucleophile was added to the reaction mixture of **12** and $TiCl_4$ at -78° C. Finally, acetate Schiff base **12** was reacted with indole to give the Schiff base ethyl ester of nortryptophan **23**.

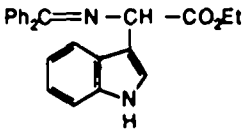
TABLE 1. Reaction of Acetate Schiff Base (12) with Furan under Various Conditions.

Entry	Furan[a]	Lewis Acid[a]	Solvent	Temp	Product(s)[b]		
Vary Lewis Acid:					**19**	**12**	$Ph_2C{=}O$
(1)	1.2	$TiCl_4$ (1.0)	CH_2Cl_2	25°C	53%	-	-
(2)	"	$AlCl_3$ (1.0)	"	"	25%	-	75%
(3)	"	$EtAlCl_2$ (1.0)	"	"	25%	-	75%
(4)	"	ZnI_2 (1.0)	"	"	0%[c]	-	100%
(5)	"	$MgBr_2{\cdot}Et_2O$ (1.0)	"	"	0%[c]	13%	87%
(6)	"	TMSOTf (1.0)	"	"	27%	9%	64%
Vary Solvent:					**20**	**12**	$Ph_2C{=}O$
(7)	1.2	$TiCl_4$ (1.0)	CH_2Cl_2	25°C	53%	-	-
(8)	"	"	$CHCl_3$	"	47%	-	-
(9)	"	"	$ClCH_2CH_2Cl$	"	44%	-	-
(10)	"	"	$Cl_2C{=}CHCl$	"	36%	-	-
(11)	"	"	CH_3NO_2	"	15%[d]	-	-
(12)	"	"	*o*-Dichlorobenzene	"	14%[d]	-	-
(13)	"	"	CCl_4	"	10%	-	-
(14)	"	"	CH_3CN	"	14%	-	-
Vary Stoichiometry, Temperature, Mode of Addition:					**19**	**12**	$Ph_2C{=}O$
(15)	1.2	$TiCl_4$ (0.1)	CH_2Cl_2	25°C	0%[c]	37%	63%
(16)	1.0	" (1.0)[e]	"	"	39%	-	-
(1)	1.2	"	"	"	53%	-	-
(17)	1.0	" (2.0)	"	"	0%[c]	-	100%
(18)	1.2	"	"	-78°→25°C	0%[c]	-	100%
(19)	10	" (1.0)	"	25°C	50%	-	-
(20)	"	"	"	0°→25°C	47%	-	-
(21)	"	" (2.0)[e]	"	25°C	29%	-	-

[a]Equivalents relative to 12. Unless otherwise noted, nucleophile added last. [b]Isolated yields unless otherwise noted. [c]HPLC yields determined from reaction mixture. [d]NMR yield determined from crude reaction product. [e]$TiCl_4$ added last.



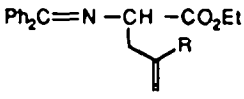
21 (R = H)
22 (R = OMe)



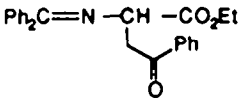
23

Silicon-Containing Nucleophiles

The reactions of various silicon-containing compounds,[14] with the glycine cation equivalent 12 were investigated as a possible entry to a number of interesting types of amino acids. Thus, allyltrimethylsilane was added to a solution of acetate 12 in CH_2Cl_2 at -78° C in the presence of varying amounts of $TiCl_4$ to determine optimal conditions for the preparation of the allylated Schiff base ester 24 (Table 2, entries 15-17). While catalytic amounts of the Lewis acid did yield product, best results were obtained when one equivalent of $TiCl_4$ was used. Using these results as a model, methallyltrimethylsilane



24 (R = H)
25 (R = CH_3)



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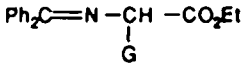
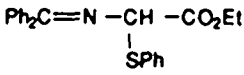


27 (G = CH_2CO_2Et)
28 (G = C≡CSiMe_3)
29 (G = Ph)

and the silyl enol ether of acetophenone (Table 2, entries 19 and 20) were reacted to yield products 25 and 26, respectively. The reactions of acetate 12 with the trimethylsilyl ketene acetal of ethyl acetate or phenyltrimethylsilane or bis(trimethylsilyl)acetylene to prepare 27, 28 or 29, respectively, were all unsucessful.

Other Glycine Cation Equivalents

Since the acetate Schiff base 12 gave only modest yields of products with either active aromatic compounds or silyl derivatives, the use of other heteroatom-substituted protected glycine derivatives (15 - 17) was explored. As in the previous experiments, furan was used as the nucleophile.



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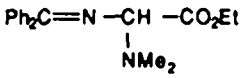

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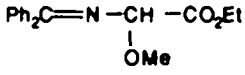

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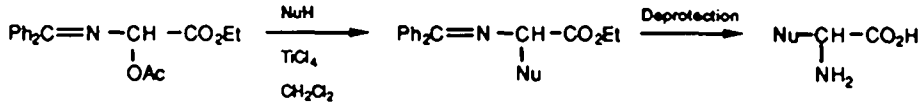
The thiophenyl Schiff base 15, which is readily prepared from acetate 12[6], did not give promising results. Thus, when 15 was reacted with furan in CH_2Cl_2 in the presence of $TiCl_4$ no reaction occured while with $HgCl_2$ only benzophenone was formed. Similarly, neither the N,N-dimethylamino Schiff base 16, which is prepared directly from the

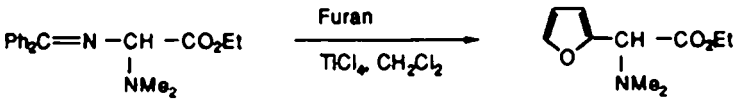
TABLE 2. Reaction of Acetate Schiff Base (12) with Various Nucleophiles and Hydrolysis to Amino Acids.[a]



12 A (19, 21-26) B (11, 31-36)

Entry	Nucleophile[b]	Eq. $TiCl_4$[b]	Temp	Scale[c] (mmol)	Product A (yield)[d]	Amino Acid B (yield)[e]
(1)	Furan (1.2)	1.0	25°C	1	**19**(53%)	-
(2)	Furan (1.0)	"	-78°C	10	" (48%)	**31** (63%)
(3)	Anisole (1.2)	1.0	-78°C	1	**21** (0%)[f]	-
(4)	"	2.0	-78°→25°C	"	" (37%)	-
(5)	"	3.0	"	"	" (24%)	-
(6)	" (1.0)	2.0	-78°C	10	" (37%)	**32** (87%)
(7)	1,3-Dimethoxybenzene (1.2)	1.0	25°C	1	**22**(29%)	-
(8)	"	2.0	-78°→25°C	"	" (30%)	-
(9)	"	3.0	"	"	" (38%)	-
(10)	"	4.0	"	"	" (31%)	-
(11)	" (1.0)	1.0	-78°C	10	" (29%)	**33** (68%)
(12)	Indole (1.2)	1.0	-78°→25°C	1	**23**(31%)	-
(13)	"	2.0	"	"	" (0%)[g]	-
(14)	"	1.0	-78°→0°C	10	" (38%)	**34** (93%)
(15)	CH_2=$CHCH_2SiMe_3$ (1.0)	0.1	-78°C	1	**24**(35%)	-
(16)	"	1.0	"	"	" (46%)	-
(17)	"	2.0	"	"	" (15%)	-
(18)	" (1.2)	1.0	-78°→25°C	61.5	" (32%)	**11** (68%)
(19)	CH_2=C(Me)CH_2SiMe_3 (1.0)	1.0	-78°→25°C	1	**25**(16%)	**35** (64%)
(20)	CH_2=C(Ph)$OSiMe_3$ (1.0)	1.0	-78°→25°C	1	**26**(41%)	**36** (87%)

[a]All reactions were run in CH_2Cl_2 and the nucleophile was added last. [b]Equivalents relative to 12. [c]Starting Schiff base 12. [d]Isolated yields unless otherwise noted. [e]Isolated yield from A. [f]Starting Schiff base 12 (18%) and benzophenone (82%) were recovered. [g]A CH_2Cl_2 soluble tan-colored viscous oil which did not contain any of product 23 was recovered.



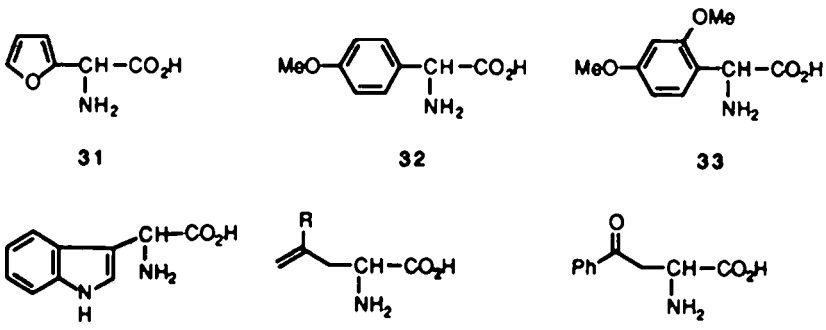
16 30

benzophenone imine of glycine ethyl ester 36, nor the quaternary salt prepared *in situ* from 16 gave the desired substitution product. Interestingly, in the former case, the substitution product 30, derived from loss of the $Ph_2C{=}N$- group, was isolated. Finally, the methoxy Schiff base 17, which is prepared from 12[6], gave only poor yields of the furan-substituted product with either one or two equivalents of $TiCl_4$.

Scale-Up and Amino Acid Isolation

Although the yields of the reactions of acetate 12 with nucleophiles were only modest, these reactions can readily be scaled-up so as to obtain quantities of the desired substitution products. Thus, reactions were carried out on 10 - 61.5 mmolar scale (3.25 - 20 g) of Schiff base acetate 12 with yields similar to those obtained on a 1 mmolar scale (Table 2, entries 2, 6, 11, 14 and 18).

The Schiff base ester substitution products were hydrolyzed to the amino acids using a two-step procedure. Imine hydrolysis was accomplished by mild acid hydrolysis in a two-phase system (1N HCl/ether) followed by separation of benzophenone and ester hydrolysis either by saponification (aq LiOH) or hydrolysis using stronger acid (6N HCl). Using these procedures, the amino acids 31 - 36 and 11 were isolated in 63-93% yield.



31 32 33

34 11 (R = H) 35 (R = CH_3) 36

In summary, reactions of acetate 12 with nucleophiles provide racemic α-aryl substituted amino acids and amino acids derived from allylsilanes or silyl enol ethers. This is an attractive route to these compounds because of the availibility of the starting acetate, the simplicity of the reaction procedure, workup and product purification, as well as the ease of scale-up.

EXPERIMENTAL

General Methods. The starting electrophilic glycine equivalents 12, 15, 16 and 17 were prepared by published procedures.[6] Ether and hexane were distilled from $LiAlH_4$; DMF and chloroform were distilled from CaH_2, and methylene chloride was distilled from P_2O_5. Other solvents were distilled from CaH_2 or were used from freshly opened bottles. Titanium tetrachloride was distilled before use. Aluminum chloride and mercuric chloride were used from freshly opened bottles. Other reagents obtained from Aldrich Chemical Company were reagent grade or spectrophotometric grade and were used without further purification. Flash chromatography columns were prepared using Merck silica gel, grade 60, 230-400

mesh, 60Å. High pressure liquid chromatography was performed on a Waters Associates Liquid Chromatograph equipped with a Varian A-25 recorder, Varian CDS 111 integrator, Perkin-Elmer LC-55 Spectrophotometer, and an Altec C-18 column (Cat. no. 600 RP). The system was operated with a wavelength of 254 nm, a flow rate of 2.0 mL/min, and upper operating pressure of 3000 psi. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 spectrometer using tetramethylsilane (TMS) as an internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer 283 infrared spectrometer. Melting points were taken in open glass capillaries with a Thomas Hoover Uni-Melt and are uncorrected. Elemental analyses were performed by Midwest Microlab of Indianapolis, IN. High resolution mass spectra were recorded at Eli Lilly and Company, Indianapolis, IN.

Preparation of Ethyl α-[(diphenylmethylene)amino]-(±)-2-furanacetate (19) from α-Acetoxyglycine Schiff Base (12) Using Different Lewis Acids. General Procedure: To a 25 mL round bottom flask, equipped with a magnetic stirring bar and a rubber septum, containing α-acetoxyglycine Schiff base **12** (325 mg, 1.0 mmol) and CH_2Cl_2 (5 mL) was added the Lewis acid (1.0 mmol) with stirring under argon. The mixture was stirred at room temperature for 30 sec., then distilled furan (82 mg, 1.2 mmol) was added. The mixture was stirred at room temperature for 8 h. At 1 h. intervals samples (0.1 mL) were withdrawn, diluted with absolute EtOH (1 mL), filtered through glass wool, and analysed by HPLC (70:30 MeOH:H_2O solvent). After stirring for 8 h, the mixture was added to saturated aqueous $NaHCO_3$ (15 mL), stirred, filtered, and extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on a 1.5 cm x 15 cm silica gel column eluted with 70:30 hexane:Et_2O.

Titanium Tetrachloride. The general procedure yielded the furanylglycine Schiff base **19** as a pale yellow oil which decomposed upon heating, yield 155 mg (53%). The furanylglycine Schiff base **19** showed the following characteristics: IR (film) 1740 (s), 1620 (m) cm^{-1}; NMR (CCl_4) δ 1.22 (t, 3H, J=7.0 Hz), 4.12 (q, 2H, J=7.0 Hz), 5.09 (s, 1H), 6.30 (m, 2H), 7.10-7.77 (m, 11H). Anal. Calcd. for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.56; H, 5.81; N, 4.27.

Aluminum Chloride. The general procedure yielded **19** (82 mg, 25%) and benzophenone (137 mg, 75%).

Ethyl Aluminum Dichloride. The general procedure using ethyl aluminum dichloride in hexane (1M solution) yielded **19** (82 mg, 25%) and benzophenone (137 mg, 75%).

Zinc Iodide. The general procedure carried out in a foil wrapped flask showed quantitative formation of benzophenone by HPLC (70:30 MeOH:H_2O).

Magnesium Bromide Etherate. The general procedure gave benzophenone (87%) and unchanged α-acetoxyglycine Schiff base **12** (13%).

Trimethylsilyl Trifluoromethanesulfonate. The general procedure yielded the furanylglycine Schiff base **19** (100 mg, 27%), benzophenone (116 mg, 64%), and unchanged starting Schiff base **12** (29 mg, 9%).

Reaction of α-Acetoxyglycine Schiff Base (12) with $TiCl_4$ and Furan in Different Solvents to Produce Ethyl α-amino-(±)-2-furanacetate (20): General Procedure. To a 25 mL round bottom flask, equipped with a magnetic stirring bar and a rubber septum, containing α-acetoxyglycine Schiff base **12** (325 mg, 1.0 mmmol) was added the solvent (5 mL). The resulting solution was stirred under argon while $TiCl_4$ (190 mg, 1.0 mmol) was added at room temperature. The mixture was stirred 30 sec., then furan (82 mg, 1.2 mmol) was added. The mixture was stirred at room temperature for 4 h, then was added to water (15 mL) and stirred for 15 min. The aqueous layer was washed with CH_2Cl_2 (3 x 5 mL), neutralized with $NaHCO_3$, and filtered through a 0.5 cm x 2 cm pad of Celite. The filter pad was washed with CH_2Cl_2 (10 mL) and the filtrate was extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extracts were dried (Na_2SO_4), filtered, and evaporated *in vacuo* to yield a yellow oil identified as ethyl furanylglycinate **20** from NMR data and by conversion to furanylglycine. Ethyl furanylglycinate **20** showed the following NMR data: NMR (CCl_4) δ 1.23 (t, 3H, J=7.1 Hz), 1.90 (broad s, 2H), 4.14 (q, 2H, J=7.1 Hz), 4.47 (s, 1H), 6.23 (m, 2H), 7.26 (d, 1H, J=2 Hz).

Methylene Chloride. The general procedure yielded **20** as a dark yellow oil (90 mg, 53%).

Chloroform. The general procedure yielded **20** as a yellow oil (79 mg, 47%).

1,2-Dichloroethane. The general procedure yielded **20** as a dark oil (74 mg, 44%).

Trichloroethylene. The general procedure yielded **20** as a yellow oil (61 mg, 36%).

Nitromethane. The general procedure gave a brown liquid (43 mg). The NMR spectrum of the liquid showed it was a 2:1 mixture of nitromethane and **20** (15%).

o-Dichlorobenzene. The general procedure gave a yellow liquid (24 mg). The NMR spectrum of the liquid showed it was ethyl furanylglycinate **20** (14%) contaminated with a small amount of o-dichlorobenzene.

Carbon Tetrachloride. The general procedure yielded **20** as a yellow oil (17 mg, 10%).

Acetonitrile. The general procedure yielded **20** as a dark oil (24 mg, 14%).

Reaction of α-Acetoxyglycine Schiff Base (12) with Furan and Titanium Tetrachloride in Methylene Chloride: Stoichiometry, Temperature and Mode of Addition: General Procedure. To a 25 mL round bottom flask, equipped with a rubber septum and magnetic stirring bar, containing α-acetoxyglycine Schiff base **12** (325 mg, 1.0 mmol) and CH_2Cl_2 (5 mL) was added $TiCl_4$ (0.1 - 2.0 mmol). The mixture was stirred 30 sec. at room temperature, then furan (1.0 - 10 mmol) was added. The mixture was stirred at room temperature for 4 h and was added to saturated aqueous $NaHCO_3$ (25 mL). The mixture was stirred 1 min, filtered through a 0.5 cm x 1 cm pad of Celite, and extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extracts were analysed by HPLC (70:30 MeOH:H_2O) and, when appropriate, purified

by flash chromatography (70:30 hexane:Et_2O) to yield the furanylglycine Schiff base **19**. Spectral and analytical data for **19** are reported above.

Catalytic $TiCl_4$, 1.2 equiv Furan, Room Temperature. Following the general procedure using $TiCl_4$ (0.1 mmol) and adding furan (1.2 mmole) last, HPLC showed a 5:3 mixture of benzophenone and unchanged starting Schiff base **12**.

1.0 equiv Furan, 1.0 equiv $TiCl_4$, Room Temperature. Following the general procedure using furan (1.0 mmole) and adding $TiCl_4$ (1.0 mmol) last, gave **19** as a pale yellow oil (130 mg, 39%).

2.0 equiv $TiCl_4$, 1.0 equiv Furan, Room Temperature. Following the general procedure using $TiCl_4$ (2.0 mmol) and adding furan (1.0 mmole) last, HPLC showed only benzophenone.

2.0 equiv $TiCl_4$, 1.2 equiv Furan, -78°C, to Room Temperature. Following the general procedure, $TiCl_4$ (2.0 mmol) was added with stirring at -78°C under argon. The mixture was stirred 2 min. at -78°C, then furan (1.2 mmol) was added. The mixture immediately turned black and a dark precipitate formed. The mixture was allowed to warm to room temperature and was worked up normally. HPLC showed only benzophenone.

1.0 equiv $TiCl_4$, 10 equiv Furan, Room Temperature. Following the general procedure using $TiCl_4$ (1.0 mmol) and adding furan (10 mmole) last, gave **19** as a pale yellow oil (167 mg, 50%).

1.0 equiv $TiCl_4$, 10 equiv Furan, 0°C, to Room Temperature. Following the general procedure, $TiCl_4$ (1.0 mmol) was added with stirring at 0°C under argon. The mixture was stirred 30 sec. at 0°C, then furan (10 mmol) was added. The mixture was allowed to warm slowly to room temperature, was stirred at room temperature for 3 h and was worked up normally to yield **19** as a pale yellow oil (157 mg, 47%).

1.0 equiv $TiCl_4$, 10 equiv Furan, Room Temperature. Following the general procedure using furan (10 mmole) and adding $TiCl_4$ (1.0 mmol) last, gave **19** as a pale yellow oil (97 mg, 29%).

Reactions of Other Aromatic Nucleophiles with α-acetoxyglycine Schiff base (12).

Preparation of Ethyl α-[(diphenylmethylene)amino]-4-methoxy-(±)-benzeneacetate (**21**). Following the general procedure for the conversion of **12** to **19**, α-acetoxyglycine Schiff base **12** was treated with $TiCl_4$ (2.0 mmol) and anisole (1.2 mmol) at -78°C for 3h, warmed to room temperature and worked up normally to give **21** as a colorless oil which decomposed upon heating (138 mg, 37%). Product **21** gave the following characteristics: IR (film) 1735 (s), 1597 (m) cm^{-1}; NMR (CCl_4) δ 1.13 (t, 3H, J=7.1 Hz); 3.12 (s, 3H); 4.03 (q, 2H, J=7.1 Hz); 4.92 (s, 1H); 6.75 (d, 2H, J=8.8 Hz); 7.00-7.80 (m, 12H). Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.34; H, 6.49; N, 3.24.

Following the same procedure as above with $TiCl_4$ (1.0 mmol) at room temperature for 4h gave anisole (quantitative), starting Schiff base **12** (18%) and benzophenone (82%).

Following the same procedure as above with $TiCl_4$ (3.0 equiv) at -78°C gave **21** as a colorless oil (97 mg, 24%).

Preparation of Ethyl α-[(diphenylmethylene)amino]-2,4-dimethoxy-(±)-benzeneacetate (**22**). Following the general procedure for the conversion of **12** to **19**, α-acetoxyglycine Schiff base **12** was treated with $TiCl_4$ and 1,3-dimethoxybenzene at room temperature for 4h to yield **22** as a colorless oil, (117 mg, 29%). Product **22** had the following characteristics: IR (film) 1735 (s), 1615 (s), 1592 (s) cm^{-1}; NMR (CCl_4) δ 1.18 (t, 3H, J=6.9 Hz), 3.62 (s, 3H), 3.75 (s, 3H), 4.05 (q, 2H, J=6.9 Hz), 5.20 (s, 1H), 6.23 (d, 1H, J=2.7 Hz), 6.39 (dd, 1H, J=2.7 Hz, J=7.6 Hz), 7.03-7.77 (m, 11H). Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.43; H, 6.47; N, 3.40.

Following the same procedure as above with $TiCl_4$ (2.0 equiv) at -78°C gave **22** as a colorless oil (120 mg, 30%).

Following the same procedure as above with $TiCl_4$ (3.0 equiv) at -78°C gave **22** as a colorless oil (157 mg, 38%).

Following the same procedure as above with $TiCl_4$ (4.0 equiv) at -78°C gave **22** as a colorless oil (125 mg, 31%).

Preparation of Ethyl α-[(diphenylmethylene)amino]-(±)-3-indoleacetate (**23**). Following the general procedure for the conversion of **12** to **19**, α-acetoxyglycine Schiff base **12** was treated with $TiCl_4$ and indole at -78°C for 3h, warmed to room temperature and worked up normally to give **23** as a white powder (120 mg, 31%), m.p. 147-9°C (dec). Product **23** gave the following characteristics: IR (CCl_4) 3410 (br, s), 1735 (s), 1622 (m) cm^{-1}; NMR (CCl_4) δ 1.09 (t, 3H, J=7.0 Hz), 3.98 (q, 2H, J=7.0 Hz). 5.23 (s, 1H), 6.73-7.60 (m, 15H), 8.50 (br s, 1H). Anal. Calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.36; H, 5.87; N, 7.26.

Following the same procedure as above with $TiCl_4$ (2.0 equiv) gave a CH_2Cl_2 soluble tan-colored viscous oil (330 mg) which did not contain any of the product **23**.

Reactions of Silicon-Containing Nucleophiles with α-Acetoxyglycine Schiff Base (12).

Reaction with Allyltrimethylsilane to Prepare Ethyl 2-[(diphenylmethylene)amino]-(±)-4-pentenoate (**24**) To a 25 mL round bottom flask, equipped with a magnetic stirring bar and rubber septum, containing the α-acetoxyglycine Schiff base **12** (325 mg, 1.0 mmol) and CH_2Cl_2 (5 mL) was added at -78°C with stirring under argon $TiCl_4$ (190 mg, 1.0 mmol). The mixture was stirred 30 sec., then allyltrimethylsilane (115 mg, 1.0 mmol) was added. The mixture was stirred at -78°C for 3 h, then poured into saturated aqueous $NaHCO_3$ (15 mL) and filtered through a 0.5 cm x 4 cm Celite pad. The pad was washed with CH_2Cl_2 (5 mL) and the filtrate was extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on a 1.5 cm x 14 cm silica gel column eluted with 70:30 hexane:Et_2O to yield allylglycine Schiff base **24** as a pale yellow oil, yield 140 mg (46%). The product **24** showed the following characteristics: IR (film) 1738 (s), 1622 (m), 1598 (m) cm^{-1}; NMR (CCl_4) δ1.23 (t, 3H, J=6.4 Hz), 2.60 (distorted t, 2H, J=6.4 Hz), 3.97 (dd, 1H, J=6.0 Hz, J=6.6 Hz), 4.08 (q, 2H, J=6.4 Hz), 4.93 (dd, 2H, J=10.5 Hz, J=15 Hz), 5.60 (m, 1H), 7.07-7.67 (m, 10H). Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.97; H, 6.86; N, 4.38.

Following the same procedure as above with $TiCl_4$ (0.1 mmol) gave **24** (107 mg, 35%).

Following the same procedure as above with $TiCl_4$ (2.0 mmol) gave **24** (46 mg, 15%).

Reaction with 2-Methyl-2-propenyltrimethylsilane to Prepare Ethyl 2-[(diphenylmethylene)-amino]-4-methyl-(±)-4-pentenoate (25). Following the procedure for the preparation of **24** using 2-methyl-2-propenyltrimethylsilane[15] gave crude product which was purified by flash chromatography (90:10 hexane:Et_2O) to yield the α-isobutenylglycine Schiff base **25** as a colorless oil (50 mg, 16%). The product **25** showed the following characteristics: IR (film) 1732 (s), 1620 (m) cm^{-1}; NMR (CCl_4) δ 1.25 (t, 3H, J=7.1 Hz), 1.49 (s, 3H), 2.50 (m, 2H), 4.10 (overlapping q, m, 3H, J=7.1 Hz), 4.64 (br s, 2H), 7.07-7.67 (m, 10H). Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.64; H, 7.09; N, 4.56.

Reaction with α-(Trimethylsiloxy)styrene to Prepare Ethyl α-[(diphenylmethylene)amino]-γ-oxo-(±)-benzenebutanoate (26). Following the procedure for the preparation of **24** on a 3 mmol scale using the silyl enol ether of acetophenone[16] yielded crude product which was purified by flash chromatography (70:30 hexane:Et_2O) to yield ethyl 2-(diphenylmethyleneamino)-4-oxo-4-phenylbutanoate **26** as a white solid (475 mg, 41%). The product was further purified by recrystalization (1:1 hexane:Et_2O) to yield white crystals of **26** (430 mg, 37% from **12**), m.p. 86-88°C. Product **26** had the following characteristics: IR (CCl_4) 1735 (s), 1682 (s), 1616 (m) cm^{-1}; NMR (CCl_4) δ 1.20 (t, 3H, J=7.1 Hz), 3.44-3.55 (overlapping d, 2H, J=7.2 Hz, J=6.0 Hz), 4.08 (q, 2H, J=7.1 Hz), 4.65 (dd, 1H, J=7.2 Hz, J=6.0 Hz), 6.87-7.98 (m, 15H). Anal. Calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.74; H, 5.99; N, 3.74.

Reactions of Other Electrophilic Glycine Equivalents with Furan in Methylene Chloride.

α-Thiophenylglycine Schiff Base (15), $TiCl_4$. To a round bottom flask, equipped with a magnetic stirring bar and rubber septum, containing the α-phenylthioglycine Schiff base **15** (375 mg, 1 mmol) and CH_2Cl_2 (10 mL) was added $TiCl_4$ (190 mg, 1.0 mmol) with stirring under argon. The mixture was stirred for 30 sec., then furan (82 mg, 1.2 mmol) was added. The mixture was stirred at room temperature for 12 h. HPLC (80:20 MeOH:H_2O solvent) showed only unchanged starting Schiff base **15** present.

α-Thiophenylglycine Schiff Base (15), $HgCl_2$. Following the same procedure as above using $HgCl_2$ (270 mg, 1.0 mmol) and stirring at room temperature for 1.5 h showed only benzophenone by HPLC.

α-Dimethylaminoglycine Schiff Base (16), $TiCl_4$. To a 25 mL round bottom flask, equipped with a magnetic stirring bar and rubber septum, containing ethyl N-(diphenylmethylene)-2-dimethylaminoglycinate **16** (310 mg, 1.0 mmol) and CH_2Cl_2 (10 mL) were added with stirring under argon $TiCl_4$ (190 mg, 1.0 mmol) and furan (82 mg, 1.2 mmol). The mixture was stirred at room temperature for 3 h, then was diluted with Et_2O (25 mL) and was extracted with water (3 x 10 mL). The aqueous extracts were neutralized with $NaHCO_3$ and filtered. The solid was washed with CH_2Cl_2 (5 mL) and the filtrate was extracted with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on a 1 cm x 10 cm silica gel column eluted with 70:30 hexane:Et_2O to yield a colorless oil (105 mg, 53%) which was identified as ethyl N,N-dimethylfuranylglycinate **30** from NMR data. Ethyl N,N-dimethylfuranylglycinate **30** had the following characteristics: NMR (CCl_4) δ 1.27 (t, 3H, J=6.8 Hz), 2.27 (s, 6H), 4.16 (q, 2H, J=6.8 Hz), 4.24 (s, 1H), 6.28 (d, 2H, J=1 Hz), 7.30 (s, 1H).

N-Alkylated α-Dimethylaminoglycine Schiff Base. To a 25 mL round bottom flask, equipped with a magnetic stirring bar and $CaCl_2$ drying tube, containing the α-dimethylaminoglycine Schiff base **16** (210 mg, 0.7 mmol) and CH_2Cl_2 (5 mL) was added with stirring iodomethane (96 mg, 0.7 mmol). The mixture was stirred at room temperature for 2 min. HPLC (70:30 MeOH:H_2O solvent) showed the disappearance of the starting Schiff base and the formation of a polar compound. Furan (48 mg, 0.7 mmol) was added to the stirred mixture. The mixture was stirred at room temperature for 24 h. HPLC (70:30 MeOH:H_2O solvent) showed benzophenone as the only product.

α-Methoxyglycine Schiff Base (17). To a 50 mL round bottom flask equipped with a magnetic stirring bar and a rubber septum was added α-methoxyglycine Schiff base **17** (300 mg, 1.0 mmol), furan (1.0 mmol), and CH_2Cl_2 (5 mL). The solution was cooled to 0°C in an ice-water bath and $TiCl_4$ (1.0 mmol) was added via syringe. After stirring at 0°C under argon for 2 h, the mixture was poured with vigorous stirring into cold (5°C) saturated aqueous $NaHCO_3$ (50 mL). The mixture was filtered through a 4.5 cm x 0.5 cm pad of packed Celite, the filter pad was washed with CH_2Cl_2 (10 mL), the filtrate was extracted with CH_2Cl_2 (3 x 30 mL) and the combined CH_2Cl_2 layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography on a 2.5 cm x 14 cm silica gel column eluted with 70:30 hexane:ether to yield benzophenone (90 mg, 50%), recovered α-methoxy Schiff base **17** (120 mg, 40%), and product **19** (33 mg, 10%). Spectral and analytical data for **19** are reported above.

Following the same procedure as above with $TiCl_4$ (2.0 mmol) gave **19** (85 mg, 25%) and benzophenone (115 mg, 64%).

Preparative Scale Synthesis of Product Schiff Bases from α-Acetoxyglycine Schiff Base (12): General Procedure. To an oven dried 100 mL round bottom flask equipped with a magnetic stirring bar and rubber septum were added the α-acetoxyglycine Schiff base **12** (3.25 g, 10 mmol) and CH_2Cl_2 (50 mL). Titanium tetrachloride (10-20 mmol) was added at -78°C with stirring under argon. The mixture was stirred for 2 min., then the nucleophile (10 mmol) was added. The mixture was stirred at -78°C for 3 h, then was poured into cold (0°C) saturated aqueous $NaHCO_3$ (50 mL). The mixture was vigorously stirred for 2 min., then filtered through a 1 cm x 4 cm pad of Celite. The filter pad was washed with CH_2Cl_2 (20 mL) and the filtrate was extracted with CH_2Cl_2 (3 x 25 mL). The CH_2Cl_2 extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (70:30 hexane:ether).

Ethyl α-[(diphenylmethylene)amino]-(±)-2-furanacetate (19). Following the general procedure, α-acetoxyglycine Schiff base **12** was mixed with $TiCl_4$ (10 mmol) and furan to yield furanylglycine Schiff base **19** as a pale yellow oil (1.60 g, 48%). Spectral and analytical data for **19** are reported above.

Ethyl α-[(diphenylmethylene)amino]-4-methoxy-(±)-benzeneacetate (21). Following the general procedure, α-acetoxyglycine Schiff base **12** was mixed with $TiCl_4$ (20 mmol) and anisole to yield p-methoxyphenylglycine Schiff base **21** as a pale yellow oil (1.38 g, 37%). Spectral and analytical data for **21** are reported above.

Ethyl α-[(diphenylmethylene)amino]-2,4-dimethoxy-(±)-benzeneacetate (22). Following the general procedure, α-acetoxyglycine Schiff base **12** was mixed with $TiCl_4$ (10 mmol) and 1,3-dimethoxybenzene for 4 h to yield 2,4-dimethoxyphenylglycine Schiff base **22** as a colorless oil (1.17 g, 29%). Spectral and analytical data for **22** are reported above.

Ethyl α-[(diphenylmethylene)amino]-(±)-3-indoleacetate (23). Following the general procedure, α-acetoxyglycine Schiff base **12** was mixed with $TiCl_4$ (10 mmol) and indole (12 mmol) to yield nortryptophan Schiff base **23** as a white powder (1.45 g, 38%). Spectral and analytical data for **23** are reported above.

Ethyl 2-[(diphenylmethylene)amino]-(±)-4-pentenoate (24). To a 250 mL round bottom flask equipped with a magnetic stirring bar and a rubber septum were added α-acetoxy glycine Schiff base (20 g, 61.5 mmol) and dichloromethane (150 mL). The solution was cooled to -78°C in a dry ice/acetone bath, then $TiCl_4$ (11.67 g, 61.5 mmol) was added over 1 min with stirring. The mixture was stirred for 1 min and then allyltrimethylsilane (8.43g, 73.8 mmol) was added dropwise with stirring over 1 min. The mixture was stirred at -78°C for 6 hours, was then warmed to room temperature and poured into saturated aqueous sodium bicarbonate (300 mL). The mixture was filtered through Celite, the Celite was rinsed with CH_2Cl_2 (75 mL), and the layers were separated. The aqueous layer was extractd with CH_2Cl_2 (3 x 100 mL). The CH_2Cl_2 layer was washed with saturated brine (1 x 75 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography on a 5 cm x 30 cm silica gel column (90:10 hexane:ether) to give the allylglycine Schiff base **24** (6.04 g, 32%). Spectral and analytical data for **24** are reported above.

Hydrolysis and Saponification of Amino Acid Ester Schiff Bases to Prepare α-Amino Acids: General Procedure. To 0.1 M aqueous HCl (50 mL) was added the Schiff base. The mixure was stirred at room temperature under argon for 3 h, then was washed with ether (3 x 25 mL) and evaporated *in vacuo*. The residue was dissolved in deionized water (2 mL) and 20% aqueous LiOH (1 mL) was added. The mixture was stirred at room temperature until it became homogeneous. The pH of the solution was adjusted to pH 2 by careful addition of 6 M HCl. Ion exchange resin [Amberlite IR-120(+), 2.5 g] was added and the mixture was allowed to stand overnight. The resin was filtered and washed with distilled water until no precipitate was observed when a sample (0.1 mL) of the aqueous wash was added to 5% ethanolic $AgNO_3$ (5 mL). The resin was added to 6 M aqueous NH_4OH (30 mL), stirred for 4 h, and filtered. The filtrate was evaporated *in vacuo* to yield the amino acid.

Preparation of α-Amino-(±)-2-furanacetic Acid (31). Following the general procedure the furanylglycine Schiff base **19** (980 mg, 2.94 mmol) was hydrolysed with 0.1 M aqueous HCl (50 mL) and saponified with 20% aqueous LiOH (1 mL) to yield furanylglycine as a dark solid. The furanylglycine was recrystalized from isopropanol (260 mg, 63%), m.p. 207-209°C (lit.[17] 209-211°C).

Preparation of α-Amino-4-methoxy-(±)-benzeneacetic Acid (32). A stirred mixture of 4-methoxyphenylglycine Schiff base **21** (650 mg, 1.74 mmol) and 6 M aqueous HCl (5 mL) was heated at gentle reflux under argon for 6.5 h. The mixture was cooled, diluted with water (25 mL), and washed with Et_2O (2 x 15 mL). The aqueous layer was evaporated *in vacuo* and the residue was redissolved in water (15 mL). The pH of the solution was adjusted to pH 7 by careful addition of 20% aqueous LiOH. The precipitate was filtered and recrystalized from water to yield 4-methoxyphenylglycine as a white solid (275 mg, 87%), m.p. 259-261°C (sub.), (lit.[17] 264-267°C, sub.).

Preparation of α-Amino-2,4-dimethoxy-(±)-benzeneacetic Acid (33). Following the general procedure 2,4-dimethoxyphenylglycine Schiff base **22** (1.02 g, 2.53 mmol) was treated with 0.1 M aqueous HCl (50 mL) and 20% aqueous LiOH (1 mL) to yield crude 2,4-dimethoxyphenylglycine which was recrystalized from isopropanol to yield the amino acid as white crystals (365 mg, 68%), m.p. 130-131°C. 2,4-Dimethoxyphenylglycine showed the following characteristics: IR (KBr pellet) 3320 (broad, s), 3110 (broad, s), 2020 (w), 1630 (m), 1590 (s), 1505 (m) cm^{-1}; NMR (D_2O, 0.25% TSP standard) δ 3.86 (s, 6H), 5.30 (s, 1H), 6.63 (d, 1H, J= 9 Hz), 6.68 (s, 1H), 7.28 (d, 1H, J= 9 Hz). MS (FAB). Calcd. for $C_{10}H_{13}NO_4$+H: 212.0923. Found: 212.0927.

Preparation of α-Amino-(±)-3-indoleacetic Acid (34). To a 250 mL round bottom flask equipped with a magnetic stirring bar were added nortryptophan Schiff base **23** (1.45 g, 3.79 mmol), ether (100 mL) and 1M aqueous hydrochloric acid (15 mL, 15 mmol). The mixture was stirred vigorously at room temperature for 4 h. The layers were separated and the etheral layer was extracted with water (3 x 10 mL). The combined aqueous layers were cooled to 4°C, then saturated aqueous lithium hydroxide monohydrate (20 mL) was added. The mixture was stirred at room temperature for 2 h at which time all of the solid had gone into solution. The solution was adjusted to pH 7 by the dropwise addition of concentrated HCl. The solution then stood overnight in an evaporating dish to allow the amino acid to crystalize. The crude product was filtered, rinsed with water (10 mL), and recrystalized from water:ethanol (2:1) to give α-aminoindoleacetic acid **34** as fine white crystals (670 mg, 93%). m.p. 210-212°C (lit.[18] 209°C).

Preparation of 2-Amino-(±)-4-pentenoic Acid (11). To a 50 mL round bottom flask equipped with a magnetic stirring bar were added allylglycine Schiff base **24** (6.04 g, 19.7 mmol), ether (5 mL) and 1 M aqueous hydrochloric acid (20 mL, 20 mmol). The mixture was stirred at room temperature for 6 hours. The layers were separated and the aqueous layer was

washed with ether (2 x 5 mL). Concentrated hydrochloric acid (17 mL) was added to the aqueous layer and the mixture was refluxed 18 hours. The mixture was evaporated *in vacuo*, dissolved in distilled water (5 mL) and applied to a 3 cm x 17 cm Amberlite + 120 ion exchange column. The column was eluted with distilled water until the eluant tested negative for chloride ion using 5% ethanolic $AgNO_3$. Then the column was eluted with concentrated ammonium hydroxide until the eluant tested negative with ninhydrin. The fractions containing allylglycine were degassed *in vacuo* and freeze dried to give allylglycine (1.53 g, 68%), mp 243-4°C dec (lit.[19] 245-50°C dec).

Preparation of 2-Amino-4-methyl-(±)-4-pentenoic Acid (35). Following the procedure for preparation of amino acid **11**, Schiff base **25** (993 mg, 3.63 mmol) was hydrolyzed with 1 M aqueous HCl (10 mL) and ether (5 mL) and then concentrated hydrochloric acid (8.5 mL). Workup and purification by chromatography with Amberlite +120 ion exchange resin gave methylallyl glycine (300 mg, 64%), m.p. 194-7°C dec (lit.[20] 214-5°C dec).

Preparation of α-Amino-γ-oxo-(±)-benzenebutanoic Acid (36). Following the general procedure Schiff base **26** (1.00 g, 2.60 mmol) was treated with 0.1 M aqueous HCl (50 mL) and 20% aqueous LiOH (1 mL) to yield 2-amino-4-oxo-4-phenylbutanoic acid. The crude amino acid was recrystalized from water to yield white crystals of 2-amino-4-oxo-4-phenylbutanoic acid (275 mg, 87%), m.p. 179-181°C (dec.), (lit.[21] 182°C, dec.).

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REFERENCES AND NOTES

1. a) 'Chemistry and Biochemistry of the Amino Acids,' ed. G.C. Barrett, Chapman and Hall, London, 1985; b) 'Amino Acids, Peptides and Proteins,' Specialist Periodical Reports, The Royal Society of Chemistry, London, 1969-1985, Vol. 1-16; c) 'Amino Acids and Peptides,' Specialist Periodical Reports, The Royal Society of Chemistry, London, 1986-1987, Vol. 17-18.
2. Lead references involving nucleophilic amino acid equivalents: a) References 3 and 6; b) T. Oesterle and G. Simchen, *Synthesis*, 1985, 403; c) K. Matsumoto, T. Moriya and M. Suzuki, *J. Synth. Org. Chem., Jpn.*, 1985, **43**, 764; d) T. Tsushima and K. Kawada, *Tetrahedron Lett*, 1985, **26**, 2445; e) J.L. Marco, J. Royer and H.-P. Husson, *Tetrahedron Lett.*, 1985, **26**, 3567; f) J. Bajgrowicz, A. El Achquar, M.-L. Roumestant, C. Pigière and P. Viallefont, *Heterocycles*, 1986, **24**, 2165; g) Y.H. Paik and P. Dowd, *J. Org. Chem.*, 1986, **51**, 2910; h) S. Sawada, T. Nakayama, N. Esaki, H. Tanaka, K. Soda and R.K. Hill, *J. Org. Chem.*, 1986, **51**, 3384; i) S. Ikegami, T. Hayama, T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, 1986, **27**, 3403; j) T. Hvidt, O.R. Martin and W.A. Szarek, *Tetrahedron Lett.*, 1986, **27**, 3807; k) J.P. Genet, D. Ferroud, S. Juge and J.R. Montes, *Tetrahedron Lett.*, 1986, **27**, 4573; l) P.K. Subramanian and R.W. Woodard, *J. Org. Chem.*, 1987, **52**, 15; m) H. Kuzuhara, N. Watanabe and M. Ando, *Chem. Commun.*, 1987, 95; n) B.D. Gray and P.W. Jeffs, *Chem. Commun.*, 1987, 1329; o) Z. Changyou, C. Daimo and J. Yaozhong, *Synth. Commun.*, 1987, **17**, 1377; p) A. Fadel and J. Salaün, *Tetrahedron Lett.*, 1987, **28**, 2243; q) L. Banfi, S. Cardani, D. Potenza and C. Scolastico, *Tetrahedron* 1987, **43**, 2317; r) P. Duhamel, J.J. Eddine and J.-Y. Valnot, *Tetrahedron Lett.*, 1987, **28**, 3801; s) S.V. Pansare and J.C. Vederas, *J. Org. Chem.*, 1987, **52**, 4804; t) Y. Ito, M. Sawamura, M. Matsuoka, Y. Matsumoto and T. Hayashi, *Tetrahedron Lett.*, 1987, **28**, 4849; u) T. Owa, M. Otsuka and M. Ohno, *Chem. Lett.*, 1988, 83; v) U. Schöllkopf and J. Schröder, *Liebigs Ann. Chem.*, 1988, 87; w) M. Gander-Coquoz and D. Seebach, *Helv. Chim Acta*, 1988, **71**, 224; x) Y. Ito, M. Sawamura and T. Hayashi, *Tetrahedron Lett.*, 1988, **29**, 239; y) I. Ojima, H.-J.C. Chen and K. Nakahashi, *J. Am. Chem. Soc.*, 1988, **110**, 278; z) Y.N. Belokon', V.I. Bakhmutov, N.I. Chernoglazova, K.A. Kochetkov, S.V. Vitt, N.S. Garbalinskaya and V.M. Belikov, *J. Chem. Soc., Perkin I*, 1988, 305; aa) J.M. McIntosh, R.L. Leavitt, P. Mishra, K.C. Cassidy, J.E. Drake and R. Chadha, *J. Org. Chem.*, 1988, **53**, 1947 and cited references.
3. a) M.J. O'Donnell, J.M. Boniece and S.E. Earp, *Tetrahedron Lett.*, 1978, 2641; b) M.J. O'Donnell and T.M. Eckrich, *Tetrahedron Lett.*, 1978, 4625; c) L. Ghosez, J.-P. Antoine, E. Deffense, M. Navarro, V. Libert, M.J. O'Donnell, W.A. Bruder, K. Willey and K. Wojciechowski, *Tetrahedron Lett.*, 1982, **23**, 4255; d) M. J. O'Donnell, B. LeClef, D. B. Rusterholz, L. Ghosez, J.-P. Antoine, M. Navarro, *Tetrahedron Lett.*, 1982, **23**, 4259;. e) M.J. O'Donnell, W. Bruder, K. Wojciechowski, L. Ghosez, M. Navarro, F. Sainte and J.-P. Antoine, *Peptides: Structure and Function, Proc. 8th Amer. Pept. Symp.* 151 (1983); f) M.J. O'Donnell, K. Wojciechowski, L. Ghosez, M. Navarro, F. Sainte and J.-P. Antoine, *Synthesis*, 1984, 313; g) M.J. O'Donnell, W.A. Bruder, T.M. Eckrich, D.F. Shullenberger and G.S. Staten, *Synthesis*, 1984, 127; h) M.J. O'Donnell, C.L. Barney and J.R. McCarthy, *Tetrahedron Lett.*, 1985, **26**, 3067; i) J.R. McCarthy, C.L. Barney, M.J. O'Donnell and J.C. Huffman, *J. Chem. Soc., Chem. Commun.*, 1987, 469.

4. Aldrich Chemical Company; Compound **3**: N-(diphenylmethylene)glycine ethyl ester, Cat. No. 22,254-2; Compound **4**: N-(diphenylmethylene)aminoacetonitrile, Cat. No. 25,265-4.
5. Lead references involving electrophilic amino acid equivalents: a) Refereace 6; b) S. Shiono and K. Harada, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1061; c) A.L. Castelhano, S. Horne, R. Billedeau and A. Krantz, *Tetrahedron Lett.*, 1986, **27**, 2435; d) B.H. Lipshutz, B. Huff and W. Vaccaro, *Tetrahedron Lett.*, 1986, **27**, 4241; e) Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu and W. Ito, *J. Am. Chem. Soc.*, 1986, **108**, 7778; f) P. Münster and W. Steglich, *Synthesis*, 1987, 223; g) T. Yamada, H. Suzuki and T. Mukaiyama, *Chem. Lett.*, 1987, 293; h) D. Ben-Ishai, I. Sataty, N. Peled and R. Goldshare, *Tetrahedron*, 1987, **43**, 439; i) U. Schöllkopf, S. Grüttner, R. Anderskewitz, E. Egert and M. Dyrbusch, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 683; j) J. Zimmermann and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1104; k) T. Kolasa, S. Sharma and M.J. Miller, *Tetrahedron Lett.*, 1987, **28**, 4973; l) R.M. Williams, P.J. Sinclair, D. Zhai and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547; m) K.E. Harding and C.S. Davis, *Tetrahedron Lett.*, 1988, **29**, 1891 and cited references.
6. M.J. O'Donnell, W.D. Bennett and R.L. Polt, *Tetrahedron Lett.*, 1985, **26**, 695.
7. M.J. O'Donnell and J.-B. Falmagne, *Tetrahedron Lett.*, 1985, **26**, 699.
8. M.J. O'Donnell and J.-B. Falmagne, *J. Chem. Soc., Chem. Commun.*, 1985, 1168.
9 Aldrich Chemical Company; Compound **12**: 2-acetoxy-N-(diphenylmethylene)glycine ethyl ester, Cat. No. 29,660-0.
10. a) 'Chemistry and Biology of β-Lactam Antibiotics,' Vol.1-3, eds. R.B. Morin and M. Gorman, Academic Press, N.Y., 1982; b) C.A. Townsend and A.M. Brown, *J. Am. Chem. Soc.*, 1983, **105**, 913; c) S. Kukolja, S.E. Drabeim, J.L. Pfeil, R.D.G. Cooper, B.J. Graves, R.E. Holmes, D.A. Neel, G.W. Huffman, J.A. Webber, M.D. Kinnick, R.T. Vasileff and B.J. Foster, *J. Med. Chem.*, 1985, **28**, 1886.
11. T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 817.
12. T.L. Gilchrist, 'Heterocyclic Chemistry,' Pitman, London, 1985, p. 144.
13. It was noted that the pale yellow reaction solution containing **12** and $TiCl_4$ in CH_2Cl_2 turned red on addition of either anisole or 1,3-dimethoxybenzene. Aryloxytitanium chlorides are normally bright orange or red solids, see: R. Feld and P.L Cowe, 'The Organic Chemistry of Titanium,' Butterworths, Washington, 1965, p. 51.
14. a) E.W. Colvin, 'Silicon in Organic Synthesis,' Butterworths, London, 1981; b) W.P. Weber, 'Silicon Reagents for Organic Synthesis,' Springer-Verlag, Berlin, 1983; c) P. Brownbridge, *Synthesis*, 1983. 1 and 85; d) J. Dunoguès, *Bull. Soc. Chim. Fr.*, 1987, 659.
15. U. Schöllkopf and H.-U. Scholz, *Synthesis*, 1976, 271.
16. H.O. House, L.J. Czuba, M. Gall and H.D. Olmstead, *J. Org. Chem.*, 1969, **34**, 2324.
17. K. Matsumoto, M. Suzuki and M. Miyoshi, *J. Org. Chem.*, 1973, **38**, 2094.
18. G. Casnati and A. Ricca, *Gazz. Chim Ital.*, 1963, **93**, 355.
19. D.J. Drinkwater and P.W.G. Smith, *J. Chem. Soc.(C)*, 1971, 1305.
20. N.F. Albertson, *J. Am. Chem. Soc.*, 1946, **68**, 450.
21. H. Kato and M. Shimo, *Nippon Kagaku Zasshi*, 1967, **88**, 224 (*Chem. Abstr.*, 1967, **67**:63985d).